Ribociclib EBC

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Subpopulation: pre-menopausal female patients

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1 Patient disposition, demographic and disease characteristics, follow-up times and PRO return rates

Table 1-1 Patient disposition (Full Analysis Set)

	Treatment Groups		
	Ribociclib + ET (N=1115)	**ET (N=1123)**	**Total (N=2238)**
Randomized	**1115**	**1123**	**2238**
Randomized but not treated	**9 (0.8)**	**51 (4.5)**	**60 (2.7)**
Treated with any treatment	**1106 (99.2)**	**1072 (95.5)**	**2178 (97.3)**
Treated with Ribociclib	1106 (99.2)	2 (0.2)	1108 (49.5)
Treated with NSAI	1106 (99.2)	1072 (95.5)	2178 (97.3)
Treated with Goserelin	1088 (97.6)	1051 (93.6)	2139 (95.6)
Still on treatment	**821 (73.6)**	**732 (65.2)**	**1553 (69.4)**
Discontinued from treatment for all the components of study treatment	**212 (19.0)**	**339 (30.2)**	**551 (24.6)**
Discontinued from Ribociclib	328 (29.4)	2 (0.2)	330 (14.7)
Discontinued from NSAI	282 (25.3)	339 (30.2)	621 (27.7)
Discontinued from Goserelin	386 (34.6)	427 (38.0)	813 (36.3)
Primary reason for discontinuation of Ribociclib			
Adverse event	179 (16.1)	0 (0.0)	179 (8.0)
Disease relapse	49 (4.4)	0 (0.0)	49 (2.2)
Lost to follow-up	2 (0.2)	0 (0.0)	2 (0.1)
Endocrine therapy discontinuation	1 (0.1)	0 (0.0)	1 (0.0)
Patient decision to discontinue treatment	45 (4.0)	0 (0.0)	45 (2.0)
Physician decision	8 (0.7)	0 (0.0)	8 (0.4)
Protocol deviation	3 (0.3)	1 (0.1)	4 (0.2)
Withdrawal by subject	35 (3.1)	0 (0.0)	35 (1.6)
Other	6 (0.5)	1 (0.1)	7 (0.3)
Primary reason for discontinuation of NSAI			
Adverse event	44 (3.9)	54 (4.8)	98 (4.4)
Death	2 (0.2)	1 (0.1)	3 (0.1)
Disease relapse	75 (6.7)	109 (9.7)	184 (8.2)
Lost to follow-up	5 (0.4)	8 (0.7)	13 (0.6)
Patient decision to discontinue treatment	69 (6.2)	66 (5.9)	135 (6.0)
Physician decision	16 (1.4)	20 (1.8)	36 (1.6)
Protocol deviation	4 (0.4)	3 (0.3)	7 (0.3)
Withdrawal by subject	57 (5.1)	74 (6.6)	131 (5.9)
Other	10 (0.9)	4 (0.4)	14 (0.6)
Primary reason for discontinuation of Goserelin			
Adverse event	36 (3.2)	41 (3.7)	77 (3.4)
Death	2 (0.2)	1 (0.1)	3 (0.1)
Disease relapse	67 (6.0)	97 (8.6)	164 (7.3)

	Treatment Groups		
	Ribociclib + ET (N=1115)	**ET (N=1123)**	**Total (N=2238)**
Lost to follow-up	3 (0.3)	5 (0.4)	8 (0.4)
Patient decision to discontinue treatment	62 (5.6)	59 (5.3)	121 (5.4)
Physician decision	17 (1.5)	17 (1.5)	34 (1.5)
Protocol deviation	5 (0.4)	3 (0.3)	8 (0.4)
Withdrawal by subject	47 (4.2)	64 (5.7)	111 (5.0)
Other	147 (13.2)	140 (12.5)	287 (12.8)
Completed treatment with Ribociclib	**778 (69.8)**	**0 (0.0)**	**778 (34.8)**
Completed treatment with NSAI	**3 (0.3)**	**1 (0.1)**	**4 (0.2)**
Completed treatment with Goserelin	**2 (0.2)**	**1 (0.1)**	**3 (0.1)**
Entered the follow-up phase	**142 (12.7)**	**199 (17.7)**	**341 (15.2)**
Discontinued from trial	**167 (15.0)**	**241 (21.5)**	**408 (18.2)**
Primary reason for discontinuation of trial			
Withdrawal by subject	110 (9.9)	171 (15.2)	281 (12.6)
Other	3 (0.3)	3 (0.3)	6 (0.3)
Death	31 (2.8)	46 (4.1)	77 (3.4)
Lost to follow-up	9 (0.8)	15 (1.3)	24 (1.1)
Physician decision	10 (0.9)	5 (0.4)	15 (0.7)
Protocol deviation	3 (0.3)	1 (0.1)	4 (0.2)
Pregnancy	1 (0.1)	0 (0.0)	1 (0.0)

ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
NSAI: Non-steroidal aromatase inhibitor
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Table 1-2 Patient demographics (Full Analysis Set)

	Treatment Groups		
	Ribociclib + ET (N=1115)	**ET (N=1123)**	**Total (N=2238)**
Age group 1 at randomization, n (%)			
<45	551 (49.4)	533 (47.5)	1084 (48.4)
45 to 54	544 (48.8)	562 (50.0)	1106 (49.4)
55 to 64	20 (1.8)	28 (2.5)	48 (2.1)
Age group 2 at randomization (median for subpopulation pre-menopausal female patients), n (%)			
<Median	551 (49.4)	533 (47.5)	1084 (48.4)
≥Median	564 (50.6)	590 (52.5)	1154 (51.6)
Age (years) at randomization			
n	1115	1123	2238
Mean ± SD	44.1 ± 6.10	44.1 ± 6.22	44.1 ± 6.16
Median	45.0	45.0	45.0
Range 1st to 3rd quartile	40.0 to 49.0	40.0 to 49.0	40.0 to 49.0
Range minimum to maximum	24.0 to 60.0	24.0 to 60.0	24.0 to 60.0
Gender, n (%)			
Female	1115 (100.0)	1123 (100.0)	2238 (100.0)
Race, n (%)			
American Indian or Alaska Native	3 (0.3)	2 (0.2)	5 (0.2)
Asian	211 (18.9)	200 (17.8)	411 (18.4)
Black or African American	16 (1.4)	22 (2.0)	38 (1.7)
Native Hawaiian or other Pacific Islander	1 (0.1)	1 (0.1)	2 (0.1)
White	754 (67.6)	757 (67.4)	1511 (67.5)
Other	72 (6.5)	82 (7.3)	154 (6.9)
Not reported	58 (5.2)	59 (5.3)	117 (5.2)
Ethnicity, n (%)			
Hispanic or Latino	102 (9.1)	105 (9.3)	207 (9.2)
Not Hispanic or Latino	900 (80.7)	888 (79.1)	1788 (79.9)
Unknown	75 (6.7)	99 (8.8)	174 (7.8)
Not reported	38 (3.4)	31 (2.8)	69 (3.1)
Geographic region, n (%)			
Europe	661 (59.3)	656 (58.4)	1317 (58.8)
North America/Australia	212 (19.0)	215 (19.1)	427 (19.1)
Asia	178 (16.0)	182 (16.2)	360 (16.1)
Latin America	64 (5.7)	70 (6.2)	134 (6.0)
Weight (kg) at baseline			
n	1106	1119	2225
Mean ± SD	69.9 ± 15.56	69.6 ± 14.60	69.8 ± 15.08
Median	67.0	66.5	66.8
Range 1st to 3rd quartile	59.0 to 78.6	59.4 to 78.0	59.0 to 78.0
Range minimum to maximum	38.4 to 149.0	41.0 to 131.9	38.4 to 149.0

	Treatment Groups		
	Ribociclib + ET (N=1115)	**ET (N=1123)**	**Total (N=2238)**
Height (cm) at baseline			
n	1101	1112	2213
Mean ± SD	163.7 ± 6.64	163.8 ± 6.68	163.7 ± 6.66
Median	163.5	164.0	164.0
Range 1st to 3rd quartile	159.0 to 168.0	159.1 to 168.0	159.0 to 168.0
Range minimum to maximum	145.0 to 186.0	144.0 to 187.0	144.0 to 187.0
Body mass index (kg/m²) at baseline			
n	1099	1111	2210
Mean ± SD	26.1 ± 5.55	26.0 ± 5.28	26.0 ± 5.41
Median	25.1	24.9	25.0
Range 1st to 3rd quartile	22.1 to 29.0	22.1 to 28.8	22.1 to 28.9
Range minimum to maximum	16.1 to 53.3	15.5 to 50.2	15.5 to 53.3
ECOG performance status at baseline, n (%)			
0	967 (86.7)	976 (86.9)	1943 (86.8)
1	146 (13.1)	146 (13.0)	292 (13.0)
Not reported	2 (0.2)	1 (0.1)	3 (0.1)

ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
ECOG: Eastern Cooperative Oncology Group
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Table 1-3 Patient baseline disease characteristics (Full Analysis Set)

	Treatment Groups		
	Ribociclib + ET (N=1115)	**ET (N=1123)**	**Total (N=2238)**
Histological grade			
At diagnosis			
G1	95 (8.5)	103 (9.2)	198 (8.8)
G2	637 (57.1)	653 (58.1)	1290 (57.6)
G3	210 (18.8)	222 (19.8)	432 (19.3)
Gx	10 (0.9)	15 (1.3)	25 (1.1)
Not done	148 (13.3)	120 (10.7)	268 (12.0)
Missing	15 (1.3)	10 (0.9)	25 (1.1)
On surgical specimen			
G1	111 (10.0)	107 (9.5)	218 (9.7)
G2	609 (54.6)	630 (56.1)	1239 (55.4)
G3	297 (26.6)	279 (24.8)	576 (25.7)
Gx	16 (1.4)	14 (1.2)	30 (1.3)
Not done	82 (7.4)	91 (8.1)	173 (7.7)
Missing	0 (0.0)	2 (0.2)	2 (0.1)
TNM-Status			
T-Status			
At diagnosis			
T0	2 (0.2)	1 (0.1)	3 (0.1)
T1a	25 (2.2)	17 (1.5)	42 (1.9)
T1b	21 (1.9)	19 (1.7)	40 (1.8)
T1c	129 (11.6)	134 (11.9)	263 (11.8)
T1mi	1 (0.1)	5 (0.4)	6 (0.3)
T2	536 (48.1)	541 (48.2)	1077 (48.1)
T3	238 (21.3)	231 (20.6)	469 (21.0)
T4a	30 (2.7)	30 (2.7)	60 (2.7)
T4b	37 (3.3)	40 (3.6)	77 (3.4)
T4c	2 (0.2)	6 (0.5)	8 (0.4)
T4d	13 (1.2)	15 (1.3)	28 (1.3)
Tis	1 (0.1)	3 (0.3)	4 (0.2)
Tx	62 (5.6)	67 (6.0)	129 (5.8)
Missing	18 (1.6)	14 (1.2)	32 (1.4)
On surgical specimen			
T0	29 (2.6)	24 (2.1)	53 (2.4)
T1a	52 (4.7)	47 (4.2)	99 (4.4)
T1b	61 (5.5)	64 (5.7)	125 (5.6)
T1c	245 (22.0)	213 (19.0)	458 (20.5)
T1mi	7 (0.6)	11 (1.0)	18 (0.8)
T2	477 (42.8)	527 (46.9)	1004 (44.9)

	Treatment Groups		
	Ribociclib + ET (N=1115)	**ET (N=1123)**	**Total (N=2238)**
T3	203 (18.2)	186 (16.6)	389 (17.4)
T4a	13 (1.2)	10 (0.9)	23 (1.0)
T4b	9 (0.8)	18 (1.6)	27 (1.2)
T4d	4 (0.4)	4 (0.4)	8 (0.4)
Tis	7 (0.6)	15 (1.3)	22 (1.0)
Tx	8 (0.7)	4 (0.4)	12 (0.5)
N-Status			
At diagnosis			
N0	286 (25.7)	288 (25.6)	574 (25.6)
N1	502 (45.0)	497 (44.3)	999 (44.6)
N2a	133 (11.9)	120 (10.7)	253 (11.3)
N2b	4 (0.4)	7 (0.6)	11 (0.5)
N3a	46 (4.1)	56 (5.0)	102 (4.6)
N3b	8 (0.7)	17 (1.5)	25 (1.1)
N3c	14 (1.3)	15 (1.3)	29 (1.3)
Nx	104 (9.3)	110 (9.8)	214 (9.6)
Missing	18 (1.6)	13 (1.2)	31 (1.4)
On surgical specimen			
N0	139 (12.5)	155 (13.8)	294 (13.1)
N0(i+)	5 (0.4)	11 (1.0)	16 (0.7)
N0(mol+)	0 (0.0)	1 (0.1)	1 (0.0)
N1a	411 (36.9)	396 (35.3)	807 (36.1)
N1b	7 (0.6)	6 (0.5)	13 (0.6)
N1c	12 (1.1)	14 (1.2)	26 (1.2)
N1mi	61 (5.5)	65 (5.8)	126 (5.6)
N2b	329 (29.5)	299 (26.6)	628 (28.1)
N2c	3 (0.3)	5 (0.4)	8 (0.4)
N3a	134 (12.0)	154 (13.7)	288 (12.9)
N3b	9 (0.8)	5 (0.4)	14 (0.6)
N3c	4 (0.4)	10 (0.9)	14 (0.6)
Nx	1 (0.1)	2 (0.2)	3 (0.1)
M-Status			
At diagnosis			
M0	1115 (100.0)	1122 (99.9)	2237 (100.0)
Missing	0 (0.0)	1 (0.1)	1 (0.0)
On surgical specimen			
Missing	1115 (100.0)	1123 (100.0)	2238 (100.0)
K67 Score			
At diagnosis			

	Treatment Groups		
	Ribociclib + ET (N=1115)	**ET (N=1123)**	**Total (N=2238)**
n	831	877	1708
Mean ± SD	28.1 ± 20.18	27.9 ± 19.49	28.0 ± 19.82
Median	25.0	22.0	23.5
Range 1st to 3rd quartile	14.0 to 38.0	14.0 to 37.0	14.0 to 37.5
Range minimum to maximum	0.0 to 97.0	0.0 to 100.0	0.0 to 100.0
On surgical specimen			
n	579	621	1200
Mean ± SD	20.3 ± 18.38	19.4 ± 18.08	19.9 ± 18.22
Median	15.0	15.0	15.0
Range 1st to 3rd quartile	5.0 to 30.0	5.0 to 27.0	5.0 to 30.0
Range minimum to maximum	0.0 to 91.0	0.0 to 98.0	0.0 to 98.0
At diagnosis			
≤14%	214 (19.2)	221 (19.7)	435 (19.4)
>14%	617 (55.3)	656 (58.4)	1273 (56.9)
Missing	284 (25.5)	246 (21.9)	530 (23.7)
On surgical specimen			
≤14%	264 (23.7)	296 (26.4)	560 (25.0)
>14%	315 (28.3)	325 (28.9)	640 (28.6)
Missing	536 (48.1)	502 (44.7)	1038 (46.4)
At diagnosis			
≤20%	393 (35.2)	422 (37.6)	815 (36.4)
>20%	438 (39.3)	455 (40.5)	893 (39.9)
Missing	284 (25.5)	246 (21.9)	530 (23.7)
On surgical specimen			
≤20%	369 (33.1)	427 (38.0)	796 (35.6)
>20%	210 (18.8)	194 (17.3)	404 (18.1)
Missing	536 (48.1)	502 (44.7)	1038 (46.4)
AJCC 8th edition anatomic stage			
IB	3 (0.3)	0 (0.0)	3 (0.1)
IIA	171 (15.3)	203 (18.1)	374 (16.7)
IIB	248 (22.2)	229 (20.4)	477 (21.3)
IIIA	451 (40.4)	416 (37.0)	867 (38.7)
IIIB	67 (6.0)	61 (5.4)	128 (5.7)
IIIC	175 (15.7)	214 (19.1)	389 (17.4)
Prior neo-/adjuvant chemotherapy			
No	83 (7.4)	84 (7.5)	167 (7.5)
Yes	1032 (92.6)	1039 (92.5)	2071 (92.5)
Time since diagnosis			

	Treatment Groups		
	Ribociclib + ET (N=1115)	**ET (N=1123)**	**Total (N=2238)**
n	1100	1109	2209
Mean ± SD	11.9 ± 3.25	12.0 ± 3.25	11.9 ± 3.25
Median	11.8	11.7	11.8
Range 1st to 3rd quartile	9.9 to 14.1	10.0 to 14.0	10.0 to 14.1
Range minimum to maximum	0.8 to 22.2	0.8 to 24.3	0.8 to 24.3
Predominant histology			
Carcinoma medullary	1 (0.1)	1 (0.1)	2 (0.1)
Invasive ductal carcinoma nos	868 (77.8)	880 (78.4)	1748 (78.1)
Invasive lobular	174 (15.6)	174 (15.5)	348 (15.5)
Mucinous	8 (0.7)	14 (1.2)	22 (1.0)
Papillary	9 (0.8)	4 (0.4)	13 (0.6)
Other	55 (4.9)	50 (4.5)	105 (4.7)
Prior surgery			
Axillary lymph node dissection	969 (86.9)	964 (85.8)	1933 (86.4)
Breast conserving surgery	381 (34.2)	391 (34.8)	772 (34.5)
Mastectomy	771 (69.1)	785 (69.9)	1556 (69.5)
Sentinel lymph node biopsy	402 (36.1)	402 (35.8)	804 (35.9)
Other	62 (5.6)	69 (6.1)	131 (5.9)
Estrogen receptor (ER) status			
Prior to surgery			
Negative	4 (0.4)	8 (0.7)	12 (0.5)
Positive	1021 (91.6)	1028 (91.5)	2049 (91.6)
Unknown	0 (0.0)	1 (0.1)	1 (0.0)
Missing	8 (0.7)	7 (0.6)	15 (0.7)
On surgical specimen			
Negative	1 (0.1)	2 (0.2)	3 (0.1)
Positive	610 (54.7)	657 (58.5)	1267 (56.6)
Unknown	1 (0.1)	1 (0.1)	2 (0.1)
Missing	45 (4.0)	39 (3.5)	84 (3.8)
Progesterone receptor (PR) status			
Prior to surgery			
Negative	81 (7.3)	85 (7.6)	166 (7.4)
Positive	942 (84.5)	944 (84.1)	1886 (84.3)
Unknown	2 (0.2)	8 (0.7)	10 (0.4)
Missing	8 (0.7)	7 (0.6)	15 (0.7)
On surgical specimen			
Negative	103 (9.2)	114 (10.2)	217 (9.7)
Positive	508 (45.6)	539 (48.0)	1047 (46.8)
Unknown	1 (0.1)	7 (0.6)	8 (0.4)
Missing	45 (4.0)	39 (3.5)	84 (3.8)
Combinations ER+PR+ vs. ER+PR- vs. ER-PR+			
ER+/PR+	972 (87.2)	959 (85.4)	1931 (86.3)

	Treatment Groups		
	Ribociclib + ET (N=1115)	**ET (N=1123)**	**Total (N=2238)**
ER+/PR-	137 (12.3)	149 (13.3)	286 (12.8)
ER-/PR+	2 (0.2)	6 (0.5)	8 (0.4)
Missing	4 (0.4)	9 (0.8)	13 (0.6)

ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
AJJC: American Joint Commission on Cancer
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Table 1-4 Drug exposure and follow-up times by endpoint and study treatment (Full Analysis Set)

	Treatment Groups		
	Ribociclib + ET (N=1115)	**ET (N=1123)**	**Total (N=2238)**
Duration of exposure (months)			
Ribociclib			
n	1106	2	1108
Mean ± SD	28.3 ± 12.82	2.0 ± 2.79	28.2 ± 12.86
Median	35.7	2.0	35.7
Range 1st to 3rd quartile	24.4 to 35.7	0.1 to 4.0	24.0 to 35.7
Range minimum to maximum	0.0 to 37.0	0.1 to 4.0	0.0 to 37.0
NSAI			
n	1106	1072	2178
Mean ± SD	40.5 ± 14.93	38.1 ± 16.57	39.3 ± 15.80
Median	45.0	44.6	44.8
Range 1st to 3rd quartile	37.5 to 50.6	31.6 to 50.4	36.9 to 50.5
Range minimum to maximum	0.0 to 60.0	0.0 to 60.0	0.0 to 60.0
Goserelin			
n	1088	1051	2139
Mean ± SD	37.2 ± 16.51	35.1 ± 17.58	36.2 ± 17.07
Median	43.4	40.5	42.3
Range 1st to 3rd quartile	29.6 to 49.7	20.4 to 49.7	24.8 to 49.7
Range minimum to maximum	0.1 to 60.8	0.3 to 60.0	0.1 to 60.8
Follow-up time (months) - Efficacy			
Overall Survival Event			
n	1115	1123	2238
Mean ± SD	41.9 ± 13.12	39.7 ± 15.45	40.8 ± 14.38
Median	44.4	44.2	44.3
Range 1st to 3rd quartile	38.1 to 49.8	36.9 to 49.7	37.7 to 49.8
Range minimum to maximum	0.0 to 60.8	0.0 to 61.3	0.0 to 61.3
First iDFS Event			
n	1115	1123	2238
Mean ± SD	39.2 ± 14.19	36.5 ± 16.38	37.9 ± 15.38
Median	44.2	44.2	44.2
Range 1st to 3rd quartile	35.7 to 49.7	33.1 to 49.7	33.4 to 49.7
Range minimum to maximum	0.0 to 60.8	0.0 to 59.5	0.0 to 60.8
Recurrence Free Survival Event			
n	1115	1123	2238
Mean ± SD	39.5 ± 13.94	36.8 ± 16.26	38.2 ± 15.21
Median	44.2	44.2	44.2
Range 1st to 3rd quartile	35.9 to 49.7	33.1 to 49.7	33.6 to 49.7
Range minimum to maximum	0.0 to 60.8	0.0 to 59.5	0.0 to 60.8

	Treatment Groups		
	Ribociclib + ET (N=1115)	**ET (N=1123)**	**Total (N=2238)**
Distant Disease Free Survival Event			
n	1115	1123	2238
Mean ± SD	39.4 ± 14.04	36.6 ± 16.31	38.0 ± 15.28
Median	44.2	44.2	44.2
Range 1st to 3rd quartile	35.9 to 49.7	33.1 to 49.7	33.4 to 49.7
Range minimum to maximum	0.0 to 60.8	0.0 to 59.5	0.0 to 60.8
Loco Regional Recurrence Free Survival Event			
n	1115	1123	2238
Mean ± SD	39.7 ± 13.76	37.3 ± 15.86	38.5 ± 14.90
Median	44.2	44.2	44.2
Range 1st to 3rd quartile	35.9 to 49.7	33.1 to 49.7	34.3 to 49.7
Range minimum to maximum	0.0 to 60.8	0.0 to 59.5	0.0 to 60.8
Follow-up time (months) - EORTC-QLQ-C30 Symptoms			
Fatigue			
n	1059	1004	2063
Mean ± SD	40.3 ± 12.29	39.6 ± 12.88	40.0 ± 12.59
Median	44.4	44.4	44.4
Range 1st to 3rd quartile	33.8 to 49.9	33.5 to 49.8	33.6 to 49.8
Range minimum to maximum	1.0 to 61.7	0.5 to 61.5	0.5 to 61.7
Nausea and Vomiting			
n	1059	1005	2064
Mean ± SD	40.3 ± 12.30	39.6 ± 12.88	40.0 ± 12.59
Median	44.4	44.4	44.4
Range 1st to 3rd quartile	33.8 to 49.9	33.5 to 49.8	33.6 to 49.8
Range minimum to maximum	1.0 to 61.7	0.5 to 61.5	0.5 to 61.7
Pain			
n	1060	1004	2064
Mean ± SD	40.3 ± 12.29	39.6 ± 12.89	40.0 ± 12.59
Median	44.4	44.4	44.4
Range 1st to 3rd quartile	33.8 to 49.9	33.5 to 49.8	33.6 to 49.8
Range minimum to maximum	1.0 to 61.7	0.5 to 61.5	0.5 to 61.7
Dyspnoea			
n	1057	1004	2061
Mean ± SD	40.3 ± 12.24	39.6 ± 12.89	40.0 ± 12.57
Median	44.4	44.4	44.4
Range 1st to 3rd quartile	33.8 to 49.9	33.5 to 49.8	33.6 to 49.8
Range minimum to maximum	1.0 to 61.7	0.5 to 61.5	0.5 to 61.7

	Treatment Groups		
	Ribociclib + ET (N=1115)	**ET (N=1123)**	**Total (N=2238)**
Insomnia			
n	1060	1005	2065
Mean ± SD	40.3 ± 12.29	39.6 ± 12.88	40.0 ± 12.58
Median	44.4	44.4	44.4
Range 1st to 3rd quartile	33.8 to 49.9	33.5 to 49.8	33.6 to 49.8
Range minimum to maximum	1.0 to 61.7	0.5 to 61.5	0.5 to 61.7
Appetite Loss			
n	1059	1005	2064
Mean ± SD	40.3 ± 12.30	39.6 ± 12.88	40.0 ± 12.59
Median	44.4	44.4	44.4
Range 1st to 3rd quartile	33.8 to 49.9	33.5 to 49.8	33.6 to 49.8
Range minimum to maximum	1.0 to 61.7	0.5 to 61.5	0.5 to 61.7
Constipation			
n	1055	1004	2059
Mean ± SD	40.3 ± 12.31	39.5 ± 12.90	39.9 ± 12.60
Median	44.4	44.4	44.4
Range 1st to 3rd quartile	33.8 to 49.9	33.5 to 49.8	33.6 to 49.8
Range minimum to maximum	1.0 to 61.7	0.5 to 61.5	0.5 to 61.7
Diarrhoea			
n	1055	1003	2058
Mean ± SD	40.3 ± 12.28	39.5 ± 12.92	40.0 ± 12.60
Median	44.4	44.4	44.4
Range 1st to 3rd quartile	33.8 to 49.9	33.5 to 49.8	33.6 to 49.8
Range minimum to maximum	1.0 to 61.7	0.5 to 61.5	0.5 to 61.7
Follow-up time (months) - EORTC-QLQ-C30 QoL			
Global Health/QoL			
n	1056	1003	2059
Mean ± SD	40.3 ± 12.28	39.6 ± 12.90	40.0 ± 12.59
Median	44.4	44.4	44.4
Range 1st to 3rd quartile	33.8 to 49.9	33.5 to 49.8	33.6 to 49.8
Range minimum to maximum	1.0 to 61.7	0.5 to 61.5	0.5 to 61.7
Physical Functioning			
n	1060	1003	2063
Mean ± SD	40.3 ± 12.29	39.6 ± 12.84	40.0 ± 12.56
Median	44.4	44.4	44.4
Range 1st to 3rd quartile	33.8 to 49.9	33.5 to 49.8	33.6 to 49.8
Range minimum to maximum	1.0 to 61.7	0.5 to 61.5	0.5 to 61.7

	Treatment Groups		
	Ribociclib + ET (N=1115)	**ET (N=1123)**	**Total (N=2238)**
Role Functioning			
n	1059	1004	2063
Mean ± SD	40.3 ± 12.29	39.6 ± 12.86	40.0 ± 12.57
Median	44.4	44.4	44.4
Range 1st to 3rd quartile	33.8 to 49.9	33.5 to 49.8	33.6 to 49.8
Range minimum to maximum	1.0 to 61.7	0.5 to 61.5	0.5 to 61.7
Emotional Functioning			
n	1056	1003	2059
Mean ± SD	40.3 ± 12.28	39.6 ± 12.90	40.0 ± 12.59
Median	44.4	44.4	44.4
Range 1st to 3rd quartile	33.8 to 49.9	33.5 to 49.8	33.6 to 49.8
Range minimum to maximum	1.0 to 61.7	0.5 to 61.5	0.5 to 61.7
Cognitive Functioning			
n	1056	1003	2059
Mean ± SD	40.3 ± 12.28	39.6 ± 12.90	40.0 ± 12.59
Median	44.4	44.4	44.4
Range 1st to 3rd quartile	33.8 to 49.9	33.5 to 49.8	33.6 to 49.8
Range minimum to maximum	1.0 to 61.7	0.5 to 61.5	0.5 to 61.7
Social Functioning			
n	1056	1002	2058
Mean ± SD	40.3 ± 12.28	39.6 ± 12.90	40.0 ± 12.59
Median	44.4	44.4	44.4
Range 1st to 3rd quartile	33.8 to 49.9	33.5 to 49.8	33.6 to 49.8
Range minimum to maximum	1.0 to 61.7	0.5 to 61.5	0.5 to 61.7
Follow-up time (months) - EORTC-QLQ-BR23 Symptoms			
Side Effects Of Systemic Therapy			
n	1060	1003	2063
Mean ± SD	40.3 ± 12.29	39.6 ± 12.86	39.9 ± 12.57
Median	44.4	44.4	44.4
Range 1st to 3rd quartile	33.8 to 49.9	33.5 to 49.8	33.6 to 49.8
Range minimum to maximum	1.0 to 61.7	0.5 to 61.5	0.5 to 61.7
Breast Symptoms			
n	1052	1001	2053
Mean ± SD	40.3 ± 12.29	39.5 ± 12.88	39.9 ± 12.58
Median	44.4	44.4	44.4
Range 1st to 3rd quartile	33.8 to 49.9	33.5 to 49.8	33.6 to 49.8
Range minimum to maximum	1.0 to 61.7	0.5 to 61.5	0.5 to 61.7

	Treatment Groups		
	Ribociclib + ET (N=1115)	**ET (N=1123)**	**Total (N=2238)**
Arm Symptoms			
n	1054	1000	2054
Mean ± SD	40.3 ± 12.28	39.5 ± 12.87	39.9 ± 12.57
Median	44.4	44.4	44.4
Range 1st to 3rd quartile	33.8 to 49.9	33.5 to 49.8	33.6 to 49.8
Range minimum to maximum	1.0 to 61.7	0.5 to 61.5	0.5 to 61.7
Being Upset With Hair Loss			
n	300	258	558
Mean ± SD	36.0 ± 12.29	36.7 ± 12.89	36.3 ± 12.57
Median	38.9	39.0	38.9
Range 1st to 3rd quartile	33.2 to 44.5	33.1 to 44.8	33.2 to 44.7
Range minimum to maximum	1.2 to 56.1	1.1 to 55.9	1.1 to 56.1
Follow-up time (months) - EORTC-QLQ-BR23 QoL			
Body Image			
n	1060	1000	2060
Mean ± SD	40.3 ± 12.29	39.6 ± 12.81	40.0 ± 12.55
Median	44.4	44.4	44.4
Range 1st to 3rd quartile	33.8 to 49.9	33.5 to 49.8	33.6 to 49.8
Range minimum to maximum	1.0 to 61.7	0.5 to 61.5	0.5 to 61.7
Sexual Functioning			
n	1047	994	2041
Mean ± SD	40.1 ± 12.48	39.4 ± 12.90	39.7 ± 12.69
Median	44.4	44.4	44.4
Range 1st to 3rd quartile	33.7 to 49.8	33.4 to 49.8	33.6 to 49.8
Range minimum to maximum	1.0 to 61.7	0.6 to 61.5	0.6 to 61.7
Sexual Enjoyment			
n	630	598	1228
Mean ± SD	36.8 ± 13.41	35.8 ± 13.93	36.3 ± 13.67
Median	39.1	38.9	39.0
Range 1st to 3rd quartile	33.1 to 45.2	27.8 to 45.1	28.2 to 45.1
Range minimum to maximum	1.0 to 61.0	0.8 to 56.0	0.8 to 61.0
Future Perspective			
n	1058	997	2055
Mean ± SD	40.3 ± 12.29	39.6 ± 12.84	39.9 ± 12.56
Median	44.4	44.4	44.4
Range 1st to 3rd quartile	33.8 to 49.9	33.5 to 49.8	33.6 to 49.8
Range minimum to maximum	1.0 to 61.7	0.5 to 61.5	0.5 to 61.7

	Treatment Groups		
	Ribociclib + ET (N=1115)	**ET (N=1123)**	**Total (N=2238)**
Follow-up time (months) - EQ-5D VAS			
EQ-5D VAS			
n	1051	999	2050
Mean ± SD	40.3 ± 12.26	39.6 ± 12.89	40.0 ± 12.57
Median	44.4	44.4	44.4
Range 1st to 3rd quartile	33.8 to 49.8	33.5 to 49.8	33.6 to 49.8
Range minimum to maximum	1.0 to 61.0	0.5 to 61.5	0.5 to 61.5
Follow-up time (months) - HADS (QoL)			
Anxiety			
n	1046	991	2037
Mean ± SD	40.2 ± 12.39	39.5 ± 12.87	39.9 ± 12.63
Median	44.4	44.4	44.4
Range 1st to 3rd quartile	33.8 to 49.8	33.4 to 49.8	33.6 to 49.8
Range minimum to maximum	1.0 to 61.7	0.5 to 61.5	0.5 to 61.7
Depression			
n	1045	991	2036
Mean ± SD	40.3 ± 12.35	39.5 ± 12.87	39.9 ± 12.61
Median	44.4	44.4	44.4
Range 1st to 3rd quartile	33.8 to 49.8	33.4 to 49.8	33.6 to 49.8
Range minimum to maximum	1.0 to 61.7	0.5 to 61.5	0.5 to 61.7

ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
OS: Overall survival
iDFS: Invasive disease-free survival
RFS: Recurrence-free survival
DDFS: Distant disease-free survival
LRRFS: Loco-regional recurrence-free survival
LRRFS: Loco-regional recurrence-free survival
EORTC-QLQ: European Organization for Research and Treatment of Cancers Core Quality of Life Questionnaire
HADS: Hospital Anxiety and Depression Scale
VAS: Visual Analogue Scale
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Table 1-5 Drug exposure and follow-up times by endpoint and study treatment (Safety Set)

	Treatment Groups		
	Ribociclib + ET (N=1108)	**ET (N=1070)**	**Total (N=2178)**
Duration of exposure (months)			
Ribociclib			
n	1108	0	1108
Mean ± SD	28.2 ± 12.86	n.a.	28.2 ± 12.86
Median	35.7	n.a.	35.7
Range 1st to 3rd quartile	24.0 to 35.7	n.a.	24.0 to 35.7
Range minimum to maximum	0.0 to 37.0	n.a.	0.0 to 37.0
NSAI			
n	1108	1070	2178
Mean ± SD	40.5 ± 14.92	38.1 ± 16.58	39.3 ± 15.80
Median	45.0	44.6	44.8
Range 1st to 3rd quartile	37.5 to 50.6	31.5 to 50.4	36.9 to 50.5
Range minimum to maximum	0.0 to 60.0	0.0 to 60.0	0.0 to 60.0
Goserelin			
n	1090	1049	2139
Mean ± SD	37.2 ± 16.52	35.1 ± 17.57	36.2 ± 17.07
Median	43.4	40.5	42.3
Range 1st to 3rd quartile	29.4 to 49.7	20.7 to 49.7	24.8 to 49.7
Range minimum to maximum	0.1 to 60.8	0.3 to 60.0	0.1 to 60.8
Follow-up time (months)			
Adverse Events			
n	1108	1070	2178
Mean ± SD	40.7 ± 14.72	38.4 ± 16.32	39.5 ± 15.57
Median	45.0	44.6	44.8
Range 1st to 3rd quartile	37.7 to 50.7	32.5 to 50.4	37.1 to 50.5
Range minimum to maximum	0.1 to 61.0	0.0 to 60.9	0.0 to 61.0

ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
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Table 1-6.1 Prior anti-cancer therapies (Full Analysis Set)

	Treatment Groups		
	Ribociclib + ET (N=1115)	**ET (N=1123)**	**Total (N=2238)**
Patients who received any prior anti-cancer therapy	**1114 (99.9)**	**1123 (100.0)**	**2237 (100.0)**
Therapy type, n (%)			
Setting, n (%)			
Biologic/targeted therapy	**1 (0.1)**	**4 (0.4)**	**5 (0.2)**
Adjuvant	0 (0.0)	3 (0.3)	3 (0.1)
Neoadjuvant	1 (0.1)	1 (0.1)	2 (0.1)
Chemotherapy	**1032 (92.6)**	**1039 (92.5)**	**2071 (92.5)**
Adjuvant	514 (46.1)	511 (45.5)	1025 (45.8)
Neoadjuvant	548 (49.1)	568 (50.6)	1116 (49.9)
Endocrine therapy	**858 (77.0)**	**822 (73.2)**	**1680 (75.1)**
Adjuvant	855 (76.7)	813 (72.4)	1668 (74.5)
Neoadjuvant	73 (6.5)	77 (6.9)	150 (6.7)
Other	**8 (0.7)**	**6 (0.5)**	**14 (0.6)**
Adjuvant	6 (0.5)	4 (0.4)	10 (0.4)
Neoadjuvant	2 (0.2)	2 (0.2)	4 (0.2)
Prior radiotherapy	**1017 (91.2)**	**1038 (92.4)**	**2055 (91.8)**
Prior surgery for breast cancer	**1114 (99.9)**	**1123 (100.0)**	**2237 (100.0)**

ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
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Table 1-6.2 Prior anti-neoplastic medications by ATC class and preferred name (Full Analysis Set)

	Treatment Groups		
	Ribociclib + ET (N=1115)	**ET (N=1123)**	**Total (N=2238)**
Patients who received any prior anti-neoplastic medication	**1085 (97.3)**	**1092 (97.2)**	**2177 (97.3)**
ATC class, n (%)			
Preferred name, n (%)			
Anthracyclines and related substances	**953 (85.5)**	**969 (86.3)**	**1922 (85.9)**
Anthracyclines and related substances	3 (0.3)	4 (0.4)	7 (0.3)
Doxorubicin	630 (56.5)	610 (54.3)	1240 (55.4)
Doxorubicin hydrochloride	25 (2.2)	21 (1.9)	46 (2.1)
Epirubicin	257 (23.0)	274 (24.4)	531 (23.7)
Epirubicin hydrochloride	22 (2.0)	39 (3.5)	61 (2.7)
Liposomal doxorubicin	3 (0.3)	2 (0.2)	5 (0.2)
Liposomal doxorubicin hydrochloride	10 (0.9)	14 (1.2)	24 (1.1)
Pegylated liposomal doxorubicin	1 (0.1)	0 (0.0)	1 (0.0)
Pegylated liposomal doxorubicin hydrochloride	2 (0.2)	3 (0.3)	5 (0.2)
Pirarubicin	5 (0.4)	5 (0.4)	10 (0.4)
Pirarubicin hydrochloride	3 (0.3)	3 (0.3)	6 (0.3)
Anti-androgens	**1 (0.1)**	**0 (0.0)**	**1 (0.0)**
Enzalutamide	1 (0.1)	0 (0.0)	1 (0.0)
Anti-estrogens	**262 (23.5)**	**243 (21.6)**	**505 (22.6)**
Fulvestrant	1 (0.1)	0 (0.0)	1 (0.0)
Tamoxifen	254 (22.8)	239 (21.3)	493 (22.0)
Tamoxifen citrate	6 (0.5)	3 (0.3)	9 (0.4)
Toremifene	1 (0.1)	1 (0.1)	2 (0.1)
Aromatase inhibitors	**672 (60.3)**	**651 (58.0)**	**1323 (59.1)**
Anastrozole	149 (13.4)	160 (14.2)	309 (13.8)
Exemestane	112 (10.0)	70 (6.2)	182 (8.1)
Letrozole	453 (40.6)	448 (39.9)	901 (40.3)
Bisphosphonates	**3 (0.3)**	**2 (0.2)**	**5 (0.2)**
Ibandronic acid	0 (0.0)	2 (0.2)	2 (0.1)
Zoledronic acid	1 (0.1)	2 (0.2)	3 (0.1)
Zoledronic acid monohydrate	2 (0.2)	0 (0.0)	2 (0.1)
Colony stimulating factors	**0 (0.0)**	**1 (0.1)**	**1 (0.0)**
Filgrastim	0 (0.0)	1 (0.1)	1 (0.0)
Detoxifying agents for antineoplastic treatment	**1 (0.1)**	**2 (0.2)**	**3 (0.1)**
Dexrazoxane hydrochloride	1 (0.1)	2 (0.2)	3 (0.1)
Folic acid analogues	**3 (0.3)**	**1 (0.1)**	**4 (0.2)**
Methotrexate	3 (0.3)	1 (0.1)	4 (0.2)
Gonadotropin releasing hormone analogues	**650 (58.3)**	**603 (53.7)**	**1253 (56.0)**

	Treatment Groups		
	Ribociclib + ET (N=1115)	**ET (N=1123)**	**Total (N=2238)**
Buserelin	2 (0.2)	4 (0.4)	6 (0.3)
Goserelin	398 (35.7)	380 (33.8)	778 (34.8)
Goserelin acetate	158 (14.2)	130 (11.6)	288 (12.9)
Leuprorelin	33 (3.0)	16 (1.4)	49 (2.2)
Leuprorelin acetate	48 (4.3)	54 (4.8)	102 (4.6)
Triptorelin	19 (1.7)	9 (0.8)	28 (1.3)
Triptorelin acetate	18 (1.6)	26 (2.3)	44 (2.0)
Gonadotropin-releasing hormones	**1 (0.1)**	**3 (0.3)**	**4 (0.2)**
Gonadorelin diacetate tetrahydrate	0 (0.0)	2 (0.2)	2 (0.1)
Leuprorelin acetate	1 (0.1)	1 (0.1)	2 (0.1)
Her2 (human epidermal growth factor receptor 2) inhibitors	**1 (0.1)**	**2 (0.2)**	**3 (0.1)**
Pertuzumab	0 (0.0)	1 (0.1)	1 (0.0)
Trastuzumab	1 (0.1)	2 (0.2)	3 (0.1)
Trastuzumab emtansine	1 (0.1)	0 (0.0)	1 (0.0)
Investigational drug	**0 (0.0)**	**2 (0.2)**	**2 (0.1)**
Investigational drug	0 (0.0)	2 (0.2)	2 (0.1)
Mammalian target of rapamycin (mtor) kinase inhibitors	**0 (0.0)**	**1 (0.1)**	**1 (0.0)**
Everolimus	0 (0.0)	1 (0.1)	1 (0.0)
Nitrogen mustard analogues	**1008 (90.4)**	**1009 (89.8)**	**2017 (90.1)**
Cyclophosphamide	1008 (90.4)	1009 (89.8)	2017 (90.1)
Other antineoplastic agents	**0 (0.0)**	**1 (0.1)**	**1 (0.0)**
Eribulin	0 (0.0)	1 (0.1)	1 (0.0)
Other immunosuppressants	**4 (0.4)**	**0 (0.0)**	**4 (0.2)**
Methotrexate	4 (0.4)	0 (0.0)	4 (0.2)
Pd-1/pdl-1 (programmed cell death protein 1/death ligand 1) inhibitors	**2 (0.2)**	**3 (0.3)**	**5 (0.2)**
Durvalumab	1 (0.1)	1 (0.1)	2 (0.1)
Pembrolizumab	1 (0.1)	2 (0.2)	3 (0.1)
Platinum compounds	**20 (1.8)**	**30 (2.7)**	**50 (2.2)**
Carboplatin	12 (1.1)	24 (2.1)	36 (1.6)
Cisplatin	7 (0.6)	5 (0.4)	12 (0.5)
Lobaplatin	0 (0.0)	1 (0.1)	1 (0.0)
Nedaplatin	1 (0.1)	0 (0.0)	1 (0.0)
Poly (adp-ribose) polymerase (parp) inhibitors	**2 (0.2)**	**0 (0.0)**	**2 (0.1)**
Olaparib	2 (0.2)	0 (0.0)	2 (0.1)
Pyrimidine analogues	**60 (5.4)**	**47 (4.2)**	**107 (4.8)**
Capecitabine	16 (1.4)	16 (1.4)	32 (1.4)
Fluorouracil	45 (4.0)	29 (2.6)	74 (3.3)
Fluorouracil sodium	0 (0.0)	1 (0.1)	1 (0.0)
Gemcitabine	1 (0.1)	1 (0.1)	2 (0.1)
Taxanes	**1004 (90.0)**	**1001 (89.1)**	**2005 (89.6)**

	Treatment Groups		
	Ribociclib + ET (N=1115)	**ET (N=1123)**	**Total (N=2238)**
Docetaxel	329 (29.5)	341 (30.4)	670 (29.9)
Paclitaxel	667 (59.8)	665 (59.2)	1332 (59.5)
Paclitaxel liposome	3 (0.3)	4 (0.4)	7 (0.3)
Paclitaxel nanoparticle albumin-bound	19 (1.7)	21 (1.9)	40 (1.8)
Vinca alkaloids and analogues	**0 (0.0)**	**2 (0.2)**	**2 (0.1)**
Vinorelbine	0 (0.0)	1 (0.1)	1 (0.0)
Vinorelbine tartrate	0 (0.0)	1 (0.1)	1 (0.0)

ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
ATC: Anatomical Therapeutic Chemical
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Table 1-7 Post treatment anti-cancer therapies (Full Analysis Set)

	Treatment Groups		
	Ribociclib + ET (N=1115)	**ET (N=1123)**	**Total (N=2238)**
Patients who received any post treatment anti-cancer therapy	**157 (14.1)**	**220 (19.6)**	**377 (16.8)**
Post treatment anti-neoplastic medications: ATC class, n (%)			
Anthracyclines and related substances	2 (0.2)	4 (0.4)	6 (0.3)
Anti-estrogens	68 (6.1)	110 (9.8)	178 (8.0)
Aromatase inhibitors	73 (6.5)	94 (8.4)	167 (7.5)
Bisphosphonates	4 (0.4)	4 (0.4)	8 (0.4)
Cyclin-dependent kinase (cdk) inhibitors	25 (2.2)	78 (6.9)	103 (4.6)
Folic acid analogues	0 (0.0)	2 (0.2)	2 (0.1)
Gonadotropin releasing hormone analogues	46 (4.1)	65 (5.8)	111 (5.0)
Gonadotropin-releasing hormones	1 (0.1)	0 (0.0)	1 (0.0)
Her2 (human epidermal growth factor receptor 2) inhibitors	5 (0.4)	9 (0.8)	14 (0.6)
Mammalian target of rapamycin (mtor) kinase inhibitors	4 (0.4)	1 (0.1)	5 (0.2)
Nitrogen mustard analogues	4 (0.4)	2 (0.2)	6 (0.3)
Other antianemic preparations	1 (0.1)	0 (0.0)	1 (0.0)
Other antineoplastic agents	5 (0.4)	16 (1.4)	21 (0.9)
Other cytotoxic antibiotics	0 (0.0)	1 (0.1)	1 (0.0)
Other drugs affecting bone structure and mineralization	5 (0.4)	7 (0.6)	12 (0.5)
Other monoclonal antibodies and antibody drug conjugates	7 (0.6)	9 (0.8)	16 (0.7)
Other protein kinase inhibitors	3 (0.3)	2 (0.2)	5 (0.2)
Pd-1/pdl-1 (programmed cell death protein 1/death ligand 1) inhibitors	6 (0.5)	9 (0.8)	15 (0.7)
Phosphatidylinositol-3-kinase (pi3k) inhibitors	3 (0.3)	1 (0.1)	4 (0.2)
Platinum compounds	16 (1.4)	23 (2.0)	39 (1.7)
Podophyllotoxin derivatives	1 (0.1)	0 (0.0)	1 (0.0)
Poly (adp-ribose) polymerase (parp) inhibitors	4 (0.4)	3 (0.3)	7 (0.3)
Pyrimidine analogues	24 (2.2)	42 (3.7)	66 (2.9)
Taxanes	17 (1.5)	26 (2.3)	43 (1.9)
Unspecified herbal and traditional medicine	0 (0.0)	2 (0.2)	2 (0.1)
Vegf/vegfr (vascular endothelial growth factor) inhibitors	2 (0.2)	6 (0.5)	8 (0.4)
Vinca alkaloids and analogues	4 (0.4)	6 (0.5)	10 (0.4)
Post treatment anti-neoplastic radiotherapy/surgery, n (%)			
Radiotherapy	10 (0.9)	18 (1.6)	28 (1.3)
Surgery	18 (1.6)	23 (2.0)	41 (1.8)

	Treatment Groups		
	Ribociclib + ET (N=1115)	**ET (N=1123)**	**Total (N=2238)**

ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
ATC: Anatomical Therapeutic Chemical
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Table 1-8 Subgroups (Full Analysis Set)

	Treatment Groups		
	Ribociclib + ET (N=1115)	**ET (N=1123)**	**Total (N=2238)**
Region, n (%)			
NA/WE/O	644 (57.8)	660 (58.8)	1304 (58.3)
ROW	471 (42.2)	463 (41.2)	934 (41.7)
Geographical region, n (%)			
Europe	661 (59.3)	656 (58.4)	1317 (58.8)
North America/Australia	212 (19.0)	215 (19.1)	427 (19.1)
Asia	178 (16.0)	182 (16.2)	360 (16.1)
Latin America	64 (5.7)	70 (6.2)	134 (6.0)
Age group 1 at randomization, n (%)			
<45	551 (49.4)	533 (47.5)	1084 (48.4)
45 to 54	544 (48.8)	562 (50.0)	1106 (49.4)
55 to 64	20 (1.8)	28 (2.5)	48 (2.1)
Age group 2 at randomization (median for subpopulation pre-menopausal female patients), n (%)			
<Median	551 (49.4)	533 (47.5)	1084 (48.4)
≥Median	564 (50.6)	590 (52.5)	1154 (51.6)
Race, n (%)			
Asian	211 (18.9)	200 (17.8)	411 (18.4)
Non-Asian	846 (75.9)	864 (76.9)	1710 (76.4)
Missing values	58 (5.2)	59 (5.3)	117 (5.2)
BMI at screening, n (%)			
≥25	554 (49.7)	545 (48.5)	1099 (49.1)
<25	545 (48.9)	566 (50.4)	1111 (49.6)
Missing values	16 (1.4)	12 (1.1)	28 (1.3)
AJCC Anatomic Stage Group, n (%)			
Group I	3 (0.3)	0 (0.0)	3 (0.1)
Group II	419 (37.6)	432 (38.5)	851 (38.0)
Group III	693 (62.2)	691 (61.5)	1384 (61.8)
Anatomic stages, n (%)			
IB	3 (0.3)	0 (0.0)	3 (0.1)
IIA	171 (15.3)	203 (18.1)	374 (16.7)
IIB	248 (22.2)	229 (20.4)	477 (21.3)
IIIA	451 (40.4)	416 (37.0)	867 (38.7)
IIIB	67 (6.0)	61 (5.4)	128 (5.7)
IIIC	175 (15.7)	214 (19.1)	389 (17.4)
Tumor category, n (%)			
T0	3 (0.3)	1 (0.1)	4 (0.2)
T1-T3	1034 (92.7)	1041 (92.7)	2075 (92.7)
>T3	75 (6.7)	78 (6.9)	153 (6.8)

	Treatment Groups		
	Ribociclib + ET (N=1115)	**ET (N=1123)**	**Total (N=2238)**
Missing values	3 (0.3)	3 (0.3)	6 (0.3)
Nodal status, n (%)			
N0	92 (8.3)	119 (10.6)	211 (9.4)
N1-N3	1023 (91.7)	1001 (89.1)	2024 (90.4)
Missing values	0 (0.0)	3 (0.3)	3 (0.1)
Histological grade at time of surgery, n (%)			
Grade 1	111 (10.0)	107 (9.5)	218 (9.7)
Grade 2	609 (54.6)	630 (56.1)	1239 (55.4)
Grade 3	297 (26.6)	279 (24.8)	576 (25.7)
Missing values	98 (8.8)	107 (9.5)	205 (9.2)
Histological subtype, n (%)			
Ductal	868 (77.8)	880 (78.4)	1748 (78.1)
Lobular	174 (15.6)	174 (15.5)	348 (15.5)
Other	73 (6.5)	69 (6.1)	142 (6.3)
Ki67 status from surgical specimen, n (%)			
Ki67≤20	530 (47.5)	576 (51.3)	1106 (49.4)
Ki67>20	424 (38.0)	396 (35.3)	820 (36.6)
Missing values	161 (14.4)	151 (13.4)	312 (13.9)
ER+PR+ vs ER-PR+ vs ER+RP, n (%)			
ER+/PR+	972 (87.2)	959 (85.4)	1931 (86.3)
ER-/PR+	2 (0.2)	6 (0.5)	8 (0.4)
ER+/PR-	137 (12.3)	149 (13.3)	286 (12.8)
Missing values	4 (0.4)	9 (0.8)	13 (0.6)
Type of NSAI, n (%)			
Letrozole	808 (72.5)	774 (68.9)	1582 (70.7)
Anastrozole	298 (26.7)	298 (26.5)	596 (26.6)
Missing values	9 (0.8)	51 (4.5)	60 (2.7)
Prior neo/adjuvant chemotherapy, n (%)			
Yes	1032 (92.6)	1039 (92.5)	2071 (92.5)
No	83 (7.4)	84 (7.5)	167 (7.5)
Prior adjuvant chemotherapy, n (%)			
Yes	514 (46.1)	511 (45.5)	1025 (45.8)
No	601 (53.9)	612 (54.5)	1213 (54.2)
Prior neoadjuvant chemotherapy, n (%)			
Yes	548 (49.1)	568 (50.6)	1116 (49.9)
No	567 (50.9)	555 (49.4)	1122 (50.1)
Prior endocrine therapy, n (%)			
Yes	858 (77.0)	822 (73.2)	1680 (75.1)
No	257 (23.0)	301 (26.8)	558 (24.9)
Prior mastectomy, n (%)			
Yes	771 (69.1)	785 (69.9)	1556 (69.5)

	Treatment Groups		
	Ribociclib + ET (N=1115)	**ET (N=1123)**	**Total (N=2238)**
No	344 (30.9)	338 (30.1)	682 (30.5)
Prior radiotherapy, n (%)			
Yes	1017 (91.2)	1038 (92.4)	2055 (91.8)
No	98 (8.8)	85 (7.6)	183 (8.2)

ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
BMI: Body mass index
AJCC: American Joint Commission on Cancer
NSAI: Non-steroidal aromatase inhibitor
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2 Efficacy

2-1 Overall survival

Table 2-1.1 Overall survival: time to event analysis (Full Analysis Set)

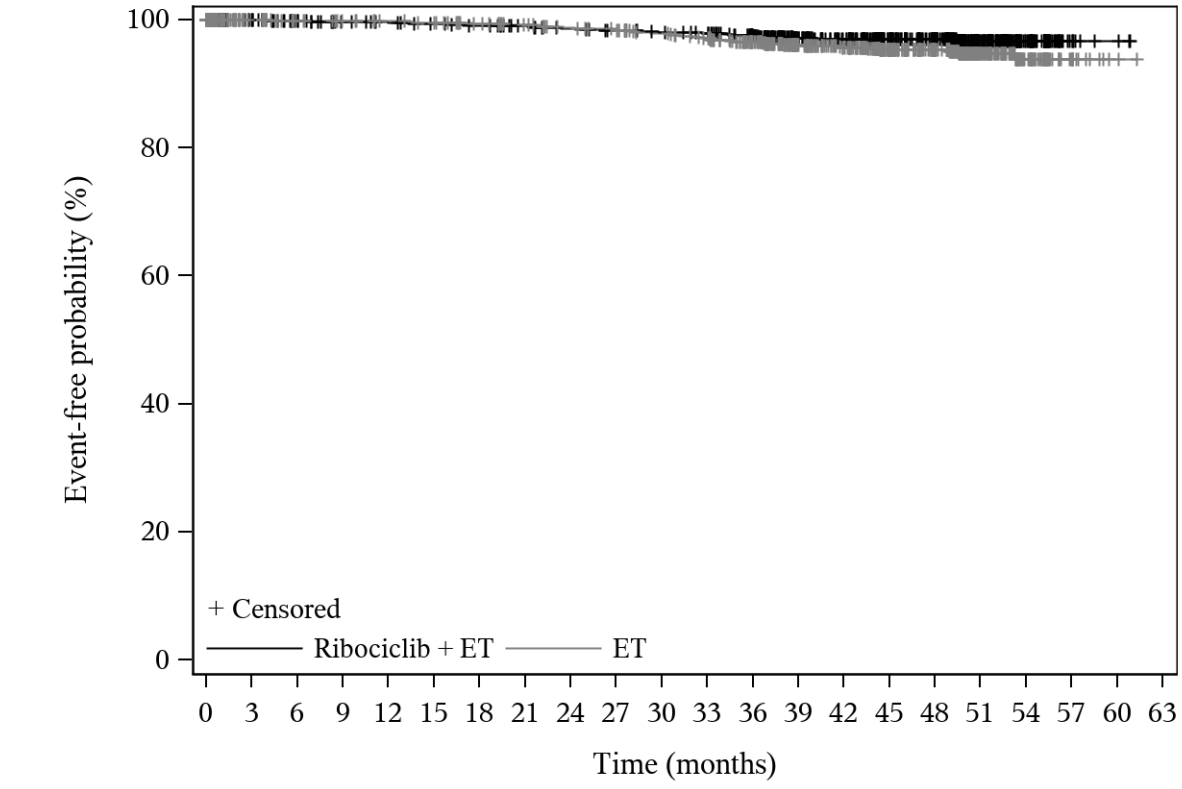
	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1115)	**ET (N = 1123)**	**HR**	**[95% CI]**	**p-value**
Time to Overall Survival Event					
N'	1115	1123			
Patients with event, n (%)					
Death (any cause)	31 (2.8)	46 (4.1)			
Patients censored, n (%)					
Any	1084 (97.2)	1077 (95.9)			
Alive	948 (85.0)	880 (78.4)			
Lost to follow-up	136 (12.2)	197 (17.5)			
Percentiles (months) [95% CI]					
25th	N.E. [N.E.]	N.E. [N.E.]			
Median	N.E. [N.E.]	N.E. [N.E.]	0.63	[0.40; 1.00]	0.049

N: Number of patients
N': Number of patients included in the analysis
n: Number and percentage of patients with event/censored
CI: Confidence interval
HR: Hazard ratio
KM: Kaplan-Meier
N.E.: Not estimable
ET: Endocrine therapy (Anastrozole/Letrozole + Goserelin)
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Analysis methods:
Median time to event and other quartiles by KM estimation, 95% CIs using the method of Brookmeyer and Crowley with linear transformation.
HR with 95% CI from stratified Cox proportional hazards model:
log(hazard ratio) = treatment
The model was stratified by AJCC Anatomic Stage Group, prior neo-/adjuvant chemotherapy and region.
ET was the reference group for treatment group comparison.
Two-sided p-value from Log-rank test, stratified by AJCC Anatomic Stage Group, prior neo-/adjuvant chemotherapy and region.

Figure 2-1.1 Overall survival: Kaplan-Meier plot (Full Analysis Set)

Time to Overall Survival Event



Ribociclib + ET	1115	1055	1034	1022	1004	989	938	738	446	84	3
ET	1123	1012	1000	984	963	941	874	686	413	84	2

Table 2-1.2 Overall survival: binary analysis (Full Analysis Set)

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1115)	**ET (N = 1123)**	**Para-meter**	**Esti-mate**	**[95% CI]**	**p-value**
Overall Survival Event						
Event, n / N' (%)	31 / 1115 (2.8)	46 / 1123 (4.1)	OR	0.66	[0.42; 1.06]	0.082
			RR	0.68	[0.43; 1.05]	
			RD	-0.01	[-0.03; 0.00]	

N: Number of patients
N': Number of patients in the analysis
n: Number of patients with event
CI: Confidence interval
OR: Odds ratio
RR: Relative risk
RD: Risk difference
CMH: Cochran-Mantel-Haenszel
ET: Endocrine therapy (Anastrozole/Letrozole + Goserelin)
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Analysis methods:
OR, RR, RD with 95% CIs estimated by CMH method, stratified by AJCC Anatomic Stage Group, prior neo-/adjuvant chemotherapy and region.
ET was the reference group for treatment group comparison.
Two-sided p-value from CMH Chi-square test, stratified by AJCC Anatomic Stage Group, prior neo-/adjuvant chemotherapy and region.

2-2 Invasive disease-free survival

Table 2-2.1 Invasive disease-free survival: time to event analysis (Full Analysis Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1115)	**ET (N = 1123)**	**HR**	**[95% CI]**	**p-value**
Time to First iDFS Event					
N'	1115	1123			
Patients with event, n (%)					
Any	99 (8.9)	136 (12.1)			
Death (any cause)	4 (0.4)	3 (0.3)			
Invasive breast recurrence event	4 (0.4)	3 (0.3)			
Regional invasive recurrence event	12 (1.1)	18 (1.6)			
Contralateral invasive recurrence event	3 (0.3)	6 (0.5)			
Distant recurrence event	66 (5.9)	103 (9.2)			
New primary malignancy event	15 (1.3)	13 (1.2)			
Patients censored, n (%)					
Any	1016 (91.1)	987 (87.9)			
Lost to follow-up	8 (0.7)	11 (1.0)			
Ongoing without event	908 (81.4)	813 (72.4)			
Withdrew consent	100 (9.0)	163 (14.5)			
Percentiles (months) [95% CI]					
25th	N.E. [N.E.]	N.E. [N.E.]			
Median	N.E. [N.E.]	N.E. [N.E.]	0.67	[0.52; 0.87]	0.002

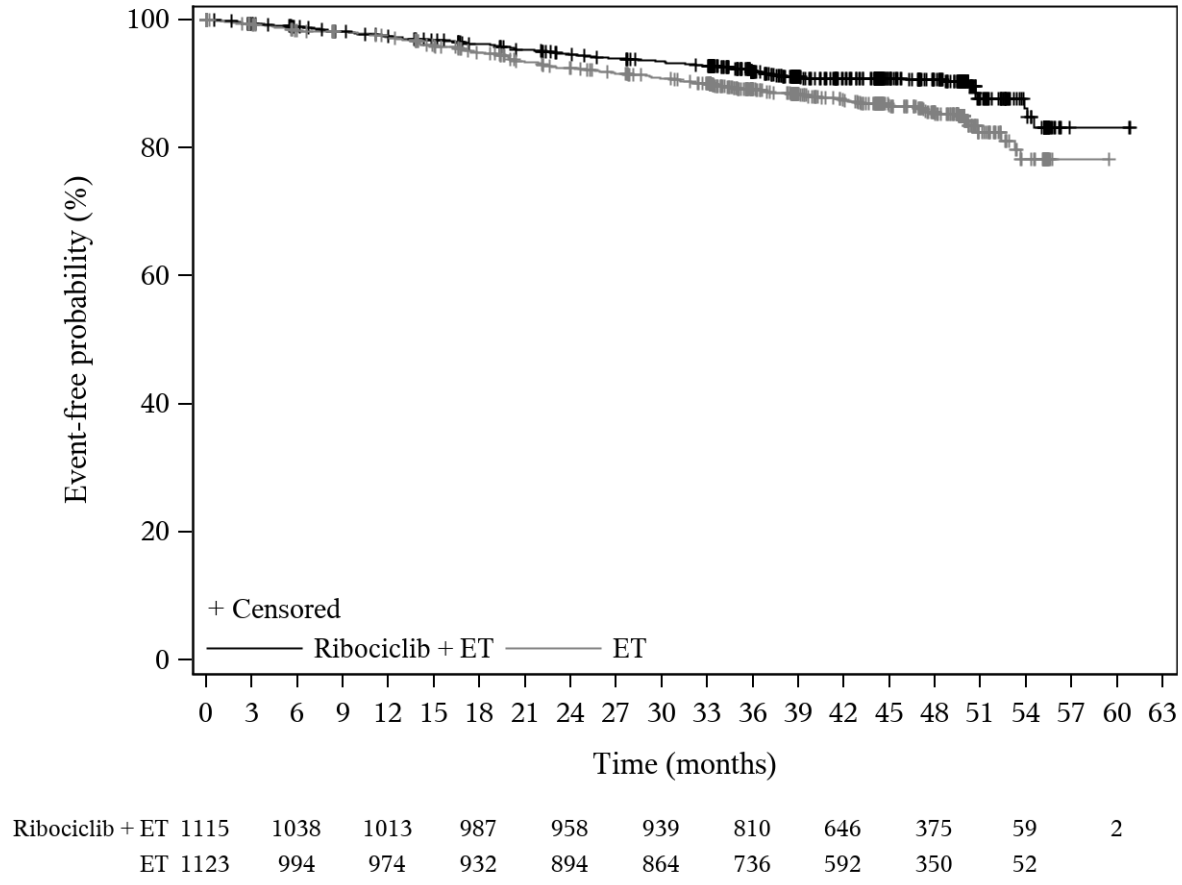
N: Number of patients
N': Number of patients included in the analysis
n: Number and percentage of patients with event/censored
CI: Confidence interval
HR: Hazard ratio
KM: Kaplan-Meier
N.E.: Not estimable
ET: Endocrine therapy (Anastrozole/Letrozole + Goserelin)
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Analysis methods:
Median time to event and other quartiles by KM estimation, 95% CIs using the method of Brookmeyer and Crowley with linear transformation.
HR with 95% CI from stratified Cox proportional hazards model:
log(hazard ratio) = treatment
The model was stratified by AJCC Anatomic Stage Group, prior neo-/adjuvant chemotherapy and region.
ET was the reference group for treatment group comparison.
Two-sided p-value from Log-rank test, stratified by AJCC Anatomic Stage Group, prior neo-/adjuvant chemotherapy and region.

Multiple events may have occurred on the same day. Therefore the sum of all event types may exceed the number of events.

Figure 2-2.1 Invasive disease-free survival: Kaplan-Meier plot (Full Analysis Set)

Time to First iDFS Event



Ribociclib + ET	1115	1038	1013	987	958	939	810	646	375	59	2
ET	1123	994	974	932	894	864	736	592	350	52	

Table 2-2.2 Invasive disease-free survival: binary analysis (Full Analysis Set)

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1115)	**ET (N = 1123)**	**Para-meter**	**Esti-mate**	**[95% CI]**	**p-value**
First iDFS Event						
Event, n / N' (%)	99 / 1115 (8.9)	136 / 1123 (12.1)	OR	0.71	[0.54; 0.93]	0.012
			RR	0.73	[0.57; 0.93]	
			RD	-0.03	[-0.06; -0.01]	

N: Number of patients
N': Number of patients in the analysis
n: Number of patients with event
CI: Confidence interval
OR: Odds ratio
RR: Relative risk
RD: Risk difference
CMH: Cochran-Mantel-Haenszel
ET: Endocrine therapy (Anastrozole/Letrozole + Goserelin)
.....

Analysis methods:
OR, RR, RD with 95% CIs estimated by CMH method, stratified by AJCC Anatomic Stage Group, prior neo-/adjuvant chemotherapy and region.
ET was the reference group for treatment group comparison.
Two-sided p-value from CMH Chi-square test, stratified by AJCC Anatomic Stage Group, prior neo-/adjuvant chemotherapy and region.

2-3 Distant disease-free survival

Table 2-3.1 Distant disease-free survival: time to event analysis (Full Analysis Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1115)	**ET (N = 1123)**	**HR**	**[95% CI]**	**p-value**
Time to Distant Disease-Free Survival Event					
N'	1115	1123			
Patients with event, n (%)					
Any	88 (7.9)	124 (11.0)			
Death (any cause)	6 (0.5)	5 (0.4)			
Distant recurrence event	67 (6.0)	106 (9.4)			
New primary malignancy event	15 (1.3)	13 (1.2)			
Patients censored, n (%)					
Any	1027 (92.1)	999 (89.0)			
Lost to follow-up	8 (0.7)	12 (1.1)			
Ongoing without event	914 (82.0)	822 (73.2)			
Withdrew consent	105 (9.4)	165 (14.7)			
Percentiles (months) [95% CI]					
25th	N.E. [N.E.]	N.E. [N.E.]			
Median	N.E. [N.E.]	N.E. [N.E.]	0.65	[0.50; 0.86]	0.002

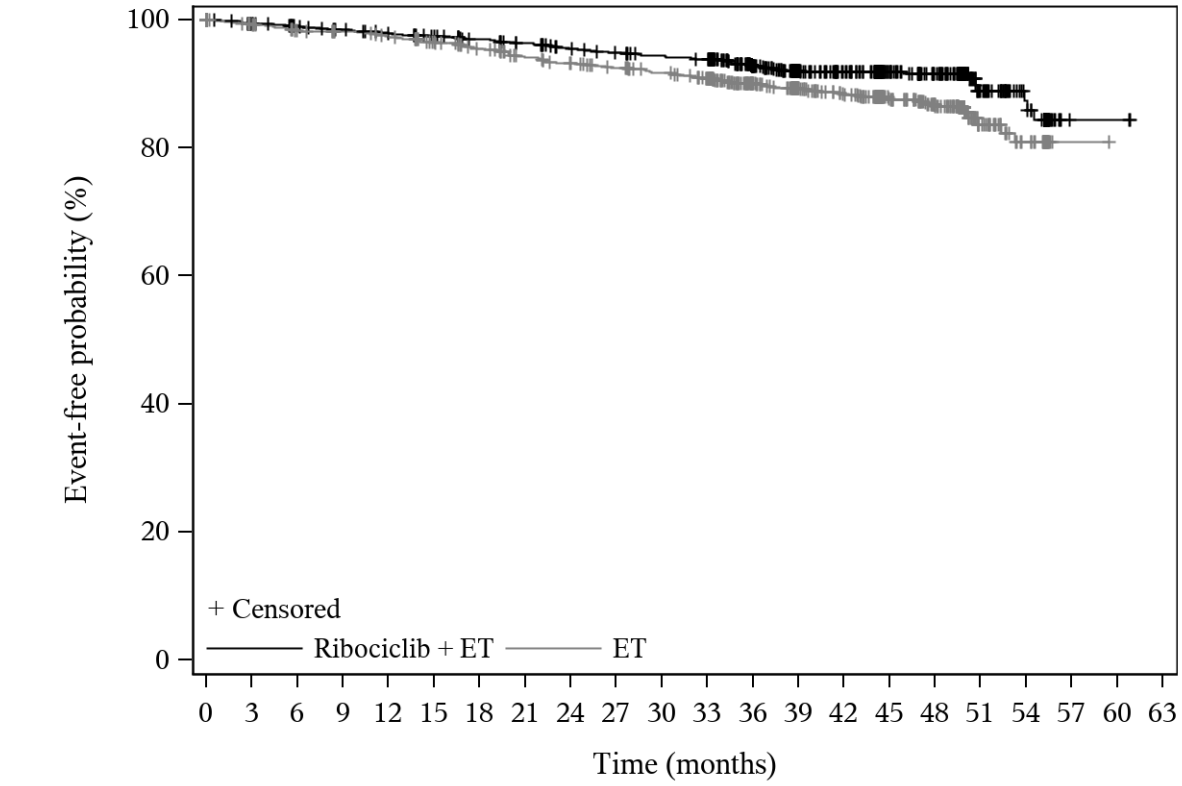
N: Number of patients
N': Number of patients included in the analysis
n: Number and percentage of patients with event/censored
CI: Confidence interval
HR: Hazard ratio
KM: Kaplan-Meier
N.E.: Not estimable
ET: Endocrine therapy (Anastrozole/Letrozole + Goserelin)
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Analysis methods:
Median time to event and other quartiles by KM estimation, 95% CIs using the method of Brookmeyer and Crowley with linear transformation.
HR with 95% CI from stratified Cox proportional hazards model:
log(hazard ratio) = treatment
The model was stratified by AJCC Anatomic Stage Group, prior neo-/adjuvant chemotherapy and region.
ET was the reference group for treatment group comparison.
Two-sided p-value from Log-rank test, stratified by AJCC Anatomic Stage Group, prior neo-/adjuvant chemotherapy and region.

Multiple events may have occurred on the same day. Therefore the sum of all event types may exceed the number of events.

Figure 2-3.1 Distant disease-free survival: Kaplan-Meier plot (Full Analysis Set)

Time to Distant Disease-Free Survival Event



Ribociclib + ET	1115	1039	1017	992	964	944	815	650	378	59	2
ET	1123	994	975	936	899	869	739	594	351	53	

Table 2-3.2 Distant disease-free survival: binary analysis (Full Analysis Set)

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1115)	**ET (N = 1123)**	**Para-meter**	**Esti-mate**	**[95% CI]**	**p-value**
Distant Disease-Free Survival Event						
Event, n / N' (%)	88 / 1115 (7.9)	124 / 1123 (11.0)	OR	0.69	[0.52; 0.92]	0.011
			RR	0.71	[0.55; 0.93]	
			RD	-0.03	[-0.06; -0.01]	

N: Number of patients
N': Number of patients in the analysis
n: Number of patients with event
CI: Confidence interval
OR: Odds ratio
RR: Relative risk
RD: Risk difference
CMH: Cochran-Mantel-Haenszel
ET: Endocrine therapy (Anastrozole/Letrozole + Goserelin)
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Analysis methods:
OR, RR, RD with 95% CIs estimated by CMH method, stratified by AJCC Anatomic Stage Group, prior neo-/adjuvant chemotherapy and region.
ET was the reference group for treatment group comparison.
Two-sided p-value from CMH Chi-square test, stratified by AJCC Anatomic Stage Group, prior neo-/adjuvant chemotherapy and region.

3 PRO

3-0 Analysis PRO

Change from baseline is analyzed based on a mixed model for repeated measures (MMRM) and includes both on- and off-treatment data in accordance with the ITT principle, whereby the values collected after an iDFS event are assigned to regular visits. All data collected will be included in the analysis, including assessments at confirmation of first recurrence and thereafter, as long as there are at least 50 patients in each arm. Missing values are not imputed.
The adjusted mean differences between the treatment groups over the entire period including the 95% confidence interval as well as the standardized mean difference (Hedges' g) with the associated confidence interval are reported. A line plot of adjusted mean change within treatment arms along with confidence limits is also produced.

3-1 EORTC QLQ-C30 Symptoms

Table 3-1.0 EORTC QLQ-C30 Symptoms: return rates (Full Analysis Set)

	Treatment groups			
	Ribociclib + ET (N = 1115)		ET (N = 1123)	
	N' (%)	Returns n (%)	N' (%)	Returns n (%)
Baseline	1115 (100.0)	1092 (97.9)	1123 (100.0)	1091 (97.2)
Week 13	1115 (100.0)	1046 (93.8)	1123 (100.0)	987 (87.9)
Week 25	1114 (99.9)	999 (89.7)	1122 (99.9)	942 (84.0)
Week 37	1112 (99.7)	1004 (90.3)	1122 (99.9)	933 (83.2)
Week 49	1112 (99.7)	988 (88.8)	1121 (99.8)	943 (84.1)
Week 61	1109 (99.5)	982 (88.5)	1119 (99.6)	924 (82.6)
Week 73	1107 (99.3)	975 (88.1)	1118 (99.6)	915 (81.8)
Week 85	1106 (99.2)	960 (86.8)	1117 (99.5)	892 (79.9)
Week 97	1103 (98.9)	952 (86.3)	1114 (99.2)	879 (78.9)
Week 121	1098 (98.5)	919 (83.7)	1108 (98.7)	858 (77.4)
Week 145	1094 (98.1)	918 (83.9)	1096 (97.6)	825 (75.3)
Week 169	1087 (97.5)	740 (68.1)	1085 (96.6)	696 (64.1)
Week 193	1085 (97.3)	620 (57.1)	1081 (96.3)	581 (53.7)
Week 217	1084 (97.2)	353 (32.6)	1078 (96.0)	331 (30.7)

	Treatment groups			
	Ribociclib + ET (N = 1115)		ET (N = 1123)	
	N' (%)	Returns n (%)	N' (%)	Returns n (%)
Week 241	1084 (97.2)	59 (5.4)	1077 (95.9)	54 (5.0)
Week 265	1084 (97.2)	2 (0.2)	1077 (95.9)	1 (0.1)

N': Number of patients who have not died until the respective visit
ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
.....

The number of returns is the number of patients with non-missing data (i.e. at least one [sub-]score present) at the respective visit.

A patients is considered to have not died until the visit if no death was documented during the study, if returns for this PRO are present at the visit or, if no returns are present for this PRO and the patient died, if the death date is after the scheduled visit date.

Percentages of returns refer to N' per group. For N' percentages refer to N per group.

Table 3-1.1 EORTC QLQ-C30 Symptoms: change from baseline analysis (Full Analysis Set)

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1115)	ET (N = 1123)	Parameter	Esti-mate	[95% CI]	p-value
QLQ-C30 - Fatigue						
	N' | Mean (SD)	**N' | Mean (SD)**				
Overall N'	1059	1004				
Baseline	1059 | 28.98 (21.49)	1004 | 28.12 (20.68)				
Week 13	1027 | 31.93 (22.32)	964 | 29.66 (21.74)				
Week 25	981 | 31.58 (22.45)	921 | 29.47 (21.76)				
Week 37	986 | 31.80 (22.42)	912 | 30.55 (22.23)				
Week 49	973 | 31.68 (22.65)	922 | 29.74 (23.47)				
Week 61	965 | 32.31 (23.47)	903 | 29.64 (22.47)				
Week 73	956 | 32.11 (22.91)	893 | 29.26 (22.35)				
Week 85	943 | 32.54 (24.01)	869 | 29.64 (23.58)				
Week 97	934 | 32.03 (23.57)	859 | 29.64 (23.18)				
Week 121	903 | 32.71 (23.99)	841 | 28.86 (22.65)				
Week 145	900 | 32.49 (23.99)	810 | 29.16 (23.56)				
Week 169	727 | 31.26 (23.18)	681 | 30.41 (23.90)				
Week 193	610 | 31.02 (23.50)	565 | 30.29 (23.87)				
Week 217	344 | 31.78 (23.14)	323 | 28.62 (23.75)				
Week 241	58 | 28.74 (26.16)	51 | 28.43 (24.31)				
Adjusted change	**Mean (SE)**	**Mean (SE)**				
Week 13	3.34 (0.56)	1.55 (0.58)	Difference	1.79	[0.21; 3.37]	0.026
			Hedges G	0.10	[0.01; 0.19]	
Week 25	3.45 (0.57)	1.20 (0.59)	Difference	2.25	[0.63; 3.86]	0.006
			Hedges G	0.13	[0.04; 0.22]	

Treatment Groups			Comparison			
	Ribociclib + ET (N = 1115)	**ET (N = 1123)**	**Parameter**	**Esti-mate**	**[95% CI]**	**p-value**
Week 37	3.64 (0.59)	2.19 (0.61)	Difference	1.45	[-0.21; 3.11]	0.087
			Hedges G	0.08	[-0.01; 0.17]	
Week 49	3.68 (0.61)	1.48 (0.62)	Difference	2.20	[0.50; 3.91]	0.011
			Hedges G	0.12	[0.03; 0.21]	
Week 61	4.56 (0.61)	1.26 (0.63)	Difference	3.30	[1.58; 5.03]	<.001
			Hedges G	0.17	[0.08; 0.26]	
Week 73	4.41 (0.62)	1.22 (0.64)	Difference	3.19	[1.44; 4.95]	<.001
			Hedges G	0.17	[0.08; 0.26]	
Week 85	4.98 (0.65)	1.36 (0.67)	Difference	3.63	[1.79; 5.46]	<.001
			Hedges G	0.18	[0.09; 0.27]	
Week 97	4.66 (0.65)	1.22 (0.67)	Difference	3.44	[1.62; 5.27]	<.001
			Hedges G	0.18	[0.08; 0.27]	
Week 121	5.32 (0.66)	0.85 (0.68)	Difference	4.46	[2.60; 6.32]	<.001
			Hedges G	0.23	[0.13; 0.32]	
Week 145	5.04 (0.67)	1.21 (0.70)	Difference	3.83	[1.93; 5.73]	<.001
			Hedges G	0.19	[0.10; 0.29]	
Week 169	3.28 (0.71)	1.39 (0.73)	Difference	1.89	[-0.11; 3.88]	0.063
			Hedges G	0.10	[-0.01; 0.20]	
Week 193	3.18 (0.74)	1.10 (0.77)	Difference	2.08	[-0.01; 4.18]	0.052
			Hedges G	0.11	[-0.00; 0.23]	
Week 217	4.62 (0.93)	0.04 (0.96)	Difference	4.58	[1.96; 7.19]	<.001
			Hedges G	0.27	[0.11; 0.42]	
Week 241	3.38 (1.91)	2.19 (2.04)	Difference	1.19	[-4.29; 6.68]	0.669
			Hedges G	0.08	[-0.29; 0.46]	
Overall effect	**4.11 (0.50)**	**1.30 (0.51)**	**Difference**	**2.81**	**[1.40; 4.21]**	**<.001**
			Hedges G	**0.17**	**[0.09; 0.26]**	

Treatment Groups			Comparison			
	Ribociclib + ET (N = 1115)	**ET (N = 1123)**	**Parameter**	**Esti-mate**	**[95% CI]**	**p-value**
QLQ-C30 - Nausea and Vomiting						
	N' | Mean (SD)	**N' | Mean (SD)**				
Overall N'	1059	1005				
Baseline	1059 | 3.29 (9.30)	1005 | 3.45 (9.31)				
Week 13	1028 | 5.07 (11.49)	965 | 3.54 (10.03)				
Week 25	981 | 4.93 (11.22)	922 | 4.34 (10.67)				
Week 37	986 | 5.02 (11.36)	913 | 4.44 (10.85)				
Week 49	973 | 5.17 (11.84)	923 | 4.93 (12.05)				
Week 61	965 | 5.01 (10.59)	904 | 4.52 (11.27)				
Week 73	956 | 5.89 (12.68)	894 | 4.85 (11.41)				
Week 85	944 | 5.35 (11.01)	870 | 4.75 (11.63)				
Week 97	932 | 6.24 (13.78)	860 | 5.25 (12.40)				
Week 121	903 | 5.89 (13.16)	842 | 5.01 (12.89)				
Week 145	900 | 6.20 (13.55)	811 | 5.26 (12.66)				
Week 169	727 | 4.84 (10.71)	683 | 5.00 (12.69)				
Week 193	610 | 4.40 (10.94)	566 | 4.83 (12.59)				
Week 217	344 | 4.17 (10.67)	323 | 4.13 (9.30)				
Week 241	58 | 5.46 (12.25)	51 | 1.96 (5.42)				
Adjusted change	**Mean (SE)**	**Mean (SE)**				
Week 13	1.85 (0.32)	0.21 (0.33)	Difference	1.64	[0.74; 2.54]	<.001
			Hedges G	0.16	[0.07; 0.25]	
Week 25	1.79 (0.33)	1.00 (0.34)	Difference	0.79	[-0.14; 1.73]	0.095
			Hedges G	0.08	[-0.01; 0.17]	
Week 37	1.95 (0.34)	1.16 (0.35)	Difference	0.79	[-0.16; 1.74]	0.103
			Hedges G	0.07	[-0.02; 0.16]	
Week 49	2.12 (0.37)	1.62 (0.38)	Difference	0.50	[-0.53; 1.53]	0.339
			Hedges G	0.04	[-0.05; 0.13]	
Week 61	2.04 (0.33)	1.21 (0.34)	Difference	0.82	[-0.12; 1.76]	0.086
			Hedges G	0.08	[-0.01; 0.17]	
Week 73	2.93 (0.37)	1.63 (0.38)	Difference	1.30	[0.26; 2.35]	0.014
			Hedges G	0.11	[0.02; 0.21]	
Week 85	2.40 (0.35)	1.52 (0.37)	Difference	0.88	[-0.11; 1.88]	0.082
			Hedges G	0.08	[-0.01; 0.17]	
Week 97	3.37 (0.41)	2.01 (0.43)	Difference	1.36	[0.19; 2.52]	0.023
			Hedges G	0.11	[0.02; 0.20]	
Week 121	3.09 (0.42)	1.73 (0.43)	Difference	1.36	[0.19; 2.54]	0.023
			Hedges G	0.11	[0.01; 0.20]	
Week 145	3.35 (0.42)	1.99 (0.44)	Difference	1.37	[0.19; 2.55]	0.023
			Hedges G	0.11	[0.01; 0.20]	
Week 169	1.81 (0.40)	1.57 (0.41)	Difference	0.24	[-0.88; 1.37]	0.675
			Hedges G	0.02	[-0.08; 0.13]	
Week 193	1.49 (0.45)	1.67 (0.46)	Difference	-0.18	[-1.44; 1.09]	0.783

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1115)	**ET (N = 1123)**	**Parameter**	**Esti-mate**	**[95% CI]**	**p-value**
			Hedges G	-0.02	[-0.13; 0.10]	
Week 217	1.06 (0.50)	1.08 (0.52)	Difference	-0.02	[-1.43; 1.39]	0.980
			Hedges G	-0.00	[-0.15; 0.15]	
Week 241	3.15 (1.08)	-0.29 (1.16)	Difference	3.44	[0.34; 6.53]	0.030
			Hedges G	0.42	[0.04; 0.80]	
Overall effect	**2.31 (0.22)**	**1.29 (0.23)**	**Difference**	**1.02**	**[0.39; 1.66]**	**0.002**
			Hedges G	**0.14**	**[0.05; 0.23]**	
QLQ-C30 - Pain						
	N' | Mean (SD)	**N' | Mean (SD)**				
Overall N'	1060	1004				
Baseline	1060 | 23.10 (22.32)	1004 | 21.51 (21.65)				
Week 13	1029 | 26.26 (24.28)	964 | 27.40 (24.54)				
Week 25	983 | 25.42 (23.63)	921 | 25.90 (23.21)				
Week 37	988 | 25.56 (23.63)	911 | 27.44 (24.59)				
Week 49	974 | 26.08 (24.18)	922 | 26.19 (23.86)				
Week 61	966 | 26.14 (23.92)	903 | 25.51 (23.59)				
Week 73	958 | 25.40 (24.42)	894 | 23.86 (22.61)				
Week 85	944 | 24.70 (24.08)	871 | 23.50 (22.87)				
Week 97	935 | 24.60 (24.22)	860 | 24.11 (23.46)				
Week 121	904 | 24.58 (24.12)	841 | 24.38 (25.34)				
Week 145	901 | 23.46 (23.96)	810 | 22.96 (23.56)				
Week 169	728 | 24.22 (23.74)	682 | 23.95 (23.88)				
Week 193	611 | 24.00 (23.65)	566 | 23.03 (23.54)				
Week 217	345 | 23.77 (23.16)	323 | 22.55 (23.23)				
Week 241	58 | 26.15 (27.41)	52 | 18.27 (26.04)				
Adjusted change	**Mean (SE)**	**Mean (SE)**				
Week 13	3.71 (0.64)	5.67 (0.66)	Difference	-1.95	[-3.75; -0.15]	0.034
			Hedges G	-0.10	[-0.18; -0.01]	
Week 25	3.32 (0.64)	3.96 (0.65)	Difference	-0.65	[-2.44; 1.14]	0.479
			Hedges G	-0.03	[-0.12; 0.06]	
Week 37	3.60 (0.66)	5.63 (0.69)	Difference	-2.03	[-3.90; -0.16]	0.033
			Hedges G	-0.10	[-0.19; -0.01]	
Week 49	4.22 (0.66)	4.42 (0.68)	Difference	-0.19	[-2.05; 1.67]	0.840
			Hedges G	-0.01	[-0.10; 0.08]	
Week 61	4.34 (0.65)	3.61 (0.67)	Difference	0.73	[-1.11; 2.57]	0.436
			Hedges G	0.04	[-0.05; 0.13]	
Week 73	3.68 (0.66)	2.22 (0.69)	Difference	1.46	[-0.41; 3.33]	0.127
			Hedges G	0.07	[-0.02; 0.16]	
Week 85	3.25 (0.67)	1.77 (0.70)	Difference	1.47	[-0.42; 3.37]	0.128
			Hedges G	0.07	[-0.02; 0.16]	
Week 97	3.16 (0.69)	2.10 (0.71)	Difference	1.06	[-0.88; 3.00]	0.285
			Hedges G	0.05	[-0.04; 0.14]	

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1115)	**ET (N = 1123)**	**Parameter**	**Esti-mate**	**[95% CI]**	**p-value**
Week 121	3.21 (0.72)	2.53 (0.74)	Difference	0.68	[-1.35; 2.70]	0.512
			Hedges G	0.03	[-0.06; 0.13]	
Week 145	2.12 (0.68)	1.21 (0.72)	Difference	0.91	[-1.03; 2.85]	0.358
			Hedges G	0.04	[-0.05; 0.14]	
Week 169	2.16 (0.74)	1.16 (0.76)	Difference	1.00	[-1.07; 3.08]	0.344
			Hedges G	0.05	[-0.05; 0.15]	
Week 193	2.03 (0.78)	0.08 (0.81)	Difference	1.95	[-0.25; 4.15]	0.083
			Hedges G	0.10	[-0.01; 0.22]	
Week 217	2.46 (0.94)	-1.22 (0.97)	Difference	3.69	[1.03; 6.34]	0.007
			Hedges G	0.21	[0.06; 0.36]	
Week 241	4.91 (2.10)	2.09 (2.22)	Difference	2.82	[-3.17; 8.82]	0.356
			Hedges G	0.18	[-0.20; 0.55]	
Overall effect	**3.30 (0.51)**	**2.52 (0.53)**	**Difference**	**0.78**	**[-0.66; 2.23]**	**0.288**
			Hedges G	**0.05**	**[-0.04; 0.13]**	
QLQ-C30 - Dyspnoea						
	N' | Mean (SD)	**N' | Mean (SD)**				
Overall N'	1057	1004				
Baseline	1057 | 10.72 (19.59)	1004 | 10.56 (18.63)				
Week 13	1024 | 12.76 (21.20)	963 | 12.08 (20.12)				
Week 25	976 | 11.78 (19.66)	919 | 12.11 (20.06)				
Week 37	985 | 13.33 (20.78)	910 | 12.23 (19.82)				
Week 49	971 | 13.39 (20.51)	921 | 12.49 (19.96)				
Week 61	963 | 14.50 (21.35)	903 | 13.58 (21.00)				
Week 73	955 | 13.61 (20.72)	892 | 12.67 (19.79)				
Week 85	943 | 13.54 (20.53)	867 | 13.99 (20.92)				
Week 97	933 | 13.68 (21.50)	859 | 14.09 (21.64)				
Week 121	902 | 14.08 (20.95)	840 | 13.77 (21.82)				
Week 145	898 | 14.63 (22.18)	807 | 13.84 (21.26)				
Week 169	726 | 13.59 (21.49)	682 | 14.57 (22.19)				
Week 193	608 | 13.38 (21.22)	564 | 14.24 (22.12)				
Week 217	343 | 12.63 (20.45)	323 | 14.55 (20.97)				
Week 241	58 | 11.49 (20.28)	51 | 11.11 (21.77)				
Adjusted change	**Mean (SE)**	**Mean (SE)**				
Week 13	2.27 (0.56)	1.55 (0.58)	Difference	0.72	[-0.86; 2.31]	0.369
			Hedges G	0.04	[-0.05; 0.13]	
Week 25	1.69 (0.57)	1.50 (0.59)	Difference	0.19	[-1.42; 1.81]	0.815
			Hedges G	0.01	[-0.08; 0.10]	
Week 37	3.14 (0.59)	1.59 (0.61)	Difference	1.55	[-0.11; 3.21]	0.068
			Hedges G	0.08	[-0.01; 0.17]	
Week 49	3.28 (0.59)	1.87 (0.60)	Difference	1.41	[-0.24; 3.06]	0.095
			Hedges G	0.08	[-0.01; 0.17]	
Week 61	4.64 (0.61)	2.92 (0.63)	Difference	1.72	[-0.01; 3.45]	0.052

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1115)	**ET (N = 1123)**	**Parameter**	**Esti-mate**	**[95% CI]**	**p-value**
			Hedges G	0.09	[-0.00; 0.18]	
Week 73	3.57 (0.60)	2.19 (0.62)	Difference	1.37	[-0.31; 3.05]	0.109
			Hedges G	0.07	[-0.02; 0.17]	
Week 85	3.70 (0.62)	3.44 (0.65)	Difference	0.26	[-1.50; 2.01]	0.775
			Hedges G	0.01	[-0.08; 0.11]	
Week 97	3.80 (0.64)	3.43 (0.66)	Difference	0.38	[-1.43; 2.19]	0.684
			Hedges G	0.02	[-0.07; 0.11]	
Week 121	4.23 (0.65)	3.27 (0.67)	Difference	0.96	[-0.87; 2.79]	0.305
			Hedges G	0.05	[-0.04; 0.14]	
Week 145	4.78 (0.67)	3.35 (0.70)	Difference	1.43	[-0.48; 3.34]	0.142
			Hedges G	0.07	[-0.02; 0.17]	
Week 169	3.64 (0.72)	3.33 (0.74)	Difference	0.31	[-1.72; 2.34]	0.765
			Hedges G	0.02	[-0.09; 0.12]	
Week 193	4.00 (0.77)	3.19 (0.79)	Difference	0.81	[-1.35; 2.98]	0.460
			Hedges G	0.04	[-0.07; 0.16]	
Week 217	3.85 (0.92)	3.25 (0.95)	Difference	0.60	[-2.00; 3.20]	0.651
			Hedges G	0.04	[-0.12; 0.19]	
Week 241	2.24 (2.11)	0.90 (2.26)	Difference	1.34	[-4.71; 7.39]	0.664
			Hedges G	0.08	[-0.29; 0.46]	
Overall effect	**3.49 (0.45)**	**2.56 (0.47)**	**Difference**	**0.93**	**[-0.34; 2.20]**	**0.150**
			Hedges G	**0.06**	**[-0.02; 0.15]**	
QLQ-C30 - Insomnia						
	N' | Mean (SD)	**N' | Mean (SD)**				
Overall N'	1060	1005				
Baseline	1060 | 33.55 (29.67)	1005 | 33.30 (29.92)				
Week 13	1027 | 36.03 (30.31)	963 | 38.01 (31.11)				
Week 25	979 | 35.61 (30.12)	921 | 36.84 (31.14)				
Week 37	986 | 35.56 (30.22)	912 | 37.54 (31.63)				
Week 49	971 | 35.02 (30.32)	923 | 36.48 (31.53)				
Week 61	965 | 35.82 (29.69)	904 | 35.58 (31.86)				
Week 73	957 | 34.24 (29.15)	892 | 36.32 (31.56)				
Week 85	943 | 35.52 (30.72)	868 | 35.83 (30.84)				
Week 97	934 | 35.33 (30.37)	860 | 36.90 (31.27)				
Week 121	902 | 33.81 (29.69)	841 | 35.39 (30.96)				
Week 145	898 | 36.15 (30.19)	811 | 33.54 (31.01)				
Week 169	727 | 34.53 (29.77)	683 | 36.02 (31.12)				
Week 193	611 | 35.46 (30.97)	565 | 36.05 (31.71)				
Week 217	345 | 35.65 (29.88)	323 | 34.98 (32.24)				
Week 241	58 | 33.91 (30.90)	51 | 33.99 (30.91)				
Adjusted change	**Mean (SE)**	**Mean (SE)**				
Week 13	2.96 (0.83)	5.01 (0.86)	Difference	-2.05	[-4.40; 0.29]	0.087
			Hedges G	-0.08	[-0.16; 0.01]	

Treatment Groups			Comparison			
	Ribociclib + ET (N = 1115)	**ET (N = 1123)**	**Parameter**	**Esti-mate**	**[95% CI]**	**p-value**
Week 25	2.91 (0.84)	3.59 (0.87)	Difference	-0.68	[-3.06; 1.70]	0.574
			Hedges G	-0.03	[-0.12; 0.06]	
Week 37	2.75 (0.87)	4.21 (0.90)	Difference	-1.47	[-3.92; 0.98]	0.240
			Hedges G	-0.05	[-0.14; 0.04]	
Week 49	2.42 (0.87)	3.26 (0.89)	Difference	-0.84	[-3.28; 1.60]	0.500
			Hedges G	-0.03	[-0.12; 0.06]	
Week 61	3.18 (0.86)	2.14 (0.89)	Difference	1.04	[-1.40; 3.47]	0.404
			Hedges G	0.04	[-0.05; 0.13]	
Week 73	1.68 (0.87)	3.34 (0.90)	Difference	-1.66	[-4.12; 0.80]	0.186
			Hedges G	-0.06	[-0.15; 0.03]	
Week 85	3.13 (0.89)	2.90 (0.92)	Difference	0.22	[-2.28; 2.73]	0.862
			Hedges G	0.01	[-0.08; 0.10]	
Week 97	3.09 (0.89)	3.75 (0.93)	Difference	-0.66	[-3.19; 1.86]	0.606
			Hedges G	-0.02	[-0.12; 0.07]	
Week 121	1.61 (0.89)	2.29 (0.92)	Difference	-0.68	[-3.19; 1.83]	0.595
			Hedges G	-0.03	[-0.12; 0.07]	
Week 145	4.31 (0.92)	0.54 (0.96)	Difference	3.76	[1.16; 6.36]	0.005
			Hedges G	0.14	[0.04; 0.23]	
Week 169	1.56 (0.99)	1.76 (1.02)	Difference	-0.20	[-3.00; 2.59]	0.886
			Hedges G	-0.01	[-0.11; 0.10]	
Week 193	2.79 (1.06)	1.77 (1.10)	Difference	1.02	[-1.98; 4.03]	0.505
			Hedges G	0.04	[-0.08; 0.15]	
Week 217	3.80 (1.35)	0.45 (1.39)	Difference	3.36	[-0.45; 7.16]	0.084
			Hedges G	0.13	[-0.02; 0.29]	
Week 241	1.18 (2.73)	1.13 (2.93)	Difference	0.05	[-7.80; 7.89]	0.990
			Hedges G	0.00	[-0.37; 0.38]	
Overall effect	**2.67 (0.65)**	**2.58 (0.67)**	**Difference**	**0.09**	**[-1.74; 1.91]**	**0.927**
			Hedges G	**0.00**	**[-0.08; 0.09]**	

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1115)	**ET (N = 1123)**	**Parameter**	**Esti-mate**	**[95% CI]**	**p-value**
QLQ-C30 - Appetite Loss						
	N' | Mean (SD)	**N' | Mean (SD)**				
Overall N'	1059	1005				
Baseline	1059 | 7.77 (18.31)	1005 | 7.63 (17.46)				
Week 13	1028 | 8.85 (18.27)	964 | 8.13 (18.28)				
Week 25	980 | 8.40 (19.08)	917 | 8.07 (18.17)				
Week 37	985 | 9.00 (18.83)	910 | 8.24 (18.08)				
Week 49	970 | 8.87 (18.28)	923 | 8.85 (19.58)				
Week 61	961 | 8.95 (18.96)	904 | 8.70 (19.10)				
Week 73	956 | 9.69 (19.33)	893 | 8.66 (18.87)				
Week 85	943 | 9.54 (19.27)	868 | 9.60 (19.61)				
Week 97	932 | 10.48 (20.29)	858 | 9.98 (20.31)				
Week 121	902 | 10.61 (20.22)	841 | 9.87 (19.83)				
Week 145	897 | 10.22 (19.63)	811 | 8.51 (18.89)				
Week 169	726 | 9.27 (19.01)	681 | 10.18 (21.33)				
Week 193	610 | 9.13 (19.26)	566 | 10.84 (21.46)				
Week 217	344 | 9.01 (18.16)	322 | 7.87 (17.85)				
Week 241	58 | 9.77 (22.52)	51 | 6.54 (14.94)				
Adjusted change	**Mean (SE)**	**Mean (SE)**				
Week 13	1.32 (0.56)	0.56 (0.57)	Difference	0.76	[-0.80; 2.32]	0.340
			Hedges G	0.04	[-0.05; 0.13]	
Week 25	0.98 (0.56)	0.40 (0.58)	Difference	0.59	[-1.00; 2.18]	0.470
			Hedges G	0.03	[-0.06; 0.12]	
Week 37	1.70 (0.56)	0.70 (0.58)	Difference	1.00	[-0.59; 2.59]	0.218
			Hedges G	0.06	[-0.03; 0.15]	
Week 49	1.58 (0.57)	1.39 (0.58)	Difference	0.19	[-1.40; 1.78]	0.816
			Hedges G	0.01	[-0.08; 0.10]	
Week 61	1.83 (0.57)	1.19 (0.59)	Difference	0.64	[-0.96; 2.25]	0.432
			Hedges G	0.04	[-0.05; 0.13]	
Week 73	2.52 (0.57)	1.36 (0.59)	Difference	1.16	[-0.45; 2.77]	0.158
			Hedges G	0.07	[-0.03; 0.16]	
Week 85	2.37 (0.57)	2.30 (0.60)	Difference	0.07	[-1.55; 1.70]	0.929
			Hedges G	0.00	[-0.09; 0.10]	
Week 97	3.37 (0.58)	2.81 (0.60)	Difference	0.56	[-1.07; 2.20]	0.498
			Hedges G	0.03	[-0.06; 0.12]	
Week 121	3.52 (0.58)	2.48 (0.60)	Difference	1.05	[-0.60; 2.70]	0.213
			Hedges G	0.06	[-0.03; 0.15]	
Week 145	3.22 (0.59)	1.33 (0.61)	Difference	1.89	[0.23; 3.56]	0.026
			Hedges G	0.11	[0.01; 0.20]	
Week 169	2.08 (0.63)	2.47 (0.66)	Difference	-0.38	[-2.17; 1.41]	0.676
			Hedges G	-0.02	[-0.13; 0.08]	
Week 193	1.94 (0.68)	3.46 (0.71)	Difference	-1.52	[-3.45; 0.40]	0.121

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1115)	**ET (N = 1123)**	**Parameter**	**Esti-mate**	**[95% CI]**	**p-value**
			Hedges G	-0.09	[-0.20; 0.02]	
Week 217	1.59 (0.86)	0.84 (0.89)	Difference	0.75	[-1.69; 3.18]	0.549
			Hedges G	0.05	[-0.11; 0.20]	
Week 241	3.26 (1.98)	2.53 (2.11)	Difference	0.73	[-4.94; 6.40]	0.801
			Hedges G	0.05	[-0.33; 0.42]	
Overall effect	**2.24 (0.39)**	**1.70 (0.40)**	**Difference**	**0.53**	**[-0.56; 1.63]**	**0.339**
			Hedges G	**0.04**	**[-0.04; 0.13]**	
QLQ-C30 - Constipation						
	N' | Mean (SD)	**N' | Mean (SD)**				
Overall N'	1055	1004				
Baseline	1055 | 10.62 (20.97)	1004 | 11.55 (21.66)				
Week 13	1022 | 15.62 (24.96)	963 | 13.05 (22.98)				
Week 25	977 | 15.01 (24.23)	922 | 11.97 (21.53)				
Week 37	982 | 16.46 (26.14)	909 | 14.30 (23.74)				
Week 49	969 | 15.65 (25.65)	921 | 14.04 (24.24)				
Week 61	960 | 15.69 (24.24)	903 | 14.47 (23.90)				
Week 73	953 | 15.70 (25.00)	892 | 14.65 (23.31)				
Week 85	936 | 15.49 (24.69)	868 | 13.48 (22.61)				
Week 97	927 | 15.14 (24.68)	859 | 15.37 (25.18)				
Week 121	898 | 16.37 (24.85)	840 | 14.37 (23.75)				
Week 145	896 | 16.15 (25.45)	810 | 13.79 (24.31)				
Week 169	724 | 12.71 (22.34)	680 | 15.49 (25.81)				
Week 193	608 | 12.23 (22.44)	566 | 15.55 (24.65)				
Week 217	343 | 11.56 (21.15)	321 | 15.78 (25.28)				
Week 241	58 | 9.20 (20.51)	51 | 11.11 (22.77)				
Adjusted change	**Mean (SE)**	**Mean (SE)**				
Week 13	4.91 (0.65)	1.79 (0.67)	Difference	3.11	[1.28; 4.95]	<.001
			Hedges G	0.15	[0.06; 0.24]	
Week 25	4.56 (0.64)	0.66 (0.65)	Difference	3.91	[2.12; 5.69]	<.001
			Hedges G	0.20	[0.11; 0.29]	
Week 37	6.17 (0.69)	3.06 (0.71)	Difference	3.11	[1.17; 5.05]	0.002
			Hedges G	0.14	[0.05; 0.24]	
Week 49	5.32 (0.70)	2.80 (0.71)	Difference	2.52	[0.56; 4.47]	0.012
			Hedges G	0.12	[0.03; 0.21]	
Week 61	5.38 (0.68)	3.19 (0.70)	Difference	2.19	[0.28; 4.11]	0.025
			Hedges G	0.10	[0.01; 0.19]	
Week 73	5.66 (0.70)	3.55 (0.72)	Difference	2.12	[0.15; 4.09]	0.035
			Hedges G	0.10	[0.01; 0.19]	
Week 85	5.32 (0.70)	2.25 (0.72)	Difference	3.07	[1.10; 5.03]	0.002
			Hedges G	0.14	[0.05; 0.24]	
Week 97	4.79 (0.72)	4.13 (0.74)	Difference	0.66	[-1.37; 2.69]	0.522
			Hedges G	0.03	[-0.06; 0.12]	

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1115)	**ET (N = 1123)**	**Parameter**	**Esti-mate**	**[95% CI]**	**p-value**
Week 121	6.24 (0.74)	3.30 (0.76)	Difference	2.94	[0.86; 5.01]	0.006
			Hedges G	0.13	[0.04; 0.23]	
Week 145	5.86 (0.75)	3.00 (0.78)	Difference	2.86	[0.74; 4.99]	0.008
			Hedges G	0.13	[0.03; 0.22]	
Week 169	2.62 (0.78)	3.27 (0.80)	Difference	-0.66	[-2.85; 1.54]	0.557
			Hedges G	-0.03	[-0.14; 0.07]	
Week 193	2.78 (0.80)	3.81 (0.82)	Difference	-1.02	[-3.27; 1.22]	0.373
			Hedges G	-0.05	[-0.17; 0.06]	
Week 217	2.77 (0.96)	4.37 (1.00)	Difference	-1.60	[-4.32; 1.12]	0.250
			Hedges G	-0.09	[-0.24; 0.06]	
Week 241	2.02 (1.75)	3.64 (1.87)	Difference	-1.62	[-6.64; 3.41]	0.528
			Hedges G	-0.12	[-0.50; 0.26]	
Overall effect	**4.60 (0.49)**	**3.06 (0.51)**	**Difference**	**1.54**	**[0.16; 2.93]**	**0.029**
			Hedges G	**0.10**	**[0.01; 0.18]**	
QLQ-C30 - Diarrhoea						
	N' | Mean (SD)	**N' | Mean (SD)**				
Overall N'	1055	1003				
Baseline	1055 | 4.55 (13.24)	1003 | 4.49 (12.76)				
Week 13	1022 | 5.90 (14.86)	959 | 4.59 (12.92)				
Week 25	974 | 5.51 (14.74)	914 | 5.07 (14.29)				
Week 37	981 | 5.71 (14.57)	906 | 5.37 (15.05)				
Week 49	967 | 6.17 (15.24)	915 | 5.46 (14.77)				
Week 61	958 | 5.74 (15.03)	900 | 6.19 (15.72)				
Week 73	949 | 6.11 (14.93)	892 | 6.05 (15.17)				
Week 85	935 | 6.52 (16.44)	868 | 6.22 (16.40)				
Week 97	927 | 6.40 (16.17)	855 | 6.90 (16.46)				
Week 121	898 | 6.20 (15.50)	838 | 7.12 (16.65)				
Week 145	895 | 6.74 (16.02)	808 | 6.93 (16.64)				
Week 169	725 | 7.17 (17.01)	680 | 7.21 (16.93)				
Week 193	605 | 7.99 (18.21)	567 | 7.35 (16.66)				
Week 217	344 | 9.01 (19.04)	323 | 5.68 (15.05)				
Week 241	58 | 5.75 (16.68)	51 | 2.61 (9.05)				
Adjusted change	**Mean (SE)**	**Mean (SE)**				
Week 13	1.43 (0.41)	0.16 (0.42)	Difference	1.27	[0.11; 2.42]	0.032
			Hedges G	0.10	[0.01; 0.18]	
Week 25	1.09 (0.44)	0.62 (0.45)	Difference	0.47	[-0.77; 1.71]	0.453
			Hedges G	0.03	[-0.06; 0.12]	
Week 37	1.30 (0.45)	0.94 (0.46)	Difference	0.36	[-0.90; 1.62]	0.578
			Hedges G	0.03	[-0.06; 0.12]	
Week 49	1.78 (0.46)	1.03 (0.47)	Difference	0.75	[-0.53; 2.03]	0.252
			Hedges G	0.05	[-0.04; 0.14]	
Week 61	1.42 (0.48)	1.72 (0.49)	Difference	-0.29	[-1.63; 1.05]	0.666

Treatment Groups			Comparison			
	Ribociclib + ET (N = 1115)	**ET (N = 1123)**	**Parameter**	**Esti-mate**	**[95% CI]**	**p-value**
			Hedges G	-0.02	[-0.11; 0.07]	
Week 73	1.60 (0.47)	1.74 (0.48)	Difference	-0.13	[-1.45; 1.19]	0.844
			Hedges G	-0.01	[-0.10; 0.08]	
Week 85	2.11 (0.51)	1.79 (0.53)	Difference	0.32	[-1.12; 1.76]	0.664
			Hedges G	0.02	[-0.07; 0.11]	
Week 97	2.03 (0.51)	2.44 (0.53)	Difference	-0.41	[-1.84; 1.03]	0.579
			Hedges G	-0.03	[-0.12; 0.07]	
Week 121	1.76 (0.50)	2.63 (0.52)	Difference	-0.86	[-2.29; 0.56]	0.234
			Hedges G	-0.06	[-0.15; 0.04]	
Week 145	2.44 (0.52)	2.58 (0.54)	Difference	-0.14	[-1.62; 1.33]	0.849
			Hedges G	-0.01	[-0.10; 0.09]	
Week 169	2.64 (0.58)	2.75 (0.60)	Difference	-0.11	[-1.75; 1.53]	0.894
			Hedges G	-0.01	[-0.11; 0.10]	
Week 193	3.20 (0.63)	3.10 (0.65)	Difference	0.10	[-1.68; 1.87]	0.915
			Hedges G	0.01	[-0.11; 0.12]	
Week 217	4.24 (0.81)	1.72 (0.84)	Difference	2.52	[0.23; 4.81]	0.031
			Hedges G	0.17	[0.02; 0.32]	
Week 241	1.84 (1.34)	0.55 (1.43)	Difference	1.30	[-2.54; 5.14]	0.508
			Hedges G	0.13	[-0.25; 0.50]	
Overall effect	**2.06 (0.32)**	**1.70 (0.33)**	**Difference**	**0.37**	**[-0.54; 1.27]**	**0.427**
			Hedges G	**0.04**	**[-0.05; 0.12]**	

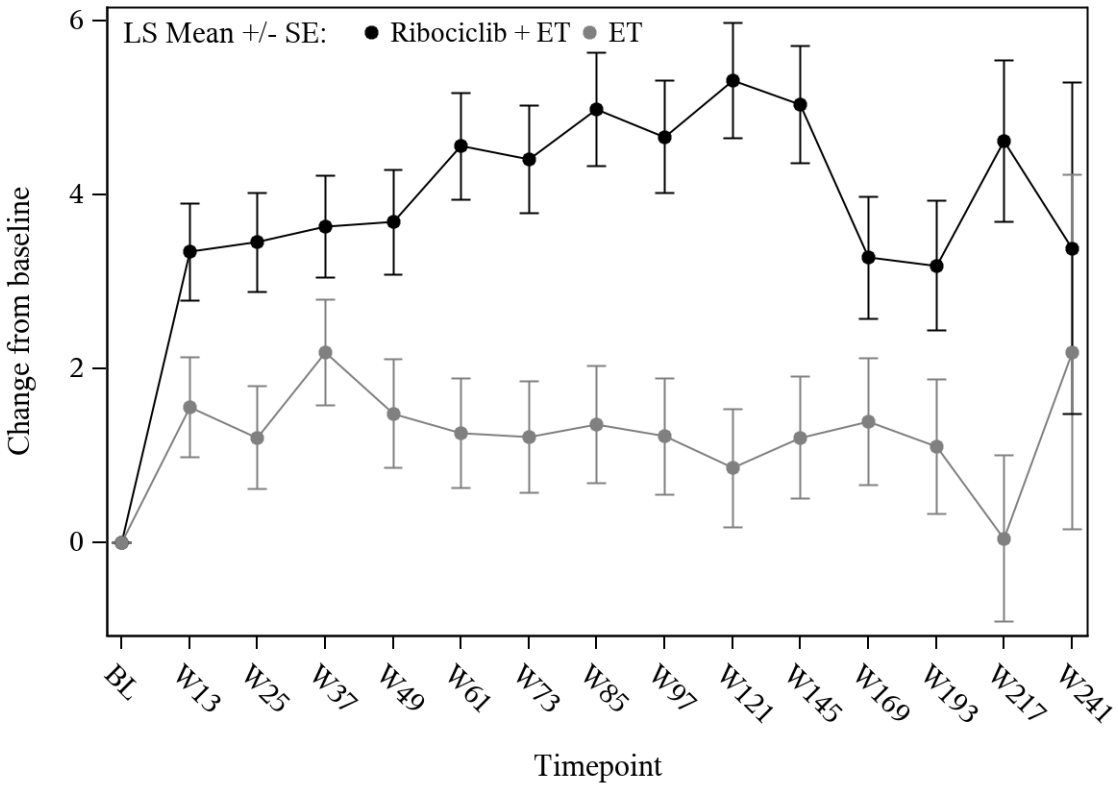
N: Number of patients
N': Number of patients in the analysis
CI: Confidence interval
SD: Standard deviation
LS Mean: Least square mean
SE: Standard error
MMRM: Mixed model for repeated measures
ET: Endocrine therapy (Anastrozole/Letrozole + Goserelin)
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Analysis methods:
Adjusted mean (LS Mean) change from baseline and difference obtained from MMRM with unstructured covariance matrix:
change from baseline = treatment + visit + treatment * visit + baseline value + AJCC Anatomic Stage + prior neo/adjuvant chemotherapy + region
ET was the reference group for treatment group comparison.
If the model did not converge for a parameter, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry.

Patients with an evaluable baseline score and at least one evaluable post-baseline score were included in the analysis.
All data collected were included in the analysis, including assessments at confirmation of first recurrence and thereafter, as long as there were at least 50 patients in each treatment group at a visit.

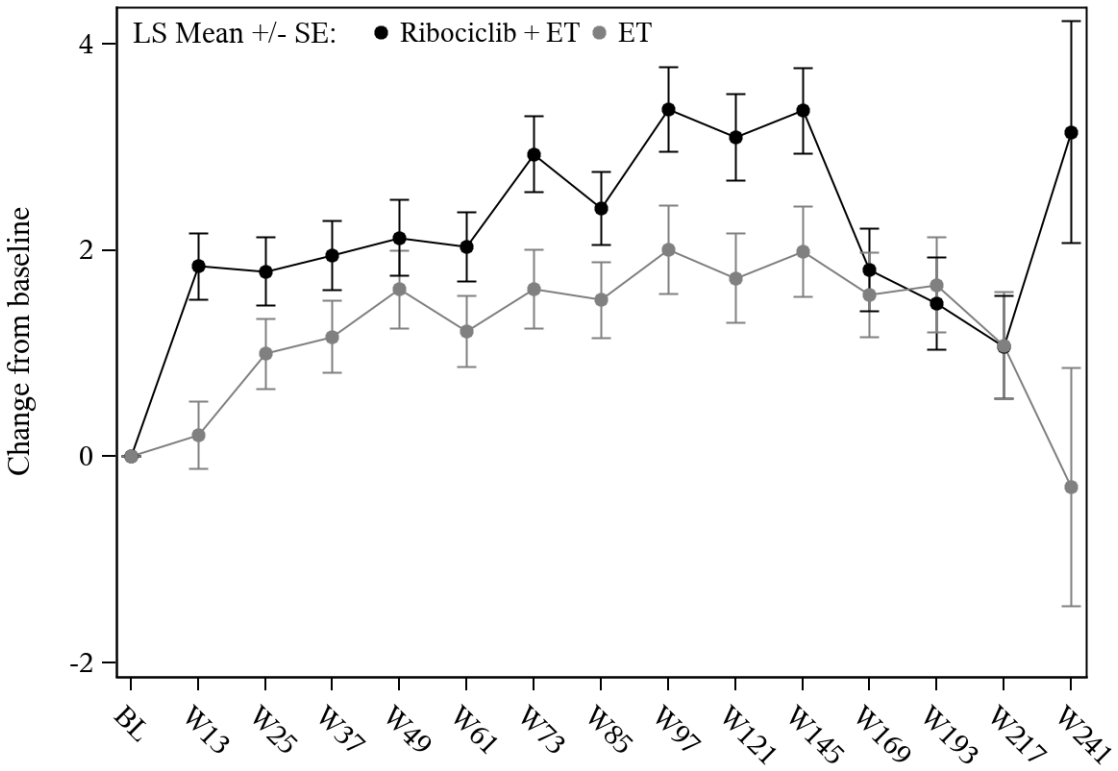
Figure 3-1.1 EORTC QLQ-C30 Symptoms: line chart of change from baseline (Full Analysis Set)

QLQ-C30 - Fatigue



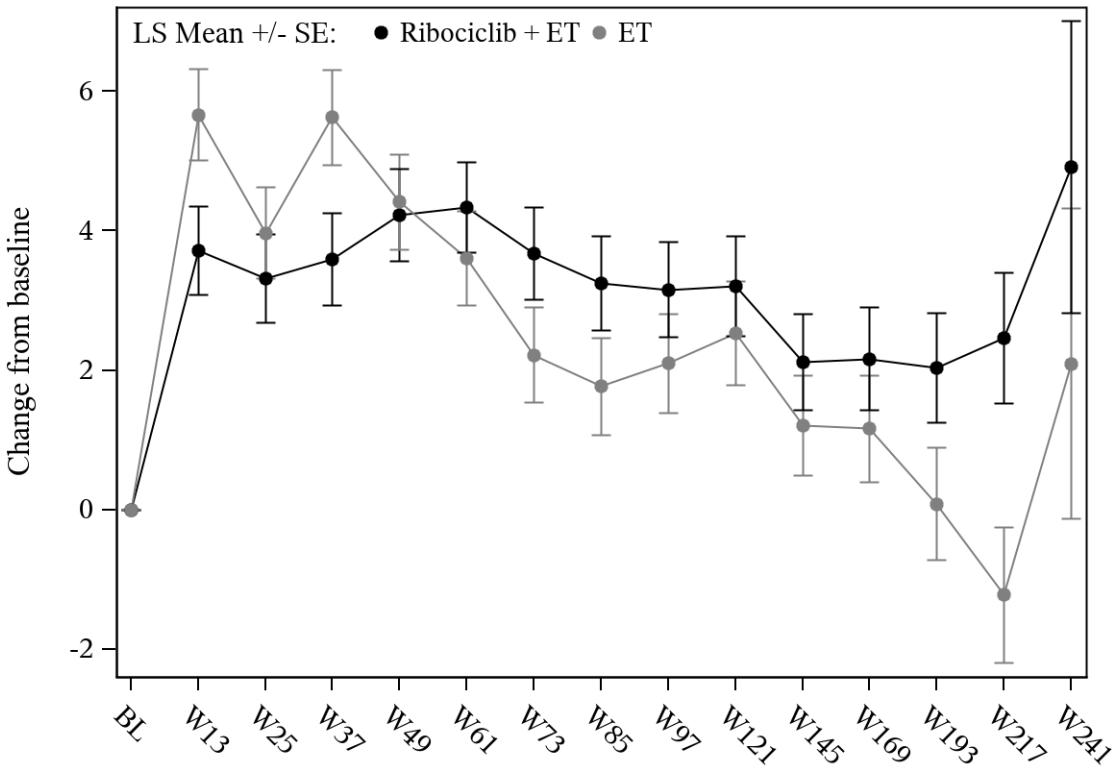
Ribociclib + ET	1059	1027	981	986	973	965	956	943	934	903	900	727	610	344	58
ET	1004	964	921	912	922	903	893	869	859	841	810	681	565	323	51

QLQ-C30 - Nausea and Vomiting



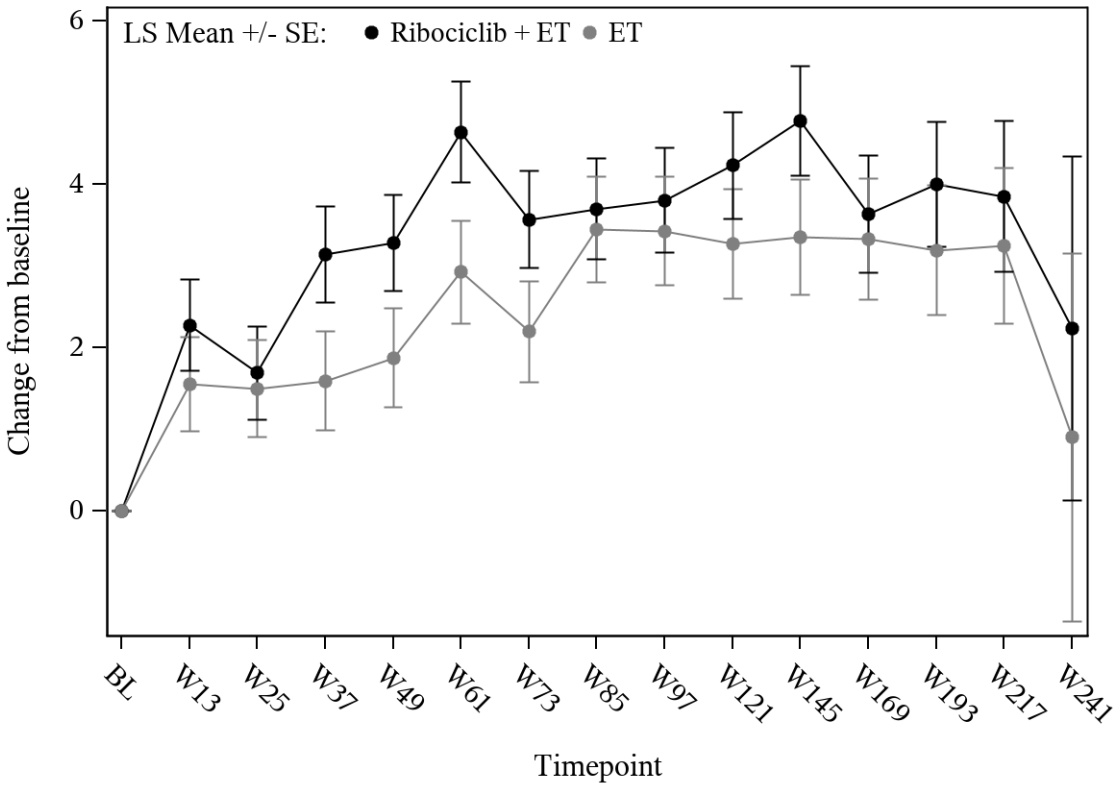
Ribociclib + ET	1059	1028	981	986	973	965	956	944	932	903	900	727	610	344	58
ET	1005	965	922	913	923	904	894	870	860	842	811	683	566	323	51

QLQ-C30 - Pain



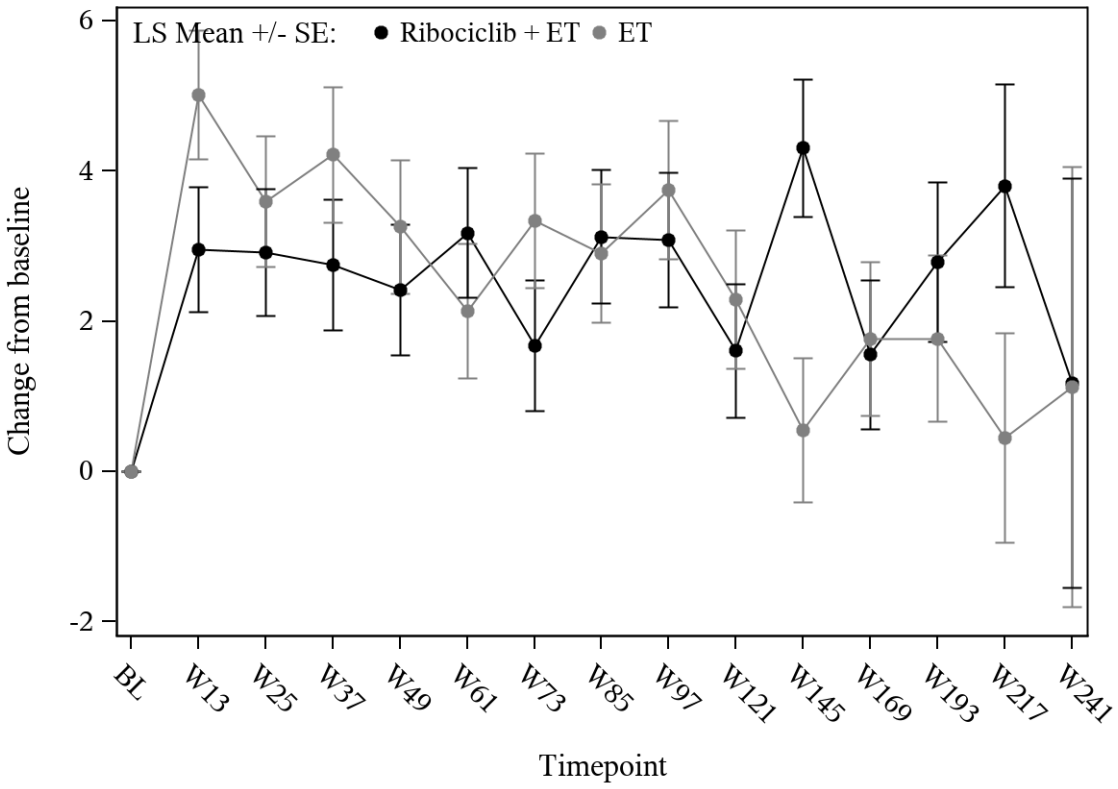
Ribociclib + ET	1060	1029	983	988	974	966	958	944	935	904	901	728	611	345	58
ET	1004	964	921	911	922	903	894	871	860	841	810	682	566	323	52

QLQ-C30 - Dyspnoea



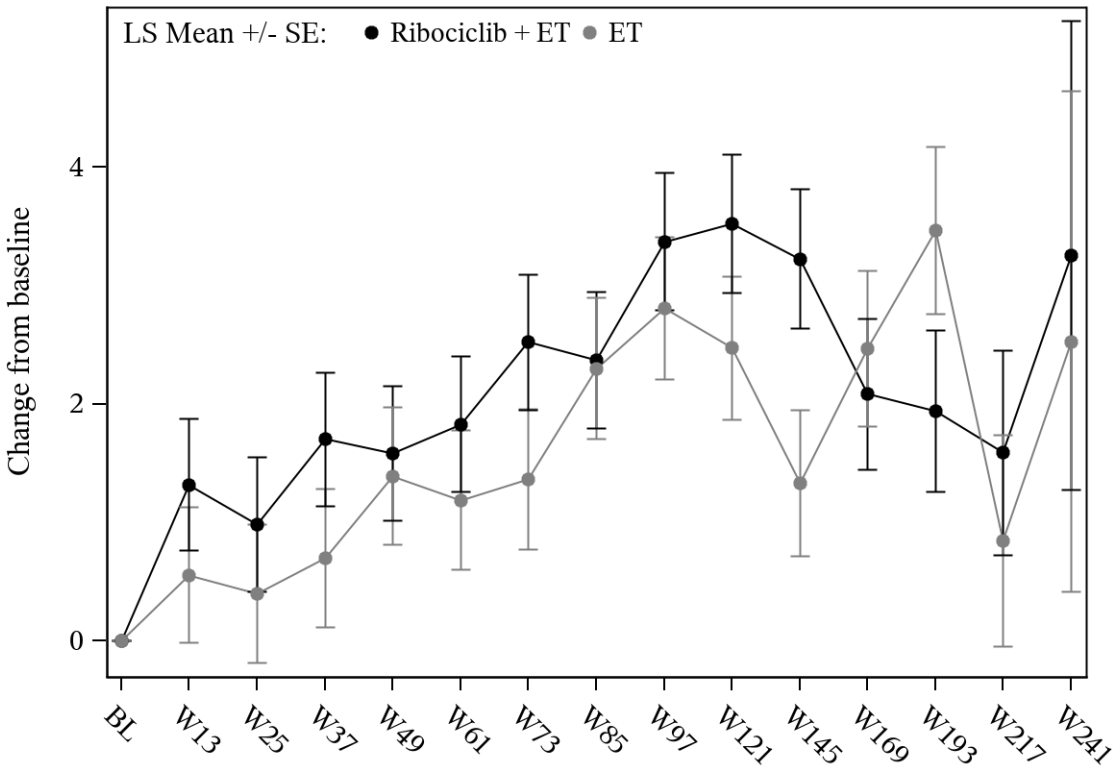
Ribociclib + ET	1057	1024	976	985	971	963	955	943	933	902	898	726	608	343	58
ET	1004	963	919	910	921	903	892	867	859	840	807	682	564	323	51

QLQ-C30 - Insomnia



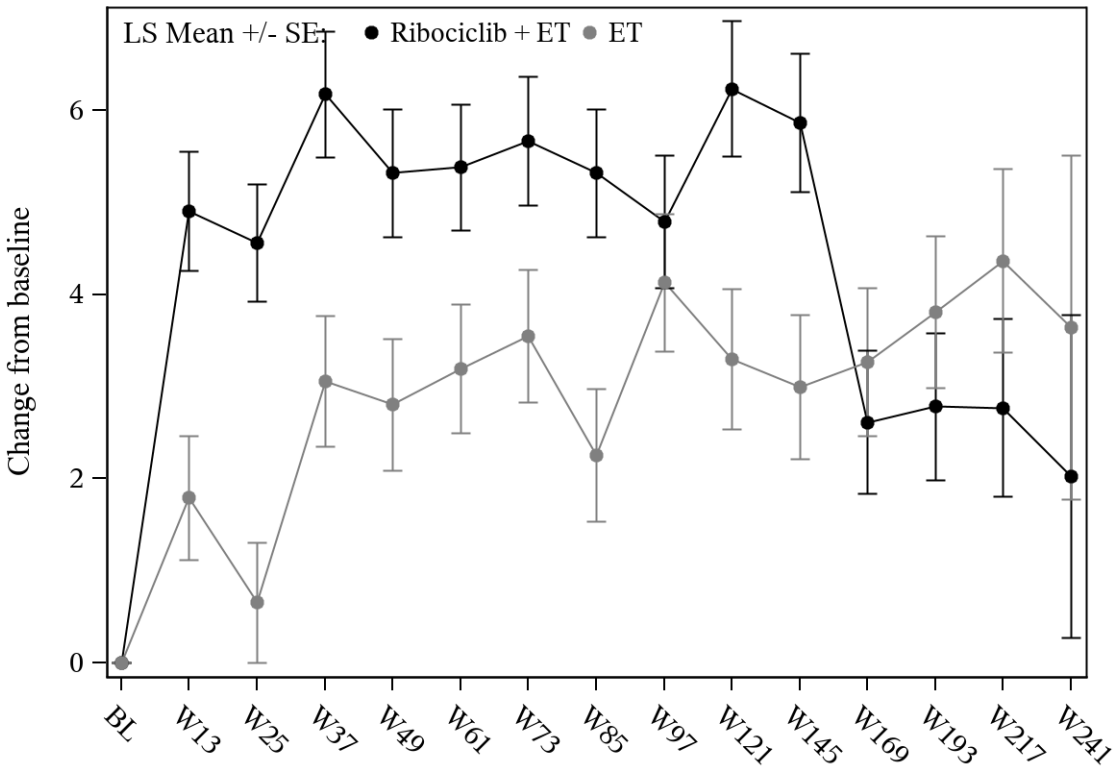
Ribociclib + ET	1060	1027	979	986	971	965	957	943	934	902	898	727	611	345	58
ET	1005	963	921	912	923	904	892	868	860	841	811	683	565	323	51

QLQ-C30 - Appetite Loss



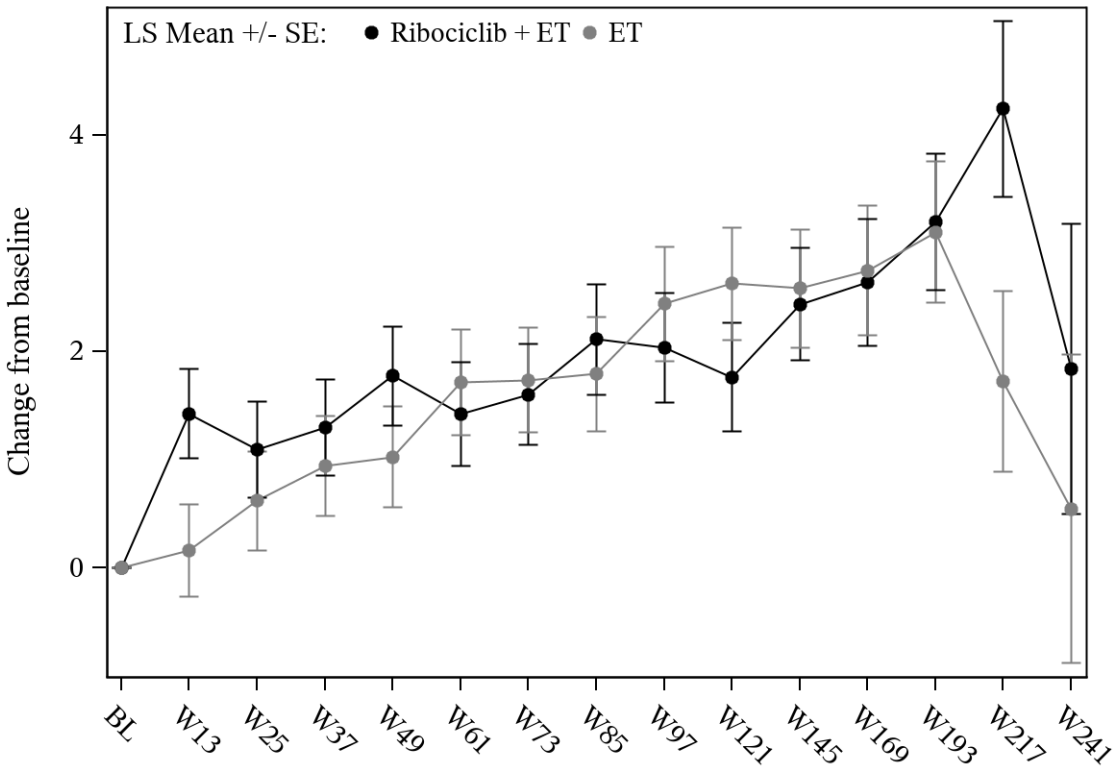
Ribociclib + ET	1059	1028	980	985	970	961	956	943	932	902	897	726	610	344	58
ET	1005	964	917	910	923	904	893	868	858	841	811	681	566	322	51

QLQ-C30 - Constipation



Ribociclib + ET	1055	1022	977	982	969	960	953	936	927	898	896	724	608	343	58
ET	1004	963	922	909	921	903	892	868	859	840	810	680	566	321	51

QLQ-C30 - Diarrhoea



Ribociclib + ET	1055	1022	974	981	967	958	949	935	927	898	895	725	605	344	58
ET	1003	959	914	906	915	900	892	868	855	838	808	680	567	323	51

3-2 EORTC QLQ-C30 QoL

Table 3-2.0 EORTC QLQ-C30 QoL: return rates (Full Analysis Set)

	Treatment groups			
	Ribociclib + ET (N = 1115)		ET (N = 1123)	
	N' (%)	Returns n (%)	N' (%)	Returns n (%)
Baseline	1115 (100.0)	1092 (97.9)	1123 (100.0)	1091 (97.2)
Week 13	1115 (100.0)	1046 (93.8)	1123 (100.0)	987 (87.9)
Week 25	1114 (99.9)	999 (89.7)	1122 (99.9)	942 (84.0)
Week 37	1112 (99.7)	1004 (90.3)	1122 (99.9)	933 (83.2)
Week 49	1112 (99.7)	988 (88.8)	1121 (99.8)	943 (84.1)
Week 61	1109 (99.5)	982 (88.5)	1119 (99.6)	925 (82.7)
Week 73	1107 (99.3)	975 (88.1)	1118 (99.6)	915 (81.8)
Week 85	1106 (99.2)	960 (86.8)	1117 (99.5)	892 (79.9)
Week 97	1103 (98.9)	952 (86.3)	1114 (99.2)	879 (78.9)
Week 121	1098 (98.5)	919 (83.7)	1108 (98.7)	858 (77.4)
Week 145	1094 (98.1)	918 (83.9)	1096 (97.6)	825 (75.3)
Week 169	1087 (97.5)	740 (68.1)	1085 (96.6)	696 (64.1)
Week 193	1085 (97.3)	620 (57.1)	1081 (96.3)	581 (53.7)
Week 217	1084 (97.2)	353 (32.6)	1078 (96.0)	331 (30.7)
Week 241	1084 (97.2)	59 (5.4)	1077 (95.9)	54 (5.0)
Week 265	1084 (97.2)	2 (0.2)	1077 (95.9)	1 (0.1)

N': Number of patients who have not died until the respective visit
ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
.....

The number of returns is the number of patients with non-missing data (i.e. at least one [sub-]score present) at the respective visit.

A patients is considered to have not died until the visit if no death was documented during the study, if returns for this PRO are present at the visit or, if no returns are present for this PRO and the patient died, if the death date is after the scheduled visit date.

Percentages of returns refer to N' per group. For N' percentages refer to N per group.

Table 3-2.1 EORTC QLQ-C30 QoL: change from baseline analysis (Full Analysis Set)

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1115)	ET (N = 1123)	Parameter	Esti-mate	[95% CI]	p-value
QLQ-C30 - Global Health/QoL						
	N' | Mean (SD)	**N' | Mean (SD)**				
Overall N'	1056	1003				
Baseline	1056 | 73.74 (17.28)	1003 | 74.37 (16.79)				
Week 13	1025 | 70.35 (18.68)	956 | 71.65 (18.99)				
Week 25	976 | 71.64 (17.90)	916 | 71.70 (18.38)				
Week 37	982 | 71.05 (18.62)	907 | 71.87 (18.57)				
Week 49	967 | 71.39 (18.29)	915 | 72.23 (18.20)				
Week 61	961 | 70.45 (19.03)	901 | 72.07 (18.40)				
Week 73	953 | 70.72 (18.76)	892 | 72.47 (18.48)				
Week 85	938 | 70.55 (19.03)	869 | 71.63 (18.92)				
Week 97	928 | 70.74 (18.92)	856 | 72.02 (19.09)				
Week 121	897 | 70.46 (19.20)	838 | 72.46 (19.22)				
Week 145	896 | 71.12 (18.73)	808 | 72.32 (19.18)				
Week 169	725 | 71.54 (18.48)	679 | 71.29 (19.91)				
Week 193	606 | 72.80 (18.09)	567 | 71.97 (19.19)				
Week 217	344 | 71.63 (18.61)	323 | 73.30 (18.69)				
Week 241	58 | 73.42 (17.27)	52 | 71.47 (20.90)				
Adjusted change	**Mean (SE)**	**Mean (SE)**				
Week 13	-3.63 (0.50)	-2.59 (0.51)	Difference	-1.03	[-2.43; 0.37]	0.148
			Hedges G	-0.07	[-0.15; 0.02]	
Week 25	-2.58 (0.49)	-2.55 (0.51)	Difference	-0.04	[-1.42; 1.35]	0.956
			Hedges G	-0.00	[-0.09; 0.09]	
Week 37	-3.31 (0.52)	-2.45 (0.53)	Difference	-0.86	[-2.32; 0.60]	0.247
			Hedges G	-0.05	[-0.14; 0.04]	
Week 49	-3.18 (0.51)	-2.11 (0.52)	Difference	-1.07	[-2.50; 0.36]	0.143
			Hedges G	-0.07	[-0.16; 0.02]	
Week 61	-4.22 (0.52)	-2.18 (0.54)	Difference	-2.04	[-3.51; -0.57]	0.006
			Hedges G	-0.13	[-0.22; -0.04]	
Week 73	-4.06 (0.53)	-2.00 (0.55)	Difference	-2.06	[-3.56; -0.57]	0.007
			Hedges G	-0.13	[-0.22; -0.03]	
Week 85	-4.35 (0.54)	-2.70 (0.56)	Difference	-1.66	[-3.18; -0.13]	0.034
			Hedges G	-0.10	[-0.19; -0.01]	
Week 97	-4.18 (0.55)	-2.33 (0.57)	Difference	-1.86	[-3.41; -0.30]	0.019
			Hedges G	-0.11	[-0.20; -0.02]	
Week 121	-4.32 (0.56)	-2.16 (0.58)	Difference	-2.16	[-3.74; -0.57]	0.008
			Hedges G	-0.13	[-0.22; -0.03]	
Week 145	-3.75 (0.55)	-2.19 (0.58)	Difference	-1.56	[-3.13; 0.01]	0.051
			Hedges G	-0.09	[-0.19; 0.00]	

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1115)	**ET (N = 1123)**	**Parameter**	**Esti-mate**	**[95% CI]**	**p-value**
Week 169	-2.91 (0.59)	-2.45 (0.61)	Difference	-0.46	[-2.13; 1.21]	0.589
			Hedges G	-0.03	[-0.13; 0.08]	
Week 193	-1.72 (0.62)	-1.89 (0.64)	Difference	0.17	[-1.59; 1.92]	0.852
			Hedges G	0.01	[-0.10; 0.13]	
Week 217	-3.16 (0.74)	-0.68 (0.77)	Difference	-2.47	[-4.57; -0.38]	0.021
			Hedges G	-0.18	[-0.33; -0.03]	
Week 241	-3.86 (1.57)	-4.71 (1.66)	Difference	0.85	[-3.64; 5.34]	0.711
			Hedges G	0.07	[-0.30; 0.45]	
Overall effect	**-3.52 (0.41)**	**-2.36 (0.42)**	**Difference**	**-1.16**	**[-2.31; -0.02]**	**0.047**
			Hedges G	**-0.09**	**[-0.17; -0.00]**	
QLQ-C30 - Physical Functioning						
	N' | Mean (SD)	**N' | Mean (SD)**				
Overall N'	1060	1003				
Baseline	1060 | 85.87 (14.27)	1003 | 86.30 (13.79)				
Week 13	1029 | 84.32 (15.85)	963 | 84.82 (14.82)				
Week 25	982 | 84.52 (15.54)	922 | 84.76 (14.94)				
Week 37	987 | 85.18 (15.30)	912 | 85.00 (14.97)				
Week 49	974 | 84.95 (15.31)	923 | 85.12 (15.17)				
Week 61	966 | 85.11 (15.28)	904 | 85.19 (15.15)				
Week 73	957 | 84.92 (15.71)	893 | 85.97 (14.70)				
Week 85	944 | 85.21 (15.79)	869 | 85.45 (15.96)				
Week 97	935 | 85.12 (16.10)	859 | 86.14 (15.13)				
Week 121	904 | 85.04 (15.92)	841 | 86.22 (15.30)				
Week 145	900 | 85.44 (15.75)	810 | 86.36 (15.47)				
Week 169	728 | 85.48 (15.46)	681 | 86.16 (15.30)				
Week 193	611 | 85.34 (15.14)	565 | 85.71 (15.69)				
Week 217	344 | 85.80 (15.17)	323 | 86.10 (14.89)				
Week 241	58 | 84.83 (19.26)	51 | 90.20 (13.69)				
Adjusted change	**Mean (SE)**	**Mean (SE)**				
Week 13	-1.58 (0.36)	-1.40 (0.37)	Difference	-0.18	[-1.20; 0.84]	0.732
			Hedges G	-0.02	[-0.10; 0.07]	
Week 25	-1.59 (0.37)	-1.27 (0.38)	Difference	-0.31	[-1.35; 0.73]	0.557
			Hedges G	-0.03	[-0.12; 0.06]	
Week 37	-1.15 (0.38)	-1.01 (0.39)	Difference	-0.14	[-1.21; 0.92]	0.794
			Hedges G	-0.01	[-0.10; 0.08]	
Week 49	-1.58 (0.39)	-1.04 (0.40)	Difference	-0.53	[-1.63; 0.56]	0.342
			Hedges G	-0.04	[-0.13; 0.05]	
Week 61	-1.43 (0.38)	-0.84 (0.40)	Difference	-0.59	[-1.67; 0.49]	0.282
			Hedges G	-0.05	[-0.14; 0.04]	
Week 73	-1.60 (0.40)	-0.36 (0.41)	Difference	-1.24	[-2.37; -0.12]	0.030
			Hedges G	-0.10	[-0.19; -0.01]	
Week 85	-1.50 (0.42)	-0.58 (0.43)	Difference	-0.92	[-2.10; 0.27]	0.128

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1115)	**ET (N = 1123)**	**Parameter**	**Esti-mate**	**[95% CI]**	**p-value**
			Hedges G	-0.07	[-0.16; 0.02]	
Week 97	-1.69 (0.42)	0.11 (0.44)	Difference	-1.80	[-2.99; -0.61]	0.003
			Hedges G	-0.14	[-0.23; -0.05]	
Week 121	-1.82 (0.43)	-0.03 (0.44)	Difference	-1.79	[-3.00; -0.59]	0.004
			Hedges G	-0.14	[-0.23; -0.05]	
Week 145	-1.29 (0.42)	0.03 (0.44)	Difference	-1.32	[-2.52; -0.12]	0.031
			Hedges G	-0.10	[-0.20; -0.01]	
Week 169	-0.97 (0.45)	0.54 (0.46)	Difference	-1.51	[-2.77; -0.25]	0.019
			Hedges G	-0.12	[-0.23; -0.02]	
Week 193	-1.48 (0.47)	0.08 (0.49)	Difference	-1.56	[-2.89; -0.24]	0.021
			Hedges G	-0.13	[-0.25; -0.02]	
Week 217	-1.09 (0.57)	0.40 (0.59)	Difference	-1.49	[-3.09; 0.12]	0.069
			Hedges G	-0.14	[-0.29; 0.01]	
Week 241	-2.34 (1.29)	1.41 (1.37)	Difference	-3.75	[-7.44; -0.06]	0.047
			Hedges G	-0.38	[-0.76; -0.00]	
Overall effect	**-1.51 (0.33)**	**-0.28 (0.34)**	**Difference**	**-1.22**	**[-2.15; -0.30]**	**0.010**
			Hedges G	**-0.11**	**[-0.20; -0.03]**	
QLQ-C30 - Role Functioning						
	N' | Mean (SD)	**N' | Mean (SD)**				
Overall N'	1059	1004				
Baseline	1059 | 82.97 (21.83)	1004 | 83.63 (20.64)				
Week 13	1027 | 80.67 (23.12)	964 | 80.52 (22.96)				
Week 25	981 | 81.35 (23.44)	921 | 81.49 (21.80)				
Week 37	986 | 81.27 (22.72)	912 | 80.14 (22.98)				
Week 49	972 | 80.47 (22.59)	922 | 81.87 (22.04)				
Week 61	965 | 80.09 (23.35)	903 | 82.17 (21.80)				
Week 73	956 | 80.42 (23.46)	894 | 81.73 (22.08)				
Week 85	944 | 80.17 (23.70)	869 | 82.34 (22.02)				
Week 97	934 | 80.35 (23.94)	860 | 82.36 (21.90)				
Week 121	903 | 80.32 (24.21)	842 | 82.05 (22.86)				
Week 145	900 | 81.83 (23.24)	811 | 82.84 (22.46)				
Week 169	727 | 82.28 (22.67)	683 | 81.72 (23.48)				
Week 193	610 | 82.76 (22.07)	565 | 82.04 (22.96)				
Week 217	344 | 82.17 (22.09)	323 | 84.11 (21.83)				
Week 241	58 | 82.18 (27.37)	52 | 87.50 (19.77)				
Adjusted change	**Mean (SE)**	**Mean (SE)**				
Week 13	-2.61 (0.63)	-2.90 (0.65)	Difference	0.29	[-1.48; 2.06]	0.750
			Hedges G	0.01	[-0.07; 0.10]	
Week 25	-2.28 (0.64)	-1.94 (0.66)	Difference	-0.34	[-2.15; 1.46]	0.707
			Hedges G	-0.02	[-0.11; 0.07]	
Week 37	-2.38 (0.64)	-3.17 (0.66)	Difference	0.79	[-1.02; 2.60]	0.394
			Hedges G	0.04	[-0.05; 0.13]	

Treatment Groups			Comparison			
	Ribociclib + ET (N = 1115)	**ET (N = 1123)**	**Parameter**	**Esti-mate**	**[95% CI]**	**p-value**
Week 49	-3.31 (0.65)	-1.65 (0.67)	Difference	-1.66	[-3.49; 0.16]	0.073
			Hedges G	-0.08	[-0.17; 0.01]	
Week 61	-3.84 (0.65)	-1.18 (0.67)	Difference	-2.67	[-4.50; -0.83]	0.004
			Hedges G	-0.13	[-0.22; -0.04]	
Week 73	-3.49 (0.65)	-2.04 (0.67)	Difference	-1.45	[-3.29; 0.39]	0.122
			Hedges G	-0.07	[-0.16; 0.02]	
Week 85	-3.89 (0.67)	-1.10 (0.69)	Difference	-2.79	[-4.67; -0.91]	0.004
			Hedges G	-0.14	[-0.23; -0.04]	
Week 97	-3.77 (0.68)	-1.12 (0.70)	Difference	-2.64	[-4.56; -0.73]	0.007
			Hedges G	-0.13	[-0.22; -0.04]	
Week 121	-3.94 (0.71)	-1.51 (0.73)	Difference	-2.43	[-4.43; -0.43]	0.017
			Hedges G	-0.11	[-0.21; -0.02]	
Week 145	-2.33 (0.68)	-0.89 (0.71)	Difference	-1.43	[-3.36; 0.49]	0.144
			Hedges G	-0.07	[-0.17; 0.02]	
Week 169	-1.64 (0.74)	-1.18 (0.76)	Difference	-0.45	[-2.54; 1.63]	0.668
			Hedges G	-0.02	[-0.13; 0.08]	
Week 193	-1.64 (0.77)	-1.22 (0.79)	Difference	-0.42	[-2.59; 1.74]	0.702
			Hedges G	-0.02	[-0.14; 0.09]	
Week 217	-2.95 (0.93)	0.88 (0.96)	Difference	-3.84	[-6.47; -1.20]	0.004
			Hedges G	-0.22	[-0.37; -0.07]	
Week 241	-2.37 (2.03)	1.56 (2.15)	Difference	-3.93	[-9.73; 1.86]	0.183
			Hedges G	-0.25	[-0.63; 0.12]	
Overall effect	**-2.89 (0.50)**	**-1.25 (0.52)**	**Difference**	**-1.64**	**[-3.06; -0.22]**	**0.023**
			Hedges G	**-0.10**	**[-0.19; -0.01]**	

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1115)	**ET (N = 1123)**	**Parameter**	**Esti-mate**	**[95% CI]**	**p-value**
QLQ-C30 - Emotional Functioning						
	N' | Mean (SD)	**N' | Mean (SD)**				
Overall N'	1056	1003				
Baseline	1056 | 77.64 (20.26)	1003 | 78.48 (19.06)				
Week 13	1024 | 73.77 (22.69)	958 | 74.17 (21.66)				
Week 25	976 | 73.74 (22.52)	918 | 74.07 (22.48)				
Week 37	982 | 73.63 (22.01)	906 | 73.27 (22.95)				
Week 49	968 | 73.43 (22.69)	916 | 72.98 (22.52)				
Week 61	961 | 71.88 (23.32)	901 | 72.86 (22.51)				
Week 73	952 | 72.43 (23.35)	892 | 73.20 (23.26)				
Week 85	940 | 72.47 (23.25)	869 | 72.69 (23.72)				
Week 97	930 | 72.24 (23.42)	856 | 73.63 (22.67)				
Week 121	898 | 72.17 (23.72)	839 | 73.32 (23.03)				
Week 145	896 | 71.68 (24.77)	808 | 73.56 (24.17)				
Week 169	725 | 72.84 (23.06)	679 | 73.09 (23.53)				
Week 193	606 | 74.06 (23.46)	567 | 72.90 (24.06)				
Week 217	344 | 73.85 (22.47)	323 | 74.79 (23.54)				
Week 241	58 | 74.57 (23.49)	52 | 77.08 (22.98)				
Adjusted change	**Mean (SE)**	**Mean (SE)**				
Week 13	-4.40 (0.62)	-4.34 (0.64)	Difference	-0.07	[-1.82; 1.68]	0.942
			Hedges G	-0.00	[-0.09; 0.08]	
Week 25	-4.90 (0.63)	-4.50 (0.65)	Difference	-0.40	[-2.17; 1.37]	0.658
			Hedges G	-0.02	[-0.11; 0.07]	
Week 37	-4.96 (0.63)	-5.18 (0.65)	Difference	0.22	[-1.55; 2.00]	0.805
			Hedges G	0.01	[-0.08; 0.10]	
Week 49	-5.32 (0.63)	-5.56 (0.65)	Difference	0.24	[-1.54; 2.01]	0.795
			Hedges G	0.01	[-0.08; 0.10]	
Week 61	-6.84 (0.63)	-5.70 (0.65)	Difference	-1.14	[-2.93; 0.64]	0.209
			Hedges G	-0.06	[-0.15; 0.03]	
Week 73	-6.37 (0.64)	-5.47 (0.66)	Difference	-0.90	[-2.69; 0.89]	0.326
			Hedges G	-0.05	[-0.14; 0.05]	
Week 85	-6.47 (0.64)	-6.12 (0.66)	Difference	-0.35	[-2.15; 1.45]	0.704
			Hedges G	-0.02	[-0.11; 0.07]	
Week 97	-6.82 (0.64)	-5.01 (0.67)	Difference	-1.81	[-3.62; 0.00]	0.050
			Hedges G	-0.09	[-0.19; 0.00]	
Week 121	-6.84 (0.65)	-5.71 (0.67)	Difference	-1.13	[-2.96; 0.69]	0.224
			Hedges G	-0.06	[-0.15; 0.04]	
Week 145	-7.37 (0.65)	-5.45 (0.68)	Difference	-1.92	[-3.76; -0.08]	0.041
			Hedges G	-0.10	[-0.19; -0.00]	
Week 169	-5.59 (0.69)	-5.10 (0.72)	Difference	-0.48	[-2.44; 1.47]	0.626
			Hedges G	-0.03	[-0.13; 0.08]	
Week 193	-4.70 (0.74)	-5.75 (0.76)	Difference	1.05	[-1.02; 3.13]	0.320

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1115)	**ET (N = 1123)**	**Parameter**	**Esti-mate**	**[95% CI]**	**p-value**
			Hedges G	0.06	[-0.06; 0.17]	
Week 217	-4.98 (0.90)	-4.42 (0.93)	Difference	-0.56	[-3.11; 1.99]	0.666
			Hedges G	-0.03	[-0.19; 0.12]	
Week 241	-6.21 (1.96)	-6.78 (2.08)	Difference	0.57	[-5.03; 6.16]	0.842
			Hedges G	0.04	[-0.34; 0.41]	
Overall effect	**-5.84 (0.49)**	**-5.36 (0.50)**	**Difference**	**-0.48**	**[-1.85; 0.89]**	**0.494**
			Hedges G	**-0.03**	**[-0.12; 0.06]**	
QLQ-C30 - Cognitive Functioning						
	N' | Mean (SD)	**N' | Mean (SD)**				
Overall N'	1056	1003				
Baseline	1056 | 81.36 (20.72)	1003 | 81.59 (20.19)				
Week 13	1024 | 78.65 (23.09)	959 | 78.75 (21.97)				
Week 25	976 | 78.16 (23.04)	918 | 78.47 (22.45)				
Week 37	982 | 76.75 (23.11)	907 | 77.31 (22.89)				
Week 49	968 | 77.44 (22.57)	916 | 76.82 (23.23)				
Week 61	961 | 75.89 (24.15)	901 | 76.06 (23.28)				
Week 73	952 | 75.63 (23.78)	892 | 77.02 (22.83)				
Week 85	940 | 75.20 (24.05)	869 | 75.78 (24.27)				
Week 97	930 | 74.25 (24.95)	856 | 75.43 (23.23)				
Week 121	899 | 74.30 (24.62)	839 | 75.31 (23.86)				
Week 145	896 | 73.88 (25.26)	808 | 75.87 (23.36)				
Week 169	725 | 75.82 (24.59)	679 | 74.47 (24.53)				
Week 193	606 | 75.41 (24.35)	567 | 74.93 (23.82)				
Week 217	344 | 75.87 (23.35)	323 | 75.90 (24.22)				
Week 241	58 | 81.03 (17.23)	52 | 78.21 (20.49)				
Adjusted change	**Mean (SE)**	**Mean (SE)**				
Week 13	-3.00 (0.57)	-3.06 (0.58)	Difference	0.06	[-1.53; 1.66]	0.936
			Hedges G	0.00	[-0.08; 0.09]	
Week 25	-3.89 (0.60)	-3.16 (0.62)	Difference	-0.72	[-2.42; 0.98]	0.404
			Hedges G	-0.04	[-0.13; 0.05]	
Week 37	-5.31 (0.62)	-4.10 (0.64)	Difference	-1.21	[-2.97; 0.54]	0.175
			Hedges G	-0.06	[-0.15; 0.03]	
Week 49	-4.81 (0.62)	-4.69 (0.64)	Difference	-0.12	[-1.88; 1.64]	0.894
			Hedges G	-0.01	[-0.10; 0.08]	
Week 61	-6.44 (0.64)	-5.39 (0.66)	Difference	-1.05	[-2.85; 0.74]	0.249
			Hedges G	-0.05	[-0.14; 0.04]	
Week 73	-6.55 (0.64)	-4.58 (0.65)	Difference	-1.97	[-3.76; -0.18]	0.031
			Hedges G	-0.10	[-0.19; -0.01]	
Week 85	-7.26 (0.66)	-5.84 (0.68)	Difference	-1.41	[-3.28; 0.45]	0.136
			Hedges G	-0.07	[-0.16; 0.02]	
Week 97	-8.24 (0.67)	-6.01 (0.69)	Difference	-2.22	[-4.11; -0.34]	0.021
			Hedges G	-0.11	[-0.20; -0.02]	

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1115)	**ET (N = 1123)**	**Parameter**	**Esti-mate**	**[95% CI]**	**p-value**
Week 121	-8.14 (0.69)	-6.48 (0.71)	Difference	-1.66	[-3.60; 0.28]	0.093
			Hedges G	-0.08	[-0.17; 0.01]	
Week 145	-8.62 (0.70)	-5.86 (0.73)	Difference	-2.76	[-4.74; -0.78]	0.006
			Hedges G	-0.13	[-0.23; -0.04]	
Week 169	-6.08 (0.74)	-5.98 (0.76)	Difference	-0.10	[-2.17; 1.98]	0.927
			Hedges G	-0.00	[-0.11; 0.10]	
Week 193	-7.12 (0.76)	-5.57 (0.79)	Difference	-1.56	[-3.71; 0.59]	0.156
			Hedges G	-0.08	[-0.20; 0.03]	
Week 217	-7.31 (0.91)	-4.77 (0.94)	Difference	-2.54	[-5.10; 0.02]	0.052
			Hedges G	-0.15	[-0.30; 0.00]	
Week 241	-4.53 (1.61)	-7.03 (1.70)	Difference	2.50	[-2.09; 7.10]	0.285
			Hedges G	0.20	[-0.17; 0.58]	
Overall effect	**-6.24 (0.51)**	**-5.18 (0.53)**	**Difference**	**-1.05**	**[-2.49; 0.38]**	**0.150**
			Hedges G	**-0.06**	**[-0.15; 0.02]**	
QLQ-C30 - Social Functioning						
	N' | Mean (SD)	**N' | Mean (SD)**				
Overall N'	1056	1002				
Baseline	1056 | 80.43 (24.30)	1002 | 81.70 (21.96)				
Week 13	1024 | 82.99 (22.39)	957 | 83.54 (22.43)				
Week 25	976 | 82.22 (23.66)	916 | 83.79 (22.29)				
Week 37	982 | 81.62 (24.17)	906 | 82.97 (22.62)				
Week 49	968 | 81.87 (22.95)	915 | 83.62 (22.16)				
Week 61	961 | 81.15 (24.59)	900 | 83.70 (22.48)				
Week 73	952 | 81.44 (24.38)	891 | 84.01 (22.42)				
Week 85	940 | 81.26 (24.13)	868 | 83.39 (22.73)				
Week 97	929 | 81.22 (24.57)	855 | 83.24 (22.91)				
Week 121	897 | 81.35 (24.89)	838 | 83.17 (23.79)				
Week 145	896 | 81.23 (24.87)	807 | 83.35 (23.05)				
Week 169	725 | 82.69 (23.95)	677 | 83.63 (22.90)				
Week 193	606 | 82.37 (24.33)	566 | 83.60 (23.24)				
Week 217	344 | 83.14 (22.77)	323 | 85.09 (22.30)				
Week 241	58 | 84.20 (23.45)	52 | 89.42 (17.47)				
Adjusted change	**Mean (SE)**	**Mean (SE)**				
Week 13	1.88 (0.60)	1.85 (0.62)	Difference	0.04	[-1.66; 1.73]	0.966
			Hedges G	0.00	[-0.09; 0.09]	
Week 25	0.66 (0.62)	1.98 (0.64)	Difference	-1.31	[-3.07; 0.45]	0.143
			Hedges G	-0.07	[-0.16; 0.02]	
Week 37	-0.07 (0.65)	1.43 (0.67)	Difference	-1.50	[-3.32; 0.33]	0.109
			Hedges G	-0.07	[-0.16; 0.02]	
Week 49	0.21 (0.63)	1.78 (0.65)	Difference	-1.56	[-3.34; 0.21]	0.084
			Hedges G	-0.08	[-0.17; 0.01]	
Week 61	-0.64 (0.65)	1.92 (0.67)	Difference	-2.56	[-4.40; -0.72]	0.006

Treatment Groups			Comparison			
	Ribociclib + ET (N = 1115)	**ET (N = 1123)**	**Parameter**	**Esti-mate**	**[95% CI]**	**p-value**
			Hedges G	-0.13	[-0.22; -0.04]	
Week 73	-0.47 (0.66)	2.04 (0.68)	Difference	-2.52	[-4.37; -0.66]	0.008
			Hedges G	-0.12	[-0.22; -0.03]	
Week 85	-0.79 (0.68)	1.42 (0.70)	Difference	-2.21	[-4.12; -0.30]	0.024
			Hedges G	-0.11	[-0.20; -0.01]	
Week 97	-1.08 (0.68)	1.25 (0.70)	Difference	-2.33	[-4.25; -0.41]	0.017
			Hedges G	-0.11	[-0.21; -0.02]	
Week 121	-1.02 (0.71)	1.07 (0.74)	Difference	-2.08	[-4.09; -0.07]	0.042
			Hedges G	-0.10	[-0.19; -0.00]	
Week 145	-1.03 (0.70)	1.31 (0.73)	Difference	-2.34	[-4.33; -0.35]	0.021
			Hedges G	-0.11	[-0.21; -0.02]	
Week 169	0.67 (0.74)	2.09 (0.76)	Difference	-1.42	[-3.49; 0.66]	0.181
			Hedges G	-0.07	[-0.18; 0.03]	
Week 193	-0.11 (0.79)	1.30 (0.81)	Difference	-1.41	[-3.63; 0.81]	0.213
			Hedges G	-0.07	[-0.19; 0.04]	
Week 217	-0.08 (0.89)	2.94 (0.92)	Difference	-3.02	[-5.53; -0.50]	0.019
			Hedges G	-0.18	[-0.33; -0.03]	
Week 241	-0.97 (1.83)	3.92 (1.94)	Difference	-4.88	[-10.11; 0.35]	0.067
			Hedges G	-0.35	[-0.73; 0.03]	
Overall effect	**-0.20 (0.51)**	**1.88 (0.53)**	**Difference**	**-2.08**	**[-3.52; -0.64]**	**0.005**
			Hedges G	**-0.12**	**[-0.21; -0.04]**	

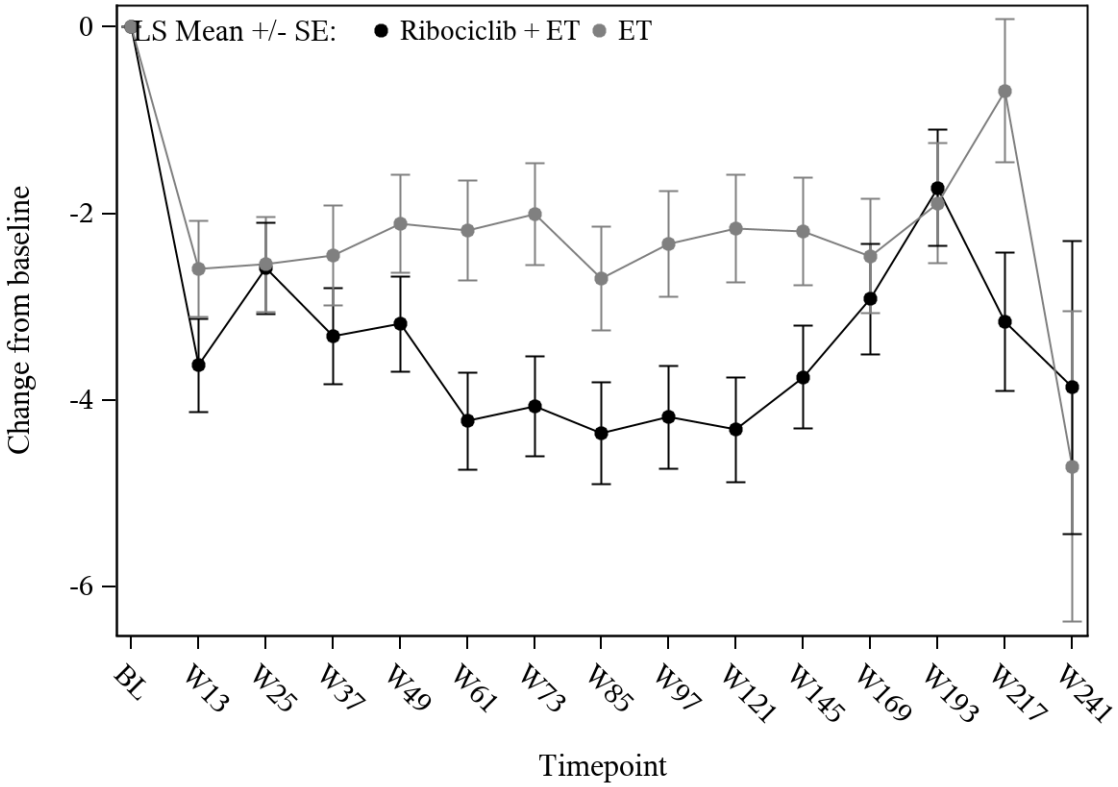
N: Number of patients
N': Number of patients in the analysis
CI: Confidence interval
SD: Standard deviation
LS Mean: Least square mean
SE: Standard error
MMRM: Mixed model for repeated measures
ET: Endocrine therapy (Anastrozole/Letrozole + Goserelin)
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Analysis methods:
Adjusted mean (LS Mean) change from baseline and difference obtained from MMRM with unstructured covariance matrix:
change from baseline = treatment + visit + treatment * visit + baseline value + AJCC Anatomic Stage + prior neo/adjuvant chemotherapy + region
ET was the reference group for treatment group comparison.
If the model did not converge for a parameter, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry.

Patients with an evaluable baseline score and at least one evaluable post-baseline score were included in the analysis.
All data collected were included in the analysis, including assessments at confirmation of first recurrence and thereafter, as long as there were at least 50 patients in each treatment group at a visit.

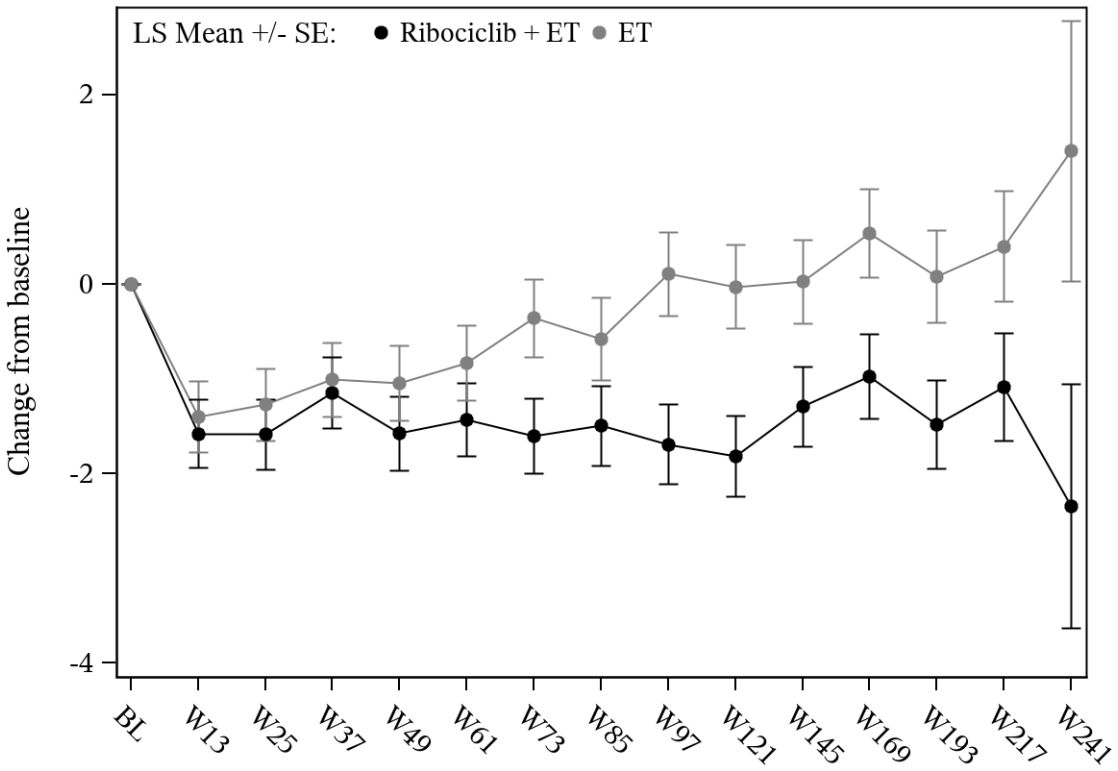
Figure 3-2.1 EORTC QLQ-C30 QoL: line chart of change from baseline (Full Analysis Set)

QLQ-C30 - Global Health/QoL



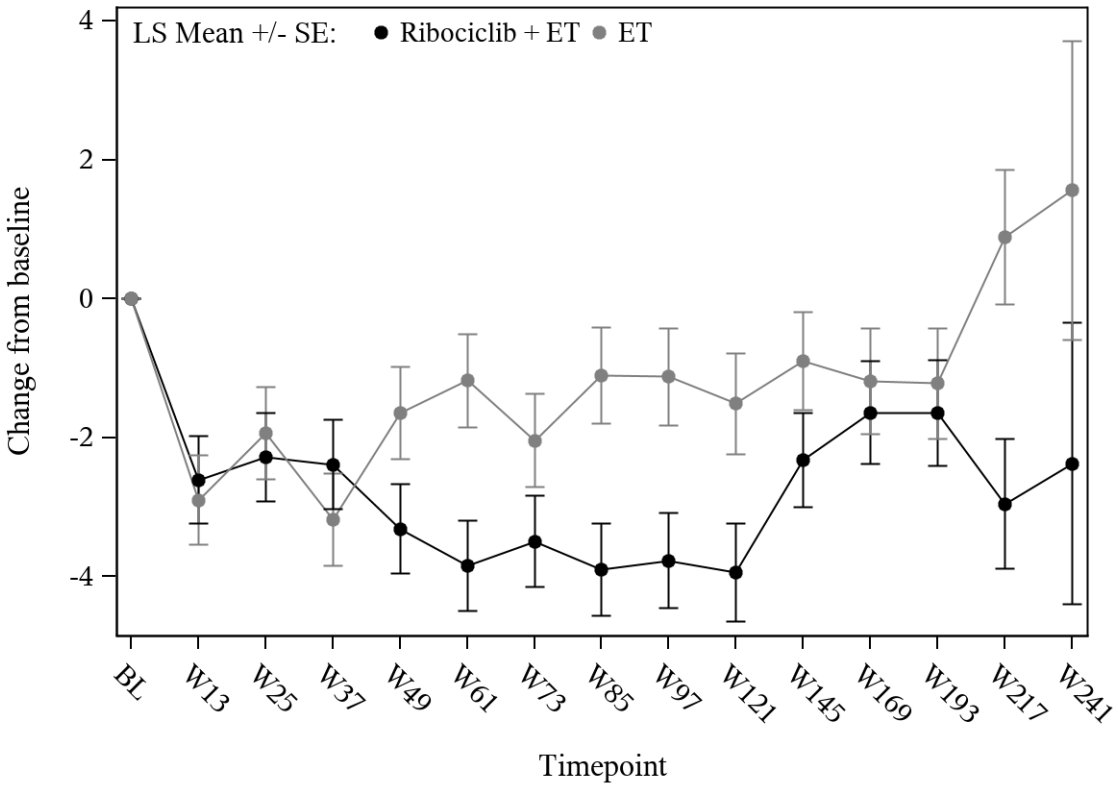
Ribociclib + ET	1056	1025	976	982	967	961	953	938	928	897	896	725	606	344	58
ET	1003	956	916	907	915	901	892	869	856	838	808	679	567	323	52

QLQ-C30 - Physical Functioning



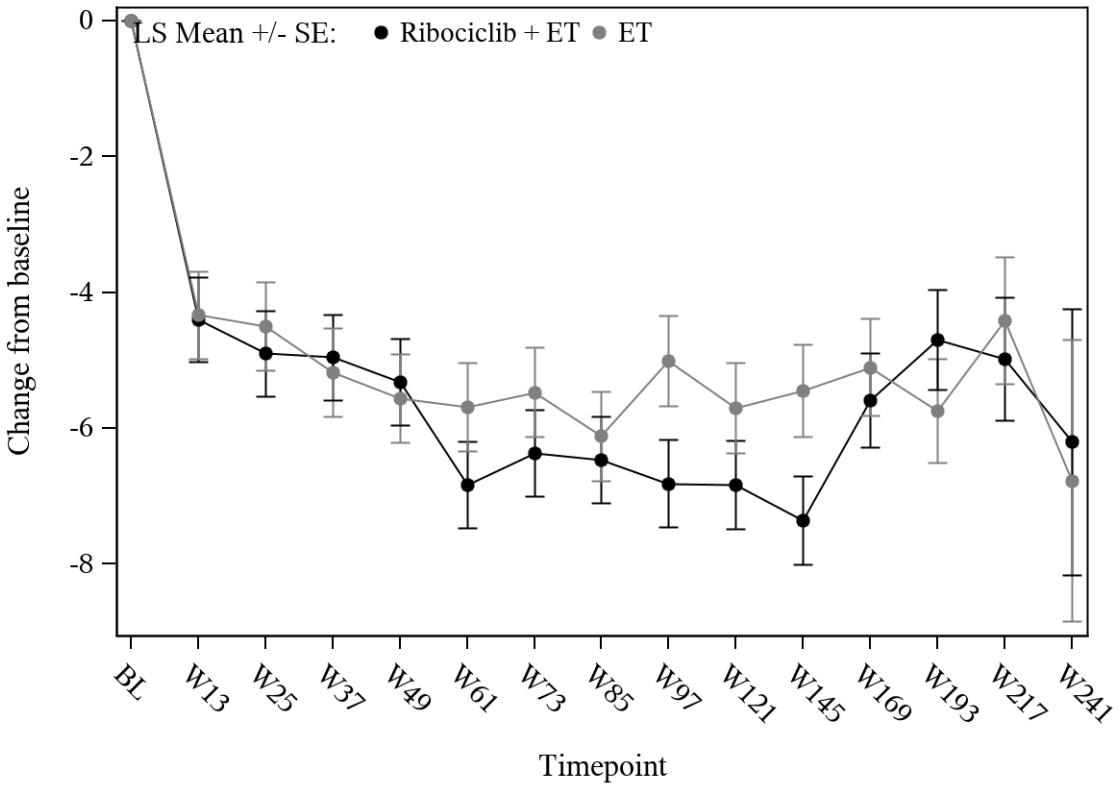
Ribociclib + ET	1060	1029	982	987	974	966	957	944	935	904	900	728	611	344	58
ET	1003	963	922	912	923	904	893	869	859	841	810	681	565	323	51

QLQ-C30 - Role Functioning



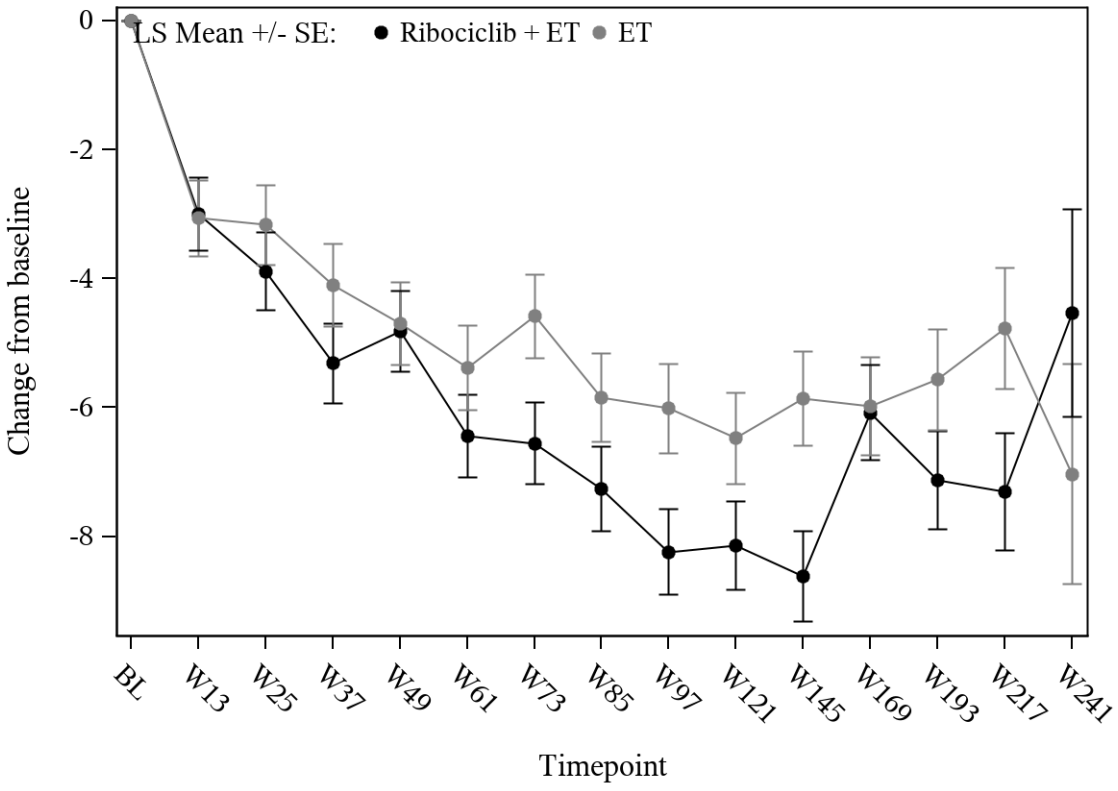
Ribociclib + ET	1059	1027	981	986	972	965	956	944	934	903	900	727	610	344	58
ET	1004	964	921	912	922	903	894	869	860	842	811	683	565	323	52

QLQ-C30 - Emotional Functioning



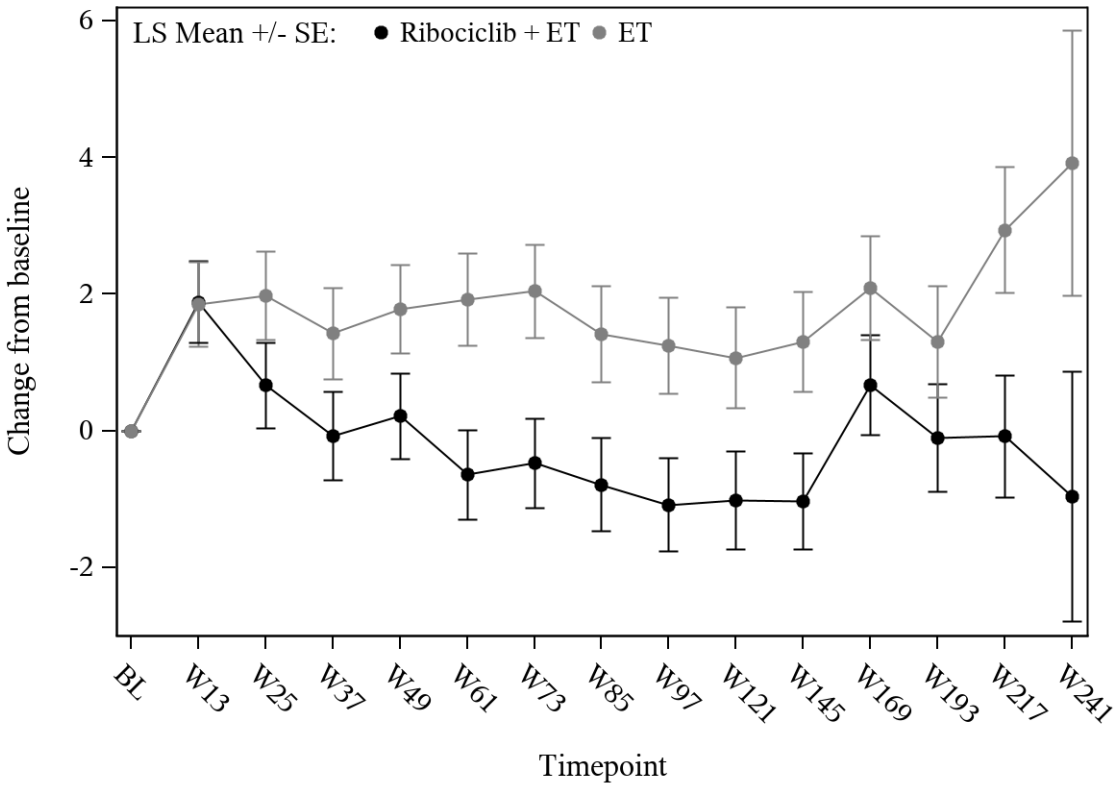
Ribociclib + ET	1056	1024	976	982	968	961	952	940	930	898	896	725	606	344	58
ET	1003	958	918	906	916	901	892	869	856	839	808	679	567	323	52

QLQ-C30 - Cognitive Functioning



Ribociclib + ET	1056	1024	976	982	968	961	952	940	930	899	896	725	606	344	58
ET	1003	959	918	907	916	901	892	869	856	839	808	679	567	323	52

QLQ-C30 - Social Functioning



Ribociclib + ET	1056	1024	976	982	968	961	952	940	929	897	896	725	606	344	58
ET	1002	957	916	906	915	900	891	868	855	838	807	677	566	323	52

3-3 EORTC QLQ-BR23 Symptoms

Table 3-3.0 EORTC QLQ-BR23 Symptoms: return rates (Full Analysis Set)

	Treatment groups			
	Ribociclib + ET (N = 1115)		ET (N = 1123)	
	N' (%)	Returns n (%)	N' (%)	Returns n (%)
Baseline	1114 (99.9)	1092 (98.0)	1123 (100.0)	1089 (97.0)
Week 13	1115 (100.0)	1043 (93.5)	1123 (100.0)	983 (87.5)
Week 25	1114 (99.9)	999 (89.7)	1122 (99.9)	943 (84.0)
Week 37	1112 (99.7)	1003 (90.2)	1122 (99.9)	932 (83.1)
Week 49	1112 (99.7)	988 (88.8)	1121 (99.8)	943 (84.1)
Week 61	1109 (99.5)	983 (88.6)	1119 (99.6)	924 (82.6)
Week 73	1107 (99.3)	973 (87.9)	1118 (99.6)	916 (81.9)
Week 85	1106 (99.2)	960 (86.8)	1117 (99.5)	895 (80.1)
Week 97	1103 (98.9)	949 (86.0)	1114 (99.2)	877 (78.7)
Week 121	1098 (98.5)	919 (83.7)	1108 (98.7)	857 (77.3)
Week 145	1094 (98.1)	915 (83.6)	1096 (97.6)	821 (74.9)
Week 169	1087 (97.5)	742 (68.3)	1085 (96.6)	695 (64.1)
Week 193	1085 (97.3)	619 (57.1)	1081 (96.3)	579 (53.6)
Week 217	1084 (97.2)	354 (32.7)	1078 (96.0)	329 (30.5)
Week 241	1084 (97.2)	59 (5.4)	1077 (95.9)	54 (5.0)
Week 265	1084 (97.2)	2 (0.2)	1077 (95.9)	1 (0.1)

N': Number of patients who have not died until the respective visit
ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
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The number of returns is the number of patients with non-missing data (i.e. at least one [sub-]score present) at the respective visit.

A patients is considered to have not died until the visit if no death was documented during the study, if returns for this PRO are present at the visit or, if no returns are present for this PRO and the patient died, if the death date is after the scheduled visit date.

Percentages of returns refer to N' per group. For N' percentages refer to N per group.

Table 3-3.1 EORTC QLQ-BR23 Symptoms: change from baseline analysis (Full Analysis Set)

Treatment Groups			Comparison			
	Ribociclib + ET (N = 1115)	ET (N = 1123)	Parameter	Esti-mate	[95% CI]	p-value
QLQ-BR23 - Side Effects Of Systemic Therapy						
	N' | Mean (SD)	**N' | Mean (SD)**				
Overall N'	1060	1003				
Baseline	1060 | 17.91 (13.11)	1003 | 17.82 (13.65)				
Week 13	1025 | 22.43 (14.54)	960 | 19.85 (13.15)				
Week 25	983 | 21.84 (14.22)	922 | 20.40 (14.20)				
Week 37	987 | 23.49 (15.23)	912 | 20.84 (14.63)				
Week 49	973 | 23.40 (15.38)	923 | 20.99 (14.48)				
Week 61	967 | 24.19 (15.73)	904 | 21.16 (14.47)				
Week 73	956 | 23.82 (15.39)	896 | 21.29 (15.07)				
Week 85	945 | 23.70 (15.89)	875 | 21.43 (15.47)				
Week 97	931 | 23.82 (16.26)	855 | 21.50 (15.59)				
Week 121	903 | 23.96 (15.92)	841 | 21.45 (15.66)				
Week 145	898 | 23.75 (16.75)	807 | 21.88 (16.18)				
Week 169	730 | 22.56 (15.93)	682 | 22.44 (16.12)				
Week 193	609 | 22.32 (15.93)	566 | 23.16 (16.76)				
Week 217	346 | 21.83 (15.32)	322 | 22.14 (15.68)				
Week 241	58 | 20.42 (15.26)	50 | 18.76 (16.92)				
Adjusted change	**Mean (SE)**	**Mean (SE)**				
Week 13	4.63 (0.36)	1.95 (0.37)	Difference	2.68	[1.66; 3.69]	<.001
			Hedges G	0.23	[0.14; 0.32]	
Week 25	4.23 (0.38)	2.37 (0.39)	Difference	1.86	[0.79; 2.93]	<.001
			Hedges G	0.16	[0.07; 0.25]	
Week 37	6.06 (0.40)	2.90 (0.42)	Difference	3.16	[2.02; 4.29]	<.001
			Hedges G	0.25	[0.16; 0.34]	
Week 49	6.03 (0.41)	3.02 (0.42)	Difference	3.01	[1.86; 4.16]	<.001
			Hedges G	0.24	[0.15; 0.33]	
Week 61	6.78 (0.41)	3.17 (0.42)	Difference	3.61	[2.45; 4.77]	<.001
			Hedges G	0.28	[0.19; 0.37]	
Week 73	6.46 (0.42)	3.42 (0.43)	Difference	3.03	[1.85; 4.22]	<.001
			Hedges G	0.23	[0.14; 0.32]	
Week 85	6.40 (0.43)	3.55 (0.44)	Difference	2.85	[1.63; 4.06]	<.001
			Hedges G	0.22	[0.12; 0.31]	
Week 97	6.73 (0.44)	3.52 (0.46)	Difference	3.21	[1.96; 4.46]	<.001
			Hedges G	0.24	[0.14; 0.33]	
Week 121	6.88 (0.45)	3.50 (0.46)	Difference	3.38	[2.12; 4.65]	<.001
			Hedges G	0.25	[0.16; 0.34]	
Week 145	6.58 (0.47)	4.01 (0.49)	Difference	2.57	[1.24; 3.90]	<.001

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1115)	**ET (N = 1123)**	**Parameter**	**Esti-mate**	**[95% CI]**	**p-value**
			Hedges G	0.18	[0.09; 0.28]	
Week 169	4.75 (0.48)	3.57 (0.49)	Difference	1.18	[-0.16; 2.52]	0.085
			Hedges G	0.09	[-0.01; 0.20]	
Week 193	4.61 (0.50)	4.29 (0.52)	Difference	0.32	[-1.10; 1.74]	0.657
			Hedges G	0.03	[-0.09; 0.14]	
Week 217	4.66 (0.61)	2.96 (0.63)	Difference	1.70	[-0.01; 3.41]	0.052
			Hedges G	0.15	[-0.00; 0.30]	
Week 241	6.07 (1.13)	3.30 (1.21)	Difference	2.77	[-0.47; 6.01]	0.094
			Hedges G	0.32	[-0.06; 0.70]	
Overall effect	**5.78 (0.35)**	**3.25 (0.36)**	**Difference**	**2.52**	**[1.53; 3.52]**	**<.001**
			Hedges G	**0.22**	**[0.13; 0.31]**	
QLQ-BR23 - Breast Symptoms						
	N' | Mean (SD)	**N' | Mean (SD)**				
Overall N'	1052	1001				
Baseline	1052 | 20.99 (18.79)	1001 | 20.07 (18.41)				
Week 13	1015 | 18.04 (17.54)	954 | 18.35 (17.97)				
Week 25	971 | 16.98 (16.99)	917 | 16.81 (17.70)				
Week 37	974 | 16.78 (17.22)	903 | 15.98 (17.21)				
Week 49	963 | 16.35 (17.85)	915 | 15.76 (17.50)				
Week 61	955 | 15.95 (17.01)	899 | 14.49 (15.59)				
Week 73	944 | 15.44 (16.79)	892 | 14.85 (16.24)				
Week 85	931 | 15.68 (17.41)	873 | 14.53 (16.04)				
Week 97	924 | 15.22 (16.42)	854 | 13.91 (15.82)				
Week 121	893 | 14.52 (16.69)	837 | 13.62 (16.27)				
Week 145	889 | 14.08 (16.13)	801 | 13.59 (16.34)				
Week 169	720 | 14.47 (16.54)	674 | 13.19 (15.96)				
Week 193	601 | 14.27 (16.87)	562 | 13.37 (16.54)				
Week 217	340 | 12.84 (14.63)	320 | 12.76 (15.83)				
Adjusted change	**Mean (SE)**	**Mean (SE)**				
Week 13	-2.53 (0.48)	-1.93 (0.49)	Difference	-0.59	[-1.93; 0.74]	0.384
			Hedges G	-0.04	[-0.13; 0.05]	
Week 25	-3.22 (0.47)	-3.53 (0.48)	Difference	0.31	[-1.02; 1.63]	0.648
			Hedges G	0.02	[-0.07; 0.11]	
Week 37	-3.59 (0.47)	-4.44 (0.49)	Difference	0.85	[-0.48; 2.18]	0.210
			Hedges G	0.06	[-0.03; 0.15]	
Week 49	-3.99 (0.49)	-4.72 (0.50)	Difference	0.73	[-0.65; 2.11]	0.300
			Hedges G	0.05	[-0.04; 0.14]	
Week 61	-4.29 (0.46)	-5.96 (0.47)	Difference	1.67	[0.38; 2.97]	0.011
			Hedges G	0.12	[0.03; 0.21]	
Week 73	-4.76 (0.46)	-5.58 (0.48)	Difference	0.82	[-0.49; 2.12]	0.220
			Hedges G	0.06	[-0.03; 0.15]	
Week 85	-4.41 (0.48)	-5.86 (0.49)	Difference	1.45	[0.11; 2.79]	0.034

Treatment Groups			Comparison			
	Ribociclib + ET (N = 1115)	**ET (N = 1123)**	**Parameter**	**Esti-mate**	**[95% CI]**	**p-value**
			Hedges G	0.10	[0.01; 0.19]	
Week 97	-4.93 (0.47)	-6.48 (0.49)	Difference	1.55	[0.21; 2.88]	0.024
			Hedges G	0.11	[0.01; 0.20]	
Week 121	-5.55 (0.49)	-6.76 (0.50)	Difference	1.21	[-0.17; 2.58]	0.086
			Hedges G	0.08	[-0.01; 0.18]	
Week 145	-6.08 (0.48)	-6.84 (0.50)	Difference	0.76	[-0.61; 2.12]	0.278
			Hedges G	0.05	[-0.04; 0.15]	
Week 169	-6.19 (0.50)	-7.62 (0.52)	Difference	1.43	[0.00; 2.85]	0.049
			Hedges G	0.11	[0.00; 0.21]	
Week 193	-6.04 (0.57)	-7.58 (0.59)	Difference	1.54	[-0.05; 3.14]	0.058
			Hedges G	0.11	[-0.00; 0.23]	
Week 217	-6.79 (0.64)	-8.27 (0.66)	Difference	1.48	[-0.32; 3.28]	0.107
			Hedges G	0.13	[-0.03; 0.28]	
Overall effect	**-4.80 (0.35)**	**-5.81 (0.36)**	**Difference**	**1.01**	**[0.04; 1.99]**	**0.041**
			Hedges G	**0.09**	**[0.00; 0.18]**	
QLQ-BR23 - Arm Symptoms						
	N' | Mean (SD)	**N' | Mean (SD)**				
Overall N'	1054	1000				
Baseline	1054 | 24.92 (21.59)	1000 | 24.80 (20.82)				
Week 13	1017 | 28.27 (22.55)	953 | 28.48 (22.85)				
Week 25	973 | 26.33 (21.86)	916 | 27.57 (22.28)				
Week 37	974 | 27.06 (22.60)	901 | 26.22 (22.60)				
Week 49	965 | 26.07 (23.18)	914 | 25.62 (22.83)				
Week 61	958 | 25.18 (22.05)	898 | 24.73 (20.96)				
Week 73	946 | 23.96 (21.39)	892 | 23.38 (20.66)				
Week 85	933 | 23.42 (21.39)	872 | 23.16 (21.71)				
Week 97	926 | 23.04 (21.72)	854 | 21.38 (20.85)				
Week 121	895 | 23.02 (21.74)	837 | 20.70 (20.84)				
Week 145	894 | 22.02 (20.78)	802 | 21.41 (20.97)				
Week 169	723 | 22.67 (22.57)	675 | 21.12 (20.89)				
Week 193	603 | 22.35 (21.78)	562 | 20.27 (20.50)				
Week 217	341 | 20.76 (19.65)	320 | 18.04 (19.39)				
Adjusted change	**Mean (SE)**	**Mean (SE)**				
Week 13	3.63 (0.59)	3.66 (0.61)	Difference	-0.03	[-1.69; 1.63]	0.970
			Hedges G	-0.00	[-0.09; 0.09]	
Week 25	1.85 (0.59)	2.58 (0.61)	Difference	-0.73	[-2.39; 0.94]	0.392
			Hedges G	-0.04	[-0.13; 0.05]	
Week 37	2.63 (0.62)	1.21 (0.64)	Difference	1.42	[-0.33; 3.16]	0.111
			Hedges G	0.07	[-0.02; 0.16]	
Week 49	1.52 (0.63)	0.56 (0.65)	Difference	0.96	[-0.82; 2.74]	0.288
			Hedges G	0.05	[-0.04; 0.14]	
Week 61	0.66 (0.59)	-0.33 (0.61)	Difference	0.99	[-0.68; 2.66]	0.247

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1115)	**ET (N = 1123)**	**Parameter**	**Esti-mate**	**[95% CI]**	**p-value**
			Hedges G	0.05	[-0.04; 0.14]	
Week 73	-0.54 (0.58)	-1.59 (0.60)	Difference	1.05	[-0.59; 2.69]	0.209
			Hedges G	0.06	[-0.03; 0.15]	
Week 85	-0.89 (0.60)	-1.97 (0.62)	Difference	1.08	[-0.60; 2.77]	0.207
			Hedges G	0.06	[-0.03; 0.15]	
Week 97	-1.30 (0.60)	-3.81 (0.62)	Difference	2.51	[0.82; 4.19]	0.004
			Hedges G	0.14	[0.05; 0.23]	
Week 121	-1.27 (0.61)	-4.46 (0.63)	Difference	3.18	[1.46; 4.90]	<.001
			Hedges G	0.17	[0.08; 0.27]	
Week 145	-2.27 (0.61)	-3.86 (0.63)	Difference	1.59	[-0.13; 3.31]	0.069
			Hedges G	0.09	[-0.01; 0.18]	
Week 169	-2.10 (0.66)	-4.81 (0.69)	Difference	2.71	[0.84; 4.59]	0.005
			Hedges G	0.15	[0.05; 0.26]	
Week 193	-2.19 (0.67)	-5.63 (0.69)	Difference	3.44	[1.55; 5.33]	<.001
			Hedges G	0.21	[0.09; 0.32]	
Week 217	-3.27 (0.77)	-8.26 (0.80)	Difference	4.99	[2.81; 7.18]	<.001
			Hedges G	0.35	[0.20; 0.50]	
Overall effect	**-0.27 (0.44)**	**-2.06 (0.46)**	**Difference**	**1.78**	**[0.54; 3.03]**	**0.005**
			Hedges G	**0.12**	**[0.04; 0.21]**	
QLQ-BR23 - Being Upset With Hair Loss						
	N' | Mean (SD)	**N' | Mean (SD)**				
Overall N'	299	256				
Baseline	299 | 22.41 (32.88)	256 | 26.69 (34.35)				
Week 13	177 | 21.28 (29.82)	147 | 20.63 (30.30)				
Week 25	175 | 24.19 (28.90)	141 | 25.53 (31.02)				
Week 37	205 | 27.64 (30.52)	160 | 25.00 (28.22)				
Week 49	210 | 30.16 (31.45)	160 | 28.13 (30.73)				
Week 61	217 | 30.11 (31.51)	173 | 27.94 (31.07)				
Week 73	200 | 33.00 (33.25)	161 | 27.95 (31.16)				
Week 85	215 | 29.61 (30.34)	162 | 30.45 (31.39)				
Week 97	200 | 29.67 (30.59)	153 | 29.63 (31.19)				
Week 121	197 | 30.46 (30.45)	156 | 28.63 (31.78)				
Week 145	204 | 30.56 (31.35)	162 | 29.63 (31.52)				
Week 169	147 | 32.88 (31.93)	120 | 33.06 (33.61)				
Week 193	91 | 32.23 (30.81)	94 | 35.11 (35.37)				
Adjusted change	**Mean (SE)**	**Mean (SE)**				
Week 13	-1.77 (1.90)	-3.86 (2.08)	Difference	2.10	[-3.44; 7.64]	0.457
			Hedges G	0.08	[-0.14; 0.30]	
Week 25	1.28 (1.91)	-1.19 (2.12)	Difference	2.47	[-3.15; 8.09]	0.389
			Hedges G	0.10	[-0.12; 0.32]	
Week 37	2.55 (1.72)	-2.49 (1.92)	Difference	5.04	[-0.02; 10.11]	0.051
			Hedges G	0.21	[-0.00; 0.41]	

Treatment Groups			Comparison			
	Ribociclib + ET (N = 1115)	**ET (N = 1123)**	**Parameter**	**Esti-mate**	**[95% CI]**	**p-value**
Week 49	5.25 (1.85)	0.44 (2.08)	Difference	4.82	[-0.65; 10.28]	0.084
			Hedges G	0.18	[-0.02; 0.39]	
Week 61	5.99 (1.80)	-0.28 (2.00)	Difference	6.27	[0.97; 11.56]	0.020
			Hedges G	0.24	[0.04; 0.44]	
Week 73	8.45 (1.95)	-0.71 (2.16)	Difference	9.17	[3.44; 14.89]	0.002
			Hedges G	0.33	[0.12; 0.54]	
Week 85	4.86 (1.84)	3.13 (2.07)	Difference	1.73	[-3.72; 7.18]	0.533
			Hedges G	0.06	[-0.14; 0.27]	
Week 97	5.16 (1.83)	2.03 (2.05)	Difference	3.13	[-2.27; 8.53]	0.256
			Hedges G	0.12	[-0.09; 0.33]	
Week 121	6.46 (1.92)	0.46 (2.13)	Difference	6.00	[0.36; 11.64]	0.037
			Hedges G	0.22	[0.01; 0.43]	
Week 145	5.92 (1.95)	3.36 (2.15)	Difference	2.56	[-3.14; 8.26]	0.377
			Hedges G	0.09	[-0.11; 0.30]	
Week 169	5.13 (2.25)	4.22 (2.48)	Difference	0.91	[-5.68; 7.50]	0.787
			Hedges G	0.03	[-0.21; 0.27]	
Week 193	2.63 (2.59)	5.22 (2.64)	Difference	-2.59	[-9.86; 4.68]	0.485
			Hedges G	-0.10	[-0.39; 0.19]	
Overall effect	**4.33 (1.30)**	**0.86 (1.42)**	**Difference**	**3.47**	**[-0.33; 7.26]**	**0.073**
			Hedges G	**0.15**	**[-0.01; 0.32]**	

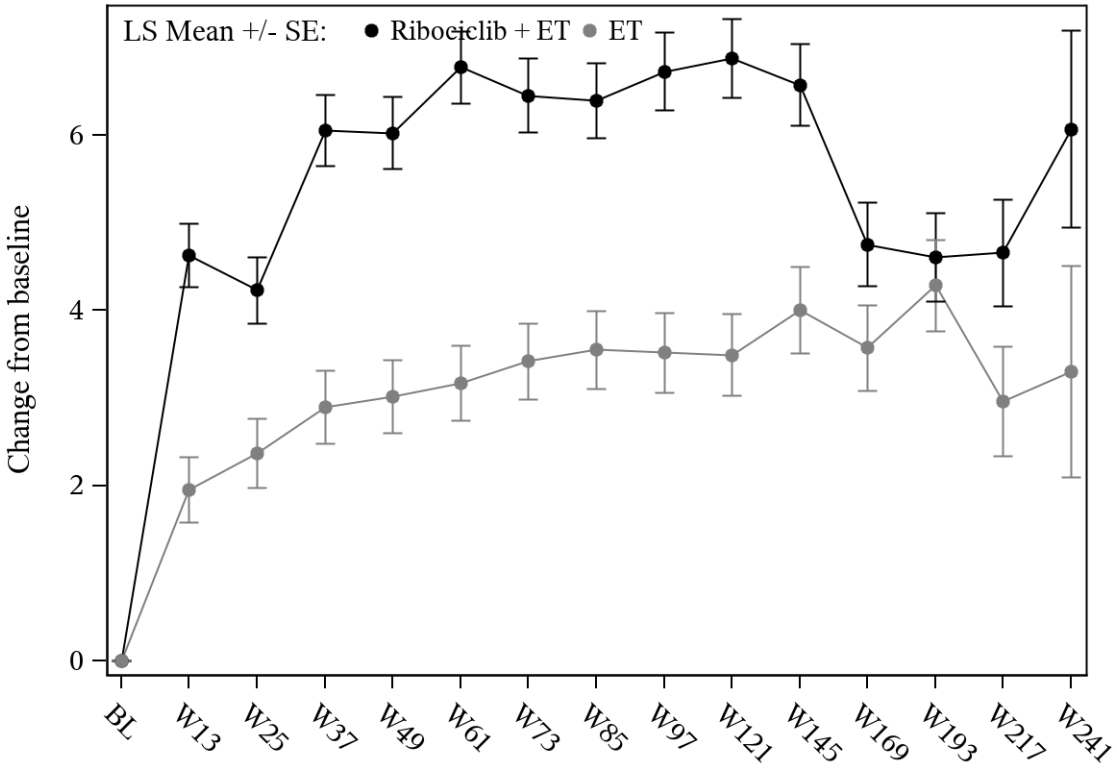
N: Number of patients
N': Number of patients in the analysis
CI: Confidence interval
SD: Standard deviation
LS Mean: Least square mean
SE: Standard error
MMRM: Mixed model for repeated measures
ET: Endocrine therapy (Anastrozole/Letrozole + Goserelin)
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Analysis methods:
Adjusted mean (LS Mean) change from baseline and difference obtained from MMRM with unstructured covariance matrix:
change from baseline = treatment + visit + treatment * visit + baseline value + AJCC Anatomic Stage + prior neo/adjuvant chemotherapy + region
ET was the reference group for treatment group comparison.
If the model did not converge for a parameter, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry.

Patients with an evaluable baseline score and at least one evaluable post-baseline score were included in the analysis.
All data collected were included in the analysis, including assessments at confirmation of first recurrence and thereafter, as long as there were at least 50 patients in each treatment group at a visit.

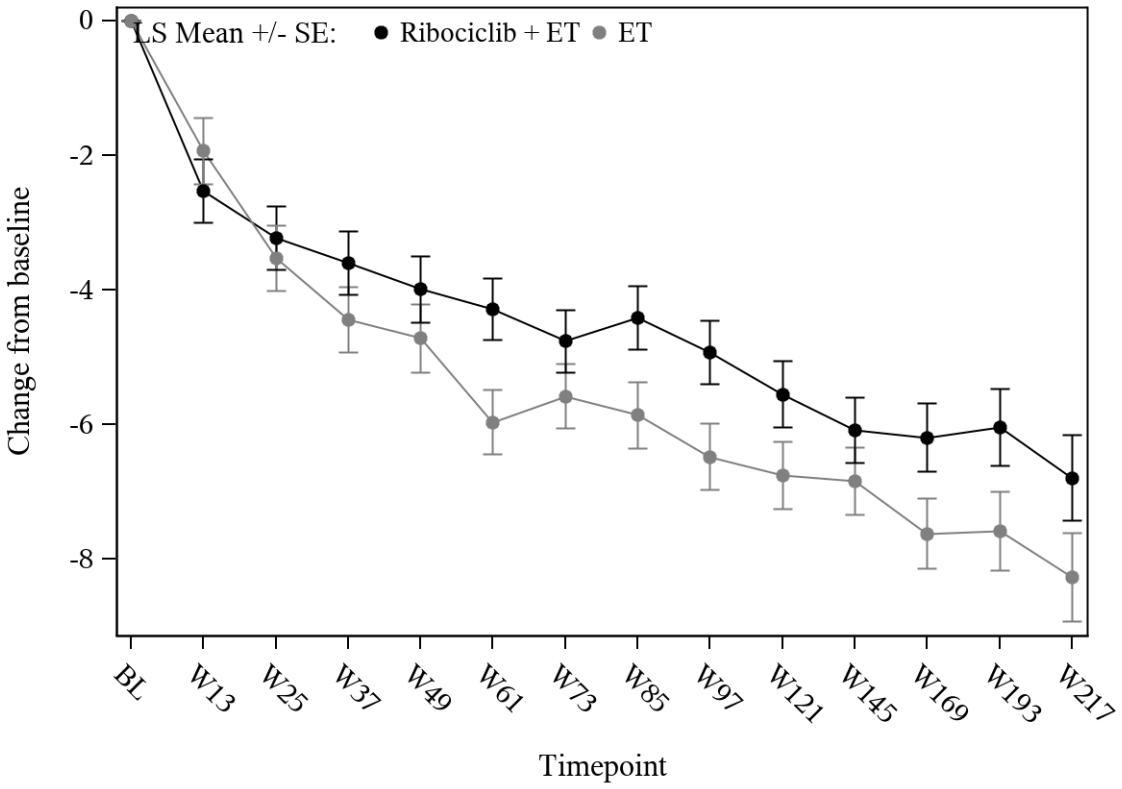
Figure 3-3.1 EORTC QLQ-BR23 Symptoms: line chart of change from baseline (Full Analysis Set)

QLQ-BR23 - Side Effects Of Systemic Therapy



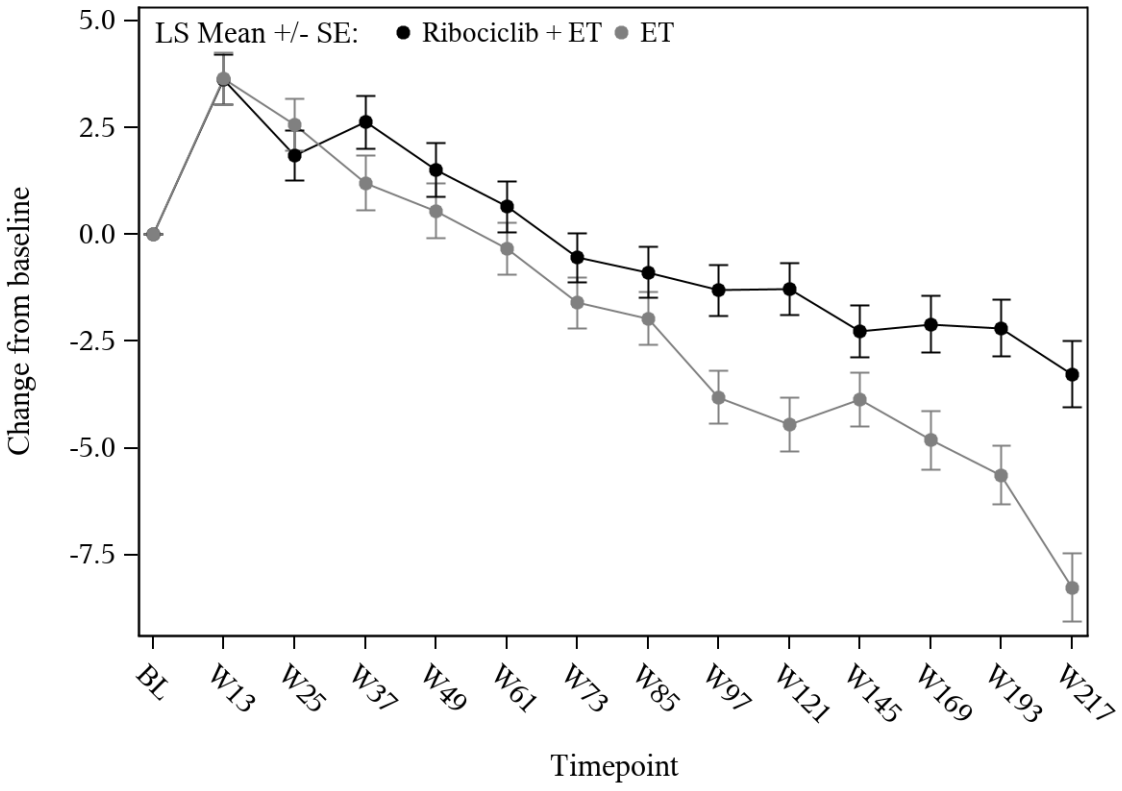
Ribociclib + ET	1060	1025	983	987	973	967	956	945	931	903	898	730	609	346	58
ET	1003	960	922	912	923	904	896	875	855	841	807	682	566	322	50

QLQ-BR23 - Breast Symptoms



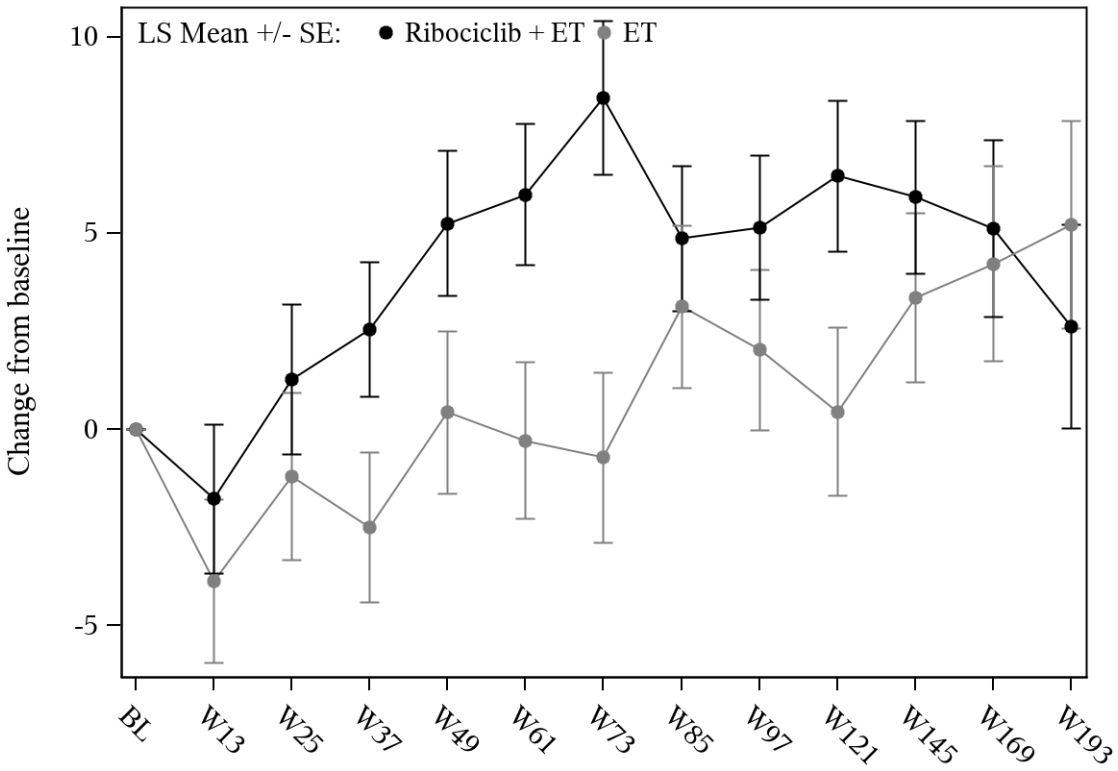
Ribociclib + ET	1052	1015	971	974	963	955	944	931	924	893	889	720	601	340
ET	1001	954	917	903	915	899	892	873	854	837	801	674	562	320

QLQ-BR23 - Arm Symptoms



Ribociclib + ET	1054	1017	973	974	965	958	946	933	926	895	894	723	603	341
ET	1000	953	916	901	914	898	892	872	854	837	802	675	562	320

QLQ-BR23 - Being Upset With Hair Loss



Ribociclib + ET	299	177	175	205	210	217	200	215	200	197	204	147	91
ET	256	147	141	160	160	173	161	162	153	156	162	120	94

3-4 EORTC QLQ-BR23 QoL

Table 3-4.0 EORTC QLQ-BR23 QoL: return rates (Full Analysis Set)

	Treatment groups			
	Ribociclib + ET (N = 1115)		ET (N = 1123)	
	N' (%)	Returns n (%)	N' (%)	Returns n (%)
Baseline	1115 (100.0)	1092 (97.9)	1123 (100.0)	1089 (97.0)
Week 13	1115 (100.0)	1041 (93.4)	1123 (100.0)	983 (87.5)
Week 25	1114 (99.9)	999 (89.7)	1122 (99.9)	942 (84.0)
Week 37	1112 (99.7)	1002 (90.1)	1122 (99.9)	932 (83.1)
Week 49	1112 (99.7)	987 (88.8)	1121 (99.8)	943 (84.1)
Week 61	1109 (99.5)	983 (88.6)	1119 (99.6)	924 (82.6)
Week 73	1107 (99.3)	972 (87.8)	1118 (99.6)	915 (81.8)
Week 85	1106 (99.2)	959 (86.7)	1117 (99.5)	894 (80.0)
Week 97	1103 (98.9)	948 (85.9)	1114 (99.2)	873 (78.4)
Week 121	1098 (98.5)	917 (83.5)	1108 (98.7)	857 (77.3)
Week 145	1094 (98.1)	915 (83.6)	1096 (97.6)	820 (74.8)
Week 169	1087 (97.5)	741 (68.2)	1085 (96.6)	693 (63.9)
Week 193	1085 (97.3)	618 (57.0)	1081 (96.3)	578 (53.5)
Week 217	1084 (97.2)	354 (32.7)	1078 (96.0)	329 (30.5)
Week 241	1084 (97.2)	59 (5.4)	1077 (95.9)	54 (5.0)
Week 265	1084 (97.2)	2 (0.2)	1077 (95.9)	1 (0.1)

N': Number of patients who have not died until the respective visit
ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
.....

The number of returns is the number of patients with non-missing data (i.e. at least one [sub-]score present) at the respective visit.

A patients is considered to have not died until the visit if no death was documented during the study, if returns for this PRO are present at the visit or, if no returns are present for this PRO and the patient died, if the death date is after the scheduled visit date.

Percentages of returns refer to N' per group. For N' percentages refer to N per group.

Table 3-4.1 EORTC QLQ-BR23 QoL: change from baseline analysis (Full Analysis Set)

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1115)	ET (N = 1123)	Parameter	Esti-mate	[95% CI]	p-value
QLQ-BR23 - Body Image						
	N' | Mean (SD)	**N' | Mean (SD)**				
Overall N'	1060	1000				
Baseline	1060 | 69.25 (28.12)	1000 | 69.58 (27.41)				
Week 13	1021 | 71.53 (26.79)	956 | 70.37 (28.10)				
Week 25	981 | 71.81 (26.48)	918 | 70.76 (27.57)				
Week 37	986 | 71.91 (27.10)	908 | 72.25 (27.04)				
Week 49	973 | 72.15 (26.79)	918 | 73.02 (27.38)				
Week 61	966 | 71.61 (26.94)	899 | 72.24 (27.20)				
Week 73	955 | 72.09 (27.12)	892 | 73.07 (27.11)				
Week 85	943 | 72.70 (26.74)	874 | 72.17 (27.84)				
Week 97	931 | 73.33 (26.56)	853 | 73.76 (26.91)				
Week 121	901 | 73.05 (26.94)	840 | 74.21 (27.32)				
Week 145	898 | 72.66 (27.64)	806 | 73.93 (28.12)				
Week 169	728 | 73.24 (27.30)	680 | 74.04 (27.79)				
Week 193	608 | 73.28 (27.76)	565 | 73.50 (27.94)				
Week 217	346 | 72.78 (27.18)	322 | 76.46 (27.41)				
Week 241	58 | 73.42 (28.29)	50 | 78.83 (20.50)				
Adjusted change	**Mean (SE)**	**Mean (SE)**				
Week 13	1.91 (0.62)	0.65 (0.64)	Difference	1.26	[-0.49; 3.02]	0.159
			Hedges G	0.06	[-0.02; 0.15]	
Week 25	1.54 (0.65)	1.28 (0.67)	Difference	0.26	[-1.57; 2.09]	0.779
			Hedges G	0.01	[-0.08; 0.10]	
Week 37	1.62 (0.65)	2.58 (0.67)	Difference	-0.95	[-2.79; 0.88]	0.308
			Hedges G	-0.05	[-0.14; 0.04]	
Week 49	1.86 (0.68)	3.39 (0.70)	Difference	-1.53	[-3.43; 0.38]	0.116
			Hedges G	-0.07	[-0.16; 0.02]	
Week 61	1.35 (0.69)	2.90 (0.71)	Difference	-1.55	[-3.49; 0.39]	0.118
			Hedges G	-0.07	[-0.16; 0.02]	
Week 73	1.57 (0.70)	3.23 (0.72)	Difference	-1.66	[-3.63; 0.31]	0.099
			Hedges G	-0.08	[-0.17; 0.01]	
Week 85	2.10 (0.71)	2.53 (0.73)	Difference	-0.42	[-2.41; 1.57]	0.677
			Hedges G	-0.02	[-0.11; 0.07]	
Week 97	2.53 (0.70)	3.90 (0.73)	Difference	-1.36	[-3.35; 0.63]	0.179
			Hedges G	-0.06	[-0.16; 0.03]	
Week 121	2.29 (0.74)	4.25 (0.76)	Difference	-1.96	[-4.04; 0.12]	0.065
			Hedges G	-0.09	[-0.18; 0.01]	
Week 145	2.22 (0.76)	3.97 (0.79)	Difference	-1.75	[-3.90; 0.40]	0.111
			Hedges G	-0.08	[-0.17; 0.02]	

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1115)	**ET (N = 1123)**	**Parameter**	**Esti-mate**	**[95% CI]**	**p-value**
Week 169	3.22 (0.79)	4.83 (0.81)	Difference	-1.61	[-3.83; 0.61]	0.154
			Hedges G	-0.08	[-0.18; 0.03]	
Week 193	2.73 (0.83)	4.13 (0.86)	Difference	-1.40	[-3.75; 0.94]	0.241
			Hedges G	-0.07	[-0.18; 0.05]	
Week 217	2.10 (0.95)	6.68 (0.98)	Difference	-4.58	[-7.26; -1.91]	<.001
			Hedges G	-0.26	[-0.41; -0.11]	
Week 241	2.58 (1.54)	4.19 (1.66)	Difference	-1.60	[-6.05; 2.84]	0.479
			Hedges G	-0.14	[-0.52; 0.24]	
Overall effect	**2.12 (0.58)**	**3.46 (0.60)**	**Difference**	**-1.35**	**[-2.98; 0.29]**	**0.106**
			Hedges G	**-0.07**	**[-0.16; 0.02]**	
QLQ-BR23 - Sexual Functioning						
	N' | Mean (SD)	**N' | Mean (SD)**				
Overall N'	1047	994				
Baseline	1047 | 25.61 (23.11)	994 | 25.12 (22.43)				
Week 13	1007 | 23.50 (21.78)	945 | 23.17 (21.43)				
Week 25	967 | 22.92 (21.94)	904 | 22.42 (21.65)				
Week 37	962 | 21.79 (21.48)	898 | 22.35 (21.68)				
Week 49	956 | 21.57 (21.45)	910 | 21.48 (21.73)				
Week 61	950 | 20.95 (22.07)	891 | 20.46 (21.03)				
Week 73	939 | 21.26 (21.98)	884 | 20.12 (20.87)				
Week 85	924 | 21.34 (21.89)	859 | 19.95 (20.78)				
Week 97	911 | 20.03 (21.83)	842 | 20.49 (20.85)				
Week 121	882 | 19.82 (21.86)	825 | 20.53 (21.78)				
Week 145	875 | 19.03 (21.53)	794 | 20.05 (21.31)				
Week 169	706 | 18.81 (21.76)	669 | 18.76 (20.28)				
Week 193	598 | 19.48 (22.23)	553 | 18.75 (20.74)				
Week 217	339 | 18.93 (22.13)	312 | 20.35 (20.48)				
Adjusted change	**Mean (SE)**	**Mean (SE)**				
Week 13	-1.92 (0.51)	-1.94 (0.53)	Difference	0.02	[-1.43; 1.47]	0.975
			Hedges G	0.00	[-0.09; 0.09]	
Week 25	-2.47 (0.55)	-2.69 (0.56)	Difference	0.22	[-1.32; 1.76]	0.777
			Hedges G	0.01	[-0.08; 0.10]	
Week 37	-3.62 (0.55)	-2.83 (0.57)	Difference	-0.79	[-2.35; 0.76]	0.316
			Hedges G	-0.05	[-0.14; 0.04]	
Week 49	-4.02 (0.56)	-3.44 (0.57)	Difference	-0.58	[-2.14; 0.99]	0.469
			Hedges G	-0.03	[-0.12; 0.06]	
Week 61	-4.57 (0.58)	-4.55 (0.59)	Difference	-0.01	[-1.64; 1.61]	0.988
			Hedges G	-0.00	[-0.09; 0.09]	
Week 73	-4.43 (0.59)	-4.92 (0.61)	Difference	0.49	[-1.18; 2.16]	0.567
			Hedges G	0.03	[-0.07; 0.12]	
Week 85	-4.26 (0.59)	-5.09 (0.61)	Difference	0.84	[-0.83; 2.50]	0.325
			Hedges G	0.05	[-0.05; 0.14]	

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1115)	**ET (N = 1123)**	**Parameter**	**Esti-mate**	**[95% CI]**	**p-value**
Week 97	-5.41 (0.60)	-4.55 (0.62)	Difference	-0.86	[-2.55; 0.83]	0.319
			Hedges G	-0.05	[-0.14; 0.05]	
Week 121	-6.08 (0.61)	-4.60 (0.63)	Difference	-1.48	[-3.20; 0.23]	0.091
			Hedges G	-0.08	[-0.18; 0.01]	
Week 145	-6.61 (0.61)	-4.97 (0.64)	Difference	-1.64	[-3.37; 0.10]	0.065
			Hedges G	-0.09	[-0.19; 0.01]	
Week 169	-6.97 (0.67)	-6.37 (0.69)	Difference	-0.59	[-2.48; 1.29]	0.535
			Hedges G	-0.03	[-0.14; 0.07]	
Week 193	-6.70 (0.70)	-6.19 (0.73)	Difference	-0.51	[-2.50; 1.48]	0.613
			Hedges G	-0.03	[-0.15; 0.09]	
Week 217	-7.84 (0.83)	-5.35 (0.86)	Difference	-2.49	[-4.83; -0.16]	0.037
			Hedges G	-0.16	[-0.32; -0.01]	
Overall effect	**-4.99 (0.44)**	**-4.42 (0.46)**	**Difference**	**-0.57**	**[-1.82; 0.68]**	**0.372**
			Hedges G	**-0.04**	**[-0.13; 0.05]**	
QLQ-BR23 - Sexual Enjoyment						
	N' | Mean (SD)	**N' | Mean (SD)**				
Overall N'	630	598				
Baseline	630 | 50.05 (30.41)	598 | 48.38 (29.58)				
Week 13	509 | 46.37 (28.42)	470 | 44.61 (28.35)				
Week 25	483 | 44.17 (28.48)	442 | 45.40 (27.40)				
Week 37	470 | 42.91 (29.29)	451 | 42.05 (26.99)				
Week 49	474 | 43.46 (28.52)	449 | 43.13 (27.42)				
Week 61	459 | 41.98 (28.89)	417 | 42.61 (27.43)				
Week 73	458 | 43.23 (28.31)	423 | 40.58 (27.92)				
Week 85	454 | 40.82 (28.67)	401 | 40.65 (29.19)				
Week 97	437 | 40.27 (29.18)	410 | 41.79 (27.36)				
Week 121	422 | 41.71 (29.66)	392 | 41.41 (27.39)				
Week 145	409 | 40.91 (30.69)	365 | 41.10 (28.45)				
Week 169	302 | 41.83 (29.10)	284 | 40.38 (27.83)				
Week 193	262 | 43.89 (29.66)	231 | 42.42 (27.79)				
Week 217	144 | 42.82 (27.22)	136 | 40.93 (27.21)				
Adjusted change	**Mean (SE)**	**Mean (SE)**				
Week 13	-4.85 (0.98)	-6.15 (1.02)	Difference	1.30	[-1.48; 4.09]	0.358
			Hedges G	0.06	[-0.07; 0.18]	
Week 25	-7.06 (1.01)	-5.88 (1.05)	Difference	-1.18	[-4.04; 1.67]	0.416
			Hedges G	-0.05	[-0.18; 0.08]	
Week 37	-8.46 (1.02)	-8.73 (1.05)	Difference	0.28	[-2.59; 3.14]	0.850
			Hedges G	0.01	[-0.12; 0.14]	
Week 49	-8.60 (1.00)	-7.94 (1.03)	Difference	-0.66	[-3.49; 2.17]	0.648
			Hedges G	-0.03	[-0.16; 0.10]	
Week 61	-10.12 (1.06)	-8.55 (1.10)	Difference	-1.57	[-4.57; 1.43]	0.305
			Hedges G	-0.07	[-0.20; 0.06]	

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1115)	**ET (N = 1123)**	**Parameter**	**Esti-mate**	**[95% CI]**	**p-value**
Week 73	-9.79 (1.08)	-10.43 (1.12)	Difference	0.64	[-2.42; 3.70]	0.682
			Hedges G	0.03	[-0.10; 0.16]	
Week 85	-10.86 (1.07)	-10.58 (1.12)	Difference	-0.28	[-3.30; 2.75]	0.858
			Hedges G	-0.01	[-0.15; 0.12]	
Week 97	-11.90 (1.09)	-10.05 (1.13)	Difference	-1.85	[-4.93; 1.23]	0.239
			Hedges G	-0.08	[-0.22; 0.05]	
Week 121	-11.37 (1.11)	-10.05 (1.15)	Difference	-1.32	[-4.45; 1.81]	0.408
			Hedges G	-0.06	[-0.20; 0.08]	
Week 145	-11.86 (1.17)	-10.18 (1.22)	Difference	-1.67	[-4.99; 1.64]	0.322
			Hedges G	-0.07	[-0.21; 0.07]	
Week 169	-12.64 (1.28)	-11.79 (1.32)	Difference	-0.85	[-4.46; 2.77]	0.646
			Hedges G	-0.04	[-0.20; 0.12]	
Week 193	-11.88 (1.37)	-10.14 (1.45)	Difference	-1.74	[-5.66; 2.18]	0.383
			Hedges G	-0.08	[-0.26; 0.10]	
Week 217	-12.81 (1.50)	-12.76 (1.55)	Difference	-0.05	[-4.28; 4.18]	0.981
			Hedges G	-0.00	[-0.24; 0.23]	
Overall effect	**-10.17 (0.78)**	**-9.48 (0.81)**	**Difference**	**-0.69**	**[-2.90; 1.52]**	**0.541**
			Hedges G	**-0.03**	**[-0.15; 0.08]**	
QLQ-BR23 - Future Perspective						
	N' | Mean (SD)	**N' | Mean (SD)**				
Overall N'	1058	997				
Baseline	1058 | 45.27 (31.62)	997 | 45.97 (31.52)				
Week 13	1014 | 50.62 (30.63)	945 | 50.55 (30.45)				
Week 25	976 | 52.77 (30.37)	909 | 54.09 (31.12)				
Week 37	982 | 54.28 (30.16)	902 | 54.25 (31.47)				
Week 49	966 | 55.24 (30.30)	912 | 55.37 (30.53)				
Week 61	960 | 54.34 (30.55)	891 | 55.52 (30.40)				
Week 73	949 | 55.74 (30.41)	886 | 56.92 (30.38)				
Week 85	939 | 56.87 (31.18)	868 | 57.10 (30.33)				
Week 97	926 | 56.48 (30.18)	849 | 57.13 (30.10)				
Week 121	897 | 57.26 (30.97)	833 | 58.54 (30.21)				
Week 145	893 | 57.07 (30.67)	799 | 59.87 (31.66)				
Week 169	726 | 57.35 (31.52)	677 | 58.00 (31.20)				
Week 193	606 | 56.49 (30.68)	561 | 59.24 (30.31)				
Week 217	344 | 58.33 (30.25)	320 | 60.31 (30.74)				
Week 241	58 | 58.05 (35.63)	50 | 61.33 (28.86)				
Adjusted change	**Mean (SE)**	**Mean (SE)**				
Week 13	5.41 (0.79)	4.94 (0.82)	Difference	0.47	[-1.76; 2.71]	0.677
			Hedges G	0.02	[-0.07; 0.11]	
Week 25	6.86 (0.83)	8.63 (0.86)	Difference	-1.77	[-4.10; 0.57]	0.138
			Hedges G	-0.07	[-0.16; 0.02]	
Week 37	8.54 (0.82)	8.73 (0.85)	Difference	-0.19	[-2.51; 2.12]	0.870

Treatment Groups			Comparison			
	Ribociclib + ET (N = 1115)	**ET (N = 1123)**	**Parameter**	**Esti-mate**	**[95% CI]**	**p-value**
			Hedges G	-0.01	[-0.10; 0.08]	
Week 49	9.28 (0.82)	9.77 (0.85)	Difference	-0.49	[-2.81; 1.83]	0.678
			Hedges G	-0.02	[-0.11; 0.07]	
Week 61	8.59 (0.84)	10.26 (0.87)	Difference	-1.67	[-4.03; 0.70]	0.168
			Hedges G	-0.06	[-0.16; 0.03]	
Week 73	9.76 (0.85)	11.53 (0.87)	Difference	-1.78	[-4.16; 0.61]	0.145
			Hedges G	-0.07	[-0.16; 0.02]	
Week 85	10.77 (0.87)	11.49 (0.90)	Difference	-0.72	[-3.17; 1.74]	0.568
			Hedges G	-0.03	[-0.12; 0.07]	
Week 97	10.41 (0.86)	11.54 (0.89)	Difference	-1.13	[-3.55; 1.29]	0.361
			Hedges G	-0.04	[-0.14; 0.05]	
Week 121	11.05 (0.89)	12.57 (0.92)	Difference	-1.52	[-4.02; 0.98]	0.235
			Hedges G	-0.06	[-0.15; 0.04]	
Week 145	11.09 (0.90)	14.14 (0.94)	Difference	-3.05	[-5.59; -0.51]	0.018
			Hedges G	-0.11	[-0.21; -0.02]	
Week 169	12.41 (0.95)	13.50 (0.99)	Difference	-1.09	[-3.78; 1.61]	0.429
			Hedges G	-0.04	[-0.15; 0.06]	
Week 193	11.78 (1.00)	14.53 (1.03)	Difference	-2.74	[-5.56; 0.07]	0.056
			Hedges G	-0.11	[-0.23; 0.00]	
Week 217	13.46 (1.24)	14.91 (1.28)	Difference	-1.45	[-4.95; 2.05]	0.416
			Hedges G	-0.06	[-0.22; 0.09]	
Week 241	10.44 (3.18)	11.75 (3.42)	Difference	-1.31	[-10.47; 7.86]	0.780
			Hedges G	-0.05	[-0.43; 0.32]	
Overall effect	**9.99 (0.67)**	**11.31 (0.70)**	**Difference**	**-1.32**	**[-3.21; 0.58]**	**0.174**
			Hedges G	**-0.06**	**[-0.15; 0.03]**	

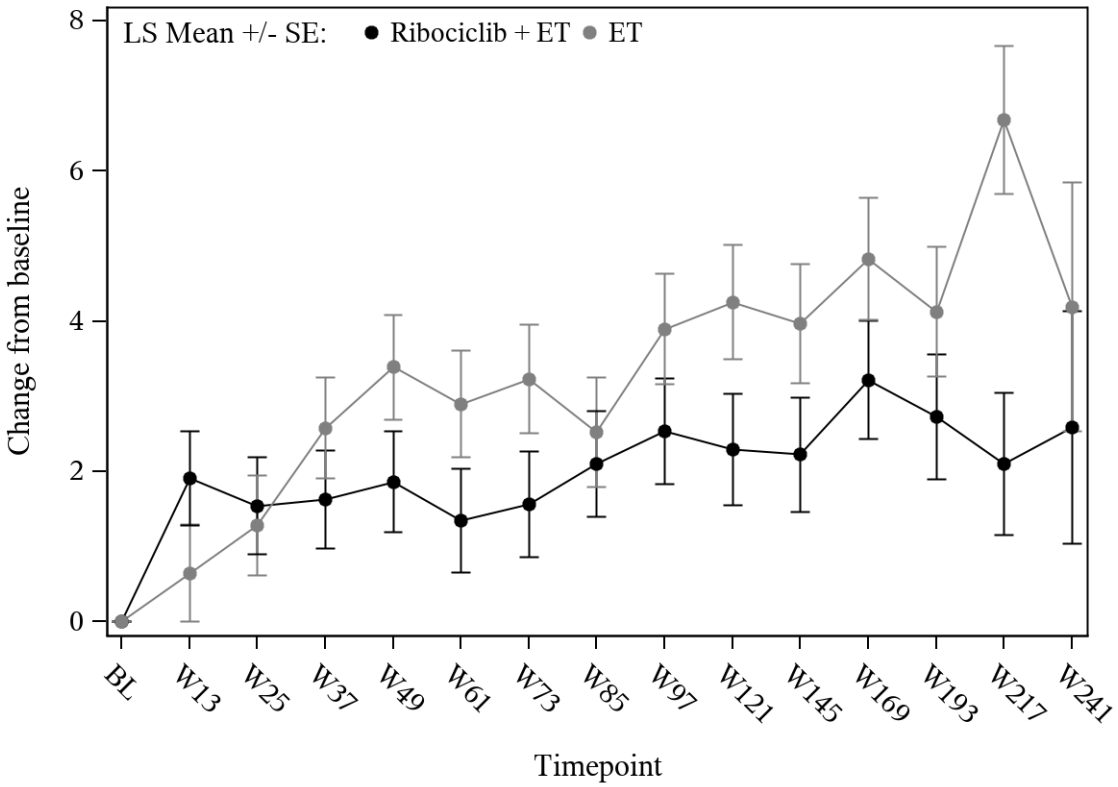
N: Number of patients
N': Number of patients in the analysis
CI: Confidence interval
SD: Standard deviation
LS Mean: Least square mean
SE: Standard error
MMRM: Mixed model for repeated measures
ET: Endocrine therapy (Anastrozole/Letrozole + Goserelin)
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Analysis methods:
Adjusted mean (LS Mean) change from baseline and difference obtained from MMRM with unstructured covariance matrix:
change from baseline = treatment + visit + treatment * visit + baseline value + AJCC Anatomic Stage + prior neo/adjuvant chemotherapy + region
ET was the reference group for treatment group comparison.
If the model did not converge for a parameter, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry.

Patients with an evaluable baseline score and at least one evaluable post-baseline score were included in the analysis.
All data collected were included in the analysis, including assessments at confirmation of first recurrence and thereafter, as long as there were at least 50 patients in each treatment group at a visit.

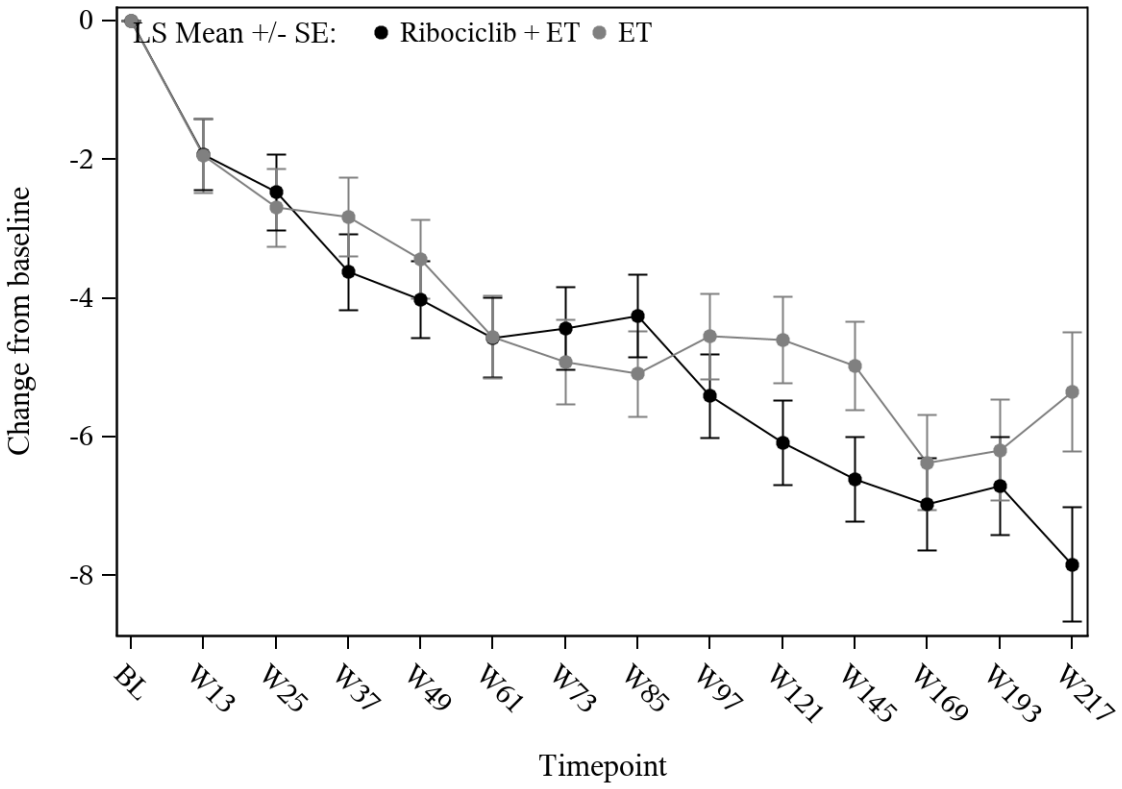
Figure 3-4.1 EORTC QLQ-BR23 QoL: line chart of change from baseline (Full Analysis Set)

QLQ-BR23 - Body Image



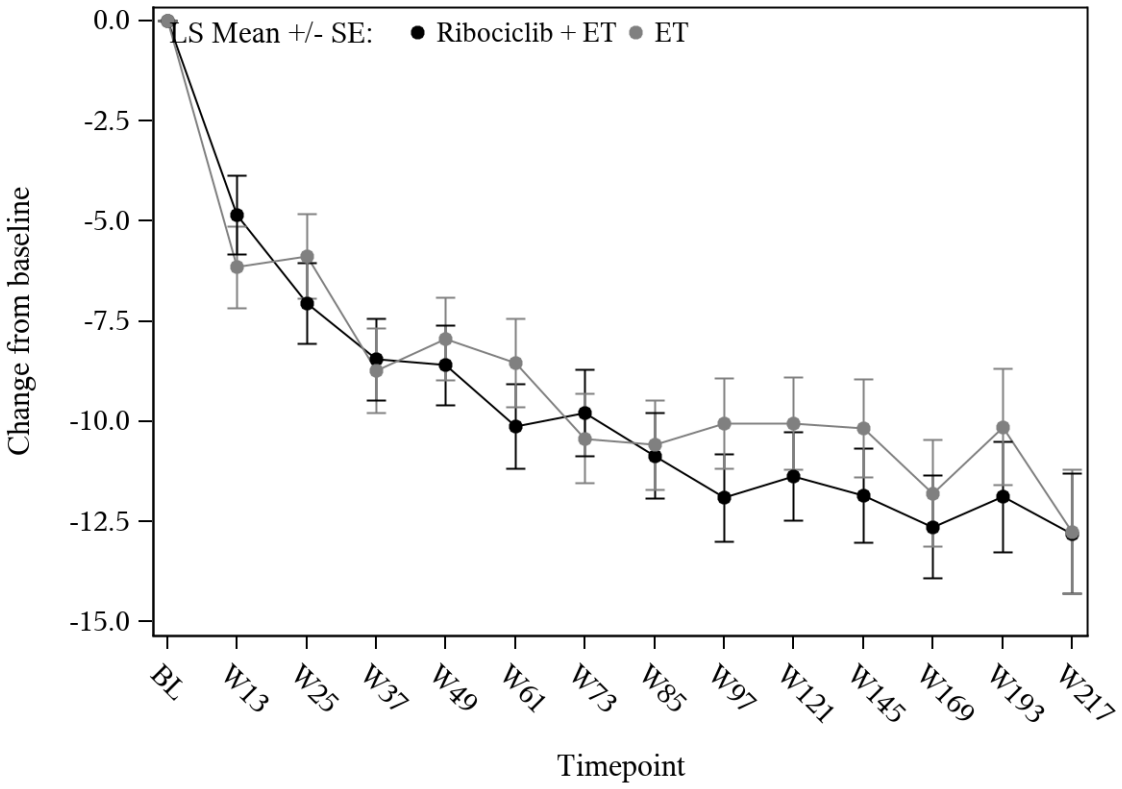
Ribociclib + ET	1060	1021	981	986	973	966	955	943	931	901	898	728	608	346	58
ET	1000	956	918	908	918	899	892	874	853	840	806	680	565	322	50

QLQ-BR23 - Sexual Functioning



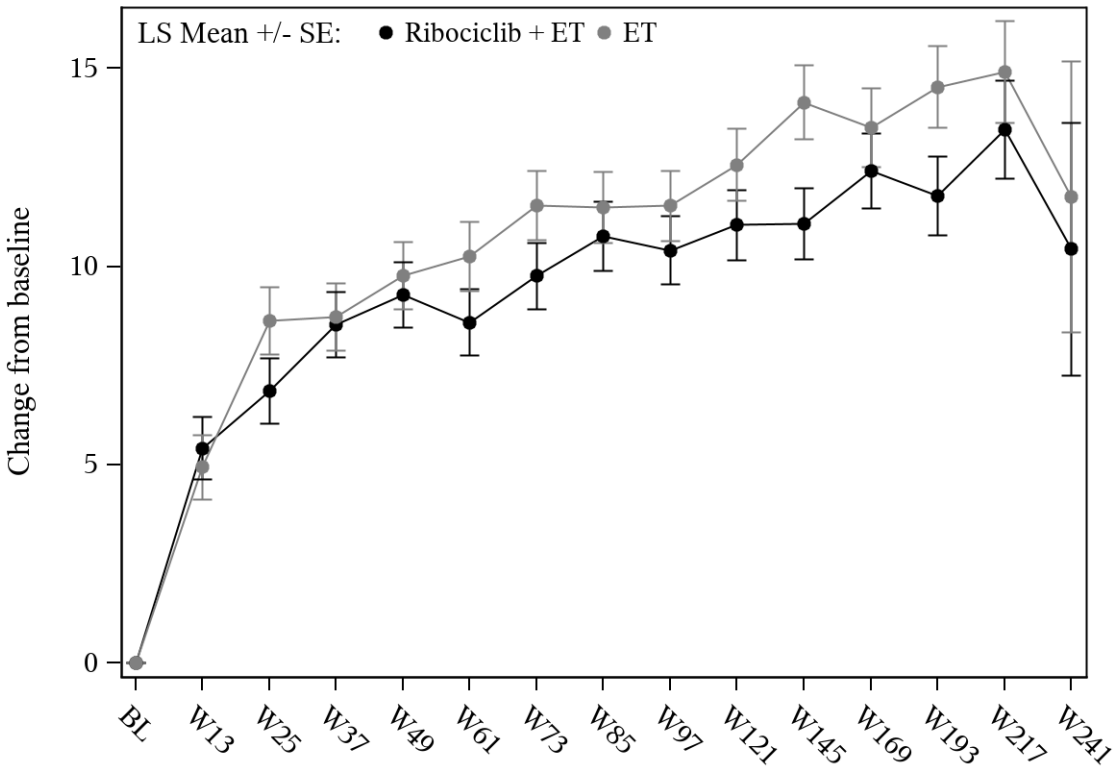
Ribociclib + ET	1047	1007	967	962	956	950	939	924	911	882	875	706	598	339
ET	994	945	904	898	910	891	884	859	842	825	794	669	553	312

QLQ-BR23 - Sexual Enjoyment



Ribociclib + ET	630	509	483	470	474	459	458	454	437	422	409	302	262	144
ET	598	470	442	451	449	417	423	401	410	392	365	284	231	136

QLQ-BR23 - Future Perspective



Ribociclib + ET	1058	1014	976	982	966	960	949	939	926	897	893	726	606	344	58
ET	997	945	909	902	912	891	886	868	849	833	799	677	561	320	50

3-5 EQ-5D VAS

Table 3-5.0 EQ-5D VAS: return rates (Full Analysis Set)

	Treatment groups			
	Ribociclib + ET (N = 1115)		ET (N = 1123)	
	N' (%)	Returns n (%)	N' (%)	Returns n (%)
Baseline	1115 (100.0)	1083 (97.1)	1123 (100.0)	1086 (96.7)
Week 13	1115 (100.0)	1034 (92.7)	1123 (100.0)	978 (87.1)
Week 25	1114 (99.9)	996 (89.4)	1122 (99.9)	939 (83.7)
Week 37	1112 (99.7)	990 (89.0)	1122 (99.9)	926 (82.5)
Week 49	1112 (99.7)	981 (88.2)	1121 (99.8)	941 (83.9)
Week 61	1109 (99.5)	980 (88.4)	1119 (99.6)	918 (82.0)
Week 73	1107 (99.3)	964 (87.1)	1118 (99.6)	909 (81.3)
Week 85	1106 (99.2)	955 (86.3)	1117 (99.5)	888 (79.5)
Week 97	1103 (98.9)	947 (85.9)	1114 (99.2)	876 (78.6)
Week 121	1098 (98.5)	911 (83.0)	1108 (98.7)	852 (76.9)
Week 145	1094 (98.1)	910 (83.2)	1096 (97.6)	820 (74.8)
Week 169	1087 (97.5)	738 (67.9)	1085 (96.6)	693 (63.9)
Week 193	1085 (97.3)	619 (57.1)	1081 (96.3)	581 (53.7)
Week 217	1084 (97.2)	350 (32.3)	1078 (96.0)	331 (30.7)
Week 241	1084 (97.2)	59 (5.4)	1077 (95.9)	55 (5.1)
Week 265	1084 (97.2)	2 (0.2)	1077 (95.9)	1 (0.1)

N': Number of patients who have not died until the respective visit
ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
.....

The number of returns is the number of patients with non-missing data (i.e. at least one [sub-]score present) at the respective visit.

A patients is considered to have not died until the visit if no death was documented during the study, if returns for this PRO are present at the visit or, if no returns are present for this PRO and the patient died, if the death date is after the scheduled visit date.

Percentages of returns refer to N' per group. For N' percentages refer to N per group.

Table 3-5.1 EQ-5D VAS: change from baseline analysis (Full Analysis Set)

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1115)	ET (N = 1123)	Parameter	Esti-mate	[95% CI]	p-value
EQ5D01-Health Today						
	N' | Mean (SD)	**N' | Mean (SD)**				
Overall N'	1051	999				
Baseline	1051 | 78.24 (14.73)	999 | 77.64 (15.08)				
Week 13	1010 | 76.43 (15.90)	953 | 76.51 (16.54)				
Week 25	974 | 77.75 (15.27)	915 | 77.48 (15.77)				
Week 37	967 | 78.93 (33.02)	905 | 77.71 (16.29)				
Week 49	960 | 78.35 (15.03)	918 | 77.92 (15.94)				
Week 61	956 | 77.37 (16.03)	895 | 77.78 (16.30)				
Week 73	942 | 77.32 (16.44)	886 | 78.34 (16.13)				
Week 85	934 | 77.46 (16.44)	868 | 77.12 (17.42)				
Week 97	925 | 77.54 (16.13)	856 | 77.98 (16.72)				
Week 121	891 | 77.53 (16.06)	833 | 78.13 (16.80)				
Week 145	888 | 77.76 (16.47)	804 | 78.32 (16.76)				
Week 169	721 | 78.14 (15.60)	678 | 77.12 (17.32)				
Week 193	604 | 78.51 (15.48)	567 | 76.70 (17.63)				
Week 217	341 | 77.24 (17.53)	324 | 77.30 (17.91)				
Week 241	57 | 78.19 (15.93)	52 | 78.48 (16.83)				
Adjusted change	**Mean (SE)**	**Mean (SE)**				
Week 13	-1.72 (0.42)	-1.37 (0.43)	Difference	-0.35	[-1.53; 0.82]	0.553
			Hedges G	-0.03	[-0.12; 0.06]	
Week 25	-0.80 (0.41)	-0.50 (0.42)	Difference	-0.29	[-1.44; 0.85]	0.614
			Hedges G	-0.02	[-0.11; 0.07]	
Week 37	0.11 (0.80)	-0.49 (0.83)	Difference	0.60	[-1.66; 2.86]	0.605
			Hedges G	0.02	[-0.07; 0.11]	
Week 49	-0.47 (0.41)	-0.16 (0.42)	Difference	-0.30	[-1.46; 0.86]	0.610
			Hedges G	-0.02	[-0.11; 0.07]	
Week 61	-1.50 (0.44)	-0.20 (0.45)	Difference	-1.30	[-2.53; -0.08]	0.037
			Hedges G	-0.10	[-0.19; -0.01]	
Week 73	-1.68 (0.45)	0.22 (0.46)	Difference	-1.90	[-3.17; -0.63]	0.003
			Hedges G	-0.14	[-0.23; -0.05]	
Week 85	-1.63 (0.46)	-1.01 (0.48)	Difference	-0.62	[-1.92; 0.69]	0.353
			Hedges G	-0.04	[-0.14; 0.05]	
Week 97	-1.58 (0.45)	-0.07 (0.47)	Difference	-1.51	[-2.78; -0.24]	0.020
			Hedges G	-0.11	[-0.20; -0.02]	
Week 121	-1.59 (0.46)	-0.03 (0.47)	Difference	-1.56	[-2.86; -0.27]	0.018
			Hedges G	-0.11	[-0.21; -0.02]	
Week 145	-1.34 (0.47)	0.06 (0.48)	Difference	-1.41	[-2.73; -0.09]	0.037
			Hedges G	-0.10	[-0.20; -0.01]	

Treatment Groups			Comparison			
	Ribociclib + ET (N = 1115)	**ET (N = 1123)**	**Parameter**	**Esti-mate**	**[95% CI]**	**p-value**
Week 169	-0.43 (0.49)	-0.53 (0.51)	Difference	0.09	[-1.29; 1.48]	0.894
			Hedges G	0.01	[-0.10; 0.11]	
Week 193	-0.21 (0.53)	-0.83 (0.54)	Difference	0.61	[-0.87; 2.10]	0.418
			Hedges G	0.05	[-0.07; 0.16]	
Week 217	-1.30 (0.65)	-0.62 (0.67)	Difference	-0.68	[-2.52; 1.16]	0.471
			Hedges G	-0.06	[-0.21; 0.10]	
Week 241	-2.15 (1.32)	-1.79 (1.40)	Difference	-0.37	[-4.15; 3.41]	0.849
			Hedges G	-0.04	[-0.41; 0.34]	
Overall effect	**-1.16 (0.37)**	**-0.52 (0.39)**	**Difference**	**-0.64**	**[-1.70; 0.41]**	**0.232**
			Hedges G	**-0.05**	**[-0.14; 0.03]**	

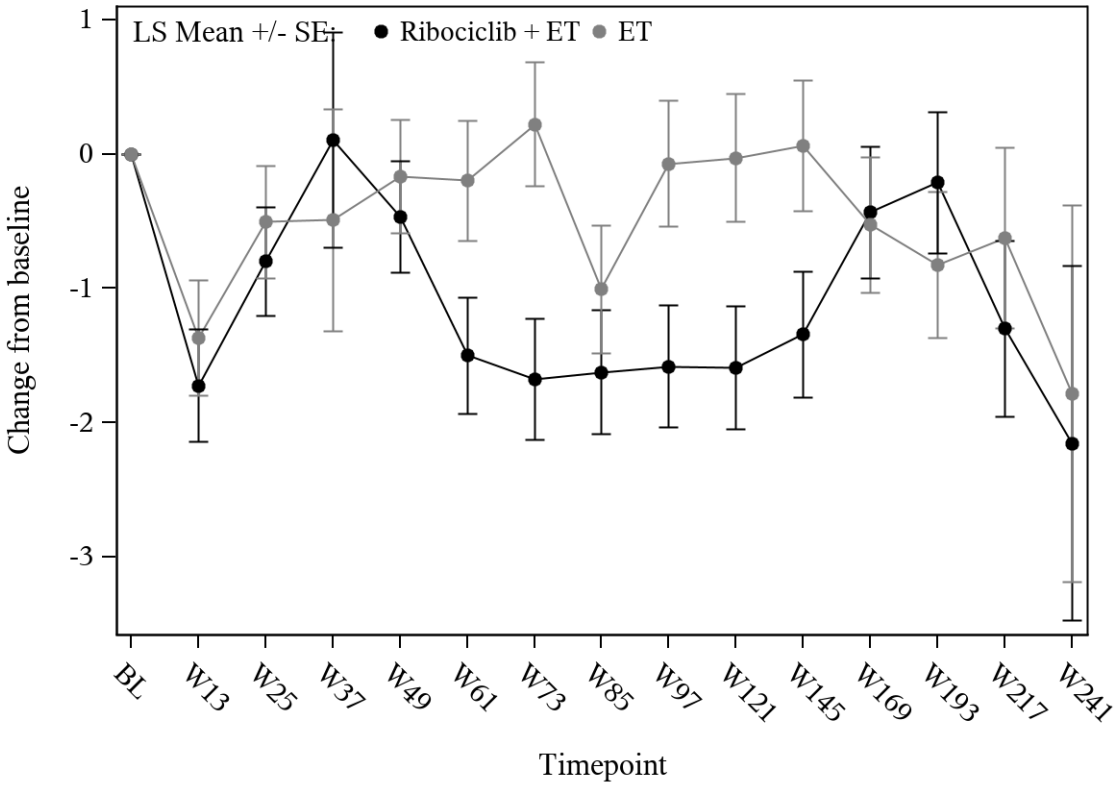
N: Number of patients
N': Number of patients in the analysis
CI: Confidence interval
SD: Standard deviation
LS Mean: Least square mean
SE: Standard error
MMRM: Mixed model for repeated measures
ET: Endocrine therapy (Anastrozole/Letrozole + Goserelin)
.....

Analysis methods:
Adjusted mean (LS Mean) change from baseline and difference obtained from MMRM with unstructured covariance matrix:
change from baseline = treatment + visit + treatment * visit + baseline value + AJCC Anatomic Stage + prior neo/adjuvant chemotherapy + region
ET was the reference group for treatment group comparison.
If the model did not converge for a parameter, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry.

Patients with an evaluable baseline score and at least one evaluable post-baseline score were included in the analysis.
All data collected were included in the analysis, including assessments at confirmation of first recurrence and thereafter, as long as there were at least 50 patients in each treatment group at a visit.

Figure 3-5.1 EQ-5D VAS: line chart of change from baseline (Full Analysis Set)

EQ5D01-Health Today



Ribociclib + ET	1051	1010	974	967	960	956	942	934	925	891	888	721	604	341	57
ET	999	953	915	905	918	895	886	868	856	833	804	678	567	324	52

3-6 HADS

Table 3-6.0 HADS: return rates (Full Analysis Set)

	Treatment groups			
	Ribociclib + ET (N = 1115)		ET (N = 1123)	
	N' (%)	Returns n (%)	N' (%)	Returns n (%)
Baseline	1115 (100.0)	1077 (96.6)	1123 (100.0)	1077 (95.9)
Week 13	1115 (100.0)	1020 (91.5)	1123 (100.0)	959 (85.4)
Week 25	1114 (99.9)	979 (87.9)	1122 (99.9)	932 (83.1)
Week 37	1112 (99.7)	989 (88.9)	1122 (99.9)	918 (81.8)
Week 49	1112 (99.7)	978 (87.9)	1121 (99.8)	933 (83.2)
Week 61	1109 (99.5)	969 (87.4)	1119 (99.6)	915 (81.8)
Week 73	1107 (99.3)	950 (85.8)	1118 (99.6)	909 (81.3)
Week 85	1106 (99.2)	945 (85.4)	1117 (99.5)	885 (79.2)
Week 97	1103 (98.9)	944 (85.6)	1114 (99.2)	867 (77.8)
Week 121	1098 (98.5)	909 (82.8)	1108 (98.7)	851 (76.8)
Week 145	1094 (98.1)	911 (83.3)	1096 (97.6)	815 (74.4)
Week 169	1087 (97.5)	739 (68.0)	1085 (96.6)	689 (63.5)
Week 193	1085 (97.3)	616 (56.8)	1081 (96.3)	576 (53.3)
Week 217	1084 (97.2)	350 (32.3)	1078 (96.0)	331 (30.7)
Week 241	1084 (97.2)	59 (5.4)	1077 (95.9)	53 (4.9)
Week 265	1084 (97.2)	2 (0.2)	1077 (95.9)	1 (0.1)

N': Number of patients who have not died until the respective visit
ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
.....

The number of returns is the number of patients with non-missing data (i.e. at least one [sub-]score present) at the respective visit.

A patients is considered to have not died until the visit if no death was documented during the study, if returns for this PRO are present at the visit or, if no returns are present for this PRO and the patient died, if the death date is after the scheduled visit date.

Percentages of returns refer to N' per group. For N' percentages refer to N per group.

Table 3-6.1 HADS: change from baseline analysis (Full Analysis Set)

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1115)	**ET (N = 1123)**	**Parameter**	**Esti-mate**	**[95% CI]**	**p-value**
HADS - Anxiety						
	N' | Mean (SD)	**N' | Mean (SD)**				
Overall N'	1046	991				
Baseline	1046 | 6.52 (3.76)	991 | 6.52 (3.76)				
Week 13	992 | 6.70 (3.98)	933 | 6.64 (4.03)				
Week 25	952 | 6.77 (4.16)	905 | 6.75 (4.09)				
Week 37	961 | 6.59 (4.14)	890 | 6.75 (4.30)				
Week 49	949 | 6.59 (4.23)	903 | 6.77 (4.23)				
Week 61	939 | 6.70 (4.46)	886 | 6.66 (4.22)				
Week 73	921 | 6.70 (4.41)	879 | 6.62 (4.41)				
Week 85	916 | 6.71 (4.34)	860 | 6.64 (4.50)				
Week 97	913 | 6.63 (4.39)	839 | 6.56 (4.46)				
Week 121	884 | 6.68 (4.30)	825 | 6.58 (4.51)				
Week 145	881 | 6.76 (4.47)	795 | 6.46 (4.48)				
Week 169	715 | 6.73 (4.48)	668 | 6.61 (4.59)				
Week 193	601 | 6.80 (4.45)	556 | 6.52 (4.63)				
Week 217	340 | 6.79 (4.55)	317 | 6.33 (4.57)				
Week 241	58 | 6.23 (4.51)	50 | 5.52 (4.08)				
Adjusted change	**Mean (SE)**	**Mean (SE)**				
Week 13	0.24 (0.09)	0.19 (0.10)	Difference	0.05	[-0.22; 0.31]	0.732
			Hedges G	0.02	[-0.07; 0.11]	
Week 25	0.37 (0.10)	0.26 (0.10)	Difference	0.11	[-0.16; 0.39]	0.423
			Hedges G	0.04	[-0.05; 0.13]	
Week 37	0.26 (0.10)	0.31 (0.11)	Difference	-0.05	[-0.34; 0.24]	0.742
			Hedges G	-0.02	[-0.11; 0.08]	
Week 49	0.31 (0.10)	0.31 (0.11)	Difference	-0.00	[-0.29; 0.29]	0.980
			Hedges G	-0.00	[-0.09; 0.09]	
Week 61	0.40 (0.11)	0.18 (0.11)	Difference	0.21	[-0.09; 0.51]	0.171
			Hedges G	0.06	[-0.03; 0.16]	
Week 73	0.46 (0.11)	0.18 (0.12)	Difference	0.27	[-0.04; 0.59]	0.089
			Hedges G	0.08	[-0.01; 0.17]	
Week 85	0.48 (0.11)	0.24 (0.12)	Difference	0.24	[-0.08; 0.56]	0.146
			Hedges G	0.07	[-0.02; 0.16]	
Week 97	0.34 (0.11)	0.16 (0.12)	Difference	0.18	[-0.14; 0.50]	0.277
			Hedges G	0.05	[-0.04; 0.15]	
Week 121	0.44 (0.12)	0.21 (0.12)	Difference	0.23	[-0.10; 0.56]	0.166
			Hedges G	0.07	[-0.03; 0.16]	
Week 145	0.49 (0.12)	0.11 (0.12)	Difference	0.38	[0.04; 0.72]	0.028
			Hedges G	0.11	[0.01; 0.20]	

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1115)	**ET (N = 1123)**	**Parameter**	**Esti-mate**	**[95% CI]**	**p-value**
Week 169	0.37 (0.13)	0.14 (0.13)	Difference	0.23	[-0.13; 0.59]	0.205
			Hedges G	0.07	[-0.04; 0.17]	
Week 193	0.51 (0.13)	0.09 (0.14)	Difference	0.42	[0.05; 0.80]	0.028
			Hedges G	0.13	[0.01; 0.25]	
Week 217	0.52 (0.16)	-0.02 (0.16)	Difference	0.54	[0.09; 0.99]	0.018
			Hedges G	0.19	[0.03; 0.34]	
Week 241	0.83 (0.30)	-0.10 (0.32)	Difference	0.93	[0.08; 1.78]	0.032
			Hedges G	0.41	[0.03; 0.80]	
Overall effect	**0.43 (0.09)**	**0.16 (0.10)**	**Difference**	**0.27**	**[0.01; 0.53]**	**0.043**
			Hedges G	**0.09**	**[0.00; 0.18]**	
HADS - Depression						
	N' | Mean (SD)	**N' | Mean (SD)**				
Overall N'	1045	991				
Baseline	1045 | 3.88 (3.31)	991 | 3.76 (3.27)				
Week 13	991 | 4.45 (3.74)	933 | 4.29 (3.59)				
Week 25	952 | 4.49 (3.86)	904 | 4.41 (3.83)				
Week 37	962 | 4.39 (3.84)	889 | 4.34 (3.92)				
Week 49	951 | 4.42 (3.86)	901 | 4.38 (3.83)				
Week 61	939 | 4.50 (4.11)	884 | 4.38 (3.81)				
Week 73	921 | 4.57 (4.03)	879 | 4.47 (3.96)				
Week 85	918 | 4.63 (4.08)	859 | 4.45 (4.04)				
Week 97	913 | 4.57 (4.18)	838 | 4.48 (3.98)				
Week 121	882 | 4.60 (4.14)	825 | 4.39 (4.03)				
Week 145	880 | 4.72 (4.33)	795 | 4.35 (3.91)				
Week 169	716 | 4.61 (4.17)	668 | 4.42 (3.92)				
Week 193	601 | 4.59 (4.18)	556 | 4.52 (4.16)				
Week 217	341 | 4.59 (4.21)	317 | 4.10 (3.89)				
Week 241	58 | 3.79 (3.91)	50 | 3.46 (3.70)				
Adjusted change	**Mean (SE)**	**Mean (SE)**				
Week 13	0.60 (0.08)	0.56 (0.09)	Difference	0.05	[-0.19; 0.29]	0.700
			Hedges G	0.02	[-0.07; 0.11]	
Week 25	0.72 (0.09)	0.63 (0.09)	Difference	0.08	[-0.17; 0.34]	0.518
			Hedges G	0.03	[-0.06; 0.12]	
Week 37	0.63 (0.09)	0.61 (0.10)	Difference	0.02	[-0.24; 0.29]	0.877
			Hedges G	0.01	[-0.08; 0.10]	
Week 49	0.74 (0.09)	0.62 (0.10)	Difference	0.12	[-0.14; 0.38]	0.371
			Hedges G	0.04	[-0.05; 0.13]	
Week 61	0.84 (0.10)	0.59 (0.10)	Difference	0.25	[-0.03; 0.53]	0.077
			Hedges G	0.08	[-0.01; 0.17]	
Week 73	0.94 (0.10)	0.70 (0.10)	Difference	0.24	[-0.05; 0.52]	0.103
			Hedges G	0.08	[-0.02; 0.17]	
Week 85	1.01 (0.10)	0.71 (0.11)	Difference	0.30	[0.01; 0.59]	0.046

Treatment Groups			Comparison			
	Ribociclib + ET (N = 1115)	**ET (N = 1123)**	**Parameter**	**Esti-mate**	**[95% CI]**	**p-value**
			Hedges G	0.09	[0.00; 0.19]	
Week 97	0.98 (0.11)	0.73 (0.11)	Difference	0.26	[-0.04; 0.55]	0.088
			Hedges G	0.08	[-0.01; 0.18]	
Week 121	1.03 (0.11)	0.66 (0.11)	Difference	0.37	[0.07; 0.67]	0.017
			Hedges G	0.12	[0.02; 0.21]	
Week 145	1.09 (0.11)	0.62 (0.11)	Difference	0.47	[0.16; 0.78]	0.003
			Hedges G	0.15	[0.05; 0.24]	
Week 169	0.95 (0.11)	0.60 (0.12)	Difference	0.35	[0.04; 0.67]	0.029
			Hedges G	0.12	[0.01; 0.22]	
Week 193	1.01 (0.12)	0.77 (0.13)	Difference	0.23	[-0.11; 0.57]	0.185
			Hedges G	0.08	[-0.04; 0.19]	
Week 217	1.25 (0.14)	0.53 (0.15)	Difference	0.72	[0.32; 1.13]	<.001
			Hedges G	0.27	[0.12; 0.43]	
Week 241	1.25 (0.25)	0.71 (0.27)	Difference	0.54	[-0.19; 1.27]	0.145
			Hedges G	0.28	[-0.10; 0.66]	
Overall effect	**0.93 (0.08)**	**0.65 (0.09)**	**Difference**	**0.29**	**[0.05; 0.52]**	**0.018**
			Hedges G	**0.10**	**[0.02; 0.19]**	

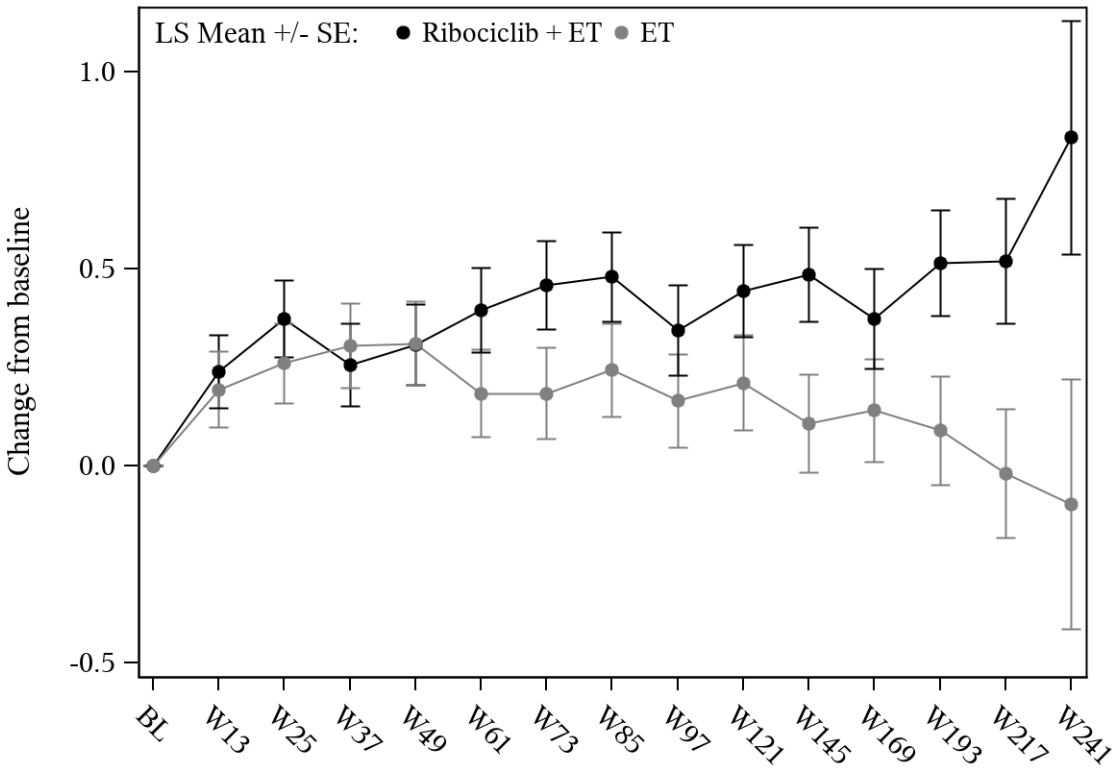
N: Number of patients
N': Number of patients in the analysis
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MMRM: Mixed model for repeated measures
ET: Endocrine therapy (Anastrozole/Letrozole + Goserelin)
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Analysis methods:
Adjusted mean (LS Mean) change from baseline and difference obtained from MMRM with unstructured covariance matrix:
change from baseline = treatment + visit + treatment * visit + baseline value + AJCC Anatomic Stage + prior neo/adjuvant chemotherapy + region
ET was the reference group for treatment group comparison.
If the model did not converge for a parameter, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry.

Patients with an evaluable baseline score and at least one evaluable post-baseline score were included in the analysis.
All data collected were included in the analysis, including assessments at confirmation of first recurrence and thereafter, as long as there were at least 50 patients in each treatment group at a visit.

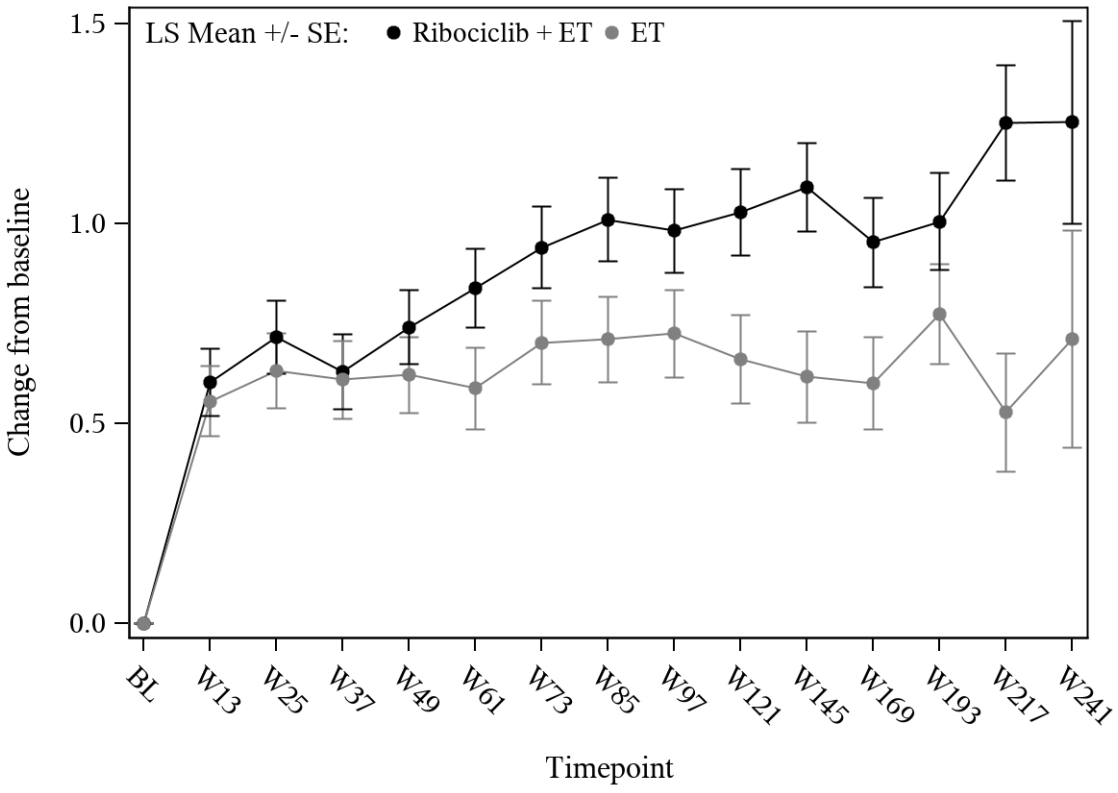
Figure 3-6.1 HADS: line chart of change from baseline (Full Analysis Set)

HADS - Anxiety



Ribociclib + ET	1046	992	952	961	949	939	921	916	913	884	881	715	601	340	58
ET	991	933	905	890	903	886	879	860	839	825	795	668	556	317	50

HADS - Depression



Ribociclib + ET	1045	991	952	962	951	939	921	918	913	882	880	716	601	341	58
ET	991	933	904	889	901	884	879	859	838	825	795	668	556	317	50

4 Adverse events

Table 4-1 Adverse events: binary analysis (Safety Set)

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1108)	ET (N = 1070)	Para-meter	Esti-mate	[95% CI]	p-value
Any adverse event, n (%)	1093 (98.6)	964 (90.1)	OR	8.01	[4.63; 13.85]	<.001
			RR	1.09	[1.07; 1.12]	<.001
			RD	0.09	[0.07; 0.10]	<.001
Any grade ≥3 adverse event, n (%)	734 (66.2)	200 (18.7)	OR	8.54	[7.00; 10.40]	<.001
			RR	3.54	[3.11; 4.04]	<.001
			RD	0.48	[0.44; 0.51]	<.001
Any serious adverse event, n (%)	145 (13.1)	105 (9.8)	OR	1.38	[1.06; 1.81]	0.017
			RR	1.33	[1.05; 1.69]	0.017
			RD	0.03	[0.01; 0.06]	0.016
Any adverse event leading to treatment discontinuation of ribociclib, n (%)	178 (16.1)	N.A.	OR	N.A.		
			RR	N.A.		
			RD	N.A.		
Any adverse event leading to treatment discontinuation of NSAI, n (%)	45 (4.1)	55 (5.1)	OR	0.78	[0.52; 1.17]	0.230
			RR	0.79	[0.54; 1.16]	0.230
			RD	-0.01	[-0.03; 0.01]	0.230
Any adverse event leading to treatment discontinuation of goserelin, n (%)	39 (3.5)	44 (4.1)	OR	0.85	[0.55; 1.32]	0.471
			RR	0.86	[0.56; 1.31]	0.471
			RD	-0.01	[-0.02; 0.01]	0.471
Any adverse event leading to treatment discontinuation of any component, n (%)	190 (17.1)	60 (5.6)	OR	3.48	[2.57; 4.72]	<.001
			RR	3.06	[2.32; 4.04]	<.001
			RD	0.12	[0.09; 0.14]	<.001

N: Number of patients
n: Number of patients with event
CI: Confidence interval
OR: Odds ratio
RR: Relative risk
RD: Risk difference
N.A.: Not applicable
ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
.....

Analysis methods:
OR with Wald 95% CI and p-value obtained from logistic regression model: logit(proportion) = treatment
RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm.
ET was the reference group for treatment group comparison.

Table 4-2 Adverse events by SOC and PT: binary analysis (Safety Set)

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1108)	ET (N = 1070)	Para-meter	Esti-mate	[95% CI]	p-value
Investigations, n (%)	742 (67.0)	390 (36.4)	OR	3.53	[2.96; 4.22]	<.001
			RR	1.84	[1.68; 2.01]	<.001
			RD	0.31	[0.27; 0.35]	<.001
Neutrophil count decreased, n (%)	308 (27.8)	28 (2.6)	OR	14.33	[9.63; 21.32]	<.001
			RR	10.62	[7.28; 15.50]	<.001
			RD	0.25	[0.22; 0.28]	<.001
SARS-CoV-2 test positive, n (%)	294 (26.5)	180 (16.8)	OR	1.79	[1.45; 2.20]	<.001
			RR	1.58	[1.34; 1.86]	<.001
			RD	0.10	[0.06; 0.13]	<.001
Alanine aminotransferase increased, n (%)	194 (17.5)	67 (6.3)	OR	3.18	[2.37; 4.25]	<.001
			RR	2.80	[2.15; 3.64]	<.001
			RD	0.11	[0.09; 0.14]	<.001
Aspartate aminotransferase increased, n (%)	172 (15.5)	63 (5.9)	OR	2.94	[2.17; 3.97]	<.001
			RR	2.64	[2.00; 3.48]	<.001
			RD	0.10	[0.07; 0.12]	<.001
White blood cell count decreased, n (%)	130 (11.7)	26 (2.4)	OR	5.34	[3.47; 8.21]	<.001
			RR	4.83	[3.20; 7.29]	<.001
			RD	0.09	[0.07; 0.11]	<.001
SARS-CoV-2 test negative, n (%)	64 (5.8)	40 (3.7)	OR	1.58	[1.05; 2.37]	0.027
			RR	1.55	[1.05; 2.27]	0.027
			RD	0.02	[0.00; 0.04]	0.025
Electrocardiogram QT prolonged, n (%)	54 (4.9)	9 (0.8)	OR	6.04	[2.97; 12.29]	<.001
			RR	5.79	[2.88; 11.68]	<.001
			RD	0.04	[0.03; 0.05]	<.001
Blood alkaline phosphatase increased, n (%)	43 (3.9)	25 (2.3)	OR	1.69	[1.02; 2.78]	0.040
			RR	1.66	[1.02; 2.70]	0.041
			RD	0.02	[0.00; 0.03]	0.037
Gamma-glutamyltransferase increased, n (%)	41 (3.7)	23 (2.1)	OR	1.75	[1.04; 2.94]	0.034
			RR	1.72	[1.04; 2.85]	0.035
			RD	0.02	[0.00; 0.03]	0.031
Weight increased, n (%)	41 (3.7)	38 (3.6)	OR	1.04	[0.67; 1.64]	0.853
			RR	1.04	[0.68; 1.61]	0.853
			RD	0.00	[-0.01; 0.02]	0.852
Lymphocyte count decreased, n (%)	32 (2.9)	14 (1.3)	OR	2.24	[1.19; 4.23]	0.012
			RR	2.21	[1.18; 4.11]	0.013
			RD	0.02	[0.00; 0.03]	0.010
Blood bilirubin increased, n (%)	28 (2.5)	13 (1.2)	OR	2.11	[1.09; 4.09]	0.028
			RR	2.08	[1.08; 3.99]	0.028

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**Para-meter**	**Esti-mate**	**[95% CI]**	**p-value**
			RD	0.01	[0.00; 0.02]	0.023
Blood magnesium decreased, n (%)	28 (2.5)	13 (1.2)	OR	2.11	[1.09; 4.09]	0.028
			RR	2.08	[1.08; 3.99]	0.028
			RD	0.01	[0.00; 0.02]	0.023
Weight decreased, n (%)	27 (2.4)	19 (1.8)	OR	1.38	[0.76; 2.50]	0.285
			RR	1.37	[0.77; 2.45]	0.286
			RD	0.01	[-0.01; 0.02]	0.282
Blood creatinine increased, n (%)	24 (2.2)	4 (0.4)	OR	5.90	[2.04; 17.06]	0.001
			RR	5.79	[2.02; 16.64]	0.001
			RD	0.02	[0.01; 0.03]	<.001
Platelet count decreased, n (%)	23 (2.1)	5 (0.5)	OR	4.52	[1.71; 11.92]	0.002
			RR	4.44	[1.70; 11.64]	0.002
			RD	0.02	[0.01; 0.03]	<.001
Lipase increased, n (%)	21 (1.9)	11 (1.0)	OR	1.86	[0.89; 3.88]	0.098
			RR	1.84	[0.89; 3.81]	0.098
			RD	0.01	[-0.00; 0.02]	0.091
Blood lactate dehydrogenase increased, n (%)	20 (1.8)	12 (1.1)	OR	1.62	[0.79; 3.33]	0.189
			RR	1.61	[0.79; 3.28]	0.189
			RD	0.01	[-0.00; 0.02]	0.183
Blood cholesterol increased, n (%)	9 (0.8)	19 (1.8)	OR	0.45	[0.20; 1.01]	0.052
			RR	0.46	[0.21; 1.01]	0.052
			RD	-0.01	[-0.02; -0.00]	0.047
Blood phosphorus increased, n (%)	18 (1.6)	10 (0.9)	OR	1.75	[0.80; 3.81]	0.158
			RR	1.74	[0.81; 3.75]	0.158
			RD	0.01	[-0.00; 0.02]	0.151
Amylase increased, n (%)	11 (1.0)	17 (1.6)	OR	0.62	[0.29; 1.33]	0.221
			RR	0.62	[0.29; 1.33]	0.221
			RD	-0.01	[-0.02; 0.00]	0.219
Blood sodium decreased, n (%)	9 (0.8)	16 (1.5)	OR	0.54	[0.24; 1.23]	0.141
			RR	0.54	[0.24; 1.22]	0.141
			RD	-0.01	[-0.02; 0.00]	0.136
Adjusted calcium decreased, n (%)	14 (1.3)	2 (0.2)	OR	6.83	[1.55; 30.14]	0.011
			RR	6.76	[1.54; 29.67]	0.011
			RD	0.01	[0.00; 0.02]	0.003
Blood calcium decreased, n (%)	13 (1.2)	5 (0.5)	OR	2.53	[0.90; 7.12]	0.079
			RR	2.51	[0.90; 7.02]	0.079
			RD	0.01	[-0.00; 0.01]	0.067
Musculoskeletal and connective tissue disorders, n (%)	716 (64.6)	712 (66.5)	OR	0.92	[0.77; 1.10]	0.346
			RR	0.97	[0.91; 1.03]	0.345
			RD	-0.02	[-0.06; 0.02]	0.345

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**Para-meter**	**Esti-mate**	**[95% CI]**	**p-value**
Arthralgia, n (%)	471 (42.5)	505 (47.2)	OR	0.83	[0.70; 0.98]	0.028
			RR	0.90	[0.82; 0.99]	0.028
			RD	-0.05	[-0.09; -0.01]	0.028
Back pain, n (%)	132 (11.9)	124 (11.6)	OR	1.03	[0.79; 1.34]	0.814
			RR	1.03	[0.82; 1.29]	0.814
			RD	0.00	[-0.02; 0.03]	0.814
Pain in extremity, n (%)	123 (11.1)	90 (8.4)	OR	1.36	[1.02; 1.81]	0.035
			RR	1.32	[1.02; 1.71]	0.035
			RD	0.03	[0.00; 0.05]	0.034
Myalgia, n (%)	104 (9.4)	99 (9.3)	OR	1.02	[0.76; 1.36]	0.914
			RR	1.01	[0.78; 1.32]	0.914
			RD	0.00	[-0.02; 0.03]	0.914
Osteoporosis, n (%)	36 (3.2)	52 (4.9)	OR	0.66	[0.43; 1.01]	0.058
			RR	0.67	[0.44; 1.01]	0.058
			RD	-0.02	[-0.03; 0.00]	0.057
Bone pain, n (%)	50 (4.5)	39 (3.6)	OR	1.25	[0.81; 1.92]	0.307
			RR	1.24	[0.82; 1.87]	0.308
			RD	0.01	[-0.01; 0.03]	0.305
Osteopenia, n (%)	35 (3.2)	47 (4.4)	OR	0.71	[0.45; 1.11]	0.132
			RR	0.72	[0.47; 1.10]	0.132
			RD	-0.01	[-0.03; 0.00]	0.131
Musculoskeletal chest pain, n (%)	44 (4.0)	31 (2.9)	OR	1.39	[0.87; 2.21]	0.171
			RR	1.37	[0.87; 2.15]	0.171
			RD	0.01	[-0.00; 0.03]	0.168
Neck pain, n (%)	42 (3.8)	24 (2.2)	OR	1.72	[1.03; 2.86]	0.037
			RR	1.69	[1.03; 2.77]	0.038
			RD	0.02	[0.00; 0.03]	0.034
Joint stiffness, n (%)	34 (3.1)	37 (3.5)	OR	0.88	[0.55; 1.42]	0.609
			RR	0.89	[0.56; 1.40]	0.609
			RD	-0.00	[-0.02; 0.01]	0.609
Muscle spasms, n (%)	29 (2.6)	18 (1.7)	OR	1.57	[0.87; 2.85]	0.136
			RR	1.56	[0.87; 2.78]	0.137
			RD	0.01	[-0.00; 0.02]	0.132
Musculoskeletal pain, n (%)	27 (2.4)	23 (2.1)	OR	1.14	[0.65; 2.00]	0.655
			RR	1.13	[0.65; 1.96]	0.655
			RD	0.00	[-0.01; 0.02]	0.654
Spinal pain, n (%)	20 (1.8)	23 (2.1)	OR	0.84	[0.46; 1.53]	0.564
			RR	0.84	[0.46; 1.52]	0.564
			RD	-0.00	[-0.02; 0.01]	0.564
Musculoskeletal stiffness, n (%)	16 (1.4)	20 (1.9)	OR	0.77	[0.40; 1.49]	0.438
			RR	0.77	[0.40; 1.48]	0.438

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**Para-meter**	**Esti-mate**	**[95% CI]**	**p-value**
			RD	-0.00	[-0.01; 0.01]	0.438
Tendonitis, n (%)	12 (1.1)	16 (1.5)	OR	0.72	[0.34; 1.53]	0.395
			RR	0.72	[0.34; 1.52]	0.395
			RD	-0.00	[-0.01; 0.01]	0.394
Osteoarthritis, n (%)	15 (1.4)	12 (1.1)	OR	1.21	[0.56; 2.60]	0.625
			RR	1.21	[0.57; 2.57]	0.625
			RD	0.00	[-0.01; 0.01]	0.624
Periarthritis, n (%)	6 (0.5)	14 (1.3)	OR	0.41	[0.16; 1.07]	0.069
			RR	0.41	[0.16; 1.07]	0.070
			RD	-0.01	[-0.02; 0.00]	0.062
General disorders and administration site conditions, n (%)	625 (56.4)	421 (39.3)	OR	1.99	[1.68; 2.37]	<.001
			RR	1.43	[1.31; 1.57]	<.001
			RD	0.17	[0.13; 0.21]	<.001
Fatigue, n (%)	238 (21.5)	144 (13.5)	OR	1.76	[1.40; 2.21]	<.001
			RR	1.60	[1.32; 1.93]	<.001
			RD	0.08	[0.05; 0.11]	<.001
Asthenia, n (%)	185 (16.7)	133 (12.4)	OR	1.41	[1.11; 1.80]	0.005
			RR	1.34	[1.09; 1.65]	0.005
			RD	0.04	[0.01; 0.07]	0.005
Pyrexia, n (%)	159 (14.4)	83 (7.8)	OR	1.99	[1.51; 2.64]	<.001
			RR	1.85	[1.44; 2.38]	<.001
			RD	0.07	[0.04; 0.09]	<.001
Influenza like illness, n (%)	65 (5.9)	21 (2.0)	OR	3.11	[1.89; 5.13]	<.001
			RR	2.99	[1.84; 4.85]	<.001
			RD	0.04	[0.02; 0.06]	<.001
Oedema peripheral, n (%)	51 (4.6)	27 (2.5)	OR	1.86	[1.16; 2.99]	0.010
			RR	1.82	[1.15; 2.89]	0.010
			RD	0.02	[0.01; 0.04]	0.009
Mucosal inflammation, n (%)	36 (3.2)	5 (0.5)	OR	7.15	[2.80; 18.30]	<.001
			RR	6.95	[2.74; 17.65]	<.001
			RD	0.03	[0.02; 0.04]	<.001
Pain, n (%)	35 (3.2)	34 (3.2)	OR	0.99	[0.62; 1.61]	0.980
			RR	0.99	[0.62; 1.58]	0.980
			RD	-0.00	[-0.01; 0.01]	0.980
Chest pain, n (%)	27 (2.4)	17 (1.6)	OR	1.55	[0.84; 2.86]	0.163
			RR	1.53	[0.84; 2.80]	0.163
			RD	0.01	[-0.00; 0.02]	0.158
Non-cardiac chest pain, n (%)	26 (2.3)	10 (0.9)	OR	2.55	[1.22; 5.31]	0.013
			RR	2.51	[1.22; 5.18]	0.013
			RD	0.01	[0.00; 0.02]	0.009

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**Para-meter**	**Esti-mate**	**[95% CI]**	**p-value**
Axillary pain, n (%)	25 (2.3)	16 (1.5)	OR	1.52	[0.81; 2.86]	0.195
			RR	1.51	[0.81; 2.81]	0.195
			RD	0.01	[-0.00; 0.02]	0.190
Peripheral swelling, n (%)	23 (2.1)	25 (2.3)	OR	0.89	[0.50; 1.57]	0.679
			RR	0.89	[0.51; 1.56]	0.679
			RD	-0.00	[-0.01; 0.01]	0.679
Chills, n (%)	18 (1.6)	10 (0.9)	OR	1.75	[0.80; 3.81]	0.158
			RR	1.74	[0.81; 3.75]	0.158
			RD	0.01	[-0.00; 0.02]	0.151
Malaise, n (%)	17 (1.5)	8 (0.7)	OR	2.07	[0.89; 4.81]	0.092
			RR	2.05	[0.89; 4.74]	0.092
			RD	0.01	[-0.00; 0.02]	0.083
Infections and infestations, n (%)	580 (52.3)	421 (39.3)	OR	1.69	[1.43; 2.01]	<.001
			RR	1.33	[1.21; 1.46]	<.001
			RD	0.13	[0.09; 0.17]	<.001
COVID-19, n (%)	306 (27.6)	189 (17.7)	OR	1.78	[1.45; 2.18]	<.001
			RR	1.56	[1.33; 1.84]	<.001
			RD	0.10	[0.06; 0.13]	<.001
Upper respiratory tract infection, n (%)	72 (6.5)	30 (2.8)	OR	2.41	[1.56; 3.72]	<.001
			RR	2.32	[1.53; 3.52]	<.001
			RD	0.04	[0.02; 0.05]	<.001
Urinary tract infection, n (%)	63 (5.7)	53 (5.0)	OR	1.16	[0.79; 1.68]	0.447
			RR	1.15	[0.80; 1.64]	0.447
			RD	0.01	[-0.01; 0.03]	0.446
Nasopharyngitis, n (%)	61 (5.5)	43 (4.0)	OR	1.39	[0.93; 2.08]	0.105
			RR	1.37	[0.94; 2.01]	0.105
			RD	0.01	[-0.00; 0.03]	0.103
Sinusitis, n (%)	35 (3.2)	14 (1.3)	OR	2.46	[1.32; 4.60]	0.005
			RR	2.41	[1.31; 4.46]	0.005
			RD	0.02	[0.01; 0.03]	0.003
Herpes zoster, n (%)	28 (2.5)	25 (2.3)	OR	1.08	[0.63; 1.87]	0.773
			RR	1.08	[0.63; 1.84]	0.773
			RD	0.00	[-0.01; 0.01]	0.773
Oral herpes, n (%)	22 (2.0)	2 (0.2)	OR	10.82	[2.54; 46.12]	0.001
			RR	10.62	[2.50; 45.06]	0.001
			RD	0.02	[0.01; 0.03]	<.001
Suspected COVID-19, n (%)	20 (1.8)	15 (1.4)	OR	1.29	[0.66; 2.54]	0.456
			RR	1.29	[0.66; 2.50]	0.456
			RD	0.00	[-0.01; 0.01]	0.453
Influenza, n (%)	18 (1.6)	11 (1.0)	OR	1.59	[0.75; 3.38]	0.229
			RR	1.58	[0.75; 3.33]	0.229

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**Para-meter**	**Esti-mate**	**[95% CI]**	**p-value**
			RD	0.01	[-0.00; 0.02]	0.223
Cystitis, n (%)	17 (1.5)	17 (1.6)	OR	0.97	[0.49; 1.90]	0.918
			RR	0.97	[0.50; 1.88]	0.918
			RD	-0.00	[-0.01; 0.01]	0.918
Pneumonia, n (%)	17 (1.5)	10 (0.9)	OR	1.65	[0.75; 3.62]	0.211
			RR	1.64	[0.76; 3.57]	0.211
			RD	0.01	[-0.00; 0.02]	0.204
Mastitis, n (%)	16 (1.4)	7 (0.7)	OR	2.22	[0.91; 5.43]	0.079
			RR	2.21	[0.91; 5.34]	0.079
			RD	0.01	[-0.00; 0.02]	0.069
Respiratory tract infection viral, n (%)	8 (0.7)	16 (1.5)	OR	0.48	[0.20; 1.12]	0.091
			RR	0.48	[0.21; 1.12]	0.091
			RD	-0.01	[-0.02; 0.00]	0.086
Bronchitis, n (%)	13 (1.2)	15 (1.4)	OR	0.84	[0.40; 1.76]	0.636
			RR	0.84	[0.40; 1.75]	0.636
			RD	-0.00	[-0.01; 0.01]	0.636
Cellulitis, n (%)	14 (1.3)	4 (0.4)	OR	3.41	[1.12; 10.39]	0.031
			RR	3.38	[1.12; 10.24]	0.031
			RD	0.01	[0.00; 0.02]	0.020
Conjunctivitis, n (%)	14 (1.3)	3 (0.3)	OR	4.55	[1.30; 15.88]	0.017
			RR	4.51	[1.30; 15.64]	0.018
			RD	0.01	[0.00; 0.02]	0.008
Gastroenteritis, n (%)	12 (1.1)	9 (0.8)	OR	1.29	[0.54; 3.08]	0.565
			RR	1.29	[0.54; 3.04]	0.565
			RD	0.00	[-0.01; 0.01]	0.563
Skin infection, n (%)	12 (1.1)	8 (0.7)	OR	1.45	[0.59; 3.57]	0.415
			RR	1.45	[0.59; 3.53]	0.415
			RD	0.00	[-0.00; 0.01]	0.410
Respiratory tract infection, n (%)	12 (1.1)	10 (0.9)	OR	1.16	[0.50; 2.70]	0.729
			RR	1.16	[0.50; 2.67]	0.729
			RD	0.00	[-0.01; 0.01]	0.729
Gastrointestinal disorders, n (%)	578 (52.2)	349 (32.6)	OR	2.25	[1.89; 2.68]	<.001
			RR	1.60	[1.44; 1.77]	<.001
			RD	0.20	[0.15; 0.24]	<.001
Nausea, n (%)	247 (22.3)	92 (8.6)	OR	3.05	[2.36; 3.94]	<.001
			RR	2.59	[2.07; 3.24]	<.001
			RD	0.14	[0.11; 0.17]	<.001
Constipation, n (%)	149 (13.4)	55 (5.1)	OR	2.87	[2.08; 3.95]	<.001
			RR	2.62	[1.94; 3.52]	<.001
			RD	0.08	[0.06; 0.11]	<.001

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**Para-meter**	**Esti-mate**	**[95% CI]**	**p-value**
Diarrhoea, n (%)	126 (11.4)	49 (4.6)	OR	2.67	[1.90; 3.76]	<.001
			RR	2.48	[1.80; 3.42]	<.001
			RD	0.07	[0.05; 0.09]	<.001
Vomiting, n (%)	82 (7.4)	47 (4.4)	OR	1.74	[1.20; 2.52]	0.003
			RR	1.68	[1.19; 2.39]	0.003
			RD	0.03	[0.01; 0.05]	0.003
Abdominal pain upper, n (%)	74 (6.7)	45 (4.2)	OR	1.63	[1.11; 2.38]	0.012
			RR	1.59	[1.11; 2.28]	0.012
			RD	0.02	[0.01; 0.04]	0.011
Abdominal pain, n (%)	71 (6.4)	62 (5.8)	OR	1.11	[0.78; 1.58]	0.550
			RR	1.11	[0.79; 1.54]	0.550
			RD	0.01	[-0.01; 0.03]	0.550
Dyspepsia, n (%)	53 (4.8)	41 (3.8)	OR	1.26	[0.83; 1.91]	0.276
			RR	1.25	[0.84; 1.86]	0.276
			RD	0.01	[-0.01; 0.03]	0.274
Dry mouth, n (%)	47 (4.2)	29 (2.7)	OR	1.59	[0.99; 2.55]	0.053
			RR	1.57	[0.99; 2.47]	0.054
			RD	0.02	[-0.00; 0.03]	0.050
Gastrooesophageal reflux disease, n (%)	45 (4.1)	23 (2.1)	OR	1.93	[1.16; 3.21]	0.012
			RR	1.89	[1.15; 3.10]	0.012
			RD	0.02	[0.00; 0.03]	0.010
Stomatitis, n (%)	45 (4.1)	10 (0.9)	OR	4.49	[2.25; 8.95]	<.001
			RR	4.35	[2.20; 8.58]	<.001
			RD	0.03	[0.02; 0.04]	<.001
Toothache, n (%)	22 (2.0)	6 (0.6)	OR	3.59	[1.45; 8.89]	0.006
			RR	3.54	[1.44; 8.70]	0.006
			RD	0.01	[0.00; 0.02]	0.003
Haemorrhoids, n (%)	20 (1.8)	13 (1.2)	OR	1.49	[0.74; 3.02]	0.263
			RR	1.49	[0.74; 2.97]	0.263
			RD	0.01	[-0.00; 0.02]	0.258
Abdominal distension, n (%)	17 (1.5)	10 (0.9)	OR	1.65	[0.75; 3.62]	0.211
			RR	1.64	[0.76; 3.57]	0.211
			RD	0.01	[-0.00; 0.02]	0.204
Mouth ulceration, n (%)	17 (1.5)	3 (0.3)	OR	5.54	[1.62; 18.97]	0.006
			RR	5.47	[1.61; 18.62]	0.007
			RD	0.01	[0.00; 0.02]	0.002
Gastritis, n (%)	16 (1.4)	8 (0.7)	OR	1.95	[0.83; 4.56]	0.126
			RR	1.93	[0.83; 4.49]	0.127
			RD	0.01	[-0.00; 0.02]	0.117
Abdominal pain lower, n (%)	10 (0.9)	12 (1.1)	OR	0.80	[0.35; 1.87]	0.610
			RR	0.80	[0.35; 1.85]	0.610

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**Para-meter**	**Esti-mate**	**[95% CI]**	**p-value**
			RD	-0.00	[-0.01; 0.01]	0.610
Blood and lymphatic system disorders, n (%)	537 (48.5)	105 (9.8)	OR	8.64	[6.84; 10.91]	<.001
			RR	4.94	[4.08; 5.98]	<.001
			RD	0.39	[0.35; 0.42]	<.001
Neutropenia, n (%)	470 (42.4)	39 (3.6)	OR	19.47	[13.84; 27.39]	<.001
			RR	11.64	[8.49; 15.96]	<.001
			RD	0.39	[0.36; 0.42]	<.001
Leukopenia, n (%)	123 (11.1)	29 (2.7)	OR	4.48	[2.96; 6.78]	<.001
			RR	4.10	[2.76; 6.08]	<.001
			RD	0.08	[0.06; 0.10]	<.001
Anaemia, n (%)	81 (7.3)	34 (3.2)	OR	2.40	[1.60; 3.62]	<.001
			RR	2.30	[1.56; 3.40]	<.001
			RD	0.04	[0.02; 0.06]	<.001
Thrombocytopenia, n (%)	36 (3.2)	21 (2.0)	OR	1.68	[0.97; 2.89]	0.063
			RR	1.66	[0.97; 2.82]	0.063
			RD	0.01	[-0.00; 0.03]	0.059
Lymphopenia, n (%)	17 (1.5)	10 (0.9)	OR	1.65	[0.75; 3.62]	0.211
			RR	1.64	[0.76; 3.57]	0.211
			RD	0.01	[-0.00; 0.02]	0.204
Nervous system disorders, n (%)	481 (43.4)	390 (36.4)	OR	1.34	[1.13; 1.59]	<.001
			RR	1.19	[1.07; 1.32]	<.001
			RD	0.07	[0.03; 0.11]	<.001
Headache, n (%)	314 (28.3)	230 (21.5)	OR	1.44	[1.19; 1.76]	<.001
			RR	1.32	[1.14; 1.53]	<.001
			RD	0.07	[0.03; 0.10]	<.001
Dizziness, n (%)	101 (9.1)	51 (4.8)	OR	2.00	[1.42; 2.84]	<.001
			RR	1.91	[1.38; 2.65]	<.001
			RD	0.04	[0.02; 0.06]	<.001
Paraesthesia, n (%)	42 (3.8)	28 (2.6)	OR	1.47	[0.90; 2.38]	0.123
			RR	1.45	[0.90; 2.32]	0.123
			RD	0.01	[-0.00; 0.03]	0.119
Dysgeusia, n (%)	26 (2.3)	8 (0.7)	OR	3.19	[1.44; 7.08]	0.004
			RR	3.14	[1.43; 6.90]	0.004
			RD	0.02	[0.01; 0.03]	0.002
Neuropathy peripheral, n (%)	21 (1.9)	24 (2.2)	OR	0.84	[0.47; 1.52]	0.569
			RR	0.84	[0.47; 1.51]	0.569
			RD	-0.00	[-0.02; 0.01]	0.569
Disturbance in attention, n (%)	21 (1.9)	10 (0.9)	OR	2.05	[0.96; 4.37]	0.064
			RR	2.03	[0.96; 4.29]	0.064
			RD	0.01	[-0.00; 0.02]	0.057

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**Para-meter**	**Esti-mate**	**[95% CI]**	**p-value**
Hypoaesthesia, n (%)	21 (1.9)	13 (1.2)	OR	1.57	[0.78; 3.15]	0.204
			RR	1.56	[0.79; 3.10]	0.204
			RD	0.01	[-0.00; 0.02]	0.199
Memory impairment, n (%)	19 (1.7)	20 (1.9)	OR	0.92	[0.49; 1.73]	0.786
			RR	0.92	[0.49; 1.71]	0.786
			RD	-0.00	[-0.01; 0.01]	0.786
Amnesia, n (%)	19 (1.7)	9 (0.8)	OR	2.06	[0.93; 4.57]	0.076
			RR	2.04	[0.93; 4.49]	0.077
			RD	0.01	[-0.00; 0.02]	0.069
Migraine, n (%)	18 (1.6)	17 (1.6)	OR	1.02	[0.52; 2.00]	0.947
			RR	1.02	[0.53; 1.97]	0.947
			RD	0.00	[-0.01; 0.01]	0.947
Anosmia, n (%)	16 (1.4)	10 (0.9)	OR	1.55	[0.70; 3.44]	0.277
			RR	1.55	[0.70; 3.39]	0.278
			RD	0.01	[-0.00; 0.01]	0.272
Carpal tunnel syndrome, n (%)	2 (0.2)	13 (1.2)	OR	0.15	[0.03; 0.65]	0.012
			RR	0.15	[0.03; 0.66]	0.012
			RD	-0.01	[-0.02; -0.00]	0.004
Peripheral sensory neuropathy, n (%)	13 (1.2)	10 (0.9)	OR	1.26	[0.55; 2.88]	0.587
			RR	1.26	[0.55; 2.85]	0.587
			RD	0.00	[-0.01; 0.01]	0.585
Sciatica, n (%)	7 (0.6)	12 (1.1)	OR	0.56	[0.22; 1.43]	0.225
			RR	0.56	[0.22; 1.43]	0.226
			RD	-0.00	[-0.01; 0.00]	0.221
Vascular disorders, n (%)	417 (37.6)	405 (37.9)	OR	0.99	[0.83; 1.18]	0.918
			RR	0.99	[0.89; 1.11]	0.918
			RD	-0.00	[-0.04; 0.04]	0.918
Hot flush, n (%)	261 (23.6)	270 (25.2)	OR	0.91	[0.75; 1.11]	0.362
			RR	0.93	[0.81; 1.08]	0.362
			RD	-0.02	[-0.05; 0.02]	0.362
Hypertension, n (%)	92 (8.3)	84 (7.9)	OR	1.06	[0.78; 1.45]	0.698
			RR	1.06	[0.80; 1.40]	0.698
			RD	0.00	[-0.02; 0.03]	0.698
Lymphoedema, n (%)	87 (7.9)	86 (8.0)	OR	0.97	[0.71; 1.33]	0.873
			RR	0.98	[0.73; 1.30]	0.873
			RD	-0.00	[-0.02; 0.02]	0.873
Skin and subcutaneous tissue disorders, n (%)	416 (37.5)	227 (21.2)	OR	2.23	[1.85; 2.70]	<.001
			RR	1.77	[1.54; 2.03]	<.001
			RD	0.16	[0.13; 0.20]	<.001
Alopecia, n (%)	155 (14.0)	47 (4.4)	OR	3.54	[2.52; 4.96]	<.001
			RR	3.18	[2.32; 4.37]	<.001

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**Para-meter**	**Esti-mate**	**[95% CI]**	**p-value**
			RD	0.10	[0.07; 0.12]	<.001
Rash, n (%)	99 (8.9)	32 (3.0)	OR	3.18	[2.12; 4.78]	<.001
			RR	2.99	[2.02; 4.41]	<.001
			RD	0.06	[0.04; 0.08]	<.001
Pruritus, n (%)	80 (7.2)	36 (3.4)	OR	2.24	[1.49; 3.34]	<.001
			RR	2.15	[1.46; 3.15]	<.001
			RD	0.04	[0.02; 0.06]	<.001
Dry skin, n (%)	44 (4.0)	14 (1.3)	OR	3.12	[1.70; 5.72]	<.001
			RR	3.04	[1.67; 5.51]	<.001
			RD	0.03	[0.01; 0.04]	<.001
Dermatitis, n (%)	15 (1.4)	7 (0.7)	OR	2.08	[0.85; 5.13]	0.110
			RR	2.07	[0.85; 5.06]	0.111
			RD	0.01	[-0.00; 0.02]	0.100
Erythema, n (%)	14 (1.3)	14 (1.3)	OR	0.97	[0.46; 2.03]	0.926
			RR	0.97	[0.46; 2.02]	0.926
			RD	-0.00	[-0.01; 0.01]	0.926
Scar pain, n (%)	7 (0.6)	14 (1.3)	OR	0.48	[0.19; 1.19]	0.114
			RR	0.48	[0.20; 1.19]	0.114
			RD	-0.01	[-0.02; 0.00]	0.108
Madarosis, n (%)	14 (1.3)	3 (0.3)	OR	4.55	[1.30; 15.88]	0.017
			RR	4.51	[1.30; 15.64]	0.018
			RD	0.01	[0.00; 0.02]	0.008
Rash maculo-papular, n (%)	12 (1.1)	3 (0.3)	OR	3.89	[1.10; 13.84]	0.036
			RR	3.86	[1.09; 13.65]	0.036
			RD	0.01	[0.00; 0.01]	0.022
Urticaria, n (%)	12 (1.1)	4 (0.4)	OR	2.92	[0.94; 9.07]	0.064
			RR	2.90	[0.94; 8.95]	0.065
			RD	0.01	[-0.00; 0.01]	0.050
Respiratory, thoracic and mediastinal disorders, n (%)	339 (30.6)	186 (17.4)	OR	2.10	[1.71; 2.57]	<.001
			RR	1.76	[1.50; 2.06]	<.001
			RD	0.13	[0.10; 0.17]	<.001
Cough, n (%)	170 (15.3)	92 (8.6)	OR	1.93	[1.47; 2.52]	<.001
			RR	1.78	[1.40; 2.27]	<.001
			RD	0.07	[0.04; 0.09]	<.001
Oropharyngeal pain, n (%)	92 (8.3)	48 (4.5)	OR	1.93	[1.35; 2.76]	<.001
			RR	1.85	[1.32; 2.60]	<.001
			RD	0.04	[0.02; 0.06]	<.001
Dyspnoea, n (%)	55 (5.0)	37 (3.5)	OR	1.46	[0.95; 2.23]	0.082
			RR	1.44	[0.95; 2.16]	0.083
			RD	0.02	[-0.00; 0.03]	0.080

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**Para-meter**	**Esti-mate**	**[95% CI]**	**p-value**
Rhinorrhoea, n (%)	39 (3.5)	11 (1.0)	OR	3.51	[1.79; 6.89]	<.001
			RR	3.42	[1.76; 6.65]	<.001
			RD	0.02	[0.01; 0.04]	<.001
Nasal congestion, n (%)	31 (2.8)	13 (1.2)	OR	2.34	[1.22; 4.50]	0.011
			RR	2.30	[1.21; 4.38]	0.011
			RD	0.02	[0.00; 0.03]	0.008
Productive cough, n (%)	22 (2.0)	10 (0.9)	OR	2.15	[1.01; 4.56]	0.046
			RR	2.12	[1.01; 4.47]	0.047
			RD	0.01	[0.00; 0.02]	0.040
Rhinitis allergic, n (%)	20 (1.8)	12 (1.1)	OR	1.62	[0.79; 3.33]	0.189
			RR	1.61	[0.79; 3.28]	0.189
			RD	0.01	[-0.00; 0.02]	0.183
Epistaxis, n (%)	18 (1.6)	8 (0.7)	OR	2.19	[0.95; 5.06]	0.066
			RR	2.17	[0.95; 4.98]	0.066
			RD	0.01	[-0.00; 0.02]	0.058
Dysphonia, n (%)	14 (1.3)	4 (0.4)	OR	3.41	[1.12; 10.39]	0.031
			RR	3.38	[1.12; 10.24]	0.031
			RD	0.01	[0.00; 0.02]	0.020
Psychiatric disorders, n (%)	306 (27.6)	322 (30.1)	OR	0.89	[0.74; 1.07]	0.202
			RR	0.92	[0.80; 1.05]	0.202
			RD	-0.02	[-0.06; 0.01]	0.202
Insomnia, n (%)	142 (12.8)	161 (15.0)	OR	0.83	[0.65; 1.06]	0.133
			RR	0.85	[0.69; 1.05]	0.133
			RD	-0.02	[-0.05; 0.01]	0.133
Anxiety, n (%)	77 (6.9)	78 (7.3)	OR	0.95	[0.69; 1.32]	0.758
			RR	0.95	[0.70; 1.29]	0.758
			RD	-0.00	[-0.03; 0.02]	0.758
Depression, n (%)	51 (4.6)	62 (5.8)	OR	0.78	[0.54; 1.15]	0.211
			RR	0.79	[0.55; 1.14]	0.211
			RD	-0.01	[-0.03; 0.01]	0.211
Sleep disorder, n (%)	23 (2.1)	20 (1.9)	OR	1.11	[0.61; 2.04]	0.729
			RR	1.11	[0.61; 2.01]	0.729
			RD	0.00	[-0.01; 0.01]	0.729
Libido decreased, n (%)	14 (1.3)	13 (1.2)	OR	1.04	[0.49; 2.22]	0.918
			RR	1.04	[0.49; 2.20]	0.918
			RD	0.00	[-0.01; 0.01]	0.918
Mood altered, n (%)	5 (0.5)	14 (1.3)	OR	0.34	[0.12; 0.95]	0.040
			RR	0.34	[0.12; 0.95]	0.040
			RD	-0.01	[-0.02; -0.00]	0.033
	308 (27.8)	143 (13.4)	OR	2.50	[2.00; 3.11]	<.001
			RR	2.08	[1.74; 2.49]	<.001

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**Para-meter**	**Esti-mate**	**[95% CI]**	**p-value**
Metabolism and nutrition disorders, n (%)			RD	0.14	[0.11; 0.18]	<.001
Hypokalaemia, n (%)	56 (5.1)	13 (1.2)	OR	4.33	[2.35; 7.96]	<.001
			RR	4.16	[2.29; 7.56]	<.001
			RD	0.04	[0.02; 0.05]	<.001
Hypocalcaemia, n (%)	54 (4.9)	6 (0.6)	OR	9.08	[3.89; 21.20]	<.001
			RR	8.69	[3.75; 20.12]	<.001
			RD	0.04	[0.03; 0.06]	<.001
Decreased appetite, n (%)	50 (4.5)	13 (1.2)	OR	3.84	[2.08; 7.12]	<.001
			RR	3.71	[2.03; 6.80]	<.001
			RD	0.03	[0.02; 0.05]	<.001
Hypomagnesaemia, n (%)	49 (4.4)	10 (0.9)	OR	4.90	[2.47; 9.73]	<.001
			RR	4.73	[2.41; 9.29]	<.001
			RD	0.03	[0.02; 0.05]	<.001
Hyperkalaemia, n (%)	31 (2.8)	10 (0.9)	OR	3.05	[1.49; 6.25]	0.002
			RR	2.99	[1.48; 6.08]	0.002
			RD	0.02	[0.01; 0.03]	0.001
Hyperglycaemia, n (%)	29 (2.6)	20 (1.9)	OR	1.41	[0.79; 2.51]	0.241
			RR	1.40	[0.80; 2.46]	0.242
			RD	0.01	[-0.00; 0.02]	0.238
Hypercalcaemia, n (%)	19 (1.7)	8 (0.7)	OR	2.32	[1.01; 5.31]	0.047
			RR	2.29	[1.01; 5.22]	0.048
			RD	0.01	[0.00; 0.02]	0.040
Hypercholesterolaemia, n (%)	16 (1.4)	17 (1.6)	OR	0.91	[0.46; 1.81]	0.782
			RR	0.91	[0.46; 1.79]	0.782
			RD	-0.00	[-0.01; 0.01]	0.782
Hypertriglyceridaemia, n (%)	15 (1.4)	8 (0.7)	OR	1.82	[0.77; 4.31]	0.173
			RR	1.81	[0.77; 4.25]	0.173
			RD	0.01	[-0.00; 0.01]	0.164
Hyperuricaemia, n (%)	15 (1.4)	6 (0.6)	OR	2.43	[0.94; 6.30]	0.067
			RR	2.41	[0.94; 6.20]	0.067
			RD	0.01	[-0.00; 0.02]	0.056
Vitamin D deficiency, n (%)	8 (0.7)	14 (1.3)	OR	0.55	[0.23; 1.31]	0.178
			RR	0.55	[0.23; 1.31]	0.178
			RD	-0.01	[-0.01; 0.00]	0.173
Hyperphosphataemia, n (%)	12 (1.1)	2 (0.2)	OR	5.85	[1.31; 26.18]	0.021
			RR	5.79	[1.30; 25.83]	0.021
			RD	0.01	[0.00; 0.02]	0.008
	202 (18.2)	214 (20.0)	OR	0.89	[0.72; 1.10]	0.294
			RR	0.91	[0.77; 1.08]	0.294

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**Para-meter**	**Esti-mate**	**[95% CI]**	**p-value**
Reproductive system and breast disorders, n (%)			RD	-0.02	[-0.05; 0.02]	0.294
Vulvovaginal dryness, n (%)	67 (6.0)	89 (8.3)	OR	0.71	[0.51; 0.99]	0.041
			RR	0.73	[0.54; 0.99]	0.041
			RD	-0.02	[-0.04; -0.00]	0.040
Breast pain, n (%)	62 (5.6)	62 (5.8)	OR	0.96	[0.67; 1.38]	0.841
			RR	0.97	[0.69; 1.36]	0.841
			RD	-0.00	[-0.02; 0.02]	0.841
Vaginal haemorrhage, n (%)	12 (1.1)	20 (1.9)	OR	0.57	[0.28; 1.18]	0.132
			RR	0.58	[0.28; 1.18]	0.132
			RD	-0.01	[-0.02; 0.00]	0.129
Dyspareunia, n (%)	6 (0.5)	19 (1.8)	OR	0.30	[0.12; 0.76]	0.011
			RR	0.30	[0.12; 0.76]	0.011
			RD	-0.01	[-0.02; -0.00]	0.007
Vaginal discharge, n (%)	9 (0.8)	11 (1.0)	OR	0.79	[0.33; 1.91]	0.599
			RR	0.79	[0.33; 1.90]	0.599
			RD	-0.00	[-0.01; 0.01]	0.598
Injury, poisoning and procedural complications, n (%)	184 (16.6)	118 (11.0)	OR	1.61	[1.25; 2.06]	<.001
			RR	1.51	[1.21; 1.87]	<.001
			RD	0.06	[0.03; 0.08]	<.001
Procedural pain, n (%)	36 (3.2)	26 (2.4)	OR	1.35	[0.81; 2.25]	0.252
			RR	1.34	[0.81; 2.20]	0.252
			RD	0.01	[-0.01; 0.02]	0.249
Contusion, n (%)	17 (1.5)	10 (0.9)	OR	1.65	[0.75; 3.62]	0.211
			RR	1.64	[0.76; 3.57]	0.211
			RD	0.01	[-0.00; 0.02]	0.204
Seroma, n (%)	12 (1.1)	6 (0.6)	OR	1.94	[0.73; 5.19]	0.186
			RR	1.93	[0.73; 5.13]	0.186
			RD	0.01	[-0.00; 0.01]	0.176
Eye disorders, n (%)	134 (12.1)	72 (6.7)	OR	1.91	[1.41; 2.57]	<.001
			RR	1.80	[1.37; 2.36]	<.001
			RD	0.05	[0.03; 0.08]	<.001
Dry eye, n (%)	47 (4.2)	16 (1.5)	OR	2.92	[1.64; 5.18]	<.001
			RR	2.84	[1.62; 4.97]	<.001
			RD	0.03	[0.01; 0.04]	<.001
Lacrimation increased, n (%)	24 (2.2)	4 (0.4)	OR	5.90	[2.04; 17.06]	0.001
			RR	5.79	[2.02; 16.64]	0.001
			RD	0.02	[0.01; 0.03]	<.001
Vision blurred, n (%)	22 (2.0)	4 (0.4)	OR	5.40	[1.85; 15.72]	0.002
			RR	5.31	[1.84; 15.36]	0.002

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1108)	ET (N = 1070)	Para-meter	Esti-mate	[95% CI]	p-value
			RD	0.02	[0.01; 0.03]	<.001
Cardiac disorders, n (%)	76 (6.9)	57 (5.3)	OR	1.31	[0.92; 1.87]	0.136
			RR	1.29	[0.92; 1.80]	0.137
			RD	0.02	[-0.00; 0.04]	0.134
Palpitations, n (%)	42 (3.8)	16 (1.5)	OR	2.60	[1.45; 4.64]	0.001
			RR	2.53	[1.43; 4.48]	0.001
			RD	0.02	[0.01; 0.04]	<.001
Tachycardia, n (%)	9 (0.8)	11 (1.0)	OR	0.79	[0.33; 1.91]	0.599
			RR	0.79	[0.33; 1.90]	0.599
			RD	-0.00	[-0.01; 0.01]	0.598
Renal and urinary disorders, n (%)	75 (6.8)	45 (4.2)	OR	1.65	[1.13; 2.42]	0.009
			RR	1.61	[1.12; 2.31]	0.010
			RD	0.03	[0.01; 0.04]	0.008
Dysuria, n (%)	15 (1.4)	13 (1.2)	OR	1.12	[0.53; 2.36]	0.774
			RR	1.11	[0.53; 2.33]	0.774
			RD	0.00	[-0.01; 0.01]	0.773
Ear and labyrinth disorders, n (%)	63 (5.7)	41 (3.8)	OR	1.51	[1.01; 2.26]	0.044
			RR	1.48	[1.01; 2.18]	0.044
			RD	0.02	[0.00; 0.04]	0.042
Vertigo, n (%)	24 (2.2)	21 (2.0)	OR	1.11	[0.61; 2.00]	0.739
			RR	1.10	[0.62; 1.97]	0.739
			RD	0.00	[-0.01; 0.01]	0.738
Tinnitus, n (%)	17 (1.5)	9 (0.8)	OR	1.84	[0.82; 4.14]	0.142
			RR	1.82	[0.82; 4.07]	0.143
			RD	0.01	[-0.00; 0.02]	0.134
Ear pain, n (%)	13 (1.2)	7 (0.7)	OR	1.80	[0.72; 4.54]	0.211
			RR	1.79	[0.72; 4.48]	0.211
			RD	0.01	[-0.00; 0.01]	0.202
Neoplasms benign, malignant and unspecified (incl cysts and polyps), n (%)	57 (5.1)	44 (4.1)	OR	1.26	[0.85; 1.89]	0.253
			RR	1.25	[0.85; 1.84]	0.253
			RD	0.01	[-0.01; 0.03]	0.251
Hepatobiliary disorders, n (%)	52 (4.7)	35 (3.3)	OR	1.46	[0.94; 2.25]	0.092
			RR	1.43	[0.94; 2.18]	0.092
			RD	0.01	[-0.00; 0.03]	0.089
Hepatic steatosis, n (%)	12 (1.1)	5 (0.5)	OR	2.33	[0.82; 6.64]	0.113
			RR	2.32	[0.82; 6.56]	0.113
			RD	0.01	[-0.00; 0.01]	0.100
Endocrine disorders, n (%)	28 (2.5)	30 (2.8)	OR	0.90	[0.53; 1.51]	0.689
			RR	0.90	[0.54; 1.50]	0.689
			RD	-0.00	[-0.02; 0.01]	0.689

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**Para-meter**	**Esti-mate**	**[95% CI]**	**p-value**
Hypothyroidism, n (%)	15 (1.4)	14 (1.3)	OR	1.04	[0.50; 2.15]	0.926
			RR	1.03	[0.50; 2.13]	0.926
			RD	0.00	[-0.01; 0.01]	0.926
Immune system disorders, n (%)	20 (1.8)	14 (1.3)	OR	1.39	[0.70; 2.76]	0.352
			RR	1.38	[0.70; 2.72]	0.352
			RD	0.00	[-0.01; 0.02]	0.349

N: Number of patients
n: Number of patients with event
CI: Confidence interval
OR: Odds ratio
RR: Relative risk
RD: Risk difference
ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
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Analysis methods:
OR with Wald 95% CI and p-value obtained from logistic regression model: logit(proportion) = treatment
RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm.
ET was the reference group for treatment group comparison.

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Table 4-3 Grade ≥3 adverse events by SOC and PT: binary analysis (Safety Set)

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1108)	ET (N = 1070)	Para-meter	Esti-mate	[95% CI]	p-value
Blood and lymphatic system disorders, n (%)	348 (31.4)	12 (1.1)	OR	40.35	[22.53; 72.26]	<.001
			RR	28.01	[15.85; 49.49]	<.001
			RD	0.30	[0.27; 0.33]	<.001
Neutropenia, n (%)	335 (30.2)	9 (0.8)	OR	51.09	[26.18; 99.69]	<.001
			RR	35.95	[18.64; 69.32]	<.001
			RD	0.29	[0.27; 0.32]	<.001
Leukopenia, n (%)	38 (3.4)	1 (0.1)	OR	37.96	[5.20; >99.99]	<.001
			RR	36.70	[5.05; 266.80]	<.001
			RD	0.03	[0.02; 0.04]	<.001
Investigations, n (%)	335 (30.2)	38 (3.6)	OR	11.77	[8.31; 16.67]	<.001
			RR	8.51	[6.15; 11.78]	<.001
			RD	0.27	[0.24; 0.30]	<.001
Neutrophil count decreased, n (%)	245 (22.1)	5 (0.5)	OR	60.47	[24.83; >99.99]	<.001
			RR	47.32	[19.60; 114.25]	<.001
			RD	0.22	[0.19; 0.24]	<.001
Alanine aminotransferase increased, n (%)	72 (6.5)	12 (1.1)	OR	6.13	[3.31; 11.36]	<.001
			RR	5.79	[3.16; 10.61]	<.001
			RD	0.05	[0.04; 0.07]	<.001
White blood cell count decreased, n (%)	56 (5.1)	3 (0.3)	OR	18.93	[5.91; 60.67]	<.001
			RR	18.03	[5.66; 57.41]	<.001
			RD	0.05	[0.03; 0.06]	<.001
Aspartate aminotransferase increased, n (%)	43 (3.9)	8 (0.7)	OR	5.36	[2.51; 11.45]	<.001
			RR	5.19	[2.45; 10.99]	<.001
			RD	0.03	[0.02; 0.04]	<.001
Infections and infestations, n (%)	57 (5.1)	29 (2.7)	OR	1.95	[1.23; 3.07]	0.004
			RR	1.90	[1.22; 2.94]	0.004
			RD	0.02	[0.01; 0.04]	0.003
Nervous system disorders, n (%)	21 (1.9)	29 (2.7)	OR	0.69	[0.39; 1.22]	0.207
			RR	0.70	[0.40; 1.22]	0.207
			RD	-0.01	[-0.02; 0.00]	0.205
Vascular disorders, n (%)	28 (2.5)	23 (2.1)	OR	1.18	[0.68; 2.06]	0.561
			RR	1.18	[0.68; 2.03]	0.561
			RD	0.00	[-0.01; 0.02]	0.560
Hypertension, n (%)	21 (1.9)	19 (1.8)	OR	1.07	[0.57; 2.00]	0.835
			RR	1.07	[0.58; 1.97]	0.835
			RD	0.00	[-0.01; 0.01]	0.835
Gastrointestinal disorders, n (%)	24 (2.2)	9 (0.8)	OR	2.61	[1.21; 5.64]	0.015
			RR	2.58	[1.20; 5.51]	0.015

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**Para-meter**	**Esti-mate**	**[95% CI]**	**p-value**
			RD	0.01	[0.00; 0.02]	0.011
General disorders and administration site conditions, n (%)	24 (2.2)	9 (0.8)	OR	2.61	[1.21; 5.64]	0.015
			RR	2.58	[1.20; 5.51]	0.015
			RD	0.01	[0.00; 0.02]	0.011
Musculoskeletal and connective tissue disorders, n (%)	23 (2.1)	22 (2.1)	OR	1.01	[0.56; 1.82]	0.974
			RR	1.01	[0.57; 1.80]	0.974
			RD	0.00	[-0.01; 0.01]	0.974
Arthralgia, n (%)	10 (0.9)	14 (1.3)	OR	0.69	[0.30; 1.55]	0.367
			RR	0.69	[0.31; 1.55]	0.367
			RD	-0.00	[-0.01; 0.00]	0.366
Injury, poisoning and procedural complications, n (%)	22 (2.0)	15 (1.4)	OR	1.42	[0.74; 2.76]	0.294
			RR	1.42	[0.74; 2.72]	0.295
			RD	0.01	[-0.00; 0.02]	0.290
Neoplasms benign, malignant and unspecified (incl cysts and polyps), n (%)	17 (1.5)	13 (1.2)	OR	1.27	[0.61; 2.62]	0.524
			RR	1.26	[0.62; 2.59]	0.524
			RD	0.00	[-0.01; 0.01]	0.522
Reproductive system and breast disorders, n (%)	16 (1.4)	8 (0.7)	OR	1.95	[0.83; 4.56]	0.126
			RR	1.93	[0.83; 4.49]	0.127
			RD	0.01	[-0.00; 0.02]	0.117
Hepatobiliary disorders, n (%)	13 (1.2)	8 (0.7)	OR	1.58	[0.65; 3.82]	0.314
			RR	1.57	[0.65; 3.77]	0.314
			RD	0.00	[-0.00; 0.01]	0.308
Metabolism and nutrition disorders, n (%)	12 (1.1)	8 (0.7)	OR	1.45	[0.59; 3.57]	0.415
			RR	1.45	[0.59; 3.53]	0.415
			RD	0.00	[-0.00; 0.01]	0.410

N: Number of patients
n: Number of patients with event
CI: Confidence interval
OR: Odds ratio
RR: Relative risk
RD: Risk difference
ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
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Analysis methods:
OR with Wald 95% CI and p-value obtained from logistic regression model: logit(proportion) = treatment
RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm.
ET was the reference group for treatment group comparison.

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Table 4-4 Serious adverse events by SOC and PT: binary analysis (Safety Set)

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1108)	ET (N = 1070)	Para-meter	Esti-mate	[95% CI]	p-value
Infections and infestations, n (%)	50 (4.5)	29 (2.7)	OR	1.70	[1.07; 2.70]	0.026
			RR	1.67	[1.06; 2.61]	0.026
			RD	0.02	[0.00; 0.03]	0.024
Injury, poisoning and procedural complications, n (%)	20 (1.8)	14 (1.3)	OR	1.39	[0.70; 2.76]	0.352
			RR	1.38	[0.70; 2.72]	0.352
			RD	0.00	[-0.01; 0.02]	0.349
Neoplasms benign, malignant and unspecified (incl cysts and polyps), n (%)	16 (1.4)	13 (1.2)	OR	1.19	[0.57; 2.49]	0.641
			RR	1.19	[0.57; 2.46]	0.641
			RD	0.00	[-0.01; 0.01]	0.640
Reproductive system and breast disorders, n (%)	16 (1.4)	6 (0.6)	OR	2.60	[1.01; 6.66]	0.047
			RR	2.58	[1.01; 6.56]	0.047
			RD	0.01	[0.00; 0.02]	0.038
Nervous system disorders, n (%)	9 (0.8)	13 (1.2)	OR	0.67	[0.28; 1.56]	0.351
			RR	0.67	[0.29; 1.56]	0.351
			RD	-0.00	[-0.01; 0.00]	0.349
Hepatobiliary disorders, n (%)	12 (1.1)	8 (0.7)	OR	1.45	[0.59; 3.57]	0.415
			RR	1.45	[0.59; 3.53]	0.415
			RD	0.00	[-0.00; 0.01]	0.410

N: Number of patients
n: Number of patients with event
CI: Confidence interval
OR: Odds ratio
RR: Relative risk
RD: Risk difference
ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
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Analysis methods:
OR with Wald 95% CI and p-value obtained from logistic regression model: logit(proportion) = treatment
RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm.
ET was the reference group for treatment group comparison.

MedDRA Version: 21.1

Table 4-5 Adverse events leading to treatment discontinuation of ribociclib, by SOC and PT: frequency table (Safety Set)

	Treatment Groups	
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**
Investigations, n (%)	88 (7.9)	0 (0.0)
Alanine aminotransferase increased, n (%)	69 (6.2)	0 (0.0)
Aspartate aminotransferase increased, n (%)	24 (2.2)	0 (0.0)
Neutrophil count decreased, n (%)	4 (0.4)	0 (0.0)
Electrocardiogram QT prolonged, n (%)	3 (0.3)	0 (0.0)
Blood bilirubin increased, n (%)	2 (0.2)	0 (0.0)
White blood cell count decreased, n (%)	2 (0.2)	0 (0.0)
Bilirubin conjugated increased, n (%)	1 (0.1)	0 (0.0)
Blood calcium increased, n (%)	1 (0.1)	0 (0.0)
Blood creatinine increased, n (%)	1 (0.1)	0 (0.0)
Blood magnesium decreased, n (%)	1 (0.1)	0 (0.0)
Blood potassium increased, n (%)	1 (0.1)	0 (0.0)
Gamma-glutamyltransferase increased, n (%)	1 (0.1)	0 (0.0)
Granulocyte count decreased, n (%)	1 (0.1)	0 (0.0)
Lipase increased, n (%)	1 (0.1)	0 (0.0)
General disorders and administration site conditions, n (%)	16 (1.4)	0 (0.0)
Fatigue, n (%)	6 (0.5)	0 (0.0)
Asthenia, n (%)	3 (0.3)	0 (0.0)
Impaired healing, n (%)	1 (0.1)	0 (0.0)
Mucosal inflammation, n (%)	1 (0.1)	0 (0.0)
Oedema peripheral, n (%)	1 (0.1)	0 (0.0)
Pyrexia, n (%)	1 (0.1)	0 (0.0)
Localised oedema, n (%)	1 (0.1)	0 (0.0)
Breast complication associated with device, n (%)	1 (0.1)	0 (0.0)
Illness, n (%)	1 (0.1)	0 (0.0)
Blood and lymphatic system disorders, n (%)	12 (1.1)	0 (0.0)
Neutropenia, n (%)	10 (0.9)	0 (0.0)
Febrile neutropenia, n (%)	2 (0.2)	0 (0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps), n (%)	10 (0.9)	0 (0.0)
Malignant melanoma, n (%)	2 (0.2)	0 (0.0)
Papillary thyroid cancer, n (%)	2 (0.2)	0 (0.0)
Colorectal cancer stage I, n (%)	1 (0.1)	0 (0.0)
Medullary thyroid cancer, n (%)	1 (0.1)	0 (0.0)
Squamous cell carcinoma of the cervix, n (%)	1 (0.1)	0 (0.0)
Nasopharyngeal cancer, n (%)	1 (0.1)	0 (0.0)
Ovarian epithelial cancer, n (%)	1 (0.1)	0 (0.0)
Malignant sweat gland neoplasm, n (%)	1 (0.1)	0 (0.0)

	Treatment Groups	
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**
Metabolism and nutrition disorders, n (%)	9 (0.8)	0 (0.0)
Hypercalcaemia, n (%)	3 (0.3)	0 (0.0)
Hypokalaemia, n (%)	2 (0.2)	0 (0.0)
Hypomagnesaemia, n (%)	2 (0.2)	0 (0.0)
Calcium deficiency, n (%)	1 (0.1)	0 (0.0)
Decreased appetite, n (%)	1 (0.1)	0 (0.0)
Skin and subcutaneous tissue disorders, n (%)	8 (0.7)	0 (0.0)
Alopecia, n (%)	2 (0.2)	0 (0.0)
Rash, n (%)	2 (0.2)	0 (0.0)
Dermatitis acneiform, n (%)	1 (0.1)	0 (0.0)
Erythema, n (%)	1 (0.1)	0 (0.0)
Nail disorder, n (%)	1 (0.1)	0 (0.0)
Psoriasis, n (%)	1 (0.1)	0 (0.0)
Skin hypopigmentation, n (%)	1 (0.1)	0 (0.0)
Hepatobiliary disorders, n (%)	7 (0.6)	0 (0.0)
Hepatotoxicity, n (%)	3 (0.3)	0 (0.0)
Cholecystitis acute, n (%)	1 (0.1)	0 (0.0)
Hepatic function abnormal, n (%)	1 (0.1)	0 (0.0)
Hyperbilirubinaemia, n (%)	1 (0.1)	0 (0.0)
Drug-induced liver injury, n (%)	1 (0.1)	0 (0.0)
Infections and infestations, n (%)	7 (0.6)	0 (0.0)
COVID-19, n (%)	2 (0.2)	0 (0.0)
Bronchopulmonary aspergillosis, n (%)	1 (0.1)	0 (0.0)
Hepatitis viral, n (%)	1 (0.1)	0 (0.0)
Mastitis, n (%)	1 (0.1)	0 (0.0)
Oral herpes, n (%)	1 (0.1)	0 (0.0)
COVID-19 pneumonia, n (%)	1 (0.1)	0 (0.0)
Musculoskeletal and connective tissue disorders, n (%)	6 (0.5)	0 (0.0)
Arthralgia, n (%)	6 (0.5)	0 (0.0)
Gastrointestinal disorders, n (%)	5 (0.5)	0 (0.0)
Nausea, n (%)	3 (0.3)	0 (0.0)
Abdominal pain upper, n (%)	1 (0.1)	0 (0.0)
Diarrhoea, n (%)	1 (0.1)	0 (0.0)
Haemorrhoids, n (%)	1 (0.1)	0 (0.0)
Nervous system disorders, n (%)	5 (0.5)	0 (0.0)
Headache, n (%)	3 (0.3)	0 (0.0)
Dizziness, n (%)	1 (0.1)	0 (0.0)
Paraesthesia, n (%)	1 (0.1)	0 (0.0)
Syncope, n (%)	1 (0.1)	0 (0.0)
Respiratory, thoracic and mediastinal disorders, n (%)	5 (0.5)	0 (0.0)
Pneumonitis, n (%)	2 (0.2)	0 (0.0)
Dyspnoea, n (%)	1 (0.1)	0 (0.0)

	Treatment Groups	
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**
Productive cough, n (%)	1 (0.1)	0 (0.0)
Pulmonary embolism, n (%)	1 (0.1)	0 (0.0)
Psychiatric disorders, n (%)	4 (0.4)	0 (0.0)
Depression, n (%)	2 (0.2)	0 (0.0)
Anxiety, n (%)	1 (0.1)	0 (0.0)
Sleep disorder, n (%)	1 (0.1)	0 (0.0)
Vascular disorders, n (%)	3 (0.3)	0 (0.0)
Hot flush, n (%)	2 (0.2)	0 (0.0)
Deep vein thrombosis, n (%)	1 (0.1)	0 (0.0)
Cardiac disorders, n (%)	2 (0.2)	0 (0.0)
Angina pectoris, n (%)	1 (0.1)	0 (0.0)
Ventricular extrasystoles, n (%)	1 (0.1)	0 (0.0)
Eye disorders, n (%)	2 (0.2)	0 (0.0)
Vision blurred, n (%)	1 (0.1)	0 (0.0)
Meibomian gland dysfunction, n (%)	1 (0.1)	0 (0.0)
Injury, poisoning and procedural complications, n (%)	1 (0.1)	0 (0.0)
Post procedural fistula, n (%)	1 (0.1)	0 (0.0)
Reproductive system and breast disorders, n (%)	1 (0.1)	0 (0.0)
Vulvovaginal dryness, n (%)	1 (0.1)	0 (0.0)
Vulvovaginal pain, n (%)	1 (0.1)	0 (0.0)

N: Number of patients
n: Number of patients with event
ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
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MedDRA Version: 21.1

Table 4-6.1 Adverse events leading to treatment discontinuation of NSAI, by SOC and PT: frequency table (Safety Set)

	Treatment Groups	
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**
Musculoskeletal and connective tissue disorders, n (%)	13 (1.2)	35 (3.3)
Arthralgia, n (%)	12 (1.1)	25 (2.3)
Bone pain, n (%)	0 (0.0)	3 (0.3)
Myalgia, n (%)	0 (0.0)	3 (0.3)
Arthropathy, n (%)	0 (0.0)	1 (0.1)
Muscular weakness, n (%)	0 (0.0)	1 (0.1)
Musculoskeletal pain, n (%)	0 (0.0)	1 (0.1)
Osteoporosis, n (%)	0 (0.0)	1 (0.1)
Trigger finger, n (%)	0 (0.0)	1 (0.1)
Joint range of motion decreased, n (%)	0 (0.0)	1 (0.1)
Osteopenia, n (%)	1 (0.1)	0 (0.0)
Limb discomfort, n (%)	0 (0.0)	1 (0.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps), n (%)	5 (0.5)	7 (0.7)
Acute myeloid leukaemia, n (%)	0 (0.0)	2 (0.2)
Malignant melanoma, n (%)	2 (0.2)	0 (0.0)
Adenocarcinoma gastric, n (%)	0 (0.0)	1 (0.1)
Adenocarcinoma of colon, n (%)	0 (0.0)	1 (0.1)
Bladder transitional cell carcinoma, n (%)	0 (0.0)	1 (0.1)
Colon cancer stage II, n (%)	0 (0.0)	1 (0.1)
Pancreatic carcinoma, n (%)	1 (0.1)	0 (0.0)
Papillary thyroid cancer, n (%)	1 (0.1)	0 (0.0)
Rectal cancer, n (%)	0 (0.0)	1 (0.1)
Ovarian epithelial cancer, n (%)	1 (0.1)	0 (0.0)
Nervous system disorders, n (%)	3 (0.3)	6 (0.6)
Headache, n (%)	1 (0.1)	2 (0.2)
Dizziness, n (%)	1 (0.1)	0 (0.0)
Epilepsy, n (%)	1 (0.1)	0 (0.0)
Memory impairment, n (%)	0 (0.0)	1 (0.1)
Migraine, n (%)	0 (0.0)	1 (0.1)
Paraesthesia, n (%)	0 (0.0)	1 (0.1)
Peripheral motor neuropathy, n (%)	0 (0.0)	1 (0.1)
Brain oedema, n (%)	1 (0.1)	0 (0.0)
General disorders and administration site conditions, n (%)	5 (0.5)	1 (0.1)
Fatigue, n (%)	2 (0.2)	1 (0.1)
Asthenia, n (%)	1 (0.1)	0 (0.0)
Oedema peripheral, n (%)	1 (0.1)	0 (0.0)
Peripheral swelling, n (%)	1 (0.1)	0 (0.0)

	Treatment Groups	
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**
Investigations, n (%)	5 (0.5)	3 (0.3)
Alanine aminotransferase increased, n (%)	3 (0.3)	1 (0.1)
Weight decreased, n (%)	1 (0.1)	0 (0.0)
Weight increased, n (%)	1 (0.1)	1 (0.1)
Hepatic enzyme increased, n (%)	0 (0.0)	1 (0.1)
Psychiatric disorders, n (%)	3 (0.3)	3 (0.3)
Depression, n (%)	2 (0.2)	0 (0.0)
Anxiety, n (%)	1 (0.1)	1 (0.1)
Mood altered, n (%)	0 (0.0)	1 (0.1)
Persistent depressive disorder, n (%)	0 (0.0)	1 (0.1)
Ear and labyrinth disorders, n (%)	0 (0.0)	2 (0.2)
Vertigo, n (%)	0 (0.0)	2 (0.2)
Infections and infestations, n (%)	2 (0.2)	0 (0.0)
COVID-19, n (%)	1 (0.1)	0 (0.0)
COVID-19 pneumonia, n (%)	1 (0.1)	0 (0.0)
Reproductive system and breast disorders, n (%)	1 (0.1)	2 (0.2)
Vaginal discharge, n (%)	0 (0.0)	1 (0.1)
Vulvovaginal dryness, n (%)	1 (0.1)	1 (0.1)
Skin and subcutaneous tissue disorders, n (%)	1 (0.1)	2 (0.2)
Rash, n (%)	0 (0.0)	1 (0.1)
Rash maculo-papular, n (%)	0 (0.0)	1 (0.1)
Skin hypopigmentation, n (%)	1 (0.1)	0 (0.0)
Vascular disorders, n (%)	2 (0.2)	0 (0.0)
Circulatory collapse, n (%)	1 (0.1)	0 (0.0)
Hot flush, n (%)	1 (0.1)	0 (0.0)
Cardiac disorders, n (%)	1 (0.1)	0 (0.0)
Cardiac arrest, n (%)	1 (0.1)	0 (0.0)
Eye disorders, n (%)	1 (0.1)	0 (0.0)
Vision blurred, n (%)	1 (0.1)	0 (0.0)
Gastrointestinal disorders, n (%)	1 (0.1)	1 (0.1)
Abdominal pain upper, n (%)	0 (0.0)	1 (0.1)
Nausea, n (%)	1 (0.1)	0 (0.0)
Hepatobiliary disorders, n (%)	1 (0.1)	0 (0.0)
Drug-induced liver injury, n (%)	1 (0.1)	0 (0.0)
Metabolism and nutrition disorders, n (%)	1 (0.1)	0 (0.0)
Hypomagnesaemia, n (%)	1 (0.1)	0 (0.0)
Respiratory, thoracic and mediastinal disorders, n (%)	1 (0.1)	0 (0.0)

	Treatment Groups	
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**
Dyspnoea, n (%)	1 (0.1)	0 (0.0)

N: Number of patients
n: Number of patients with event
ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
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MedDRA Version: 21.1

Table 4-6.2 Adverse events leading to treatment discontinuation of goserelin, by SOC and PT: frequency table (Safety Set)

	Treatment Groups	
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**
Musculoskeletal and connective tissue disorders, n (%)	6 (0.5)	19 (1.8)
Arthralgia, n (%)	6 (0.5)	11 (1.0)
Bone pain, n (%)	0 (0.0)	2 (0.2)
Myalgia, n (%)	0 (0.0)	2 (0.2)
Arthropathy, n (%)	0 (0.0)	1 (0.1)
Musculoskeletal pain, n (%)	0 (0.0)	1 (0.1)
Osteoporosis, n (%)	0 (0.0)	1 (0.1)
Trigger finger, n (%)	0 (0.0)	1 (0.1)
Limb discomfort, n (%)	0 (0.0)	1 (0.1)
General disorders and administration site conditions, n (%)	8 (0.7)	3 (0.3)
Fatigue, n (%)	4 (0.4)	2 (0.2)
Asthenia, n (%)	1 (0.1)	0 (0.0)
Drug ineffective, n (%)	1 (0.1)	0 (0.0)
Oedema peripheral, n (%)	1 (0.1)	0 (0.0)
Peripheral swelling, n (%)	1 (0.1)	0 (0.0)
Administration site pain, n (%)	0 (0.0)	1 (0.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps), n (%)	5 (0.5)	7 (0.7)
Acute myeloid leukaemia, n (%)	0 (0.0)	2 (0.2)
Malignant melanoma, n (%)	2 (0.2)	0 (0.0)
Adenocarcinoma gastric, n (%)	0 (0.0)	1 (0.1)
Adenocarcinoma of colon, n (%)	0 (0.0)	1 (0.1)
Bladder transitional cell carcinoma, n (%)	0 (0.0)	1 (0.1)
Colon cancer stage II, n (%)	0 (0.0)	1 (0.1)
Pancreatic carcinoma, n (%)	1 (0.1)	0 (0.0)
Papillary thyroid cancer, n (%)	1 (0.1)	0 (0.0)
Rectal cancer, n (%)	0 (0.0)	1 (0.1)
Ovarian epithelial cancer, n (%)	1 (0.1)	0 (0.0)
Nervous system disorders, n (%)	3 (0.3)	6 (0.6)
Headache, n (%)	1 (0.1)	2 (0.2)
Dizziness, n (%)	1 (0.1)	0 (0.0)
Memory impairment, n (%)	0 (0.0)	1 (0.1)
Migraine, n (%)	0 (0.0)	1 (0.1)
Paraesthesia, n (%)	0 (0.0)	1 (0.1)
Peripheral motor neuropathy, n (%)	0 (0.0)	1 (0.1)
Brain oedema, n (%)	1 (0.1)	0 (0.0)
Investigations, n (%)	5 (0.5)	1 (0.1)
Alanine aminotransferase increased, n (%)	2 (0.2)	0 (0.0)

	Treatment Groups	
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**
Aspartate aminotransferase increased, n (%)	1 (0.1)	0 (0.0)
Weight decreased, n (%)	1 (0.1)	0 (0.0)
Weight increased, n (%)	1 (0.1)	1 (0.1)
Reproductive system and breast disorders, n (%)	1 (0.1)	4 (0.4)
Intermenstrual bleeding, n (%)	0 (0.0)	1 (0.1)
Vaginal discharge, n (%)	0 (0.0)	1 (0.1)
Vulvovaginal dryness, n (%)	1 (0.1)	1 (0.1)
Heavy menstrual bleeding, n (%)	0 (0.0)	1 (0.1)
Psychiatric disorders, n (%)	3 (0.3)	3 (0.3)
Depression, n (%)	2 (0.2)	0 (0.0)
Anxiety, n (%)	1 (0.1)	1 (0.1)
Depressed mood, n (%)	0 (0.0)	1 (0.1)
Persistent depressive disorder, n (%)	0 (0.0)	1 (0.1)
Ear and labyrinth disorders, n (%)	0 (0.0)	2 (0.2)
Vertigo, n (%)	0 (0.0)	2 (0.2)
Gastrointestinal disorders, n (%)	0 (0.0)	2 (0.2)
Abdominal pain, n (%)	0 (0.0)	1 (0.1)
Diarrhoea, n (%)	0 (0.0)	1 (0.1)
Infections and infestations, n (%)	2 (0.2)	0 (0.0)
COVID-19, n (%)	1 (0.1)	0 (0.0)
COVID-19 pneumonia, n (%)	1 (0.1)	0 (0.0)
Vascular disorders, n (%)	2 (0.2)	0 (0.0)
Circulatory collapse, n (%)	1 (0.1)	0 (0.0)
Hot flush, n (%)	1 (0.1)	0 (0.0)
Cardiac disorders, n (%)	1 (0.1)	0 (0.0)
Cardiac arrest, n (%)	1 (0.1)	0 (0.0)
Congenital, familial and genetic disorders, n (%)	0 (0.0)	1 (0.1)
BRCA1 gene mutation, n (%)	0 (0.0)	1 (0.1)
BRCA2 gene mutation, n (%)	0 (0.0)	1 (0.1)
Hepatobiliary disorders, n (%)	0 (0.0)	1 (0.1)
Hyperbilirubinaemia, n (%)	0 (0.0)	1 (0.1)
Metabolism and nutrition disorders, n (%)	1 (0.1)	0 (0.0)
Hypomagnesaemia, n (%)	1 (0.1)	0 (0.0)
Respiratory, thoracic and mediastinal disorders, n (%)	1 (0.1)	0 (0.0)
Dyspnoea, n (%)	1 (0.1)	0 (0.0)
Skin and subcutaneous tissue disorders, n (%)	1 (0.1)	1 (0.1)
Rash maculo-papular, n (%)	0 (0.0)	1 (0.1)
Skin hypopigmentation, n (%)	1 (0.1)	0 (0.0)

N: Number of patients
n: Number of patients with event
ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
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Table 4-7 Adverse events leading to treatment discontinuation of any component, by SOC and PT: frequency table (Safety Set)

	Treatment Groups	
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**
Investigations, n (%)	89 (8.0)	3 (0.3)
Alanine aminotransferase increased, n (%)	69 (6.2)	1 (0.1)
Aspartate aminotransferase increased, n (%)	25 (2.3)	0 (0.0)
Neutrophil count decreased, n (%)	4 (0.4)	0 (0.0)
Electrocardiogram QT prolonged, n (%)	3 (0.3)	0 (0.0)
Blood bilirubin increased, n (%)	2 (0.2)	0 (0.0)
White blood cell count decreased, n (%)	2 (0.2)	0 (0.0)
Bilirubin conjugated increased, n (%)	1 (0.1)	0 (0.0)
Blood calcium increased, n (%)	1 (0.1)	0 (0.0)
Blood creatinine increased, n (%)	1 (0.1)	0 (0.0)
Blood magnesium decreased, n (%)	1 (0.1)	0 (0.0)
Blood potassium increased, n (%)	1 (0.1)	0 (0.0)
Gamma-glutamyltransferase increased, n (%)	1 (0.1)	0 (0.0)
Granulocyte count decreased, n (%)	1 (0.1)	0 (0.0)
Lipase increased, n (%)	1 (0.1)	0 (0.0)
Weight decreased, n (%)	1 (0.1)	0 (0.0)
Weight increased, n (%)	1 (0.1)	1 (0.1)
Hepatic enzyme increased, n (%)	0 (0.0)	1 (0.1)
Musculoskeletal and connective tissue disorders, n (%)	13 (1.2)	35 (3.3)
Arthralgia, n (%)	12 (1.1)	25 (2.3)
Bone pain, n (%)	0 (0.0)	3 (0.3)
Myalgia, n (%)	0 (0.0)	3 (0.3)
Arthropathy, n (%)	0 (0.0)	1 (0.1)
Muscular weakness, n (%)	0 (0.0)	1 (0.1)
Musculoskeletal pain, n (%)	0 (0.0)	1 (0.1)
Osteoporosis, n (%)	0 (0.0)	1 (0.1)
Trigger finger, n (%)	0 (0.0)	1 (0.1)
Joint range of motion decreased, n (%)	0 (0.0)	1 (0.1)
Osteopenia, n (%)	1 (0.1)	0 (0.0)
Limb discomfort, n (%)	0 (0.0)	1 (0.1)
General disorders and administration site conditions, n (%)	20 (1.8)	3 (0.3)
Fatigue, n (%)	8 (0.7)	2 (0.2)
Asthenia, n (%)	3 (0.3)	0 (0.0)
Drug ineffective, n (%)	1 (0.1)	0 (0.0)
Impaired healing, n (%)	1 (0.1)	0 (0.0)
Mucosal inflammation, n (%)	1 (0.1)	0 (0.0)
Oedema peripheral, n (%)	1 (0.1)	0 (0.0)
Pyrexia, n (%)	1 (0.1)	0 (0.0)

	Treatment Groups	
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**
Peripheral swelling, n (%)	1 (0.1)	0 (0.0)
Localised oedema, n (%)	1 (0.1)	0 (0.0)
Administration site pain, n (%)	0 (0.0)	1 (0.1)
Breast complication associated with device, n (%)	1 (0.1)	0 (0.0)
Illness, n (%)	1 (0.1)	0 (0.0)
Blood and lymphatic system disorders, n (%)	12 (1.1)	0 (0.0)
Neutropenia, n (%)	10 (0.9)	0 (0.0)
Febrile neutropenia, n (%)	2 (0.2)	0 (0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps), n (%)	11 (1.0)	7 (0.7)
Acute myeloid leukaemia, n (%)	0 (0.0)	2 (0.2)
Malignant melanoma, n (%)	2 (0.2)	0 (0.0)
Papillary thyroid cancer, n (%)	2 (0.2)	0 (0.0)
Adenocarcinoma gastric, n (%)	0 (0.0)	1 (0.1)
Adenocarcinoma of colon, n (%)	0 (0.0)	1 (0.1)
Bladder transitional cell carcinoma, n (%)	0 (0.0)	1 (0.1)
Colon cancer stage II, n (%)	0 (0.0)	1 (0.1)
Colorectal cancer stage I, n (%)	1 (0.1)	0 (0.0)
Medullary thyroid cancer, n (%)	1 (0.1)	0 (0.0)
Pancreatic carcinoma, n (%)	1 (0.1)	0 (0.0)
Rectal cancer, n (%)	0 (0.0)	1 (0.1)
Squamous cell carcinoma of the cervix, n (%)	1 (0.1)	0 (0.0)
Nasopharyngeal cancer, n (%)	1 (0.1)	0 (0.0)
Ovarian epithelial cancer, n (%)	1 (0.1)	0 (0.0)
Malignant sweat gland neoplasm, n (%)	1 (0.1)	0 (0.0)
Metabolism and nutrition disorders, n (%)	9 (0.8)	0 (0.0)
Hypercalcaemia, n (%)	3 (0.3)	0 (0.0)
Hypokalaemia, n (%)	2 (0.2)	0 (0.0)
Hypomagnesaemia, n (%)	2 (0.2)	0 (0.0)
Calcium deficiency, n (%)	1 (0.1)	0 (0.0)
Decreased appetite, n (%)	1 (0.1)	0 (0.0)
Hepatobiliary disorders, n (%)	8 (0.7)	1 (0.1)
Hepatotoxicity, n (%)	3 (0.3)	0 (0.0)
Drug-induced liver injury, n (%)	2 (0.2)	0 (0.0)
Cholecystitis acute, n (%)	1 (0.1)	0 (0.0)
Hepatic function abnormal, n (%)	1 (0.1)	0 (0.0)
Hyperbilirubinaemia, n (%)	1 (0.1)	1 (0.1)
Nervous system disorders, n (%)	6 (0.5)	8 (0.7)
Headache, n (%)	3 (0.3)	4 (0.4)
Dizziness, n (%)	2 (0.2)	0 (0.0)
Epilepsy, n (%)	1 (0.1)	0 (0.0)
Memory impairment, n (%)	0 (0.0)	1 (0.1)

	Treatment Groups	
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**
Migraine, n (%)	0 (0.0)	1 (0.1)
Paraesthesia, n (%)	1 (0.1)	1 (0.1)
Peripheral motor neuropathy, n (%)	0 (0.0)	1 (0.1)
Syncope, n (%)	1 (0.1)	0 (0.0)
Brain oedema, n (%)	1 (0.1)	0 (0.0)
Skin and subcutaneous tissue disorders, n (%)	8 (0.7)	2 (0.2)
Alopecia, n (%)	2 (0.2)	0 (0.0)
Rash, n (%)	2 (0.2)	1 (0.1)
Dermatitis acneiform, n (%)	1 (0.1)	0 (0.0)
Erythema, n (%)	1 (0.1)	0 (0.0)
Nail disorder, n (%)	1 (0.1)	0 (0.0)
Psoriasis, n (%)	1 (0.1)	0 (0.0)
Rash maculo-papular, n (%)	0 (0.0)	1 (0.1)
Skin hypopigmentation, n (%)	1 (0.1)	0 (0.0)
Infections and infestations, n (%)	7 (0.6)	0 (0.0)
COVID-19, n (%)	2 (0.2)	0 (0.0)
Bronchopulmonary aspergillosis, n (%)	1 (0.1)	0 (0.0)
Hepatitis viral, n (%)	1 (0.1)	0 (0.0)
Mastitis, n (%)	1 (0.1)	0 (0.0)
Oral herpes, n (%)	1 (0.1)	0 (0.0)
COVID-19 pneumonia, n (%)	1 (0.1)	0 (0.0)
Gastrointestinal disorders, n (%)	6 (0.5)	3 (0.3)
Nausea, n (%)	4 (0.4)	0 (0.0)
Abdominal pain, n (%)	0 (0.0)	1 (0.1)
Abdominal pain upper, n (%)	1 (0.1)	1 (0.1)
Diarrhoea, n (%)	1 (0.1)	1 (0.1)
Haemorrhoids, n (%)	1 (0.1)	0 (0.0)
Respiratory, thoracic and mediastinal disorders, n (%)	5 (0.5)	0 (0.0)
Pneumonitis, n (%)	2 (0.2)	0 (0.0)
Dyspnoea, n (%)	1 (0.1)	0 (0.0)
Productive cough, n (%)	1 (0.1)	0 (0.0)
Pulmonary embolism, n (%)	1 (0.1)	0 (0.0)
Vascular disorders, n (%)	5 (0.5)	0 (0.0)
Hot flush, n (%)	3 (0.3)	0 (0.0)
Circulatory collapse, n (%)	1 (0.1)	0 (0.0)
Deep vein thrombosis, n (%)	1 (0.1)	0 (0.0)
Psychiatric disorders, n (%)	4 (0.4)	4 (0.4)
Depression, n (%)	2 (0.2)	0 (0.0)
Anxiety, n (%)	1 (0.1)	1 (0.1)
Depressed mood, n (%)	0 (0.0)	1 (0.1)
Mood altered, n (%)	0 (0.0)	1 (0.1)
Sleep disorder, n (%)	1 (0.1)	0 (0.0)

	Treatment Groups	
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**
Persistent depressive disorder, n (%)	0 (0.0)	1 (0.1)
Reproductive system and breast disorders, n (%)	2 (0.2)	4 (0.4)
Vulvovaginal dryness, n (%)	2 (0.2)	1 (0.1)
Intermenstrual bleeding, n (%)	0 (0.0)	1 (0.1)
Vaginal discharge, n (%)	0 (0.0)	1 (0.1)
Vulvovaginal pain, n (%)	1 (0.1)	0 (0.0)
Heavy menstrual bleeding, n (%)	0 (0.0)	1 (0.1)
Cardiac disorders, n (%)	3 (0.3)	0 (0.0)
Angina pectoris, n (%)	1 (0.1)	0 (0.0)
Cardiac arrest, n (%)	1 (0.1)	0 (0.0)
Ventricular extrasystoles, n (%)	1 (0.1)	0 (0.0)
Ear and labyrinth disorders, n (%)	0 (0.0)	2 (0.2)
Vertigo, n (%)	0 (0.0)	2 (0.2)
Eye disorders, n (%)	2 (0.2)	0 (0.0)
Vision blurred, n (%)	1 (0.1)	0 (0.0)
Meibomian gland dysfunction, n (%)	1 (0.1)	0 (0.0)
Congenital, familial and genetic disorders, n (%)	0 (0.0)	1 (0.1)
BRCA1 gene mutation, n (%)	0 (0.0)	1 (0.1)
BRCA2 gene mutation, n (%)	0 (0.0)	1 (0.1)
Injury, poisoning and procedural complications, n (%)	1 (0.1)	0 (0.0)
Post procedural fistula, n (%)	1 (0.1)	0 (0.0)

N: Number of patients
n: Number of patients with event
ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
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Table 4-8 Adverse events of special interest: binary analysis (Safety Set)

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1108)	ET (N = 1070)	Para-meter	Esti-mate	[95% CI]	p-value
Hepatobiliary toxicity, n (%)	270 (24.4)	125 (11.7)	OR	2.44	[1.93; 3.07]	<.001
			RR	2.09	[1.72; 2.53]	<.001
			RD	0.13	[0.10; 0.16]	<.001
Serious hepatobiliary toxicity, n (%)	10 (0.9)	3 (0.3)	OR	3.24	[0.89; 11.80]	0.075
			RR	3.22	[0.89; 11.66]	0.075
			RD	0.01	[-0.00; 0.01]	0.057
Grade ≥3: hepatobiliary toxicity, n (%)	75 (6.8)	21 (2.0)	OR	3.63	[2.22; 5.93]	<.001
			RR	3.45	[2.14; 5.55]	<.001
			RD	0.05	[0.03; 0.07]	<.001
ILD Pneumonitis, n (%)	16 (1.4)	5 (0.5)	OR	3.12	[1.14; 8.55]	0.027
			RR	3.09	[1.14; 8.41]	0.027
			RD	0.01	[0.00; 0.02]	0.018
Serious iLD Pneumonitis, n (%)	2 (0.2)	1 (0.1)	OR	1.93	[0.18; 21.35]	0.591
			RR	1.93	[0.18; 21.27]	0.591
			RD	0.00	[-0.00; 0.00]	0.582
Grade ≥3: iLD Pneumonitis, n (%)	0 (0.0)	2 (0.2)	OR	N.E.	N.E.	N.E.
			RR	0.19	[0.01; 4.02]	0.288
			RD	-0.00	[-0.00; 0.00]	0.157
Infections, n (%)	581 (52.4)	423 (39.5)	OR	1.69	[1.42; 2.00]	<.001
			RR	1.33	[1.21; 1.46]	<.001
			RD	0.13	[0.09; 0.17]	<.001
Serious infections, n (%)	50 (4.5)	29 (2.7)	OR	1.70	[1.07; 2.70]	0.026
			RR	1.67	[1.06; 2.61]	0.026
			RD	0.02	[0.00; 0.03]	0.024
Grade ≥3: infections, n (%)	57 (5.1)	29 (2.7)	OR	1.95	[1.23; 3.07]	0.004
			RR	1.90	[1.22; 2.94]	0.004
			RD	0.02	[0.01; 0.04]	0.003
Myelosuppression - Anaemia, n (%)	85 (7.7)	35 (3.3)	OR	2.46	[1.64; 3.68]	<.001
			RR	2.35	[1.60; 3.45]	<.001
			RD	0.04	[0.03; 0.06]	<.001
Grade ≥3: myelosuppression - Anaemia, n (%)	3 (0.3)	1 (0.1)	OR	2.90	[0.30; 27.94]	0.357
			RR	2.90	[0.30; 27.81]	0.357
			RD	0.00	[-0.00; 0.01]	0.330
Myelosuppression - Leukopenia, n (%)	256 (23.1)	68 (6.4)	OR	4.43	[3.34; 5.87]	<.001
			RR	3.64	[2.82; 4.69]	<.001
			RD	0.17	[0.14; 0.20]	<.001
	99 (8.9)	4 (0.4)	OR	26.14	[9.59; 71.27]	<.001
			RR	23.90	[8.83; 64.71]	<.001

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**Para-meter**	**Esti-mate**	**[95% CI]**	**p-value**
Grade ≥3: myelosuppression - Leukopenia, n (%)			RD	0.09	[0.07; 0.10]	<.001
Myelosuppression - Neutropenia, n (%)	739 (66.7)	66 (6.2)	OR	30.46	[23.05; 40.25]	<.001
			RR	10.81	[8.53; 13.71]	<.001
			RD	0.61	[0.57; 0.64]	<.001
Serious myelosuppression - Neutropenia, n (%)	1 (0.1)	0 (0.0)	OR	N.E.	N.E.	N.E.
			RR	2.90	[0.12; 71.04]	0.515
			RD	0.00	[-0.00; 0.00]	0.317
Grade ≥3: myelosuppression - Neutropenia, n (%)	561 (50.6)	14 (1.3)	OR	77.36	[45.07; >99.99]	<.001
			RR	38.70	[22.92; 65.33]	<.001
			RD	0.49	[0.46; 0.52]	<.001
Myelosuppression - Other, n (%)	0 (0.0)	0 (0.0)	OR	N.E.	N.E.	N.E.
			RD	N.E.	N.E.	N.E.
			RR	N.E.	N.E.	N.E.
Myelosuppression - Thrombocytopenia, n (%)	58 (5.2)	26 (2.4)	OR	2.22	[1.39; 3.55]	<.001
			RR	2.15	[1.37; 3.40]	<.001
			RD	0.03	[0.01; 0.04]	<.001
Grade ≥3: myelosuppression - Thrombocytopenia, n (%)	2 (0.2)	2 (0.2)	OR	0.97	[0.14; 6.87]	0.972
			RR	0.97	[0.14; 6.84]	0.972
			RD	-0.00	[-0.00; 0.00]	0.972
QT interval prolongation, n (%)	67 (6.0)	21 (2.0)	OR	3.21	[1.95; 5.29]	<.001
			RR	3.08	[1.90; 4.99]	<.001
			RD	0.04	[0.02; 0.06]	<.001
Serious qT interval prolongation, n (%)	4 (0.4)	1 (0.1)	OR	3.87	[0.43; 34.71]	0.226
			RR	3.86	[0.43; 34.50]	0.226
			RD	0.00	[-0.00; 0.01]	0.187
Grade ≥3: qT interval prolongation, n (%)	13 (1.2)	9 (0.8)	OR	1.40	[0.60; 3.29]	0.440
			RR	1.39	[0.60; 3.25]	0.441
			RD	0.00	[-0.01; 0.01]	0.437
Renal toxicity, n (%)	33 (3.0)	10 (0.9)	OR	3.25	[1.60; 6.63]	0.001
			RR	3.19	[1.58; 6.43]	0.001
			RD	0.02	[0.01; 0.03]	<.001
Reproductive toxicity, n (%)	1 (0.1)	3 (0.3)	OR	0.32	[0.03; 3.09]	0.326
			RR	0.32	[0.03; 3.09]	0.326
			RD	-0.00	[-0.01; 0.00]	0.304
Serious reproductive toxicity, n (%)	0 (0.0)	1 (0.1)	OR	N.E.	N.E.	N.E.
			RR	0.32	[0.01; 7.89]	0.487
			RD	-0.00	[-0.00; 0.00]	0.317
	21 (1.9)	17 (1.6)	OR	1.20	[0.63; 2.28]	0.585
			RR	1.19	[0.63; 2.25]	0.585

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**Para-meter**	**Esti-mate**	**[95% CI]**	**p-value**
Second Primary Malignancies, n (%)			RD	0.00	[-0.01; 0.01]	0.584
Serious second Primary Malignancies, n (%)	13 (1.2)	12 (1.1)	OR	1.05	[0.48; 2.30]	0.910
			RR	1.05	[0.48; 2.28]	0.910
			RD	0.00	[-0.01; 0.01]	0.910
Grade ≥3: second Primary Malignancies, n (%)	14 (1.3)	11 (1.0)	OR	1.23	[0.56; 2.73]	0.607
			RR	1.23	[0.56; 2.70]	0.607
			RD	0.00	[-0.01; 0.01]	0.605

N: Number of patients
n: Number of patients with event
N.E.: Not estimable
CI: Confidence interval
OR: Odds ratio
RR: Relative risk
RD: Risk difference
ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
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Analysis methods:
OR with Wald 95% CI and p-value obtained from logistic regression model: logit(proportion) = treatment
RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm.
ET was the reference group for treatment group comparison.

5 Subgroup analysis

5-1 Subgroup analysis for efficacy

5-1.1 Overall survival

Table 5-1.1.1 Overall survival: time to event analysis - subgroup analysis (Full Analysis Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1115)	ET (N = 1123)	HR	[95% CI]	p-value
Time to Overall Survival Event					
	n / N' (%)	n / N' (%)			
Region					
Interaction test	**p = 0.817**				
NA/WE/O	16 / 644 (2.5)	23 / 660 (3.5)	0.68	[0.36; 1.28]	0.227
ROW	15 / 471 (3.2)	23 / 463 (5.0)	0.61	[0.32; 1.16]	0.128
Geographical region					
Interaction test	**p = 0.965**				
Europe	23 / 661 (3.5)	28 / 656 (4.3)	0.80	[0.46; 1.39]	0.424
North America/Australia	6 / 212 (2.8)	8 / 215 (3.7)	0.62	[0.22; 1.80]	0.377
Asia	0 / 178 (0.0)	6 / 182 (3.3)	N.E.	N.E.	0.012
Latin America	2 / 64 (3.1)	4 / 70 (5.7)	0.56	[0.10; 3.05]	0.495
Age group 1 at randomization					
Interaction test	**p = 0.801**				
<45	18 / 551 (3.3)	23 / 533 (4.3)	0.69	[0.37; 1.28]	0.239
45 to 54	12 / 544 (2.2)	19 / 562 (3.4)	0.64	[0.31; 1.31]	0.217
55 to 64	1 / 20 (5.0)	4 / 28 (14.3)	0.33	[0.04; 2.98]	0.301
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)					
Interaction test	**p = 0.698**				
<Median	18 / 551 (3.3)	23 / 533 (4.3)	0.69	[0.37; 1.28]	0.239
≥Median	13 / 564 (2.3)	23 / 590 (3.9)	0.58	[0.29; 1.14]	0.106
Race					
Interaction test	**p = 0.132**				
Asian	2 / 211 (0.9)	8 / 200 (4.0)	0.22	[0.05; 1.02]	0.033
Non-Asian	28 / 846 (3.3)	36 / 864 (4.2)	0.75	[0.46; 1.23]	0.259
BMI at screening					
Interaction test	**p = 0.767**				
≥25	16 / 554 (2.9)	21 / 545 (3.9)	0.71	[0.37; 1.36]	0.300
<25	15 / 545 (2.8)	24 / 566 (4.2)	0.61	[0.32; 1.17]	0.135

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1115)	**ET (N = 1123)**	**HR**	**[95% CI]**	**p-value**
AJCC Anatomic Stage Group					
Interaction test	**p = 0.501**				
Group I/II	4 / 422 (0.9)	9 / 432 (2.1)	0.44	[0.13; 1.42]	0.157
Group III	27 / 693 (3.9)	37 / 691 (5.4)	0.68	[0.41; 1.11]	0.123
Anatomic stages					
Interaction test	**p = 0.999**				
IA/IB/IIA	0 / 174 (0.0)	3 / 203 (1.5)	N.E.	N.E.	0.092
IIB	4 / 248 (1.6)	6 / 229 (2.6)	0.61	[0.17; 2.17]	0.443
IIIA	15 / 451 (3.3)	18 / 416 (4.3)	0.73	[0.37; 1.46]	0.377
IIIB	4 / 67 (6.0)	5 / 61 (8.2)	0.69	[0.19; 2.59]	0.585
IIIC	8 / 175 (4.6)	14 / 214 (6.5)	0.62	[0.26; 1.48]	0.279
Nodal status					
Interaction test	**p = 0.982**				
N0	0 / 92 (0.0)	5 / 119 (4.2)	N.E.	N.E.	0.045
N1-N3	31 / 1023 (3.0)	41 / 1001 (4.1)	0.70	[0.44; 1.11]	0.127
Histological grade at time of surgery					
Interaction test	**p = 0.261**				
Grade 1	2 / 111 (1.8)	1 / 107 (0.9)	1.79	[0.16; 19.74]	0.630
Grade 2	9 / 609 (1.5)	22 / 630 (3.5)	0.39	[0.18; 0.85]	0.014
Grade 3	14 / 297 (4.7)	16 / 279 (5.7)	0.81	[0.40; 1.67]	0.572
Histological subtype					
Interaction test	**p = 0.539**				
Ductal	23 / 868 (2.6)	38 / 880 (4.3)	0.58	[0.34; 0.97]	0.034
Lobular	8 / 174 (4.6)	7 / 174 (4.0)	1.11	[0.40; 3.06]	0.841
Other	0 / 73 (0.0)	1 / 69 (1.4)	N.E.	N.E.	0.300
Ki67 status from surgical specimen					
Interaction test	**p = 0.706**				
Ki67≤20	12 / 530 (2.3)	18 / 576 (3.1)	0.69	[0.33; 1.43]	0.312
Ki67>20	15 / 424 (3.5)	23 / 396 (5.8)	0.57	[0.30; 1.09]	0.084
Type of NSAI					
Interaction test	**p = 0.714**				
Letrozole	22 / 808 (2.7)	34 / 774 (4.4)	0.61	[0.36; 1.04]	0.066
Anastrozole	9 / 298 (3.0)	12 / 298 (4.0)	0.74	[0.31; 1.76]	0.494
Prior neo/adjuvant chemotherapy					
Interaction test	**p = 0.363**				
Yes	29 / 1032 (2.8)	45 / 1039 (4.3)	0.61	[0.38; 0.98]	0.038
No	2 / 83 (2.4)	1 / 84 (1.2)	1.89	[0.17; 20.83]	0.597
Prior adjuvant chemotherapy					
Interaction test	**p = 0.566**				
Yes	7 / 514 (1.4)	13 / 511 (2.5)	0.51	[0.20; 1.28]	0.142
No	24 / 601 (4.0)	33 / 612 (5.4)	0.69	[0.41; 1.18]	0.172

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1115)	**ET (N = 1123)**	**HR**	**[95% CI]**	**p-value**
Prior neoadjuvant chemotherapy					
Interaction test	**p = 0.760**				
Yes	23 / 548 (4.2)	33 / 568 (5.8)	0.68	[0.40; 1.15]	0.147
No	8 / 567 (1.4)	13 / 555 (2.3)	0.58	[0.24; 1.39]	0.213
Prior endocrine therapy					
Interaction test	**p = 0.607**				
Yes	22 / 858 (2.6)	28 / 822 (3.4)	0.71	[0.41; 1.25]	0.234
No	9 / 257 (3.5)	18 / 301 (6.0)	0.55	[0.25; 1.23]	0.139
Prior mastectomy					
Interaction test	**p = 0.962**				
Yes	25 / 771 (3.2)	37 / 785 (4.7)	0.65	[0.39; 1.07]	0.088
No	6 / 344 (1.7)	9 / 338 (2.7)	0.62	[0.22; 1.75]	0.366
Prior radiotherapy					
Interaction test	**p = 0.212**				
Yes	28 / 1017 (2.8)	45 / 1038 (4.3)	0.60	[0.37; 0.96]	0.030
No	3 / 98 (3.1)	1 / 85 (1.2)	2.54	[0.26; 24.39]	0.403

N: Number of patients
N': Number of patients included in the analysis
n: Number and percentage of patients with event
CI: Confidence interval
HR: Hazard ratio
KM: Kaplan-Meier
N.E.: Not estimable
ET: Endocrine therapy (Anastrozole/Letrozole + Goserelin)
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Analysis method for interaction test:
p-value from Cox proportional hazards model:
log(hazard ratio) = treatment + subgroup factor + treatment * subgroup factor

Analysis methods for within-subgroup analysis:
HR with 95% CI from Cox proportional hazards model:
log(hazard ratio) = treatment
ET was the reference group for treatment group comparison.
Two-sided p-value from Log-rank test.

5-1.2 Invasive disease-free survival

Table 5-1.2.1 Invasive disease-free survival: time to event analysis - subgroup analysis (Full Analysis Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1115)	ET (N = 1123)	HR	[95% CI]	p-value
Time to First iDFS Event					
	n / N' (%)	n / N' (%)			
Region					
Interaction test	**p = 0.247**				
NA/WE/O	58 / 644 (9.0)	71 / 660 (10.8)	0.78	[0.55; 1.10]	0.158
ROW	41 / 471 (8.7)	65 / 463 (14.0)	0.58	[0.39; 0.85]	0.005
Geographical region					
Interaction test	**p = 0.630**				
Europe	50 / 661 (7.6)	82 / 656 (12.5)	0.58	[0.41; 0.83]	0.002
North America/Australia	26 / 212 (12.3)	26 / 215 (12.1)	0.81	[0.47; 1.40]	0.454
Asia	15 / 178 (8.4)	18 / 182 (9.9)	0.77	[0.39; 1.53]	0.460
Latin America	8 / 64 (12.5)	10 / 70 (14.3)	0.95	[0.37; 2.42]	0.917
Age group 1 at randomization					
Interaction test	**p = 0.625**				
<45	53 / 551 (9.6)	66 / 533 (12.4)	0.70	[0.49; 1.00]	0.049
45 to 54	44 / 544 (8.1)	62 / 562 (11.0)	0.70	[0.48; 1.03]	0.069
55 to 64	2 / 20 (10.0)	8 / 28 (28.6)	0.33	[0.07; 1.57]	0.145
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)					
Interaction test	**p = 0.818**				
<Median	53 / 551 (9.6)	66 / 533 (12.4)	0.70	[0.49; 1.00]	0.049
≥Median	46 / 564 (8.2)	70 / 590 (11.9)	0.65	[0.45; 0.95]	0.025
Race					
Interaction test	**p = 0.176**				
Asian	24 / 211 (11.4)	21 / 200 (10.5)	0.98	[0.55; 1.76]	0.951
Non-Asian	70 / 846 (8.3)	109 / 864 (12.6)	0.61	[0.45; 0.83]	0.001
BMI at screening					
Interaction test	**p = 0.290**				
≥25	58 / 554 (10.5)	69 / 545 (12.7)	0.77	[0.54; 1.09]	0.138
<25	40 / 545 (7.3)	66 / 566 (11.7)	0.58	[0.39; 0.86]	0.006
AJCC Anatomic Stage Group					
Interaction test	**p = 0.462**				
Group I/II	24 / 422 (5.7)	41 / 432 (9.5)	0.57	[0.35; 0.95]	0.029
Group III	75 / 693 (10.8)	95 / 691 (13.7)	0.72	[0.53; 0.97]	0.031

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1115)	**ET (N = 1123)**	**HR**	**[95% CI]**	**p-value**
Anatomic stages					
Interaction test	**p = 0.304**				
IA/IB/IIA	4 / 174 (2.3)	17 / 203 (8.4)	0.24	[0.08; 0.73]	0.006
IIB	20 / 248 (8.1)	24 / 229 (10.5)	0.77	[0.43; 1.40]	0.395
IIIA	41 / 451 (9.1)	41 / 416 (9.9)	0.86	[0.55; 1.32]	0.479
IIIB	6 / 67 (9.0)	10 / 61 (16.4)	0.50	[0.18; 1.38]	0.173
IIIC	28 / 175 (16.0)	44 / 214 (20.6)	0.68	[0.43; 1.10]	0.115
Nodal status					
Interaction test	**p = 0.085**				
N0	3 / 92 (3.3)	15 / 119 (12.6)	0.24	[0.07; 0.83]	0.014
N1-N3	96 / 1023 (9.4)	120 / 1001 (12.0)	0.73	[0.56; 0.95]	0.019
Histological grade at time of surgery					
Interaction test	**p = 0.547**				
Grade 1	6 / 111 (5.4)	8 / 107 (7.5)	0.69	[0.24; 2.00]	0.493
Grade 2	46 / 609 (7.6)	71 / 630 (11.3)	0.61	[0.42; 0.89]	0.009
Grade 3	39 / 297 (13.1)	42 / 279 (15.1)	0.84	[0.54; 1.30]	0.430
Histological subtype					
Interaction test	**p = 0.183**				
Ductal	72 / 868 (8.3)	109 / 880 (12.4)	0.61	[0.45; 0.82]	0.001
Lobular	22 / 174 (12.6)	19 / 174 (10.9)	1.15	[0.62; 2.13]	0.650
Other	5 / 73 (6.8)	8 / 69 (11.6)	0.57	[0.19; 1.74]	0.318
Ki67 status from surgical specimen					
Interaction test	**p = 0.476**				
Ki67≤20	37 / 530 (7.0)	56 / 576 (9.7)	0.67	[0.44; 1.01]	0.055
Ki67>20	41 / 424 (9.7)	64 / 396 (16.2)	0.54	[0.37; 0.81]	0.002
Type of NSAI					
Interaction test	**p = 0.377**				
Letrozole	73 / 808 (9.0)	92 / 774 (11.9)	0.73	[0.54; 1.00]	0.048
Anastrozole	26 / 298 (8.7)	44 / 298 (14.8)	0.57	[0.35; 0.92]	0.020
Prior neo/adjuvant chemotherapy					
Interaction test	**p = 0.127**				
Yes	90 / 1032 (8.7)	130 / 1039 (12.5)	0.64	[0.49; 0.84]	0.001
No	9 / 83 (10.8)	6 / 84 (7.1)	1.49	[0.53; 4.20]	0.443
Prior adjuvant chemotherapy					
Interaction test	**p = 0.574**				
Yes	36 / 514 (7.0)	45 / 511 (8.8)	0.75	[0.48; 1.17]	0.200
No	63 / 601 (10.5)	91 / 612 (14.9)	0.64	[0.47; 0.89]	0.007
Prior neoadjuvant chemotherapy					
Interaction test	**p = 0.273**				
Yes	57 / 548 (10.4)	88 / 568 (15.5)	0.61	[0.43; 0.85]	0.003
No	42 / 567 (7.4)	48 / 555 (8.6)	0.82	[0.54; 1.23]	0.333

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1115)	**ET (N = 1123)**	**HR**	**[95% CI]**	**p-value**
Prior endocrine therapy					
Interaction test	**p = 0.418**				
Yes	70 / 858 (8.2)	97 / 822 (11.8)	0.64	[0.47; 0.87]	0.004
No	29 / 257 (11.3)	39 / 301 (13.0)	0.81	[0.50; 1.31]	0.391
Prior mastectomy					
Interaction test	**p = 0.528**				
Yes	76 / 771 (9.9)	100 / 785 (12.7)	0.72	[0.53; 0.96]	0.027
No	23 / 344 (6.7)	36 / 338 (10.7)	0.59	[0.35; 1.00]	0.045
Prior radiotherapy					
Interaction test	**p = 0.300**				
Yes	88 / 1017 (8.7)	127 / 1038 (12.2)	0.65	[0.50; 0.86]	0.002
No	11 / 98 (11.2)	9 / 85 (10.6)	1.05	[0.44; 2.55]	0.905

N: Number of patients
N': Number of patients included in the analysis
n: Number and percentage of patients with event
CI: Confidence interval
HR: Hazard ratio
KM: Kaplan-Meier
ET: Endocrine therapy (Anastrozole/Letrozole + Goserelin)
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Analysis method for interaction test:
p-value from Cox proportional hazards model:
log(hazard ratio) = treatment + subgroup factor + treatment * subgroup factor

Analysis methods for within-subgroup analysis:
HR with 95% CI from Cox proportional hazards model:
log(hazard ratio) = treatment
ET was the reference group for treatment group comparison.
Two-sided p-value from Log-rank test.

5-2 Subgroup analysis for PRO

5-2.1 EORTC QLQ-C30 Symptoms

Table 5-2.1.1.1 QLQ-C30 - Fatigue: change from baseline analysis - subgroup analysis (Full Analysis Set)

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1115)	ET (N = 1123)	Parameter	Esti-mate	[95% CI]	p-value
QLQ-C30 - Fatigue						
	N' | LS Mean (SE)	N' | LS Mean (SE)				
Region						
Interaction test	**p = 0.005**					
NA/WE/O	599 | 5.07 (0.68)	577 | 0.82 (0.70)	Difference	4.25	[2.34; 6.17]	<.001
			Hedges G	0.25	[0.14; 0.37]	
ROW	460 | 2.71 (0.66)	427 | 2.08 (0.69)	Difference	0.63	[-1.24; 2.50]	0.510
			Hedges G	0.04	[-0.09; 0.18]	
Geographical region						
Interaction test	**N.E.**					
Europe	618 | 5.12 (0.65)	592 | 2.38 (0.66)	Difference	2.74	[0.93; 4.56]	0.003
			Hedges G	0.17	[0.06; 0.28]	
North America/Australia	203 | 2.52 (1.00)	177 | -2.63 (1.09)	Difference	5.15	[2.24; 8.06]	<.001
			Hedges G	0.36	[0.15; 0.56]	
Asia	175 | N.E.	166 | N.E.	Difference	N.E.	[N.E.]	N.E.
			Hedges G	N.E.	[N.E.]	
Latin America	63 | 5.84 (1.93)	69 | 3.65 (1.82)	Difference	2.19	[-3.07; 7.44]	0.412
			Hedges G	0.14	[-0.20; 0.49]	
Age group 1 at randomization						
Interaction test	**p = 0.990**					
<45	525 | 4.09 (0.69)	458 | 0.90 (0.73)	Difference	3.19	[1.21; 5.16]	0.002
			Hedges G	0.20	[0.08; 0.33]	
45 to 54	514 | 4.31 (0.68)	519 | 1.98 (0.69)	Difference	2.33	[0.43; 4.23]	0.016
			Hedges G	0.15	[0.03; 0.27]	
55 to 64	20 | N.E.	27 | N.E.	Difference	N.E.	[N.E.]	N.E.
			Hedges G	N.E.	[N.E.]	
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)						
Interaction test	**N.E.**					
<Median	525 | 4.07 (0.72)	458 | 1.18 (0.77)	Difference	2.89	[0.83; 4.96]	0.006
			Hedges G	0.18	[0.05; 0.30]	
≥Median	534 | 4.08 (0.69)	546 | 1.56 (0.69)	Difference	2.52	[0.61; 4.43]	0.010
			Hedges G	0.16	[0.04; 0.28]	

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1115)	**ET (N = 1123)**	**Parameter**	**Esti-mate**	**[95% CI]**	**p-value**
Race						
Interaction test	**p = 0.267**					
Asian	206 | 1.22 (0.97)	180 | -0.03 (1.04)	Difference	1.25	[-1.55; 4.06]	0.380
			Hedges G	0.09	[-0.11; 0.29]	
Non-Asian	802 | 4.64 (0.56)	772 | 1.52 (0.57)	Difference	3.12	[1.56; 4.69]	<.001
			Hedges G	0.20	[0.10; 0.30]	
BMI at screening						
Interaction test	**p = 0.175**					
≥25	529 | 5.97 (0.75)	488 | 2.31 (0.78)	Difference	3.66	[1.53; 5.78]	<.001
			Hedges G	0.21	[0.09; 0.34]	
<25	518 | 2.06 (0.65)	505 | 0.22 (0.66)	Difference	1.84	[0.01; 3.67]	0.048
			Hedges G	0.12	[0.00; 0.25]	
AJCC Anatomic Stage Group						
Interaction test	**p = <.001**					
Group I/II	394 | 2.54 (0.79)	398 | 3.75 (0.79)	Difference	-1.20	[-3.40; 0.99]	0.282
			Hedges G	-0.08	[-0.22; 0.06]	
Group III	665 | 4.97 (0.60)	606 | -0.22 (0.64)	Difference	5.18	[3.46; 6.91]	<.001
			Hedges G	0.33	[0.22; 0.44]	
Anatomic stages						
Interaction test	**p = <.001**					
IA/IB/IIA	163 | 0.91 (1.19)	188 | 3.51 (1.13)	Difference	-2.60	[-5.84; 0.64]	0.116
			Hedges G	-0.17	[-0.38; 0.04]	
IIB	231 | 3.68 (1.05)	210 | 3.89 (1.10)	Difference	-0.21	[-3.20; 2.77]	0.888
			Hedges G	-0.01	[-0.20; 0.17]	
IIIA	433 | 5.59 (0.75)	368 | -0.02 (0.82)	Difference	5.62	[3.43; 7.80]	<.001
			Hedges G	0.36	[0.22; 0.50]	
IIIB	63 | 5.49 (2.07)	52 | 0.25 (2.29)	Difference	5.24	[-0.92; 11.40]	0.095
			Hedges G	0.32	[-0.05; 0.69]	
IIIC	169 | 3.32 (1.19)	186 | -0.57 (1.14)	Difference	3.89	[0.66; 7.13]	0.018
			Hedges G	0.25	[0.04; 0.46]	
Nodal status						
Interaction test	**p = 0.164**					
N0	84 | 2.89 (1.45)	109 | 2.78 (1.29)	Difference	0.11	[-3.72; 3.94]	0.955
			Hedges G	0.01	[-0.28; 0.29]	
N1-N3	975 | 4.14 (0.52)	892 | 1.02 (0.54)	Difference	3.12	[1.64; 4.59]	<.001
			Hedges G	0.19	[0.10; 0.28]	

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1115)	**ET (N = 1123)**	**Parameter**	**Esti-mate**	**[95% CI]**	**p-value**
Histological grade at time of surgery						
Interaction test	**p = 0.084**					
Grade 1	106 | 1.76 (1.55)	97 | 3.17 (1.64)	Difference	-1.42	[-5.86; 3.02]	0.530
			Hedges G	-0.09	[-0.36; 0.19]	
Grade 2	579 | 4.58 (0.65)	558 | 1.05 (0.66)	Difference	3.53	[1.71; 5.35]	<.001
			Hedges G	0.23	[0.11; 0.34]	
Grade 3	282 | 4.53 (0.90)	252 | 0.61 (0.95)	Difference	3.92	[1.36; 6.49]	0.003
			Hedges G	0.26	[0.09; 0.43]	
Histological subtype						
Interaction test	**p = 0.474**					
Ductal	822 | 4.61 (0.54)	786 | 1.43 (0.56)	Difference	3.18	[1.66; 4.70]	<.001
			Hedges G	0.20	[0.11; 0.30]	
Lobular	168 | 2.11 (1.26)	156 | 1.27 (1.33)	Difference	0.83	[-2.77; 4.43]	0.649
			Hedges G	0.05	[-0.17; 0.27]	
Other	69 | 0.98 (1.83)	62 | 1.75 (1.98)	Difference	-0.78	[-6.13; 4.58]	0.775
			Hedges G	-0.05	[-0.39; 0.29]	
Ki67 status from surgical specimen						
Interaction test	**p = 0.236**					
Ki67≤20	510 | 3.94 (0.71)	517 | 1.82 (0.71)	Difference	2.12	[0.16; 4.09]	0.034
			Hedges G	0.13	[0.01; 0.25]	
Ki67>20	400 | 5.16 (0.76)	358 | 1.31 (0.81)	Difference	3.86	[1.68; 6.04]	<.001
			Hedges G	0.25	[0.11; 0.40]	
Type of NSAI						
Interaction test	**p = 0.059**					
Letrozole	775 | 4.00 (0.58)	720 | 2.08 (0.61)	Difference	1.92	[0.27; 3.56]	0.022
			Hedges G	0.12	[0.02; 0.22]	
Anastrozole	284 | 4.46 (0.96)	282 | -0.62 (0.97)	Difference	5.08	[2.40; 7.77]	<.001
			Hedges G	0.31	[0.15; 0.48]	
Prior neo/adjuvant chemotherapy						
Interaction test	**p = 0.145**					
Yes	984 | 4.25 (0.50)	926 | 1.24 (0.52)	Difference	3.00	[1.59; 4.42]	<.001
			Hedges G	0.19	[0.10; 0.28]	
No	75 | 1.66 (1.61)	78 | 3.15 (1.62)	Difference	-1.48	[-5.99; 3.03]	0.517
			Hedges G	-0.11	[-0.42; 0.21]	
Prior adjuvant chemotherapy						
Interaction test	**p = 0.771**					
Yes	494 | 4.22 (0.72)	463 | 1.23 (0.74)	Difference	2.99	[0.97; 5.01]	0.004
			Hedges G	0.19	[0.06; 0.31]	
No	565 | 4.05 (0.69)	541 | 1.51 (0.71)	Difference	2.54	[0.59; 4.49]	0.011
			Hedges G	0.15	[0.04; 0.27]	

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1115)	ET (N = 1123)	Parameter	Esti-mate	[95% CI]	p-value
Prior neoadjuvant chemotherapy						
Interaction test	**p = 0.642**					
Yes	520 | 4.11 (0.73)	501 | 1.10 (0.74)	Difference	3.01	[0.97; 5.05]	0.004
			Hedges G	0.18	[0.06; 0.30]	
No	539 | 3.84 (0.68)	503 | 1.56 (0.71)	Difference	2.28	[0.35; 4.20]	0.020
			Hedges G	0.14	[0.02; 0.27]	
Prior endocrine therapy						
Interaction test	**p = 0.522**					
Yes	815 | 4.05 (0.57)	734 | 1.61 (0.61)	Difference	2.44	[0.81; 4.08]	0.003
			Hedges G	0.15	[0.05; 0.25]	
No	244 | 4.15 (1.02)	270 | 0.83 (0.98)	Difference	3.32	[0.54; 6.09]	0.019
			Hedges G	0.21	[0.03; 0.38]	
Prior mastectomy						
Interaction test	**p = 0.021**					
Yes	737 | 4.34 (0.60)	699 | 0.49 (0.61)	Difference	3.86	[2.18; 5.53]	<.001
			Hedges G	0.24	[0.13; 0.34]	
No	322 | 3.55 (0.91)	305 | 3.35 (0.94)	Difference	0.20	[-2.37; 2.77]	0.879
			Hedges G	0.01	[-0.14; 0.17]	
Prior radiotherapy						
Interaction test	**p = 0.614**					
Yes	970 | 4.11 (0.51)	922 | 1.35 (0.52)	Difference	2.77	[1.34; 4.19]	<.001
			Hedges G	0.17	[0.08; 0.27]	
No	89 | 3.56 (1.52)	82 | 1.75 (1.61)	Difference	1.80	[-2.58; 6.18]	0.417
			Hedges G	0.12	[-0.18; 0.42]	

N: Number of patients
N': Number of patients in the analysis
CI: Confidence interval
SD: Standard deviation
LS Mean: Least square mean
SE: Standard error
MMRM: Mixed model for repeated measures
N.E.: Not estimable
ET: Endocrine therapy (Anastrozole/Letrozole + Goserelin)
.....

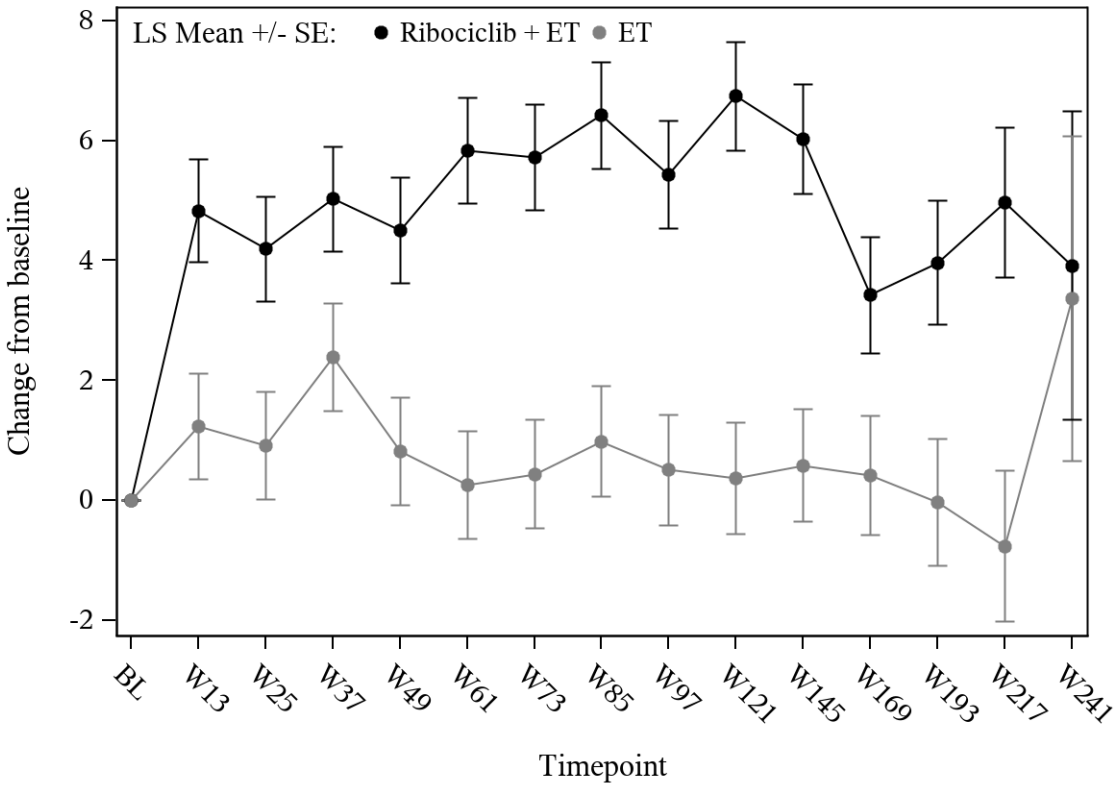
Analysis method for interaction test:
p-value from MMRM with unstructured covariance matrix:
change from baseline = treatment + visit + treatment * visit + subgroup factor + treatment * subgroup factor + subgroup factor * visit + treatment * subgroup factor * visit + baseline value
If the model did not converge for a parameter*subgroup factor, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry. If the model did still not converge, interactions were removed in the order treatment * subgroup factor * visit, subgroup factor * visit.

Analysis methods for within-subgroup analysis:
Adjusted mean (LS Mean) change from baseline and overall effect obtained from MMRM with unstructured covariance matrix:
change from baseline = treatment + visit + treatment * visit + baseline value
ET was the reference group for treatment group comparison.
If the model did not converge for a parameter*subgroup factor, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry.

Patients with an evaluable baseline score and at least one evaluable post-baseline score were included in the analysis.
All data collected were included in the analysis, including assessments at confirmation of first recurrence and thereafter, as long as there were at least 50 patients in each treatment group at a visit in the overall (sub-)population.

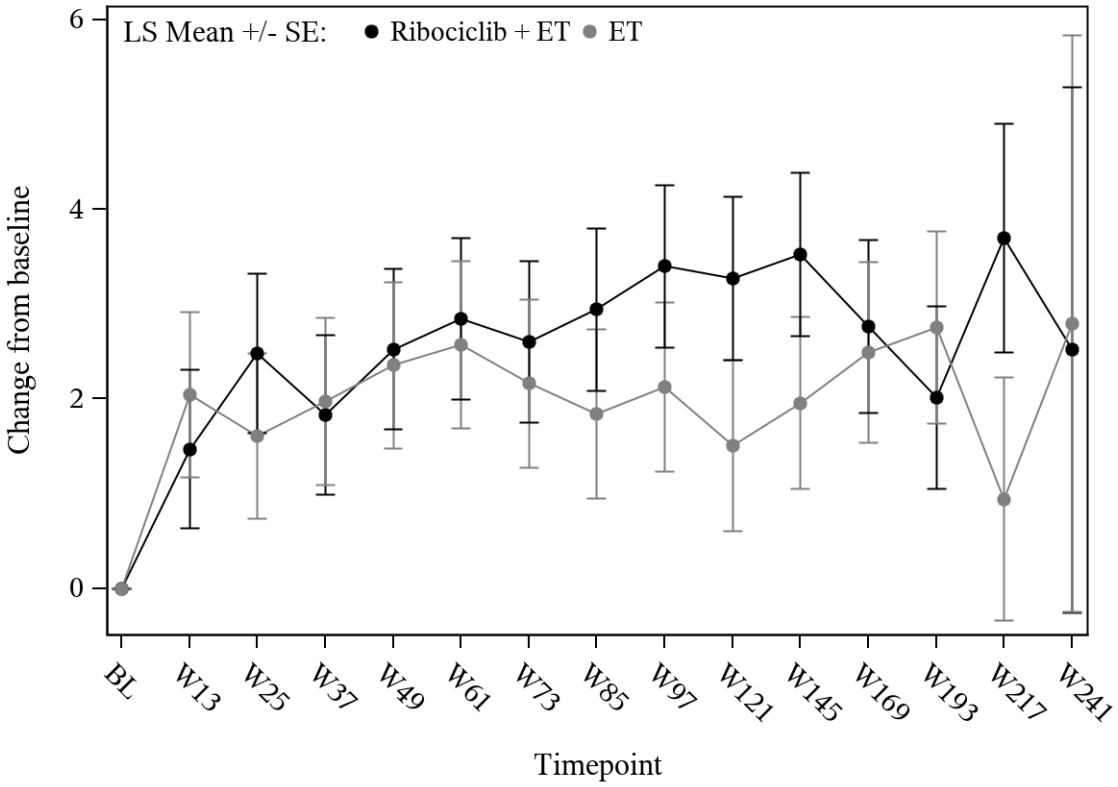
Figure 5-2.1.1.1 QLQ-C30 - Fatigue: line chart of change from baseline - subgroup analysis (Full Analysis Set)

QLQ-C30 - Fatigue
Region: NA/WE/O



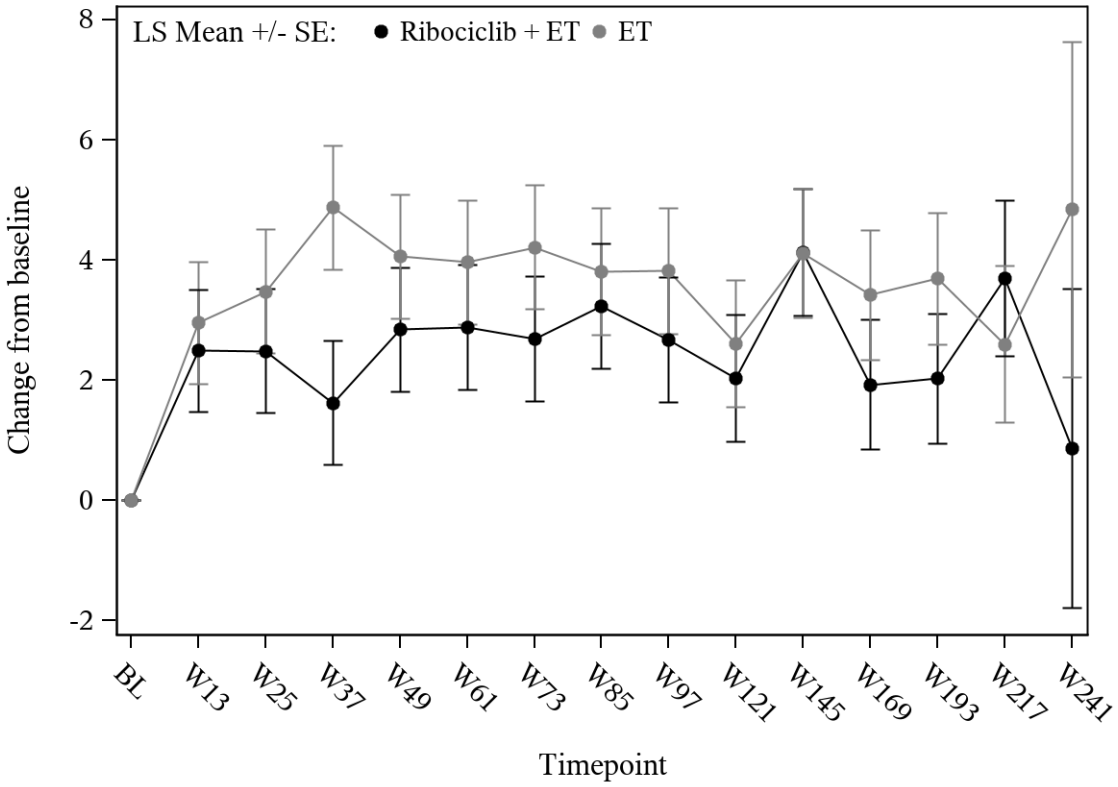
Ribociclib + ET	599	567	530	539	529	529	520	510	504	481	482	386	317	190	35
ET	577	539	503	506	511	501	495	474	471	461	441	365	305	188	32

QLQ-C30 - Fatigue
Region: ROW



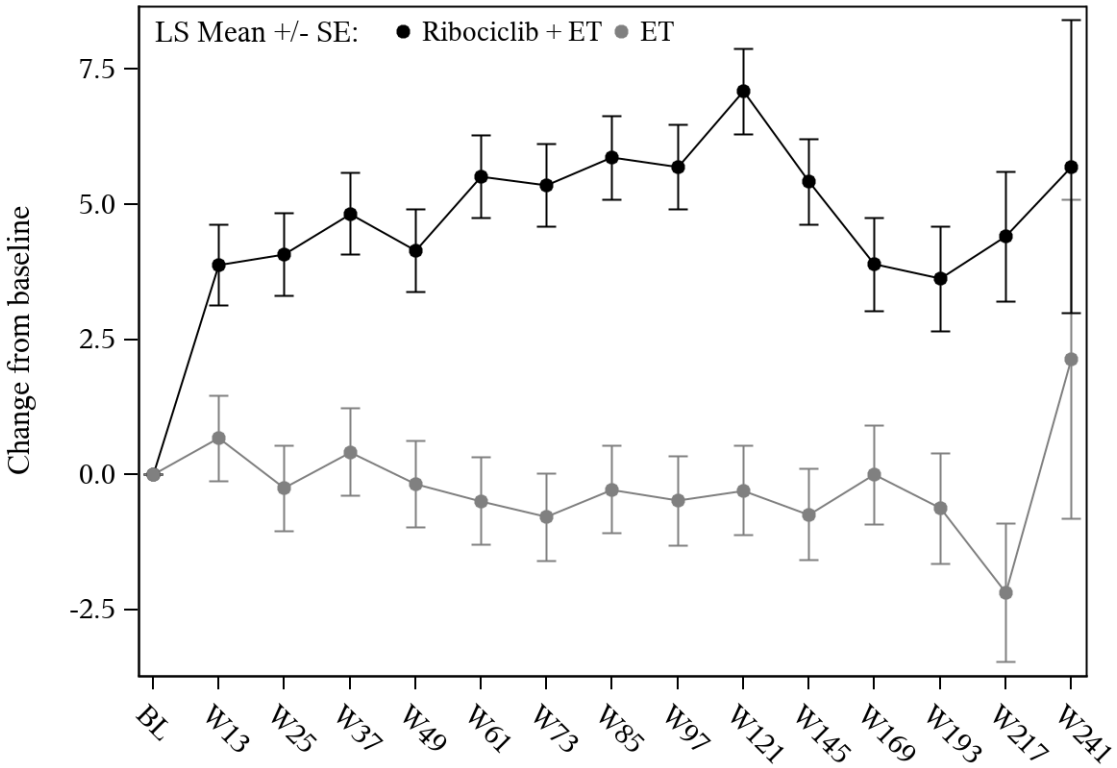
Ribociclib + ET	460	460	451	447	444	436	436	433	430	422	418	341	293	154	23
ET	427	425	418	406	411	402	398	395	388	380	369	316	260	135	19

QLQ-C30 - Fatigue
AJCC Anatomic Stage Group: Group I/II



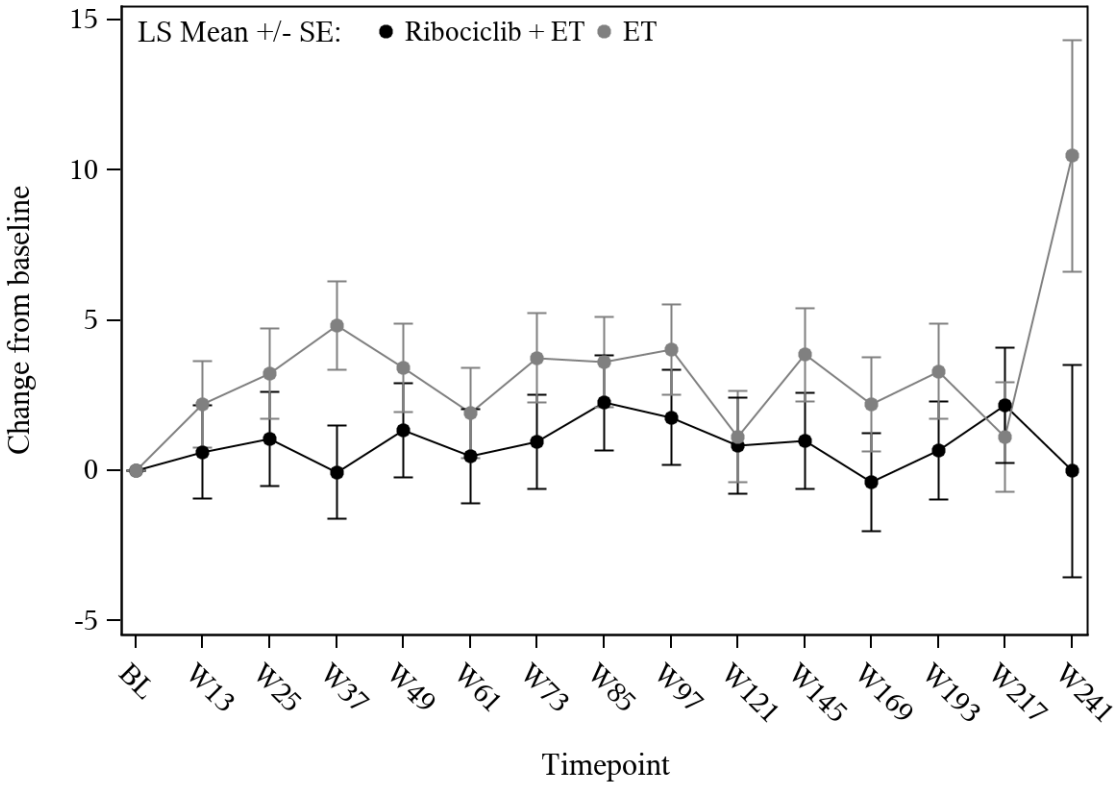
Ribociclib + ET	394	384	368	365	362	360	356	355	352	341	340	315	315	176	31
ET	398	381	350	365	367	359	360	341	346	334	321	315	302	175	28

QLQ-C30 - Fatigue
AJCC Anatomic Stage Group: Group III



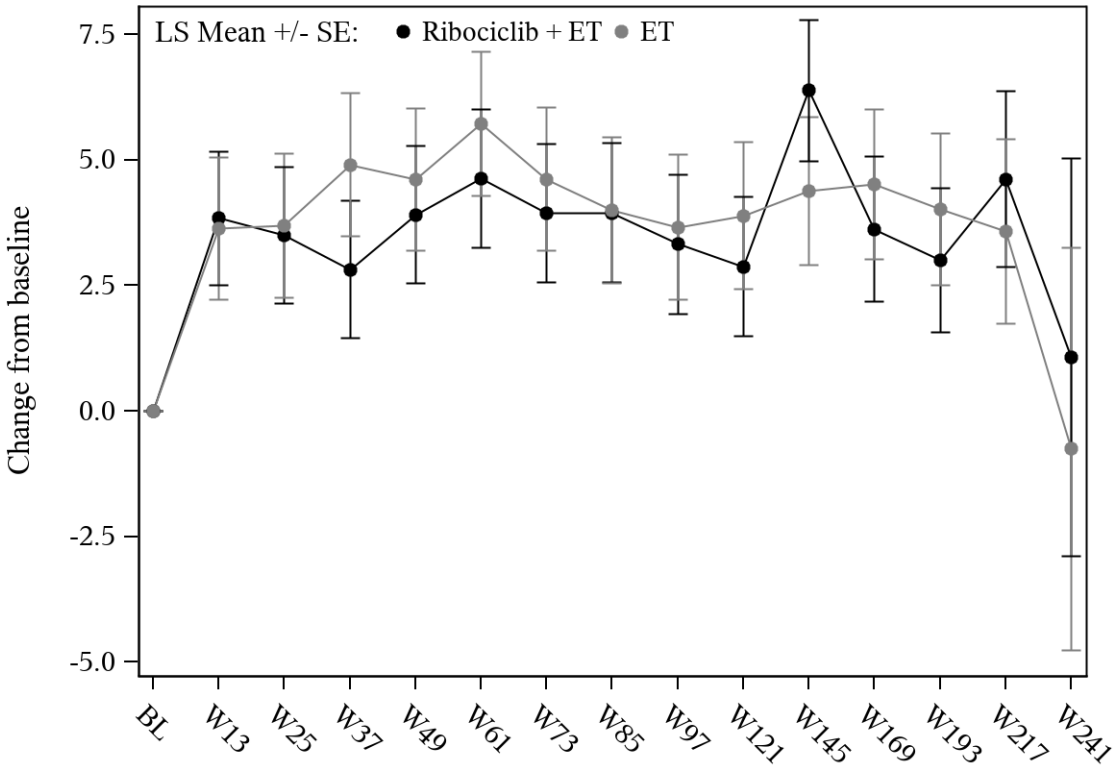
Ribociclib + ET	665	643	613	621	611	605	600	588	582	562	560	412	295	168	27
ET	606	583	571	547	555	544	533	528	513	507	489	366	263	148	23

QLQ-C30 - Fatigue
Anatomic stages: IA/IB/IIA



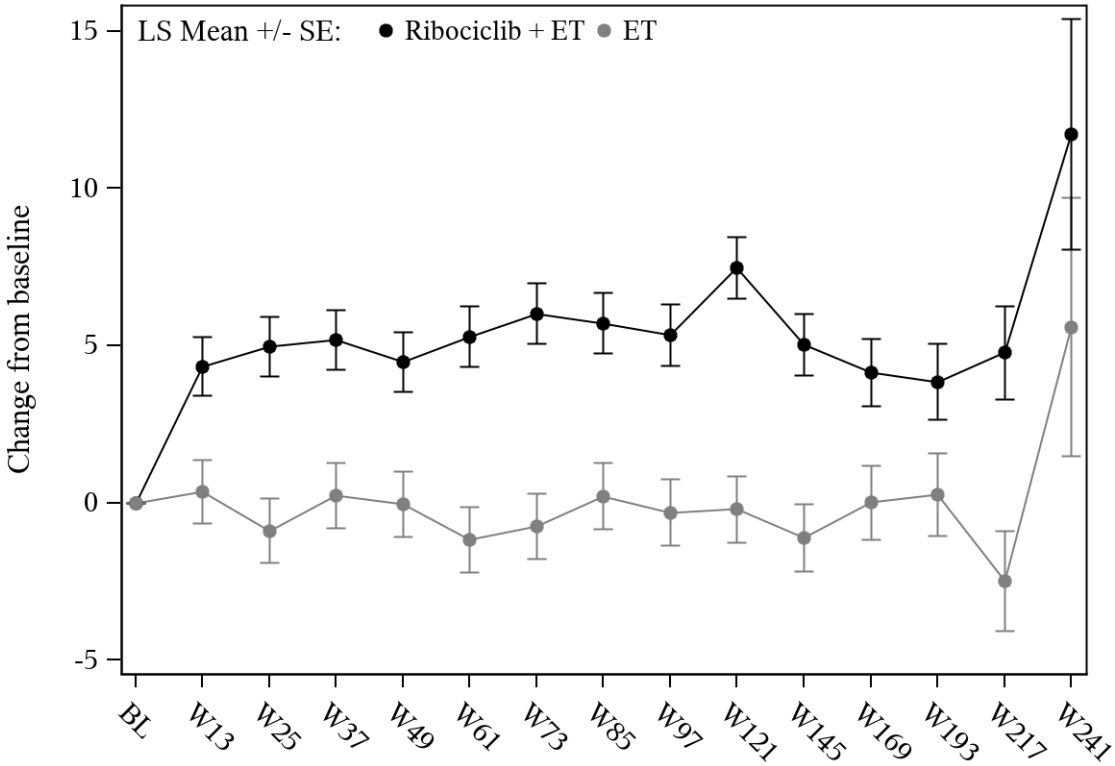
Ribociclib + ET	163	159	154	154	153	155	151	152	148	142	143	138	135	79	17
ET	188	183	160	169	170	166	169	161	161	155	147	147	139	87	14

QLQ-C30 - Fatigue
Anatomic stages: IIB



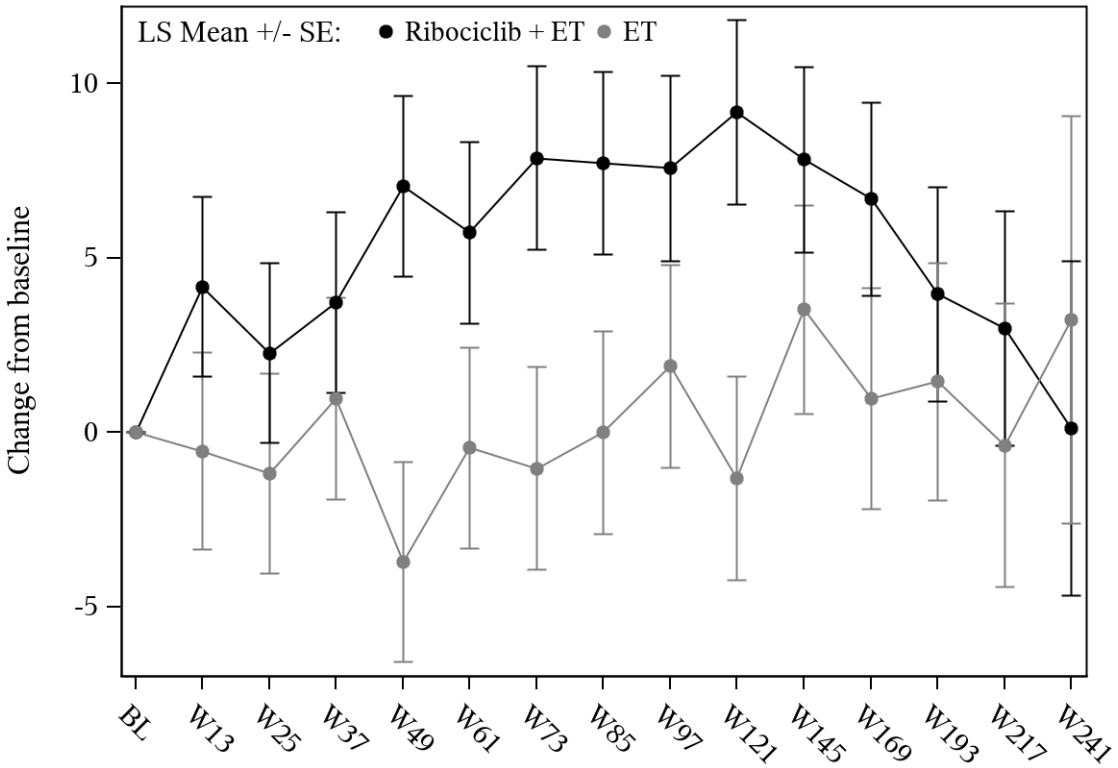
Ribociclib + ET	231	225	214	211	209	205	205	203	204	199	197	177	180	97	14
ET	210	198	190	196	197	193	191	180	185	179	174	168	163	88	14

QLQ-C30 - Fatigue
Anatomic stages: IIIA



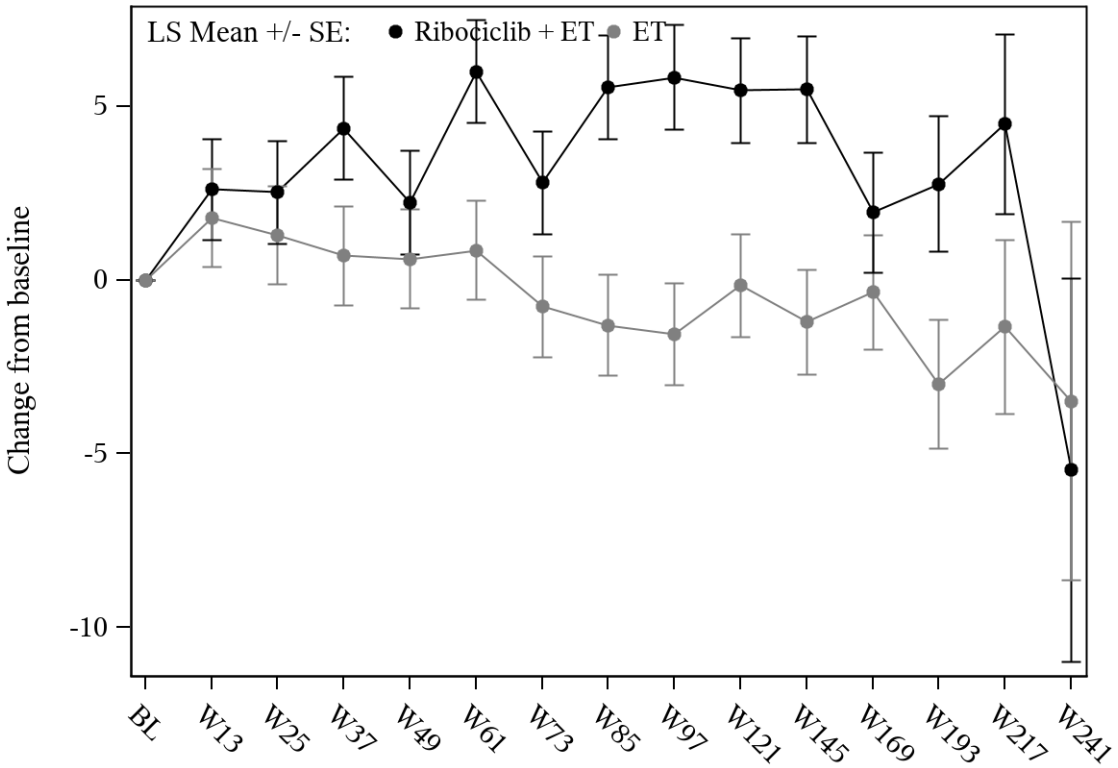
Ribociclib + ET	433	416	391	400	393	389	385	375	374	357	360	269	197	112	15
ET	368	355	343	330	336	329	327	322	313	308	304	225	162	99	12

QLQ-C30 - Fatigue
Anatomic stages: IIIB



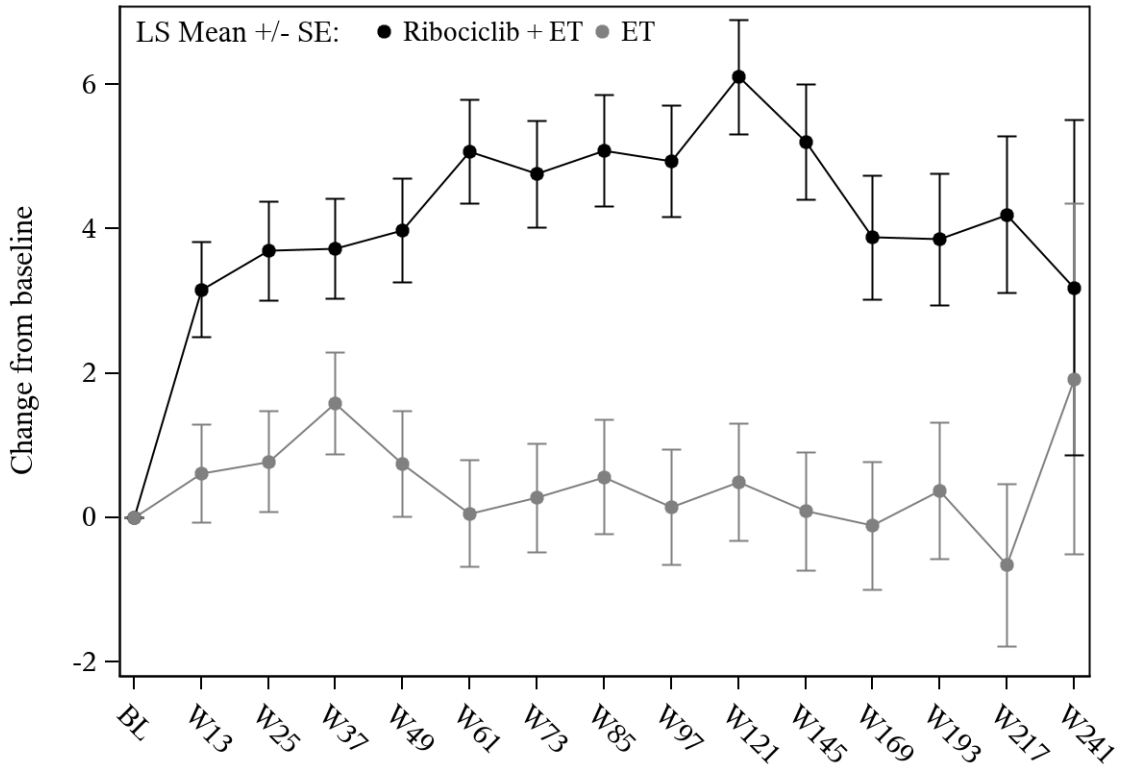
Ribociclib + ET	63	61	62	61	60	59	58	59	56	57	57	46	31	23	6
ET	52	52	49	47	49	49	46	47	47	46	42	33	25	14	4

QLQ-C30 - Fatigue
Anatomic stages: IIIC



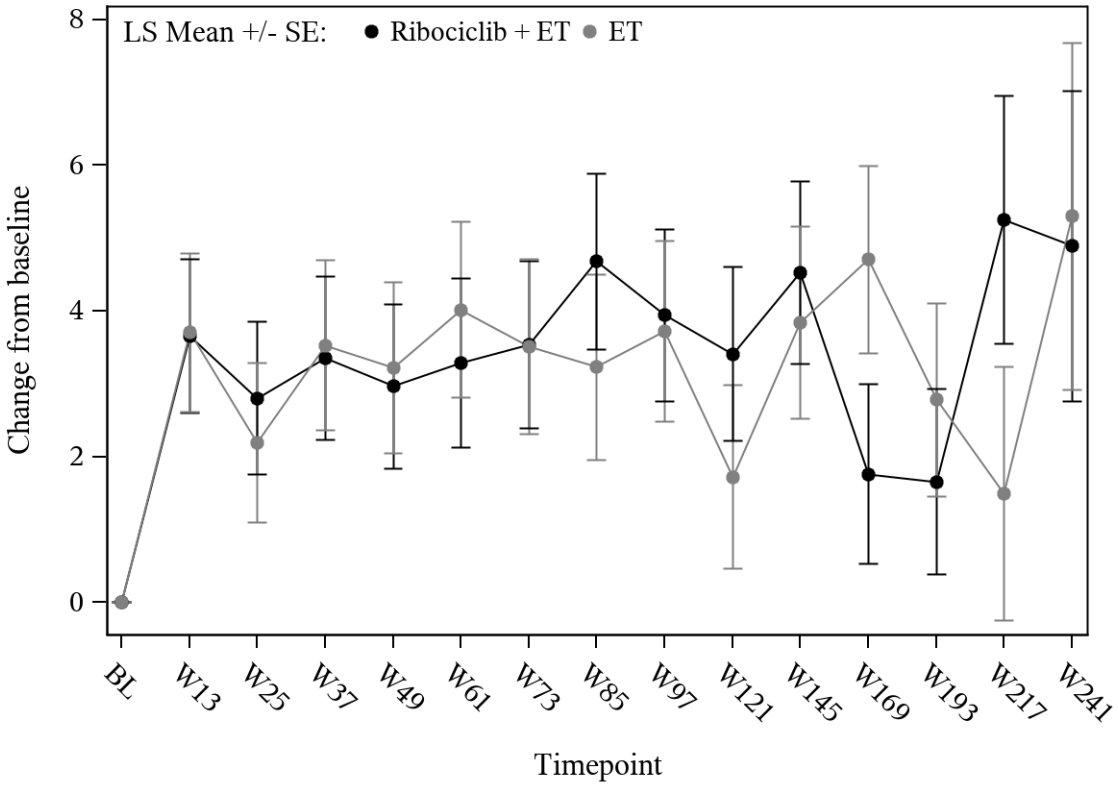
Ribociclib + ET	169	166	160	160	158	157	157	154	152	148	143	97	67	33	6
ET	186	176	179	170	170	166	160	159	153	153	143	108	76	35	7

QLQ-C30 - Fatigue
Prior mastectomy: Yes



Ribociclib + ET	737	711	680	679	668	665	657	648	640	619	613	490	404	232	40
ET	699	666	650	637	647	631	624	610	599	590	560	461	376	213	37

QLQ-C30 - Fatigue
Prior mastectomy: No



Ribociclib + ET	322	316	301	307	305	300	299	295	294	284	287	237	206	112	18
ET	305	298	271	275	275	272	269	259	260	251	250	220	189	110	14

Table 5-2.1.2.1 QLQ-C30 - Nausea and Vomiting: change from baseline analysis - subgroup analysis (Full Analysis Set)

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1115)	ET (N = 1123)	Parameter	Esti-mate	[95% CI]	p-value
QLQ-C30 - Nausea and Vomiting						
	N' | LS Mean (SE)	N' | LS Mean (SE)				
Region						
Interaction test	**p = 0.027**					
NA/WE/O	599 | 2.93 (0.31)	578 | 1.31 (0.32)	Difference	1.62	[0.75; 2.50]	<.001
			Hedges G	0.21	[0.10; 0.33]	
ROW	460 | 1.47 (0.31)	427 | 1.23 (0.33)	Difference	0.24	[-0.64; 1.13]	0.589
			Hedges G	0.04	[-0.10; 0.17]	
Geographical region						
Interaction test	**N.E.**					
Europe	618 | 2.57 (0.32)	593 | 1.58 (0.32)	Difference	0.99	[0.11; 1.88]	0.028
			Hedges G	0.13	[0.01; 0.24]	
North America/Australia	203 | 2.44 (0.45)	177 | 0.85 (0.50)	Difference	1.59	[0.28; 2.90]	0.018
			Hedges G	0.24	[0.04; 0.45]	
Asia	175 | N.E.	166 | N.E.	Difference	N.E.	[N.E.]	N.E.
			Hedges G	N.E.	[N.E.]	
Latin America	63 | 1.53 (0.95)	69 | 0.46 (0.89)	Difference	1.07	[-1.51; 3.65]	0.414
			Hedges G	0.14	[-0.20; 0.48]	
Age group 1 at randomization						
Interaction test	**p = 0.493**					
<45	525 | 2.25 (0.33)	459 | 1.63 (0.34)	Difference	0.62	[-0.32; 1.55]	0.196
			Hedges G	0.08	[-0.04; 0.21]	
45 to 54	514 | 2.28 (0.34)	519 | 1.01 (0.34)	Difference	1.27	[0.33; 2.21]	0.008
			Hedges G	0.16	[0.04; 0.29]	
55 to 64	20 | N.E.	27 | N.E.	Difference	N.E.	[N.E.]	N.E.
			Hedges G	N.E.	[N.E.]	
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)						
Interaction test	**p = 0.425**					
<Median	525 | 2.34 (0.32)	459 | 1.53 (0.33)	Difference	0.81	[-0.09; 1.71]	0.077
			Hedges G	0.11	[-0.01; 0.24]	
≥Median	534 | 2.38 (0.32)	546 | 1.14 (0.32)	Difference	1.24	[0.34; 2.13]	0.007
			Hedges G	0.17	[0.05; 0.28]	

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1115)	**ET (N = 1123)**	**Parameter**	**Esti-mate**	**[95% CI]**	**p-value**
Race						
Interaction test	**p = 0.912**					
Asian	206 | 1.95 (0.50)	180 | 1.31 (0.54)	Difference	0.64	[-0.82; 2.10]	0.389
			Hedges G	0.09	[-0.11; 0.29]	
Non-Asian	802 | 2.21 (0.25)	773 | 1.35 (0.26)	Difference	0.87	[0.15; 1.58]	0.018
			Hedges G	0.12	[0.02; 0.22]	
BMI at screening						
Interaction test	**p = 0.170**					
≥25	529 | 2.99 (0.35)	489 | 1.63 (0.37)	Difference	1.36	[0.37; 2.35]	0.007
			Hedges G	0.17	[0.05; 0.29]	
<25	518 | 1.65 (0.28)	505 | 1.02 (0.28)	Difference	0.63	[-0.15; 1.41]	0.113
			Hedges G	0.10	[-0.02; 0.22]	
AJCC Anatomic Stage Group						
Interaction test	**p = 0.003**					
Group I/II	394 | 2.06 (0.33)	399 | 1.87 (0.33)	Difference	0.19	[-0.74; 1.12]	0.689
			Hedges G	0.03	[-0.11; 0.17]	
Group III	665 | 2.51 (0.30)	606 | 0.95 (0.32)	Difference	1.57	[0.70; 2.44]	<.001
			Hedges G	0.20	[0.09; 0.31]	
Anatomic stages						
Interaction test	**N.E.**					
IA/IB/IIA	163 | 1.57 (0.51)	189 | 2.09 (0.49)	Difference	-0.52	[-1.91; 0.86]	0.456
			Hedges G	-0.08	[-0.29; 0.13]	
IIB	231 | 2.50 (0.47)	210 | 1.46 (0.49)	Difference	1.04	[-0.29; 2.37]	0.124
			Hedges G	0.15	[-0.04; 0.33]	
IIIA	433 | 2.77 (0.39)	368 | 0.84 (0.42)	Difference	1.93	[0.81; 3.06]	<.001
			Hedges G	0.24	[0.10; 0.38]	
IIIB	63 | 2.79 (1.24)	52 | 0.28 (1.38)	Difference	2.51	[-1.17; 6.18]	0.179
			Hedges G	0.25	[-0.12; 0.62]	
IIIC	169 | 1.21 (0.59)	186 | 1.24 (0.56)	Difference	-0.03	[-1.62; 1.57]	0.975
			Hedges G	-0.00	[-0.21; 0.20]	
Nodal status						
Interaction test	**p = 0.685**					
N0	84 | 1.47 (0.73)	110 | 1.04 (0.65)	Difference	0.43	[-1.49; 2.36]	0.657
			Hedges G	0.06	[-0.22; 0.35]	
N1-N3	975 | 2.28 (0.24)	892 | 1.31 (0.25)	Difference	0.97	[0.31; 1.64]	0.004
			Hedges G	0.13	[0.04; 0.22]	

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1115)	**ET (N = 1123)**	**Parameter**	**Esti-mate**	**[95% CI]**	**p-value**
Histological grade at time of surgery						
Interaction test	**p = 0.788**					
Grade 1	106 | 2.12 (0.69)	97 | 1.52 (0.73)	Difference	0.60	[-1.38; 2.57]	0.552
			Hedges G	0.08	[-0.19; 0.36]	
Grade 2	579 | 2.36 (0.31)	559 | 1.33 (0.31)	Difference	1.03	[0.17; 1.89]	0.019
			Hedges G	0.14	[0.02; 0.26]	
Grade 3	282 | 2.12 (0.39)	252 | 1.56 (0.41)	Difference	0.56	[-0.55; 1.66]	0.324
			Hedges G	0.09	[-0.08; 0.26]	
Histological subtype						
Interaction test	**N.E.**					
Ductal	822 | 2.29 (0.26)	787 | 1.27 (0.27)	Difference	1.02	[0.28; 1.76]	0.007
			Hedges G	0.14	[0.04; 0.23]	
Lobular	168 | 2.61 (0.66)	156 | 0.93 (0.71)	Difference	1.67	[-0.24; 3.58]	0.086
			Hedges G	0.19	[-0.03; 0.41]	
Other	69 | N.E.	62 | N.E.	Difference	N.E.	[N.E.]	N.E.
			Hedges G	N.E.	[N.E.]	
Ki67 status from surgical specimen						
Interaction test	**p = 0.390**					
Ki67≤20	510 | 2.52 (0.31)	517 | 1.59 (0.31)	Difference	0.94	[0.07; 1.81]	0.034
			Hedges G	0.13	[0.01; 0.25]	
Ki67>20	400 | 2.02 (0.37)	359 | 1.63 (0.39)	Difference	0.39	[-0.66; 1.44]	0.470
			Hedges G	0.05	[-0.09; 0.20]	
Type of NSAI						
Interaction test	**p = 0.242**					
Letrozole	775 | 2.48 (0.28)	721 | 1.33 (0.30)	Difference	1.15	[0.34; 1.95]	0.005
			Hedges G	0.14	[0.04; 0.25]	
Anastrozole	284 | 1.73 (0.42)	282 | 1.37 (0.43)	Difference	0.35	[-0.83; 1.53]	0.555
			Hedges G	0.05	[-0.12; 0.21]	
Prior neo/adjuvant chemotherapy						
Interaction test	**p = 0.822**					
Yes	984 | 2.18 (0.25)	927 | 1.29 (0.25)	Difference	0.89	[0.19; 1.58]	0.012
			Hedges G	0.11	[0.03; 0.20]	
No	75 | 3.17 (0.77)	78 | 1.94 (0.78)	Difference	1.23	[-0.93; 3.39]	0.263
			Hedges G	0.18	[-0.14; 0.50]	
Prior adjuvant chemotherapy						
Interaction test	**p = 0.105**					
Yes	494 | 1.76 (0.30)	463 | 1.32 (0.31)	Difference	0.44	[-0.40; 1.29]	0.305
			Hedges G	0.07	[-0.06; 0.19]	
No	565 | 2.82 (0.33)	542 | 1.25 (0.34)	Difference	1.57	[0.63; 2.50]	0.001
			Hedges G	0.20	[0.08; 0.32]	

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1115)	ET (N = 1123)	Parameter	Esti-mate	[95% CI]	p-value
Prior neoadjuvant chemotherapy						
Interaction test	**p = 0.143**					
Yes	520 | 2.53 (0.36)	502 | 1.16 (0.36)	Difference	1.37	[0.37; 2.37]	0.007
			Hedges G	0.17	[0.05; 0.29]	
No	539 | 2.04 (0.31)	503 | 1.53 (0.32)	Difference	0.51	[-0.36; 1.39]	0.250
			Hedges G	0.07	[-0.05; 0.19]	
Prior endocrine therapy						
Interaction test	**p = 0.694**					
Yes	815 | 2.39 (0.27)	735 | 1.33 (0.29)	Difference	1.05	[0.27; 1.83]	0.008
			Hedges G	0.14	[0.04; 0.23]	
No	244 | 1.90 (0.47)	270 | 1.36 (0.44)	Difference	0.54	[-0.73; 1.80]	0.404
			Hedges G	0.07	[-0.10; 0.25]	
Prior mastectomy						
Interaction test	**p = 0.542**					
Yes	737 | 2.42 (0.29)	699 | 1.38 (0.30)	Difference	1.04	[0.23; 1.85]	0.012
			Hedges G	0.13	[0.03; 0.24]	
No	322 | 1.92 (0.40)	306 | 1.29 (0.42)	Difference	0.63	[-0.50; 1.77]	0.272
			Hedges G	0.09	[-0.07; 0.24]	
Prior radiotherapy						
Interaction test	**p = 0.474**					
Yes	970 | 2.17 (0.25)	923 | 1.19 (0.26)	Difference	0.98	[0.28; 1.69]	0.006
			Hedges G	0.13	[0.04; 0.22]	
No	89 | 2.60 (0.70)	82 | 2.47 (0.74)	Difference	0.13	[-1.88; 2.15]	0.895
			Hedges G	0.02	[-0.28; 0.32]	

N: Number of patients
N': Number of patients in the analysis
CI: Confidence interval
SD: Standard deviation
LS Mean: Least square mean
SE: Standard error
MMRM: Mixed model for repeated measures
N.E.: Not estimable
ET: Endocrine therapy (Anastrozole/Letrozole + Goserelin)
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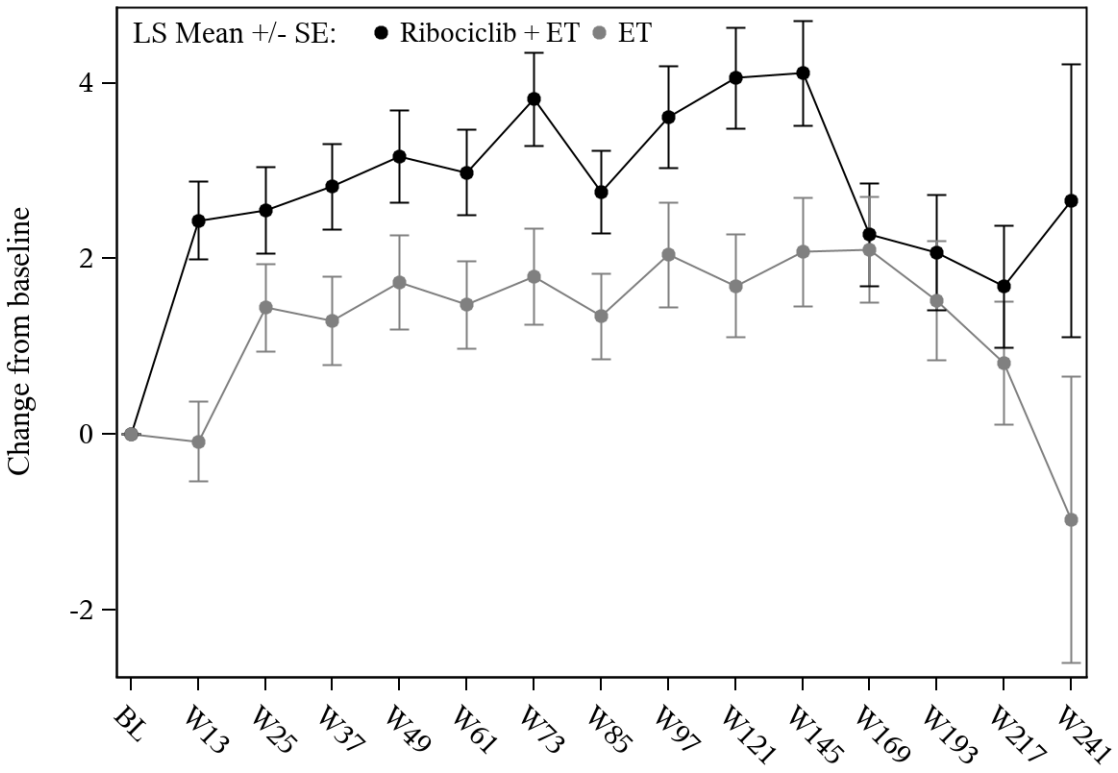
Analysis method for interaction test:
p-value from MMRM with unstructured covariance matrix:
change from baseline = treatment + visit + treatment * visit + subgroup factor + treatment * subgroup factor + subgroup factor * visit + treatment * subgroup factor * visit + baseline value
If the model did not converge for a parameter*subgroup factor, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry. If the model did still not converge, interactions were removed in the order treatment * subgroup factor * visit, subgroup factor * visit.

Analysis methods for within-subgroup analysis:
Adjusted mean (LS Mean) change from baseline and overall effect obtained from MMRM with unstructured covariance matrix:
change from baseline = treatment + visit + treatment * visit + baseline value
ET was the reference group for treatment group comparison.
If the model did not converge for a parameter*subgroup factor, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry.

Patients with an evaluable baseline score and at least one evaluable post-baseline score were included in the analysis.
All data collected were included in the analysis, including assessments at confirmation of first recurrence and thereafter, as long as there were at least 50 patients in each treatment group at a visit in the overall (sub-)population.

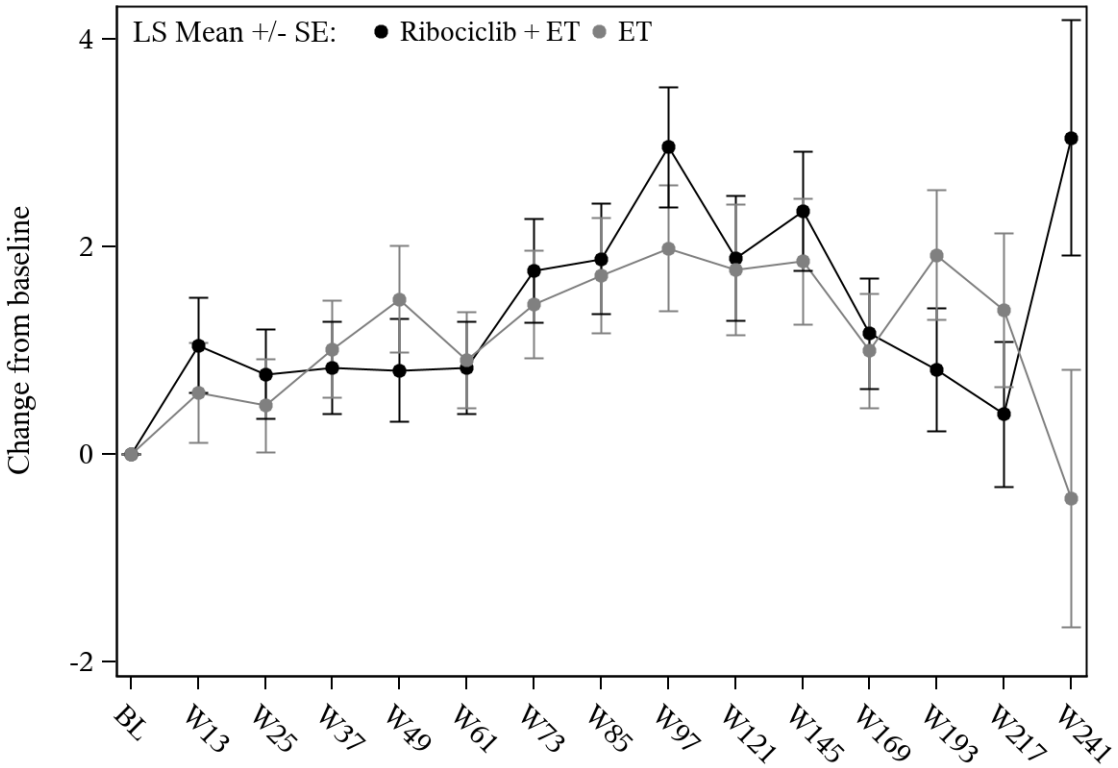
Figure 5-2.1.2.1 QLQ-C30 - Nausea and Vomiting: line chart of change from baseline - subgroup analysis (Full Analysis Set)

QLQ-C30 - Nausea and Vomiting
Region: NA/WE/O



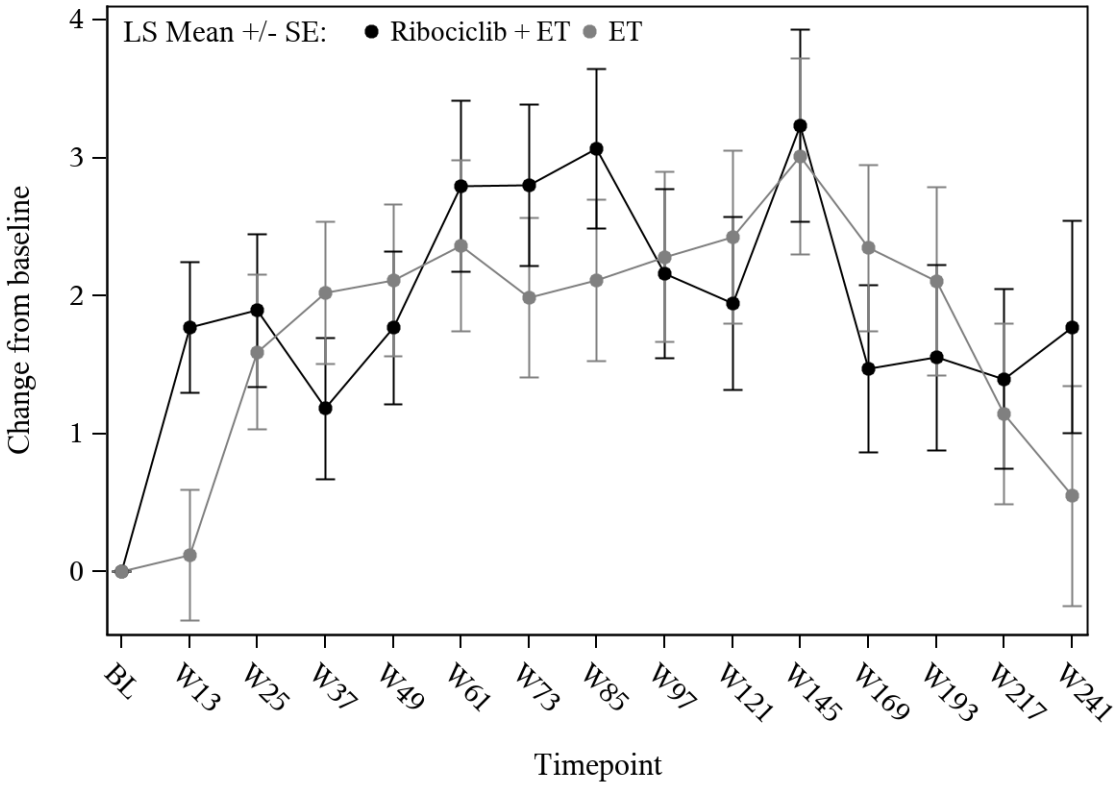
Ribociclib + ET	599	568	530	539	529	529	520	511	502	481	482	386	317	190	35
ET	578	540	504	507	512	502	496	475	472	462	442	367	306	188	32

QLQ-C30 - Nausea and Vomiting
Region: ROW



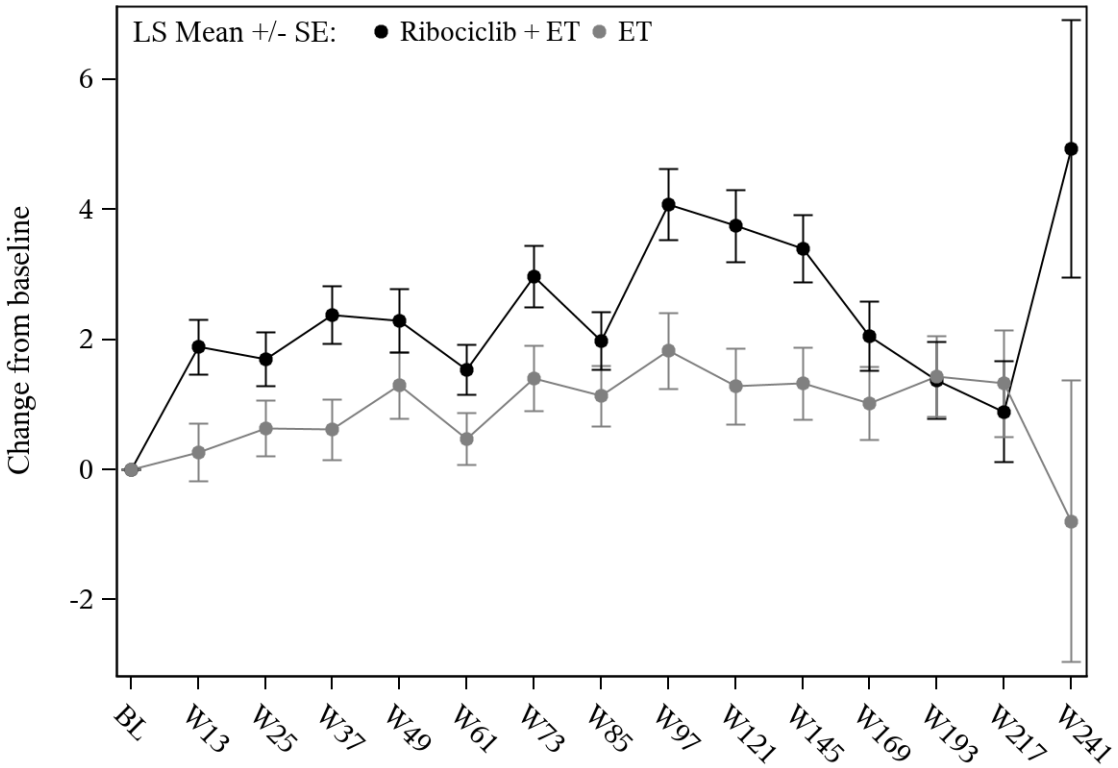
Ribociclib + ET	460	460	451	447	444	436	436	433	430	422	418	341	293	154	23
ET	427	425	418	406	411	402	398	395	388	380	369	316	260	135	19

QLQ-C30 - Nausea and Vomiting
AJCC Anatomic Stage Group: Group I/II



Ribociclib + ET	394	384	368	365	362	360	356	355	351	341	340	315	315	176	31
ET	399	382	351	366	368	360	361	342	347	335	322	317	303	175	28

QLQ-C30 - Nausea and Vomiting
AJCC Anatomic Stage Group: Group III



Ribociclib + ET	665	644	613	621	611	605	600	589	581	562	560	412	295	168	27
ET	606	583	571	547	555	544	533	528	513	507	489	366	263	148	23

Table 5-2.1.3.1 QLQ-C30 - Pain: change from baseline analysis - subgroup analysis (Full Analysis Set)

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1115)	ET (N = 1123)	Parameter	Esti-mate	[95% CI]	p-value
QLQ-C30 - Pain						
	N' | LS Mean (SE)	N' | LS Mean (SE)				
Region						
Interaction test	**p = 0.049**					
NA/WE/O	600 | 5.05 (0.73)	578 | 2.55 (0.75)	Difference	2.50	[0.44; 4.56]	0.017
			Hedges G	0.14	[0.02; 0.25]	
ROW	460 | 1.49 (0.68)	426 | 2.14 (0.72)	Difference	-0.65	[-2.60; 1.30]	0.513
			Hedges G	-0.04	[-0.18; 0.09]	
Geographical region						
Interaction test	**p = 0.076**					
Europe	619 | 4.35 (0.68)	593 | 3.95 (0.69)	Difference	0.40	[-1.50; 2.30]	0.677
			Hedges G	0.02	[-0.09; 0.14]	
North America/Australia	203 | 2.84 (1.01)	177 | -1.59 (1.11)	Difference	4.43	[1.48; 7.38]	0.003
			Hedges G	0.30	[0.10; 0.51]	
Asia	175 | N.E.	166 | N.E.	Difference	N.E.	[N.E.]	N.E.
			Hedges G	N.E.	[N.E.]	
Latin America	63 | 3.90 (2.21)	68 | 6.72 (2.10)	Difference	-2.82	[-8.86; 3.22]	0.358
			Hedges G	-0.16	[-0.50; 0.18]	
Age group 1 at randomization						
Interaction test	**p = 0.939**					
<45	525 | N.E.	459 | N.E.	Difference	N.E.	[N.E.]	N.E.
			Hedges G	N.E.	[N.E.]	
45 to 54	515 | 3.79 (0.74)	518 | 2.79 (0.75)	Difference	1.00	[-1.08; 3.07]	0.347
			Hedges G	0.06	[-0.06; 0.18]	
55 to 64	20 | 1.41 (3.59)	27 | -3.02 (3.16)	Difference	4.44	[-5.22; 14.10]	0.360
			Hedges G	0.27	[-0.31; 0.85]	
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)						
Interaction test	**p = 0.945**					
<Median	525 | 2.63 (0.70)	459 | 2.30 (0.74)	Difference	0.33	[-1.67; 2.33]	0.746
			Hedges G	0.02	[-0.10; 0.15]	
≥Median	535 | 3.81 (0.75)	545 | 2.68 (0.75)	Difference	1.13	[-0.95; 3.20]	0.287
			Hedges G	0.06	[-0.05; 0.18]	

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1115)	**ET (N = 1123)**	**Parameter**	**Esti-mate**	**[95% CI]**	**p-value**
Race						
Interaction test	**p = 0.998**					
Asian	206 | -0.64 (0.91)	180 | -1.18 (0.98)	Difference	0.54	[-2.09; 3.17]	0.688
			Hedges G	0.04	[-0.16; 0.24]	
Non-Asian	803 | 3.69 (0.57)	772 | 3.06 (0.58)	Difference	0.62	[-0.98; 2.23]	0.445
			Hedges G	0.04	[-0.06; 0.14]	
BMI at screening						
Interaction test	**p = 0.617**					
≥25	530 | 5.08 (0.78)	488 | 3.76 (0.82)	Difference	1.32	[-0.91; 3.56]	0.245
			Hedges G	0.07	[-0.05; 0.20]	
<25	518 | 1.16 (0.65)	505 | 1.30 (0.66)	Difference	-0.14	[-1.95; 1.66]	0.876
			Hedges G	-0.01	[-0.13; 0.11]	
AJCC Anatomic Stage Group						
Interaction test	**p = <.001**					
Group I/II	395 | 2.46 (0.81)	398 | 5.48 (0.82)	Difference	-3.02	[-5.28; -0.76]	0.009
			Hedges G	-0.19	[-0.33; -0.05]	
Group III	665 | 3.80 (0.67)	606 | 0.58 (0.70)	Difference	3.22	[1.31; 5.12]	<.001
			Hedges G	0.19	[0.08; 0.30]	
Anatomic stages						
Interaction test	**p = <.001**					
IA/IB/IIA	164 | 0.77 (1.22)	189 | 7.20 (1.17)	Difference	-6.43	[-9.76; -3.10]	<.001
			Hedges G	-0.41	[-0.62; -0.19]	
IIB	231 | 3.53 (1.03)	209 | 3.96 (1.08)	Difference	-0.43	[-3.37; 2.52]	0.776
			Hedges G	-0.03	[-0.21; 0.16]	
IIIA	433 | 4.29 (0.80)	368 | 1.38 (0.87)	Difference	2.92	[0.60; 5.23]	0.014
			Hedges G	0.18	[0.04; 0.31]	
IIIB	63 | 3.32 (2.25)	52 | 2.19 (2.49)	Difference	1.13	[-5.59; 7.86]	0.739
			Hedges G	0.06	[-0.30; 0.43]	
IIIC	169 | 3.35 (1.24)	186 | -1.56 (1.18)	Difference	4.91	[1.55; 8.27]	0.004
			Hedges G	0.31	[0.10; 0.51]	
Nodal status						
Interaction test	**p = 0.606**					
N0	84 | 4.64 (1.51)	110 | 4.59 (1.33)	Difference	0.05	[-3.93; 4.04]	0.978
			Hedges G	0.00	[-0.28; 0.29]	
N1-N3	976 | 3.25 (0.55)	891 | 2.31 (0.57)	Difference	0.94	[-0.62; 2.49]	0.239
			Hedges G	0.05	[-0.04; 0.15]	

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1115)	**ET (N = 1123)**	**Parameter**	**Esti-mate**	**[95% CI]**	**p-value**
Histological grade at time of surgery						
Interaction test	**p = 0.854**					
Grade 1	106 | 3.00 (1.44)	97 | 3.39 (1.52)	Difference	-0.40	[-4.53; 3.74]	0.850
			Hedges G	-0.03	[-0.30; 0.25]	
Grade 2	580 | 2.90 (0.66)	559 | 2.18 (0.68)	Difference	0.72	[-1.14; 2.59]	0.446
			Hedges G	0.05	[-0.07; 0.16]	
Grade 3	282 | 3.80 (0.94)	251 | 2.71 (0.99)	Difference	1.09	[-1.59; 3.77]	0.426
			Hedges G	0.07	[-0.10; 0.24]	
Histological subtype						
Interaction test	**p = 0.810**					
Ductal	823 | 3.05 (0.56)	787 | 2.59 (0.58)	Difference	0.46	[-1.12; 2.04]	0.565
			Hedges G	0.03	[-0.07; 0.13]	
Lobular	168 | 4.24 (1.33)	156 | 1.77 (1.38)	Difference	2.46	[-1.32; 6.25]	0.201
			Hedges G	0.14	[-0.08; 0.36]	
Other	69 | 4.80 (1.89)	61 | 3.07 (2.08)	Difference	1.73	[-3.83; 7.29]	0.539
			Hedges G	0.11	[-0.24; 0.45]	
Ki67 status from surgical specimen						
Interaction test	**p = 0.935**					
Ki67≤20	510 | 2.93 (0.70)	517 | 2.41 (0.70)	Difference	0.52	[-1.43; 2.47]	0.599
			Hedges G	0.03	[-0.09; 0.16]	
Ki67>20	401 | 3.57 (0.79)	358 | 3.32 (0.84)	Difference	0.25	[-2.03; 2.52]	0.832
			Hedges G	0.02	[-0.13; 0.16]	
Type of NSAI						
Interaction test	**p = 0.099**					
Letrozole	775 | 3.00 (0.58)	720 | 3.15 (0.61)	Difference	-0.15	[-1.81; 1.51]	0.858
			Hedges G	-0.01	[-0.11; 0.09]	
Anastrozole	285 | 4.26 (1.04)	282 | 1.38 (1.05)	Difference	2.88	[-0.02; 5.78]	0.052
			Hedges G	0.16	[-0.00; 0.33]	
Prior neo/adjuvant chemotherapy						
Interaction test	**p = 0.547**					
Yes	985 | 3.31 (0.52)	926 | 2.44 (0.54)	Difference	0.87	[-0.60; 2.34]	0.247
			Hedges G	0.05	[-0.04; 0.14]	
No	75 | 2.50 (1.73)	78 | 3.03 (1.74)	Difference	-0.53	[-5.38; 4.32]	0.830
			Hedges G	-0.03	[-0.35; 0.28]	
Prior adjuvant chemotherapy						
Interaction test	**p = 0.415**					
Yes	495 | 3.76 (0.71)	462 | 2.43 (0.73)	Difference	1.33	[-0.67; 3.33]	0.191
			Hedges G	0.08	[-0.04; 0.21]	
No	565 | 2.80 (0.70)	542 | 2.58 (0.72)	Difference	0.23	[-1.74; 2.20]	0.820
			Hedges G	0.01	[-0.10; 0.13]	

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1115)	ET (N = 1123)	Parameter	Esti-mate	[95% CI]	p-value
Prior neoadjuvant chemotherapy						
Interaction test	**p = 0.679**					
Yes	520 | 2.88 (0.75)	502 | 2.49 (0.77)	Difference	0.38	[-1.72; 2.48]	0.721
			Hedges G	0.02	[-0.10; 0.14]	
No	540 | 3.68 (0.70)	502 | 2.72 (0.73)	Difference	0.96	[-1.03; 2.96]	0.343
			Hedges G	0.06	[-0.06; 0.18]	
Prior endocrine therapy						
Interaction test	**p = 0.019**					
Yes	816 | 3.18 (0.59)	734 | 1.86 (0.63)	Difference	1.31	[-0.38; 3.01]	0.129
			Hedges G	0.08	[-0.02; 0.18]	
No	244 | 3.26 (1.05)	270 | 4.77 (1.01)	Difference	-1.51	[-4.37; 1.36]	0.302
			Hedges G	-0.09	[-0.26; 0.08]	
Prior mastectomy						
Interaction test	**p = 0.013**					
Yes	737 | 3.38 (0.60)	698 | 1.50 (0.61)	Difference	1.88	[0.20; 3.55]	0.029
			Hedges G	0.12	[0.01; 0.22]	
No	323 | 3.03 (0.95)	306 | 5.09 (0.99)	Difference	-2.06	[-4.75; 0.64]	0.134
			Hedges G	-0.12	[-0.28; 0.04]	
Prior radiotherapy						
Interaction test	**p = 0.629**					
Yes	971 | 3.51 (0.55)	922 | 2.57 (0.56)	Difference	0.94	[-0.60; 2.48]	0.232
			Hedges G	0.05	[-0.04; 0.15]	
No	89 | 1.35 (1.62)	82 | 1.84 (1.71)	Difference	-0.50	[-5.15; 4.16]	0.834
			Hedges G	-0.03	[-0.33; 0.27]	

N: Number of patients
N': Number of patients in the analysis
CI: Confidence interval
SD: Standard deviation
LS Mean: Least square mean
SE: Standard error
MMRM: Mixed model for repeated measures
N.E.: Not estimable
ET: Endocrine therapy (Anastrozole/Letrozole + Goserelin)
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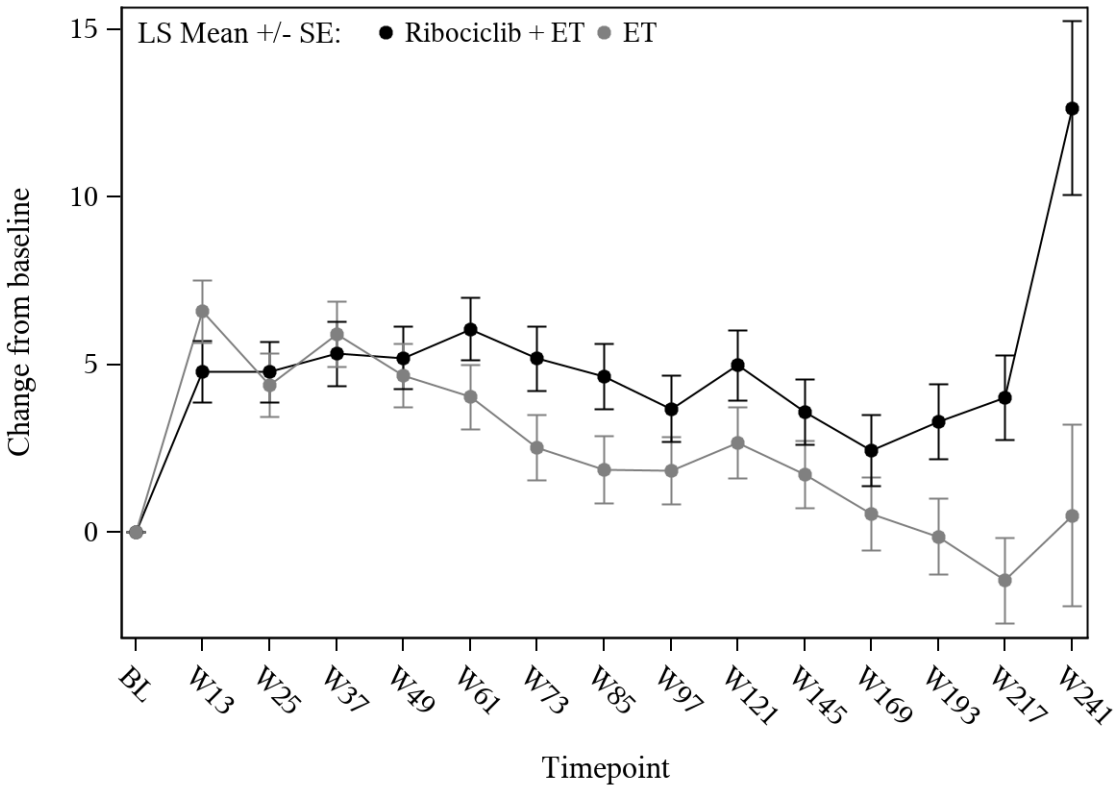
Analysis method for interaction test:
p-value from MMRM with unstructured covariance matrix:
change from baseline = treatment + visit + treatment * visit + subgroup factor + treatment * subgroup factor + subgroup factor * visit + treatment * subgroup factor * visit + baseline value
If the model did not converge for a parameter*subgroup factor, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry. If the model did still not converge, interactions were removed in the order treatment * subgroup factor * visit, subgroup factor * visit.

Analysis methods for within-subgroup analysis:
Adjusted mean (LS Mean) change from baseline and overall effect obtained from MMRM with unstructured covariance matrix:
change from baseline = treatment + visit + treatment * visit + baseline value
ET was the reference group for treatment group comparison.
If the model did not converge for a parameter*subgroup factor, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry.

Patients with an evaluable baseline score and at least one evaluable post-baseline score were included in the analysis.
All data collected were included in the analysis, including assessments at confirmation of first recurrence and thereafter, as long as there were at least 50 patients in each treatment group at a visit in the overall (sub-)population.

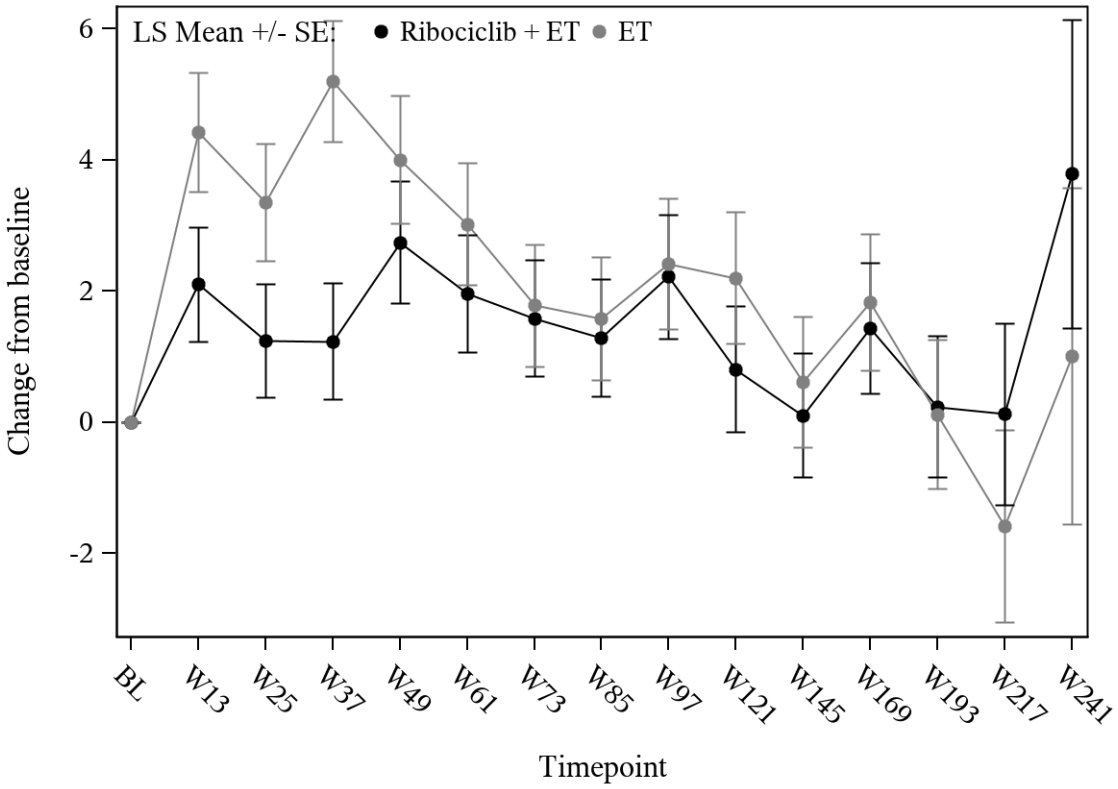
Figure 5-2.1.3.1 QLQ-C30 - Pain: line chart of change from baseline - subgroup analysis (Full Analysis Set)

QLQ-C30 - Pain
Region: NA/WE/O



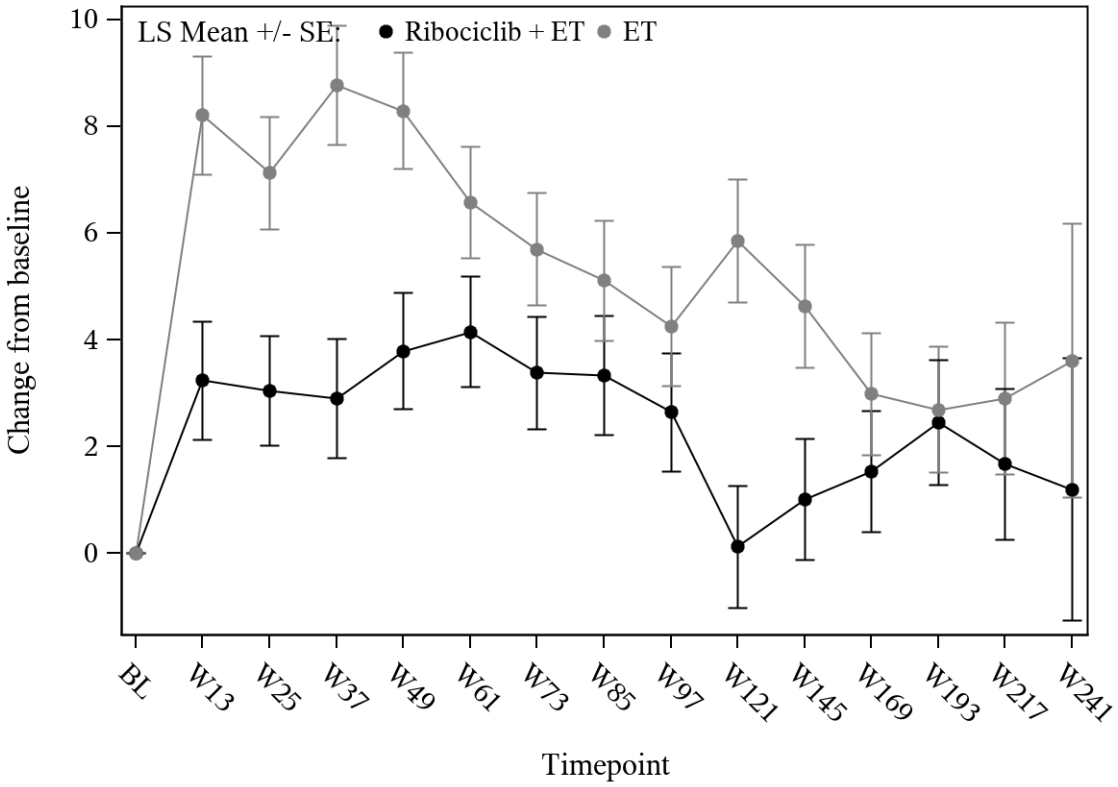
Ribociclib + ET	600	569	532	541	530	530	522	511	505	482	483	387	318	191	35
ET	578	540	504	506	512	502	497	477	473	462	442	367	306	188	33

QLQ-C30 - Pain
Region: ROW



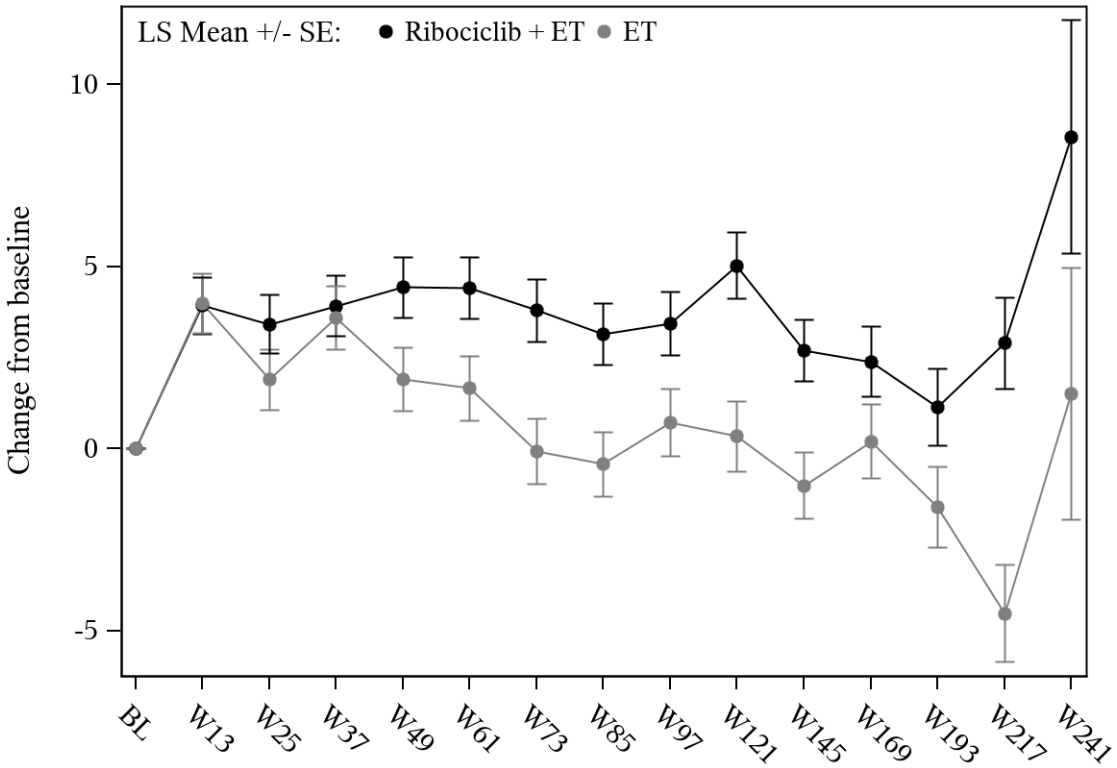
Ribociclib + ET	460	460	451	447	444	436	436	433	430	422	418	341	293	154	23
ET	426	424	417	405	410	401	397	394	387	379	368	315	260	135	19

QLQ-C30 - Pain
AJCC Anatomic Stage Group: Group I/II



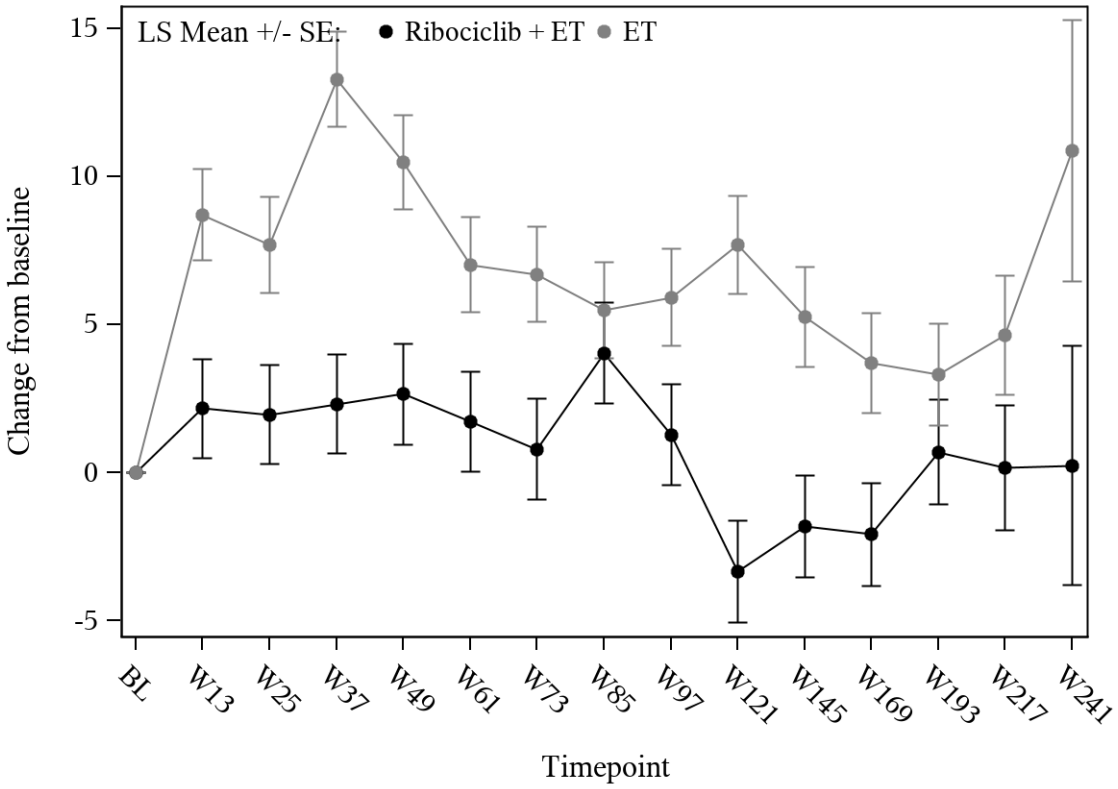
Ribociclib + ET	395	385	370	367	362	361	357	356	353	342	341	316	316	177	31
ET	398	381	350	364	367	359	361	342	346	334	321	316	302	175	28

QLQ-C30 - Pain
AJCC Anatomic Stage Group: Group III



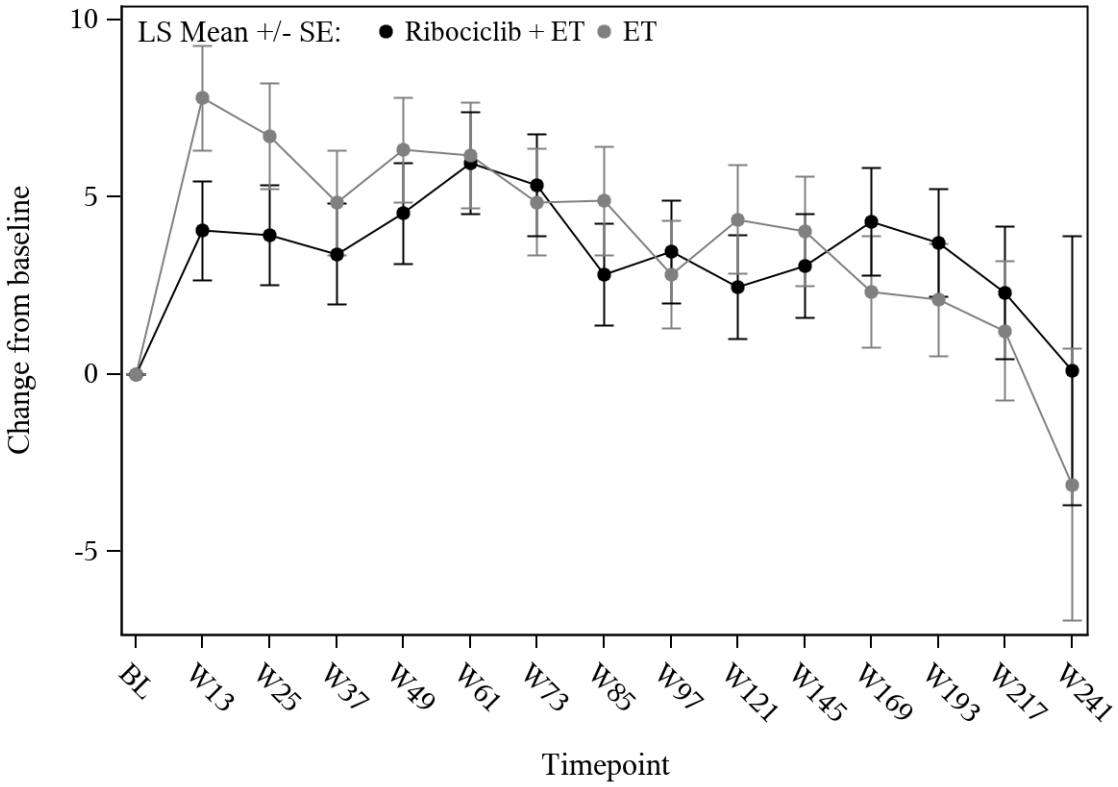
Ribociclib + ET	665	644	613	621	612	605	601	588	582	562	560	412	295	168	27
ET	606	583	571	547	555	544	533	529	514	507	489	366	264	148	24

QLQ-C30 - Pain
Anatomic stages: IA/IB/IIA



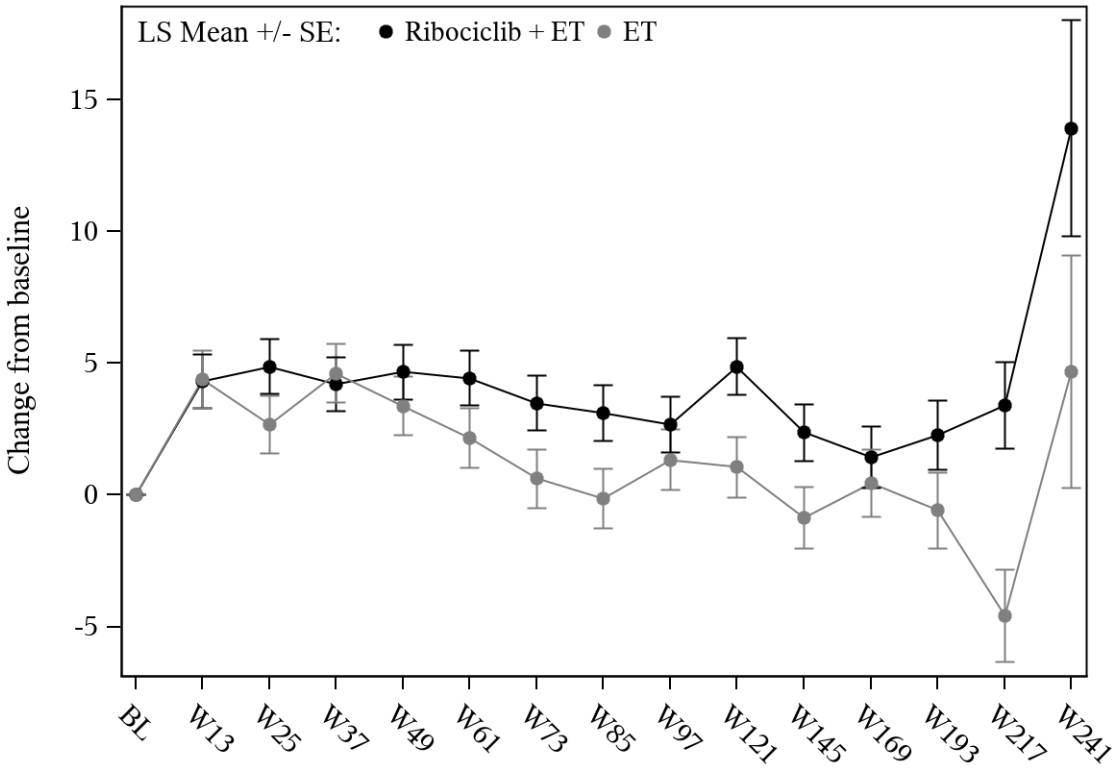
Ribociclib + ET	164	160	156	156	153	156	152	152	149	143	144	139	136	80	17
ET	189	184	161	169	171	167	170	162	162	156	148	148	140	87	14

QLQ-C30 - Pain
Anatomic stages: IIB



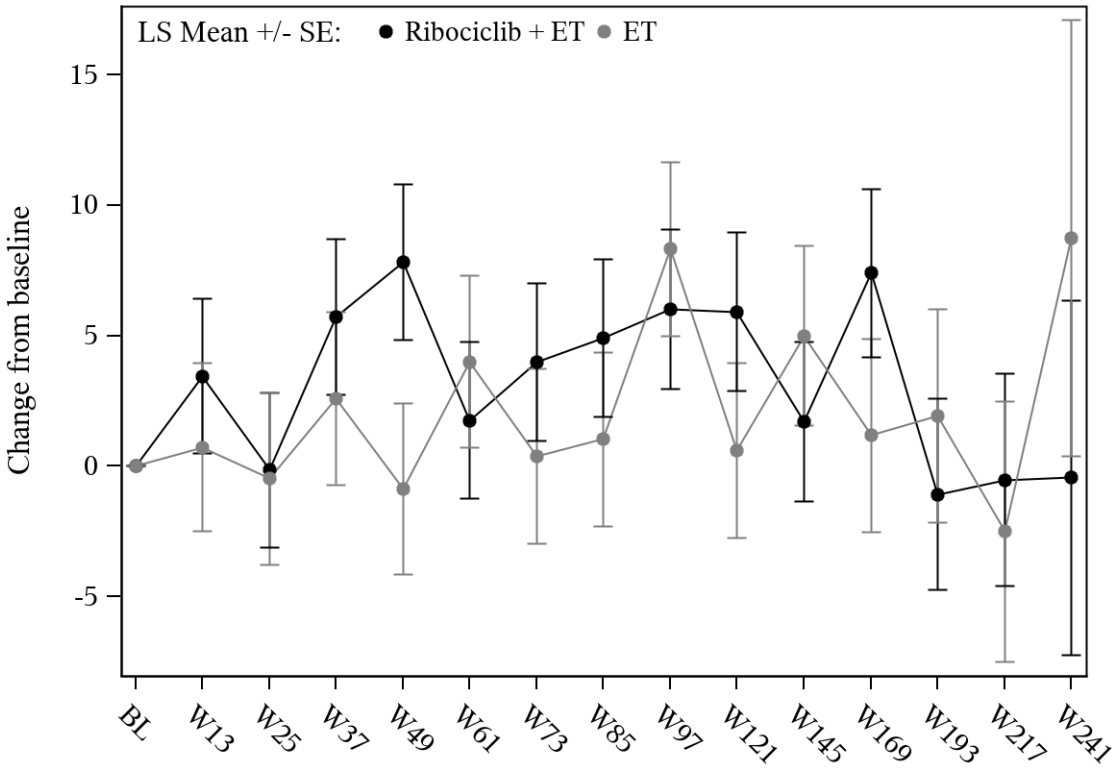
Ribociclib + ET	231	225	214	211	209	205	205	204	204	199	197	177	180	97	14
ET	209	197	189	195	196	192	191	180	184	178	173	168	162	88	14

QLQ-C30 - Pain
Anatomic stages: IIIA



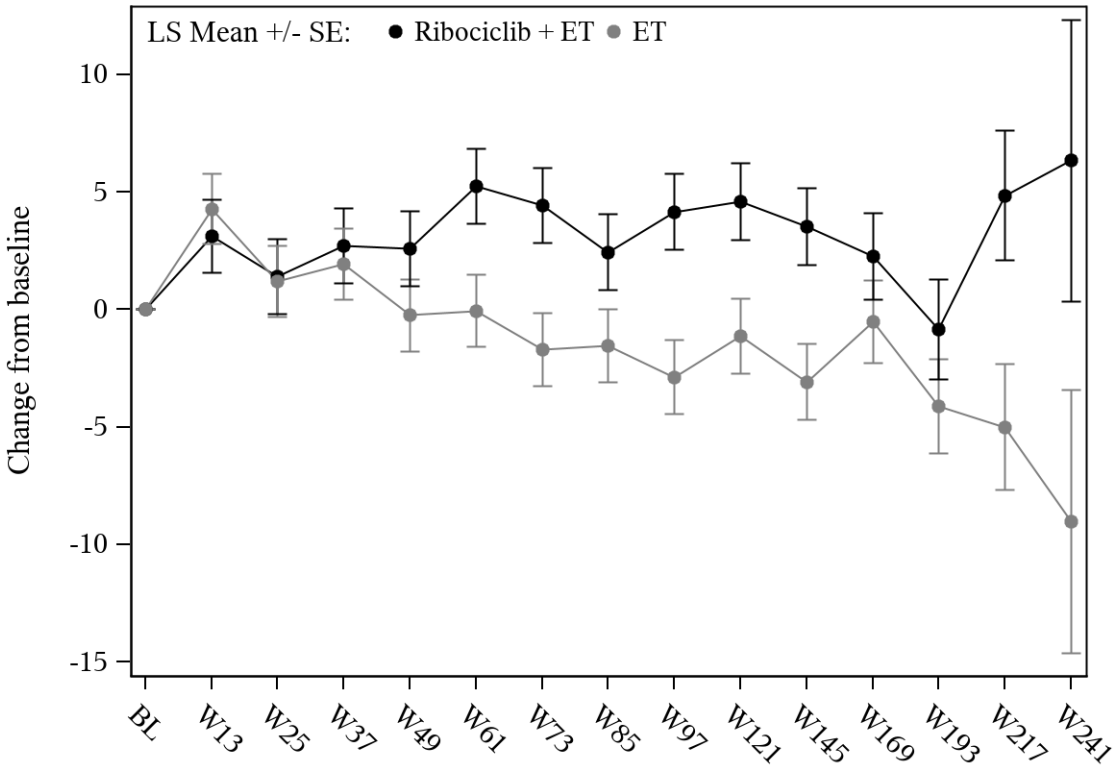
Ribociclib + ET	433	416	391	400	394	389	386	375	374	357	360	269	197	112	15
ET	368	355	343	330	336	329	327	322	314	308	304	225	163	99	13

QLQ-C30 - Pain
Anatomic stages: IIIB



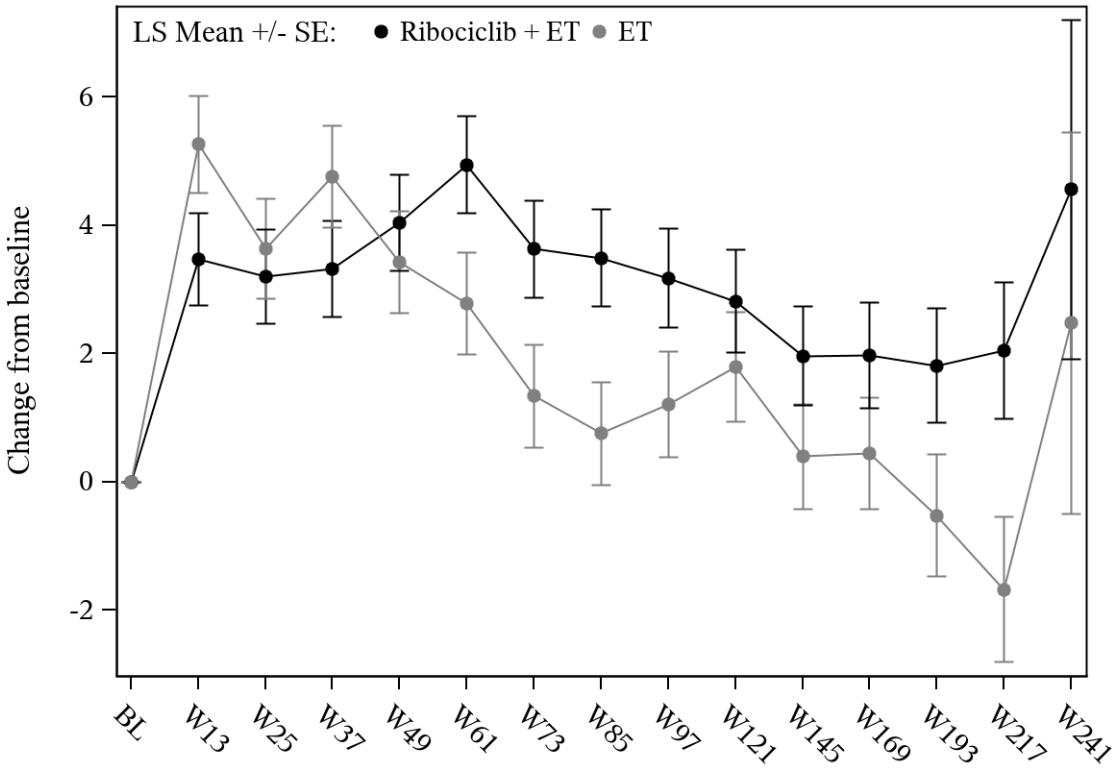
Ribociclib + ET	63	62	62	61	60	59	58	59	56	57	57	46	31	23	6
ET	52	52	49	47	49	49	46	47	47	46	42	33	25	14	4

QLQ-C30 - Pain
Anatomic stages: IIIC



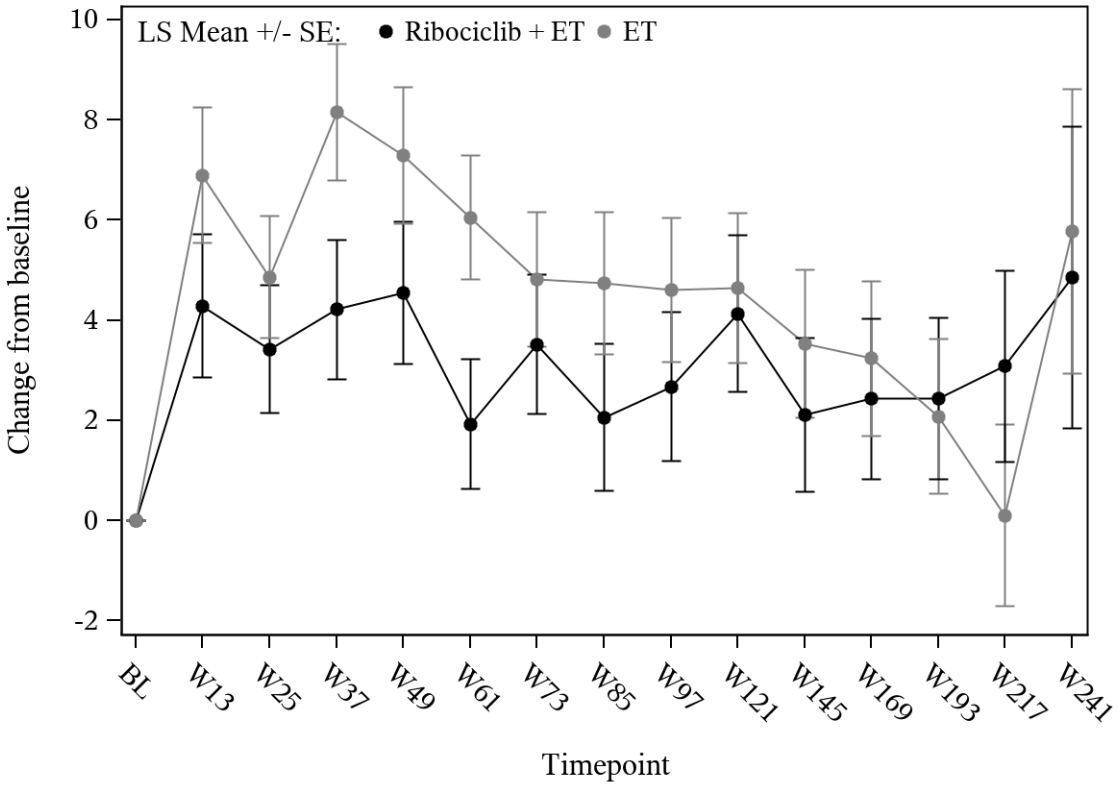
Ribociclib + ET	169	166	160	160	158	157	157	154	152	148	143	97	67	33	6
ET	186	176	179	170	170	166	160	160	153	153	143	108	76	35	7

QLQ-C30 - Pain
Prior endocrine therapy: Yes



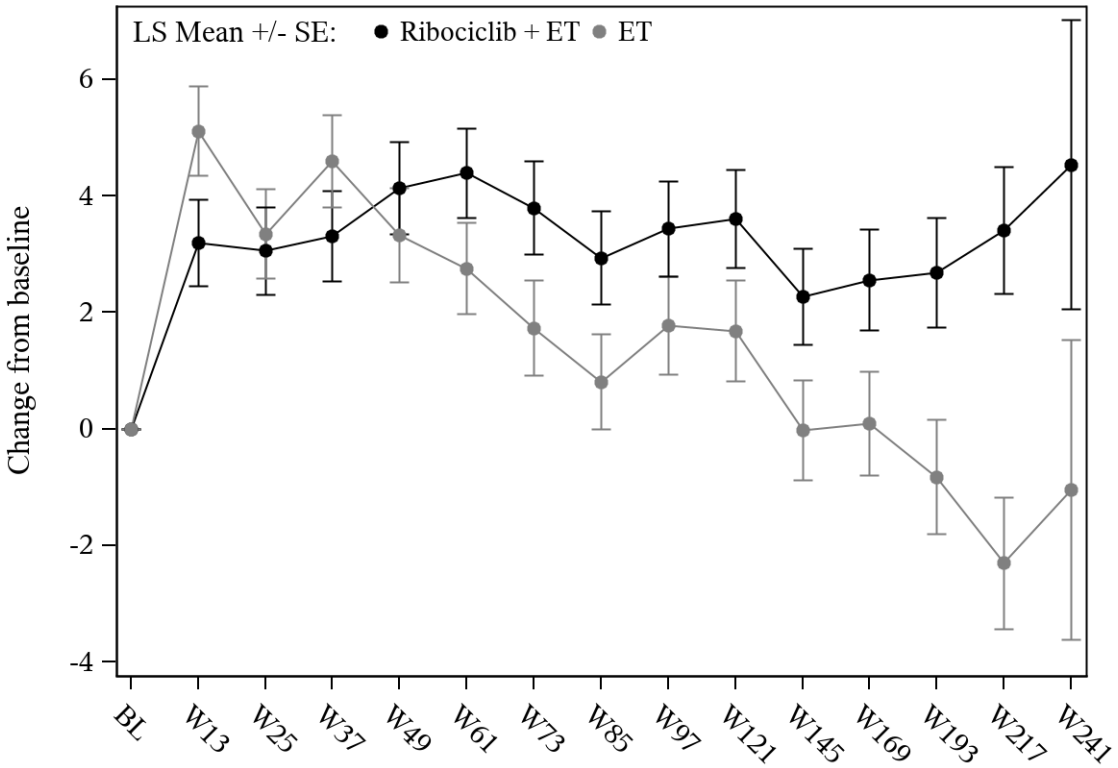
Ribociclib + ET	816	791	759	756	751	748	742	731	723	710	706	568	469	261	42
ET	734	701	679	675	678	668	663	647	635	624	605	505	407	229	33

QLQ-C30 - Pain
Prior endocrine therapy: No



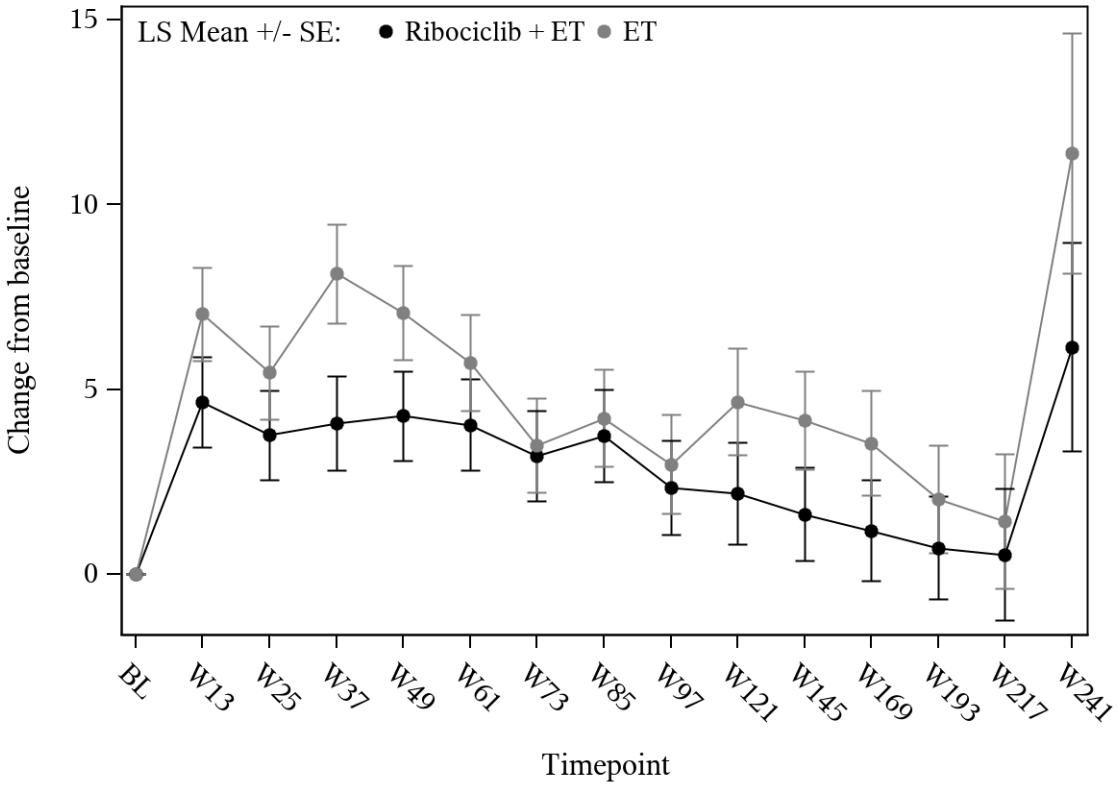
Ribociclib + ET	244	238	224	232	223	218	216	213	212	194	195	160	142	84	16
ET	270	263	242	236	244	235	231	224	225	217	205	177	159	94	19

QLQ-C30 - Pain
Prior mastectomy: Yes



Ribociclib + ET	737	711	680	679	669	665	658	649	640	619	613	490	404	232	40
ET	698	665	649	635	646	630	624	612	599	589	559	460	376	213	38

QLQ-C30 - Pain
Prior mastectomy: No



Ribociclib + ET	323	318	303	309	305	301	300	295	295	285	288	238	207	113	18
ET	306	299	272	276	276	273	270	259	261	252	251	222	190	110	14

Table 5-2.1.4.1 QLQ-C30 - Dyspnoea: change from baseline analysis - subgroup analysis (Full Analysis Set)

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1115)	ET (N = 1123)	Parameter	Esti-mate	[95% CI]	p-value
QLQ-C30 - Dyspnoea						
	N' | LS Mean (SE)	**N' | LS Mean (SE)**				
Region						
Interaction test	**p = 0.297**					
NA/WE/O	597 | 3.97 (0.62)	577 | 2.27 (0.64)	Difference	1.69	[-0.06; 3.45]	0.058
			Hedges G	0.11	[-0.00; 0.23]	
ROW	460 | 2.66 (0.61)	427 | 2.65 (0.64)	Difference	0.01	[-1.72; 1.74]	0.991
			Hedges G	0.00	[-0.13; 0.13]	
Geographical region						
Interaction test	**p = 0.723**					
Europe	617 | 3.81 (0.45)	592 | 3.66 (0.45)	Difference	0.15	[-1.11; 1.41]	0.816
			Hedges G	0.01	[-0.10; 0.13]	
North America/Australia	202 | 3.37 (0.63)	177 | 1.63 (0.72)	Difference	1.75	[-0.14; 3.63]	0.069
			Hedges G	0.19	[-0.01; 0.39]	
Asia	175 | N.E.	166 | N.E.	Difference	N.E.	[N.E.]	N.E.
			Hedges G	N.E.	[N.E.]	
Latin America	63 | 3.40 (1.02)	69 | 1.06 (0.94)	Difference	2.34	[-0.41; 5.09]	0.095
			Hedges G	0.29	[-0.05; 0.64]	
Age group 1 at randomization						
Interaction test	**p = 0.679**					
<45	524 | 2.64 (0.62)	458 | 1.98 (0.66)	Difference	0.66	[-1.11; 2.44]	0.463
			Hedges G	0.05	[-0.08; 0.17]	
45 to 54	513 | 4.21 (0.62)	519 | 3.23 (0.63)	Difference	0.98	[-0.76; 2.72]	0.268
			Hedges G	0.07	[-0.05; 0.19]	
55 to 64	20 | N.E.	27 | N.E.	Difference	N.E.	[N.E.]	N.E.
			Hedges G	N.E.	[N.E.]	
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)						
Interaction test	**p = 0.804**					
<Median	524 | 2.64 (0.62)	458 | 1.98 (0.66)	Difference	0.66	[-1.11; 2.44]	0.463
			Hedges G	0.05	[-0.08; 0.17]	
≥Median	533 | 4.30 (0.61)	546 | 3.21 (0.62)	Difference	1.09	[-0.61; 2.79]	0.210
			Hedges G	0.08	[-0.04; 0.20]	

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1115)	**ET (N = 1123)**	**Parameter**	**Esti-mate**	**[95% CI]**	**p-value**
Race						
Interaction test	**p = 0.750**					
Asian	206 | 1.19 (0.91)	180 | 0.97 (0.98)	Difference	0.22	[-2.41; 2.85]	0.869
			Hedges G	0.02	[-0.18; 0.22]	
Non-Asian	800 | 4.03 (0.49)	772 | 3.15 (0.50)	Difference	0.88	[-0.49; 2.25]	0.210
			Hedges G	0.06	[-0.04; 0.16]	
BMI at screening						
Interaction test	**p = 0.610**					
≥25	528 | 4.76 (0.66)	488 | 3.63 (0.69)	Difference	1.13	[-0.74; 3.00]	0.235
			Hedges G	0.07	[-0.05; 0.20]	
<25	517 | 2.51 (0.61)	505 | 1.82 (0.62)	Difference	0.68	[-1.04; 2.40]	0.436
			Hedges G	0.05	[-0.07; 0.17]	
AJCC Anatomic Stage Group						
Interaction test	**p = 0.035**					
Group I/II	394 | 3.20 (0.71)	398 | 3.80 (0.71)	Difference	-0.60	[-2.57; 1.36]	0.545
			Hedges G	-0.04	[-0.18; 0.10]	
Group III	663 | 3.52 (0.57)	606 | 1.65 (0.61)	Difference	1.88	[0.24; 3.51]	0.025
			Hedges G	0.13	[0.02; 0.24]	
Anatomic stages						
Interaction test	**p = 0.020**					
IA/IB/IIA	163 | 2.00 (1.02)	188 | 2.96 (0.98)	Difference	-0.96	[-3.74; 1.82]	0.499
			Hedges G	-0.07	[-0.28; 0.14]	
IIB	231 | 4.18 (0.99)	210 | 5.25 (1.03)	Difference	-1.07	[-3.87; 1.73]	0.455
			Hedges G	-0.07	[-0.26; 0.12]	
IIIA	431 | 3.92 (0.70)	368 | 1.58 (0.76)	Difference	2.34	[0.32; 4.36]	0.023
			Hedges G	0.16	[0.02; 0.30]	
IIIB	63 | 2.11 (1.88)	52 | 1.34 (2.09)	Difference	0.77	[-4.83; 6.37]	0.786
			Hedges G	0.05	[-0.32; 0.42]	
IIIC	169 | N.E.	186 | N.E.	Difference	N.E.	[N.E.]	N.E.
			Hedges G	N.E.	[N.E.]	
Nodal status						
Interaction test	**p = 0.057**					
N0	84 | 1.97 (1.39)	109 | 5.05 (1.24)	Difference	-3.08	[-6.77; 0.61]	0.101
			Hedges G	-0.24	[-0.52; 0.05]	
N1-N3	973 | 3.52 (0.46)	892 | 2.38 (0.48)	Difference	1.14	[-0.17; 2.45]	0.089
			Hedges G	0.08	[-0.01; 0.17]	

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1115)	**ET (N = 1123)**	**Parameter**	**Esti-mate**	**[95% CI]**	**p-value**
Histological grade at time of surgery						
Interaction test	**p = 0.857**					
Grade 1	105 | 2.76 (1.32)	97 | 2.40 (1.38)	Difference	0.36	[-3.41; 4.13]	0.852
			Hedges G	0.03	[-0.25; 0.30]	
Grade 2	579 | 3.73 (0.58)	558 | 2.53 (0.60)	Difference	1.20	[-0.44; 2.83]	0.152
			Hedges G	0.09	[-0.03; 0.20]	
Grade 3	281 | 3.17 (0.85)	252 | 2.39 (0.89)	Difference	0.78	[-1.63; 3.19]	0.523
			Hedges G	0.06	[-0.11; 0.23]	
Histological subtype						
Interaction test	**N.E.**					
Ductal	821 | N.E.	786 | N.E.	Difference	N.E.	[N.E.]	N.E.
			Hedges G	N.E.	[N.E.]	
Lobular	167 | 2.26 (1.14)	156 | 2.15 (1.21)	Difference	0.11	[-3.17; 3.38]	0.949
			Hedges G	0.01	[-0.21; 0.23]	
Other	69 | 3.98 (1.64)	62 | 2.25 (1.74)	Difference	1.74	[-3.00; 6.48]	0.469
			Hedges G	0.13	[-0.22; 0.47]	
Ki67 status from surgical specimen						
Interaction test	**p = 0.836**					
Ki67≤20	509 | 2.99 (0.60)	517 | 2.06 (0.60)	Difference	0.93	[-0.74; 2.60]	0.274
			Hedges G	0.07	[-0.05; 0.19]	
Ki67>20	399 | 4.96 (0.72)	358 | 4.23 (0.77)	Difference	0.73	[-1.35; 2.81]	0.493
			Hedges G	0.05	[-0.09; 0.19]	
Type of NSAI						
Interaction test	**p = 0.316**					
Letrozole	775 | 3.29 (0.52)	720 | 2.74 (0.56)	Difference	0.56	[-0.94; 2.05]	0.467
			Hedges G	0.04	[-0.06; 0.14]	
Anastrozole	282 | 4.29 (0.85)	282 | 2.40 (0.86)	Difference	1.89	[-0.49; 4.26]	0.119
			Hedges G	0.13	[-0.03; 0.30]	
Prior neo/adjuvant chemotherapy						
Interaction test	**N.E.**					
Yes	982 | 3.28 (0.47)	926 | 2.41 (0.49)	Difference	0.87	[-0.47; 2.20]	0.203
			Hedges G	0.06	[-0.03; 0.15]	
No	75 | 5.42 (1.35)	78 | 4.36 (1.36)	Difference	1.06	[-2.72; 4.84]	0.580
			Hedges G	0.09	[-0.23; 0.41]	
Prior adjuvant chemotherapy						
Interaction test	**p = 0.104**					
Yes	493 | 3.64 (0.64)	463 | 1.57 (0.66)	Difference	2.07	[0.27; 3.87]	0.024
			Hedges G	0.15	[0.02; 0.27]	
No	564 | 3.13 (0.62)	541 | 3.65 (0.64)	Difference	-0.52	[-2.27; 1.23]	0.561
			Hedges G	-0.03	[-0.15; 0.08]	

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1115)	**ET (N = 1123)**	**Parameter**	**Esti-mate**	**[95% CI]**	**p-value**
Prior neoadjuvant chemotherapy						
Interaction test	**p = 0.133**					
Yes	519 | 2.80 (0.65)	501 | 3.33 (0.66)	Difference	-0.54	[-2.36; 1.28]	0.563
			Hedges G	-0.04	[-0.16; 0.09]	
No	538 | 3.98 (0.60)	503 | 2.08 (0.62)	Difference	1.89	[0.21; 3.58]	0.028
			Hedges G	0.14	[0.01; 0.26]	
Prior endocrine therapy						
Interaction test	**N.E.**					
Yes	813 | 3.80 (0.52)	734 | 2.71 (0.56)	Difference	1.09	[-0.41; 2.60]	0.155
			Hedges G	0.07	[-0.03; 0.17]	
No	244 | 1.92 (0.83)	270 | 2.21 (0.80)	Difference	-0.29	[-2.55; 1.97]	0.800
			Hedges G	-0.02	[-0.20; 0.15]	
Prior mastectomy						
Interaction test	**p = 0.460**					
Yes	735 | 3.41 (0.54)	699 | 2.31 (0.55)	Difference	1.10	[-0.41; 2.62]	0.153
			Hedges G	0.08	[-0.03; 0.18]	
No	322 | 3.76 (0.79)	305 | 3.19 (0.83)	Difference	0.57	[-1.68; 2.83]	0.617
			Hedges G	0.04	[-0.12; 0.20]	
Prior radiotherapy						
Interaction test	**p = 0.584**					
Yes	968 | N.E.	922 | N.E.	Difference	N.E.	[N.E.]	N.E.
			Hedges G	N.E.	[N.E.]	
No	89 | 4.06 (1.30)	82 | 4.12 (1.37)	Difference	-0.06	[-3.80; 3.68]	0.975
			Hedges G	-0.00	[-0.30; 0.30]	

N: Number of patients
N': Number of patients in the analysis
CI: Confidence interval
SD: Standard deviation
LS Mean: Least square mean
SE: Standard error
MMRM: Mixed model for repeated measures
N.E.: Not estimable
ET: Endocrine therapy (Anastrozole/Letrozole + Goserelin)
.....

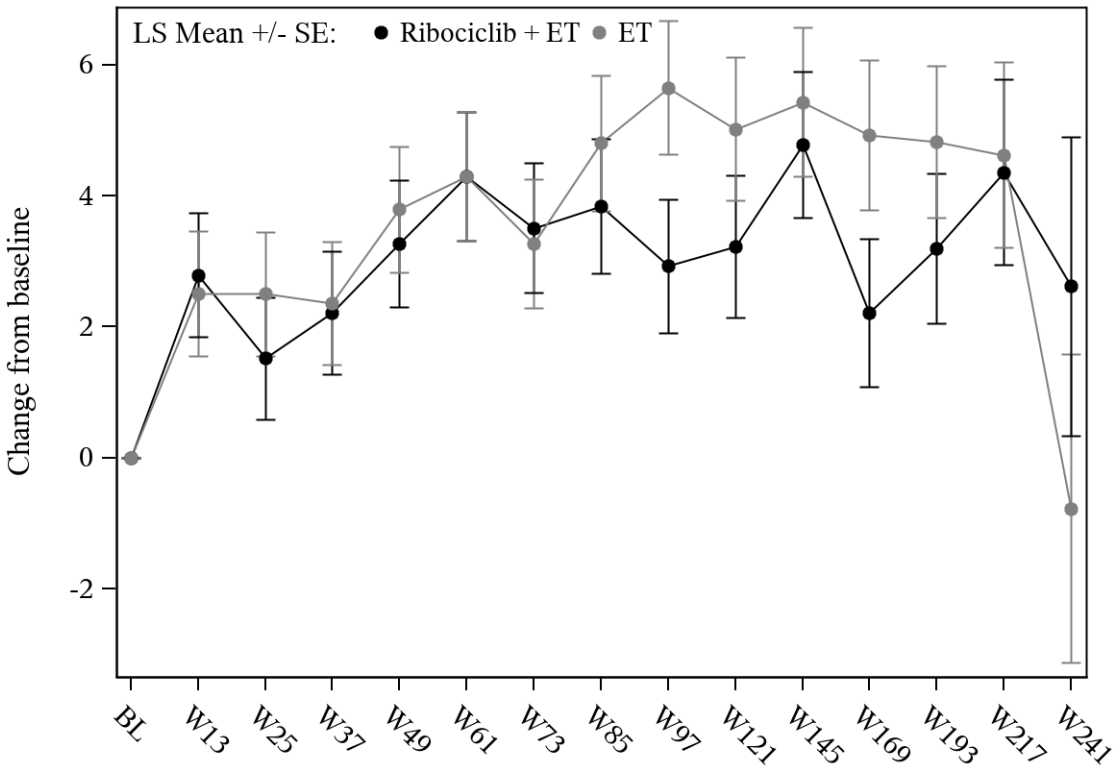
Analysis method for interaction test:
p-value from MMRM with unstructured covariance matrix:
change from baseline = treatment + visit + treatment * visit + subgroup factor + treatment * subgroup factor + subgroup factor * visit + treatment * subgroup factor * visit + baseline value
If the model did not converge for a parameter*subgroup factor, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry. If the model did still not converge, interactions were removed in the order treatment * subgroup factor * visit, subgroup factor * visit.

Analysis methods for within-subgroup analysis:
Adjusted mean (LS Mean) change from baseline and overall effect obtained from MMRM with unstructured covariance matrix:
change from baseline = treatment + visit + treatment * visit + baseline value
ET was the reference group for treatment group comparison.
If the model did not converge for a parameter*subgroup factor, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry.

Patients with an evaluable baseline score and at least one evaluable post-baseline score were included in the analysis.
All data collected were included in the analysis, including assessments at confirmation of first recurrence and thereafter, as long as there were at least 50 patients in each treatment group at a visit in the overall (sub-)population.

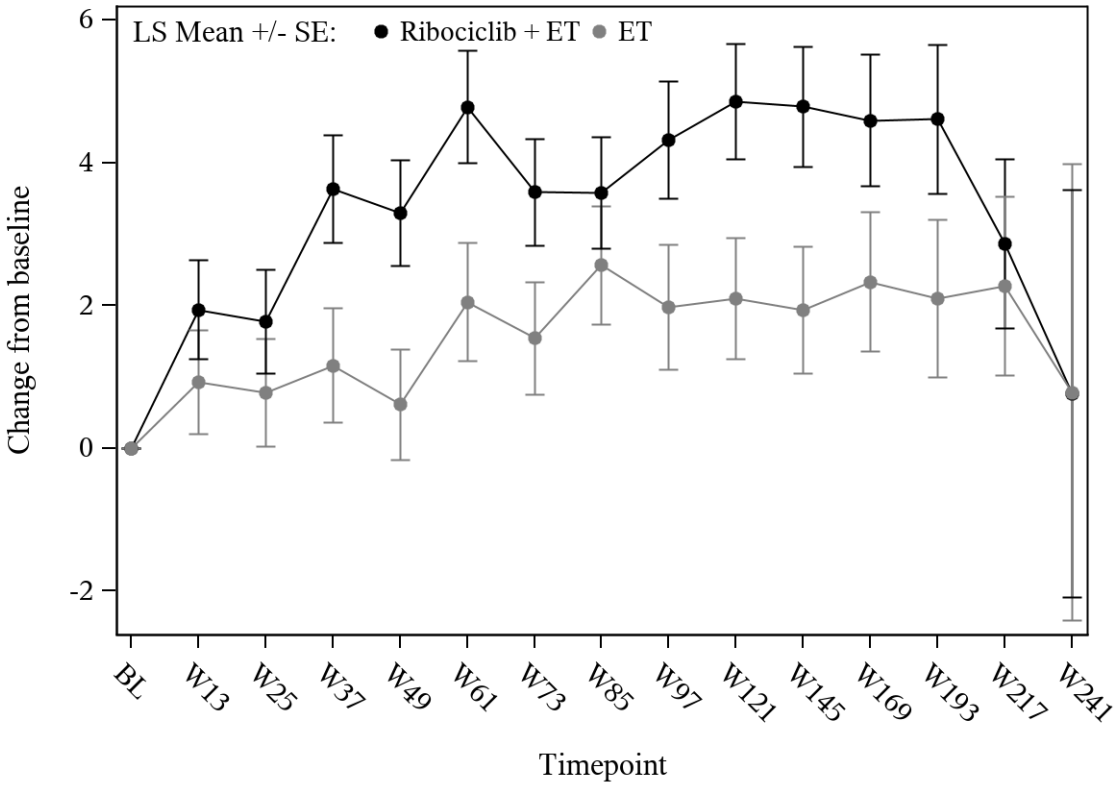
Figure 5-2.1.4.1 QLQ-C30 - Dyspnoea: line chart of change from baseline - subgroup analysis (Full Analysis Set)

QLQ-C30 - Dyspnoea
AJCC Anatomic Stage Group: Group I/II



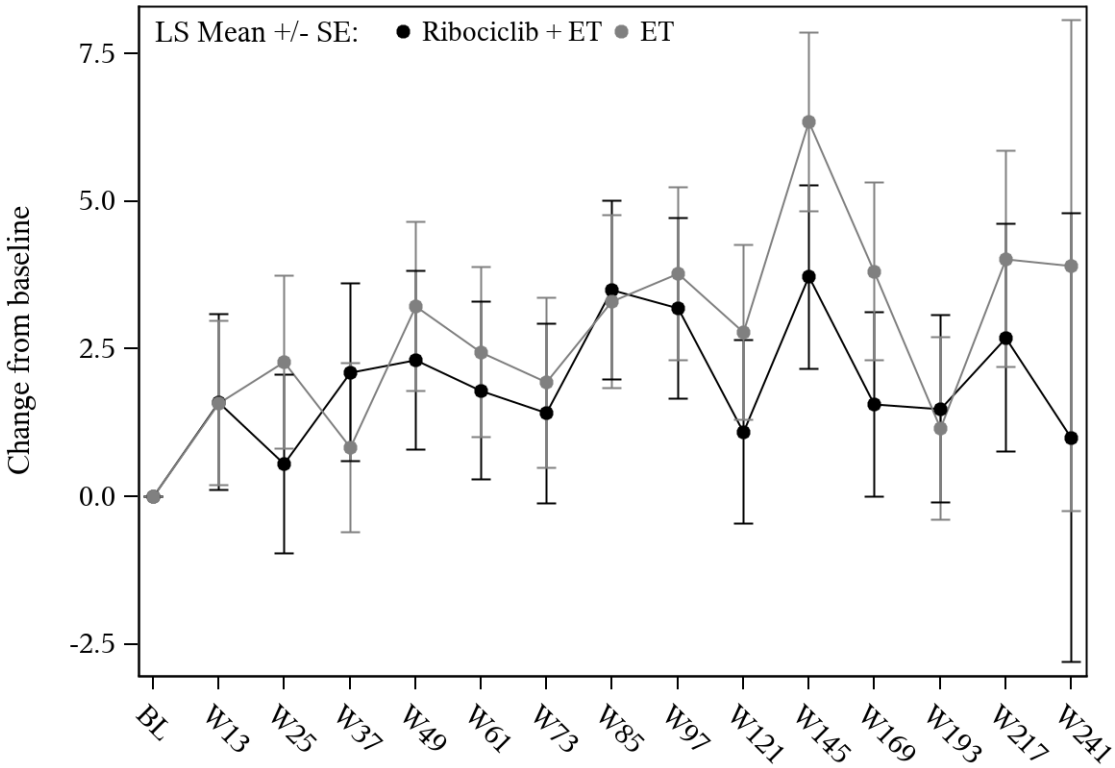
Ribociclib + ET	394	383	367	365	361	360	356	355	352	341	339	315	314	176	31
ET	398	381	349	364	367	359	360	340	346	333	320	316	301	175	28

QLQ-C30 - Dyspnoea
AJCC Anatomic Stage Group: Group III



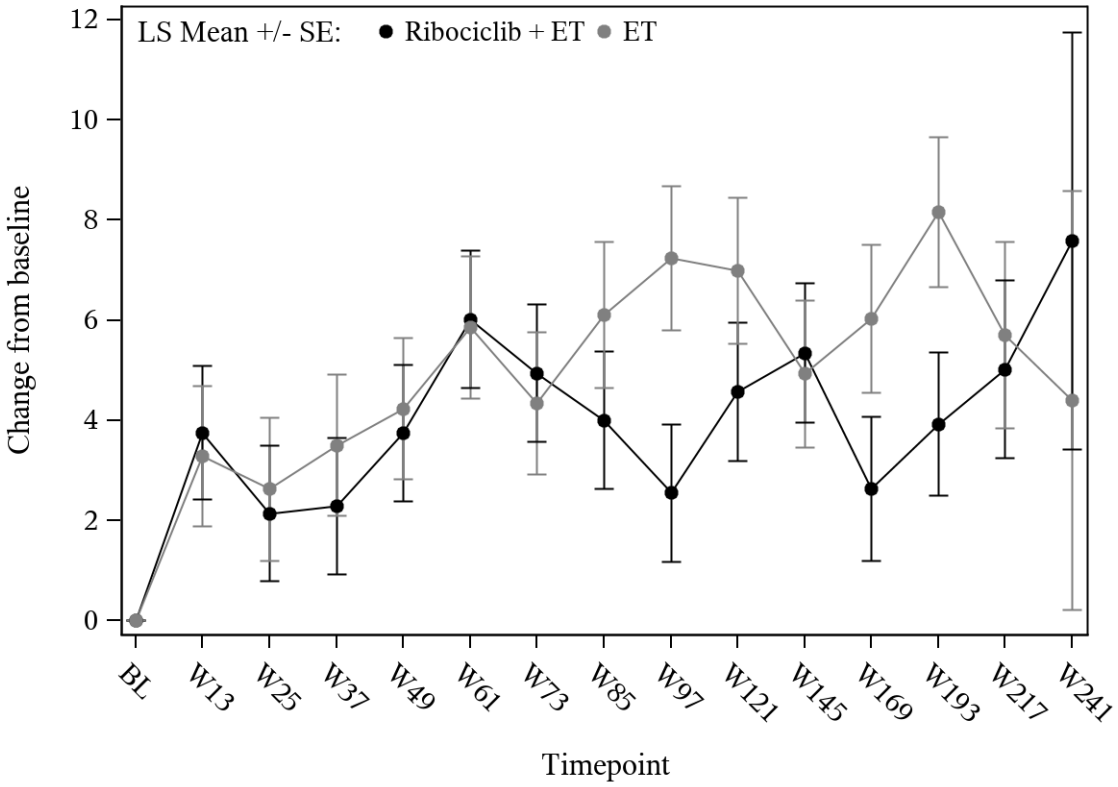
Ribociclib + ET	663	641	609	620	610	603	599	588	581	561	559	411	294	167	27
ET	606	582	570	546	554	544	532	527	513	507	487	366	263	148	23

QLQ-C30 - Dyspnoea
Anatomic stages: IA/IB/IIA



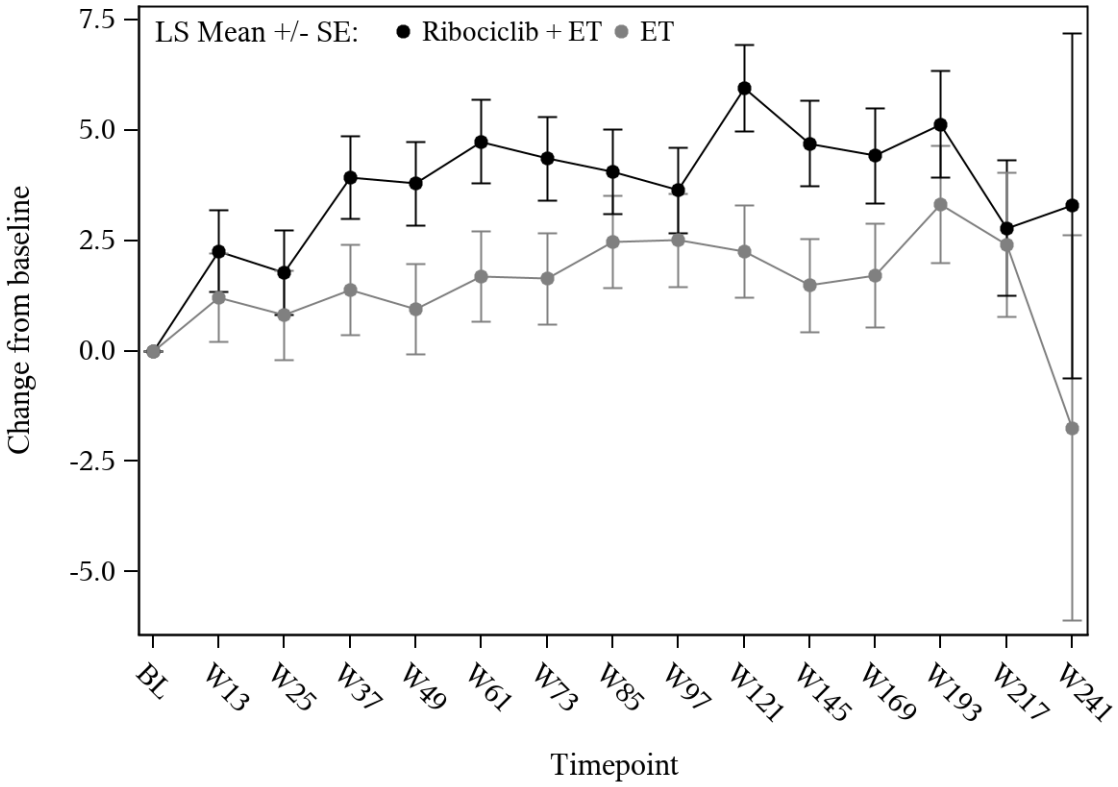
Ribociclib + ET	163	159	153	154	153	155	151	152	148	142	142	138	135	79	17
ET	188	183	160	169	170	166	169	161	161	155	146	147	138	87	14

QLQ-C30 - Dyspnoea
Anatomic stages: IIB



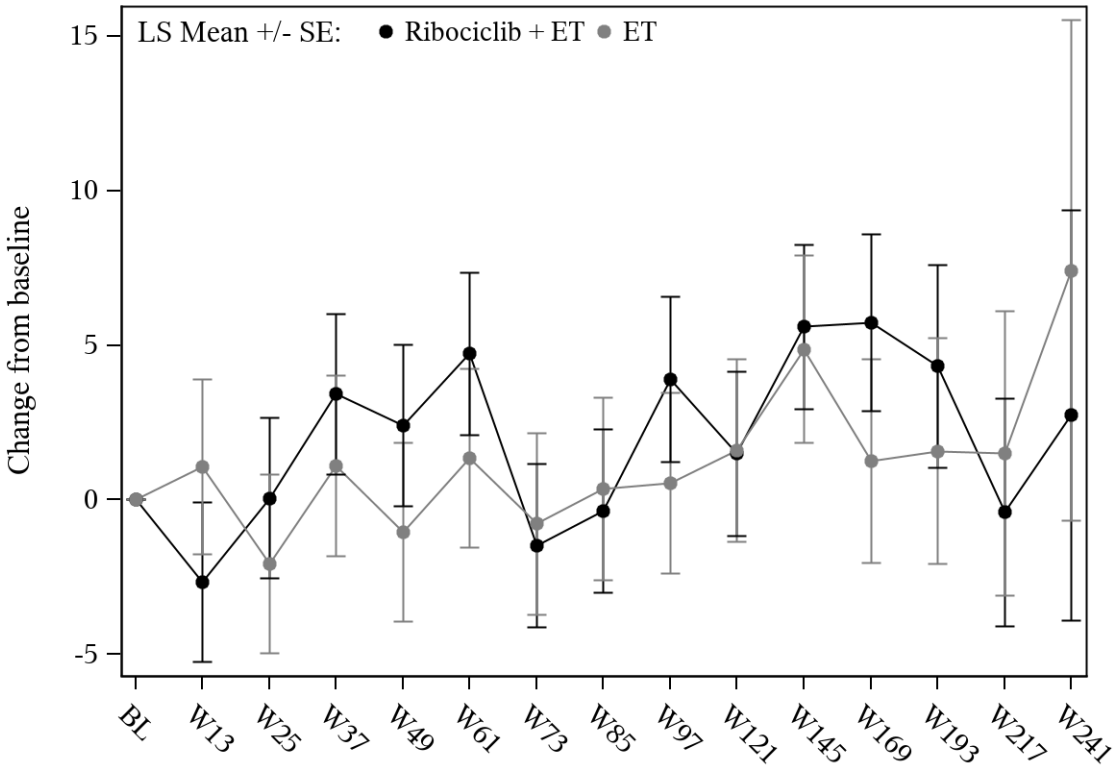
Ribociclib + ET	231	224	214	211	208	205	205	203	204	199	197	177	179	97	14
ET	210	198	189	195	197	193	191	179	185	178	174	169	163	88	14

QLQ-C30 - Dyspnoea
Anatomic stages: IIIA



Ribociclib + ET	431	413	388	399	392	387	384	375	373	356	359	268	196	111	15
ET	368	354	342	330	335	329	326	322	313	308	304	225	162	99	12

QLQ-C30 - Dyspnoea
Anatomic stages: IIIB



Ribociclib + ET	63	62	62	61	60	59	58	59	56	57	57	46	31	23	6
ET	52	52	49	47	49	49	46	46	47	46	42	33	25	14	4

QLQ-C30 - Dyspnoea
Anatomic stages: IIIC

The figure is not displayed as the model did not converge.

Table 5-2.1.5.1 QLQ-C30 - Insomnia: change from baseline analysis - subgroup analysis (Full Analysis Set)

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1115)	ET (N = 1123)	Parameter	Esti-mate	[95% CI]	p-value
QLQ-C30 - Insomnia						
	N' | LS Mean (SE)	N' | LS Mean (SE)				
Region						
Interaction test	**p = 0.011**					
NA/WE/O	600 | 3.08 (0.88)	578 | 1.09 (0.90)	Difference	1.99	[-0.47; 4.46]	0.113
			Hedges G	0.09	[-0.02; 0.21]	
ROW	460 | 1.95 (0.93)	427 | 4.91 (0.98)	Difference	-2.95	[-5.61; -0.30]	0.029
			Hedges G	-0.15	[-0.28; -0.01]	
Geographical region						
Interaction test	**p = 0.012**					
Europe	619 | 3.50 (0.64)	593 | 4.53 (0.65)	Difference	-1.03	[-2.82; 0.77]	0.263
			Hedges G	-0.06	[-0.18; 0.05]	
North America/Australia	203 | 0.22 (1.01)	177 | -3.53 (1.14)	Difference	3.74	[0.74; 6.75]	0.015
			Hedges G	0.25	[0.05; 0.45]	
Asia	175 | N.E.	166 | N.E.	Difference	N.E.	[N.E.]	N.E.
			Hedges G	N.E.	[N.E.]	
Latin America	63 | 1.74 (1.94)	69 | -0.86 (1.81)	Difference	2.60	[-2.66; 7.86]	0.329
			Hedges G	0.17	[-0.17; 0.51]	
Age group 1 at randomization						
Interaction test	**p = 0.992**					
<45	525 | N.E.	459 | N.E.	Difference	N.E.	[N.E.]	N.E.
			Hedges G	N.E.	[N.E.]	
45 to 54	515 | 2.26 (0.90)	519 | 2.64 (0.91)	Difference	-0.38	[-2.89; 2.13]	0.764
			Hedges G	-0.02	[-0.14; 0.10]	
55 to 64	20 | N.E.	27 | N.E.	Difference	N.E.	[N.E.]	N.E.
			Hedges G	N.E.	[N.E.]	
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)						
Interaction test	**p = 0.579**					
<Median	525 | 3.23 (0.94)	459 | 2.61 (1.00)	Difference	0.62	[-2.07; 3.31]	0.650
			Hedges G	0.03	[-0.10; 0.15]	
≥Median	535 | 2.38 (0.89)	546 | 2.62 (0.90)	Difference	-0.24	[-2.73; 2.24]	0.849
			Hedges G	-0.01	[-0.13; 0.11]	

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1115)	**ET (N = 1123)**	**Parameter**	**Esti-mate**	**[95% CI]**	**p-value**
Race						
Interaction test	**p = 0.584**					
Asian	206 | 1.07 (1.35)	180 | 1.96 (1.45)	Difference	-0.89	[-4.79; 3.02]	0.656
			Hedges G	-0.05	[-0.25; 0.15]	
Non-Asian	803 | 3.33 (0.72)	773 | 2.84 (0.73)	Difference	0.49	[-1.52; 2.50]	0.634
			Hedges G	0.02	[-0.07; 0.12]	
BMI at screening						
Interaction test	**p = 0.242**					
≥25	530 | 3.88 (0.92)	489 | 2.95 (0.97)	Difference	0.93	[-1.69; 3.55]	0.487
			Hedges G	0.04	[-0.08; 0.17]	
<25	518 | 1.33 (0.90)	505 | 2.37 (0.92)	Difference	-1.04	[-3.57; 1.49]	0.421
			Hedges G	-0.05	[-0.17; 0.07]	
AJCC Anatomic Stage Group						
Interaction test	**p = 0.009**					
Group I/II	395 | 3.65 (1.06)	399 | 6.54 (1.06)	Difference	-2.89	[-5.84; 0.05]	0.054
			Hedges G	-0.14	[-0.28; 0.00]	
Group III	665 | 1.73 (0.81)	606 | -0.22 (0.86)	Difference	1.94	[-0.38; 4.27]	0.101
			Hedges G	0.09	[-0.02; 0.20]	
Anatomic stages						
Interaction test	**p = 0.072**					
IA/IB/IIA	164 | 1.00 (1.54)	189 | 6.21 (1.48)	Difference	-5.21	[-9.42; -1.00]	0.015
			Hedges G	-0.26	[-0.47; -0.05]	
IIB	231 | 5.08 (1.42)	210 | 6.85 (1.48)	Difference	-1.77	[-5.80; 2.26]	0.388
			Hedges G	-0.08	[-0.27; 0.10]	
IIIA	433 | 2.23 (1.01)	368 | 0.35 (1.10)	Difference	1.89	[-1.05; 4.83]	0.208
			Hedges G	0.09	[-0.05; 0.23]	
IIIB	63 | 4.70 (2.61)	52 | 0.34 (2.89)	Difference	4.36	[-3.36; 12.08]	0.266
			Hedges G	0.21	[-0.16; 0.58]	
IIIC	169 | 0.39 (1.58)	186 | -0.41 (1.51)	Difference	0.80	[-3.50; 5.10]	0.715
			Hedges G	0.04	[-0.17; 0.25]	
Nodal status						
Interaction test	**p = 0.973**					
N0	84 | 4.11 (2.29)	110 | 4.14 (2.02)	Difference	-0.03	[-6.05; 6.00]	0.993
			Hedges G	-0.00	[-0.29; 0.28]	
N1-N3	976 | 2.23 (0.68)	892 | 2.36 (0.71)	Difference	-0.12	[-2.04; 1.79]	0.899
			Hedges G	-0.01	[-0.10; 0.08]	

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1115)	**ET (N = 1123)**	**Parameter**	**Esti-mate**	**[95% CI]**	**p-value**
Histological grade at time of surgery						
Interaction test	**p = 0.395**					
Grade 1	106 | 0.53 (1.94)	97 | 3.86 (2.05)	Difference	-3.33	[-8.89; 2.23]	0.239
			Hedges G	-0.17	[-0.44; 0.11]	
Grade 2	580 | 3.12 (0.84)	559 | 2.72 (0.86)	Difference	0.40	[-1.95; 2.75]	0.740
			Hedges G	0.02	[-0.10; 0.14]	
Grade 3	282 | 2.13 (1.23)	252 | 1.40 (1.29)	Difference	0.73	[-2.77; 4.23]	0.682
			Hedges G	0.04	[-0.13; 0.21]	
Histological subtype						
Interaction test	**p = 0.208**					
Ductal	823 | 2.69 (0.54)	787 | 2.28 (0.56)	Difference	0.41	[-1.12; 1.94]	0.600
			Hedges G	0.03	[-0.07; 0.12]	
Lobular	168 | 2.55 (1.30)	156 | 5.40 (1.41)	Difference	-2.85	[-6.63; 0.93]	0.139
			Hedges G	-0.16	[-0.38; 0.05]	
Other	69 | 0.13 (2.12)	62 | 3.69 (2.48)	Difference	-3.56	[-10.02; 2.90]	0.278
			Hedges G	-0.19	[-0.53; 0.15]	
Ki67 status from surgical specimen						
Interaction test	**p = 0.415**					
Ki67≤20	510 | 3.42 (0.92)	517 | 3.74 (0.91)	Difference	-0.32	[-2.86; 2.23]	0.807
			Hedges G	-0.02	[-0.14; 0.11]	
Ki67>20	401 | 3.14 (0.99)	359 | 1.83 (1.05)	Difference	1.31	[-1.52; 4.15]	0.364
			Hedges G	0.07	[-0.08; 0.21]	
Type of NSAI						
Interaction test	**p = 0.117**					
Letrozole	775 | 2.11 (0.75)	721 | 3.12 (0.79)	Difference	-1.02	[-3.16; 1.13]	0.353
			Hedges G	-0.05	[-0.15; 0.05]	
Anastrozole	285 | 3.95 (1.23)	282 | 1.86 (1.24)	Difference	2.09	[-1.33; 5.52]	0.231
			Hedges G	0.10	[-0.06; 0.27]	
Prior neo/adjuvant chemotherapy						
Interaction test	**p = 0.733**					
Yes	985 | 2.30 (0.51)	927 | 2.39 (0.53)	Difference	-0.08	[-1.52; 1.35]	0.908
			Hedges G	-0.01	[-0.09; 0.08]	
No	75 | 4.54 (1.74)	78 | 6.43 (1.79)	Difference	-1.89	[-6.83; 3.04]	0.450
			Hedges G	-0.12	[-0.44; 0.19]	
Prior adjuvant chemotherapy						
Interaction test	**p = 0.586**					
Yes	495 | 1.42 (0.91)	463 | 2.21 (0.94)	Difference	-0.79	[-3.35; 1.77]	0.545
			Hedges G	-0.04	[-0.17; 0.09]	
No	565 | 3.69 (0.92)	542 | 2.87 (0.94)	Difference	0.82	[-1.76; 3.40]	0.533
			Hedges G	0.04	[-0.08; 0.16]	

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1115)	ET (N = 1123)	Parameter	Esti-mate	[95% CI]	p-value
Prior neoadjuvant chemotherapy						
Interaction test	**p = 0.254**					
Yes	520 | 3.38 (0.94)	502 | 1.93 (0.97)	Difference	1.45	[-1.20; 4.10]	0.284
			Hedges G	0.07	[-0.06; 0.19]	
No	540 | 2.22 (0.89)	503 | 3.25 (0.93)	Difference	-1.04	[-3.55; 1.48]	0.418
			Hedges G	-0.05	[-0.17; 0.07]	
Prior endocrine therapy						
Interaction test	**p = 0.963**					
Yes	816 | 1.93 (0.73)	735 | 2.08 (0.77)	Difference	-0.15	[-2.23; 1.93]	0.888
			Hedges G	-0.01	[-0.11; 0.09]	
No	244 | 4.86 (1.36)	270 | 4.91 (1.29)	Difference	-0.04	[-3.73; 3.64]	0.981
			Hedges G	-0.00	[-0.18; 0.17]	
Prior mastectomy						
Interaction test	**p = 0.218**					
Yes	737 | 2.78 (0.78)	699 | 1.91 (0.80)	Difference	0.87	[-1.32; 3.06]	0.435
			Hedges G	0.04	[-0.06; 0.14]	
No	323 | 2.27 (1.14)	306 | 3.91 (1.19)	Difference	-1.64	[-4.87; 1.59]	0.319
			Hedges G	-0.08	[-0.24; 0.08]	
Prior radiotherapy						
Interaction test	**p = 0.597**					
Yes	971 | 2.16 (0.68)	923 | 2.19 (0.70)	Difference	-0.03	[-1.94; 1.89]	0.980
			Hedges G	-0.00	[-0.09; 0.09]	
No	89 | 7.67 (2.30)	82 | 6.54 (2.42)	Difference	1.12	[-5.48; 7.72]	0.738
			Hedges G	0.05	[-0.25; 0.35]	

N: Number of patients
N': Number of patients in the analysis
CI: Confidence interval
SD: Standard deviation
LS Mean: Least square mean
SE: Standard error
MMRM: Mixed model for repeated measures
N.E.: Not estimable
ET: Endocrine therapy (Anastrozole/Letrozole + Goserelin)
.....

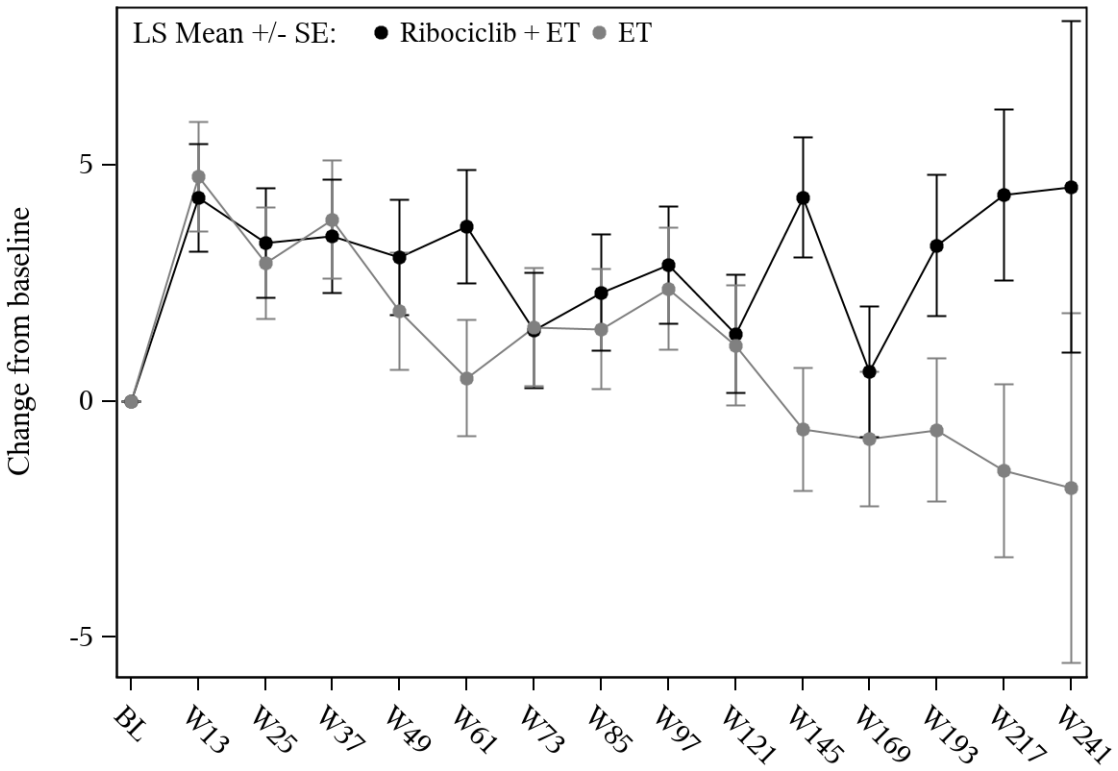
Analysis method for interaction test:
p-value from MMRM with unstructured covariance matrix:
change from baseline = treatment + visit + treatment * visit + subgroup factor + treatment * subgroup factor + subgroup factor * visit + treatment * subgroup factor * visit + baseline value
If the model did not converge for a parameter*subgroup factor, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry. If the model did still not converge, interactions were removed in the order treatment * subgroup factor * visit, subgroup factor * visit.

Analysis methods for within-subgroup analysis:
Adjusted mean (LS Mean) change from baseline and overall effect obtained from MMRM with unstructured covariance matrix:
change from baseline = treatment + visit + treatment * visit + baseline value
ET was the reference group for treatment group comparison.
If the model did not converge for a parameter*subgroup factor, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry.

Patients with an evaluable baseline score and at least one evaluable post-baseline score were included in the analysis.
All data collected were included in the analysis, including assessments at confirmation of first recurrence and thereafter, as long as there were at least 50 patients in each treatment group at a visit in the overall (sub-)population.

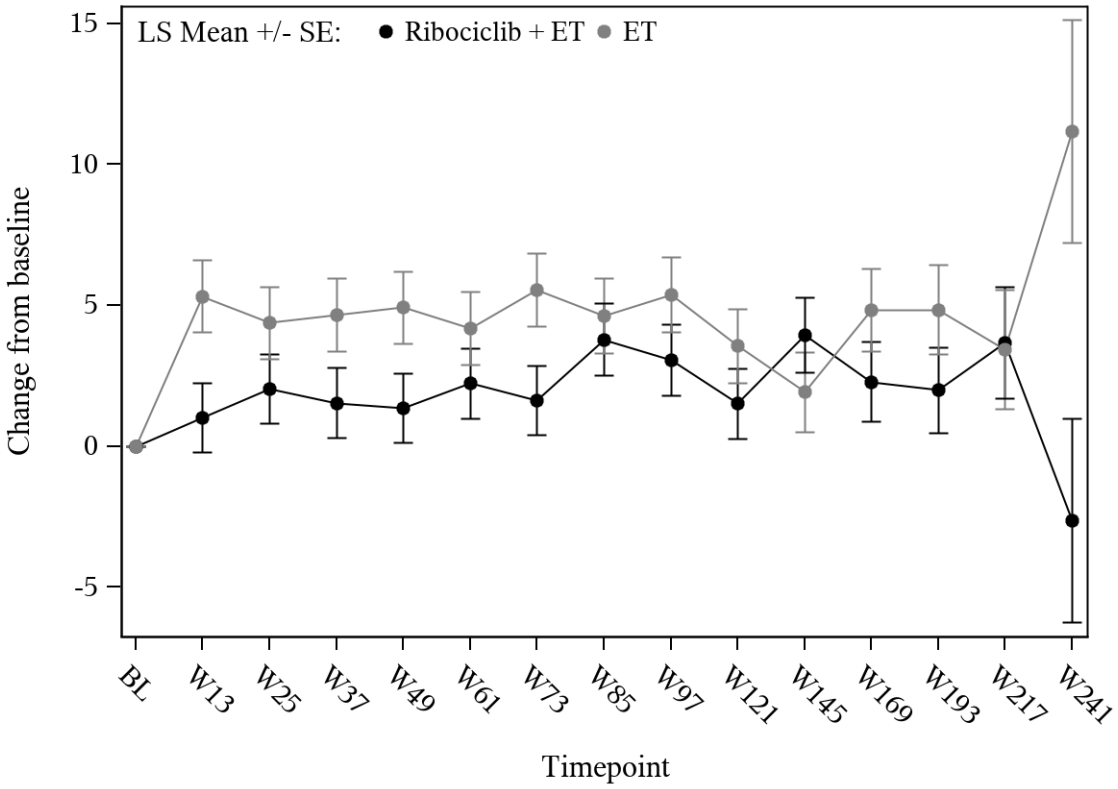
Figure 5-2.1.5.1 QLQ-C30 - Insomnia: line chart of change from baseline - subgroup analysis (Full Analysis Set)

QLQ-C30 - Insomnia
Region: NA/WE/O



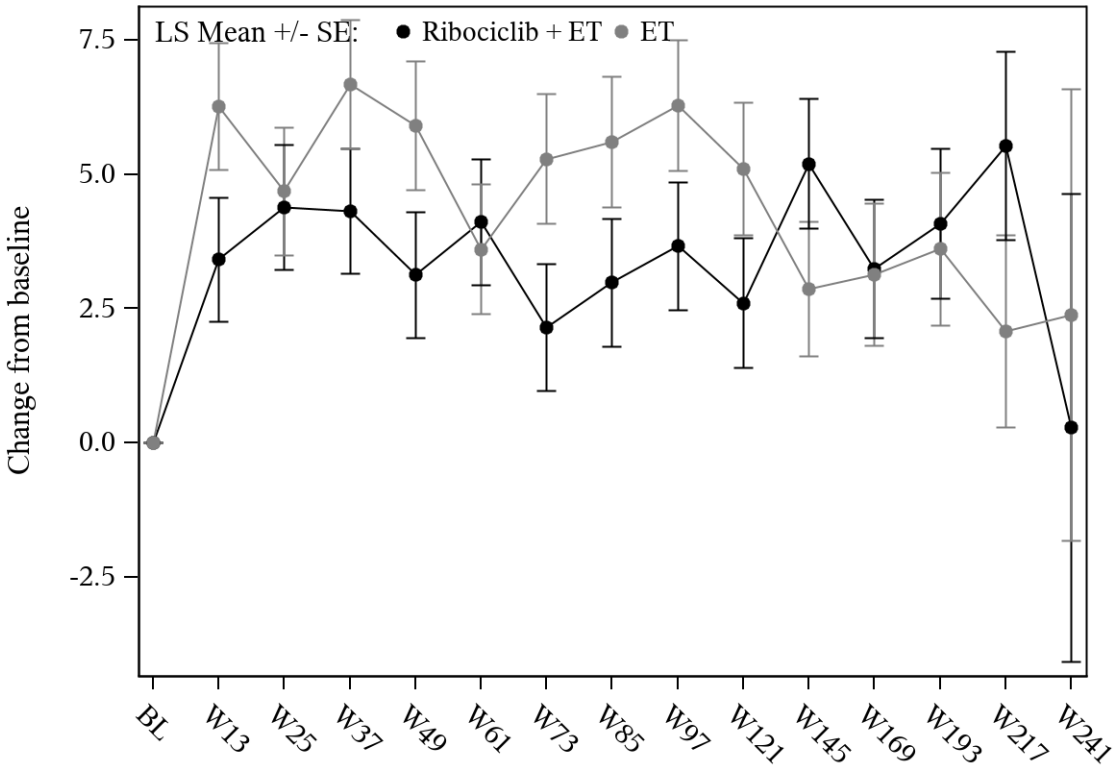
Ribociclib + ET	600	567	529	539	527	529	521	510	505	481	481	386	318	191	35
ET	578	540	504	506	512	502	494	474	472	462	442	367	306	188	32

QLQ-C30 - Insomnia
Region: ROW



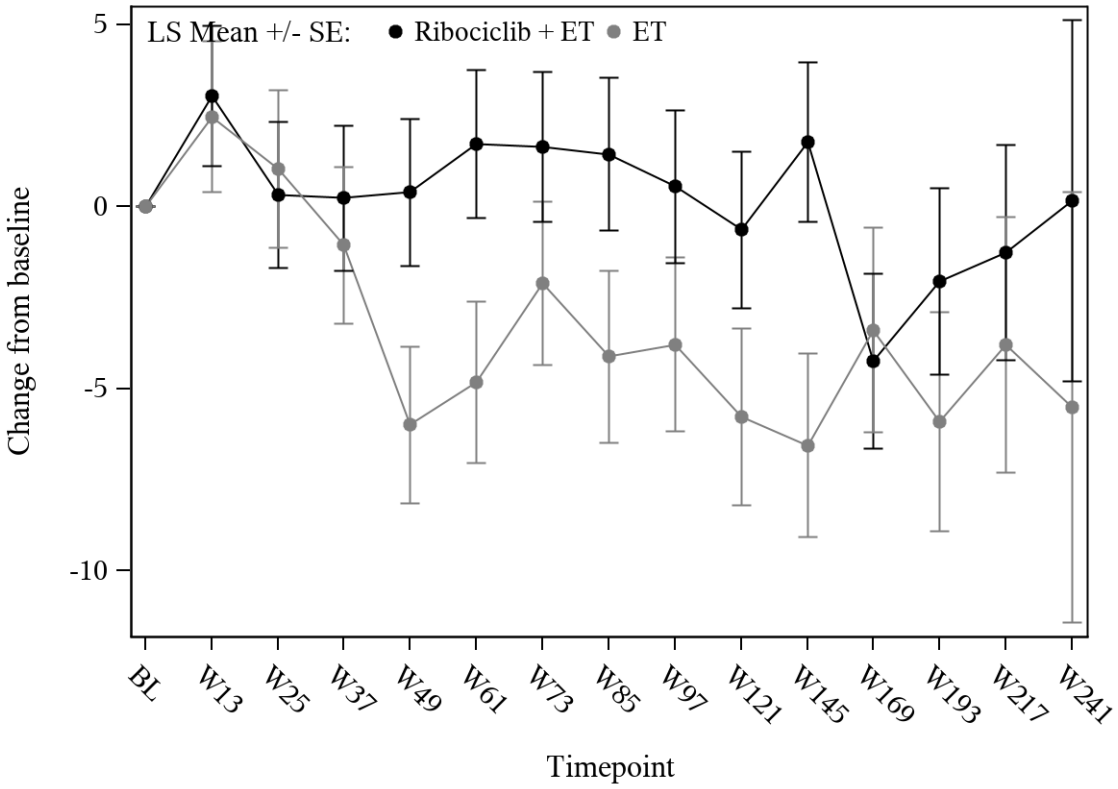
Ribociclib + ET	460	460	450	447	444	436	436	433	429	421	417	341	293	154	23
ET	427	423	417	406	411	402	398	394	388	379	369	316	259	135	19

QLQ-C30 - Insomnia
Geographical region: Europe



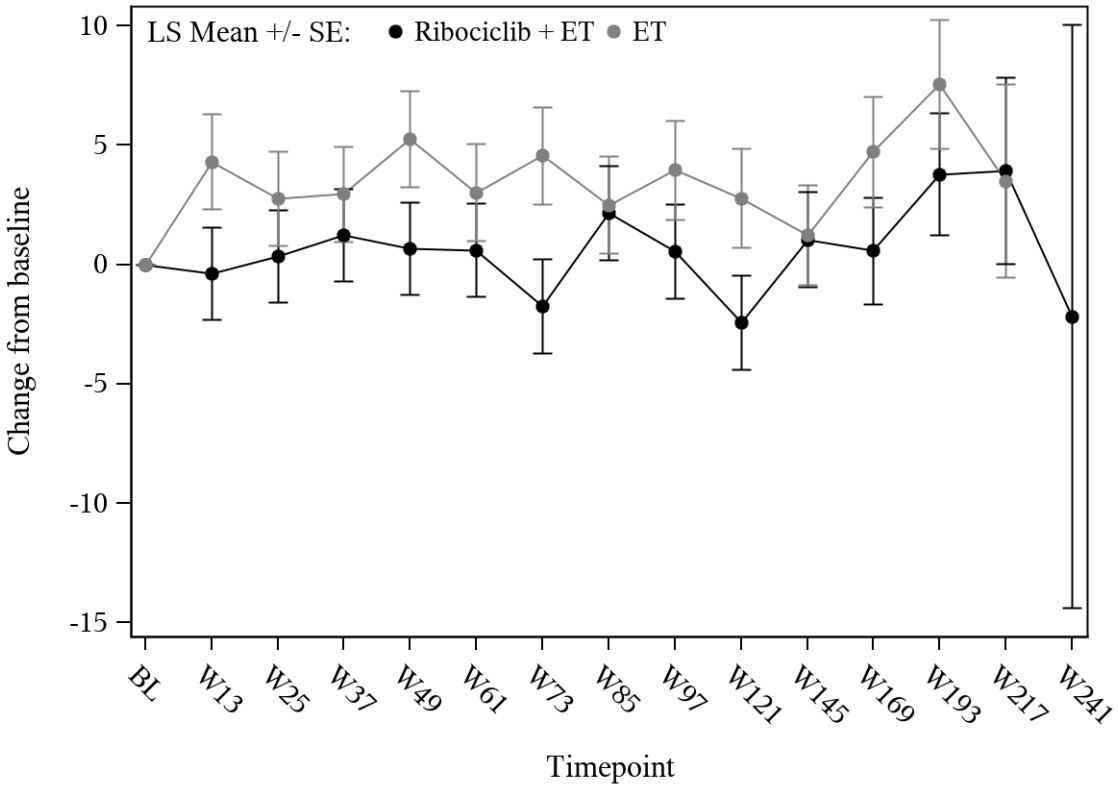
Ribociclib + ET	619	598	577	580	567	569	565	559	550	536	536	451	382	225	31
ET	593	566	543	536	546	544	533	528	526	513	498	434	365	217	34

QLQ-C30 - Insomnia
Geographical region: North America/Australia



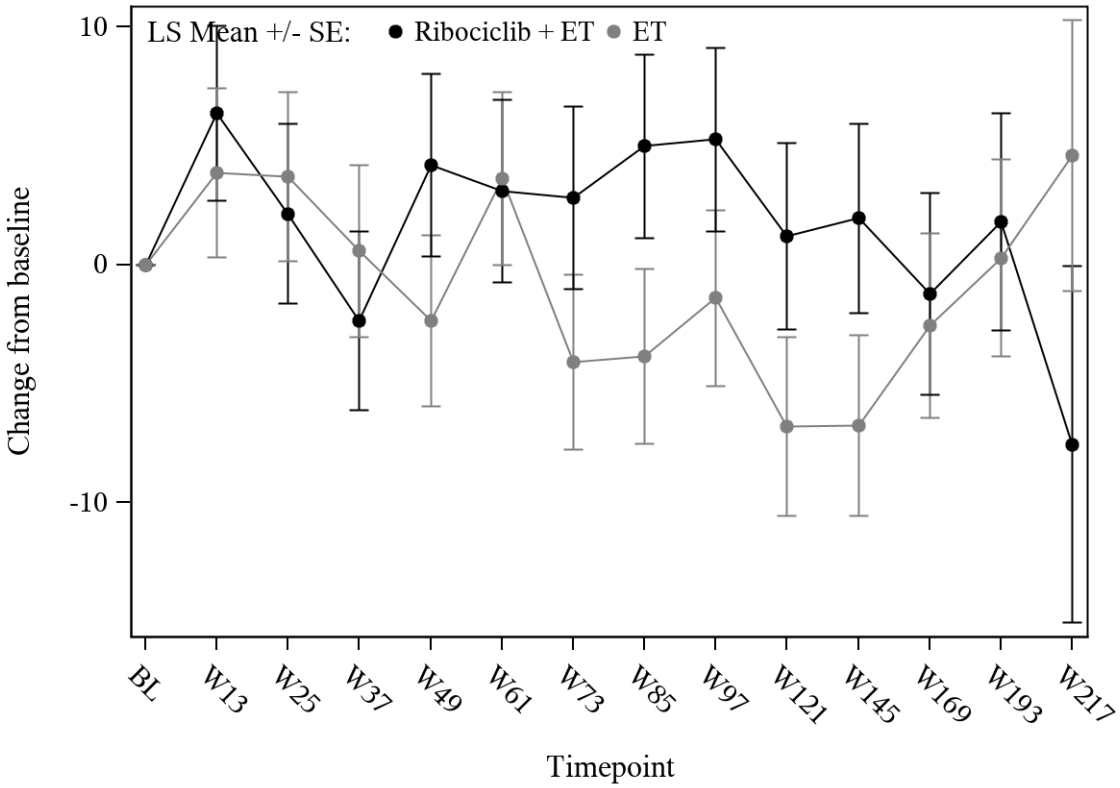
Ribociclib + ET	203	191	171	175	175	169	167	159	161	149	147	116	102	75	24
ET	177	164	147	153	152	142	141	123	121	119	109	84	74	53	17

QLQ-C30 - Insomnia
Geographical region: Asia



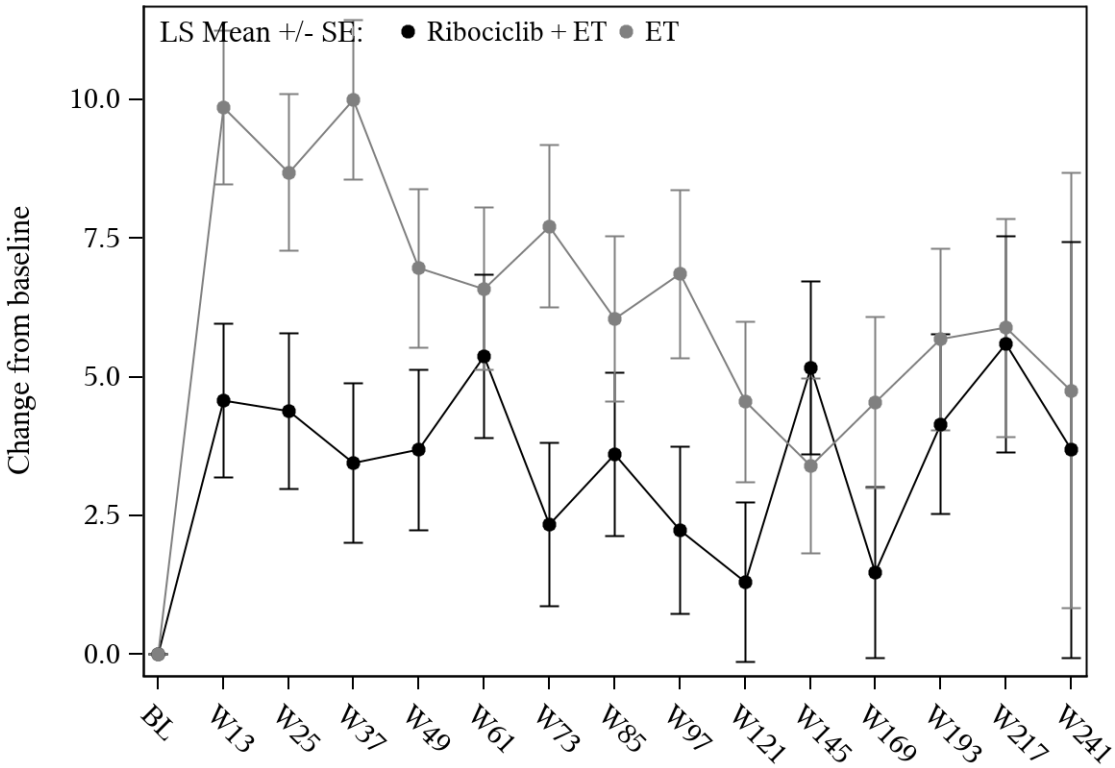
Ribociclib + ET	175	175	173	171	171	169	167	167	166	162	162	116	89	33	3
ET	166	165	163	159	159	154	155	154	150	150	146	110	79	31	

QLQ-C30 - Insomnia
Geographical region: Latin America



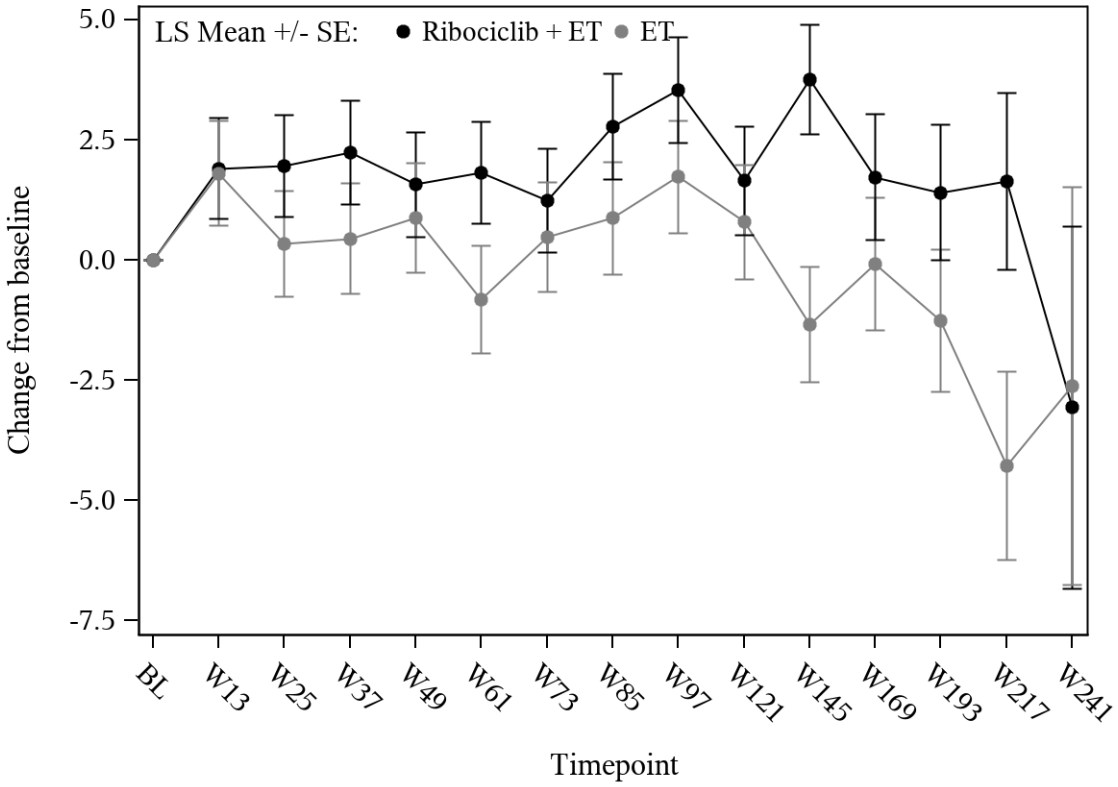
Ribociclib + ET	63	63	58	60	58	58	58	58	57	55	53	44	38	12
ET	69	68	68	64	66	64	63	63	63	59	58	55	47	22

QLQ-C30 - Insomnia
AJCC Anatomic Stage Group: Group I/II



Ribociclib + ET	395	384	367	365	361	361	357	355	353	342	339	315	316	177	31
ET	399	382	351	366	368	360	360	342	347	335	322	317	302	175	28

QLQ-C30 - Insomnia
AJCC Anatomic Stage Group: Group III



Ribociclib + ET	665	643	612	621	610	604	600	588	581	560	559	412	295	168	27
ET	606	581	570	546	555	544	532	526	513	506	489	366	263	148	23

Table 5-2.1.6.1 QLQ-C30 - Appetite Loss: change from baseline analysis - subgroup analysis (Full Analysis Set)

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1115)	ET (N = 1123)	Parameter	Esti-mate	[95% CI]	p-value
QLQ-C30 - Appetite Loss						
	N' | LS Mean (SE)	**N' | LS Mean (SE)**				
Region						
Interaction test	**p = 0.343**					
NA/WE/O	599 | 3.14 (0.54)	578 | 2.09 (0.55)	Difference	1.05	[-0.45; 2.56]	0.170
			Hedges G	0.08	[-0.03; 0.19]	
ROW	460 | 1.10 (0.56)	427 | 1.26 (0.59)	Difference	-0.15	[-1.75; 1.44]	0.852
			Hedges G	-0.01	[-0.14; 0.12]	
Geographical region						
Interaction test	**p = 0.996**					
Europe	618 | 2.68 (0.53)	593 | 2.06 (0.53)	Difference	0.62	[-0.85; 2.10]	0.406
			Hedges G	0.05	[-0.06; 0.16]	
North America/Australia	203 | 1.98 (0.75)	177 | 1.45 (0.83)	Difference	0.54	[-1.65; 2.73]	0.630
			Hedges G	0.05	[-0.15; 0.25]	
Asia	175 | N.E.	166 | N.E.	Difference	N.E.	[N.E.]	N.E.
			Hedges G	N.E.	[N.E.]	
Latin America	63 | 4.13 (1.53)	69 | 3.57 (1.43)	Difference	0.56	[-3.59; 4.71]	0.790
			Hedges G	0.05	[-0.30; 0.39]	
Age group 1 at randomization						
Interaction test	**N.E.**					
<45	525 | 2.79 (0.54)	459 | 1.97 (0.57)	Difference	0.83	[-0.73; 2.38]	0.297
			Hedges G	0.07	[-0.06; 0.19]	
45 to 54	514 | 1.92 (0.56)	519 | 1.16 (0.57)	Difference	0.77	[-0.80; 2.33]	0.336
			Hedges G	0.06	[-0.06; 0.18]	
55 to 64	20 | N.E.	27 | N.E.	Difference	N.E.	[N.E.]	N.E.
			Hedges G	N.E.	[N.E.]	
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)						
Interaction test	**p = 0.663**					
<Median	525 | 3.11 (0.57)	459 | 1.82 (0.60)	Difference	1.29	[-0.32; 2.91]	0.115
			Hedges G	0.10	[-0.02; 0.23]	
≥Median	534 | 1.56 (0.53)	546 | 1.34 (0.54)	Difference	0.21	[-1.28; 1.71]	0.778
			Hedges G	0.02	[-0.10; 0.14]	

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1115)	**ET (N = 1123)**	**Parameter**	**Esti-mate**	**[95% CI]**	**p-value**
Race						
Interaction test	**p = 0.867**					
Asian	206 | -0.04 (0.79)	180 | -0.50 (0.85)	Difference	0.46	[-1.84; 2.75]	0.695
			Hedges G	0.04	[-0.16; 0.24]	
Non-Asian	802 | 2.55 (0.43)	773 | 2.26 (0.44)	Difference	0.28	[-0.93; 1.50]	0.647
			Hedges G	0.02	[-0.08; 0.12]	
BMI at screening						
Interaction test	**p = 0.276**					
≥25	529 | 4.09 (0.54)	489 | 3.12 (0.57)	Difference	0.97	[-0.56; 2.51]	0.214
			Hedges G	0.08	[-0.05; 0.20]	
<25	518 | 0.28 (0.57)	505 | 0.32 (0.58)	Difference	-0.04	[-1.63; 1.54]	0.957
			Hedges G	-0.00	[-0.13; 0.12]	
AJCC Anatomic Stage Group						
Interaction test	**p = 0.294**					
Group I/II	394 | 2.10 (0.66)	399 | 2.36 (0.66)	Difference	-0.26	[-2.10; 1.58]	0.782
			Hedges G	-0.02	[-0.16; 0.12]	
Group III	665 | 2.35 (0.48)	606 | 1.25 (0.51)	Difference	1.10	[-0.28; 2.48]	0.117
			Hedges G	0.09	[-0.02; 0.20]	
Anatomic stages						
Interaction test	**N.E.**					
IA/IB/IIA	163 | 0.09 (0.95)	189 | 1.49 (0.91)	Difference	-1.40	[-4.00; 1.21]	0.293
			Hedges G	-0.11	[-0.32; 0.10]	
IIB	231 | 3.78 (0.92)	210 | 2.97 (0.95)	Difference	0.81	[-1.79; 3.41]	0.542
			Hedges G	0.06	[-0.13; 0.25]	
IIIA	433 | 2.81 (0.61)	368 | 1.48 (0.66)	Difference	1.33	[-0.44; 3.10]	0.141
			Hedges G	0.10	[-0.03; 0.24]	
IIIB	63 | 3.70 (1.54)	52 | 2.97 (1.72)	Difference	0.72	[-3.87; 5.32]	0.755
			Hedges G	0.06	[-0.31; 0.43]	
IIIC	169 | 0.97 (0.94)	186 | 0.16 (0.90)	Difference	0.81	[-1.74; 3.36]	0.531
			Hedges G	0.07	[-0.14; 0.27]	
Nodal status						
Interaction test	**p = 0.617**					
N0	84 | -0.46 (1.15)	110 | -1.39 (1.03)	Difference	0.93	[-2.14; 3.99]	0.550
			Hedges G	0.09	[-0.20; 0.37]	
N1-N3	975 | 2.52 (0.41)	892 | 2.07 (0.43)	Difference	0.45	[-0.73; 1.63]	0.452
			Hedges G	0.03	[-0.06; 0.13]	

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1115)	**ET (N = 1123)**	**Parameter**	**Esti-mate**	**[95% CI]**	**p-value**
Histological grade at time of surgery						
Interaction test	**p = 0.838**					
Grade 1	106 | 2.10 (1.22)	97 | 2.08 (1.28)	Difference	0.02	[-3.47; 3.50]	0.992
			Hedges G	0.00	[-0.27; 0.28]	
Grade 2	579 | 2.17 (0.51)	559 | 1.32 (0.52)	Difference	0.86	[-0.58; 2.29]	0.241
			Hedges G	0.07	[-0.05; 0.19]	
Grade 3	282 | 2.21 (0.68)	252 | 1.83 (0.71)	Difference	0.38	[-1.54; 2.30]	0.696
			Hedges G	0.03	[-0.14; 0.20]	
Histological subtype						
Interaction test	**p = 0.428**					
Ductal	822 | 2.66 (0.43)	787 | 1.86 (0.45)	Difference	0.80	[-0.42; 2.02]	0.197
			Hedges G	0.06	[-0.03; 0.16]	
Lobular	168 | N.E.	156 | N.E.	Difference	N.E.	[N.E.]	N.E.
			Hedges G	N.E.	[N.E.]	
Other	69 | 0.80 (1.70)	62 | 3.43 (1.90)	Difference	-2.63	[-7.67; 2.42]	0.305
			Hedges G	-0.18	[-0.52; 0.16]	
Ki67 status from surgical specimen						
Interaction test	**p = 0.907**					
Ki67≤20	510 | 2.15 (0.52)	517 | 1.59 (0.52)	Difference	0.56	[-0.89; 2.00]	0.449
			Hedges G	0.05	[-0.08; 0.17]	
Ki67>20	400 | 2.26 (0.64)	359 | 1.82 (0.68)	Difference	0.44	[-1.40; 2.28]	0.635
			Hedges G	0.03	[-0.11; 0.18]	
Type of NSAI						
Interaction test	**p = 0.524**					
Letrozole	775 | 2.14 (0.45)	721 | 1.86 (0.48)	Difference	0.28	[-1.00; 1.57]	0.666
			Hedges G	0.02	[-0.08; 0.12]	
Anastrozole	284 | 2.24 (0.72)	282 | 0.79 (0.72)	Difference	1.45	[-0.56; 3.45]	0.156
			Hedges G	0.12	[-0.05; 0.28]	
Prior neo/adjuvant chemotherapy						
Interaction test	**p = 0.291**					
Yes	984 | 2.39 (0.41)	927 | 2.05 (0.42)	Difference	0.34	[-0.81; 1.49]	0.564
			Hedges G	0.03	[-0.06; 0.12]	
No	75 | -0.14 (1.24)	78 | -2.26 (1.26)	Difference	2.12	[-1.39; 5.63]	0.234
			Hedges G	0.19	[-0.12; 0.51]	
Prior adjuvant chemotherapy						
Interaction test	**p = 0.242**					
Yes	494 | 1.95 (0.57)	463 | 1.90 (0.60)	Difference	0.05	[-1.58; 1.67]	0.955
			Hedges G	0.00	[-0.12; 0.13]	
No	565 | 2.54 (0.53)	542 | 1.34 (0.55)	Difference	1.20	[-0.30; 2.69]	0.116
			Hedges G	0.09	[-0.02; 0.21]	

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1115)	ET (N = 1123)	Parameter	Esti-mate	[95% CI]	p-value
Prior neoadjuvant chemotherapy						
Interaction test	**p = 0.407**					
Yes	520 | 2.85 (0.56)	502 | 1.75 (0.57)	Difference	1.10	[-0.47; 2.67]	0.169
			Hedges G	0.09	[-0.04; 0.21]	
No	539 | 1.73 (0.55)	503 | 1.52 (0.57)	Difference	0.21	[-1.34; 1.76]	0.786
			Hedges G	0.02	[-0.10; 0.14]	
Prior endocrine therapy						
Interaction test	**p = 0.521**					
Yes	815 | 2.50 (0.45)	735 | 1.68 (0.48)	Difference	0.82	[-0.47; 2.12]	0.213
			Hedges G	0.06	[-0.04; 0.16]	
No	244 | 1.32 (0.80)	270 | 1.72 (0.77)	Difference	-0.40	[-2.59; 1.78]	0.717
			Hedges G	-0.03	[-0.21; 0.14]	
Prior mastectomy						
Interaction test	**N.E.**					
Yes	737 | 2.15 (0.47)	699 | 0.98 (0.48)	Difference	1.17	[-0.14; 2.48]	0.081
			Hedges G	0.09	[-0.01; 0.20]	
No	322 | 2.50 (0.71)	306 | 3.09 (0.74)	Difference	-0.59	[-2.60; 1.42]	0.565
			Hedges G	-0.05	[-0.20; 0.11]	
Prior radiotherapy						
Interaction test	**p = 0.309**					
Yes	970 | 2.21 (0.41)	923 | 1.85 (0.42)	Difference	0.36	[-0.80; 1.52]	0.546
			Hedges G	0.03	[-0.06; 0.12]	
No	89 | 1.98 (1.19)	82 | -0.04 (1.26)	Difference	2.02	[-1.42; 5.45]	0.248
			Hedges G	0.18	[-0.12; 0.48]	

N: Number of patients
N': Number of patients in the analysis
CI: Confidence interval
SD: Standard deviation
LS Mean: Least square mean
SE: Standard error
MMRM: Mixed model for repeated measures
N.E.: Not estimable
ET: Endocrine therapy (Anastrozole/Letrozole + Goserelin)
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Analysis method for interaction test:
p-value from MMRM with unstructured covariance matrix:
change from baseline = treatment + visit + treatment * visit + subgroup factor + treatment * subgroup factor + subgroup factor * visit + treatment * subgroup factor * visit + baseline value
If the model did not converge for a parameter*subgroup factor, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry. If the model did still not converge, interactions were removed in the order treatment * subgroup factor * visit, subgroup factor * visit.

Analysis methods for within-subgroup analysis:
Adjusted mean (LS Mean) change from baseline and overall effect obtained from MMRM with unstructured covariance matrix:
change from baseline = treatment + visit + treatment * visit + baseline value
ET was the reference group for treatment group comparison.
If the model did not converge for a parameter*subgroup factor, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry.

Patients with an evaluable baseline score and at least one evaluable post-baseline score were included in the analysis.
All data collected were included in the analysis, including assessments at confirmation of first recurrence and thereafter, as long as there were at least 50 patients in each treatment group at a visit in the overall (sub-)population.

Table 5-2.1.7.1 QLQ-C30 - Constipation: change from baseline analysis - subgroup analysis (Full Analysis Set)

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1115)	ET (N = 1123)	Parameter	Esti-mate	[95% CI]	p-value
QLQ-C30 - Constipation						
	N' | LS Mean (SE)	**N' | LS Mean (SE)**				
Region						
Interaction test	**p = 0.065**					
NA/WE/O	596 | 5.39 (0.69)	577 | 2.66 (0.70)	Difference	2.74	[0.81; 4.66]	0.005
			Hedges G	0.16	[0.05; 0.28]	
ROW	459 | 3.55 (0.67)	427 | 3.39 (0.70)	Difference	0.15	[-1.76; 2.07]	0.875
			Hedges G	0.01	[-0.12; 0.14]	
Geographical region						
Interaction test	**p = 0.731**					
Europe	615 | 5.34 (0.66)	593 | 3.46 (0.67)	Difference	1.88	[0.04; 3.73]	0.046
			Hedges G	0.12	[0.00; 0.23]	
North America/Australia	202 | 3.92 (1.06)	176 | 2.04 (1.16)	Difference	1.88	[-1.21; 4.97]	0.232
			Hedges G	0.12	[-0.08; 0.33]	
Asia	175 | N.E.	166 | N.E.	Difference	N.E.	[N.E.]	N.E.
			Hedges G	N.E.	[N.E.]	
Latin America	63 | 3.53 (1.96)	69 | 4.80 (1.83)	Difference	-1.27	[-6.58; 4.04]	0.637
			Hedges G	-0.08	[-0.42; 0.26]	
Age group 1 at randomization						
Interaction test	**N.E.**					
<45	523 | 4.73 (0.69)	458 | 2.62 (0.73)	Difference	2.12	[0.16; 4.08]	0.034
			Hedges G	0.14	[0.01; 0.26]	
45 to 54	512 | 4.86 (0.72)	519 | 3.51 (0.73)	Difference	1.35	[-0.65; 3.35]	0.185
			Hedges G	0.08	[-0.04; 0.20]	
55 to 64	20 | N.E.	27 | N.E.	Difference	N.E.	[N.E.]	N.E.
			Hedges G	N.E.	[N.E.]	
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)						
Interaction test	**p = 0.518**					
<Median	523 | 4.73 (0.69)	458 | 2.62 (0.73)	Difference	2.12	[0.16; 4.08]	0.034
			Hedges G	0.14	[0.01; 0.26]	
≥Median	532 | 4.55 (0.70)	546 | 3.56 (0.71)	Difference	0.98	[-0.97; 2.93]	0.322
			Hedges G	0.06	[-0.06; 0.18]	

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1115)	**ET (N = 1123)**	**Parameter**	**Esti-mate**	**[95% CI]**	**p-value**
Race						
Interaction test	**p = 0.968**					
Asian	206 | 3.48 (1.00)	180 | 1.90 (1.07)	Difference	1.58	[-1.30; 4.46]	0.281
			Hedges G	0.11	[-0.09; 0.31]	
Non-Asian	798 | 5.03 (0.57)	772 | 3.41 (0.58)	Difference	1.63	[0.03; 3.22]	0.046
			Hedges G	0.10	[0.00; 0.20]	
BMI at screening						
Interaction test	**p = 0.962**					
≥25	527 | 5.63 (0.74)	489 | 4.25 (0.78)	Difference	1.38	[-0.73; 3.49]	0.199
			Hedges G	0.08	[-0.04; 0.20]	
<25	516 | 3.68 (0.66)	504 | 2.22 (0.67)	Difference	1.46	[-0.38; 3.30]	0.119
			Hedges G	0.10	[-0.03; 0.22]	
AJCC Anatomic Stage Group						
Interaction test	**p = <.001**					
Group I/II	392 | 3.41 (0.80)	398 | 4.94 (0.80)	Difference	-1.53	[-3.76; 0.69]	0.177
			Hedges G	-0.10	[-0.24; 0.04]	
Group III	663 | 5.30 (0.63)	606 | 1.89 (0.66)	Difference	3.41	[1.62; 5.19]	<.001
			Hedges G	0.21	[0.10; 0.32]	
Anatomic stages						
Interaction test	**p = 0.003**					
IA/IB/IIA	162 | 3.04 (1.11)	189 | 4.98 (1.06)	Difference	-1.94	[-4.97; 1.09]	0.209
			Hedges G	-0.13	[-0.34; 0.08]	
IIB	230 | 3.69 (1.13)	209 | 4.84 (1.17)	Difference	-1.15	[-4.35; 2.05]	0.480
			Hedges G	-0.07	[-0.25; 0.12]	
IIIA	432 | 6.37 (0.78)	368 | 2.01 (0.84)	Difference	4.36	[2.11; 6.61]	<.001
			Hedges G	0.27	[0.13; 0.41]	
IIIB	63 | 4.00 (2.17)	52 | 2.69 (2.41)	Difference	1.31	[-5.19; 7.82]	0.690
			Hedges G	0.07	[-0.29; 0.44]	
IIIC	168 | 3.79 (1.19)	186 | 1.03 (1.14)	Difference	2.76	[-0.47; 6.00]	0.094
			Hedges G	0.18	[-0.03; 0.39]	
Nodal status						
Interaction test	**p = 0.810**					
N0	84 | 5.37 (1.62)	110 | 4.14 (1.44)	Difference	1.23	[-3.06; 5.51]	0.574
			Hedges G	0.08	[-0.20; 0.37]	
N1-N3	971 | N.E.	891 | N.E.	Difference	N.E.	[N.E.]	N.E.
			Hedges G	N.E.	[N.E.]	

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1115)	**ET (N = 1123)**	**Parameter**	**Esti-mate**	**[95% CI]**	**p-value**
Histological grade at time of surgery						
Interaction test	**p = 0.955**					
Grade 1	106 | 5.34 (1.58)	97 | 4.23 (1.67)	Difference	1.11	[-3.43; 5.64]	0.630
			Hedges G	0.07	[-0.21; 0.34]	
Grade 2	577 | 4.98 (0.66)	559 | 3.13 (0.68)	Difference	1.85	[-0.02; 3.71]	0.052
			Hedges G	0.12	[-0.00; 0.23]	
Grade 3	282 | 4.15 (0.91)	252 | 2.29 (0.95)	Difference	1.86	[-0.73; 4.44]	0.160
			Hedges G	0.12	[-0.05; 0.29]	
Histological subtype						
Interaction test	**N.E.**					
Ductal	819 | N.E.	786 | N.E.	Difference	N.E.	[N.E.]	N.E.
			Hedges G	N.E.	[N.E.]	
Lobular	167 | 7.29 (1.29)	156 | 3.73 (1.37)	Difference	3.56	[-0.14; 7.26]	0.059
			Hedges G	0.21	[-0.01; 0.43]	
Other	69 | 2.40 (1.97)	62 | 1.14 (2.22)	Difference	1.26	[-4.61; 7.13]	0.672
			Hedges G	0.07	[-0.27; 0.42]	
Ki67 status from surgical specimen						
Interaction test	**p = 0.408**					
Ki67≤20	508 | 5.25 (0.69)	517 | 3.30 (0.68)	Difference	1.95	[0.04; 3.86]	0.045
			Hedges G	0.13	[0.00; 0.25]	
Ki67>20	399 | 3.86 (0.78)	359 | 3.19 (0.83)	Difference	0.67	[-1.57; 2.91]	0.559
			Hedges G	0.04	[-0.10; 0.19]	
Type of NSAI						
Interaction test	**p = 0.279**					
Letrozole	772 | 4.44 (0.56)	720 | 2.47 (0.59)	Difference	1.97	[0.39; 3.56]	0.015
			Hedges G	0.13	[0.02; 0.23]	
Anastrozole	283 | 4.98 (1.03)	282 | 4.90 (1.04)	Difference	0.08	[-2.80; 2.95]	0.959
			Hedges G	0.00	[-0.16; 0.17]	
Prior neo/adjuvant chemotherapy						
Interaction test	**p = 0.008**					
Yes	980 | 4.86 (0.51)	926 | 2.84 (0.53)	Difference	2.02	[0.57; 3.47]	0.006
			Hedges G	0.13	[0.04; 0.22]	
No	75 | 0.77 (1.61)	78 | 6.45 (1.64)	Difference	-5.68	[-10.23; -1.14]	0.015
			Hedges G	-0.40	[-0.72; -0.08]	
Prior adjuvant chemotherapy						
Interaction test	**p = 0.192**					
Yes	494 | 5.54 (0.71)	462 | 2.85 (0.74)	Difference	2.68	[0.67; 4.70]	0.009
			Hedges G	0.17	[0.04; 0.30]	
No	561 | 3.81 (0.68)	542 | 3.28 (0.69)	Difference	0.54	[-1.37; 2.44]	0.580
			Hedges G	0.03	[-0.08; 0.15]	

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1115)	ET (N = 1123)	Parameter	Esti-mate	[95% CI]	p-value
Prior neoadjuvant chemotherapy						
Interaction test	**p = 0.548**					
Yes	516 | 4.48 (0.71)	502 | 2.58 (0.72)	Difference	1.91	[-0.09; 3.90]	0.061
			Hedges G	0.12	[-0.01; 0.24]	
No	539 | 4.69 (0.68)	502 | 3.58 (0.71)	Difference	1.12	[-0.81; 3.05]	0.255
			Hedges G	0.07	[-0.05; 0.19]	
Prior endocrine therapy						
Interaction test	**p = 0.850**					
Yes	812 | 4.64 (0.56)	734 | 3.21 (0.59)	Difference	1.43	[-0.17; 3.02]	0.079
			Hedges G	0.09	[-0.01; 0.19]	
No	243 | 4.62 (1.02)	270 | 2.76 (0.98)	Difference	1.86	[-0.92; 4.64]	0.190
			Hedges G	0.12	[-0.06; 0.29]	
Prior mastectomy						
Interaction test	**p = 0.038**					
Yes	733 | 4.88 (0.60)	698 | 2.34 (0.62)	Difference	2.54	[0.85; 4.23]	0.003
			Hedges G	0.16	[0.05; 0.26]	
No	322 | 3.97 (0.83)	306 | 4.71 (0.87)	Difference	-0.75	[-3.11; 1.62]	0.536
			Hedges G	-0.05	[-0.21; 0.11]	
Prior radiotherapy						
Interaction test	**p = 0.510**					
Yes	966 | 4.89 (0.52)	922 | 3.20 (0.53)	Difference	1.69	[0.24; 3.15]	0.022
			Hedges G	0.11	[0.01; 0.20]	
No	89 | 1.72 (1.61)	82 | 2.14 (1.71)	Difference	-0.42	[-5.06; 4.22]	0.857
			Hedges G	-0.03	[-0.33; 0.27]	

N: Number of patients
N': Number of patients in the analysis
CI: Confidence interval
SD: Standard deviation
LS Mean: Least square mean
SE: Standard error
MMRM: Mixed model for repeated measures
N.E.: Not estimable
ET: Endocrine therapy (Anastrozole/Letrozole + Goserelin)
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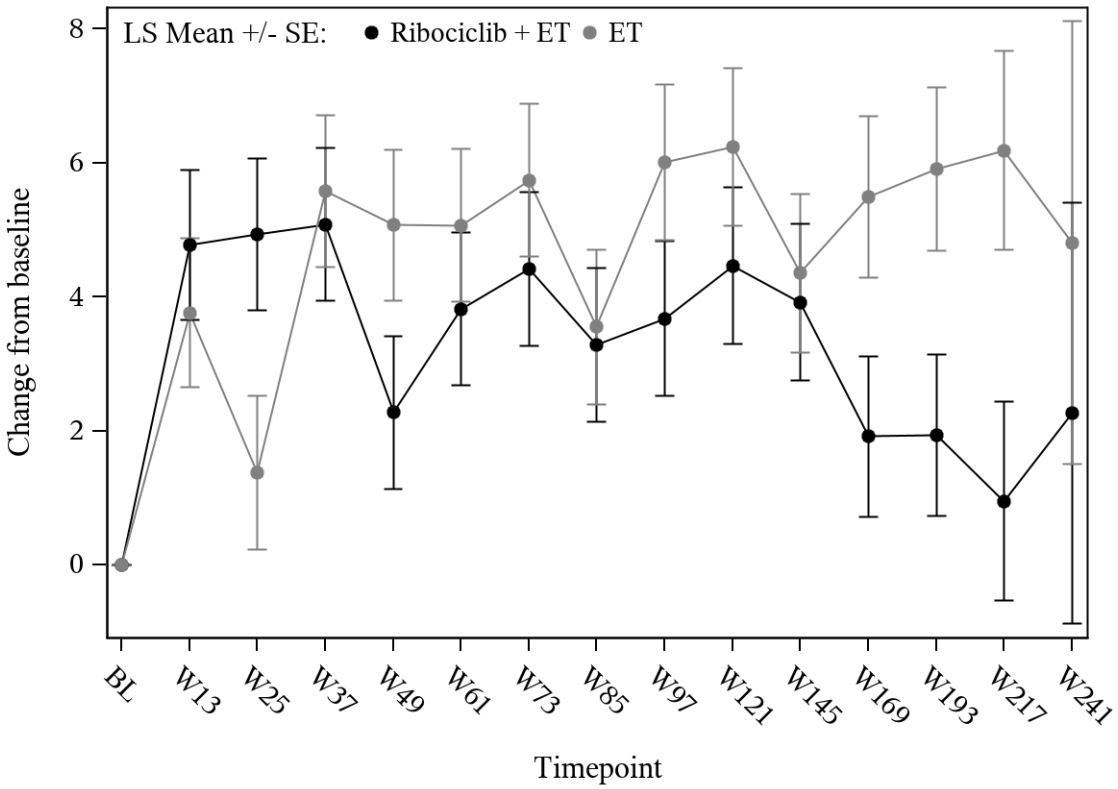
Analysis method for interaction test:
p-value from MMRM with unstructured covariance matrix:
change from baseline = treatment + visit + treatment * visit + subgroup factor + treatment * subgroup factor + subgroup factor * visit + treatment * subgroup factor * visit + baseline value
If the model did not converge for a parameter*subgroup factor, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry. If the model did still not converge, interactions were removed in the order treatment * subgroup factor * visit, subgroup factor * visit.

Analysis methods for within-subgroup analysis:
Adjusted mean (LS Mean) change from baseline and overall effect obtained from MMRM with unstructured covariance matrix:
change from baseline = treatment + visit + treatment * visit + baseline value
ET was the reference group for treatment group comparison.
If the model did not converge for a parameter*subgroup factor, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry.

Patients with an evaluable baseline score and at least one evaluable post-baseline score were included in the analysis.
All data collected were included in the analysis, including assessments at confirmation of first recurrence and thereafter, as long as there were at least 50 patients in each treatment group at a visit in the overall (sub-)population.

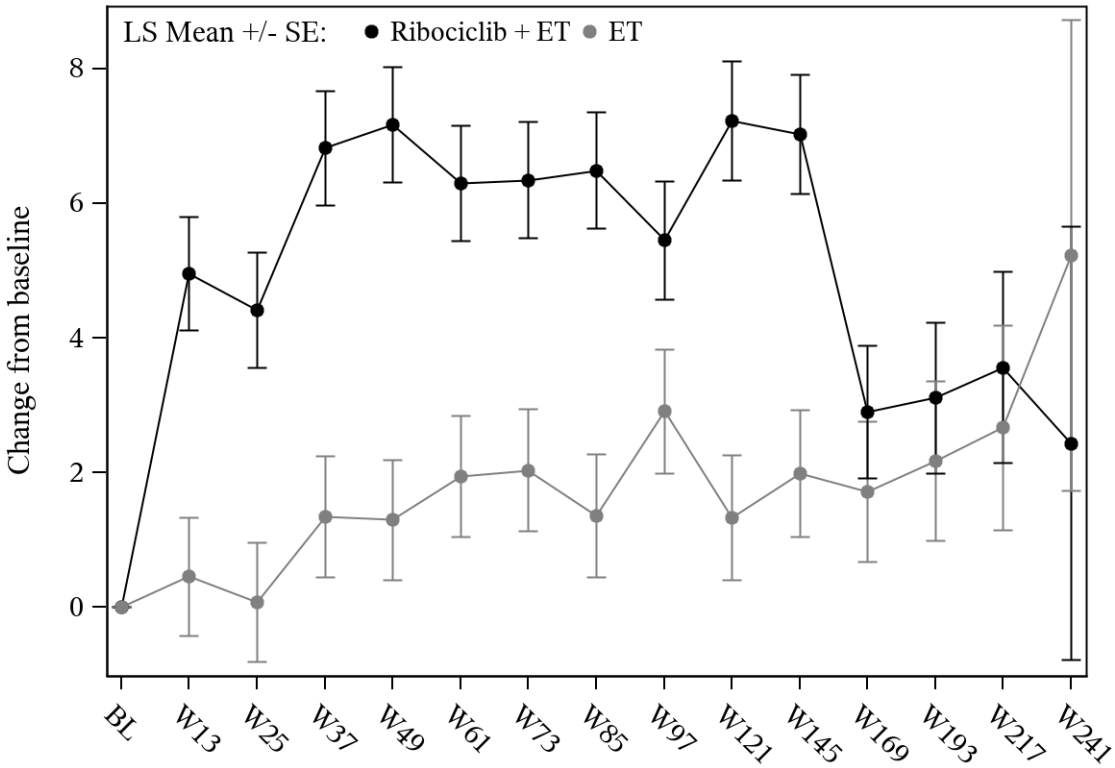
Figure 5-2.1.7.1 QLQ-C30 - Constipation: line chart of change from baseline - subgroup analysis (Full Analysis Set)

QLQ-C30 - Constipation
AJCC Anatomic Stage Group: Group I/II



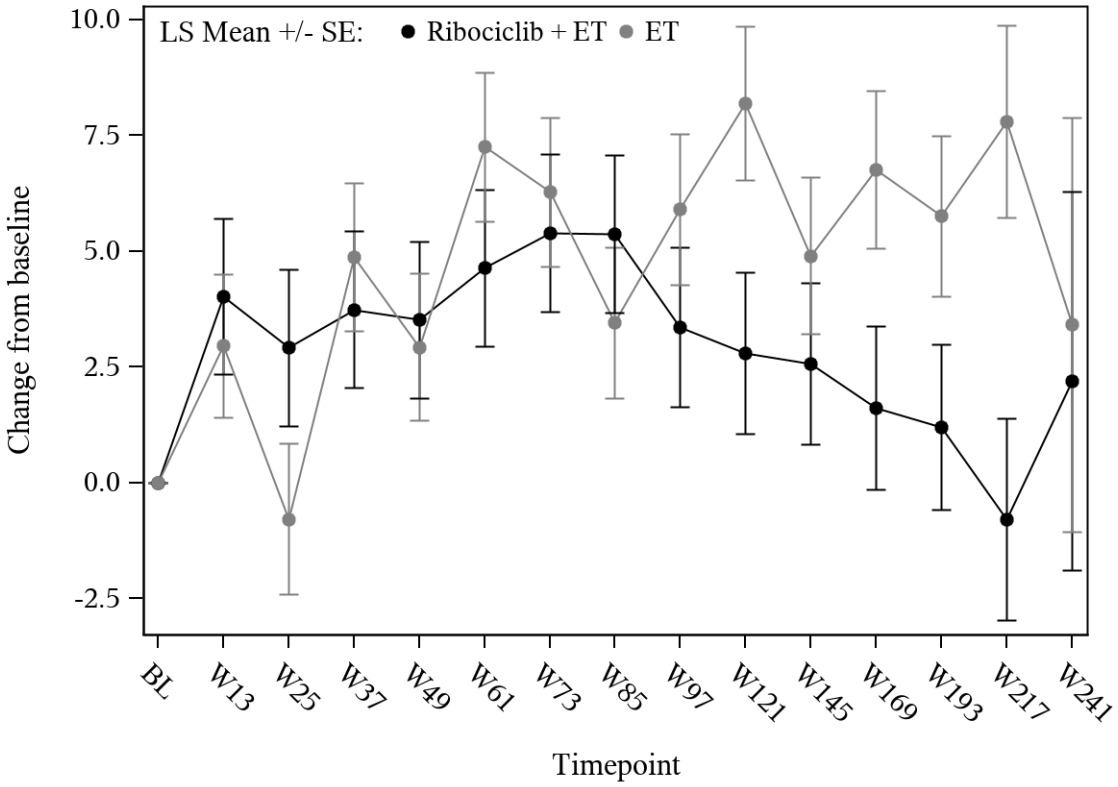
Ribociclib + ET	392	381	366	363	360	358	354	349	349	338	337	313	314	175	31
ET	398	381	351	364	368	359	359	341	346	334	321	315	303	174	28

QLQ-C30 - Constipation
AJCC Anatomic Stage Group: Group III



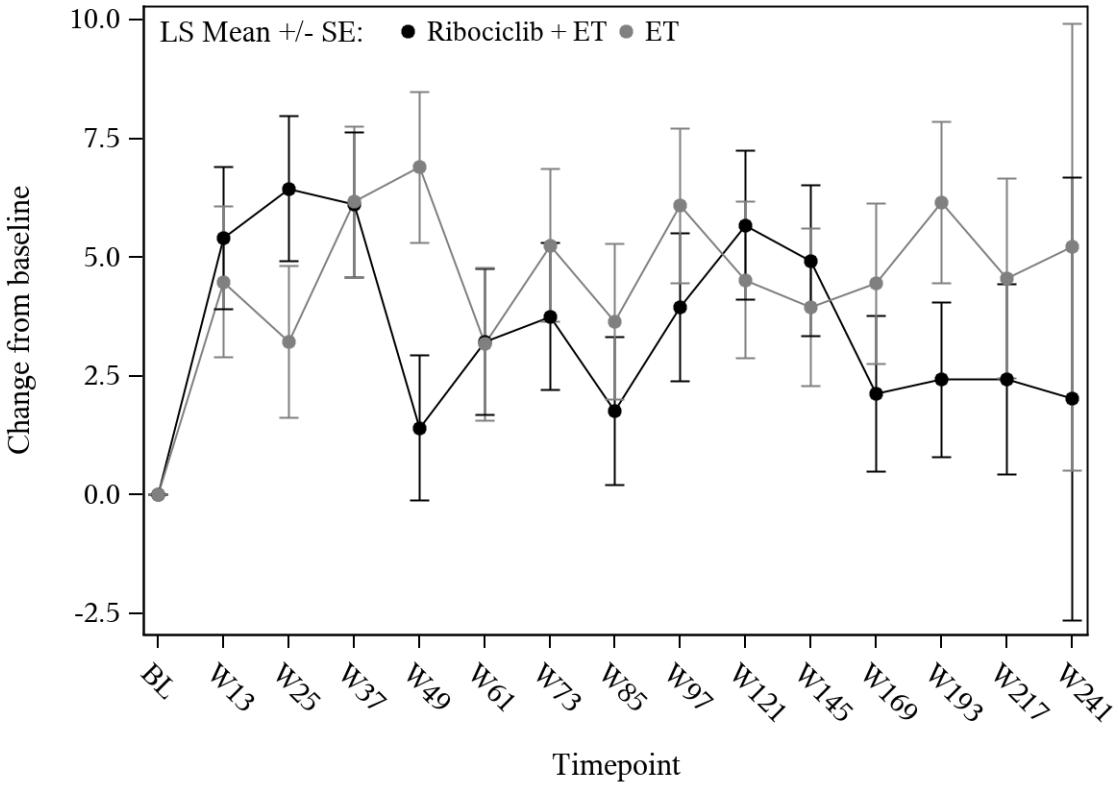
Ribociclib + ET	663	641	611	619	609	602	599	587	578	560	559	411	294	168	27
ET	606	582	571	545	553	544	533	527	513	506	489	365	263	147	23

QLQ-C30 - Constipation
Anatomic stages: IA/IB/IIA



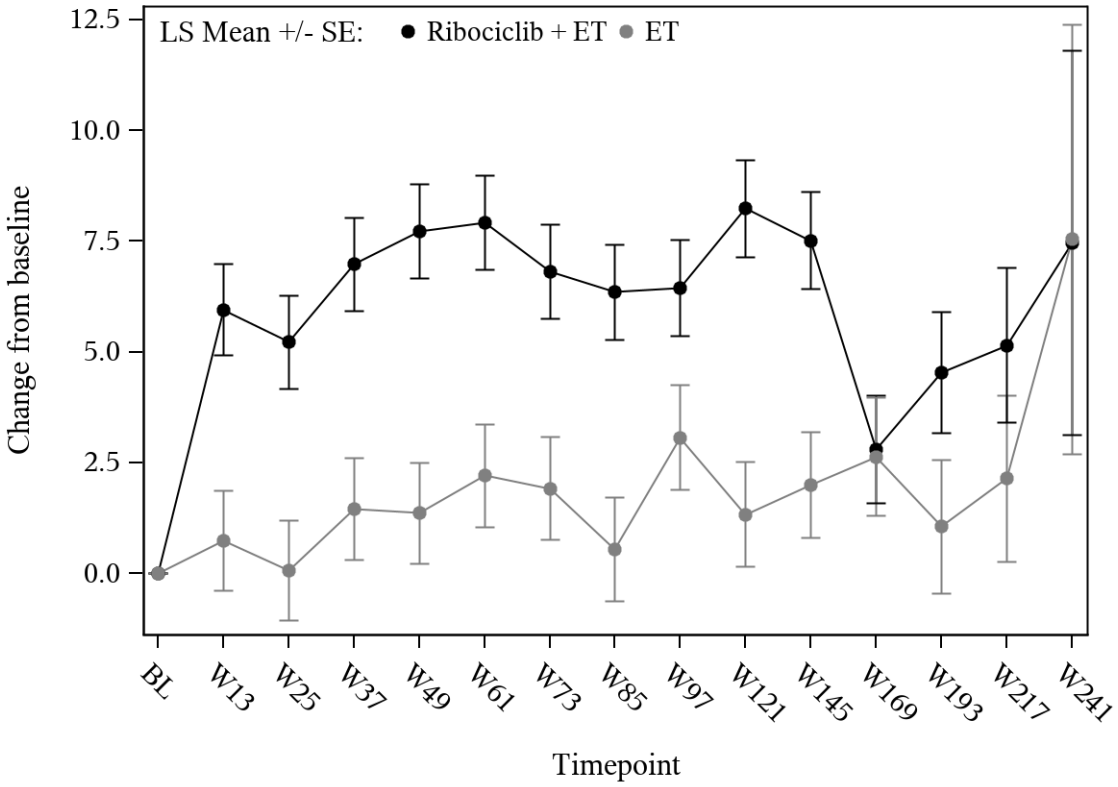
Ribociclib + ET	162	157	153	153	152	154	150	150	146	140	142	137	134	78	17
ET	189	184	161	169	171	167	169	162	162	156	148	147	140	86	14

QLQ-C30 - Constipation
Anatomic stages: IIB



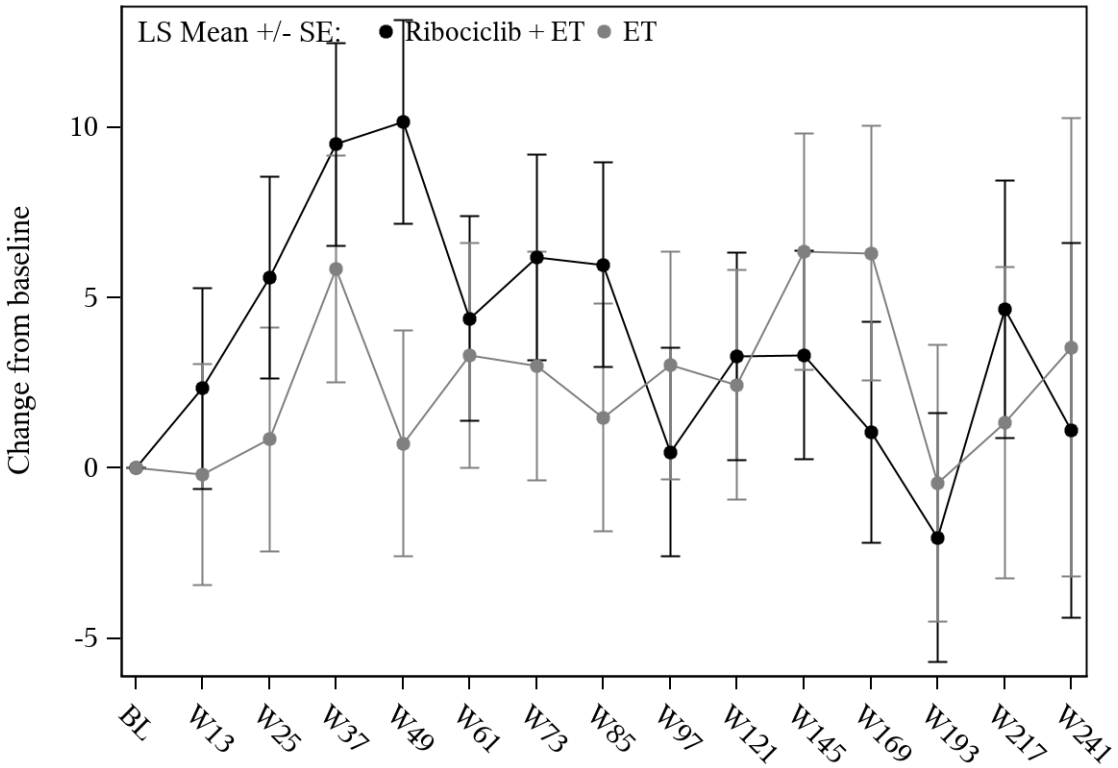
Ribociclib + ET	230	224	213	210	208	204	204	199	203	198	195	176	180	97	14
ET	209	197	190	195	197	192	190	179	184	178	173	168	163	88	14

QLQ-C30 - Constipation
Anatomic stages: IIIA



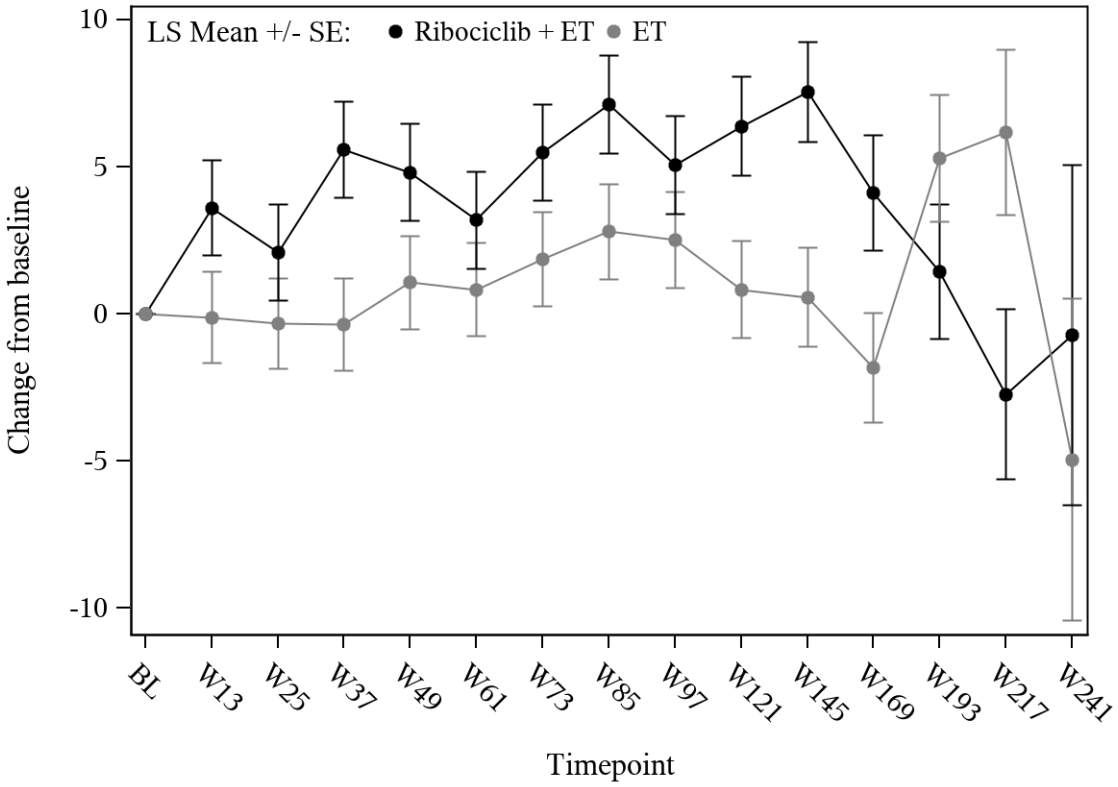
Ribociclib + ET	432	414	390	399	392	388	385	375	371	356	360	269	197	112	15
ET	368	355	343	328	335	329	327	321	313	307	304	224	162	98	12

QLQ-C30 - Constipation
Anatomic stages: IIIB



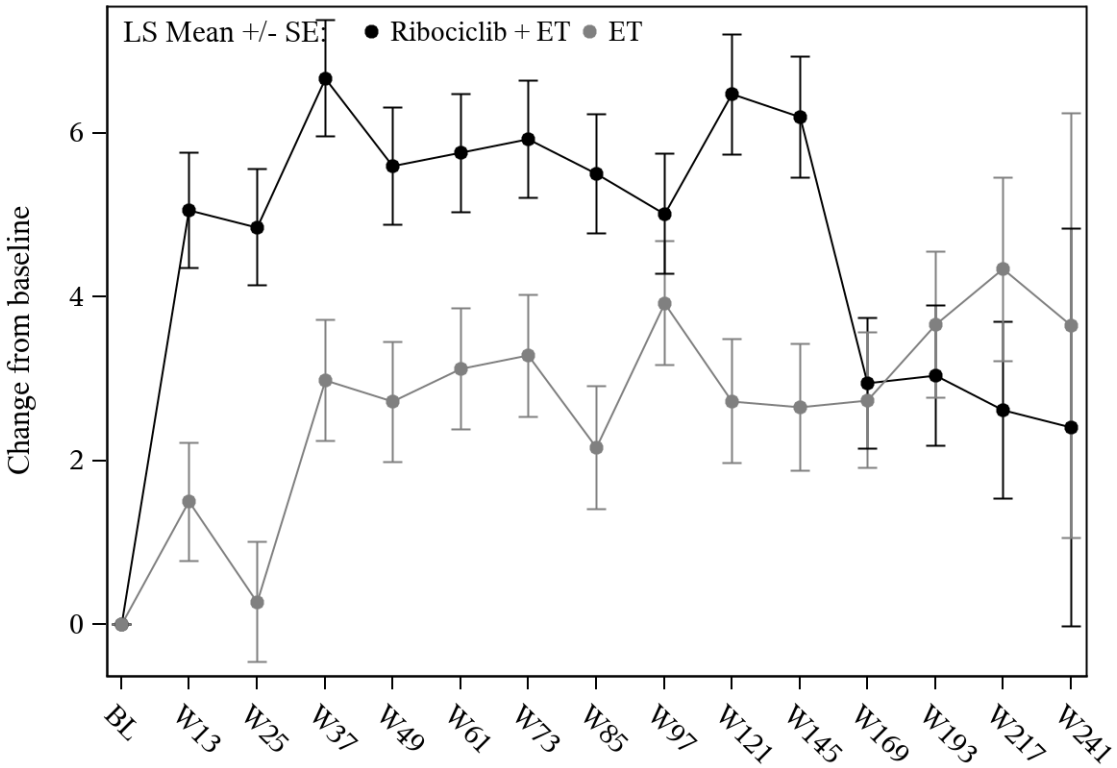
Ribociclib + ET	63	62	62	61	60	59	58	59	56	57	57	46	31	23	6
ET	52	52	49	47	48	49	46	47	47	46	42	33	25	14	4

QLQ-C30 - Constipation
Anatomic stages: IIIC



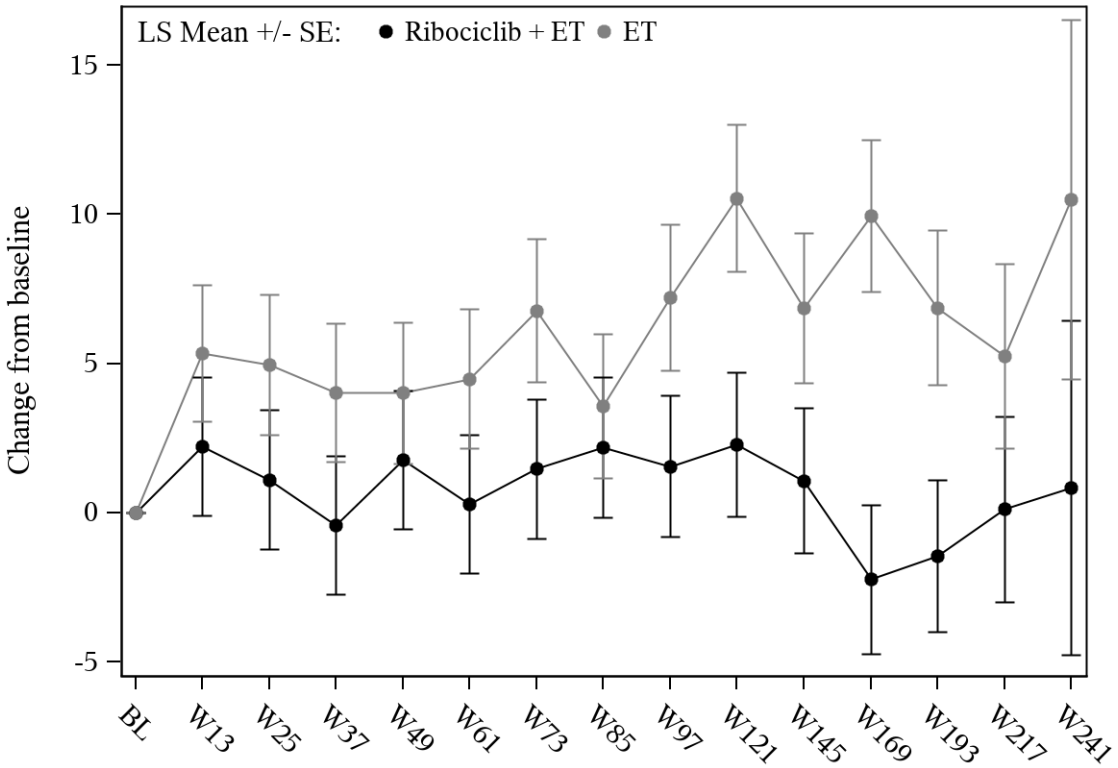
Ribociclib + ET	168	165	159	159	157	155	156	153	151	147	142	96	66	33	6
ET	186	175	179	170	170	166	160	159	153	153	143	108	76	35	7

QLQ-C30 - Constipation
Prior neo/adjuvant chemotherapy: Yes



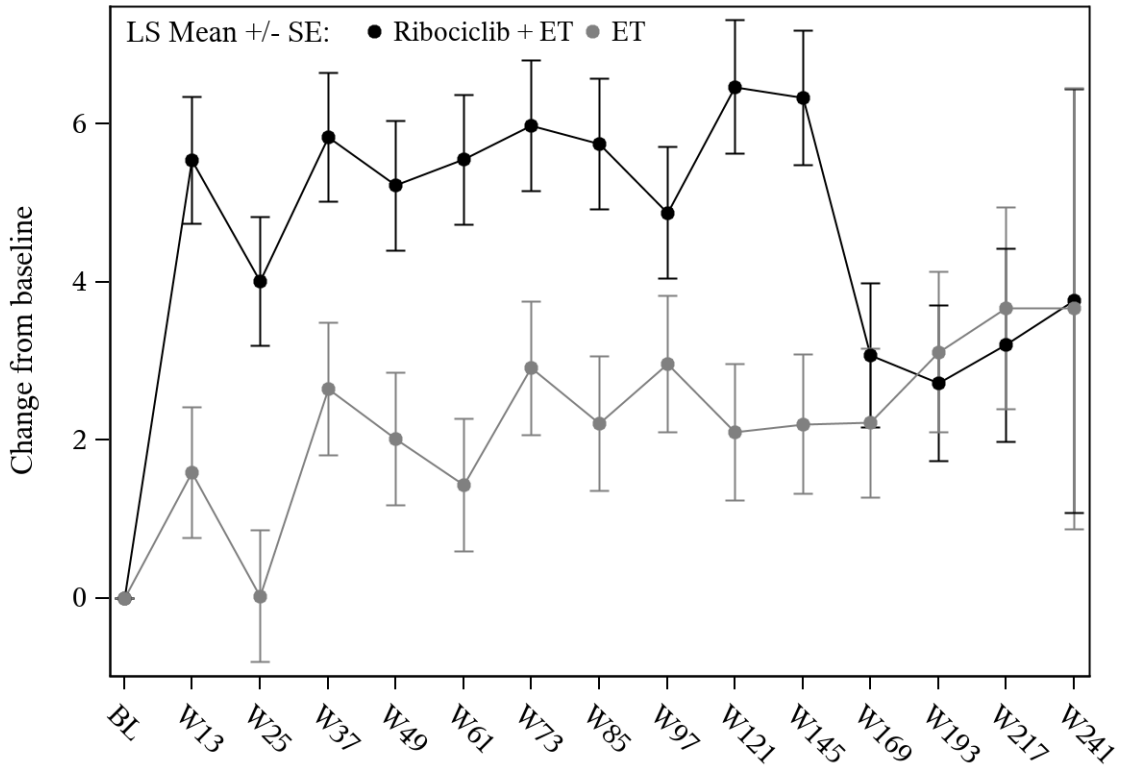
Ribociclib + ET	980	948	907	909	896	887	882	866	858	833	833	664	551	311	51
ET	926	887	853	836	852	832	826	803	796	778	751	622	511	288	45

QLQ-C30 - Constipation
Prior neo/adjuvant chemotherapy: No



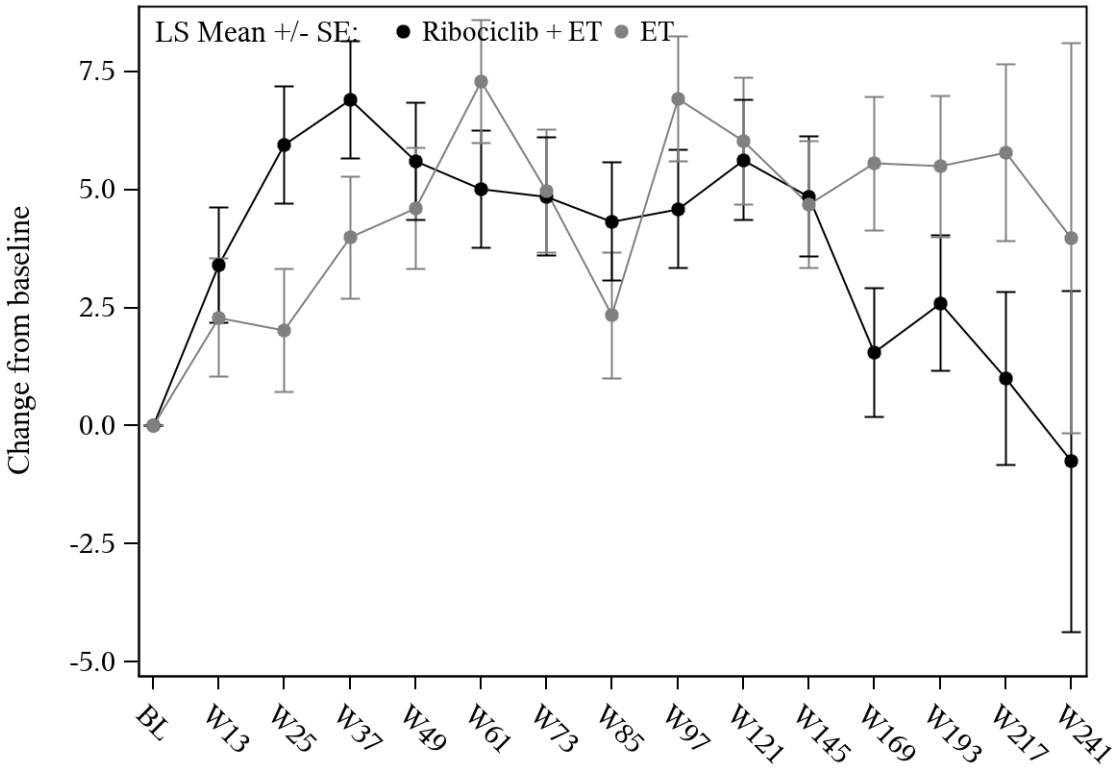
Ribociclib + ET	75	74	70	73	73	73	71	70	69	65	63	60	57	32	7
ET	78	76	69	73	69	71	66	65	63	62	59	58	55	33	6

QLQ-C30 - Constipation
Prior mastectomy: Yes



Ribociclib + ET	733	707	676	675	664	660	654	643	634	615	609	487	402	231	40
ET	698	665	650	635	645	630	622	608	598	588	559	459	376	212	37

QLQ-C30 - Constipation
Prior mastectomy: No



Ribociclib + ET	322	315	301	307	305	300	299	293	293	283	287	237	206	112	18
ET	306	298	272	274	276	273	270	260	261	252	251	221	190	109	14

Table 5-2.1.8.1 QLQ-C30 - Diarrhoea: change from baseline analysis - subgroup analysis (Full Analysis Set)

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1115)	ET (N = 1123)	Parameter	Esti-mate	[95% CI]	p-value
QLQ-C30 - Diarrhoea						
	N' | LS Mean (SE)	**N' | LS Mean (SE)**				
Region						
Interaction test	**p = 0.297**					
NA/WE/O	596 | 2.33 (0.44)	576 | 2.36 (0.45)	Difference	-0.03	[-1.28; 1.22]	0.962
			Hedges G	-0.00	[-0.12; 0.11]	
ROW	459 | 2.07 (0.47)	427 | 1.23 (0.49)	Difference	0.84	[-0.50; 2.18]	0.219
			Hedges G	0.08	[-0.05; 0.21]	
Geographical region						
Interaction test	**p = 0.151**					
Europe	615 | 2.48 (0.43)	592 | 2.80 (0.43)	Difference	-0.32	[-1.51; 0.86]	0.594
			Hedges G	-0.03	[-0.14; 0.08]	
North America/Australia	203 | 0.63 (0.62)	176 | -0.35 (0.69)	Difference	0.98	[-0.84; 2.80]	0.292
			Hedges G	0.11	[-0.09; 0.31]	
Asia	174 | N.E.	166 | N.E.	Difference	N.E.	[N.E.]	N.E.
			Hedges G	N.E.	[N.E.]	
Latin America	63 | 3.41 (1.17)	69 | 0.82 (1.10)	Difference	2.59	[-0.58; 5.75]	0.108
			Hedges G	0.28	[-0.06; 0.63]	
Age group 1 at randomization						
Interaction test	**N.E.**					
<45	524 | 1.72 (0.44)	458 | 2.04 (0.46)	Difference	-0.32	[-1.57; 0.93]	0.616
			Hedges G	-0.03	[-0.16; 0.09]	
45 to 54	511 | 2.27 (0.47)	518 | 1.09 (0.47)	Difference	1.19	[-0.12; 2.49]	0.074
			Hedges G	0.11	[-0.01; 0.23]	
55 to 64	20 | 5.02 (2.59)	27 | 5.01 (2.28)	Difference	0.01	[-6.95; 6.97]	0.998
			Hedges G	0.00	[-0.58; 0.58]	
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)						
Interaction test	**p = 0.129**					
<Median	524 | 1.60 (0.42)	458 | 1.95 (0.45)	Difference	-0.35	[-1.55; 0.85]	0.563
			Hedges G	-0.04	[-0.16; 0.09]	
≥Median	531 | 2.47 (0.46)	545 | 1.50 (0.45)	Difference	0.97	[-0.29; 2.24]	0.130
			Hedges G	0.09	[-0.03; 0.21]	

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1115)	**ET (N = 1123)**	**Parameter**	**Esti-mate**	**[95% CI]**	**p-value**
Race						
Interaction test	**p = 0.009**					
Asian	205 | 2.01 (0.69)	180 | -0.59 (0.74)	Difference	2.60	[0.62; 4.58]	0.010
			Hedges G	0.26	[0.06; 0.46]	
Non-Asian	799 | 1.96 (0.35)	771 | 2.31 (0.36)	Difference	-0.35	[-1.33; 0.64]	0.490
			Hedges G	-0.03	[-0.13; 0.06]	
BMI at screening						
Interaction test	**p = 0.781**					
≥25	526 | 2.62 (0.50)	488 | 2.22 (0.52)	Difference	0.40	[-1.01; 1.82]	0.575
			Hedges G	0.04	[-0.09; 0.16]	
<25	517 | 1.76 (0.40)	504 | 1.42 (0.41)	Difference	0.33	[-0.80; 1.46]	0.564
			Hedges G	0.04	[-0.09; 0.16]	
AJCC Anatomic Stage Group						
Interaction test	**p = 0.165**					
Group I/II	393 | 1.83 (0.49)	399 | 2.24 (0.49)	Difference	-0.41	[-1.78; 0.95]	0.553
			Hedges G	-0.04	[-0.18; 0.10]	
Group III	662 | 2.03 (0.42)	604 | 1.07 (0.44)	Difference	0.96	[-0.22; 2.15]	0.112
			Hedges G	0.09	[-0.02; 0.20]	
Anatomic stages						
Interaction test	**p = 0.171**					
IA/IB/IIA	163 | 1.27 (0.78)	189 | 2.21 (0.75)	Difference	-0.93	[-3.06; 1.19]	0.387
			Hedges G	-0.09	[-0.30; 0.12]	
IIB	230 | 2.66 (0.65)	210 | 2.27 (0.68)	Difference	0.39	[-1.46; 2.25]	0.677
			Hedges G	0.04	[-0.15; 0.23]	
IIIA	432 | 2.17 (0.53)	366 | 1.38 (0.57)	Difference	0.79	[-0.73; 2.32]	0.306
			Hedges G	0.07	[-0.07; 0.21]	
IIIB	62 | -0.55 (1.08)	52 | 0.09 (1.20)	Difference	-0.64	[-3.86; 2.59]	0.697
			Hedges G	-0.07	[-0.44; 0.30]	
IIIC	168 | 3.24 (0.77)	186 | 0.94 (0.73)	Difference	2.30	[0.22; 4.38]	0.031
			Hedges G	0.23	[0.02; 0.44]	
Nodal status						
Interaction test	**p = 0.788**					
N0	84 | 3.32 (1.04)	110 | 2.02 (0.95)	Difference	1.30	[-1.48; 4.07]	0.359
			Hedges G	0.13	[-0.15; 0.42]	
N1-N3	971 | 1.89 (0.34)	890 | 1.55 (0.35)	Difference	0.33	[-0.62; 1.29]	0.491
			Hedges G	0.03	[-0.06; 0.12]	

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1115)	**ET (N = 1123)**	**Parameter**	**Esti-mate**	**[95% CI]**	**p-value**
Histological grade at time of surgery						
Interaction test	**p = 0.966**					
Grade 1	104 | 1.80 (0.85)	97 | 1.47 (0.89)	Difference	0.33	[-2.11; 2.76]	0.792
			Hedges G	0.04	[-0.24; 0.31]	
Grade 2	578 | 1.69 (0.41)	557 | 1.51 (0.42)	Difference	0.18	[-0.97; 1.33]	0.762
			Hedges G	0.02	[-0.10; 0.13]	
Grade 3	281 | 2.75 (0.64)	252 | 2.36 (0.67)	Difference	0.39	[-1.42; 2.21]	0.670
			Hedges G	0.04	[-0.13; 0.21]	
Histological subtype						
Interaction test	**p = 0.052**					
Ductal	819 | 2.22 (0.35)	786 | 1.29 (0.36)	Difference	0.92	[-0.06; 1.91]	0.066
			Hedges G	0.09	[-0.01; 0.19]	
Lobular	168 | 1.83 (0.92)	156 | 3.28 (0.95)	Difference	-1.45	[-4.06; 1.15]	0.273
			Hedges G	-0.12	[-0.34; 0.10]	
Other	68 | 0.99 (1.15)	61 | 1.91 (1.33)	Difference	-0.92	[-4.40; 2.56]	0.602
			Hedges G	-0.09	[-0.44; 0.25]	
Ki67 status from surgical specimen						
Interaction test	**p = 0.928**					
Ki67≤20	508 | 2.27 (0.45)	517 | 1.79 (0.44)	Difference	0.48	[-0.75; 1.72]	0.443
			Hedges G	0.05	[-0.07; 0.17]	
Ki67>20	398 | 2.27 (0.50)	359 | 1.89 (0.54)	Difference	0.38	[-1.06; 1.82]	0.605
			Hedges G	0.04	[-0.10; 0.18]	
Type of NSAI						
Interaction test	**p = 0.371**					
Letrozole	772 | 2.46 (0.39)	720 | 2.27 (0.41)	Difference	0.19	[-0.91; 1.29]	0.732
			Hedges G	0.02	[-0.08; 0.12]	
Anastrozole	283 | 1.66 (0.60)	281 | 0.77 (0.61)	Difference	0.89	[-0.80; 2.58]	0.301
			Hedges G	0.09	[-0.08; 0.25]	
Prior neo/adjuvant chemotherapy						
Interaction test	**p = 0.044**					
Yes	980 | 1.84 (0.33)	926 | 1.65 (0.34)	Difference	0.19	[-0.74; 1.13]	0.686
			Hedges G	0.02	[-0.07; 0.11]	
No	75 | 4.51 (1.15)	77 | 1.10 (1.17)	Difference	3.41	[0.16; 6.67]	0.040
			Hedges G	0.34	[0.02; 0.66]	
Prior adjuvant chemotherapy						
Interaction test	**p = 0.999**					
Yes	493 | 1.49 (0.44)	462 | 1.21 (0.46)	Difference	0.28	[-0.96; 1.53]	0.655
			Hedges G	0.03	[-0.10; 0.16]	
No	562 | 2.62 (0.45)	541 | 2.16 (0.46)	Difference	0.46	[-0.81; 1.72]	0.482
			Hedges G	0.04	[-0.08; 0.16]	

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1115)	ET (N = 1123)	Parameter	Esti-mate	[95% CI]	p-value
Prior neoadjuvant chemotherapy						
Interaction test	**p = 0.359**					
Yes	517 | 1.89 (0.46)	502 | 1.98 (0.47)	Difference	-0.09	[-1.38; 1.20]	0.892
			Hedges G	-0.01	[-0.13; 0.11]	
No	538 | 2.09 (0.43)	501 | 1.39 (0.45)	Difference	0.70	[-0.51; 1.91]	0.257
			Hedges G	0.07	[-0.05; 0.19]	
Prior endocrine therapy						
Interaction test	**p = 0.625**					
Yes	811 | 1.89 (0.34)	734 | 1.57 (0.36)	Difference	0.32	[-0.64; 1.28]	0.513
			Hedges G	0.03	[-0.07; 0.13]	
No	244 | 1.93 (0.69)	269 | 1.26 (0.66)	Difference	0.67	[-1.21; 2.56]	0.483
			Hedges G	0.06	[-0.11; 0.24]	
Prior mastectomy						
Interaction test	**p = 0.638**					
Yes	734 | 2.00 (0.36)	698 | 1.58 (0.37)	Difference	0.42	[-0.60; 1.43]	0.419
			Hedges G	0.04	[-0.06; 0.15]	
No	321 | 1.16 (0.59)	305 | 1.92 (0.62)	Difference	-0.76	[-2.43; 0.92]	0.375
			Hedges G	-0.07	[-0.23; 0.09]	
Prior radiotherapy						
Interaction test	**p = 0.351**					
Yes	966 | 1.78 (0.33)	921 | 1.60 (0.34)	Difference	0.18	[-0.75; 1.12]	0.698
			Hedges G	0.02	[-0.07; 0.11]	
No	89 | 3.69 (1.08)	82 | 2.70 (1.14)	Difference	0.99	[-2.12; 4.10]	0.530
			Hedges G	0.10	[-0.20; 0.40]	

N: Number of patients
N': Number of patients in the analysis
CI: Confidence interval
SD: Standard deviation
LS Mean: Least square mean
SE: Standard error
MMRM: Mixed model for repeated measures
N.E.: Not estimable
ET: Endocrine therapy (Anastrozole/Letrozole + Goserelin)
.....

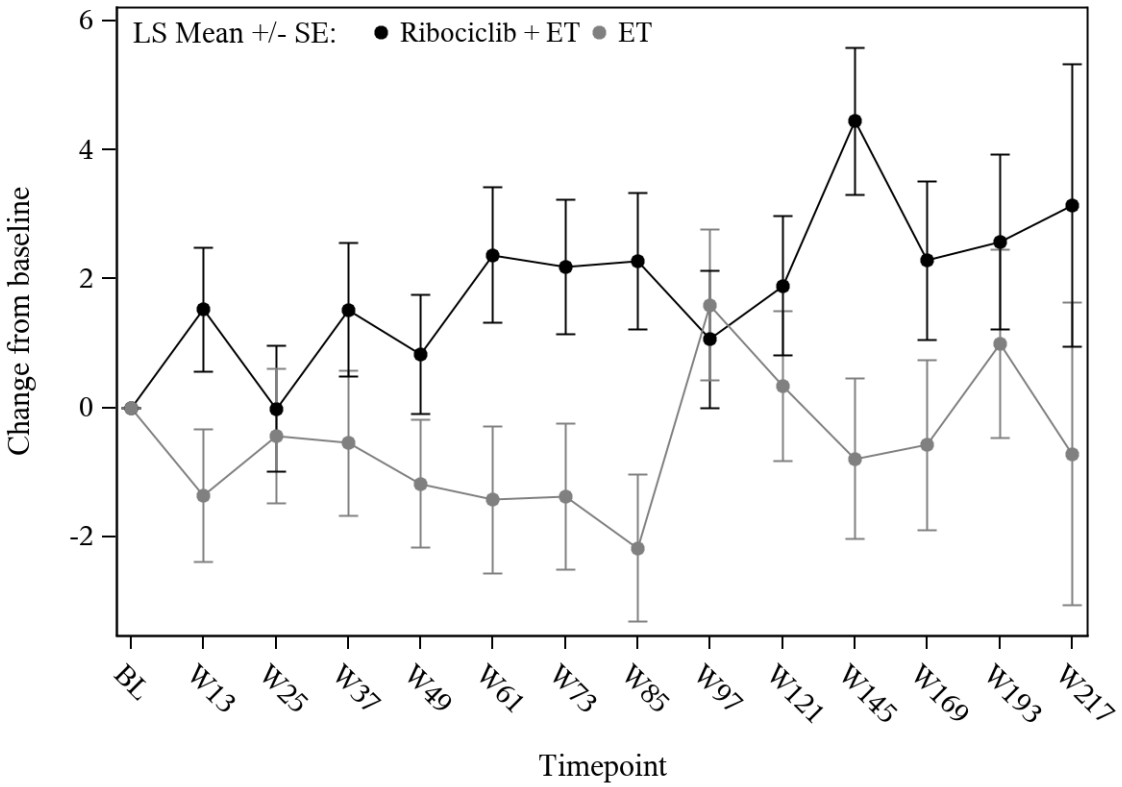
Analysis method for interaction test:
p-value from MMRM with unstructured covariance matrix:
change from baseline = treatment + visit + treatment * visit + subgroup factor + treatment * subgroup factor + subgroup factor * visit + treatment * subgroup factor * visit + baseline value
If the model did not converge for a parameter*subgroup factor, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry. If the model did still not converge, interactions were removed in the order treatment * subgroup factor * visit, subgroup factor * visit.

Analysis methods for within-subgroup analysis:
Adjusted mean (LS Mean) change from baseline and overall effect obtained from MMRM with unstructured covariance matrix:
change from baseline = treatment + visit + treatment * visit + baseline value
ET was the reference group for treatment group comparison.
If the model did not converge for a parameter*subgroup factor, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry.

Patients with an evaluable baseline score and at least one evaluable post-baseline score were included in the analysis.
All data collected were included in the analysis, including assessments at confirmation of first recurrence and thereafter, as long as there were at least 50 patients in each treatment group at a visit in the overall (sub-)population.

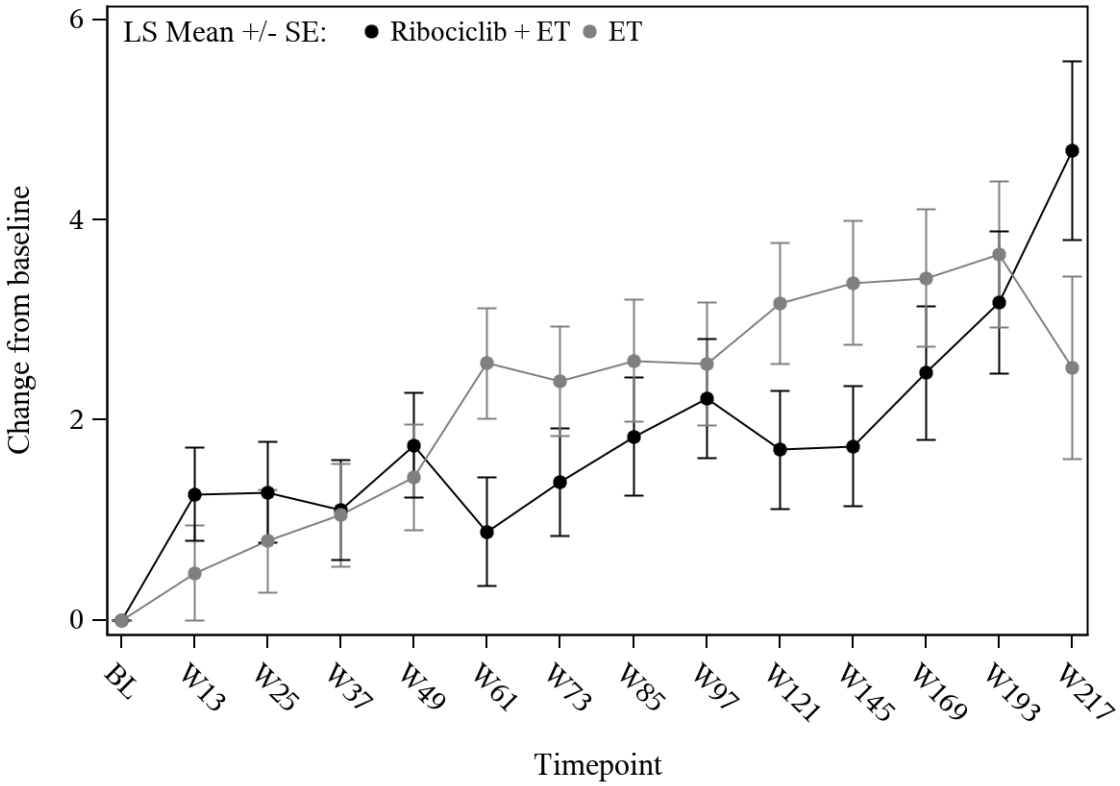
Figure 5-2.1.8.1 QLQ-C30 - Diarrhoea: line chart of change from baseline - subgroup analysis (Full Analysis Set)

QLQ-C30 - Diarrhoea
Race: Asian



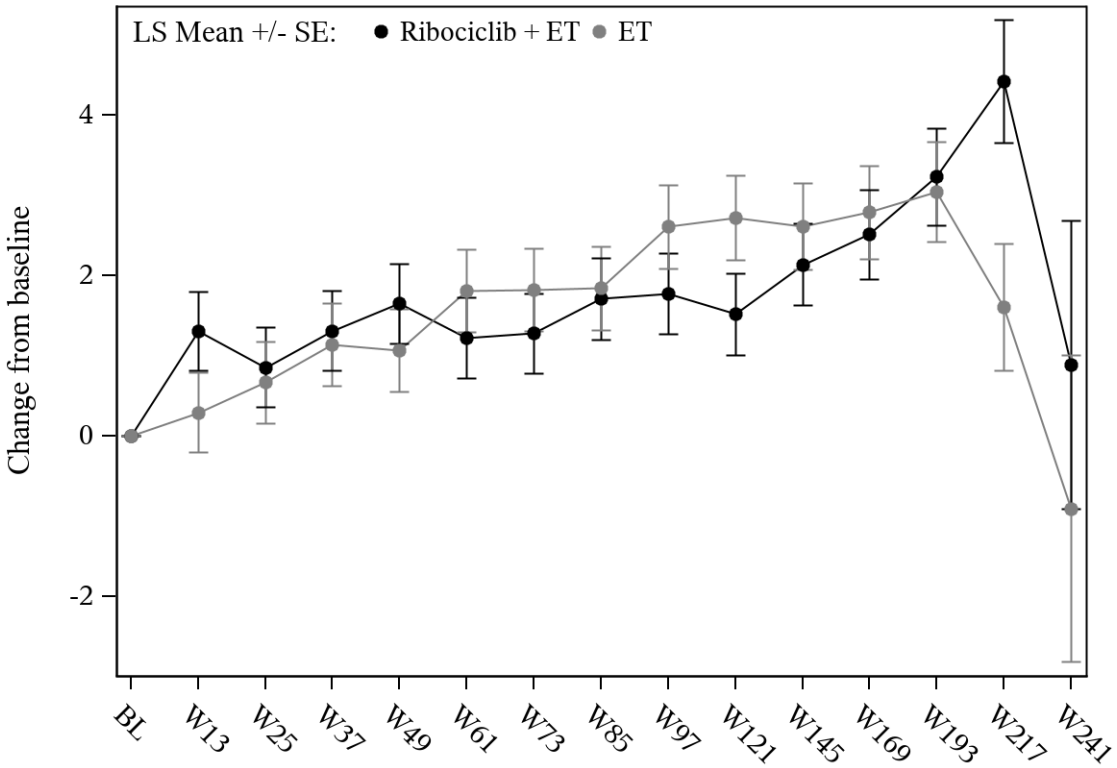
Ribociclib + ET	205	203	200	200	200	195	195	194	192	185	184	133	100	40
ET	180	178	175	170	173	166	168	166	160	161	153	116	87	35

QLQ-C30 - Diarrhoea
Race: Non-Asian



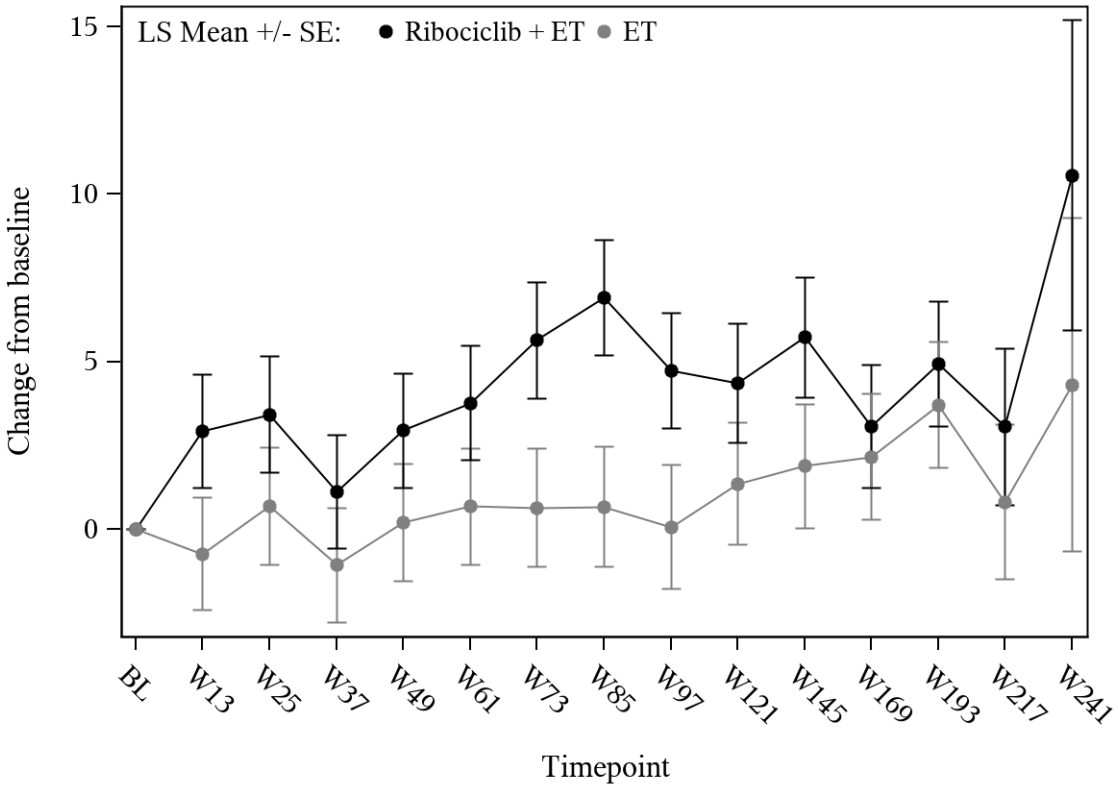
Ribociclib + ET	799	770	729	736	723	720	709	698	692	672	670	560	476	287
ET	771	733	692	691	697	690	681	659	652	638	617	529	447	274

QLQ-C30 - Diarrhoea
Prior neo/adjuvant chemotherapy: Yes



Ribociclib + ET	980	948	904	907	894	885	878	865	857	833	832	665	548	312	51
ET	926	884	846	834	847	830	826	804	796	777	749	623	511	290	45

QLQ-C30 - Diarrhoea
Prior neo/adjuvant chemotherapy: No



Ribociclib + ET	75	74	70	74	73	73	71	70	70	65	63	60	57	32	7
ET	77	75	68	72	68	70	66	64	59	61	59	57	56	33	6

5-2.2 EORTC QLQ-C30 QoL

Table 5-2.2.1.1 QLQ-C30 - Global Health/QoL: change from baseline analysis - subgroup analysis (Full Analysis Set)

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1115)	ET (N = 1123)	Parameter	Esti-mate	[95% CI]	p-value
QLQ-C30 - Global Health/QoL						
	N' | LS Mean (SE)	N' | LS Mean (SE)				
Region						
Interaction test	**p = 0.430**					
NA/WE/O	596 | -4.17 (0.56)	576 | -2.64 (0.57)	Difference	-1.53	[-3.09; 0.03]	0.054
			Hedges G	-0.11	[-0.23; 0.00]	
ROW	460 | -2.72 (0.59)	427 | -1.94 (0.62)	Difference	-0.78	[-2.45; 0.90]	0.362
			Hedges G	-0.06	[-0.19; 0.07]	
Geographical region						
Interaction test	**N.E.**					
Europe	615 | -3.99 (0.52)	592 | -3.04 (0.53)	Difference	-0.95	[-2.41; 0.52]	0.206
			Hedges G	-0.07	[-0.19; 0.04]	
North America/Australia	203 | -2.41 (0.81)	176 | -0.89 (0.89)	Difference	-1.52	[-3.89; 0.85]	0.208
			Hedges G	-0.13	[-0.33; 0.07]	
Asia	175 | N.E.	166 | N.E.	Difference	N.E.	[N.E.]	N.E.
			Hedges G	N.E.	[N.E.]	
Latin America	63 | -3.15 (1.45)	69 | -1.80 (1.37)	Difference	-1.35	[-5.31; 2.60]	0.499
			Hedges G	-0.12	[-0.46; 0.22]	
Age group 1 at randomization						
Interaction test	**N.E.**					
<45	523 | -3.68 (0.55)	458 | -1.92 (0.58)	Difference	-1.76	[-3.32; -0.20]	0.027
			Hedges G	-0.14	[-0.27; -0.02]	
45 to 54	513 | -3.54 (0.58)	518 | -2.73 (0.59)	Difference	-0.81	[-2.43; 0.82]	0.329
			Hedges G	-0.06	[-0.18; 0.06]	
55 to 64	20 | -0.49 (2.95)	27 | 0.05 (2.58)	Difference	-0.54	[-8.44; 7.35]	0.891
			Hedges G	-0.04	[-0.62; 0.54]	
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)						
Interaction test	**p = 0.396**					
<Median	523 | -3.81 (0.56)	458 | -1.98 (0.60)	Difference	-1.83	[-3.44; -0.22]	0.026
			Hedges G	-0.14	[-0.27; -0.02]	
≥Median	533 | -3.46 (0.58)	545 | -2.70 (0.58)	Difference	-0.76	[-2.38; 0.86]	0.358
			Hedges G	-0.06	[-0.18; 0.06]	

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1115)	**ET (N = 1123)**	**Parameter**	**Esti-mate**	**[95% CI]**	**p-value**
Race						
Interaction test	**p = 0.750**					
Asian	206 | -2.49 (0.92)	180 | -0.65 (0.99)	Difference	-1.85	[-4.49; 0.80]	0.171
			Hedges G	-0.14	[-0.34; 0.06]	
Non-Asian	800 | -3.68 (0.45)	771 | -2.37 (0.46)	Difference	-1.31	[-2.56; -0.06]	0.040
			Hedges G	-0.10	[-0.20; -0.00]	
BMI at screening						
Interaction test	**p = 0.214**					
≥25	527 | -4.73 (0.59)	488 | -2.92 (0.62)	Difference	-1.81	[-3.50; -0.12]	0.035
			Hedges G	-0.13	[-0.26; -0.01]	
<25	517 | -2.34 (0.55)	504 | -1.77 (0.56)	Difference	-0.56	[-2.11; 0.98]	0.474
			Hedges G	-0.04	[-0.17; 0.08]	
AJCC Anatomic Stage Group						
Interaction test	**p = 0.040**					
Group I/II	394 | -2.39 (0.65)	399 | -2.73 (0.65)	Difference	0.34	[-1.47; 2.14]	0.716
			Hedges G	0.03	[-0.11; 0.17]	
Group III	662 | -4.02 (0.52)	604 | -2.12 (0.55)	Difference	-1.90	[-3.39; -0.42]	0.012
			Hedges G	-0.14	[-0.25; -0.03]	
Anatomic stages						
Interaction test	**p = 0.004**					
IA/IB/IIA	164 | 0.87 (0.94)	189 | -2.45 (0.90)	Difference	3.32	[0.77; 5.88]	0.011
			Hedges G	0.27	[0.06; 0.48]	
IIB	230 | -4.41 (0.85)	210 | -2.80 (0.88)	Difference	-1.61	[-4.02; 0.79]	0.188
			Hedges G	-0.13	[-0.31; 0.06]	
IIIA	433 | -4.80 (0.64)	366 | -2.34 (0.69)	Difference	-2.47	[-4.32; -0.61]	0.009
			Hedges G	-0.19	[-0.32; -0.05]	
IIIB	62 | -2.90 (1.68)	52 | -5.26 (1.86)	Difference	2.36	[-2.67; 7.40]	0.354
			Hedges G	0.18	[-0.19; 0.54]	
IIIC	167 | -3.02 (1.00)	186 | -1.03 (0.95)	Difference	-1.99	[-4.71; 0.73]	0.151
			Hedges G	-0.15	[-0.36; 0.06]	
Nodal status						
Interaction test	**p = 0.011**					
N0	84 | -0.29 (1.33)	110 | -2.27 (1.19)	Difference	1.98	[-1.53; 5.50]	0.267
			Hedges G	0.16	[-0.12; 0.45]	
N1-N3	972 | -3.76 (0.42)	890 | -2.34 (0.44)	Difference	-1.43	[-2.61; -0.24]	0.018
			Hedges G	-0.11	[-0.20; -0.02]	

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1115)	**ET (N = 1123)**	**Parameter**	**Esti-mate**	**[95% CI]**	**p-value**
Histological grade at time of surgery						
Interaction test	**p = 0.354**					
Grade 1	104 | -3.18 (1.18)	97 | -3.69 (1.24)	Difference	0.51	[-2.87; 3.89]	0.768
			Hedges G	0.04	[-0.23; 0.32]	
Grade 2	579 | -3.55 (0.53)	557 | -1.41 (0.55)	Difference	-2.14	[-3.63; -0.64]	0.005
			Hedges G	-0.17	[-0.28; -0.05]	
Grade 3	281 | -3.62 (0.73)	252 | -2.29 (0.77)	Difference	-1.33	[-3.42; 0.76]	0.211
			Hedges G	-0.11	[-0.28; 0.06]	
Histological subtype						
Interaction test	**p = 0.579**					
Ductal	820 | -3.46 (0.45)	786 | -2.35 (0.46)	Difference	-1.10	[-2.37; 0.16]	0.088
			Hedges G	-0.09	[-0.18; 0.01]	
Lobular	168 | -2.84 (1.01)	156 | -2.44 (1.05)	Difference	-0.40	[-3.27; 2.47]	0.785
			Hedges G	-0.03	[-0.25; 0.19]	
Other	68 | -3.98 (1.49)	61 | -0.60 (1.64)	Difference	-3.38	[-7.76; 1.00]	0.129
			Hedges G	-0.27	[-0.62; 0.08]	
Ki67 status from surgical specimen						
Interaction test	**p = 0.434**					
Ki67≤20	509 | -3.68 (0.57)	517 | -1.93 (0.57)	Difference	-1.75	[-3.33; -0.18]	0.029
			Hedges G	-0.14	[-0.26; -0.01]	
Ki67>20	398 | -3.51 (0.63)	359 | -2.70 (0.67)	Difference	-0.81	[-2.62; 1.01]	0.383
			Hedges G	-0.06	[-0.21; 0.08]	
Type of NSAI						
Interaction test	**p = 0.064**					
Letrozole	772 | -3.17 (0.47)	720 | -2.56 (0.49)	Difference	-0.62	[-1.94; 0.71]	0.363
			Hedges G	-0.05	[-0.15; 0.05]	
Anastrozole	284 | -4.53 (0.78)	281 | -1.56 (0.78)	Difference	-2.97	[-5.14; -0.81]	0.007
			Hedges G	-0.23	[-0.39; -0.06]	
Prior neo/adjuvant chemotherapy						
Interaction test	**p = 0.450**					
Yes	981 | -3.61 (0.42)	926 | -2.30 (0.43)	Difference	-1.30	[-2.48; -0.13]	0.029
			Hedges G	-0.10	[-0.19; -0.01]	
No	75 | -1.97 (1.43)	77 | -2.13 (1.44)	Difference	0.17	[-3.85; 4.18]	0.935
			Hedges G	0.01	[-0.30; 0.33]	
Prior adjuvant chemotherapy						
Interaction test	**p = 0.967**					
Yes	494 | -3.48 (0.57)	462 | -2.24 (0.60)	Difference	-1.24	[-2.87; 0.38]	0.133
			Hedges G	-0.10	[-0.22; 0.03]	
No	562 | -3.55 (0.56)	541 | -2.24 (0.58)	Difference	-1.31	[-2.90; 0.27]	0.103
			Hedges G	-0.10	[-0.22; 0.02]	

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1115)	ET (N = 1123)	Parameter	Esti-mate	[95% CI]	p-value
Prior neoadjuvant chemotherapy						
Interaction test	**p = 0.845**					
Yes	517 | -3.55 (0.58)	502 | -2.18 (0.59)	Difference	-1.36	[-3.00; 0.27]	0.101
			Hedges G	-0.10	[-0.23; 0.02]	
No	539 | -3.40 (0.56)	501 | -2.38 (0.58)	Difference	-1.02	[-2.59; 0.56]	0.206
			Hedges G	-0.08	[-0.20; 0.04]	
Prior endocrine therapy						
Interaction test	**p = 0.874**					
Yes	812 | -3.94 (0.45)	734 | -2.73 (0.48)	Difference	-1.21	[-2.51; 0.09]	0.068
			Hedges G	-0.09	[-0.19; 0.01]	
No	244 | -2.20 (0.88)	269 | -1.29 (0.85)	Difference	-0.91	[-3.32; 1.50]	0.457
			Hedges G	-0.07	[-0.24; 0.11]	
Prior mastectomy						
Interaction test	**p = 0.003**					
Yes	734 | -3.73 (0.48)	698 | -1.45 (0.50)	Difference	-2.28	[-3.64; -0.92]	0.001
			Hedges G	-0.17	[-0.28; -0.07]	
No	322 | -2.93 (0.74)	305 | -4.46 (0.77)	Difference	1.53	[-0.57; 3.63]	0.152
			Hedges G	0.11	[-0.04; 0.27]	
Prior radiotherapy						
Interaction test	**p = 0.789**					
Yes	967 | -3.59 (0.43)	921 | -2.52 (0.44)	Difference	-1.08	[-2.28; 0.12]	0.079
			Hedges G	-0.08	[-0.17; 0.01]	
No	89 | -1.88 (1.34)	82 | 1.45 (1.41)	Difference	-3.33	[-7.17; 0.51]	0.089
			Hedges G	-0.26	[-0.56; 0.04]	

N: Number of patients
N': Number of patients in the analysis
CI: Confidence interval
SD: Standard deviation
LS Mean: Least square mean
SE: Standard error
MMRM: Mixed model for repeated measures
N.E.: Not estimable
ET: Endocrine therapy (Anastrozole/Letrozole + Goserelin)
.....

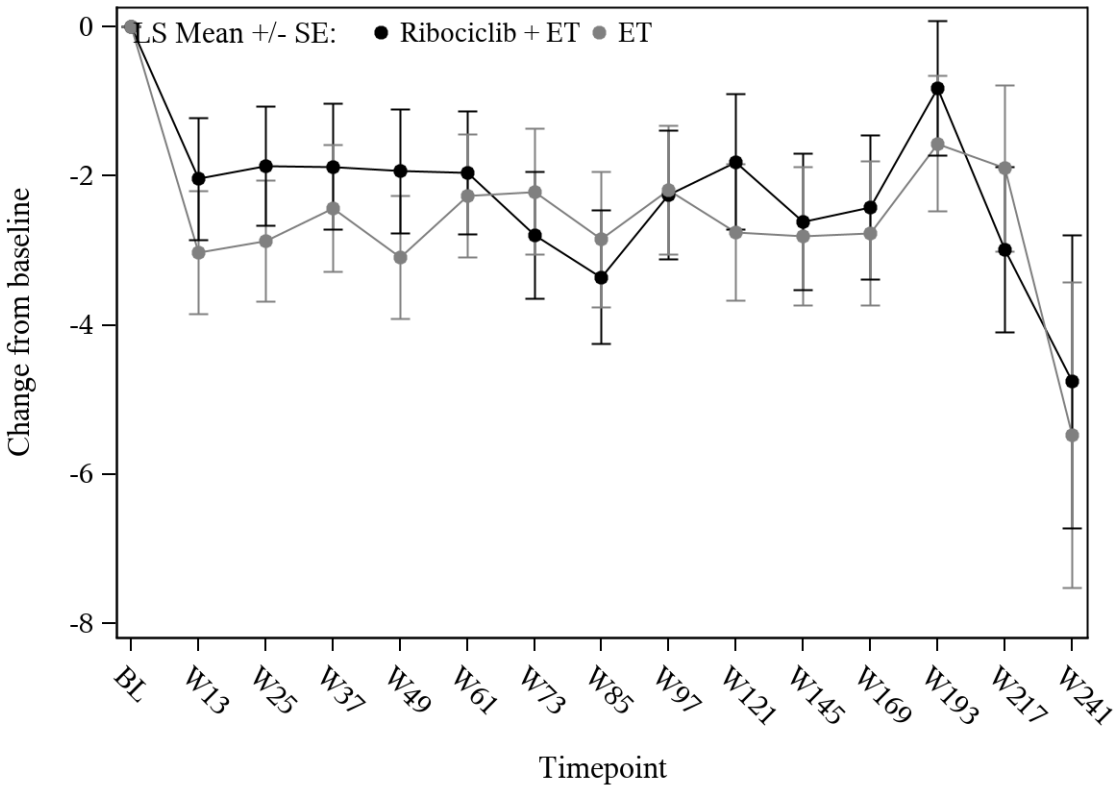
Analysis method for interaction test:
p-value from MMRM with unstructured covariance matrix:
change from baseline = treatment + visit + treatment * visit + subgroup factor + treatment * subgroup factor + subgroup factor * visit + treatment * subgroup factor * visit + baseline value
If the model did not converge for a parameter*subgroup factor, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry. If the model did still not converge, interactions were removed in the order treatment * subgroup factor * visit, subgroup factor * visit.

Analysis methods for within-subgroup analysis:
Adjusted mean (LS Mean) change from baseline and overall effect obtained from MMRM with unstructured covariance matrix:
change from baseline = treatment + visit + treatment * visit + baseline value
ET was the reference group for treatment group comparison.
If the model did not converge for a parameter*subgroup factor, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry.

Patients with an evaluable baseline score and at least one evaluable post-baseline score were included in the analysis.
All data collected were included in the analysis, including assessments at confirmation of first recurrence and thereafter, as long as there were at least 50 patients in each treatment group at a visit in the overall (sub-)population.

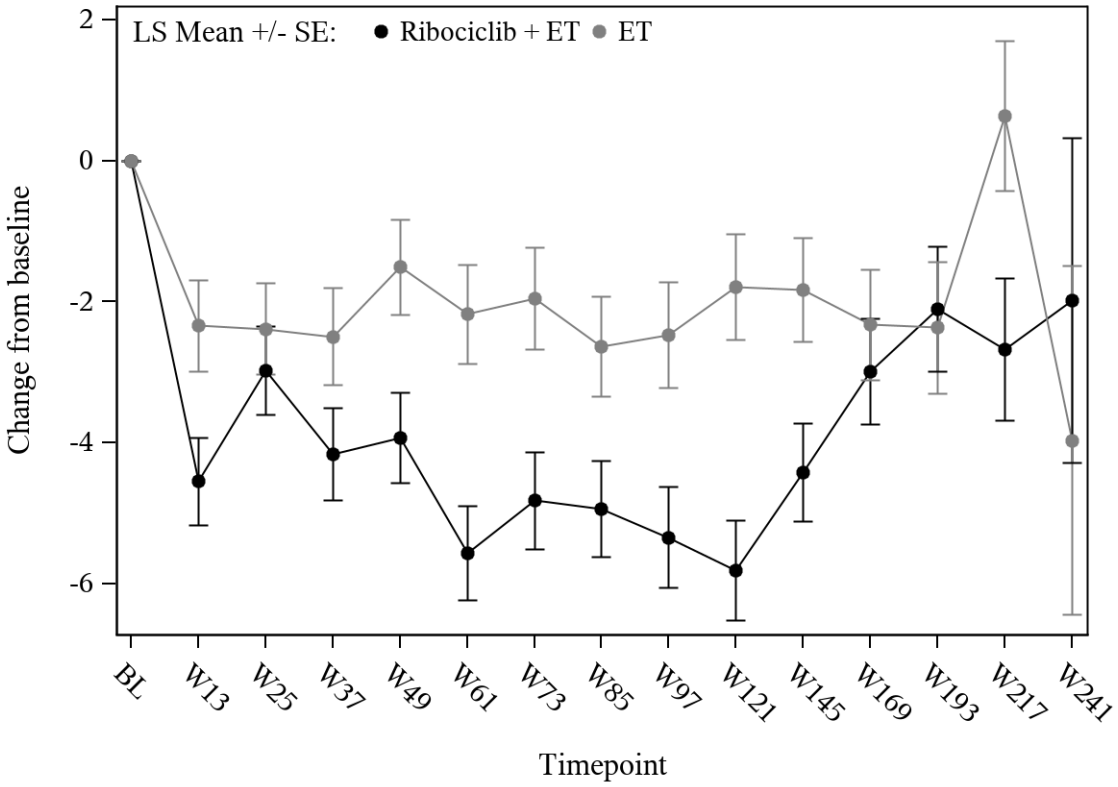
Figure 5-2.2.1.1 QLQ-C30 - Global Health/QoL: line chart of change from baseline - subgroup analysis (Full Analysis Set)

QLQ-C30 - Global Health/QoL
AJCC Anatomic Stage Group: Group I/II



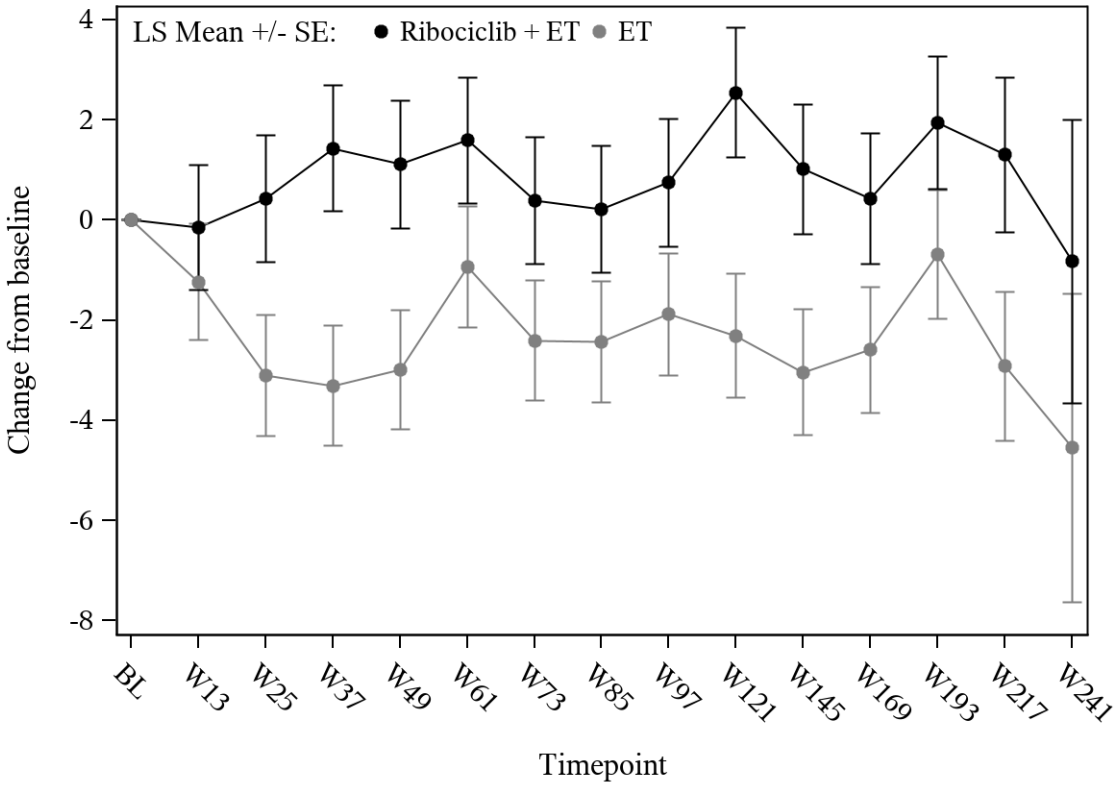
Ribociclib + ET	394	384	367	367	360	360	354	356	352	341	339	316	314	177	31
ET	399	381	349	363	366	359	361	342	344	334	322	316	303	175	28

QLQ-C30 - Global Health/QoL
AJCC Anatomic Stage Group: Group III



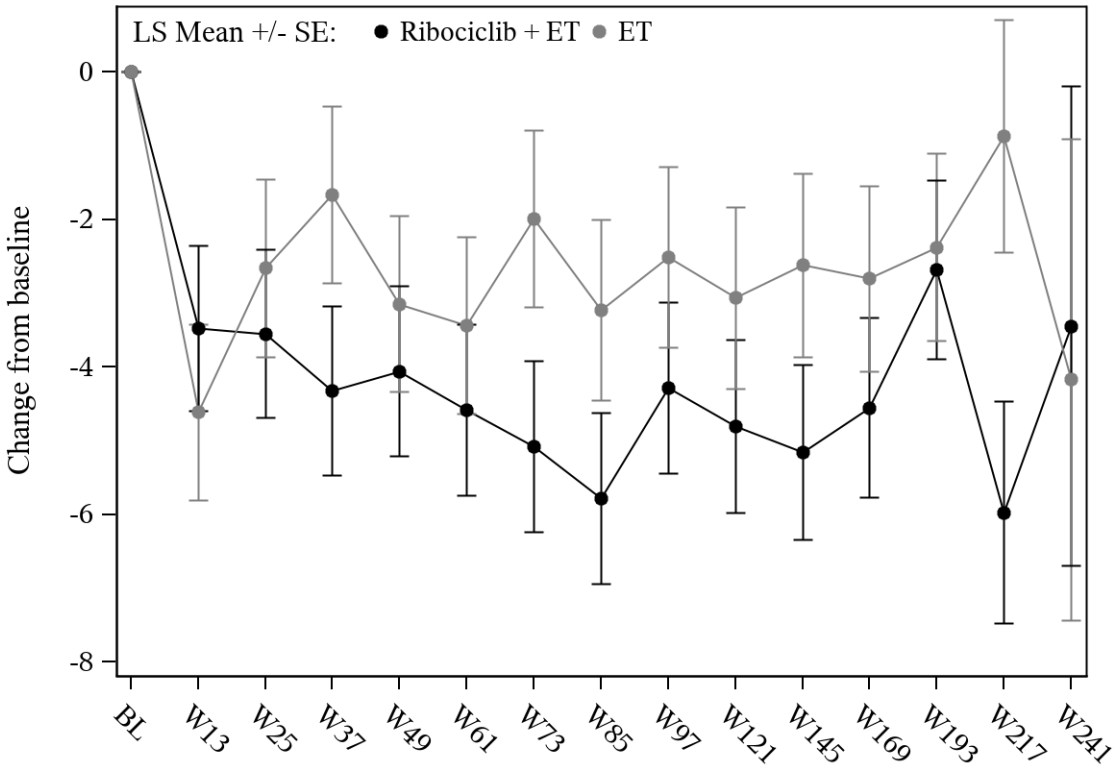
Ribociclib + ET	662	641	609	615	607	601	599	582	576	556	557	409	292	167	27
ET	604	575	567	544	549	542	531	527	512	504	486	363	264	148	24

QLQ-C30 - Global Health/QoL
Anatomic stages: IA/IB/IIA



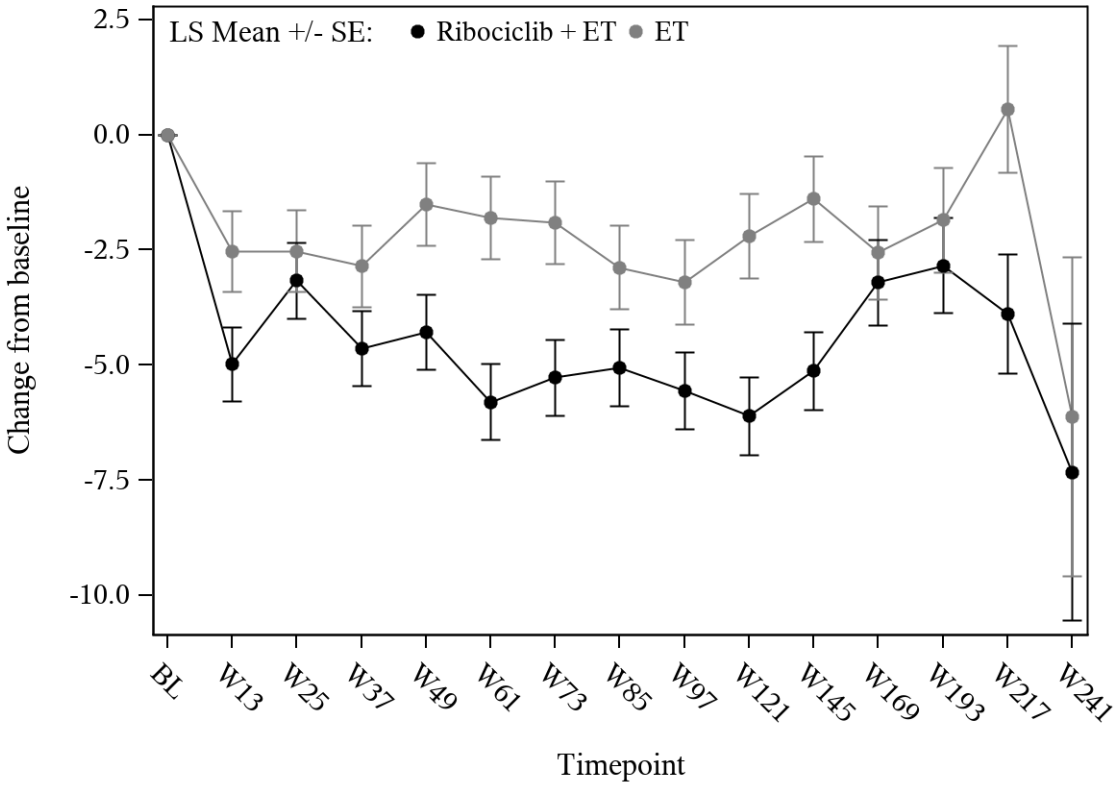
Ribociclib + ET	164	160	154	156	152	156	151	152	148	142	143	139	134	80	17
ET	189	183	161	169	170	167	170	162	162	155	148	148	140	87	14

QLQ-C30 - Global Health/QoL
Anatomic stages: IIB



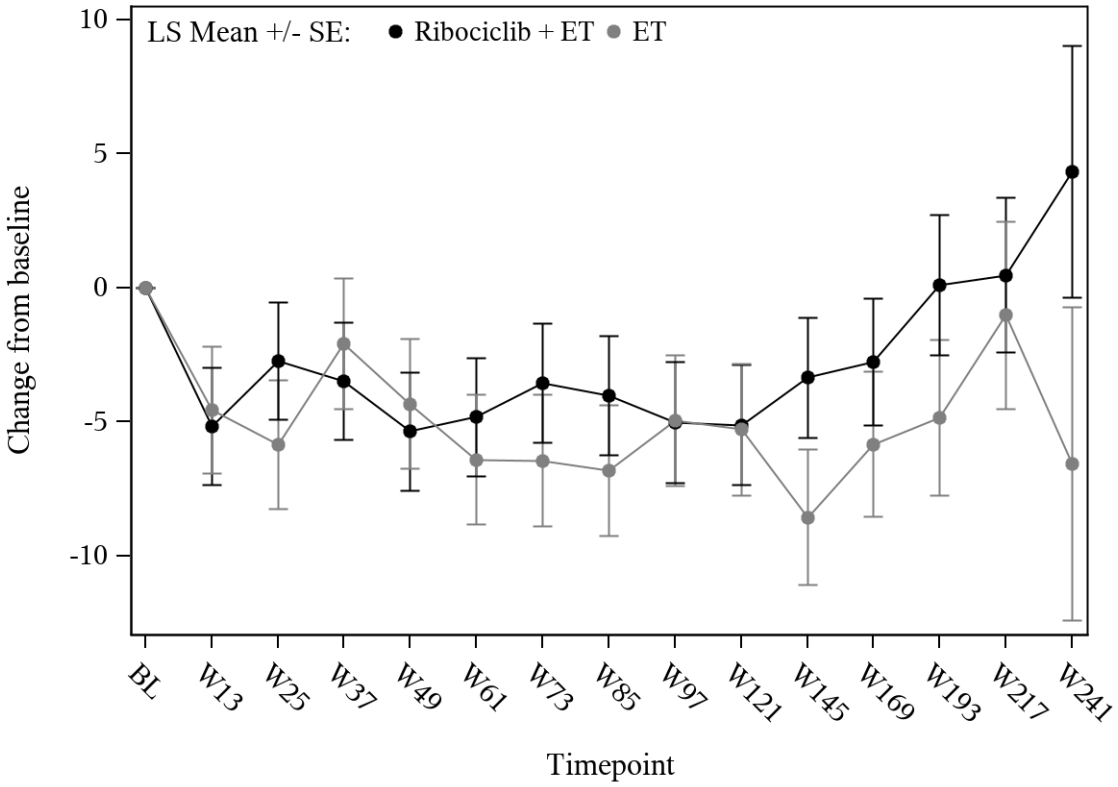
Ribociclib + ET	230	224	213	211	208	204	203	204	204	199	196	177	180	97	14
ET	210	198	188	194	196	192	191	180	182	179	174	168	163	88	14

QLQ-C30 - Global Health/QoL
Anatomic stages: IIIA



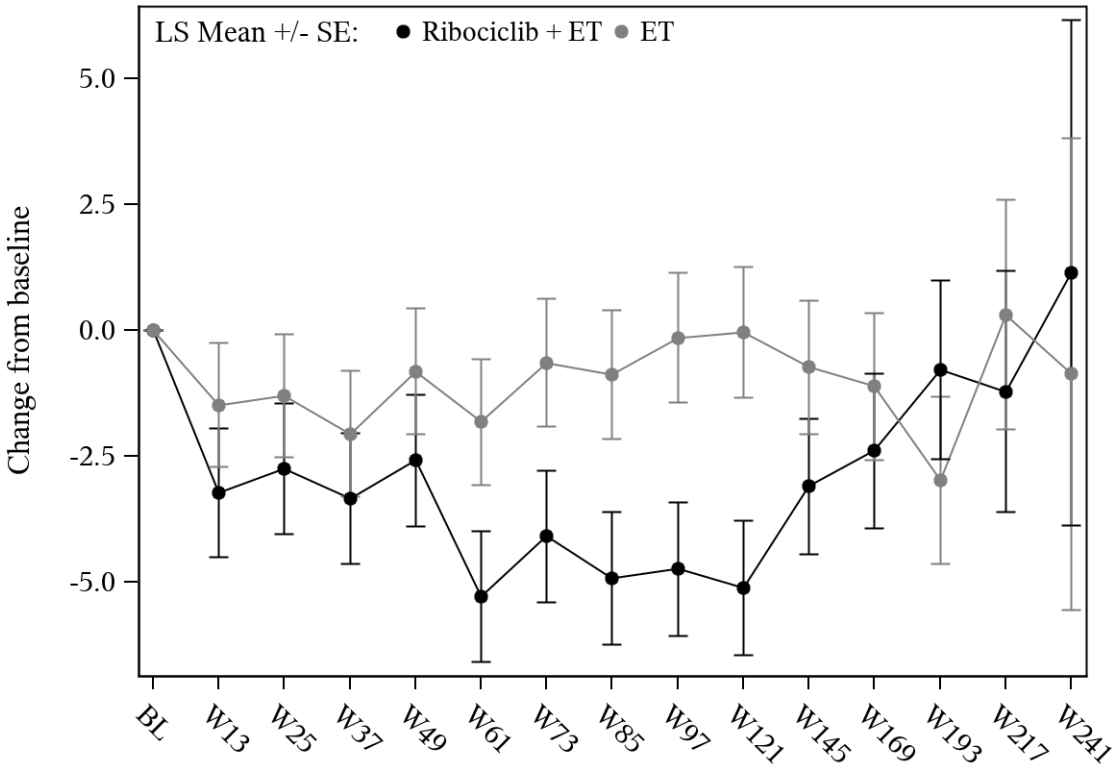
Ribociclib + ET	433	416	391	398	393	387	387	372	372	354	360	268	196	112	15
ET	366	348	340	328	330	327	325	321	312	305	302	223	163	99	13

QLQ-C30 - Global Health/QoL
Anatomic stages: IIIB



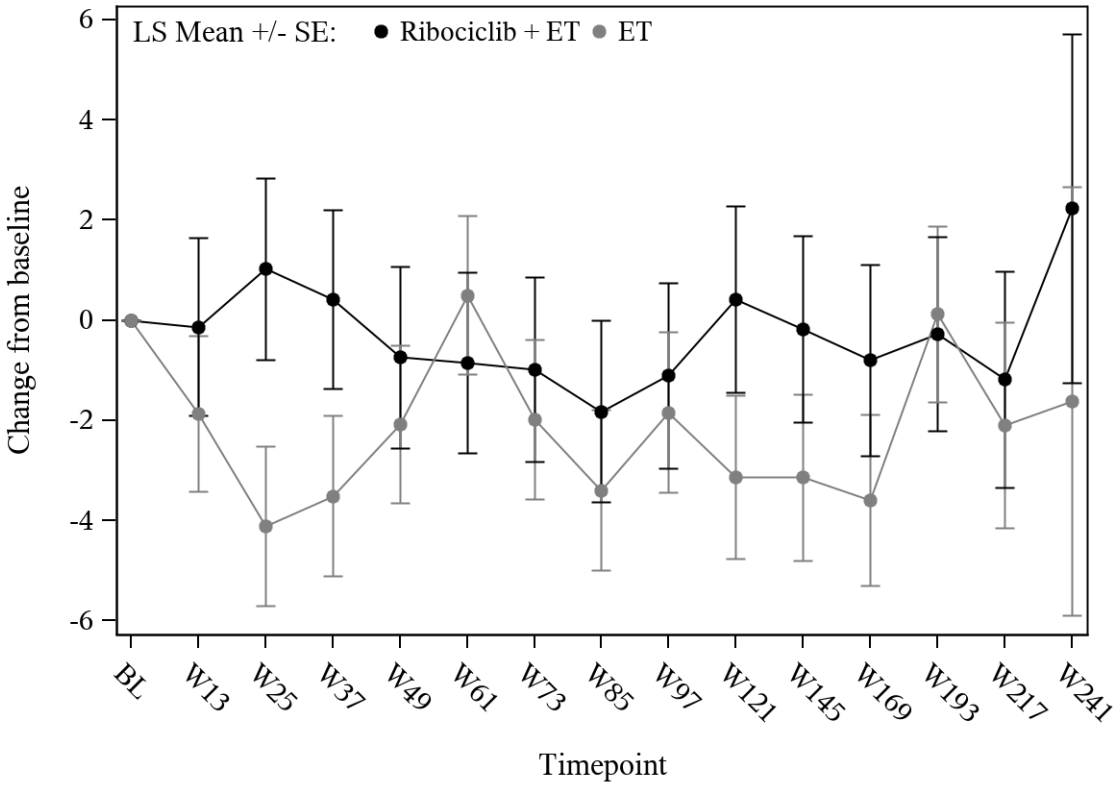
Ribociclib + ET	62	60	60	60	59	58	57	58	56	57	57	46	31	23	6
ET	52	52	49	47	49	49	46	47	47	46	42	33	25	14	4

QLQ-C30 - Global Health/QoL
Anatomic stages: IIIC



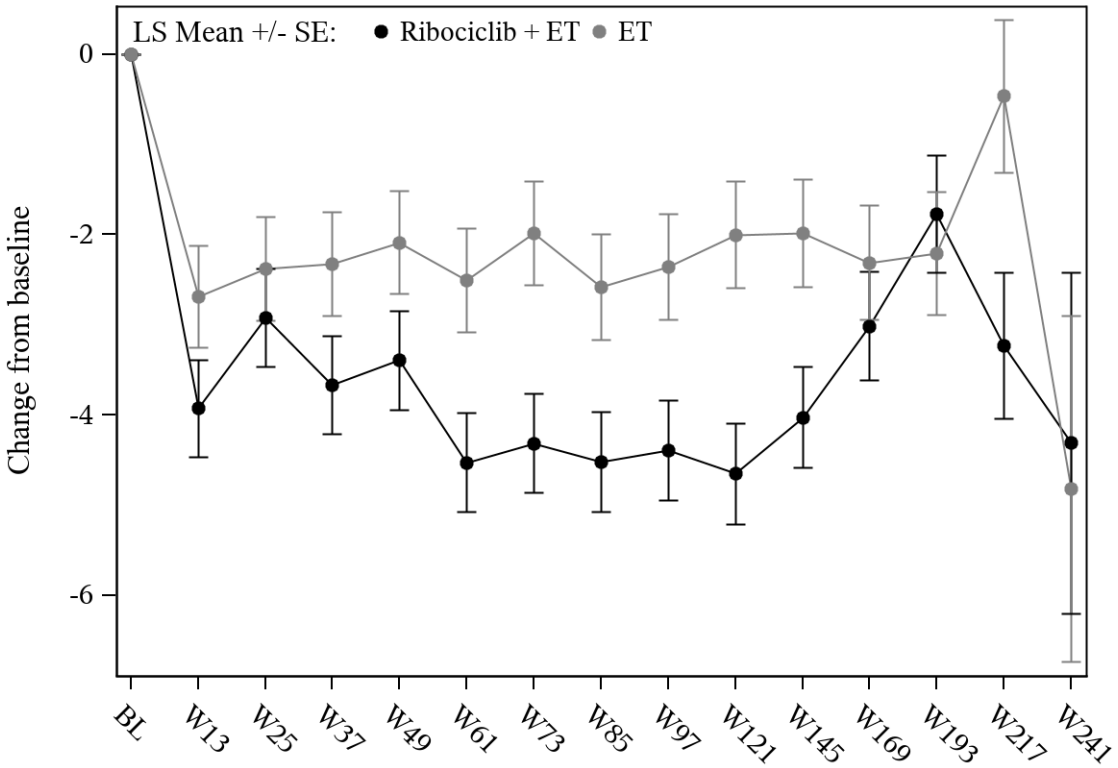
Ribociclib + ET	167	165	158	157	155	156	155	152	148	145	140	95	65	32	6
ET	186	175	178	169	170	166	160	159	153	153	142	107	76	35	7

QLQ-C30 - Global Health/QoL
Nodal status: N0



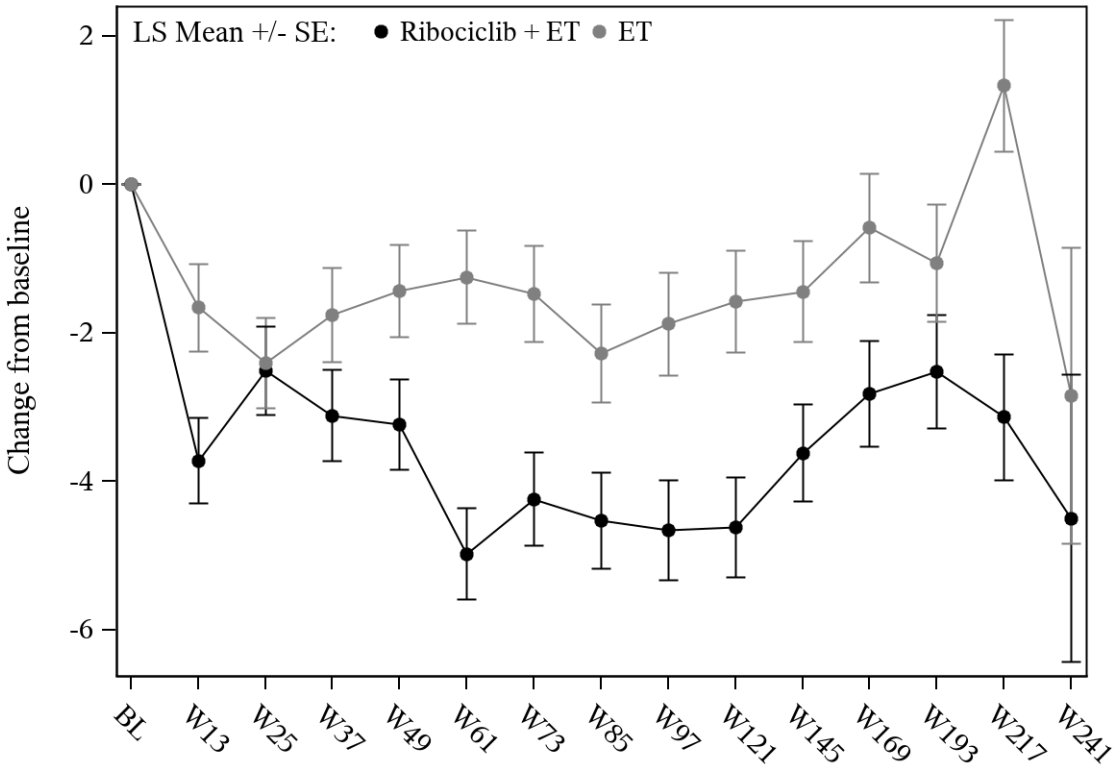
Ribociclib + ET	84	83	77	82	77	78	74	78	73	71	72	66	64	45	13
ET	110	108	98	98	104	102	100	97	98	93	87	81	75	47	8

QLQ-C30 - Global Health/QoL
Nodal status: N1-N3



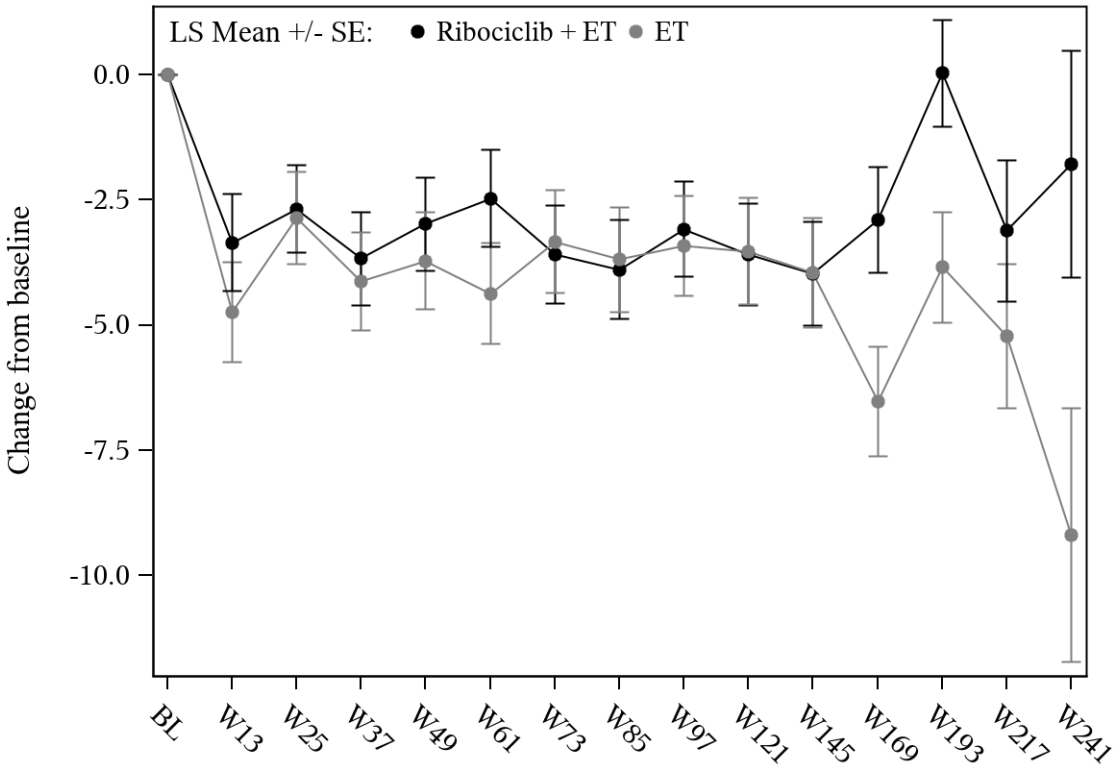
Ribociclib + ET	972	942	899	900	890	883	879	860	855	826	824	659	542	299	45
ET	890	845	815	806	810	797	790	770	756	743	719	596	490	274	44

QLQ-C30 - Global Health/QoL
Prior mastectomy: Yes



Ribociclib + ET	734	708	674	674	664	662	653	644	633	614	611	487	401	231	40
ET	698	658	647	634	642	630	623	611	596	587	558	457	377	213	38

QLQ-C30 - Global Health/QoL
Prior mastectomy: No



Ribociclib + ET	322	317	302	308	303	299	300	294	295	283	285	238	205	113	18
ET	305	298	269	273	273	271	269	258	260	251	250	222	190	110	14

Table 5-2.2.2.1 QLQ-C30 - Physical Functioning: change from baseline analysis - subgroup analysis (Full Analysis Set)

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1115)	ET (N = 1123)	Parameter	Esti-mate	[95% CI]	p-value
QLQ-C30 - Physical Functioning						
	N' | LS Mean (SE)	**N' | LS Mean (SE)**				
Region						
Interaction test	**p = 0.028**					
NA/WE/O	600 | -2.45 (0.42)	576 | -0.62 (0.43)	Difference	-1.83	[-3.02; -0.64]	0.003
			Hedges G	-0.18	[-0.29; -0.06]	
ROW	460 | -0.26 (0.46)	427 | -0.08 (0.48)	Difference	-0.18	[-1.47; 1.12]	0.789
			Hedges G	-0.02	[-0.15; 0.11]	
Geographical region						
Interaction test	**p = 0.233**					
Europe	619 | -2.76 (0.42)	592 | -1.21 (0.43)	Difference	-1.55	[-2.73; -0.36]	0.010
			Hedges G	-0.15	[-0.26; -0.03]	
North America/Australia	203 | -1.89 (0.63)	176 | 0.43 (0.69)	Difference	-2.32	[-4.16; -0.49]	0.013
			Hedges G	-0.26	[-0.46; -0.05]	
Asia	175 | N.E.	166 | N.E.	Difference	N.E.	[N.E.]	N.E.
			Hedges G	N.E.	[N.E.]	
Latin America	63 | 3.19 (1.24)	69 | 0.92 (1.17)	Difference	2.28	[-1.11; 5.66]	0.185
			Hedges G	0.23	[-0.11; 0.57]	
Age group 1 at randomization						
Interaction test	**p = 0.911**					
<45	525 | -0.94 (0.42)	458 | 0.37 (0.45)	Difference	-1.31	[-2.52; -0.11]	0.032
			Hedges G	-0.14	[-0.26; -0.01]	
45 to 54	515 | -2.26 (0.47)	518 | -0.72 (0.47)	Difference	-1.54	[-2.85; -0.23]	0.022
			Hedges G	-0.14	[-0.27; -0.02]	
55 to 64	20 | N.E.	27 | N.E.	Difference	N.E.	[N.E.]	N.E.
			Hedges G	N.E.	[N.E.]	
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)						
Interaction test	**p = 0.994**					
<Median	525 | -0.98 (0.41)	458 | 0.28 (0.44)	Difference	-1.26	[-2.44; -0.08]	0.036
			Hedges G	-0.13	[-0.26; -0.01]	
≥Median	535 | -2.13 (0.46)	545 | -0.78 (0.46)	Difference	-1.35	[-2.63; -0.07]	0.039
			Hedges G	-0.13	[-0.25; -0.01]	

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1115)	**ET (N = 1123)**	**Parameter**	**Esti-mate**	**[95% CI]**	**p-value**
Race						
Interaction test	**p = 0.805**					
Asian	206 | 0.65 (0.65)	180 | 1.75 (0.70)	Difference	-1.10	[-2.97; 0.77]	0.248
			Hedges G	-0.12	[-0.32; 0.08]	
Non-Asian	803 | -1.77 (0.37)	771 | -0.88 (0.38)	Difference	-0.89	[-1.93; 0.15]	0.093
			Hedges G	-0.08	[-0.18; 0.01]	
BMI at screening						
Interaction test	**p = 0.277**					
≥25	530 | -2.55 (0.52)	489 | -0.87 (0.55)	Difference	-1.68	[-3.16; -0.20]	0.026
			Hedges G	-0.14	[-0.26; -0.02]	
<25	518 | -0.21 (0.39)	503 | 0.37 (0.39)	Difference	-0.58	[-1.66; 0.51]	0.296
			Hedges G	-0.07	[-0.19; 0.06]	
AJCC Anatomic Stage Group						
Interaction test	**p = 0.011**					
Group I/II	395 | -1.00 (0.51)	397 | -1.24 (0.52)	Difference	0.23	[-1.20; 1.66]	0.749
			Hedges G	0.02	[-0.12; 0.16]	
Group III	665 | -1.93 (0.43)	606 | 0.36 (0.46)	Difference	-2.29	[-3.52; -1.06]	<.001
			Hedges G	-0.20	[-0.32; -0.09]	
Anatomic stages						
Interaction test	**p = 0.070**					
IA/IB/IIA	164 | -0.41 (0.75)	188 | -1.08 (0.71)	Difference	0.67	[-1.37; 2.70]	0.519
			Hedges G	0.07	[-0.14; 0.28]	
IIB	231 | -1.40 (0.68)	209 | -1.61 (0.71)	Difference	0.21	[-1.72; 2.14]	0.830
			Hedges G	0.02	[-0.17; 0.21]	
IIIA	433 | -2.11 (0.48)	368 | 0.55 (0.52)	Difference	-2.66	[-4.05; -1.27]	<.001
			Hedges G	-0.27	[-0.41; -0.13]	
IIIB	63 | -1.62 (1.53)	52 | -0.89 (1.70)	Difference	-0.72	[-5.32; 3.87]	0.756
			Hedges G	-0.06	[-0.43; 0.31]	
IIIC	169 | -1.86 (0.77)	186 | 0.63 (0.74)	Difference	-2.49	[-4.60; -0.39]	0.020
			Hedges G	-0.25	[-0.46; -0.04]	
Nodal status						
Interaction test	**p = 0.942**					
N0	84 | -0.22 (1.03)	110 | 0.57 (0.92)	Difference	-0.79	[-3.52; 1.95]	0.571
			Hedges G	-0.08	[-0.37; 0.20]	
N1-N3	976 | N.E.	890 | N.E.	Difference	N.E.	[N.E.]	N.E.
			Hedges G	N.E.	[N.E.]	

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1115)	**ET (N = 1123)**	**Parameter**	**Esti-mate**	**[95% CI]**	**p-value**
Histological grade at time of surgery						
Interaction test	**p = 0.224**					
Grade 1	106 | -0.73 (0.98)	97 | -1.53 (1.03)	Difference	0.80	[-2.00; 3.59]	0.574
			Hedges G	0.08	[-0.20; 0.35]	
Grade 2	580 | -1.37 (0.43)	558 | -0.32 (0.44)	Difference	-1.04	[-2.24; 0.15]	0.088
			Hedges G	-0.10	[-0.22; 0.01]	
Grade 3	282 | -2.01 (0.60)	252 | 0.15 (0.63)	Difference	-2.16	[-3.87; -0.44]	0.014
			Hedges G	-0.21	[-0.38; -0.04]	
Histological subtype						
Interaction test	**N.E.**					
Ductal	823 | -1.44 (0.34)	785 | -0.09 (0.35)	Difference	-1.35	[-2.32; -0.38]	0.006
			Hedges G	-0.14	[-0.23; -0.04]	
Lobular	168 | -1.67 (0.86)	156 | -1.28 (0.90)	Difference	-0.39	[-2.85; 2.07]	0.755
			Hedges G	-0.03	[-0.25; 0.18]	
Other	69 | -1.84 (1.27)	62 | -0.23 (1.37)	Difference	-1.61	[-5.30; 2.08]	0.389
			Hedges G	-0.15	[-0.49; 0.19]	
Ki67 status from surgical specimen						
Interaction test	**p = 0.804**					
Ki67≤20	510 | -1.34 (0.46)	516 | -0.28 (0.46)	Difference	-1.06	[-2.34; 0.21]	0.102
			Hedges G	-0.10	[-0.22; 0.02]	
Ki67>20	401 | -1.90 (0.51)	359 | -0.63 (0.54)	Difference	-1.27	[-2.73; 0.20]	0.089
			Hedges G	-0.12	[-0.27; 0.02]	
Type of NSAI						
Interaction test	**p = 0.406**					
Letrozole	775 | -1.25 (0.39)	719 | -0.27 (0.41)	Difference	-0.98	[-2.09; 0.14]	0.086
			Hedges G	-0.09	[-0.19; 0.01]	
Anastrozole	285 | -2.21 (0.60)	282 | -0.43 (0.61)	Difference	-1.77	[-3.46; -0.09]	0.040
			Hedges G	-0.17	[-0.34; -0.01]	
Prior neo/adjuvant chemotherapy						
Interaction test	**p = 0.922**					
Yes	985 | -1.38 (0.33)	925 | -0.17 (0.34)	Difference	-1.21	[-2.13; -0.29]	0.010
			Hedges G	-0.12	[-0.21; -0.03]	
No	75 | -2.95 (1.05)	78 | -1.92 (1.06)	Difference	-1.03	[-3.98; 1.92]	0.491
			Hedges G	-0.11	[-0.43; 0.21]	
Prior adjuvant chemotherapy						
Interaction test	**p = 0.833**					
Yes	495 | -1.53 (0.44)	462 | -0.33 (0.45)	Difference	-1.20	[-2.44; 0.04]	0.058
			Hedges G	-0.12	[-0.25; 0.00]	
No	565 | -1.68 (0.48)	541 | -0.27 (0.50)	Difference	-1.41	[-2.76; -0.05]	0.042
			Hedges G	-0.12	[-0.24; -0.00]	

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1115)	ET (N = 1123)	Parameter	Esti-mate	[95% CI]	p-value
Prior neoadjuvant chemotherapy						
Interaction test	**p = 0.810**					
Yes	520 | -1.42 (0.51)	501 | 0.01 (0.52)	Difference	-1.43	[-2.86; -0.00]	0.049
			Hedges G	-0.12	[-0.25; -0.00]	
No	540 | -1.76 (0.42)	502 | -0.66 (0.44)	Difference	-1.10	[-2.29; 0.09]	0.069
			Hedges G	-0.11	[-0.23; 0.01]	
Prior endocrine therapy						
Interaction test	**p = 0.646**					
Yes	816 | -1.51 (0.35)	733 | -0.43 (0.37)	Difference	-1.09	[-2.09; -0.08]	0.035
			Hedges G	-0.11	[-0.21; -0.01]	
No	244 | -1.52 (0.67)	270 | -0.00 (0.64)	Difference	-1.52	[-3.33; 0.29]	0.100
			Hedges G	-0.15	[-0.32; 0.03]	
Prior mastectomy						
Interaction test	**p = 0.233**					
Yes	737 | -1.43 (0.37)	697 | 0.22 (0.38)	Difference	-1.65	[-2.71; -0.60]	0.002
			Hedges G	-0.16	[-0.27; -0.06]	
No	323 | -1.79 (0.59)	306 | -1.31 (0.61)	Difference	-0.48	[-2.14; 1.18]	0.569
			Hedges G	-0.05	[-0.20; 0.11]	
Prior radiotherapy						
Interaction test	**p = 0.699**					
Yes	971 | -1.63 (0.33)	922 | -0.34 (0.34)	Difference	-1.29	[-2.21; -0.37]	0.006
			Hedges G	-0.13	[-0.22; -0.04]	
No	89 | -0.82 (1.02)	81 | 0.02 (1.08)	Difference	-0.84	[-3.79; 2.10]	0.572
			Hedges G	-0.09	[-0.39; 0.21]	

N: Number of patients
N': Number of patients in the analysis
CI: Confidence interval
SD: Standard deviation
LS Mean: Least square mean
SE: Standard error
MMRM: Mixed model for repeated measures
N.E.: Not estimable
ET: Endocrine therapy (Anastrozole/Letrozole + Goserelin)
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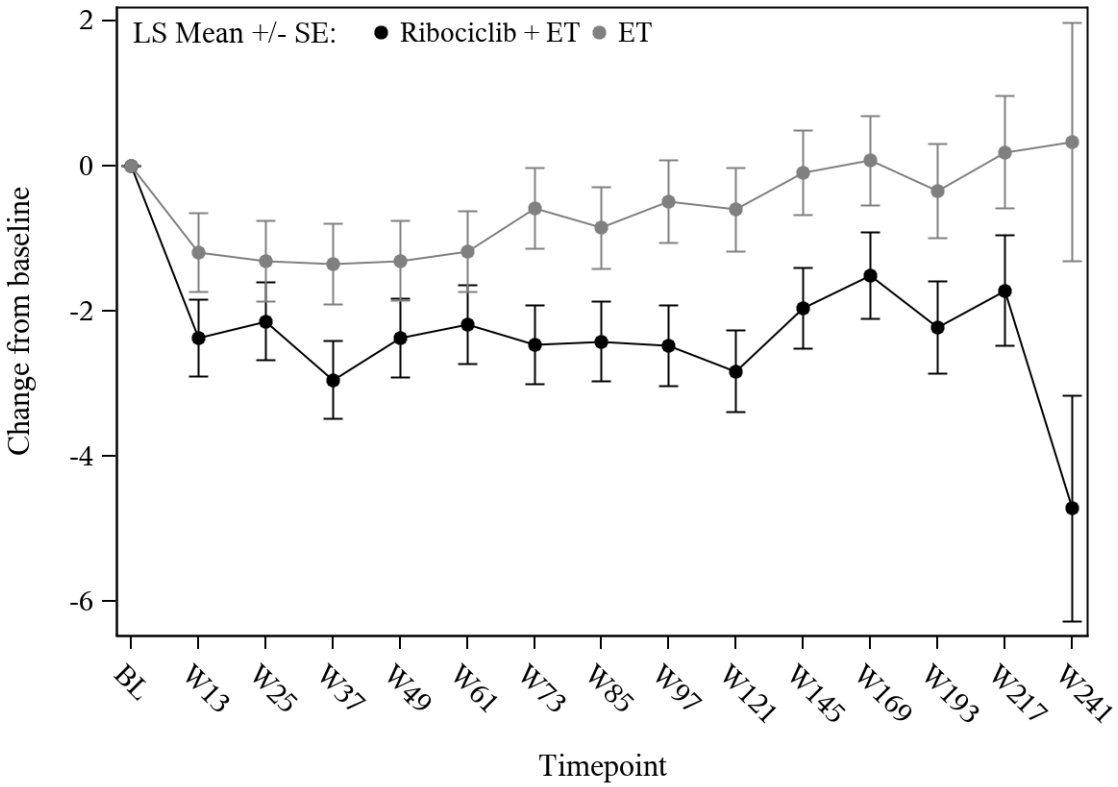
Analysis method for interaction test:
p-value from MMRM with unstructured covariance matrix:
change from baseline = treatment + visit + treatment * visit + subgroup factor + treatment * subgroup factor + subgroup factor * visit + treatment * subgroup factor * visit + baseline value
If the model did not converge for a parameter*subgroup factor, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry. If the model did still not converge, interactions were removed in the order treatment * subgroup factor * visit, subgroup factor * visit.

Analysis methods for within-subgroup analysis:
Adjusted mean (LS Mean) change from baseline and overall effect obtained from MMRM with unstructured covariance matrix:
change from baseline = treatment + visit + treatment * visit + baseline value
ET was the reference group for treatment group comparison.
If the model did not converge for a parameter*subgroup factor, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry.

Patients with an evaluable baseline score and at least one evaluable post-baseline score were included in the analysis.
All data collected were included in the analysis, including assessments at confirmation of first recurrence and thereafter, as long as there were at least 50 patients in each treatment group at a visit in the overall (sub-)population.

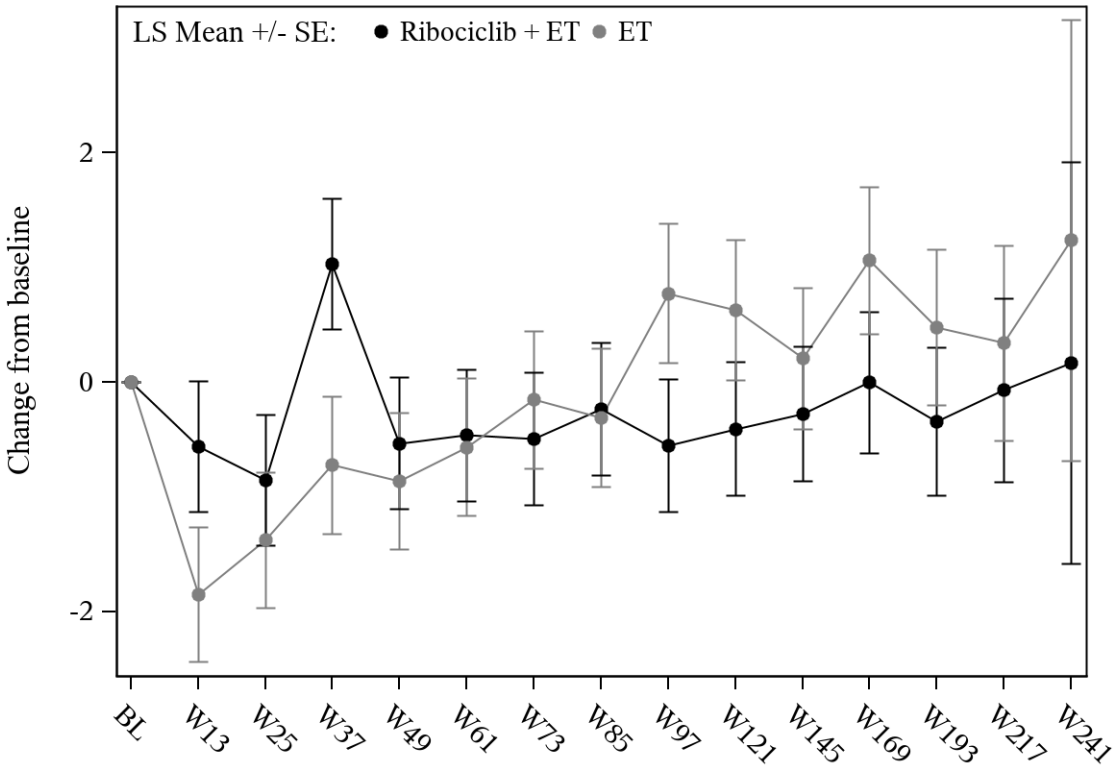
Figure 5-2.2.2.1 QLQ-C30 - Physical Functioning: line chart of change from baseline - subgroup analysis (Full Analysis Set)

QLQ-C30 - Physical Functioning
Region: NA/WE/O



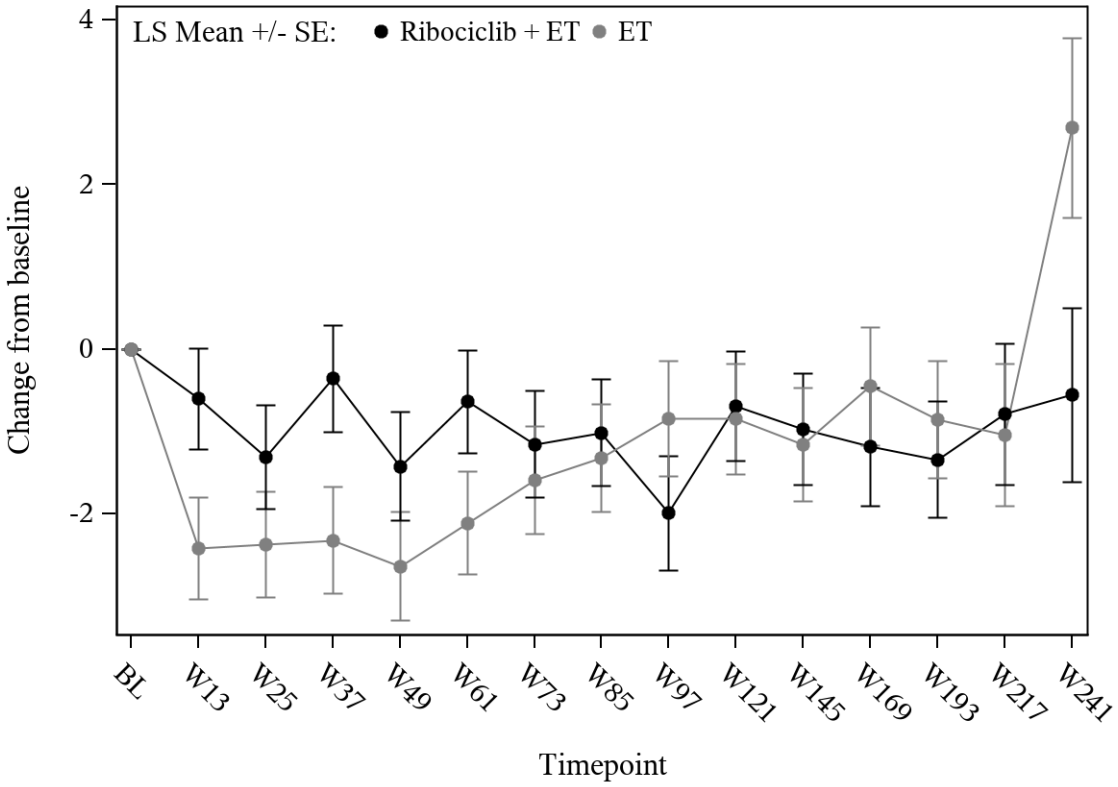
Ribociclib + ET	600	569	531	540	530	530	521	511	505	482	482	387	318	191	35
ET	576	538	504	506	512	502	495	474	471	461	441	365	305	188	32

QLQ-C30 - Physical Functioning
Region: ROW



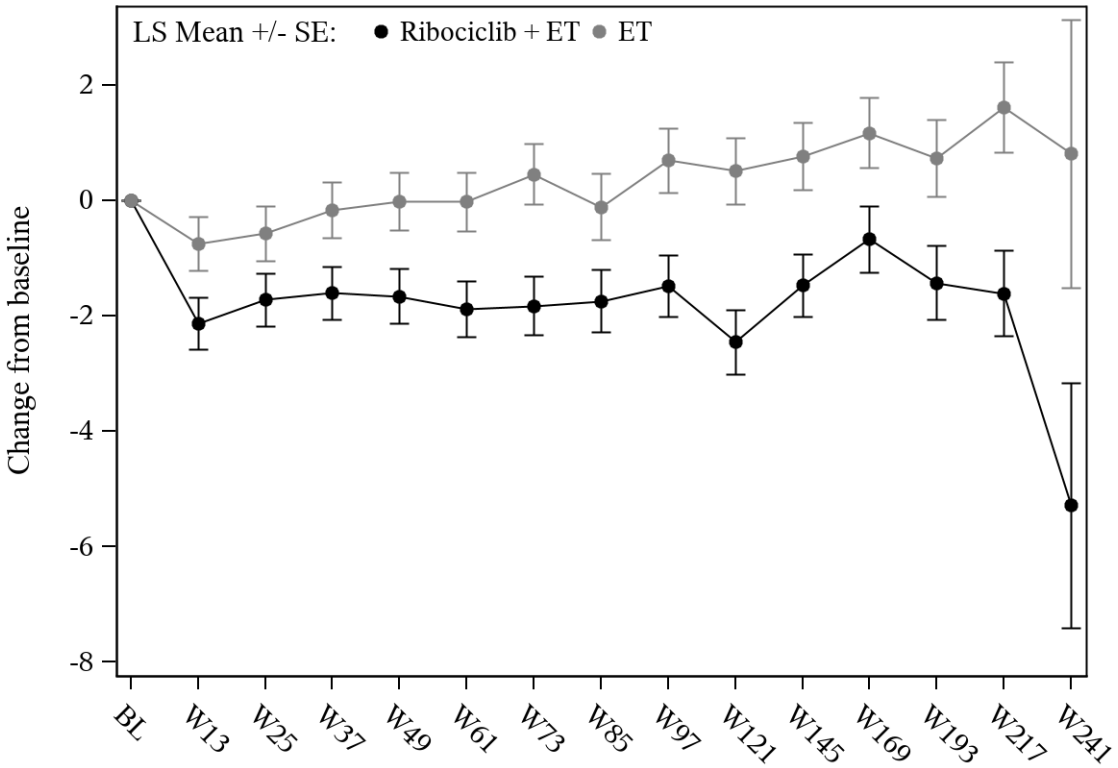
Ribociclib + ET	460	460	451	447	444	436	436	433	430	422	418	341	293	153	23
ET	427	425	418	406	411	402	398	395	388	380	369	316	260	135	19

QLQ-C30 - Physical Functioning
AJCC Anatomic Stage Group: Group I/II



Ribociclib + ET	395	385	369	366	362	361	357	355	353	342	340	316	316	177	31
ET	397	380	351	365	368	359	360	341	346	334	321	315	302	175	28

QLQ-C30 - Physical Functioning
AJCC Anatomic Stage Group: Group III



Ribociclib + ET	665	644	613	621	612	605	600	589	582	562	560	412	295	167	27
ET	606	583	571	547	555	545	533	528	513	507	489	366	263	148	23

Table 5-2.2.3.1 QLQ-C30 - Role Functioning: change from baseline analysis - subgroup analysis (Full Analysis Set)

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1115)	ET (N = 1123)	Parameter	Esti-mate	[95% CI]	p-value
QLQ-C30 - Role Functioning						
	N' | LS Mean (SE)	N' | LS Mean (SE)				
Region						
Interaction test	**p = 0.030**					
NA/WE/O	599 | -4.16 (0.72)	577 | -1.06 (0.73)	Difference	-3.10	[-5.11; -1.09]	0.003
			Hedges G	-0.18	[-0.29; -0.06]	
ROW	460 | -1.22 (0.67)	427 | -1.26 (0.70)	Difference	0.04	[-1.87; 1.94]	0.971
			Hedges G	0.00	[-0.13; 0.13]	
Geographical region						
Interaction test	**p = 0.056**					
Europe	618 | -3.38 (0.66)	593 | -2.27 (0.67)	Difference	-1.11	[-2.96; 0.74]	0.241
			Hedges G	-0.07	[-0.18; 0.05]	
North America/Australia	203 | -3.15 (1.08)	176 | 2.34 (1.19)	Difference	-5.49	[-8.65; -2.33]	<.001
			Hedges G	-0.35	[-0.55; -0.15]	
Asia	175 | N.E.	166 | N.E.	Difference	N.E.	[N.E.]	N.E.
			Hedges G	N.E.	[N.E.]	
Latin America	63 | -2.40 (1.98)	69 | -3.82 (1.86)	Difference	1.42	[-3.96; 6.80]	0.602
			Hedges G	0.09	[-0.25; 0.43]	
Age group 1 at randomization						
Interaction test	**N.E.**					
<45	525 | -2.40 (0.69)	459 | -1.55 (0.73)	Difference	-0.85	[-2.82; 1.12]	0.397
			Hedges G	-0.05	[-0.18; 0.07]	
45 to 54	514 | -3.53 (0.72)	519 | -1.15 (0.73)	Difference	-2.38	[-4.39; -0.37]	0.020
			Hedges G	-0.14	[-0.27; -0.02]	
55 to 64	20 | 0.46 (4.08)	26 | 1.23 (3.61)	Difference	-0.77	[-11.78; 10.23]	0.888
			Hedges G	-0.04	[-0.63; 0.54]	
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)						
Interaction test	**p = 0.114**					
<Median	525 | -1.86 (0.53)	459 | -1.62 (0.56)	Difference	-0.24	[-1.75; 1.26]	0.751
			Hedges G	-0.02	[-0.15; 0.10]	
≥Median	534 | -3.03 (0.53)	545 | -1.06 (0.54)	Difference	-1.97	[-3.44; -0.50]	0.009
			Hedges G	-0.16	[-0.28; -0.04]	

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1115)	**ET (N = 1123)**	**Parameter**	**Esti-mate**	**[95% CI]**	**p-value**
Race						
Interaction test	**p = 0.874**					
Asian	206 | -1.70 (1.02)	180 | -0.59 (1.10)	Difference	-1.10	[-4.06; 1.85]	0.463
			Hedges G	-0.07	[-0.27; 0.13]	
Non-Asian	802 | -3.00 (0.57)	772 | -1.64 (0.58)	Difference	-1.36	[-2.95; 0.23]	0.094
			Hedges G	-0.08	[-0.18; 0.01]	
BMI at screening						
Interaction test	**p = 0.435**					
≥25	529 | -4.75 (0.76)	489 | -2.45 (0.80)	Difference	-2.30	[-4.47; -0.13]	0.038
			Hedges G	-0.13	[-0.25; -0.01]	
<25	518 | -0.74 (0.63)	504 | 0.04 (0.65)	Difference	-0.78	[-2.56; 1.00]	0.389
			Hedges G	-0.05	[-0.18; 0.07]	
AJCC Anatomic Stage Group						
Interaction test	**p = <.001**					
Group I/II	394 | -0.80 (0.83)	399 | -3.32 (0.83)	Difference	2.52	[0.23; 4.81]	0.031
			Hedges G	0.15	[0.01; 0.29]	
Group III	665 | -4.14 (0.63)	605 | 0.23 (0.67)	Difference	-4.37	[-6.17; -2.57]	<.001
			Hedges G	-0.27	[-0.38; -0.16]	
Anatomic stages						
Interaction test	**p = <.001**					
IA/IB/IIA	163 | 2.35 (0.89)	189 | -0.87 (0.86)	Difference	3.22	[0.78; 5.66]	0.010
			Hedges G	0.28	[0.07; 0.49]	
IIB	231 | -2.49 (0.83)	210 | -5.07 (0.86)	Difference	2.58	[0.22; 4.94]	0.033
			Hedges G	0.20	[0.02; 0.39]	
IIIA	433 | -4.62 (0.59)	368 | -0.48 (0.64)	Difference	-4.14	[-5.84; -2.45]	<.001
			Hedges G	-0.34	[-0.48; -0.20]	
IIIB	63 | 0.01 (1.75)	52 | 2.68 (1.97)	Difference	-2.67	[-7.90; 2.57]	0.315
			Hedges G	-0.19	[-0.56; 0.18]	
IIIC	169 | -4.00 (0.95)	185 | -0.09 (0.91)	Difference	-3.91	[-6.50; -1.31]	0.003
			Hedges G	-0.31	[-0.52; -0.11]	
Nodal status						
Interaction test	**p = 0.264**					
N0	84 | 2.46 (1.57)	110 | 2.35 (1.39)	Difference	0.11	[-4.03; 4.25]	0.960
			Hedges G	0.01	[-0.28; 0.29]	
N1-N3	975 | -3.53 (0.53)	891 | -1.61 (0.56)	Difference	-1.92	[-3.43; -0.41]	0.013
			Hedges G	-0.12	[-0.21; -0.02]	

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1115)	**ET (N = 1123)**	**Parameter**	**Esti-mate**	**[95% CI]**	**p-value**
Histological grade at time of surgery						
Interaction test	**p = 0.523**					
Grade 1	106 | -1.88 (1.48)	97 | -2.20 (1.56)	Difference	0.32	[-3.91; 4.55]	0.882
			Hedges G	0.02	[-0.25; 0.30]	
Grade 2	579 | -2.85 (0.66)	558 | -1.10 (0.68)	Difference	-1.75	[-3.60; 0.11]	0.065
			Hedges G	-0.11	[-0.23; 0.01]	
Grade 3	282 | -3.51 (0.93)	252 | -0.81 (0.98)	Difference	-2.70	[-5.36; -0.05]	0.046
			Hedges G	-0.17	[-0.34; -0.00]	
Histological subtype						
Interaction test	**p = 0.954**					
Ductal	822 | -2.84 (0.55)	786 | -1.30 (0.57)	Difference	-1.54	[-3.09; 0.01]	0.052
			Hedges G	-0.10	[-0.19; 0.00]	
Lobular	168 | -2.46 (1.33)	156 | -0.93 (1.38)	Difference	-1.53	[-5.30; 2.24]	0.426
			Hedges G	-0.09	[-0.31; 0.13]	
Other	69 | -2.94 (1.90)	62 | -1.92 (2.05)	Difference	-1.02	[-6.56; 4.51]	0.715
			Hedges G	-0.06	[-0.41; 0.28]	
Ki67 status from surgical specimen						
Interaction test	**p = 0.807**					
Ki67≤20	510 | -3.19 (0.70)	517 | -1.95 (0.69)	Difference	-1.24	[-3.16; 0.69]	0.207
			Hedges G	-0.08	[-0.20; 0.04]	
Ki67>20	400 | -3.05 (0.79)	358 | -1.42 (0.84)	Difference	-1.63	[-3.90; 0.64]	0.159
			Hedges G	-0.10	[-0.25; 0.04]	
Type of NSAI						
Interaction test	**p = 0.029**					
Letrozole	775 | -2.12 (0.58)	721 | -1.52 (0.61)	Difference	-0.59	[-2.24; 1.05]	0.480
			Hedges G	-0.04	[-0.14; 0.06]	
Anastrozole	284 | -5.19 (0.98)	281 | -0.78 (0.99)	Difference	-4.41	[-7.13; -1.68]	0.002
			Hedges G	-0.27	[-0.43; -0.10]	
Prior neo/adjuvant chemotherapy						
Interaction test	**N.E.**					
Yes	984 | -3.08 (0.51)	926 | -1.47 (0.53)	Difference	-1.61	[-3.07; -0.16]	0.029
			Hedges G	-0.10	[-0.19; -0.01]	
No	75 | 0.58 (1.76)	78 | 0.97 (1.77)	Difference	-0.40	[-5.33; 4.53]	0.874
			Hedges G	-0.03	[-0.34; 0.29]	
Prior adjuvant chemotherapy						
Interaction test	**p = 0.539**					
Yes	494 | -3.71 (0.71)	462 | -1.59 (0.74)	Difference	-2.12	[-4.13; -0.11]	0.039
			Hedges G	-0.13	[-0.26; -0.01]	
No	565 | -2.57 (0.71)	542 | -0.98 (0.73)	Difference	-1.59	[-3.58; 0.40]	0.117
			Hedges G	-0.09	[-0.21; 0.02]	

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1115)	ET (N = 1123)	Parameter	Esti-mate	[95% CI]	p-value
Prior neoadjuvant chemotherapy						
Interaction test	**p = 0.949**					
Yes	520 | -2.57 (0.72)	502 | -1.00 (0.74)	Difference	-1.57	[-3.60; 0.46]	0.129
			Hedges G	-0.09	[-0.22; 0.03]	
No	539 | -3.14 (0.69)	502 | -1.56 (0.72)	Difference	-1.58	[-3.55; 0.39]	0.115
			Hedges G	-0.10	[-0.22; 0.02]	
Prior endocrine therapy						
Interaction test	**p = 0.423**					
Yes	815 | -3.61 (0.57)	734 | -1.63 (0.61)	Difference	-1.98	[-3.62; -0.35]	0.017
			Hedges G	-0.12	[-0.22; -0.02]	
No	244 | -0.80 (1.04)	270 | -0.15 (1.00)	Difference	-0.65	[-3.49; 2.19]	0.655
			Hedges G	-0.04	[-0.21; 0.13]	
Prior mastectomy						
Interaction test	**p = 0.034**					
Yes	737 | -3.14 (0.60)	699 | -0.43 (0.62)	Difference	-2.72	[-4.40; -1.03]	0.002
			Hedges G	-0.17	[-0.27; -0.06]	
No	322 | -2.70 (0.89)	305 | -2.95 (0.93)	Difference	0.26	[-2.27; 2.78]	0.842
			Hedges G	0.02	[-0.14; 0.17]	
Prior radiotherapy						
Interaction test	**p = 0.407**					
Yes	970 | -3.33 (0.52)	922 | -1.64 (0.53)	Difference	-1.70	[-3.15; -0.24]	0.023
			Hedges G	-0.10	[-0.20; -0.01]	
No	89 | 2.01 (1.63)	82 | 1.91 (1.73)	Difference	0.10	[-4.60; 4.79]	0.968
			Hedges G	0.01	[-0.29; 0.31]	

N: Number of patients
N': Number of patients in the analysis
CI: Confidence interval
SD: Standard deviation
LS Mean: Least square mean
SE: Standard error
MMRM: Mixed model for repeated measures
N.E.: Not estimable
ET: Endocrine therapy (Anastrozole/Letrozole + Goserelin)
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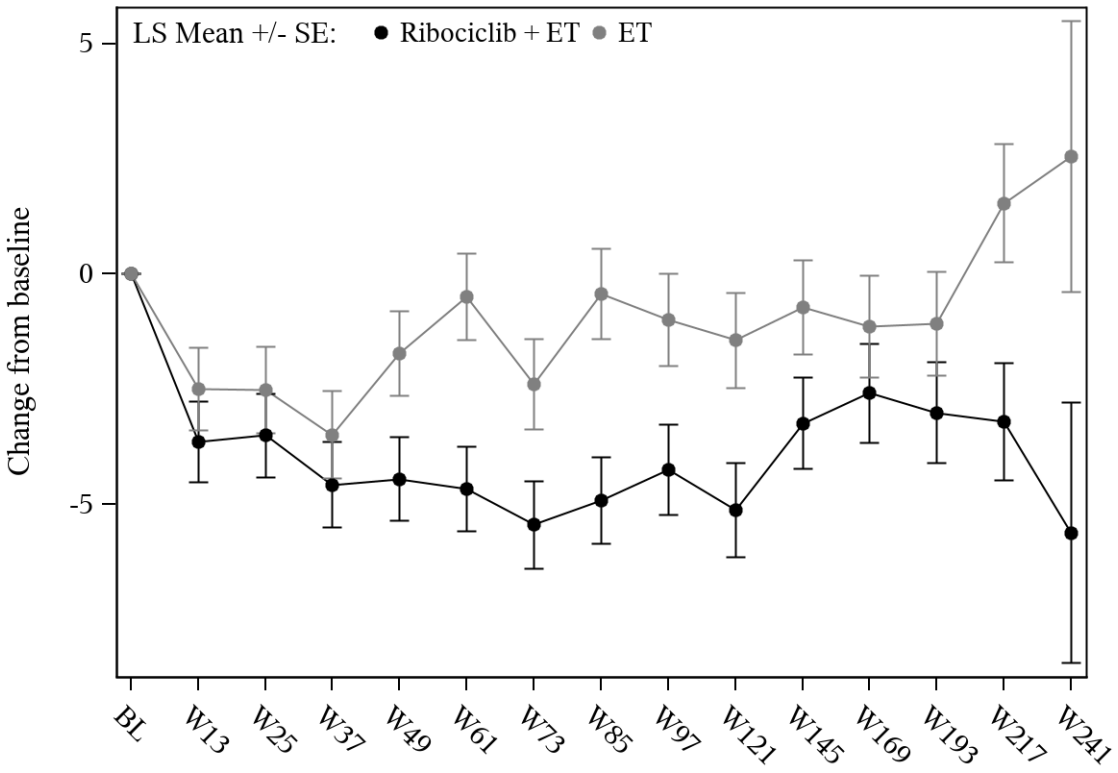
Analysis method for interaction test:
p-value from MMRM with unstructured covariance matrix:
change from baseline = treatment + visit + treatment * visit + subgroup factor + treatment * subgroup factor + subgroup factor * visit + treatment * subgroup factor * visit + baseline value
If the model did not converge for a parameter*subgroup factor, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry. If the model did still not converge, interactions were removed in the order treatment * subgroup factor * visit, subgroup factor * visit.

Analysis methods for within-subgroup analysis:
Adjusted mean (LS Mean) change from baseline and overall effect obtained from MMRM with unstructured covariance matrix:
change from baseline = treatment + visit + treatment * visit + baseline value
ET was the reference group for treatment group comparison.
If the model did not converge for a parameter*subgroup factor, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry.

Patients with an evaluable baseline score and at least one evaluable post-baseline score were included in the analysis.
All data collected were included in the analysis, including assessments at confirmation of first recurrence and thereafter, as long as there were at least 50 patients in each treatment group at a visit in the overall (sub-)population.

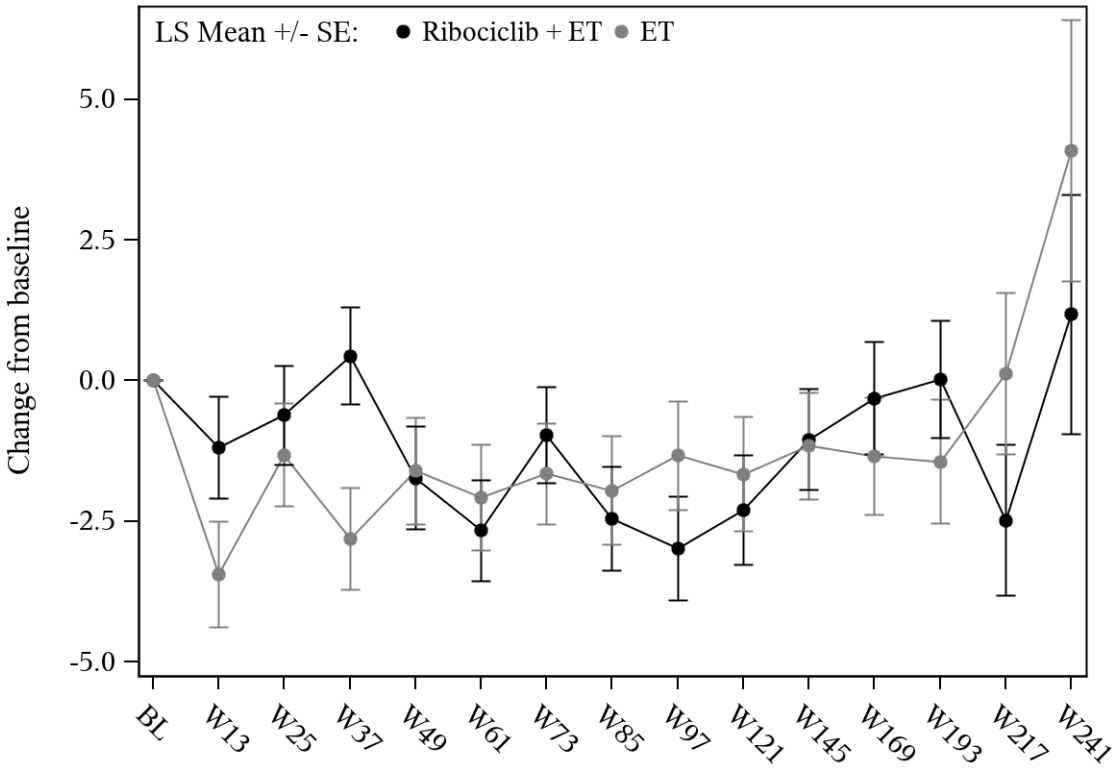
Figure 5-2.2.3.1 QLQ-C30 - Role Functioning: line chart of change from baseline - subgroup analysis (Full Analysis Set)

QLQ-C30 - Role Functioning
Region: NA/WE/O



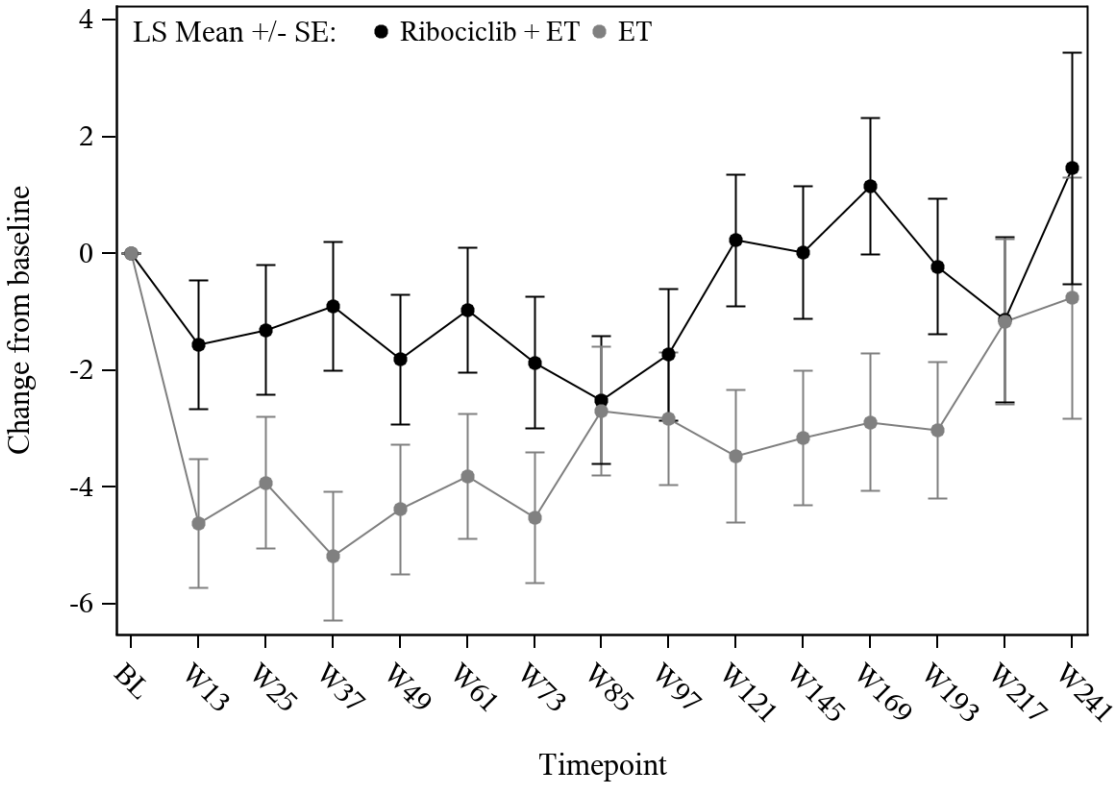
Ribociclib + ET	599	567	530	539	528	529	520	511	504	481	482	386	317	190	35
ET	577	539	503	506	511	501	496	475	472	462	442	367	306	188	33

QLQ-C30 - Role Functioning
Region: ROW



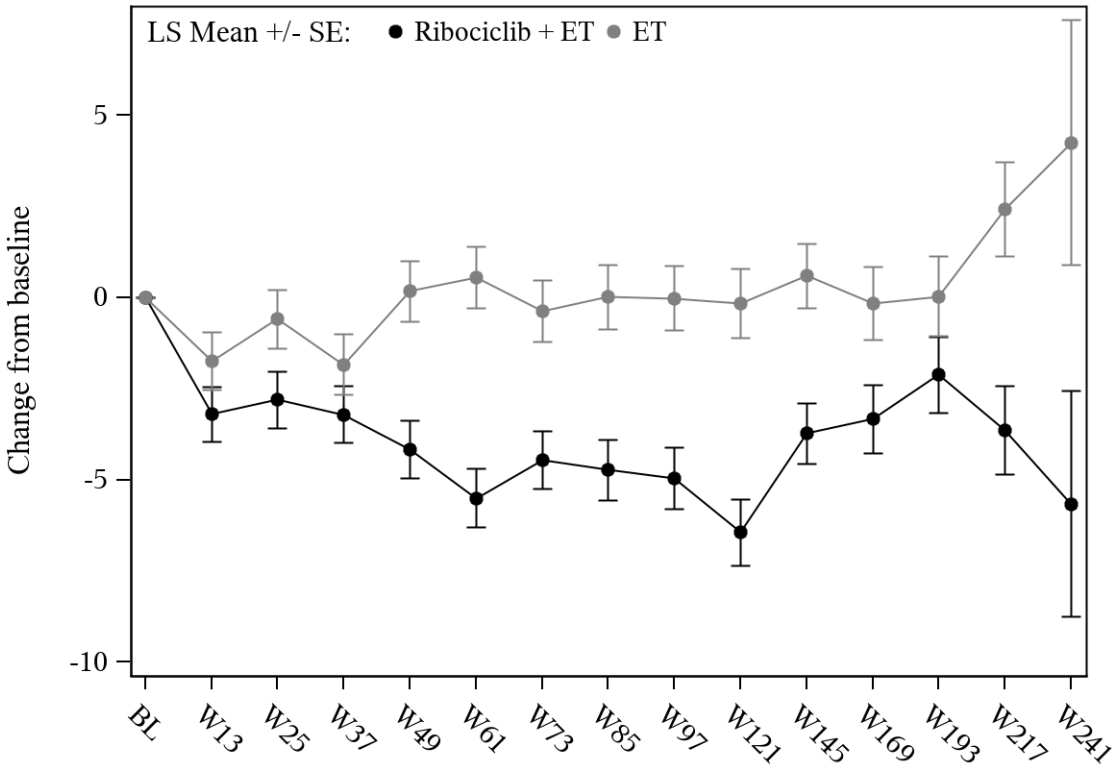
Ribociclib + ET	460	460	451	447	444	436	436	433	430	422	418	341	293	154	23
ET	427	425	418	406	411	402	398	394	388	380	369	316	259	135	19

QLQ-C30 - Role Functioning
AJCC Anatomic Stage Group: Group I/II



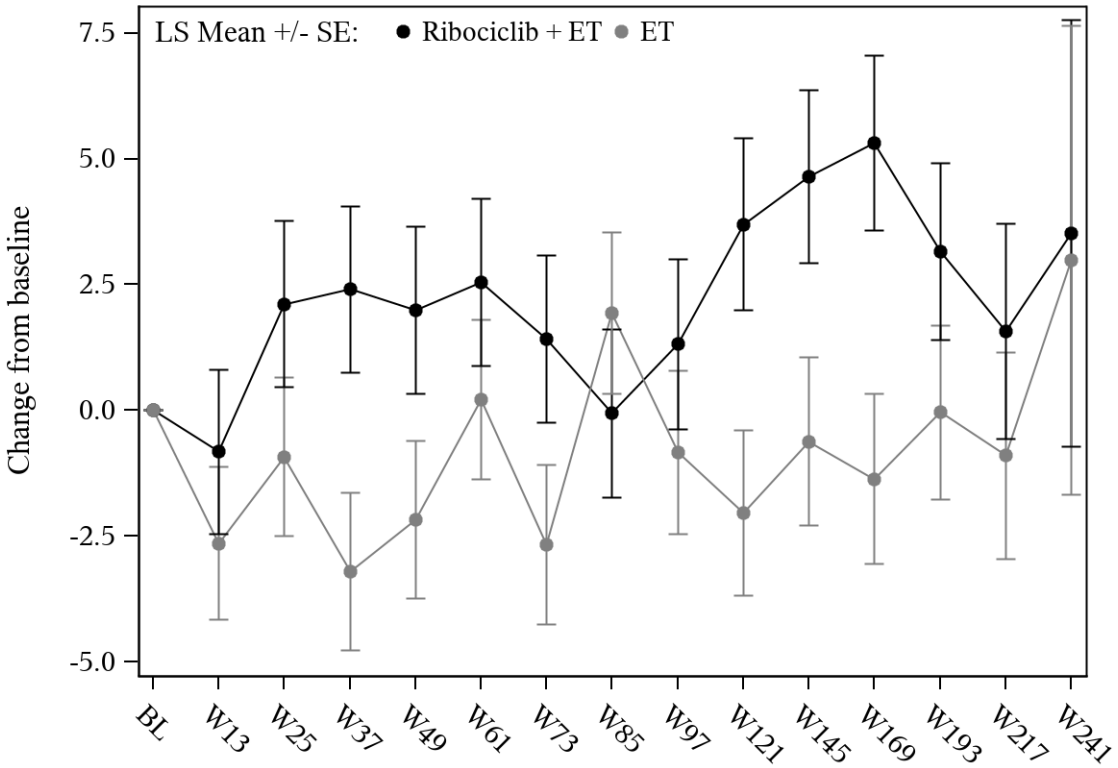
Ribociclib + ET	394	384	368	365	362	360	356	355	352	341	340	315	315	176	31
ET	399	382	351	366	368	360	361	342	347	335	322	317	302	175	28

QLQ-C30 - Role Functioning
AJCC Anatomic Stage Group: Group III



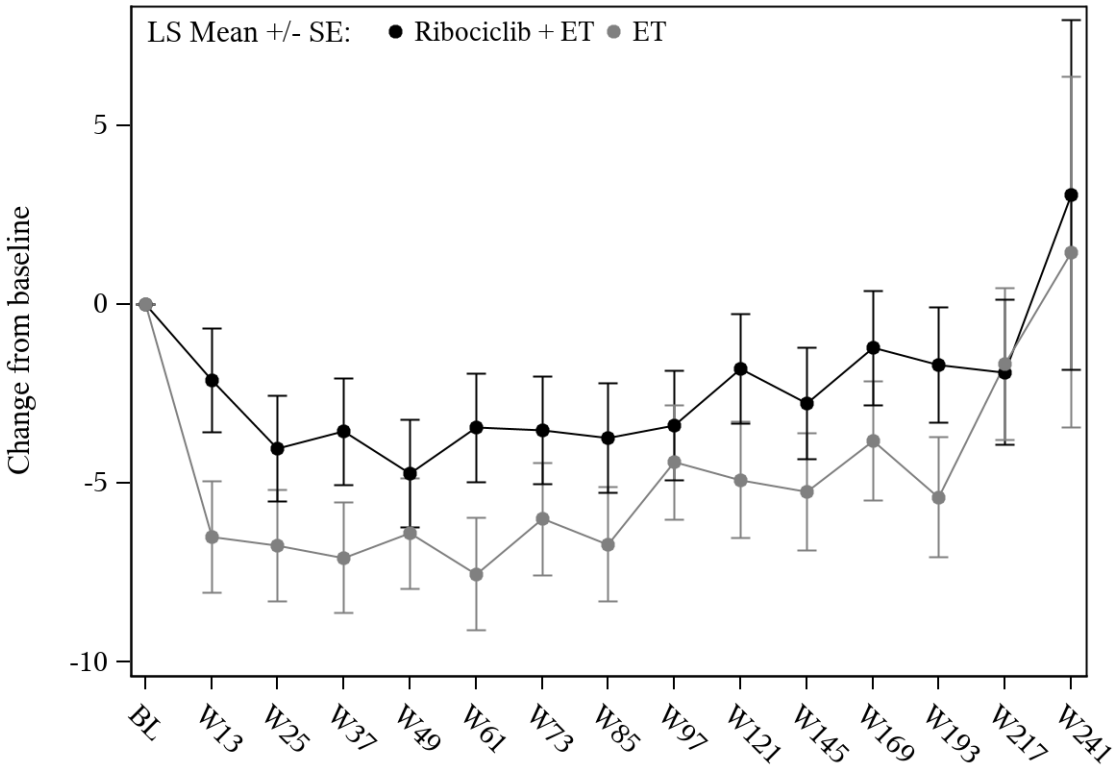
Ribociclib + ET	665	643	613	621	610	605	600	589	582	562	560	412	295	168	27
ET	605	582	570	546	554	543	533	527	513	507	489	366	263	148	24

QLQ-C30 - Role Functioning
Anatomic stages: IA/IB/IIA



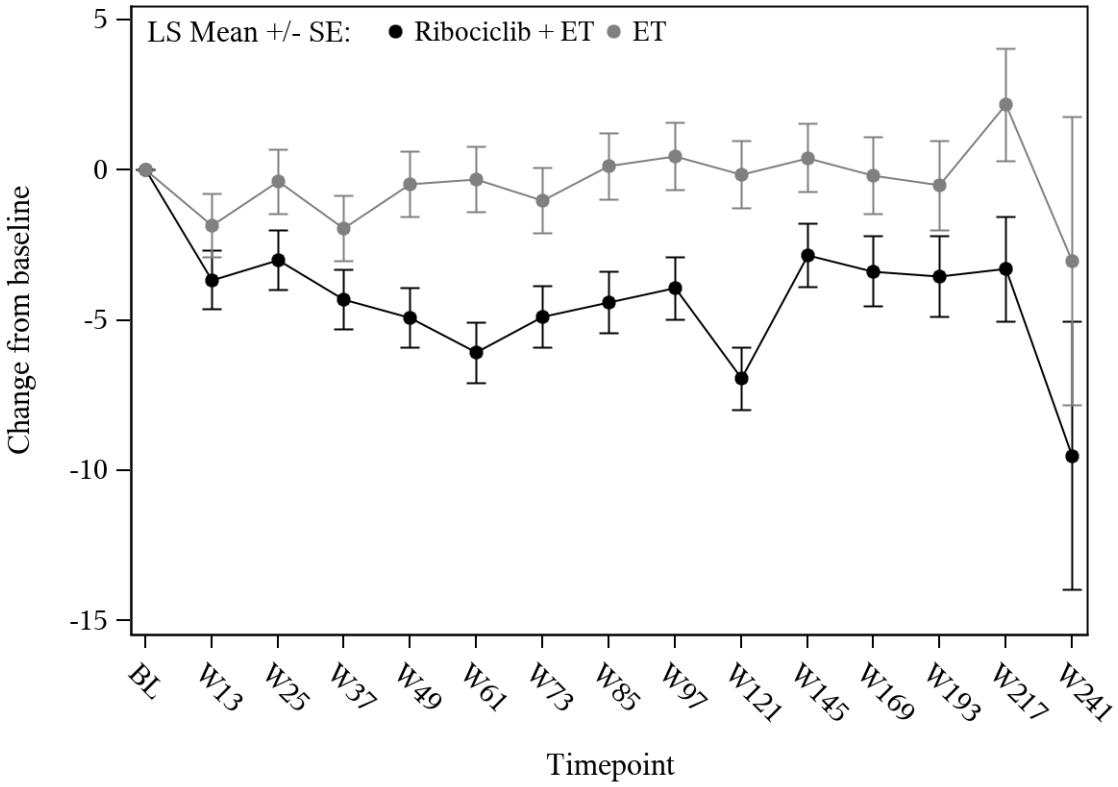
Ribociclib + ET	163	159	154	154	153	155	151	152	148	142	143	138	135	79	17
ET	189	184	161	170	171	167	170	162	162	156	148	148	139	87	14

QLQ-C30 - Role Functioning
Anatomic stages: IIB



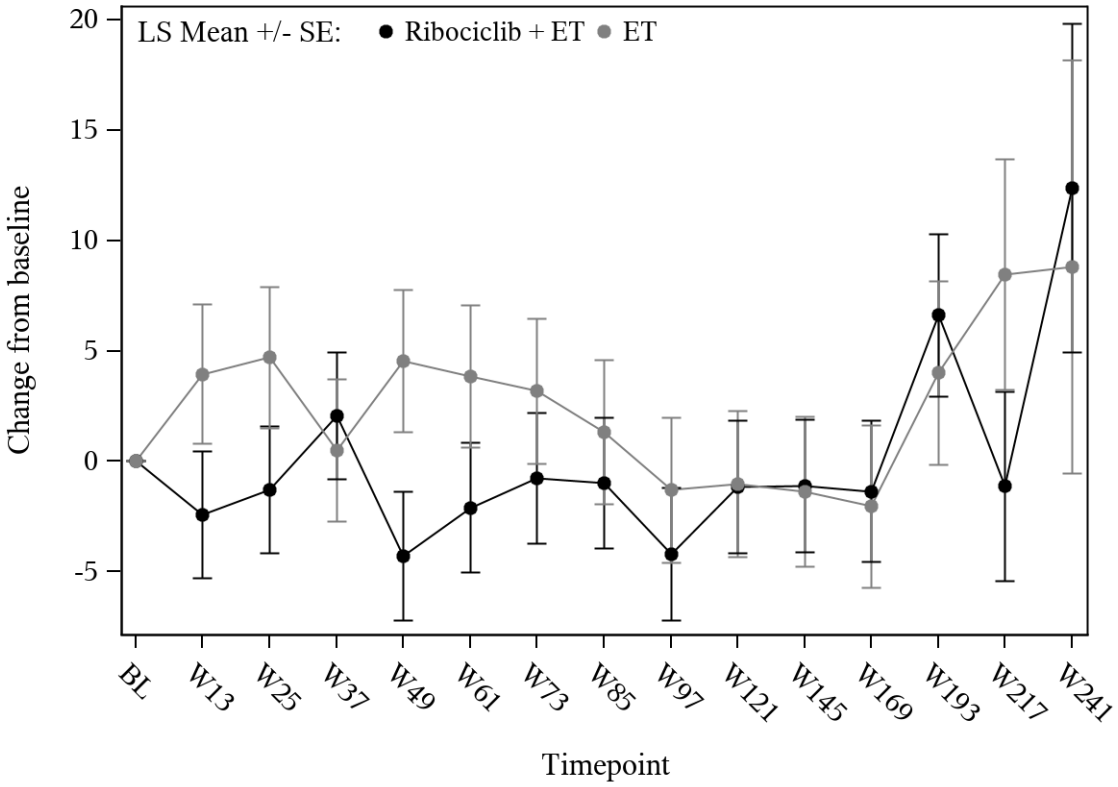
Ribociclib + ET	231	225	214	211	209	205	205	203	204	199	197	177	180	97	14
ET	210	198	190	196	197	193	191	180	185	179	174	169	163	88	14

QLQ-C30 - Role Functioning
Anatomic stages: IIIA



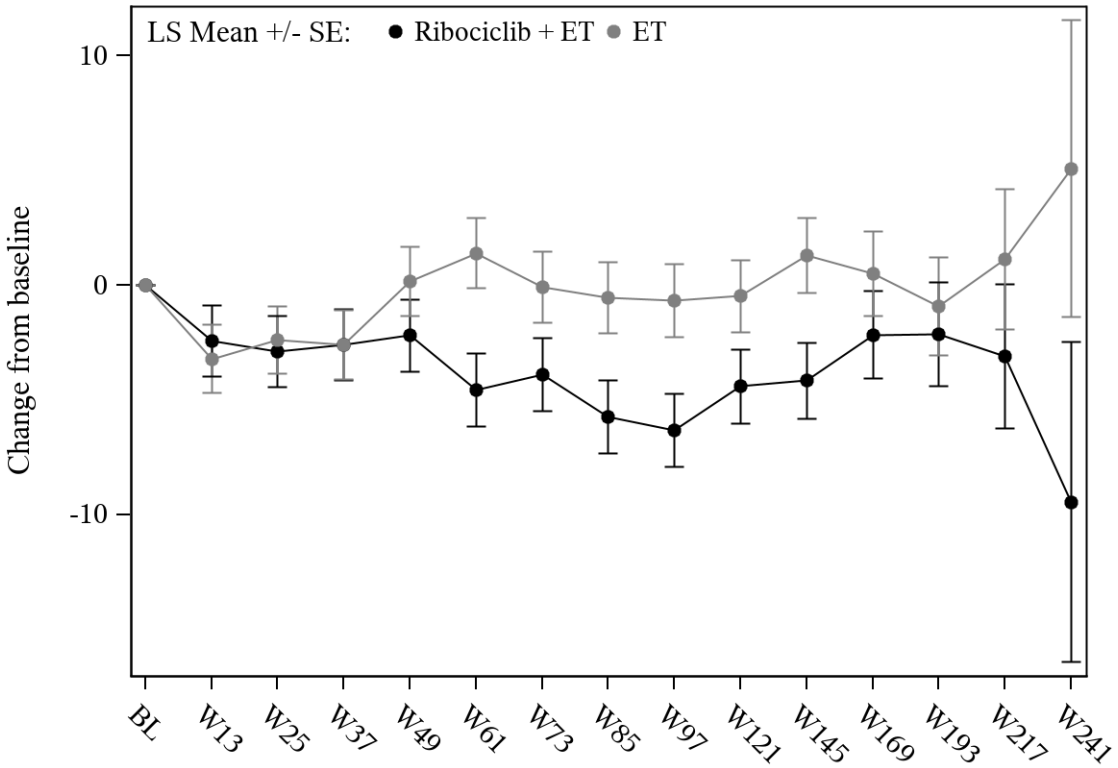
Ribociclib + ET	433	416	391	400	392	389	385	376	374	357	360	269	197	112	15
ET	368	355	343	330	336	329	327	321	313	308	304	225	162	99	13

QLQ-C30 - Role Functioning
Anatomic stages: IIIB



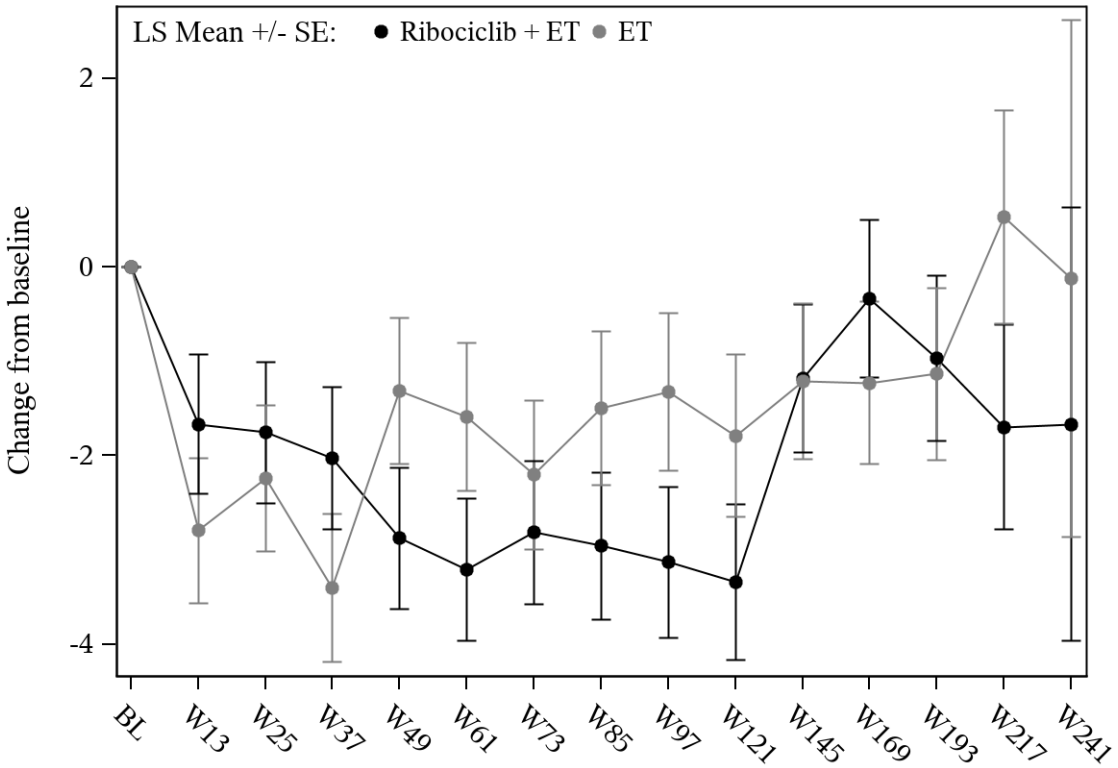
Ribociclib + ET	63	62	62	61	60	59	58	59	56	57	57	46	31	23	6
ET	52	52	49	47	49	49	46	47	47	46	42	33	25	14	4

QLQ-C30 - Role Functioning
Anatomic stages: IIIC



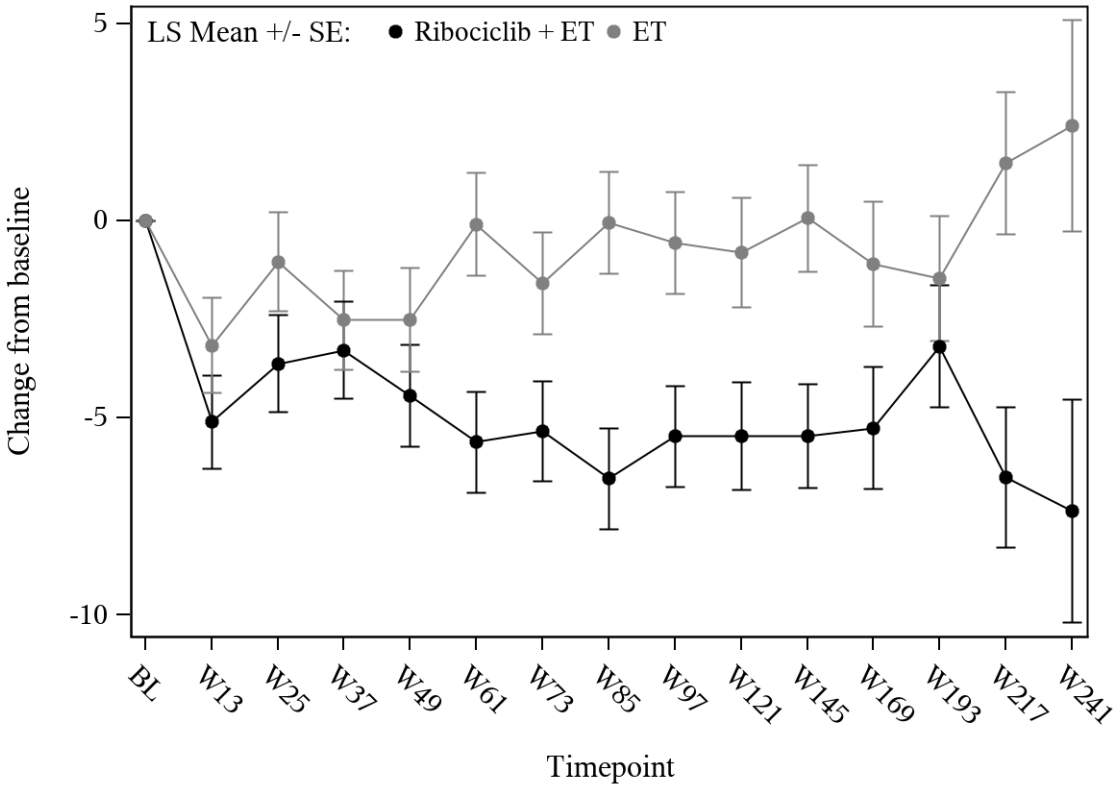
Ribociclib + ET	169	165	160	160	158	157	157	154	152	148	143	97	67	33	6
ET	185	175	178	169	169	165	160	159	153	153	143	108	76	35	7

QLQ-C30 - Role Functioning
Type of NSAI: Letrozole



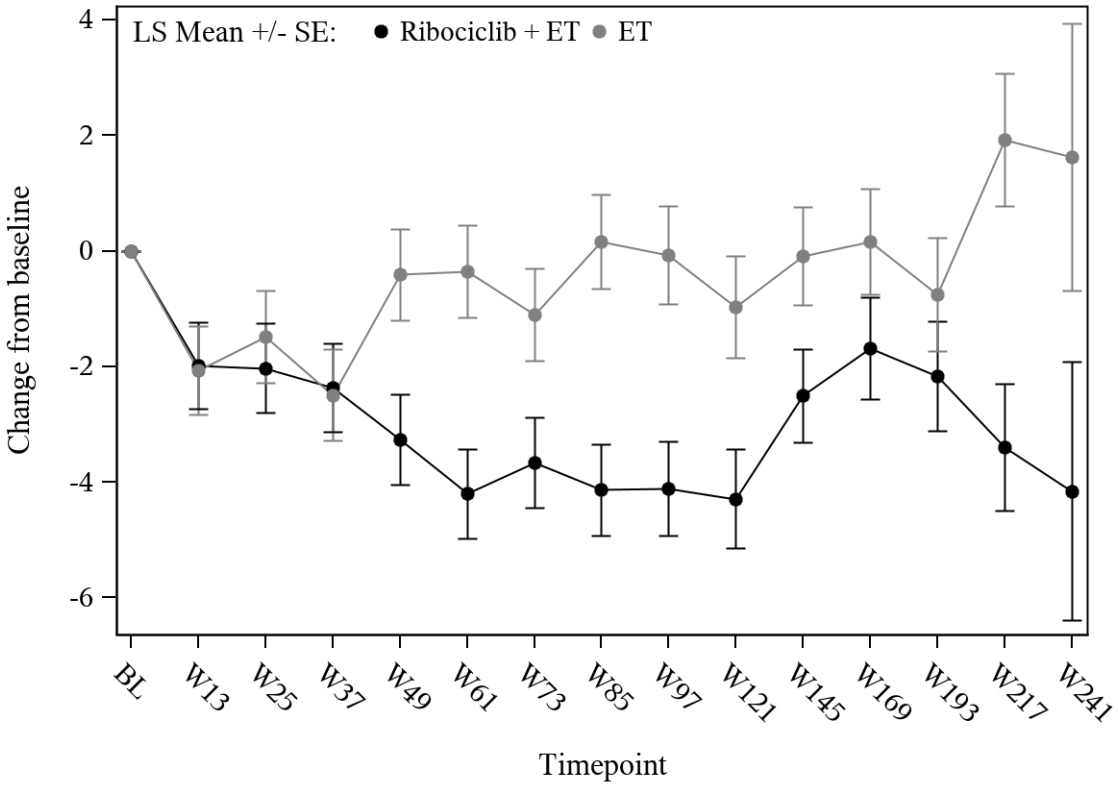
Ribociclib + ET	775	752	717	724	710	710	704	699	695	666	663	538	455	255	37
ET	721	693	672	661	671	657	649	630	628	615	594	507	416	234	26

QLQ-C30 - Role Functioning
Type of NSAI: Anastrozole



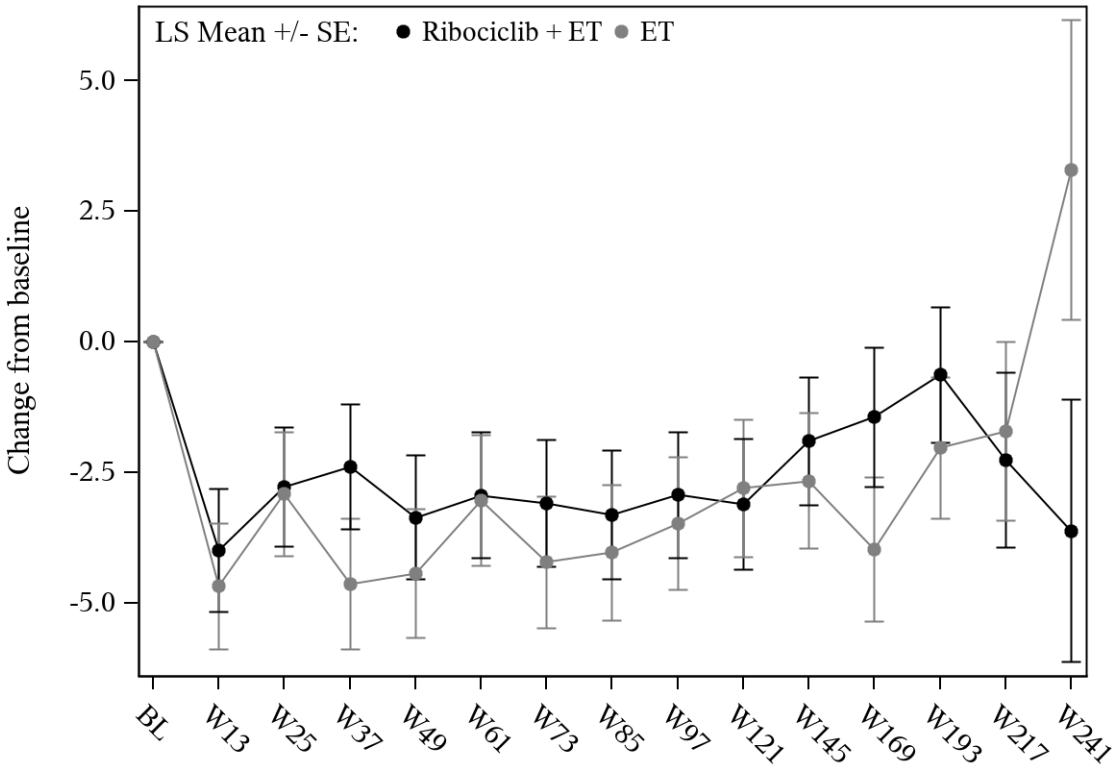
Ribociclib + ET	284	275	264	262	262	255	252	245	239	237	237	189	155	89	21
ET	281	269	249	251	251	246	245	239	232	227	217	176	149	89	26

QLQ-C30 - Role Functioning
Prior mastectomy: Yes



Ribociclib + ET	737	710	680	679	667	665	657	649	640	619	613	490	404	232	40
ET	699	666	650	637	647	631	624	610	599	590	560	461	376	213	38

QLQ-C30 - Role Functioning
Prior mastectomy: No



Ribociclib + ET	322	317	301	307	305	300	299	295	294	284	287	237	206	112	18
ET	305	298	271	275	275	272	270	259	261	252	251	222	189	110	14

Table 5-2.2.4.1 QLQ-C30 - Emotional Functioning: change from baseline analysis - subgroup analysis (Full Analysis Set)

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1115)	ET (N = 1123)	Parameter	Esti-mate	[95% CI]	p-value
QLQ-C30 - Emotional Functioning						
	N' | LS Mean (SE)	N' | LS Mean (SE)				
Region						
Interaction test	**p = 0.012**					
NA/WE/O	596 | -7.47 (0.72)	576 | -5.27 (0.74)	Difference	-2.20	[-4.23; -0.18]	0.033
			Hedges G	-0.12	[-0.24; -0.01]	
ROW	460 | -4.05 (0.70)	427 | -5.67 (0.73)	Difference	1.62	[-0.37; 3.61]	0.110
			Hedges G	0.11	[-0.02; 0.24]	
Geographical region						
Interaction test	**p = 0.305**					
Europe	615 | -6.93 (0.68)	592 | -6.26 (0.69)	Difference	-0.67	[-2.57; 1.24]	0.491
			Hedges G	-0.04	[-0.15; 0.07]	
North America/Australia	203 | -5.08 (1.02)	176 | -1.95 (1.11)	Difference	-3.12	[-6.08; -0.16]	0.039
			Hedges G	-0.21	[-0.42; -0.01]	
Asia	175 | N.E.	166 | N.E.	Difference	N.E.	[N.E.]	N.E.
			Hedges G	N.E.	[N.E.]	
Latin America	63 | -2.57 (1.99)	69 | -4.24 (1.88)	Difference	1.67	[-3.74; 7.08]	0.543
			Hedges G	0.11	[-0.24; 0.45]	
Age group 1 at randomization						
Interaction test	**N.E.**					
<45	524 | -5.11 (0.70)	458 | -4.70 (0.75)	Difference	-0.42	[-2.43; 1.59]	0.685
			Hedges G	-0.03	[-0.15; 0.10]	
45 to 54	512 | N.E.	518 | N.E.	Difference	N.E.	[N.E.]	N.E.
			Hedges G	N.E.	[N.E.]	
55 to 64	20 | -2.56 (3.19)	27 | -2.63 (2.81)	Difference	0.07	[-8.49; 8.62]	0.987
			Hedges G	0.00	[-0.57; 0.58]	
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)						
Interaction test	**p = 0.681**					
<Median	524 | -5.15 (0.74)	458 | -4.97 (0.78)	Difference	-0.17	[-2.29; 1.94]	0.873
			Hedges G	-0.01	[-0.14; 0.12]	
≥Median	532 | -6.88 (0.72)	545 | -5.85 (0.72)	Difference	-1.03	[-3.03; 0.96]	0.310
			Hedges G	-0.06	[-0.18; 0.06]	

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1115)	**ET (N = 1123)**	**Parameter**	**Esti-mate**	**[95% CI]**	**p-value**
Race						
Interaction test	**p = 0.712**					
Asian	206 | -4.46 (0.94)	180 | -4.58 (1.01)	Difference	0.11	[-2.60; 2.82]	0.936
			Hedges G	0.01	[-0.19; 0.21]	
Non-Asian	799 | -5.84 (0.57)	771 | -5.48 (0.58)	Difference	-0.36	[-1.95; 1.24]	0.661
			Hedges G	-0.02	[-0.12; 0.08]	
BMI at screening						
Interaction test	**p = 0.579**					
≥25	526 | -7.78 (0.75)	488 | -6.94 (0.78)	Difference	-0.84	[-2.96; 1.27]	0.434
			Hedges G	-0.05	[-0.17; 0.07]	
<25	518 | -4.19 (0.69)	504 | -3.83 (0.70)	Difference	-0.37	[-2.31; 1.57]	0.710
			Hedges G	-0.02	[-0.15; 0.10]	
AJCC Anatomic Stage Group						
Interaction test	**p = 0.005**					
Group I/II	393 | N.E.	399 | N.E.	Difference	N.E.	[N.E.]	N.E.
			Hedges G	N.E.	[N.E.]	
Group III	663 | N.E.	604 | N.E.	Difference	N.E.	[N.E.]	N.E.
			Hedges G	N.E.	[N.E.]	
Anatomic stages						
Interaction test	**p = 0.035**					
IA/IB/IIA	163 | -3.63 (1.25)	189 | -7.38 (1.19)	Difference	3.75	[0.35; 7.14]	0.031
			Hedges G	0.23	[0.02; 0.44]	
IIB	230 | -7.38 (1.05)	210 | -7.76 (1.09)	Difference	0.38	[-2.60; 3.36]	0.802
			Hedges G	0.02	[-0.16; 0.21]	
IIIA	433 | -6.50 (0.77)	366 | -4.15 (0.84)	Difference	-2.35	[-4.59; -0.12]	0.039
			Hedges G	-0.15	[-0.29; -0.01]	
IIIB	62 | -6.07 (2.03)	52 | -5.05 (2.24)	Difference	-1.01	[-7.06; 5.03]	0.740
			Hedges G	-0.06	[-0.43; 0.31]	
IIIC	168 | -4.41 (1.16)	186 | -3.04 (1.11)	Difference	-1.37	[-4.52; 1.78]	0.392
			Hedges G	-0.09	[-0.30; 0.12]	
Nodal status						
Interaction test	**p = 0.048**					
N0	84 | -3.93 (1.66)	110 | -7.65 (1.48)	Difference	3.72	[-0.68; 8.13]	0.097
			Hedges G	0.24	[-0.04; 0.53]	
N1-N3	972 | N.E.	890 | N.E.	Difference	N.E.	[N.E.]	N.E.
			Hedges G	N.E.	[N.E.]	

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1115)	**ET (N = 1123)**	**Parameter**	**Esti-mate**	**[95% CI]**	**p-value**
Histological grade at time of surgery						
Interaction test	**p = 0.435**					
Grade 1	104 | -5.74 (1.54)	97 | -5.95 (1.61)	Difference	0.21	[-4.20; 4.62]	0.925
			Hedges G	0.01	[-0.26; 0.29]	
Grade 2	578 | -6.09 (0.66)	557 | -4.81 (0.68)	Difference	-1.28	[-3.14; 0.58]	0.177
			Hedges G	-0.08	[-0.20; 0.04]	
Grade 3	282 | -5.83 (0.89)	252 | -6.40 (0.94)	Difference	0.56	[-1.99; 3.11]	0.665
			Hedges G	0.04	[-0.13; 0.21]	
Histological subtype						
Interaction test	**p = 0.218**					
Ductal	820 | -6.33 (0.55)	786 | -5.48 (0.56)	Difference	-0.85	[-2.38; 0.69]	0.278
			Hedges G	-0.05	[-0.15; 0.04]	
Lobular	168 | -4.18 (1.30)	156 | -6.56 (1.35)	Difference	2.38	[-1.31; 6.07]	0.205
			Hedges G	0.14	[-0.08; 0.36]	
Other	68 | -3.23 (1.76)	61 | -1.09 (1.92)	Difference	-2.14	[-7.29; 3.00]	0.411
			Hedges G	-0.15	[-0.49; 0.20]	
Ki67 status from surgical specimen						
Interaction test	**p = 0.110**					
Ki67≤20	509 | -5.27 (0.70)	517 | -5.86 (0.70)	Difference	0.59	[-1.36; 2.54]	0.553
			Hedges G	0.04	[-0.09; 0.16]	
Ki67>20	398 | -6.37 (0.77)	359 | -4.58 (0.82)	Difference	-1.78	[-3.99; 0.42]	0.112
			Hedges G	-0.12	[-0.26; 0.03]	
Type of NSAI						
Interaction test	**p = 0.628**					
Letrozole	773 | -6.09 (0.60)	720 | -5.99 (0.63)	Difference	-0.10	[-1.80; 1.60]	0.909
			Hedges G	-0.01	[-0.11; 0.10]	
Anastrozole	283 | -5.30 (0.98)	281 | -4.52 (0.98)	Difference	-0.78	[-3.50; 1.94]	0.574
			Hedges G	-0.05	[-0.21; 0.12]	
Prior neo/adjuvant chemotherapy						
Interaction test	**p = 0.638**					
Yes	981 | -5.92 (0.51)	926 | -5.22 (0.53)	Difference	-0.70	[-2.14; 0.75]	0.346
			Hedges G	-0.04	[-0.13; 0.05]	
No	75 | -4.62 (1.79)	77 | -5.28 (1.80)	Difference	0.66	[-4.41; 5.73]	0.797
			Hedges G	0.04	[-0.28; 0.36]	
Prior adjuvant chemotherapy						
Interaction test	**p = 0.579**					
Yes	494 | -6.74 (0.71)	462 | -5.56 (0.74)	Difference	-1.18	[-3.19; 0.84]	0.251
			Hedges G	-0.07	[-0.20; 0.05]	
No	562 | -5.46 (0.72)	541 | -5.02 (0.74)	Difference	-0.44	[-2.46; 1.59]	0.672
			Hedges G	-0.03	[-0.14; 0.09]	

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1115)	ET (N = 1123)	Parameter	Esti-mate	[95% CI]	p-value
Prior neoadjuvant chemotherapy						
Interaction test	**p = 0.601**					
Yes	517 | -5.57 (0.74)	502 | -4.92 (0.76)	Difference	-0.65	[-2.73; 1.44]	0.541
			Hedges G	-0.04	[-0.16; 0.08]	
No	539 | -6.67 (0.68)	501 | -5.58 (0.71)	Difference	-1.09	[-3.02; 0.84]	0.268
			Hedges G	-0.07	[-0.19; 0.05]	
Prior endocrine therapy						
Interaction test	**p = 0.558**					
Yes	812 | -5.76 (0.59)	734 | -4.92 (0.62)	Difference	-0.84	[-2.52; 0.83]	0.323
			Hedges G	-0.05	[-0.15; 0.05]	
No	244 | -6.75 (1.04)	269 | -7.11 (1.00)	Difference	0.36	[-2.47; 3.19]	0.801
			Hedges G	0.02	[-0.15; 0.20]	
Prior mastectomy						
Interaction test	**p = 0.005**					
Yes	735 | -5.90 (0.61)	698 | -4.17 (0.62)	Difference	-1.73	[-3.43; -0.02]	0.047
			Hedges G	-0.10	[-0.21; -0.00]	
No	321 | -6.05 (0.93)	305 | -8.54 (0.97)	Difference	2.49	[-0.15; 5.12]	0.064
			Hedges G	0.15	[-0.01; 0.31]	
Prior radiotherapy						
Interaction test	**p = 0.701**					
Yes	967 | -5.91 (0.53)	921 | -5.47 (0.55)	Difference	-0.44	[-1.94; 1.07]	0.569
			Hedges G	-0.03	[-0.12; 0.06]	
No	89 | -6.25 (1.81)	82 | -5.26 (1.90)	Difference	-0.99	[-6.18; 4.19]	0.706
			Hedges G	-0.06	[-0.36; 0.24]	

N: Number of patients
N': Number of patients in the analysis
CI: Confidence interval
SD: Standard deviation
LS Mean: Least square mean
SE: Standard error
MMRM: Mixed model for repeated measures
N.E.: Not estimable
ET: Endocrine therapy (Anastrozole/Letrozole + Goserelin)
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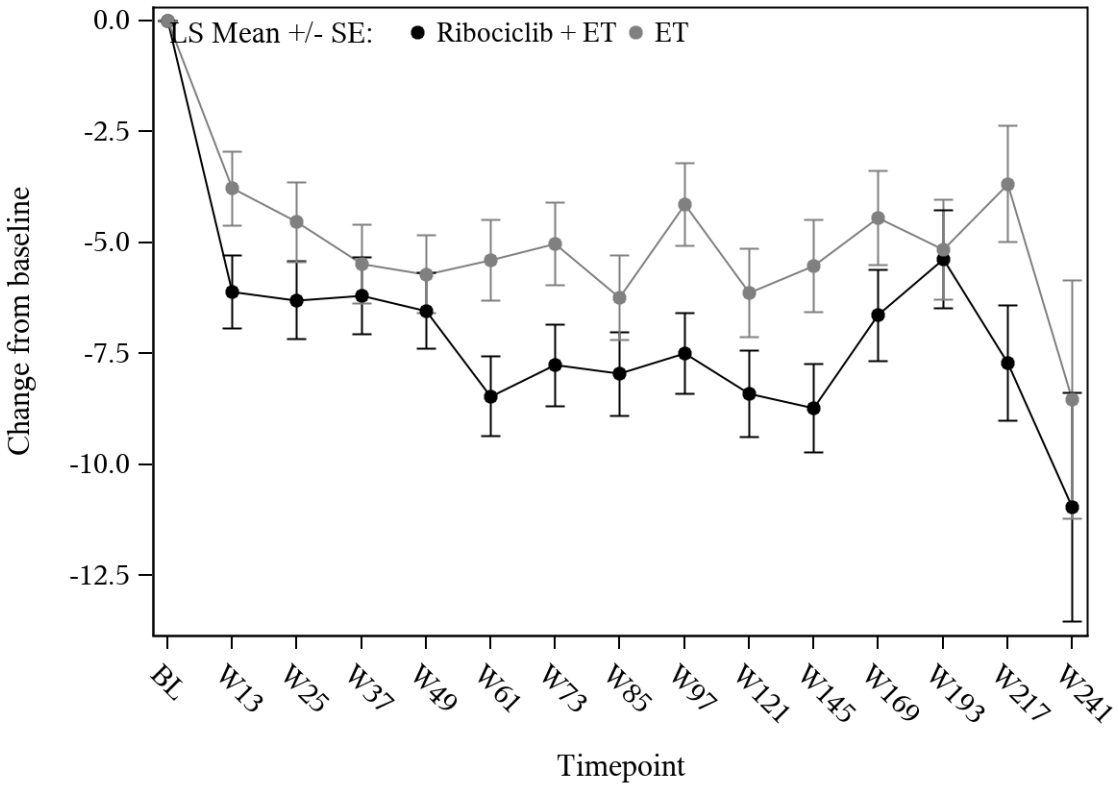
Analysis method for interaction test:
p-value from MMRM with unstructured covariance matrix:
change from baseline = treatment + visit + treatment * visit + subgroup factor + treatment * subgroup factor + subgroup factor * visit + treatment * subgroup factor * visit + baseline value
If the model did not converge for a parameter*subgroup factor, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry. If the model did still not converge, interactions were removed in the order treatment * subgroup factor * visit, subgroup factor * visit.

Analysis methods for within-subgroup analysis:
Adjusted mean (LS Mean) change from baseline and overall effect obtained from MMRM with unstructured covariance matrix:
change from baseline = treatment + visit + treatment * visit + baseline value
ET was the reference group for treatment group comparison.
If the model did not converge for a parameter*subgroup factor, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry.

Patients with an evaluable baseline score and at least one evaluable post-baseline score were included in the analysis.
All data collected were included in the analysis, including assessments at confirmation of first recurrence and thereafter, as long as there were at least 50 patients in each treatment group at a visit in the overall (sub-)population.

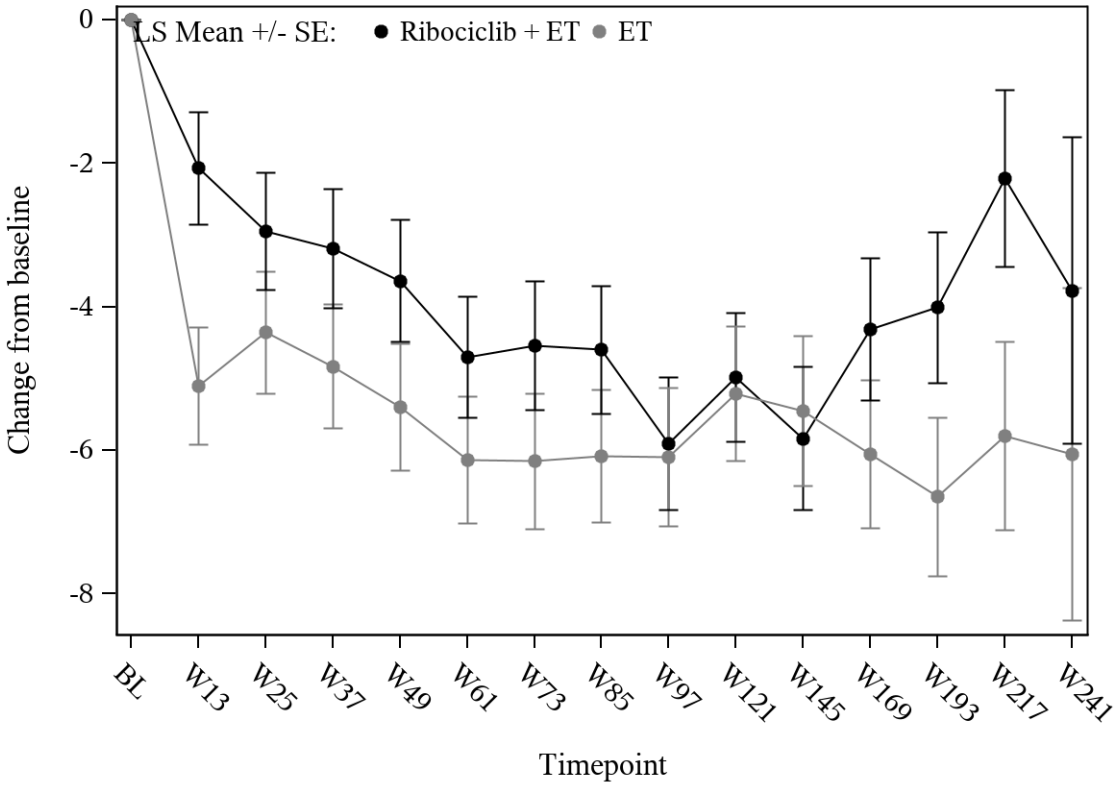
Figure 5-2.2.4.1 QLQ-C30 - Emotional Functioning: line chart of change from baseline - subgroup analysis (Full Analysis Set)

QLQ-C30 - Emotional Functioning
Region: NA/WE/O



Ribociclib + ET	596	564	526	535	524	525	517	507	500	476	478	384	314	190	35
ET	576	533	500	502	505	499	494	474	469	459	439	363	306	188	33

QLQ-C30 - Emotional Functioning
Region: ROW



Ribociclib + ET	460	460	450	447	444	436	435	433	430	422	418	341	292	154	23
ET	427	425	418	404	411	402	398	395	387	380	369	316	261	135	19

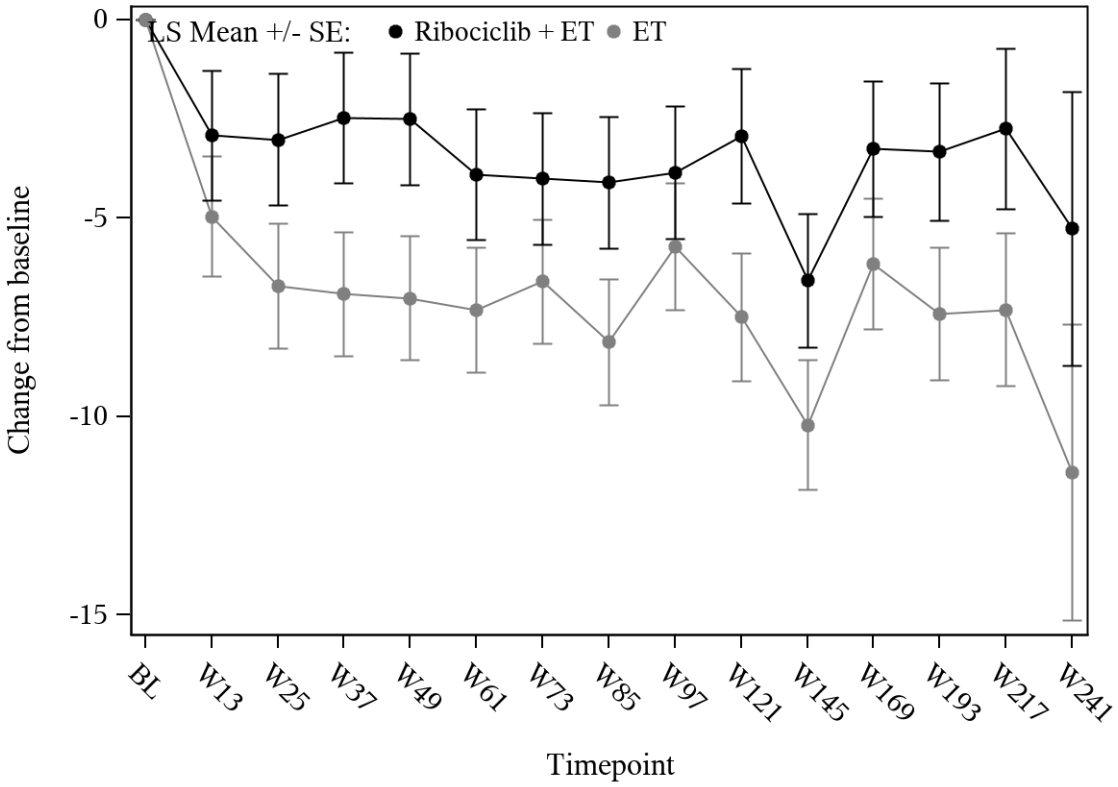
QLQ-C30 - Emotional Functioning
AJCC Anatomic Stage Group: Group I/II

The figure is not displayed as the model did not converge.

QLQ-C30 - Emotional Functioning
AJCC Anatomic Stage Group: Group III

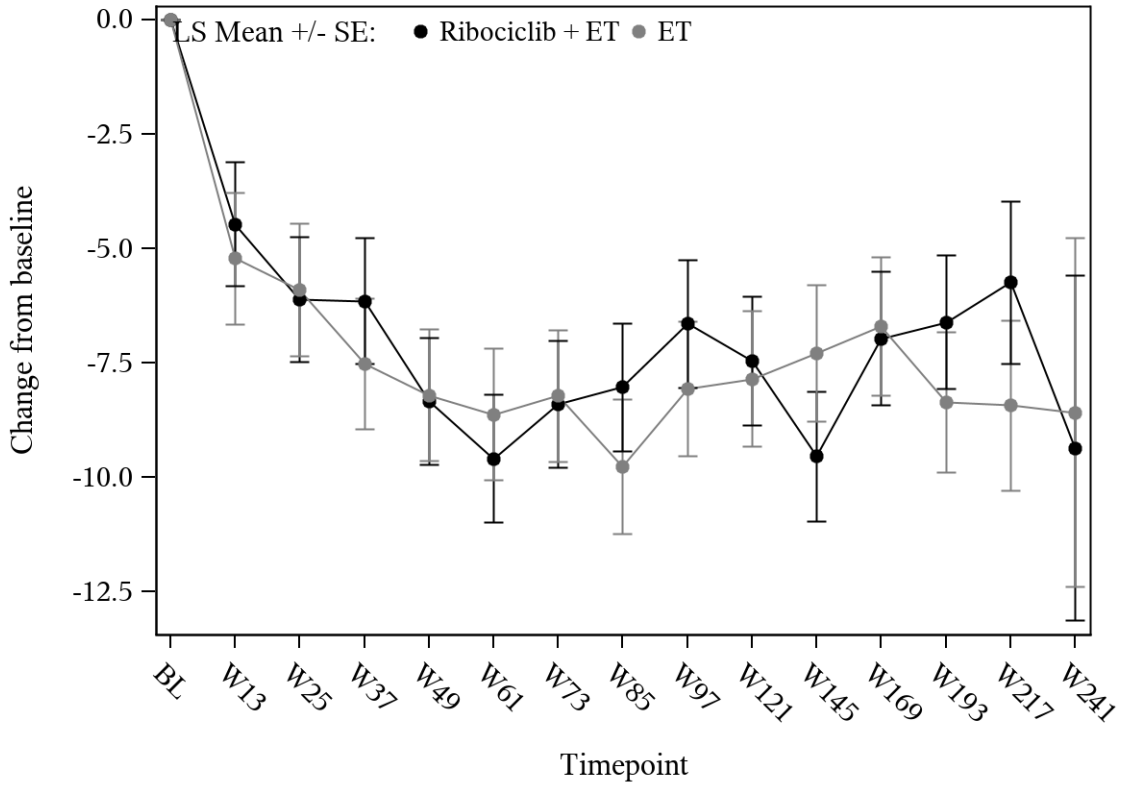
The figure is not displayed as the model did not converge.

QLQ-C30 - Emotional Functioning
Anatomic stages: IA/IB/IIA



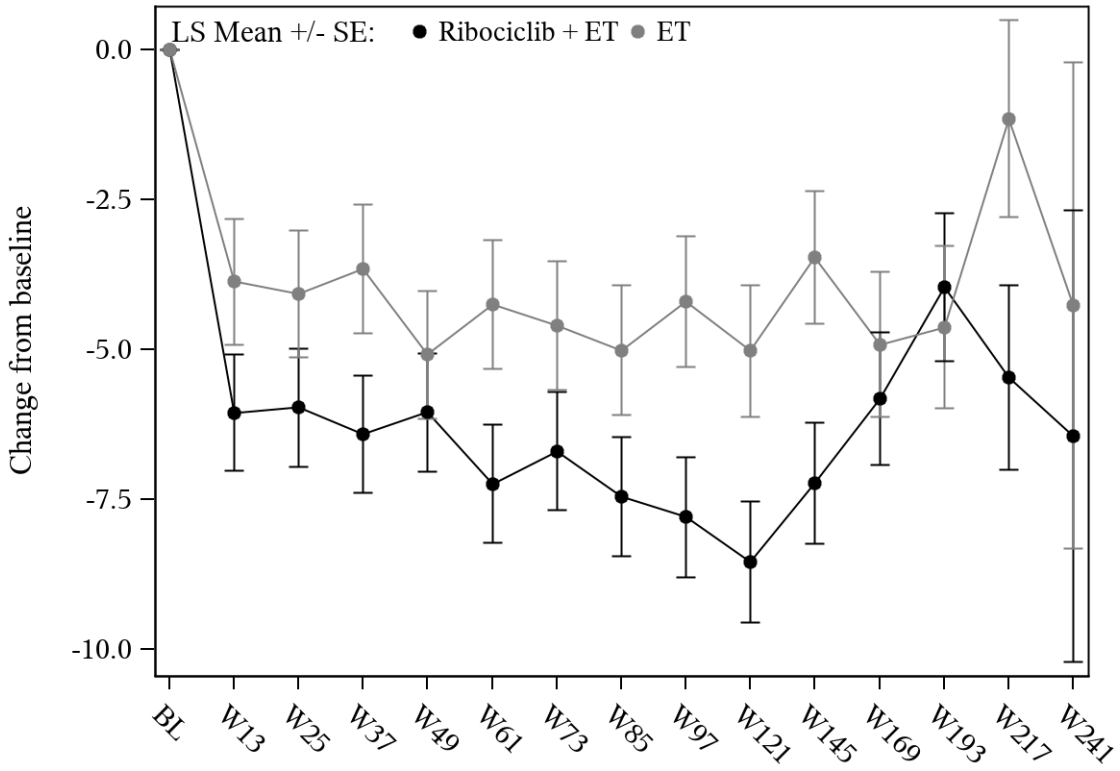
Ribociclib + ET	163	159	153	155	152	155	150	152	147	141	142	138	133	79	17
ET	189	183	161	168	170	167	170	162	162	156	148	148	140	87	14

QLQ-C30 - Emotional Functioning
Anatomic stages: IIB



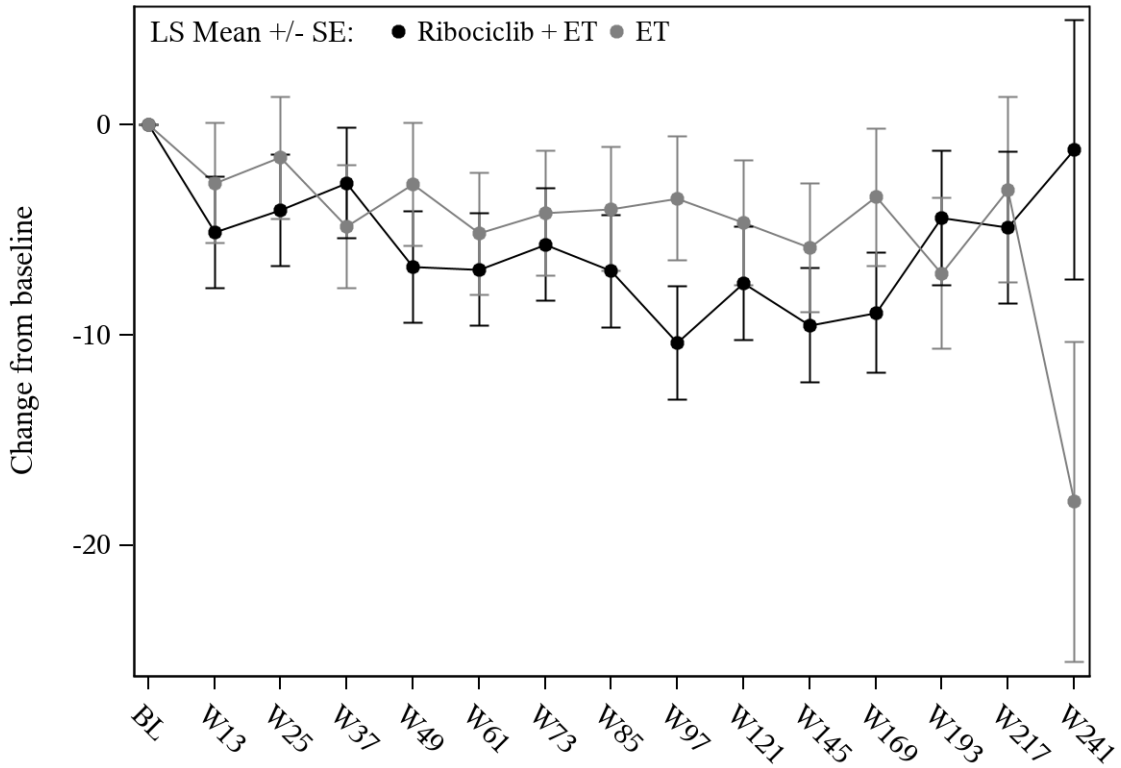
Ribociclib + ET	230	224	213	211	208	204	203	204	204	199	196	177	180	97	14
ET	210	198	189	194	196	192	191	180	182	179	174	168	163	88	14

QLQ-C30 - Emotional Functioning
Anatomic stages: IIIA



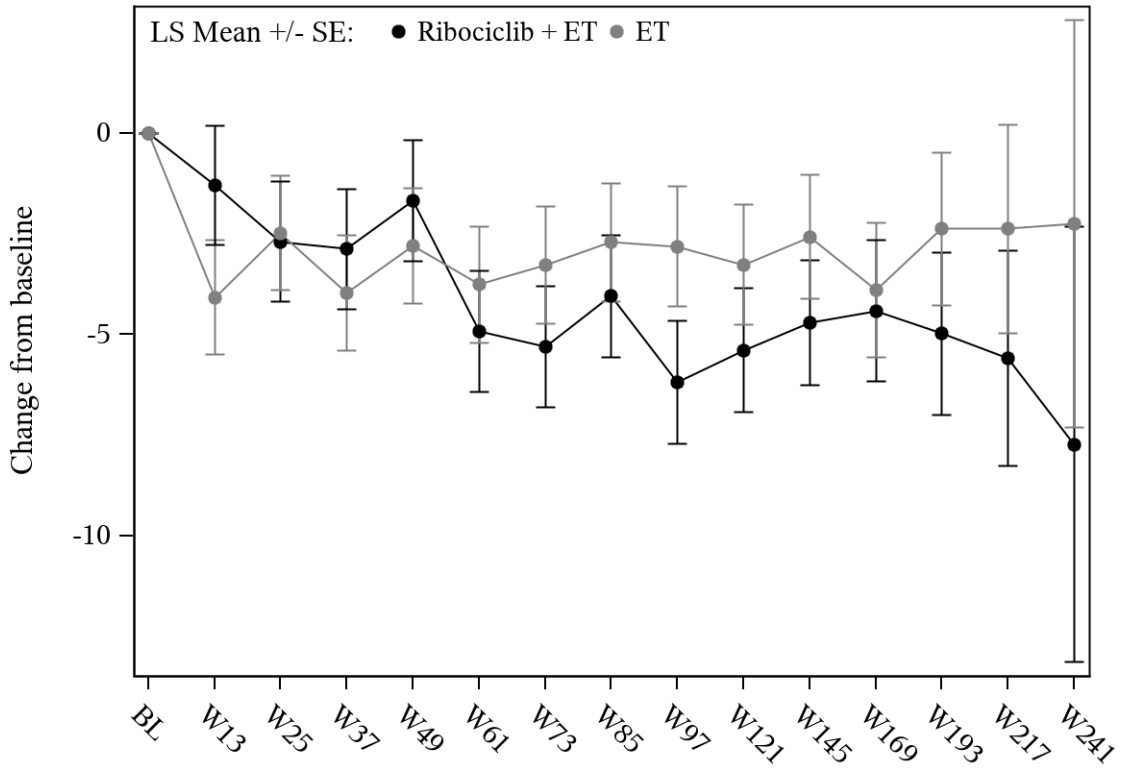
Ribociclib + ET	433	416	391	398	393	388	386	373	373	355	360	268	197	112	15
ET	366	349	341	328	331	327	325	321	312	305	302	223	163	99	13

QLQ-C30 - Emotional Functioning
Anatomic stages: IIIB



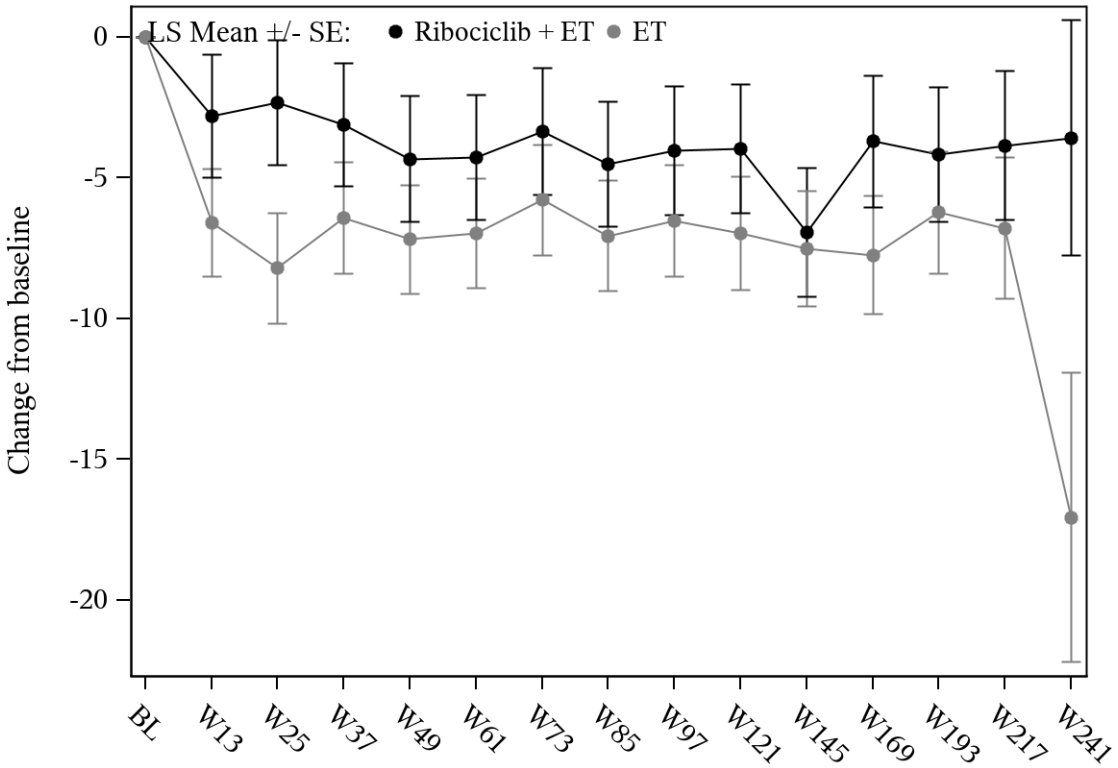
	BL	W13	W25	W37	W49	W61	W73	W85	W97	W121	W145	W169	W193	W217	W241
Ribociclib + ET	62	60	60	60	59	58	57	58	56	57	57	46	31	23	6
ET	52	52	49	47	49	49	46	47	47	46	42	33	25	14	4

QLQ-C30 - Emotional Functioning
Anatomic stages: IIIC



Ribociclib + ET	168	165	159	158	156	156	156	153	150	146	141	96	65	33	6
ET	186	176	178	169	170	166	160	159	153	153	142	107	76	35	7

QLQ-C30 - Emotional Functioning
Nodal status: N0

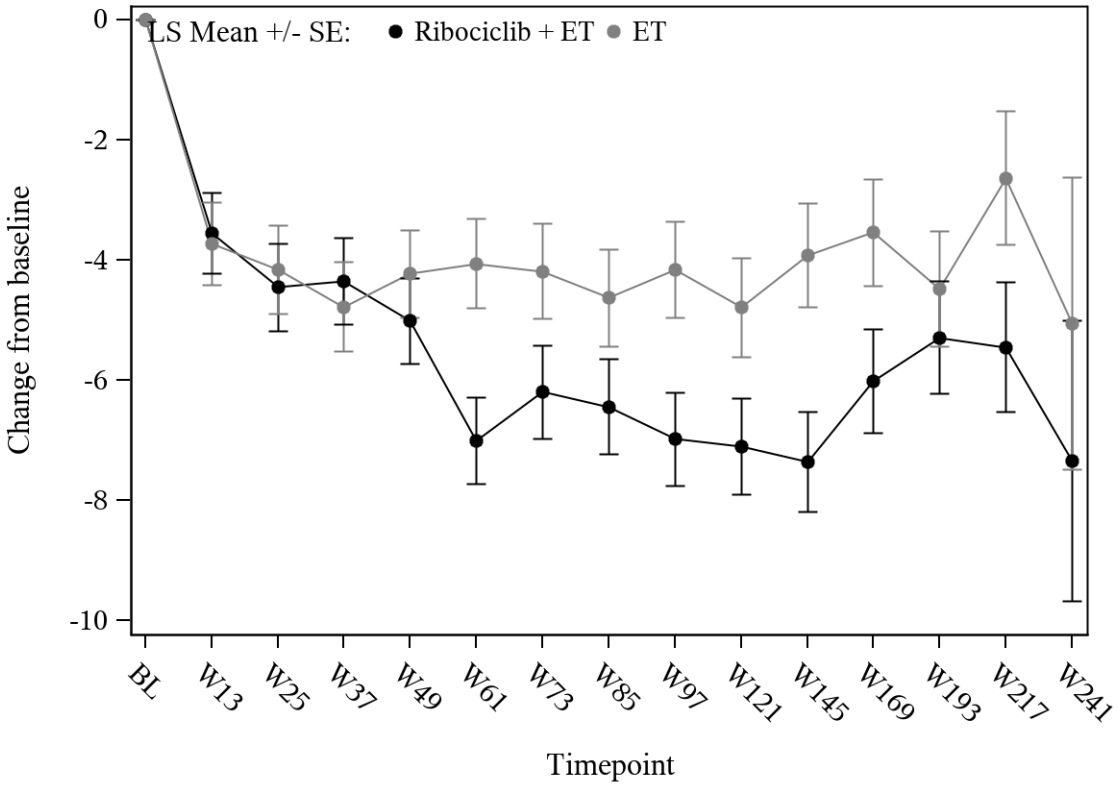


Ribociclib + ET	84	83	77	82	77	78	74	78	73	71	72	66	64	45	13
ET	110	108	98	97	104	102	100	97	98	93	87	81	75	47	8

QLQ-C30 - Emotional Functioning
Nodal status: N1-N3

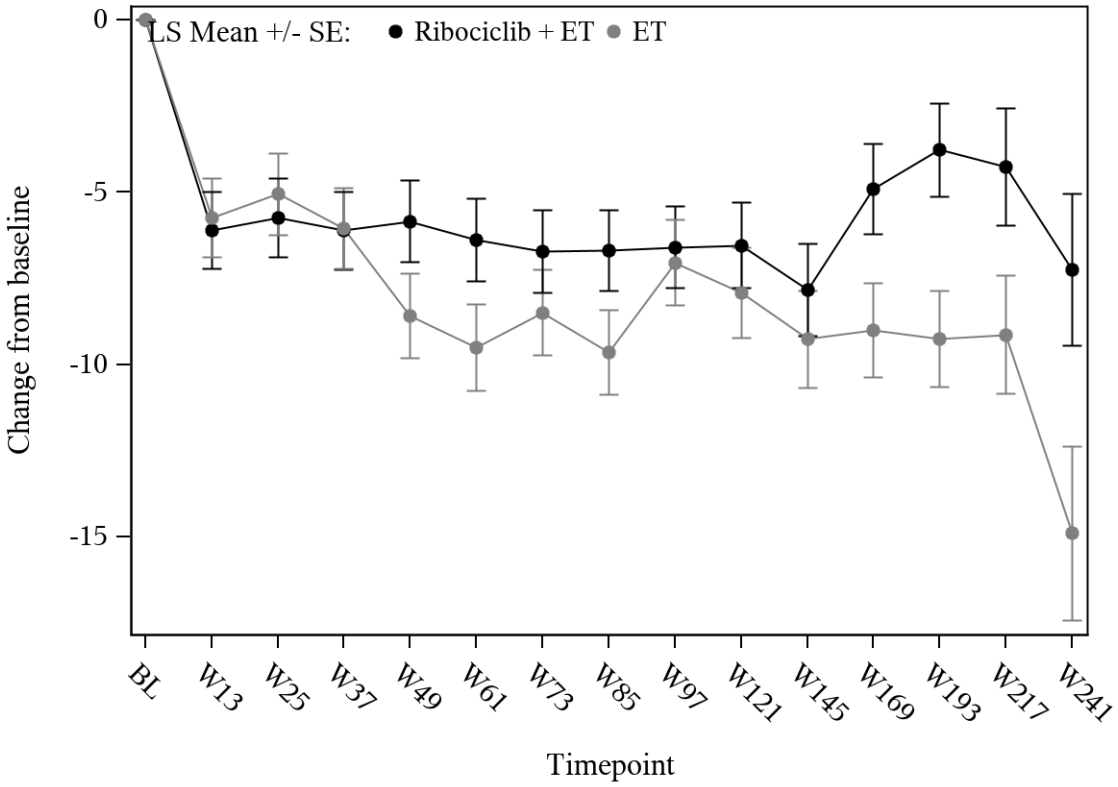
The figure is not displayed as the model did not converge.

QLQ-C30 - Emotional Functioning
Prior mastectomy: Yes



Ribociclib + ET	735	708	675	675	665	662	653	646	636	616	612	488	401	232	40
ET	698	660	648	634	643	630	623	611	596	588	558	457	377	213	38

QLQ-C30 - Emotional Functioning
Prior mastectomy: No



Ribociclib + ET	321	316	301	307	303	299	299	294	294	282	284	237	205	112	18
ET	305	298	270	272	273	271	269	258	260	251	250	222	190	110	14

Table 5-2.2.5.1 QLQ-C30 - Cognitive Functioning: change from baseline analysis - subgroup analysis (Full Analysis Set)

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1115)	ET (N = 1123)	Parameter	Esti-mate	[95% CI]	p-value
QLQ-C30 - Cognitive Functioning						
	N' | LS Mean (SE)	N' | LS Mean (SE)				
Region						
Interaction test	**p = 0.110**					
NA/WE/O	596 | -7.10 (0.72)	576 | -5.01 (0.74)	Difference	-2.09	[-4.11; -0.06]	0.043
			Hedges G	-0.12	[-0.23; -0.00]	
ROW	460 | -5.10 (0.70)	427 | -5.28 (0.74)	Difference	0.18	[-1.82; 2.18]	0.862
			Hedges G	0.01	[-0.12; 0.14]	
Geographical region						
Interaction test	**p = 0.841**					
Europe	615 | N.E.	592 | N.E.	Difference	N.E.	[N.E.]	N.E.
			Hedges G	N.E.	[N.E.]	
North America/Australia	203 | -4.03 (1.05)	176 | -3.11 (1.15)	Difference	-0.92	[-3.99; 2.15]	0.556
			Hedges G	-0.06	[-0.26; 0.14]	
Asia	175 | N.E.	166 | N.E.	Difference	N.E.	[N.E.]	N.E.
			Hedges G	N.E.	[N.E.]	
Latin America	63 | -6.25 (2.14)	69 | -6.16 (2.01)	Difference	-0.09	[-5.90; 5.72]	0.976
			Hedges G	-0.01	[-0.35; 0.34]	
Age group 1 at randomization						
Interaction test	**p = 0.893**					
<45	524 | -5.43 (0.71)	458 | -4.42 (0.75)	Difference	-1.01	[-3.04; 1.02]	0.329
			Hedges G	-0.06	[-0.19; 0.06]	
45 to 54	512 | -7.27 (0.74)	518 | -6.01 (0.74)	Difference	-1.26	[-3.31; 0.79]	0.229
			Hedges G	-0.08	[-0.20; 0.05]	
55 to 64	20 | -5.22 (2.89)	27 | -3.36 (2.55)	Difference	-1.86	[-9.63; 5.92]	0.632
			Hedges G	-0.14	[-0.72; 0.44]	
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)						
Interaction test	**p = 0.903**					
<Median	524 | -5.43 (0.71)	458 | -4.42 (0.75)	Difference	-1.01	[-3.04; 1.02]	0.329
			Hedges G	-0.06	[-0.19; 0.06]	
≥Median	532 | -7.20 (0.72)	545 | -5.86 (0.72)	Difference	-1.34	[-3.33; 0.64]	0.185
			Hedges G	-0.08	[-0.20; 0.04]	

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1115)	**ET (N = 1123)**	**Parameter**	**Esti-mate**	**[95% CI]**	**p-value**
Race						
Interaction test	**p = 0.821**					
Asian	206 | -2.88 (0.95)	180 | -1.53 (1.02)	Difference	-1.35	[-4.10; 1.40]	0.335
			Hedges G	-0.10	[-0.30; 0.10]	
Non-Asian	799 | -7.25 (0.60)	771 | -6.27 (0.61)	Difference	-0.98	[-2.65; 0.69]	0.251
			Hedges G	-0.06	[-0.16; 0.04]	
BMI at screening						
Interaction test	**p = 0.334**					
≥25	526 | -7.18 (0.75)	488 | -7.14 (0.78)	Difference	-0.04	[-2.16; 2.09]	0.973
			Hedges G	-0.00	[-0.13; 0.12]	
<25	518 | -5.20 (0.70)	504 | -3.37 (0.71)	Difference	-1.83	[-3.79; 0.14]	0.068
			Hedges G	-0.11	[-0.24; 0.01]	
AJCC Anatomic Stage Group						
Interaction test	**p = 0.002**					
Group I/II	393 | -6.31 (0.90)	399 | -7.91 (0.90)	Difference	1.60	[-0.91; 4.11]	0.210
			Hedges G	0.09	[-0.05; 0.23]	
Group III	663 | -6.00 (0.61)	604 | -3.59 (0.64)	Difference	-2.41	[-4.15; -0.67]	0.007
			Hedges G	-0.15	[-0.26; -0.04]	
Anatomic stages						
Interaction test	**p = 0.010**					
IA/IB/IIA	163 | -3.55 (1.28)	189 | -7.54 (1.21)	Difference	3.99	[0.53; 7.45]	0.024
			Hedges G	0.24	[0.03; 0.45]	
IIB	230 | -8.03 (1.18)	210 | -7.86 (1.23)	Difference	-0.17	[-3.51; 3.18]	0.923
			Hedges G	-0.01	[-0.20; 0.18]	
IIIA	433 | -6.42 (0.76)	366 | -3.48 (0.83)	Difference	-2.94	[-5.15; -0.73]	0.009
			Hedges G	-0.19	[-0.33; -0.05]	
IIIB	62 | -4.66 (2.05)	52 | -2.68 (2.27)	Difference	-1.98	[-8.17; 4.22]	0.528
			Hedges G	-0.12	[-0.49; 0.25]	
IIIC	168 | -6.23 (1.20)	186 | -3.16 (1.14)	Difference	-3.07	[-6.32; 0.19]	0.065
			Hedges G	-0.20	[-0.41; 0.01]	
Nodal status						
Interaction test	**p = 0.006**					
N0	84 | -2.21 (1.67)	110 | -7.65 (1.49)	Difference	5.44	[1.04; 9.85]	0.016
			Hedges G	0.35	[0.07; 0.64]	
N1-N3	972 | -6.73 (0.53)	890 | -4.96 (0.55)	Difference	-1.77	[-3.27; -0.27]	0.021
			Hedges G	-0.11	[-0.20; -0.02]	

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1115)	**ET (N = 1123)**	**Parameter**	**Esti-mate**	**[95% CI]**	**p-value**
Histological grade at time of surgery						
Interaction test	**p = 0.324**					
Grade 1	104 | -7.57 (1.73)	97 | -7.47 (1.81)	Difference	-0.09	[-5.04; 4.86]	0.971
			Hedges G	-0.01	[-0.28; 0.27]	
Grade 2	578 | -6.91 (0.68)	557 | -4.67 (0.70)	Difference	-2.24	[-4.16; -0.33]	0.022
			Hedges G	-0.14	[-0.25; -0.02]	
Grade 3	282 | -4.80 (0.93)	252 | -4.88 (0.98)	Difference	0.08	[-2.57; 2.73]	0.953
			Hedges G	0.01	[-0.16; 0.18]	
Histological subtype						
Interaction test	**p = 0.173**					
Ductal	820 | N.E.	786 | N.E.	Difference	N.E.	[N.E.]	N.E.
			Hedges G	N.E.	[N.E.]	
Lobular	168 | -5.32 (1.05)	156 | -8.01 (1.09)	Difference	2.69	[-0.29; 5.66]	0.077
			Hedges G	0.20	[-0.02; 0.42]	
Other	68 | -4.57 (1.58)	61 | -2.99 (1.82)	Difference	-1.59	[-6.35; 3.18]	0.511
			Hedges G	-0.12	[-0.46; 0.23]	
Ki67 status from surgical specimen						
Interaction test	**p = 0.359**					
Ki67≤20	509 | -6.25 (0.74)	517 | -5.48 (0.73)	Difference	-0.78	[-2.81; 1.26]	0.455
			Hedges G	-0.05	[-0.17; 0.08]	
Ki67>20	398 | -6.85 (0.83)	359 | -4.59 (0.88)	Difference	-2.26	[-4.62; 0.11]	0.061
			Hedges G	-0.14	[-0.28; 0.01]	
Type of NSAI						
Interaction test	**p = 0.390**					
Letrozole	773 | -5.87 (0.58)	720 | -5.22 (0.61)	Difference	-0.65	[-2.30; 1.00]	0.438
			Hedges G	-0.04	[-0.14; 0.06]	
Anastrozole	283 | -7.05 (1.04)	281 | -4.88 (1.05)	Difference	-2.17	[-5.07; 0.73]	0.142
			Hedges G	-0.12	[-0.29; 0.04]	
Prior neo/adjuvant chemotherapy						
Interaction test	**p = 0.080**					
Yes	981 | -6.28 (0.52)	926 | -4.78 (0.54)	Difference	-1.50	[-2.97; -0.02]	0.046
			Hedges G	-0.09	[-0.18; -0.00]	
No	75 | -6.76 (1.89)	77 | -10.12 (1.91)	Difference	3.36	[-1.95; 8.67]	0.214
			Hedges G	0.20	[-0.12; 0.52]	
Prior adjuvant chemotherapy						
Interaction test	**p = 0.487**					
Yes	494 | -6.68 (0.72)	462 | -4.82 (0.75)	Difference	-1.86	[-3.91; 0.18]	0.074
			Hedges G	-0.12	[-0.24; 0.01]	
No	562 | -5.71 (0.72)	541 | -5.46 (0.73)	Difference	-0.24	[-2.26; 1.77]	0.812
			Hedges G	-0.01	[-0.13; 0.10]	

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1115)	ET (N = 1123)	Parameter	Esti-mate	[95% CI]	p-value
Prior neoadjuvant chemotherapy						
Interaction test	**N.E.**					
Yes	517 | -5.44 (0.73)	502 | -4.47 (0.75)	Difference	-0.97	[-3.02; 1.09]	0.356
			Hedges G	-0.06	[-0.18; 0.06]	
No	539 | -6.94 (0.71)	501 | -5.93 (0.74)	Difference	-1.01	[-3.04; 1.01]	0.325
			Hedges G	-0.06	[-0.18; 0.06]	
Prior endocrine therapy						
Interaction test	**p = 0.726**					
Yes	812 | -5.94 (0.58)	734 | -4.72 (0.62)	Difference	-1.22	[-2.89; 0.45]	0.151
			Hedges G	-0.07	[-0.17; 0.03]	
No	244 | -7.63 (1.09)	269 | -6.55 (1.05)	Difference	-1.07	[-4.05; 1.90]	0.478
			Hedges G	-0.06	[-0.24; 0.11]	
Prior mastectomy						
Interaction test	**p = 0.073**					
Yes	735 | -6.47 (0.59)	698 | -4.43 (0.61)	Difference	-2.05	[-3.71; -0.38]	0.016
			Hedges G	-0.13	[-0.23; -0.02]	
No	321 | -5.87 (0.95)	305 | -6.91 (0.99)	Difference	1.04	[-1.66; 3.73]	0.449
			Hedges G	0.06	[-0.10; 0.22]	
Prior radiotherapy						
Interaction test	**p = 0.151**					
Yes	967 | -6.35 (0.53)	921 | -4.93 (0.55)	Difference	-1.42	[-2.92; 0.07]	0.062
			Hedges G	-0.09	[-0.18; 0.00]	
No	89 | -5.76 (1.59)	82 | -7.91 (1.68)	Difference	2.15	[-2.42; 6.71]	0.354
			Hedges G	0.14	[-0.16; 0.44]	

N: Number of patients
N': Number of patients in the analysis
CI: Confidence interval
SD: Standard deviation
LS Mean: Least square mean
SE: Standard error
MMRM: Mixed model for repeated measures
N.E.: Not estimable
ET: Endocrine therapy (Anastrozole/Letrozole + Goserelin)
.....

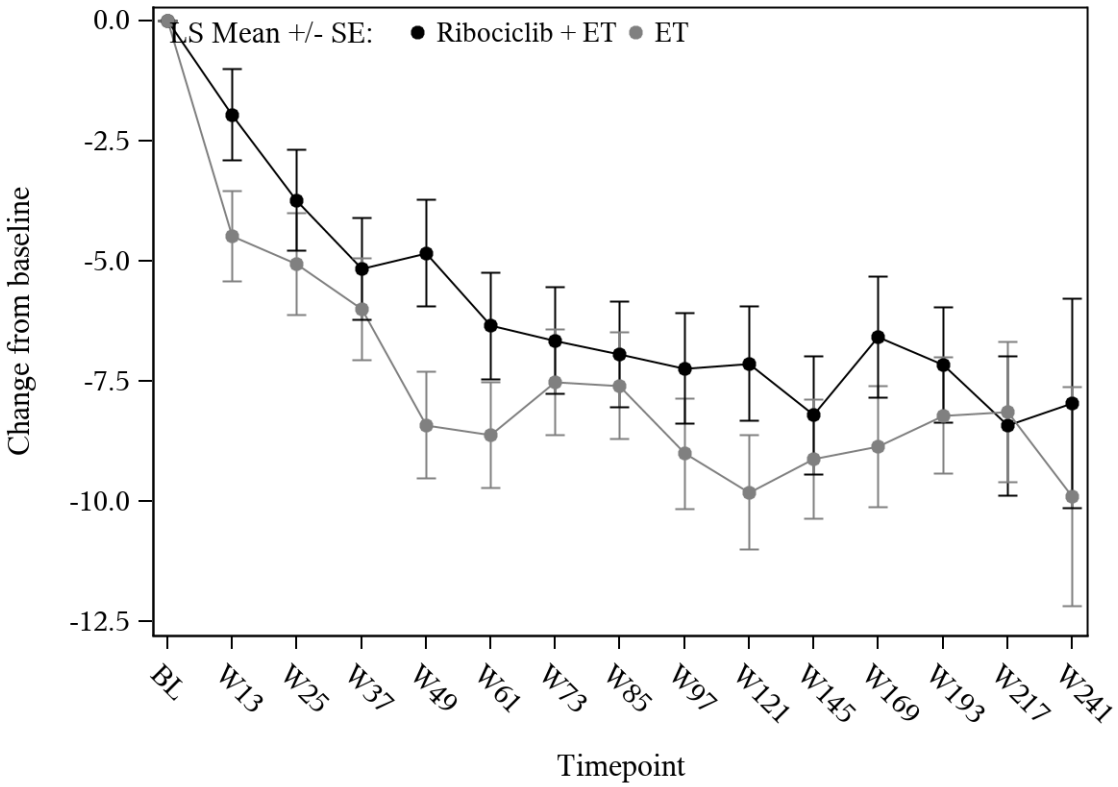
Analysis method for interaction test:
p-value from MMRM with unstructured covariance matrix:
change from baseline = treatment + visit + treatment * visit + subgroup factor + treatment * subgroup factor + subgroup factor * visit + treatment * subgroup factor * visit + baseline value
If the model did not converge for a parameter*subgroup factor, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry. If the model did still not converge, interactions were removed in the order treatment * subgroup factor * visit, subgroup factor * visit.

Analysis methods for within-subgroup analysis:
Adjusted mean (LS Mean) change from baseline and overall effect obtained from MMRM with unstructured covariance matrix:
change from baseline = treatment + visit + treatment * visit + baseline value
ET was the reference group for treatment group comparison.
If the model did not converge for a parameter*subgroup factor, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry.

Patients with an evaluable baseline score and at least one evaluable post-baseline score were included in the analysis.
All data collected were included in the analysis, including assessments at confirmation of first recurrence and thereafter, as long as there were at least 50 patients in each treatment group at a visit in the overall (sub-)population.

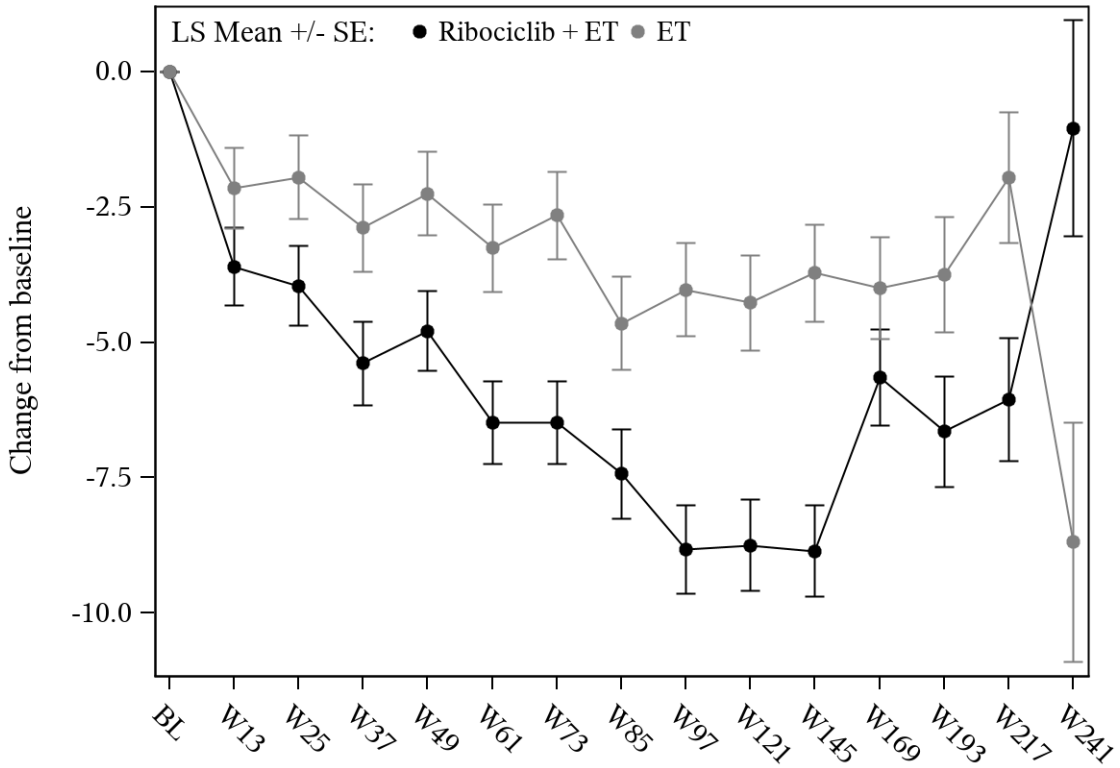
Figure 5-2.2.5.1 QLQ-C30 - Cognitive Functioning: line chart of change from baseline - subgroup analysis (Full Analysis Set)

QLQ-C30 - Cognitive Functioning
AJCC Anatomic Stage Group: Group I/II



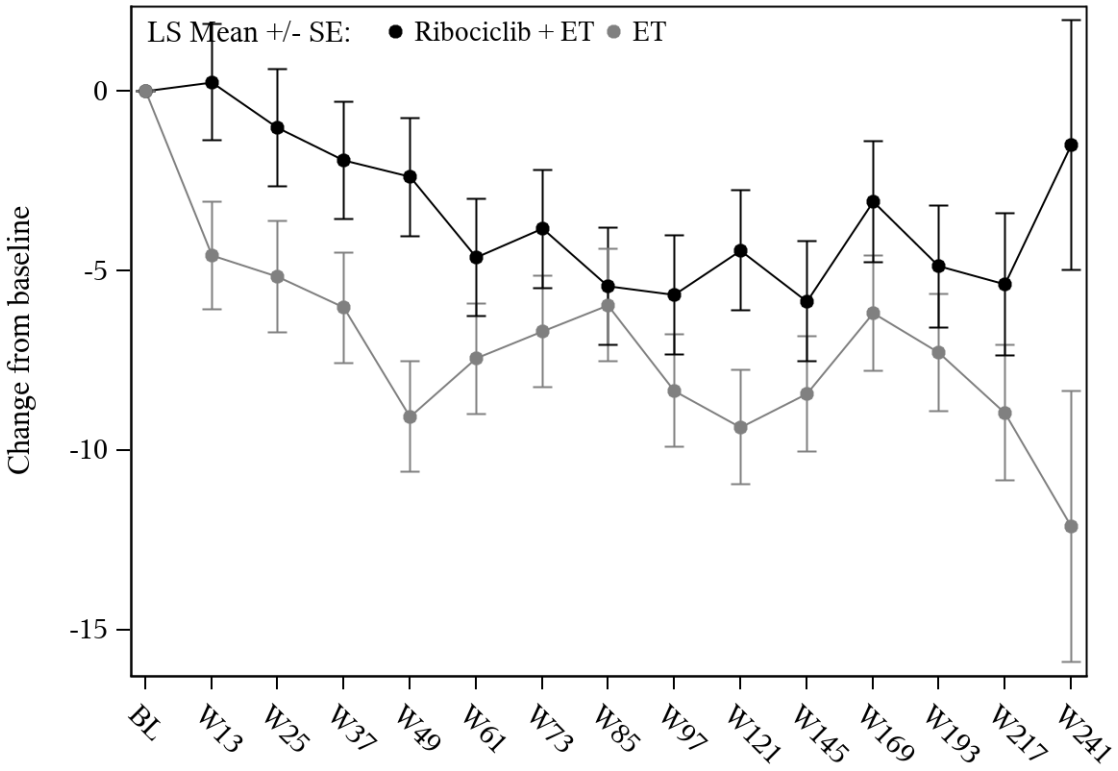
Ribociclib + ET	393	383	366	366	360	359	353	356	351	340	338	315	313	176	31
ET	399	381	350	363	366	359	361	342	344	335	322	316	303	175	28

QLQ-C30 - Cognitive Functioning
AJCC Anatomic Stage Group: Group III



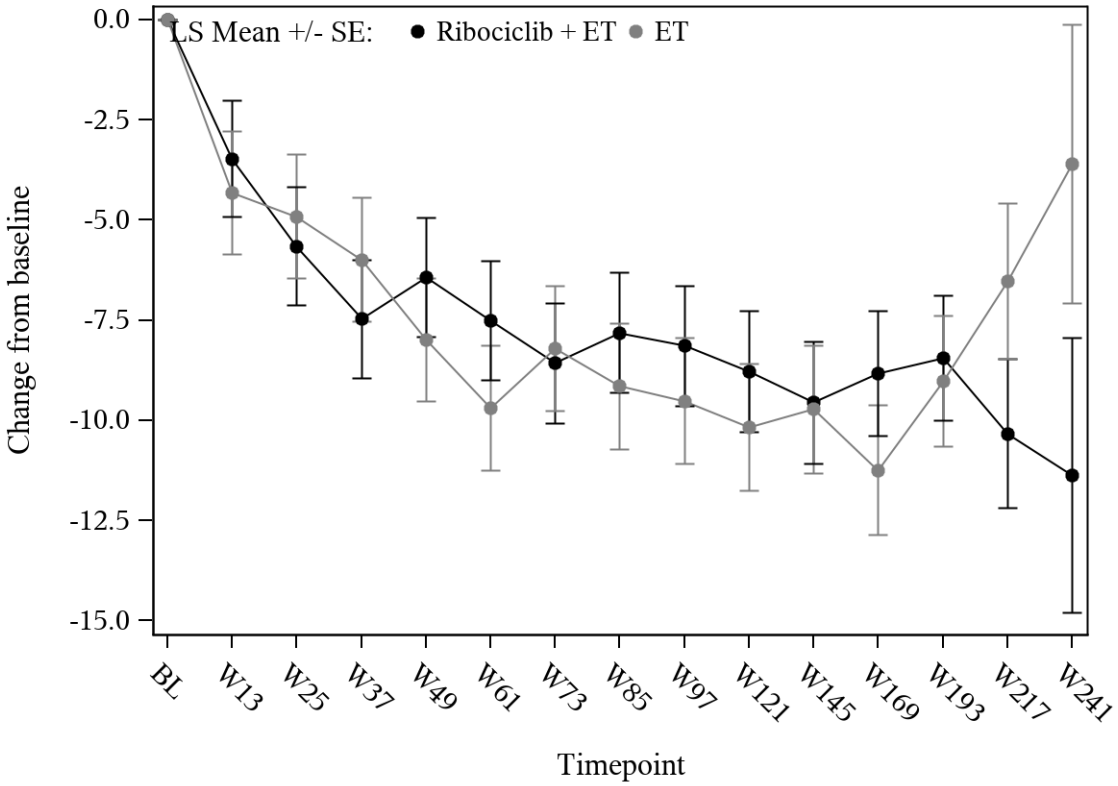
Ribociclib + ET	663	641	610	616	608	602	599	584	579	559	558	410	293	168	27
ET	604	578	568	544	550	542	531	527	512	504	486	363	264	148	24

QLQ-C30 - Cognitive Functioning
Anatomic stages: IA/IB/IIA



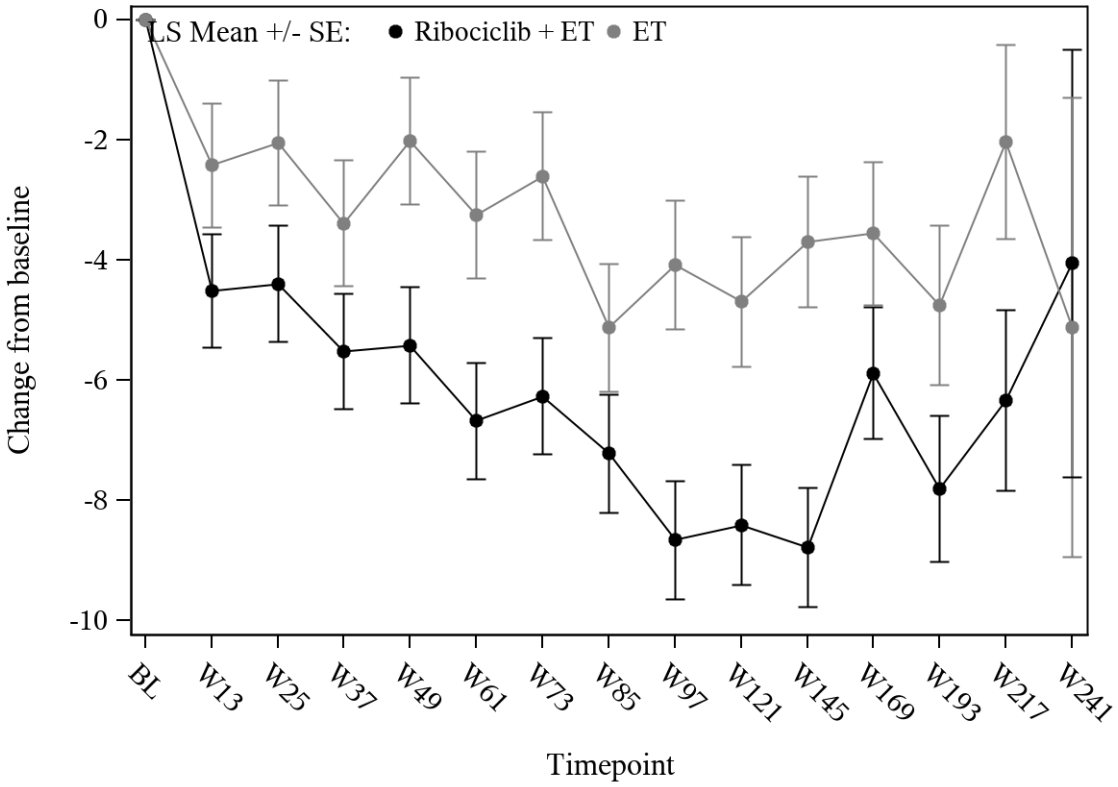
Ribociclib + ET	163	159	153	155	152	155	150	152	147	141	142	138	133	79	17
ET	189	183	161	169	170	167	170	162	162	156	148	148	140	87	14

QLQ-C30 - Cognitive Functioning
Anatomic stages: IIB



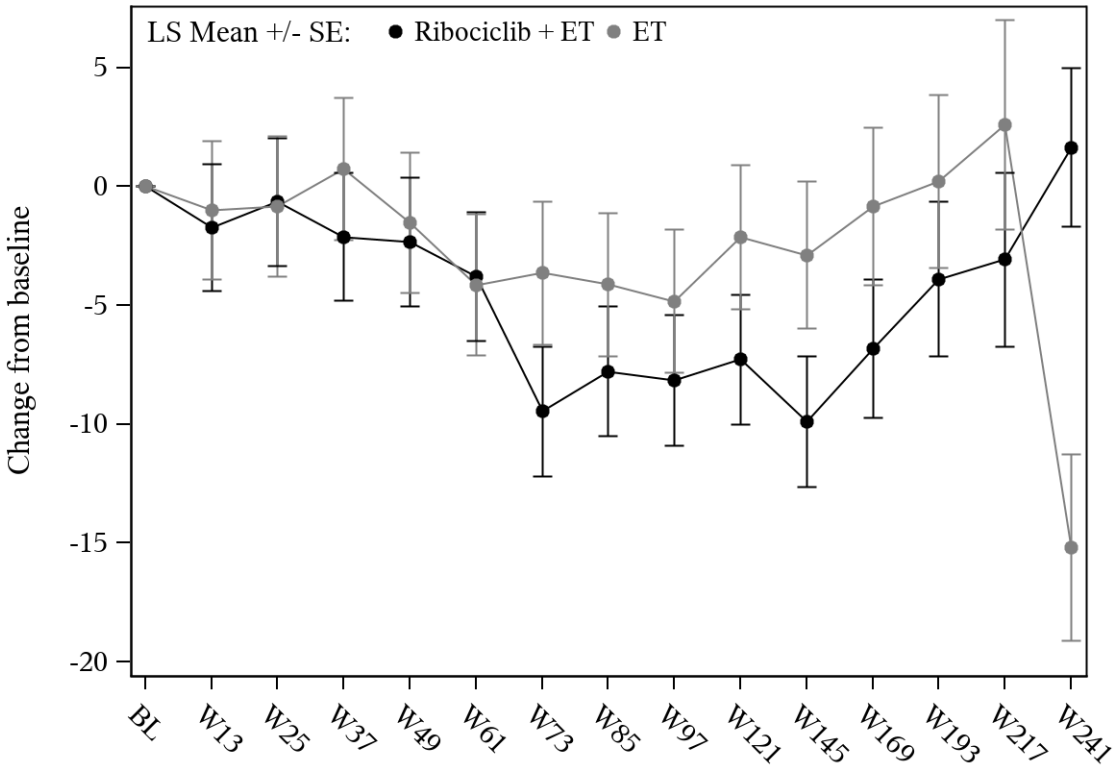
Ribociclib + ET	230	224	213	211	208	204	203	204	204	199	196	177	180	97	14
ET	210	198	189	194	196	192	191	180	182	179	174	168	163	88	14

QLQ-C30 - Cognitive Functioning
Anatomic stages: IIIA



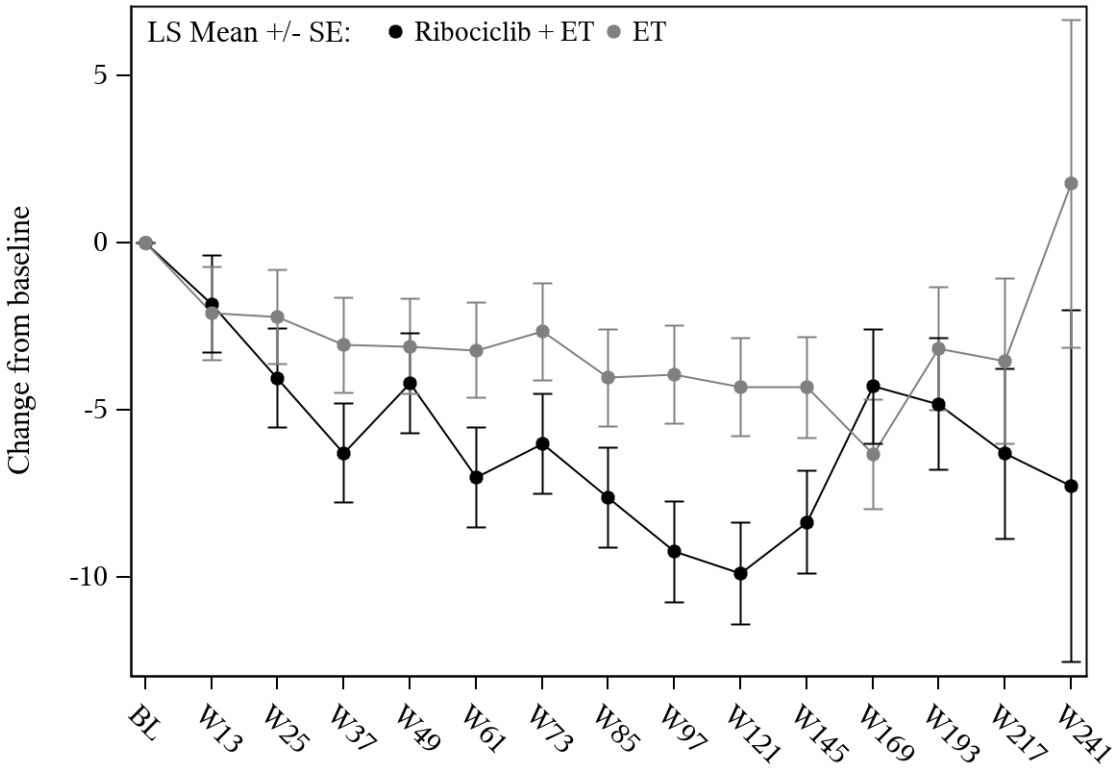
Ribociclib + ET	433	416	391	398	393	388	386	373	373	355	360	268	197	112	15
ET	366	350	341	328	331	327	325	321	312	305	302	223	163	99	13

QLQ-C30 - Cognitive Functioning
Anatomic stages: IIIB



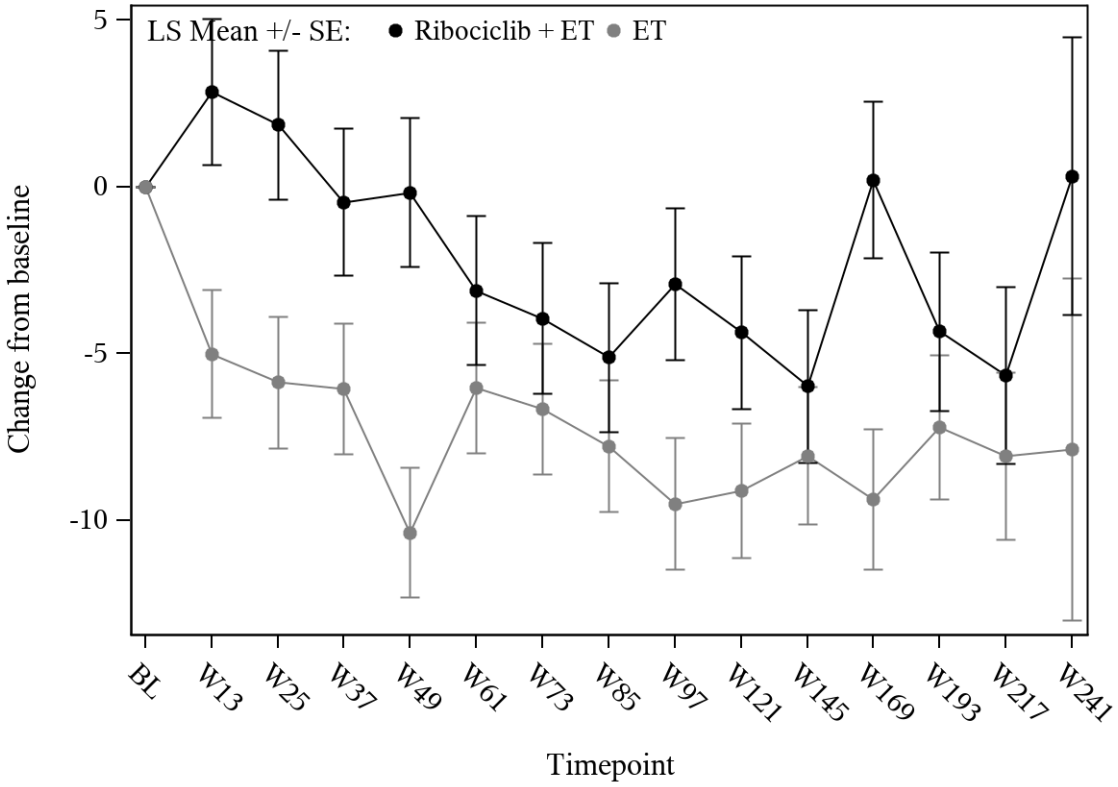
Ribociclib + ET	62	60	60	60	59	58	57	58	56	57	57	46	31	23	6
ET	52	52	49	47	49	49	46	47	47	46	42	33	25	14	4

QLQ-C30 - Cognitive Functioning
Anatomic stages: IIIC



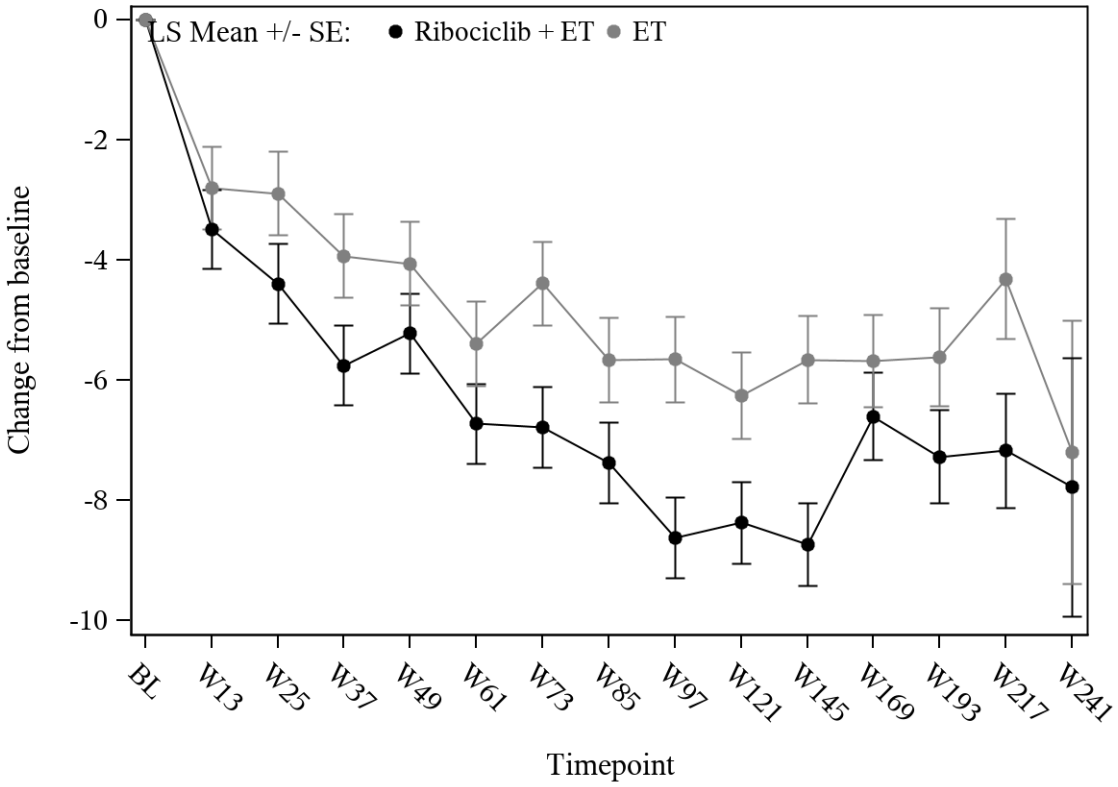
Ribociclib + ET	168	165	159	158	156	156	156	153	150	147	141	96	65	33	6
ET	186	176	178	169	170	166	160	159	153	153	142	107	76	35	7

QLQ-C30 - Cognitive Functioning
Nodal status: N0



Ribociclib + ET	84	83	77	82	77	78	74	78	73	71	72	66	64	45	13
ET	110	108	98	98	104	102	100	97	98	93	87	81	75	47	8

QLQ-C30 - Cognitive Functioning
Nodal status: N1-N3



Ribociclib + ET	972	941	899	900	891	883	878	862	857	828	824	659	542	299	45
ET	890	848	817	806	811	797	790	770	756	744	719	596	490	274	44

Table 5-2.2.6.1 QLQ-C30 - Social Functioning: change from baseline analysis - subgroup analysis (Full Analysis Set)

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1115)	ET (N = 1123)	Parameter	Esti-mate	[95% CI]	p-value
QLQ-C30 - Social Functioning						
	N' | LS Mean (SE)	N' | LS Mean (SE)				
Region						
Interaction test	**p = 0.144**					
NA/WE/O	596 | -1.02 (0.73)	575 | 2.03 (0.74)	Difference	-3.04	[-5.09; -1.00]	0.004
			Hedges G	-0.17	[-0.29; -0.06]	
ROW	460 | 1.17 (0.68)	427 | 2.12 (0.71)	Difference	-0.95	[-2.88; 0.99]	0.336
			Hedges G	-0.06	[-0.20; 0.07]	
Geographical region						
Interaction test	**p = 0.617**					
Europe	615 | -1.49 (0.69)	591 | 0.41 (0.70)	Difference	-1.91	[-3.84; 0.02]	0.053
			Hedges G	-0.11	[-0.22; 0.00]	
North America/Australia	203 | 1.64 (1.10)	176 | 4.59 (1.20)	Difference	-2.95	[-6.16; 0.26]	0.072
			Hedges G	-0.19	[-0.39; 0.02]	
Asia	175 | N.E.	166 | N.E.	Difference	N.E.	[N.E.]	N.E.
			Hedges G	N.E.	[N.E.]	
Latin America	63 | 1.02 (1.57)	69 | -0.31 (1.48)	Difference	1.34	[-2.94; 5.61]	0.538
			Hedges G	0.11	[-0.23; 0.45]	
Age group 1 at randomization						
Interaction test	**p = 0.795**					
<45	524 | 0.15 (0.74)	458 | 2.05 (0.79)	Difference	-1.89	[-4.02; 0.23]	0.081
			Hedges G	-0.11	[-0.24; 0.01]	
45 to 54	512 | -0.67 (0.72)	517 | 1.50 (0.73)	Difference	-2.17	[-4.18; -0.17]	0.034
			Hedges G	-0.13	[-0.25; -0.01]	
55 to 64	20 | 1.64 (3.93)	27 | 1.34 (3.43)	Difference	0.30	[-10.22; 10.81]	0.954
			Hedges G	0.02	[-0.56; 0.60]	
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)						
Interaction test	**p = 0.795**					
<Median	524 | 0.23 (0.76)	458 | 1.92 (0.81)	Difference	-1.69	[-3.86; 0.48]	0.128
			Hedges G	-0.10	[-0.22; 0.03]	
≥Median	532 | -0.48 (0.69)	544 | 1.67 (0.69)	Difference	-2.15	[-4.07; -0.23]	0.028
			Hedges G	-0.13	[-0.25; -0.01]	

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1115)	**ET (N = 1123)**	**Parameter**	**Esti-mate**	**[95% CI]**	**p-value**
Race						
Interaction test	**p = 0.515**					
Asian	206 | 2.06 (1.07)	180 | 4.79 (1.15)	Difference	-2.72	[-5.82; 0.38]	0.085
			Hedges G	-0.18	[-0.38; 0.02]	
Non-Asian	799 | -0.30 (0.60)	770 | 1.20 (0.61)	Difference	-1.50	[-3.16; 0.17]	0.079
			Hedges G	-0.09	[-0.19; 0.01]	
BMI at screening						
Interaction test	**p = 0.651**					
≥25	526 | -1.65 (0.77)	487 | 0.28 (0.81)	Difference	-1.93	[-4.13; 0.27]	0.086
			Hedges G	-0.11	[-0.23; 0.02]	
<25	518 | 1.28 (0.67)	504 | 3.40 (0.68)	Difference	-2.12	[-3.99; -0.25]	0.026
			Hedges G	-0.14	[-0.26; -0.02]	
AJCC Anatomic Stage Group						
Interaction test	**p = 0.071**					
Group I/II	393 | 0.04 (0.83)	398 | 0.34 (0.83)	Difference	-0.30	[-2.62; 2.02]	0.800
			Hedges G	-0.02	[-0.16; 0.12]	
Group III	663 | -0.25 (0.64)	604 | 3.19 (0.68)	Difference	-3.44	[-5.27; -1.60]	<.001
			Hedges G	-0.21	[-0.32; -0.10]	
Anatomic stages						
Interaction test	**N.E.**					
IA/IB/IIA	163 | 2.23 (1.23)	188 | 1.16 (1.17)	Difference	1.07	[-2.26; 4.40]	0.527
			Hedges G	0.07	[-0.14; 0.28]	
IIB	230 | -1.53 (1.12)	210 | -0.48 (1.17)	Difference	-1.05	[-4.24; 2.15]	0.520
			Hedges G	-0.06	[-0.25; 0.13]	
IIIA	433 | -0.33 (0.83)	366 | 3.17 (0.91)	Difference	-3.50	[-5.92; -1.08]	0.005
			Hedges G	-0.20	[-0.34; -0.06]	
IIIB	62 | -1.94 (1.82)	52 | -0.62 (2.00)	Difference	-1.32	[-6.71; 4.08]	0.629
			Hedges G	-0.09	[-0.46; 0.28]	
IIIC	168 | 0.30 (1.18)	186 | 2.92 (1.13)	Difference	-2.62	[-5.84; 0.60]	0.110
			Hedges G	-0.17	[-0.38; 0.04]	
Nodal status						
Interaction test	**p = 0.729**					
N0	84 | 1.78 (1.58)	110 | 2.27 (1.41)	Difference	-0.49	[-4.68; 3.70]	0.817
			Hedges G	-0.03	[-0.32; 0.25]	
N1-N3	972 | -0.41 (0.54)	889 | 1.58 (0.57)	Difference	-2.00	[-3.54; -0.46]	0.011
			Hedges G	-0.12	[-0.21; -0.03]	

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1115)	**ET (N = 1123)**	**Parameter**	**Esti-mate**	**[95% CI]**	**p-value**
Histological grade at time of surgery						
Interaction test	**p = 0.655**					
Grade 1	104 | 0.16 (1.43)	97 | 0.31 (1.50)	Difference	-0.15	[-4.25; 3.94]	0.942
			Hedges G	-0.01	[-0.29; 0.27]	
Grade 2	578 | -0.12 (0.70)	556 | 2.03 (0.72)	Difference	-2.15	[-4.12; -0.17]	0.033
			Hedges G	-0.13	[-0.24; -0.01]	
Grade 3	282 | -0.48 (1.00)	252 | 2.03 (1.05)	Difference	-2.51	[-5.35; 0.33]	0.083
			Hedges G	-0.15	[-0.32; 0.02]	
Histological subtype						
Interaction test	**N.E.**					
Ductal	820 | -0.45 (0.57)	785 | 1.67 (0.58)	Difference	-2.13	[-3.72; -0.53]	0.009
			Hedges G	-0.13	[-0.23; -0.03]	
Lobular	168 | 1.25 (1.42)	156 | 0.70 (1.47)	Difference	0.55	[-3.49; 4.58]	0.789
			Hedges G	0.03	[-0.19; 0.25]	
Other	68 | -0.87 (1.72)	61 | 5.02 (1.91)	Difference	-5.89	[-10.97; -0.80]	0.024
			Hedges G	-0.40	[-0.75; -0.06]	
Ki67 status from surgical specimen						
Interaction test	**p = 0.403**					
Ki67≤20	509 | 0.31 (0.75)	516 | 1.50 (0.75)	Difference	-1.19	[-3.27; 0.89]	0.261
			Hedges G	-0.07	[-0.19; 0.05]	
Ki67>20	398 | -0.87 (0.80)	359 | 1.49 (0.84)	Difference	-2.36	[-4.64; -0.09]	0.042
			Hedges G	-0.15	[-0.29; -0.01]	
Type of NSAI						
Interaction test	**p = 0.583**					
Letrozole	773 | -0.36 (0.59)	719 | 1.55 (0.62)	Difference	-1.91	[-3.59; -0.22]	0.027
			Hedges G	-0.11	[-0.22; -0.01]	
Anastrozole	283 | 0.09 (0.99)	281 | 2.91 (1.00)	Difference	-2.82	[-5.58; -0.06]	0.045
			Hedges G	-0.17	[-0.33; -0.00]	
Prior neo/adjuvant chemotherapy						
Interaction test	**p = 0.955**					
Yes	981 | -0.01 (0.53)	925 | 1.89 (0.55)	Difference	-1.90	[-3.40; -0.40]	0.013
			Hedges G	-0.11	[-0.20; -0.02]	
No	75 | -1.98 (1.60)	77 | -0.40 (1.62)	Difference	-1.57	[-6.07; 2.93]	0.490
			Hedges G	-0.11	[-0.43; 0.21]	
Prior adjuvant chemotherapy						
Interaction test	**p = 0.877**					
Yes	494 | -0.04 (0.72)	461 | 2.47 (0.75)	Difference	-2.51	[-4.55; -0.47]	0.016
			Hedges G	-0.16	[-0.28; -0.03]	
No	562 | -0.09 (0.72)	541 | 1.45 (0.74)	Difference	-1.54	[-3.57; 0.49]	0.136
			Hedges G	-0.09	[-0.21; 0.03]	

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1115)	ET (N = 1123)	Parameter	Esti-mate	[95% CI]	p-value
Prior neoadjuvant chemotherapy						
Interaction test	**p = 0.645**					
Yes	517 | 0.56 (0.75)	502 | 2.64 (0.77)	Difference	-2.09	[-4.20; 0.03]	0.053
			Hedges G	-0.12	[-0.24; 0.00]	
No	539 | -0.92 (0.69)	500 | 1.57 (0.72)	Difference	-2.49	[-4.45; -0.52]	0.013
			Hedges G	-0.15	[-0.28; -0.03]	
Prior endocrine therapy						
Interaction test	**p = 0.666**					
Yes	812 | -0.22 (0.59)	733 | 2.04 (0.62)	Difference	-2.25	[-3.94; -0.57]	0.009
			Hedges G	-0.13	[-0.23; -0.03]	
No	244 | 0.07 (1.02)	269 | 1.58 (0.98)	Difference	-1.50	[-4.29; 1.28]	0.290
			Hedges G	-0.09	[-0.27; 0.08]	
Prior mastectomy						
Interaction test	**p = 0.031**					
Yes	735 | -0.52 (0.62)	698 | 2.70 (0.64)	Difference	-3.21	[-4.97; -1.46]	<.001
			Hedges G	-0.19	[-0.29; -0.09]	
No	321 | 0.12 (0.92)	304 | -0.19 (0.96)	Difference	0.31	[-2.29; 2.91]	0.815
			Hedges G	0.02	[-0.14; 0.18]	
Prior radiotherapy						
Interaction test	**p = 0.747**					
Yes	967 | -0.30 (0.54)	920 | 1.73 (0.55)	Difference	-2.03	[-3.54; -0.52]	0.008
			Hedges G	-0.12	[-0.21; -0.03]	
No	89 | 0.47 (1.56)	82 | 1.63 (1.65)	Difference	-1.16	[-5.65; 3.32]	0.610
			Hedges G	-0.08	[-0.38; 0.22]	

N: Number of patients
N': Number of patients in the analysis
CI: Confidence interval
SD: Standard deviation
LS Mean: Least square mean
SE: Standard error
MMRM: Mixed model for repeated measures
N.E.: Not estimable
ET: Endocrine therapy (Anastrozole/Letrozole + Goserelin)
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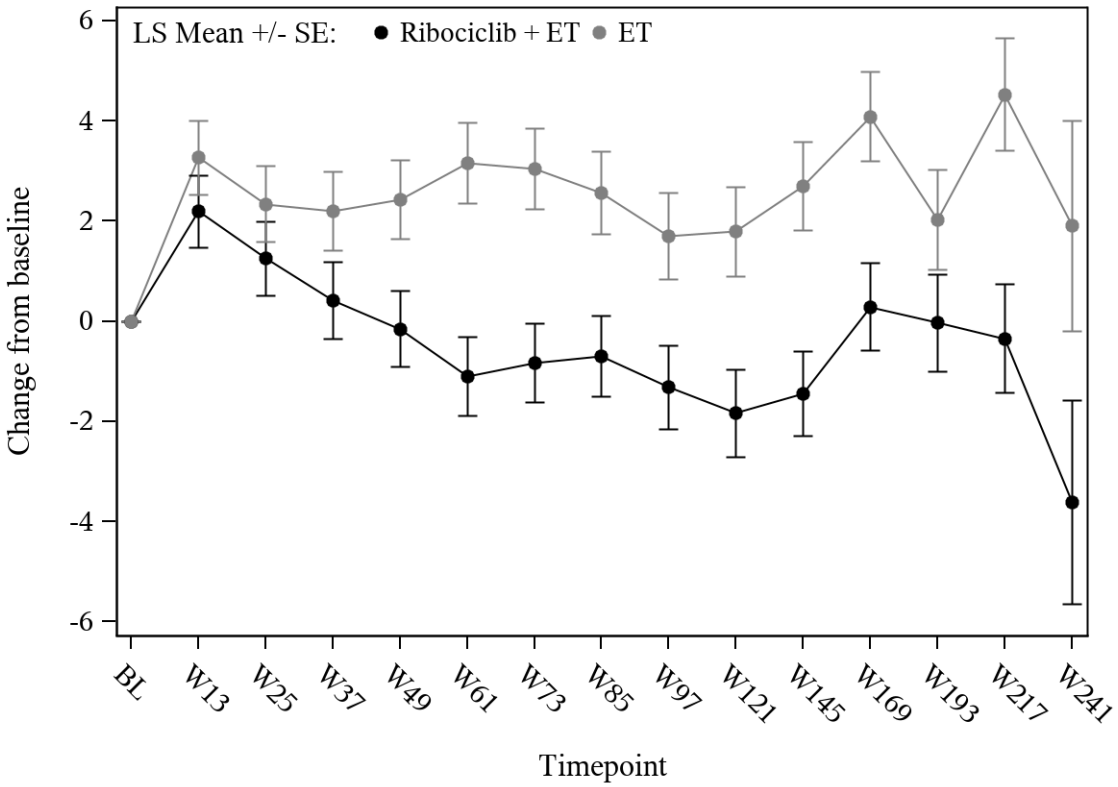
Analysis method for interaction test:
p-value from MMRM with unstructured covariance matrix:
change from baseline = treatment + visit + treatment * visit + subgroup factor + treatment * subgroup factor + subgroup factor * visit + treatment * subgroup factor * visit + baseline value
If the model did not converge for a parameter*subgroup factor, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry. If the model did still not converge, interactions were removed in the order treatment * subgroup factor * visit, subgroup factor * visit.

Analysis methods for within-subgroup analysis:
Adjusted mean (LS Mean) change from baseline and overall effect obtained from MMRM with unstructured covariance matrix:
change from baseline = treatment + visit + treatment * visit + baseline value
ET was the reference group for treatment group comparison.
If the model did not converge for a parameter*subgroup factor, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry.

Patients with an evaluable baseline score and at least one evaluable post-baseline score were included in the analysis.
All data collected were included in the analysis, including assessments at confirmation of first recurrence and thereafter, as long as there were at least 50 patients in each treatment group at a visit in the overall (sub-)population.

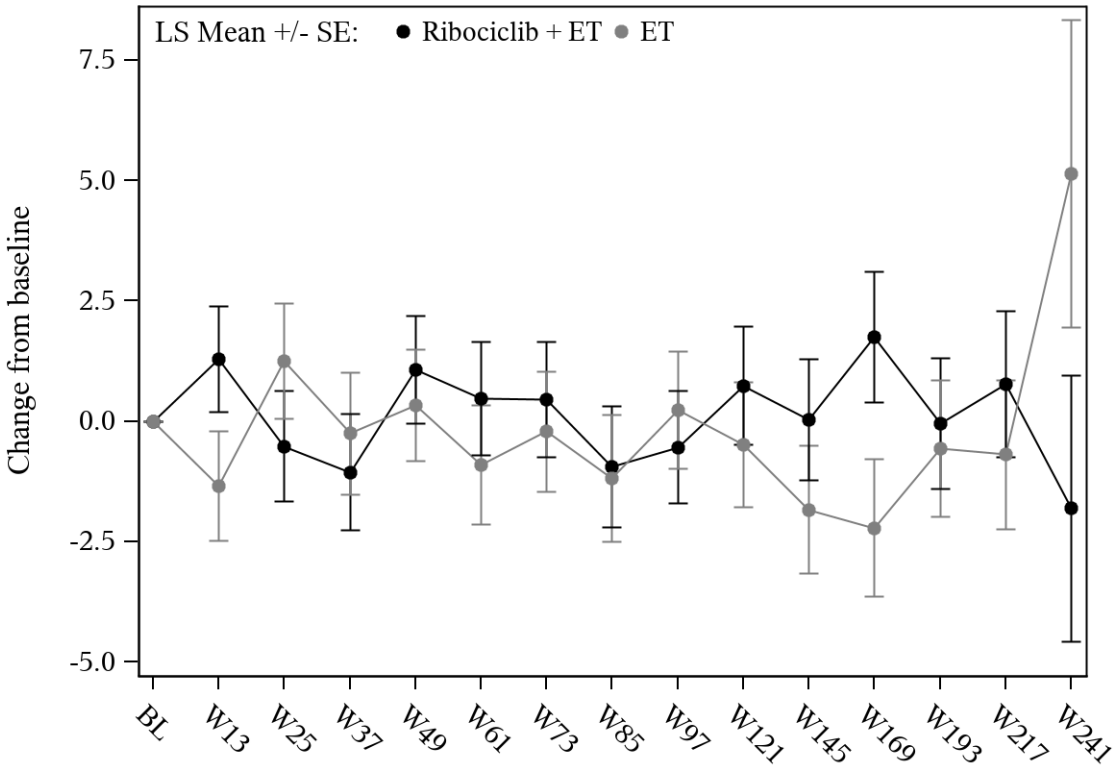
Figure 5-2.2.6.1 QLQ-C30 - Social Functioning: line chart of change from baseline - subgroup analysis (Full Analysis Set)

QLQ-C30 - Social Functioning
Prior mastectomy: Yes



Ribociclib + ET	735	708	675	675	665	662	653	646	635	615	612	488	401	232	40
ET	698	660	648	634	643	630	623	611	596	588	558	456	377	213	38

QLQ-C30 - Social Functioning
Prior mastectomy: No



Ribociclib + ET	321	316	301	307	303	299	299	294	294	282	284	237	205	112	18
ET	304	297	268	272	272	270	268	257	259	250	249	221	189	110	14

5-2.3 EORTC QLQ-BR23 Symptoms

Table 5-2.3.1.1 QLQ-BR23 - Side Effects Of Systemic Therapy: change from baseline analysis - subgroup analysis (Full Analysis Set)

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1115)	ET (N = 1123)	Parameter	Esti-mate	[95% CI]	p-value
QLQ-BR23 - Side Effects Of Systemic Therapy						
	N' | LS Mean (SE)	N' | LS Mean (SE)				
Region						
Interaction test	**p = 0.050**					
NA/WE/O	600 | 6.03 (0.47)	576 | 2.76 (0.48)	Difference	3.27	[1.95; 4.60]	<.001
			Hedges G	0.28	[0.17; 0.40]	
ROW	460 | 5.45 (0.53)	427 | 3.89 (0.55)	Difference	1.56	[0.06; 3.06]	0.041
			Hedges G	0.14	[0.01; 0.27]	
Geographical region						
Interaction test	**p = 0.389**					
Europe	619 | 5.87 (0.35)	594 | 3.61 (0.35)	Difference	2.25	[1.28; 3.22]	<.001
			Hedges G	0.26	[0.15; 0.37]	
North America/Australia	203 | 3.90 (0.51)	174 | 1.00 (0.58)	Difference	2.90	[1.38; 4.42]	<.001
			Hedges G	0.39	[0.18; 0.59]	
Asia	175 | N.E.	166 | N.E.	Difference	N.E.	[N.E.]	N.E.
			Hedges G	N.E.	[N.E.]	
Latin America	63 | 8.78 (1.18)	69 | 5.43 (1.11)	Difference	3.36	[0.14; 6.57]	0.041
			Hedges G	0.36	[0.02; 0.70]	
Age group 1 at randomization						
Interaction test	**N.E.**					
<45	525 | 5.65 (0.48)	460 | 2.58 (0.51)	Difference	3.07	[1.69; 4.45]	<.001
			Hedges G	0.28	[0.15; 0.40]	
45 to 54	515 | 5.56 (0.48)	516 | 3.87 (0.48)	Difference	1.69	[0.35; 3.02]	0.013
			Hedges G	0.15	[0.03; 0.28]	
55 to 64	20 | 9.21 (2.67)	27 | 3.06 (2.29)	Difference	6.15	[-1.00; 13.31]	0.090
			Hedges G	0.51	[-0.08; 1.10]	
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)						
Interaction test	**p = 0.213**					
<Median	525 | N.E.	460 | N.E.	Difference	N.E.	[N.E.]	N.E.
			Hedges G	N.E.	[N.E.]	
≥Median	535 | 5.73 (0.48)	543 | 3.79 (0.48)	Difference	1.93	[0.61; 3.26]	0.004
			Hedges G	0.17	[0.05; 0.29]	

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1115)	**ET (N = 1123)**	**Parameter**	**Esti-mate**	**[95% CI]**	**p-value**
Race						
Interaction test	**p = 0.687**					
Asian	206 | 5.33 (0.76)	180 | 3.16 (0.82)	Difference	2.17	[-0.04; 4.38]	0.054
			Hedges G	0.20	[-0.00; 0.40]	
Non-Asian	803 | 5.81 (0.39)	771 | 3.39 (0.40)	Difference	2.42	[1.32; 3.51]	<.001
			Hedges G	0.22	[0.12; 0.32]	
BMI at screening						
Interaction test	**p = 0.290**					
≥25	530 | 6.81 (0.52)	486 | 3.99 (0.55)	Difference	2.82	[1.32; 4.31]	<.001
			Hedges G	0.23	[0.11; 0.36]	
<25	518 | 4.57 (0.47)	506 | 2.69 (0.48)	Difference	1.87	[0.56; 3.19]	0.005
			Hedges G	0.17	[0.05; 0.30]	
AJCC Anatomic Stage Group						
Interaction test	**p = 0.002**					
Group I/II	395 | 5.26 (0.58)	397 | 4.53 (0.58)	Difference	0.73	[-0.89; 2.35]	0.377
			Hedges G	0.06	[-0.08; 0.20]	
Group III	665 | 5.97 (0.43)	606 | 2.36 (0.46)	Difference	3.61	[2.37; 4.84]	<.001
			Hedges G	0.32	[0.21; 0.43]	
Anatomic stages						
Interaction test	**p = 0.005**					
IA/IB/IIA	164 | 2.68 (0.82)	189 | 4.44 (0.78)	Difference	-1.76	[-4.00; 0.47]	0.122
			Hedges G	-0.17	[-0.37; 0.04]	
IIB	231 | 7.07 (0.73)	208 | 4.70 (0.77)	Difference	2.37	[0.29; 4.46]	0.026
			Hedges G	0.21	[0.03; 0.40]	
IIIA	433 | 6.35 (0.53)	368 | 2.59 (0.57)	Difference	3.76	[2.23; 5.29]	<.001
			Hedges G	0.34	[0.20; 0.48]	
IIIB	63 | 6.63 (1.48)	52 | 1.31 (1.63)	Difference	5.32	[0.94; 9.70]	0.018
			Hedges G	0.45	[0.08; 0.82]	
IIIC	169 | 4.94 (0.81)	186 | 2.29 (0.78)	Difference	2.66	[0.44; 4.88]	0.019
			Hedges G	0.25	[0.04; 0.46]	
Nodal status						
Interaction test	**p = 0.398**					
N0	84 | 4.00 (1.15)	111 | 2.88 (1.00)	Difference	1.12	[-1.89; 4.13]	0.463
			Hedges G	0.11	[-0.18; 0.39]	
N1-N3	976 | 5.91 (0.37)	889 | 3.40 (0.39)	Difference	2.51	[1.46; 3.57]	<.001
			Hedges G	0.22	[0.13; 0.31]	

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1115)	**ET (N = 1123)**	**Parameter**	**Esti-mate**	**[95% CI]**	**p-value**
Histological grade at time of surgery						
Interaction test	**p = 0.474**					
Grade 1	106 | 5.98 (1.07)	97 | 4.95 (1.12)	Difference	1.04	[-2.02; 4.09]	0.503
			Hedges G	0.09	[-0.18; 0.37]	
Grade 2	580 | 6.01 (0.45)	558 | 3.04 (0.46)	Difference	2.97	[1.70; 4.24]	<.001
			Hedges G	0.27	[0.16; 0.39]	
Grade 3	282 | 5.37 (0.68)	250 | 2.98 (0.72)	Difference	2.38	[0.44; 4.32]	0.016
			Hedges G	0.21	[0.04; 0.38]	
Histological subtype						
Interaction test	**p = 0.705**					
Ductal	823 | N.E.	786 | N.E.	Difference	N.E.	[N.E.]	N.E.
			Hedges G	N.E.	[N.E.]	
Lobular	168 | 6.30 (0.91)	155 | 3.38 (0.96)	Difference	2.92	[0.32; 5.52]	0.028
			Hedges G	0.25	[0.03; 0.47]	
Other	69 | 5.31 (1.28)	62 | 0.91 (1.41)	Difference	4.40	[0.64; 8.16]	0.022
			Hedges G	0.40	[0.06; 0.75]	
Ki67 status from surgical specimen						
Interaction test	**p = 0.550**					
Ki67≤20	510 | 6.90 (0.51)	519 | 4.27 (0.50)	Difference	2.63	[1.23; 4.04]	<.001
			Hedges G	0.23	[0.11; 0.35]	
Ki67>20	401 | 5.45 (0.53)	357 | 2.23 (0.56)	Difference	3.23	[1.71; 4.74]	<.001
			Hedges G	0.30	[0.16; 0.45]	
Type of NSAI						
Interaction test	**N.E.**					
Letrozole	775 | 5.52 (0.41)	719 | 3.63 (0.43)	Difference	1.89	[0.72; 3.06]	0.002
			Hedges G	0.16	[0.06; 0.27]	
Anastrozole	285 | 6.46 (0.68)	282 | 2.29 (0.69)	Difference	4.16	[2.27; 6.06]	<.001
			Hedges G	0.36	[0.20; 0.53]	
Prior neo/adjuvant chemotherapy						
Interaction test	**p = 0.258**					
Yes	985 | 5.51 (0.35)	925 | 2.95 (0.36)	Difference	2.55	[1.56; 3.54]	<.001
			Hedges G	0.23	[0.14; 0.32]	
No	75 | 7.66 (1.20)	78 | 7.03 (1.20)	Difference	0.64	[-2.72; 4.00]	0.708
			Hedges G	0.06	[-0.26; 0.38]	
Prior adjuvant chemotherapy						
Interaction test	**p = 0.947**					
Yes	495 | 5.20 (0.51)	459 | 2.72 (0.53)	Difference	2.48	[1.04; 3.92]	<.001
			Hedges G	0.22	[0.09; 0.35]	
No	565 | 6.23 (0.49)	544 | 3.74 (0.50)	Difference	2.49	[1.12; 3.87]	<.001
			Hedges G	0.21	[0.10; 0.33]	

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1115)	ET (N = 1123)	Parameter	Esti-mate	[95% CI]	p-value
Prior neoadjuvant chemotherapy						
Interaction test	**p = 0.851**					
Yes	520 | 5.86 (0.50)	503 | 3.26 (0.51)	Difference	2.60	[1.18; 4.01]	<.001
			Hedges G	0.23	[0.10; 0.35]	
No	540 | 5.71 (0.49)	500 | 3.30 (0.51)	Difference	2.40	[1.02; 3.79]	<.001
			Hedges G	0.21	[0.09; 0.33]	
Prior endocrine therapy						
Interaction test	**p = 0.999**					
Yes	816 | 5.61 (0.40)	734 | 3.12 (0.42)	Difference	2.49	[1.35; 3.64]	<.001
			Hedges G	0.22	[0.12; 0.32]	
No	244 | 6.07 (0.73)	269 | 3.81 (0.70)	Difference	2.27	[0.27; 4.26]	0.026
			Hedges G	0.20	[0.02; 0.37]	
Prior mastectomy						
Interaction test	**p = 0.128**					
Yes	737 | 5.71 (0.40)	700 | 2.85 (0.41)	Difference	2.86	[1.73; 3.99]	<.001
			Hedges G	0.26	[0.16; 0.37]	
No	323 | 5.58 (0.61)	303 | 4.28 (0.65)	Difference	1.30	[-0.45; 3.05]	0.146
			Hedges G	0.12	[-0.04; 0.27]	
Prior radiotherapy						
Interaction test	**p = 0.569**					
Yes	971 | 5.67 (0.37)	920 | 3.29 (0.38)	Difference	2.38	[1.33; 3.42]	<.001
			Hedges G	0.21	[0.12; 0.30]	
No	89 | 6.09 (1.22)	83 | 3.26 (1.28)	Difference	2.83	[-0.67; 6.32]	0.112
			Hedges G	0.24	[-0.06; 0.54]	

N: Number of patients
N': Number of patients in the analysis
CI: Confidence interval
SD: Standard deviation
LS Mean: Least square mean
SE: Standard error
MMRM: Mixed model for repeated measures
N.E.: Not estimable
ET: Endocrine therapy (Anastrozole/Letrozole + Goserelin)
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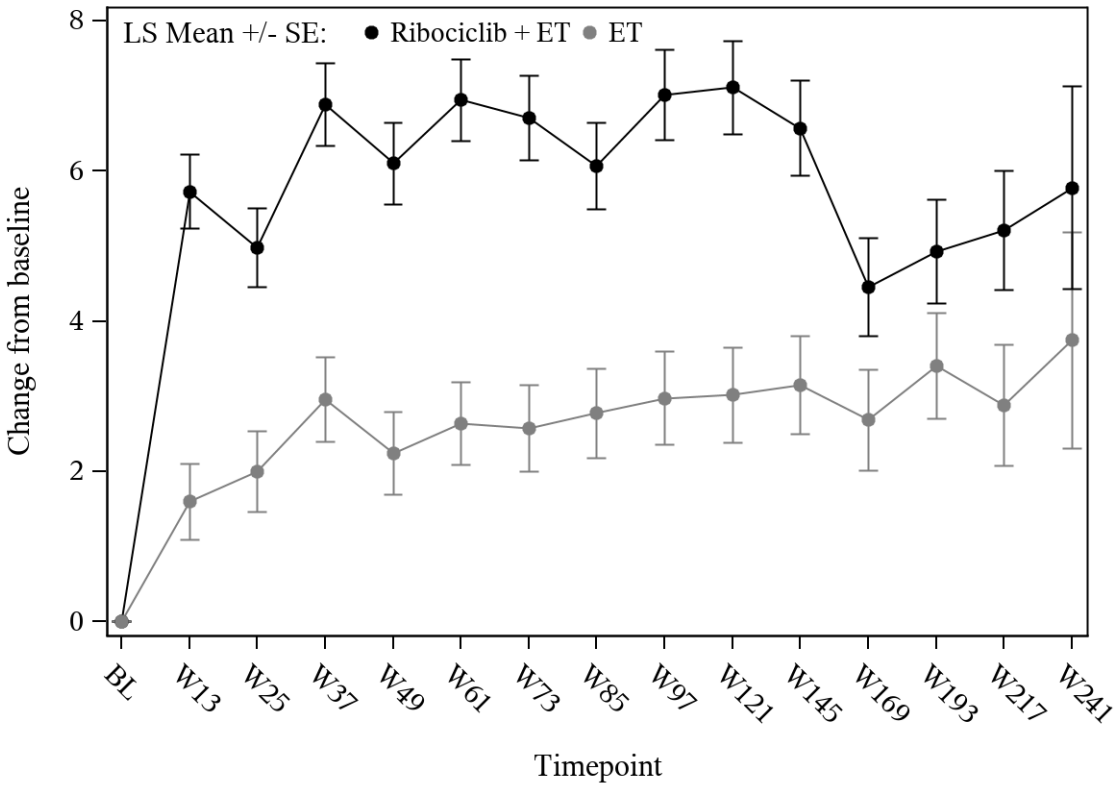
Analysis method for interaction test:
p-value from MMRM with unstructured covariance matrix:
change from baseline = treatment + visit + treatment * visit + subgroup factor + treatment * subgroup factor + subgroup factor * visit + treatment * subgroup factor * visit + baseline value
If the model did not converge for a parameter*subgroup factor, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry. If the model did still not converge, interactions were removed in the order treatment * subgroup factor * visit, subgroup factor * visit.

Analysis methods for within-subgroup analysis:
Adjusted mean (LS Mean) change from baseline and overall effect obtained from MMRM with unstructured covariance matrix:
change from baseline = treatment + visit + treatment * visit + baseline value
ET was the reference group for treatment group comparison.
If the model did not converge for a parameter*subgroup factor, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry.

Patients with an evaluable baseline score and at least one evaluable post-baseline score were included in the analysis.
All data collected were included in the analysis, including assessments at confirmation of first recurrence and thereafter, as long as there were at least 50 patients in each treatment group at a visit in the overall (sub-)population.

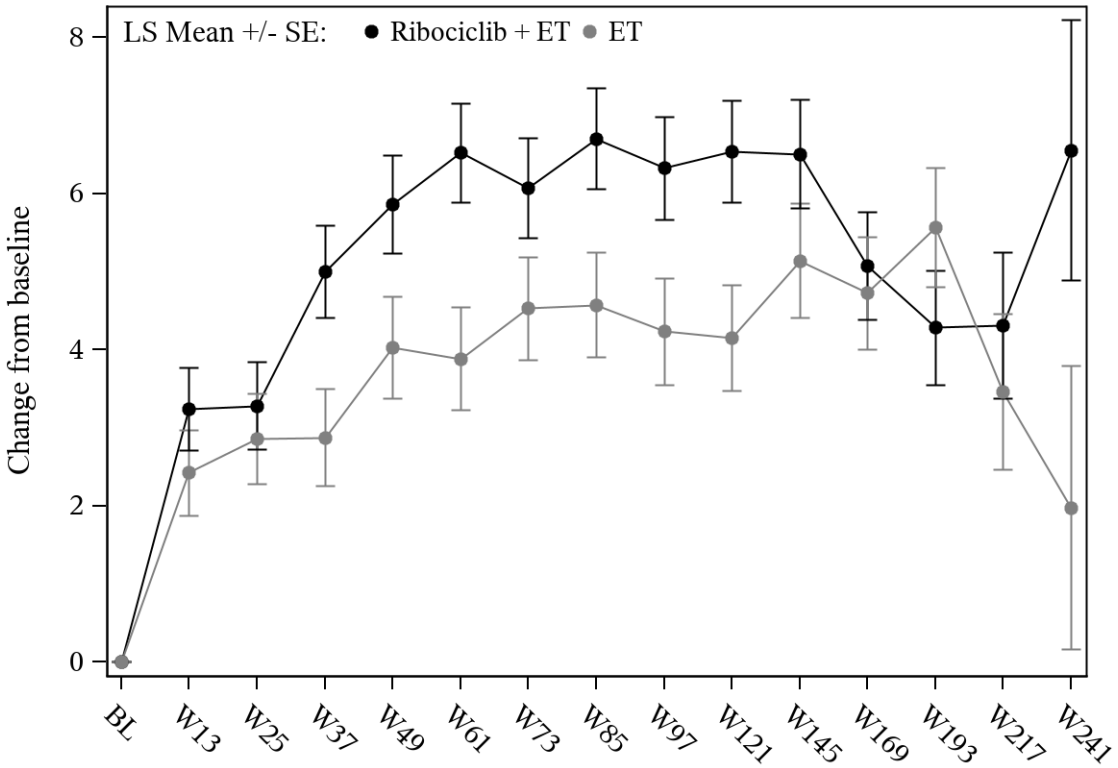
Figure 5-2.3.1.1 QLQ-BR23 - Side Effects Of Systemic Therapy: line chart of change from baseline - subgroup analysis (Full Analysis Set)

QLQ-BR23 - Side Effects Of Systemic Therapy
Region: NA/WE/O



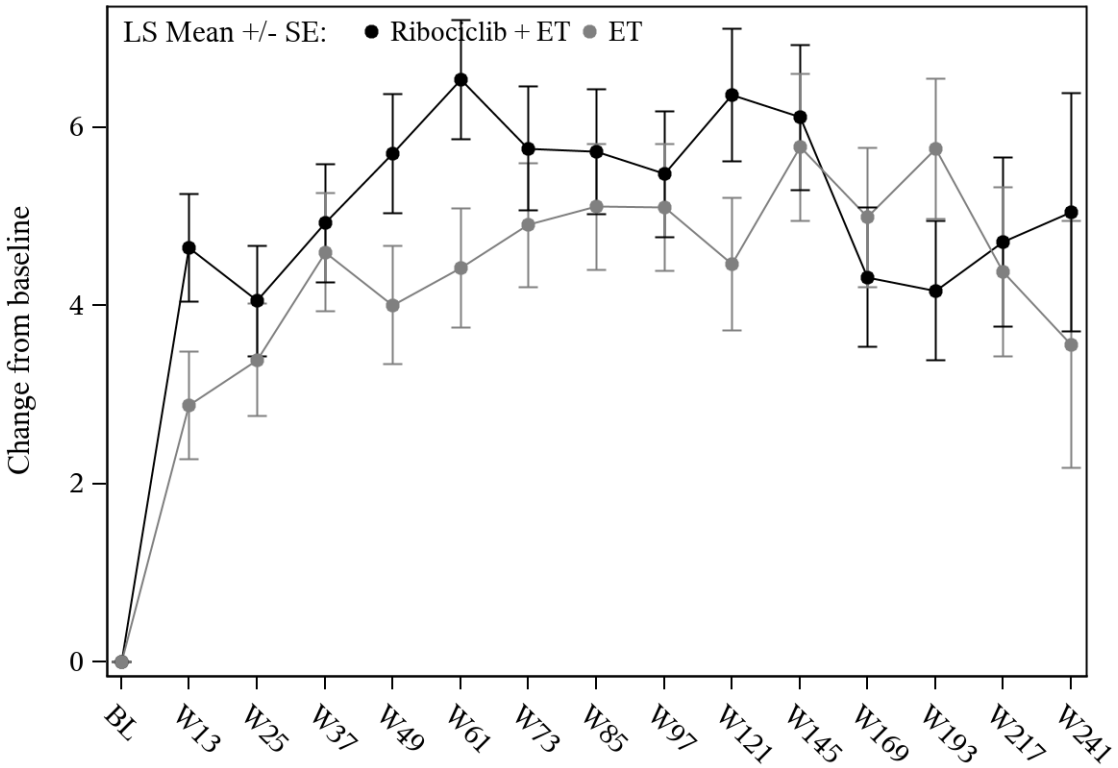
Ribociclib + ET	600	565	532	541	529	531	520	512	501	481	480	389	316	192	35
ET	576	536	504	507	512	502	498	479	467	461	438	366	304	188	31

QLQ-BR23 - Side Effects Of Systemic Therapy
Region: ROW



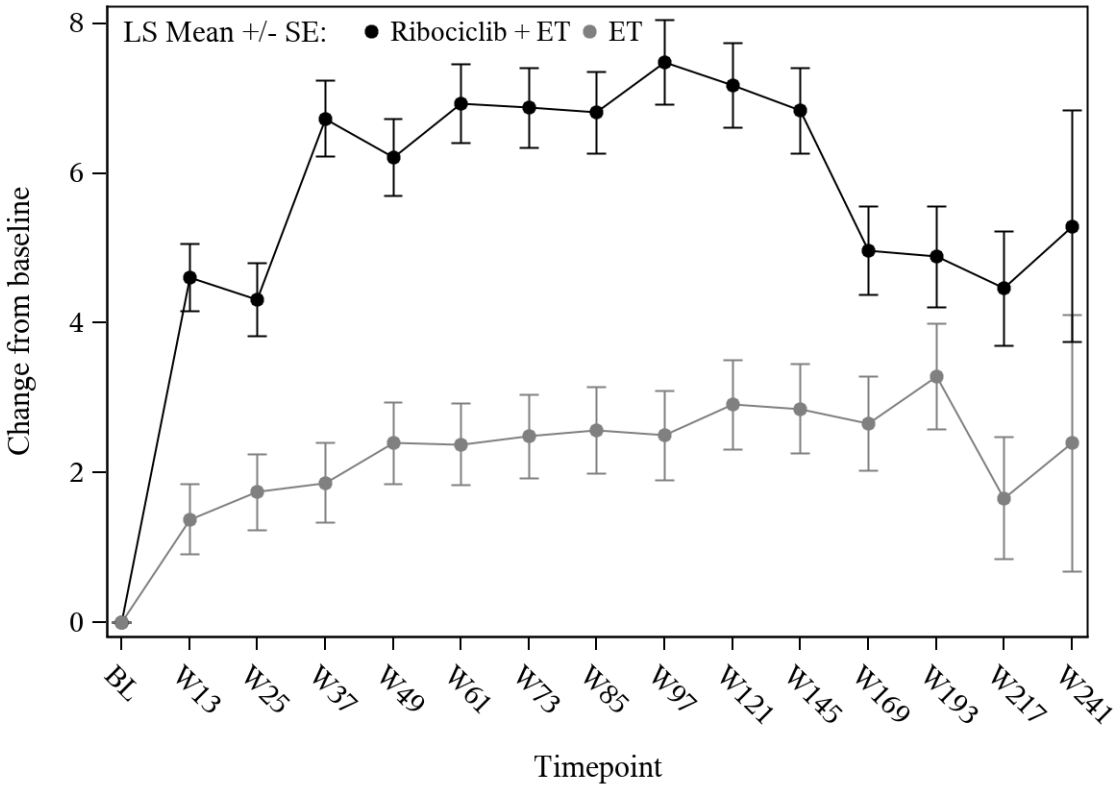
Ribociclib + ET	460	460	451	446	444	436	436	433	430	422	418	341	293	154	23
ET	427	424	418	405	411	402	398	396	388	380	369	316	262	134	19

QLQ-BR23 - Side Effects Of Systemic Therapy
AJCC Anatomic Stage Group: Group I/II



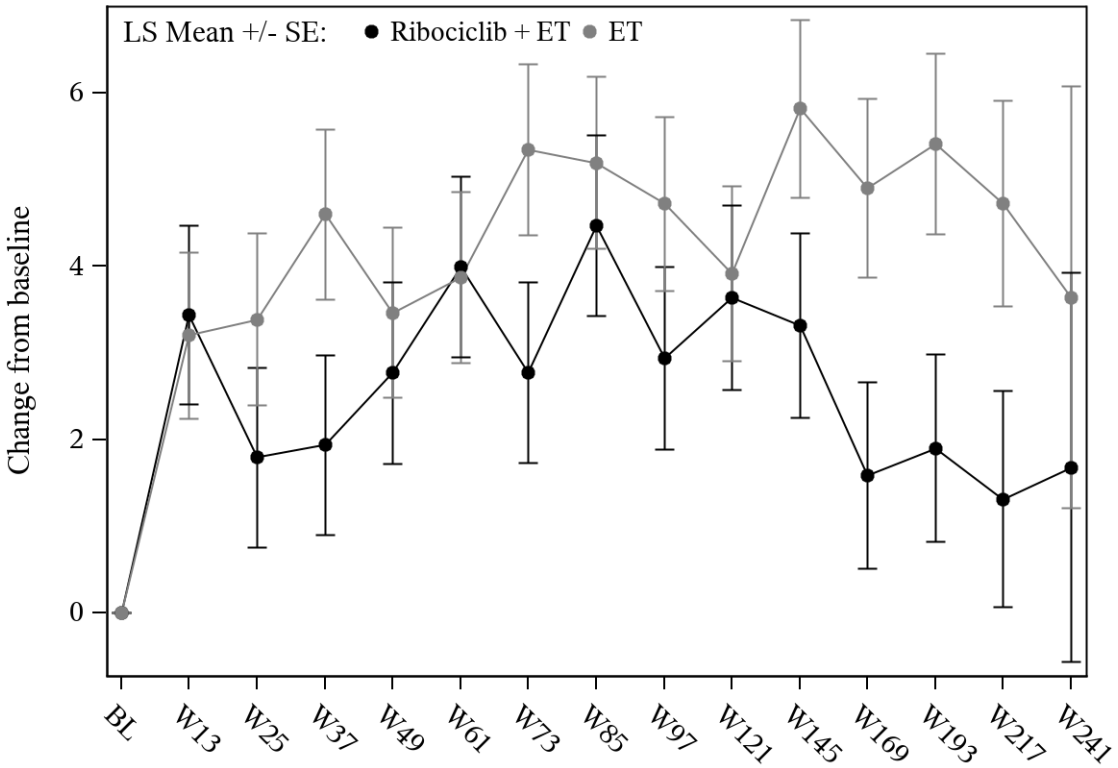
Ribociclib + ET	395	385	371	367	361	361	357	357	351	341	341	316	314	177	31
ET	397	380	352	365	368	359	361	344	342	335	321	317	303	175	27

QLQ-BR23 - Side Effects Of Systemic Therapy
AJCC Anatomic Stage Group: Group III



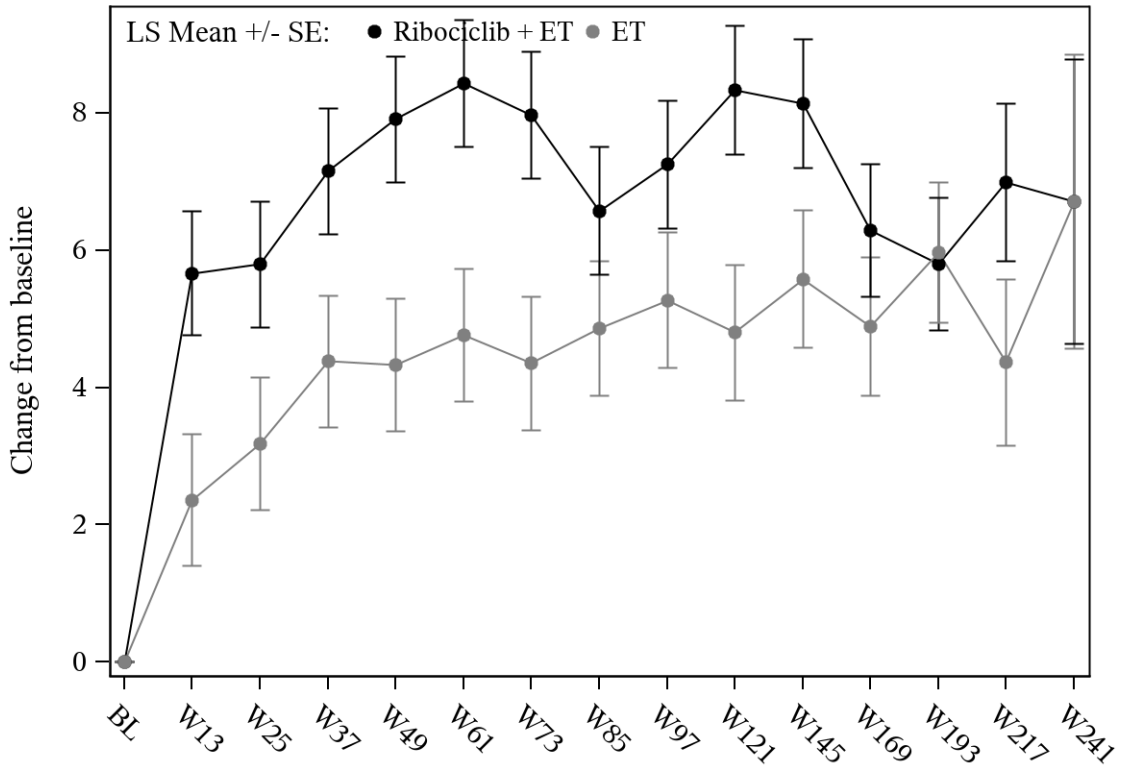
Ribociclib + ET	665	640	612	620	612	606	599	588	580	562	557	414	295	169	27
ET	606	580	570	547	555	545	535	531	513	506	486	365	263	147	23

QLQ-BR23 - Side Effects Of Systemic Therapy
Anatomic stages: IA/IB/IIA



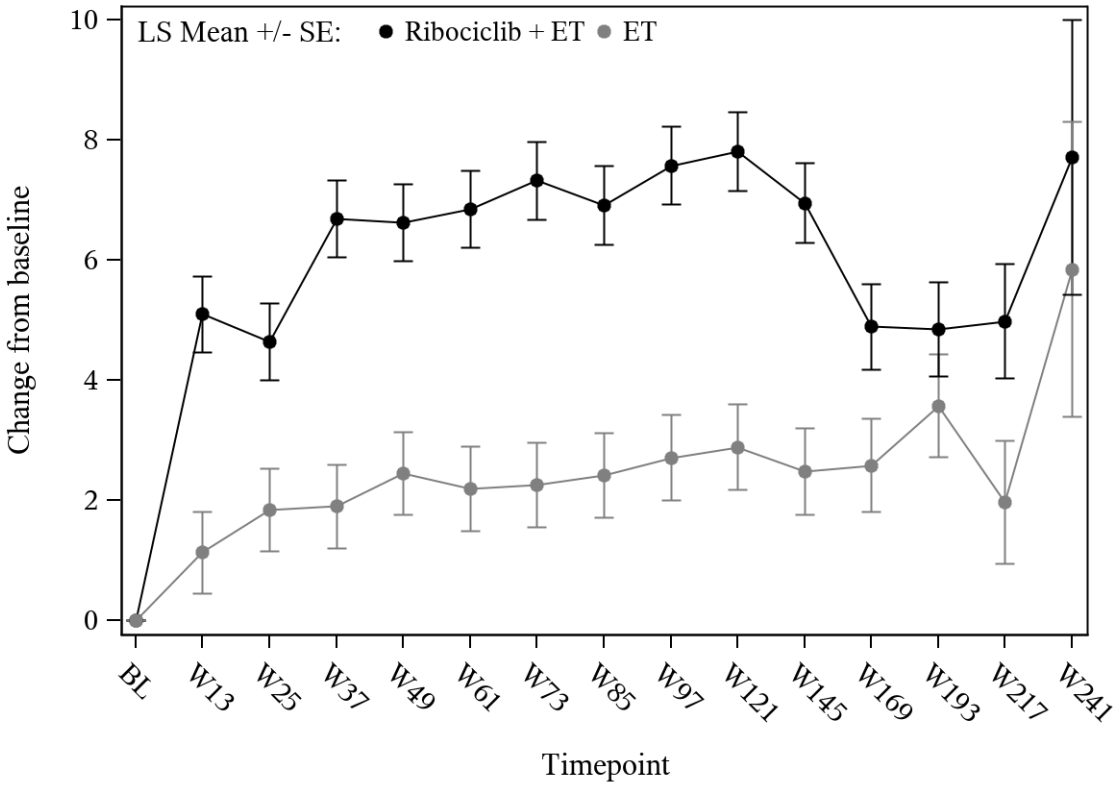
Ribociclib + ET	164	160	156	157	152	156	152	153	147	142	144	139	134	80	17
ET	189	184	162	170	172	168	170	163	161	157	150	148	141	88	14

QLQ-BR23 - Side Effects Of Systemic Therapy
Anatomic stages: IIB



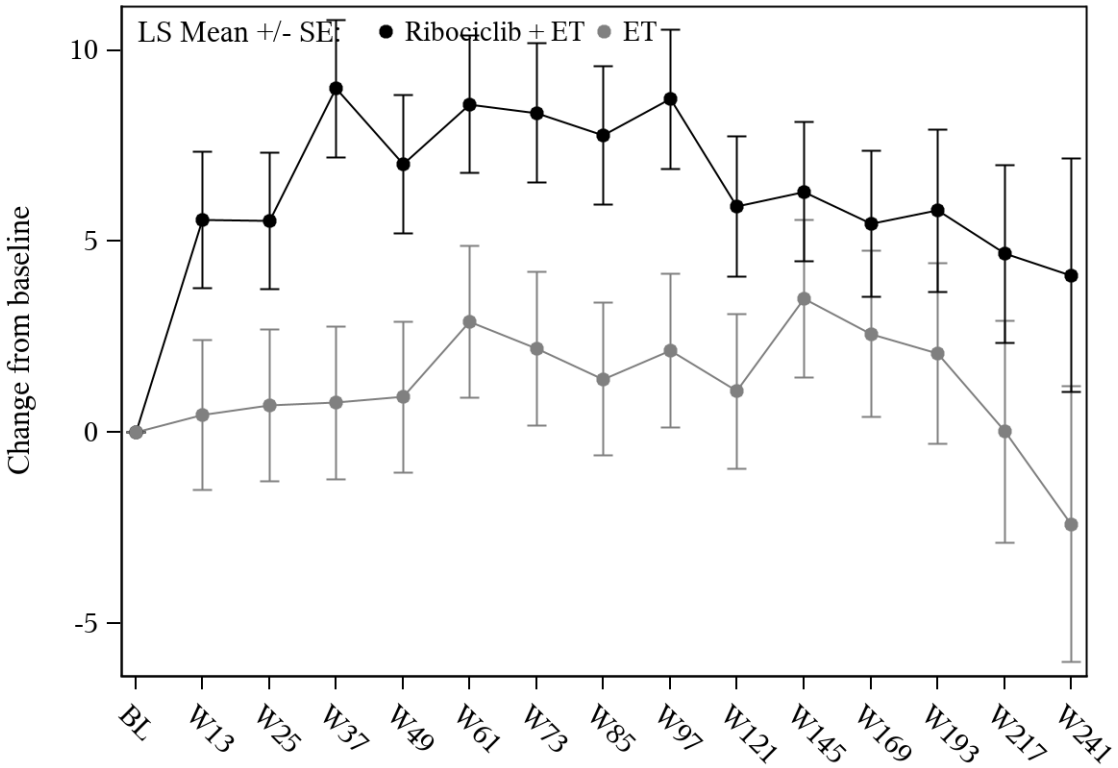
Ribociclib + ET	231	225	215	210	209	205	205	204	204	199	197	177	180	97	14
ET	208	196	190	195	196	191	191	181	181	178	171	169	162	87	13

QLQ-BR23 - Side Effects Of Systemic Therapy
Anatomic stages: IIIA



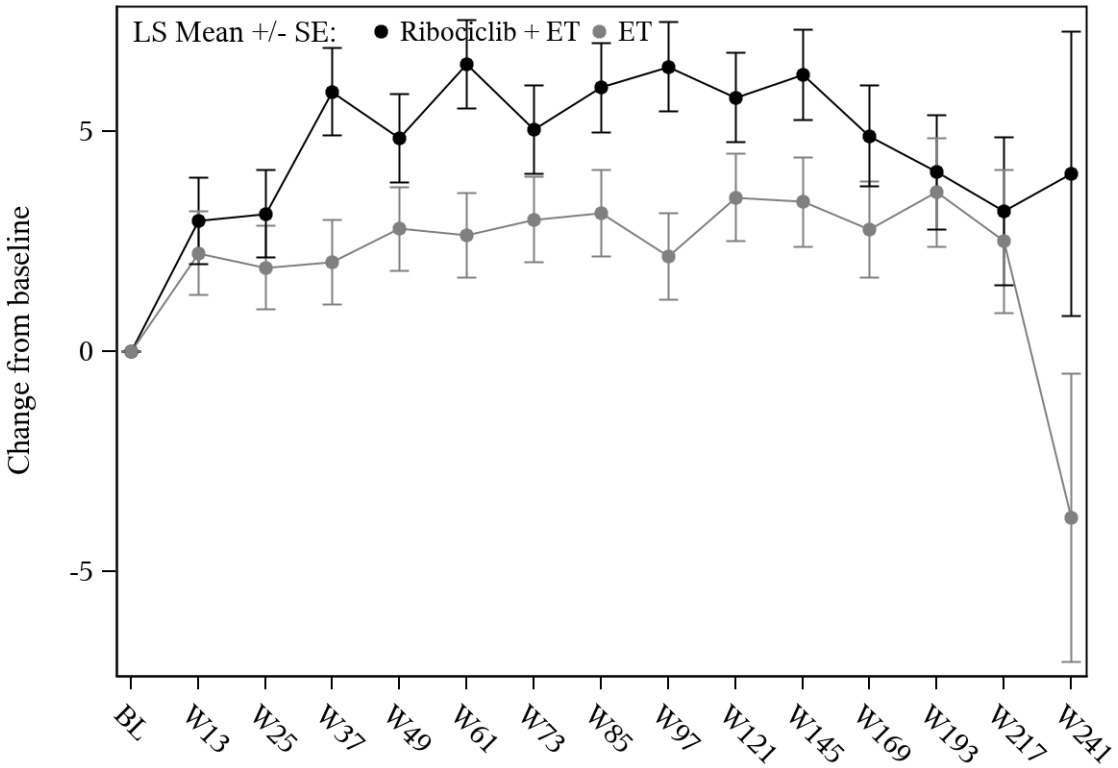
Ribociclib + ET	433	412	391	400	394	391	385	375	372	356	359	271	197	113	15
ET	368	351	343	329	335	329	327	324	313	307	302	224	163	99	13

QLQ-BR23 - Side Effects Of Systemic Therapy
Anatomic stages: IIIB



Ribociclib + ET	63	62	62	61	60	59	58	59	56	57	57	46	31	23	6
ET	52	52	49	47	49	49	46	48	47	46	42	33	25	13	4

QLQ-BR23 - Side Effects Of Systemic Therapy
Anatomic stages: IIIC



Ribociclib + ET	169	166	159	159	158	156	156	154	152	149	141	97	67	33	6
ET	186	177	178	171	171	167	162	159	153	153	142	108	75	35	6

Table 5-2.3.2.1 QLQ-BR23 - Breast Symptoms: change from baseline analysis - subgroup analysis (Full Analysis Set)

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1115)	ET (N = 1123)	Parameter	Esti-mate	[95% CI]	p-value
QLQ-BR23 - Breast Symptoms						
	N' | LS Mean (SE)	N' | LS Mean (SE)				
Region						
Interaction test	**p = 0.746**					
NA/WE/O	594 | -4.90 (0.50)	574 | -5.99 (0.50)	Difference	1.09	[-0.30; 2.48]	0.123
			Hedges G	0.09	[-0.02; 0.21]	
ROW	458 | -4.86 (0.47)	427 | -5.63 (0.49)	Difference	0.77	[-0.56; 2.10]	0.256
			Hedges G	0.08	[-0.06; 0.21]	
Geographical region						
Interaction test	**p = 0.202**					
Europe	613 | -4.74 (0.48)	592 | -5.20 (0.49)	Difference	0.46	[-0.88; 1.80]	0.500
			Hedges G	0.04	[-0.07; 0.15]	
North America/Australia	201 | -5.10 (0.71)	174 | -8.20 (0.77)	Difference	3.10	[1.04; 5.16]	0.003
			Hedges G	0.31	[0.10; 0.51]	
Asia	175 | -4.56 (0.70)	166 | -5.04 (0.72)	Difference	0.48	[-1.49; 2.44]	0.635
			Hedges G	0.05	[-0.16; 0.26]	
Latin America	63 | -4.56 (1.47)	69 | -7.44 (1.40)	Difference	2.88	[-1.14; 6.90]	0.159
			Hedges G	0.25	[-0.10; 0.59]	
Age group 1 at randomization						
Interaction test	**p = 0.487**					
<45	519 | -4.76 (0.51)	460 | -6.38 (0.54)	Difference	1.63	[0.17; 3.08]	0.028
			Hedges G	0.14	[0.01; 0.27]	
45 to 54	513 | -4.77 (0.48)	514 | -5.36 (0.48)	Difference	0.60	[-0.74; 1.93]	0.382
			Hedges G	0.05	[-0.07; 0.18]	
55 to 64	20 | -6.64 (2.27)	27 | -5.91 (1.96)	Difference	-0.73	[-6.78; 5.31]	0.808
			Hedges G	-0.07	[-0.65; 0.51]	
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)						
Interaction test	**p = 0.305**					
<Median	519 | -4.76 (0.51)	460 | -6.37 (0.54)	Difference	1.61	[0.15; 3.07]	0.031
			Hedges G	0.14	[0.01; 0.26]	
≥Median	533 | -4.85 (0.47)	541 | -5.36 (0.47)	Difference	0.51	[-0.79; 1.82]	0.442
			Hedges G	0.05	[-0.07; 0.17]	

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1115)	**ET (N = 1123)**	**Parameter**	**Esti-mate**	**[95% CI]**	**p-value**
Race						
Interaction test	**p = 0.982**					
Asian	206 | -4.81 (0.64)	180 | -5.79 (0.69)	Difference	0.98	[-0.87; 2.84]	0.298
			Hedges G	0.11	[-0.09; 0.31]	
Non-Asian	795 | -4.71 (0.42)	769 | -5.58 (0.42)	Difference	0.88	[-0.29; 2.04]	0.139
			Hedges G	0.07	[-0.02; 0.17]	
BMI at screening						
Interaction test	**p = 0.203**					
≥25	523 | -3.95 (0.53)	485 | -5.54 (0.55)	Difference	1.59	[0.08; 3.10]	0.039
			Hedges G	0.13	[0.01; 0.25]	
<25	517 | -5.69 (0.45)	505 | -6.00 (0.46)	Difference	0.31	[-0.95; 1.57]	0.628
			Hedges G	0.03	[-0.09; 0.15]	
AJCC Anatomic Stage Group						
Interaction test	**p = 0.020**					
Group I/II	392 | -5.77 (0.59)	395 | -5.25 (0.59)	Difference	-0.52	[-2.16; 1.12]	0.534
			Hedges G	-0.04	[-0.18; 0.10]	
Group III	660 | -4.23 (0.42)	606 | -6.17 (0.44)	Difference	1.93	[0.73; 3.14]	0.002
			Hedges G	0.18	[0.07; 0.29]	
Anatomic stages						
Interaction test	**p = 0.029**					
IA/IB/IIA	163 | -8.52 (0.90)	188 | -6.47 (0.85)	Difference	-2.04	[-4.48; 0.39]	0.100
			Hedges G	-0.18	[-0.39; 0.03]	
IIB	229 | -3.61 (0.79)	207 | -4.25 (0.82)	Difference	0.64	[-1.59; 2.88]	0.573
			Hedges G	0.05	[-0.13; 0.24]	
IIIA	430 | -3.81 (0.51)	368 | -6.44 (0.56)	Difference	2.63	[1.14; 4.11]	<.001
			Hedges G	0.25	[0.11; 0.39]	
IIIB	62 | -4.33 (1.71)	52 | -4.64 (1.87)	Difference	0.30	[-4.75; 5.35]	0.906
			Hedges G	0.02	[-0.35; 0.39]	
IIIC	168 | -5.43 (0.80)	186 | -6.07 (0.77)	Difference	0.65	[-1.54; 2.84]	0.562
			Hedges G	0.06	[-0.15; 0.27]	
Nodal status						
Interaction test	**p = 0.991**					
N0	83 | -5.53 (1.19)	111 | -6.49 (1.03)	Difference	0.96	[-2.14; 4.06]	0.542
			Hedges G	0.09	[-0.20; 0.37]	
N1-N3	969 | -4.72 (0.36)	887 | -5.71 (0.38)	Difference	0.99	[-0.04; 2.02]	0.060
			Hedges G	0.09	[-0.00; 0.18]	

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1115)	**ET (N = 1123)**	**Parameter**	**Esti-mate**	**[95% CI]**	**p-value**
Histological grade at time of surgery						
Interaction test	**p = 0.655**					
Grade 1	104 | -4.75 (0.95)	96 | -4.66 (1.00)	Difference	-0.09	[-2.81; 2.62]	0.945
			Hedges G	-0.01	[-0.29; 0.27]	
Grade 2	577 | -5.02 (0.48)	558 | -6.56 (0.50)	Difference	1.54	[0.18; 2.90]	0.026
			Hedges G	0.13	[0.02; 0.25]	
Grade 3	279 | -4.34 (0.66)	250 | -5.19 (0.69)	Difference	0.84	[-1.04; 2.73]	0.380
			Hedges G	0.08	[-0.09; 0.25]	
Histological subtype						
Interaction test	**p = 0.932**					
Ductal	816 | -5.01 (0.39)	785 | -5.93 (0.40)	Difference	0.92	[-0.18; 2.01]	0.101
			Hedges G	0.08	[-0.02; 0.18]	
Lobular	168 | -3.58 (0.93)	154 | -4.91 (0.96)	Difference	1.33	[-1.30; 3.96]	0.322
			Hedges G	0.11	[-0.11; 0.33]	
Other	68 | -4.82 (1.22)	62 | -6.88 (1.27)	Difference	2.05	[-1.43; 5.54]	0.246
			Hedges G	0.20	[-0.14; 0.55]	
Ki67 status from surgical specimen						
Interaction test	**p = 0.067**					
Ki67≤20	509 | -5.51 (0.51)	517 | -5.45 (0.50)	Difference	-0.06	[-1.46; 1.34]	0.933
			Hedges G	-0.01	[-0.13; 0.12]	
Ki67>20	395 | -4.04 (0.56)	357 | -5.85 (0.60)	Difference	1.82	[0.21; 3.43]	0.027
			Hedges G	0.16	[0.02; 0.31]	
Type of NSAI						
Interaction test	**p = 0.250**					
Letrozole	768 | -5.08 (0.40)	718 | -5.71 (0.41)	Difference	0.63	[-0.49; 1.76]	0.271
			Hedges G	0.06	[-0.04; 0.16]	
Anastrozole	284 | -4.11 (0.69)	281 | -6.02 (0.70)	Difference	1.91	[-0.02; 3.85]	0.053
			Hedges G	0.16	[-0.00; 0.33]	
Prior neo/adjuvant chemotherapy						
Interaction test	**p = 0.186**					
Yes	977 | -4.40 (0.36)	924 | -5.59 (0.37)	Difference	1.20	[0.18; 2.21]	0.021
			Hedges G	0.11	[0.02; 0.20]	
No	75 | -9.69 (1.21)	77 | -8.82 (1.23)	Difference	-0.87	[-4.28; 2.55]	0.617
			Hedges G	-0.08	[-0.40; 0.24]	
Prior adjuvant chemotherapy						
Interaction test	**p = 0.764**					
Yes	493 | -3.41 (0.49)	459 | -4.53 (0.51)	Difference	1.13	[-0.26; 2.52]	0.112
			Hedges G	0.10	[-0.02; 0.23]	
No	559 | -6.06 (0.49)	542 | -6.94 (0.50)	Difference	0.89	[-0.48; 2.25]	0.203
			Hedges G	0.08	[-0.04; 0.20]	

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1115)	ET (N = 1123)	Parameter	Esti-mate	[95% CI]	p-value
Prior neoadjuvant chemotherapy						
Interaction test	**p = 0.684**					
Yes	514 | -5.33 (0.51)	502 | -6.56 (0.51)	Difference	1.23	[-0.18; 2.64]	0.088
			Hedges G	0.11	[-0.02; 0.23]	
No	538 | -4.34 (0.48)	499 | -5.10 (0.49)	Difference	0.77	[-0.58; 2.11]	0.263
			Hedges G	0.07	[-0.05; 0.19]	
Prior endocrine therapy						
Interaction test	**p = 0.962**					
Yes	810 | -4.37 (0.40)	733 | -5.34 (0.42)	Difference	0.97	[-0.16; 2.09]	0.092
			Hedges G	0.09	[-0.01; 0.19]	
No	242 | -6.29 (0.73)	268 | -7.13 (0.69)	Difference	0.84	[-1.13; 2.81]	0.405
			Hedges G	0.07	[-0.10; 0.25]	
Prior mastectomy						
Interaction test	**p = 0.522**					
Yes	731 | -4.36 (0.40)	699 | -5.14 (0.41)	Difference	0.78	[-0.35; 1.90]	0.177
			Hedges G	0.07	[-0.03; 0.18]	
No	321 | -5.78 (0.67)	302 | -7.23 (0.70)	Difference	1.45	[-0.46; 3.36]	0.136
			Hedges G	0.12	[-0.04; 0.28]	
Prior radiotherapy						
Interaction test	**p = 0.047**					
Yes	963 | -4.74 (0.37)	918 | -6.04 (0.38)	Difference	1.30	[0.27; 2.33]	0.013
			Hedges G	0.11	[0.02; 0.20]	
No	89 | -5.83 (0.99)	83 | -3.57 (1.04)	Difference	-2.26	[-5.10; 0.57]	0.117
			Hedges G	-0.24	[-0.54; 0.06]	

N: Number of patients
N': Number of patients in the analysis
CI: Confidence interval
SD: Standard deviation
LS Mean: Least square mean
SE: Standard error
MMRM: Mixed model for repeated measures
ET: Endocrine therapy (Anastrozole/Letrozole + Goserelin)
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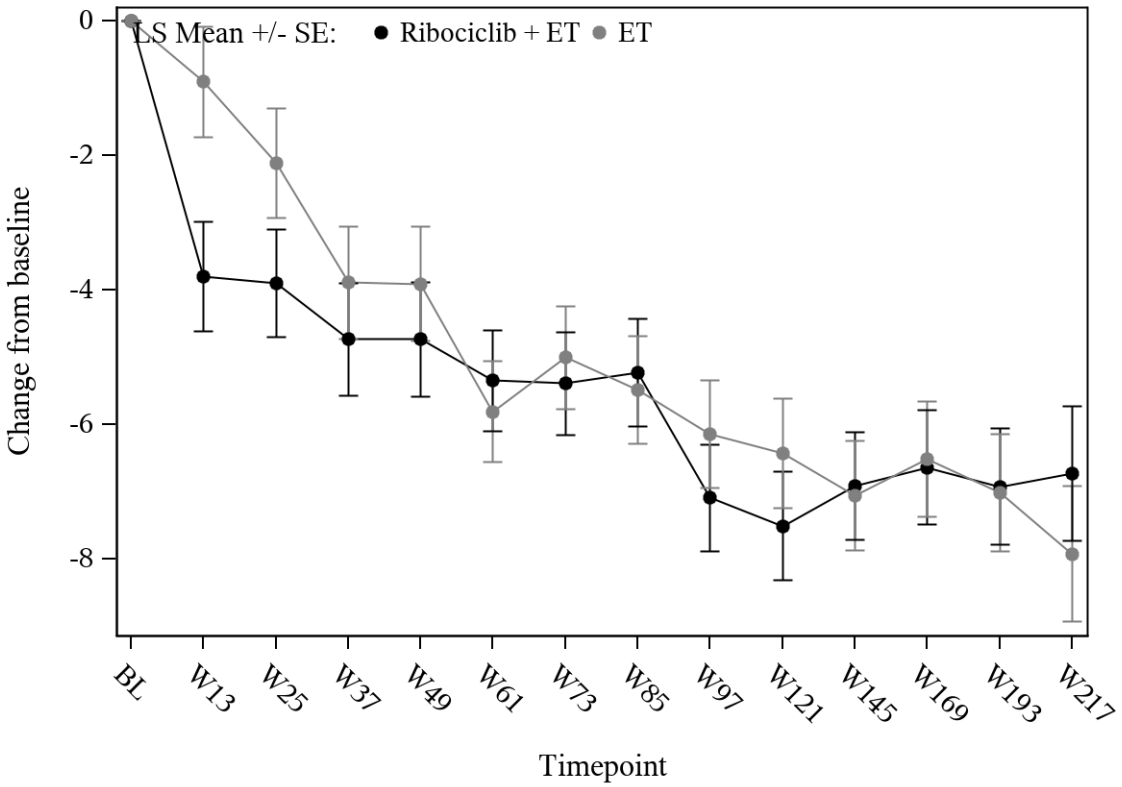
Analysis method for interaction test:
p-value from MMRM with unstructured covariance matrix:
change from baseline = treatment + visit + treatment * visit + subgroup factor + treatment * subgroup factor + subgroup factor * visit + treatment * subgroup factor * visit + baseline value
If the model did not converge for a parameter*subgroup factor, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry. If the model did still not converge, interactions were removed in the order treatment * subgroup factor * visit, subgroup factor * visit.

Analysis methods for within-subgroup analysis:
Adjusted mean (LS Mean) change from baseline and overall effect obtained from MMRM with unstructured covariance matrix:
change from baseline = treatment + visit + treatment * visit + baseline value
ET was the reference group for treatment group comparison.
If the model did not converge for a parameter*subgroup factor, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry.

Patients with an evaluable baseline score and at least one evaluable post-baseline score were included in the analysis.
All data collected were included in the analysis, including assessments at confirmation of first recurrence and thereafter, as long as there were at least 50 patients in each treatment group at a visit in the overall (sub-)population.

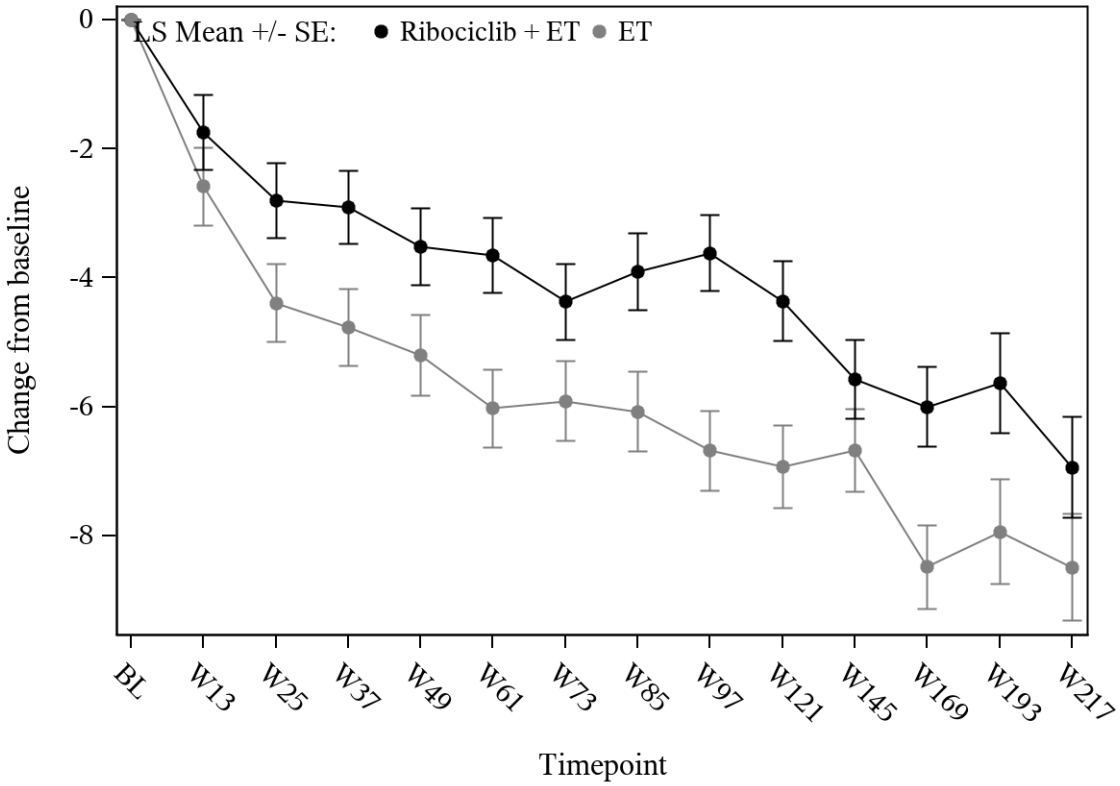
Figure 5-2.3.2.1 QLQ-BR23 - Breast Symptoms: line chart of change from baseline - subgroup analysis (Full Analysis Set)

QLQ-BR23 - Breast Symptoms
AJCC Anatomic Stage Group: Group I/II



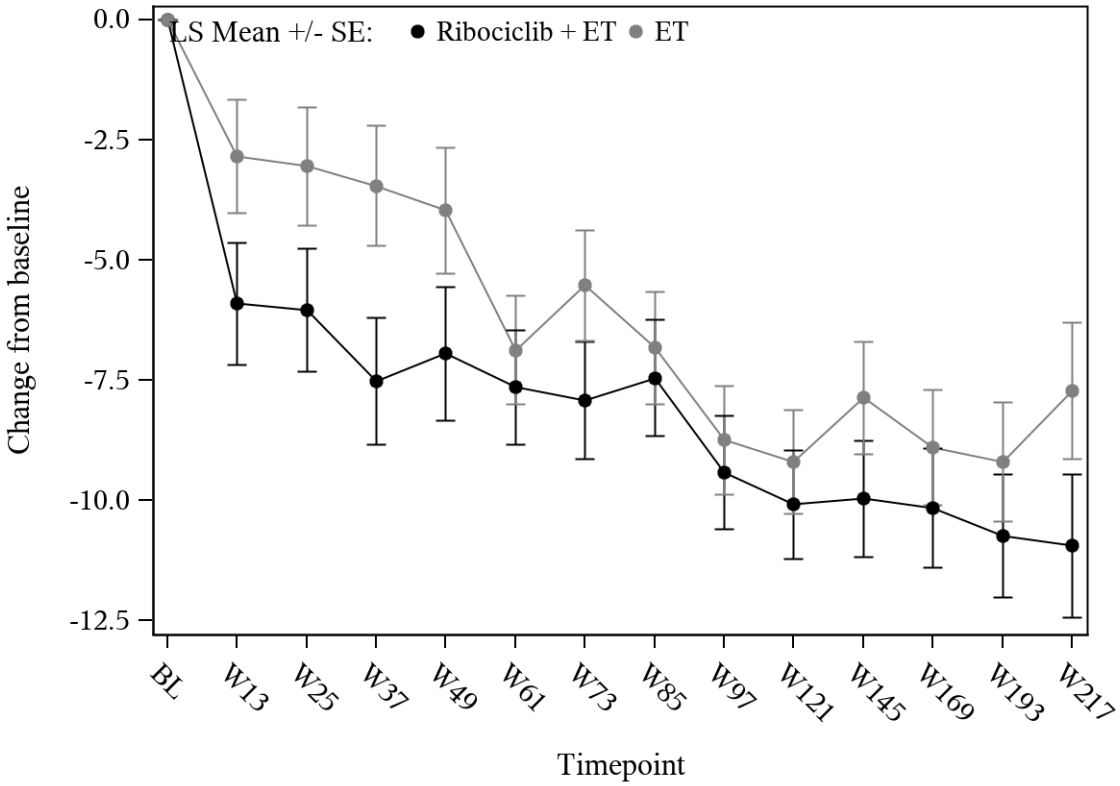
Ribociclib + ET	392	384	366	364	358	358	351	352	350	340	338	314	314	175
ET	395	377	348	357	365	356	358	342	340	331	318	312	300	175

QLQ-BR23 - Breast Symptoms
AJCC Anatomic Stage Group: Group III



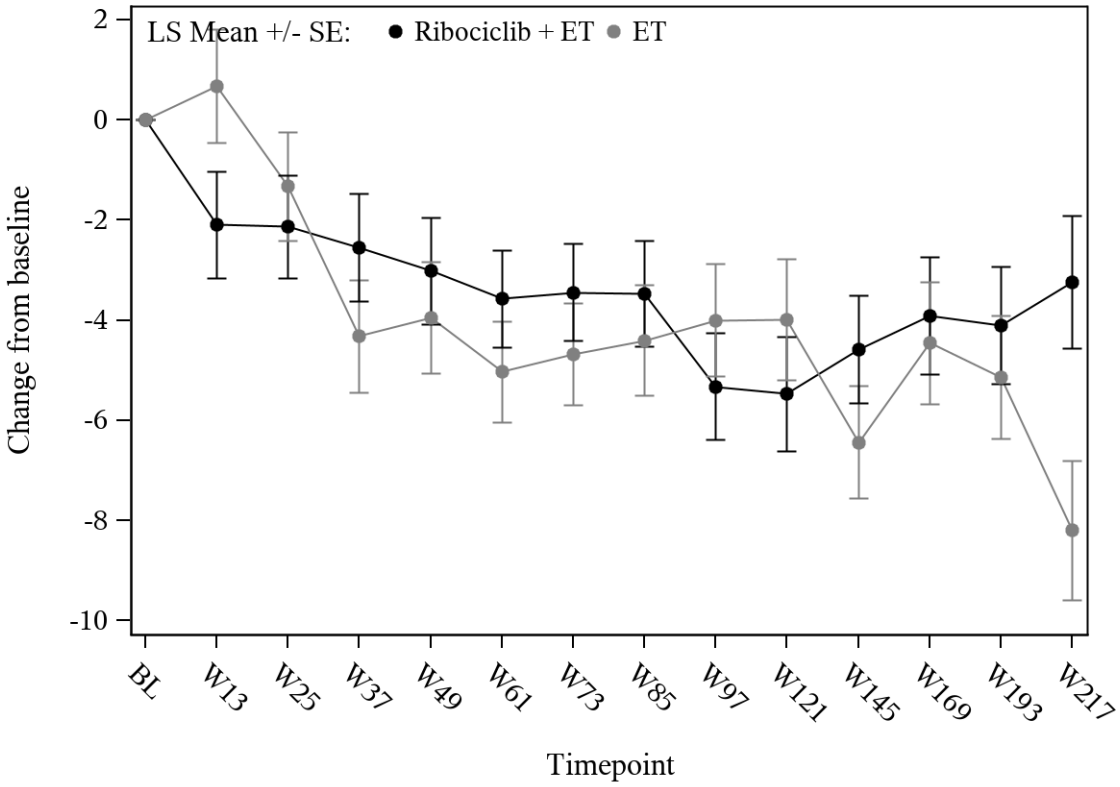
Ribociclib + ET	660	631	605	610	605	597	593	579	574	553	551	406	287	165
ET	606	577	569	546	550	543	534	531	514	506	483	362	262	145

QLQ-BR23 - Breast Symptoms
Anatomic stages: IA/IB/IIA



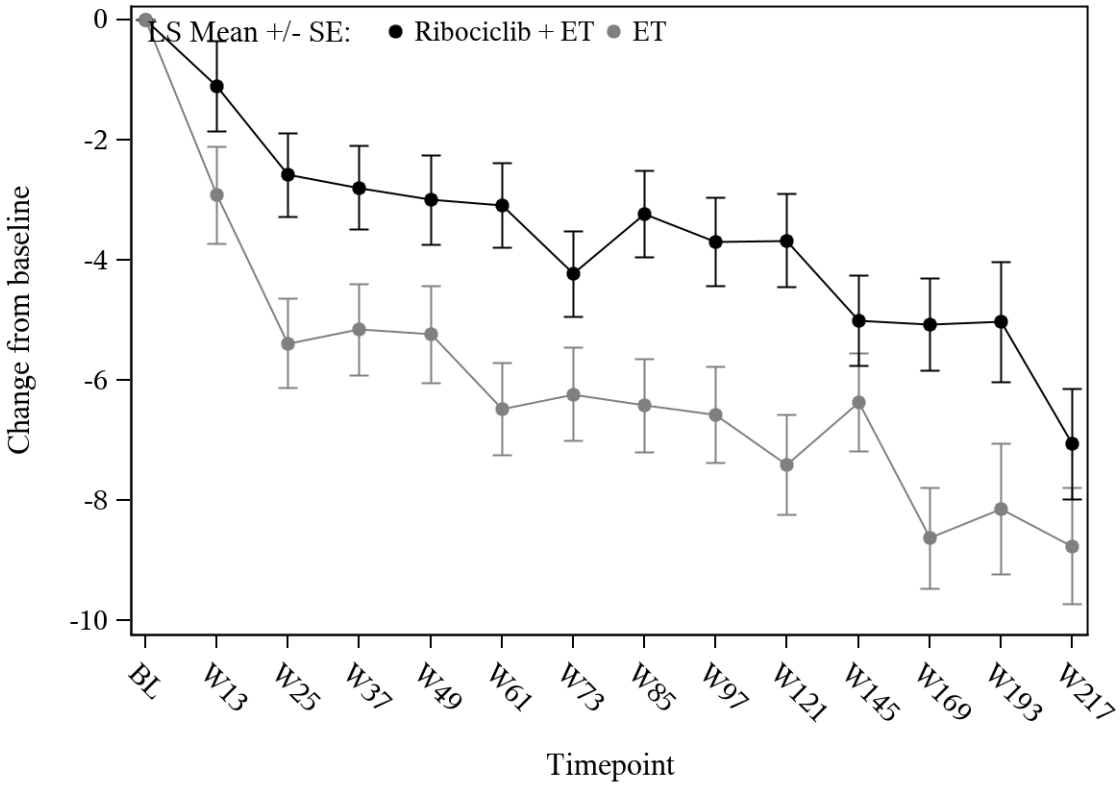
Ribociclib + ET	163	159	154	156	151	155	150	150	147	142	143	138	134	79
ET	188	183	161	166	170	166	169	162	160	156	149	146	140	88

QLQ-BR23 - Breast Symptoms
Anatomic stages: IIB



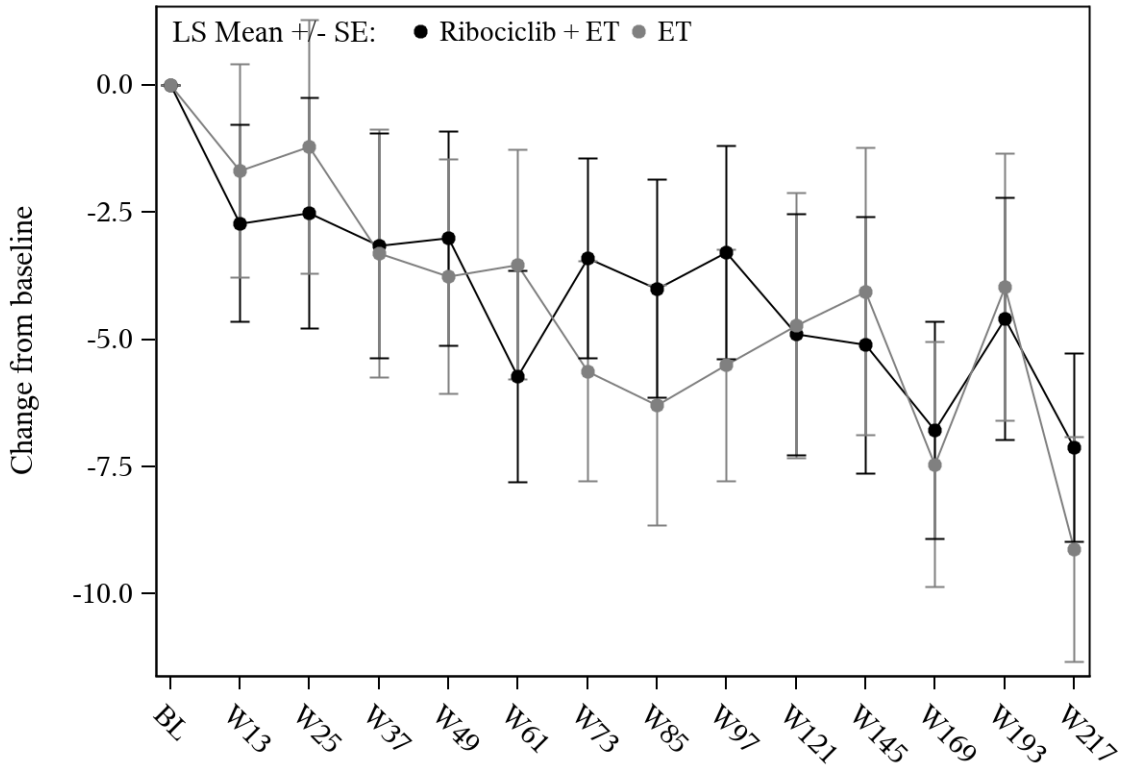
Ribociclib + ET	229	225	212	208	207	203	201	202	203	198	195	176	180	96
ET	207	194	187	191	195	190	189	180	180	175	169	166	160	87

QLQ-BR23 - Breast Symptoms
Anatomic stages: IIIA



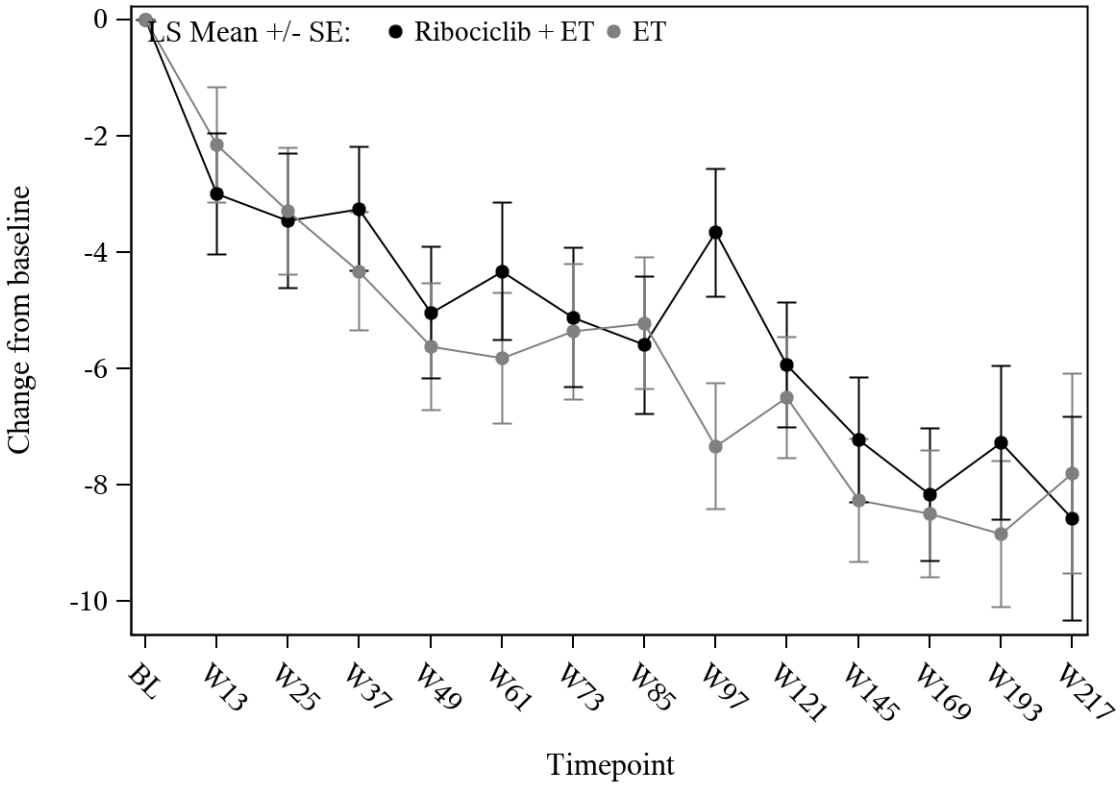
Ribociclib + ET	430	409	387	394	389	387	382	370	368	349	355	266	190	109
ET	368	349	342	329	331	327	327	324	314	307	301	222	162	98

QLQ-BR23 - Breast Symptoms
Anatomic stages: IIIB



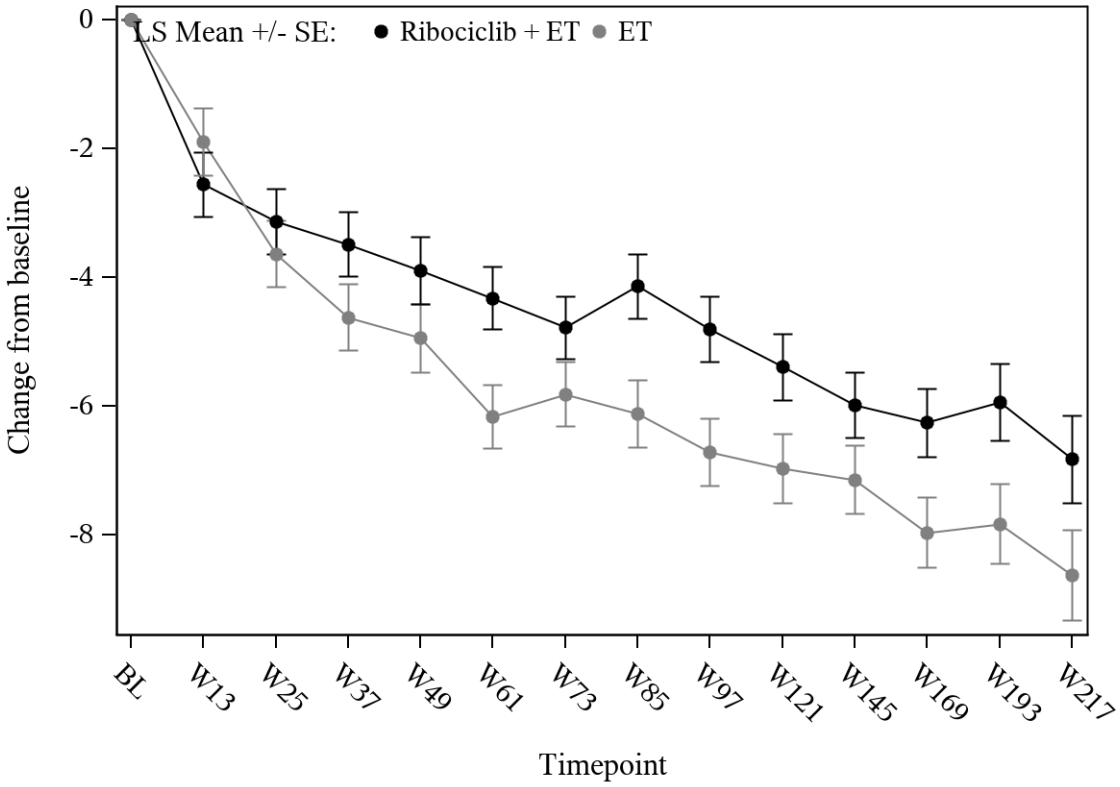
Ribociclib + ET	62	59	60	60	59	57	57	58	55	56	57	45	31	23
ET	52	52	48	47	49	49	46	48	47	46	42	33	25	13

QLQ-BR23 - Breast Symptoms
Anatomic stages: IIIC



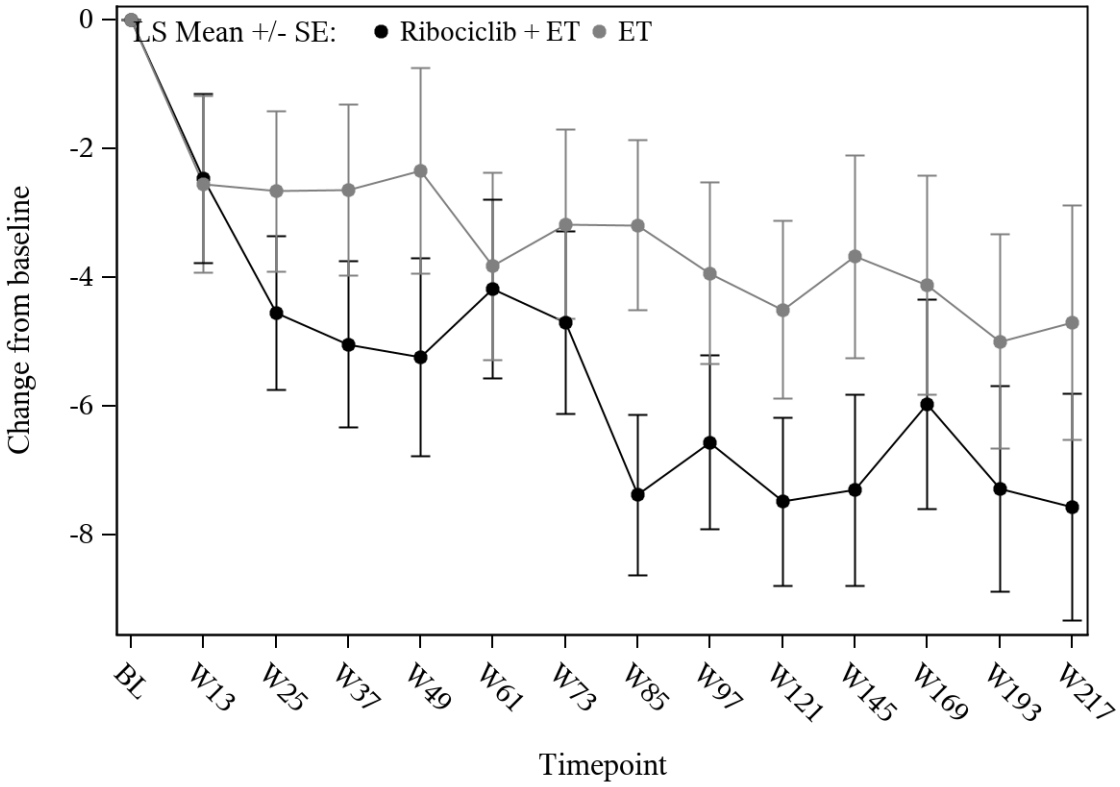
Ribociclib + ET	168	163	158	156	157	153	154	151	151	148	139	95	66	33
ET	186	176	179	170	170	167	161	159	153	153	140	107	75	34

QLQ-BR23 - Breast Symptoms
Prior radiotherapy: Yes



Ribociclib + ET	963	928	887	891	881	870	864	849	847	814	813	650	535	297
ET	918	875	841	824	838	822	816	801	782	767	735	609	500	279

QLQ-BR23 - Breast Symptoms
Prior radiotherapy: No



Ribociclib + ET	89	87	84	83	82	85	80	82	77	79	76	70	66	43
ET	83	79	76	79	77	77	76	72	72	70	66	65	62	41

Table 5-2.3.3.1 QLQ-BR23 - Arm Symptoms: change from baseline analysis - subgroup analysis (Full Analysis Set)

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1115)	ET (N = 1123)	Parameter	Esti-mate	[95% CI]	p-value
QLQ-BR23 - Arm Symptoms						
	N' | LS Mean (SE)	**N' | LS Mean (SE)**				
Region						
Interaction test	**p = 0.130**					
NA/WE/O	594 | 0.08 (0.61)	573 | -2.58 (0.62)	Difference	2.66	[0.96; 4.37]	0.002
			Hedges G	0.18	[0.06; 0.29]	
ROW	460 | -0.66 (0.64)	427 | -1.37 (0.67)	Difference	0.71	[-1.12; 2.53]	0.445
			Hedges G	0.05	[-0.08; 0.18]	
Geographical region						
Interaction test	**p = 0.167**					
Europe	615 | 0.87 (0.59)	591 | -1.78 (0.60)	Difference	2.66	[1.00; 4.31]	0.002
			Hedges G	0.18	[0.07; 0.29]	
North America/Australia	201 | -1.12 (0.87)	174 | -3.84 (0.95)	Difference	2.72	[0.20; 5.24]	0.035
			Hedges G	0.22	[0.02; 0.42]	
Asia	175 | -2.11 (1.05)	166 | -2.27 (1.08)	Difference	0.16	[-2.81; 3.13]	0.918
			Hedges G	0.01	[-0.20; 0.22]	
Latin America	63 | -1.77 (2.08)	69 | -0.26 (1.96)	Difference	-1.51	[-7.16; 4.15]	0.599
			Hedges G	-0.09	[-0.43; 0.25]	
Age group 1 at randomization						
Interaction test	**N.E.**					
<45	521 | -0.38 (0.62)	459 | -2.50 (0.67)	Difference	2.12	[0.33; 3.91]	0.020
			Hedges G	0.15	[0.02; 0.27]	
45 to 54	513 | -0.13 (0.62)	514 | -1.76 (0.62)	Difference	1.63	[-0.09; 3.34]	0.063
			Hedges G	0.12	[-0.01; 0.24]	
55 to 64	20 | 1.66 (3.78)	27 | -1.67 (3.26)	Difference	3.33	[-6.74; 13.40]	0.508
			Hedges G	0.20	[-0.38; 0.78]	
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)						
Interaction test	**p = 0.765**					
<Median	521 | -0.40 (0.63)	459 | -2.55 (0.67)	Difference	2.14	[0.34; 3.95]	0.020
			Hedges G	0.15	[0.02; 0.27]	
≥Median	533 | -0.06 (0.62)	541 | -1.74 (0.62)	Difference	1.68	[-0.03; 3.40]	0.055
			Hedges G	0.12	[-0.00; 0.24]	

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1115)	**ET (N = 1123)**	**Parameter**	**Esti-mate**	**[95% CI]**	**p-value**
Race						
Interaction test	**p = 0.346**					
Asian	206 | -1.82 (0.98)	180 | -2.54 (1.05)	Difference	0.72	[-2.11; 3.54]	0.617
			Hedges G	0.05	[-0.15; 0.25]	
Non-Asian	797 | 0.06 (0.51)	768 | -2.08 (0.52)	Difference	2.14	[0.72; 3.57]	0.003
			Hedges G	0.15	[0.05; 0.25]	
BMI at screening						
Interaction test	**p = 0.950**					
≥25	525 | 1.35 (0.67)	484 | -0.36 (0.69)	Difference	1.71	[-0.18; 3.59]	0.077
			Hedges G	0.11	[-0.01; 0.24]	
<25	517 | -2.08 (0.58)	505 | -3.70 (0.59)	Difference	1.62	[-0.00; 3.24]	0.050
			Hedges G	0.12	[-0.00; 0.25]	
AJCC Anatomic Stage Group						
Interaction test	**p = 0.148**					
Group I/II	393 | -0.74 (0.73)	394 | -1.16 (0.74)	Difference	0.42	[-1.62; 2.46]	0.687
			Hedges G	0.03	[-0.11; 0.17]	
Group III	661 | -0.14 (0.55)	606 | -2.56 (0.58)	Difference	2.42	[0.84; 3.99]	0.003
			Hedges G	0.17	[0.06; 0.28]	
Anatomic stages						
Interaction test	**p = 0.353**					
IA/IB/IIA	163 | -1.84 (1.09)	187 | -0.94 (1.03)	Difference	-0.90	[-3.85; 2.06]	0.550
			Hedges G	-0.06	[-0.27; 0.15]	
IIB	230 | 0.09 (1.00)	207 | -1.33 (1.05)	Difference	1.43	[-1.42; 4.27]	0.325
			Hedges G	0.09	[-0.09; 0.28]	
IIIA	431 | 0.13 (0.69)	368 | -3.00 (0.75)	Difference	3.13	[1.13; 5.13]	0.002
			Hedges G	0.22	[0.08; 0.36]	
IIIB	62 | -0.19 (2.18)	52 | -1.78 (2.38)	Difference	1.60	[-4.89; 8.08]	0.627
			Hedges G	0.09	[-0.28; 0.46]	
IIIC	168 | -0.57 (1.00)	186 | -1.89 (0.96)	Difference	1.32	[-1.41; 4.05]	0.343
			Hedges G	0.10	[-0.11; 0.31]	
Nodal status						
Interaction test	**p = 0.871**					
N0	83 | 0.11 (1.38)	110 | -1.70 (1.21)	Difference	1.82	[-1.82; 5.45]	0.325
			Hedges G	0.14	[-0.14; 0.43]	
N1-N3	971 | -0.37 (0.47)	887 | -2.08 (0.49)	Difference	1.72	[0.39; 3.04]	0.011
			Hedges G	0.12	[0.03; 0.21]	

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1115)	**ET (N = 1123)**	**Parameter**	**Esti-mate**	**[95% CI]**	**p-value**
Histological grade at time of surgery						
Interaction test	**p = 0.509**					
Grade 1	105 | -0.65 (1.43)	96 | -0.41 (1.52)	Difference	-0.25	[-4.37; 3.87]	0.905
			Hedges G	-0.02	[-0.29; 0.26]	
Grade 2	577 | -0.86 (0.59)	557 | -3.30 (0.61)	Difference	2.44	[0.77; 4.11]	0.004
			Hedges G	0.17	[0.05; 0.29]	
Grade 3	280 | 1.32 (0.85)	250 | -1.18 (0.90)	Difference	2.49	[0.06; 4.93]	0.045
			Hedges G	0.18	[0.00; 0.35]	
Histological subtype						
Interaction test	**p = 0.314**					
Ductal	819 | -0.48 (0.50)	784 | -1.99 (0.52)	Difference	1.51	[0.10; 2.93]	0.036
			Hedges G	0.10	[0.01; 0.20]	
Lobular	167 | 0.55 (1.13)	154 | -0.99 (1.16)	Difference	1.54	[-1.64; 4.73]	0.341
			Hedges G	0.11	[-0.11; 0.33]	
Other	68 | 0.10 (1.62)	62 | -5.37 (1.70)	Difference	5.47	[0.83; 10.10]	0.021
			Hedges G	0.41	[0.06; 0.76]	
Ki67 status from surgical specimen						
Interaction test	**p = 0.612**					
Ki67≤20	509 | -0.15 (0.66)	517 | -1.65 (0.65)	Difference	1.50	[-0.31; 3.31]	0.105
			Hedges G	0.10	[-0.02; 0.22]	
Ki67>20	397 | -0.14 (0.73)	356 | -2.31 (0.77)	Difference	2.17	[0.08; 4.25]	0.042
			Hedges G	0.15	[0.01; 0.29]	
Type of NSAI						
Interaction test	**p = 0.380**					
Letrozole	769 | -0.71 (0.51)	717 | -2.17 (0.53)	Difference	1.46	[0.01; 2.91]	0.049
			Hedges G	0.10	[0.00; 0.20]	
Anastrozole	285 | 1.03 (0.87)	281 | -1.73 (0.89)	Difference	2.76	[0.32; 5.21]	0.027
			Hedges G	0.19	[0.02; 0.35]	
Prior neo/adjuvant chemotherapy						
Interaction test	**p = 0.687**					
Yes	979 | -0.19 (0.46)	923 | -2.08 (0.47)	Difference	1.89	[0.59; 3.19]	0.004
			Hedges G	0.13	[0.04; 0.22]	
No	75 | -1.19 (1.57)	77 | -2.15 (1.59)	Difference	0.96	[-3.46; 5.39]	0.667
			Hedges G	0.07	[-0.25; 0.39]	
Prior adjuvant chemotherapy						
Interaction test	**p = 0.103**					
Yes	494 | 0.53 (0.65)	459 | -2.37 (0.67)	Difference	2.89	[1.07; 4.72]	0.002
			Hedges G	0.20	[0.07; 0.33]	
No	560 | -0.98 (0.61)	541 | -1.82 (0.62)	Difference	0.84	[-0.87; 2.55]	0.334
			Hedges G	0.06	[-0.06; 0.18]	

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1115)	ET (N = 1123)	Parameter	Esti-mate	[95% CI]	p-value
Prior neoadjuvant chemotherapy						
Interaction test	**p = 0.188**					
Yes	515 | -1.12 (0.63)	501 | -2.06 (0.65)	Difference	0.94	[-0.83; 2.72]	0.298
			Hedges G	0.07	[-0.06; 0.19]	
No	539 | 0.53 (0.62)	499 | -2.04 (0.64)	Difference	2.57	[0.82; 4.32]	0.004
			Hedges G	0.18	[0.06; 0.30]	
Prior endocrine therapy						
Interaction test	**p = 0.384**					
Yes	813 | -0.26 (0.50)	732 | -2.41 (0.53)	Difference	2.15	[0.72; 3.57]	0.003
			Hedges G	0.15	[0.05; 0.25]	
No	241 | -0.26 (0.96)	268 | -1.11 (0.91)	Difference	0.85	[-1.75; 3.45]	0.522
			Hedges G	0.06	[-0.12; 0.23]	
Prior mastectomy						
Interaction test	**p = 0.596**					
Yes	733 | -0.68 (0.52)	699 | -2.71 (0.53)	Difference	2.03	[0.58; 3.49]	0.006
			Hedges G	0.15	[0.04; 0.25]	
No	321 | 0.63 (0.84)	301 | -0.68 (0.88)	Difference	1.31	[-1.09; 3.71]	0.286
			Hedges G	0.09	[-0.07; 0.24]	
Prior radiotherapy						
Interaction test	**p = 0.822**					
Yes	965 | 0.05 (0.46)	917 | -1.79 (0.48)	Difference	1.83	[0.53; 3.14]	0.006
			Hedges G	0.13	[0.04; 0.22]	
No	89 | -3.71 (1.42)	83 | -5.15 (1.49)	Difference	1.44	[-2.62; 5.51]	0.484
			Hedges G	0.11	[-0.19; 0.41]	

N: Number of patients
N': Number of patients in the analysis
CI: Confidence interval
SD: Standard deviation
LS Mean: Least square mean
SE: Standard error
MMRM: Mixed model for repeated measures
N.E.: Not estimable
ET: Endocrine therapy (Anastrozole/Letrozole + Goserelin)
.....

Analysis method for interaction test:
p-value from MMRM with unstructured covariance matrix:
change from baseline = treatment + visit + treatment * visit + subgroup factor + treatment * subgroup factor + subgroup factor * visit + treatment * subgroup factor * visit + baseline value
If the model did not converge for a parameter*subgroup factor, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry. If the model did still not converge, interactions were removed in the order treatment * subgroup factor * visit, subgroup factor * visit.

Analysis methods for within-subgroup analysis:
Adjusted mean (LS Mean) change from baseline and overall effect obtained from MMRM with unstructured covariance matrix:
change from baseline = treatment + visit + treatment * visit + baseline value
ET was the reference group for treatment group comparison.
If the model did not converge for a parameter*subgroup factor, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry.

Patients with an evaluable baseline score and at least one evaluable post-baseline score were included in the analysis.
All data collected were included in the analysis, including assessments at confirmation of first recurrence and thereafter, as long as there were at least 50 patients in each treatment group at a visit in the overall (sub-)population.

Table 5-2.3.4.1 QLQ-BR23 - Being Upset With Hair Loss: change from baseline analysis - subgroup analysis (Full Analysis Set)

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1115)	ET (N = 1123)	Parameter	Esti-mate	[95% CI]	p-value
QLQ-BR23 - Being Upset With Hair Loss						
	N' | LS Mean (SE)	N' | LS Mean (SE)				
Region						
Interaction test	**p = 0.082**					
NA/WE/O	145 | 7.52 (2.07)	117 | 0.54 (2.35)	Difference	6.98	[0.80; 13.16]	0.027
			Hedges G	0.28	[0.03; 0.52]	
ROW	154 | 1.10 (1.68)	139 | 1.04 (1.77)	Difference	0.06	[-4.74; 4.87]	0.979
			Hedges G	0.00	[-0.23; 0.23]	
Geographical region						
Interaction test	**p = 0.392**					
Europe	131 | 2.70 (2.16)	129 | -0.01 (2.20)	Difference	2.72	[-3.35; 8.78]	0.379
			Hedges G	0.11	[-0.13; 0.35]	
North America/Australia	57 | 5.29 (2.97)	30 | -1.78 (4.20)	Difference	7.06	[-3.16; 17.29]	0.173
			Hedges G	0.31	[-0.13; 0.75]	
Asia	82 | 2.75 (2.27)	73 | 2.64 (2.42)	Difference	0.11	[-6.44; 6.67]	0.972
			Hedges G	0.01	[-0.31; 0.32]	
Latin America	29 | 9.31 (3.08)	24 | -0.16 (3.44)	Difference	9.47	[0.13; 18.80]	0.047
			Hedges G	0.56	[0.01; 1.11]	
Age group 1 at randomization						
Interaction test	**p = 0.871**					
<45	143 | 3.27 (1.42)	131 | 0.75 (1.50)	Difference	2.53	[-1.54; 6.60]	0.223
			Hedges G	0.15	[-0.09; 0.39]	
45 to 54	150 | 4.79 (1.59)	117 | 1.56 (1.85)	Difference	3.23	[-1.58; 8.05]	0.188
			Hedges G	0.16	[-0.08; 0.41]	
55 to 64	6 | 18.30 (8.53)	8 | 22.99 (6.49)	Difference	-4.68	[-29.03; 19.66]	0.680
			Hedges G	-0.23	[-1.29; 0.83]	
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)						
Interaction test	**p = 0.902**					
<Median	143 | 3.20 (1.79)	131 | 0.03 (1.88)	Difference	3.17	[-1.93; 8.27]	0.223
			Hedges G	0.15	[-0.09; 0.39]	
≥Median	156 | 5.04 (1.91)	125 | 1.78 (2.16)	Difference	3.26	[-2.43; 8.94]	0.260
			Hedges G	0.14	[-0.10; 0.37]	

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1115)	**ET (N = 1123)**	**Parameter**	**Esti-mate**	**[95% CI]**	**p-value**
Race						
Interaction test	**p = 0.896**					
Asian	96 | 3.77 (2.26)	77 | 1.86 (2.53)	Difference	1.91	[-4.78; 8.60]	0.574
			Hedges G	0.09	[-0.21; 0.39]	
Non-Asian	195 | 3.52 (1.64)	170 | 0.95 (1.77)	Difference	2.57	[-2.18; 7.32]	0.288
			Hedges G	0.11	[-0.09; 0.32]	
BMI at screening						
Interaction test	**p = 0.551**					
≥25	159 | 5.96 (1.86)	131 | 3.81 (2.03)	Difference	2.15	[-3.28; 7.58]	0.436
			Hedges G	0.09	[-0.14; 0.32]	
<25	139 | 2.05 (1.90)	120 | -2.32 (2.09)	Difference	4.37	[-1.18; 9.92]	0.122
			Hedges G	0.19	[-0.05; 0.44]	
AJCC Anatomic Stage Group						
Interaction test	**p = 0.342**					
Group I/II	90 | 5.06 (2.59)	97 | 3.25 (2.54)	Difference	1.81	[-5.39; 9.01]	0.620
			Hedges G	0.07	[-0.21; 0.36]	
Group III	209 | 4.33 (1.50)	159 | -0.64 (1.72)	Difference	4.96	[0.47; 9.45]	0.030
			Hedges G	0.23	[0.02; 0.44]	
Anatomic stages						
Interaction test	**p = 0.764**					
IA/IB/IIA	46 | 5.37 (2.80)	48 | 6.83 (2.86)	Difference	-1.46	[-9.42; 6.50]	0.717
			Hedges G	-0.08	[-0.48; 0.33]	
IIB	44 | 5.15 (3.38)	49 | 2.49 (3.28)	Difference	2.66	[-6.81; 12.13]	0.578
			Hedges G	0.12	[-0.29; 0.52]	
IIIA	125 | 3.86 (1.53)	97 | -2.36 (1.77)	Difference	6.22	[1.61; 10.83]	0.008
			Hedges G	0.36	[0.09; 0.63]	
IIIB	21 | 8.82 (5.11)	10 | 4.85 (7.18)	Difference	3.98	[-14.35; 22.30]	0.660
			Hedges G	0.17	[-0.58; 0.92]	
IIIC	63 | 3.21 (1.96)	52 | 1.93 (2.15)	Difference	1.27	[-4.48; 7.03]	0.662
			Hedges G	0.08	[-0.29; 0.45]	
Nodal status						
Interaction test	**p = 0.742**					
N0	26 | 6.95 (3.60)	28 | 6.48 (3.36)	Difference	0.47	[-9.49; 10.43]	0.925
			Hedges G	0.03	[-0.51; 0.56]	
N1-N3	273 | 4.02 (1.40)	227 | 0.52 (1.55)	Difference	3.50	[-0.59; 7.60]	0.093
			Hedges G	0.15	[-0.03; 0.33]	

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1115)	**ET (N = 1123)**	**Parameter**	**Esti-mate**	**[95% CI]**	**p-value**
Histological grade at time of surgery						
Interaction test	**p = 0.630**					
Grade 1	32 | 6.28 (4.18)	25 | 7.70 (4.86)	Difference	-1.42	[-14.31; 11.47]	0.826
			Hedges G	-0.06	[-0.58; 0.46]	
Grade 2	167 | 3.44 (1.79)	143 | 0.23 (1.97)	Difference	3.21	[-2.03; 8.45]	0.229
			Hedges G	0.14	[-0.09; 0.36]	
Grade 3	76 | 6.39 (2.55)	60 | 3.01 (2.86)	Difference	3.39	[-4.18; 10.96]	0.377
			Hedges G	0.15	[-0.19; 0.49]	
Histological subtype						
Interaction test	**p = 0.620**					
Ductal	243 | 4.60 (1.43)	199 | 0.89 (1.60)	Difference	3.71	[-0.52; 7.93]	0.086
			Hedges G	0.16	[-0.02; 0.35]	
Lobular	34 | -0.09 (4.65)	32 | 2.54 (4.79)	Difference	-2.63	[-16.10; 10.84]	0.698
			Hedges G	-0.10	[-0.58; 0.39]	
Other	22 | 2.94 (4.21)	25 | -1.46 (3.95)	Difference	4.40	[-7.28; 16.08]	0.452
			Hedges G	0.22	[-0.35; 0.80]	
Ki67 status from surgical specimen						
Interaction test	**p = 0.322**					
Ki67≤20	149 | 5.42 (1.97)	141 | 0.97 (2.04)	Difference	4.46	[-1.13; 10.05]	0.118
			Hedges G	0.18	[-0.05; 0.42]	
Ki67>20	111 | 1.77 (1.94)	96 | 1.57 (2.12)	Difference	0.20	[-5.46; 5.87]	0.943
			Hedges G	0.01	[-0.26; 0.28]	
Type of NSAI						
Interaction test	**p = 0.358**					
Letrozole	214 | 5.63 (1.56)	184 | 3.43 (1.69)	Difference	2.20	[-2.33; 6.72]	0.341
			Hedges G	0.10	[-0.10; 0.29]	
Anastrozole	85 | 0.23 (2.45)	71 | -5.60 (2.74)	Difference	5.83	[-1.44; 13.10]	0.115
			Hedges G	0.25	[-0.06; 0.57]	
Prior neo/adjuvant chemotherapy						
Interaction test	**p = 0.807**					
Yes	272 | 3.24 (1.38)	231 | 0.08 (1.51)	Difference	3.17	[-0.86; 7.19]	0.123
			Hedges G	0.14	[-0.04; 0.31]	
No	27 | 15.29 (4.12)	25 | 6.35 (4.36)	Difference	8.93	[-3.31; 21.18]	0.149
			Hedges G	0.41	[-0.14; 0.96]	
Prior adjuvant chemotherapy						
Interaction test	**p = 0.939**					
Yes	146 | 3.16 (1.93)	126 | 0.03 (2.10)	Difference	3.13	[-2.48; 8.74]	0.274
			Hedges G	0.13	[-0.11; 0.37]	
No	153 | 5.23 (1.82)	130 | 1.74 (1.99)	Difference	3.49	[-1.82; 8.81]	0.197
			Hedges G	0.15	[-0.08; 0.39]	

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1115)	**ET (N = 1123)**	**Parameter**	**Esti-mate**	**[95% CI]**	**p-value**
Prior neoadjuvant chemotherapy						
Interaction test	**p = 0.756**					
Yes	138 | 3.01 (1.85)	121 | -0.81 (1.98)	Difference	3.82	[-1.52; 9.15]	0.160
			Hedges G	0.18	[-0.07; 0.42]	
No	161 | 5.08 (1.86)	135 | 2.27 (2.06)	Difference	2.81	[-2.66; 8.29]	0.312
			Hedges G	0.12	[-0.11; 0.35]	
Prior endocrine therapy						
Interaction test	**p = 0.168**					
Yes	217 | 3.30 (1.51)	177 | 1.51 (1.69)	Difference	1.79	[-2.67; 6.24]	0.431
			Hedges G	0.08	[-0.12; 0.28]	
No	82 | 7.50 (2.77)	79 | -0.60 (2.82)	Difference	8.11	[0.28; 15.93]	0.042
			Hedges G	0.32	[0.01; 0.63]	
Prior mastectomy						
Interaction test	**p = 0.068**					
Yes	203 | 4.29 (1.62)	181 | -1.20 (1.74)	Difference	5.49	[0.80; 10.18]	0.022
			Hedges G	0.24	[0.03; 0.44]	
No	96 | 3.71 (2.29)	75 | 5.94 (2.58)	Difference	-2.23	[-9.04; 4.58]	0.518
			Hedges G	-0.10	[-0.40; 0.20]	
Prior radiotherapy						
Interaction test	**p = 0.986**					
Yes	275 | 4.77 (1.38)	231 | 1.57 (1.51)	Difference	3.21	[-0.81; 7.23]	0.118
			Hedges G	0.14	[-0.04; 0.32]	
No	24 | -3.31 (4.68)	25 | -5.71 (4.62)	Difference	2.40	[-10.90; 15.70]	0.718
			Hedges G	0.10	[-0.46; 0.66]	

N: Number of patients
N': Number of patients in the analysis
CI: Confidence interval
SD: Standard deviation
LS Mean: Least square mean
SE: Standard error
MMRM: Mixed model for repeated measures
ET: Endocrine therapy (Anastrozole/Letrozole + Goserelin)
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Analysis method for interaction test:
p-value from MMRM with unstructured covariance matrix:
change from baseline = treatment + visit + treatment * visit + subgroup factor + treatment * subgroup factor + subgroup factor * visit + treatment * subgroup factor * visit + baseline value
If the model did not converge for a parameter*subgroup factor, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry. If the model did still not converge, interactions were removed in the order treatment * subgroup factor * visit, subgroup factor * visit.

Analysis methods for within-subgroup analysis:
Adjusted mean (LS Mean) change from baseline and overall effect obtained from MMRM with unstructured covariance matrix:
change from baseline = treatment + visit + treatment * visit + baseline value
ET was the reference group for treatment group comparison.
If the model did not converge for a parameter*subgroup factor, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry.

Patients with an evaluable baseline score and at least one evaluable post-baseline score were included in the analysis.
All data collected were included in the analysis, including assessments at confirmation of first recurrence and thereafter, as long as there were at least 50 patients in each treatment group at a visit in the overall (sub-)population.

5-2.4 EORTC QLQ-BR23 QoL

Table 5-2.4.1.1 QLQ-BR23 - Body Image: change from baseline analysis - subgroup analysis (Full Analysis Set)

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1115)	ET (N = 1123)	Parameter	Esti-mate	[95% CI]	p-value
QLQ-BR23 - Body Image						
	N' | LS Mean (SE)	N' | LS Mean (SE)				
Region						
Interaction test	**p = 0.169**					
NA/WE/O	600 | 1.47 (0.79)	573 | 3.77 (0.81)	Difference	-2.30	[-4.52; -0.08]	0.042
			Hedges G	-0.12	[-0.23; -0.00]	
ROW	460 | 3.09 (0.84)	427 | 3.04 (0.87)	Difference	0.04	[-2.33; 2.42]	0.972
			Hedges G	0.00	[-0.13; 0.13]	
Geographical region						
Interaction test	**p = 0.661**					
Europe	619 | 2.32 (0.75)	593 | 3.41 (0.77)	Difference	-1.09	[-3.21; 1.02]	0.310
			Hedges G	-0.06	[-0.17; 0.05]	
North America/Australia	203 | 2.48 (1.19)	172 | 4.86 (1.31)	Difference	-2.38	[-5.87; 1.11]	0.180
			Hedges G	-0.14	[-0.34; 0.06]	
Asia	175 | N.E.	166 | N.E.	Difference	N.E.	[N.E.]	N.E.
			Hedges G	N.E.	[N.E.]	
Latin America	63 | 6.87 (2.16)	69 | 9.31 (2.05)	Difference	-2.44	[-8.36; 3.49]	0.418
			Hedges G	-0.14	[-0.48; 0.20]	
Age group 1 at randomization						
Interaction test	**p = 0.909**					
<45	525 | N.E.	459 | N.E.	Difference	N.E.	[N.E.]	N.E.
			Hedges G	N.E.	[N.E.]	
45 to 54	515 | N.E.	514 | N.E.	Difference	N.E.	[N.E.]	N.E.
			Hedges G	N.E.	[N.E.]	
55 to 64	20 | -0.63 (3.08)	27 | 1.93 (2.75)	Difference	-2.56	[-10.87; 5.75]	0.538
			Hedges G	-0.18	[-0.76; 0.40]	
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)						
Interaction test	**p = 0.914**					
<Median	525 | 3.58 (0.81)	459 | 5.30 (0.86)	Difference	-1.72	[-4.04; 0.60]	0.147
			Hedges G	-0.09	[-0.22; 0.03]	
≥Median	535 | 0.94 (0.77)	541 | 2.22 (0.77)	Difference	-1.28	[-3.42; 0.86]	0.241
			Hedges G	-0.07	[-0.19; 0.05]	

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1115)	**ET (N = 1123)**	**Parameter**	**Esti-mate**	**[95% CI]**	**p-value**
Race						
Interaction test	**p = 0.929**					
Asian	206 | -0.13 (1.16)	180 | 1.21 (1.25)	Difference	-1.34	[-4.69; 2.00]	0.430
			Hedges G	-0.08	[-0.28; 0.12]	
Non-Asian	803 | 2.78 (0.66)	768 | 4.06 (0.68)	Difference	-1.28	[-3.13; 0.57]	0.175
			Hedges G	-0.07	[-0.17; 0.03]	
BMI at screening						
Interaction test	**p = 0.724**					
≥25	530 | 1.17 (0.88)	484 | 2.25 (0.93)	Difference	-1.08	[-3.59; 1.43]	0.398
			Hedges G	-0.05	[-0.18; 0.07]	
<25	518 | 3.07 (0.76)	505 | 4.65 (0.78)	Difference	-1.57	[-3.71; 0.57]	0.149
			Hedges G	-0.09	[-0.21; 0.03]	
AJCC Anatomic Stage Group						
Interaction test	**p = 0.459**					
Group I/II	395 | 1.67 (1.00)	396 | 2.31 (1.00)	Difference	-0.63	[-3.41; 2.15]	0.655
			Hedges G	-0.03	[-0.17; 0.11]	
Group III	665 | 2.62 (0.70)	604 | 4.31 (0.74)	Difference	-1.70	[-3.70; 0.30]	0.096
			Hedges G	-0.09	[-0.20; 0.02]	
Anatomic stages						
Interaction test	**p = 0.577**					
IA/IB/IIA	164 | 3.19 (1.43)	188 | 5.29 (1.36)	Difference	-2.10	[-5.99; 1.79]	0.290
			Hedges G	-0.11	[-0.32; 0.10]	
IIB	231 | 0.86 (1.29)	208 | -0.42 (1.35)	Difference	1.28	[-2.39; 4.95]	0.493
			Hedges G	0.07	[-0.12; 0.25]	
IIIA	433 | 3.11 (0.85)	367 | 4.90 (0.92)	Difference	-1.79	[-4.25; 0.67]	0.153
			Hedges G	-0.10	[-0.24; 0.04]	
IIIB	63 | 3.10 (2.26)	52 | 5.43 (2.49)	Difference	-2.33	[-9.01; 4.36]	0.492
			Hedges G	-0.13	[-0.50; 0.24]	
IIIC	169 | 0.72 (1.33)	185 | 3.80 (1.29)	Difference	-3.08	[-6.73; 0.56]	0.097
			Hedges G	-0.18	[-0.39; 0.03]	
Nodal status						
Interaction test	**p = 0.696**					
N0	84 | 4.47 (2.00)	110 | 6.83 (1.77)	Difference	-2.36	[-7.62; 2.90]	0.378
			Hedges G	-0.13	[-0.41; 0.16]	
N1-N3	976 | 2.02 (0.58)	887 | 3.22 (0.61)	Difference	-1.21	[-2.87; 0.45]	0.154
			Hedges G	-0.07	[-0.16; 0.02]	

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1115)	**ET (N = 1123)**	**Parameter**	**Esti-mate**	**[95% CI]**	**p-value**
Histological grade at time of surgery						
Interaction test	**p = 0.586**					
Grade 1	106 | 2.48 (1.72)	97 | 1.72 (1.82)	Difference	0.75	[-4.17; 5.68]	0.764
			Hedges G	0.04	[-0.23; 0.32]	
Grade 2	580 | 1.64 (0.77)	556 | 3.54 (0.79)	Difference	-1.91	[-4.08; 0.26]	0.085
			Hedges G	-0.10	[-0.22; 0.01]	
Grade 3	282 | 2.82 (1.11)	249 | 5.02 (1.17)	Difference	-2.20	[-5.37; 0.97]	0.173
			Hedges G	-0.12	[-0.29; 0.05]	
Histological subtype						
Interaction test	**N.E.**					
Ductal	823 | N.E.	783 | N.E.	Difference	N.E.	[N.E.]	N.E.
			Hedges G	N.E.	[N.E.]	
Lobular	168 | 3.26 (1.44)	155 | 3.76 (1.51)	Difference	-0.50	[-4.61; 3.61]	0.812
			Hedges G	-0.03	[-0.24; 0.19]	
Other	69 | 1.10 (2.30)	62 | 3.12 (2.44)	Difference	-2.02	[-8.66; 4.63]	0.549
			Hedges G	-0.11	[-0.45; 0.24]	
Ki67 status from surgical specimen						
Interaction test	**p = 0.694**					
Ki67≤20	510 | 1.55 (0.82)	518 | 3.50 (0.82)	Difference	-1.95	[-4.23; 0.33]	0.093
			Hedges G	-0.10	[-0.23; 0.02]	
Ki67>20	401 | 2.26 (0.88)	356 | 3.54 (0.94)	Difference	-1.27	[-3.81; 1.26]	0.324
			Hedges G	-0.07	[-0.21; 0.07]	
Type of NSAI						
Interaction test	**p = 0.519**					
Letrozole	775 | 2.20 (0.67)	718 | 3.28 (0.70)	Difference	-1.08	[-2.99; 0.84]	0.270
			Hedges G	-0.06	[-0.16; 0.04]	
Anastrozole	285 | 1.60 (1.13)	280 | 3.81 (1.15)	Difference	-2.21	[-5.38; 0.95]	0.170
			Hedges G	-0.12	[-0.28; 0.05]	
Prior neo/adjuvant chemotherapy						
Interaction test	**p = 0.590**					
Yes	985 | 2.56 (0.58)	922 | 4.13 (0.61)	Difference	-1.57	[-3.22; 0.08]	0.063
			Hedges G	-0.09	[-0.18; 0.00]	
No	75 | -1.87 (1.91)	78 | -1.60 (1.92)	Difference	-0.27	[-5.63; 5.09]	0.921
			Hedges G	-0.02	[-0.33; 0.30]	
Prior adjuvant chemotherapy						
Interaction test	**p = 0.822**					
Yes	495 | 3.16 (0.85)	458 | 4.60 (0.89)	Difference	-1.44	[-3.86; 0.97]	0.242
			Hedges G	-0.08	[-0.20; 0.05]	
No	565 | 1.29 (0.78)	542 | 2.68 (0.80)	Difference	-1.39	[-3.59; 0.81]	0.216
			Hedges G	-0.07	[-0.19; 0.04]	

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1115)	ET (N = 1123)	Parameter	Esti-mate	[95% CI]	p-value
Prior neoadjuvant chemotherapy						
Interaction test	**p = 0.891**					
Yes	520 | 2.06 (0.79)	501 | 3.67 (0.81)	Difference	-1.61	[-3.83; 0.61]	0.155
			Hedges G	-0.09	[-0.21; 0.03]	
No	540 | 2.36 (0.79)	499 | 3.68 (0.82)	Difference	-1.32	[-3.55; 0.91]	0.246
			Hedges G	-0.07	[-0.19; 0.05]	
Prior endocrine therapy						
Interaction test	**p = 0.671**					
Yes	816 | 2.39 (0.64)	731 | 3.67 (0.68)	Difference	-1.28	[-3.11; 0.56]	0.173
			Hedges G	-0.07	[-0.17; 0.03]	
No	244 | 1.84 (1.14)	269 | 3.49 (1.09)	Difference	-1.65	[-4.76; 1.45]	0.296
			Hedges G	-0.09	[-0.27; 0.08]	
Prior mastectomy						
Interaction test	**p = 0.053**					
Yes	737 | 2.04 (0.69)	697 | 4.33 (0.71)	Difference	-2.29	[-4.23; -0.35]	0.021
			Hedges G	-0.12	[-0.23; -0.02]	
No	323 | 2.36 (1.05)	303 | 1.66 (1.09)	Difference	0.70	[-2.27; 3.67]	0.643
			Hedges G	0.04	[-0.12; 0.19]	
Prior radiotherapy						
Interaction test	**p = 0.910**					
Yes	971 | 2.10 (0.59)	918 | 3.61 (0.61)	Difference	-1.51	[-3.17; 0.16]	0.076
			Hedges G	-0.08	[-0.17; 0.01]	
No	89 | 3.04 (2.06)	82 | 4.31 (2.16)	Difference	-1.27	[-7.16; 4.62]	0.670
			Hedges G	-0.07	[-0.37; 0.23]	

N: Number of patients
N': Number of patients in the analysis
CI: Confidence interval
SD: Standard deviation
LS Mean: Least square mean
SE: Standard error
MMRM: Mixed model for repeated measures
N.E.: Not estimable
ET: Endocrine therapy (Anastrozole/Letrozole + Goserelin)
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Analysis method for interaction test:
p-value from MMRM with unstructured covariance matrix:
change from baseline = treatment + visit + treatment * visit + subgroup factor + treatment * subgroup factor + subgroup factor * visit + treatment * subgroup factor * visit + baseline value
If the model did not converge for a parameter*subgroup factor, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry. If the model did still not converge, interactions were removed in the order treatment * subgroup factor * visit, subgroup factor * visit.

Analysis methods for within-subgroup analysis:
Adjusted mean (LS Mean) change from baseline and overall effect obtained from MMRM with unstructured covariance matrix:
change from baseline = treatment + visit + treatment * visit + baseline value
ET was the reference group for treatment group comparison.
If the model did not converge for a parameter*subgroup factor, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry.

Patients with an evaluable baseline score and at least one evaluable post-baseline score were included in the analysis.
All data collected were included in the analysis, including assessments at confirmation of first recurrence and thereafter, as long as there were at least 50 patients in each treatment group at a visit in the overall (sub-)population.

Table 5-2.4.2.1 QLQ-BR23 - Sexual Functioning: change from baseline analysis - subgroup analysis (Full Analysis Set)

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1115)	ET (N = 1123)	Parameter	Esti-mate	[95% CI]	p-value
QLQ-BR23 - Sexual Functioning						
	N' | LS Mean (SE)	N' | LS Mean (SE)				
Region						
Interaction test	**p = 0.799**					
NA/WE/O	589 | -4.01 (0.63)	568 | -3.60 (0.64)	Difference	-0.41	[-2.18; 1.35]	0.645
			Hedges G	-0.03	[-0.14; 0.09]	
ROW	458 | -6.28 (0.62)	426 | -5.53 (0.64)	Difference	-0.75	[-2.49; 1.00]	0.401
			Hedges G	-0.06	[-0.19; 0.08]	
Geographical region						
Interaction test	**p = 0.450**					
Europe	608 | -4.76 (0.60)	586 | -4.73 (0.61)	Difference	-0.03	[-1.71; 1.65]	0.974
			Hedges G	-0.00	[-0.12; 0.11]	
North America/Australia	203 | -4.83 (1.08)	174 | -2.88 (1.18)	Difference	-1.95	[-5.09; 1.19]	0.223
			Hedges G	-0.13	[-0.33; 0.08]	
Asia	175 | -4.13 (0.79)	165 | -3.77 (0.82)	Difference	-0.36	[-2.61; 1.89]	0.754
			Hedges G	-0.03	[-0.25; 0.18]	
Latin America	61 | -10.25 (1.92)	69 | -6.90 (1.79)	Difference	-3.35	[-8.55; 1.84]	0.204
			Hedges G	-0.22	[-0.57; 0.12]	
Age group 1 at randomization						
Interaction test	**p = 0.392**					
<45	518 | -5.27 (0.61)	460 | -4.60 (0.65)	Difference	-0.66	[-2.42; 1.09]	0.458
			Hedges G	-0.05	[-0.17; 0.08]	
45 to 54	510 | -4.68 (0.62)	507 | -4.44 (0.62)	Difference	-0.23	[-1.96; 1.49]	0.791
			Hedges G	-0.02	[-0.14; 0.11]	
55 to 64	19 | -6.24 (2.35)	27 | -2.28 (2.00)	Difference	-3.96	[-10.20; 2.29]	0.208
			Hedges G	-0.38	[-0.97; 0.21]	
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)						
Interaction test	**p = 0.815**					
<Median	518 | -5.33 (0.64)	460 | -4.56 (0.68)	Difference	-0.78	[-2.61; 1.06]	0.408
			Hedges G	-0.05	[-0.18; 0.07]	
≥Median	529 | -4.76 (0.62)	534 | -4.30 (0.62)	Difference	-0.46	[-2.18; 1.26]	0.600
			Hedges G	-0.03	[-0.15; 0.09]	

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1115)	**ET (N = 1123)**	**Parameter**	**Esti-mate**	**[95% CI]**	**p-value**
Race						
Interaction test	**p = 0.378**					
Asian	206 | -3.65 (0.78)	179 | -4.12 (0.84)	Difference	0.47	[-1.77; 2.71]	0.680
			Hedges G	0.04	[-0.16; 0.24]	
Non-Asian	791 | -5.19 (0.52)	764 | -4.23 (0.54)	Difference	-0.96	[-2.43; 0.51]	0.199
			Hedges G	-0.07	[-0.16; 0.03]	
BMI at screening						
Interaction test	**p = 0.767**					
≥25	517 | -5.46 (0.64)	482 | -4.66 (0.66)	Difference	-0.80	[-2.60; 1.00]	0.384
			Hedges G	-0.06	[-0.18; 0.07]	
<25	518 | -4.51 (0.63)	501 | -4.02 (0.64)	Difference	-0.48	[-2.25; 1.28]	0.592
			Hedges G	-0.03	[-0.16; 0.09]	
AJCC Anatomic Stage Group						
Interaction test	**p = 0.242**					
Group I/II	389 | -5.05 (0.73)	391 | -5.47 (0.73)	Difference	0.42	[-1.61; 2.45]	0.686
			Hedges G	0.03	[-0.11; 0.17]	
Group III	658 | -4.99 (0.56)	603 | -3.85 (0.59)	Difference	-1.13	[-2.73; 0.47]	0.166
			Hedges G	-0.08	[-0.19; 0.03]	
Anatomic stages						
Interaction test	**p = 0.632**					
IA/IB/IIA	164 | -4.58 (1.06)	185 | -4.71 (1.02)	Difference	0.13	[-2.77; 3.02]	0.932
			Hedges G	0.01	[-0.20; 0.22]	
IIB	225 | -5.39 (1.00)	206 | -6.16 (1.04)	Difference	0.77	[-2.07; 3.60]	0.596
			Hedges G	0.05	[-0.14; 0.24]	
IIIA	430 | -5.07 (0.70)	367 | -4.22 (0.76)	Difference	-0.86	[-2.89; 1.17]	0.408
			Hedges G	-0.06	[-0.20; 0.08]	
IIIB	61 | -6.98 (1.87)	52 | -7.50 (2.04)	Difference	0.52	[-4.97; 6.02]	0.851
			Hedges G	0.04	[-0.33; 0.41]	
IIIC	167 | -4.03 (1.10)	184 | -1.68 (1.06)	Difference	-2.36	[-5.38; 0.66]	0.125
			Hedges G	-0.16	[-0.37; 0.05]	
Nodal status						
Interaction test	**p = 0.819**					
N0	84 | -5.11 (1.54)	109 | -5.21 (1.35)	Difference	0.09	[-3.95; 4.13]	0.964
			Hedges G	0.01	[-0.28; 0.29]	
N1-N3	963 | -4.99 (0.47)	882 | -4.38 (0.49)	Difference	-0.61	[-1.93; 0.72]	0.370
			Hedges G	-0.04	[-0.13; 0.05]	

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1115)	**ET (N = 1123)**	**Parameter**	**Esti-mate**	**[95% CI]**	**p-value**
Histological grade at time of surgery						
Interaction test	**p = 0.029**					
Grade 1	104 | -5.94 (1.30)	97 | -7.20 (1.36)	Difference	1.26	[-2.47; 4.98]	0.506
			Hedges G	0.09	[-0.18; 0.37]	
Grade 2	572 | -5.97 (0.60)	552 | -3.89 (0.62)	Difference	-2.07	[-3.77; -0.37]	0.017
			Hedges G	-0.14	[-0.26; -0.03]	
Grade 3	279 | -2.84 (0.88)	249 | -4.39 (0.93)	Difference	1.55	[-0.97; 4.07]	0.227
			Hedges G	0.11	[-0.07; 0.28]	
Histological subtype						
Interaction test	**p = 0.423**					
Ductal	813 | -4.87 (0.48)	778 | -4.75 (0.50)	Difference	-0.12	[-1.48; 1.24]	0.864
			Hedges G	-0.01	[-0.11; 0.09]	
Lobular	166 | -4.94 (1.05)	155 | -2.58 (1.08)	Difference	-2.36	[-5.33; 0.61]	0.119
			Hedges G	-0.17	[-0.39; 0.04]	
Other	68 | -6.59 (1.92)	61 | -5.61 (2.03)	Difference	-0.97	[-6.52; 4.57]	0.728
			Hedges G	-0.06	[-0.41; 0.28]	
Ki67 status from surgical specimen						
Interaction test	**p = 0.125**					
Ki67≤20	500 | -5.81 (0.63)	516 | -4.16 (0.62)	Difference	-1.66	[-3.40; 0.08]	0.062
			Hedges G	-0.12	[-0.24; 0.01]	
Ki67>20	398 | -4.49 (0.73)	351 | -4.87 (0.79)	Difference	0.37	[-1.74; 2.48]	0.730
			Hedges G	0.03	[-0.12; 0.17]	
Type of NSAI						
Interaction test	**p = 0.315**					
Letrozole	764 | -4.65 (0.52)	711 | -4.46 (0.54)	Difference	-0.19	[-1.67; 1.28]	0.797
			Hedges G	-0.01	[-0.12; 0.09]	
Anastrozole	283 | -5.98 (0.86)	281 | -4.34 (0.88)	Difference	-1.64	[-4.06; 0.77]	0.182
			Hedges G	-0.11	[-0.28; 0.05]	
Prior neo/adjuvant chemotherapy						
Interaction test	**p = 0.891**					
Yes	972 | -4.84 (0.47)	918 | -4.29 (0.48)	Difference	-0.55	[-1.86; 0.75]	0.406
			Hedges G	-0.04	[-0.13; 0.05]	
No	75 | -7.25 (1.59)	76 | -6.29 (1.63)	Difference	-0.96	[-5.46; 3.54]	0.674
			Hedges G	-0.07	[-0.39; 0.25]	
Prior adjuvant chemotherapy						
Interaction test	**p = 0.668**					
Yes	487 | -4.04 (0.65)	454 | -3.75 (0.67)	Difference	-0.29	[-2.12; 1.55]	0.759
			Hedges G	-0.02	[-0.15; 0.11]	
No	560 | -5.86 (0.61)	540 | -5.02 (0.63)	Difference	-0.85	[-2.57; 0.88]	0.336
			Hedges G	-0.06	[-0.18; 0.06]	

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1115)	ET (N = 1123)	Parameter	Esti-mate	[95% CI]	p-value
Prior neoadjuvant chemotherapy						
Interaction test	**p = 0.718**					
Yes	515 | -5.71 (0.64)	500 | -4.90 (0.66)	Difference	-0.81	[-2.61; 0.99]	0.378
			Hedges G	-0.06	[-0.18; 0.07]	
No	532 | -4.34 (0.62)	494 | -3.98 (0.64)	Difference	-0.36	[-2.11; 1.39]	0.687
			Hedges G	-0.03	[-0.15; 0.10]	
Prior endocrine therapy						
Interaction test	**p = 0.436**					
Yes	804 | -5.17 (0.50)	728 | -4.27 (0.53)	Difference	-0.89	[-2.32; 0.54]	0.221
			Hedges G	-0.06	[-0.16; 0.04]	
No	243 | -4.55 (0.97)	266 | -4.80 (0.93)	Difference	0.24	[-2.40; 2.89]	0.856
			Hedges G	0.02	[-0.16; 0.19]	
Prior mastectomy						
Interaction test	**p = 0.931**					
Yes	729 | -4.91 (0.52)	696 | -4.31 (0.54)	Difference	-0.60	[-2.07; 0.87]	0.421
			Hedges G	-0.04	[-0.15; 0.06]	
No	318 | -5.19 (0.84)	298 | -4.72 (0.88)	Difference	-0.46	[-2.86; 1.93]	0.703
			Hedges G	-0.03	[-0.19; 0.13]	
Prior radiotherapy						
Interaction test	**p = 0.390**					
Yes	958 | -5.16 (0.47)	911 | -4.40 (0.48)	Difference	-0.76	[-2.07; 0.55]	0.255
			Hedges G	-0.05	[-0.14; 0.04]	
No	89 | -3.40 (1.58)	83 | -4.74 (1.64)	Difference	1.35	[-3.15; 5.84]	0.555
			Hedges G	0.09	[-0.21; 0.39]	

N: Number of patients
N': Number of patients in the analysis
CI: Confidence interval
SD: Standard deviation
LS Mean: Least square mean
SE: Standard error
MMRM: Mixed model for repeated measures
ET: Endocrine therapy (Anastrozole/Letrozole + Goserelin)
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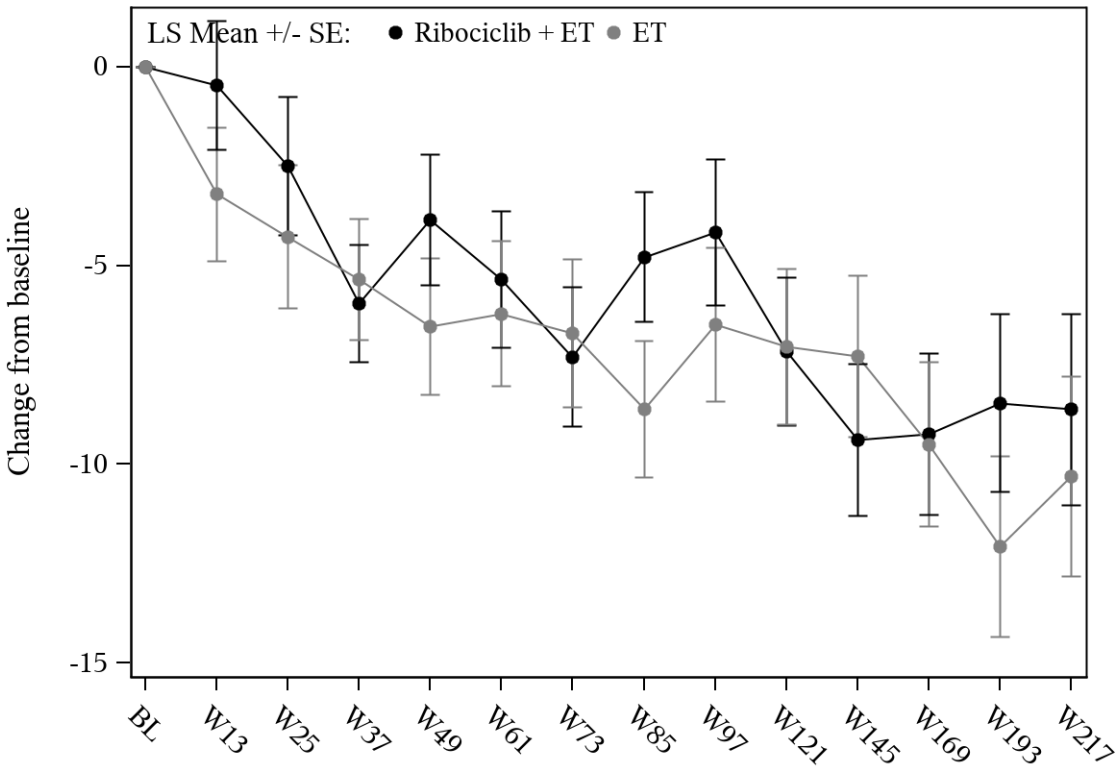
Analysis method for interaction test:
p-value from MMRM with unstructured covariance matrix:
change from baseline = treatment + visit + treatment * visit + subgroup factor + treatment * subgroup factor + subgroup factor * visit + treatment * subgroup factor * visit + baseline value
If the model did not converge for a parameter*subgroup factor, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry. If the model did still not converge, interactions were removed in the order treatment * subgroup factor * visit, subgroup factor * visit.

Analysis methods for within-subgroup analysis:
Adjusted mean (LS Mean) change from baseline and overall effect obtained from MMRM with unstructured covariance matrix:
change from baseline = treatment + visit + treatment * visit + baseline value
ET was the reference group for treatment group comparison.
If the model did not converge for a parameter*subgroup factor, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry.

Patients with an evaluable baseline score and at least one evaluable post-baseline score were included in the analysis.
All data collected were included in the analysis, including assessments at confirmation of first recurrence and thereafter, as long as there were at least 50 patients in each treatment group at a visit in the overall (sub-)population.

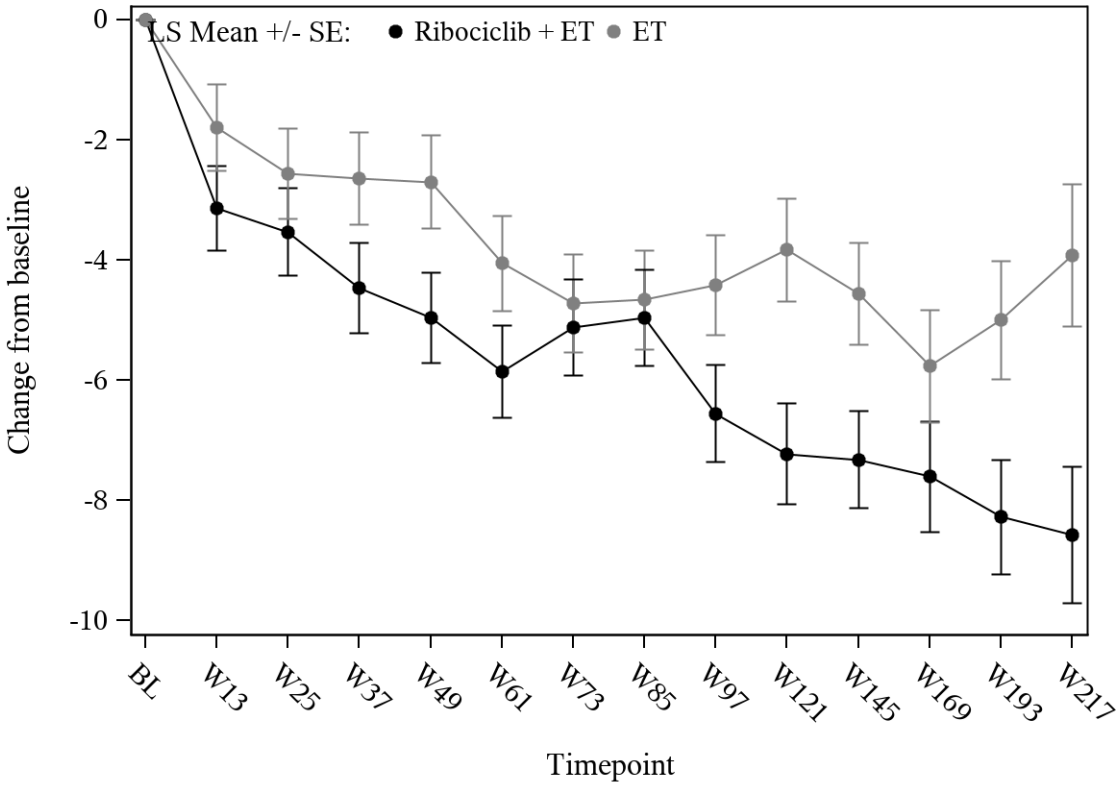
Figure 5-2.4.2.1 QLQ-BR23 - Sexual Functioning: line chart of change from baseline - subgroup analysis (Full Analysis Set)

QLQ-BR23 - Sexual Functioning
Histological grade at time of surgery: Grade 1



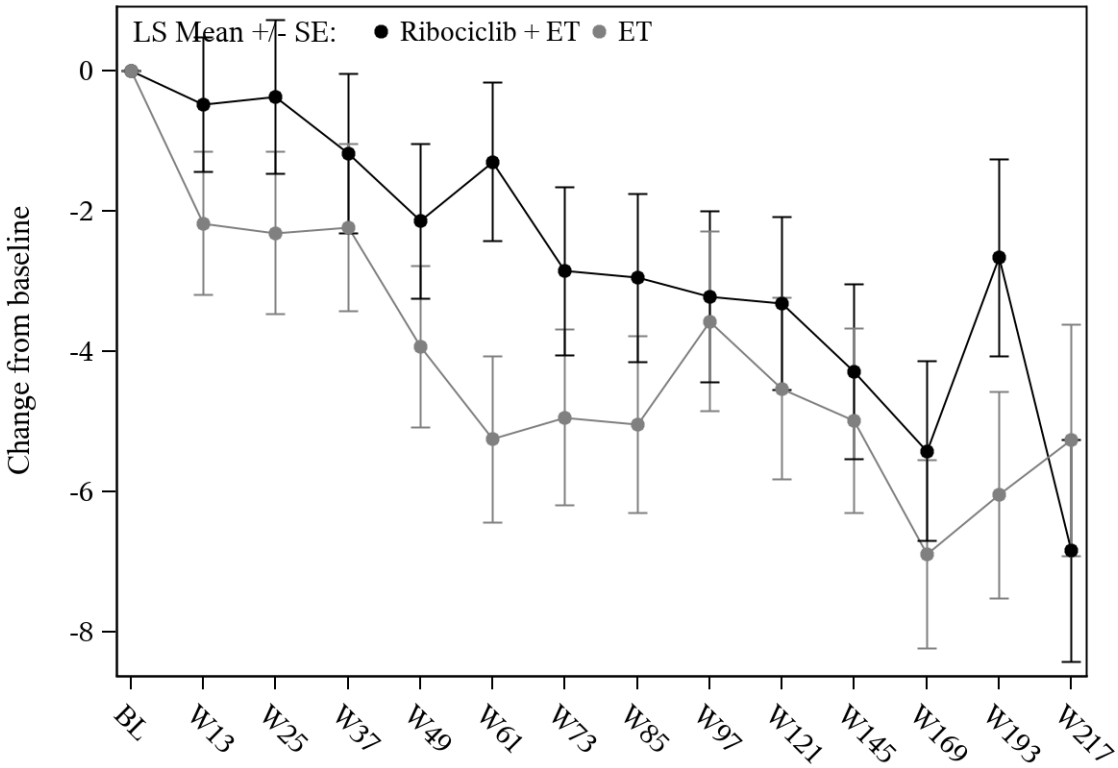
Ribociclib + ET	104	99	102	97	97	99	99	93	94	93	93	74	64	36
ET	97	91	93	91	89	86	86	86	83	85	82	76	65	33

QLQ-BR23 - Sexual Functioning
Histological grade at time of surgery: Grade 2



Ribociclib + ET	572	551	529	533	526	528	520	511	507	486	490	403	338	190
ET	552	530	498	494	502	491	486	470	466	454	443	381	306	171

QLQ-BR23 - Sexual Functioning
Histological grade at time of surgery: Grade 3



Ribociclib + ET	279	266	247	247	250	242	239	238	230	227	218	171	143	82
ET	249	236	222	223	229	223	221	214	205	203	192	155	132	77

Table 5-2.4.3.1 QLQ-BR23 - Sexual Enjoyment: change from baseline analysis - subgroup analysis (Full Analysis Set)

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1115)	ET (N = 1123)	Parameter	Esti-mate	[95% CI]	p-value
QLQ-BR23 - Sexual Enjoyment						
	N' | LS Mean (SE)	**N' | LS Mean (SE)**				
Region						
Interaction test	**p = 0.287**					
NA/WE/O	355 | -8.37 (1.03)	353 | -8.62 (1.04)	Difference	0.25	[-2.62; 3.12]	0.862
			Hedges G	0.01	[-0.13; 0.16]	
ROW	275 | -12.70 (1.20)	245 | -10.65 (1.27)	Difference	-2.06	[-5.49; 1.38]	0.240
			Hedges G	-0.10	[-0.28; 0.07]	
Geographical region						
Interaction test	**p = 0.782**					
Europe	387 | -9.84 (0.97)	361 | -9.60 (1.01)	Difference	-0.25	[-3.01; 2.51]	0.859
			Hedges G	-0.01	[-0.16; 0.13]	
North America/Australia	118 | -7.33 (1.80)	110 | -7.37 (1.88)	Difference	0.04	[-5.09; 5.18]	0.987
			Hedges G	0.00	[-0.26; 0.26]	
Asia	79 | -12.79 (1.78)	79 | -10.05 (1.83)	Difference	-2.74	[-7.78; 2.30]	0.284
			Hedges G	-0.17	[-0.48; 0.14]	
Latin America	46 | -14.24 (2.84)	48 | -11.09 (2.74)	Difference	-3.15	[-11.00; 4.70]	0.427
			Hedges G	-0.16	[-0.57; 0.24]	
Age group 1 at randomization						
Interaction test	**p = 0.860**					
<45	333 | -10.28 (0.82)	292 | -9.36 (0.89)	Difference	-0.92	[-3.30; 1.45]	0.445
			Hedges G	-0.06	[-0.22; 0.10]	
45 to 54	288 | -9.35 (0.90)	290 | -8.89 (0.91)	Difference	-0.46	[-2.98; 2.05]	0.718
			Hedges G	-0.03	[-0.19; 0.13]	
55 to 64	9 | -1.34 (4.32)	16 | -5.39 (3.20)	Difference	4.05	[-7.25; 15.36]	0.465
			Hedges G	0.31	[-0.51; 1.13]	
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)						
Interaction test	**p = 0.627**					
<Median	333 | -10.84 (1.09)	292 | -9.44 (1.17)	Difference	-1.40	[-4.53; 1.74]	0.381
			Hedges G	-0.07	[-0.23; 0.09]	
≥Median	297 | -9.57 (1.16)	306 | -9.36 (1.15)	Difference	-0.21	[-3.42; 3.01]	0.900
			Hedges G	-0.01	[-0.17; 0.15]	

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1115)	**ET (N = 1123)**	**Parameter**	**Esti-mate**	**[95% CI]**	**p-value**
Race						
Interaction test	**p = 0.655**					
Asian	94 | -9.72 (1.82)	87 | -9.97 (1.92)	Difference	0.25	[-4.98; 5.47]	0.926
			Hedges G	0.01	[-0.28; 0.31]	
Non-Asian	504 | -10.30 (0.85)	476 | -8.92 (0.88)	Difference	-1.37	[-3.78; 1.04]	0.264
			Hedges G	-0.07	[-0.20; 0.05]	
BMI at screening						
Interaction test	**p = 0.737**					
≥25	306 | -11.38 (1.13)	284 | -9.93 (1.18)	Difference	-1.45	[-4.66; 1.76]	0.376
			Hedges G	-0.07	[-0.23; 0.09]	
<25	316 | -9.52 (1.12)	306 | -9.05 (1.15)	Difference	-0.48	[-3.64; 2.69]	0.767
			Hedges G	-0.02	[-0.18; 0.13]	
AJCC Anatomic Stage Group						
Interaction test	**p = 0.692**					
Group I/II	239 | -11.30 (1.33)	234 | -11.07 (1.36)	Difference	-0.23	[-3.97; 3.50]	0.902
			Hedges G	-0.01	[-0.19; 0.17]	
Group III	391 | -9.71 (1.00)	364 | -8.38 (1.04)	Difference	-1.33	[-4.17; 1.50]	0.356
			Hedges G	-0.07	[-0.21; 0.08]	
Anatomic stages						
Interaction test	**p = 0.312**					
IA/IB/IIA	105 | -10.36 (1.91)	113 | -7.66 (1.88)	Difference	-2.70	[-7.98; 2.59]	0.315
			Hedges G	-0.14	[-0.40; 0.13]	
IIB	134 | -11.74 (1.72)	121 | -13.94 (1.83)	Difference	2.20	[-2.75; 7.15]	0.382
			Hedges G	0.11	[-0.14; 0.36]	
IIIA	245 | -8.84 (1.21)	235 | -8.78 (1.23)	Difference	-0.07	[-3.45; 3.32]	0.970
			Hedges G	-0.00	[-0.18; 0.18]	
IIIB	37 | -12.85 (3.52)	32 | -13.62 (3.90)	Difference	0.78	[-9.72; 11.28]	0.883
			Hedges G	0.04	[-0.44; 0.51]	
IIIC	109 | -10.58 (1.79)	97 | -5.50 (1.91)	Difference	-5.07	[-10.23; 0.08]	0.054
			Hedges G	-0.27	[-0.55; 0.00]	
Nodal status						
Interaction test	**p = 0.307**					
N0	53 | -10.72 (2.79)	69 | -7.22 (2.49)	Difference	-3.50	[-10.91; 3.91]	0.351
			Hedges G	-0.17	[-0.53; 0.19]	
N1-N3	577 | -10.21 (0.83)	527 | -9.74 (0.87)	Difference	-0.47	[-2.83; 1.88]	0.693
			Hedges G	-0.02	[-0.14; 0.09]	

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1115)	**ET (N = 1123)**	**Parameter**	**Esti-mate**	**[95% CI]**	**p-value**
Histological grade at time of surgery						
Interaction test	**p = 0.651**					
Grade 1	55 | -10.59 (2.25)	61 | -9.22 (2.16)	Difference	-1.37	[-7.56; 4.82]	0.662
			Hedges G	-0.08	[-0.45; 0.28]	
Grade 2	341 | -11.03 (1.07)	333 | -8.77 (1.09)	Difference	-2.26	[-5.26; 0.74]	0.140
			Hedges G	-0.11	[-0.27; 0.04]	
Grade 3	172 | -10.61 (1.51)	146 | -10.58 (1.66)	Difference	-0.03	[-4.46; 4.39]	0.988
			Hedges G	-0.00	[-0.22; 0.22]	
Histological subtype						
Interaction test	**p = 0.410**					
Ductal	491 | -10.24 (0.90)	472 | -9.54 (0.93)	Difference	-0.69	[-3.23; 1.84]	0.592
			Hedges G	-0.03	[-0.16; 0.09]	
Lobular	88 | -9.12 (1.74)	86 | -9.87 (1.75)	Difference	0.75	[-4.12; 5.62]	0.761
			Hedges G	0.05	[-0.25; 0.34]	
Other	51 | -11.48 (2.45)	40 | -5.23 (2.76)	Difference	-6.25	[-13.59; 1.09]	0.094
			Hedges G	-0.36	[-0.77; 0.06]	
Ki67 status from surgical specimen						
Interaction test	**p = 0.689**					
Ki67≤20	286 | -11.52 (1.12)	302 | -9.72 (1.10)	Difference	-1.81	[-4.88; 1.27]	0.249
			Hedges G	-0.10	[-0.26; 0.07]	
Ki67>20	262 | -9.88 (1.28)	216 | -8.73 (1.41)	Difference	-1.15	[-4.89; 2.59]	0.545
			Hedges G	-0.06	[-0.24; 0.12]	
Type of NSAI						
Interaction test	**p = 0.578**					
Letrozole	449 | -10.63 (0.96)	419 | -9.26 (1.00)	Difference	-1.37	[-4.09; 1.35]	0.323
			Hedges G	-0.07	[-0.20; 0.07]	
Anastrozole	181 | -9.56 (1.42)	178 | -9.57 (1.42)	Difference	0.01	[-3.95; 3.96]	0.998
			Hedges G	0.00	[-0.21; 0.21]	
Prior neo/adjuvant chemotherapy						
Interaction test	**p = 0.616**					
Yes	580 | -10.05 (0.83)	548 | -9.37 (0.86)	Difference	-0.68	[-3.02; 1.67]	0.571
			Hedges G	-0.03	[-0.15; 0.08]	
No	50 | -13.12 (2.80)	50 | -9.94 (2.83)	Difference	-3.18	[-11.08; 4.72]	0.426
			Hedges G	-0.16	[-0.55; 0.23]	
Prior adjuvant chemotherapy						
Interaction test	**p = 0.076**					
Yes	283 | -7.68 (1.18)	275 | -9.04 (1.20)	Difference	1.36	[-1.95; 4.67]	0.419
			Hedges G	0.07	[-0.10; 0.23]	
No	347 | -12.55 (1.08)	323 | -9.78 (1.12)	Difference	-2.77	[-5.82; 0.28]	0.075
			Hedges G	-0.14	[-0.29; 0.01]	

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1115)	ET (N = 1123)	Parameter	Esti-mate	[95% CI]	p-value
Prior neoadjuvant chemotherapy						
Interaction test	**p = 0.252**					
Yes	316 | -12.55 (1.15)	297 | -10.28 (1.19)	Difference	-2.27	[-5.51; 0.98]	0.170
			Hedges G	-0.11	[-0.27; 0.05]	
No	314 | -8.09 (1.10)	301 | -8.51 (1.13)	Difference	0.42	[-2.68; 3.53]	0.788
			Hedges G	0.02	[-0.14; 0.18]	
Prior endocrine therapy						
Interaction test	**p = 0.870**					
Yes	482 | -10.15 (0.91)	433 | -8.99 (0.97)	Difference	-1.16	[-3.77; 1.46]	0.386
			Hedges G	-0.06	[-0.19; 0.07]	
No	148 | -11.02 (1.61)	165 | -10.18 (1.53)	Difference	-0.84	[-5.20; 3.53]	0.707
			Hedges G	-0.04	[-0.26; 0.18]	
Prior mastectomy						
Interaction test	**p = 0.932**					
Yes	434 | -10.37 (0.95)	424 | -9.44 (0.97)	Difference	-0.93	[-3.59; 1.73]	0.493
			Hedges G	-0.05	[-0.18; 0.09]	
No	196 | -10.01 (1.45)	174 | -9.45 (1.55)	Difference	-0.56	[-4.73; 3.62]	0.793
			Hedges G	-0.03	[-0.23; 0.18]	
Prior radiotherapy						
Interaction test	**p = 0.938**					
Yes	571 | -10.55 (0.84)	545 | -9.66 (0.86)	Difference	-0.89	[-3.25; 1.46]	0.457
			Hedges G	-0.04	[-0.16; 0.07]	
No	59 | -7.62 (2.47)	53 | -6.96 (2.65)	Difference	-0.66	[-7.85; 6.53]	0.856
			Hedges G	-0.03	[-0.41; 0.34]	

N: Number of patients
N': Number of patients in the analysis
CI: Confidence interval
SD: Standard deviation
LS Mean: Least square mean
SE: Standard error
MMRM: Mixed model for repeated measures
ET: Endocrine therapy (Anastrozole/Letrozole + Goserelin)
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Analysis method for interaction test:
p-value from MMRM with unstructured covariance matrix:
change from baseline = treatment + visit + treatment * visit + subgroup factor + treatment * subgroup factor + subgroup factor * visit + treatment * subgroup factor * visit + baseline value
If the model did not converge for a parameter*subgroup factor, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry. If the model did still not converge, interactions were removed in the order treatment * subgroup factor * visit, subgroup factor * visit.

Analysis methods for within-subgroup analysis:
Adjusted mean (LS Mean) change from baseline and overall effect obtained from MMRM with unstructured covariance matrix:
change from baseline = treatment + visit + treatment * visit + baseline value
ET was the reference group for treatment group comparison.
If the model did not converge for a parameter*subgroup factor, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry.

Patients with an evaluable baseline score and at least one evaluable post-baseline score were included in the analysis.
All data collected were included in the analysis, including assessments at confirmation of first recurrence and thereafter, as long as there were at least 50 patients in each treatment group at a visit in the overall (sub-)population.

Table 5-2.4.4.1 QLQ-BR23 - Future Perspective: change from baseline analysis - subgroup analysis (Full Analysis Set)

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1115)	ET (N = 1123)	Parameter	Esti-mate	[95% CI]	p-value
QLQ-BR23 - Future Perspective						
	N' | LS Mean (SE)	**N' | LS Mean (SE)**				
Region						
Interaction test	**p = 0.072**					
NA/WE/O	599 | 7.99 (0.86)	571 | 10.70 (0.88)	Difference	-2.70	[-5.12; -0.28]	0.028
			Hedges G	-0.13	[-0.24; -0.01]	
ROW	459 | 12.66 (0.96)	426 | 11.99 (1.01)	Difference	0.67	[-2.06; 3.40]	0.629
			Hedges G	0.03	[-0.10; 0.16]	
Geographical region						
Interaction test	**p = 0.328**					
Europe	618 | 11.04 (0.86)	591 | 11.74 (0.88)	Difference	-0.70	[-3.11; 1.71]	0.569
			Hedges G	-0.03	[-0.15; 0.08]	
North America/Australia	203 | 7.56 (1.34)	172 | 12.45 (1.49)	Difference	-4.89	[-8.83; -0.95]	0.015
			Hedges G	-0.25	[-0.46; -0.05]	
Asia	174 | N.E.	166 | N.E.	Difference	N.E.	[N.E.]	N.E.
			Hedges G	N.E.	[N.E.]	
Latin America	63 | 17.58 (2.98)	68 | 16.95 (2.83)	Difference	0.63	[-7.51; 8.78]	0.878
			Hedges G	0.03	[-0.32; 0.37]	
Age group 1 at randomization						
Interaction test	**N.E.**					
<45	525 | 11.31 (0.93)	459 | 12.06 (0.99)	Difference	-0.75	[-3.42; 1.92]	0.582
			Hedges G	-0.04	[-0.16; 0.09]	
45 to 54	513 | 8.69 (0.90)	511 | 10.85 (0.92)	Difference	-2.16	[-4.69; 0.36]	0.093
			Hedges G	-0.11	[-0.23; 0.02]	
55 to 64	20 | 8.49 (4.20)	27 | 7.18 (3.72)	Difference	1.31	[-10.12; 12.74]	0.818
			Hedges G	0.07	[-0.51; 0.65]	
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)						
Interaction test	**p = 0.511**					
<Median	525 | 11.28 (0.98)	459 | 12.44 (1.04)	Difference	-1.15	[-3.96; 1.65]	0.420
			Hedges G	-0.05	[-0.18; 0.07]	
≥Median	533 | 8.72 (0.90)	538 | 10.45 (0.91)	Difference	-1.73	[-4.24; 0.78]	0.177
			Hedges G	-0.08	[-0.20; 0.04]	

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1115)	**ET (N = 1123)**	**Parameter**	**Esti-mate**	**[95% CI]**	**p-value**
Race						
Interaction test	**p = 0.946**					
Asian	205 | 6.18 (1.30)	180 | 7.35 (1.40)	Difference	-1.17	[-4.92; 2.58]	0.539
			Hedges G	-0.06	[-0.26; 0.14]	
Non-Asian	803 | 10.83 (0.74)	765 | 11.86 (0.76)	Difference	-1.03	[-3.11; 1.05]	0.333
			Hedges G	-0.05	[-0.15; 0.05]	
BMI at screening						
Interaction test	**p = 0.624**					
≥25	529 | 8.35 (0.91)	482 | 9.17 (0.97)	Difference	-0.82	[-3.43; 1.79]	0.538
			Hedges G	-0.04	[-0.16; 0.08]	
<25	517 | 11.91 (0.91)	504 | 13.36 (0.92)	Difference	-1.46	[-4.00; 1.08]	0.261
			Hedges G	-0.07	[-0.19; 0.05]	
AJCC Anatomic Stage Group						
Interaction test	**p = 0.025**					
Group I/II	395 | 11.12 (1.07)	394 | 10.68 (1.08)	Difference	0.43	[-2.56; 3.43]	0.777
			Hedges G	0.02	[-0.12; 0.16]	
Group III	663 | 9.30 (0.86)	603 | 12.08 (0.91)	Difference	-2.77	[-5.24; -0.30]	0.028
			Hedges G	-0.12	[-0.23; -0.01]	
Anatomic stages						
Interaction test	**p = 0.167**					
IA/IB/IIA	164 | 14.54 (1.65)	186 | 11.26 (1.58)	Difference	3.28	[-1.21; 7.77]	0.152
			Hedges G	0.15	[-0.06; 0.36]	
IIB	231 | 8.50 (1.33)	208 | 10.25 (1.40)	Difference	-1.74	[-5.55; 2.06]	0.368
			Hedges G	-0.09	[-0.27; 0.10]	
IIIA	432 | 7.90 (1.04)	366 | 11.65 (1.13)	Difference	-3.76	[-6.78; -0.73]	0.015
			Hedges G	-0.17	[-0.31; -0.03]	
IIIB	62 | 12.94 (2.52)	52 | 14.45 (2.81)	Difference	-1.51	[-9.17; 6.15]	0.697
			Hedges G	-0.07	[-0.44; 0.30]	
IIIC	169 | 10.64 (1.58)	185 | 12.20 (1.53)	Difference	-1.56	[-5.89; 2.76]	0.477
			Hedges G	-0.08	[-0.28; 0.13]	
Nodal status						
Interaction test	**p = 0.008**					
N0	84 | 18.42 (2.23)	109 | 11.57 (1.99)	Difference	6.86	[0.96; 12.76]	0.023
			Hedges G	0.33	[0.05; 0.62]	
N1-N3	974 | 9.18 (0.67)	885 | 11.28 (0.70)	Difference	-2.10	[-4.01; -0.19]	0.031
			Hedges G	-0.10	[-0.19; -0.01]	

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1115)	**ET (N = 1123)**	**Parameter**	**Esti-mate**	**[95% CI]**	**p-value**
Histological grade at time of surgery						
Interaction test	**p = 0.696**					
Grade 1	106 | 8.73 (1.88)	97 | 12.15 (1.99)	Difference	-3.43	[-8.83; 1.98]	0.213
			Hedges G	-0.18	[-0.45; 0.10]	
Grade 2	580 | 10.40 (0.87)	553 | 11.41 (0.90)	Difference	-1.01	[-3.47; 1.45]	0.422
			Hedges G	-0.05	[-0.16; 0.07]	
Grade 3	281 | 9.30 (1.21)	249 | 11.32 (1.28)	Difference	-2.03	[-5.48; 1.43]	0.250
			Hedges G	-0.10	[-0.27; 0.07]	
Histological subtype						
Interaction test	**p = 0.811**					
Ductal	821 | N.E.	781 | N.E.	Difference	N.E.	[N.E.]	N.E.
			Hedges G	N.E.	[N.E.]	
Lobular	168 | 11.43 (1.60)	154 | 13.19 (1.70)	Difference	-1.76	[-6.35; 2.83]	0.451
			Hedges G	-0.08	[-0.30; 0.13]	
Other	69 | 8.93 (2.58)	62 | 13.94 (2.85)	Difference	-5.01	[-12.63; 2.60]	0.195
			Hedges G	-0.23	[-0.57; 0.12]	
Ki67 status from surgical specimen						
Interaction test	**p = 0.684**					
Ki67≤20	509 | 9.64 (0.92)	517 | 10.91 (0.91)	Difference	-1.28	[-3.82; 1.27]	0.325
			Hedges G	-0.06	[-0.18; 0.06]	
Ki67>20	401 | 10.38 (1.01)	354 | 12.42 (1.08)	Difference	-2.04	[-4.95; 0.87]	0.169
			Hedges G	-0.10	[-0.24; 0.04]	
Type of NSAI						
Interaction test	**p = 0.730**					
Letrozole	774 | 9.69 (0.77)	716 | 10.84 (0.82)	Difference	-1.15	[-3.35; 1.06]	0.307
			Hedges G	-0.05	[-0.15; 0.05]	
Anastrozole	284 | 10.79 (1.27)	279 | 12.47 (1.28)	Difference	-1.68	[-5.22; 1.86]	0.352
			Hedges G	-0.08	[-0.24; 0.09]	
Prior neo/adjuvant chemotherapy						
Interaction test	**p = 0.395**					
Yes	983 | 9.92 (0.67)	920 | 11.43 (0.69)	Difference	-1.51	[-3.40; 0.37]	0.116
			Hedges G	-0.07	[-0.16; 0.02]	
No	75 | 12.04 (2.62)	77 | 10.75 (2.63)	Difference	1.29	[-6.07; 8.65]	0.730
			Hedges G	0.06	[-0.26; 0.37]	
Prior adjuvant chemotherapy						
Interaction test	**p = 0.371**					
Yes	494 | 8.77 (0.95)	456 | 10.82 (0.99)	Difference	-2.06	[-4.75; 0.63]	0.133
			Hedges G	-0.10	[-0.22; 0.03]	
No	564 | 10.98 (0.92)	541 | 11.56 (0.95)	Difference	-0.58	[-3.18; 2.02]	0.662
			Hedges G	-0.03	[-0.14; 0.09]	

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1115)	ET (N = 1123)	Parameter	Esti-mate	[95% CI]	p-value
Prior neoadjuvant chemotherapy						
Interaction test	**p = 0.940**					
Yes	519 | 11.02 (0.92)	501 | 11.52 (0.94)	Difference	-0.50	[-3.08; 2.08]	0.705
			Hedges G	-0.02	[-0.15; 0.10]	
No	539 | 9.13 (0.90)	496 | 11.04 (0.94)	Difference	-1.91	[-4.45; 0.64]	0.143
			Hedges G	-0.09	[-0.21; 0.03]	
Prior endocrine therapy						
Interaction test	**p = 0.882**					
Yes	814 | N.E.	729 | N.E.	Difference	N.E.	[N.E.]	N.E.
			Hedges G	N.E.	[N.E.]	
No	244 | 7.81 (1.43)	268 | 8.57 (1.37)	Difference	-0.77	[-4.66; 3.13]	0.700
			Hedges G	-0.03	[-0.21; 0.14]	
Prior mastectomy						
Interaction test	**p = 0.011**					
Yes	735 | 9.15 (0.81)	697 | 12.26 (0.83)	Difference	-3.12	[-5.38; -0.85]	0.007
			Hedges G	-0.14	[-0.25; -0.04]	
No	323 | 11.93 (1.20)	300 | 9.99 (1.26)	Difference	1.94	[-1.48; 5.36]	0.266
			Hedges G	0.09	[-0.07; 0.25]	
Prior radiotherapy						
Interaction test	**p = 0.876**					
Yes	969 | 9.88 (0.68)	915 | 11.26 (0.70)	Difference	-1.38	[-3.29; 0.52]	0.155
			Hedges G	-0.07	[-0.16; 0.02]	
No	89 | 11.37 (2.05)	82 | 12.19 (2.17)	Difference	-0.82	[-6.72; 5.09]	0.785
			Hedges G	-0.04	[-0.34; 0.26]	

N: Number of patients
N': Number of patients in the analysis
CI: Confidence interval
SD: Standard deviation
LS Mean: Least square mean
SE: Standard error
MMRM: Mixed model for repeated measures
N.E.: Not estimable
ET: Endocrine therapy (Anastrozole/Letrozole + Goserelin)
.....

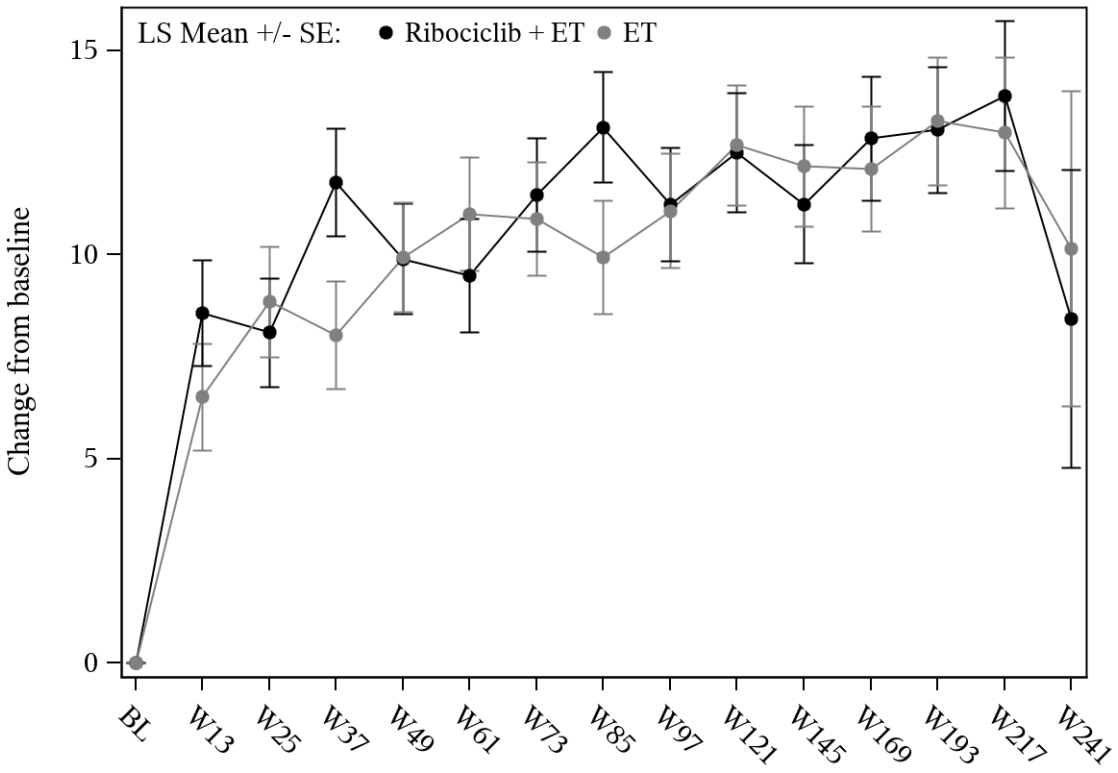
Analysis method for interaction test:
p-value from MMRM with unstructured covariance matrix:
change from baseline = treatment + visit + treatment * visit + subgroup factor + treatment * subgroup factor + subgroup factor * visit + treatment * subgroup factor * visit + baseline value
If the model did not converge for a parameter*subgroup factor, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry. If the model did still not converge, interactions were removed in the order treatment * subgroup factor * visit, subgroup factor * visit.

Analysis methods for within-subgroup analysis:
Adjusted mean (LS Mean) change from baseline and overall effect obtained from MMRM with unstructured covariance matrix:
change from baseline = treatment + visit + treatment * visit + baseline value
ET was the reference group for treatment group comparison.
If the model did not converge for a parameter*subgroup factor, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry.

Patients with an evaluable baseline score and at least one evaluable post-baseline score were included in the analysis.
All data collected were included in the analysis, including assessments at confirmation of first recurrence and thereafter, as long as there were at least 50 patients in each treatment group at a visit in the overall (sub-)population.

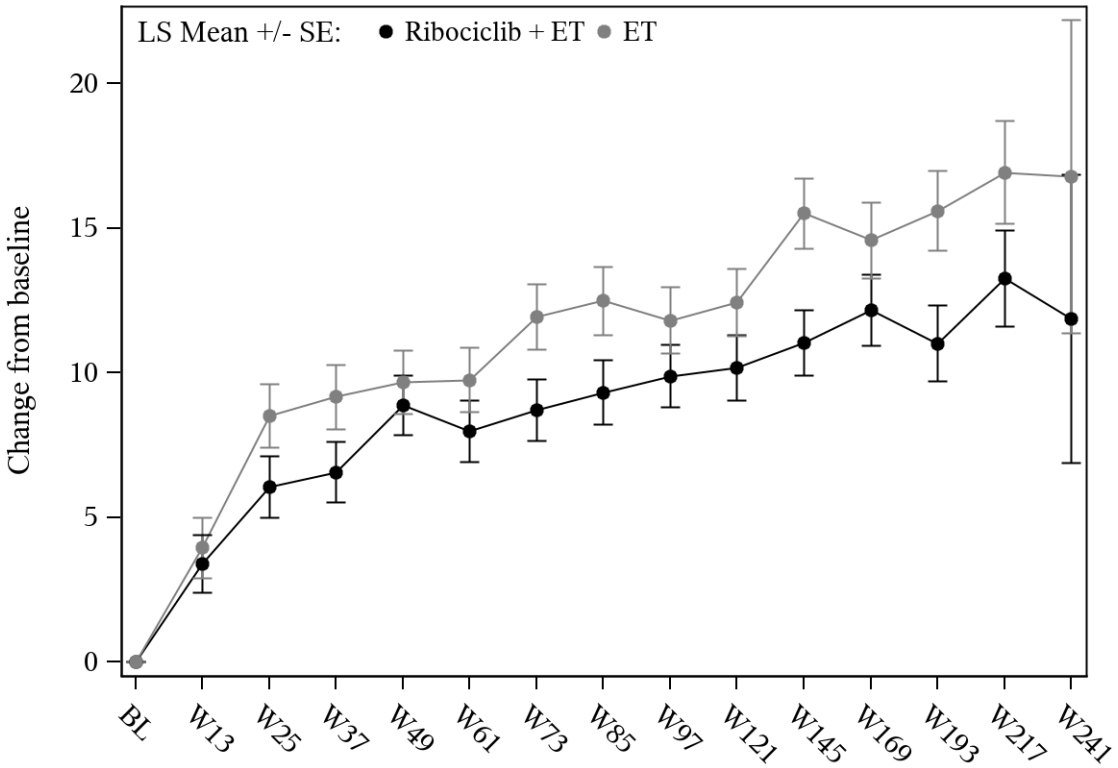
Figure 5-2.4.4.1 QLQ-BR23 - Future Perspective: line chart of change from baseline - subgroup analysis (Full Analysis Set)

QLQ-BR23 - Future Perspective
AJCC Anatomic Stage Group: Group I/II



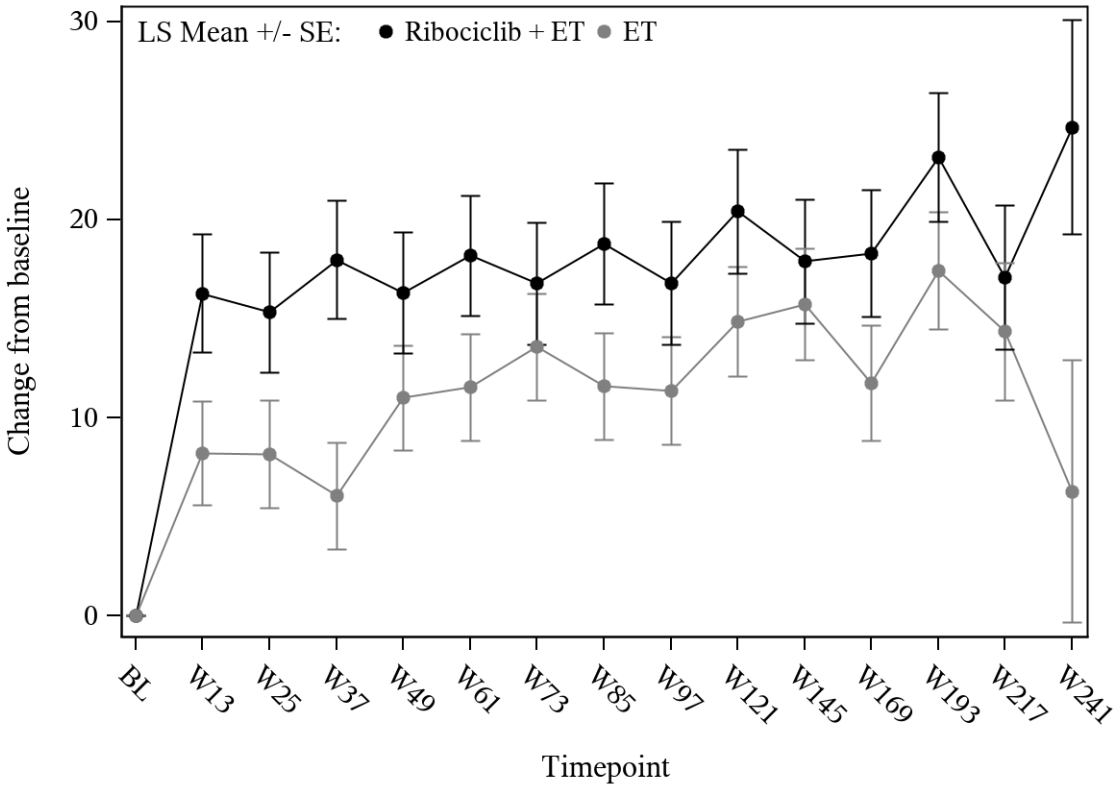
Ribociclib + ET	395	384	369	365	357	359	355	357	348	340	339	314	312	177	31
ET	394	373	345	362	363	352	357	339	338	330	316	314	299	173	27

QLQ-BR23 - Future Perspective
AJCC Anatomic Stage Group: Group III



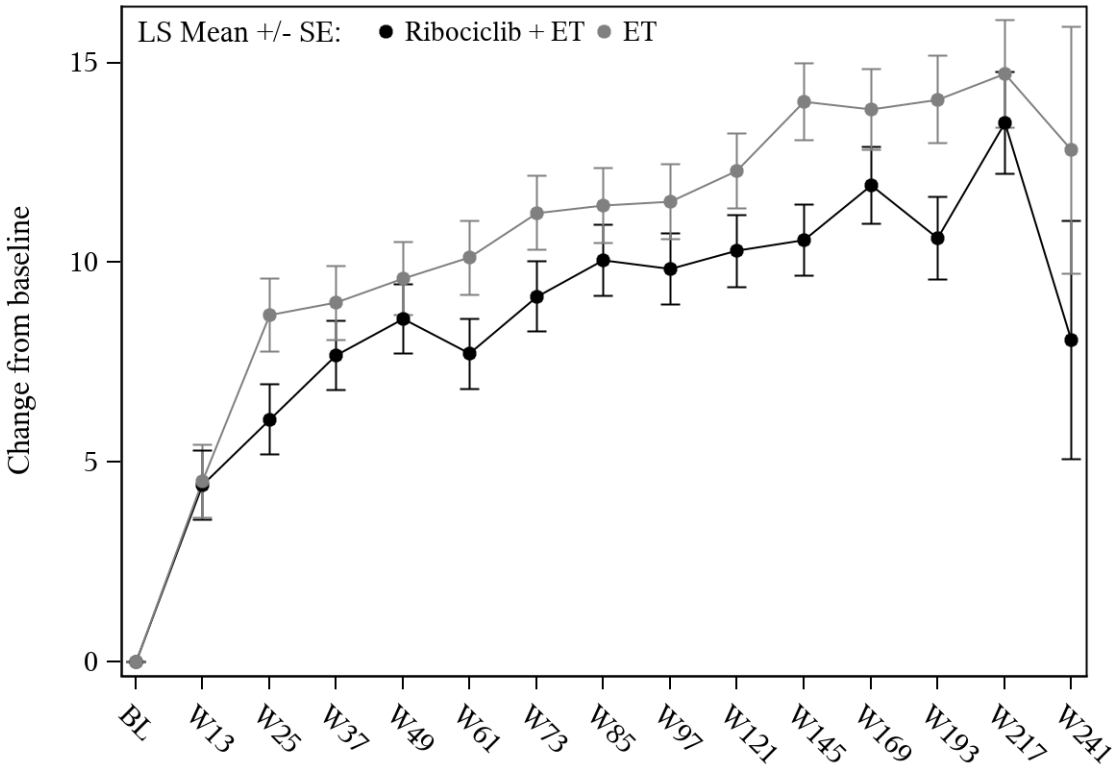
Ribociclib + ET	663	630	607	617	609	601	594	582	578	557	554	412	294	167	27
ET	603	572	564	540	549	539	529	529	511	503	483	363	262	147	23

QLQ-BR23 - Future Perspective
Nodal status: N0



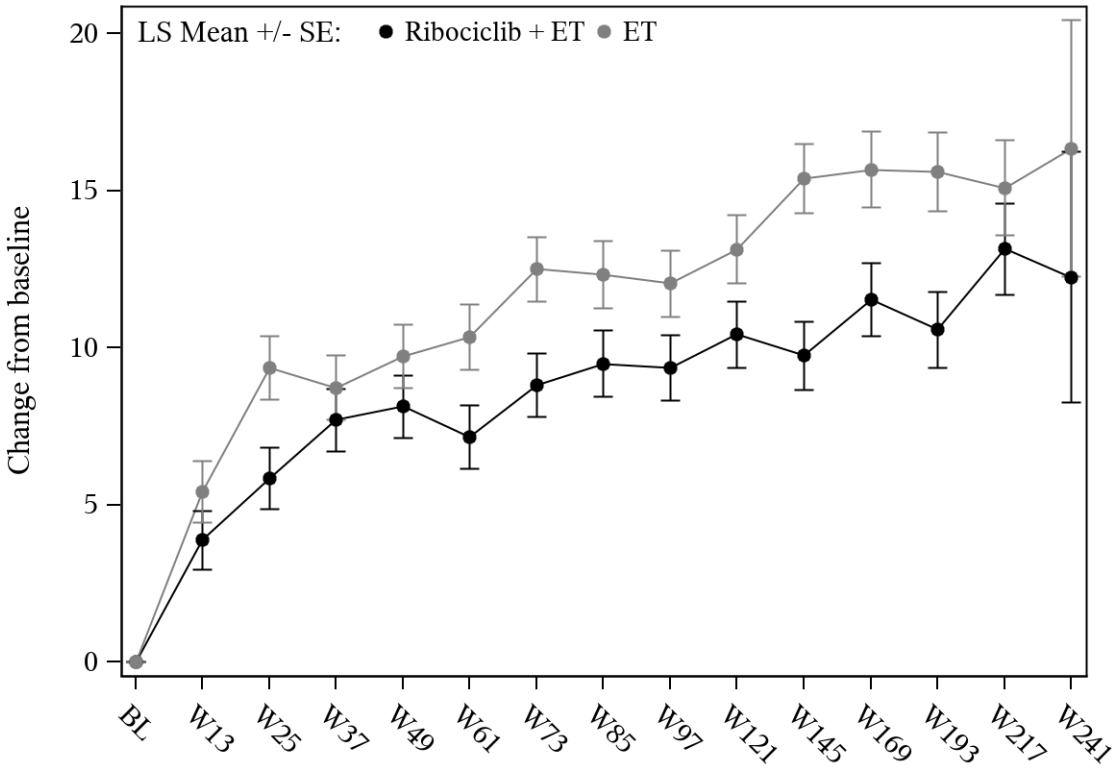
Ribociclib + ET	84	83	78	82	76	77	74	78	73	71	72	65	64	45	13
ET	109	107	96	97	103	99	98	96	94	91	85	79	74	46	8

QLQ-BR23 - Future Perspective
Nodal status: N1-N3



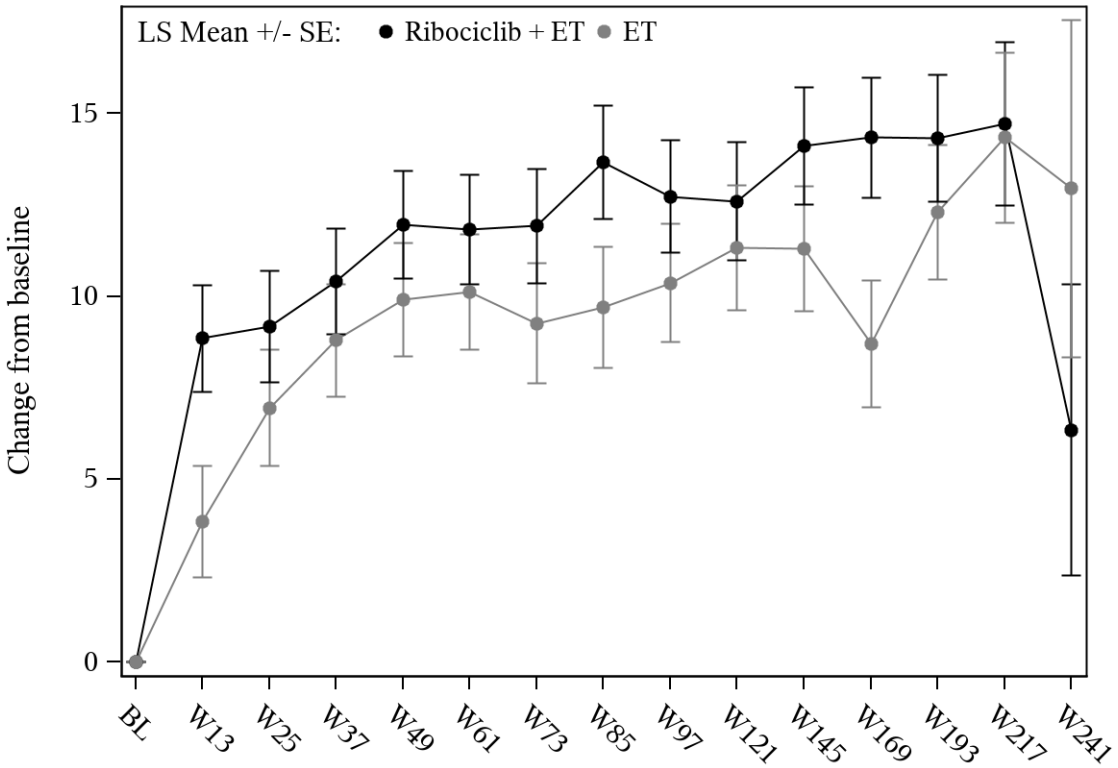
Ribociclib + ET	974	931	898	900	890	883	875	861	853	826	821	661	542	299	45
ET	885	835	811	802	808	790	786	770	753	740	712	596	485	272	42

QLQ-BR23 - Future Perspective
Prior mastectomy: Yes



Ribociclib + ET	735	698	675	675	664	661	649	644	634	614	609	490	401	231	40
ET	697	654	642	631	641	624	619	612	594	584	556	459	375	213	38

QLQ-BR23 - Future Perspective
Prior mastectomy: No



Ribociclib + ET	323	316	301	307	302	299	300	295	292	283	284	236	205	113	18
ET	300	291	267	271	271	267	267	256	255	249	243	218	186	107	12

5-2.5 EQ-5D VAS

Table 5-2.5.1.1 EQ5D01-Health Today: change from baseline analysis - subgroup analysis (Full Analysis Set)

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1115)	ET (N = 1123)	Parameter	Esti-mate	[95% CI]	p-value
EQ5D01-Health Today						
	N' | LS Mean (SE)	N' | LS Mean (SE)				
Region						
Interaction test	**p = 0.431**					
NA/WE/O	592 | -1.04 (0.51)	572 | 0.02 (0.52)	Difference	-1.06	[-2.49; 0.38]	0.150
			Hedges G	-0.08	[-0.20; 0.03]	
ROW	459 | -1.26 (0.53)	427 | -1.24 (0.55)	Difference	-0.02	[-1.53; 1.49]	0.978
			Hedges G	-0.00	[-0.13; 0.13]	
Geographical region						
Interaction test	**p = 0.299**					
Europe	610 | -1.39 (0.51)	587 | -1.14 (0.52)	Difference	-0.25	[-1.69; 1.19]	0.731
			Hedges G	-0.02	[-0.13; 0.09]	
North America/Australia	203 | 0.06 (0.75)	177 | 2.45 (0.81)	Difference	-2.39	[-4.57; -0.22]	0.031
			Hedges G	-0.22	[-0.42; -0.02]	
Asia	175 | N.E.	166 | N.E.	Difference	N.E.	[N.E.]	N.E.
			Hedges G	N.E.	[N.E.]	
Latin America	63 | 0.03 (1.27)	69 | -1.30 (1.20)	Difference	1.33	[-2.14; 4.79]	0.450
			Hedges G	0.13	[-0.21; 0.47]	
Age group 1 at randomization						
Interaction test	**p = 0.620**					
<45	523 | N.E.	460 | N.E.	Difference	N.E.	[N.E.]	N.E.
			Hedges G	N.E.	[N.E.]	
45 to 54	508 | -1.17 (0.39)	512 | -0.56 (0.40)	Difference	-0.61	[-1.71; 0.48]	0.273
			Hedges G	-0.07	[-0.19; 0.05]	
55 to 64	20 | -0.49 (2.02)	27 | 0.83 (1.81)	Difference	-1.32	[-6.80; 4.16]	0.630
			Hedges G	-0.14	[-0.72; 0.44]	
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)						
Interaction test	**p = 0.754**					
<Median	523 | -1.10 (0.54)	460 | -0.50 (0.57)	Difference	-0.60	[-2.13; 0.94]	0.446
			Hedges G	-0.05	[-0.17; 0.08]	
≥Median	528 | -1.43 (0.51)	539 | -0.56 (0.51)	Difference	-0.87	[-2.29; 0.55]	0.230
			Hedges G	-0.07	[-0.19; 0.05]	

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1115)	**ET (N = 1123)**	**Parameter**	**Esti-mate**	**[95% CI]**	**p-value**
Race						
Interaction test	**p = 0.132**					
Asian	206 | -2.56 (0.74)	180 | -0.17 (0.80)	Difference	-2.39	[-4.54; -0.24]	0.030
			Hedges G	-0.22	[-0.42; -0.02]	
Non-Asian	794 | -0.72 (0.42)	769 | -0.50 (0.43)	Difference	-0.22	[-1.39; 0.96]	0.714
			Hedges G	-0.02	[-0.12; 0.08]	
BMI at screening						
Interaction test	**p = 0.546**					
≥25	527 | -1.64 (0.56)	487 | -0.91 (0.59)	Difference	-0.73	[-2.33; 0.88]	0.375
			Hedges G	-0.06	[-0.18; 0.07]	
<25	512 | -0.45 (0.48)	501 | -0.28 (0.49)	Difference	-0.17	[-1.52; 1.18]	0.804
			Hedges G	-0.02	[-0.14; 0.11]	
AJCC Anatomic Stage Group						
Interaction test	**p = 0.012**					
Group I/II	394 | 0.36 (0.56)	397 | -0.78 (0.56)	Difference	1.14	[-0.43; 2.71]	0.155
			Hedges G	0.10	[-0.04; 0.24]	
Group III	657 | -2.09 (0.49)	602 | -0.38 (0.52)	Difference	-1.70	[-3.11; -0.29]	0.018
			Hedges G	-0.13	[-0.24; -0.02]	
Anatomic stages						
Interaction test	**p = 0.022**					
IA/IB/IIA	162 | 1.55 (0.83)	187 | -1.34 (0.79)	Difference	2.89	[0.63; 5.14]	0.012
			Hedges G	0.27	[0.06; 0.48]	
IIB	232 | -0.71 (0.74)	210 | -0.40 (0.77)	Difference	-0.31	[-2.42; 1.79]	0.770
			Hedges G	-0.03	[-0.21; 0.16]	
IIIA	429 | -1.91 (0.62)	367 | -0.58 (0.68)	Difference	-1.33	[-3.14; 0.47]	0.147
			Hedges G	-0.10	[-0.24; 0.04]	
IIIB	61 | -1.41 (1.53)	51 | -0.17 (1.69)	Difference	-1.24	[-5.76; 3.27]	0.586
			Hedges G	-0.10	[-0.48; 0.27]	
IIIC	167 | -2.66 (0.85)	184 | 0.37 (0.82)	Difference	-3.03	[-5.35; -0.71]	0.011
			Hedges G	-0.27	[-0.49; -0.06]	
Nodal status						
Interaction test	**p = 0.022**					
N0	84 | 1.46 (0.86)	110 | -1.74 (0.78)	Difference	3.20	[0.91; 5.49]	0.006
			Hedges G	0.40	[0.11; 0.69]	
N1-N3	967 | -1.20 (0.28)	886 | -0.24 (0.30)	Difference	-0.96	[-1.76; -0.15]	0.020
			Hedges G	-0.11	[-0.20; -0.02]	

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1115)	**ET (N = 1123)**	**Parameter**	**Esti-mate**	**[95% CI]**	**p-value**
Histological grade at time of surgery						
Interaction test	**p = 0.311**					
Grade 1	105 | -1.43 (1.04)	97 | -2.74 (1.10)	Difference	1.31	[-1.69; 4.31]	0.390
			Hedges G	0.12	[-0.15; 0.40]	
Grade 2	573 | -1.09 (0.49)	554 | -0.44 (0.50)	Difference	-0.64	[-2.03; 0.74]	0.361
			Hedges G	-0.05	[-0.17; 0.06]	
Grade 3	282 | -1.38 (0.69)	251 | 0.18 (0.73)	Difference	-1.57	[-3.55; 0.41]	0.120
			Hedges G	-0.14	[-0.31; 0.04]	
Histological subtype						
Interaction test	**N.E.**					
Ductal	819 | N.E.	783 | N.E.	Difference	N.E.	[N.E.]	N.E.
			Hedges G	N.E.	[N.E.]	
Lobular	165 | 0.52 (1.12)	154 | 0.36 (1.16)	Difference	0.17	[-3.01; 3.34]	0.918
			Hedges G	0.01	[-0.21; 0.23]	
Other	67 | 0.40 (1.36)	62 | 0.20 (1.48)	Difference	0.20	[-3.77; 4.18]	0.920
			Hedges G	0.02	[-0.33; 0.36]	
Ki67 status from surgical specimen						
Interaction test	**p = 0.439**					
Ki67≤20	503 | -0.87 (0.53)	515 | -0.80 (0.52)	Difference	-0.07	[-1.53; 1.39]	0.923
			Hedges G	-0.01	[-0.13; 0.12]	
Ki67>20	399 | -1.61 (0.58)	358 | -0.52 (0.62)	Difference	-1.08	[-2.74; 0.57]	0.200
			Hedges G	-0.09	[-0.24; 0.05]	
Type of NSAI						
Interaction test	**N.E.**					
Letrozole	767 | -0.93 (0.45)	715 | -0.84 (0.46)	Difference	-0.10	[-1.36; 1.16]	0.880
			Hedges G	-0.01	[-0.11; 0.09]	
Anastrozole	284 | -1.81 (0.66)	282 | 0.11 (0.66)	Difference	-1.92	[-3.76; -0.08]	0.041
			Hedges G	-0.17	[-0.34; -0.01]	
Prior neo/adjuvant chemotherapy						
Interaction test	**p = 0.164**					
Yes	976 | -1.24 (0.37)	922 | -0.38 (0.38)	Difference	-0.86	[-1.89; 0.17]	0.100
			Hedges G	-0.08	[-0.17; 0.01]	
No	75 | 0.46 (1.82)	77 | -2.16 (1.83)	Difference	2.62	[-2.48; 7.72]	0.312
			Hedges G	0.16	[-0.15; 0.48]	
Prior adjuvant chemotherapy						
Interaction test	**p = 0.674**					
Yes	487 | -1.06 (0.53)	464 | -0.20 (0.55)	Difference	-0.86	[-2.36; 0.64]	0.261
			Hedges G	-0.07	[-0.20; 0.05]	
No	564 | -1.25 (0.52)	535 | -0.83 (0.53)	Difference	-0.42	[-1.88; 1.03]	0.569
			Hedges G	-0.03	[-0.15; 0.08]	

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1115)	ET (N = 1123)	Parameter	Esti-mate	[95% CI]	p-value
Prior neoadjuvant chemotherapy						
Interaction test	**p = 0.488**					
Yes	519 | -1.60 (0.52)	496 | -0.40 (0.54)	Difference	-1.19	[-2.66; 0.28]	0.111
			Hedges G	-0.10	[-0.22; 0.02]	
No	532 | -0.79 (0.53)	503 | -0.56 (0.54)	Difference	-0.23	[-1.71; 1.26]	0.765
			Hedges G	-0.02	[-0.14; 0.10]	
Prior endocrine therapy						
Interaction test	**p = 0.634**					
Yes	807 | -1.14 (0.43)	731 | -0.60 (0.45)	Difference	-0.54	[-1.77; 0.68]	0.383
			Hedges G	-0.04	[-0.14; 0.06]	
No	244 | -1.16 (0.75)	268 | -0.51 (0.72)	Difference	-0.65	[-2.69; 1.39]	0.531
			Hedges G	-0.06	[-0.23; 0.12]	
Prior mastectomy						
Interaction test	**p = <.001**					
Yes	730 | -1.46 (0.45)	695 | 0.43 (0.46)	Difference	-1.89	[-3.15; -0.63]	0.003
			Hedges G	-0.16	[-0.26; -0.05]	
No	321 | -0.30 (0.61)	304 | -2.39 (0.64)	Difference	2.09	[0.36; 3.82]	0.018
			Hedges G	0.19	[0.03; 0.35]	
Prior radiotherapy						
Interaction test	**p = 0.479**					
Yes	962 | N.E.	918 | N.E.	Difference	N.E.	[N.E.]	N.E.
			Hedges G	N.E.	[N.E.]	
No	89 | -1.22 (1.19)	81 | 0.66 (1.25)	Difference	-1.88	[-5.30; 1.53]	0.278
			Hedges G	-0.17	[-0.47; 0.13]	

N: Number of patients
N': Number of patients in the analysis
CI: Confidence interval
SD: Standard deviation
LS Mean: Least square mean
SE: Standard error
MMRM: Mixed model for repeated measures
N.E.: Not estimable
ET: Endocrine therapy (Anastrozole/Letrozole + Goserelin)
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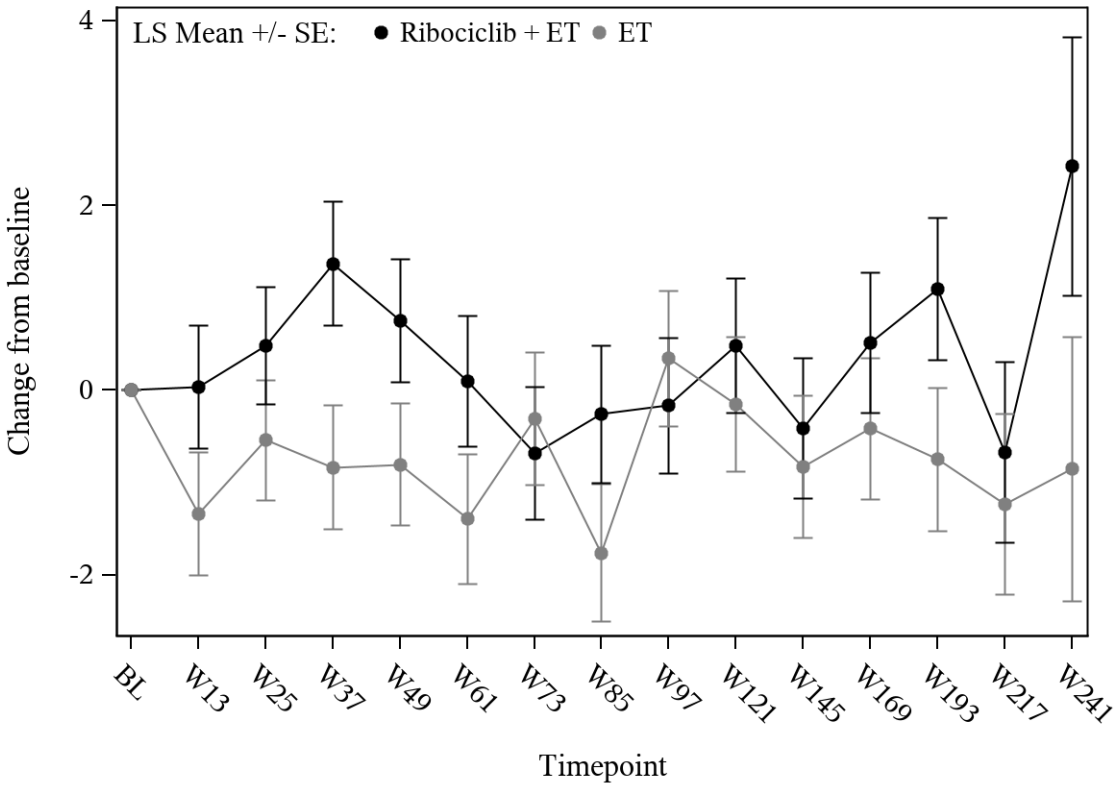
Analysis method for interaction test:
p-value from MMRM with unstructured covariance matrix:
change from baseline = treatment + visit + treatment * visit + subgroup factor + treatment * subgroup factor + subgroup factor * visit + treatment * subgroup factor * visit + baseline value
If the model did not converge for a parameter*subgroup factor, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry. If the model did still not converge, interactions were removed in the order treatment * subgroup factor * visit, subgroup factor * visit.

Analysis methods for within-subgroup analysis:
Adjusted mean (LS Mean) change from baseline and overall effect obtained from MMRM with unstructured covariance matrix:
change from baseline = treatment + visit + treatment * visit + baseline value
ET was the reference group for treatment group comparison.
If the model did not converge for a parameter*subgroup factor, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry.

Patients with an evaluable baseline score and at least one evaluable post-baseline score were included in the analysis.
All data collected were included in the analysis, including assessments at confirmation of first recurrence and thereafter, as long as there were at least 50 patients in each treatment group at a visit in the overall (sub-)population.

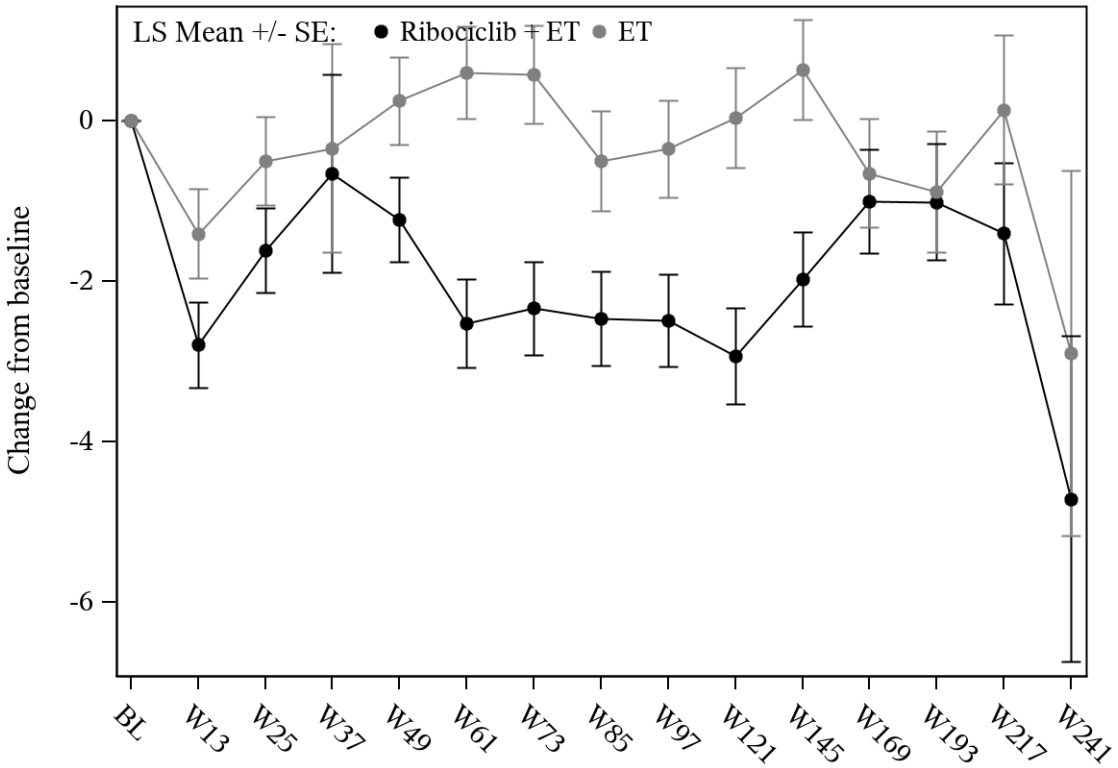
Figure 5-2.5.1.1 EQ5D01-Health Today: line chart of change from baseline - subgroup analysis (Full Analysis Set)

EQ5D01-Health Today
AJCC Anatomic Stage Group: Group I/II



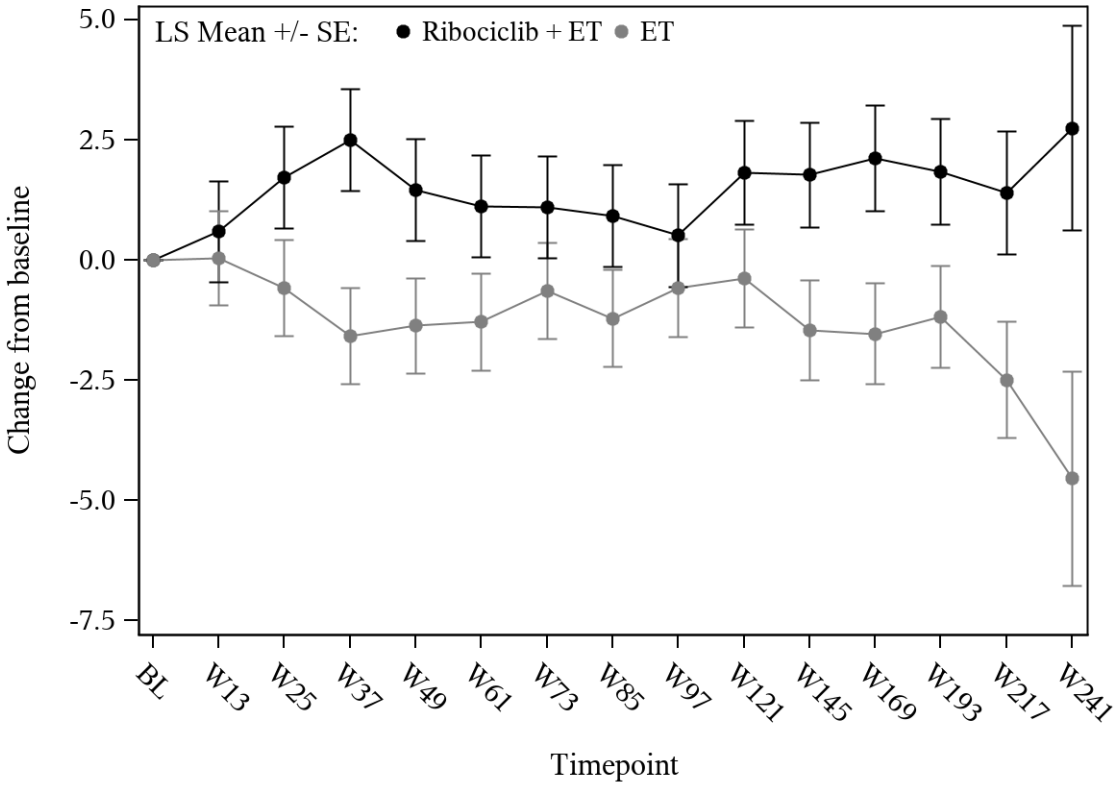
Ribociclib + ET	394	381	370	366	360	359	354	354	350	340	339	314	314	175	30
ET	397	378	351	364	367	358	360	343	345	333	322	315	305	176	28

EQ5D01-Health Today
AJCC Anatomic Stage Group: Group III



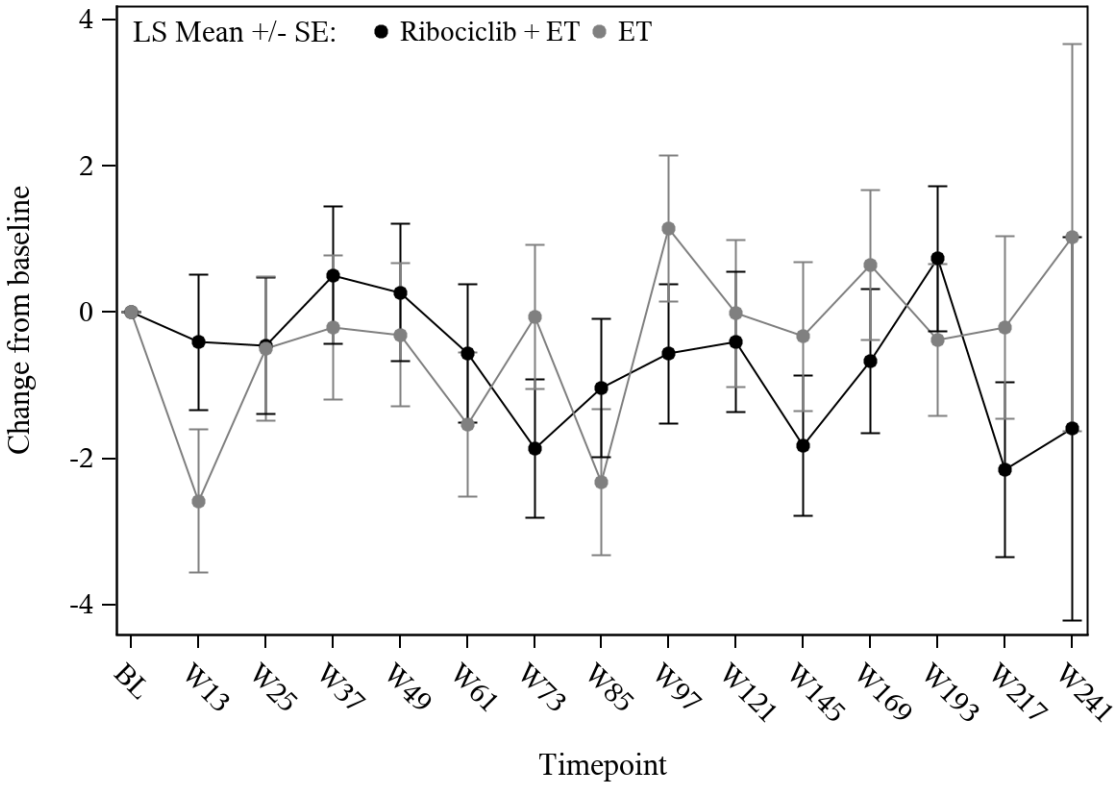
Ribociclib + ET	657	629	604	601	600	597	588	580	575	551	549	407	290	166	27
ET	602	575	564	541	551	537	526	525	511	500	482	363	262	148	24

EQ5D01-Health Today
Anatomic stages: IA/IB/IIA



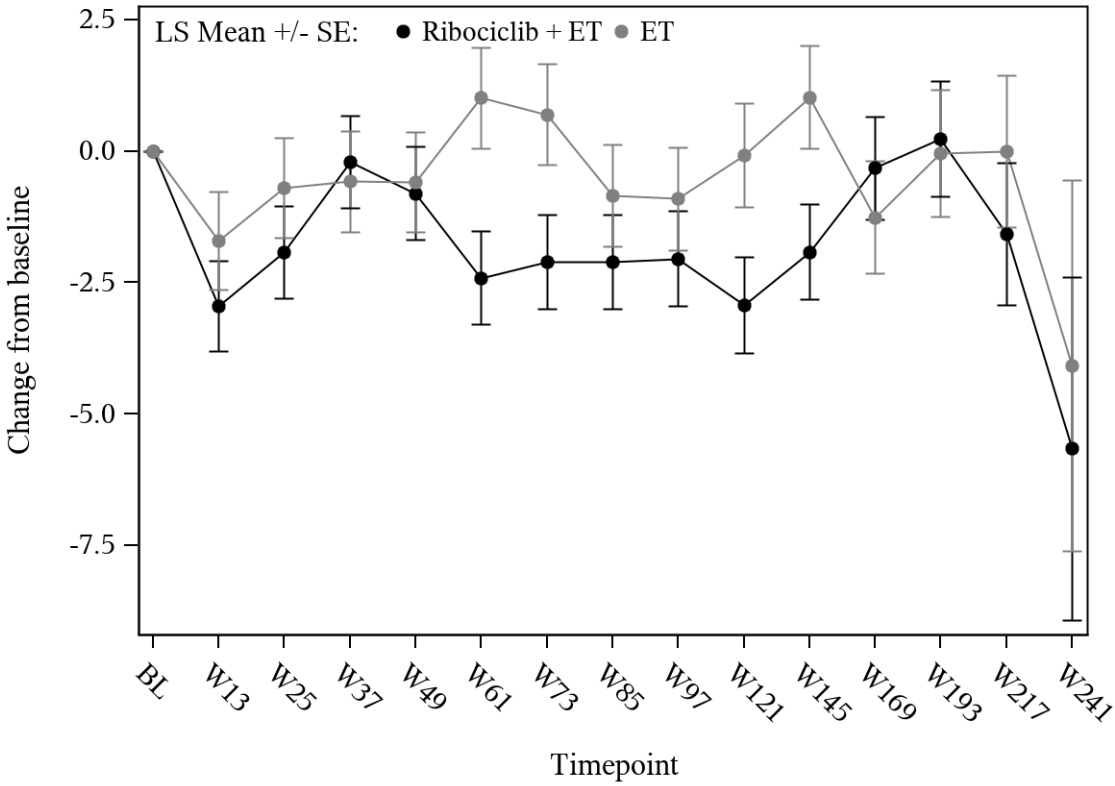
Ribociclib + ET	162	157	154	155	151	154	151	151	148	141	141	136	135	79	16
ET	187	181	161	169	170	165	169	161	162	155	149	147	141	88	14

EQ5D01-Health Today
Anatomic stages: IIB



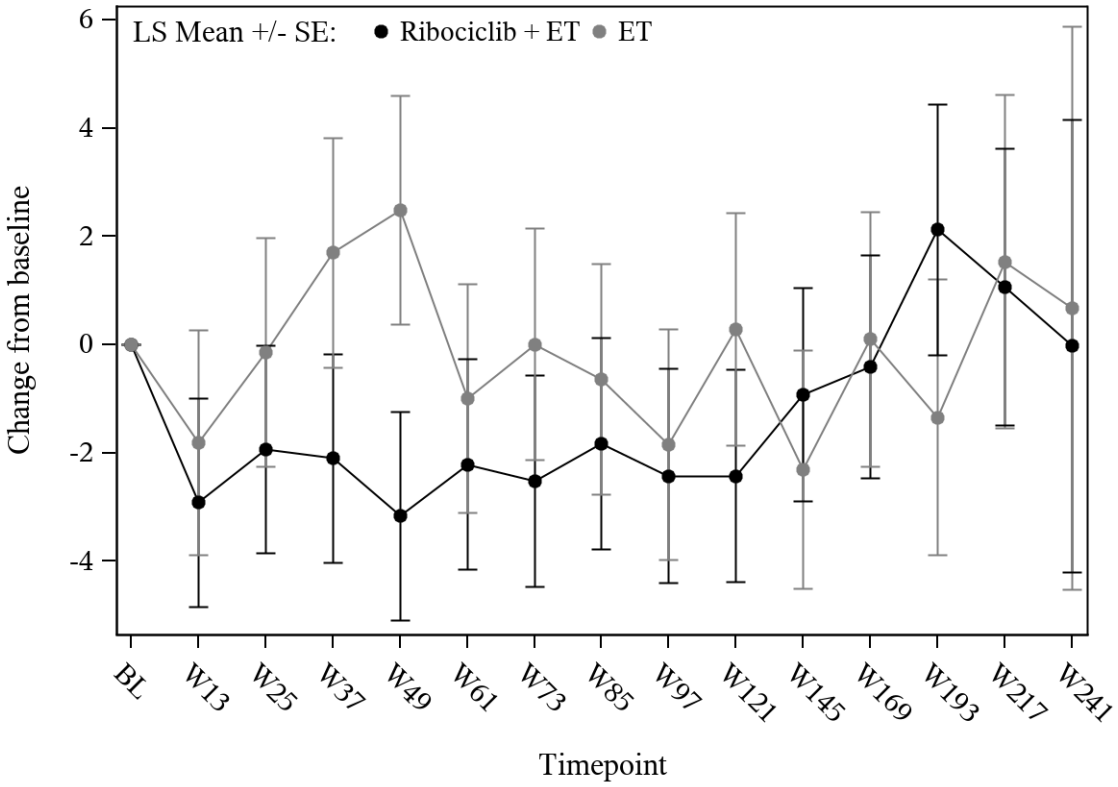
Ribociclib + ET	232	224	216	211	209	205	203	203	202	199	198	178	179	96	14
ET	210	197	190	195	197	193	191	182	183	178	173	168	164	88	14

EQ5D01-Health Today
Anatomic stages: IIIA



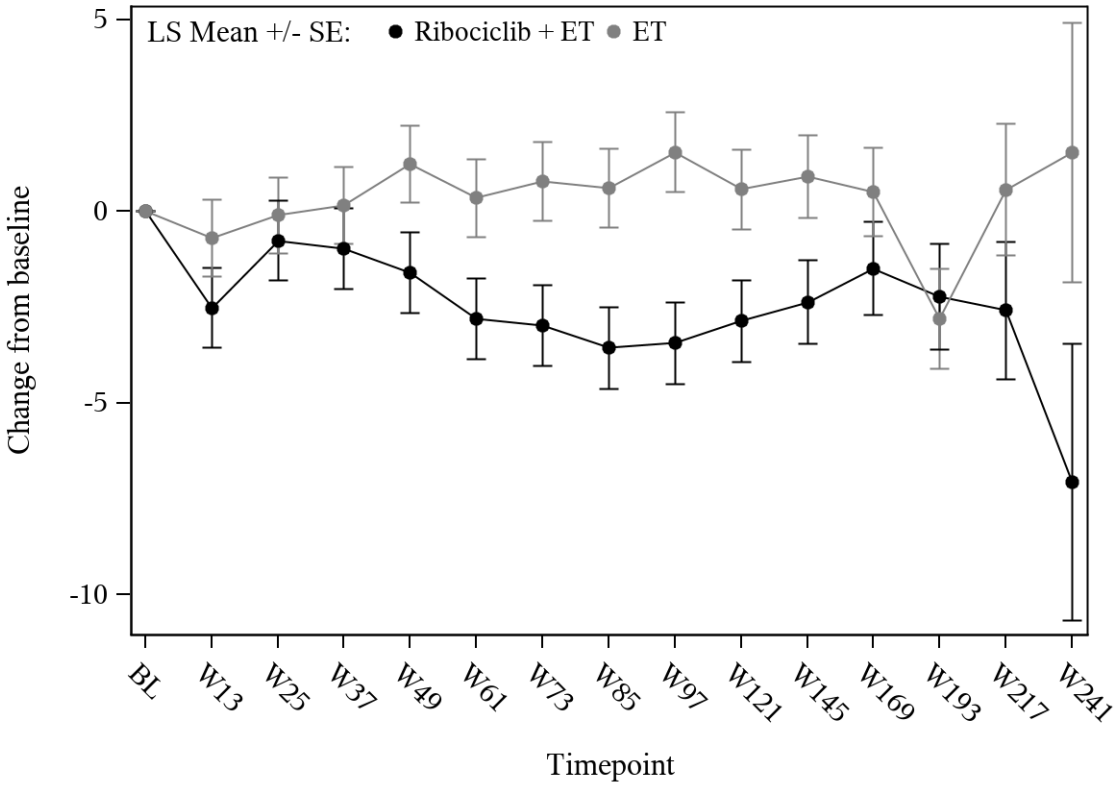
Ribociclib + ET	429	407	385	388	387	385	380	371	370	348	354	266	194	110	15
ET	367	349	339	327	335	326	323	321	313	305	299	223	161	98	13

EQ5D01-Health Today
Anatomic stages: IIIB



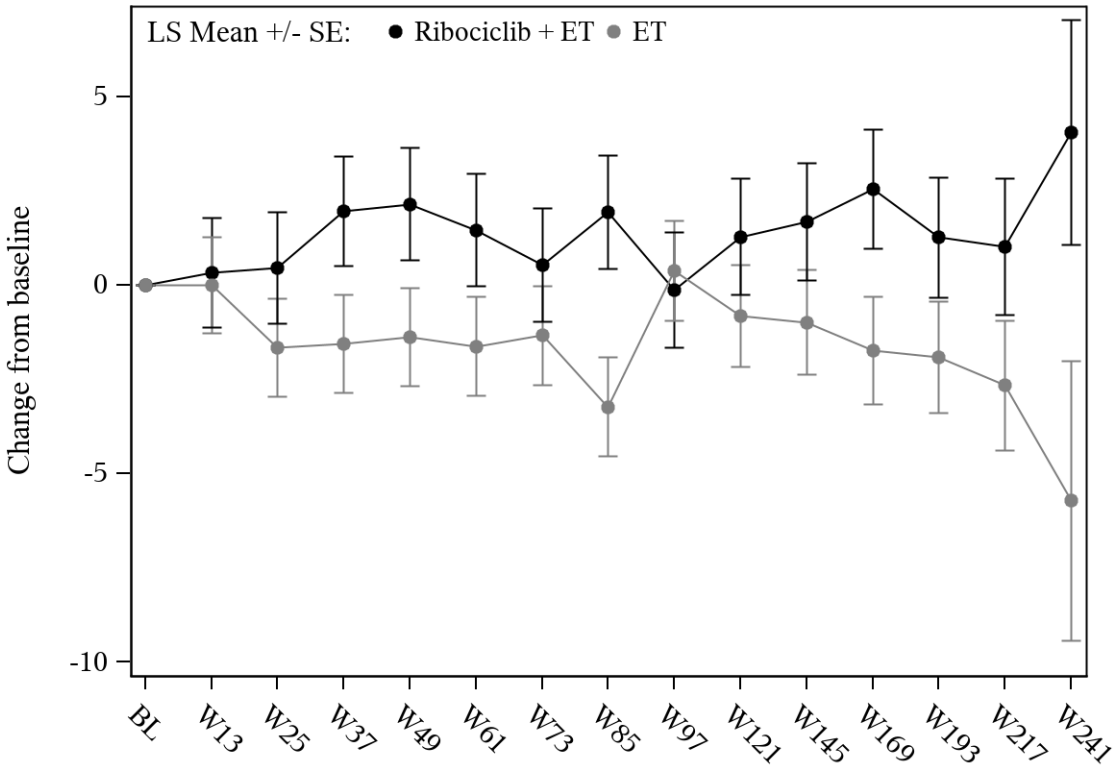
Ribociclib + ET	61	59	60	58	58	57	56	57	54	56	55	45	30	23	6
ET	51	51	48	47	48	49	46	47	47	46	42	32	25	14	4

EQ5D01-Health Today
Anatomic stages: IIIC



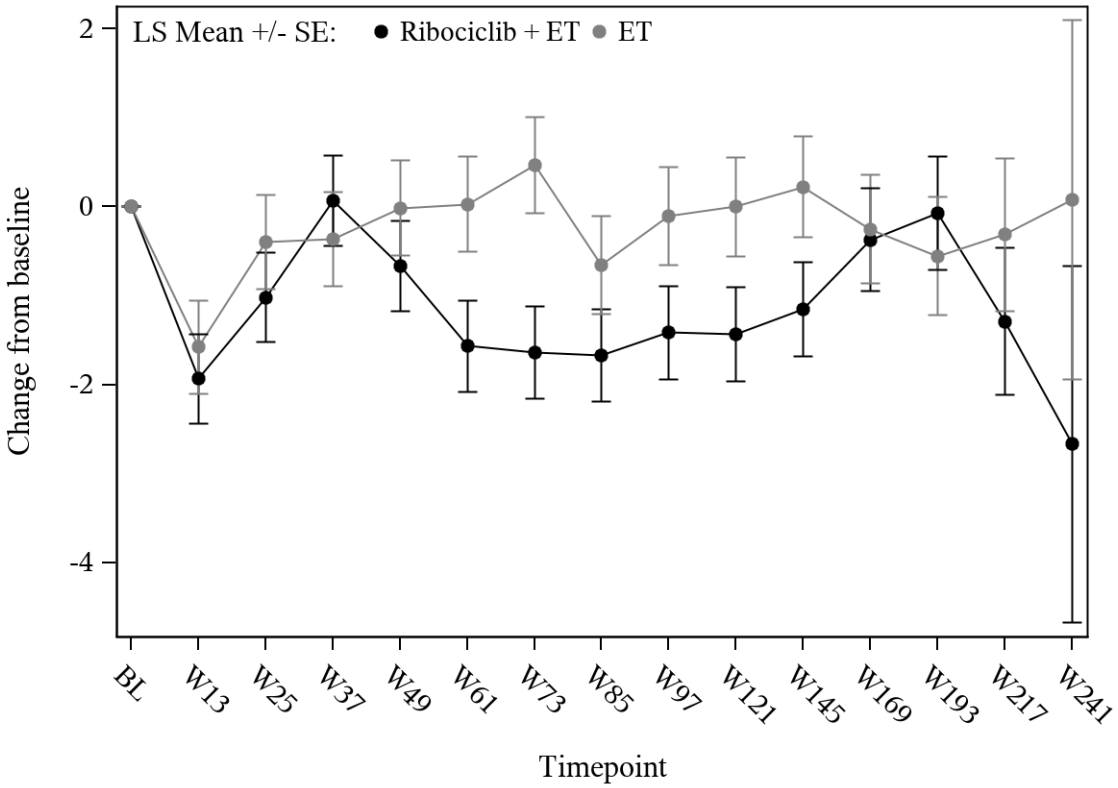
Ribociclib + ET	167	163	159	155	155	155	152	152	151	147	140	96	66	33	6
ET	184	175	177	167	168	162	157	157	151	149	141	108	76	36	7

EQ5D01-Health Today
Nodal status: N0



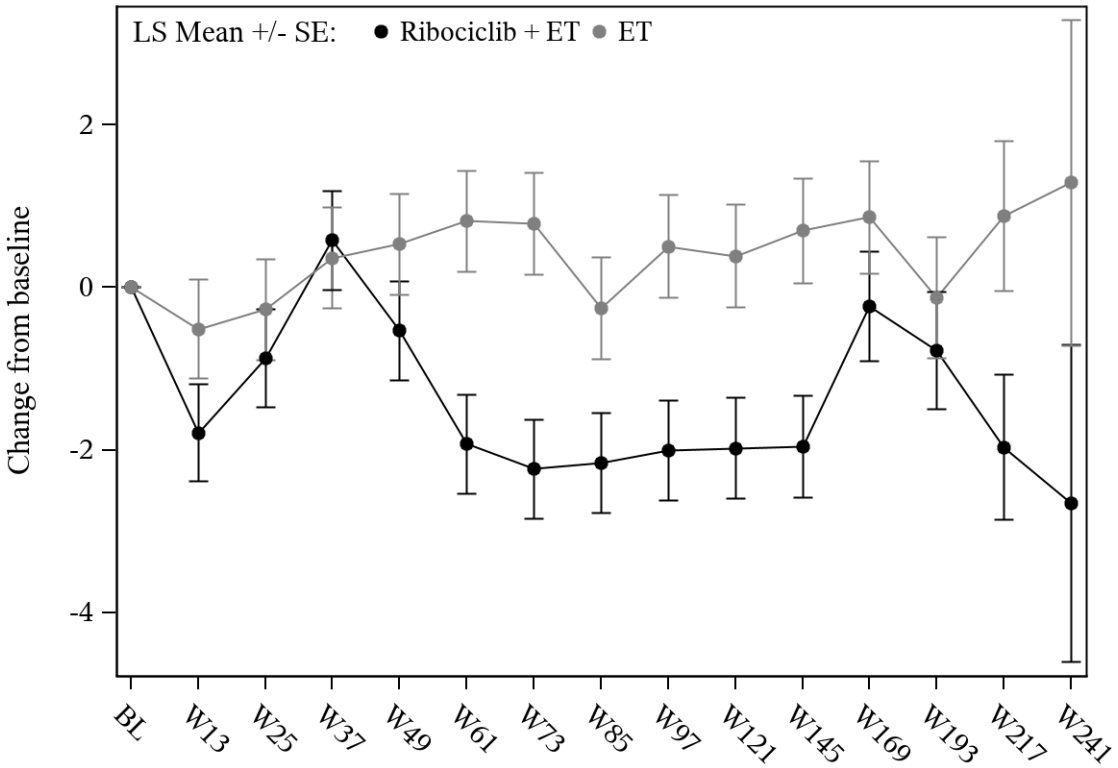
	BL	W13	W25	W37	W49	W61	W73	W85	W97	W121	W145	W169	W193	W217	W241
Ribociclib + ET	84	82	77	82	76	78	74	77	73	71	71	66	65	45	13
ET	110	108	98	97	104	100	99	99	98	93	87	80	76	48	8

EQ5D01-Health Today
Nodal status: N1-N3



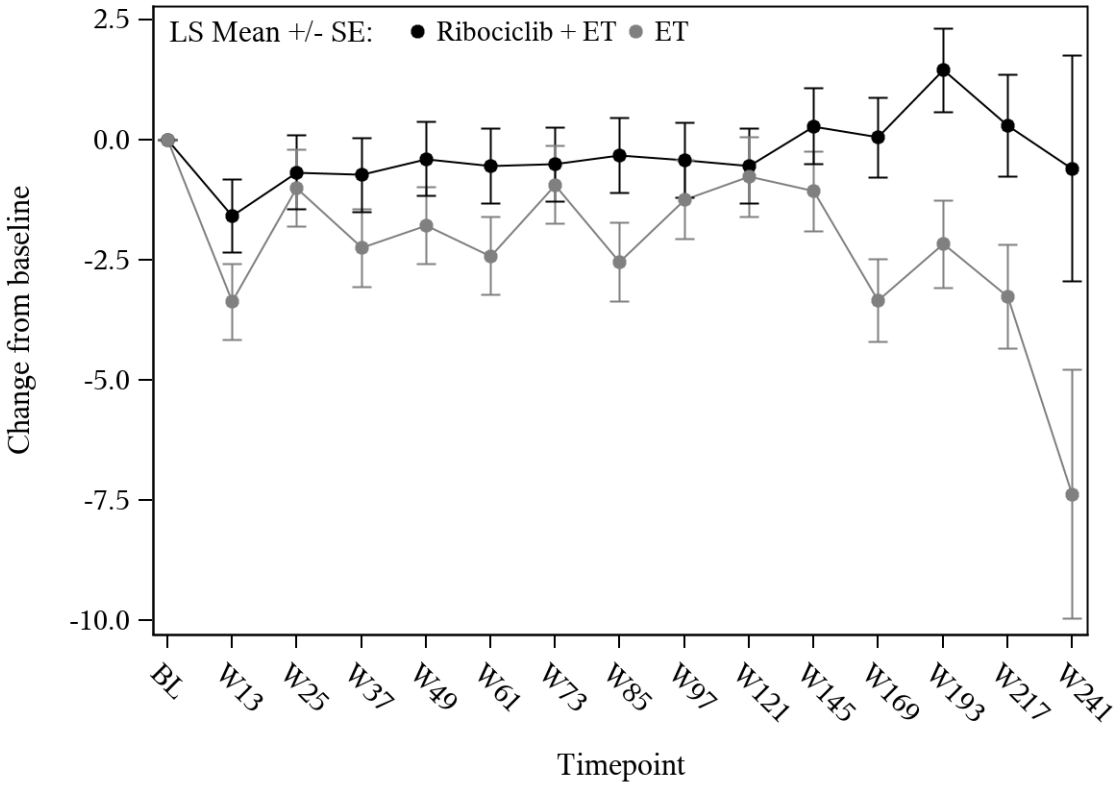
Ribociclib + ET	967	928	897	885	884	878	868	857	852	820	817	655	539	296	44
ET	886	842	814	805	813	793	785	767	756	738	715	596	489	274	44

EQ5D01-Health Today
Prior mastectomy: Yes



Ribociclib + ET	730	697	674	665	658	658	643	641	630	607	604	485	400	230	40
ET	695	660	644	631	643	625	619	611	597	586	557	460	379	215	38

EQ5D01-Health Today
Prior mastectomy: No



Ribociclib + ET	321	313	300	302	302	298	299	293	295	284	284	236	204	111	17
ET	304	293	271	274	275	270	267	257	259	247	247	218	188	109	14

5-2.6 HADS

Table 5-2.6.1.1 HADS - Anxiety: change from baseline analysis - subgroup analysis (Full Analysis Set)

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1115)	ET (N = 1123)	Parameter	Esti-mate	[95% CI]	p-value
HADS - Anxiety						
	N' | LS Mean (SE)	**N' | LS Mean (SE)**				
Region						
Interaction test	**p = 0.014**					
NA/WE/O	587 | 0.58 (0.12)	564 | 0.05 (0.12)	Difference	0.53	[0.20; 0.86]	0.002
			Hedges G	0.18	[0.07; 0.30]	
ROW	459 | 0.19 (0.13)	427 | 0.27 (0.13)	Difference	-0.08	[-0.44; 0.28]	0.652
			Hedges G	-0.03	[-0.16; 0.10]	
Geographical region						
Interaction test	**p = 0.300**					
Europe	606 | 0.56 (0.12)	580 | 0.32 (0.12)	Difference	0.24	[-0.09; 0.57]	0.160
			Hedges G	0.08	[-0.03; 0.20]	
North America/Australia	202 | 0.15 (0.18)	176 | -0.55 (0.19)	Difference	0.71	[0.20; 1.22]	0.007
			Hedges G	0.28	[0.08; 0.48]	
Asia	175 | N.E.	166 | N.E.	Difference	N.E.	[N.E.]	N.E.
			Hedges G	N.E.	[N.E.]	
Latin America	63 | 0.18 (0.35)	69 | -0.00 (0.33)	Difference	0.18	[-0.78; 1.14]	0.715
			Hedges G	0.06	[-0.28; 0.41]	
Age group 1 at randomization						
Interaction test	**N.E.**					
<45	522 | 0.22 (0.12)	456 | 0.11 (0.13)	Difference	0.11	[-0.25; 0.47]	0.548
			Hedges G	0.04	[-0.09; 0.16]	
45 to 54	504 | 0.61 (0.12)	508 | 0.20 (0.12)	Difference	0.41	[0.07; 0.76]	0.019
			Hedges G	0.15	[0.02; 0.27]	
55 to 64	20 | -0.20 (0.58)	27 | -0.60 (0.51)	Difference	0.40	[-1.15; 1.96]	0.605
			Hedges G	0.15	[-0.43; 0.73]	
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)						
Interaction test	**p = 0.382**					
<Median	522 | 0.25 (0.13)	456 | 0.08 (0.14)	Difference	0.16	[-0.21; 0.54]	0.392
			Hedges G	0.05	[-0.07; 0.18]	
≥Median	524 | 0.62 (0.13)	535 | 0.22 (0.13)	Difference	0.40	[0.05; 0.76]	0.027
			Hedges G	0.14	[0.02; 0.26]	

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1115)	**ET (N = 1123)**	**Parameter**	**Esti-mate**	**[95% CI]**	**p-value**
Race						
Interaction test	**p = 0.712**					
Asian	206 | 0.27 (0.19)	180 | 0.18 (0.21)	Difference	0.09	[-0.47; 0.65]	0.759
			Hedges G	0.03	[-0.17; 0.23]	
Non-Asian	792 | 0.39 (0.10)	762 | 0.19 (0.11)	Difference	0.20	[-0.09; 0.49]	0.178
			Hedges G	0.07	[-0.03; 0.17]	
BMI at screening						
Interaction test	**p = 0.140**					
≥25	520 | 0.78 (0.13)	483 | 0.31 (0.14)	Difference	0.47	[0.09; 0.85]	0.015
			Hedges G	0.15	[0.03; 0.28]	
<25	514 | 0.05 (0.13)	498 | 0.04 (0.13)	Difference	0.01	[-0.34; 0.37]	0.937
			Hedges G	0.00	[-0.12; 0.13]	
AJCC Anatomic Stage Group						
Interaction test	**p = 0.004**					
Group I/II	392 | 0.21 (0.15)	393 | 0.40 (0.15)	Difference	-0.19	[-0.61; 0.24]	0.383
			Hedges G	-0.06	[-0.20; 0.08]	
Group III	654 | 0.58 (0.11)	598 | -0.00 (0.12)	Difference	0.58	[0.26; 0.91]	<.001
			Hedges G	0.20	[0.09; 0.31]	
Anatomic stages						
Interaction test	**p = 0.024**					
IA/IB/IIA	163 | -0.19 (0.22)	187 | 0.37 (0.21)	Difference	-0.56	[-1.16; 0.04]	0.066
			Hedges G	-0.20	[-0.41; 0.01]	
IIB	229 | 0.44 (0.19)	206 | 0.37 (0.20)	Difference	0.07	[-0.46; 0.61]	0.792
			Hedges G	0.03	[-0.16; 0.21]	
IIIA	430 | 0.68 (0.13)	363 | -0.03 (0.15)	Difference	0.71	[0.31; 1.10]	<.001
			Hedges G	0.25	[0.11; 0.39]	
IIIB	60 | 0.73 (0.39)	50 | 0.32 (0.43)	Difference	0.41	[-0.75; 1.56]	0.486
			Hedges G	0.13	[-0.24; 0.51]	
IIIC	164 | 0.33 (0.22)	185 | -0.14 (0.21)	Difference	0.46	[-0.13; 1.06]	0.127
			Hedges G	0.16	[-0.05; 0.37]	
Nodal status						
Interaction test	**p = 0.011**					
N0	84 | -0.47 (0.29)	108 | 0.32 (0.26)	Difference	-0.78	[-1.56; -0.01]	0.048
			Hedges G	-0.29	[-0.58; -0.00]	
N1-N3	962 | 0.49 (0.09)	880 | 0.13 (0.10)	Difference	0.36	[0.10; 0.62]	0.007
			Hedges G	0.13	[0.04; 0.22]	

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1115)	**ET (N = 1123)**	**Parameter**	**Esti-mate**	**[95% CI]**	**p-value**
Histological grade at time of surgery						
Interaction test	**p = 0.416**					
Grade 1	104 | 0.33 (0.27)	96 | 0.27 (0.28)	Difference	0.06	[-0.71; 0.82]	0.887
			Hedges G	0.02	[-0.26; 0.30]	
Grade 2	573 | 0.50 (0.12)	547 | 0.09 (0.12)	Difference	0.41	[0.08; 0.74]	0.016
			Hedges G	0.14	[0.03; 0.26]	
Grade 3	278 | 0.24 (0.16)	251 | 0.18 (0.16)	Difference	0.06	[-0.39; 0.51]	0.790
			Hedges G	0.02	[-0.15; 0.19]	
Histological subtype						
Interaction test	**N.E.**					
Ductal	815 | 0.42 (0.08)	778 | 0.18 (0.08)	Difference	0.24	[0.02; 0.46]	0.031
			Hedges G	0.11	[0.01; 0.21]	
Lobular	165 | 0.29 (0.18)	152 | 0.18 (0.19)	Difference	0.11	[-0.41; 0.63]	0.681
			Hedges G	0.05	[-0.17; 0.27]	
Other	66 | 0.12 (0.30)	61 | -0.31 (0.34)	Difference	0.43	[-0.47; 1.33]	0.344
			Hedges G	0.17	[-0.18; 0.52]	
Ki67 status from surgical specimen						
Interaction test	**p = 0.180**					
Ki67≤20	501 | 0.38 (0.13)	511 | 0.34 (0.13)	Difference	0.04	[-0.32; 0.39]	0.831
			Hedges G	0.01	[-0.11; 0.14]	
Ki67>20	396 | 0.43 (0.15)	353 | 0.02 (0.15)	Difference	0.42	[-0.00; 0.83]	0.050
			Hedges G	0.14	[-0.00; 0.29]	
Type of NSAI						
Interaction test	**p = 0.298**					
Letrozole	762 | 0.43 (0.11)	710 | 0.30 (0.11)	Difference	0.13	[-0.17; 0.43]	0.407
			Hedges G	0.04	[-0.06; 0.15]	
Anastrozole	284 | 0.32 (0.18)	280 | -0.13 (0.18)	Difference	0.45	[-0.05; 0.95]	0.077
			Hedges G	0.15	[-0.02; 0.31]	
Prior neo/adjuvant chemotherapy						
Interaction test	**p = 0.443**					
Yes	972 | 0.42 (0.09)	913 | 0.11 (0.10)	Difference	0.31	[0.05; 0.57]	0.019
			Hedges G	0.11	[0.02; 0.20]	
No	74 | 0.05 (0.32)	78 | 0.09 (0.32)	Difference	-0.04	[-0.94; 0.85]	0.922
			Hedges G	-0.02	[-0.33; 0.30]	
Prior adjuvant chemotherapy						
Interaction test	**p = 0.413**					
Yes	489 | 0.51 (0.13)	457 | 0.11 (0.13)	Difference	0.40	[0.04; 0.76]	0.028
			Hedges G	0.14	[0.02; 0.27]	
No	557 | 0.32 (0.12)	534 | 0.18 (0.12)	Difference	0.14	[-0.19; 0.48]	0.402
			Hedges G	0.05	[-0.07; 0.17]	

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1115)	ET (N = 1123)	Parameter	Esti-mate	[95% CI]	p-value
Prior neoadjuvant chemotherapy						
Interaction test	**p = 0.561**					
Yes	513 | 0.33 (0.13)	494 | 0.14 (0.13)	Difference	0.19	[-0.17; 0.55]	0.304
			Hedges G	0.06	[-0.06; 0.19]	
No	533 | 0.54 (0.13)	497 | 0.18 (0.14)	Difference	0.36	[-0.01; 0.73]	0.057
			Hedges G	0.12	[-0.00; 0.24]	
Prior endocrine therapy						
Interaction test	**p = 0.673**					
Yes	806 | 0.38 (0.10)	723 | 0.13 (0.11)	Difference	0.25	[-0.05; 0.55]	0.097
			Hedges G	0.09	[-0.02; 0.19]	
No	240 | 0.59 (0.19)	268 | 0.22 (0.18)	Difference	0.37	[-0.15; 0.89]	0.166
			Hedges G	0.12	[-0.05; 0.30]	
Prior mastectomy						
Interaction test	**p = 0.001**					
Yes	727 | 0.47 (0.11)	690 | -0.05 (0.11)	Difference	0.53	[0.22; 0.84]	<.001
			Hedges G	0.18	[0.08; 0.28]	
No	319 | 0.34 (0.17)	301 | 0.71 (0.18)	Difference	-0.38	[-0.86; 0.10]	0.123
			Hedges G	-0.12	[-0.28; 0.03]	
Prior radiotherapy						
Interaction test	**p = 0.370**					
Yes	957 | 0.41 (0.09)	908 | 0.18 (0.09)	Difference	0.22	[-0.03; 0.48]	0.086
			Hedges G	0.08	[-0.01; 0.17]	
No	89 | 0.35 (0.30)	83 | -0.24 (0.31)	Difference	0.59	[-0.26; 1.44]	0.175
			Hedges G	0.21	[-0.09; 0.51]	

N: Number of patients
N': Number of patients in the analysis
CI: Confidence interval
SD: Standard deviation
LS Mean: Least square mean
SE: Standard error
MMRM: Mixed model for repeated measures
N.E.: Not estimable
ET: Endocrine therapy (Anastrozole/Letrozole + Goserelin)
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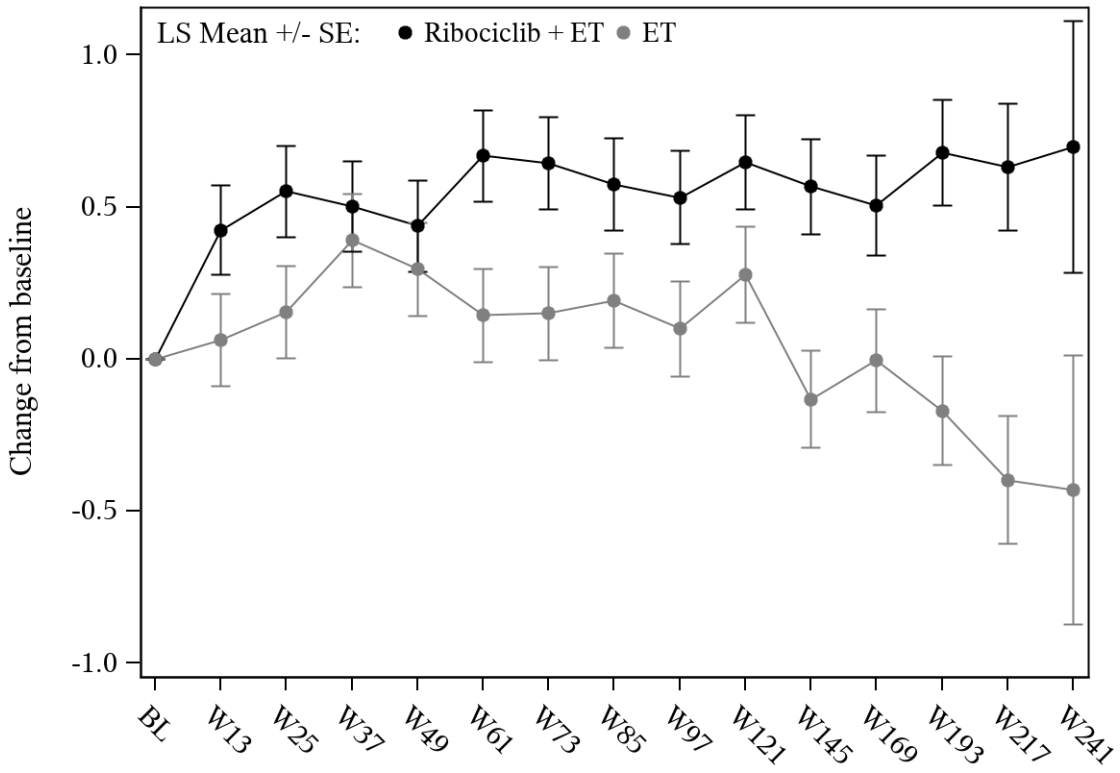
Analysis method for interaction test:
p-value from MMRM with unstructured covariance matrix:
change from baseline = treatment + visit + treatment * visit + subgroup factor + treatment * subgroup factor + subgroup factor * visit + treatment * subgroup factor * visit + baseline value
If the model did not converge for a parameter*subgroup factor, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry. If the model did still not converge, interactions were removed in the order treatment * subgroup factor * visit, subgroup factor * visit.

Analysis methods for within-subgroup analysis:
Adjusted mean (LS Mean) change from baseline and overall effect obtained from MMRM with unstructured covariance matrix:
change from baseline = treatment + visit + treatment * visit + baseline value
ET was the reference group for treatment group comparison.
If the model did not converge for a parameter*subgroup factor, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry.

Patients with an evaluable baseline score and at least one evaluable post-baseline score were included in the analysis.
All data collected were included in the analysis, including assessments at confirmation of first recurrence and thereafter, as long as there were at least 50 patients in each treatment group at a visit in the overall (sub-)population.

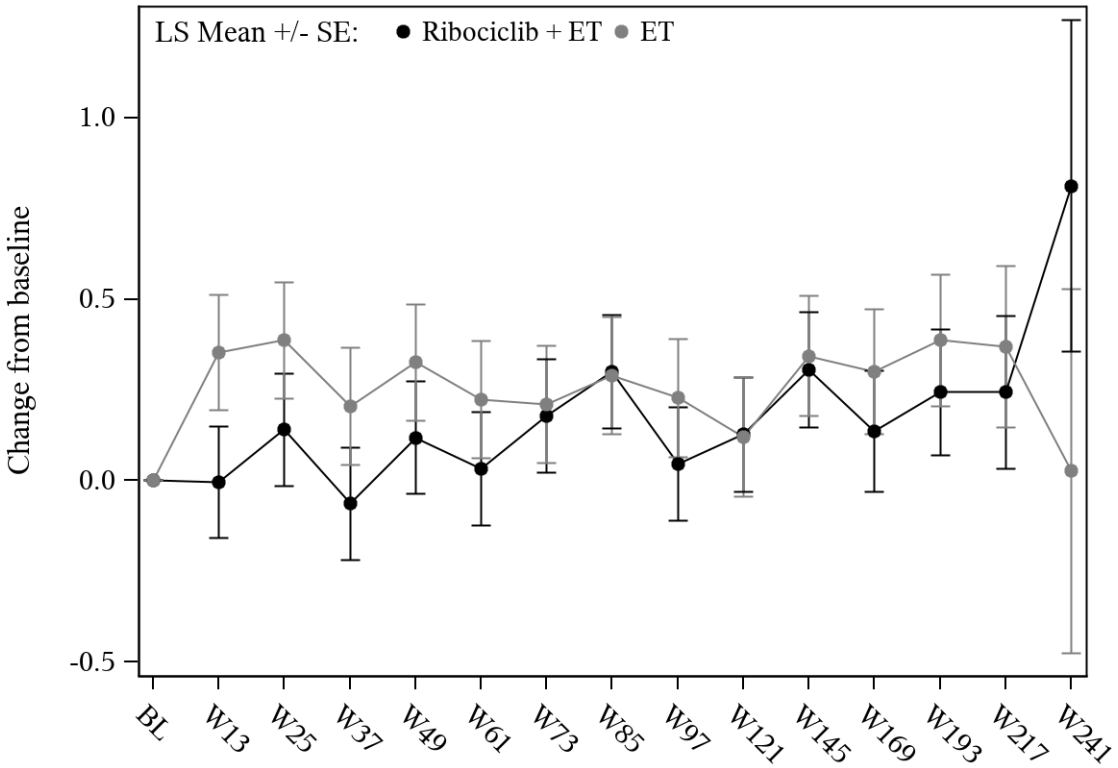
Figure 5-2.6.1.1 HADS - Anxiety: line chart of change from baseline - subgroup analysis (Full Analysis Set)

HADS - Anxiety
Region: NA/WE/O



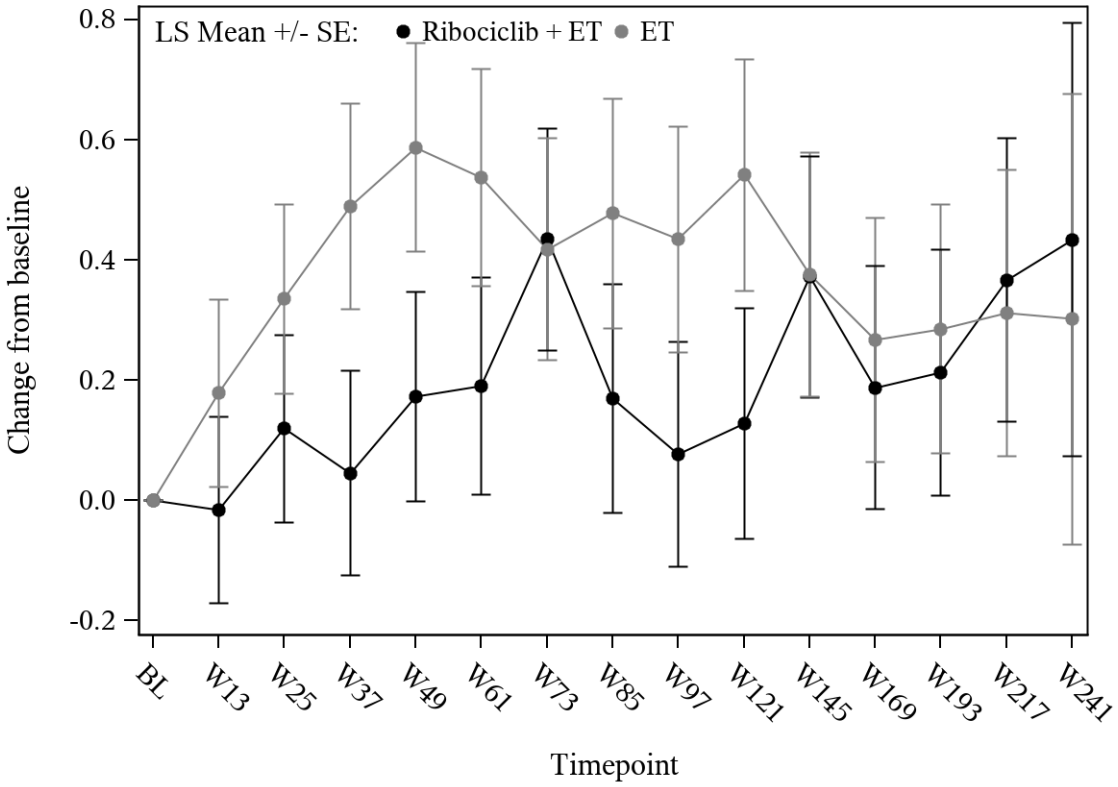
	BL	W13	W25	W37	W49	W61	W73	W85	W97	W121	W145	W169	W193	W217	W241
Ribociclib + ET	587	534	503	515	507	505	486	488	484	463	464	375	309	186	35
ET	564	509	489	484	493	484	481	465	452	445	427	352	295	182	31

HADS - Anxiety
Region: ROW



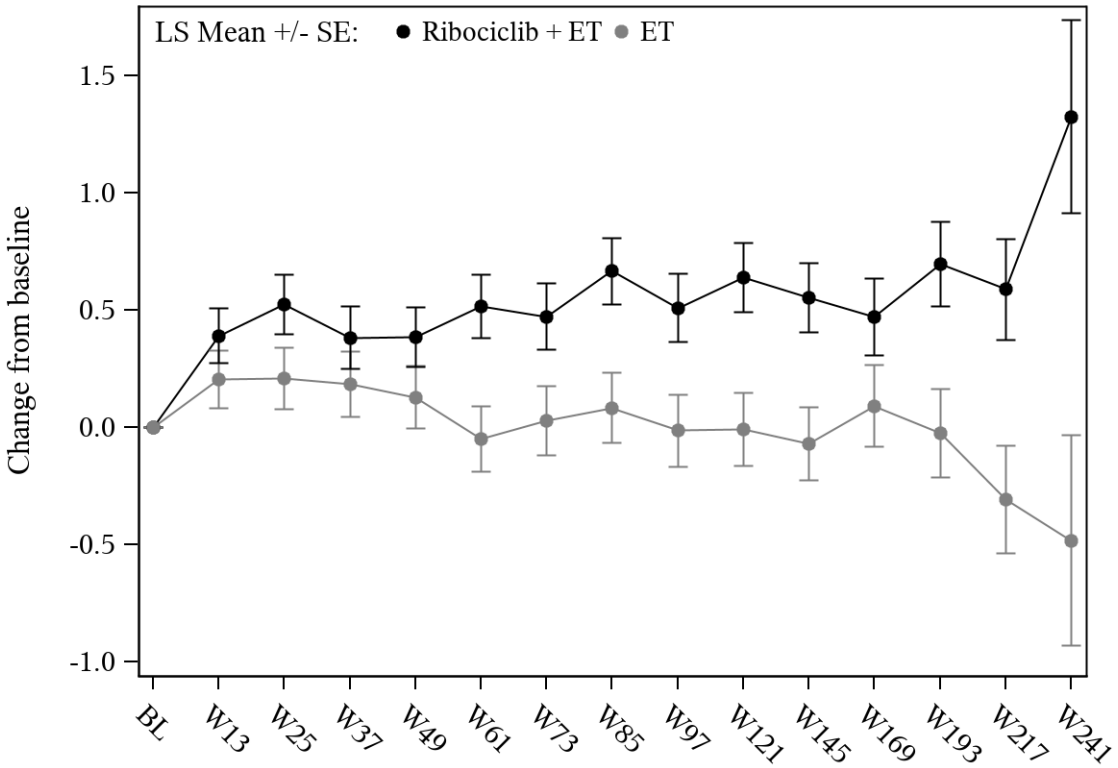
Ribociclib + ET	459	458	449	446	442	434	435	428	429	421	417	340	292	154	23
ET	427	424	416	406	410	402	398	395	387	380	368	316	261	135	19

HADS - Anxiety
AJCC Anatomic Stage Group: Group I/II



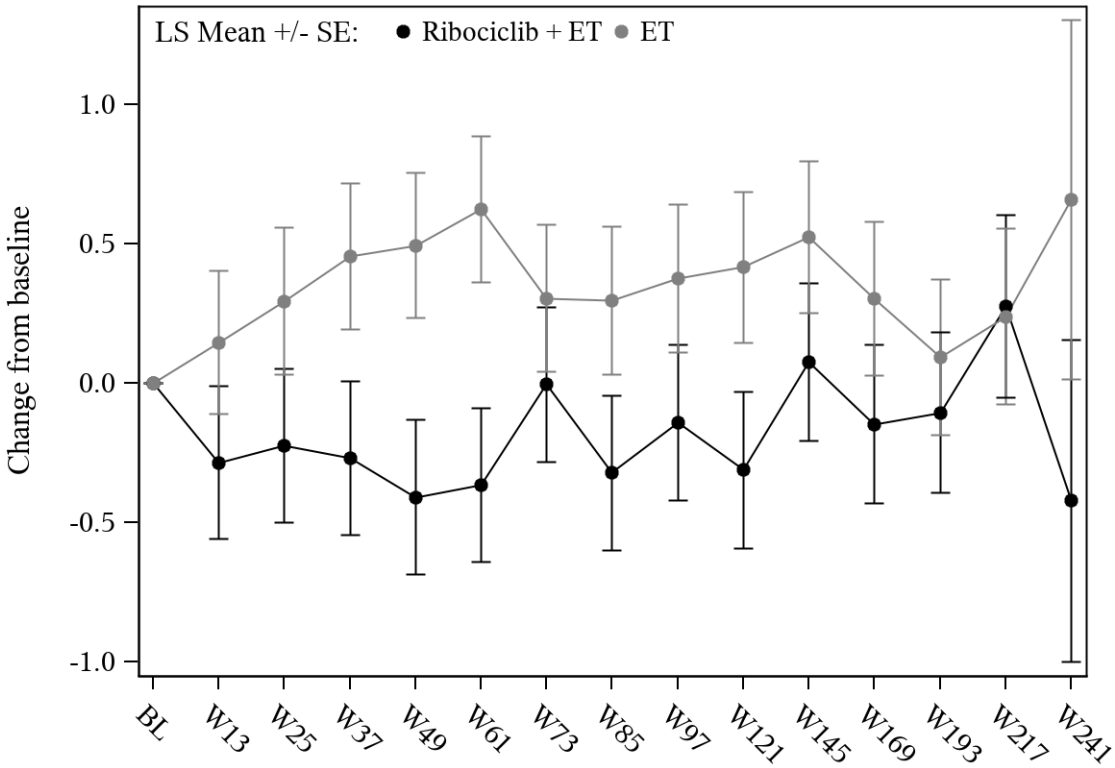
Ribociclib + ET	392	376	362	360	354	354	347	346	345	336	336	311	313	176	31
ET	393	370	346	354	360	351	355	336	339	328	316	310	297	173	27

HADS - Anxiety
AJCC Anatomic Stage Group: Group III



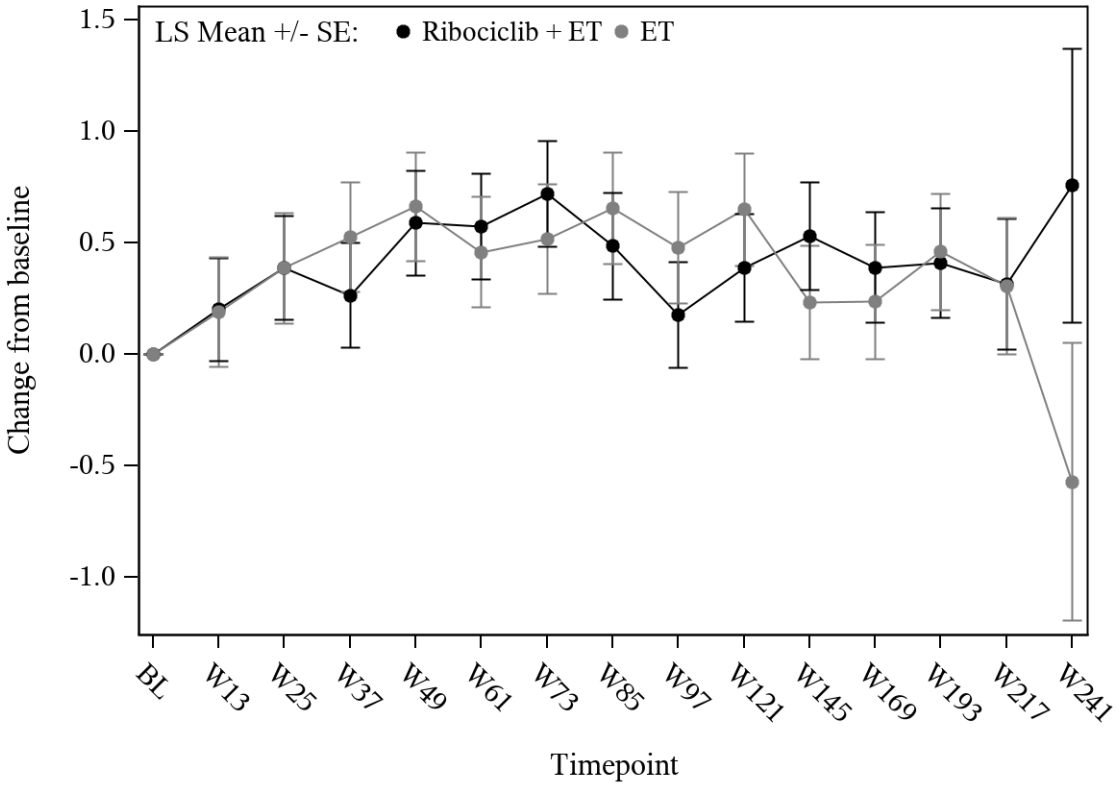
Ribociclib + ET	654	616	590	601	595	585	574	570	568	548	545	404	288	164	27
ET	598	563	559	536	543	535	524	524	500	497	479	358	259	144	23

HADS - Anxiety
Anatomic stages: IA/IB/IIA



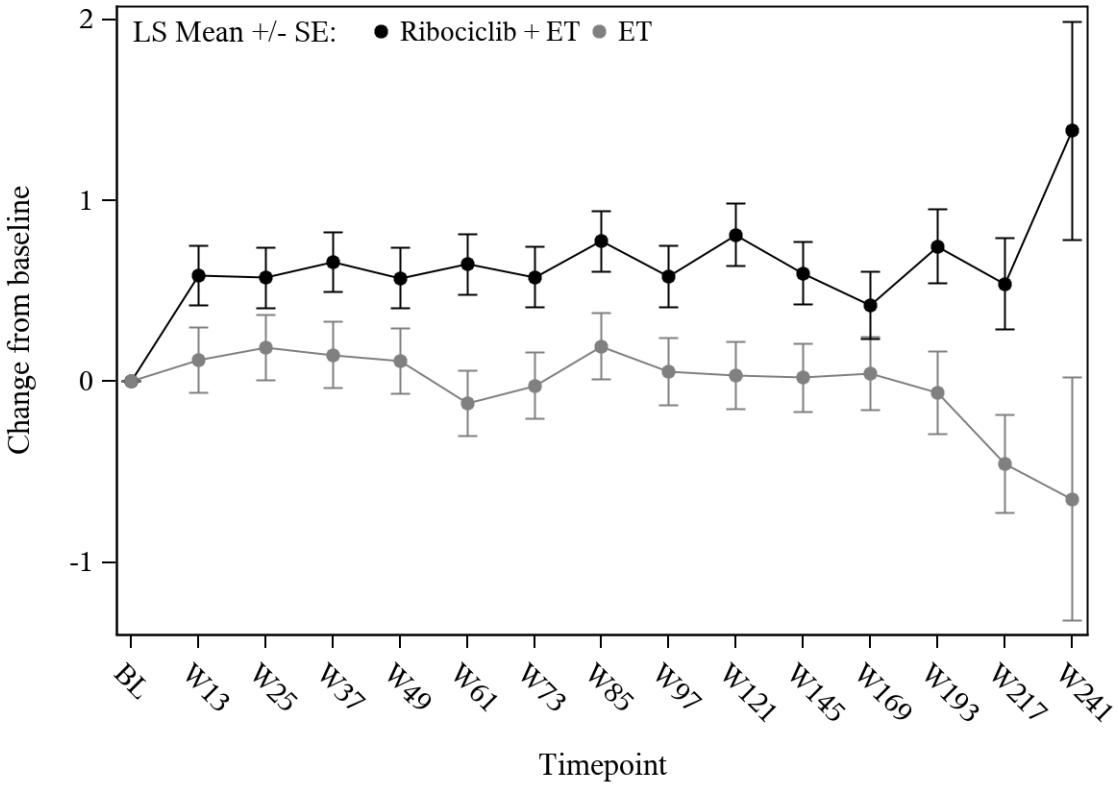
Ribociclib + ET	163	159	153	154	150	155	149	151	145	141	141	136	134	80	17
ET	187	178	158	164	167	164	166	158	159	153	146	144	137	85	13

HADS - Anxiety
Anatomic stages: IIB



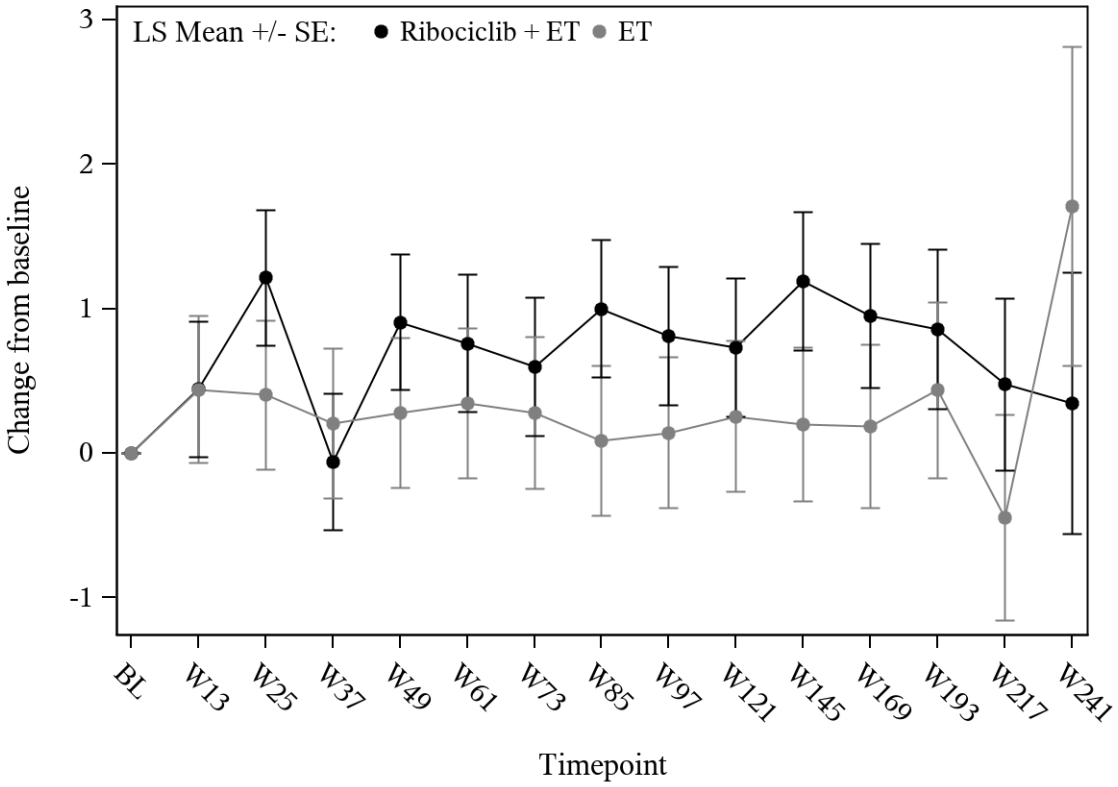
Ribociclib + ET	229	217	209	206	204	199	198	195	200	195	195	175	179	96	14
ET	206	192	188	190	193	187	189	178	180	175	170	166	160	88	14

HADS - Anxiety
Anatomic stages: IIIA



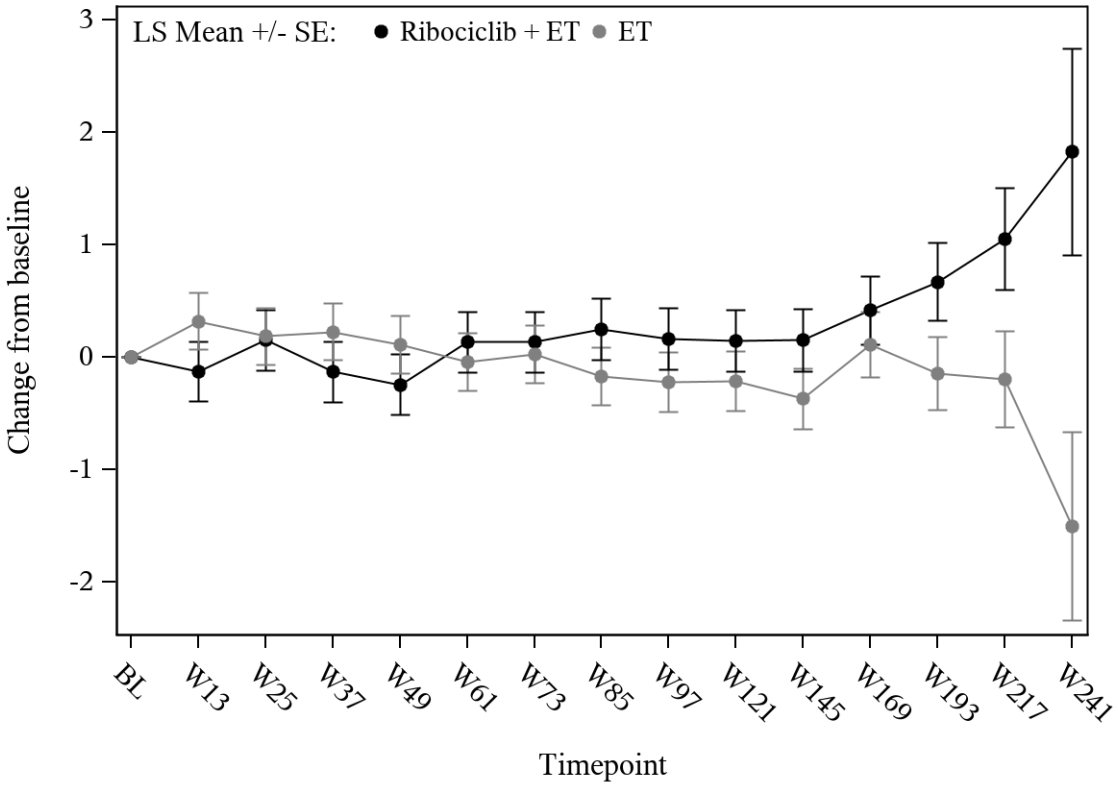
Ribociclib + ET	430	402	382	391	386	381	372	366	368	351	354	266	195	110	15
ET	363	337	334	321	328	323	319	317	302	300	294	217	157	95	12

HADS - Anxiety
Anatomic stages: IIIB



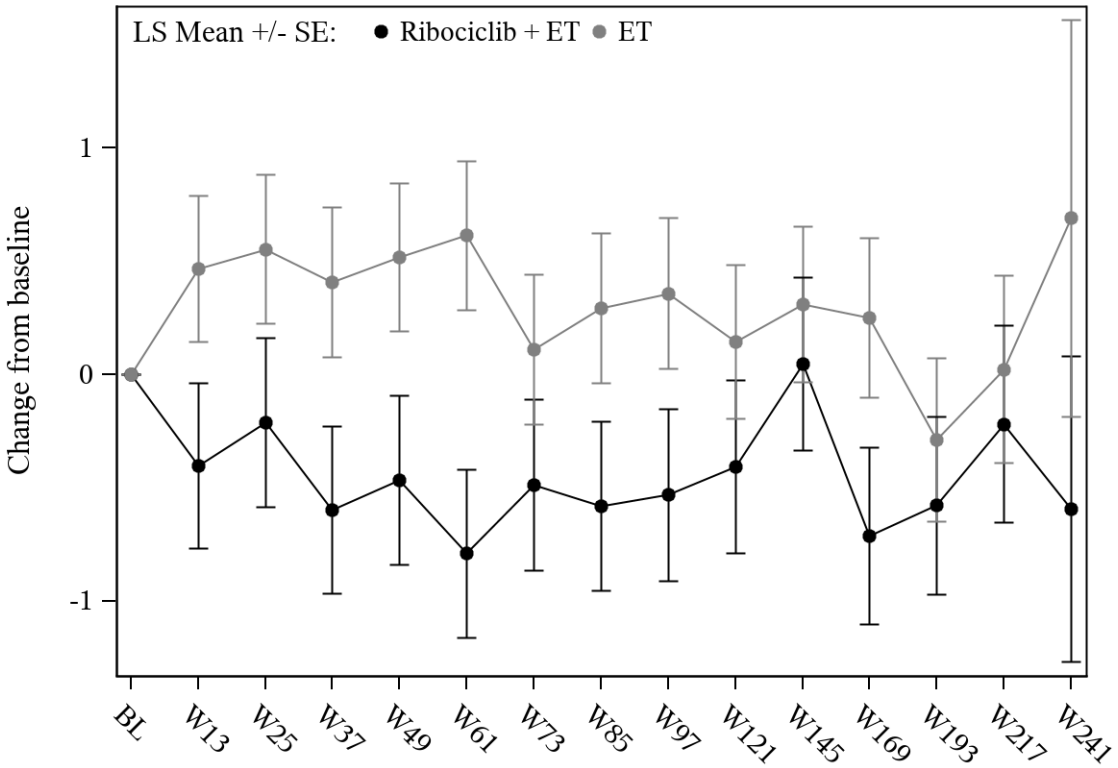
Ribociclib + ET	60	58	58	56	57	54	54	56	53	55	55	44	30	23	6
ET	50	50	48	46	47	48	45	47	46	46	42	32	25	14	4

HADS - Anxiety
Anatomic stages: IIIC



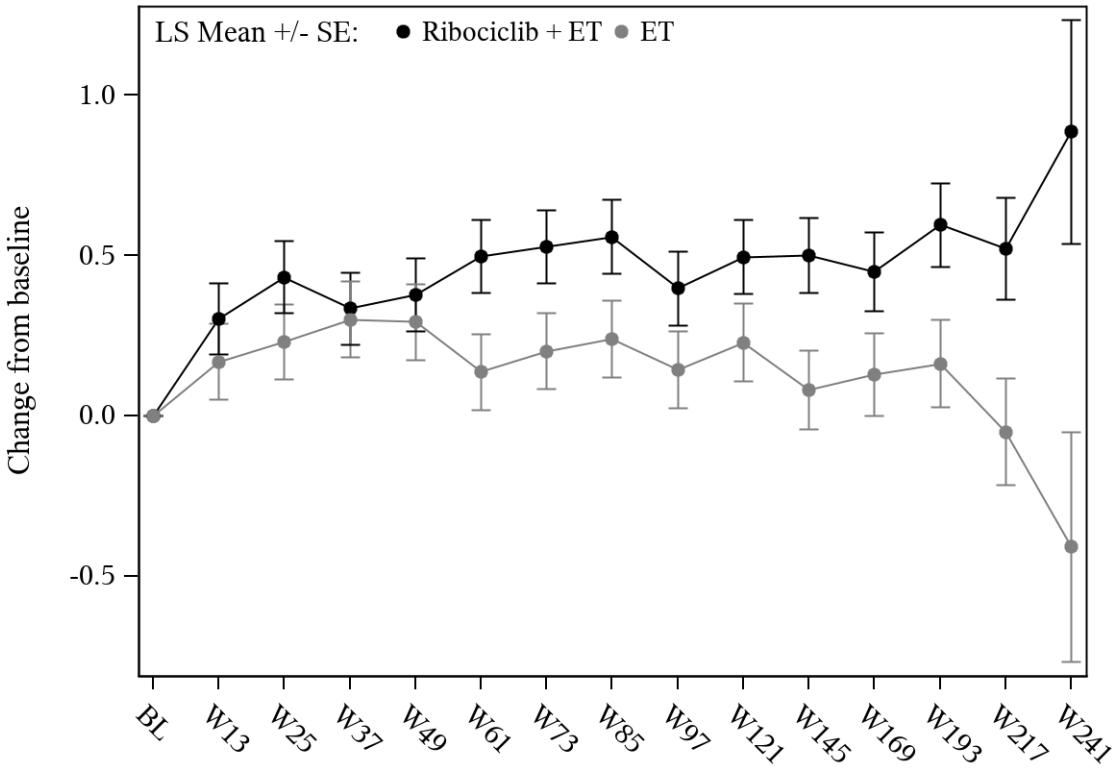
Ribociclib + ET	164	156	150	154	152	150	148	148	147	142	136	94	63	31	6
ET	185	176	177	169	168	164	160	160	152	151	143	109	77	35	7

HADS - Anxiety
Nodal status: N0



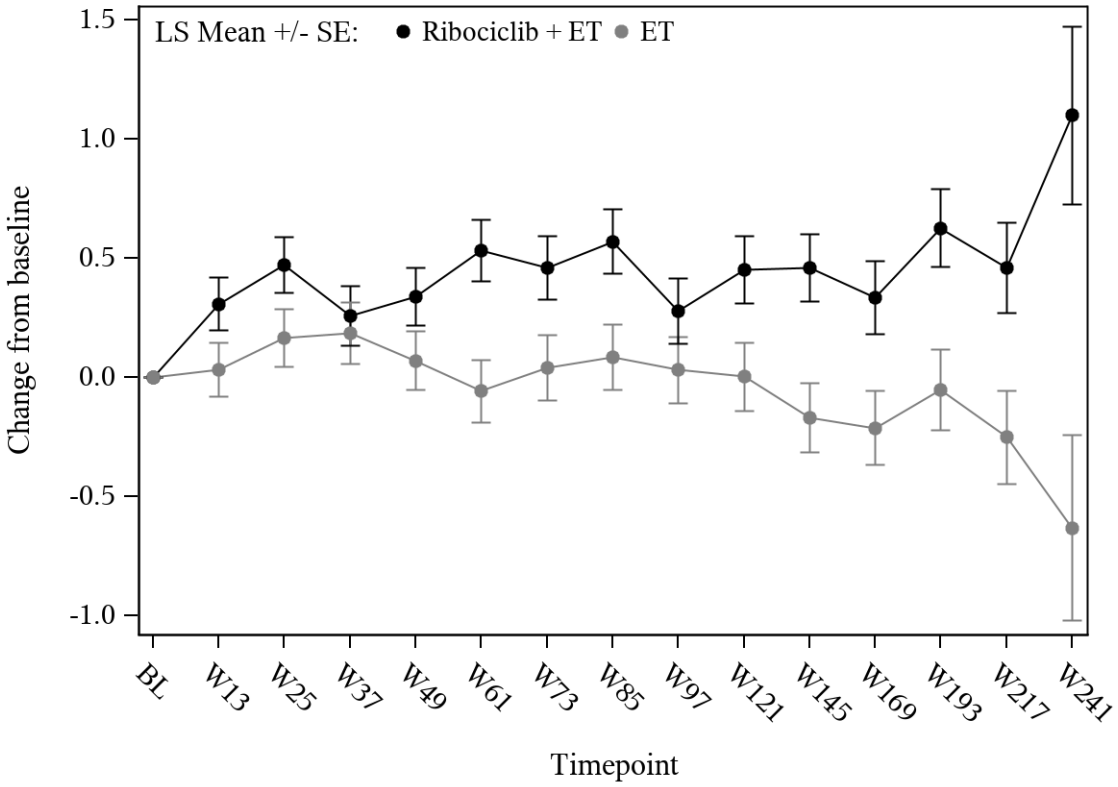
Ribociclib + ET	84	83	76	81	76	78	73	77	73	71	72	66	65	45	13
ET	108	106	97	95	102	100	97	97	96	91	85	78	73	45	7

HADS - Anxiety
Nodal status: N1-N3



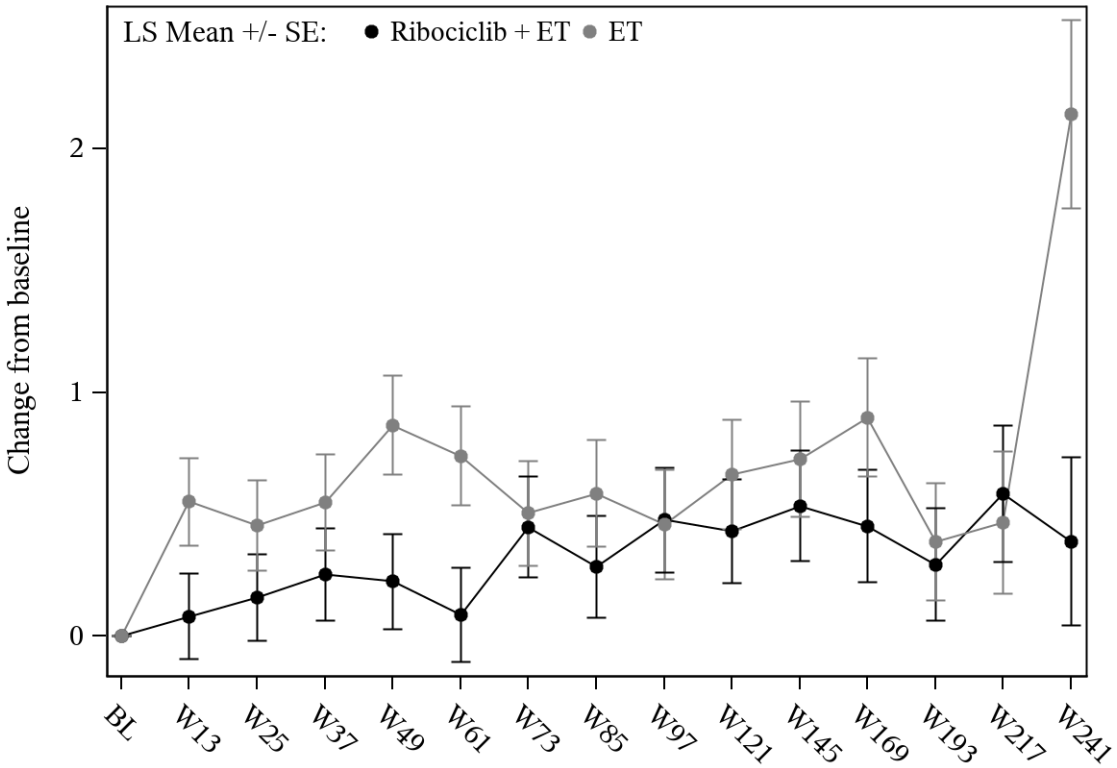
Ribociclib + ET	962	909	876	880	873	861	848	839	840	813	809	649	536	295	45
ET	880	824	805	792	800	784	780	761	741	732	708	588	481	270	43

HADS - Anxiety
Prior mastectomy: Yes



Ribociclib + ET	727	680	655	662	652	645	631	628	625	603	599	480	396	227	40
ET	690	647	637	624	636	620	614	606	588	581	551	453	371	212	37

HADS - Anxiety
Prior mastectomy: No



Ribociclib + ET	319	312	297	299	297	294	290	288	288	281	282	235	205	113	18
ET	301	286	268	266	267	266	265	254	251	244	244	215	185	105	13

Table 5-2.6.2.1 HADS - Depression: change from baseline analysis - subgroup analysis (Full Analysis Set)

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1115)	ET (N = 1123)	Parameter	Esti-mate	[95% CI]	p-value
HADS - Depression						
	N' | LS Mean (SE)	**N' | LS Mean (SE)**				
Region						
Interaction test	**p = 0.562**					
NA/WE/O	586 | 1.01 (0.11)	564 | 0.69 (0.11)	Difference	0.31	[0.00; 0.63]	0.048
			Hedges G	0.12	[0.00; 0.23]	
ROW	459 | 0.78 (0.11)	427 | 0.60 (0.12)	Difference	0.18	[-0.14; 0.50]	0.275
			Hedges G	0.07	[-0.06; 0.21]	
Geographical region						
Interaction test	**N.E.**					
Europe	604 | 1.15 (0.09)	580 | 0.83 (0.09)	Difference	0.32	[0.08; 0.56]	0.010
			Hedges G	0.15	[0.04; 0.26]	
North America/Australia	203 | 0.52 (0.13)	176 | 0.31 (0.14)	Difference	0.20	[-0.17; 0.58]	0.282
			Hedges G	0.11	[-0.09; 0.31]	
Asia	175 | N.E.	166 | N.E.	Difference	N.E.	[N.E.]	N.E.
			Hedges G	N.E.	[N.E.]	
Latin America	63 | 1.10 (0.21)	69 | 0.34 (0.20)	Difference	0.77	[0.18; 1.35]	0.011
			Hedges G	0.45	[0.11; 0.80]	
Age group 1 at randomization						
Interaction test	**p = 0.855**					
<45	522 | 0.81 (0.11)	456 | 0.57 (0.12)	Difference	0.24	[-0.08; 0.56]	0.141
			Hedges G	0.09	[-0.03; 0.22]	
45 to 54	503 | 1.03 (0.12)	508 | 0.72 (0.12)	Difference	0.31	[-0.01; 0.64]	0.060
			Hedges G	0.12	[-0.01; 0.24]	
55 to 64	20 | 0.89 (0.52)	27 | 0.75 (0.45)	Difference	0.14	[-1.26; 1.53]	0.843
			Hedges G	0.06	[-0.52; 0.64]	
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)						
Interaction test	**p = 0.781**					
<Median	522 | 0.77 (0.12)	456 | 0.57 (0.12)	Difference	0.20	[-0.14; 0.53]	0.244
			Hedges G	0.07	[-0.05; 0.20]	
≥Median	523 | 1.06 (0.12)	535 | 0.72 (0.12)	Difference	0.34	[0.00; 0.68]	0.047
			Hedges G	0.12	[0.00; 0.24]	

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1115)	**ET (N = 1123)**	**Parameter**	**Esti-mate**	**[95% CI]**	**p-value**
Race						
Interaction test	**p = 0.453**					
Asian	206 | 0.33 (0.18)	180 | 0.23 (0.19)	Difference	0.10	[-0.41; 0.62]	0.696
			Hedges G	0.04	[-0.16; 0.24]	
Non-Asian	791 | 1.06 (0.09)	762 | 0.72 (0.10)	Difference	0.34	[0.07; 0.60]	0.012
			Hedges G	0.13	[0.03; 0.23]	
BMI at screening						
Interaction test	**p = 0.272**					
≥25	520 | 1.30 (0.13)	483 | 0.88 (0.13)	Difference	0.42	[0.06; 0.78]	0.022
			Hedges G	0.15	[0.02; 0.27]	
<25	513 | 0.55 (0.11)	498 | 0.43 (0.11)	Difference	0.12	[-0.19; 0.43]	0.443
			Hedges G	0.05	[-0.08; 0.17]	
AJCC Anatomic Stage Group						
Interaction test	**p = 0.040**					
Group I/II	391 | 0.97 (0.13)	393 | 0.97 (0.13)	Difference	-0.00	[-0.38; 0.37]	0.984
			Hedges G	-0.00	[-0.14; 0.14]	
Group III	654 | 0.90 (0.11)	598 | 0.42 (0.11)	Difference	0.48	[0.17; 0.79]	0.002
			Hedges G	0.17	[0.06; 0.29]	
Anatomic stages						
Interaction test	**N.E.**					
IA/IB/IIA	163 | 0.67 (0.19)	187 | 0.84 (0.18)	Difference	-0.17	[-0.69; 0.35]	0.528
			Hedges G	-0.07	[-0.28; 0.14]	
IIB	228 | 1.15 (0.17)	206 | 1.06 (0.18)	Difference	0.08	[-0.40; 0.57]	0.734
			Hedges G	0.03	[-0.16; 0.22]	
IIIA	429 | 0.97 (0.12)	363 | 0.54 (0.14)	Difference	0.43	[0.07; 0.79]	0.019
			Hedges G	0.17	[0.03; 0.31]	
IIIB	60 | 1.06 (0.37)	50 | 0.65 (0.40)	Difference	0.41	[-0.69; 1.51]	0.460
			Hedges G	0.14	[-0.23; 0.52]	
IIIC	165 | 0.69 (0.20)	185 | 0.07 (0.19)	Difference	0.62	[0.06; 1.17]	0.029
			Hedges G	0.23	[0.02; 0.45]	
Nodal status						
Interaction test	**p = 0.234**					
N0	84 | 0.70 (0.26)	108 | 0.88 (0.23)	Difference	-0.18	[-0.87; 0.50]	0.598
			Hedges G	-0.08	[-0.36; 0.21]	
N1-N3	961 | 0.94 (0.08)	880 | 0.62 (0.09)	Difference	0.32	[0.09; 0.56]	0.008
			Hedges G	0.12	[0.03; 0.22]	

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1115)	**ET (N = 1123)**	**Parameter**	**Esti-mate**	**[95% CI]**	**p-value**
Histological grade at time of surgery						
Interaction test	**p = 0.635**					
Grade 1	104 | 0.89 (0.26)	96 | 0.79 (0.27)	Difference	0.10	[-0.65; 0.84]	0.795
			Hedges G	0.04	[-0.24; 0.31]	
Grade 2	573 | 1.01 (0.11)	547 | 0.63 (0.12)	Difference	0.39	[0.07; 0.71]	0.018
			Hedges G	0.14	[0.02; 0.26]	
Grade 3	277 | 0.69 (0.15)	251 | 0.51 (0.16)	Difference	0.18	[-0.25; 0.61]	0.422
			Hedges G	0.07	[-0.10; 0.24]	
Histological subtype						
Interaction test	**p = 0.329**					
Ductal	815 | N.E.	778 | N.E.	Difference	N.E.	[N.E.]	N.E.
			Hedges G	N.E.	[N.E.]	
Lobular	165 | 0.67 (0.20)	152 | 0.67 (0.21)	Difference	0.00	[-0.56; 0.57]	0.990
			Hedges G	0.00	[-0.22; 0.22]	
Other	65 | 0.23 (0.33)	61 | 0.38 (0.35)	Difference	-0.15	[-1.10; 0.80]	0.760
			Hedges G	-0.05	[-0.40; 0.29]	
Ki67 status from surgical specimen						
Interaction test	**p = 0.912**					
Ki67≤20	502 | 0.93 (0.12)	511 | 0.62 (0.12)	Difference	0.31	[-0.03; 0.65]	0.075
			Hedges G	0.11	[-0.01; 0.24]	
Ki67>20	394 | 0.97 (0.13)	353 | 0.63 (0.14)	Difference	0.34	[-0.03; 0.70]	0.071
			Hedges G	0.13	[-0.01; 0.28]	
Type of NSAI						
Interaction test	**p = 0.389**					
Letrozole	760 | 0.85 (0.10)	710 | 0.66 (0.10)	Difference	0.19	[-0.08; 0.47]	0.170
			Hedges G	0.07	[-0.03; 0.17]	
Anastrozole	285 | 1.11 (0.17)	280 | 0.67 (0.17)	Difference	0.43	[-0.04; 0.91]	0.072
			Hedges G	0.15	[-0.01; 0.32]	
Prior neo/adjuvant chemotherapy						
Interaction test	**p = 0.440**					
Yes	971 | 0.91 (0.08)	913 | 0.62 (0.09)	Difference	0.29	[0.06; 0.53]	0.015
			Hedges G	0.11	[0.02; 0.20]	
No	74 | 0.90 (0.26)	78 | 0.88 (0.26)	Difference	0.02	[-0.72; 0.76]	0.955
			Hedges G	0.01	[-0.31; 0.33]	
Prior adjuvant chemotherapy						
Interaction test	**p = 0.835**					
Yes	487 | 0.91 (0.12)	457 | 0.69 (0.13)	Difference	0.23	[-0.12; 0.57]	0.194
			Hedges G	0.08	[-0.04; 0.21]	
No	558 | 0.94 (0.12)	534 | 0.64 (0.12)	Difference	0.29	[-0.03; 0.62]	0.078
			Hedges G	0.11	[-0.01; 0.23]	

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1115)	ET (N = 1123)	Parameter	Esti-mate	[95% CI]	p-value
Prior neoadjuvant chemotherapy						
Interaction test	**p = 0.488**					
Yes	514 | 0.91 (0.12)	494 | 0.61 (0.12)	Difference	0.30	[-0.04; 0.64]	0.081
			Hedges G	0.11	[-0.01; 0.23]	
No	531 | 0.93 (0.12)	497 | 0.71 (0.12)	Difference	0.22	[-0.11; 0.55]	0.198
			Hedges G	0.08	[-0.04; 0.20]	
Prior endocrine therapy						
Interaction test	**p = 0.578**					
Yes	807 | 0.93 (0.10)	723 | 0.68 (0.10)	Difference	0.25	[-0.02; 0.53]	0.070
			Hedges G	0.09	[-0.01; 0.19]	
No	238 | 0.92 (0.17)	268 | 0.60 (0.17)	Difference	0.32	[-0.15; 0.79]	0.183
			Hedges G	0.12	[-0.06; 0.29]	
Prior mastectomy						
Interaction test	**p = 0.007**					
Yes	726 | 0.91 (0.10)	690 | 0.46 (0.10)	Difference	0.46	[0.17; 0.74]	0.002
			Hedges G	0.17	[0.06; 0.27]	
No	319 | 0.89 (0.15)	301 | 1.07 (0.15)	Difference	-0.18	[-0.60; 0.23]	0.387
			Hedges G	-0.07	[-0.23; 0.09]	
Prior radiotherapy						
Interaction test	**p = 0.850**					
Yes	956 | N.E.	908 | N.E.	Difference	N.E.	[N.E.]	N.E.
			Hedges G	N.E.	[N.E.]	
No	89 | 0.82 (0.28)	83 | 0.43 (0.29)	Difference	0.39	[-0.40; 1.18]	0.332
			Hedges G	0.15	[-0.15; 0.45]	

N: Number of patients
N': Number of patients in the analysis
CI: Confidence interval
SD: Standard deviation
LS Mean: Least square mean
SE: Standard error
MMRM: Mixed model for repeated measures
N.E.: Not estimable
ET: Endocrine therapy (Anastrozole/Letrozole + Goserelin)
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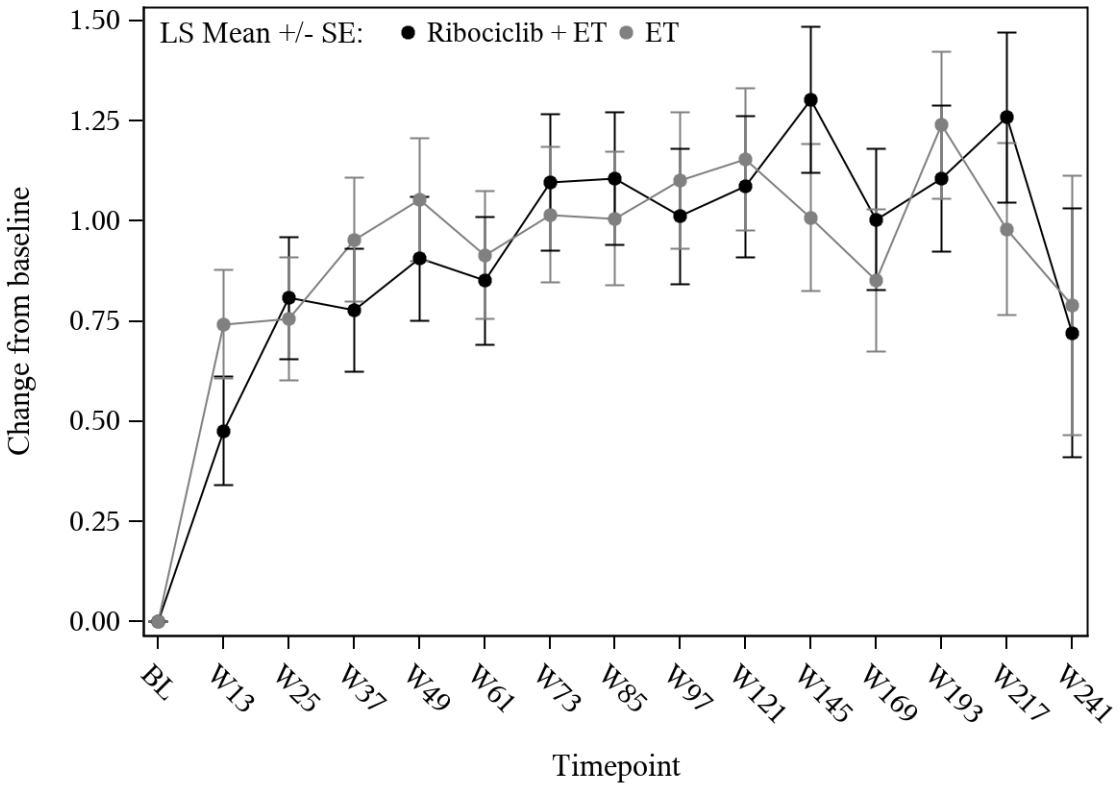
Analysis method for interaction test:
p-value from MMRM with unstructured covariance matrix:
change from baseline = treatment + visit + treatment * visit + subgroup factor + treatment * subgroup factor + subgroup factor * visit + treatment * subgroup factor * visit + baseline value
If the model did not converge for a parameter*subgroup factor, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry. If the model did still not converge, interactions were removed in the order treatment * subgroup factor * visit, subgroup factor * visit.

Analysis methods for within-subgroup analysis:
Adjusted mean (LS Mean) change from baseline and overall effect obtained from MMRM with unstructured covariance matrix:
change from baseline = treatment + visit + treatment * visit + baseline value
ET was the reference group for treatment group comparison.
If the model did not converge for a parameter*subgroup factor, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry.

Patients with an evaluable baseline score and at least one evaluable post-baseline score were included in the analysis.
All data collected were included in the analysis, including assessments at confirmation of first recurrence and thereafter, as long as there were at least 50 patients in each treatment group at a visit in the overall (sub-)population.

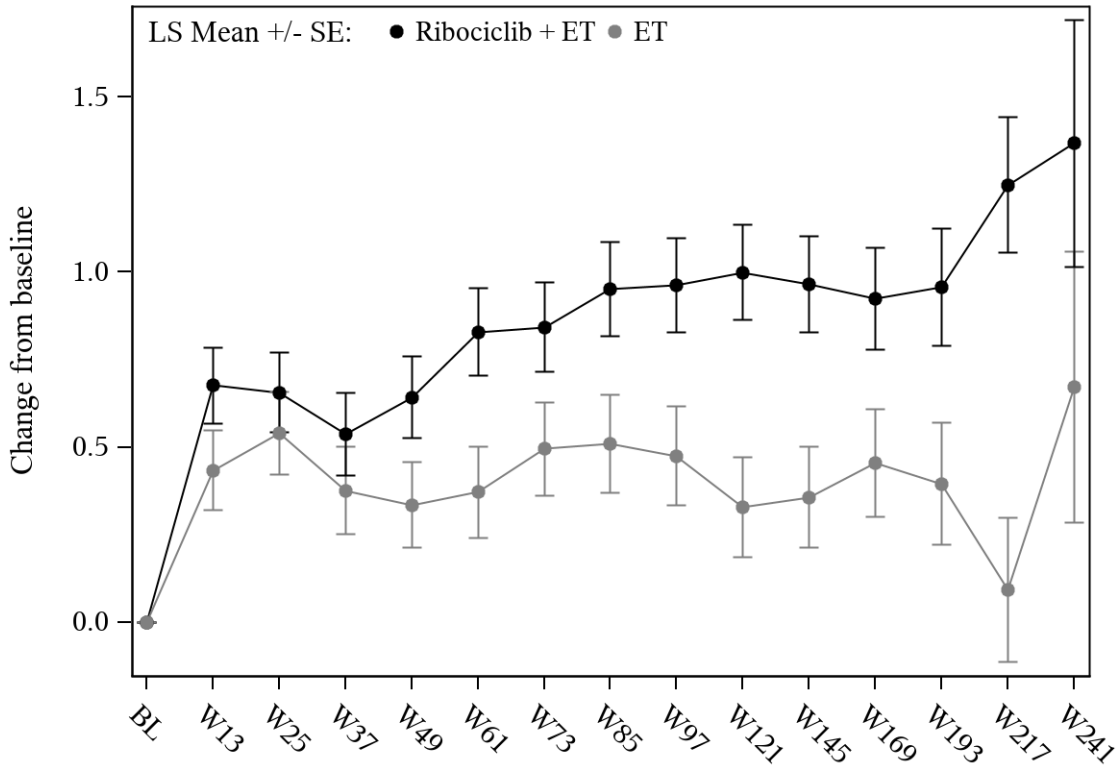
Figure 5-2.6.2.1 HADS - Depression: line chart of change from baseline - subgroup analysis (Full Analysis Set)

HADS - Depression
AJCC Anatomic Stage Group: Group I/II



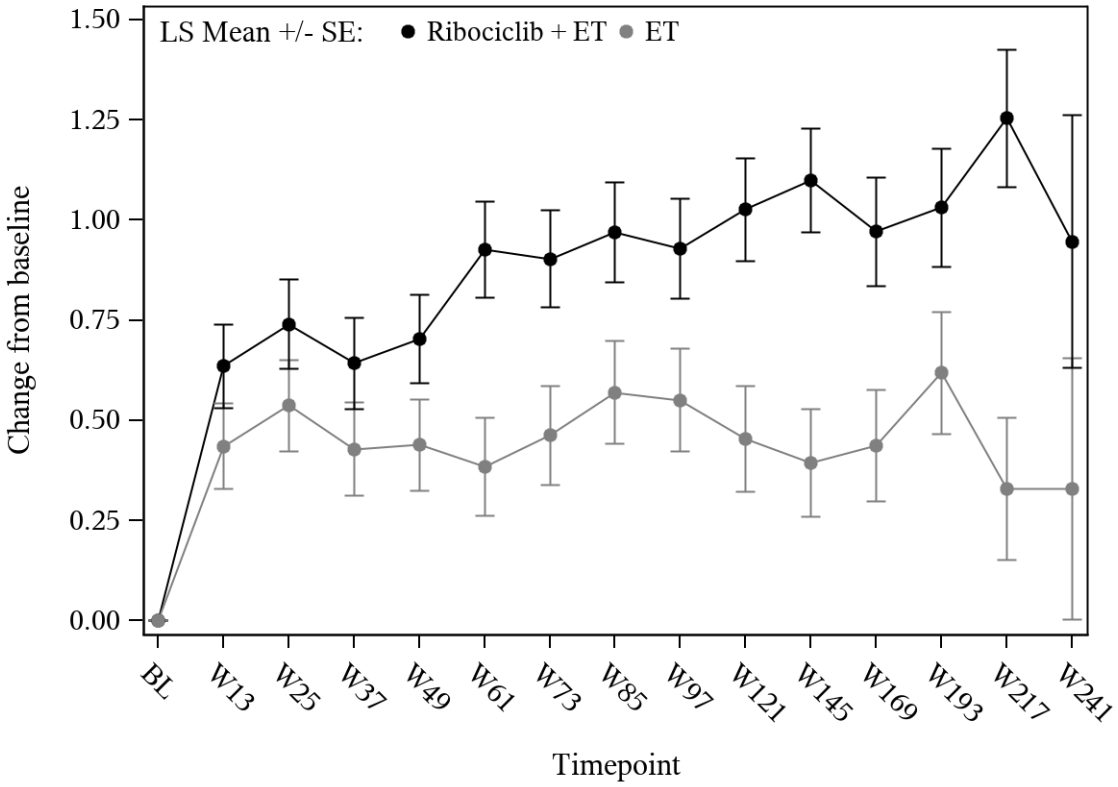
Ribociclib + ET	391	376	362	361	355	354	346	346	345	335	334	311	313	176	31
ET	393	370	346	353	359	351	355	335	337	328	316	310	297	172	27

HADS - Depression
AJCC Anatomic Stage Group: Group III



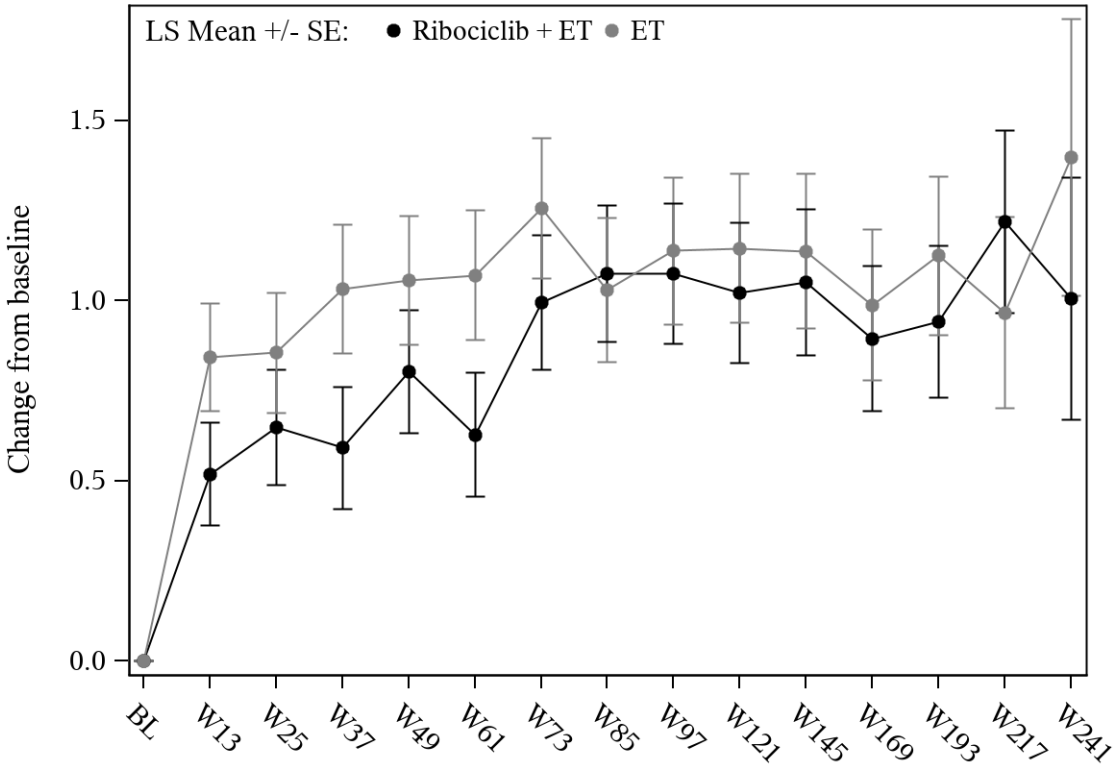
Ribociclib + ET	654	615	590	601	596	585	575	572	568	547	546	405	288	165	27
ET	598	563	558	536	542	533	524	524	501	497	479	358	259	145	23

HADS - Depression
Prior mastectomy: Yes



Ribociclib + ET	726	679	655	662	653	645	631	630	624	601	598	481	396	228	40
ET	690	647	636	623	635	618	614	605	588	581	551	453	371	212	37

HADS - Depression
Prior mastectomy: No



Ribociclib + ET	319	312	297	300	298	294	290	288	289	281	282	235	205	113	18
ET	301	286	268	266	266	266	265	254	250	244	244	215	185	105	13

5-3 Subgroup analysis for safety
5-3.1 Subgroup analysis for adverse events

Table 5-3.1.1 Any adverse event: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	ET (N = 1070)	RR	[95% CI]	p-value
Any adverse event					
	n / N (%)	n / N (%)			
Region					
Interaction test	**p = 0.372**				
NA/WE/O	632 / 640 (98.8)	581 / 627 (92.7)	1.07	[1.04; 1.09]	<.001
ROW	461 / 468 (98.5)	383 / 443 (86.5)	1.14	[1.10; 1.18]	<.001
Geographical region					
Interaction test	**p = 0.719**				
Europe	640 / 654 (97.9)	567 / 638 (88.9)	1.10	[1.07; 1.13]	<.001
North America/Australia	213 / 213 (100.0)	176 / 194 (90.7)	1.10	[1.05; 1.15]	<.001
Asia	178 / 178 (100.0)	155 / 168 (92.3)	1.08	[1.04; 1.13]	<.001
Latin America	62 / 63 (98.4)	66 / 70 (94.3)	1.04	[0.98; 1.11]	0.201
Age group 1 at randomization					
Interaction test	**p = 0.329**				
<45	539 / 549 (98.2)	434 / 496 (87.5)	1.12	[1.08; 1.16]	<.001
45 to 54	535 / 539 (99.3)	504 / 546 (92.3)	1.08	[1.05; 1.10]	<.001
55 to 64	19 / 20 (95.0)	26 / 28 (92.9)	1.02	[0.89; 1.18]	0.756
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)					
Interaction test	**p = 0.763**				
<Median	539 / 549 (98.2)	434 / 496 (87.5)	1.12	[1.08; 1.16]	<.001
≥Median	554 / 559 (99.1)	530 / 574 (92.3)	1.07	[1.05; 1.10]	<.001
Race					
Interaction test	**N.E.**				
Asian	211 / 211 (100.0)	172 / 186 (92.5)	1.08	[1.04; 1.13]	<.001
Non-Asian	825 / 840 (98.2)	737 / 827 (89.1)	1.10	[1.07; 1.13]	<.001
BMI at screening					
Interaction test	**p = 0.684**				
≥25	544 / 551 (98.7)	480 / 523 (91.8)	1.08	[1.05; 1.11]	<.001
<25	534 / 542 (98.5)	473 / 535 (88.4)	1.11	[1.08; 1.15]	<.001
AJCC Anatomic Stage Group					
Interaction test	**p = 0.271**				
Group I/II	410 / 417 (98.3)	382 / 418 (91.4)	1.08	[1.04; 1.11]	<.001
Group III	683 / 691 (98.8)	582 / 652 (89.3)	1.11	[1.08; 1.14]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Anatomic stages					
Interaction test	**p = 0.713**				
IA/IB/IIA	169 / 171 (98.8)	182 / 198 (91.9)	1.08	[1.03; 1.12]	0.001
IIB	241 / 246 (98.0)	200 / 220 (90.9)	1.08	[1.03; 1.13]	0.001
IIIA	444 / 451 (98.4)	354 / 393 (90.1)	1.09	[1.06; 1.13]	<.001
IIIB	67 / 67 (100.0)	47 / 59 (79.7)	1.26	[1.10; 1.43]	<.001
IIIC	172 / 173 (99.4)	181 / 200 (90.5)	1.10	[1.05; 1.15]	<.001
Nodal status					
Interaction test	**N.E.**				
N0	91 / 91 (100.0)	107 / 117 (91.5)	1.09	[1.03; 1.16]	0.002
N1-N3	1002 / 1017 (98.5)	854 / 950 (89.9)	1.10	[1.07; 1.12]	<.001
Histological grade at time of surgery					
Interaction test	**p = 0.978**				
Grade 1	109 / 110 (99.1)	92 / 100 (92.0)	1.08	[1.01; 1.14]	0.016
Grade 2	596 / 604 (98.7)	539 / 601 (89.7)	1.10	[1.07; 1.13]	<.001
Grade 3	294 / 297 (99.0)	247 / 266 (92.9)	1.07	[1.03; 1.10]	<.001
Histological subtype					
Interaction test	**p = 0.589**				
Ductal	853 / 863 (98.8)	755 / 835 (90.4)	1.09	[1.07; 1.12]	<.001
Lobular	170 / 172 (98.8)	153 / 169 (90.5)	1.09	[1.04; 1.15]	<.001
Other	70 / 73 (95.9)	56 / 66 (84.8)	1.13	[1.01; 1.26]	0.033
Ki67 status from surgical specimen					
Interaction test	**p = 0.274**				
Ki67≤20	519 / 527 (98.5)	511 / 552 (92.6)	1.06	[1.04; 1.09]	<.001
Ki67>20	415 / 422 (98.3)	325 / 378 (86.0)	1.14	[1.10; 1.19]	<.001
Type of NSAI					
Interaction test	**p = 0.465**				
Letrozole	798 / 809 (98.6)	688 / 773 (89.0)	1.11	[1.08; 1.14]	<.001
Anastrozole	295 / 299 (98.7)	276 / 297 (92.9)	1.06	[1.03; 1.10]	<.001
Prior neo/adjuvant chemotherapy					
Interaction test	**N.E.**				
Yes	1014 / 1029 (98.5)	888 / 987 (90.0)	1.10	[1.07; 1.12]	<.001
No	79 / 79 (100.0)	76 / 83 (91.6)	1.09	[1.02; 1.17]	0.008
Prior adjuvant chemotherapy					
Interaction test	**p = 0.360**				
Yes	505 / 513 (98.4)	445 / 488 (91.2)	1.08	[1.05; 1.11]	<.001
No	588 / 595 (98.8)	519 / 582 (89.2)	1.11	[1.08; 1.14]	<.001
Prior neoadjuvant chemotherapy					
Interaction test	**p = 0.442**				
Yes	539 / 546 (98.7)	477 / 538 (88.7)	1.11	[1.08; 1.15]	<.001
No	554 / 562 (98.6)	487 / 532 (91.5)	1.08	[1.05; 1.11]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Prior endocrine therapy					
Interaction test	**p = 0.521**				
Yes	840 / 853 (98.5)	708 / 789 (89.7)	1.10	[1.07; 1.13]	<.001
No	253 / 255 (99.2)	256 / 281 (91.1)	1.09	[1.05; 1.13]	<.001
Prior mastectomy					
Interaction test	**p = 0.598**				
Yes	758 / 769 (98.6)	674 / 745 (90.5)	1.09	[1.06; 1.12]	<.001
No	335 / 339 (98.8)	290 / 325 (89.2)	1.11	[1.06; 1.15]	<.001
Prior radiotherapy					
Interaction test	**p = 0.808**				
Yes	997 / 1011 (98.6)	886 / 987 (89.8)	1.10	[1.07; 1.12]	<.001
No	96 / 97 (99.0)	78 / 83 (94.0)	1.05	[0.99; 1.12]	0.081

N: Number of patients
n: Number of patients with event
N.E.: Not estimable
CI: Confidence interval
RR: Relative risk
ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
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Analysis method for interaction test:
p-value from logistic regression model.
logit(proportion) = treatment + subgroup factor + treatment * subgroup factor

Analysis method for within subgroup analysis:
RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm.
ET was the reference group for treatment group comparison.

Table 5-3.1.2 Any grade ≥3 adverse event: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	ET (N = 1070)	RR	[95% CI]	p-value
Any grade >=3 adverse event					
	n / N (%)	n / N (%)			
Region					
Interaction test	**p = 0.233**				
NA/WE/O	406 / 640 (63.4)	115 / 627 (18.3)	3.46	[2.90; 4.12]	<.001
ROW	328 / 468 (70.1)	85 / 443 (19.2)	3.65	[2.99; 4.46]	<.001
Geographical region					
Interaction test	**p = 0.003**				
Europe	416 / 654 (63.6)	111 / 638 (17.4)	3.66	[3.06; 4.37]	<.001
North America/Australia	142 / 213 (66.7)	39 / 194 (20.1)	3.32	[2.47; 4.46]	<.001
Asia	143 / 178 (80.3)	32 / 168 (19.0)	4.22	[3.06; 5.81]	<.001
Latin America	33 / 63 (52.4)	18 / 70 (25.7)	2.04	[1.28; 3.24]	0.003
Age group 1 at randomization					
Interaction test	**p = 0.304**				
<45	377 / 549 (68.7)	91 / 496 (18.3)	3.74	[3.08; 4.54]	<.001
45 to 54	343 / 539 (63.6)	99 / 546 (18.1)	3.51	[2.90; 4.24]	<.001
55 to 64	14 / 20 (70.0)	10 / 28 (35.7)	1.96	[1.10; 3.48]	0.022
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)					
Interaction test	**p = 0.203**				
<Median	377 / 549 (68.7)	91 / 496 (18.3)	3.74	[3.08; 4.54]	<.001
≥Median	357 / 559 (63.9)	109 / 574 (19.0)	3.36	[2.81; 4.03]	<.001
Race					
Interaction test	**p = 0.004**				
Asian	169 / 211 (80.1)	36 / 186 (19.4)	4.14	[3.06; 5.59]	<.001
Non-Asian	534 / 840 (63.6)	155 / 827 (18.7)	3.39	[2.92; 3.94]	<.001
BMI at screening					
Interaction test	**p = <.001**				
≥25	317 / 551 (57.5)	108 / 523 (20.7)	2.79	[2.32; 3.34]	<.001
<25	407 / 542 (75.1)	89 / 535 (16.6)	4.51	[3.71; 5.49]	<.001
AJCC Anatomic Stage Group					
Interaction test	**p = 0.126**				
Group I/II	259 / 417 (62.1)	79 / 418 (18.9)	3.29	[2.66; 4.06]	<.001
Group III	475 / 691 (68.7)	121 / 652 (18.6)	3.70	[3.13; 4.38]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Anatomic stages					
Interaction test	**p = 0.238**				
IA/IB/IIA	111 / 171 (64.9)	42 / 198 (21.2)	3.06	[2.29; 4.09]	<.001
IIB	148 / 246 (60.2)	37 / 220 (16.8)	3.58	[2.62; 4.88]	<.001
IIIA	308 / 451 (68.3)	60 / 393 (15.3)	4.47	[3.51; 5.69]	<.001
IIIB	46 / 67 (68.7)	12 / 59 (20.3)	3.38	[1.99; 5.74]	<.001
IIIC	121 / 173 (69.9)	49 / 200 (24.5)	2.85	[2.20; 3.71]	<.001
Nodal status					
Interaction test	**p = 0.826**				
N0	63 / 91 (69.2)	23 / 117 (19.7)	3.52	[2.38; 5.21]	<.001
N1-N3	671 / 1017 (66.0)	176 / 950 (18.5)	3.56	[3.09; 4.10]	<.001
Histological grade at time of surgery					
Interaction test	**p = 0.728**				
Grade 1	70 / 110 (63.6)	16 / 100 (16.0)	3.98	[2.48; 6.37]	<.001
Grade 2	408 / 604 (67.5)	113 / 601 (18.8)	3.59	[3.02; 4.28]	<.001
Grade 3	190 / 297 (64.0)	51 / 266 (19.2)	3.34	[2.57; 4.33]	<.001
Histological subtype					
Interaction test	**p = 0.327**				
Ductal	567 / 863 (65.7)	159 / 835 (19.0)	3.45	[2.98; 4.00]	<.001
Lobular	123 / 172 (71.5)	29 / 169 (17.2)	4.17	[2.95; 5.88]	<.001
Other	44 / 73 (60.3)	12 / 66 (18.2)	3.32	[1.92; 5.71]	<.001
Ki67 status from surgical specimen					
Interaction test	**p = 0.925**				
Ki67≤20	354 / 527 (67.2)	102 / 552 (18.5)	3.64	[3.02; 4.37]	<.001
Ki67>20	285 / 422 (67.5)	72 / 378 (19.0)	3.55	[2.85; 4.41]	<.001
Type of NSAI					
Interaction test	**p = 0.483**				
Letrozole	537 / 809 (66.4)	140 / 773 (18.1)	3.67	[3.13; 4.29]	<.001
Anastrozole	197 / 299 (65.9)	60 / 297 (20.2)	3.26	[2.56; 4.15]	<.001
Prior neo/adjuvant chemotherapy					
Interaction test	**p = 0.327**				
Yes	683 / 1029 (66.4)	181 / 987 (18.3)	3.62	[3.15; 4.16]	<.001
No	51 / 79 (64.6)	19 / 83 (22.9)	2.82	[1.84; 4.32]	<.001
Prior adjuvant chemotherapy					
Interaction test	**p = 0.558**				
Yes	333 / 513 (64.9)	82 / 488 (16.8)	3.86	[3.14; 4.75]	<.001
No	401 / 595 (67.4)	118 / 582 (20.3)	3.32	[2.80; 3.94]	<.001
Prior neoadjuvant chemotherapy					
Interaction test	**p = 0.871**				
Yes	371 / 546 (67.9)	108 / 538 (20.1)	3.38	[2.83; 4.05]	<.001
No	363 / 562 (64.6)	92 / 532 (17.3)	3.74	[3.07; 4.54]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Prior endocrine therapy					
Interaction test	**p = 0.326**				
Yes	561 / 853 (65.8)	137 / 789 (17.4)	3.79	[3.23; 4.44]	<.001
No	173 / 255 (67.8)	63 / 281 (22.4)	3.03	[2.40; 3.82]	<.001
Prior mastectomy					
Interaction test	**p = 0.666**				
Yes	527 / 769 (68.5)	147 / 745 (19.7)	3.47	[2.98; 4.05]	<.001
No	207 / 339 (61.1)	53 / 325 (16.3)	3.74	[2.89; 4.86]	<.001
Prior radiotherapy					
Interaction test	**p = 0.550**				
Yes	667 / 1011 (66.0)	180 / 987 (18.2)	3.62	[3.15; 4.16]	<.001
No	67 / 97 (69.1)	20 / 83 (24.1)	2.87	[1.91; 4.30]	<.001

N: Number of patients
n: Number of patients with event
CI: Confidence interval
RR: Relative risk
ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
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Analysis method for interaction test:
p-value from logistic regression model.
logit(proportion) = treatment + subgroup factor + treatment * subgroup factor

Analysis method for within subgroup analysis:
RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm.
ET was the reference group for treatment group comparison.

Table 5-3.1.3 Any serious adverse event: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	ET (N = 1070)	RR	[95% CI]	p-value
Any serious adverse event					
	n / N (%)	n / N (%)			
Region					
Interaction test	**p = 0.810**				
NA/WE/O	77 / 640 (12.0)	58 / 627 (9.3)	1.30	[0.94; 1.80]	0.110
ROW	68 / 468 (14.5)	47 / 443 (10.6)	1.37	[0.97; 1.94]	0.077
Geographical region					
Interaction test	**p = 0.211**				
Europe	92 / 654 (14.1)	60 / 638 (9.4)	1.50	[1.10; 2.03]	0.010
North America/Australia	27 / 213 (12.7)	18 / 194 (9.3)	1.37	[0.78; 2.40]	0.278
Asia	20 / 178 (11.2)	24 / 168 (14.3)	0.79	[0.45; 1.37]	0.396
Latin America	6 / 63 (9.5)	3 / 70 (4.3)	2.22	[0.58; 8.52]	0.244
Age group 1 at randomization					
Interaction test	**p = 0.945**				
<45	67 / 549 (12.2)	43 / 496 (8.7)	1.41	[0.98; 2.02]	0.065
45 to 54	72 / 539 (13.4)	56 / 546 (10.3)	1.30	[0.94; 1.81]	0.115
55 to 64	6 / 20 (30.0)	6 / 28 (21.4)	1.40	[0.53; 3.71]	0.499
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)					
Interaction test	**p = 0.745**				
<Median	67 / 549 (12.2)	43 / 496 (8.7)	1.41	[0.98; 2.02]	0.065
≥Median	78 / 559 (14.0)	62 / 574 (10.8)	1.29	[0.95; 1.77]	0.108
Race					
Interaction test	**p = 0.021**				
Asian	22 / 211 (10.4)	25 / 186 (13.4)	0.78	[0.45; 1.33]	0.355
Non-Asian	120 / 840 (14.3)	75 / 827 (9.1)	1.58	[1.20; 2.07]	0.001
BMI at screening					
Interaction test	**p = 0.843**				
≥25	81 / 551 (14.7)	57 / 523 (10.9)	1.35	[0.98; 1.85]	0.064
<25	63 / 542 (11.6)	48 / 535 (9.0)	1.30	[0.91; 1.85]	0.154
AJCC Anatomic Stage Group					
Interaction test	**p = 0.326**				
Group I/II	52 / 417 (12.5)	33 / 418 (7.9)	1.58	[1.04; 2.39]	0.031
Group III	93 / 691 (13.5)	72 / 652 (11.0)	1.22	[0.91; 1.63]	0.179

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Anatomic stages					
Interaction test	**p = 0.174**				
IA/IB/IIA	17 / 171 (9.9)	17 / 198 (8.6)	1.16	[0.61; 2.20]	0.654
IIB	35 / 246 (14.2)	16 / 220 (7.3)	1.96	[1.11; 3.43]	0.019
IIIA	60 / 451 (13.3)	33 / 393 (8.4)	1.58	[1.06; 2.37]	0.025
IIIB	6 / 67 (9.0)	9 / 59 (15.3)	0.59	[0.22; 1.55]	0.283
IIIC	27 / 173 (15.6)	30 / 200 (15.0)	1.04	[0.64; 1.68]	0.871
Nodal status					
Interaction test	**p = 0.384**				
N0	12 / 91 (13.2)	8 / 117 (6.8)	1.93	[0.82; 4.52]	0.131
N1-N3	133 / 1017 (13.1)	96 / 950 (10.1)	1.29	[1.01; 1.66]	0.041
Histological grade at time of surgery					
Interaction test	**p = 0.715**				
Grade 1	9 / 110 (8.2)	7 / 100 (7.0)	1.17	[0.45; 3.02]	0.748
Grade 2	85 / 604 (14.1)	56 / 601 (9.3)	1.51	[1.10; 2.08]	0.011
Grade 3	40 / 297 (13.5)	29 / 266 (10.9)	1.24	[0.79; 1.93]	0.356
Histological subtype					
Interaction test	**p = 0.014**				
Ductal	98 / 863 (11.4)	87 / 835 (10.4)	1.09	[0.83; 1.43]	0.536
Lobular	34 / 172 (19.8)	12 / 169 (7.1)	2.78	[1.49; 5.19]	0.001
Other	13 / 73 (17.8)	6 / 66 (9.1)	1.96	[0.79; 4.86]	0.147
Ki67 status from surgical specimen					
Interaction test	**p = 0.973**				
Ki67≤20	66 / 527 (12.5)	49 / 552 (8.9)	1.41	[0.99; 2.00]	0.054
Ki67>20	62 / 422 (14.7)	40 / 378 (10.6)	1.39	[0.96; 2.01]	0.084
Type of NSAI					
Interaction test	**p = 0.901**				
Letrozole	107 / 809 (13.2)	76 / 773 (9.8)	1.35	[1.02; 1.77]	0.036
Anastrozole	38 / 299 (12.7)	29 / 297 (9.8)	1.30	[0.83; 2.05]	0.257
Prior neo/adjuvant chemotherapy					
Interaction test	**p = 0.113**				
Yes	130 / 1029 (12.6)	99 / 987 (10.0)	1.26	[0.98; 1.61]	0.066
No	15 / 79 (19.0)	6 / 83 (7.2)	2.63	[1.07; 6.43]	0.034
Prior adjuvant chemotherapy					
Interaction test	**p = 0.631**				
Yes	62 / 513 (12.1)	41 / 488 (8.4)	1.44	[0.99; 2.09]	0.057
No	83 / 595 (13.9)	64 / 582 (11.0)	1.27	[0.93; 1.72]	0.127
Prior neoadjuvant chemotherapy					
Interaction test	**p = 0.291**				
Yes	72 / 546 (13.2)	60 / 538 (11.2)	1.18	[0.86; 1.63]	0.307
No	73 / 562 (13.0)	45 / 532 (8.5)	1.54	[1.08; 2.18]	0.017

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Prior endocrine therapy					
Interaction test	**p = 0.640**				
Yes	112 / 853 (13.1)	75 / 789 (9.5)	1.38	[1.05; 1.82]	0.022
No	33 / 255 (12.9)	30 / 281 (10.7)	1.21	[0.76; 1.93]	0.417
Prior mastectomy					
Interaction test	**p = 0.762**				
Yes	109 / 769 (14.2)	81 / 745 (10.9)	1.30	[1.00; 1.71]	0.054
No	36 / 339 (10.6)	24 / 325 (7.4)	1.44	[0.88; 2.36]	0.149
Prior radiotherapy					
Interaction test	**p = 0.462**				
Yes	127 / 1011 (12.6)	96 / 987 (9.7)	1.29	[1.01; 1.66]	0.045
No	18 / 97 (18.6)	9 / 83 (10.8)	1.71	[0.81; 3.60]	0.157

N: Number of patients
n: Number of patients with event
CI: Confidence interval
RR: Relative risk
ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
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Analysis method for interaction test:
p-value from logistic regression model.
logit(proportion) = treatment + subgroup factor + treatment * subgroup factor

Analysis method for within subgroup analysis:
RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm.
ET was the reference group for treatment group comparison.

Table 5-3.1.4 Any adverse event leading to treatment discontinuation of ribociclib: binary analysis - subgroup analysis (Safety Set)

Analysis not performed as these events could not occur in treatment arm ET.

Table 5-3.1.5 Any adverse event leading to treatment discontinuation of NSAI: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	ET (N = 1070)	RR	[95% CI]	p-value
Any adverse event leading to treatment discontinuation of NSAI					
	n / N (%)	n / N (%)			
Region					
Interaction test	**p = 0.339**				
NA/WE/O	35 / 640 (5.5)	47 / 627 (7.5)	0.73	[0.48; 1.11]	0.144
ROW	10 / 468 (2.1)	8 / 443 (1.8)	1.18	[0.47; 2.97]	0.720
Geographical region					
Interaction test	**p = 0.519**				
Europe	23 / 654 (3.5)	32 / 638 (5.0)	0.70	[0.41; 1.18]	0.185
North America/Australia	17 / 213 (8.0)	20 / 194 (10.3)	0.77	[0.42; 1.43]	0.416
Asia	4 / 178 (2.2)	1 / 168 (0.6)	3.78	[0.43; 33.44]	0.233
Latin America	1 / 63 (1.6)	2 / 70 (2.9)	0.56	[0.05; 5.98]	0.628
Age group 1 at randomization					
Interaction test	**p = 0.161**				
<45	15 / 549 (2.7)	20 / 496 (4.0)	0.68	[0.35; 1.31]	0.247
45 to 54	26 / 539 (4.8)	34 / 546 (6.2)	0.77	[0.47; 1.27]	0.313
55 to 64	4 / 20 (20.0)	1 / 28 (3.6)	5.60	[0.68; 46.41]	0.110
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)					
Interaction test	**p = 0.536**				
<Median	15 / 549 (2.7)	20 / 496 (4.0)	0.68	[0.35; 1.31]	0.247
≥Median	30 / 559 (5.4)	35 / 574 (6.1)	0.88	[0.55; 1.41]	0.597
Race					
Interaction test	**p = 0.356**				
Asian	5 / 211 (2.4)	3 / 186 (1.6)	1.47	[0.36; 6.06]	0.595
Non-Asian	36 / 840 (4.3)	48 / 827 (5.8)	0.74	[0.48; 1.13]	0.158
BMI at screening					
Interaction test	**p = 0.839**				
≥25	26 / 551 (4.7)	33 / 523 (6.3)	0.75	[0.45; 1.23]	0.255
<25	18 / 542 (3.3)	22 / 535 (4.1)	0.81	[0.44; 1.49]	0.493
AJCC Anatomic Stage Group					
Interaction test	**p = 0.167**				
Group I/II	17 / 417 (4.1)	29 / 418 (6.9)	0.59	[0.33; 1.05]	0.074
Group III	28 / 691 (4.1)	26 / 652 (4.0)	1.02	[0.60; 1.71]	0.952

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Anatomic stages					
Interaction test	**p = 0.510**				
IA/IB/IIA	6 / 171 (3.5)	18 / 198 (9.1)	0.39	[0.16; 0.95]	0.038
IIB	11 / 246 (4.5)	11 / 220 (5.0)	0.89	[0.40; 2.02]	0.788
IIIA	22 / 451 (4.9)	19 / 393 (4.8)	1.01	[0.55; 1.84]	0.977
IIIB	2 / 67 (3.0)	2 / 59 (3.4)	0.88	[0.13; 6.06]	0.897
IIIC	4 / 173 (2.3)	5 / 200 (2.5)	0.92	[0.25; 3.39]	0.906
Nodal status					
Interaction test	**p = 0.110**				
N0	2 / 91 (2.2)	10 / 117 (8.5)	0.26	[0.06; 1.14]	0.075
N1-N3	43 / 1017 (4.2)	45 / 950 (4.7)	0.89	[0.59; 1.34]	0.586
Histological grade at time of surgery					
Interaction test	**p = 0.720**				
Grade 1	3 / 110 (2.7)	5 / 100 (5.0)	0.55	[0.13; 2.22]	0.398
Grade 2	26 / 604 (4.3)	30 / 601 (5.0)	0.86	[0.52; 1.44]	0.571
Grade 3	13 / 297 (4.4)	18 / 266 (6.8)	0.65	[0.32; 1.29]	0.219
Histological subtype					
Interaction test	**p = 0.431**				
Ductal	35 / 863 (4.1)	39 / 835 (4.7)	0.87	[0.56; 1.36]	0.535
Lobular	7 / 172 (4.1)	14 / 169 (8.3)	0.49	[0.20; 1.19]	0.114
Other	3 / 73 (4.1)	2 / 66 (3.0)	1.36	[0.23; 7.87]	0.734
Ki67 status from surgical specimen					
Interaction test	**p = 0.886**				
Ki67≤20	17 / 527 (3.2)	25 / 552 (4.5)	0.71	[0.39; 1.30]	0.271
Ki67>20	17 / 422 (4.0)	20 / 378 (5.3)	0.76	[0.40; 1.43]	0.397
Type of NSAI					
Interaction test	**p = 0.209**				
Letrozole	27 / 809 (3.3)	39 / 773 (5.0)	0.66	[0.41; 1.07]	0.092
Anastrozole	18 / 299 (6.0)	16 / 297 (5.4)	1.12	[0.58; 2.15]	0.739
Prior neo/adjuvant chemotherapy					
Interaction test	**p = 0.379**				
Yes	40 / 1029 (3.9)	45 / 987 (4.6)	0.85	[0.56; 1.29]	0.453
No	5 / 79 (6.3)	10 / 83 (12.0)	0.53	[0.19; 1.47]	0.220
Prior adjuvant chemotherapy					
Interaction test	**p = 0.958**				
Yes	21 / 513 (4.1)	25 / 488 (5.1)	0.80	[0.45; 1.41]	0.438
No	24 / 595 (4.0)	30 / 582 (5.2)	0.78	[0.46; 1.32]	0.359
Prior neoadjuvant chemotherapy					
Interaction test	**p = 0.470**				
Yes	19 / 546 (3.5)	20 / 538 (3.7)	0.94	[0.51; 1.73]	0.834
No	26 / 562 (4.6)	35 / 532 (6.6)	0.70	[0.43; 1.15]	0.162

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Prior endocrine therapy					
Interaction test	**p = 0.728**				
Yes	31 / 853 (3.6)	34 / 789 (4.3)	0.84	[0.52; 1.36]	0.484
No	14 / 255 (5.5)	21 / 281 (7.5)	0.73	[0.38; 1.41]	0.356
Prior mastectomy					
Interaction test	**p = 0.224**				
Yes	32 / 769 (4.2)	33 / 745 (4.4)	0.94	[0.58; 1.51]	0.797
No	13 / 339 (3.8)	22 / 325 (6.8)	0.57	[0.29; 1.11]	0.096
Prior radiotherapy					
Interaction test	**p = 0.904**				
Yes	41 / 1011 (4.1)	51 / 987 (5.2)	0.78	[0.53; 1.17]	0.237
No	4 / 97 (4.1)	4 / 83 (4.8)	0.86	[0.22; 3.32]	0.822

N: Number of patients
n: Number of patients with event
CI: Confidence interval
RR: Relative risk
ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
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Analysis method for interaction test:
p-value from logistic regression model.
logit(proportion) = treatment + subgroup factor + treatment * subgroup factor

Analysis method for within subgroup analysis:
RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm.
ET was the reference group for treatment group comparison.

Table 5-3.1.6 Any adverse event leading to treatment discontinuation of goserelin: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	ET (N = 1070)	RR	[95% CI]	p-value
Any adverse event leading to treatment discontinuation of goserelin					
	n / N (%)	n / N (%)			
Region					
Interaction test	**p = 0.183**				
NA/WE/O	29 / 640 (4.5)	38 / 627 (6.1)	0.75	[0.47; 1.20]	0.226
ROW	10 / 468 (2.1)	6 / 443 (1.4)	1.58	[0.58; 4.30]	0.373
Geographical region					
Interaction test	**p = 0.916**				
Europe	20 / 654 (3.1)	27 / 638 (4.2)	0.72	[0.41; 1.28]	0.262
North America/Australia	14 / 213 (6.6)	15 / 194 (7.7)	0.85	[0.42; 1.72]	0.650
Asia	4 / 178 (2.2)	0 / 168 (0.0)	8.50	[0.46; >99.99]	0.150
Latin America	1 / 63 (1.6)	2 / 70 (2.9)	0.56	[0.05; 5.98]	0.628
Age group 1 at randomization					
Interaction test	**p = 0.088**				
<45	10 / 549 (1.8)	17 / 496 (3.4)	0.53	[0.25; 1.15]	0.108
45 to 54	25 / 539 (4.6)	26 / 546 (4.8)	0.97	[0.57; 1.66]	0.923
55 to 64	4 / 20 (20.0)	1 / 28 (3.6)	5.60	[0.68; 46.41]	0.110
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)					
Interaction test	**p = 0.123**				
<Median	10 / 549 (1.8)	17 / 496 (3.4)	0.53	[0.25; 1.15]	0.108
≥Median	29 / 559 (5.2)	27 / 574 (4.7)	1.10	[0.66; 1.84]	0.707
Race					
Interaction test	**p = 0.242**				
Asian	5 / 211 (2.4)	2 / 186 (1.1)	2.20	[0.43; 11.22]	0.341
Non-Asian	32 / 840 (3.8)	39 / 827 (4.7)	0.81	[0.51; 1.28]	0.361
BMI at screening					
Interaction test	**p = 0.995**				
≥25	22 / 551 (4.0)	25 / 523 (4.8)	0.84	[0.48; 1.46]	0.529
<25	16 / 542 (3.0)	19 / 535 (3.6)	0.83	[0.43; 1.60]	0.580
AJCC Anatomic Stage Group					
Interaction test	**p = 0.165**				
Group I/II	14 / 417 (3.4)	23 / 418 (5.5)	0.61	[0.32; 1.17]	0.137
Group III	25 / 691 (3.6)	21 / 652 (3.2)	1.12	[0.64; 1.99]	0.689

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Anatomic stages					
Interaction test	**p = 0.638**				
IA/IB/IIA	5 / 171 (2.9)	13 / 198 (6.6)	0.45	[0.16; 1.22]	0.117
IIB	9 / 246 (3.7)	10 / 220 (4.5)	0.80	[0.33; 1.94]	0.630
IIIA	19 / 451 (4.2)	14 / 393 (3.6)	1.18	[0.60; 2.33]	0.627
IIIB	2 / 67 (3.0)	2 / 59 (3.4)	0.88	[0.13; 6.06]	0.897
IIIC	4 / 173 (2.3)	5 / 200 (2.5)	0.92	[0.25; 3.39]	0.906
Nodal status					
Interaction test	**p = 0.123**				
N0	1 / 91 (1.1)	7 / 117 (6.0)	0.18	[0.02; 1.47]	0.110
N1-N3	38 / 1017 (3.7)	37 / 950 (3.9)	0.96	[0.62; 1.50]	0.855
Histological grade at time of surgery					
Interaction test	**p = 0.685**				
Grade 1	3 / 110 (2.7)	6 / 100 (6.0)	0.45	[0.12; 1.77]	0.256
Grade 2	21 / 604 (3.5)	24 / 601 (4.0)	0.87	[0.49; 1.55]	0.637
Grade 3	12 / 297 (4.0)	14 / 266 (5.3)	0.77	[0.36; 1.63]	0.491
Histological subtype					
Interaction test	**p = 0.290**				
Ductal	30 / 863 (3.5)	31 / 835 (3.7)	0.94	[0.57; 1.53]	0.794
Lobular	6 / 172 (3.5)	12 / 169 (7.1)	0.49	[0.19; 1.28]	0.145
Other	3 / 73 (4.1)	1 / 66 (1.5)	2.71	[0.29; 25.44]	0.382
Ki67 status from surgical specimen					
Interaction test	**p = 0.476**				
Ki67≤20	16 / 527 (3.0)	23 / 552 (4.2)	0.73	[0.39; 1.36]	0.322
Ki67>20	15 / 422 (3.6)	13 / 378 (3.4)	1.03	[0.50; 2.14]	0.929
Type of NSAI					
Interaction test	**p = 0.478**				
Letrozole	25 / 809 (3.1)	31 / 773 (4.0)	0.77	[0.46; 1.29]	0.324
Anastrozole	14 / 299 (4.7)	13 / 297 (4.4)	1.07	[0.51; 2.24]	0.858
Prior neo/adjuvant chemotherapy					
Interaction test	**p = 0.127**				
Yes	36 / 1029 (3.5)	35 / 987 (3.5)	0.99	[0.62; 1.56]	0.954
No	3 / 79 (3.8)	9 / 83 (10.8)	0.35	[0.10; 1.25]	0.105
Prior adjuvant chemotherapy					
Interaction test	**p = 0.635**				
Yes	20 / 513 (3.9)	20 / 488 (4.1)	0.95	[0.52; 1.75]	0.872
No	19 / 595 (3.2)	24 / 582 (4.1)	0.77	[0.43; 1.40]	0.396
Prior neoadjuvant chemotherapy					
Interaction test	**p = 0.447**				
Yes	16 / 546 (2.9)	15 / 538 (2.8)	1.05	[0.52; 2.10]	0.888
No	23 / 562 (4.1)	29 / 532 (5.5)	0.75	[0.44; 1.28]	0.293

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Prior endocrine therapy					
Interaction test	**p = 0.576**				
Yes	25 / 853 (2.9)	29 / 789 (3.7)	0.80	[0.47; 1.35]	0.399
No	14 / 255 (5.5)	15 / 281 (5.3)	1.03	[0.51; 2.09]	0.938
Prior mastectomy					
Interaction test	**p = 0.429**				
Yes	27 / 769 (3.5)	27 / 745 (3.6)	0.97	[0.57; 1.64]	0.906
No	12 / 339 (3.5)	17 / 325 (5.2)	0.68	[0.33; 1.39]	0.290
Prior radiotherapy					
Interaction test	**p = 0.643**				
Yes	36 / 1011 (3.6)	42 / 987 (4.3)	0.84	[0.54; 1.29]	0.424
No	3 / 97 (3.1)	2 / 83 (2.4)	1.28	[0.22; 7.50]	0.782

N: Number of patients
n: Number of patients with event
CI: Confidence interval
RR: Relative risk
ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
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Analysis method for interaction test:
p-value from logistic regression model.
logit(proportion) = treatment + subgroup factor + treatment * subgroup factor

Analysis method for within subgroup analysis:
RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm.
ET was the reference group for treatment group comparison.

Table 5-3.1.7 Any adverse event leading to treatment discontinuation of any component: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	ET (N = 1070)	RR	[95% CI]	p-value
Any adverse event leading to treatment discontinuation of any component					
	n / N (%)	n / N (%)			
Region					
Interaction test	**p = <.001**				
NA/WE/O	115 / 640 (18.0)	52 / 627 (8.3)	2.17	[1.59; 2.95]	<.001
ROW	75 / 468 (16.0)	8 / 443 (1.8)	8.87	[4.33; 18.18]	<.001
Geographical region					
Interaction test	**p = 0.037**				
Europe	120 / 654 (18.3)	36 / 638 (5.6)	3.25	[2.28; 4.64]	<.001
North America/Australia	39 / 213 (18.3)	21 / 194 (10.8)	1.69	[1.03; 2.77]	0.037
Asia	23 / 178 (12.9)	1 / 168 (0.6)	21.71	[2.96; >99.99]	0.002
Latin America	8 / 63 (12.7)	2 / 70 (2.9)	4.44	[0.98; 20.15]	0.053
Age group 1 at randomization					
Interaction test	**p = 0.571**				
<45	78 / 549 (14.2)	22 / 496 (4.4)	3.20	[2.03; 5.06]	<.001
45 to 54	104 / 539 (19.3)	36 / 546 (6.6)	2.93	[2.04; 4.19]	<.001
55 to 64	8 / 20 (40.0)	2 / 28 (7.1)	5.60	[1.33; 23.62]	0.019
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)					
Interaction test	**p = 0.976**				
<Median	78 / 549 (14.2)	22 / 496 (4.4)	3.20	[2.03; 5.06]	<.001
≥Median	112 / 559 (20.0)	38 / 574 (6.6)	3.03	[2.13; 4.29]	<.001
Race					
Interaction test	**p = 0.094**				
Asian	28 / 211 (13.3)	3 / 186 (1.6)	8.23	[2.54; 26.62]	<.001
Non-Asian	151 / 840 (18.0)	53 / 827 (6.4)	2.80	[2.08; 3.78]	<.001
BMI at screening					
Interaction test	**p = 0.882**				
≥25	114 / 551 (20.7)	36 / 523 (6.9)	3.01	[2.11; 4.29]	<.001
<25	74 / 542 (13.7)	24 / 535 (4.5)	3.04	[1.95; 4.75]	<.001
AJCC Anatomic Stage Group					
Interaction test	**p = 0.298**				
Group I/II	77 / 417 (18.5)	30 / 418 (7.2)	2.57	[1.73; 3.84]	<.001
Group III	113 / 691 (16.4)	30 / 652 (4.6)	3.55	[2.41; 5.24]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Anatomic stages					
Interaction test	**p = 0.432**				
IA/IB/IIA	29 / 171 (17.0)	18 / 198 (9.1)	1.87	[1.07; 3.24]	0.027
IIB	48 / 246 (19.5)	12 / 220 (5.5)	3.58	[1.95; 6.56]	<.001
IIIA	78 / 451 (17.3)	21 / 393 (5.3)	3.24	[2.04; 5.14]	<.001
IIIB	9 / 67 (13.4)	2 / 59 (3.4)	3.96	[0.89; 17.61]	0.070
IIIC	26 / 173 (15.0)	7 / 200 (3.5)	4.29	[1.91; 9.65]	<.001
Nodal status					
Interaction test	**p = 0.161**				
N0	14 / 91 (15.4)	10 / 117 (8.5)	1.80	[0.84; 3.86]	0.132
N1-N3	176 / 1017 (17.3)	50 / 950 (5.3)	3.29	[2.43; 4.44]	<.001
Histological grade at time of surgery					
Interaction test	**p = 0.507**				
Grade 1	16 / 110 (14.5)	6 / 100 (6.0)	2.42	[0.99; 5.95]	0.053
Grade 2	107 / 604 (17.7)	33 / 601 (5.5)	3.23	[2.22; 4.69]	<.001
Grade 3	48 / 297 (16.2)	19 / 266 (7.1)	2.26	[1.37; 3.75]	0.002
Histological subtype					
Interaction test	**p = 0.306**				
Ductal	144 / 863 (16.7)	44 / 835 (5.3)	3.17	[2.29; 4.38]	<.001
Lobular	31 / 172 (18.0)	14 / 169 (8.3)	2.18	[1.20; 3.94]	0.010
Other	15 / 73 (20.5)	2 / 66 (3.0)	6.78	[1.61; 28.54]	0.009
Ki67 status from surgical specimen					
Interaction test	**p = 0.660**				
Ki67≤20	85 / 527 (16.1)	27 / 552 (4.9)	3.30	[2.17; 5.00]	<.001
Ki67>20	67 / 422 (15.9)	21 / 378 (5.6)	2.86	[1.79; 4.57]	<.001
Type of NSAI					
Interaction test	**p = 0.539**				
Letrozole	139 / 809 (17.2)	41 / 773 (5.3)	3.24	[2.32; 4.52]	<.001
Anastrozole	51 / 299 (17.1)	19 / 297 (6.4)	2.67	[1.61; 4.40]	<.001
Prior neo/adjuvant chemotherapy					
Interaction test	**p = 0.784**				
Yes	166 / 1029 (16.1)	50 / 987 (5.1)	3.18	[2.35; 4.32]	<.001
No	24 / 79 (30.4)	10 / 83 (12.0)	2.52	[1.29; 4.93]	0.007
Prior adjuvant chemotherapy					
Interaction test	**p = 0.566**				
Yes	80 / 513 (15.6)	27 / 488 (5.5)	2.82	[1.86; 4.28]	<.001
No	110 / 595 (18.5)	33 / 582 (5.7)	3.26	[2.25; 4.73]	<.001
Prior neoadjuvant chemotherapy					
Interaction test	**p = 0.181**				
Yes	90 / 546 (16.5)	23 / 538 (4.3)	3.86	[2.48; 6.00]	<.001
No	100 / 562 (17.8)	37 / 532 (7.0)	2.56	[1.79; 3.66]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Prior endocrine therapy					
Interaction test	**p = 0.099**				
Yes	145 / 853 (17.0)	37 / 789 (4.7)	3.62	[2.56; 5.13]	<.001
No	45 / 255 (17.6)	23 / 281 (8.2)	2.16	[1.34; 3.46]	0.001
Prior mastectomy					
Interaction test	**p = 0.470**				
Yes	127 / 769 (16.5)	37 / 745 (5.0)	3.33	[2.34; 4.73]	<.001
No	63 / 339 (18.6)	23 / 325 (7.1)	2.63	[1.67; 4.13]	<.001
Prior radiotherapy					
Interaction test	**p = 0.289**				
Yes	167 / 1011 (16.5)	56 / 987 (5.7)	2.91	[2.18; 3.89]	<.001
No	23 / 97 (23.7)	4 / 83 (4.8)	4.92	[1.77; 13.65]	0.002

N: Number of patients
n: Number of patients with event
CI: Confidence interval
RR: Relative risk
ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
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Analysis method for interaction test:
p-value from logistic regression model.
logit(proportion) = treatment + subgroup factor + treatment * subgroup factor

Analysis method for within subgroup analysis:
RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm.
ET was the reference group for treatment group comparison.

5-3.2 Subgroup analysis for adverse events by SOC and PT

Table 5-3.2.1 SOC investigations: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	ET (N = 1070)	RR	[95% CI]	p-value
Investigations					
	n / N (%)	n / N (%)			
Region					
Interaction test	**p = 0.150**				
NA/WE/O	423 / 640 (66.1)	207 / 627 (33.0)	2.00	[1.77; 2.27]	<.001
ROW	319 / 468 (68.2)	183 / 443 (41.3)	1.65	[1.45; 1.87]	<.001
Geographical region					
Interaction test	**p = 0.018**				
Europe	398 / 654 (60.9)	214 / 638 (33.5)	1.81	[1.60; 2.06]	<.001
North America/Australia	155 / 213 (72.8)	71 / 194 (36.6)	1.99	[1.62; 2.43]	<.001
Asia	153 / 178 (86.0)	80 / 168 (47.6)	1.81	[1.52; 2.14]	<.001
Latin America	36 / 63 (57.1)	25 / 70 (35.7)	1.60	[1.09; 2.34]	0.015
Age group 1 at randomization					
Interaction test	**p = 0.848**				
<45	360 / 549 (65.6)	168 / 496 (33.9)	1.94	[1.69; 2.22]	<.001
45 to 54	366 / 539 (67.9)	205 / 546 (37.5)	1.81	[1.60; 2.04]	<.001
55 to 64	16 / 20 (80.0)	17 / 28 (60.7)	1.32	[0.91; 1.91]	0.144
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)					
Interaction test	**p = 0.645**				
<Median	360 / 549 (65.6)	168 / 496 (33.9)	1.94	[1.69; 2.22]	<.001
≥Median	382 / 559 (68.3)	222 / 574 (38.7)	1.77	[1.57; 1.99]	<.001
Race					
Interaction test	**p = 0.016**				
Asian	177 / 211 (83.9)	87 / 186 (46.8)	1.79	[1.52; 2.11]	<.001
Non-Asian	528 / 840 (62.9)	288 / 827 (34.8)	1.80	[1.62; 2.01]	<.001
BMI at screening					
Interaction test	**p = 0.880**				
≥25	369 / 551 (67.0)	193 / 523 (36.9)	1.81	[1.60; 2.06]	<.001
<25	360 / 542 (66.4)	191 / 535 (35.7)	1.86	[1.64; 2.12]	<.001
AJCC Anatomic Stage Group					
Interaction test	**p = 0.781**				
Group I/II	266 / 417 (63.8)	136 / 418 (32.5)	1.96	[1.68; 2.29]	<.001
Group III	476 / 691 (68.9)	254 / 652 (39.0)	1.77	[1.59; 1.97]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Anatomic stages					
Interaction test	**p = 0.006**				
IA/IB/IIA	108 / 171 (63.2)	56 / 198 (28.3)	2.23	[1.74; 2.87]	<.001
IIB	158 / 246 (64.2)	80 / 220 (36.4)	1.77	[1.45; 2.15]	<.001
IIIA	294 / 451 (65.2)	166 / 393 (42.2)	1.54	[1.35; 1.76]	<.001
IIIB	48 / 67 (71.6)	20 / 59 (33.9)	2.11	[1.44; 3.11]	<.001
IIIC	134 / 173 (77.5)	68 / 200 (34.0)	2.28	[1.85; 2.81]	<.001
Nodal status					
Interaction test	**p = 0.107**				
N0	61 / 91 (67.0)	31 / 117 (26.5)	2.53	[1.81; 3.53]	<.001
N1-N3	681 / 1017 (67.0)	357 / 950 (37.6)	1.78	[1.62; 1.95]	<.001
Histological grade at time of surgery					
Interaction test	**p = 0.828**				
Grade 1	73 / 110 (66.4)	35 / 100 (35.0)	1.90	[1.41; 2.56]	<.001
Grade 2	417 / 604 (69.0)	213 / 601 (35.4)	1.95	[1.73; 2.20]	<.001
Grade 3	203 / 297 (68.4)	100 / 266 (37.6)	1.82	[1.53; 2.16]	<.001
Histological subtype					
Interaction test	**p = 0.891**				
Ductal	574 / 863 (66.5)	298 / 835 (35.7)	1.86	[1.68; 2.07]	<.001
Lobular	115 / 172 (66.9)	61 / 169 (36.1)	1.85	[1.48; 2.32]	<.001
Other	53 / 73 (72.6)	31 / 66 (47.0)	1.55	[1.15; 2.07]	0.004
Ki67 status from surgical specimen					
Interaction test	**p = 0.834**				
Ki67≤20	366 / 527 (69.4)	214 / 552 (38.8)	1.79	[1.59; 2.02]	<.001
Ki67>20	267 / 422 (63.3)	126 / 378 (33.3)	1.90	[1.62; 2.23]	<.001
Type of NSAI					
Interaction test	**p = 0.920**				
Letrozole	542 / 809 (67.0)	283 / 773 (36.6)	1.83	[1.65; 2.03]	<.001
Anastrozole	200 / 299 (66.9)	107 / 297 (36.0)	1.86	[1.56; 2.20]	<.001
Prior neo/adjuvant chemotherapy					
Interaction test	**p = 0.470**				
Yes	688 / 1029 (66.9)	354 / 987 (35.9)	1.86	[1.70; 2.05]	<.001
No	54 / 79 (68.4)	36 / 83 (43.4)	1.58	[1.18; 2.10]	0.002
Prior adjuvant chemotherapy					
Interaction test	**p = 0.033**				
Yes	338 / 513 (65.9)	196 / 488 (40.2)	1.64	[1.45; 1.86]	<.001
No	404 / 595 (67.9)	194 / 582 (33.3)	2.04	[1.79; 2.31]	<.001
Prior neoadjuvant chemotherapy					
Interaction test	**p = 0.035**				
Yes	371 / 546 (67.9)	178 / 538 (33.1)	2.05	[1.80; 2.35]	<.001
No	371 / 562 (66.0)	212 / 532 (39.8)	1.66	[1.47; 1.87]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Prior endocrine therapy					
Interaction test	**p = 0.106**				
Yes	580 / 853 (68.0)	281 / 789 (35.6)	1.91	[1.72; 2.12]	<.001
No	162 / 255 (63.5)	109 / 281 (38.8)	1.64	[1.38; 1.95]	<.001
Prior mastectomy					
Interaction test	**p = 0.152**				
Yes	519 / 769 (67.5)	290 / 745 (38.9)	1.73	[1.56; 1.92]	<.001
No	223 / 339 (65.8)	100 / 325 (30.8)	2.14	[1.79; 2.56]	<.001
Prior radiotherapy					
Interaction test	**p = 0.442**				
Yes	671 / 1011 (66.4)	349 / 987 (35.4)	1.88	[1.71; 2.06]	<.001
No	71 / 97 (73.2)	41 / 83 (49.4)	1.48	[1.16; 1.90]	0.002

N: Number of patients
n: Number of patients with event
CI: Confidence interval
RR: Relative risk
ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
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Analysis method for interaction test:
p-value from logistic regression model.
logit(proportion) = treatment + subgroup factor + treatment * subgroup factor

Analysis method for within subgroup analysis:
RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm.
ET was the reference group for treatment group comparison.

Table 5-3.2.2 PT neutrophil count decreased: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	ET (N = 1070)	RR	[95% CI]	p-value
Neutrophil count decreased					
	n / N (%)	n / N (%)			
Region					
Interaction test	**p = 0.017**				
NA/WE/O	173 / 640 (27.0)	9 / 627 (1.4)	18.83	[9.72; 36.47]	<.001
ROW	135 / 468 (28.8)	19 / 443 (4.3)	6.73	[4.24; 10.68]	<.001
Geographical region					
Interaction test	**p = 0.783**				
Europe	102 / 654 (15.6)	7 / 638 (1.1)	14.21	[6.66; 30.33]	<.001
North America/Australia	75 / 213 (35.2)	5 / 194 (2.6)	13.66	[5.64; 33.07]	<.001
Asia	127 / 178 (71.3)	16 / 168 (9.5)	7.49	[4.66; 12.05]	<.001
Latin America	4 / 63 (6.3)	0 / 70 (0.0)	9.98	[0.55; >99.99]	0.120
Age group 1 at randomization					
Interaction test	**p = 0.811**				
<45	161 / 549 (29.3)	15 / 496 (3.0)	9.70	[5.79; 16.23]	<.001
45 to 54	142 / 539 (26.3)	13 / 546 (2.4)	11.06	[6.35; 19.28]	<.001
55 to 64	5 / 20 (25.0)	0 / 28 (0.0)	15.19	[0.89; >99.99]	0.060
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)					
Interaction test	**p = 0.720**				
<Median	161 / 549 (29.3)	15 / 496 (3.0)	9.70	[5.79; 16.23]	<.001
≥Median	147 / 559 (26.3)	13 / 574 (2.3)	11.61	[6.67; 20.23]	<.001
Race					
Interaction test	**p = 0.582**				
Asian	139 / 211 (65.9)	16 / 186 (8.6)	7.66	[4.75; 12.36]	<.001
Non-Asian	162 / 840 (19.3)	12 / 827 (1.5)	13.29	[7.45; 23.70]	<.001
BMI at screening					
Interaction test	**p = 0.933**				
≥25	119 / 551 (21.6)	10 / 523 (1.9)	11.30	[5.99; 21.30]	<.001
<25	183 / 542 (33.8)	18 / 535 (3.4)	10.04	[6.28; 16.04]	<.001
AJCC Anatomic Stage Group					
Interaction test	**p = 0.767**				
Group I/II	98 / 417 (23.5)	8 / 418 (1.9)	12.28	[6.05; 24.92]	<.001
Group III	210 / 691 (30.4)	20 / 652 (3.1)	9.91	[6.34; 15.48]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Anatomic stages					
Interaction test	**p = 0.885**				
IA/IB/IIA	36 / 171 (21.1)	2 / 198 (1.0)	20.84	[5.09; 85.29]	<.001
IIB	62 / 246 (25.2)	6 / 220 (2.7)	9.24	[4.08; 20.94]	<.001
IIIA	130 / 451 (28.8)	11 / 393 (2.8)	10.30	[5.65; 18.77]	<.001
IIIB	9 / 67 (13.4)	1 / 59 (1.7)	7.93	[1.03; 60.72]	0.046
IIIC	71 / 173 (41.0)	8 / 200 (4.0)	10.26	[5.08; 20.70]	<.001
Nodal status					
Interaction test	**p = 0.442**				
N0	19 / 91 (20.9)	1 / 117 (0.9)	24.43	[3.33; >99.99]	0.002
N1-N3	289 / 1017 (28.4)	27 / 950 (2.8)	10.00	[6.81; 14.68]	<.001
Histological grade at time of surgery					
Interaction test	**p = 0.436**				
Grade 1	32 / 110 (29.1)	4 / 100 (4.0)	7.27	[2.67; 19.84]	<.001
Grade 2	167 / 604 (27.6)	15 / 601 (2.5)	11.08	[6.61; 18.56]	<.001
Grade 3	95 / 297 (32.0)	5 / 266 (1.9)	17.02	[7.03; 41.19]	<.001
Histological subtype					
Interaction test	**p = 0.858**				
Ductal	240 / 863 (27.8)	26 / 835 (3.1)	8.93	[6.03; 13.24]	<.001
Lobular	46 / 172 (26.7)	0 / 169 (0.0)	91.39	[5.68; >99.99]	0.001
Other	22 / 73 (30.1)	2 / 66 (3.0)	9.95	[2.43; 40.68]	0.001
Ki67 status from surgical specimen					
Interaction test	**p = 0.230**				
Ki67≤20	174 / 527 (33.0)	15 / 552 (2.7)	12.15	[7.27; 20.31]	<.001
Ki67>20	93 / 422 (22.0)	10 / 378 (2.6)	8.33	[4.40; 15.76]	<.001
Type of NSAI					
Interaction test	**p = 0.134**				
Letrozole	229 / 809 (28.3)	17 / 773 (2.2)	12.87	[7.94; 20.86]	<.001
Anastrozole	79 / 299 (26.4)	11 / 297 (3.7)	7.13	[3.88; 13.13]	<.001
Prior neo/adjuvant chemotherapy					
Interaction test	**p = 0.983**				
Yes	296 / 1029 (28.8)	27 / 987 (2.7)	10.52	[7.16; 15.44]	<.001
No	12 / 79 (15.2)	1 / 83 (1.2)	12.61	[1.68; 94.72]	0.014
Prior adjuvant chemotherapy					
Interaction test	**p = 0.198**				
Yes	156 / 513 (30.4)	18 / 488 (3.7)	8.24	[5.14; 13.22]	<.001
No	152 / 595 (25.5)	10 / 582 (1.7)	14.87	[7.92; 27.90]	<.001
Prior neoadjuvant chemotherapy					
Interaction test	**p = 0.690**				
Yes	152 / 546 (27.8)	13 / 538 (2.4)	11.52	[6.62; 20.04]	<.001
No	156 / 562 (27.8)	15 / 532 (2.8)	9.84	[5.87; 16.50]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Prior endocrine therapy					
Interaction test	**p = 0.118**				
Yes	239 / 853 (28.0)	17 / 789 (2.2)	13.00	[8.03; 21.07]	<.001
No	69 / 255 (27.1)	11 / 281 (3.9)	6.91	[3.74; 12.76]	<.001
Prior mastectomy					
Interaction test	**p = 0.177**				
Yes	224 / 769 (29.1)	24 / 745 (3.2)	9.04	[6.01; 13.61]	<.001
No	84 / 339 (24.8)	4 / 325 (1.2)	20.13	[7.47; 54.26]	<.001
Prior radiotherapy					
Interaction test	**p = 0.052**				
Yes	295 / 1011 (29.2)	25 / 987 (2.5)	11.52	[7.73; 17.16]	<.001
No	13 / 97 (13.4)	3 / 83 (3.6)	3.71	[1.09; 12.57]	0.035

N: Number of patients
n: Number of patients with event
CI: Confidence interval
RR: Relative risk
ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
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Analysis method for interaction test:
p-value from logistic regression model.
logit(proportion) = treatment + subgroup factor + treatment * subgroup factor

Analysis method for within subgroup analysis:
RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm.
ET was the reference group for treatment group comparison.

Table 5-3.2.3 PT sars-cov-2 test positive: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	ET (N = 1070)	RR	[95% CI]	p-value
SARS-CoV-2 test positive					
	n / N (%)	n / N (%)			
Region					
Interaction test	**p = 0.023**				
NA/WE/O	182 / 640 (28.4)	96 / 627 (15.3)	1.86	[1.49; 2.32]	<.001
ROW	112 / 468 (23.9)	84 / 443 (19.0)	1.26	[0.98; 1.62]	0.069
Geographical region					
Interaction test	**p = 0.696**				
Europe	155 / 654 (23.7)	92 / 638 (14.4)	1.64	[1.30; 2.08]	<.001
North America/Australia	61 / 213 (28.6)	31 / 194 (16.0)	1.79	[1.22; 2.64]	0.003
Asia	64 / 178 (36.0)	44 / 168 (26.2)	1.37	[1.00; 1.89]	0.053
Latin America	14 / 63 (22.2)	13 / 70 (18.6)	1.20	[0.61; 2.35]	0.602
Age group 1 at randomization					
Interaction test	**p = 0.071**				
<45	157 / 549 (28.6)	75 / 496 (15.1)	1.89	[1.48; 2.42]	<.001
45 to 54	134 / 539 (24.9)	99 / 546 (18.1)	1.37	[1.09; 1.73]	0.007
55 to 64	3 / 20 (15.0)	6 / 28 (21.4)	0.70	[0.20; 2.47]	0.579
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)					
Interaction test	**p = 0.041**				
<Median	157 / 549 (28.6)	75 / 496 (15.1)	1.89	[1.48; 2.42]	<.001
≥Median	137 / 559 (24.5)	105 / 574 (18.3)	1.34	[1.07; 1.68]	0.011
Race					
Interaction test	**p = 0.460**				
Asian	73 / 211 (34.6)	48 / 186 (25.8)	1.34	[0.99; 1.82]	0.061
Non-Asian	204 / 840 (24.3)	123 / 827 (14.9)	1.63	[1.33; 2.00]	<.001
BMI at screening					
Interaction test	**p = 0.141**				
≥25	133 / 551 (24.1)	92 / 523 (17.6)	1.37	[1.08; 1.74]	0.009
<25	154 / 542 (28.4)	87 / 535 (16.3)	1.75	[1.38; 2.21]	<.001
AJCC Anatomic Stage Group					
Interaction test	**p = 0.912**				
Group I/II	99 / 417 (23.7)	63 / 418 (15.1)	1.58	[1.18; 2.10]	0.002
Group III	195 / 691 (28.2)	117 / 652 (17.9)	1.57	[1.28; 1.93]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Anatomic stages					
Interaction test	**p = 0.227**				
IA/IB/IIA	42 / 171 (24.6)	21 / 198 (10.6)	2.32	[1.43; 3.75]	<.001
IIB	57 / 246 (23.2)	42 / 220 (19.1)	1.21	[0.85; 1.73]	0.284
IIIA	119 / 451 (26.4)	71 / 393 (18.1)	1.46	[1.13; 1.90]	0.004
IIIB	16 / 67 (23.9)	8 / 59 (13.6)	1.76	[0.81; 3.82]	0.151
IIIC	60 / 173 (34.7)	38 / 200 (19.0)	1.83	[1.28; 2.59]	<.001
Nodal status					
Interaction test	**p = 0.249**				
N0	19 / 91 (20.9)	10 / 117 (8.5)	2.44	[1.19; 4.99]	0.014
N1-N3	275 / 1017 (27.0)	169 / 950 (17.8)	1.52	[1.28; 1.80]	<.001
Histological grade at time of surgery					
Interaction test	**p = 0.474**				
Grade 1	26 / 110 (23.6)	18 / 100 (18.0)	1.31	[0.77; 2.25]	0.320
Grade 2	160 / 604 (26.5)	99 / 601 (16.5)	1.61	[1.29; 2.01]	<.001
Grade 3	90 / 297 (30.3)	43 / 266 (16.2)	1.87	[1.36; 2.59]	<.001
Histological subtype					
Interaction test	**p = 0.884**				
Ductal	230 / 863 (26.7)	139 / 835 (16.6)	1.60	[1.33; 1.93]	<.001
Lobular	41 / 172 (23.8)	28 / 169 (16.6)	1.44	[0.93; 2.21]	0.098
Other	23 / 73 (31.5)	13 / 66 (19.7)	1.60	[0.88; 2.89]	0.121
Ki67 status from surgical specimen					
Interaction test	**p = 0.093**				
Ki67≤20	140 / 527 (26.6)	108 / 552 (19.6)	1.36	[1.09; 1.69]	0.007
Ki67>20	105 / 422 (24.9)	49 / 378 (13.0)	1.92	[1.41; 2.62]	<.001
Type of NSAI					
Interaction test	**p = 0.817**				
Letrozole	208 / 809 (25.7)	127 / 773 (16.4)	1.56	[1.28; 1.91]	<.001
Anastrozole	86 / 299 (28.8)	53 / 297 (17.8)	1.61	[1.19; 2.18]	0.002
Prior neo/adjuvant chemotherapy					
Interaction test	**p = 0.260**				
Yes	272 / 1029 (26.4)	170 / 987 (17.2)	1.53	[1.29; 1.82]	<.001
No	22 / 79 (27.8)	10 / 83 (12.0)	2.31	[1.17; 4.57]	0.016
Prior adjuvant chemotherapy					
Interaction test	**p = 0.576**				
Yes	144 / 513 (28.1)	92 / 488 (18.9)	1.49	[1.18; 1.87]	<.001
No	150 / 595 (25.2)	88 / 582 (15.1)	1.67	[1.32; 2.11]	<.001
Prior neoadjuvant chemotherapy					
Interaction test	**p = 0.646**				
Yes	136 / 546 (24.9)	88 / 538 (16.4)	1.52	[1.20; 1.94]	<.001
No	158 / 562 (28.1)	92 / 532 (17.3)	1.63	[1.29; 2.04]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Prior endocrine therapy					
Interaction test	**p = 0.718**				
Yes	234 / 853 (27.4)	136 / 789 (17.2)	1.59	[1.32; 1.92]	<.001
No	60 / 255 (23.5)	44 / 281 (15.7)	1.50	[1.06; 2.13]	0.023
Prior mastectomy					
Interaction test	**p = 0.177**				
Yes	204 / 769 (26.5)	135 / 745 (18.1)	1.46	[1.21; 1.78]	<.001
No	90 / 339 (26.5)	45 / 325 (13.8)	1.92	[1.39; 2.65]	<.001
Prior radiotherapy					
Interaction test	**p = 0.508**				
Yes	267 / 1011 (26.4)	168 / 987 (17.0)	1.55	[1.31; 1.84]	<.001
No	27 / 97 (27.8)	12 / 83 (14.5)	1.93	[1.04; 3.56]	0.036

N: Number of patients
n: Number of patients with event
CI: Confidence interval
RR: Relative risk
ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
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Analysis method for interaction test:
p-value from logistic regression model.
logit(proportion) = treatment + subgroup factor + treatment * subgroup factor

Analysis method for within subgroup analysis:
RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm.
ET was the reference group for treatment group comparison.

Table 5-3.2.4 PT alanine aminotransferase increased: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	ET (N = 1070)	RR	[95% CI]	p-value
Alanine aminotransferase increased					
	n / N (%)	n / N (%)			
Region					
Interaction test	**p = 0.911**				
NA/WE/O	77 / 640 (12.0)	25 / 627 (4.0)	3.02	[1.95; 4.67]	<.001
ROW	117 / 468 (25.0)	42 / 443 (9.5)	2.64	[1.90; 3.66]	<.001
Geographical region					
Interaction test	**p = 0.705**				
Europe	99 / 654 (15.1)	34 / 638 (5.3)	2.84	[1.95; 4.13]	<.001
North America/Australia	35 / 213 (16.4)	12 / 194 (6.2)	2.66	[1.42; 4.97]	0.002
Asia	43 / 178 (24.2)	17 / 168 (10.1)	2.39	[1.42; 4.02]	0.001
Latin America	17 / 63 (27.0)	4 / 70 (5.7)	4.72	[1.68; 13.29]	0.003
Age group 1 at randomization					
Interaction test	**p = 0.331**				
<45	91 / 549 (16.6)	34 / 496 (6.9)	2.42	[1.66; 3.52]	<.001
45 to 54	95 / 539 (17.6)	31 / 546 (5.7)	3.10	[2.11; 4.57]	<.001
55 to 64	8 / 20 (40.0)	2 / 28 (7.1)	5.60	[1.33; 23.62]	0.019
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)					
Interaction test	**p = 0.289**				
<Median	91 / 549 (16.6)	34 / 496 (6.9)	2.42	[1.66; 3.52]	<.001
≥Median	103 / 559 (18.4)	33 / 574 (5.7)	3.20	[2.20; 4.66]	<.001
Race					
Interaction test	**p = 0.187**				
Asian	46 / 211 (21.8)	20 / 186 (10.8)	2.03	[1.25; 3.30]	0.004
Non-Asian	145 / 840 (17.3)	45 / 827 (5.4)	3.17	[2.30; 4.37]	<.001
BMI at screening					
Interaction test	**p = 0.226**				
≥25	120 / 551 (21.8)	37 / 523 (7.1)	3.08	[2.17; 4.36]	<.001
<25	71 / 542 (13.1)	30 / 535 (5.6)	2.34	[1.55; 3.52]	<.001
AJCC Anatomic Stage Group					
Interaction test	**p = 0.221**				
Group I/II	74 / 417 (17.7)	21 / 418 (5.0)	3.53	[2.22; 5.62]	<.001
Group III	120 / 691 (17.4)	46 / 652 (7.1)	2.46	[1.78; 3.40]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Anatomic stages					
Interaction test	**p = 0.023**				
IA/IB/IIA	32 / 171 (18.7)	7 / 198 (3.5)	5.29	[2.40; 11.68]	<.001
IIB	42 / 246 (17.1)	14 / 220 (6.4)	2.68	[1.51; 4.78]	<.001
IIIA	70 / 451 (15.5)	35 / 393 (8.9)	1.74	[1.19; 2.55]	0.004
IIIB	15 / 67 (22.4)	2 / 59 (3.4)	6.60	[1.58; 27.69]	0.010
IIIC	35 / 173 (20.2)	9 / 200 (4.5)	4.50	[2.22; 9.09]	<.001
Nodal status					
Interaction test	**p = 0.044**				
N0	20 / 91 (22.0)	3 / 117 (2.6)	8.57	[2.63; 27.96]	<.001
N1-N3	174 / 1017 (17.1)	64 / 950 (6.7)	2.54	[1.93; 3.34]	<.001
Histological grade at time of surgery					
Interaction test	**p = 0.661**				
Grade 1	15 / 110 (13.6)	3 / 100 (3.0)	4.55	[1.36; 15.24]	0.014
Grade 2	107 / 604 (17.7)	39 / 601 (6.5)	2.73	[1.93; 3.87]	<.001
Grade 3	51 / 297 (17.2)	19 / 266 (7.1)	2.40	[1.46; 3.96]	<.001
Histological subtype					
Interaction test	**p = 0.407**				
Ductal	148 / 863 (17.1)	56 / 835 (6.7)	2.56	[1.91; 3.43]	<.001
Lobular	32 / 172 (18.6)	7 / 169 (4.1)	4.49	[2.04; 9.89]	<.001
Other	14 / 73 (19.2)	4 / 66 (6.1)	3.16	[1.10; 9.13]	0.033
Ki67 status from surgical specimen					
Interaction test	**p = 0.324**				
Ki67≤20	89 / 527 (16.9)	37 / 552 (6.7)	2.52	[1.75; 3.63]	<.001
Ki67>20	79 / 422 (18.7)	21 / 378 (5.6)	3.37	[2.13; 5.34]	<.001
Type of NSAI					
Interaction test	**p = 0.598**				
Letrozole	151 / 809 (18.7)	50 / 773 (6.5)	2.89	[2.13; 3.91]	<.001
Anastrozole	43 / 299 (14.4)	17 / 297 (5.7)	2.51	[1.47; 4.30]	<.001
Prior neo/adjuvant chemotherapy					
Interaction test	**p = 0.988**				
Yes	174 / 1029 (16.9)	59 / 987 (6.0)	2.83	[2.13; 3.75]	<.001
No	20 / 79 (25.3)	8 / 83 (9.6)	2.63	[1.23; 5.62]	0.013
Prior adjuvant chemotherapy					
Interaction test	**p = 0.174**				
Yes	90 / 513 (17.5)	37 / 488 (7.6)	2.31	[1.61; 3.32]	<.001
No	104 / 595 (17.5)	30 / 582 (5.2)	3.39	[2.30; 5.01]	<.001
Prior neoadjuvant chemotherapy					
Interaction test	**p = 0.296**				
Yes	91 / 546 (16.7)	27 / 538 (5.0)	3.32	[2.20; 5.02]	<.001
No	103 / 562 (18.3)	40 / 532 (7.5)	2.44	[1.73; 3.44]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Prior endocrine therapy					
Interaction test	**p = 0.930**				
Yes	136 / 853 (15.9)	44 / 789 (5.6)	2.86	[2.06; 3.96]	<.001
No	58 / 255 (22.7)	23 / 281 (8.2)	2.78	[1.77; 4.37]	<.001
Prior mastectomy					
Interaction test	**p = 0.269**				
Yes	131 / 769 (17.0)	50 / 745 (6.7)	2.54	[1.86; 3.46]	<.001
No	63 / 339 (18.6)	17 / 325 (5.2)	3.55	[2.13; 5.94]	<.001
Prior radiotherapy					
Interaction test	**p = 0.998**				
Yes	167 / 1011 (16.5)	58 / 987 (5.9)	2.81	[2.11; 3.74]	<.001
No	27 / 97 (27.8)	9 / 83 (10.8)	2.57	[1.28; 5.14]	0.008

N: Number of patients
n: Number of patients with event
CI: Confidence interval
RR: Relative risk
ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
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Analysis method for interaction test:
p-value from logistic regression model.
logit(proportion) = treatment + subgroup factor + treatment * subgroup factor

Analysis method for within subgroup analysis:
RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm.
ET was the reference group for treatment group comparison.

Table 5-3.2.5 PT aspartate aminotransferase increased: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	ET (N = 1070)	RR	[95% CI]	p-value
Aspartate aminotransferase increased					
	n / N (%)	n / N (%)			
Region					
Interaction test	**p = 0.759**				
NA/WE/O	61 / 640 (9.5)	20 / 627 (3.2)	2.99	[1.83; 4.89]	<.001
ROW	111 / 468 (23.7)	43 / 443 (9.7)	2.44	[1.76; 3.39]	<.001
Geographical region					
Interaction test	**p = 0.968**				
Europe	91 / 654 (13.9)	32 / 638 (5.0)	2.77	[1.88; 4.09]	<.001
North America/Australia	29 / 213 (13.6)	10 / 194 (5.2)	2.64	[1.32; 5.28]	0.006
Asia	39 / 178 (21.9)	14 / 168 (8.3)	2.63	[1.48; 4.66]	<.001
Latin America	13 / 63 (20.6)	7 / 70 (10.0)	2.06	[0.88; 4.84]	0.096
Age group 1 at randomization					
Interaction test	**p = 0.705**				
<45	88 / 549 (16.0)	27 / 496 (5.4)	2.94	[1.95; 4.45]	<.001
45 to 54	76 / 539 (14.1)	32 / 546 (5.9)	2.41	[1.62; 3.57]	<.001
55 to 64	8 / 20 (40.0)	4 / 28 (14.3)	2.80	[0.98; 8.03]	0.056
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)					
Interaction test	**p = 0.465**				
<Median	88 / 549 (16.0)	27 / 496 (5.4)	2.94	[1.95; 4.45]	<.001
≥Median	84 / 559 (15.0)	36 / 574 (6.3)	2.40	[1.65; 3.48]	<.001
Race					
Interaction test	**p = 0.511**				
Asian	42 / 211 (19.9)	17 / 186 (9.1)	2.18	[1.28; 3.69]	0.004
Non-Asian	128 / 840 (15.2)	45 / 827 (5.4)	2.80	[2.02; 3.88]	<.001
BMI at screening					
Interaction test	**p = 0.661**				
≥25	98 / 551 (17.8)	34 / 523 (6.5)	2.74	[1.89; 3.97]	<.001
<25	73 / 542 (13.5)	29 / 535 (5.4)	2.48	[1.64; 3.76]	<.001
AJCC Anatomic Stage Group					
Interaction test	**p = 0.938**				
Group I/II	60 / 417 (14.4)	23 / 418 (5.5)	2.61	[1.65; 4.15]	<.001
Group III	112 / 691 (16.2)	40 / 652 (6.1)	2.64	[1.87; 3.73]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Anatomic stages					
Interaction test	**p = 0.272**				
IA/IB/IIA	26 / 171 (15.2)	9 / 198 (4.5)	3.35	[1.61; 6.94]	0.001
IIB	34 / 246 (13.8)	14 / 220 (6.4)	2.17	[1.20; 3.94]	0.011
IIIA	64 / 451 (14.2)	28 / 393 (7.1)	1.99	[1.30; 3.04]	0.001
IIIB	16 / 67 (23.9)	3 / 59 (5.1)	4.70	[1.44; 15.32]	0.010
IIIC	32 / 173 (18.5)	9 / 200 (4.5)	4.11	[2.02; 8.37]	<.001
Nodal status					
Interaction test	**p = 0.334**				
N0	16 / 91 (17.6)	5 / 117 (4.3)	4.11	[1.57; 10.81]	0.004
N1-N3	156 / 1017 (15.3)	58 / 950 (6.1)	2.51	[1.88; 3.35]	<.001
Histological grade at time of surgery					
Interaction test	**p = 0.872**				
Grade 1	15 / 110 (13.6)	6 / 100 (6.0)	2.27	[0.92; 5.63]	0.076
Grade 2	90 / 604 (14.9)	34 / 601 (5.7)	2.63	[1.80; 3.84]	<.001
Grade 3	52 / 297 (17.5)	16 / 266 (6.0)	2.91	[1.70; 4.97]	<.001
Histological subtype					
Interaction test	**p = 0.499**				
Ductal	130 / 863 (15.1)	52 / 835 (6.2)	2.42	[1.78; 3.29]	<.001
Lobular	28 / 172 (16.3)	7 / 169 (4.1)	3.93	[1.76; 8.75]	<.001
Other	14 / 73 (19.2)	4 / 66 (6.1)	3.16	[1.10; 9.13]	0.033
Ki67 status from surgical specimen					
Interaction test	**p = 0.689**				
Ki67≤20	81 / 527 (15.4)	34 / 552 (6.2)	2.50	[1.70; 3.66]	<.001
Ki67>20	69 / 422 (16.4)	22 / 378 (5.8)	2.81	[1.77; 4.45]	<.001
Type of NSAI					
Interaction test	**p = 0.836**				
Letrozole	136 / 809 (16.8)	49 / 773 (6.3)	2.65	[1.94; 3.62]	<.001
Anastrozole	36 / 299 (12.0)	14 / 297 (4.7)	2.55	[1.41; 4.64]	0.002
Prior neo/adjuvant chemotherapy					
Interaction test	**p = 0.634**				
Yes	154 / 1029 (15.0)	54 / 987 (5.5)	2.74	[2.03; 3.68]	<.001
No	18 / 79 (22.8)	9 / 83 (10.8)	2.10	[1.00; 4.40]	0.049
Prior adjuvant chemotherapy					
Interaction test	**p = 0.635**				
Yes	75 / 513 (14.6)	29 / 488 (5.9)	2.46	[1.63; 3.71]	<.001
No	97 / 595 (16.3)	34 / 582 (5.8)	2.79	[1.92; 4.05]	<.001
Prior neoadjuvant chemotherapy					
Interaction test	**p = 0.544**				
Yes	85 / 546 (15.6)	29 / 538 (5.4)	2.89	[1.93; 4.33]	<.001
No	87 / 562 (15.5)	34 / 532 (6.4)	2.42	[1.66; 3.54]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Prior endocrine therapy					
Interaction test	**p = 0.205**				
Yes	128 / 853 (15.0)	39 / 789 (4.9)	3.04	[2.15; 4.29]	<.001
No	44 / 255 (17.3)	24 / 281 (8.5)	2.02	[1.27; 3.22]	0.003
Prior mastectomy					
Interaction test	**p = 0.653**				
Yes	115 / 769 (15.0)	44 / 745 (5.9)	2.53	[1.82; 3.53]	<.001
No	57 / 339 (16.8)	19 / 325 (5.8)	2.88	[1.75; 4.72]	<.001
Prior radiotherapy					
Interaction test	**p = 0.604**				
Yes	148 / 1011 (14.6)	53 / 987 (5.4)	2.73	[2.02; 3.68]	<.001
No	24 / 97 (24.7)	10 / 83 (12.0)	2.05	[1.04; 4.04]	0.037

N: Number of patients
n: Number of patients with event
CI: Confidence interval
RR: Relative risk
ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
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Analysis method for interaction test:
p-value from logistic regression model.
logit(proportion) = treatment + subgroup factor + treatment * subgroup factor

Analysis method for within subgroup analysis:
RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm.
ET was the reference group for treatment group comparison.

Table 5-3.2.6 PT white blood cell count decreased: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	ET (N = 1070)	RR	[95% CI]	p-value
White blood cell count decreased					
	n / N (%)	n / N (%)			
Region					
Interaction test	**p = 0.712**				
NA/WE/O	56 / 640 (8.8)	10 / 627 (1.6)	5.49	[2.82; 10.66]	<.001
ROW	74 / 468 (15.8)	16 / 443 (3.6)	4.38	[2.59; 7.40]	<.001
Geographical region					
Interaction test	**p = 0.459**				
Europe	30 / 654 (4.6)	3 / 638 (0.5)	9.76	[2.99; 31.80]	<.001
North America/Australia	32 / 213 (15.0)	8 / 194 (4.1)	3.64	[1.72; 7.71]	<.001
Asia	65 / 178 (36.5)	15 / 168 (8.9)	4.09	[2.43; 6.88]	<.001
Latin America	3 / 63 (4.8)	0 / 70 (0.0)	7.77	[0.41; >99.99]	0.172
Age group 1 at randomization					
Interaction test	**p = 0.390**				
<45	75 / 549 (13.7)	18 / 496 (3.6)	3.76	[2.28; 6.21]	<.001
45 to 54	52 / 539 (9.6)	7 / 546 (1.3)	7.53	[3.45; 16.42]	<.001
55 to 64	3 / 20 (15.0)	1 / 28 (3.6)	4.20	[0.47; 37.50]	0.199
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)					
Interaction test	**p = 0.195**				
<Median	75 / 549 (13.7)	18 / 496 (3.6)	3.76	[2.28; 6.21]	<.001
≥Median	55 / 559 (9.8)	8 / 574 (1.4)	7.06	[3.39; 14.68]	<.001
Race					
Interaction test	**p = 0.916**				
Asian	69 / 211 (32.7)	15 / 186 (8.1)	4.05	[2.40; 6.84]	<.001
Non-Asian	61 / 840 (7.3)	11 / 827 (1.3)	5.46	[2.89; 10.30]	<.001
BMI at screening					
Interaction test	**p = 0.633**				
≥25	50 / 551 (9.1)	8 / 523 (1.5)	5.93	[2.84; 12.39]	<.001
<25	78 / 542 (14.4)	17 / 535 (3.2)	4.53	[2.72; 7.55]	<.001
AJCC Anatomic Stage Group					
Interaction test	**p = 0.447**				
Group I/II	34 / 417 (8.2)	5 / 418 (1.2)	6.82	[2.69; 17.26]	<.001
Group III	96 / 691 (13.9)	21 / 652 (3.2)	4.31	[2.72; 6.83]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Anatomic stages					
Interaction test	**p = 0.646**				
IA/IB/IIA	11 / 171 (6.4)	0 / 198 (0.0)	26.61	[1.58; >99.99]	0.023
IIB	23 / 246 (9.3)	5 / 220 (2.3)	4.11	[1.59; 10.64]	0.004
IIIA	60 / 451 (13.3)	14 / 393 (3.6)	3.73	[2.12; 6.58]	<.001
IIIB	2 / 67 (3.0)	0 / 59 (0.0)	4.41	[0.22; 90.08]	0.335
IIIC	34 / 173 (19.7)	7 / 200 (3.5)	5.62	[2.55; 12.34]	<.001
Nodal status					
Interaction test	**p = 0.390**				
N0	9 / 91 (9.9)	1 / 117 (0.9)	11.57	[1.49; 89.68]	0.019
N1-N3	121 / 1017 (11.9)	25 / 950 (2.6)	4.52	[2.97; 6.89]	<.001
Histological grade at time of surgery					
Interaction test	**p = 0.162**				
Grade 1	7 / 110 (6.4)	3 / 100 (3.0)	2.12	[0.56; 7.98]	0.266
Grade 2	70 / 604 (11.6)	15 / 601 (2.5)	4.64	[2.69; 8.02]	<.001
Grade 3	44 / 297 (14.8)	4 / 266 (1.5)	9.85	[3.59; 27.05]	<.001
Histological subtype					
Interaction test	**p = 0.435**				
Ductal	100 / 863 (11.6)	23 / 835 (2.8)	4.21	[2.70; 6.55]	<.001
Lobular	18 / 172 (10.5)	2 / 169 (1.2)	8.84	[2.08; 37.52]	0.003
Other	12 / 73 (16.4)	1 / 66 (1.5)	10.85	[1.45; 81.19]	0.020
Ki67 status from surgical specimen					
Interaction test	**p = 0.323**				
Ki67≤20	61 / 527 (11.6)	10 / 552 (1.8)	6.39	[3.31; 12.34]	<.001
Ki67>20	49 / 422 (11.6)	11 / 378 (2.9)	3.99	[2.11; 7.56]	<.001
Type of NSAI					
Interaction test	**p = 0.634**				
Letrozole	84 / 809 (10.4)	15 / 773 (1.9)	5.35	[3.12; 9.19]	<.001
Anastrozole	46 / 299 (15.4)	11 / 297 (3.7)	4.15	[2.19; 7.86]	<.001
Prior neo/adjuvant chemotherapy					
Interaction test	**N.E.**				
Yes	126 / 1029 (12.2)	26 / 987 (2.6)	4.65	[3.08; 7.03]	<.001
No	4 / 79 (5.1)	0 / 83 (0.0)	9.45	[0.52; >99.99]	0.130
Prior adjuvant chemotherapy					
Interaction test	**p = 0.306**				
Yes	66 / 513 (12.9)	16 / 488 (3.3)	3.92	[2.31; 6.68]	<.001
No	64 / 595 (10.8)	10 / 582 (1.7)	6.26	[3.25; 12.07]	<.001
Prior neoadjuvant chemotherapy					
Interaction test	**p = 0.370**				
Yes	66 / 546 (12.1)	16 / 538 (3.0)	4.06	[2.39; 6.93]	<.001
No	64 / 562 (11.4)	10 / 532 (1.9)	6.06	[3.14; 11.67]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Prior endocrine therapy					
Interaction test	**p = 0.961**				
Yes	104 / 853 (12.2)	20 / 789 (2.5)	4.81	[3.01; 7.69]	<.001
No	26 / 255 (10.2)	6 / 281 (2.1)	4.78	[2.00; 11.41]	<.001
Prior mastectomy					
Interaction test	**p = 0.162**				
Yes	92 / 769 (12.0)	22 / 745 (3.0)	4.05	[2.57; 6.38]	<.001
No	38 / 339 (11.2)	4 / 325 (1.2)	9.11	[3.29; 25.23]	<.001
Prior radiotherapy					
Interaction test	**p = 0.528**				
Yes	127 / 1011 (12.6)	25 / 987 (2.5)	4.96	[3.26; 7.55]	<.001
No	3 / 97 (3.1)	1 / 83 (1.2)	2.57	[0.27; 24.21]	0.410

N: Number of patients
n: Number of patients with event
N.E.: Not estimable
CI: Confidence interval
RR: Relative risk
ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
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Analysis method for interaction test:
p-value from logistic regression model.
logit(proportion) = treatment + subgroup factor + treatment * subgroup factor

Analysis method for within subgroup analysis:
RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm.
ET was the reference group for treatment group comparison.

Table 5-3.2.7 PT sars-cov-2 test negative: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	ET (N = 1070)	RR	[95% CI]	p-value
SARS-CoV-2 test negative					
	n / N (%)	n / N (%)			
Region					
Interaction test	**p = 0.910**				
NA/WE/O	34 / 640 (5.3)	22 / 627 (3.5)	1.51	[0.90; 2.56]	0.121
ROW	30 / 468 (6.4)	18 / 443 (4.1)	1.58	[0.89; 2.79]	0.117
Geographical region					
Interaction test	**p = 0.972**				
Europe	35 / 654 (5.4)	24 / 638 (3.8)	1.42	[0.86; 2.36]	0.174
North America/Australia	17 / 213 (8.0)	10 / 194 (5.2)	1.55	[0.73; 3.30]	0.257
Asia	10 / 178 (5.6)	6 / 168 (3.6)	1.57	[0.58; 4.23]	0.370
Latin America	2 / 63 (3.2)	0 / 70 (0.0)	5.55	[0.27; >99.99]	0.266
Age group 1 at randomization					
Interaction test	**p = 0.965**				
<45	28 / 549 (5.1)	17 / 496 (3.4)	1.49	[0.82; 2.69]	0.187
45 to 54	34 / 539 (6.3)	21 / 546 (3.8)	1.64	[0.96; 2.79]	0.068
55 to 64	2 / 20 (10.0)	2 / 28 (7.1)	1.40	[0.21; 9.12]	0.725
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)					
Interaction test	**p = 0.838**				
<Median	28 / 549 (5.1)	17 / 496 (3.4)	1.49	[0.82; 2.69]	0.187
≥Median	36 / 559 (6.4)	23 / 574 (4.0)	1.61	[0.97; 2.68]	0.068
Race					
Interaction test	**p = 0.815**				
Asian	12 / 211 (5.7)	6 / 186 (3.2)	1.76	[0.68; 4.60]	0.247
Non-Asian	52 / 840 (6.2)	33 / 827 (4.0)	1.55	[1.01; 2.37]	0.043
BMI at screening					
Interaction test	**p = 0.163**				
≥25	35 / 551 (6.4)	27 / 523 (5.2)	1.23	[0.76; 2.00]	0.405
<25	29 / 542 (5.4)	13 / 535 (2.4)	2.20	[1.16; 4.19]	0.016
AJCC Anatomic Stage Group					
Interaction test	**p = 0.737**				
Group I/II	22 / 417 (5.3)	13 / 418 (3.1)	1.70	[0.87; 3.32]	0.123
Group III	42 / 691 (6.1)	27 / 652 (4.1)	1.47	[0.92; 2.35]	0.111

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Anatomic stages					
Interaction test	**p = 0.759**				
IA/IB/IIA	9 / 171 (5.3)	5 / 198 (2.5)	2.08	[0.71; 6.10]	0.180
IIB	13 / 246 (5.3)	8 / 220 (3.6)	1.45	[0.61; 3.44]	0.395
IIIA	26 / 451 (5.8)	13 / 393 (3.3)	1.74	[0.91; 3.34]	0.095
IIIB	4 / 67 (6.0)	5 / 59 (8.5)	0.70	[0.20; 2.50]	0.588
IIIC	12 / 173 (6.9)	9 / 200 (4.5)	1.54	[0.67; 3.57]	0.313
Nodal status					
Interaction test	**p = 0.511**				
N0	5 / 91 (5.5)	6 / 117 (5.1)	1.07	[0.34; 3.40]	0.907
N1-N3	59 / 1017 (5.8)	34 / 950 (3.6)	1.62	[1.07; 2.45]	0.022
Histological grade at time of surgery					
Interaction test	**p = 0.275**				
Grade 1	5 / 110 (4.5)	1 / 100 (1.0)	4.55	[0.54; 38.25]	0.164
Grade 2	32 / 604 (5.3)	25 / 601 (4.2)	1.27	[0.76; 2.12]	0.353
Grade 3	23 / 297 (7.7)	9 / 266 (3.4)	2.29	[1.08; 4.86]	0.031
Histological subtype					
Interaction test	**p = 0.947**				
Ductal	44 / 863 (5.1)	27 / 835 (3.2)	1.58	[0.99; 2.52]	0.057
Lobular	11 / 172 (6.4)	8 / 169 (4.7)	1.35	[0.56; 3.28]	0.506
Other	9 / 73 (12.3)	5 / 66 (7.6)	1.63	[0.57; 4.61]	0.359
Ki67 status from surgical specimen					
Interaction test	**p = 0.659**				
Ki67≤20	24 / 527 (4.6)	20 / 552 (3.6)	1.26	[0.70; 2.25]	0.441
Ki67>20	27 / 422 (6.4)	16 / 378 (4.2)	1.51	[0.83; 2.76]	0.179
Type of NSAI					
Interaction test	**p = 0.631**				
Letrozole	41 / 809 (5.1)	27 / 773 (3.5)	1.45	[0.90; 2.33]	0.125
Anastrozole	23 / 299 (7.7)	13 / 297 (4.4)	1.76	[0.91; 3.40]	0.094
Prior neo/adjuvant chemotherapy					
Interaction test	**N.E.**				
Yes	54 / 1029 (5.2)	40 / 987 (4.1)	1.29	[0.87; 1.93]	0.205
No	10 / 79 (12.7)	0 / 83 (0.0)	22.05	[1.31; >99.99]	0.032
Prior adjuvant chemotherapy					
Interaction test	**p = 0.029**				
Yes	25 / 513 (4.9)	24 / 488 (4.9)	0.99	[0.57; 1.71]	0.974
No	39 / 595 (6.6)	16 / 582 (2.7)	2.38	[1.35; 4.22]	0.003
Prior neoadjuvant chemotherapy					
Interaction test	**p = 0.638**				
Yes	30 / 546 (5.5)	21 / 538 (3.9)	1.41	[0.82; 2.43]	0.219
No	34 / 562 (6.0)	19 / 532 (3.6)	1.69	[0.98; 2.93]	0.060

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Prior endocrine therapy					
Interaction test	**p = 0.339**				
Yes	48 / 853 (5.6)	25 / 789 (3.2)	1.78	[1.11; 2.85]	0.017
No	16 / 255 (6.3)	15 / 281 (5.3)	1.18	[0.59; 2.33]	0.643
Prior mastectomy					
Interaction test	**p = 0.972**				
Yes	48 / 769 (6.2)	30 / 745 (4.0)	1.55	[0.99; 2.42]	0.053
No	16 / 339 (4.7)	10 / 325 (3.1)	1.53	[0.71; 3.33]	0.279
Prior radiotherapy					
Interaction test	**p = 0.503**				
Yes	52 / 1011 (5.1)	35 / 987 (3.5)	1.45	[0.95; 2.21]	0.082
No	12 / 97 (12.4)	5 / 83 (6.0)	2.05	[0.75; 5.59]	0.159

N: Number of patients
n: Number of patients with event
N.E.: Not estimable
CI: Confidence interval
RR: Relative risk
ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
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Analysis method for interaction test:
p-value from logistic regression model.
logit(proportion) = treatment + subgroup factor + treatment * subgroup factor

Analysis method for within subgroup analysis:
RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm.
ET was the reference group for treatment group comparison.

Table 5-3.2.8 PT electrocardiogram qt prolonged: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	ET (N = 1070)	RR	[95% CI]	p-value
Electrocardiogram QT prolonged					
	n / N (%)	n / N (%)			
Region					
Interaction test	**p = 0.900**				
NA/WE/O	17 / 640 (2.7)	3 / 627 (0.5)	5.55	[1.64; 18.85]	0.006
ROW	37 / 468 (7.9)	6 / 443 (1.4)	5.84	[2.49; 13.69]	<.001
Geographical region					
Interaction test	**p = 0.952**				
Europe	27 / 654 (4.1)	6 / 638 (0.9)	4.39	[1.82; 10.56]	<.001
North America/Australia	5 / 213 (2.3)	1 / 194 (0.5)	4.55	[0.54; 38.64]	0.165
Asia	12 / 178 (6.7)	2 / 168 (1.2)	5.66	[1.29; 24.93]	0.022
Latin America	10 / 63 (15.9)	0 / 70 (0.0)	23.30	[1.39; >99.99]	0.028
Age group 1 at randomization					
Interaction test	**p = 0.881**				
<45	27 / 549 (4.9)	4 / 496 (0.8)	6.10	[2.15; 17.31]	<.001
45 to 54	27 / 539 (5.0)	5 / 546 (0.9)	5.47	[2.12; 14.10]	<.001
55 to 64	0 / 20 (0.0)	0 / 28 (0.0)	N.E.	N.E.	N.E.
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)					
Interaction test	**p = 0.894**				
<Median	27 / 549 (4.9)	4 / 496 (0.8)	6.10	[2.15; 17.31]	<.001
≥Median	27 / 559 (4.8)	5 / 574 (0.9)	5.54	[2.15; 14.30]	<.001
Race					
Interaction test	**p = 0.800**				
Asian	14 / 211 (6.6)	2 / 186 (1.1)	6.17	[1.42; 26.80]	0.015
Non-Asian	36 / 840 (4.3)	7 / 827 (0.8)	5.06	[2.27; 11.31]	<.001
BMI at screening					
Interaction test	**p = 0.719**				
≥25	28 / 551 (5.1)	4 / 523 (0.8)	6.64	[2.35; 18.81]	<.001
<25	26 / 542 (4.8)	5 / 535 (0.9)	5.13	[1.99; 13.27]	<.001
AJCC Anatomic Stage Group					
Interaction test	**p = 0.778**				
Group I/II	14 / 417 (3.4)	2 / 418 (0.5)	7.02	[1.60; 30.68]	0.010
Group III	40 / 691 (5.8)	7 / 652 (1.1)	5.39	[2.43; 11.95]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Anatomic stages					
Interaction test	**p = 0.806**				
IA/IB/IIA	6 / 171 (3.5)	2 / 198 (1.0)	3.47	[0.71; 16.99]	0.124
IIB	8 / 246 (3.3)	0 / 220 (0.0)	15.21	[0.88; >99.99]	0.061
IIIA	23 / 451 (5.1)	5 / 393 (1.3)	4.01	[1.54; 10.44]	0.004
IIIB	9 / 67 (13.4)	1 / 59 (1.7)	7.93	[1.03; 60.72]	0.046
IIIC	8 / 173 (4.6)	1 / 200 (0.5)	9.25	[1.17; 73.21]	0.035
Nodal status					
Interaction test	**p = 0.916**				
N0	5 / 91 (5.5)	1 / 117 (0.9)	6.43	[0.76; 54.07]	0.087
N1-N3	49 / 1017 (4.8)	8 / 950 (0.8)	5.72	[2.72; 12.02]	<.001
Histological grade at time of surgery					
Interaction test	**p = 0.351**				
Grade 1	5 / 110 (4.5)	0 / 100 (0.0)	10.01	[0.56; >99.99]	0.117
Grade 2	33 / 604 (5.5)	8 / 601 (1.3)	4.10	[1.91; 8.81]	<.001
Grade 3	13 / 297 (4.4)	1 / 266 (0.4)	11.64	[1.53; 88.40]	0.018
Histological subtype					
Interaction test	**p = 0.346**				
Ductal	42 / 863 (4.9)	7 / 835 (0.8)	5.81	[2.62; 12.85]	<.001
Lobular	5 / 172 (2.9)	2 / 169 (1.2)	2.46	[0.48; 12.49]	0.279
Other	7 / 73 (9.6)	0 / 66 (0.0)	13.58	[0.79; >99.99]	0.072
Ki67 status from surgical specimen					
Interaction test	**p = 0.164**				
Ki67≤20	27 / 527 (5.1)	7 / 552 (1.3)	4.04	[1.77; 9.20]	<.001
Ki67>20	21 / 422 (5.0)	1 / 378 (0.3)	18.81	[2.54; >99.99]	0.004
Type of NSAI					
Interaction test	**N.E.**				
Letrozole	44 / 809 (5.4)	9 / 773 (1.2)	4.67	[2.30; 9.50]	<.001
Anastrozole	10 / 299 (3.3)	0 / 297 (0.0)	20.86	[1.23; >99.99]	0.036
Prior neo/adjuvant chemotherapy					
Interaction test	**N.E.**				
Yes	52 / 1029 (5.1)	9 / 987 (0.9)	5.54	[2.75; 11.18]	<.001
No	2 / 79 (2.5)	0 / 83 (0.0)	5.25	[0.26; >99.99]	0.282
Prior adjuvant chemotherapy					
Interaction test	**p = 0.024**				
Yes	19 / 513 (3.7)	7 / 488 (1.4)	2.58	[1.10; 6.09]	0.030
No	35 / 595 (5.9)	2 / 582 (0.3)	17.12	[4.14; 70.84]	<.001
Prior neoadjuvant chemotherapy					
Interaction test	**p = 0.090**				
Yes	34 / 546 (6.2)	3 / 538 (0.6)	11.17	[3.45; 36.14]	<.001
No	20 / 562 (3.6)	6 / 532 (1.1)	3.16	[1.28; 7.80]	0.013

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Prior endocrine therapy					
Interaction test	**p = 0.841**				
Yes	42 / 853 (4.9)	7 / 789 (0.9)	5.55	[2.51; 12.28]	<.001
No	12 / 255 (4.7)	2 / 281 (0.7)	6.61	[1.49; 29.26]	0.013
Prior mastectomy					
Interaction test	**p = 0.341**				
Yes	33 / 769 (4.3)	7 / 745 (0.9)	4.57	[2.03; 10.26]	<.001
No	21 / 339 (6.2)	2 / 325 (0.6)	10.07	[2.38; 42.59]	0.002
Prior radiotherapy					
Interaction test	**p = 0.458**				
Yes	51 / 1011 (5.0)	8 / 987 (0.8)	6.22	[2.97; 13.05]	<.001
No	3 / 97 (3.1)	1 / 83 (1.2)	2.57	[0.27; 24.21]	0.410

N: Number of patients
n: Number of patients with event
N.E.: Not estimable
CI: Confidence interval
RR: Relative risk
ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
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Analysis method for interaction test:
p-value from logistic regression model.
logit(proportion) = treatment + subgroup factor + treatment * subgroup factor

Analysis method for within subgroup analysis:
RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm.
ET was the reference group for treatment group comparison.

Table 5-3.2.9 PT blood alkaline phosphatase increased: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	ET (N = 1070)	RR	[95% CI]	p-value
Blood alkaline phosphatase increased					
	n / N (%)	n / N (%)			
Region					
Interaction test	**p = 0.488**				
NA/WE/O	24 / 640 (3.8)	12 / 627 (1.9)	1.96	[0.99; 3.88]	0.054
ROW	19 / 468 (4.1)	13 / 443 (2.9)	1.38	[0.69; 2.77]	0.359
Geographical region					
Interaction test	**p = 0.878**				
Europe	27 / 654 (4.1)	17 / 638 (2.7)	1.55	[0.85; 2.81]	0.151
North America/Australia	10 / 213 (4.7)	5 / 194 (2.6)	1.82	[0.63; 5.24]	0.266
Asia	3 / 178 (1.7)	0 / 168 (0.0)	6.61	[0.34; >99.99]	0.210
Latin America	3 / 63 (4.8)	3 / 70 (4.3)	1.11	[0.23; 5.31]	0.895
Age group 1 at randomization					
Interaction test	**p = 0.443**				
<45	21 / 549 (3.8)	10 / 496 (2.0)	1.90	[0.90; 3.99]	0.091
45 to 54	19 / 539 (3.5)	15 / 546 (2.7)	1.28	[0.66; 2.50]	0.463
55 to 64	3 / 20 (15.0)	0 / 28 (0.0)	9.67	[0.53; >99.99]	0.126
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)					
Interaction test	**p = 0.648**				
<Median	21 / 549 (3.8)	10 / 496 (2.0)	1.90	[0.90; 3.99]	0.091
≥Median	22 / 559 (3.9)	15 / 574 (2.6)	1.51	[0.79; 2.87]	0.214
Race					
Interaction test	**p = 0.459**				
Asian	4 / 211 (1.9)	1 / 186 (0.5)	3.53	[0.40; 31.27]	0.258
Non-Asian	35 / 840 (4.2)	23 / 827 (2.8)	1.50	[0.89; 2.51]	0.126
BMI at screening					
Interaction test	**p = 0.090**				
≥25	33 / 551 (6.0)	14 / 523 (2.7)	2.24	[1.21; 4.13]	0.010
<25	9 / 542 (1.7)	10 / 535 (1.9)	0.89	[0.36; 2.17]	0.795
AJCC Anatomic Stage Group					
Interaction test	**p = 0.165**				
Group I/II	16 / 417 (3.8)	14 / 418 (3.3)	1.15	[0.57; 2.32]	0.705
Group III	27 / 691 (3.9)	11 / 652 (1.7)	2.32	[1.16; 4.63]	0.018

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Anatomic stages					
Interaction test	**p = 0.659**				
IA/IB/IIA	6 / 171 (3.5)	6 / 198 (3.0)	1.16	[0.38; 3.52]	0.796
IIB	10 / 246 (4.1)	8 / 220 (3.6)	1.12	[0.45; 2.78]	0.811
IIIA	11 / 451 (2.4)	9 / 393 (2.3)	1.07	[0.45; 2.54]	0.887
IIIB	7 / 67 (10.4)	2 / 59 (3.4)	3.08	[0.67; 14.26]	0.150
IIIC	9 / 173 (5.2)	0 / 200 (0.0)	21.95	[1.29; >99.99]	0.033
Nodal status					
Interaction test	**p = 0.952**				
N0	5 / 91 (5.5)	4 / 117 (3.4)	1.61	[0.44; 5.81]	0.470
N1-N3	38 / 1017 (3.7)	21 / 950 (2.2)	1.69	[1.00; 2.86]	0.050
Histological grade at time of surgery					
Interaction test	**p = 0.993**				
Grade 1	2 / 110 (1.8)	1 / 100 (1.0)	1.82	[0.17; 19.75]	0.623
Grade 2	22 / 604 (3.6)	14 / 601 (2.3)	1.56	[0.81; 3.03]	0.185
Grade 3	16 / 297 (5.4)	9 / 266 (3.4)	1.59	[0.72; 3.54]	0.254
Histological subtype					
Interaction test	**p = 0.849**				
Ductal	32 / 863 (3.7)	20 / 835 (2.4)	1.55	[0.89; 2.68]	0.120
Lobular	8 / 172 (4.7)	4 / 169 (2.4)	1.97	[0.60; 6.40]	0.262
Other	3 / 73 (4.1)	1 / 66 (1.5)	2.71	[0.29; 25.44]	0.382
Ki67 status from surgical specimen					
Interaction test	**p = 0.352**				
Ki67≤20	24 / 527 (4.6)	12 / 552 (2.2)	2.09	[1.06; 4.15]	0.034
Ki67>20	11 / 422 (2.6)	8 / 378 (2.1)	1.23	[0.50; 3.03]	0.650
Type of NSAI					
Interaction test	**p = 0.240**				
Letrozole	31 / 809 (3.8)	21 / 773 (2.7)	1.41	[0.82; 2.43]	0.216
Anastrozole	12 / 299 (4.0)	4 / 297 (1.3)	2.98	[0.97; 9.13]	0.056
Prior neo/adjuvant chemotherapy					
Interaction test	**p = 0.137**				
Yes	39 / 1029 (3.8)	19 / 987 (1.9)	1.97	[1.15; 3.38]	0.014
No	4 / 79 (5.1)	6 / 83 (7.2)	0.70	[0.21; 2.39]	0.570
Prior adjuvant chemotherapy					
Interaction test	**p = 0.381**				
Yes	18 / 513 (3.5)	13 / 488 (2.7)	1.32	[0.65; 2.66]	0.442
No	25 / 595 (4.2)	12 / 582 (2.1)	2.04	[1.03; 4.02]	0.040
Prior neoadjuvant chemotherapy					
Interaction test	**p = 0.048**				
Yes	24 / 546 (4.4)	8 / 538 (1.5)	2.96	[1.34; 6.52]	0.007
No	19 / 562 (3.4)	17 / 532 (3.2)	1.06	[0.56; 2.01]	0.864

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Prior endocrine therapy					
Interaction test	**p = 0.454**				
Yes	25 / 853 (2.9)	11 / 789 (1.4)	2.10	[1.04; 4.24]	0.038
No	18 / 255 (7.1)	14 / 281 (5.0)	1.42	[0.72; 2.79]	0.314
Prior mastectomy					
Interaction test	**p = 0.490**				
Yes	33 / 769 (4.3)	21 / 745 (2.8)	1.52	[0.89; 2.61]	0.126
No	10 / 339 (2.9)	4 / 325 (1.2)	2.40	[0.76; 7.57]	0.136
Prior radiotherapy					
Interaction test	**p = 0.086**				
Yes	36 / 1011 (3.6)	17 / 987 (1.7)	2.07	[1.17; 3.66]	0.013
No	7 / 97 (7.2)	8 / 83 (9.6)	0.75	[0.28; 1.98]	0.559

N: Number of patients
n: Number of patients with event
CI: Confidence interval
RR: Relative risk
ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
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Analysis method for interaction test:
p-value from logistic regression model.
logit(proportion) = treatment + subgroup factor + treatment * subgroup factor

Analysis method for within subgroup analysis:
RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm.
ET was the reference group for treatment group comparison.

Table 5-3.2.10 PT gamma-glutamyltransferase increased: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	ET (N = 1070)	RR	[95% CI]	p-value
Gamma-glutamyltransferase increased					
	n / N (%)	n / N (%)			
Region					
Interaction test	**p = 0.285**				
NA/WE/O	19 / 640 (3.0)	14 / 627 (2.2)	1.33	[0.67; 2.63]	0.413
ROW	22 / 468 (4.7)	9 / 443 (2.0)	2.31	[1.08; 4.97]	0.032
Geographical region					
Interaction test	**p = 0.721**				
Europe	28 / 654 (4.3)	15 / 638 (2.4)	1.82	[0.98; 3.38]	0.057
North America/Australia	7 / 213 (3.3)	6 / 194 (3.1)	1.06	[0.36; 3.11]	0.912
Asia	4 / 178 (2.2)	1 / 168 (0.6)	3.78	[0.43; 33.44]	0.233
Latin America	2 / 63 (3.2)	1 / 70 (1.4)	2.22	[0.21; 23.92]	0.510
Age group 1 at randomization					
Interaction test	**p = 0.314**				
<45	20 / 549 (3.6)	6 / 496 (1.2)	3.01	[1.22; 7.44]	0.017
45 to 54	19 / 539 (3.5)	14 / 546 (2.6)	1.37	[0.70; 2.71]	0.359
55 to 64	2 / 20 (10.0)	3 / 28 (10.7)	0.93	[0.17; 5.08]	0.936
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)					
Interaction test	**p = 0.125**				
<Median	20 / 549 (3.6)	6 / 496 (1.2)	3.01	[1.22; 7.44]	0.017
≥Median	21 / 559 (3.8)	17 / 574 (3.0)	1.27	[0.68; 2.38]	0.459
Race					
Interaction test	**p = 0.809**				
Asian	5 / 211 (2.4)	3 / 186 (1.6)	1.47	[0.36; 6.06]	0.595
Non-Asian	34 / 840 (4.0)	19 / 827 (2.3)	1.76	[1.01; 3.06]	0.045
BMI at screening					
Interaction test	**p = 0.187**				
≥25	31 / 551 (5.6)	13 / 523 (2.5)	2.26	[1.20; 4.28]	0.012
<25	10 / 542 (1.8)	9 / 535 (1.7)	1.10	[0.45; 2.68]	0.839
AJCC Anatomic Stage Group					
Interaction test	**p = 0.588**				
Group I/II	20 / 417 (4.8)	10 / 418 (2.4)	2.00	[0.95; 4.23]	0.068
Group III	21 / 691 (3.0)	13 / 652 (2.0)	1.52	[0.77; 3.02]	0.227

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Anatomic stages					
Interaction test	**p = 0.558**				
IA/IB/IIA	9 / 171 (5.3)	5 / 198 (2.5)	2.08	[0.71; 6.10]	0.180
IIB	11 / 246 (4.5)	5 / 220 (2.3)	1.97	[0.69; 5.57]	0.203
IIIA	13 / 451 (2.9)	11 / 393 (2.8)	1.03	[0.47; 2.27]	0.942
IIIB	4 / 67 (6.0)	1 / 59 (1.7)	3.52	[0.40; 30.64]	0.254
IIIC	4 / 173 (2.3)	1 / 200 (0.5)	4.62	[0.52; 40.98]	0.169
Nodal status					
Interaction test	**p = 0.419**				
N0	5 / 91 (5.5)	2 / 117 (1.7)	3.21	[0.64; 16.19]	0.157
N1-N3	36 / 1017 (3.5)	21 / 950 (2.2)	1.60	[0.94; 2.72]	0.082
Histological grade at time of surgery					
Interaction test	**p = 0.891**				
Grade 1	3 / 110 (2.7)	2 / 100 (2.0)	1.36	[0.23; 7.99]	0.731
Grade 2	19 / 604 (3.1)	14 / 601 (2.3)	1.35	[0.68; 2.67]	0.387
Grade 3	12 / 297 (4.0)	6 / 266 (2.3)	1.79	[0.68; 4.71]	0.237
Histological subtype					
Interaction test	**p = 0.183**				
Ductal	32 / 863 (3.7)	19 / 835 (2.3)	1.63	[0.93; 2.85]	0.087
Lobular	2 / 172 (1.2)	4 / 169 (2.4)	0.49	[0.09; 2.65]	0.408
Other	7 / 73 (9.6)	0 / 66 (0.0)	13.58	[0.79; >99.99]	0.072
Ki67 status from surgical specimen					
Interaction test	**p = 0.869**				
Ki67≤20	20 / 527 (3.8)	10 / 552 (1.8)	2.09	[0.99; 4.43]	0.053
Ki67>20	17 / 422 (4.0)	8 / 378 (2.1)	1.90	[0.83; 4.36]	0.128
Type of NSAI					
Interaction test	**p = 0.196**				
Letrozole	33 / 809 (4.1)	15 / 773 (1.9)	2.10	[1.15; 3.84]	0.016
Anastrozole	8 / 299 (2.7)	8 / 297 (2.7)	0.99	[0.38; 2.61]	0.989
Prior neo/adjuvant chemotherapy					
Interaction test	**p = 0.555**				
Yes	34 / 1029 (3.3)	20 / 987 (2.0)	1.63	[0.95; 2.81]	0.079
No	7 / 79 (8.9)	3 / 83 (3.6)	2.45	[0.66; 9.15]	0.182
Prior adjuvant chemotherapy					
Interaction test	**p = 0.343**				
Yes	15 / 513 (2.9)	11 / 488 (2.3)	1.30	[0.60; 2.80]	0.507
No	26 / 595 (4.4)	12 / 582 (2.1)	2.12	[1.08; 4.16]	0.029
Prior neoadjuvant chemotherapy					
Interaction test	**p = 0.995**				
Yes	21 / 546 (3.8)	12 / 538 (2.2)	1.72	[0.86; 3.47]	0.127
No	20 / 562 (3.6)	11 / 532 (2.1)	1.72	[0.83; 3.56]	0.143

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Prior endocrine therapy					
Interaction test	**p = 0.522**				
Yes	27 / 853 (3.2)	16 / 789 (2.0)	1.56	[0.85; 2.87]	0.153
No	14 / 255 (5.5)	7 / 281 (2.5)	2.20	[0.90; 5.37]	0.082
Prior mastectomy					
Interaction test	**p = 0.037**				
Yes	23 / 769 (3.0)	19 / 745 (2.6)	1.17	[0.64; 2.14]	0.602
No	18 / 339 (5.3)	4 / 325 (1.2)	4.31	[1.48; 12.61]	0.008
Prior radiotherapy					
Interaction test	**p = 0.839**				
Yes	34 / 1011 (3.4)	19 / 987 (1.9)	1.75	[1.00; 3.04]	0.049
No	7 / 97 (7.2)	4 / 83 (4.8)	1.50	[0.45; 4.94]	0.507

N: Number of patients
n: Number of patients with event
CI: Confidence interval
RR: Relative risk
ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
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Analysis method for interaction test:
p-value from logistic regression model.
logit(proportion) = treatment + subgroup factor + treatment * subgroup factor

Analysis method for within subgroup analysis:
RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm.
ET was the reference group for treatment group comparison.

Table 5-3.2.11 PT lymphocyte count decreased: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	ET (N = 1070)	RR	[95% CI]	p-value
Lymphocyte count decreased					
	n / N (%)	n / N (%)			
Region					
Interaction test	**p = 0.233**				
NA/WE/O	19 / 640 (3.0)	11 / 627 (1.8)	1.69	[0.81; 3.53]	0.160
ROW	13 / 468 (2.8)	3 / 443 (0.7)	4.10	[1.18; 14.30]	0.027
Geographical region					
Interaction test	**p = 0.336**				
Europe	8 / 654 (1.2)	3 / 638 (0.5)	2.60	[0.69; 9.76]	0.156
North America/Australia	11 / 213 (5.2)	8 / 194 (4.1)	1.25	[0.51; 3.05]	0.620
Asia	12 / 178 (6.7)	3 / 168 (1.8)	3.78	[1.08; 13.14]	0.037
Latin America	1 / 63 (1.6)	0 / 70 (0.0)	3.33	[0.14; 80.25]	0.459
Age group 1 at randomization					
Interaction test	**p = 0.130**				
<45	15 / 549 (2.7)	9 / 496 (1.8)	1.51	[0.66; 3.41]	0.326
45 to 54	17 / 539 (3.2)	4 / 546 (0.7)	4.31	[1.46; 12.71]	0.008
55 to 64	0 / 20 (0.0)	1 / 28 (3.6)	0.46	[0.02; 10.75]	0.629
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)					
Interaction test	**p = 0.200**				
<Median	15 / 549 (2.7)	9 / 496 (1.8)	1.51	[0.66; 3.41]	0.326
≥Median	17 / 559 (3.0)	5 / 574 (0.9)	3.49	[1.30; 9.40]	0.013
Race					
Interaction test	**p = 0.398**				
Asian	14 / 211 (6.6)	4 / 186 (2.2)	3.09	[1.03; 9.21]	0.043
Non-Asian	18 / 840 (2.1)	10 / 827 (1.2)	1.77	[0.82; 3.82]	0.144
BMI at screening					
Interaction test	**p = 0.162**				
≥25	15 / 551 (2.7)	3 / 523 (0.6)	4.75	[1.38; 16.30]	0.013
<25	15 / 542 (2.8)	9 / 535 (1.7)	1.65	[0.73; 3.73]	0.233
AJCC Anatomic Stage Group					
Interaction test	**p = 0.673**				
Group I/II	7 / 417 (1.7)	4 / 418 (1.0)	1.75	[0.52; 5.95]	0.367
Group III	25 / 691 (3.6)	10 / 652 (1.5)	2.36	[1.14; 4.87]	0.020

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Anatomic stages					
Interaction test	**p = 0.226**				
IA/IB/IIA	2 / 171 (1.2)	2 / 198 (1.0)	1.16	[0.16; 8.13]	0.883
IIB	5 / 246 (2.0)	2 / 220 (0.9)	2.24	[0.44; 11.41]	0.333
IIIA	14 / 451 (3.1)	9 / 393 (2.3)	1.36	[0.59; 3.10]	0.471
IIIB	0 / 67 (0.0)	0 / 59 (0.0)	N.E.	N.E.	N.E.
IIIC	11 / 173 (6.4)	1 / 200 (0.5)	12.72	[1.66; 97.50]	0.014
Nodal status					
Interaction test	**N.E.**				
N0	0 / 91 (0.0)	0 / 117 (0.0)	N.E.	N.E.	N.E.
N1-N3	32 / 1017 (3.1)	14 / 950 (1.5)	2.14	[1.15; 3.98]	0.017
Histological grade at time of surgery					
Interaction test	**p = 0.429**				
Grade 1	3 / 110 (2.7)	3 / 100 (3.0)	0.91	[0.19; 4.40]	0.906
Grade 2	20 / 604 (3.3)	7 / 601 (1.2)	2.84	[1.21; 6.67]	0.016
Grade 3	7 / 297 (2.4)	2 / 266 (0.8)	3.13	[0.66; 14.96]	0.152
Histological subtype					
Interaction test	**p = 0.110**				
Ductal	25 / 863 (2.9)	9 / 835 (1.1)	2.69	[1.26; 5.72]	0.010
Lobular	4 / 172 (2.3)	5 / 169 (3.0)	0.79	[0.21; 2.88]	0.716
Other	3 / 73 (4.1)	0 / 66 (0.0)	6.34	[0.33; >99.99]	0.219
Ki67 status from surgical specimen					
Interaction test	**p = 0.520**				
Ki67≤20	13 / 527 (2.5)	4 / 552 (0.7)	3.40	[1.12; 10.37]	0.031
Ki67>20	14 / 422 (3.3)	6 / 378 (1.6)	2.09	[0.81; 5.38]	0.127
Type of NSAI					
Interaction test	**p = 0.949**				
Letrozole	19 / 809 (2.3)	8 / 773 (1.0)	2.27	[1.00; 5.15]	0.050
Anastrozole	13 / 299 (4.3)	6 / 297 (2.0)	2.15	[0.83; 5.59]	0.115
Prior neo/adjuvant chemotherapy					
Interaction test	**p = 0.217**				
Yes	31 / 1029 (3.0)	12 / 987 (1.2)	2.48	[1.28; 4.80]	0.007
No	1 / 79 (1.3)	2 / 83 (2.4)	0.53	[0.05; 5.68]	0.596
Prior adjuvant chemotherapy					
Interaction test	**p = 0.930**				
Yes	9 / 513 (1.8)	4 / 488 (0.8)	2.14	[0.66; 6.90]	0.203
No	23 / 595 (3.9)	10 / 582 (1.7)	2.25	[1.08; 4.69]	0.030
Prior neoadjuvant chemotherapy					
Interaction test	**p = 0.401**				
Yes	22 / 546 (4.0)	8 / 538 (1.5)	2.71	[1.22; 6.03]	0.015
No	10 / 562 (1.8)	6 / 532 (1.1)	1.58	[0.58; 4.31]	0.374

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Prior endocrine therapy					
Interaction test	**N.E.**				
Yes	24 / 853 (2.8)	14 / 789 (1.8)	1.59	[0.83; 3.04]	0.166
No	8 / 255 (3.1)	0 / 281 (0.0)	18.73	[1.09; >99.99]	0.044
Prior mastectomy					
Interaction test	**p = 0.144**				
Yes	23 / 769 (3.0)	13 / 745 (1.7)	1.71	[0.87; 3.36]	0.116
No	9 / 339 (2.7)	1 / 325 (0.3)	8.63	[1.10; 67.72]	0.040
Prior radiotherapy					
Interaction test	**N.E.**				
Yes	32 / 1011 (3.2)	14 / 987 (1.4)	2.23	[1.20; 4.16]	0.011
No	0 / 97 (0.0)	0 / 83 (0.0)	N.E.	N.E.	N.E.

N: Number of patients
n: Number of patients with event
N.E.: Not estimable
CI: Confidence interval
RR: Relative risk
ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
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Analysis method for interaction test:
p-value from logistic regression model.
logit(proportion) = treatment + subgroup factor + treatment * subgroup factor

Analysis method for within subgroup analysis:
RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm.
ET was the reference group for treatment group comparison.

Table 5-3.2.12 PT blood bilirubin increased: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	ET (N = 1070)	RR	[95% CI]	p-value
Blood bilirubin increased					
	n / N (%)	n / N (%)			
Region					
Interaction test	**p = 0.297**				
NA/WE/O	11 / 640 (1.7)	3 / 627 (0.5)	3.59	[1.01; 12.81]	0.049
ROW	17 / 468 (3.6)	10 / 443 (2.3)	1.61	[0.74; 3.48]	0.226
Geographical region					
Interaction test	**p = 0.475**				
Europe	13 / 654 (2.0)	9 / 638 (1.4)	1.41	[0.61; 3.27]	0.425
North America/Australia	6 / 213 (2.8)	1 / 194 (0.5)	5.46	[0.66; 44.99]	0.114
Asia	7 / 178 (3.9)	3 / 168 (1.8)	2.20	[0.58; 8.38]	0.247
Latin America	2 / 63 (3.2)	0 / 70 (0.0)	5.55	[0.27; >99.99]	0.266
Age group 1 at randomization					
Interaction test	**p = 0.159**				
<45	15 / 549 (2.7)	4 / 496 (0.8)	3.39	[1.13; 10.14]	0.029
45 to 54	11 / 539 (2.0)	9 / 546 (1.6)	1.24	[0.52; 2.96]	0.632
55 to 64	2 / 20 (10.0)	0 / 28 (0.0)	6.90	[0.35; >99.99]	0.204
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)					
Interaction test	**p = 0.242**				
<Median	15 / 549 (2.7)	4 / 496 (0.8)	3.39	[1.13; 10.14]	0.029
≥Median	13 / 559 (2.3)	9 / 574 (1.6)	1.48	[0.64; 3.44]	0.359
Race					
Interaction test	**p = 0.951**				
Asian	7 / 211 (3.3)	3 / 186 (1.6)	2.06	[0.54; 7.84]	0.291
Non-Asian	20 / 840 (2.4)	10 / 827 (1.2)	1.97	[0.93; 4.18]	0.078
BMI at screening					
Interaction test	**p = 0.614**				
≥25	13 / 551 (2.4)	7 / 523 (1.3)	1.76	[0.71; 4.38]	0.223
<25	15 / 542 (2.8)	6 / 535 (1.1)	2.47	[0.96; 6.31]	0.059
AJCC Anatomic Stage Group					
Interaction test	**p = 0.377**				
Group I/II	10 / 417 (2.4)	3 / 418 (0.7)	3.34	[0.93; 12.05]	0.065
Group III	18 / 691 (2.6)	10 / 652 (1.5)	1.70	[0.79; 3.65]	0.175

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Anatomic stages					
Interaction test	**p = 0.739**				
IA/IB/IIA	5 / 171 (2.9)	1 / 198 (0.5)	5.79	[0.68; 49.07]	0.107
IIB	5 / 246 (2.0)	2 / 220 (0.9)	2.24	[0.44; 11.41]	0.333
IIIA	7 / 451 (1.6)	5 / 393 (1.3)	1.22	[0.39; 3.81]	0.732
IIIB	4 / 67 (6.0)	1 / 59 (1.7)	3.52	[0.40; 30.64]	0.254
IIIC	7 / 173 (4.0)	4 / 200 (2.0)	2.02	[0.60; 6.79]	0.254
Nodal status					
Interaction test	**N.E.**				
N0	3 / 91 (3.3)	0 / 117 (0.0)	8.98	[0.47; >99.99]	0.145
N1-N3	25 / 1017 (2.5)	13 / 950 (1.4)	1.80	[0.92; 3.49]	0.084
Histological grade at time of surgery					
Interaction test	**p = 0.129**				
Grade 1	1 / 110 (0.9)	3 / 100 (3.0)	0.30	[0.03; 2.87]	0.298
Grade 2	14 / 604 (2.3)	4 / 601 (0.7)	3.48	[1.15; 10.52]	0.027
Grade 3	9 / 297 (3.0)	6 / 266 (2.3)	1.34	[0.48; 3.72]	0.570
Histological subtype					
Interaction test	**p = 0.065**				
Ductal	20 / 863 (2.3)	8 / 835 (1.0)	2.42	[1.07; 5.46]	0.034
Lobular	7 / 172 (4.1)	1 / 169 (0.6)	6.88	[0.86; 55.30]	0.070
Other	1 / 73 (1.4)	4 / 66 (6.1)	0.23	[0.03; 1.97]	0.178
Ki67 status from surgical specimen					
Interaction test	**p = 0.264**				
Ki67≤20	13 / 527 (2.5)	9 / 552 (1.6)	1.51	[0.65; 3.51]	0.335
Ki67>20	12 / 422 (2.8)	3 / 378 (0.8)	3.58	[1.02; 12.60]	0.047
Type of NSAI					
Interaction test	**p = 0.537**				
Letrozole	24 / 809 (3.0)	12 / 773 (1.6)	1.91	[0.96; 3.79]	0.064
Anastrozole	4 / 299 (1.3)	1 / 297 (0.3)	3.97	[0.45; 35.34]	0.216
Prior neo/adjuvant chemotherapy					
Interaction test	**p = 0.235**				
Yes	27 / 1029 (2.6)	11 / 987 (1.1)	2.35	[1.17; 4.72]	0.016
No	1 / 79 (1.3)	2 / 83 (2.4)	0.53	[0.05; 5.68]	0.596
Prior adjuvant chemotherapy					
Interaction test	**p = 0.514**				
Yes	14 / 513 (2.7)	5 / 488 (1.0)	2.66	[0.97; 7.34]	0.058
No	14 / 595 (2.4)	8 / 582 (1.4)	1.71	[0.72; 4.05]	0.221
Prior neoadjuvant chemotherapy					
Interaction test	**p = 0.865**				
Yes	14 / 546 (2.6)	7 / 538 (1.3)	1.97	[0.80; 4.84]	0.139
No	14 / 562 (2.5)	6 / 532 (1.1)	2.21	[0.86; 5.71]	0.102

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Prior endocrine therapy					
Interaction test	**p = 0.293**				
Yes	19 / 853 (2.2)	6 / 789 (0.8)	2.93	[1.18; 7.30]	0.021
No	9 / 255 (3.5)	7 / 281 (2.5)	1.42	[0.54; 3.75]	0.483
Prior mastectomy					
Interaction test	**p = 0.723**				
Yes	20 / 769 (2.6)	10 / 745 (1.3)	1.94	[0.91; 4.11]	0.085
No	8 / 339 (2.4)	3 / 325 (0.9)	2.56	[0.68; 9.55]	0.163
Prior radiotherapy					
Interaction test	**p = 0.116**				
Yes	23 / 1011 (2.3)	8 / 987 (0.8)	2.81	[1.26; 6.24]	0.011
No	5 / 97 (5.2)	5 / 83 (6.0)	0.86	[0.26; 2.85]	0.800

N: Number of patients
n: Number of patients with event
N.E.: Not estimable
CI: Confidence interval
RR: Relative risk
ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
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Analysis method for interaction test:
p-value from logistic regression model.
logit(proportion) = treatment + subgroup factor + treatment * subgroup factor

Analysis method for within subgroup analysis:
RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm.
ET was the reference group for treatment group comparison.

Table 5-3.2.13 PT blood magnesium decreased: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	ET (N = 1070)	RR	[95% CI]	p-value
Blood magnesium decreased					
	n / N (%)	n / N (%)			
Region					
Interaction test	**N.E.**				
NA/WE/O	10 / 640 (1.6)	0 / 627 (0.0)	20.57	[1.21; >99.99]	0.037
ROW	18 / 468 (3.8)	13 / 443 (2.9)	1.31	[0.65; 2.64]	0.450
Geographical region					
Interaction test	**N.E.**				
Europe	27 / 654 (4.1)	13 / 638 (2.0)	2.03	[1.05; 3.89]	0.034
North America/Australia	0 / 213 (0.0)	0 / 194 (0.0)	N.E.	N.E.	N.E.
Asia	1 / 178 (0.6)	0 / 168 (0.0)	2.83	[0.12; 69.05]	0.523
Latin America	0 / 63 (0.0)	0 / 70 (0.0)	N.E.	N.E.	N.E.
Age group 1 at randomization					
Interaction test	**p = 0.479**				
<45	7 / 549 (1.3)	5 / 496 (1.0)	1.26	[0.40; 3.96]	0.687
45 to 54	18 / 539 (3.3)	7 / 546 (1.3)	2.60	[1.10; 6.19]	0.030
55 to 64	3 / 20 (15.0)	1 / 28 (3.6)	4.20	[0.47; 37.50]	0.199
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)					
Interaction test	**p = 0.282**				
<Median	7 / 549 (1.3)	5 / 496 (1.0)	1.26	[0.40; 3.96]	0.687
≥Median	21 / 559 (3.8)	8 / 574 (1.4)	2.70	[1.20; 6.03]	0.016
Race					
Interaction test	**N.E.**				
Asian	1 / 211 (0.5)	0 / 186 (0.0)	2.65	[0.11; 64.57]	0.550
Non-Asian	26 / 840 (3.1)	13 / 827 (1.6)	1.97	[1.02; 3.81]	0.044
BMI at screening					
Interaction test	**p = 0.897**				
≥25	19 / 551 (3.4)	9 / 523 (1.7)	2.00	[0.91; 4.39]	0.082
<25	9 / 542 (1.7)	4 / 535 (0.7)	2.22	[0.69; 7.17]	0.182
AJCC Anatomic Stage Group					
Interaction test	**p = 0.584**				
Group I/II	15 / 417 (3.6)	6 / 418 (1.4)	2.51	[0.98; 6.40]	0.055
Group III	13 / 691 (1.9)	7 / 652 (1.1)	1.75	[0.70; 4.36]	0.228

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Anatomic stages					
Interaction test	**p = 0.854**				
IA/IB/IIA	5 / 171 (2.9)	3 / 198 (1.5)	1.93	[0.47; 7.96]	0.363
IIB	10 / 246 (4.1)	3 / 220 (1.4)	2.98	[0.83; 10.69]	0.094
IIIA	6 / 451 (1.3)	3 / 393 (0.8)	1.74	[0.44; 6.92]	0.430
IIIB	6 / 67 (9.0)	4 / 59 (6.8)	1.32	[0.39; 4.46]	0.654
IIIC	1 / 173 (0.6)	0 / 200 (0.0)	3.47	[0.14; 84.52]	0.446
Nodal status					
Interaction test	**p = 0.175**				
N0	6 / 91 (6.6)	1 / 117 (0.9)	7.71	[0.95; 62.95]	0.056
N1-N3	22 / 1017 (2.2)	12 / 950 (1.3)	1.71	[0.85; 3.44]	0.131
Histological grade at time of surgery					
Interaction test	**p = 0.780**				
Grade 1	4 / 110 (3.6)	1 / 100 (1.0)	3.64	[0.41; 31.99]	0.245
Grade 2	19 / 604 (3.1)	10 / 601 (1.7)	1.89	[0.89; 4.03]	0.099
Grade 3	3 / 297 (1.0)	2 / 266 (0.8)	1.34	[0.23; 7.98]	0.745
Histological subtype					
Interaction test	**p = 0.935**				
Ductal	20 / 863 (2.3)	10 / 835 (1.2)	1.94	[0.91; 4.11]	0.086
Lobular	5 / 172 (2.9)	2 / 169 (1.2)	2.46	[0.48; 12.49]	0.279
Other	3 / 73 (4.1)	1 / 66 (1.5)	2.71	[0.29; 25.44]	0.382
Ki67 status from surgical specimen					
Interaction test	**p = 0.302**				
Ki67≤20	13 / 527 (2.5)	9 / 552 (1.6)	1.51	[0.65; 3.51]	0.335
Ki67>20	14 / 422 (3.3)	4 / 378 (1.1)	3.14	[1.04; 9.44]	0.042
Type of NSAI					
Interaction test	**N.E.**				
Letrozole	22 / 809 (2.7)	13 / 773 (1.7)	1.62	[0.82; 3.19]	0.165
Anastrozole	6 / 299 (2.0)	0 / 297 (0.0)	12.91	[0.73; >99.99]	0.081
Prior neo/adjuvant chemotherapy					
Interaction test	**p = 0.965**				
Yes	20 / 1029 (1.9)	9 / 987 (0.9)	2.13	[0.98; 4.66]	0.058
No	8 / 79 (10.1)	4 / 83 (4.8)	2.10	[0.66; 6.70]	0.210
Prior adjuvant chemotherapy					
Interaction test	**p = 0.446**				
Yes	10 / 513 (1.9)	3 / 488 (0.6)	3.17	[0.88; 11.45]	0.078
No	18 / 595 (3.0)	10 / 582 (1.7)	1.76	[0.82; 3.78]	0.147
Prior neoadjuvant chemotherapy					
Interaction test	**p = 0.547**				
Yes	12 / 546 (2.2)	7 / 538 (1.3)	1.69	[0.67; 4.26]	0.266
No	16 / 562 (2.8)	6 / 532 (1.1)	2.52	[1.00; 6.40]	0.051

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Prior endocrine therapy					
Interaction test	**p = 0.183**				
Yes	14 / 853 (1.6)	3 / 789 (0.4)	4.32	[1.25; 14.96]	0.021
No	14 / 255 (5.5)	10 / 281 (3.6)	1.54	[0.70; 3.41]	0.284
Prior mastectomy					
Interaction test	**N.E.**				
Yes	22 / 769 (2.9)	13 / 745 (1.7)	1.64	[0.83; 3.23]	0.153
No	6 / 339 (1.8)	0 / 325 (0.0)	12.46	[0.71; >99.99]	0.085
Prior radiotherapy					
Interaction test	**p = 0.146**				
Yes	17 / 1011 (1.7)	5 / 987 (0.5)	3.32	[1.23; 8.96]	0.018
No	11 / 97 (11.3)	8 / 83 (9.6)	1.18	[0.50; 2.79]	0.712

N: Number of patients
n: Number of patients with event
N.E.: Not estimable
CI: Confidence interval
RR: Relative risk
ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
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Analysis method for interaction test:
p-value from logistic regression model.
logit(proportion) = treatment + subgroup factor + treatment * subgroup factor

Analysis method for within subgroup analysis:
RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm.
ET was the reference group for treatment group comparison.

Table 5-3.2.14 PT blood creatinine increased: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	ET (N = 1070)	RR	[95% CI]	p-value
Blood creatinine increased					
	n / N (%)	n / N (%)			
Region					
Interaction test	**p = 0.395**				
NA/WE/O	17 / 640 (2.7)	2 / 627 (0.3)	8.33	[1.93; 35.89]	0.004
ROW	7 / 468 (1.5)	2 / 443 (0.5)	3.31	[0.69; 15.86]	0.134
Geographical region					
Interaction test	**p = 0.707**				
Europe	18 / 654 (2.8)	3 / 638 (0.5)	5.85	[1.73; 19.77]	0.004
North America/Australia	4 / 213 (1.9)	1 / 194 (0.5)	3.64	[0.41; 32.31]	0.246
Asia	2 / 178 (1.1)	0 / 168 (0.0)	4.72	[0.23; 97.61]	0.315
Latin America	0 / 63 (0.0)	0 / 70 (0.0)	N.E.	N.E.	N.E.
Age group 1 at randomization					
Interaction test	**N.E.**				
<45	13 / 549 (2.4)	0 / 496 (0.0)	24.40	[1.45; >99.99]	0.026
45 to 54	11 / 539 (2.0)	3 / 546 (0.5)	3.71	[1.04; 13.24]	0.043
55 to 64	0 / 20 (0.0)	1 / 28 (3.6)	0.46	[0.02; 10.75]	0.629
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)					
Interaction test	**N.E.**				
<Median	13 / 549 (2.4)	0 / 496 (0.0)	24.40	[1.45; >99.99]	0.026
≥Median	11 / 559 (2.0)	4 / 574 (0.7)	2.82	[0.90; 8.82]	0.074
Race					
Interaction test	**N.E.**				
Asian	3 / 211 (1.4)	0 / 186 (0.0)	6.17	[0.32; >99.99]	0.228
Non-Asian	20 / 840 (2.4)	4 / 827 (0.5)	4.92	[1.69; 14.34]	0.003
BMI at screening					
Interaction test	**N.E.**				
≥25	14 / 551 (2.5)	0 / 523 (0.0)	27.53	[1.65; >99.99]	0.021
<25	9 / 542 (1.7)	4 / 535 (0.7)	2.22	[0.69; 7.17]	0.182
AJCC Anatomic Stage Group					
Interaction test	**p = 0.968**				
Group I/II	6 / 417 (1.4)	1 / 418 (0.2)	6.01	[0.73; 49.74]	0.096
Group III	18 / 691 (2.6)	3 / 652 (0.5)	5.66	[1.68; 19.13]	0.005

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Anatomic stages					
Interaction test	**p = 0.875**				
IA/IB/IIA	2 / 171 (1.2)	0 / 198 (0.0)	5.78	[0.28; >99.99]	0.256
IIB	4 / 246 (1.6)	1 / 220 (0.5)	3.58	[0.40; 31.76]	0.253
IIIA	10 / 451 (2.2)	3 / 393 (0.8)	2.90	[0.81; 10.48]	0.103
IIIB	4 / 67 (6.0)	0 / 59 (0.0)	7.94	[0.44; >99.99]	0.162
IIIC	4 / 173 (2.3)	0 / 200 (0.0)	10.40	[0.56; >99.99]	0.115
Nodal status					
Interaction test	**N.E.**				
N0	1 / 91 (1.1)	0 / 117 (0.0)	3.85	[0.16; 93.36]	0.408
N1-N3	23 / 1017 (2.3)	4 / 950 (0.4)	5.37	[1.86; 15.47]	0.002
Histological grade at time of surgery					
Interaction test	**p = 0.193**				
Grade 1	3 / 110 (2.7)	2 / 100 (2.0)	1.36	[0.23; 7.99]	0.731
Grade 2	16 / 604 (2.6)	1 / 601 (0.2)	15.92	[2.12; >99.99]	0.007
Grade 3	3 / 297 (1.0)	1 / 266 (0.4)	2.69	[0.28; 25.67]	0.391
Histological subtype					
Interaction test	**p = 0.240**				
Ductal	19 / 863 (2.2)	2 / 835 (0.2)	9.19	[2.15; 39.34]	0.003
Lobular	5 / 172 (2.9)	2 / 169 (1.2)	2.46	[0.48; 12.49]	0.279
Other	0 / 73 (0.0)	0 / 66 (0.0)	N.E.	N.E.	N.E.
Ki67 status from surgical specimen					
Interaction test	**p = 0.683**				
Ki67≤20	12 / 527 (2.3)	2 / 552 (0.4)	6.28	[1.41; 27.95]	0.016
Ki67>20	9 / 422 (2.1)	2 / 378 (0.5)	4.03	[0.88; 18.54]	0.073
Type of NSAI					
Interaction test	**p = 0.976**				
Letrozole	18 / 809 (2.2)	3 / 773 (0.4)	5.73	[1.70; 19.39]	0.005
Anastrozole	6 / 299 (2.0)	1 / 297 (0.3)	5.96	[0.72; 49.20]	0.097
Prior neo/adjuvant chemotherapy					
Interaction test	**p = 0.205**				
Yes	23 / 1029 (2.2)	3 / 987 (0.3)	7.35	[2.22; 24.41]	0.001
No	1 / 79 (1.3)	1 / 83 (1.2)	1.05	[0.07; 16.51]	0.972
Prior adjuvant chemotherapy					
Interaction test	**p = 0.765**				
Yes	8 / 513 (1.6)	1 / 488 (0.2)	7.61	[0.96; 60.62]	0.055
No	16 / 595 (2.7)	3 / 582 (0.5)	5.22	[1.53; 17.81]	0.008
Prior neoadjuvant chemotherapy					
Interaction test	**p = 0.605**				
Yes	15 / 546 (2.7)	2 / 538 (0.4)	7.39	[1.70; 32.16]	0.008
No	9 / 562 (1.6)	2 / 532 (0.4)	4.26	[0.92; 19.62]	0.063

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Prior endocrine therapy					
Interaction test	**N.E.**				
Yes	19 / 853 (2.2)	4 / 789 (0.5)	4.39	[1.50; 12.86]	0.007
No	5 / 255 (2.0)	0 / 281 (0.0)	12.12	[0.67; >99.99]	0.091
Prior mastectomy					
Interaction test	**N.E.**				
Yes	16 / 769 (2.1)	4 / 745 (0.5)	3.88	[1.30; 11.54]	0.015
No	8 / 339 (2.4)	0 / 325 (0.0)	16.30	[0.94; >99.99]	0.055
Prior radiotherapy					
Interaction test	**N.E.**				
Yes	20 / 1011 (2.0)	4 / 987 (0.4)	4.88	[1.67; 14.23]	0.004
No	4 / 97 (4.1)	0 / 83 (0.0)	7.71	[0.42; >99.99]	0.168

N: Number of patients
n: Number of patients with event
N.E.: Not estimable
CI: Confidence interval
RR: Relative risk
ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
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Analysis method for interaction test:
p-value from logistic regression model.
logit(proportion) = treatment + subgroup factor + treatment * subgroup factor

Analysis method for within subgroup analysis:
RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm.
ET was the reference group for treatment group comparison.

Table 5-3.2.15 PT platelet count decreased: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	ET (N = 1070)	RR	[95% CI]	p-value
Platelet count decreased					
	n / N (%)	n / N (%)			
Region					
Interaction test	**p = 0.913**				
NA/WE/O	13 / 640 (2.0)	3 / 627 (0.5)	4.25	[1.22; 14.83]	0.023
ROW	10 / 468 (2.1)	2 / 443 (0.5)	4.73	[1.04; 21.48]	0.044
Geographical region					
Interaction test	**p = 0.405**				
Europe	3 / 654 (0.5)	2 / 638 (0.3)	1.46	[0.25; 8.73]	0.676
North America/Australia	10 / 213 (4.7)	2 / 194 (1.0)	4.55	[1.01; 20.53]	0.048
Asia	9 / 178 (5.1)	1 / 168 (0.6)	8.49	[1.09; 66.33]	0.041
Latin America	1 / 63 (1.6)	0 / 70 (0.0)	3.33	[0.14; 80.25]	0.459
Age group 1 at randomization					
Interaction test	**p = 0.397**				
<45	14 / 549 (2.6)	2 / 496 (0.4)	6.32	[1.44; 27.69]	0.014
45 to 54	8 / 539 (1.5)	3 / 546 (0.5)	2.70	[0.72; 10.13]	0.141
55 to 64	1 / 20 (5.0)	0 / 28 (0.0)	4.14	[0.18; 96.77]	0.377
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)					
Interaction test	**p = 0.470**				
<Median	14 / 549 (2.6)	2 / 496 (0.4)	6.32	[1.44; 27.69]	0.014
≥Median	9 / 559 (1.6)	3 / 574 (0.5)	3.08	[0.84; 11.32]	0.090
Race					
Interaction test	**p = 0.306**				
Asian	11 / 211 (5.2)	1 / 186 (0.5)	9.70	[1.26; 74.39]	0.029
Non-Asian	12 / 840 (1.4)	4 / 827 (0.5)	2.95	[0.96; 9.12]	0.060
BMI at screening					
Interaction test	**p = 0.060**				
≥25	7 / 551 (1.3)	4 / 523 (0.8)	1.66	[0.49; 5.64]	0.416
<25	16 / 542 (3.0)	1 / 535 (0.2)	15.79	[2.10; >99.99]	0.007
AJCC Anatomic Stage Group					
Interaction test	**p = 0.900**				
Group I/II	5 / 417 (1.2)	1 / 418 (0.2)	5.01	[0.59; 42.72]	0.140
Group III	18 / 691 (2.6)	4 / 652 (0.6)	4.25	[1.44; 12.48]	0.009

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Anatomic stages					
Interaction test	**p = 0.919**				
IA/IB/IIA	1 / 171 (0.6)	0 / 198 (0.0)	3.47	[0.14; 84.65]	0.445
IIB	4 / 246 (1.6)	1 / 220 (0.5)	3.58	[0.40; 31.76]	0.253
IIIA	12 / 451 (2.7)	3 / 393 (0.8)	3.49	[0.99; 12.26]	0.052
IIIB	1 / 67 (1.5)	0 / 59 (0.0)	2.65	[0.11; 63.76]	0.549
IIIC	5 / 173 (2.9)	1 / 200 (0.5)	5.78	[0.68; 49.00]	0.108
Nodal status					
Interaction test	**N.E.**				
N0	1 / 91 (1.1)	0 / 117 (0.0)	3.85	[0.16; 93.36]	0.408
N1-N3	22 / 1017 (2.2)	5 / 950 (0.5)	4.11	[1.56; 10.81]	0.004
Histological grade at time of surgery					
Interaction test	**p = 0.596**				
Grade 1	4 / 110 (3.6)	1 / 100 (1.0)	3.64	[0.41; 31.99]	0.245
Grade 2	14 / 604 (2.3)	2 / 601 (0.3)	6.97	[1.59; 30.51]	0.010
Grade 3	5 / 297 (1.7)	2 / 266 (0.8)	2.24	[0.44; 11.44]	0.333
Histological subtype					
Interaction test	**p = 0.065**				
Ductal	19 / 863 (2.2)	3 / 835 (0.4)	6.13	[1.82; 20.63]	0.003
Lobular	1 / 172 (0.6)	2 / 169 (1.2)	0.49	[0.04; 5.37]	0.560
Other	3 / 73 (4.1)	0 / 66 (0.0)	6.34	[0.33; >99.99]	0.219
Ki67 status from surgical specimen					
Interaction test	**p = 0.784**				
Ki67≤20	9 / 527 (1.7)	3 / 552 (0.5)	3.14	[0.86; 11.54]	0.085
Ki67>20	5 / 422 (1.2)	1 / 378 (0.3)	4.48	[0.53; 38.16]	0.170
Type of NSAI					
Interaction test	**p = 0.428**				
Letrozole	14 / 809 (1.7)	2 / 773 (0.3)	6.69	[1.53; 29.33]	0.012
Anastrozole	9 / 299 (3.0)	3 / 297 (1.0)	2.98	[0.81; 10.90]	0.099
Prior neo/adjuvant chemotherapy					
Interaction test	**N.E.**				
Yes	22 / 1029 (2.1)	5 / 987 (0.5)	4.22	[1.60; 11.10]	0.004
No	1 / 79 (1.3)	0 / 83 (0.0)	3.15	[0.13; 76.20]	0.480
Prior adjuvant chemotherapy					
Interaction test	**p = 0.733**				
Yes	12 / 513 (2.3)	3 / 488 (0.6)	3.81	[1.08; 13.40]	0.038
No	11 / 595 (1.8)	2 / 582 (0.3)	5.38	[1.20; 24.17]	0.028
Prior neoadjuvant chemotherapy					
Interaction test	**p = 0.651**				
Yes	11 / 546 (2.0)	3 / 538 (0.6)	3.61	[1.01; 12.88]	0.048
No	12 / 562 (2.1)	2 / 532 (0.4)	5.68	[1.28; 25.26]	0.023

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Prior endocrine therapy					
Interaction test	**p = 0.656**				
Yes	17 / 853 (2.0)	3 / 789 (0.4)	5.24	[1.54; 17.82]	0.008
No	6 / 255 (2.4)	2 / 281 (0.7)	3.31	[0.67; 16.23]	0.141
Prior mastectomy					
Interaction test	**N.E.**				
Yes	18 / 769 (2.3)	5 / 745 (0.7)	3.49	[1.30; 9.35]	0.013
No	5 / 339 (1.5)	0 / 325 (0.0)	10.55	[0.59; >99.99]	0.110
Prior radiotherapy					
Interaction test	**N.E.**				
Yes	23 / 1011 (2.3)	5 / 987 (0.5)	4.49	[1.71; 11.77]	0.002
No	0 / 97 (0.0)	0 / 83 (0.0)	N.E.	N.E.	N.E.

N: Number of patients
n: Number of patients with event
N.E.: Not estimable
CI: Confidence interval
RR: Relative risk
ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
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Analysis method for interaction test:
p-value from logistic regression model.
logit(proportion) = treatment + subgroup factor + treatment * subgroup factor

Analysis method for within subgroup analysis:
RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm.
ET was the reference group for treatment group comparison.

Table 5-3.2.16 PT adjusted calcium decreased: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Adjusted calcium decreased					
	n / N (%)	**n / N (%)**			
Region					
Interaction test	**N.E.**				
NA/WE/O	3 / 640 (0.5)	0 / 627 (0.0)	6.86	[0.35; >99.99]	0.203
ROW	11 / 468 (2.4)	2 / 443 (0.5)	5.21	[1.16; 23.36]	0.031
Geographical region					
The subgroup analysis is not presented as all subgroups have less than 10 events.					
Age group 1 at randomization					
Interaction test	**p = 0.752**				
<45	9 / 549 (1.6)	1 / 496 (0.2)	8.13	[1.03; 63.95]	0.046
45 to 54	5 / 539 (0.9)	1 / 546 (0.2)	5.06	[0.59; 43.21]	0.138
55 to 64	0 / 20 (0.0)	0 / 28 (0.0)	N.E.	N.E.	N.E.
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)					
Interaction test	**p = 0.759**				
<Median	9 / 549 (1.6)	1 / 496 (0.2)	8.13	[1.03; 63.95]	0.046
≥Median	5 / 559 (0.9)	1 / 574 (0.2)	5.13	[0.60; 43.81]	0.135
Race					
The subgroup analysis is not presented as all subgroups have less than 10 events.					
BMI at screening					
Interaction test	**N.E.**				
≥25	1 / 551 (0.2)	2 / 523 (0.4)	0.47	[0.04; 5.22]	0.542
<25	13 / 542 (2.4)	0 / 535 (0.0)	26.65	[1.59; >99.99]	0.023
AJCC Anatomic Stage Group					
Interaction test	**p = 0.423**				
Group I/II	3 / 417 (0.7)	1 / 418 (0.2)	3.01	[0.31; 28.79]	0.339
Group III	11 / 691 (1.6)	1 / 652 (0.2)	10.38	[1.34; 80.17]	0.025
Anatomic stages					
The subgroup analysis is not presented as all subgroups have less than 10 events.					

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Nodal status					
Interaction test	**p = 0.200**				
N0	1 / 91 (1.1)	1 / 117 (0.9)	1.29	[0.08; 20.28]	0.858
N1-N3	13 / 1017 (1.3)	1 / 950 (0.1)	12.14	[1.59; 92.65]	0.016
Histological grade at time of surgery					
Interaction test	**N.E.**				
Grade 1	1 / 110 (0.9)	0 / 100 (0.0)	2.73	[0.11; 66.25]	0.537
Grade 2	9 / 604 (1.5)	2 / 601 (0.3)	4.48	[0.97; 20.64]	0.054
Grade 3	2 / 297 (0.7)	0 / 266 (0.0)	4.48	[0.22; 92.89]	0.332
Histological subtype					
Interaction test	**N.E.**				
Ductal	12 / 863 (1.4)	2 / 835 (0.2)	5.81	[1.30; 25.86]	0.021
Lobular	1 / 172 (0.6)	0 / 169 (0.0)	2.95	[0.12; 71.86]	0.507
Other	1 / 73 (1.4)	0 / 66 (0.0)	2.72	[0.11; 65.54]	0.538
Ki67 status from surgical specimen					
Interaction test	**p = 0.526**				
Ki67≤20	9 / 527 (1.7)	1 / 552 (0.2)	9.43	[1.20; 74.15]	0.033
Ki67>20	4 / 422 (0.9)	1 / 378 (0.3)	3.58	[0.40; 31.92]	0.253
Type of NSAI					
Interaction test	**N.E.**				
Letrozole	9 / 809 (1.1)	2 / 773 (0.3)	4.30	[0.93; 19.84]	0.062
Anastrozole	5 / 299 (1.7)	0 / 297 (0.0)	10.93	[0.61; >99.99]	0.105
Prior neo/adjuvant chemotherapy					
Interaction test	**N.E.**				
Yes	14 / 1029 (1.4)	2 / 987 (0.2)	6.71	[1.53; 29.47]	0.012
No	0 / 79 (0.0)	0 / 83 (0.0)	N.E.	N.E.	N.E.
Prior adjuvant chemotherapy					
The subgroup analysis is not presented as all subgroups have less than 10 events.					
Prior neoadjuvant chemotherapy					
The subgroup analysis is not presented as all subgroups have less than 10 events.					
Prior endocrine therapy					
Interaction test	**N.E.**				
Yes	8 / 853 (0.9)	2 / 789 (0.3)	3.70	[0.79; 17.37]	0.097
No	6 / 255 (2.4)	0 / 281 (0.0)	14.32	[0.81; >99.99]	0.069

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Prior mastectomy					
Interaction test	**p = 0.260**				
Yes	12 / 769 (1.6)	1 / 745 (0.1)	11.63	[1.52; 89.18]	0.018
No	2 / 339 (0.6)	1 / 325 (0.3)	1.92	[0.17; 21.04]	0.594
Prior radiotherapy					
Interaction test	**p = 0.233**				
Yes	12 / 1011 (1.2)	1 / 987 (0.1)	11.72	[1.53; 89.93]	0.018
No	2 / 97 (2.1)	1 / 83 (1.2)	1.71	[0.16; 18.54]	0.658

N: Number of patients
n: Number of patients with event
N.E.: Not estimable
CI: Confidence interval
RR: Relative risk
ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
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Analysis method for interaction test:
p-value from logistic regression model.
logit(proportion) = treatment + subgroup factor + treatment * subgroup factor

Analysis method for within subgroup analysis:
RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm.
ET was the reference group for treatment group comparison.

Table 5-3.2.17 PT arthralgia: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	ET (N = 1070)	RR	[95% CI]	p-value
Arthralgia					
	n / N (%)	n / N (%)			
Region					
Interaction test	**p = 0.069**				
NA/WE/O	339 / 640 (53.0)	342 / 627 (54.5)	0.97	[0.88; 1.08]	0.574
ROW	132 / 468 (28.2)	163 / 443 (36.8)	0.77	[0.63; 0.93]	0.006
Geographical region					
Interaction test	**p = 0.011**				
Europe	291 / 654 (44.5)	298 / 638 (46.7)	0.95	[0.85; 1.07]	0.425
North America/Australia	108 / 213 (50.7)	94 / 194 (48.5)	1.05	[0.86; 1.27]	0.651
Asia	47 / 178 (26.4)	74 / 168 (44.0)	0.60	[0.44; 0.81]	<.001
Latin America	25 / 63 (39.7)	39 / 70 (55.7)	0.71	[0.49; 1.03]	0.072
Age group 1 at randomization					
Interaction test	**p = 0.810**				
<45	222 / 549 (40.4)	216 / 496 (43.5)	0.93	[0.81; 1.07]	0.308
45 to 54	242 / 539 (44.9)	278 / 546 (50.9)	0.88	[0.78; 1.00]	0.048
55 to 64	7 / 20 (35.0)	11 / 28 (39.3)	0.89	[0.42; 1.89]	0.764
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)					
Interaction test	**p = 0.543**				
<Median	222 / 549 (40.4)	216 / 496 (43.5)	0.93	[0.81; 1.07]	0.308
≥Median	249 / 559 (44.5)	289 / 574 (50.3)	0.88	[0.78; 1.00]	0.051
Race					
Interaction test	**p = 0.067**				
Asian	67 / 211 (31.8)	83 / 186 (44.6)	0.71	[0.55; 0.92]	0.009
Non-Asian	371 / 840 (44.2)	391 / 827 (47.3)	0.93	[0.84; 1.04]	0.202
BMI at screening					
Interaction test	**p = 0.786**				
≥25	248 / 551 (45.0)	258 / 523 (49.3)	0.91	[0.80; 1.04]	0.156
<25	214 / 542 (39.5)	240 / 535 (44.9)	0.88	[0.76; 1.01]	0.075
AJCC Anatomic Stage Group					
Interaction test	**p = 0.722**				
Group I/II	184 / 417 (44.1)	200 / 418 (47.8)	0.92	[0.80; 1.07]	0.281
Group III	287 / 691 (41.5)	305 / 652 (46.8)	0.89	[0.79; 1.00]	0.053

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Anatomic stages					
Interaction test	**p = 0.688**				
IA/IB/IIA	77 / 171 (45.0)	101 / 198 (51.0)	0.88	[0.71; 1.09]	0.255
IIB	107 / 246 (43.5)	99 / 220 (45.0)	0.97	[0.79; 1.19]	0.744
IIIA	184 / 451 (40.8)	192 / 393 (48.9)	0.84	[0.72; 0.97]	0.019
IIIB	30 / 67 (44.8)	28 / 59 (47.5)	0.94	[0.65; 1.38]	0.763
IIIC	73 / 173 (42.2)	85 / 200 (42.5)	0.99	[0.78; 1.26]	0.953
Nodal status					
Interaction test	**p = 0.437**				
N0	37 / 91 (40.7)	59 / 117 (50.4)	0.81	[0.59; 1.10]	0.168
N1-N3	434 / 1017 (42.7)	444 / 950 (46.7)	0.91	[0.83; 1.01]	0.070
Histological grade at time of surgery					
Interaction test	**p = 0.216**				
Grade 1	51 / 110 (46.4)	45 / 100 (45.0)	1.03	[0.77; 1.38]	0.843
Grade 2	266 / 604 (44.0)	274 / 601 (45.6)	0.97	[0.85; 1.09]	0.588
Grade 3	120 / 297 (40.4)	133 / 266 (50.0)	0.81	[0.67; 0.97]	0.023
Histological subtype					
Interaction test	**p = 0.595**				
Ductal	371 / 863 (43.0)	393 / 835 (47.1)	0.91	[0.82; 1.01]	0.092
Lobular	74 / 172 (43.0)	80 / 169 (47.3)	0.91	[0.72; 1.15]	0.424
Other	26 / 73 (35.6)	32 / 66 (48.5)	0.73	[0.49; 1.09]	0.127
Ki67 status from surgical specimen					
Interaction test	**p = 0.417**				
Ki67≤20	223 / 527 (42.3)	271 / 552 (49.1)	0.86	[0.76; 0.98]	0.026
Ki67>20	174 / 422 (41.2)	167 / 378 (44.2)	0.93	[0.79; 1.10]	0.400
Type of NSAI					
Interaction test	**p = 0.211**				
Letrozole	338 / 809 (41.8)	346 / 773 (44.8)	0.93	[0.83; 1.04]	0.232
Anastrozole	133 / 299 (44.5)	159 / 297 (53.5)	0.83	[0.70; 0.98]	0.028
Prior neo/adjuvant chemotherapy					
Interaction test	**p = 0.892**				
Yes	443 / 1029 (43.1)	471 / 987 (47.7)	0.90	[0.82; 0.99]	0.035
No	28 / 79 (35.4)	34 / 83 (41.0)	0.87	[0.58; 1.28]	0.471
Prior adjuvant chemotherapy					
Interaction test	**p = 0.543**				
Yes	234 / 513 (45.6)	239 / 488 (49.0)	0.93	[0.82; 1.06]	0.287
No	237 / 595 (39.8)	266 / 582 (45.7)	0.87	[0.76; 1.00]	0.042
Prior neoadjuvant chemotherapy					
Interaction test	**p = 0.434**				
Yes	219 / 546 (40.1)	250 / 538 (46.5)	0.86	[0.75; 0.99]	0.035
No	252 / 562 (44.8)	255 / 532 (47.9)	0.94	[0.82; 1.06]	0.305

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Prior endocrine therapy					
Interaction test	**p = 0.003**				
Yes	372 / 853 (43.6)	352 / 789 (44.6)	0.98	[0.88; 1.09]	0.683
No	99 / 255 (38.8)	153 / 281 (54.4)	0.71	[0.59; 0.86]	<.001
Prior mastectomy					
Interaction test	**p = 0.791**				
Yes	323 / 769 (42.0)	345 / 745 (46.3)	0.91	[0.81; 1.02]	0.092
No	148 / 339 (43.7)	160 / 325 (49.2)	0.89	[0.75; 1.04]	0.150
Prior radiotherapy					
Interaction test	**p = 0.606**				
Yes	431 / 1011 (42.6)	470 / 987 (47.6)	0.90	[0.81; 0.99]	0.025
No	40 / 97 (41.2)	35 / 83 (42.2)	0.98	[0.69; 1.38]	0.899

N: Number of patients
n: Number of patients with event
CI: Confidence interval
RR: Relative risk
ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
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Analysis method for interaction test:
p-value from logistic regression model.
logit(proportion) = treatment + subgroup factor + treatment * subgroup factor

Analysis method for within subgroup analysis:
RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm.
ET was the reference group for treatment group comparison.

Table 5-3.2.18 PT pain in extremity: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	ET (N = 1070)	RR	[95% CI]	p-value
Pain in extremity					
	n / N (%)	n / N (%)			
Region					
Interaction test	**p = 0.388**				
NA/WE/O	95 / 640 (14.8)	66 / 627 (10.5)	1.41	[1.05; 1.89]	0.022
ROW	28 / 468 (6.0)	24 / 443 (5.4)	1.10	[0.65; 1.88]	0.713
Geographical region					
Interaction test	**p = 0.816**				
Europe	70 / 654 (10.7)	49 / 638 (7.7)	1.39	[0.98; 1.97]	0.062
North America/Australia	39 / 213 (18.3)	28 / 194 (14.4)	1.27	[0.81; 1.98]	0.294
Asia	8 / 178 (4.5)	5 / 168 (3.0)	1.51	[0.50; 4.52]	0.462
Latin America	6 / 63 (9.5)	8 / 70 (11.4)	0.83	[0.31; 2.27]	0.721
Age group 1 at randomization					
Interaction test	**p = 0.915**				
<45	57 / 549 (10.4)	39 / 496 (7.9)	1.32	[0.90; 1.95]	0.161
45 to 54	64 / 539 (11.9)	48 / 546 (8.8)	1.35	[0.95; 1.93]	0.097
55 to 64	2 / 20 (10.0)	3 / 28 (10.7)	0.93	[0.17; 5.08]	0.936
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)					
Interaction test	**p = 0.969**				
<Median	57 / 549 (10.4)	39 / 496 (7.9)	1.32	[0.90; 1.95]	0.161
≥Median	66 / 559 (11.8)	51 / 574 (8.9)	1.33	[0.94; 1.88]	0.108
Race					
Interaction test	**p = 0.599**				
Asian	13 / 211 (6.2)	7 / 186 (3.8)	1.64	[0.67; 4.02]	0.282
Non-Asian	103 / 840 (12.3)	81 / 827 (9.8)	1.25	[0.95; 1.65]	0.109
BMI at screening					
Interaction test	**p = 0.064**				
≥25	72 / 551 (13.1)	62 / 523 (11.9)	1.10	[0.80; 1.51]	0.548
<25	50 / 542 (9.2)	26 / 535 (4.9)	1.90	[1.20; 3.00]	0.006
AJCC Anatomic Stage Group					
Interaction test	**p = 0.670**				
Group I/II	48 / 417 (11.5)	39 / 418 (9.3)	1.23	[0.83; 1.84]	0.304
Group III	75 / 691 (10.9)	51 / 652 (7.8)	1.39	[0.99; 1.95]	0.058

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Anatomic stages					
Interaction test	**p = 0.649**				
IA/IB/IIA	19 / 171 (11.1)	22 / 198 (11.1)	1.00	[0.56; 1.78]	1.000
IIB	29 / 246 (11.8)	17 / 220 (7.7)	1.53	[0.86; 2.70]	0.147
IIIA	50 / 451 (11.1)	32 / 393 (8.1)	1.36	[0.89; 2.08]	0.152
IIIB	8 / 67 (11.9)	8 / 59 (13.6)	0.88	[0.35; 2.20]	0.785
IIIC	17 / 173 (9.8)	11 / 200 (5.5)	1.79	[0.86; 3.71]	0.120
Nodal status					
Interaction test	**p = 0.932**				
N0	10 / 91 (11.0)	10 / 117 (8.5)	1.29	[0.56; 2.96]	0.554
N1-N3	113 / 1017 (11.1)	79 / 950 (8.3)	1.34	[1.02; 1.76]	0.038
Histological grade at time of surgery					
Interaction test	**p = 0.404**				
Grade 1	9 / 110 (8.2)	8 / 100 (8.0)	1.02	[0.41; 2.55]	0.962
Grade 2	80 / 604 (13.2)	48 / 601 (8.0)	1.66	[1.18; 2.33]	0.004
Grade 3	29 / 297 (9.8)	22 / 266 (8.3)	1.18	[0.70; 2.00]	0.538
Histological subtype					
Interaction test	**p = 0.835**				
Ductal	102 / 863 (11.8)	73 / 835 (8.7)	1.35	[1.02; 1.80]	0.038
Lobular	17 / 172 (9.9)	13 / 169 (7.7)	1.28	[0.64; 2.56]	0.477
Other	4 / 73 (5.5)	4 / 66 (6.1)	0.90	[0.24; 3.47]	0.883
Ki67 status from surgical specimen					
Interaction test	**p = 0.868**				
Ki67≤20	50 / 527 (9.5)	42 / 552 (7.6)	1.25	[0.84; 1.85]	0.270
Ki67>20	41 / 422 (9.7)	31 / 378 (8.2)	1.18	[0.76; 1.85]	0.456
Type of NSAI					
Interaction test	**p = 0.567**				
Letrozole	79 / 809 (9.8)	60 / 773 (7.8)	1.26	[0.91; 1.73]	0.161
Anastrozole	44 / 299 (14.7)	30 / 297 (10.1)	1.46	[0.94; 2.25]	0.090
Prior neo/adjuvant chemotherapy					
Interaction test	**p = 0.296**				
Yes	118 / 1029 (11.5)	83 / 987 (8.4)	1.36	[1.04; 1.78]	0.023
No	5 / 79 (6.3)	7 / 83 (8.4)	0.75	[0.25; 2.27]	0.611
Prior adjuvant chemotherapy					
Interaction test	**p = 0.164**				
Yes	68 / 513 (13.3)	41 / 488 (8.4)	1.58	[1.09; 2.28]	0.015
No	55 / 595 (9.2)	49 / 582 (8.4)	1.10	[0.76; 1.59]	0.618
Prior neoadjuvant chemotherapy					
Interaction test	**p = 0.298**				
Yes	52 / 546 (9.5)	45 / 538 (8.4)	1.14	[0.78; 1.67]	0.504
No	71 / 562 (12.6)	45 / 532 (8.5)	1.49	[1.05; 2.13]	0.026

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Prior endocrine therapy					
Interaction test	**p = 0.344**				
Yes	98 / 853 (11.5)	64 / 789 (8.1)	1.42	[1.05; 1.91]	0.023
No	25 / 255 (9.8)	26 / 281 (9.3)	1.06	[0.63; 1.79]	0.828
Prior mastectomy					
Interaction test	**p = 0.054**				
Yes	92 / 769 (12.0)	57 / 745 (7.7)	1.56	[1.14; 2.14]	0.005
No	31 / 339 (9.1)	33 / 325 (10.2)	0.90	[0.57; 1.44]	0.660
Prior radiotherapy					
Interaction test	**p = 0.119**				
Yes	114 / 1011 (11.3)	79 / 987 (8.0)	1.41	[1.07; 1.85]	0.014
No	9 / 97 (9.3)	11 / 83 (13.3)	0.70	[0.31; 1.61]	0.400

N: Number of patients
n: Number of patients with event
CI: Confidence interval
RR: Relative risk
ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
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Analysis method for interaction test:
p-value from logistic regression model.
logit(proportion) = treatment + subgroup factor + treatment * subgroup factor

Analysis method for within subgroup analysis:
RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm.
ET was the reference group for treatment group comparison.

Table 5-3.2.19 PT neck pain: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	ET (N = 1070)	RR	[95% CI]	p-value
Neck pain					
	n / N (%)	n / N (%)			
Region					
Interaction test	**p = 0.692**				
NA/WE/O	33 / 640 (5.2)	20 / 627 (3.2)	1.62	[0.94; 2.79]	0.084
ROW	9 / 468 (1.9)	4 / 443 (0.9)	2.13	[0.66; 6.87]	0.206
Geographical region					
Interaction test	**p = 0.659**				
Europe	26 / 654 (4.0)	18 / 638 (2.8)	1.41	[0.78; 2.54]	0.255
North America/Australia	13 / 213 (6.1)	5 / 194 (2.6)	2.37	[0.86; 6.52]	0.095
Asia	1 / 178 (0.6)	0 / 168 (0.0)	2.83	[0.12; 69.05]	0.523
Latin America	2 / 63 (3.2)	1 / 70 (1.4)	2.22	[0.21; 23.92]	0.510
Age group 1 at randomization					
Interaction test	**p = 0.333**				
<45	21 / 549 (3.8)	8 / 496 (1.6)	2.37	[1.06; 5.31]	0.036
45 to 54	21 / 539 (3.9)	15 / 546 (2.7)	1.42	[0.74; 2.72]	0.293
55 to 64	0 / 20 (0.0)	1 / 28 (3.6)	0.46	[0.02; 10.75]	0.629
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)					
Interaction test	**p = 0.284**				
<Median	21 / 549 (3.8)	8 / 496 (1.6)	2.37	[1.06; 5.31]	0.036
≥Median	21 / 559 (3.8)	16 / 574 (2.8)	1.35	[0.71; 2.56]	0.361
Race					
Interaction test	**p = 0.683**				
Asian	1 / 211 (0.5)	1 / 186 (0.5)	0.88	[0.06; 13.99]	0.929
Non-Asian	35 / 840 (4.2)	22 / 827 (2.7)	1.57	[0.93; 2.65]	0.094
BMI at screening					
Interaction test	**p = 0.510**				
≥25	24 / 551 (4.4)	11 / 523 (2.1)	2.07	[1.02; 4.19]	0.043
<25	18 / 542 (3.3)	12 / 535 (2.2)	1.48	[0.72; 3.04]	0.286
AJCC Anatomic Stage Group					
Interaction test	**p = 0.061**				
Group I/II	8 / 417 (1.9)	10 / 418 (2.4)	0.80	[0.32; 2.01]	0.638
Group III	34 / 691 (4.9)	14 / 652 (2.1)	2.29	[1.24; 4.23]	0.008

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Anatomic stages					
Interaction test	**p = 0.259**				
IA/IB/IIA	3 / 171 (1.8)	5 / 198 (2.5)	0.69	[0.17; 2.86]	0.614
IIB	5 / 246 (2.0)	5 / 220 (2.3)	0.89	[0.26; 3.05]	0.858
IIIA	25 / 451 (5.5)	9 / 393 (2.3)	2.42	[1.14; 5.12]	0.021
IIIB	0 / 67 (0.0)	1 / 59 (1.7)	0.29	[0.01; 7.08]	0.451
IIIC	9 / 173 (5.2)	4 / 200 (2.0)	2.60	[0.82; 8.30]	0.106
Nodal status					
Interaction test	**p = 0.435**				
N0	2 / 91 (2.2)	3 / 117 (2.6)	0.86	[0.15; 5.02]	0.864
N1-N3	40 / 1017 (3.9)	21 / 950 (2.2)	1.78	[1.06; 2.99]	0.030
Histological grade at time of surgery					
Interaction test	**p = 0.525**				
Grade 1	5 / 110 (4.5)	1 / 100 (1.0)	4.55	[0.54; 38.25]	0.164
Grade 2	23 / 604 (3.8)	11 / 601 (1.8)	2.08	[1.02; 4.23]	0.043
Grade 3	12 / 297 (4.0)	8 / 266 (3.0)	1.34	[0.56; 3.24]	0.510
Histological subtype					
Interaction test	**p = 0.675**				
Ductal	37 / 863 (4.3)	22 / 835 (2.6)	1.63	[0.97; 2.73]	0.066
Lobular	4 / 172 (2.3)	1 / 169 (0.6)	3.93	[0.44; 34.80]	0.219
Other	1 / 73 (1.4)	1 / 66 (1.5)	0.90	[0.06; 14.17]	0.943
Ki67 status from surgical specimen					
Interaction test	**p = 0.430**				
Ki67≤20	16 / 527 (3.0)	9 / 552 (1.6)	1.86	[0.83; 4.18]	0.131
Ki67>20	16 / 422 (3.8)	12 / 378 (3.2)	1.19	[0.57; 2.49]	0.636
Type of NSAI					
Interaction test	**p = 0.631**				
Letrozole	26 / 809 (3.2)	16 / 773 (2.1)	1.55	[0.84; 2.87]	0.161
Anastrozole	16 / 299 (5.4)	8 / 297 (2.7)	1.99	[0.86; 4.57]	0.106
Prior neo/adjuvant chemotherapy					
Interaction test	**N.E.**				
Yes	41 / 1029 (4.0)	24 / 987 (2.4)	1.64	[1.00; 2.69]	0.051
No	1 / 79 (1.3)	0 / 83 (0.0)	3.15	[0.13; 76.20]	0.480
Prior adjuvant chemotherapy					
Interaction test	**p = 0.261**				
Yes	22 / 513 (4.3)	9 / 488 (1.8)	2.33	[1.08; 5.00]	0.031
No	20 / 595 (3.4)	15 / 582 (2.6)	1.30	[0.67; 2.52]	0.430
Prior neoadjuvant chemotherapy					
Interaction test	**p = 0.200**				
Yes	19 / 546 (3.5)	15 / 538 (2.8)	1.25	[0.64; 2.43]	0.515
No	23 / 562 (4.1)	9 / 532 (1.7)	2.42	[1.13; 5.18]	0.023

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Prior endocrine therapy					
Interaction test	**p = 0.084**				
Yes	30 / 853 (3.5)	21 / 789 (2.7)	1.32	[0.76; 2.29]	0.320
No	12 / 255 (4.7)	3 / 281 (1.1)	4.41	[1.26; 15.44]	0.020
Prior mastectomy					
Interaction test	**p = 0.386**				
Yes	32 / 769 (4.2)	16 / 745 (2.1)	1.94	[1.07; 3.50]	0.028
No	10 / 339 (2.9)	8 / 325 (2.5)	1.20	[0.48; 3.00]	0.699
Prior radiotherapy					
Interaction test	**p = 0.241**				
Yes	41 / 1011 (4.1)	22 / 987 (2.2)	1.82	[1.09; 3.03]	0.022
No	1 / 97 (1.0)	2 / 83 (2.4)	0.43	[0.04; 4.63]	0.485

N: Number of patients
n: Number of patients with event
N.E.: Not estimable
CI: Confidence interval
RR: Relative risk
ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
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Analysis method for interaction test:
p-value from logistic regression model.
logit(proportion) = treatment + subgroup factor + treatment * subgroup factor

Analysis method for within subgroup analysis:
RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm.
ET was the reference group for treatment group comparison.

Table 5-3.2.20 SOC general disorders and administration site conditions: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	ET (N = 1070)	RR	[95% CI]	p-value
General disorders and administration site conditions					
	n / N (%)	n / N (%)			
Region					
Interaction test	**p = 0.014**				
NA/WE/O	446 / 640 (69.7)	298 / 627 (47.5)	1.47	[1.33; 1.62]	<.001
ROW	179 / 468 (38.2)	123 / 443 (27.8)	1.38	[1.14; 1.66]	<.001
Geographical region					
Interaction test	**p = 0.033**				
Europe	378 / 654 (57.8)	268 / 638 (42.0)	1.38	[1.23; 1.54]	<.001
North America/Australia	142 / 213 (66.7)	78 / 194 (40.2)	1.66	[1.36; 2.02]	<.001
Asia	88 / 178 (49.4)	54 / 168 (32.1)	1.54	[1.18; 2.01]	0.001
Latin America	17 / 63 (27.0)	21 / 70 (30.0)	0.90	[0.52; 1.55]	0.701
Age group 1 at randomization					
Interaction test	**p = 0.588**				
<45	299 / 549 (54.5)	188 / 496 (37.9)	1.44	[1.25; 1.65]	<.001
45 to 54	316 / 539 (58.6)	220 / 546 (40.3)	1.46	[1.28; 1.65]	<.001
55 to 64	10 / 20 (50.0)	13 / 28 (46.4)	1.08	[0.60; 1.95]	0.806
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)					
Interaction test	**p = 0.801**				
<Median	299 / 549 (54.5)	188 / 496 (37.9)	1.44	[1.25; 1.65]	<.001
≥Median	326 / 559 (58.3)	233 / 574 (40.6)	1.44	[1.27; 1.62]	<.001
Race					
Interaction test	**p = 0.279**				
Asian	112 / 211 (53.1)	60 / 186 (32.3)	1.65	[1.29; 2.10]	<.001
Non-Asian	464 / 840 (55.2)	331 / 827 (40.0)	1.38	[1.24; 1.53]	<.001
BMI at screening					
Interaction test	**p = 0.680**				
≥25	310 / 551 (56.3)	202 / 523 (38.6)	1.46	[1.28; 1.66]	<.001
<25	303 / 542 (55.9)	214 / 535 (40.0)	1.40	[1.23; 1.59]	<.001
AJCC Anatomic Stage Group					
Interaction test	**p = 0.897**				
Group I/II	232 / 417 (55.6)	160 / 418 (38.3)	1.45	[1.25; 1.69]	<.001
Group III	393 / 691 (56.9)	261 / 652 (40.0)	1.42	[1.27; 1.59]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Anatomic stages					
Interaction test	**p = 0.790**				
IA/IB/IIA	84 / 171 (49.1)	72 / 198 (36.4)	1.35	[1.06; 1.72]	0.014
IIB	148 / 246 (60.2)	88 / 220 (40.0)	1.50	[1.24; 1.82]	<.001
IIIA	260 / 451 (57.6)	162 / 393 (41.2)	1.40	[1.21; 1.61]	<.001
IIIB	32 / 67 (47.8)	15 / 59 (25.4)	1.88	[1.14; 3.11]	0.014
IIIC	101 / 173 (58.4)	84 / 200 (42.0)	1.39	[1.13; 1.71]	0.002
Nodal status					
Interaction test	**p = 0.440**				
N0	43 / 91 (47.3)	42 / 117 (35.9)	1.32	[0.95; 1.82]	0.098
N1-N3	582 / 1017 (57.2)	379 / 950 (39.9)	1.43	[1.31; 1.58]	<.001
Histological grade at time of surgery					
Interaction test	**p = 0.693**				
Grade 1	64 / 110 (58.2)	34 / 100 (34.0)	1.71	[1.25; 2.35]	<.001
Grade 2	346 / 604 (57.3)	236 / 601 (39.3)	1.46	[1.29; 1.65]	<.001
Grade 3	170 / 297 (57.2)	103 / 266 (38.7)	1.48	[1.23; 1.77]	<.001
Histological subtype					
Interaction test	**p = 0.137**				
Ductal	486 / 863 (56.3)	342 / 835 (41.0)	1.37	[1.24; 1.52]	<.001
Lobular	102 / 172 (59.3)	55 / 169 (32.5)	1.82	[1.42; 2.34]	<.001
Other	37 / 73 (50.7)	24 / 66 (36.4)	1.39	[0.94; 2.06]	0.096
Ki67 status from surgical specimen					
Interaction test	**p = 0.647**				
Ki67≤20	297 / 527 (56.4)	211 / 552 (38.2)	1.47	[1.29; 1.68]	<.001
Ki67>20	227 / 422 (53.8)	143 / 378 (37.8)	1.42	[1.22; 1.66]	<.001
Type of NSAI					
Interaction test	**p = 0.197**				
Letrozole	445 / 809 (55.0)	280 / 773 (36.2)	1.52	[1.36; 1.70]	<.001
Anastrozole	180 / 299 (60.2)	141 / 297 (47.5)	1.27	[1.09; 1.47]	0.002
Prior neo/adjuvant chemotherapy					
Interaction test	**p = 0.131**				
Yes	578 / 1029 (56.2)	395 / 987 (40.0)	1.40	[1.28; 1.54]	<.001
No	47 / 79 (59.5)	26 / 83 (31.3)	1.90	[1.32; 2.74]	<.001
Prior adjuvant chemotherapy					
Interaction test	**p = 0.922**				
Yes	301 / 513 (58.7)	204 / 488 (41.8)	1.40	[1.24; 1.59]	<.001
No	324 / 595 (54.5)	217 / 582 (37.3)	1.46	[1.28; 1.66]	<.001
Prior neoadjuvant chemotherapy					
Interaction test	**p = 0.312**				
Yes	291 / 546 (53.3)	207 / 538 (38.5)	1.39	[1.21; 1.58]	<.001
No	334 / 562 (59.4)	214 / 532 (40.2)	1.48	[1.31; 1.67]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Prior endocrine therapy					
Interaction test	**p = 0.159**				
Yes	479 / 853 (56.2)	294 / 789 (37.3)	1.51	[1.35; 1.68]	<.001
No	146 / 255 (57.3)	127 / 281 (45.2)	1.27	[1.07; 1.50]	0.005
Prior mastectomy					
Interaction test	**p = 0.620**				
Yes	438 / 769 (57.0)	292 / 745 (39.2)	1.45	[1.30; 1.62]	<.001
No	187 / 339 (55.2)	129 / 325 (39.7)	1.39	[1.18; 1.64]	<.001
Prior radiotherapy					
Interaction test	**p = 0.479**				
Yes	576 / 1011 (57.0)	389 / 987 (39.4)	1.45	[1.32; 1.59]	<.001
No	49 / 97 (50.5)	32 / 83 (38.6)	1.31	[0.94; 1.83]	0.114

N: Number of patients
n: Number of patients with event
CI: Confidence interval
RR: Relative risk
ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
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Analysis method for interaction test:
p-value from logistic regression model.
logit(proportion) = treatment + subgroup factor + treatment * subgroup factor

Analysis method for within subgroup analysis:
RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm.
ET was the reference group for treatment group comparison.

Table 5-3.2.21 PT fatigue: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	ET (N = 1070)	RR	[95% CI]	p-value
Fatigue					
	n / N (%)	n / N (%)			
Region					
Interaction test	**p = 0.056**				
NA/WE/O	195 / 640 (30.5)	110 / 627 (17.5)	1.74	[1.41; 2.13]	<.001
ROW	43 / 468 (9.2)	34 / 443 (7.7)	1.20	[0.78; 1.84]	0.413
Geographical region					
Interaction test	**p = 0.526**				
Europe	115 / 654 (17.6)	75 / 638 (11.8)	1.50	[1.14; 1.96]	0.003
North America/Australia	89 / 213 (41.8)	47 / 194 (24.2)	1.72	[1.28; 2.32]	<.001
Asia	27 / 178 (15.2)	15 / 168 (8.9)	1.70	[0.94; 3.08]	0.081
Latin America	7 / 63 (11.1)	7 / 70 (10.0)	1.11	[0.41; 2.99]	0.835
Age group 1 at randomization					
Interaction test	**p = 0.299**				
<45	114 / 549 (20.8)	56 / 496 (11.3)	1.84	[1.37; 2.47]	<.001
45 to 54	120 / 539 (22.3)	81 / 546 (14.8)	1.50	[1.16; 1.94]	0.002
55 to 64	4 / 20 (20.0)	7 / 28 (25.0)	0.80	[0.27; 2.37]	0.687
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)					
Interaction test	**p = 0.252**				
<Median	114 / 549 (20.8)	56 / 496 (11.3)	1.84	[1.37; 2.47]	<.001
≥Median	124 / 559 (22.2)	88 / 574 (15.3)	1.45	[1.13; 1.85]	0.003
Race					
Interaction test	**p = 0.658**				
Asian	40 / 211 (19.0)	19 / 186 (10.2)	1.86	[1.12; 3.09]	0.017
Non-Asian	192 / 840 (22.9)	118 / 827 (14.3)	1.60	[1.30; 1.97]	<.001
BMI at screening					
Interaction test	**p = 0.935**				
≥25	121 / 551 (22.0)	73 / 523 (14.0)	1.57	[1.21; 2.05]	<.001
<25	112 / 542 (20.7)	71 / 535 (13.3)	1.56	[1.19; 2.04]	0.001
AJCC Anatomic Stage Group					
Interaction test	**p = 0.199**				
Group I/II	76 / 417 (18.2)	56 / 418 (13.4)	1.36	[0.99; 1.87]	0.057
Group III	162 / 691 (23.4)	88 / 652 (13.5)	1.74	[1.37; 2.20]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Anatomic stages					
Interaction test	**p = 0.446**				
IA/IB/IIA	29 / 171 (17.0)	28 / 198 (14.1)	1.20	[0.74; 1.93]	0.456
IIB	47 / 246 (19.1)	28 / 220 (12.7)	1.50	[0.98; 2.31]	0.065
IIIA	108 / 451 (23.9)	57 / 393 (14.5)	1.65	[1.23; 2.21]	<.001
IIIB	13 / 67 (19.4)	3 / 59 (5.1)	3.82	[1.14; 12.74]	0.029
IIIC	41 / 173 (23.7)	28 / 200 (14.0)	1.69	[1.10; 2.62]	0.018
Nodal status					
Interaction test	**p = 0.131**				
N0	14 / 91 (15.4)	18 / 117 (15.4)	1.00	[0.53; 1.90]	1.000
N1-N3	224 / 1017 (22.0)	126 / 950 (13.3)	1.66	[1.36; 2.03]	<.001
Histological grade at time of surgery					
Interaction test	**p = 0.894**				
Grade 1	16 / 110 (14.5)	10 / 100 (10.0)	1.45	[0.69; 3.06]	0.322
Grade 2	144 / 604 (23.8)	85 / 601 (14.1)	1.69	[1.32; 2.15]	<.001
Grade 3	65 / 297 (21.9)	35 / 266 (13.2)	1.66	[1.14; 2.42]	0.008
Histological subtype					
Interaction test	**p = 0.459**				
Ductal	183 / 863 (21.2)	114 / 835 (13.7)	1.55	[1.25; 1.92]	<.001
Lobular	46 / 172 (26.7)	23 / 169 (13.6)	1.97	[1.25; 3.09]	0.003
Other	9 / 73 (12.3)	7 / 66 (10.6)	1.16	[0.46; 2.95]	0.751
Ki67 status from surgical specimen					
Interaction test	**p = 0.625**				
Ki67≤20	97 / 527 (18.4)	60 / 552 (10.9)	1.69	[1.26; 2.28]	<.001
Ki67>20	71 / 422 (16.8)	42 / 378 (11.1)	1.51	[1.06; 2.16]	0.022
Type of NSAI					
Interaction test	**p = 0.222**				
Letrozole	164 / 809 (20.3)	89 / 773 (11.5)	1.76	[1.39; 2.23]	<.001
Anastrozole	74 / 299 (24.7)	55 / 297 (18.5)	1.34	[0.98; 1.82]	0.067
Prior neo/adjuvant chemotherapy					
Interaction test	**p = 0.153**				
Yes	226 / 1029 (22.0)	131 / 987 (13.3)	1.65	[1.36; 2.01]	<.001
No	12 / 79 (15.2)	13 / 83 (15.7)	0.97	[0.47; 2.00]	0.934
Prior adjuvant chemotherapy					
Interaction test	**p = 0.623**				
Yes	122 / 513 (23.8)	70 / 488 (14.3)	1.66	[1.27; 2.16]	<.001
No	116 / 595 (19.5)	74 / 582 (12.7)	1.53	[1.17; 2.01]	0.002
Prior neoadjuvant chemotherapy					
Interaction test	**p = 0.794**				
Yes	109 / 546 (20.0)	65 / 538 (12.1)	1.65	[1.24; 2.19]	<.001
No	129 / 562 (23.0)	79 / 532 (14.8)	1.55	[1.20; 1.99]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Prior endocrine therapy					
Interaction test	**p = 0.174**				
Yes	183 / 853 (21.5)	97 / 789 (12.3)	1.75	[1.39; 2.19]	<.001
No	55 / 255 (21.6)	47 / 281 (16.7)	1.29	[0.91; 1.83]	0.155
Prior mastectomy					
Interaction test	**p = 0.742**				
Yes	163 / 769 (21.2)	101 / 745 (13.6)	1.56	[1.25; 1.96]	<.001
No	75 / 339 (22.1)	43 / 325 (13.2)	1.67	[1.19; 2.36]	0.003
Prior radiotherapy					
Interaction test	**p = 0.124**				
Yes	222 / 1011 (22.0)	130 / 987 (13.2)	1.67	[1.37; 2.03]	<.001
No	16 / 97 (16.5)	14 / 83 (16.9)	0.98	[0.51; 1.88]	0.947

N: Number of patients
n: Number of patients with event
CI: Confidence interval
RR: Relative risk
ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
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Analysis method for interaction test:
p-value from logistic regression model.
logit(proportion) = treatment + subgroup factor + treatment * subgroup factor

Analysis method for within subgroup analysis:
RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm.
ET was the reference group for treatment group comparison.

Table 5-3.2.22 PT asthenia: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	ET (N = 1070)	RR	[95% CI]	p-value
Asthenia					
	n / N (%)	n / N (%)			
Region					
Interaction test	**p = 0.901**				
NA/WE/O	146 / 640 (22.8)	106 / 627 (16.9)	1.35	[1.08; 1.69]	0.009
ROW	39 / 468 (8.3)	27 / 443 (6.1)	1.37	[0.85; 2.19]	0.195
Geographical region					
Interaction test	**p = 0.189**				
Europe	176 / 654 (26.9)	119 / 638 (18.7)	1.44	[1.17; 1.77]	<.001
North America/Australia	2 / 213 (0.9)	4 / 194 (2.1)	0.46	[0.08; 2.46]	0.361
Asia	2 / 178 (1.1)	1 / 168 (0.6)	1.89	[0.17; 20.63]	0.603
Latin America	5 / 63 (7.9)	9 / 70 (12.9)	0.62	[0.22; 1.74]	0.363
Age group 1 at randomization					
Interaction test	**p = 0.525**				
<45	80 / 549 (14.6)	61 / 496 (12.3)	1.18	[0.87; 1.62]	0.284
45 to 54	102 / 539 (18.9)	69 / 546 (12.6)	1.50	[1.13; 1.98]	0.005
55 to 64	3 / 20 (15.0)	3 / 28 (10.7)	1.40	[0.31; 6.24]	0.659
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)					
Interaction test	**p = 0.253**				
<Median	80 / 549 (14.6)	61 / 496 (12.3)	1.18	[0.87; 1.62]	0.284
≥Median	105 / 559 (18.8)	72 / 574 (12.5)	1.50	[1.14; 1.97]	0.004
Race					
Interaction test	**p = 0.984**				
Asian	3 / 211 (1.4)	2 / 186 (1.1)	1.32	[0.22; 7.83]	0.758
Non-Asian	143 / 840 (17.0)	109 / 827 (13.2)	1.29	[1.03; 1.63]	0.029
BMI at screening					
Interaction test	**p = 0.606**				
≥25	92 / 551 (16.7)	69 / 523 (13.2)	1.27	[0.95; 1.69]	0.109
<25	89 / 542 (16.4)	62 / 535 (11.6)	1.42	[1.05; 1.92]	0.023
AJCC Anatomic Stage Group					
Interaction test	**p = 0.801**				
Group I/II	83 / 417 (19.9)	64 / 418 (15.3)	1.30	[0.97; 1.75]	0.083
Group III	102 / 691 (14.8)	69 / 652 (10.6)	1.39	[1.05; 1.86]	0.023

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Anatomic stages					
Interaction test	**p = 0.727**				
IA/IB/IIA	34 / 171 (19.9)	32 / 198 (16.2)	1.23	[0.79; 1.90]	0.353
IIB	49 / 246 (19.9)	32 / 220 (14.5)	1.37	[0.91; 2.06]	0.130
IIIA	64 / 451 (14.2)	47 / 393 (12.0)	1.19	[0.84; 1.69]	0.340
IIIB	14 / 67 (20.9)	7 / 59 (11.9)	1.76	[0.76; 4.07]	0.185
IIIC	24 / 173 (13.9)	15 / 200 (7.5)	1.85	[1.00; 3.41]	0.049
Nodal status					
Interaction test	**p = 0.604**				
N0	17 / 91 (18.7)	19 / 117 (16.2)	1.15	[0.63; 2.08]	0.644
N1-N3	168 / 1017 (16.5)	114 / 950 (12.0)	1.38	[1.10; 1.72]	0.005
Histological grade at time of surgery					
Interaction test	**p = 0.671**				
Grade 1	21 / 110 (19.1)	10 / 100 (10.0)	1.91	[0.95; 3.85]	0.071
Grade 2	101 / 604 (16.7)	74 / 601 (12.3)	1.36	[1.03; 1.79]	0.031
Grade 3	41 / 297 (13.8)	26 / 266 (9.8)	1.41	[0.89; 2.24]	0.144
Histological subtype					
Interaction test	**p = 0.533**				
Ductal	142 / 863 (16.5)	107 / 835 (12.8)	1.28	[1.02; 1.62]	0.035
Lobular	31 / 172 (18.0)	17 / 169 (10.1)	1.79	[1.03; 3.11]	0.038
Other	12 / 73 (16.4)	9 / 66 (13.6)	1.21	[0.54; 2.68]	0.646
Ki67 status from surgical specimen					
Interaction test	**p = 0.597**				
Ki67≤20	104 / 527 (19.7)	77 / 552 (13.9)	1.41	[1.08; 1.85]	0.012
Ki67>20	75 / 422 (17.8)	53 / 378 (14.0)	1.27	[0.92; 1.75]	0.150
Type of NSAI					
Interaction test	**p = 0.322**				
Letrozole	136 / 809 (16.8)	103 / 773 (13.3)	1.26	[1.00; 1.60]	0.054
Anastrozole	49 / 299 (16.4)	30 / 297 (10.1)	1.62	[1.06; 2.48]	0.026
Prior neo/adjuvant chemotherapy					
Interaction test	**p = 0.027**				
Yes	166 / 1029 (16.1)	127 / 987 (12.9)	1.25	[1.01; 1.55]	0.038
No	19 / 79 (24.1)	6 / 83 (7.2)	3.33	[1.40; 7.90]	0.006
Prior adjuvant chemotherapy					
Interaction test	**p = 0.385**				
Yes	93 / 513 (18.1)	60 / 488 (12.3)	1.47	[1.09; 1.99]	0.011
No	92 / 595 (15.5)	73 / 582 (12.5)	1.23	[0.93; 1.64]	0.150
Prior neoadjuvant chemotherapy					
Interaction test	**p = 0.044**				
Yes	75 / 546 (13.7)	69 / 538 (12.8)	1.07	[0.79; 1.45]	0.659
No	110 / 562 (19.6)	64 / 532 (12.0)	1.63	[1.22; 2.16]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Prior endocrine therapy					
Interaction test	**p = 0.864**				
Yes	141 / 853 (16.5)	98 / 789 (12.4)	1.33	[1.05; 1.69]	0.019
No	44 / 255 (17.3)	35 / 281 (12.5)	1.39	[0.92; 2.09]	0.119
Prior mastectomy					
Interaction test	**p = 0.002**				
Yes	130 / 769 (16.9)	73 / 745 (9.8)	1.73	[1.32; 2.26]	<.001
No	55 / 339 (16.2)	60 / 325 (18.5)	0.88	[0.63; 1.23]	0.447
Prior radiotherapy					
Interaction test	**p = 0.819**				
Yes	165 / 1011 (16.3)	121 / 987 (12.3)	1.33	[1.07; 1.65]	0.010
No	20 / 97 (20.6)	12 / 83 (14.5)	1.43	[0.74; 2.74]	0.287

N: Number of patients
n: Number of patients with event
CI: Confidence interval
RR: Relative risk
ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
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Analysis method for interaction test:
p-value from logistic regression model.
logit(proportion) = treatment + subgroup factor + treatment * subgroup factor

Analysis method for within subgroup analysis:
RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm.
ET was the reference group for treatment group comparison.

Table 5-3.2.23 PT pyrexia: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	ET (N = 1070)	RR	[95% CI]	p-value
Pyrexia					
	n / N (%)	n / N (%)			
Region					
Interaction test	**p = 0.358**				
NA/WE/O	89 / 640 (13.9)	52 / 627 (8.3)	1.68	[1.21; 2.32]	0.002
ROW	70 / 468 (15.0)	31 / 443 (7.0)	2.14	[1.43; 3.20]	<.001
Geographical region					
Interaction test	**p = 0.182**				
Europe	70 / 654 (10.7)	48 / 638 (7.5)	1.42	[1.00; 2.02]	0.049
North America/Australia	41 / 213 (19.2)	14 / 194 (7.2)	2.67	[1.50; 4.74]	<.001
Asia	46 / 178 (25.8)	20 / 168 (11.9)	2.17	[1.34; 3.51]	0.002
Latin America	2 / 63 (3.2)	1 / 70 (1.4)	2.22	[0.21; 23.92]	0.510
Age group 1 at randomization					
Interaction test	**p = 0.208**				
<45	88 / 549 (16.0)	37 / 496 (7.5)	2.15	[1.49; 3.09]	<.001
45 to 54	71 / 539 (13.2)	46 / 546 (8.4)	1.56	[1.10; 2.22]	0.013
55 to 64	0 / 20 (0.0)	0 / 28 (0.0)	N.E.	N.E.	N.E.
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)					
Interaction test	**p = 0.224**				
<Median	88 / 549 (16.0)	37 / 496 (7.5)	2.15	[1.49; 3.09]	<.001
≥Median	71 / 559 (12.7)	46 / 574 (8.0)	1.58	[1.11; 2.25]	0.010
Race					
Interaction test	**p = 0.181**				
Asian	53 / 211 (25.1)	20 / 186 (10.8)	2.34	[1.45; 3.76]	<.001
Non-Asian	103 / 840 (12.3)	60 / 827 (7.3)	1.69	[1.25; 2.29]	<.001
BMI at screening					
Interaction test	**p = 0.645**				
≥25	76 / 551 (13.8)	37 / 523 (7.1)	1.95	[1.34; 2.83]	<.001
<25	80 / 542 (14.8)	46 / 535 (8.6)	1.72	[1.22; 2.42]	0.002
AJCC Anatomic Stage Group					
Interaction test	**p = 0.416**				
Group I/II	45 / 417 (10.8)	20 / 418 (4.8)	2.26	[1.36; 3.75]	0.002
Group III	114 / 691 (16.5)	63 / 652 (9.7)	1.71	[1.28; 2.28]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Anatomic stages					
Interaction test	**p = 0.410**				
IA/IB/IIA	17 / 171 (9.9)	4 / 198 (2.0)	4.92	[1.69; 14.34]	0.004
IIB	28 / 246 (11.4)	16 / 220 (7.3)	1.57	[0.87; 2.81]	0.135
IIIA	68 / 451 (15.1)	35 / 393 (8.9)	1.69	[1.15; 2.49]	0.007
IIIB	7 / 67 (10.4)	2 / 59 (3.4)	3.08	[0.67; 14.26]	0.150
IIIC	39 / 173 (22.5)	26 / 200 (13.0)	1.73	[1.10; 2.73]	0.017
Nodal status					
Interaction test	**p = 0.352**				
N0	8 / 91 (8.8)	3 / 117 (2.6)	3.43	[0.94; 12.56]	0.063
N1-N3	151 / 1017 (14.8)	80 / 950 (8.4)	1.76	[1.36; 2.28]	<.001
Histological grade at time of surgery					
Interaction test	**p = 0.826**				
Grade 1	14 / 110 (12.7)	5 / 100 (5.0)	2.55	[0.95; 6.81]	0.063
Grade 2	86 / 604 (14.2)	40 / 601 (6.7)	2.14	[1.50; 3.06]	<.001
Grade 3	51 / 297 (17.2)	25 / 266 (9.4)	1.83	[1.17; 2.86]	0.009
Histological subtype					
Interaction test	**p = 0.636**				
Ductal	127 / 863 (14.7)	68 / 835 (8.1)	1.81	[1.37; 2.39]	<.001
Lobular	19 / 172 (11.0)	7 / 169 (4.1)	2.67	[1.15; 6.18]	0.022
Other	13 / 73 (17.8)	8 / 66 (12.1)	1.47	[0.65; 3.32]	0.355
Ki67 status from surgical specimen					
Interaction test	**p = 0.245**				
Ki67≤20	66 / 527 (12.5)	43 / 552 (7.8)	1.61	[1.12; 2.32]	0.011
Ki67>20	73 / 422 (17.3)	30 / 378 (7.9)	2.18	[1.46; 3.26]	<.001
Type of NSAI					
Interaction test	**p = 0.131**				
Letrozole	114 / 809 (14.1)	51 / 773 (6.6)	2.14	[1.56; 2.93]	<.001
Anastrozole	45 / 299 (15.1)	32 / 297 (10.8)	1.40	[0.91; 2.13]	0.122
Prior neo/adjuvant chemotherapy					
Interaction test	**p = 0.235**				
Yes	148 / 1029 (14.4)	80 / 987 (8.1)	1.77	[1.37; 2.30]	<.001
No	11 / 79 (13.9)	3 / 83 (3.6)	3.85	[1.12; 13.30]	0.033
Prior adjuvant chemotherapy					
Interaction test	**p = 0.360**				
Yes	81 / 513 (15.8)	47 / 488 (9.6)	1.64	[1.17; 2.30]	0.004
No	78 / 595 (13.1)	36 / 582 (6.2)	2.12	[1.45; 3.09]	<.001
Prior neoadjuvant chemotherapy					
Interaction test	**p = 0.797**				
Yes	71 / 546 (13.0)	39 / 538 (7.2)	1.79	[1.24; 2.60]	0.002
No	88 / 562 (15.7)	44 / 532 (8.3)	1.89	[1.34; 2.66]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Prior endocrine therapy					
Interaction test	**p = 0.216**				
Yes	127 / 853 (14.9)	58 / 789 (7.4)	2.03	[1.51; 2.72]	<.001
No	32 / 255 (12.5)	25 / 281 (8.9)	1.41	[0.86; 2.31]	0.173
Prior mastectomy					
Interaction test	**p = 0.196**				
Yes	114 / 769 (14.8)	66 / 745 (8.9)	1.67	[1.26; 2.23]	<.001
No	45 / 339 (13.3)	17 / 325 (5.2)	2.54	[1.48; 4.34]	<.001
Prior radiotherapy					
Interaction test	**p = 0.843**				
Yes	149 / 1011 (14.7)	78 / 987 (7.9)	1.86	[1.44; 2.42]	<.001
No	10 / 97 (10.3)	5 / 83 (6.0)	1.71	[0.61; 4.81]	0.308

N: Number of patients
n: Number of patients with event
N.E.: Not estimable
CI: Confidence interval
RR: Relative risk
ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
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Analysis method for interaction test:
p-value from logistic regression model.
logit(proportion) = treatment + subgroup factor + treatment * subgroup factor

Analysis method for within subgroup analysis:
RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm.
ET was the reference group for treatment group comparison.

Table 5-3.2.24 PT influenza like illness: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	ET (N = 1070)	RR	[95% CI]	p-value
Influenza like illness					
	n / N (%)	n / N (%)			
Region					
Interaction test	**p = 0.198**				
NA/WE/O	54 / 640 (8.4)	15 / 627 (2.4)	3.53	[2.01; 6.18]	<.001
ROW	11 / 468 (2.4)	6 / 443 (1.4)	1.74	[0.65; 4.65]	0.273
Geographical region					
Interaction test	**p = 0.238**				
Europe	19 / 654 (2.9)	10 / 638 (1.6)	1.85	[0.87; 3.96]	0.111
North America/Australia	37 / 213 (17.4)	8 / 194 (4.1)	4.21	[2.01; 8.82]	<.001
Asia	9 / 178 (5.1)	3 / 168 (1.8)	2.83	[0.78; 10.28]	0.114
Latin America	0 / 63 (0.0)	0 / 70 (0.0)	N.E.	N.E.	N.E.
Age group 1 at randomization					
Interaction test	**p = 0.307**				
<45	39 / 549 (7.1)	8 / 496 (1.6)	4.40	[2.08; 9.33]	<.001
45 to 54	25 / 539 (4.6)	12 / 546 (2.2)	2.11	[1.07; 4.16]	0.031
55 to 64	1 / 20 (5.0)	1 / 28 (3.6)	1.40	[0.09; 21.08]	0.808
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)					
Interaction test	**p = 0.128**				
<Median	39 / 549 (7.1)	8 / 496 (1.6)	4.40	[2.08; 9.33]	<.001
≥Median	26 / 559 (4.7)	13 / 574 (2.3)	2.05	[1.07; 3.96]	0.031
Race					
Interaction test	**p = 0.660**				
Asian	11 / 211 (5.2)	4 / 186 (2.2)	2.42	[0.79; 7.48]	0.124
Non-Asian	52 / 840 (6.2)	16 / 827 (1.9)	3.20	[1.84; 5.56]	<.001
BMI at screening					
Interaction test	**p = 0.176**				
≥25	27 / 551 (4.9)	12 / 523 (2.3)	2.14	[1.09; 4.17]	0.026
<25	38 / 542 (7.0)	9 / 535 (1.7)	4.17	[2.04; 8.53]	<.001
AJCC Anatomic Stage Group					
Interaction test	**p = 0.588**				
Group I/II	25 / 417 (6.0)	7 / 418 (1.7)	3.58	[1.57; 8.19]	0.003
Group III	40 / 691 (5.8)	14 / 652 (2.1)	2.70	[1.48; 4.91]	0.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Anatomic stages					
Interaction test	**p = 0.362**				
IA/IB/IIA	9 / 171 (5.3)	5 / 198 (2.5)	2.08	[0.71; 6.10]	0.180
IIB	16 / 246 (6.5)	2 / 220 (0.9)	7.15	[1.66; 30.77]	0.008
IIIA	30 / 451 (6.7)	7 / 393 (1.8)	3.73	[1.66; 8.41]	0.001
IIIB	2 / 67 (3.0)	2 / 59 (3.4)	0.88	[0.13; 6.06]	0.897
IIIC	8 / 173 (4.6)	5 / 200 (2.5)	1.85	[0.62; 5.55]	0.273
Nodal status					
Interaction test	**p = 0.612**				
N0	4 / 91 (4.4)	1 / 117 (0.9)	5.14	[0.58; 45.23]	0.140
N1-N3	61 / 1017 (6.0)	20 / 950 (2.1)	2.85	[1.73; 4.68]	<.001
Histological grade at time of surgery					
Interaction test	**p = 0.622**				
Grade 1	8 / 110 (7.3)	1 / 100 (1.0)	7.27	[0.93; 57.13]	0.059
Grade 2	34 / 604 (5.6)	11 / 601 (1.8)	3.08	[1.57; 6.01]	0.001
Grade 3	19 / 297 (6.4)	7 / 266 (2.6)	2.43	[1.04; 5.69]	0.041
Histological subtype					
Interaction test	**p = 0.145**				
Ductal	52 / 863 (6.0)	20 / 835 (2.4)	2.52	[1.52; 4.18]	<.001
Lobular	12 / 172 (7.0)	1 / 169 (0.6)	11.79	[1.55; 89.68]	0.017
Other	1 / 73 (1.4)	0 / 66 (0.0)	2.72	[0.11; 65.54]	0.538
Ki67 status from surgical specimen					
Interaction test	**p = 0.133**				
Ki67≤20	25 / 527 (4.7)	11 / 552 (2.0)	2.38	[1.18; 4.79]	0.015
Ki67>20	23 / 422 (5.5)	3 / 378 (0.8)	6.87	[2.08; 22.69]	0.002
Type of NSAI					
Interaction test	**p = 0.878**				
Letrozole	40 / 809 (4.9)	13 / 773 (1.7)	2.94	[1.58; 5.45]	<.001
Anastrozole	25 / 299 (8.4)	8 / 297 (2.7)	3.10	[1.42; 6.77]	0.004
Prior neo/adjuvant chemotherapy					
Interaction test	**p = 0.756**				
Yes	63 / 1029 (6.1)	20 / 987 (2.0)	3.02	[1.84; 4.96]	<.001
No	2 / 79 (2.5)	1 / 83 (1.2)	2.10	[0.19; 22.72]	0.541
Prior adjuvant chemotherapy					
Interaction test	**p = 0.672**				
Yes	34 / 513 (6.6)	12 / 488 (2.5)	2.70	[1.41; 5.14]	0.003
No	31 / 595 (5.2)	9 / 582 (1.5)	3.37	[1.62; 7.01]	0.001
Prior neoadjuvant chemotherapy					
Interaction test	**p = 0.739**				
Yes	30 / 546 (5.5)	9 / 538 (1.7)	3.28	[1.57; 6.85]	0.002
No	35 / 562 (6.2)	12 / 532 (2.3)	2.76	[1.45; 5.26]	0.002

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Prior endocrine therapy					
Interaction test	**p = 0.194**				
Yes	54 / 853 (6.3)	14 / 789 (1.8)	3.57	[2.00; 6.37]	<.001
No	11 / 255 (4.3)	7 / 281 (2.5)	1.73	[0.68; 4.40]	0.248
Prior mastectomy					
Interaction test	**p = 0.053**				
Yes	46 / 769 (6.0)	10 / 745 (1.3)	4.46	[2.27; 8.76]	<.001
No	19 / 339 (5.6)	11 / 325 (3.4)	1.66	[0.80; 3.43]	0.174
Prior radiotherapy					
Interaction test	**p = 0.493**				
Yes	61 / 1011 (6.0)	19 / 987 (1.9)	3.13	[1.89; 5.21]	<.001
No	4 / 97 (4.1)	2 / 83 (2.4)	1.71	[0.32; 9.11]	0.529

N: Number of patients
n: Number of patients with event
N.E.: Not estimable
CI: Confidence interval
RR: Relative risk
ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
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Analysis method for interaction test:
p-value from logistic regression model.
logit(proportion) = treatment + subgroup factor + treatment * subgroup factor

Analysis method for within subgroup analysis:
RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm.
ET was the reference group for treatment group comparison.

Table 5-3.2.25 PT oedema peripheral: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	ET (N = 1070)	RR	[95% CI]	p-value
Oedema peripheral					
	n / N (%)	n / N (%)			
Region					
Interaction test	**p = 0.713**				
NA/WE/O	41 / 640 (6.4)	21 / 627 (3.3)	1.91	[1.14; 3.20]	0.013
ROW	10 / 468 (2.1)	6 / 443 (1.4)	1.58	[0.58; 4.30]	0.373
Geographical region					
Interaction test	**p = 0.463**				
Europe	30 / 654 (4.6)	15 / 638 (2.4)	1.95	[1.06; 3.59]	0.032
North America/Australia	13 / 213 (6.1)	6 / 194 (3.1)	1.97	[0.77; 5.09]	0.160
Asia	8 / 178 (4.5)	1 / 168 (0.6)	7.55	[0.95; 59.73]	0.055
Latin America	0 / 63 (0.0)	5 / 70 (7.1)	0.10	[<0.01; 1.79]	0.118
Age group 1 at randomization					
Interaction test	**p = 0.572**				
<45	19 / 549 (3.5)	11 / 496 (2.2)	1.56	[0.75; 3.25]	0.234
45 to 54	32 / 539 (5.9)	16 / 546 (2.9)	2.03	[1.13; 3.65]	0.019
55 to 64	0 / 20 (0.0)	0 / 28 (0.0)	N.E.	N.E.	N.E.
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)					
Interaction test	**p = 0.554**				
<Median	19 / 549 (3.5)	11 / 496 (2.2)	1.56	[0.75; 3.25]	0.234
≥Median	32 / 559 (5.7)	16 / 574 (2.8)	2.05	[1.14; 3.70]	0.017
Race					
Interaction test	**p = 0.186**				
Asian	8 / 211 (3.8)	1 / 186 (0.5)	7.05	[0.89; 55.86]	0.064
Non-Asian	39 / 840 (4.6)	23 / 827 (2.8)	1.67	[1.01; 2.77]	0.047
BMI at screening					
Interaction test	**p = 0.598**				
≥25	34 / 551 (6.2)	17 / 523 (3.3)	1.90	[1.07; 3.36]	0.027
<25	15 / 542 (2.8)	10 / 535 (1.9)	1.48	[0.67; 3.27]	0.331
AJCC Anatomic Stage Group					
Interaction test	**p = 0.858**				
Group I/II	19 / 417 (4.6)	11 / 418 (2.6)	1.73	[0.83; 3.59]	0.141
Group III	32 / 691 (4.6)	16 / 652 (2.5)	1.89	[1.05; 3.41]	0.035

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Anatomic stages					
Interaction test	**p = 0.661**				
IA/IB/IIA	8 / 171 (4.7)	3 / 198 (1.5)	3.09	[0.83; 11.46]	0.092
IIB	11 / 246 (4.5)	8 / 220 (3.6)	1.23	[0.50; 3.00]	0.650
IIIA	20 / 451 (4.4)	8 / 393 (2.0)	2.18	[0.97; 4.89]	0.059
IIIB	6 / 67 (9.0)	2 / 59 (3.4)	2.64	[0.55; 12.59]	0.223
IIIC	6 / 173 (3.5)	6 / 200 (3.0)	1.16	[0.38; 3.52]	0.798
Nodal status					
Interaction test	**p = 0.151**				
N0	6 / 91 (6.6)	1 / 117 (0.9)	7.71	[0.95; 62.95]	0.056
N1-N3	45 / 1017 (4.4)	26 / 950 (2.7)	1.62	[1.01; 2.60]	0.047
Histological grade at time of surgery					
Interaction test	**p = 0.125**				
Grade 1	8 / 110 (7.3)	1 / 100 (1.0)	7.27	[0.93; 57.13]	0.059
Grade 2	32 / 604 (5.3)	16 / 601 (2.7)	1.99	[1.10; 3.59]	0.022
Grade 3	9 / 297 (3.0)	9 / 266 (3.4)	0.90	[0.36; 2.22]	0.812
Histological subtype					
Interaction test	**p = 0.225**				
Ductal	37 / 863 (4.3)	22 / 835 (2.6)	1.63	[0.97; 2.73]	0.066
Lobular	11 / 172 (6.4)	2 / 169 (1.2)	5.40	[1.22; 24.02]	0.027
Other	3 / 73 (4.1)	3 / 66 (4.5)	0.90	[0.19; 4.33]	0.900
Ki67 status from surgical specimen					
Interaction test	**p = 0.414**				
Ki67≤20	26 / 527 (4.9)	11 / 552 (2.0)	2.48	[1.24; 4.96]	0.011
Ki67>20	18 / 422 (4.3)	10 / 378 (2.6)	1.61	[0.75; 3.45]	0.218
Type of NSAI					
Interaction test	**p = 0.009**				
Letrozole	40 / 809 (4.9)	13 / 773 (1.7)	2.94	[1.58; 5.45]	<.001
Anastrozole	11 / 299 (3.7)	14 / 297 (4.7)	0.78	[0.36; 1.69]	0.530
Prior neo/adjuvant chemotherapy					
Interaction test	**p = 0.910**				
Yes	49 / 1029 (4.8)	26 / 987 (2.6)	1.81	[1.13; 2.88]	0.013
No	2 / 79 (2.5)	1 / 83 (1.2)	2.10	[0.19; 22.72]	0.541
Prior adjuvant chemotherapy					
Interaction test	**p = 0.788**				
Yes	27 / 513 (5.3)	15 / 488 (3.1)	1.71	[0.92; 3.18]	0.089
No	24 / 595 (4.0)	12 / 582 (2.1)	1.96	[0.99; 3.87]	0.054
Prior neoadjuvant chemotherapy					
Interaction test	**p = 0.855**				
Yes	23 / 546 (4.2)	13 / 538 (2.4)	1.74	[0.89; 3.41]	0.104
No	28 / 562 (5.0)	14 / 532 (2.6)	1.89	[1.01; 3.56]	0.047

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Prior endocrine therapy					
Interaction test	**p = 0.300**				
Yes	38 / 853 (4.5)	16 / 789 (2.0)	2.20	[1.23; 3.91]	0.007
No	13 / 255 (5.1)	11 / 281 (3.9)	1.30	[0.59; 2.85]	0.509
Prior mastectomy					
Interaction test	**p = 0.904**				
Yes	37 / 769 (4.8)	20 / 745 (2.7)	1.79	[1.05; 3.06]	0.032
No	14 / 339 (4.1)	7 / 325 (2.2)	1.92	[0.78; 4.69]	0.154
Prior radiotherapy					
Interaction test	**p = 0.307**				
Yes	45 / 1011 (4.5)	26 / 987 (2.6)	1.69	[1.05; 2.72]	0.030
No	6 / 97 (6.2)	1 / 83 (1.2)	5.13	[0.63; 41.78]	0.126

N: Number of patients
n: Number of patients with event
N.E.: Not estimable
CI: Confidence interval
RR: Relative risk
ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
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Analysis method for interaction test:
p-value from logistic regression model.
logit(proportion) = treatment + subgroup factor + treatment * subgroup factor

Analysis method for within subgroup analysis:
RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm.
ET was the reference group for treatment group comparison.

Table 5-3.2.26 PT mucosal inflammation: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	ET (N = 1070)	RR	[95% CI]	p-value
Mucosal inflammation					
	n / N (%)	n / N (%)			
Region					
Interaction test	**p = 0.002**				
NA/WE/O	33 / 640 (5.2)	1 / 627 (0.2)	32.33	[4.44; >99.99]	<.001
ROW	3 / 468 (0.6)	4 / 443 (0.9)	0.71	[0.16; 3.15]	0.653
Geographical region					
Interaction test	**p = 0.006**				
Europe	24 / 654 (3.7)	1 / 638 (0.2)	23.41	[3.18; >99.99]	0.002
North America/Australia	9 / 213 (4.2)	0 / 194 (0.0)	17.31	[1.01; >99.99]	0.049
Asia	3 / 178 (1.7)	4 / 168 (2.4)	0.71	[0.16; 3.12]	0.648
Latin America	0 / 63 (0.0)	0 / 70 (0.0)	N.E.	N.E.	N.E.
Age group 1 at randomization					
Interaction test	**p = 0.372**				
<45	16 / 549 (2.9)	1 / 496 (0.2)	14.46	[1.92; >99.99]	0.009
45 to 54	20 / 539 (3.7)	4 / 546 (0.7)	5.06	[1.74; 14.72]	0.003
55 to 64	0 / 20 (0.0)	0 / 28 (0.0)	N.E.	N.E.	N.E.
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)					
Interaction test	**p = 0.377**				
<Median	16 / 549 (2.9)	1 / 496 (0.2)	14.46	[1.92; >99.99]	0.009
≥Median	20 / 559 (3.6)	4 / 574 (0.7)	5.13	[1.77; 14.93]	0.003
Race					
Interaction test	**p = 0.004**				
Asian	4 / 211 (1.9)	4 / 186 (2.2)	0.88	[0.22; 3.48]	0.857
Non-Asian	30 / 840 (3.6)	1 / 827 (0.1)	29.54	[4.04; >99.99]	<.001
BMI at screening					
Interaction test	**p = 0.192**				
≥25	19 / 551 (3.4)	1 / 523 (0.2)	18.03	[2.42; >99.99]	0.005
<25	16 / 542 (3.0)	4 / 535 (0.7)	3.95	[1.33; 11.73]	0.013
AJCC Anatomic Stage Group					
Interaction test	**N.E.**				
Group I/II	12 / 417 (2.9)	0 / 418 (0.0)	25.06	[1.49; >99.99]	0.025
Group III	24 / 691 (3.5)	5 / 652 (0.8)	4.53	[1.74; 11.80]	0.002

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Anatomic stages					
Interaction test	**p = 0.528**				
IA/IB/IIA	5 / 171 (2.9)	0 / 198 (0.0)	12.73	[0.71; >99.99]	0.084
IIB	7 / 246 (2.8)	0 / 220 (0.0)	13.42	[0.77; >99.99]	0.075
IIIA	12 / 451 (2.7)	1 / 393 (0.3)	10.46	[1.37; 80.06]	0.024
IIIB	2 / 67 (3.0)	1 / 59 (1.7)	1.76	[0.16; 18.93]	0.640
IIIC	10 / 173 (5.8)	3 / 200 (1.5)	3.85	[1.08; 13.78]	0.038
Nodal status					
Interaction test	**N.E.**				
N0	3 / 91 (3.3)	0 / 117 (0.0)	8.98	[0.47; >99.99]	0.145
N1-N3	33 / 1017 (3.2)	5 / 950 (0.5)	6.17	[2.42; 15.73]	<.001
Histological grade at time of surgery					
Interaction test	**p = 0.313**				
Grade 1	3 / 110 (2.7)	0 / 100 (0.0)	6.37	[0.33; >99.99]	0.219
Grade 2	14 / 604 (2.3)	3 / 601 (0.5)	4.64	[1.34; 16.08]	0.015
Grade 3	17 / 297 (5.7)	1 / 266 (0.4)	15.23	[2.04; >99.99]	0.008
Histological subtype					
Interaction test	**p = 0.197**				
Ductal	26 / 863 (3.0)	4 / 835 (0.5)	6.29	[2.20; 17.94]	<.001
Lobular	9 / 172 (5.2)	0 / 169 (0.0)	18.67	[1.10; >99.99]	0.043
Other	1 / 73 (1.4)	1 / 66 (1.5)	0.90	[0.06; 14.17]	0.943
Ki67 status from surgical specimen					
Interaction test	**p = 0.994**				
Ki67≤20	14 / 527 (2.7)	3 / 552 (0.5)	4.89	[1.41; 16.91]	0.012
Ki67>20	11 / 422 (2.6)	2 / 378 (0.5)	4.93	[1.10; 22.08]	0.037
Type of NSAI					
Interaction test	**N.E.**				
Letrozole	26 / 809 (3.2)	5 / 773 (0.6)	4.97	[1.92; 12.87]	<.001
Anastrozole	10 / 299 (3.3)	0 / 297 (0.0)	20.86	[1.23; >99.99]	0.036
Prior neo/adjuvant chemotherapy					
Interaction test	**N.E.**				
Yes	34 / 1029 (3.3)	5 / 987 (0.5)	6.52	[2.56; 16.61]	<.001
No	2 / 79 (2.5)	0 / 83 (0.0)	5.25	[0.26; >99.99]	0.282
Prior adjuvant chemotherapy					
Interaction test	**p = 0.385**				
Yes	22 / 513 (4.3)	2 / 488 (0.4)	10.46	[2.47; 44.26]	0.001
No	14 / 595 (2.4)	3 / 582 (0.5)	4.56	[1.32; 15.80]	0.017
Prior neoadjuvant chemotherapy					
Interaction test	**p = 0.079**				
Yes	12 / 546 (2.2)	4 / 538 (0.7)	2.96	[0.96; 9.11]	0.059
No	24 / 562 (4.3)	1 / 532 (0.2)	22.72	[3.08; >99.99]	0.002

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Prior endocrine therapy					
Interaction test	**p = 0.664**				
Yes	32 / 853 (3.8)	4 / 789 (0.5)	7.40	[2.63; 20.83]	<.001
No	4 / 255 (1.6)	1 / 281 (0.4)	4.41	[0.50; 39.18]	0.183
Prior mastectomy					
Interaction test	**p = 0.925**				
Yes	28 / 769 (3.6)	4 / 745 (0.5)	6.78	[2.39; 19.24]	<.001
No	8 / 339 (2.4)	1 / 325 (0.3)	7.67	[0.96; 60.98]	0.054
Prior radiotherapy					
Interaction test	**N.E.**				
Yes	34 / 1011 (3.4)	5 / 987 (0.5)	6.64	[2.61; 16.90]	<.001
No	2 / 97 (2.1)	0 / 83 (0.0)	4.29	[0.21; 88.03]	0.345

N: Number of patients
n: Number of patients with event
N.E.: Not estimable
CI: Confidence interval
RR: Relative risk
ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
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Analysis method for interaction test:
p-value from logistic regression model.
logit(proportion) = treatment + subgroup factor + treatment * subgroup factor

Analysis method for within subgroup analysis:
RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm.
ET was the reference group for treatment group comparison.

Table 5-3.2.27 PT non-cardiac chest pain: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Non-cardiac chest pain					
	n / N (%)	**n / N (%)**			
Region					
Interaction test	**p = 0.301**				
NA/WE/O	22 / 640 (3.4)	7 / 627 (1.1)	3.08	[1.32; 7.16]	0.009
ROW	4 / 468 (0.9)	3 / 443 (0.7)	1.26	[0.28; 5.61]	0.760
Geographical region					
Interaction test	**p = 0.365**				
Europe	11 / 654 (1.7)	2 / 638 (0.3)	5.37	[1.19; 24.11]	0.028
North America/Australia	15 / 213 (7.0)	6 / 194 (3.1)	2.28	[0.90; 5.75]	0.082
Asia	0 / 178 (0.0)	2 / 168 (1.2)	0.19	[<0.01; 3.90]	0.281
Latin America	0 / 63 (0.0)	0 / 70 (0.0)	N.E.	N.E.	N.E.
Age group 1 at randomization					
Interaction test	**p = 0.524**				
<45	12 / 549 (2.2)	5 / 496 (1.0)	2.17	[0.77; 6.11]	0.143
45 to 54	14 / 539 (2.6)	4 / 546 (0.7)	3.55	[1.17; 10.70]	0.025
55 to 64	0 / 20 (0.0)	1 / 28 (3.6)	0.46	[0.02; 10.75]	0.629
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)					
Interaction test	**p = 0.702**				
<Median	12 / 549 (2.2)	5 / 496 (1.0)	2.17	[0.77; 6.11]	0.143
≥Median	14 / 559 (2.5)	5 / 574 (0.9)	2.88	[1.04; 7.93]	0.041
Race					
Interaction test	**p = 0.097**				
Asian	2 / 211 (0.9)	3 / 186 (1.6)	0.59	[0.10; 3.48]	0.558
Non-Asian	22 / 840 (2.6)	7 / 827 (0.8)	3.09	[1.33; 7.20]	0.009
BMI at screening					
Interaction test	**p = 0.707**				
≥25	12 / 551 (2.2)	4 / 523 (0.8)	2.85	[0.92; 8.77]	0.068
<25	13 / 542 (2.4)	6 / 535 (1.1)	2.14	[0.82; 5.59]	0.121
AJCC Anatomic Stage Group					
Interaction test	**p = 0.338**				
Group I/II	12 / 417 (2.9)	3 / 418 (0.7)	4.01	[1.14; 14.11]	0.030
Group III	14 / 691 (2.0)	7 / 652 (1.1)	1.89	[0.77; 4.65]	0.167

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Anatomic stages					
Interaction test	**p = 0.758**				
IA/IB/IIA	5 / 171 (2.9)	0 / 198 (0.0)	12.73	[0.71; >99.99]	0.084
IIB	7 / 246 (2.8)	3 / 220 (1.4)	2.09	[0.55; 7.97]	0.282
IIIA	11 / 451 (2.4)	4 / 393 (1.0)	2.40	[0.77; 7.47]	0.132
IIIB	0 / 67 (0.0)	0 / 59 (0.0)	N.E.	N.E.	N.E.
IIIC	3 / 173 (1.7)	3 / 200 (1.5)	1.16	[0.24; 5.65]	0.858
Nodal status					
Interaction test	**N.E.**				
N0	2 / 91 (2.2)	0 / 117 (0.0)	6.41	[0.31; >99.99]	0.228
N1-N3	24 / 1017 (2.4)	10 / 950 (1.1)	2.24	[1.08; 4.66]	0.031
Histological grade at time of surgery					
Interaction test	**p = 0.963**				
Grade 1	3 / 110 (2.7)	0 / 100 (0.0)	6.37	[0.33; >99.99]	0.219
Grade 2	15 / 604 (2.5)	7 / 601 (1.2)	2.13	[0.88; 5.19]	0.095
Grade 3	5 / 297 (1.7)	2 / 266 (0.8)	2.24	[0.44; 11.44]	0.333
Histological subtype					
Interaction test	**p = 0.853**				
Ductal	23 / 863 (2.7)	9 / 835 (1.1)	2.47	[1.15; 5.31]	0.020
Lobular	2 / 172 (1.2)	1 / 169 (0.6)	1.97	[0.18; 21.47]	0.580
Other	1 / 73 (1.4)	0 / 66 (0.0)	2.72	[0.11; 65.54]	0.538
Ki67 status from surgical specimen					
Interaction test	**p = 0.514**				
Ki67≤20	8 / 527 (1.5)	3 / 552 (0.5)	2.79	[0.75; 10.47]	0.128
Ki67>20	12 / 422 (2.8)	2 / 378 (0.5)	5.37	[1.21; 23.86]	0.027
Type of NSAI					
Interaction test	**p = 0.892**				
Letrozole	14 / 809 (1.7)	5 / 773 (0.6)	2.68	[0.97; 7.39]	0.058
Anastrozole	12 / 299 (4.0)	5 / 297 (1.7)	2.38	[0.85; 6.68]	0.099
Prior neo/adjuvant chemotherapy					
Interaction test	**N.E.**				
Yes	25 / 1029 (2.4)	10 / 987 (1.0)	2.40	[1.16; 4.97]	0.019
No	1 / 79 (1.3)	0 / 83 (0.0)	3.15	[0.13; 76.20]	0.480
Prior adjuvant chemotherapy					
Interaction test	**p = 0.972**				
Yes	13 / 513 (2.5)	5 / 488 (1.0)	2.47	[0.89; 6.89]	0.083
No	13 / 595 (2.2)	5 / 582 (0.9)	2.54	[0.91; 7.09]	0.074
Prior neoadjuvant chemotherapy					
Interaction test	**p = 0.876**				
Yes	12 / 546 (2.2)	5 / 538 (0.9)	2.36	[0.84; 6.67]	0.104
No	14 / 562 (2.5)	5 / 532 (0.9)	2.65	[0.96; 7.31]	0.060

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Prior endocrine therapy					
Interaction test	**p = 0.871**				
Yes	16 / 853 (1.9)	6 / 789 (0.8)	2.47	[0.97; 6.27]	0.058
No	10 / 255 (3.9)	4 / 281 (1.4)	2.75	[0.87; 8.68]	0.083
Prior mastectomy					
Interaction test	**p = 0.523**				
Yes	21 / 769 (2.7)	9 / 745 (1.2)	2.26	[1.04; 4.90]	0.039
No	5 / 339 (1.5)	1 / 325 (0.3)	4.79	[0.56; 40.81]	0.151
Prior radiotherapy					
Interaction test	**N.E.**				
Yes	23 / 1011 (2.3)	10 / 987 (1.0)	2.25	[1.07; 4.69]	0.032
No	3 / 97 (3.1)	0 / 83 (0.0)	6.00	[0.31; >99.99]	0.234

N: Number of patients
n: Number of patients with event
N.E.: Not estimable
CI: Confidence interval
RR: Relative risk
ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
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Analysis method for interaction test:
p-value from logistic regression model.
logit(proportion) = treatment + subgroup factor + treatment * subgroup factor

Analysis method for within subgroup analysis:
RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm.
ET was the reference group for treatment group comparison.

Table 5-3.2.28 SOC infections and infestations: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	ET (N = 1070)	RR	[95% CI]	p-value
Infections and infestations					
	n / N (%)	n / N (%)			
Region					
Interaction test	**p = 0.015**				
NA/WE/O	363 / 640 (56.7)	246 / 627 (39.2)	1.45	[1.28; 1.63]	<.001
ROW	217 / 468 (46.4)	175 / 443 (39.5)	1.17	[1.01; 1.36]	0.037
Geographical region					
Interaction test	**p = 0.020**				
Europe	310 / 654 (47.4)	242 / 638 (37.9)	1.25	[1.10; 1.42]	<.001
North America/Australia	137 / 213 (64.3)	74 / 194 (38.1)	1.69	[1.37; 2.07]	<.001
Asia	103 / 178 (57.9)	74 / 168 (44.0)	1.31	[1.06; 1.62]	0.011
Latin America	30 / 63 (47.6)	31 / 70 (44.3)	1.08	[0.74; 1.56]	0.700
Age group 1 at randomization					
Interaction test	**p = 0.064**				
<45	293 / 549 (53.4)	181 / 496 (36.5)	1.46	[1.27; 1.68]	<.001
45 to 54	281 / 539 (52.1)	228 / 546 (41.8)	1.25	[1.10; 1.42]	<.001
55 to 64	6 / 20 (30.0)	12 / 28 (42.9)	0.70	[0.32; 1.55]	0.379
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)					
Interaction test	**p = 0.080**				
<Median	293 / 549 (53.4)	181 / 496 (36.5)	1.46	[1.27; 1.68]	<.001
≥Median	287 / 559 (51.3)	240 / 574 (41.8)	1.23	[1.08; 1.39]	0.001
Race					
Interaction test	**p = 0.768**				
Asian	121 / 211 (57.3)	81 / 186 (43.5)	1.32	[1.08; 1.61]	0.007
Non-Asian	426 / 840 (50.7)	320 / 827 (38.7)	1.31	[1.18; 1.46]	<.001
BMI at screening					
Interaction test	**p = 0.519**				
≥25	286 / 551 (51.9)	212 / 523 (40.5)	1.28	[1.12; 1.46]	<.001
<25	284 / 542 (52.4)	205 / 535 (38.3)	1.37	[1.20; 1.56]	<.001
AJCC Anatomic Stage Group					
Interaction test	**p = 0.333**				
Group I/II	214 / 417 (51.3)	150 / 418 (35.9)	1.43	[1.22; 1.68]	<.001
Group III	366 / 691 (53.0)	271 / 652 (41.6)	1.27	[1.14; 1.43]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Anatomic stages					
Interaction test	**p = 0.121**				
IA/IB/IIA	82 / 171 (48.0)	62 / 198 (31.3)	1.53	[1.18; 1.98]	0.001
IIB	132 / 246 (53.7)	88 / 220 (40.0)	1.34	[1.10; 1.64]	0.004
IIIA	227 / 451 (50.3)	173 / 393 (44.0)	1.14	[0.99; 1.32]	0.069
IIIB	36 / 67 (53.7)	21 / 59 (35.6)	1.51	[1.00; 2.27]	0.048
IIIC	103 / 173 (59.5)	77 / 200 (38.5)	1.55	[1.25; 1.92]	<.001
Nodal status					
Interaction test	**p = 0.211**				
N0	44 / 91 (48.4)	33 / 117 (28.2)	1.71	[1.20; 2.45]	0.003
N1-N3	536 / 1017 (52.7)	387 / 950 (40.7)	1.29	[1.17; 1.42]	<.001
Histological grade at time of surgery					
Interaction test	**p = 0.713**				
Grade 1	51 / 110 (46.4)	35 / 100 (35.0)	1.32	[0.95; 1.85]	0.099
Grade 2	326 / 604 (54.0)	243 / 601 (40.4)	1.33	[1.18; 1.51]	<.001
Grade 3	166 / 297 (55.9)	103 / 266 (38.7)	1.44	[1.20; 1.73]	<.001
Histological subtype					
Interaction test	**p = 0.439**				
Ductal	462 / 863 (53.5)	331 / 835 (39.6)	1.35	[1.22; 1.50]	<.001
Lobular	84 / 172 (48.8)	61 / 169 (36.1)	1.35	[1.05; 1.74]	0.019
Other	34 / 73 (46.6)	29 / 66 (43.9)	1.06	[0.73; 1.53]	0.756
Ki67 status from surgical specimen					
Interaction test	**p = 0.257**				
Ki67≤20	271 / 527 (51.4)	228 / 552 (41.3)	1.24	[1.09; 1.42]	<.001
Ki67>20	216 / 422 (51.2)	136 / 378 (36.0)	1.42	[1.21; 1.68]	<.001
Type of NSAI					
Interaction test	**p = 0.902**				
Letrozole	411 / 809 (50.8)	291 / 773 (37.6)	1.35	[1.21; 1.51]	<.001
Anastrozole	169 / 299 (56.5)	130 / 297 (43.8)	1.29	[1.10; 1.52]	0.002
Prior neo/adjuvant chemotherapy					
Interaction test	**p = 0.936**				
Yes	545 / 1029 (53.0)	394 / 987 (39.9)	1.33	[1.21; 1.46]	<.001
No	35 / 79 (44.3)	27 / 83 (32.5)	1.36	[0.92; 2.02]	0.127
Prior adjuvant chemotherapy					
Interaction test	**p = 0.685**				
Yes	281 / 513 (54.8)	208 / 488 (42.6)	1.29	[1.13; 1.46]	<.001
No	299 / 595 (50.3)	213 / 582 (36.6)	1.37	[1.20; 1.57]	<.001
Prior neoadjuvant chemotherapy					
Interaction test	**p = 0.776**				
Yes	282 / 546 (51.6)	205 / 538 (38.1)	1.36	[1.18; 1.55]	<.001
No	298 / 562 (53.0)	216 / 532 (40.6)	1.31	[1.15; 1.49]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Prior endocrine therapy					
Interaction test	**p = 0.834**				
Yes	445 / 853 (52.2)	311 / 789 (39.4)	1.32	[1.19; 1.47]	<.001
No	135 / 255 (52.9)	110 / 281 (39.1)	1.35	[1.12; 1.63]	0.001
Prior mastectomy					
Interaction test	**p = 0.971**				
Yes	416 / 769 (54.1)	305 / 745 (40.9)	1.32	[1.19; 1.47]	<.001
No	164 / 339 (48.4)	116 / 325 (35.7)	1.36	[1.13; 1.63]	0.001
Prior radiotherapy					
Interaction test	**p = 0.956**				
Yes	528 / 1011 (52.2)	387 / 987 (39.2)	1.33	[1.21; 1.47]	<.001
No	52 / 97 (53.6)	34 / 83 (41.0)	1.31	[0.95; 1.80]	0.097

N: Number of patients
n: Number of patients with event
CI: Confidence interval
RR: Relative risk
ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
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Analysis method for interaction test:
p-value from logistic regression model.
logit(proportion) = treatment + subgroup factor + treatment * subgroup factor

Analysis method for within subgroup analysis:
RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm.
ET was the reference group for treatment group comparison.

Table 5-3.2.29 PT covid-19: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	ET (N = 1070)	RR	[95% CI]	p-value
COVID-19					
	n / N (%)	n / N (%)			
Region					
Interaction test	**p = 0.014**				
NA/WE/O	195 / 640 (30.5)	104 / 627 (16.6)	1.84	[1.49; 2.27]	<.001
ROW	111 / 468 (23.7)	85 / 443 (19.2)	1.24	[0.96; 1.59]	0.098
Geographical region					
Interaction test	**p = 0.229**				
Europe	164 / 654 (25.1)	95 / 638 (14.9)	1.68	[1.34; 2.12]	<.001
North America/Australia	65 / 213 (30.5)	34 / 194 (17.5)	1.74	[1.21; 2.51]	0.003
Asia	64 / 178 (36.0)	43 / 168 (25.6)	1.40	[1.02; 1.94]	0.040
Latin America	13 / 63 (20.6)	17 / 70 (24.3)	0.85	[0.45; 1.61]	0.616
Age group 1 at randomization					
Interaction test	**p = 0.272**				
<45	163 / 549 (29.7)	85 / 496 (17.1)	1.73	[1.37; 2.19]	<.001
45 to 54	141 / 539 (26.2)	100 / 546 (18.3)	1.43	[1.14; 1.79]	0.002
55 to 64	2 / 20 (10.0)	4 / 28 (14.3)	0.70	[0.14; 3.46]	0.662
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)					
Interaction test	**p = 0.193**				
<Median	163 / 549 (29.7)	85 / 496 (17.1)	1.73	[1.37; 2.19]	<.001
≥Median	143 / 559 (25.6)	104 / 574 (18.1)	1.41	[1.13; 1.77]	0.003
Race					
Interaction test	**p = 0.537**				
Asian	74 / 211 (35.1)	48 / 186 (25.8)	1.36	[1.00; 1.84]	0.049
Non-Asian	214 / 840 (25.5)	131 / 827 (15.8)	1.61	[1.32; 1.95]	<.001
BMI at screening					
Interaction test	**p = 0.177**				
≥25	141 / 551 (25.6)	97 / 523 (18.5)	1.38	[1.10; 1.74]	0.006
<25	158 / 542 (29.2)	91 / 535 (17.0)	1.71	[1.36; 2.15]	<.001
AJCC Anatomic Stage Group					
Interaction test	**p = 0.602**				
Group I/II	104 / 417 (24.9)	70 / 418 (16.7)	1.49	[1.14; 1.95]	0.004
Group III	202 / 691 (29.2)	119 / 652 (18.3)	1.60	[1.31; 1.96]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Anatomic stages					
Interaction test	**p = 0.093**				
IA/IB/IIA	44 / 171 (25.7)	23 / 198 (11.6)	2.22	[1.40; 3.51]	<.001
IIB	60 / 246 (24.4)	47 / 220 (21.4)	1.14	[0.82; 1.60]	0.439
IIIA	123 / 451 (27.3)	73 / 393 (18.6)	1.47	[1.14; 1.90]	0.003
IIIB	15 / 67 (22.4)	9 / 59 (15.3)	1.47	[0.69; 3.10]	0.315
IIIC	64 / 173 (37.0)	37 / 200 (18.5)	2.00	[1.41; 2.84]	<.001
Nodal status					
Interaction test	**p = 0.382**				
N0	20 / 91 (22.0)	12 / 117 (10.3)	2.14	[1.11; 4.15]	0.024
N1-N3	286 / 1017 (28.1)	176 / 950 (18.5)	1.52	[1.29; 1.79]	<.001
Histological grade at time of surgery					
Interaction test	**p = 0.326**				
Grade 1	28 / 110 (25.5)	18 / 100 (18.0)	1.41	[0.84; 2.39]	0.197
Grade 2	165 / 604 (27.3)	108 / 601 (18.0)	1.52	[1.23; 1.88]	<.001
Grade 3	93 / 297 (31.3)	42 / 266 (15.8)	1.98	[1.43; 2.74]	<.001
Histological subtype					
Interaction test	**p = 0.785**				
Ductal	241 / 863 (27.9)	146 / 835 (17.5)	1.60	[1.33; 1.92]	<.001
Lobular	42 / 172 (24.4)	30 / 169 (17.8)	1.38	[0.91; 2.09]	0.135
Other	23 / 73 (31.5)	13 / 66 (19.7)	1.60	[0.88; 2.89]	0.121
Ki67 status from surgical specimen					
Interaction test	**p = 0.068**				
Ki67≤20	143 / 527 (27.1)	111 / 552 (20.1)	1.35	[1.09; 1.68]	0.007
Ki67>20	114 / 422 (27.0)	53 / 378 (14.0)	1.93	[1.43; 2.59]	<.001
Type of NSAI					
Interaction test	**p = 0.664**				
Letrozole	214 / 809 (26.5)	133 / 773 (17.2)	1.54	[1.27; 1.86]	<.001
Anastrozole	92 / 299 (30.8)	56 / 297 (18.9)	1.63	[1.22; 2.18]	<.001
Prior neo/adjuvant chemotherapy					
Interaction test	**p = 0.256**				
Yes	284 / 1029 (27.6)	179 / 987 (18.1)	1.52	[1.29; 1.80]	<.001
No	22 / 79 (27.8)	10 / 83 (12.0)	2.31	[1.17; 4.57]	0.016
Prior adjuvant chemotherapy					
Interaction test	**p = 0.304**				
Yes	148 / 513 (28.8)	99 / 488 (20.3)	1.42	[1.14; 1.78]	0.002
No	158 / 595 (26.6)	90 / 582 (15.5)	1.72	[1.36; 2.17]	<.001
Prior neoadjuvant chemotherapy					
Interaction test	**p = 0.975**				
Yes	144 / 546 (26.4)	90 / 538 (16.7)	1.58	[1.25; 1.99]	<.001
No	162 / 562 (28.8)	99 / 532 (18.6)	1.55	[1.24; 1.93]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Prior endocrine therapy					
Interaction test	**p = 0.638**				
Yes	246 / 853 (28.8)	144 / 789 (18.3)	1.58	[1.32; 1.89]	<.001
No	60 / 255 (23.5)	45 / 281 (16.0)	1.47	[1.04; 2.08]	0.030
Prior mastectomy					
Interaction test	**p = 0.370**				
Yes	215 / 769 (28.0)	140 / 745 (18.8)	1.49	[1.23; 1.79]	<.001
No	91 / 339 (26.8)	49 / 325 (15.1)	1.78	[1.30; 2.43]	<.001
Prior radiotherapy					
Interaction test	**p = 0.568**				
Yes	278 / 1011 (27.5)	176 / 987 (17.8)	1.54	[1.30; 1.82]	<.001
No	28 / 97 (28.9)	13 / 83 (15.7)	1.84	[1.02; 3.32]	0.042

N: Number of patients
n: Number of patients with event
CI: Confidence interval
RR: Relative risk
ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
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Analysis method for interaction test:
p-value from logistic regression model.
logit(proportion) = treatment + subgroup factor + treatment * subgroup factor

Analysis method for within subgroup analysis:
RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm.
ET was the reference group for treatment group comparison.

Table 5-3.2.30 PT upper respiratory tract infection: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	ET (N = 1070)	RR	[95% CI]	p-value
Upper respiratory tract infection					
	n / N (%)	n / N (%)			
Region					
Interaction test	**p = 0.157**				
NA/WE/O	37 / 640 (5.8)	11 / 627 (1.8)	3.30	[1.70; 6.40]	<.001
ROW	35 / 468 (7.5)	19 / 443 (4.3)	1.74	[1.01; 3.00]	0.045
Geographical region					
Interaction test	**p = 0.871**				
Europe	20 / 654 (3.1)	8 / 638 (1.3)	2.44	[1.08; 5.50]	0.032
North America/Australia	25 / 213 (11.7)	8 / 194 (4.1)	2.85	[1.32; 6.16]	0.008
Asia	25 / 178 (14.0)	13 / 168 (7.7)	1.82	[0.96; 3.43]	0.066
Latin America	2 / 63 (3.2)	1 / 70 (1.4)	2.22	[0.21; 23.92]	0.510
Age group 1 at randomization					
Interaction test	**p = 0.407**				
<45	43 / 549 (7.8)	14 / 496 (2.8)	2.77	[1.54; 5.01]	<.001
45 to 54	29 / 539 (5.4)	15 / 546 (2.7)	1.96	[1.06; 3.61]	0.031
55 to 64	0 / 20 (0.0)	1 / 28 (3.6)	0.46	[0.02; 10.75]	0.629
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)					
Interaction test	**p = 0.338**				
<Median	43 / 549 (7.8)	14 / 496 (2.8)	2.77	[1.54; 5.01]	<.001
≥Median	29 / 559 (5.2)	16 / 574 (2.8)	1.86	[1.02; 3.39]	0.042
Race					
Interaction test	**p = 0.320**				
Asian	25 / 211 (11.8)	13 / 186 (7.0)	1.70	[0.89; 3.22]	0.106
Non-Asian	47 / 840 (5.6)	17 / 827 (2.1)	2.72	[1.58; 4.70]	<.001
BMI at screening					
Interaction test	**p = 0.017**				
≥25	27 / 551 (4.9)	19 / 523 (3.6)	1.35	[0.76; 2.40]	0.307
<25	43 / 542 (7.9)	11 / 535 (2.1)	3.86	[2.01; 7.40]	<.001
AJCC Anatomic Stage Group					
Interaction test	**p = 0.279**				
Group I/II	16 / 417 (3.8)	4 / 418 (1.0)	4.01	[1.35; 11.89]	0.012
Group III	56 / 691 (8.1)	26 / 652 (4.0)	2.03	[1.29; 3.20]	0.002

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Anatomic stages					
Interaction test	**p = 0.199**				
IA/IB/IIA	5 / 171 (2.9)	3 / 198 (1.5)	1.93	[0.47; 7.96]	0.363
IIB	11 / 246 (4.5)	1 / 220 (0.5)	9.84	[1.28; 75.58]	0.028
IIIA	30 / 451 (6.7)	18 / 393 (4.6)	1.45	[0.82; 2.56]	0.198
IIIB	9 / 67 (13.4)	1 / 59 (1.7)	7.93	[1.03; 60.72]	0.046
IIIC	17 / 173 (9.8)	7 / 200 (3.5)	2.81	[1.19; 6.61]	0.018
Nodal status					
Interaction test	**p = 0.255**				
N0	2 / 91 (2.2)	3 / 117 (2.6)	0.86	[0.15; 5.02]	0.864
N1-N3	70 / 1017 (6.9)	27 / 950 (2.8)	2.42	[1.57; 3.74]	<.001
Histological grade at time of surgery					
Interaction test	**p = 0.810**				
Grade 1	3 / 110 (2.7)	2 / 100 (2.0)	1.36	[0.23; 7.99]	0.731
Grade 2	42 / 604 (7.0)	17 / 601 (2.8)	2.46	[1.42; 4.27]	0.001
Grade 3	25 / 297 (8.4)	10 / 266 (3.8)	2.24	[1.10; 4.57]	0.027
Histological subtype					
Interaction test	**p = 0.123**				
Ductal	54 / 863 (6.3)	22 / 835 (2.6)	2.37	[1.46; 3.86]	<.001
Lobular	12 / 172 (7.0)	2 / 169 (1.2)	5.90	[1.34; 25.95]	0.019
Other	6 / 73 (8.2)	6 / 66 (9.1)	0.90	[0.31; 2.67]	0.855
Ki67 status from surgical specimen					
Interaction test	**p = 0.022**				
Ki67≤20	39 / 527 (7.4)	12 / 552 (2.2)	3.40	[1.80; 6.43]	<.001
Ki67>20	23 / 422 (5.5)	17 / 378 (4.5)	1.21	[0.66; 2.23]	0.538
Type of NSAI					
Interaction test	**p = 0.744**				
Letrozole	51 / 809 (6.3)	20 / 773 (2.6)	2.44	[1.47; 4.05]	<.001
Anastrozole	21 / 299 (7.0)	10 / 297 (3.4)	2.09	[1.00; 4.35]	0.050
Prior neo/adjuvant chemotherapy					
Interaction test	**p = 0.404**				
Yes	70 / 1029 (6.8)	28 / 987 (2.8)	2.40	[1.56; 3.68]	<.001
No	2 / 79 (2.5)	2 / 83 (2.4)	1.05	[0.15; 7.28]	0.960
Prior adjuvant chemotherapy					
Interaction test	**p = 0.285**				
Yes	33 / 513 (6.4)	17 / 488 (3.5)	1.85	[1.04; 3.27]	0.036
No	39 / 595 (6.6)	13 / 582 (2.2)	2.93	[1.58; 5.44]	<.001
Prior neoadjuvant chemotherapy					
Interaction test	**p = 0.443**				
Yes	41 / 546 (7.5)	15 / 538 (2.8)	2.69	[1.51; 4.81]	<.001
No	31 / 562 (5.5)	15 / 532 (2.8)	1.96	[1.07; 3.58]	0.030

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Prior endocrine therapy					
Interaction test	**p = 0.516**				
Yes	57 / 853 (6.7)	21 / 789 (2.7)	2.51	[1.54; 4.10]	<.001
No	15 / 255 (5.9)	9 / 281 (3.2)	1.84	[0.82; 4.12]	0.141
Prior mastectomy					
Interaction test	**p = 0.715**				
Yes	60 / 769 (7.8)	26 / 745 (3.5)	2.24	[1.43; 3.50]	<.001
No	12 / 339 (3.5)	4 / 325 (1.2)	2.88	[0.94; 8.83]	0.065
Prior radiotherapy					
Interaction test	**p = 0.148**				
Yes	71 / 1011 (7.0)	28 / 987 (2.8)	2.48	[1.61; 3.80]	<.001
No	1 / 97 (1.0)	2 / 83 (2.4)	0.43	[0.04; 4.63]	0.485

N: Number of patients
n: Number of patients with event
CI: Confidence interval
RR: Relative risk
ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
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Analysis method for interaction test:
p-value from logistic regression model.
logit(proportion) = treatment + subgroup factor + treatment * subgroup factor

Analysis method for within subgroup analysis:
RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm.
ET was the reference group for treatment group comparison.

Table 5-3.2.31 PT sinusitis: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	ET (N = 1070)	RR	[95% CI]	p-value
Sinusitis					
	n / N (%)	n / N (%)			
Region					
Interaction test	**p = 0.577**				
NA/WE/O	25 / 640 (3.9)	9 / 627 (1.4)	2.72	[1.28; 5.78]	0.009
ROW	10 / 468 (2.1)	5 / 443 (1.1)	1.89	[0.65; 5.50]	0.240
Geographical region					
Interaction test	**p = 0.308**				
Europe	21 / 654 (3.2)	6 / 638 (0.9)	3.41	[1.39; 8.40]	0.008
North America/Australia	11 / 213 (5.2)	5 / 194 (2.6)	2.00	[0.71; 5.66]	0.190
Asia	1 / 178 (0.6)	0 / 168 (0.0)	2.83	[0.12; 69.05]	0.523
Latin America	2 / 63 (3.2)	3 / 70 (4.3)	0.74	[0.13; 4.29]	0.738
Age group 1 at randomization					
Interaction test	**p = 0.530**				
<45	20 / 549 (3.6)	9 / 496 (1.8)	2.01	[0.92; 4.37]	0.079
45 to 54	15 / 539 (2.8)	5 / 546 (0.9)	3.04	[1.11; 8.30]	0.030
55 to 64	0 / 20 (0.0)	0 / 28 (0.0)	N.E.	N.E.	N.E.
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)					
Interaction test	**p = 0.517**				
<Median	20 / 549 (3.6)	9 / 496 (1.8)	2.01	[0.92; 4.37]	0.079
≥Median	15 / 559 (2.7)	5 / 574 (0.9)	3.08	[1.13; 8.42]	0.028
Race					
Interaction test	**N.E.**				
Asian	3 / 211 (1.4)	0 / 186 (0.0)	6.17	[0.32; >99.99]	0.228
Non-Asian	32 / 840 (3.8)	14 / 827 (1.7)	2.25	[1.21; 4.19]	0.010
BMI at screening					
Interaction test	**p = 0.407**				
≥25	18 / 551 (3.3)	5 / 523 (1.0)	3.42	[1.28; 9.14]	0.014
<25	16 / 542 (3.0)	8 / 535 (1.5)	1.97	[0.85; 4.57]	0.113
AJCC Anatomic Stage Group					
Interaction test	**p = 0.984**				
Group I/II	17 / 417 (4.1)	7 / 418 (1.7)	2.43	[1.02; 5.81]	0.045
Group III	18 / 691 (2.6)	7 / 652 (1.1)	2.43	[1.02; 5.77]	0.045

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Anatomic stages					
Interaction test	**p = 0.269**				
IA/IB/IIA	4 / 171 (2.3)	5 / 198 (2.5)	0.93	[0.25; 3.39]	0.908
IIB	13 / 246 (5.3)	2 / 220 (0.9)	5.81	[1.33; 25.47]	0.020
IIIA	13 / 451 (2.9)	6 / 393 (1.5)	1.89	[0.72; 4.92]	0.193
IIIB	1 / 67 (1.5)	0 / 59 (0.0)	2.65	[0.11; 63.76]	0.549
IIIC	4 / 173 (2.3)	1 / 200 (0.5)	4.62	[0.52; 40.98]	0.169
Nodal status					
Interaction test	**p = 0.221**				
N0	2 / 91 (2.2)	3 / 117 (2.6)	0.86	[0.15; 5.02]	0.864
N1-N3	33 / 1017 (3.2)	11 / 950 (1.2)	2.80	[1.42; 5.51]	0.003
Histological grade at time of surgery					
Interaction test	**p = 0.699**				
Grade 1	4 / 110 (3.6)	0 / 100 (0.0)	8.19	[0.45; >99.99]	0.157
Grade 2	17 / 604 (2.8)	9 / 601 (1.5)	1.88	[0.84; 4.18]	0.122
Grade 3	11 / 297 (3.7)	4 / 266 (1.5)	2.46	[0.79; 7.64]	0.119
Histological subtype					
Interaction test	**p = 0.655**				
Ductal	28 / 863 (3.2)	12 / 835 (1.4)	2.26	[1.16; 4.41]	0.017
Lobular	3 / 172 (1.7)	2 / 169 (1.2)	1.47	[0.25; 8.71]	0.669
Other	4 / 73 (5.5)	0 / 66 (0.0)	8.15	[0.45; >99.99]	0.157
Ki67 status from surgical specimen					
Interaction test	**p = 0.649**				
Ki67≤20	11 / 527 (2.1)	5 / 552 (0.9)	2.30	[0.81; 6.59]	0.119
Ki67>20	11 / 422 (2.6)	6 / 378 (1.6)	1.64	[0.61; 4.40]	0.324
Type of NSAI					
Interaction test	**p = 0.027**				
Letrozole	23 / 809 (2.8)	4 / 773 (0.5)	5.49	[1.91; 15.81]	0.002
Anastrozole	12 / 299 (4.0)	10 / 297 (3.4)	1.19	[0.52; 2.72]	0.676
Prior neo/adjuvant chemotherapy					
Interaction test	**p = 0.905**				
Yes	33 / 1029 (3.2)	13 / 987 (1.3)	2.43	[1.29; 4.60]	0.006
No	2 / 79 (2.5)	1 / 83 (1.2)	2.10	[0.19; 22.72]	0.541
Prior adjuvant chemotherapy					
Interaction test	**p = 0.958**				
Yes	18 / 513 (3.5)	7 / 488 (1.4)	2.45	[1.03; 5.80]	0.042
No	17 / 595 (2.9)	7 / 582 (1.2)	2.38	[0.99; 5.69]	0.052
Prior neoadjuvant chemotherapy					
Interaction test	**p = 0.956**				
Yes	15 / 546 (2.7)	6 / 538 (1.1)	2.46	[0.96; 6.30]	0.060
No	20 / 562 (3.6)	8 / 532 (1.5)	2.37	[1.05; 5.33]	0.037

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Prior endocrine therapy					
Interaction test	**p = 0.991**				
Yes	24 / 853 (2.8)	9 / 789 (1.1)	2.47	[1.15; 5.27]	0.020
No	11 / 255 (4.3)	5 / 281 (1.8)	2.42	[0.85; 6.88]	0.096
Prior mastectomy					
Interaction test	**p = 0.768**				
Yes	26 / 769 (3.4)	11 / 745 (1.5)	2.29	[1.14; 4.60]	0.020
No	9 / 339 (2.7)	3 / 325 (0.9)	2.88	[0.79; 10.53]	0.111
Prior radiotherapy					
Interaction test	**p = 0.565**				
Yes	30 / 1011 (3.0)	13 / 987 (1.3)	2.25	[1.18; 4.29]	0.014
No	5 / 97 (5.2)	1 / 83 (1.2)	4.28	[0.51; 35.89]	0.180

N: Number of patients
n: Number of patients with event
N.E.: Not estimable
CI: Confidence interval
RR: Relative risk
ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
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Analysis method for interaction test:
p-value from logistic regression model.
logit(proportion) = treatment + subgroup factor + treatment * subgroup factor

Analysis method for within subgroup analysis:
RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm.
ET was the reference group for treatment group comparison.

Table 5-3.2.32 PT oral herpes: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	ET (N = 1070)	RR	[95% CI]	p-value
Oral herpes					
	n / N (%)	n / N (%)			
Region					
Interaction test	**N.E.**				
NA/WE/O	20 / 640 (3.1)	2 / 627 (0.3)	9.80	[2.30; 41.74]	0.002
ROW	2 / 468 (0.4)	0 / 443 (0.0)	4.73	[0.23; 98.32]	0.315
Geographical region					
Interaction test	**N.E.**				
Europe	16 / 654 (2.4)	0 / 638 (0.0)	32.19	[1.94; >99.99]	0.016
North America/Australia	6 / 213 (2.8)	2 / 194 (1.0)	2.73	[0.56; 13.38]	0.215
Asia	0 / 178 (0.0)	0 / 168 (0.0)	N.E.	N.E.	N.E.
Latin America	0 / 63 (0.0)	0 / 70 (0.0)	N.E.	N.E.	N.E.
Age group 1 at randomization					
Interaction test	**p = 0.644**				
<45	8 / 549 (1.5)	1 / 496 (0.2)	7.23	[0.91; 57.58]	0.062
45 to 54	14 / 539 (2.6)	1 / 546 (0.2)	14.18	[1.87; >99.99]	0.010
55 to 64	0 / 20 (0.0)	0 / 28 (0.0)	N.E.	N.E.	N.E.
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)					
Interaction test	**p = 0.638**				
<Median	8 / 549 (1.5)	1 / 496 (0.2)	7.23	[0.91; 57.58]	0.062
≥Median	14 / 559 (2.5)	1 / 574 (0.2)	14.38	[1.90; >99.99]	0.010
Race					
Interaction test	**N.E.**				
Asian	0 / 211 (0.0)	0 / 186 (0.0)	N.E.	N.E.	N.E.
Non-Asian	19 / 840 (2.3)	2 / 827 (0.2)	9.35	[2.19; 40.03]	0.003
BMI at screening					
Interaction test	**N.E.**				
≥25	11 / 551 (2.0)	0 / 523 (0.0)	21.83	[1.29; >99.99]	0.033
<25	10 / 542 (1.8)	2 / 535 (0.4)	4.94	[1.09; 22.42]	0.039
AJCC Anatomic Stage Group					
Interaction test	**N.E.**				
Group I/II	11 / 417 (2.6)	2 / 418 (0.5)	5.51	[1.23; 24.72]	0.026
Group III	11 / 691 (1.6)	0 / 652 (0.0)	21.70	[1.28; >99.99]	0.033

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Anatomic stages					
Interaction test	**N.E.**				
IA/IB/IIA	3 / 171 (1.8)	0 / 198 (0.0)	8.10	[0.42; >99.99]	0.165
IIB	8 / 246 (3.3)	2 / 220 (0.9)	3.58	[0.77; 16.67]	0.104
IIIA	8 / 451 (1.8)	0 / 393 (0.0)	14.82	[0.86; >99.99]	0.064
IIIB	1 / 67 (1.5)	0 / 59 (0.0)	2.65	[0.11; 63.76]	0.549
IIIC	2 / 173 (1.2)	0 / 200 (0.0)	5.78	[0.28; >99.99]	0.257
Nodal status					
Interaction test	**N.E.**				
N0	0 / 91 (0.0)	0 / 117 (0.0)	N.E.	N.E.	N.E.
N1-N3	22 / 1017 (2.2)	2 / 950 (0.2)	10.28	[2.42; 43.58]	0.002
Histological grade at time of surgery					
Interaction test	**N.E.**				
Grade 1	2 / 110 (1.8)	0 / 100 (0.0)	4.55	[0.22; 93.64]	0.326
Grade 2	14 / 604 (2.3)	0 / 601 (0.0)	28.86	[1.73; >99.99]	0.019
Grade 3	6 / 297 (2.0)	2 / 266 (0.8)	2.69	[0.55; 13.20]	0.224
Histological subtype					
Interaction test	**N.E.**				
Ductal	18 / 863 (2.1)	2 / 835 (0.2)	8.71	[2.03; 37.41]	0.004
Lobular	4 / 172 (2.3)	0 / 169 (0.0)	8.84	[0.48; >99.99]	0.143
Other	0 / 73 (0.0)	0 / 66 (0.0)	N.E.	N.E.	N.E.
Ki67 status from surgical specimen					
Interaction test	**N.E.**				
Ki67≤20	12 / 527 (2.3)	0 / 552 (0.0)	26.18	[1.55; >99.99]	0.023
Ki67>20	6 / 422 (1.4)	0 / 378 (0.0)	11.65	[0.66; >99.99]	0.094
Type of NSAI					
Interaction test	**p = 0.629**				
Letrozole	15 / 809 (1.9)	1 / 773 (0.1)	14.33	[1.90; >99.99]	0.010
Anastrozole	7 / 299 (2.3)	1 / 297 (0.3)	6.95	[0.86; 56.17]	0.069
Prior neo/adjuvant chemotherapy					
Interaction test	**N.E.**				
Yes	22 / 1029 (2.1)	2 / 987 (0.2)	10.55	[2.49; 44.75]	0.001
No	0 / 79 (0.0)	0 / 83 (0.0)	N.E.	N.E.	N.E.
Prior adjuvant chemotherapy					
Interaction test	**N.E.**				
Yes	14 / 513 (2.7)	2 / 488 (0.4)	6.66	[1.52; 29.15]	0.012
No	8 / 595 (1.3)	0 / 582 (0.0)	16.63	[0.96; >99.99]	0.053
Prior neoadjuvant chemotherapy					
Interaction test	**N.E.**				
Yes	9 / 546 (1.6)	0 / 538 (0.0)	18.72	[1.09; >99.99]	0.043
No	13 / 562 (2.3)	2 / 532 (0.4)	6.15	[1.40; 27.14]	0.016

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Prior endocrine therapy					
Interaction test	**N.E.**				
Yes	18 / 853 (2.1)	2 / 789 (0.3)	8.32	[1.94; 35.76]	0.004
No	4 / 255 (1.6)	0 / 281 (0.0)	9.91	[0.54; >99.99]	0.123
Prior mastectomy					
Interaction test	**N.E.**				
Yes	14 / 769 (1.8)	2 / 745 (0.3)	6.78	[1.55; 29.74]	0.011
No	8 / 339 (2.4)	0 / 325 (0.0)	16.30	[0.94; >99.99]	0.055
Prior radiotherapy					
Interaction test	**N.E.**				
Yes	22 / 1011 (2.2)	2 / 987 (0.2)	10.74	[2.53; 45.55]	0.001
No	0 / 97 (0.0)	0 / 83 (0.0)	N.E.	N.E.	N.E.

N: Number of patients
n: Number of patients with event
N.E.: Not estimable
CI: Confidence interval
RR: Relative risk
ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
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Analysis method for interaction test:
p-value from logistic regression model.
logit(proportion) = treatment + subgroup factor + treatment * subgroup factor

Analysis method for within subgroup analysis:
RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm.
ET was the reference group for treatment group comparison.

Table 5-3.2.33 PT cellulitis: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	ET (N = 1070)	RR	[95% CI]	p-value
Cellulitis					
	n / N (%)	n / N (%)			
Region					
Interaction test	**p = 0.594**				
NA/WE/O	12 / 640 (1.9)	3 / 627 (0.5)	3.92	[1.11; 13.82]	0.034
ROW	2 / 468 (0.4)	1 / 443 (0.2)	1.89	[0.17; 20.80]	0.602
Geographical region					
The subgroup analysis is not presented as all subgroups have less than 10 events.					
Age group 1 at randomization					
Interaction test	**p = 0.963**				
<45	4 / 549 (0.7)	1 / 496 (0.2)	3.61	[0.41; 32.22]	0.250
45 to 54	10 / 539 (1.9)	3 / 546 (0.5)	3.38	[0.93; 12.20]	0.063
55 to 64	0 / 20 (0.0)	0 / 28 (0.0)	N.E.	N.E.	N.E.
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)					
Interaction test	**p = 0.971**				
<Median	4 / 549 (0.7)	1 / 496 (0.2)	3.61	[0.41; 32.22]	0.250
≥Median	10 / 559 (1.8)	3 / 574 (0.5)	3.42	[0.95; 12.37]	0.061
Race					
Interaction test	**N.E.**				
Asian	5 / 211 (2.4)	0 / 186 (0.0)	9.70	[0.54; >99.99]	0.123
Non-Asian	8 / 840 (1.0)	4 / 827 (0.5)	1.97	[0.60; 6.51]	0.267
BMI at screening					
Interaction test	**N.E.**				
≥25	11 / 551 (2.0)	4 / 523 (0.8)	2.61	[0.84; 8.15]	0.098
<25	2 / 542 (0.4)	0 / 535 (0.0)	4.94	[0.24; >99.99]	0.302
AJCC Anatomic Stage Group					
Interaction test	**p = 0.854**				
Group I/II	4 / 417 (1.0)	1 / 418 (0.2)	4.01	[0.45; 35.72]	0.213
Group III	10 / 691 (1.4)	3 / 652 (0.5)	3.15	[0.87; 11.38]	0.081
Anatomic stages					
Interaction test	**p = 0.955**				
IA/IB/IIA	1 / 171 (0.6)	0 / 198 (0.0)	3.47	[0.14; 84.65]	0.445
IIB	3 / 246 (1.2)	1 / 220 (0.5)	2.68	[0.28; 25.60]	0.391
IIIA	8 / 451 (1.8)	2 / 393 (0.5)	3.49	[0.74; 16.32]	0.113
IIIB	0 / 67 (0.0)	0 / 59 (0.0)	N.E.	N.E.	N.E.
IIIC	2 / 173 (1.2)	1 / 200 (0.5)	2.31	[0.21; 25.28]	0.492

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Nodal status					
Interaction test	**N.E.**				
N0	1 / 91 (1.1)	0 / 117 (0.0)	3.85	[0.16; 93.36]	0.408
N1-N3	13 / 1017 (1.3)	4 / 950 (0.4)	3.04	[0.99; 9.28]	0.051
Histological grade at time of surgery					
Interaction test	**p = 0.083**				
Grade 1	2 / 110 (1.8)	0 / 100 (0.0)	4.55	[0.22; 93.64]	0.326
Grade 2	9 / 604 (1.5)	1 / 601 (0.2)	8.96	[1.14; 70.47]	0.037
Grade 3	3 / 297 (1.0)	3 / 266 (1.1)	0.90	[0.18; 4.40]	0.892
Histological subtype					
Interaction test	**N.E.**				
Ductal	13 / 863 (1.5)	3 / 835 (0.4)	4.19	[1.20; 14.66]	0.025
Lobular	1 / 172 (0.6)	0 / 169 (0.0)	2.95	[0.12; 71.86]	0.507
Other	0 / 73 (0.0)	1 / 66 (1.5)	0.30	[0.01; 7.28]	0.461
Ki67 status from surgical specimen					
Interaction test	**p = 0.748**				
Ki67≤20	8 / 527 (1.5)	2 / 552 (0.4)	4.19	[0.89; 19.64]	0.069
Ki67>20	3 / 422 (0.7)	1 / 378 (0.3)	2.69	[0.28; 25.72]	0.391
Type of NSAI					
Interaction test	**p = 0.450**				
Letrozole	10 / 809 (1.2)	2 / 773 (0.3)	4.78	[1.05; 21.73]	0.043
Anastrozole	4 / 299 (1.3)	2 / 297 (0.7)	1.99	[0.37; 10.76]	0.426
Prior neo/adjuvant chemotherapy					
Interaction test	**N.E.**				
Yes	14 / 1029 (1.4)	4 / 987 (0.4)	3.36	[1.11; 10.16]	0.032
No	0 / 79 (0.0)	0 / 83 (0.0)	N.E.	N.E.	N.E.
Prior adjuvant chemotherapy					
Interaction test	**p = 0.858**				
Yes	3 / 513 (0.6)	1 / 488 (0.2)	2.85	[0.30; 27.34]	0.363
No	11 / 595 (1.8)	3 / 582 (0.5)	3.59	[1.01; 12.79]	0.049
Prior neoadjuvant chemotherapy					
Interaction test	**p = 0.849**				
Yes	11 / 546 (2.0)	3 / 538 (0.6)	3.61	[1.01; 12.88]	0.048
No	3 / 562 (0.5)	1 / 532 (0.2)	2.84	[0.30; 27.22]	0.365
Prior endocrine therapy					
Interaction test	**N.E.**				
Yes	10 / 853 (1.2)	4 / 789 (0.5)	2.31	[0.73; 7.34]	0.155
No	4 / 255 (1.6)	0 / 281 (0.0)	9.91	[0.54; >99.99]	0.123
Prior mastectomy					
Interaction test	**p = 0.150**				
Yes	12 / 769 (1.6)	2 / 745 (0.3)	5.81	[1.31; 25.88]	0.021
No	2 / 339 (0.6)	2 / 325 (0.6)	0.96	[0.14; 6.77]	0.966

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Prior radiotherapy					
Interaction test	**N.E.**				
Yes	13 / 1011 (1.3)	4 / 987 (0.4)	3.17	[1.04; 9.70]	0.043
No	1 / 97 (1.0)	0 / 83 (0.0)	2.57	[0.11; 62.29]	0.561

N: Number of patients
n: Number of patients with event
N.E.: Not estimable
CI: Confidence interval
RR: Relative risk
ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
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Analysis method for interaction test:
p-value from logistic regression model.
logit(proportion) = treatment + subgroup factor + treatment * subgroup factor

Analysis method for within subgroup analysis:
RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm.
ET was the reference group for treatment group comparison.

Table 5-3.2.34 PT conjunctivitis: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Conjunctivitis					
	n / N (%)	**n / N (%)**			
Region					
Interaction test	**N.E.**				
NA/WE/O	11 / 640 (1.7)	3 / 627 (0.5)	3.59	[1.01; 12.81]	0.049
ROW	3 / 468 (0.6)	0 / 443 (0.0)	6.63	[0.34; >99.99]	0.211
Geographical region					
Interaction test	**N.E.**				
Europe	11 / 654 (1.7)	3 / 638 (0.5)	3.58	[1.00; 12.76]	0.050
North America/Australia	2 / 213 (0.9)	0 / 194 (0.0)	4.56	[0.22; 94.31]	0.327
Asia	1 / 178 (0.6)	0 / 168 (0.0)	2.83	[0.12; 69.05]	0.523
Latin America	0 / 63 (0.0)	0 / 70 (0.0)	N.E.	N.E.	N.E.
Age group 1 at randomization					
The subgroup analysis is not presented as all subgroups have less than 10 events.					
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)					
The subgroup analysis is not presented as all subgroups have less than 10 events.					
Race					
Interaction test	**N.E.**				
Asian	1 / 211 (0.5)	0 / 186 (0.0)	2.65	[0.11; 64.57]	0.550
Non-Asian	13 / 840 (1.5)	3 / 827 (0.4)	4.27	[1.22; 14.92]	0.023
BMI at screening					
Interaction test	**p = 0.636**				
≥25	3 / 551 (0.5)	1 / 523 (0.2)	2.85	[0.30; 27.29]	0.364
<25	11 / 542 (2.0)	2 / 535 (0.4)	5.43	[1.21; 24.38]	0.027
AJCC Anatomic Stage Group					
Interaction test	**p = 0.903**				
Group I/II	4 / 417 (1.0)	1 / 418 (0.2)	4.01	[0.45; 35.72]	0.213
Group III	10 / 691 (1.4)	2 / 652 (0.3)	4.72	[1.04; 21.45]	0.045
Anatomic stages					
The subgroup analysis is not presented as all subgroups have less than 10 events.					

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Nodal status					
Interaction test	**N.E.**				
N0	0 / 91 (0.0)	0 / 117 (0.0)	N.E.	N.E.	N.E.
N1-N3	14 / 1017 (1.4)	3 / 950 (0.3)	4.36	[1.26; 15.12]	0.020
Histological grade at time of surgery					
Interaction test	**p = 0.399**				
Grade 1	1 / 110 (0.9)	0 / 100 (0.0)	2.73	[0.11; 66.25]	0.537
Grade 2	10 / 604 (1.7)	1 / 601 (0.2)	9.95	[1.28; 77.49]	0.028
Grade 3	3 / 297 (1.0)	1 / 266 (0.4)	2.69	[0.28; 25.67]	0.391
Histological subtype					
Interaction test	**p = 0.672**				
Ductal	11 / 863 (1.3)	2 / 835 (0.2)	5.32	[1.18; 23.94]	0.029
Lobular	3 / 172 (1.7)	1 / 169 (0.6)	2.95	[0.31; 28.06]	0.347
Other	0 / 73 (0.0)	0 / 66 (0.0)	N.E.	N.E.	N.E.
Ki67 status from surgical specimen					
The subgroup analysis is not presented as all subgroups have less than 10 events.					
Type of NSAI					
Interaction test	**p = 0.089**				
Letrozole	12 / 809 (1.5)	1 / 773 (0.1)	11.47	[1.49; 87.97]	0.019
Anastrozole	2 / 299 (0.7)	2 / 297 (0.7)	0.99	[0.14; 7.01]	0.995
Prior neo/adjuvant chemotherapy					
Interaction test	**N.E.**				
Yes	13 / 1029 (1.3)	3 / 987 (0.3)	4.16	[1.19; 14.54]	0.026
No	1 / 79 (1.3)	0 / 83 (0.0)	3.15	[0.13; 76.20]	0.480
Prior adjuvant chemotherapy					
The subgroup analysis is not presented as all subgroups have less than 10 events.					
Prior neoadjuvant chemotherapy					
The subgroup analysis is not presented as all subgroups have less than 10 events.					
Prior endocrine therapy					
Interaction test	**p = 0.054**				
Yes	13 / 853 (1.5)	1 / 789 (0.1)	12.02	[1.58; 91.71]	0.016
No	1 / 255 (0.4)	2 / 281 (0.7)	0.55	[0.05; 6.04]	0.626

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Prior mastectomy					
Interaction test	**N.E.**				
Yes	10 / 769 (1.3)	3 / 745 (0.4)	3.23	[0.89; 11.69]	0.074
No	4 / 339 (1.2)	0 / 325 (0.0)	8.63	[0.47; >99.99]	0.148
Prior radiotherapy					
Interaction test	**N.E.**				
Yes	13 / 1011 (1.3)	3 / 987 (0.3)	4.23	[1.21; 14.80]	0.024
No	1 / 97 (1.0)	0 / 83 (0.0)	2.57	[0.11; 62.29]	0.561

N: Number of patients
n: Number of patients with event
N.E.: Not estimable
CI: Confidence interval
RR: Relative risk
ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
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Analysis method for interaction test:
p-value from logistic regression model.
logit(proportion) = treatment + subgroup factor + treatment * subgroup factor

Analysis method for within subgroup analysis:
RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm.
ET was the reference group for treatment group comparison.

Table 5-3.2.35 SOC gastrointestinal disorders: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	ET (N = 1070)	RR	[95% CI]	p-value
Gastrointestinal disorders					
	n / N (%)	n / N (%)			
Region					
Interaction test	**p = <.001**				
NA/WE/O	409 / 640 (63.9)	230 / 627 (36.7)	1.74	[1.55; 1.96]	<.001
ROW	169 / 468 (36.1)	119 / 443 (26.9)	1.34	[1.11; 1.63]	0.003
Geographical region					
Interaction test	**p = 0.001**				
Europe	310 / 654 (47.4)	188 / 638 (29.5)	1.61	[1.39; 1.86]	<.001
North America/Australia	162 / 213 (76.1)	82 / 194 (42.3)	1.80	[1.50; 2.16]	<.001
Asia	82 / 178 (46.1)	51 / 168 (30.4)	1.52	[1.15; 2.01]	0.003
Latin America	24 / 63 (38.1)	28 / 70 (40.0)	0.95	[0.62; 1.46]	0.822
Age group 1 at randomization					
Interaction test	**p = 0.557**				
<45	279 / 549 (50.8)	152 / 496 (30.6)	1.66	[1.42; 1.94]	<.001
45 to 54	291 / 539 (54.0)	187 / 546 (34.2)	1.58	[1.37; 1.81]	<.001
55 to 64	8 / 20 (40.0)	10 / 28 (35.7)	1.12	[0.54; 2.33]	0.761
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)					
Interaction test	**p = 0.734**				
<Median	279 / 549 (50.8)	152 / 496 (30.6)	1.66	[1.42; 1.94]	<.001
≥Median	299 / 559 (53.5)	197 / 574 (34.3)	1.56	[1.36; 1.79]	<.001
Race					
Interaction test	**p = 0.933**				
Asian	106 / 211 (50.2)	57 / 186 (30.6)	1.64	[1.27; 2.11]	<.001
Non-Asian	435 / 840 (51.8)	268 / 827 (32.4)	1.60	[1.42; 1.80]	<.001
BMI at screening					
Interaction test	**p = 0.972**				
≥25	298 / 551 (54.1)	180 / 523 (34.4)	1.57	[1.36; 1.81]	<.001
<25	272 / 542 (50.2)	165 / 535 (30.8)	1.63	[1.40; 1.89]	<.001
AJCC Anatomic Stage Group					
Interaction test	**p = 0.809**				
Group I/II	220 / 417 (52.8)	136 / 418 (32.5)	1.62	[1.37; 1.91]	<.001
Group III	358 / 691 (51.8)	213 / 652 (32.7)	1.59	[1.39; 1.81]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Anatomic stages					
Interaction test	**p = 0.788**				
IA/IB/IIA	81 / 171 (47.4)	63 / 198 (31.8)	1.49	[1.15; 1.93]	0.002
IIB	139 / 246 (56.5)	73 / 220 (33.2)	1.70	[1.37; 2.12]	<.001
IIIA	240 / 451 (53.2)	138 / 393 (35.1)	1.52	[1.29; 1.78]	<.001
IIIB	33 / 67 (49.3)	15 / 59 (25.4)	1.94	[1.17; 3.19]	0.010
IIIC	85 / 173 (49.1)	60 / 200 (30.0)	1.64	[1.26; 2.12]	<.001
Nodal status					
Interaction test	**p = 0.083**				
N0	50 / 91 (54.9)	29 / 117 (24.8)	2.22	[1.54; 3.20]	<.001
N1-N3	528 / 1017 (51.9)	318 / 950 (33.5)	1.55	[1.39; 1.73]	<.001
Histological grade at time of surgery					
Interaction test	**p = 0.349**				
Grade 1	58 / 110 (52.7)	25 / 100 (25.0)	2.11	[1.44; 3.09]	<.001
Grade 2	317 / 604 (52.5)	198 / 601 (32.9)	1.59	[1.39; 1.83]	<.001
Grade 3	161 / 297 (54.2)	98 / 266 (36.8)	1.47	[1.22; 1.78]	<.001
Histological subtype					
Interaction test	**p = 0.084**				
Ductal	451 / 863 (52.3)	258 / 835 (30.9)	1.69	[1.50; 1.91]	<.001
Lobular	95 / 172 (55.2)	64 / 169 (37.9)	1.46	[1.15; 1.85]	0.002
Other	32 / 73 (43.8)	27 / 66 (40.9)	1.07	[0.73; 1.58]	0.728
Ki67 status from surgical specimen					
Interaction test	**p = 0.460**				
Ki67≤20	263 / 527 (49.9)	165 / 552 (29.9)	1.67	[1.43; 1.95]	<.001
Ki67>20	202 / 422 (47.9)	118 / 378 (31.2)	1.53	[1.28; 1.84]	<.001
Type of NSAI					
Interaction test	**p = 0.694**				
Letrozole	407 / 809 (50.3)	235 / 773 (30.4)	1.65	[1.46; 1.88]	<.001
Anastrozole	171 / 299 (57.2)	114 / 297 (38.4)	1.49	[1.25; 1.77]	<.001
Prior neo/adjuvant chemotherapy					
Interaction test	**p = 0.719**				
Yes	538 / 1029 (52.3)	321 / 987 (32.5)	1.61	[1.44; 1.79]	<.001
No	40 / 79 (50.6)	28 / 83 (33.7)	1.50	[1.03; 2.18]	0.032
Prior adjuvant chemotherapy					
Interaction test	**p = 0.144**				
Yes	266 / 513 (51.9)	173 / 488 (35.5)	1.46	[1.26; 1.69]	<.001
No	312 / 595 (52.4)	176 / 582 (30.2)	1.73	[1.50; 2.00]	<.001
Prior neoadjuvant chemotherapy					
Interaction test	**p = 0.123**				
Yes	282 / 546 (51.6)	157 / 538 (29.2)	1.77	[1.52; 2.07]	<.001
No	296 / 562 (52.7)	192 / 532 (36.1)	1.46	[1.27; 1.67]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Prior endocrine therapy					
Interaction test	**p = 0.135**				
Yes	449 / 853 (52.6)	247 / 789 (31.3)	1.68	[1.49; 1.90]	<.001
No	129 / 255 (50.6)	102 / 281 (36.3)	1.39	[1.14; 1.70]	<.001
Prior mastectomy					
Interaction test	**p = 0.521**				
Yes	401 / 769 (52.1)	249 / 745 (33.4)	1.56	[1.38; 1.76]	<.001
No	177 / 339 (52.2)	100 / 325 (30.8)	1.70	[1.40; 2.06]	<.001
Prior radiotherapy					
Interaction test	**p = 0.539**				
Yes	536 / 1011 (53.0)	325 / 987 (32.9)	1.61	[1.45; 1.79]	<.001
No	42 / 97 (43.3)	24 / 83 (28.9)	1.50	[1.00; 2.25]	0.052

N: Number of patients
n: Number of patients with event
CI: Confidence interval
RR: Relative risk
ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
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Analysis method for interaction test:
p-value from logistic regression model.
logit(proportion) = treatment + subgroup factor + treatment * subgroup factor

Analysis method for within subgroup analysis:
RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm.
ET was the reference group for treatment group comparison.

Table 5-3.2.36 PT nausea: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	ET (N = 1070)	RR	[95% CI]	p-value
Nausea					
	n / N (%)	n / N (%)			
Region					
Interaction test	**p = 0.585**				
NA/WE/O	200 / 640 (31.3)	75 / 627 (12.0)	2.61	[2.05; 3.33]	<.001
ROW	47 / 468 (10.0)	17 / 443 (3.8)	2.62	[1.53; 4.49]	<.001
Geographical region					
Interaction test	**p = 0.299**				
Europe	120 / 654 (18.3)	45 / 638 (7.1)	2.60	[1.88; 3.60]	<.001
North America/Australia	100 / 213 (46.9)	33 / 194 (17.0)	2.76	[1.96; 3.89]	<.001
Asia	19 / 178 (10.7)	10 / 168 (6.0)	1.79	[0.86; 3.74]	0.120
Latin America	8 / 63 (12.7)	4 / 70 (5.7)	2.22	[0.70; 7.02]	0.174
Age group 1 at randomization					
Interaction test	**p = 0.044**				
<45	127 / 549 (23.1)	43 / 496 (8.7)	2.67	[1.93; 3.69]	<.001
45 to 54	119 / 539 (22.1)	43 / 546 (7.9)	2.80	[2.02; 3.89]	<.001
55 to 64	1 / 20 (5.0)	6 / 28 (21.4)	0.23	[0.03; 1.79]	0.162
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)					
Interaction test	**p = 0.762**				
<Median	127 / 549 (23.1)	43 / 496 (8.7)	2.67	[1.93; 3.69]	<.001
≥Median	120 / 559 (21.5)	49 / 574 (8.5)	2.51	[1.84; 3.43]	<.001
Race					
Interaction test	**p = 0.990**				
Asian	33 / 211 (15.6)	10 / 186 (5.4)	2.91	[1.47; 5.74]	0.002
Non-Asian	207 / 840 (24.6)	75 / 827 (9.1)	2.72	[2.12; 3.48]	<.001
BMI at screening					
Interaction test	**p = 0.937**				
≥25	124 / 551 (22.5)	44 / 523 (8.4)	2.67	[1.94; 3.69]	<.001
<25	120 / 542 (22.1)	45 / 535 (8.4)	2.63	[1.91; 3.63]	<.001
AJCC Anatomic Stage Group					
Interaction test	**p = 0.928**				
Group I/II	92 / 417 (22.1)	36 / 418 (8.6)	2.56	[1.79; 3.67]	<.001
Group III	155 / 691 (22.4)	56 / 652 (8.6)	2.61	[1.96; 3.48]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Anatomic stages					
Interaction test	**p = 0.443**				
IA/IB/IIA	30 / 171 (17.5)	19 / 198 (9.6)	1.83	[1.07; 3.13]	0.028
IIB	62 / 246 (25.2)	17 / 220 (7.7)	3.26	[1.97; 5.40]	<.001
IIIA	103 / 451 (22.8)	36 / 393 (9.2)	2.49	[1.75; 3.55]	<.001
IIIB	16 / 67 (23.9)	3 / 59 (5.1)	4.70	[1.44; 15.32]	0.010
IIIC	36 / 173 (20.8)	17 / 200 (8.5)	2.45	[1.43; 4.20]	0.001
Nodal status					
Interaction test	**p = 0.715**				
N0	17 / 91 (18.7)	7 / 117 (6.0)	3.12	[1.35; 7.21]	0.008
N1-N3	230 / 1017 (22.6)	84 / 950 (8.8)	2.56	[2.02; 3.23]	<.001
Histological grade at time of surgery					
Interaction test	**p = 0.353**				
Grade 1	24 / 110 (21.8)	6 / 100 (6.0)	3.64	[1.55; 8.53]	0.003
Grade 2	136 / 604 (22.5)	59 / 601 (9.8)	2.29	[1.73; 3.05]	<.001
Grade 3	72 / 297 (24.2)	20 / 266 (7.5)	3.22	[2.02; 5.14]	<.001
Histological subtype					
Interaction test	**p = 0.030**				
Ductal	195 / 863 (22.6)	73 / 835 (8.7)	2.58	[2.01; 3.32]	<.001
Lobular	42 / 172 (24.4)	10 / 169 (5.9)	4.13	[2.14; 7.95]	<.001
Other	10 / 73 (13.7)	9 / 66 (13.6)	1.00	[0.44; 2.32]	0.991
Ki67 status from surgical specimen					
Interaction test	**p = 0.031**				
Ki67≤20	105 / 527 (19.9)	29 / 552 (5.3)	3.79	[2.56; 5.62]	<.001
Ki67>20	78 / 422 (18.5)	34 / 378 (9.0)	2.05	[1.41; 3.00]	<.001
Type of NSAI					
Interaction test	**p = 0.300**				
Letrozole	163 / 809 (20.1)	53 / 773 (6.9)	2.94	[2.19; 3.94]	<.001
Anastrozole	84 / 299 (28.1)	39 / 297 (13.1)	2.14	[1.52; 3.02]	<.001
Prior neo/adjuvant chemotherapy					
Interaction test	**p = 0.346**				
Yes	228 / 1029 (22.2)	87 / 987 (8.8)	2.51	[2.00; 3.17]	<.001
No	19 / 79 (24.1)	5 / 83 (6.0)	3.99	[1.57; 10.18]	0.004
Prior adjuvant chemotherapy					
Interaction test	**p = 0.224**				
Yes	122 / 513 (23.8)	52 / 488 (10.7)	2.23	[1.65; 3.01]	<.001
No	125 / 595 (21.0)	40 / 582 (6.9)	3.06	[2.18; 4.28]	<.001
Prior neoadjuvant chemotherapy					
Interaction test	**p = 0.297**				
Yes	109 / 546 (20.0)	35 / 538 (6.5)	3.07	[2.14; 4.41]	<.001
No	138 / 562 (24.6)	57 / 532 (10.7)	2.29	[1.72; 3.05]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Prior endocrine therapy					
Interaction test	**p = 0.207**				
Yes	197 / 853 (23.1)	65 / 789 (8.2)	2.80	[2.15; 3.65]	<.001
No	50 / 255 (19.6)	27 / 281 (9.6)	2.04	[1.32; 3.16]	0.001
Prior mastectomy					
Interaction test	**p = 0.713**				
Yes	174 / 769 (22.6)	67 / 745 (9.0)	2.52	[1.93; 3.27]	<.001
No	73 / 339 (21.5)	25 / 325 (7.7)	2.80	[1.82; 4.29]	<.001
Prior radiotherapy					
Interaction test	**p = 0.260**				
Yes	231 / 1011 (22.8)	84 / 987 (8.5)	2.68	[2.12; 3.39]	<.001
No	16 / 97 (16.5)	8 / 83 (9.6)	1.71	[0.77; 3.80]	0.186

N: Number of patients
n: Number of patients with event
CI: Confidence interval
RR: Relative risk
ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
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Analysis method for interaction test:
p-value from logistic regression model.
logit(proportion) = treatment + subgroup factor + treatment * subgroup factor

Analysis method for within subgroup analysis:
RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm.
ET was the reference group for treatment group comparison.

Table 5-3.2.37 PT constipation: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	ET (N = 1070)	RR	[95% CI]	p-value
Constipation					
	n / N (%)	n / N (%)			
Region					
Interaction test	**p = 0.002**				
NA/WE/O	118 / 640 (18.4)	33 / 627 (5.3)	3.50	[2.42; 5.07]	<.001
ROW	31 / 468 (6.6)	22 / 443 (5.0)	1.33	[0.78; 2.27]	0.287
Geographical region					
Interaction test	**p = 0.070**				
Europe	85 / 654 (13.0)	23 / 638 (3.6)	3.61	[2.30; 5.64]	<.001
North America/Australia	41 / 213 (19.2)	17 / 194 (8.8)	2.20	[1.29; 3.74]	0.004
Asia	17 / 178 (9.6)	7 / 168 (4.2)	2.29	[0.98; 5.39]	0.057
Latin America	6 / 63 (9.5)	8 / 70 (11.4)	0.83	[0.31; 2.27]	0.721
Age group 1 at randomization					
Interaction test	**p = 0.514**				
<45	68 / 549 (12.4)	23 / 496 (4.6)	2.67	[1.69; 4.22]	<.001
45 to 54	80 / 539 (14.8)	30 / 546 (5.5)	2.70	[1.81; 4.04]	<.001
55 to 64	1 / 20 (5.0)	2 / 28 (7.1)	0.70	[0.07; 7.20]	0.764
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)					
Interaction test	**p = 0.969**				
<Median	68 / 549 (12.4)	23 / 496 (4.6)	2.67	[1.69; 4.22]	<.001
≥Median	81 / 559 (14.5)	32 / 574 (5.6)	2.60	[1.76; 3.85]	<.001
Race					
Interaction test	**p = 0.886**				
Asian	24 / 211 (11.4)	8 / 186 (4.3)	2.64	[1.22; 5.74]	0.014
Non-Asian	112 / 840 (13.3)	45 / 827 (5.4)	2.45	[1.76; 3.42]	<.001
BMI at screening					
Interaction test	**p = 0.514**				
≥25	79 / 551 (14.3)	31 / 523 (5.9)	2.42	[1.63; 3.60]	<.001
<25	70 / 542 (12.9)	23 / 535 (4.3)	3.00	[1.90; 4.74]	<.001
AJCC Anatomic Stage Group					
Interaction test	**p = 0.556**				
Group I/II	56 / 417 (13.4)	19 / 418 (4.5)	2.95	[1.79; 4.88]	<.001
Group III	93 / 691 (13.5)	36 / 652 (5.5)	2.44	[1.68; 3.53]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Anatomic stages					
Interaction test	**p = 0.738**				
IA/IB/IIA	20 / 171 (11.7)	7 / 198 (3.5)	3.31	[1.43; 7.63]	0.005
IIB	36 / 246 (14.6)	12 / 220 (5.5)	2.68	[1.43; 5.02]	0.002
IIIA	60 / 451 (13.3)	24 / 393 (6.1)	2.18	[1.38; 3.43]	<.001
IIIB	8 / 67 (11.9)	4 / 59 (6.8)	1.76	[0.56; 5.55]	0.334
IIIC	25 / 173 (14.5)	8 / 200 (4.0)	3.61	[1.67; 7.80]	0.001
Nodal status					
Interaction test	**p = 0.090**				
N0	11 / 91 (12.1)	1 / 117 (0.9)	14.14	[1.86; >99.99]	0.010
N1-N3	138 / 1017 (13.6)	54 / 950 (5.7)	2.39	[1.77; 3.23]	<.001
Histological grade at time of surgery					
Interaction test	**p = 0.843**				
Grade 1	15 / 110 (13.6)	4 / 100 (4.0)	3.41	[1.17; 9.93]	0.025
Grade 2	87 / 604 (14.4)	36 / 601 (6.0)	2.40	[1.66; 3.49]	<.001
Grade 3	34 / 297 (11.4)	12 / 266 (4.5)	2.54	[1.34; 4.80]	0.004
Histological subtype					
Interaction test	**p = 0.571**				
Ductal	109 / 863 (12.6)	44 / 835 (5.3)	2.40	[1.71; 3.36]	<.001
Lobular	32 / 172 (18.6)	11 / 169 (6.5)	2.86	[1.49; 5.48]	0.002
Other	8 / 73 (11.0)	0 / 66 (0.0)	15.39	[0.91; >99.99]	0.059
Ki67 status from surgical specimen					
Interaction test	**p = 0.935**				
Ki67≤20	64 / 527 (12.1)	26 / 552 (4.7)	2.58	[1.66; 4.00]	<.001
Ki67>20	53 / 422 (12.6)	19 / 378 (5.0)	2.50	[1.51; 4.14]	<.001
Type of NSAI					
Interaction test	**p = 0.184**				
Letrozole	101 / 809 (12.5)	31 / 773 (4.0)	3.11	[2.11; 4.60]	<.001
Anastrozole	48 / 299 (16.1)	24 / 297 (8.1)	1.99	[1.25; 3.16]	0.004
Prior neo/adjuvant chemotherapy					
Interaction test	**p = 0.853**				
Yes	143 / 1029 (13.9)	53 / 987 (5.4)	2.59	[1.91; 3.50]	<.001
No	6 / 79 (7.6)	2 / 83 (2.4)	3.15	[0.66; 15.16]	0.152
Prior adjuvant chemotherapy					
Interaction test	**p = 0.941**				
Yes	68 / 513 (13.3)	25 / 488 (5.1)	2.59	[1.66; 4.02]	<.001
No	81 / 595 (13.6)	30 / 582 (5.2)	2.64	[1.76; 3.95]	<.001
Prior neoadjuvant chemotherapy					
Interaction test	**p = 0.906**				
Yes	78 / 546 (14.3)	29 / 538 (5.4)	2.65	[1.76; 3.99]	<.001
No	71 / 562 (12.6)	26 / 532 (4.9)	2.58	[1.68; 3.99]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Prior endocrine therapy					
Interaction test	**p = 0.093**				
Yes	119 / 853 (14.0)	36 / 789 (4.6)	3.06	[2.13; 4.38]	<.001
No	30 / 255 (11.8)	19 / 281 (6.8)	1.74	[1.00; 3.01]	0.048
Prior mastectomy					
Interaction test	**p = 0.189**				
Yes	108 / 769 (14.0)	45 / 745 (6.0)	2.33	[1.67; 3.24]	<.001
No	41 / 339 (12.1)	10 / 325 (3.1)	3.93	[2.00; 7.71]	<.001
Prior radiotherapy					
Interaction test	**p = 0.825**				
Yes	138 / 1011 (13.6)	51 / 987 (5.2)	2.64	[1.94; 3.60]	<.001
No	11 / 97 (11.3)	4 / 83 (4.8)	2.35	[0.78; 7.11]	0.129

N: Number of patients
n: Number of patients with event
CI: Confidence interval
RR: Relative risk
ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
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Analysis method for interaction test:
p-value from logistic regression model.
logit(proportion) = treatment + subgroup factor + treatment * subgroup factor

Analysis method for within subgroup analysis:
RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm.
ET was the reference group for treatment group comparison.

Table 5-3.2.38 PT diarrhoea: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	ET (N = 1070)	RR	[95% CI]	p-value
Diarrhoea					
	n / N (%)	n / N (%)			
Region					
Interaction test	**p = 0.502**				
NA/WE/O	95 / 640 (14.8)	40 / 627 (6.4)	2.33	[1.64; 3.31]	<.001
ROW	31 / 468 (6.6)	9 / 443 (2.0)	3.26	[1.57; 6.77]	0.002
Geographical region					
Interaction test	**p = 0.213**				
Europe	63 / 654 (9.6)	33 / 638 (5.2)	1.86	[1.24; 2.80]	0.003
North America/Australia	41 / 213 (19.2)	11 / 194 (5.7)	3.39	[1.80; 6.42]	<.001
Asia	15 / 178 (8.4)	3 / 168 (1.8)	4.72	[1.39; 16.01]	0.013
Latin America	7 / 63 (11.1)	2 / 70 (2.9)	3.89	[0.84; 18.03]	0.083
Age group 1 at randomization					
Interaction test	**p = 0.434**				
<45	64 / 549 (11.7)	20 / 496 (4.0)	2.89	[1.78; 4.71]	<.001
45 to 54	61 / 539 (11.3)	27 / 546 (4.9)	2.29	[1.48; 3.54]	<.001
55 to 64	1 / 20 (5.0)	2 / 28 (7.1)	0.70	[0.07; 7.20]	0.764
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)					
Interaction test	**p = 0.407**				
<Median	64 / 549 (11.7)	20 / 496 (4.0)	2.89	[1.78; 4.71]	<.001
≥Median	62 / 559 (11.1)	29 / 574 (5.1)	2.20	[1.43; 3.36]	<.001
Race					
Interaction test	**p = 0.125**				
Asian	21 / 211 (10.0)	3 / 186 (1.6)	6.17	[1.87; 20.36]	0.003
Non-Asian	98 / 840 (11.7)	42 / 827 (5.1)	2.30	[1.62; 3.25]	<.001
BMI at screening					
Interaction test	**p = 0.428**				
≥25	73 / 551 (13.2)	31 / 523 (5.9)	2.24	[1.49; 3.34]	<.001
<25	52 / 542 (9.6)	17 / 535 (3.2)	3.02	[1.77; 5.15]	<.001
AJCC Anatomic Stage Group					
Interaction test	**p = 0.281**				
Group I/II	55 / 417 (13.2)	18 / 418 (4.3)	3.06	[1.83; 5.12]	<.001
Group III	71 / 691 (10.3)	31 / 652 (4.8)	2.16	[1.44; 3.25]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Anatomic stages					
Interaction test	**p = 0.106**				
IA/IB/IIA	20 / 171 (11.7)	13 / 198 (6.6)	1.78	[0.91; 3.47]	0.090
IIB	35 / 246 (14.2)	5 / 220 (2.3)	6.26	[2.50; 15.70]	<.001
IIIA	44 / 451 (9.8)	21 / 393 (5.3)	1.83	[1.11; 3.02]	0.019
IIIB	6 / 67 (9.0)	0 / 59 (0.0)	11.47	[0.66; >99.99]	0.094
IIIC	21 / 173 (12.1)	10 / 200 (5.0)	2.43	[1.18; 5.01]	0.016
Nodal status					
Interaction test	**p = 0.922**				
N0	12 / 91 (13.2)	6 / 117 (5.1)	2.57	[1.00; 6.59]	0.049
N1-N3	114 / 1017 (11.2)	43 / 950 (4.5)	2.48	[1.76; 3.48]	<.001
Histological grade at time of surgery					
Interaction test	**p = 0.664**				
Grade 1	12 / 110 (10.9)	3 / 100 (3.0)	3.64	[1.06; 12.51]	0.041
Grade 2	69 / 604 (11.4)	30 / 601 (5.0)	2.29	[1.51; 3.46]	<.001
Grade 3	37 / 297 (12.5)	11 / 266 (4.1)	3.01	[1.57; 5.78]	<.001
Histological subtype					
Interaction test	**p = 0.658**				
Ductal	98 / 863 (11.4)	41 / 835 (4.9)	2.31	[1.63; 3.29]	<.001
Lobular	19 / 172 (11.0)	5 / 169 (3.0)	3.73	[1.43; 9.77]	0.007
Other	9 / 73 (12.3)	3 / 66 (4.5)	2.71	[0.77; 9.60]	0.122
Ki67 status from surgical specimen					
Interaction test	**p = 0.073**				
Ki67≤20	50 / 527 (9.5)	13 / 552 (2.4)	4.03	[2.21; 7.33]	<.001
Ki67>20	50 / 422 (11.8)	23 / 378 (6.1)	1.95	[1.21; 3.13]	0.006
Type of NSAI					
Interaction test	**p = 0.339**				
Letrozole	88 / 809 (10.9)	30 / 773 (3.9)	2.80	[1.87; 4.19]	<.001
Anastrozole	38 / 299 (12.7)	19 / 297 (6.4)	1.99	[1.17; 3.36]	0.011
Prior neo/adjuvant chemotherapy					
Interaction test	**p = 0.462**				
Yes	118 / 1029 (11.5)	44 / 987 (4.5)	2.57	[1.84; 3.60]	<.001
No	8 / 79 (10.1)	5 / 83 (6.0)	1.68	[0.57; 4.92]	0.343
Prior adjuvant chemotherapy					
Interaction test	**p = 0.096**				
Yes	69 / 513 (13.5)	20 / 488 (4.1)	3.28	[2.03; 5.31]	<.001
No	57 / 595 (9.6)	29 / 582 (5.0)	1.92	[1.25; 2.96]	0.003
Prior neoadjuvant chemotherapy					
Interaction test	**p = 0.304**				
Yes	53 / 546 (9.7)	25 / 538 (4.6)	2.09	[1.32; 3.31]	0.002
No	73 / 562 (13.0)	24 / 532 (4.5)	2.88	[1.84; 4.50]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Prior endocrine therapy					
Interaction test	**p = 0.408**				
Yes	105 / 853 (12.3)	37 / 789 (4.7)	2.62	[1.83; 3.77]	<.001
No	21 / 255 (8.2)	12 / 281 (4.3)	1.93	[0.97; 3.84]	0.062
Prior mastectomy					
Interaction test	**p = 0.997**				
Yes	80 / 769 (10.4)	31 / 745 (4.2)	2.50	[1.67; 3.74]	<.001
No	46 / 339 (13.6)	18 / 325 (5.5)	2.45	[1.45; 4.13]	<.001
Prior radiotherapy					
Interaction test	**p = 0.922**				
Yes	115 / 1011 (11.4)	45 / 987 (4.6)	2.49	[1.79; 3.48]	<.001
No	11 / 97 (11.3)	4 / 83 (4.8)	2.35	[0.78; 7.11]	0.129

N: Number of patients
n: Number of patients with event
CI: Confidence interval
RR: Relative risk
ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
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Analysis method for interaction test:
p-value from logistic regression model.
logit(proportion) = treatment + subgroup factor + treatment * subgroup factor

Analysis method for within subgroup analysis:
RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm.
ET was the reference group for treatment group comparison.

Table 5-3.2.39 PT vomiting: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	ET (N = 1070)	RR	[95% CI]	p-value
Vomiting					
	n / N (%)	n / N (%)			
Region					
Interaction test	**p = 0.828**				
NA/WE/O	65 / 640 (10.2)	37 / 627 (5.9)	1.72	[1.17; 2.54]	0.006
ROW	17 / 468 (3.6)	10 / 443 (2.3)	1.61	[0.74; 3.48]	0.226
Geographical region					
Interaction test	**p = 0.218**				
Europe	48 / 654 (7.3)	26 / 638 (4.1)	1.80	[1.13; 2.87]	0.013
North America/Australia	26 / 213 (12.2)	13 / 194 (6.7)	1.82	[0.96; 3.44]	0.065
Asia	4 / 178 (2.2)	7 / 168 (4.2)	0.54	[0.16; 1.81]	0.317
Latin America	4 / 63 (6.3)	1 / 70 (1.4)	4.44	[0.51; 38.72]	0.177
Age group 1 at randomization					
Interaction test	**p = 0.623**				
<45	43 / 549 (7.8)	19 / 496 (3.8)	2.04	[1.21; 3.46]	0.008
45 to 54	37 / 539 (6.9)	26 / 546 (4.8)	1.44	[0.89; 2.35]	0.141
55 to 64	2 / 20 (10.0)	2 / 28 (7.1)	1.40	[0.21; 9.12]	0.725
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)					
Interaction test	**p = 0.322**				
<Median	43 / 549 (7.8)	19 / 496 (3.8)	2.04	[1.21; 3.46]	0.008
≥Median	39 / 559 (7.0)	28 / 574 (4.9)	1.43	[0.89; 2.29]	0.137
Race					
Interaction test	**p = 0.237**				
Asian	8 / 211 (3.8)	7 / 186 (3.8)	1.01	[0.37; 2.72]	0.988
Non-Asian	71 / 840 (8.5)	37 / 827 (4.5)	1.89	[1.28; 2.78]	0.001
BMI at screening					
Interaction test	**p = 0.902**				
≥25	45 / 551 (8.2)	25 / 523 (4.8)	1.71	[1.06; 2.74]	0.027
<25	35 / 542 (6.5)	21 / 535 (3.9)	1.65	[0.97; 2.79]	0.064
AJCC Anatomic Stage Group					
Interaction test	**p = 0.780**				
Group I/II	30 / 417 (7.2)	19 / 418 (4.5)	1.58	[0.91; 2.77]	0.107
Group III	52 / 691 (7.5)	28 / 652 (4.3)	1.75	[1.12; 2.74]	0.014

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Anatomic stages					
Interaction test	**p = 0.054**				
IA/IB/IIA	7 / 171 (4.1)	13 / 198 (6.6)	0.62	[0.25; 1.53]	0.301
IIB	23 / 246 (9.3)	6 / 220 (2.7)	3.43	[1.42; 8.26]	0.006
IIIA	36 / 451 (8.0)	19 / 393 (4.8)	1.65	[0.96; 2.83]	0.068
IIIB	7 / 67 (10.4)	0 / 59 (0.0)	13.24	[0.77; >99.99]	0.075
IIIC	9 / 173 (5.2)	9 / 200 (4.5)	1.16	[0.47; 2.85]	0.752
Nodal status					
Interaction test	**p = 0.523**				
N0	6 / 91 (6.6)	3 / 117 (2.6)	2.57	[0.66; 10.00]	0.173
N1-N3	76 / 1017 (7.5)	44 / 950 (4.6)	1.61	[1.13; 2.31]	0.009
Histological grade at time of surgery					
Interaction test	**p = 0.234**				
Grade 1	11 / 110 (10.0)	3 / 100 (3.0)	3.33	[0.96; 11.61]	0.059
Grade 2	44 / 604 (7.3)	26 / 601 (4.3)	1.68	[1.05; 2.70]	0.030
Grade 3	19 / 297 (6.4)	16 / 266 (6.0)	1.06	[0.56; 2.03]	0.851
Histological subtype					
Interaction test	**p = 0.716**				
Ductal	66 / 863 (7.6)	37 / 835 (4.4)	1.73	[1.17; 2.55]	0.006
Lobular	13 / 172 (7.6)	7 / 169 (4.1)	1.82	[0.75; 4.46]	0.187
Other	3 / 73 (4.1)	3 / 66 (4.5)	0.90	[0.19; 4.33]	0.900
Ki67 status from surgical specimen					
Interaction test	**p = 0.063**				
Ki67≤20	40 / 527 (7.6)	18 / 552 (3.3)	2.33	[1.35; 4.01]	0.002
Ki67>20	26 / 422 (6.2)	21 / 378 (5.6)	1.11	[0.63; 1.94]	0.716
Type of NSAI					
Interaction test	**p = 0.385**				
Letrozole	56 / 809 (6.9)	35 / 773 (4.5)	1.53	[1.01; 2.31]	0.043
Anastrozole	26 / 299 (8.7)	12 / 297 (4.0)	2.15	[1.11; 4.18]	0.024
Prior neo/adjuvant chemotherapy					
Interaction test	**p = 0.025**				
Yes	81 / 1029 (7.9)	41 / 987 (4.2)	1.89	[1.31; 2.73]	<.001
No	1 / 79 (1.3)	6 / 83 (7.2)	0.18	[0.02; 1.42]	0.103
Prior adjuvant chemotherapy					
Interaction test	**p = 0.887**				
Yes	45 / 513 (8.8)	25 / 488 (5.1)	1.71	[1.07; 2.75]	0.026
No	37 / 595 (6.2)	22 / 582 (3.8)	1.65	[0.98; 2.75]	0.058
Prior neoadjuvant chemotherapy					
Interaction test	**p = 0.318**				
Yes	38 / 546 (7.0)	18 / 538 (3.3)	2.08	[1.20; 3.60]	0.009
No	44 / 562 (7.8)	29 / 532 (5.5)	1.44	[0.91; 2.26]	0.118

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Prior endocrine therapy					
Interaction test	**p = 0.953**				
Yes	64 / 853 (7.5)	35 / 789 (4.4)	1.69	[1.13; 2.52]	0.010
No	18 / 255 (7.1)	12 / 281 (4.3)	1.65	[0.81; 3.36]	0.166
Prior mastectomy					
Interaction test	**p = 0.426**				
Yes	56 / 769 (7.3)	29 / 745 (3.9)	1.87	[1.21; 2.90]	0.005
No	26 / 339 (7.7)	18 / 325 (5.5)	1.38	[0.77; 2.48]	0.272
Prior radiotherapy					
Interaction test	**p = 0.093**				
Yes	80 / 1011 (7.9)	43 / 987 (4.4)	1.82	[1.27; 2.60]	0.001
No	2 / 97 (2.1)	4 / 83 (4.8)	0.43	[0.08; 2.28]	0.320

N: Number of patients
n: Number of patients with event
CI: Confidence interval
RR: Relative risk
ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
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Analysis method for interaction test:
p-value from logistic regression model.
logit(proportion) = treatment + subgroup factor + treatment * subgroup factor

Analysis method for within subgroup analysis:
RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm.
ET was the reference group for treatment group comparison.

Table 5-3.2.40 PT abdominal pain upper: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	ET (N = 1070)	RR	[95% CI]	p-value
Abdominal pain upper					
	n / N (%)	n / N (%)			
Region					
Interaction test	**p = 0.938**				
NA/WE/O	54 / 640 (8.4)	33 / 627 (5.3)	1.60	[1.05; 2.44]	0.027
ROW	20 / 468 (4.3)	12 / 443 (2.7)	1.58	[0.78; 3.19]	0.204
Geographical region					
Interaction test	**p = 0.938**				
Europe	56 / 654 (8.6)	34 / 638 (5.3)	1.61	[1.06; 2.43]	0.024
North America/Australia	11 / 213 (5.2)	7 / 194 (3.6)	1.43	[0.57; 3.62]	0.449
Asia	5 / 178 (2.8)	2 / 168 (1.2)	2.36	[0.46; 12.00]	0.301
Latin America	2 / 63 (3.2)	2 / 70 (2.9)	1.11	[0.16; 7.66]	0.915
Age group 1 at randomization					
Interaction test	**p = 0.992**				
<45	39 / 549 (7.1)	22 / 496 (4.4)	1.60	[0.96; 2.66]	0.069
45 to 54	35 / 539 (6.5)	22 / 546 (4.0)	1.61	[0.96; 2.71]	0.072
55 to 64	0 / 20 (0.0)	1 / 28 (3.6)	0.46	[0.02; 10.75]	0.629
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)					
Interaction test	**p = 0.940**				
<Median	39 / 549 (7.1)	22 / 496 (4.4)	1.60	[0.96; 2.66]	0.069
≥Median	35 / 559 (6.3)	23 / 574 (4.0)	1.56	[0.94; 2.61]	0.088
Race					
Interaction test	**p = 0.214**				
Asian	9 / 211 (4.3)	2 / 186 (1.1)	3.97	[0.87; 18.13]	0.075
Non-Asian	59 / 840 (7.0)	40 / 827 (4.8)	1.45	[0.98; 2.14]	0.061
BMI at screening					
Interaction test	**p = 0.499**				
≥25	35 / 551 (6.4)	18 / 523 (3.4)	1.85	[1.06; 3.22]	0.031
<25	39 / 542 (7.2)	27 / 535 (5.0)	1.43	[0.89; 2.29]	0.144
AJCC Anatomic Stage Group					
Interaction test	**p = 0.342**				
Group I/II	24 / 417 (5.8)	19 / 418 (4.5)	1.27	[0.70; 2.28]	0.430
Group III	50 / 691 (7.2)	26 / 652 (4.0)	1.81	[1.14; 2.88]	0.011

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Anatomic stages					
Interaction test	**p = 0.509**				
IA/IB/IIA	12 / 171 (7.0)	14 / 198 (7.1)	0.99	[0.47; 2.09]	0.984
IIB	12 / 246 (4.9)	5 / 220 (2.3)	2.15	[0.77; 6.00]	0.145
IIIA	37 / 451 (8.2)	15 / 393 (3.8)	2.15	[1.20; 3.86]	0.010
IIIB	5 / 67 (7.5)	4 / 59 (6.8)	1.10	[0.31; 3.91]	0.882
IIIC	8 / 173 (4.6)	7 / 200 (3.5)	1.32	[0.49; 3.57]	0.583
Nodal status					
Interaction test	**p = 0.776**				
N0	10 / 91 (11.0)	7 / 117 (6.0)	1.84	[0.73; 4.64]	0.198
N1-N3	64 / 1017 (6.3)	37 / 950 (3.9)	1.62	[1.09; 2.40]	0.017
Histological grade at time of surgery					
Interaction test	**p = 0.642**				
Grade 1	8 / 110 (7.3)	3 / 100 (3.0)	2.42	[0.66; 8.89]	0.182
Grade 2	41 / 604 (6.8)	25 / 601 (4.2)	1.63	[1.01; 2.65]	0.048
Grade 3	15 / 297 (5.1)	11 / 266 (4.1)	1.22	[0.57; 2.61]	0.606
Histological subtype					
Interaction test	**p = 0.116**				
Ductal	54 / 863 (6.3)	27 / 835 (3.2)	1.94	[1.23; 3.04]	0.004
Lobular	14 / 172 (8.1)	9 / 169 (5.3)	1.53	[0.68; 3.44]	0.305
Other	6 / 73 (8.2)	9 / 66 (13.6)	0.60	[0.23; 1.60]	0.310
Ki67 status from surgical specimen					
Interaction test	**p = 0.493**				
Ki67≤20	38 / 527 (7.2)	24 / 552 (4.3)	1.66	[1.01; 2.73]	0.046
Ki67>20	24 / 422 (5.7)	17 / 378 (4.5)	1.26	[0.69; 2.32]	0.447
Type of NSAI					
Interaction test	**p = 0.567**				
Letrozole	53 / 809 (6.6)	34 / 773 (4.4)	1.49	[0.98; 2.27]	0.063
Anastrozole	21 / 299 (7.0)	11 / 297 (3.7)	1.90	[0.93; 3.86]	0.078
Prior neo/adjuvant chemotherapy					
Interaction test	**p = 0.330**				
Yes	71 / 1029 (6.9)	41 / 987 (4.2)	1.66	[1.14; 2.42]	0.008
No	3 / 79 (3.8)	4 / 83 (4.8)	0.79	[0.18; 3.41]	0.750
Prior adjuvant chemotherapy					
Interaction test	**p = 0.808**				
Yes	35 / 513 (6.8)	22 / 488 (4.5)	1.51	[0.90; 2.54]	0.117
No	39 / 595 (6.6)	23 / 582 (4.0)	1.66	[1.00; 2.74]	0.048
Prior neoadjuvant chemotherapy					
Interaction test	**p = 0.274**				
Yes	38 / 546 (7.0)	19 / 538 (3.5)	1.97	[1.15; 3.37]	0.013
No	36 / 562 (6.4)	26 / 532 (4.9)	1.31	[0.80; 2.14]	0.279

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Prior endocrine therapy					
Interaction test	**p = 0.535**				
Yes	60 / 853 (7.0)	33 / 789 (4.2)	1.68	[1.11; 2.54]	0.014
No	14 / 255 (5.5)	12 / 281 (4.3)	1.29	[0.61; 2.73]	0.513
Prior mastectomy					
Interaction test	**p = 0.513**				
Yes	50 / 769 (6.5)	33 / 745 (4.4)	1.47	[0.96; 2.25]	0.079
No	24 / 339 (7.1)	12 / 325 (3.7)	1.92	[0.98; 3.77]	0.059
Prior radiotherapy					
Interaction test	**p = 0.868**				
Yes	69 / 1011 (6.8)	42 / 987 (4.3)	1.60	[1.10; 2.33]	0.013
No	5 / 97 (5.2)	3 / 83 (3.6)	1.43	[0.35; 5.79]	0.619

N: Number of patients
n: Number of patients with event
CI: Confidence interval
RR: Relative risk
ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
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Analysis method for interaction test:
p-value from logistic regression model.
logit(proportion) = treatment + subgroup factor + treatment * subgroup factor

Analysis method for within subgroup analysis:
RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm.
ET was the reference group for treatment group comparison.

Table 5-3.2.41 PT gastrooesophageal reflux disease: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	ET (N = 1070)	RR	[95% CI]	p-value
Gastrooesophageal reflux disease					
	n / N (%)	n / N (%)			
Region					
Interaction test	**p = 0.815**				
NA/WE/O	34 / 640 (5.3)	17 / 627 (2.7)	1.96	[1.11; 3.47]	0.021
ROW	11 / 468 (2.4)	6 / 443 (1.4)	1.74	[0.65; 4.65]	0.273
Geographical region					
Interaction test	**p = 0.293**				
Europe	18 / 654 (2.8)	13 / 638 (2.0)	1.35	[0.67; 2.73]	0.403
North America/Australia	19 / 213 (8.9)	7 / 194 (3.6)	2.47	[1.06; 5.75]	0.036
Asia	7 / 178 (3.9)	1 / 168 (0.6)	6.61	[0.82; 53.13]	0.076
Latin America	1 / 63 (1.6)	2 / 70 (2.9)	0.56	[0.05; 5.98]	0.628
Age group 1 at randomization					
Interaction test	**p = 0.170**				
<45	24 / 549 (4.4)	6 / 496 (1.2)	3.61	[1.49; 8.77]	0.004
45 to 54	20 / 539 (3.7)	16 / 546 (2.9)	1.27	[0.66; 2.42]	0.474
55 to 64	1 / 20 (5.0)	1 / 28 (3.6)	1.40	[0.09; 21.08]	0.808
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)					
Interaction test	**p = 0.059**				
<Median	24 / 549 (4.4)	6 / 496 (1.2)	3.61	[1.49; 8.77]	0.004
≥Median	21 / 559 (3.8)	17 / 574 (3.0)	1.27	[0.68; 2.38]	0.459
Race					
Interaction test	**p = 0.057**				
Asian	11 / 211 (5.2)	1 / 186 (0.5)	9.70	[1.26; 74.39]	0.029
Non-Asian	27 / 840 (3.2)	21 / 827 (2.5)	1.27	[0.72; 2.22]	0.411
BMI at screening					
Interaction test	**p = 0.758**				
≥25	26 / 551 (4.7)	14 / 523 (2.7)	1.76	[0.93; 3.34]	0.082
<25	17 / 542 (3.1)	8 / 535 (1.5)	2.10	[0.91; 4.82]	0.081
AJCC Anatomic Stage Group					
Interaction test	**p = 0.589**				
Group I/II	18 / 417 (4.3)	8 / 418 (1.9)	2.26	[0.99; 5.13]	0.052
Group III	27 / 691 (3.9)	15 / 652 (2.3)	1.70	[0.91; 3.16]	0.095

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Anatomic stages					
Interaction test	**p = 0.784**				
IA/IB/IIA	5 / 171 (2.9)	2 / 198 (1.0)	2.89	[0.57; 14.73]	0.200
IIB	13 / 246 (5.3)	6 / 220 (2.7)	1.94	[0.75; 5.01]	0.172
IIIA	20 / 451 (4.4)	10 / 393 (2.5)	1.74	[0.83; 3.68]	0.145
IIIB	0 / 67 (0.0)	3 / 59 (5.1)	0.13	[<0.01; 2.39]	0.168
IIIC	7 / 173 (4.0)	2 / 200 (1.0)	4.05	[0.85; 19.22]	0.079
Nodal status					
Interaction test	**p = 0.342**				
N0	4 / 91 (4.4)	1 / 117 (0.9)	5.14	[0.58; 45.23]	0.140
N1-N3	41 / 1017 (4.0)	22 / 950 (2.3)	1.74	[1.04; 2.90]	0.033
Histological grade at time of surgery					
Interaction test	**p = 0.899**				
Grade 1	3 / 110 (2.7)	1 / 100 (1.0)	2.73	[0.29; 25.80]	0.381
Grade 2	28 / 604 (4.6)	11 / 601 (1.8)	2.53	[1.27; 5.04]	0.008
Grade 3	13 / 297 (4.4)	6 / 266 (2.3)	1.94	[0.75; 5.03]	0.173
Histological subtype					
Interaction test	**p = 0.432**				
Ductal	40 / 863 (4.6)	18 / 835 (2.2)	2.15	[1.24; 3.72]	0.006
Lobular	5 / 172 (2.9)	4 / 169 (2.4)	1.23	[0.34; 4.50]	0.756
Other	0 / 73 (0.0)	1 / 66 (1.5)	0.30	[0.01; 7.28]	0.461
Ki67 status from surgical specimen					
Interaction test	**p = 0.345**				
Ki67≤20	15 / 527 (2.8)	11 / 552 (2.0)	1.43	[0.66; 3.08]	0.363
Ki67>20	17 / 422 (4.0)	6 / 378 (1.6)	2.54	[1.01; 6.37]	0.047
Type of NSAI					
Interaction test	**p = 0.611**				
Letrozole	31 / 809 (3.8)	17 / 773 (2.2)	1.74	[0.97; 3.12]	0.062
Anastrozole	14 / 299 (4.7)	6 / 297 (2.0)	2.32	[0.90; 5.95]	0.081
Prior neo/adjuvant chemotherapy					
Interaction test	**N.E.**				
Yes	44 / 1029 (4.3)	23 / 987 (2.3)	1.83	[1.12; 3.02]	0.017
No	1 / 79 (1.3)	0 / 83 (0.0)	3.15	[0.13; 76.20]	0.480
Prior adjuvant chemotherapy					
Interaction test	**p = 0.305**				
Yes	18 / 513 (3.5)	12 / 488 (2.5)	1.43	[0.69; 2.93]	0.333
No	27 / 595 (4.5)	11 / 582 (1.9)	2.40	[1.20; 4.79]	0.013
Prior neoadjuvant chemotherapy					
Interaction test	**p = 0.381**				
Yes	26 / 546 (4.8)	11 / 538 (2.0)	2.33	[1.16; 4.67]	0.017
No	19 / 562 (3.4)	12 / 532 (2.3)	1.50	[0.73; 3.06]	0.266

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Prior endocrine therapy					
Interaction test	**p = 0.574**				
Yes	32 / 853 (3.8)	17 / 789 (2.2)	1.74	[0.97; 3.11]	0.061
No	13 / 255 (5.1)	6 / 281 (2.1)	2.39	[0.92; 6.19]	0.073
Prior mastectomy					
Interaction test	**p = 0.978**				
Yes	33 / 769 (4.3)	17 / 745 (2.3)	1.88	[1.06; 3.35]	0.032
No	12 / 339 (3.5)	6 / 325 (1.8)	1.92	[0.73; 5.05]	0.188
Prior radiotherapy					
Interaction test	**N.E.**				
Yes	41 / 1011 (4.1)	23 / 987 (2.3)	1.74	[1.05; 2.88]	0.031
No	4 / 97 (4.1)	0 / 83 (0.0)	7.71	[0.42; >99.99]	0.168

N: Number of patients
n: Number of patients with event
N.E.: Not estimable
CI: Confidence interval
RR: Relative risk
ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
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Analysis method for interaction test:
p-value from logistic regression model.
logit(proportion) = treatment + subgroup factor + treatment * subgroup factor

Analysis method for within subgroup analysis:
RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm.
ET was the reference group for treatment group comparison.

Table 5-3.2.42 PT stomatitis: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	ET (N = 1070)	RR	[95% CI]	p-value
Stomatitis					
	n / N (%)	n / N (%)			
Region					
Interaction test	**p = 0.818**				
NA/WE/O	34 / 640 (5.3)	8 / 627 (1.3)	4.16	[1.94; 8.92]	<.001
ROW	11 / 468 (2.4)	2 / 443 (0.5)	5.21	[1.16; 23.36]	0.031
Geographical region					
Interaction test	**p = 0.948**				
Europe	20 / 654 (3.1)	4 / 638 (0.6)	4.88	[1.68; 14.19]	0.004
North America/Australia	16 / 213 (7.5)	4 / 194 (2.1)	3.64	[1.24; 10.71]	0.019
Asia	9 / 178 (5.1)	2 / 168 (1.2)	4.25	[0.93; 19.37]	0.062
Latin America	0 / 63 (0.0)	0 / 70 (0.0)	N.E.	N.E.	N.E.
Age group 1 at randomization					
Interaction test	**p = 0.684**				
<45	28 / 549 (5.1)	5 / 496 (1.0)	5.06	[1.97; 13.00]	<.001
45 to 54	16 / 539 (3.0)	4 / 546 (0.7)	4.05	[1.36; 12.04]	0.012
55 to 64	1 / 20 (5.0)	1 / 28 (3.6)	1.40	[0.09; 21.08]	0.808
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)					
Interaction test	**p = 0.581**				
<Median	28 / 549 (5.1)	5 / 496 (1.0)	5.06	[1.97; 13.00]	<.001
≥Median	17 / 559 (3.0)	5 / 574 (0.9)	3.49	[1.30; 9.40]	0.013
Race					
Interaction test	**p = 0.832**				
Asian	12 / 211 (5.7)	3 / 186 (1.6)	3.53	[1.01; 12.30]	0.048
Non-Asian	30 / 840 (3.6)	7 / 827 (0.8)	4.22	[1.86; 9.55]	<.001
BMI at screening					
Interaction test	**p = 0.673**				
≥25	23 / 551 (4.2)	6 / 523 (1.1)	3.64	[1.49; 8.86]	0.004
<25	20 / 542 (3.7)	4 / 535 (0.7)	4.94	[1.70; 14.34]	0.003
AJCC Anatomic Stage Group					
Interaction test	**p = 0.502**				
Group I/II	18 / 417 (4.3)	3 / 418 (0.7)	6.01	[1.79; 20.26]	0.004
Group III	27 / 691 (3.9)	7 / 652 (1.1)	3.64	[1.60; 8.30]	0.002

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Anatomic stages					
Interaction test	**p = 0.776**				
IA/IB/IIA	9 / 171 (5.3)	0 / 198 (0.0)	21.98	[1.29; >99.99]	0.033
IIB	9 / 246 (3.7)	3 / 220 (1.4)	2.68	[0.74; 9.78]	0.135
IIIA	19 / 451 (4.2)	4 / 393 (1.0)	4.14	[1.42; 12.06]	0.009
IIIB	2 / 67 (3.0)	0 / 59 (0.0)	4.41	[0.22; 90.08]	0.335
IIIC	6 / 173 (3.5)	3 / 200 (1.5)	2.31	[0.59; 9.11]	0.231
Nodal status					
Interaction test	**N.E.**				
N0	4 / 91 (4.4)	0 / 117 (0.0)	11.54	[0.63; >99.99]	0.099
N1-N3	41 / 1017 (4.0)	10 / 950 (1.1)	3.83	[1.93; 7.60]	<.001
Histological grade at time of surgery					
Interaction test	**p = 0.848**				
Grade 1	7 / 110 (6.4)	1 / 100 (1.0)	6.36	[0.80; 50.82]	0.081
Grade 2	21 / 604 (3.5)	6 / 601 (1.0)	3.48	[1.42; 8.57]	0.007
Grade 3	11 / 297 (3.7)	3 / 266 (1.1)	3.28	[0.93; 11.65]	0.066
Histological subtype					
Interaction test	**p = 0.105**				
Ductal	38 / 863 (4.4)	7 / 835 (0.8)	5.25	[2.36; 11.70]	<.001
Lobular	4 / 172 (2.3)	3 / 169 (1.8)	1.31	[0.30; 5.77]	0.721
Other	3 / 73 (4.1)	0 / 66 (0.0)	6.34	[0.33; >99.99]	0.219
Ki67 status from surgical specimen					
Interaction test	**p = 0.625**				
Ki67≤20	25 / 527 (4.7)	5 / 552 (0.9)	5.24	[2.02; 13.58]	<.001
Ki67>20	12 / 422 (2.8)	3 / 378 (0.8)	3.58	[1.02; 12.60]	0.047
Type of NSAI					
Interaction test	**p = 0.591**				
Letrozole	28 / 809 (3.5)	7 / 773 (0.9)	3.82	[1.68; 8.70]	0.001
Anastrozole	17 / 299 (5.7)	3 / 297 (1.0)	5.63	[1.67; 19.01]	0.005
Prior neo/adjuvant chemotherapy					
Interaction test	**N.E.**				
Yes	43 / 1029 (4.2)	10 / 987 (1.0)	4.12	[2.08; 8.16]	<.001
No	2 / 79 (2.5)	0 / 83 (0.0)	5.25	[0.26; >99.99]	0.282
Prior adjuvant chemotherapy					
Interaction test	**p = 0.366**				
Yes	16 / 513 (3.1)	5 / 488 (1.0)	3.04	[1.12; 8.25]	0.029
No	29 / 595 (4.9)	5 / 582 (0.9)	5.67	[2.21; 14.56]	<.001
Prior neoadjuvant chemotherapy					
Interaction test	**p = 0.352**				
Yes	29 / 546 (5.3)	5 / 538 (0.9)	5.72	[2.23; 14.65]	<.001
No	16 / 562 (2.8)	5 / 532 (0.9)	3.03	[1.12; 8.21]	0.029

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Prior endocrine therapy					
Interaction test	**p = 0.459**				
Yes	37 / 853 (4.3)	9 / 789 (1.1)	3.80	[1.85; 7.83]	<.001
No	8 / 255 (3.1)	1 / 281 (0.4)	8.82	[1.11; 70.00]	0.040
Prior mastectomy					
Interaction test	**p = 0.172**				
Yes	30 / 769 (3.9)	9 / 745 (1.2)	3.23	[1.54; 6.76]	0.002
No	15 / 339 (4.4)	1 / 325 (0.3)	14.38	[1.91; >99.99]	0.010
Prior radiotherapy					
Interaction test	**N.E.**				
Yes	41 / 1011 (4.1)	10 / 987 (1.0)	4.00	[2.02; 7.95]	<.001
No	4 / 97 (4.1)	0 / 83 (0.0)	7.71	[0.42; >99.99]	0.168

N: Number of patients
n: Number of patients with event
N.E.: Not estimable
CI: Confidence interval
RR: Relative risk
ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
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Analysis method for interaction test:
p-value from logistic regression model.
logit(proportion) = treatment + subgroup factor + treatment * subgroup factor

Analysis method for within subgroup analysis:
RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm.
ET was the reference group for treatment group comparison.

Table 5-3.2.43 PT toothache: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	ET (N = 1070)	RR	[95% CI]	p-value
Toothache					
	n / N (%)	n / N (%)			
Region					
Interaction test	**p = 0.178**				
NA/WE/O	11 / 640 (1.7)	5 / 627 (0.8)	2.16	[0.75; 6.17]	0.152
ROW	11 / 468 (2.4)	1 / 443 (0.2)	10.41	[1.35; 80.32]	0.025
Geographical region					
Interaction test	**p = 0.558**				
Europe	8 / 654 (1.2)	3 / 638 (0.5)	2.60	[0.69; 9.76]	0.156
North America/Australia	5 / 213 (2.3)	2 / 194 (1.0)	2.28	[0.45; 11.60]	0.322
Asia	9 / 178 (5.1)	1 / 168 (0.6)	8.49	[1.09; 66.33]	0.041
Latin America	0 / 63 (0.0)	0 / 70 (0.0)	N.E.	N.E.	N.E.
Age group 1 at randomization					
Interaction test	**p = 0.265**				
<45	10 / 549 (1.8)	1 / 496 (0.2)	9.03	[1.16; 70.32]	0.036
45 to 54	12 / 539 (2.2)	5 / 546 (0.9)	2.43	[0.86; 6.85]	0.093
55 to 64	0 / 20 (0.0)	0 / 28 (0.0)	N.E.	N.E.	N.E.
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)					
Interaction test	**p = 0.269**				
<Median	10 / 549 (1.8)	1 / 496 (0.2)	9.03	[1.16; 70.32]	0.036
≥Median	12 / 559 (2.1)	5 / 574 (0.9)	2.46	[0.87; 6.95]	0.088
Race					
Interaction test	**p = 0.314**				
Asian	10 / 211 (4.7)	1 / 186 (0.5)	8.82	[1.14; 68.21]	0.037
Non-Asian	11 / 840 (1.3)	4 / 827 (0.5)	2.71	[0.87; 8.47]	0.087
BMI at screening					
Interaction test	**p = 0.253**				
≥25	9 / 551 (1.6)	4 / 523 (0.8)	2.14	[0.66; 6.89]	0.204
<25	13 / 542 (2.4)	2 / 535 (0.4)	6.42	[1.45; 28.30]	0.014
AJCC Anatomic Stage Group					
Interaction test	**p = 0.813**				
Group I/II	6 / 417 (1.4)	2 / 418 (0.5)	3.01	[0.61; 14.81]	0.176
Group III	16 / 691 (2.3)	4 / 652 (0.6)	3.77	[1.27; 11.23]	0.017

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Anatomic stages					
Interaction test	**p = 0.513**				
IA/IB/IIA	0 / 171 (0.0)	1 / 198 (0.5)	0.39	[0.02; 9.41]	0.559
IIB	6 / 246 (2.4)	1 / 220 (0.5)	5.37	[0.65; 44.22]	0.118
IIIA	14 / 451 (3.1)	2 / 393 (0.5)	6.10	[1.39; 26.67]	0.016
IIIB	1 / 67 (1.5)	1 / 59 (1.7)	0.88	[0.06; 13.77]	0.928
IIIC	1 / 173 (0.6)	1 / 200 (0.5)	1.16	[0.07; 18.34]	0.918
Nodal status					
Interaction test	**N.E.**				
N0	0 / 91 (0.0)	0 / 117 (0.0)	N.E.	N.E.	N.E.
N1-N3	22 / 1017 (2.2)	6 / 950 (0.6)	3.43	[1.39; 8.41]	0.007
Histological grade at time of surgery					
Interaction test	**p = 0.790**				
Grade 1	2 / 110 (1.8)	1 / 100 (1.0)	1.82	[0.17; 19.75]	0.623
Grade 2	12 / 604 (2.0)	3 / 601 (0.5)	3.98	[1.13; 14.03]	0.032
Grade 3	6 / 297 (2.0)	1 / 266 (0.4)	5.37	[0.65; 44.35]	0.118
Histological subtype					
Interaction test	**p = 0.294**				
Ductal	18 / 863 (2.1)	3 / 835 (0.4)	5.81	[1.72; 19.64]	0.005
Lobular	3 / 172 (1.7)	2 / 169 (1.2)	1.47	[0.25; 8.71]	0.669
Other	1 / 73 (1.4)	1 / 66 (1.5)	0.90	[0.06; 14.17]	0.943
Ki67 status from surgical specimen					
Interaction test	**p = 0.995**				
Ki67≤20	12 / 527 (2.3)	4 / 552 (0.7)	3.14	[1.02; 9.68]	0.046
Ki67>20	7 / 422 (1.7)	2 / 378 (0.5)	3.14	[0.66; 15.00]	0.153
Type of NSAI					
Interaction test	**p = 0.319**				
Letrozole	16 / 809 (2.0)	3 / 773 (0.4)	5.10	[1.49; 17.42]	0.009
Anastrozole	6 / 299 (2.0)	3 / 297 (1.0)	1.99	[0.50; 7.87]	0.328
Prior neo/adjuvant chemotherapy					
Interaction test	**N.E.**				
Yes	21 / 1029 (2.0)	6 / 987 (0.6)	3.36	[1.36; 8.28]	0.009
No	1 / 79 (1.3)	0 / 83 (0.0)	3.15	[0.13; 76.20]	0.480
Prior adjuvant chemotherapy					
Interaction test	**p = 0.424**				
Yes	15 / 513 (2.9)	3 / 488 (0.6)	4.76	[1.39; 16.33]	0.013
No	7 / 595 (1.2)	3 / 582 (0.5)	2.28	[0.59; 8.78]	0.230
Prior neoadjuvant chemotherapy					
Interaction test	**p = 0.570**				
Yes	8 / 546 (1.5)	3 / 538 (0.6)	2.63	[0.70; 9.85]	0.152
No	14 / 562 (2.5)	3 / 532 (0.6)	4.42	[1.28; 15.29]	0.019

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Prior endocrine therapy					
Interaction test	**p = 0.956**				
Yes	19 / 853 (2.2)	5 / 789 (0.6)	3.51	[1.32; 9.37]	0.012
No	3 / 255 (1.2)	1 / 281 (0.4)	3.31	[0.35; 31.58]	0.299
Prior mastectomy					
Interaction test	**p = 0.944**				
Yes	18 / 769 (2.3)	5 / 745 (0.7)	3.49	[1.30; 9.35]	0.013
No	4 / 339 (1.2)	1 / 325 (0.3)	3.83	[0.43; 34.13]	0.228
Prior radiotherapy					
Interaction test	**p = 0.293**				
Yes	21 / 1011 (2.1)	5 / 987 (0.5)	4.10	[1.55; 10.83]	0.004
No	1 / 97 (1.0)	1 / 83 (1.2)	0.86	[0.05; 13.47]	0.912

N: Number of patients
n: Number of patients with event
N.E.: Not estimable
CI: Confidence interval
RR: Relative risk
ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
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Analysis method for interaction test:
p-value from logistic regression model.
logit(proportion) = treatment + subgroup factor + treatment * subgroup factor

Analysis method for within subgroup analysis:
RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm.
ET was the reference group for treatment group comparison.

Table 5-3.2.44 PT mouth ulceration: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	ET (N = 1070)	RR	[95% CI]	p-value
Mouth ulceration					
	n / N (%)	n / N (%)			
Region					
Interaction test	**N.E.**				
NA/WE/O	12 / 640 (1.9)	3 / 627 (0.5)	3.92	[1.11; 13.82]	0.034
ROW	5 / 468 (1.1)	0 / 443 (0.0)	10.41	[0.58; >99.99]	0.112
Geographical region					
Interaction test	**N.E.**				
Europe	8 / 654 (1.2)	3 / 638 (0.5)	2.60	[0.69; 9.76]	0.156
North America/Australia	6 / 213 (2.8)	0 / 194 (0.0)	11.85	[0.67; >99.99]	0.091
Asia	3 / 178 (1.7)	0 / 168 (0.0)	6.61	[0.34; >99.99]	0.210
Latin America	0 / 63 (0.0)	0 / 70 (0.0)	N.E.	N.E.	N.E.
Age group 1 at randomization					
Interaction test	**p = 0.601**				
<45	9 / 549 (1.6)	2 / 496 (0.4)	4.07	[0.88; 18.73]	0.072
45 to 54	8 / 539 (1.5)	1 / 546 (0.2)	8.10	[1.02; 64.57]	0.048
55 to 64	0 / 20 (0.0)	0 / 28 (0.0)	N.E.	N.E.	N.E.
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)					
Interaction test	**p = 0.594**				
<Median	9 / 549 (1.6)	2 / 496 (0.4)	4.07	[0.88; 18.73]	0.072
≥Median	8 / 559 (1.4)	1 / 574 (0.2)	8.21	[1.03; 65.46]	0.047
Race					
Interaction test	**N.E.**				
Asian	4 / 211 (1.9)	0 / 186 (0.0)	7.94	[0.43; >99.99]	0.164
Non-Asian	13 / 840 (1.5)	3 / 827 (0.4)	4.27	[1.22; 14.92]	0.023
BMI at screening					
Interaction test	**p = 0.779**				
≥25	10 / 551 (1.8)	2 / 523 (0.4)	4.75	[1.04; 21.56]	0.044
<25	7 / 542 (1.3)	1 / 535 (0.2)	6.91	[0.85; 55.97]	0.070
AJCC Anatomic Stage Group					
Interaction test	**N.E.**				
Group I/II	4 / 417 (1.0)	0 / 418 (0.0)	9.02	[0.49; >99.99]	0.140
Group III	13 / 691 (1.9)	3 / 652 (0.5)	4.09	[1.17; 14.28]	0.027

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Anatomic stages					
Interaction test	**p = 0.902**				
IA/IB/IIA	0 / 171 (0.0)	0 / 198 (0.0)	N.E.	N.E.	N.E.
IIB	4 / 246 (1.6)	0 / 220 (0.0)	8.05	[0.44; >99.99]	0.161
IIIA	9 / 451 (2.0)	2 / 393 (0.5)	3.92	[0.85; 18.04]	0.079
IIIB	0 / 67 (0.0)	0 / 59 (0.0)	N.E.	N.E.	N.E.
IIIC	4 / 173 (2.3)	1 / 200 (0.5)	4.62	[0.52; 40.98]	0.169
Nodal status					
Interaction test	**N.E.**				
N0	0 / 91 (0.0)	0 / 117 (0.0)	N.E.	N.E.	N.E.
N1-N3	17 / 1017 (1.7)	3 / 950 (0.3)	5.29	[1.56; 18.00]	0.008
Histological grade at time of surgery					
Interaction test	**N.E.**				
Grade 1	0 / 110 (0.0)	1 / 100 (1.0)	0.30	[0.01; 7.36]	0.463
Grade 2	15 / 604 (2.5)	2 / 601 (0.3)	7.46	[1.71; 32.49]	0.007
Grade 3	2 / 297 (0.7)	0 / 266 (0.0)	4.48	[0.22; 92.89]	0.332
Histological subtype					
Interaction test	**N.E.**				
Ductal	13 / 863 (1.5)	3 / 835 (0.4)	4.19	[1.20; 14.66]	0.025
Lobular	3 / 172 (1.7)	0 / 169 (0.0)	6.88	[0.36; >99.99]	0.201
Other	1 / 73 (1.4)	0 / 66 (0.0)	2.72	[0.11; 65.54]	0.538
Ki67 status from surgical specimen					
The subgroup analysis is not presented as all subgroups have less than 10 events.					
Type of NSAI					
Interaction test	**p = 0.564**				
Letrozole	9 / 809 (1.1)	1 / 773 (0.1)	8.60	[1.09; 67.72]	0.041
Anastrozole	8 / 299 (2.7)	2 / 297 (0.7)	3.97	[0.85; 18.55]	0.079
Prior neo/adjuvant chemotherapy					
Interaction test	**N.E.**				
Yes	16 / 1029 (1.6)	3 / 987 (0.3)	5.12	[1.50; 17.50]	0.009
No	1 / 79 (1.3)	0 / 83 (0.0)	3.15	[0.13; 76.20]	0.480
Prior adjuvant chemotherapy					
Interaction test	**p = 0.550**				
Yes	9 / 513 (1.8)	1 / 488 (0.2)	8.56	[1.09; 67.32]	0.041
No	8 / 595 (1.3)	2 / 582 (0.3)	3.91	[0.83; 18.35]	0.084
Prior neoadjuvant chemotherapy					
Interaction test	**p = 0.558**				
Yes	8 / 546 (1.5)	2 / 538 (0.4)	3.94	[0.84; 18.48]	0.082
No	9 / 562 (1.6)	1 / 532 (0.2)	8.52	[1.08; 67.02]	0.042

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Prior endocrine therapy					
Interaction test	**N.E.**				
Yes	15 / 853 (1.8)	3 / 789 (0.4)	4.62	[1.34; 15.91]	0.015
No	2 / 255 (0.8)	0 / 281 (0.0)	5.51	[0.27; >99.99]	0.270
Prior mastectomy					
Interaction test	**p = 0.236**				
Yes	12 / 769 (1.6)	1 / 745 (0.1)	11.63	[1.52; 89.18]	0.018
No	5 / 339 (1.5)	2 / 325 (0.6)	2.40	[0.47; 12.27]	0.294
Prior radiotherapy					
Interaction test	**N.E.**				
Yes	16 / 1011 (1.6)	3 / 987 (0.3)	5.21	[1.52; 17.81]	0.009
No	1 / 97 (1.0)	0 / 83 (0.0)	2.57	[0.11; 62.29]	0.561

N: Number of patients
n: Number of patients with event
N.E.: Not estimable
CI: Confidence interval
RR: Relative risk
ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
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Analysis method for interaction test:
p-value from logistic regression model.
logit(proportion) = treatment + subgroup factor + treatment * subgroup factor

Analysis method for within subgroup analysis:
RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm.
ET was the reference group for treatment group comparison.

Table 5-3.2.45 SOC blood and lymphatic system disorders: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	ET (N = 1070)	RR	[95% CI]	p-value
Blood and lymphatic system disorders					
	n / N (%)	n / N (%)			
Region					
Interaction test	**p = 0.457**				
NA/WE/O	289 / 640 (45.2)	50 / 627 (8.0)	5.66	[4.28; 7.49]	<.001
ROW	248 / 468 (53.0)	55 / 443 (12.4)	4.27	[3.29; 5.54]	<.001
Geographical region					
Interaction test	**p = 0.910**				
Europe	372 / 654 (56.9)	77 / 638 (12.1)	4.71	[3.78; 5.87]	<.001
North America/Australia	88 / 213 (41.3)	15 / 194 (7.7)	5.34	[3.20; 8.91]	<.001
Asia	41 / 178 (23.0)	6 / 168 (3.6)	6.45	[2.81; 14.80]	<.001
Latin America	36 / 63 (57.1)	7 / 70 (10.0)	5.71	[2.74; 11.91]	<.001
Age group 1 at randomization					
Interaction test	**p = 0.847**				
<45	265 / 549 (48.3)	49 / 496 (9.9)	4.89	[3.69; 6.46]	<.001
45 to 54	262 / 539 (48.6)	52 / 546 (9.5)	5.10	[3.89; 6.70]	<.001
55 to 64	10 / 20 (50.0)	4 / 28 (14.3)	3.50	[1.28; 9.59]	0.015
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)					
Interaction test	**p = 0.902**				
<Median	265 / 549 (48.3)	49 / 496 (9.9)	4.89	[3.69; 6.46]	<.001
≥Median	272 / 559 (48.7)	56 / 574 (9.8)	4.99	[3.83; 6.49]	<.001
Race					
Interaction test	**p = 0.827**				
Asian	58 / 211 (27.5)	8 / 186 (4.3)	6.39	[3.13; 13.03]	<.001
Non-Asian	445 / 840 (53.0)	90 / 827 (10.9)	4.87	[3.96; 5.98]	<.001
BMI at screening					
Interaction test	**p = 0.438**				
≥25	248 / 551 (45.0)	49 / 523 (9.4)	4.80	[3.62; 6.37]	<.001
<25	283 / 542 (52.2)	55 / 535 (10.3)	5.08	[3.90; 6.61]	<.001
AJCC Anatomic Stage Group					
Interaction test	**p = 0.123**				
Group I/II	206 / 417 (49.4)	51 / 418 (12.2)	4.05	[3.08; 5.33]	<.001
Group III	331 / 691 (47.9)	54 / 652 (8.3)	5.78	[4.43; 7.55]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Anatomic stages					
Interaction test	**p = 0.373**				
IA/IB/IIA	88 / 171 (51.5)	23 / 198 (11.6)	4.43	[2.94; 6.68]	<.001
IIB	118 / 246 (48.0)	28 / 220 (12.7)	3.77	[2.60; 5.45]	<.001
IIIA	219 / 451 (48.6)	29 / 393 (7.4)	6.58	[4.58; 9.46]	<.001
IIIB	39 / 67 (58.2)	10 / 59 (16.9)	3.43	[1.88; 6.26]	<.001
IIIC	73 / 173 (42.2)	15 / 200 (7.5)	5.63	[3.35; 9.44]	<.001
Nodal status					
Interaction test	**p = 0.302**				
N0	52 / 91 (57.1)	20 / 117 (17.1)	3.34	[2.16; 5.17]	<.001
N1-N3	485 / 1017 (47.7)	85 / 950 (8.9)	5.33	[4.31; 6.59]	<.001
Histological grade at time of surgery					
Interaction test	**p = 0.930**				
Grade 1	56 / 110 (50.9)	12 / 100 (12.0)	4.24	[2.42; 7.44]	<.001
Grade 2	296 / 604 (49.0)	65 / 601 (10.8)	4.53	[3.55; 5.78]	<.001
Grade 3	131 / 297 (44.1)	22 / 266 (8.3)	5.33	[3.50; 8.12]	<.001
Histological subtype					
Interaction test	**p = 0.687**				
Ductal	418 / 863 (48.4)	83 / 835 (9.9)	4.87	[3.93; 6.04]	<.001
Lobular	84 / 172 (48.8)	14 / 169 (8.3)	5.90	[3.49; 9.96]	<.001
Other	35 / 73 (47.9)	8 / 66 (12.1)	3.96	[1.98; 7.90]	<.001
Ki67 status from surgical specimen					
Interaction test	**p = 0.012**				
Ki67≤20	239 / 527 (45.4)	62 / 552 (11.2)	4.04	[3.14; 5.20]	<.001
Ki67>20	228 / 422 (54.0)	32 / 378 (8.5)	6.38	[4.53; 8.99]	<.001
Type of NSAI					
Interaction test	**p = 0.763**				
Letrozole	391 / 809 (48.3)	77 / 773 (10.0)	4.85	[3.88; 6.07]	<.001
Anastrozole	146 / 299 (48.8)	28 / 297 (9.4)	5.18	[3.57; 7.51]	<.001
Prior neo/adjuvant chemotherapy					
Interaction test	**p = 0.407**				
Yes	487 / 1029 (47.3)	88 / 987 (8.9)	5.31	[4.30; 6.55]	<.001
No	50 / 79 (63.3)	17 / 83 (20.5)	3.09	[1.96; 4.88]	<.001
Prior adjuvant chemotherapy					
Interaction test	**p = 0.895**				
Yes	226 / 513 (44.1)	41 / 488 (8.4)	5.24	[3.85; 7.14]	<.001
No	311 / 595 (52.3)	64 / 582 (11.0)	4.75	[3.73; 6.06]	<.001
Prior neoadjuvant chemotherapy					
Interaction test	**p = 0.287**				
Yes	274 / 546 (50.2)	50 / 538 (9.3)	5.40	[4.09; 7.12]	<.001
No	263 / 562 (46.8)	55 / 532 (10.3)	4.53	[3.47; 5.90]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Prior endocrine therapy					
Interaction test	**p = 0.074**				
Yes	399 / 853 (46.8)	62 / 789 (7.9)	5.95	[4.64; 7.64]	<.001
No	138 / 255 (54.1)	43 / 281 (15.3)	3.54	[2.63; 4.76]	<.001
Prior mastectomy					
Interaction test	**p = 0.187**				
Yes	370 / 769 (48.1)	79 / 745 (10.6)	4.54	[3.64; 5.66]	<.001
No	167 / 339 (49.3)	26 / 325 (8.0)	6.16	[4.19; 9.04]	<.001
Prior radiotherapy					
Interaction test	**p = 0.018**				
Yes	475 / 1011 (47.0)	81 / 987 (8.2)	5.72	[4.60; 7.12]	<.001
No	62 / 97 (63.9)	24 / 83 (28.9)	2.21	[1.53; 3.20]	<.001

N: Number of patients
n: Number of patients with event
CI: Confidence interval
RR: Relative risk
ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
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Analysis method for interaction test:
p-value from logistic regression model.
logit(proportion) = treatment + subgroup factor + treatment * subgroup factor

Analysis method for within subgroup analysis:
RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm.
ET was the reference group for treatment group comparison.

Table 5-3.2.46 PT neutropenia: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	ET (N = 1070)	RR	[95% CI]	p-value
Neutropenia					
	n / N (%)	n / N (%)			
Region					
Interaction test	**p = 0.058**				
NA/WE/O	246 / 640 (38.4)	13 / 627 (2.1)	18.54	[10.73; 32.03]	<.001
ROW	224 / 468 (47.9)	26 / 443 (5.9)	8.16	[5.55; 11.98]	<.001
Geographical region					
Interaction test	**p = 0.400**				
Europe	342 / 654 (52.3)	32 / 638 (5.0)	10.43	[7.38; 14.73]	<.001
North America/Australia	71 / 213 (33.3)	2 / 194 (1.0)	32.33	[8.04; >99.99]	<.001
Asia	24 / 178 (13.5)	0 / 168 (0.0)	46.26	[2.84; >99.99]	0.007
Latin America	33 / 63 (52.4)	5 / 70 (7.1)	7.33	[3.05; 17.62]	<.001
Age group 1 at randomization					
Interaction test	**p = 0.957**				
<45	237 / 549 (43.2)	19 / 496 (3.8)	11.27	[7.18; 17.70]	<.001
45 to 54	226 / 539 (41.9)	19 / 546 (3.5)	12.05	[7.66; 18.95]	<.001
55 to 64	7 / 20 (35.0)	1 / 28 (3.6)	9.80	[1.31; 73.52]	0.026
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)					
Interaction test	**p = 0.914**				
<Median	237 / 549 (43.2)	19 / 496 (3.8)	11.27	[7.18; 17.70]	<.001
≥Median	233 / 559 (41.7)	20 / 574 (3.5)	11.96	[7.69; 18.60]	<.001
Race					
Interaction test	**N.E.**				
Asian	39 / 211 (18.5)	0 / 186 (0.0)	69.68	[4.31; >99.99]	0.003
Non-Asian	405 / 840 (48.2)	37 / 827 (4.5)	10.78	[7.80; 14.88]	<.001
BMI at screening					
Interaction test	**p = 0.427**				
≥25	215 / 551 (39.0)	14 / 523 (2.7)	14.58	[8.60; 24.70]	<.001
<25	250 / 542 (46.1)	25 / 535 (4.7)	9.87	[6.66; 14.63]	<.001
AJCC Anatomic Stage Group					
Interaction test	**p = 0.198**				
Group I/II	181 / 417 (43.4)	20 / 418 (4.8)	9.07	[5.83; 14.11]	<.001
Group III	289 / 691 (41.8)	19 / 652 (2.9)	14.35	[9.14; 22.55]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Anatomic stages					
Interaction test	**p = 0.258**				
IA/IB/IIA	77 / 171 (45.0)	8 / 198 (4.0)	11.14	[5.54; 22.41]	<.001
IIB	104 / 246 (42.3)	12 / 220 (5.5)	7.75	[4.39; 13.69]	<.001
IIIA	190 / 451 (42.1)	10 / 393 (2.5)	16.56	[8.89; 30.82]	<.001
IIIB	37 / 67 (55.2)	6 / 59 (10.2)	5.43	[2.47; 11.95]	<.001
IIIC	62 / 173 (35.8)	3 / 200 (1.5)	23.89	[7.64; 74.75]	<.001
Nodal status					
Interaction test	**p = 0.013**				
N0	45 / 91 (49.5)	12 / 117 (10.3)	4.82	[2.71; 8.57]	<.001
N1-N3	425 / 1017 (41.8)	27 / 950 (2.8)	14.70	[10.07; 21.48]	<.001
Histological grade at time of surgery					
Interaction test	**p = 0.710**				
Grade 1	52 / 110 (47.3)	3 / 100 (3.0)	15.76	[5.08; 48.87]	<.001
Grade 2	261 / 604 (43.2)	23 / 601 (3.8)	11.29	[7.49; 17.03]	<.001
Grade 3	107 / 297 (36.0)	9 / 266 (3.4)	10.65	[5.50; 20.60]	<.001
Histological subtype					
Interaction test	**p = 0.488**				
Ductal	370 / 863 (42.9)	30 / 835 (3.6)	11.93	[8.33; 17.10]	<.001
Lobular	71 / 172 (41.3)	5 / 169 (3.0)	13.95	[5.78; 33.69]	<.001
Other	29 / 73 (39.7)	4 / 66 (6.1)	6.55	[2.43; 17.66]	<.001
Ki67 status from surgical specimen					
Interaction test	**p = 0.164**				
Ki67≤20	210 / 527 (39.8)	23 / 552 (4.2)	9.56	[6.32; 14.46]	<.001
Ki67>20	202 / 422 (47.9)	13 / 378 (3.4)	13.92	[8.08; 23.96]	<.001
Type of NSAI					
Interaction test	**p = 0.696**				
Letrozole	343 / 809 (42.4)	27 / 773 (3.5)	12.14	[8.31; 17.73]	<.001
Anastrozole	127 / 299 (42.5)	12 / 297 (4.0)	10.51	[5.95; 18.58]	<.001
Prior neo/adjuvant chemotherapy					
Interaction test	**p = 0.727**				
Yes	425 / 1029 (41.3)	33 / 987 (3.3)	12.35	[8.76; 17.41]	<.001
No	45 / 79 (57.0)	6 / 83 (7.2)	7.88	[3.56; 17.43]	<.001
Prior adjuvant chemotherapy					
Interaction test	**p = 0.274**				
Yes	193 / 513 (37.6)	11 / 488 (2.3)	16.69	[9.21; 30.25]	<.001
No	277 / 595 (46.6)	28 / 582 (4.8)	9.68	[6.67; 14.03]	<.001
Prior neoadjuvant chemotherapy					
Interaction test	**p = 0.637**				
Yes	245 / 546 (44.9)	23 / 538 (4.3)	10.50	[6.96; 15.82]	<.001
No	225 / 562 (40.0)	16 / 532 (3.0)	13.31	[8.13; 21.80]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Prior endocrine therapy					
Interaction test	**p = 0.504**				
Yes	351 / 853 (41.1)	25 / 789 (3.2)	12.99	[8.76; 19.26]	<.001
No	119 / 255 (46.7)	14 / 281 (5.0)	9.37	[5.53; 15.87]	<.001
Prior mastectomy					
Interaction test	**p = 0.487**				
Yes	317 / 769 (41.2)	28 / 745 (3.8)	10.97	[7.55; 15.93]	<.001
No	153 / 339 (45.1)	11 / 325 (3.4)	13.33	[7.37; 24.12]	<.001
Prior radiotherapy					
Interaction test	**p = 0.194**				
Yes	416 / 1011 (41.1)	31 / 987 (3.1)	13.10	[9.19; 18.67]	<.001
No	54 / 97 (55.7)	8 / 83 (9.6)	5.78	[2.92; 11.43]	<.001

N: Number of patients
n: Number of patients with event
N.E.: Not estimable
CI: Confidence interval
RR: Relative risk
ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
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Analysis method for interaction test:
p-value from logistic regression model.
logit(proportion) = treatment + subgroup factor + treatment * subgroup factor

Analysis method for within subgroup analysis:
RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm.
ET was the reference group for treatment group comparison.

Table 5-3.2.47 PT leukopenia: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	ET (N = 1070)	RR	[95% CI]	p-value
Leukopenia					
	n / N (%)	n / N (%)			
Region					
Interaction test	**p = 0.650**				
NA/WE/O	45 / 640 (7.0)	9 / 627 (1.4)	4.90	[2.42; 9.94]	<.001
ROW	78 / 468 (16.7)	20 / 443 (4.5)	3.69	[2.30; 5.93]	<.001
Geographical region					
Interaction test	**p = 0.285**				
Europe	107 / 654 (16.4)	25 / 638 (3.9)	4.18	[2.74; 6.36]	<.001
North America/Australia	10 / 213 (4.7)	1 / 194 (0.5)	9.11	[1.18; 70.50]	0.034
Asia	2 / 178 (1.1)	0 / 168 (0.0)	4.72	[0.23; 97.61]	0.315
Latin America	4 / 63 (6.3)	3 / 70 (4.3)	1.48	[0.34; 6.36]	0.597
Age group 1 at randomization					
Interaction test	**p = 0.663**				
<45	62 / 549 (11.3)	15 / 496 (3.0)	3.73	[2.15; 6.48]	<.001
45 to 54	55 / 539 (10.2)	13 / 546 (2.4)	4.29	[2.37; 7.75]	<.001
55 to 64	6 / 20 (30.0)	1 / 28 (3.6)	8.40	[1.09; 64.46]	0.041
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)					
Interaction test	**p = 0.666**				
<Median	62 / 549 (11.3)	15 / 496 (3.0)	3.73	[2.15; 6.48]	<.001
≥Median	61 / 559 (10.9)	14 / 574 (2.4)	4.47	[2.53; 7.90]	<.001
Race					
Interaction test	**N.E.**				
Asian	3 / 211 (1.4)	0 / 186 (0.0)	6.17	[0.32; >99.99]	0.228
Non-Asian	112 / 840 (13.3)	27 / 827 (3.3)	4.08	[2.71; 6.15]	<.001
BMI at screening					
Interaction test	**p = 0.298**				
≥25	65 / 551 (11.8)	12 / 523 (2.3)	5.14	[2.81; 9.41]	<.001
<25	58 / 542 (10.7)	17 / 535 (3.2)	3.37	[1.99; 5.71]	<.001
AJCC Anatomic Stage Group					
Interaction test	**p = 0.399**				
Group I/II	47 / 417 (11.3)	14 / 418 (3.3)	3.37	[1.88; 6.02]	<.001
Group III	76 / 691 (11.0)	15 / 652 (2.3)	4.78	[2.78; 8.23]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Anatomic stages					
Interaction test	**p = 0.855**				
IA/IB/IIA	18 / 171 (10.5)	7 / 198 (3.5)	2.98	[1.27; 6.96]	0.012
IIB	29 / 246 (11.8)	7 / 220 (3.2)	3.70	[1.66; 8.29]	0.001
IIIA	49 / 451 (10.9)	8 / 393 (2.0)	5.34	[2.56; 11.13]	<.001
IIIB	17 / 67 (25.4)	5 / 59 (8.5)	2.99	[1.18; 7.62]	0.021
IIIC	10 / 173 (5.8)	2 / 200 (1.0)	5.78	[1.28; 26.02]	0.022
Nodal status					
Interaction test	**p = 0.106**				
N0	13 / 91 (14.3)	8 / 117 (6.8)	2.09	[0.90; 4.83]	0.084
N1-N3	110 / 1017 (10.8)	21 / 950 (2.2)	4.89	[3.09; 7.74]	<.001
Histological grade at time of surgery					
Interaction test	**p = 0.584**				
Grade 1	12 / 110 (10.9)	1 / 100 (1.0)	10.91	[1.44; 82.40]	0.021
Grade 2	77 / 604 (12.7)	21 / 601 (3.5)	3.65	[2.28; 5.83]	<.001
Grade 3	25 / 297 (8.4)	5 / 266 (1.9)	4.48	[1.74; 11.53]	0.002
Histological subtype					
Interaction test	**p = 0.866**				
Ductal	92 / 863 (10.7)	23 / 835 (2.8)	3.87	[2.48; 6.05]	<.001
Lobular	21 / 172 (12.2)	4 / 169 (2.4)	5.16	[1.81; 14.71]	0.002
Other	10 / 73 (13.7)	2 / 66 (3.0)	4.52	[1.03; 19.88]	0.046
Ki67 status from surgical specimen					
Interaction test	**p = 0.343**				
Ki67≤20	56 / 527 (10.6)	18 / 552 (3.3)	3.26	[1.94; 5.47]	<.001
Ki67>20	54 / 422 (12.8)	10 / 378 (2.6)	4.84	[2.50; 9.36]	<.001
Type of NSAI					
Interaction test	**p = 0.637**				
Letrozole	89 / 809 (11.0)	22 / 773 (2.8)	3.87	[2.45; 6.10]	<.001
Anastrozole	34 / 299 (11.4)	7 / 297 (2.4)	4.82	[2.17; 10.71]	<.001
Prior neo/adjuvant chemotherapy					
Interaction test	**p = 0.769**				
Yes	103 / 1029 (10.0)	24 / 987 (2.4)	4.12	[2.66; 6.36]	<.001
No	20 / 79 (25.3)	5 / 83 (6.0)	4.20	[1.66; 10.65]	0.002
Prior adjuvant chemotherapy					
Interaction test	**p = 0.457**				
Yes	40 / 513 (7.8)	11 / 488 (2.3)	3.46	[1.80; 6.66]	<.001
No	83 / 595 (13.9)	18 / 582 (3.1)	4.51	[2.74; 7.41]	<.001
Prior neoadjuvant chemotherapy					
Interaction test	**p = 0.403**				
Yes	68 / 546 (12.5)	14 / 538 (2.6)	4.79	[2.73; 8.40]	<.001
No	55 / 562 (9.8)	15 / 532 (2.8)	3.47	[1.99; 6.07]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Prior endocrine therapy					
Interaction test	**p = 0.679**				
Yes	80 / 853 (9.4)	16 / 789 (2.0)	4.62	[2.73; 7.84]	<.001
No	43 / 255 (16.9)	13 / 281 (4.6)	3.64	[2.01; 6.62]	<.001
Prior mastectomy					
Interaction test	**p = 0.302**				
Yes	95 / 769 (12.4)	20 / 745 (2.7)	4.60	[2.87; 7.37]	<.001
No	28 / 339 (8.3)	9 / 325 (2.8)	2.98	[1.43; 6.22]	0.004
Prior radiotherapy					
Interaction test	**p = 0.393**				
Yes	94 / 1011 (9.3)	24 / 987 (2.4)	3.82	[2.46; 5.93]	<.001
No	29 / 97 (29.9)	5 / 83 (6.0)	4.96	[2.01; 12.24]	<.001

N: Number of patients
n: Number of patients with event
N.E.: Not estimable
CI: Confidence interval
RR: Relative risk
ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
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Analysis method for interaction test:
p-value from logistic regression model.
logit(proportion) = treatment + subgroup factor + treatment * subgroup factor

Analysis method for within subgroup analysis:
RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm.
ET was the reference group for treatment group comparison.

Table 5-3.2.48 PT anaemia: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	ET (N = 1070)	RR	[95% CI]	p-value
Anaemia					
	n / N (%)	n / N (%)			
Region					
Interaction test	**p = 0.329**				
NA/WE/O	37 / 640 (5.8)	19 / 627 (3.0)	1.91	[1.11; 3.28]	0.020
ROW	44 / 468 (9.4)	15 / 443 (3.4)	2.78	[1.57; 4.92]	<.001
Geographical region					
Interaction test	**p = 0.798**				
Europe	44 / 654 (6.7)	23 / 638 (3.6)	1.87	[1.14; 3.05]	0.013
North America/Australia	15 / 213 (7.0)	5 / 194 (2.6)	2.73	[1.01; 7.38]	0.047
Asia	13 / 178 (7.3)	6 / 168 (3.6)	2.04	[0.80; 5.26]	0.138
Latin America	9 / 63 (14.3)	0 / 70 (0.0)	21.08	[1.25; >99.99]	0.034
Age group 1 at randomization					
Interaction test	**p = 0.972**				
<45	37 / 549 (6.7)	15 / 496 (3.0)	2.23	[1.24; 4.01]	0.008
45 to 54	41 / 539 (7.6)	19 / 546 (3.5)	2.19	[1.29; 3.72]	0.004
55 to 64	3 / 20 (15.0)	0 / 28 (0.0)	9.67	[0.53; >99.99]	0.126
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)					
Interaction test	**p = 0.860**				
<Median	37 / 549 (6.7)	15 / 496 (3.0)	2.23	[1.24; 4.01]	0.008
≥Median	44 / 559 (7.9)	19 / 574 (3.3)	2.38	[1.41; 4.02]	0.001
Race					
Interaction test	**p = 0.487**				
Asian	14 / 211 (6.6)	7 / 186 (3.8)	1.76	[0.73; 4.27]	0.210
Non-Asian	66 / 840 (7.9)	26 / 827 (3.1)	2.50	[1.60; 3.89]	<.001
BMI at screening					
Interaction test	**p = 0.067**				
≥25	43 / 551 (7.8)	11 / 523 (2.1)	3.71	[1.93; 7.12]	<.001
<25	38 / 542 (7.0)	22 / 535 (4.1)	1.70	[1.02; 2.84]	0.041
AJCC Anatomic Stage Group					
Interaction test	**p = 0.585**				
Group I/II	28 / 417 (6.7)	14 / 418 (3.3)	2.00	[1.07; 3.75]	0.030
Group III	53 / 691 (7.7)	20 / 652 (3.1)	2.50	[1.51; 4.14]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Anatomic stages					
Interaction test	**p = 0.705**				
IA/IB/IIA	12 / 171 (7.0)	7 / 198 (3.5)	1.98	[0.80; 4.93]	0.140
IIB	16 / 246 (6.5)	7 / 220 (3.2)	2.04	[0.86; 4.88]	0.107
IIIA	31 / 451 (6.9)	10 / 393 (2.5)	2.70	[1.34; 5.44]	0.005
IIIB	11 / 67 (16.4)	2 / 59 (3.4)	4.84	[1.12; 20.97]	0.035
IIIC	11 / 173 (6.4)	8 / 200 (4.0)	1.59	[0.65; 3.86]	0.306
Nodal status					
Interaction test	**p = 0.807**				
N0	10 / 91 (11.0)	5 / 117 (4.3)	2.57	[0.91; 7.26]	0.075
N1-N3	71 / 1017 (7.0)	29 / 950 (3.1)	2.29	[1.50; 3.49]	<.001
Histological grade at time of surgery					
Interaction test	**p = 0.270**				
Grade 1	5 / 110 (4.5)	2 / 100 (2.0)	2.27	[0.45; 11.45]	0.320
Grade 2	43 / 604 (7.1)	24 / 601 (4.0)	1.78	[1.10; 2.90]	0.020
Grade 3	27 / 297 (9.1)	6 / 266 (2.3)	4.03	[1.69; 9.61]	0.002
Histological subtype					
Interaction test	**p = 0.974**				
Ductal	63 / 863 (7.3)	27 / 835 (3.2)	2.26	[1.45; 3.51]	<.001
Lobular	12 / 172 (7.0)	5 / 169 (3.0)	2.36	[0.85; 6.55]	0.100
Other	6 / 73 (8.2)	2 / 66 (3.0)	2.71	[0.57; 12.98]	0.212
Ki67 status from surgical specimen					
Interaction test	**p = 0.012**				
Ki67≤20	38 / 527 (7.2)	24 / 552 (4.3)	1.66	[1.01; 2.73]	0.046
Ki67>20	39 / 422 (9.2)	6 / 378 (1.6)	5.82	[2.49; 13.60]	<.001
Type of NSAI					
Interaction test	**p = 0.244**				
Letrozole	59 / 809 (7.3)	28 / 773 (3.6)	2.01	[1.30; 3.12]	0.002
Anastrozole	22 / 299 (7.4)	6 / 297 (2.0)	3.64	[1.50; 8.85]	0.004
Prior neo/adjuvant chemotherapy					
Interaction test	**p = 0.330**				
Yes	73 / 1029 (7.1)	28 / 987 (2.8)	2.50	[1.63; 3.83]	<.001
No	8 / 79 (10.1)	6 / 83 (7.2)	1.40	[0.51; 3.86]	0.514
Prior adjuvant chemotherapy					
Interaction test	**p = 0.427**				
Yes	28 / 513 (5.5)	14 / 488 (2.9)	1.90	[1.01; 3.57]	0.045
No	53 / 595 (8.9)	20 / 582 (3.4)	2.59	[1.57; 4.28]	<.001
Prior neoadjuvant chemotherapy					
Interaction test	**p = 0.210**				
Yes	45 / 546 (8.2)	15 / 538 (2.8)	2.96	[1.67; 5.24]	<.001
No	36 / 562 (6.4)	19 / 532 (3.6)	1.79	[1.04; 3.09]	0.035

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Prior endocrine therapy					
Interaction test	**p = 0.313**				
Yes	53 / 853 (6.2)	24 / 789 (3.0)	2.04	[1.27; 3.28]	0.003
No	28 / 255 (11.0)	10 / 281 (3.6)	3.09	[1.53; 6.22]	0.002
Prior mastectomy					
Interaction test	**p = 0.479**				
Yes	59 / 769 (7.7)	27 / 745 (3.6)	2.12	[1.36; 3.30]	<.001
No	22 / 339 (6.5)	7 / 325 (2.2)	3.01	[1.30; 6.96]	0.010
Prior radiotherapy					
Interaction test	**p = 0.283**				
Yes	64 / 1011 (6.3)	30 / 987 (3.0)	2.08	[1.36; 3.18]	<.001
No	17 / 97 (17.5)	4 / 83 (4.8)	3.64	[1.27; 10.38]	0.016

N: Number of patients
n: Number of patients with event
CI: Confidence interval
RR: Relative risk
ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
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Analysis method for interaction test:
p-value from logistic regression model.
logit(proportion) = treatment + subgroup factor + treatment * subgroup factor

Analysis method for within subgroup analysis:
RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm.
ET was the reference group for treatment group comparison.

Table 5-3.2.49 SOC nervous system disorders: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	ET (N = 1070)	RR	[95% CI]	p-value
Nervous system disorders					
	n / N (%)	n / N (%)			
Region					
Interaction test	**p = 0.006**				
NA/WE/O	347 / 640 (54.2)	262 / 627 (41.8)	1.30	[1.15; 1.46]	<.001
ROW	134 / 468 (28.6)	128 / 443 (28.9)	0.99	[0.81; 1.22]	0.931
Geographical region					
Interaction test	**p = 0.005**				
Europe	276 / 654 (42.2)	231 / 638 (36.2)	1.17	[1.02; 1.34]	0.028
North America/Australia	131 / 213 (61.5)	79 / 194 (40.7)	1.51	[1.24; 1.85]	<.001
Asia	56 / 178 (31.5)	54 / 168 (32.1)	0.98	[0.72; 1.33]	0.892
Latin America	18 / 63 (28.6)	26 / 70 (37.1)	0.77	[0.47; 1.26]	0.299
Age group 1 at randomization					
Interaction test	**p = 0.940**				
<45	236 / 549 (43.0)	176 / 496 (35.5)	1.21	[1.04; 1.41]	0.014
45 to 54	238 / 539 (44.2)	205 / 546 (37.5)	1.18	[1.02; 1.36]	0.027
55 to 64	7 / 20 (35.0)	9 / 28 (32.1)	1.09	[0.49; 2.43]	0.836
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)					
Interaction test	**p = 0.805**				
<Median	236 / 549 (43.0)	176 / 496 (35.5)	1.21	[1.04; 1.41]	0.014
≥Median	245 / 559 (43.8)	214 / 574 (37.3)	1.18	[1.02; 1.35]	0.025
Race					
Interaction test	**p = 0.453**				
Asian	77 / 211 (36.5)	61 / 186 (32.8)	1.11	[0.85; 1.46]	0.442
Non-Asian	372 / 840 (44.3)	299 / 827 (36.2)	1.22	[1.09; 1.38]	<.001
BMI at screening					
Interaction test	**p = 0.295**				
≥25	234 / 551 (42.5)	198 / 523 (37.9)	1.12	[0.97; 1.30]	0.125
<25	237 / 542 (43.7)	186 / 535 (34.8)	1.26	[1.08; 1.46]	0.003
AJCC Anatomic Stage Group					
Interaction test	**p = 0.278**				
Group I/II	180 / 417 (43.2)	163 / 418 (39.0)	1.11	[0.94; 1.30]	0.221
Group III	301 / 691 (43.6)	227 / 652 (34.8)	1.25	[1.09; 1.43]	0.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Anatomic stages					
Interaction test	**p = 0.425**				
IA/IB/IIA	78 / 171 (45.6)	71 / 198 (35.9)	1.27	[0.99; 1.63]	0.057
IIB	102 / 246 (41.5)	92 / 220 (41.8)	0.99	[0.80; 1.23]	0.938
IIIA	203 / 451 (45.0)	146 / 393 (37.2)	1.21	[1.03; 1.43]	0.022
IIIB	23 / 67 (34.3)	13 / 59 (22.0)	1.56	[0.87; 2.79]	0.136
IIIC	75 / 173 (43.4)	68 / 200 (34.0)	1.28	[0.99; 1.65]	0.064
Nodal status					
Interaction test	**p = 0.520**				
N0	37 / 91 (40.7)	35 / 117 (29.9)	1.36	[0.94; 1.97]	0.106
N1-N3	444 / 1017 (43.7)	352 / 950 (37.1)	1.18	[1.06; 1.31]	0.003
Histological grade at time of surgery					
Interaction test	**p = 0.611**				
Grade 1	44 / 110 (40.0)	31 / 100 (31.0)	1.29	[0.89; 1.87]	0.179
Grade 2	271 / 604 (44.9)	210 / 601 (34.9)	1.28	[1.12; 1.48]	<.001
Grade 3	136 / 297 (45.8)	108 / 266 (40.6)	1.13	[0.93; 1.37]	0.217
Histological subtype					
Interaction test	**p = 0.310**				
Ductal	371 / 863 (43.0)	309 / 835 (37.0)	1.16	[1.03; 1.31]	0.012
Lobular	80 / 172 (46.5)	55 / 169 (32.5)	1.43	[1.09; 1.87]	0.009
Other	30 / 73 (41.1)	26 / 66 (39.4)	1.04	[0.69; 1.57]	0.838
Ki67 status from surgical specimen					
Interaction test	**p = 0.405**				
Ki67≤20	204 / 527 (38.7)	191 / 552 (34.6)	1.12	[0.96; 1.31]	0.162
Ki67>20	180 / 422 (42.7)	131 / 378 (34.7)	1.23	[1.03; 1.47]	0.022
Type of NSAI					
Interaction test	**p = 0.658**				
Letrozole	335 / 809 (41.4)	271 / 773 (35.1)	1.18	[1.04; 1.34]	0.010
Anastrozole	146 / 299 (48.8)	119 / 297 (40.1)	1.22	[1.02; 1.46]	0.032
Prior neo/adjuvant chemotherapy					
Interaction test	**p = 0.399**				
Yes	450 / 1029 (43.7)	358 / 987 (36.3)	1.21	[1.08; 1.34]	<.001
No	31 / 79 (39.2)	32 / 83 (38.6)	1.02	[0.69; 1.50]	0.929
Prior adjuvant chemotherapy					
Interaction test	**p = 0.875**				
Yes	239 / 513 (46.6)	191 / 488 (39.1)	1.19	[1.03; 1.38]	0.018
No	242 / 595 (40.7)	199 / 582 (34.2)	1.19	[1.03; 1.38]	0.022
Prior neoadjuvant chemotherapy					
Interaction test	**p = 0.754**				
Yes	222 / 546 (40.7)	179 / 538 (33.3)	1.22	[1.04; 1.43]	0.012
No	259 / 562 (46.1)	211 / 532 (39.7)	1.16	[1.01; 1.33]	0.033

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Prior endocrine therapy					
Interaction test	**p = 0.120**				
Yes	377 / 853 (44.2)	279 / 789 (35.4)	1.25	[1.11; 1.41]	<.001
No	104 / 255 (40.8)	111 / 281 (39.5)	1.03	[0.84; 1.27]	0.762
Prior mastectomy					
Interaction test	**p = 0.072**				
Yes	341 / 769 (44.3)	260 / 745 (34.9)	1.27	[1.12; 1.44]	<.001
No	140 / 339 (41.3)	130 / 325 (40.0)	1.03	[0.86; 1.24]	0.734
Prior radiotherapy					
Interaction test	**p = 0.526**				
Yes	436 / 1011 (43.1)	361 / 987 (36.6)	1.18	[1.06; 1.31]	0.003
No	45 / 97 (46.4)	29 / 83 (34.9)	1.33	[0.92; 1.91]	0.126

N: Number of patients
n: Number of patients with event
CI: Confidence interval
RR: Relative risk
ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
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Analysis method for interaction test:
p-value from logistic regression model.
logit(proportion) = treatment + subgroup factor + treatment * subgroup factor

Analysis method for within subgroup analysis:
RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm.
ET was the reference group for treatment group comparison.

Table 5-3.2.50 PT headache: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	ET (N = 1070)	RR	[95% CI]	p-value
Headache					
	n / N (%)	n / N (%)			
Region					
Interaction test	**p = 0.009**				
NA/WE/O	226 / 640 (35.3)	148 / 627 (23.6)	1.50	[1.26; 1.78]	<.001
ROW	88 / 468 (18.8)	82 / 443 (18.5)	1.02	[0.77; 1.33]	0.910
Geographical region					
Interaction test	**p = 0.004**				
Europe	173 / 654 (26.5)	136 / 638 (21.3)	1.24	[1.02; 1.51]	0.031
North America/Australia	90 / 213 (42.3)	42 / 194 (21.6)	1.95	[1.43; 2.66]	<.001
Asia	40 / 178 (22.5)	33 / 168 (19.6)	1.14	[0.76; 1.72]	0.520
Latin America	11 / 63 (17.5)	19 / 70 (27.1)	0.64	[0.33; 1.24]	0.190
Age group 1 at randomization					
Interaction test	**p = 0.531**				
<45	158 / 549 (28.8)	100 / 496 (20.2)	1.43	[1.15; 1.78]	0.001
45 to 54	150 / 539 (27.8)	125 / 546 (22.9)	1.22	[0.99; 1.49]	0.062
55 to 64	6 / 20 (30.0)	5 / 28 (17.9)	1.68	[0.59; 4.75]	0.328
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)					
Interaction test	**p = 0.342**				
<Median	158 / 549 (28.8)	100 / 496 (20.2)	1.43	[1.15; 1.78]	0.001
≥Median	156 / 559 (27.9)	130 / 574 (22.6)	1.23	[1.01; 1.51]	0.042
Race					
Interaction test	**p = 0.736**				
Asian	58 / 211 (27.5)	36 / 186 (19.4)	1.42	[0.98; 2.05]	0.060
Non-Asian	237 / 840 (28.2)	177 / 827 (21.4)	1.32	[1.11; 1.56]	0.001
BMI at screening					
Interaction test	**p = 0.288**				
≥25	149 / 551 (27.0)	118 / 523 (22.6)	1.20	[0.97; 1.48]	0.091
<25	157 / 542 (29.0)	110 / 535 (20.6)	1.41	[1.14; 1.74]	0.002
AJCC Anatomic Stage Group					
Interaction test	**p = 0.146**				
Group I/II	116 / 417 (27.8)	101 / 418 (24.2)	1.15	[0.92; 1.45]	0.229
Group III	198 / 691 (28.7)	129 / 652 (19.8)	1.45	[1.19; 1.76]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Anatomic stages					
Interaction test	**p = 0.375**				
IA/IB/IIA	51 / 171 (29.8)	43 / 198 (21.7)	1.37	[0.97; 1.95]	0.076
IIB	65 / 246 (26.4)	58 / 220 (26.4)	1.00	[0.74; 1.36]	0.988
IIIA	141 / 451 (31.3)	85 / 393 (21.6)	1.45	[1.15; 1.82]	0.002
IIIB	13 / 67 (19.4)	10 / 59 (16.9)	1.14	[0.54; 2.41]	0.723
IIIC	44 / 173 (25.4)	34 / 200 (17.0)	1.50	[1.00; 2.23]	0.048
Nodal status					
Interaction test	**p = 0.742**				
N0	22 / 91 (24.2)	23 / 117 (19.7)	1.23	[0.73; 2.06]	0.432
N1-N3	292 / 1017 (28.7)	205 / 950 (21.6)	1.33	[1.14; 1.55]	<.001
Histological grade at time of surgery					
Interaction test	**p = 0.657**				
Grade 1	28 / 110 (25.5)	14 / 100 (14.0)	1.82	[1.02; 3.25]	0.044
Grade 2	181 / 604 (30.0)	134 / 601 (22.3)	1.34	[1.11; 1.63]	0.003
Grade 3	85 / 297 (28.6)	57 / 266 (21.4)	1.34	[1.00; 1.79]	0.052
Histological subtype					
Interaction test	**p = 0.558**				
Ductal	240 / 863 (27.8)	180 / 835 (21.6)	1.29	[1.09; 1.53]	0.003
Lobular	54 / 172 (31.4)	34 / 169 (20.1)	1.56	[1.07; 2.27]	0.019
Other	20 / 73 (27.4)	16 / 66 (24.2)	1.13	[0.64; 1.99]	0.672
Ki67 status from surgical specimen					
Interaction test	**p = 0.930**				
Ki67≤20	132 / 527 (25.0)	106 / 552 (19.2)	1.30	[1.04; 1.64]	0.021
Ki67>20	114 / 422 (27.0)	80 / 378 (21.2)	1.28	[0.99; 1.64]	0.056
Type of NSAI					
Interaction test	**p = 0.252**				
Letrozole	204 / 809 (25.2)	155 / 773 (20.1)	1.26	[1.05; 1.51]	0.015
Anastrozole	110 / 299 (36.8)	75 / 297 (25.3)	1.46	[1.14; 1.86]	0.003
Prior neo/adjuvant chemotherapy					
Interaction test	**p = 0.218**				
Yes	296 / 1029 (28.8)	210 / 987 (21.3)	1.35	[1.16; 1.58]	<.001
No	18 / 79 (22.8)	20 / 83 (24.1)	0.95	[0.54; 1.65]	0.844
Prior adjuvant chemotherapy					
Interaction test	**p = 0.316**				
Yes	163 / 513 (31.8)	110 / 488 (22.5)	1.41	[1.15; 1.73]	0.001
No	151 / 595 (25.4)	120 / 582 (20.6)	1.23	[1.00; 1.52]	0.053
Prior neoadjuvant chemotherapy					
Interaction test	**p = 0.894**				
Yes	140 / 546 (25.6)	105 / 538 (19.5)	1.31	[1.05; 1.64]	0.017
No	174 / 562 (31.0)	125 / 532 (23.5)	1.32	[1.08; 1.60]	0.006

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Prior endocrine therapy					
Interaction test	**p = 0.334**				
Yes	241 / 853 (28.3)	161 / 789 (20.4)	1.38	[1.16; 1.65]	<.001
No	73 / 255 (28.6)	69 / 281 (24.6)	1.17	[0.88; 1.55]	0.286
Prior mastectomy					
Interaction test	**p = 0.885**				
Yes	218 / 769 (28.3)	159 / 745 (21.3)	1.33	[1.11; 1.59]	0.002
No	96 / 339 (28.3)	71 / 325 (21.8)	1.30	[0.99; 1.69]	0.056
Prior radiotherapy					
Interaction test	**p = 0.866**				
Yes	288 / 1011 (28.5)	214 / 987 (21.7)	1.31	[1.13; 1.53]	<.001
No	26 / 97 (26.8)	16 / 83 (19.3)	1.39	[0.80; 2.41]	0.240

N: Number of patients
n: Number of patients with event
CI: Confidence interval
RR: Relative risk
ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
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Analysis method for interaction test:
p-value from logistic regression model.
logit(proportion) = treatment + subgroup factor + treatment * subgroup factor

Analysis method for within subgroup analysis:
RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm.
ET was the reference group for treatment group comparison.

Table 5-3.2.51 PT dizziness: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	ET (N = 1070)	RR	[95% CI]	p-value
Dizziness					
	n / N (%)	n / N (%)			
Region					
Interaction test	**p = 0.471**				
NA/WE/O	68 / 640 (10.6)	32 / 627 (5.1)	2.08	[1.39; 3.12]	<.001
ROW	33 / 468 (7.1)	19 / 443 (4.3)	1.64	[0.95; 2.85]	0.076
Geographical region					
Interaction test	**p = 0.027**				
Europe	40 / 654 (6.1)	26 / 638 (4.1)	1.50	[0.93; 2.43]	0.098
North America/Australia	40 / 213 (18.8)	8 / 194 (4.1)	4.55	[2.19; 9.49]	<.001
Asia	19 / 178 (10.7)	15 / 168 (8.9)	1.20	[0.63; 2.27]	0.586
Latin America	2 / 63 (3.2)	2 / 70 (2.9)	1.11	[0.16; 7.66]	0.915
Age group 1 at randomization					
Interaction test	**p = 0.368**				
<45	54 / 549 (9.8)	22 / 496 (4.4)	2.22	[1.37; 3.59]	0.001
45 to 54	47 / 539 (8.7)	29 / 546 (5.3)	1.64	[1.05; 2.57]	0.030
55 to 64	0 / 20 (0.0)	0 / 28 (0.0)	N.E.	N.E.	N.E.
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)					
Interaction test	**p = 0.387**				
<Median	54 / 549 (9.8)	22 / 496 (4.4)	2.22	[1.37; 3.59]	0.001
≥Median	47 / 559 (8.4)	29 / 574 (5.1)	1.66	[1.06; 2.60]	0.026
Race					
Interaction test	**p = 0.141**				
Asian	23 / 211 (10.9)	15 / 186 (8.1)	1.35	[0.73; 2.51]	0.341
Non-Asian	76 / 840 (9.0)	31 / 827 (3.7)	2.41	[1.61; 3.62]	<.001
BMI at screening					
Interaction test	**p = 0.337**				
≥25	52 / 551 (9.4)	21 / 523 (4.0)	2.35	[1.44; 3.85]	<.001
<25	48 / 542 (8.9)	28 / 535 (5.2)	1.69	[1.08; 2.66]	0.022
AJCC Anatomic Stage Group					
Interaction test	**p = 0.623**				
Group I/II	38 / 417 (9.1)	22 / 418 (5.3)	1.73	[1.04; 2.88]	0.034
Group III	63 / 691 (9.1)	29 / 652 (4.4)	2.05	[1.34; 3.14]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Anatomic stages					
Interaction test	**p = 0.321**				
IA/IB/IIA	17 / 171 (9.9)	9 / 198 (4.5)	2.19	[1.00; 4.78]	0.050
IIB	21 / 246 (8.5)	13 / 220 (5.9)	1.44	[0.74; 2.82]	0.280
IIIA	45 / 451 (10.0)	16 / 393 (4.1)	2.45	[1.41; 4.27]	0.002
IIIB	2 / 67 (3.0)	4 / 59 (6.8)	0.44	[0.08; 2.32]	0.333
IIIC	16 / 173 (9.2)	9 / 200 (4.5)	2.06	[0.93; 4.53]	0.074
Nodal status					
Interaction test	**p = 0.169**				
N0	3 / 91 (3.3)	5 / 117 (4.3)	0.77	[0.19; 3.14]	0.717
N1-N3	98 / 1017 (9.6)	44 / 950 (4.6)	2.08	[1.47; 2.94]	<.001
Histological grade at time of surgery					
Interaction test	**p = 0.979**				
Grade 1	10 / 110 (9.1)	4 / 100 (4.0)	2.27	[0.74; 7.02]	0.154
Grade 2	64 / 604 (10.6)	29 / 601 (4.8)	2.20	[1.44; 3.36]	<.001
Grade 3	27 / 297 (9.1)	10 / 266 (3.8)	2.42	[1.19; 4.90]	0.014
Histological subtype					
Interaction test	**p = 0.405**				
Ductal	84 / 863 (9.7)	41 / 835 (4.9)	1.98	[1.38; 2.84]	<.001
Lobular	15 / 172 (8.7)	7 / 169 (4.1)	2.11	[0.88; 5.03]	0.094
Other	2 / 73 (2.7)	3 / 66 (4.5)	0.60	[0.10; 3.50]	0.572
Ki67 status from surgical specimen					
Interaction test	**p = 0.234**				
Ki67≤20	39 / 527 (7.4)	29 / 552 (5.3)	1.41	[0.88; 2.24]	0.149
Ki67>20	35 / 422 (8.3)	14 / 378 (3.7)	2.24	[1.22; 4.10]	0.009
Type of NSAI					
Interaction test	**p = 0.820**				
Letrozole	72 / 809 (8.9)	35 / 773 (4.5)	1.97	[1.33; 2.91]	<.001
Anastrozole	29 / 299 (9.7)	16 / 297 (5.4)	1.80	[1.00; 3.24]	0.050
Prior neo/adjuvant chemotherapy					
Interaction test	**p = 0.290**				
Yes	93 / 1029 (9.0)	49 / 987 (5.0)	1.82	[1.30; 2.54]	<.001
No	8 / 79 (10.1)	2 / 83 (2.4)	4.20	[0.92; 19.19]	0.064
Prior adjuvant chemotherapy					
Interaction test	**p = 0.570**				
Yes	49 / 513 (9.6)	22 / 488 (4.5)	2.12	[1.30; 3.45]	0.003
No	52 / 595 (8.7)	29 / 582 (5.0)	1.75	[1.13; 2.72]	0.012
Prior neoadjuvant chemotherapy					
Interaction test	**p = 0.269**				
Yes	49 / 546 (9.0)	30 / 538 (5.6)	1.61	[1.04; 2.50]	0.033
No	52 / 562 (9.3)	21 / 532 (3.9)	2.34	[1.43; 3.84]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Prior endocrine therapy					
Interaction test	**p = 0.048**				
Yes	90 / 853 (10.6)	38 / 789 (4.8)	2.19	[1.52; 3.16]	<.001
No	11 / 255 (4.3)	13 / 281 (4.6)	0.93	[0.43; 2.04]	0.861
Prior mastectomy					
Interaction test	**p = 0.212**				
Yes	64 / 769 (8.3)	27 / 745 (3.6)	2.30	[1.48; 3.56]	<.001
No	37 / 339 (10.9)	24 / 325 (7.4)	1.48	[0.90; 2.41]	0.119
Prior radiotherapy					
Interaction test	**p = 0.355**				
Yes	95 / 1011 (9.4)	50 / 987 (5.1)	1.85	[1.33; 2.58]	<.001
No	6 / 97 (6.2)	1 / 83 (1.2)	5.13	[0.63; 41.78]	0.126

N: Number of patients
n: Number of patients with event
N.E.: Not estimable
CI: Confidence interval
RR: Relative risk
ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
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Analysis method for interaction test:
p-value from logistic regression model.
logit(proportion) = treatment + subgroup factor + treatment * subgroup factor

Analysis method for within subgroup analysis:
RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm.
ET was the reference group for treatment group comparison.

Table 5-3.2.52 PT dysgeusia: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	ET (N = 1070)	RR	[95% CI]	p-value
Dysgeusia					
	n / N (%)	n / N (%)			
Region					
Interaction test	**p = 0.646**				
NA/WE/O	24 / 640 (3.8)	7 / 627 (1.1)	3.36	[1.46; 7.74]	0.004
ROW	2 / 468 (0.4)	1 / 443 (0.2)	1.89	[0.17; 20.80]	0.602
Geographical region					
Interaction test	**p = 0.246**				
Europe	15 / 654 (2.3)	6 / 638 (0.9)	2.44	[0.95; 6.25]	0.063
North America/Australia	10 / 213 (4.7)	1 / 194 (0.5)	9.11	[1.18; 70.50]	0.034
Asia	0 / 178 (0.0)	1 / 168 (0.6)	0.31	[0.01; 7.67]	0.478
Latin America	1 / 63 (1.6)	0 / 70 (0.0)	3.33	[0.14; 80.25]	0.459
Age group 1 at randomization					
Interaction test	**p = 0.809**				
<45	12 / 549 (2.2)	4 / 496 (0.8)	2.71	[0.88; 8.35]	0.082
45 to 54	13 / 539 (2.4)	4 / 546 (0.7)	3.29	[1.08; 10.03]	0.036
55 to 64	1 / 20 (5.0)	0 / 28 (0.0)	4.14	[0.18; 96.77]	0.377
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)					
Interaction test	**p = 0.725**				
<Median	12 / 549 (2.2)	4 / 496 (0.8)	2.71	[0.88; 8.35]	0.082
≥Median	14 / 559 (2.5)	4 / 574 (0.7)	3.59	[1.19; 10.85]	0.023
Race					
Interaction test	**N.E.**				
Asian	0 / 211 (0.0)	1 / 186 (0.5)	0.29	[0.01; 7.17]	0.453
Non-Asian	25 / 840 (3.0)	6 / 827 (0.7)	4.10	[1.69; 9.95]	0.002
BMI at screening					
Interaction test	**p = 0.808**				
≥25	12 / 551 (2.2)	4 / 523 (0.8)	2.85	[0.92; 8.77]	0.068
<25	14 / 542 (2.6)	4 / 535 (0.7)	3.45	[1.14; 10.43]	0.028
AJCC Anatomic Stage Group					
Interaction test	**p = 0.076**				
Group I/II	13 / 417 (3.1)	1 / 418 (0.2)	13.03	[1.71; 99.16]	0.013
Group III	13 / 691 (1.9)	7 / 652 (1.1)	1.75	[0.70; 4.36]	0.228

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Anatomic stages					
Interaction test	**p = 0.259**				
IA/IB/IIA	3 / 171 (1.8)	0 / 198 (0.0)	8.10	[0.42; >99.99]	0.165
IIB	10 / 246 (4.1)	1 / 220 (0.5)	8.94	[1.15; 69.30]	0.036
IIIA	9 / 451 (2.0)	3 / 393 (0.8)	2.61	[0.71; 9.59]	0.147
IIIB	0 / 67 (0.0)	0 / 59 (0.0)	N.E.	N.E.	N.E.
IIIC	4 / 173 (2.3)	4 / 200 (2.0)	1.16	[0.29; 4.55]	0.836
Nodal status					
Interaction test	**N.E.**				
N0	3 / 91 (3.3)	0 / 117 (0.0)	8.98	[0.47; >99.99]	0.145
N1-N3	23 / 1017 (2.3)	8 / 950 (0.8)	2.69	[1.21; 5.97]	0.015
Histological grade at time of surgery					
Interaction test	**p = 0.193**				
Grade 1	2 / 110 (1.8)	0 / 100 (0.0)	4.55	[0.22; 93.64]	0.326
Grade 2	15 / 604 (2.5)	3 / 601 (0.5)	4.98	[1.45; 17.10]	0.011
Grade 3	7 / 297 (2.4)	4 / 266 (1.5)	1.57	[0.46; 5.29]	0.469
Histological subtype					
Interaction test	**p = 0.979**				
Ductal	18 / 863 (2.1)	6 / 835 (0.7)	2.90	[1.16; 7.28]	0.023
Lobular	6 / 172 (3.5)	2 / 169 (1.2)	2.95	[0.60; 14.40]	0.182
Other	2 / 73 (2.7)	0 / 66 (0.0)	4.53	[0.22; 92.61]	0.327
Ki67 status from surgical specimen					
Interaction test	**p = 0.711**				
Ki67≤20	12 / 527 (2.3)	5 / 552 (0.9)	2.51	[0.89; 7.09]	0.081
Ki67>20	8 / 422 (1.9)	2 / 378 (0.5)	3.58	[0.77; 16.77]	0.105
Type of NSAI					
Interaction test	**p = 0.915**				
Letrozole	16 / 809 (2.0)	5 / 773 (0.6)	3.06	[1.13; 8.31]	0.028
Anastrozole	10 / 299 (3.3)	3 / 297 (1.0)	3.31	[0.92; 11.91]	0.067
Prior neo/adjuvant chemotherapy					
Interaction test	**p = 0.731**				
Yes	24 / 1029 (2.3)	7 / 987 (0.7)	3.29	[1.42; 7.60]	0.005
No	2 / 79 (2.5)	1 / 83 (1.2)	2.10	[0.19; 22.72]	0.541
Prior adjuvant chemotherapy					
Interaction test	**p = 0.121**				
Yes	18 / 513 (3.5)	3 / 488 (0.6)	5.71	[1.69; 19.25]	0.005
No	8 / 595 (1.3)	5 / 582 (0.9)	1.57	[0.52; 4.76]	0.430
Prior neoadjuvant chemotherapy					
Interaction test	**p = 0.050**				
Yes	6 / 546 (1.1)	5 / 538 (0.9)	1.18	[0.36; 3.85]	0.781
No	20 / 562 (3.6)	3 / 532 (0.6)	6.31	[1.89; 21.11]	0.003

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Prior endocrine therapy					
Interaction test	**p = 0.329**				
Yes	19 / 853 (2.2)	7 / 789 (0.9)	2.51	[1.06; 5.94]	0.036
No	7 / 255 (2.7)	1 / 281 (0.4)	7.71	[0.96; 62.27]	0.055
Prior mastectomy					
Interaction test	**p = 0.412**				
Yes	20 / 769 (2.6)	5 / 745 (0.7)	3.88	[1.46; 10.27]	0.006
No	6 / 339 (1.8)	3 / 325 (0.9)	1.92	[0.48; 7.60]	0.354
Prior radiotherapy					
Interaction test	**N.E.**				
Yes	19 / 1011 (1.9)	8 / 987 (0.8)	2.32	[1.02; 5.27]	0.045
No	7 / 97 (7.2)	0 / 83 (0.0)	12.86	[0.75; >99.99]	0.079

N: Number of patients
n: Number of patients with event
N.E.: Not estimable
CI: Confidence interval
RR: Relative risk
ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
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Analysis method for interaction test:
p-value from logistic regression model.
logit(proportion) = treatment + subgroup factor + treatment * subgroup factor

Analysis method for within subgroup analysis:
RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm.
ET was the reference group for treatment group comparison.

Table 5-3.2.53 PT carpal tunnel syndrome: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	ET (N = 1070)	RR	[95% CI]	p-value
Carpal tunnel syndrome					
	n / N (%)	n / N (%)			
Region					
Interaction test	N.E.				
NA/WE/O	2 / 640 (0.3)	10 / 627 (1.6)	0.20	[0.04; 0.89]	0.035
ROW	0 / 468 (0.0)	3 / 443 (0.7)	0.14	[<0.01; 2.61]	0.185
Geographical region					
Interaction test	N.E.				
Europe	2 / 654 (0.3)	10 / 638 (1.6)	0.20	[0.04; 0.89]	0.034
North America/Australia	0 / 213 (0.0)	1 / 194 (0.5)	0.30	[0.01; 7.41]	0.465
Asia	0 / 178 (0.0)	2 / 168 (1.2)	0.19	[<0.01; 3.90]	0.281
Latin America	0 / 63 (0.0)	0 / 70 (0.0)	N.E.	N.E.	N.E.
Age group 1 at randomization					
Interaction test	N.E.				
<45	0 / 549 (0.0)	4 / 496 (0.8)	0.10	[<0.01; 1.86]	0.123
45 to 54	2 / 539 (0.4)	9 / 546 (1.6)	0.23	[0.05; 1.04]	0.056
55 to 64	0 / 20 (0.0)	0 / 28 (0.0)	N.E.	N.E.	N.E.
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)					
Interaction test	N.E.				
<Median	0 / 549 (0.0)	4 / 496 (0.8)	0.10	[<0.01; 1.86]	0.123
≥Median	2 / 559 (0.4)	9 / 574 (1.6)	0.23	[0.05; 1.05]	0.058
Race					
The subgroup analysis is not presented as all subgroups have less than 10 events.					
BMI at screening					
The subgroup analysis is not presented as all subgroups have less than 10 events.					
AJCC Anatomic Stage Group					
Interaction test	N.E.				
Group I/II	0 / 417 (0.0)	4 / 418 (1.0)	0.11	[<0.01; 2.06]	0.141
Group III	2 / 691 (0.3)	9 / 652 (1.4)	0.21	[0.05; 0.97]	0.045
Anatomic stages					
The subgroup analysis is not presented as all subgroups have less than 10 events.					

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Nodal status					
Interaction test	**N.E.**				
N0	0 / 91 (0.0)	0 / 117 (0.0)	N.E.	N.E.	N.E.
N1-N3	2 / 1017 (0.2)	13 / 950 (1.4)	0.14	[0.03; 0.64]	0.011
Histological grade at time of surgery					
The subgroup analysis is not presented as all subgroups have less than 10 events.					
Histological subtype					
Interaction test	**N.E.**				
Ductal	2 / 863 (0.2)	12 / 835 (1.4)	0.16	[0.04; 0.72]	0.017
Lobular	0 / 172 (0.0)	1 / 169 (0.6)	0.33	[0.01; 7.98]	0.493
Other	0 / 73 (0.0)	0 / 66 (0.0)	N.E.	N.E.	N.E.
Ki67 status from surgical specimen					
The subgroup analysis is not presented as all subgroups have less than 10 events.					
Type of NSAI					
Interaction test	**N.E.**				
Letrozole	0 / 809 (0.0)	10 / 773 (1.3)	0.05	[<0.01; 0.78]	0.033
Anastrozole	2 / 299 (0.7)	3 / 297 (1.0)	0.66	[0.11; 3.93]	0.650
Prior neo/adjuvant chemotherapy					
Interaction test	**N.E.**				
Yes	2 / 1029 (0.2)	13 / 987 (1.3)	0.15	[0.03; 0.65]	0.012
No	0 / 79 (0.0)	0 / 83 (0.0)	N.E.	N.E.	N.E.
Prior adjuvant chemotherapy					
The subgroup analysis is not presented as all subgroups have less than 10 events.					
Prior neoadjuvant chemotherapy					
The subgroup analysis is not presented as all subgroups have less than 10 events.					
Prior endocrine therapy					
Interaction test	**p = 0.241**				
Yes	1 / 853 (0.1)	11 / 789 (1.4)	0.08	[0.01; 0.65]	0.018
No	1 / 255 (0.4)	2 / 281 (0.7)	0.55	[0.05; 6.04]	0.626
Prior mastectomy					
Interaction test	**N.E.**				
Yes	2 / 769 (0.3)	8 / 745 (1.1)	0.24	[0.05; 1.14]	0.072
No	0 / 339 (0.0)	5 / 325 (1.5)	0.09	[<0.01; 1.57]	0.098

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Prior radiotherapy					
Interaction test	**N.E.**				
Yes	1 / 1011 (0.1)	13 / 987 (1.3)	0.08	[<0.01; 0.57]	0.013
No	1 / 97 (1.0)	0 / 83 (0.0)	2.57	[0.11; 62.29]	0.561

N: Number of patients
n: Number of patients with event
N.E.: Not estimable
CI: Confidence interval
RR: Relative risk
ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
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Analysis method for interaction test:
p-value from logistic regression model.
logit(proportion) = treatment + subgroup factor + treatment * subgroup factor

Analysis method for within subgroup analysis:
RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm.
ET was the reference group for treatment group comparison.

Table 5-3.2.54 SOC skin and subcutaneous tissue disorders: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	ET (N = 1070)	RR	[95% CI]	p-value
Skin and subcutaneous tissue disorders					
	n / N (%)	n / N (%)			
Region					
Interaction test	**p = 0.603**				
NA/WE/O	281 / 640 (43.9)	156 / 627 (24.9)	1.76	[1.50; 2.07]	<.001
ROW	135 / 468 (28.8)	71 / 443 (16.0)	1.80	[1.39; 2.33]	<.001
Geographical region					
Interaction test	**p = 0.777**				
Europe	225 / 654 (34.4)	126 / 638 (19.7)	1.74	[1.44; 2.10]	<.001
North America/Australia	103 / 213 (48.4)	52 / 194 (26.8)	1.80	[1.38; 2.37]	<.001
Asia	72 / 178 (40.4)	42 / 168 (25.0)	1.62	[1.18; 2.22]	0.003
Latin America	16 / 63 (25.4)	7 / 70 (10.0)	2.54	[1.12; 5.77]	0.026
Age group 1 at randomization					
Interaction test	**p = 0.119**				
<45	199 / 549 (36.2)	93 / 496 (18.8)	1.93	[1.56; 2.39]	<.001
45 to 54	211 / 539 (39.1)	123 / 546 (22.5)	1.74	[1.44; 2.10]	<.001
55 to 64	6 / 20 (30.0)	11 / 28 (39.3)	0.76	[0.34; 1.72]	0.515
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)					
Interaction test	**p = 0.392**				
<Median	199 / 549 (36.2)	93 / 496 (18.8)	1.93	[1.56; 2.39]	<.001
≥Median	217 / 559 (38.8)	134 / 574 (23.3)	1.66	[1.39; 1.99]	<.001
Race					
Interaction test	**p = 0.908**				
Asian	90 / 211 (42.7)	48 / 186 (25.8)	1.65	[1.24; 2.21]	<.001
Non-Asian	296 / 840 (35.2)	164 / 827 (19.8)	1.78	[1.51; 2.10]	<.001
BMI at screening					
Interaction test	**p = 0.330**				
≥25	197 / 551 (35.8)	113 / 523 (21.6)	1.65	[1.36; 2.02]	<.001
<25	210 / 542 (38.7)	110 / 535 (20.6)	1.88	[1.55; 2.30]	<.001
AJCC Anatomic Stage Group					
Interaction test	**p = 0.568**				
Group I/II	164 / 417 (39.3)	89 / 418 (21.3)	1.85	[1.48; 2.30]	<.001
Group III	252 / 691 (36.5)	138 / 652 (21.2)	1.72	[1.44; 2.06]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Anatomic stages					
Interaction test	**p = 0.513**				
IA/IB/IIA	66 / 171 (38.6)	40 / 198 (20.2)	1.91	[1.37; 2.67]	<.001
IIB	98 / 246 (39.8)	49 / 220 (22.3)	1.79	[1.34; 2.39]	<.001
IIIA	167 / 451 (37.0)	90 / 393 (22.9)	1.62	[1.30; 2.01]	<.001
IIIB	19 / 67 (28.4)	13 / 59 (22.0)	1.29	[0.70; 2.37]	0.419
IIIC	66 / 173 (38.2)	35 / 200 (17.5)	2.18	[1.53; 3.11]	<.001
Nodal status					
Interaction test	**p = 0.148**				
N0	37 / 91 (40.7)	19 / 117 (16.2)	2.50	[1.55; 4.05]	<.001
N1-N3	379 / 1017 (37.3)	206 / 950 (21.7)	1.72	[1.49; 1.99]	<.001
Histological grade at time of surgery					
Interaction test	**p = 0.970**				
Grade 1	41 / 110 (37.3)	22 / 100 (22.0)	1.69	[1.09; 2.63]	0.019
Grade 2	218 / 604 (36.1)	119 / 601 (19.8)	1.82	[1.50; 2.21]	<.001
Grade 3	126 / 297 (42.4)	65 / 266 (24.4)	1.74	[1.35; 2.23]	<.001
Histological subtype					
Interaction test	**p = 0.319**				
Ductal	326 / 863 (37.8)	171 / 835 (20.5)	1.84	[1.57; 2.16]	<.001
Lobular	64 / 172 (37.2)	45 / 169 (26.6)	1.40	[1.02; 1.92]	0.038
Other	26 / 73 (35.6)	11 / 66 (16.7)	2.14	[1.15; 3.98]	0.017
Ki67 status from surgical specimen					
Interaction test	**p = 0.322**				
Ki67≤20	209 / 527 (39.7)	114 / 552 (20.7)	1.92	[1.58; 2.33]	<.001
Ki67>20	140 / 422 (33.2)	74 / 378 (19.6)	1.69	[1.33; 2.17]	<.001
Type of NSAI					
Interaction test	**p = 0.780**				
Letrozole	297 / 809 (36.7)	157 / 773 (20.3)	1.81	[1.53; 2.13]	<.001
Anastrozole	119 / 299 (39.8)	70 / 297 (23.6)	1.69	[1.32; 2.16]	<.001
Prior neo/adjuvant chemotherapy					
Interaction test	**p = 0.644**				
Yes	387 / 1029 (37.6)	212 / 987 (21.5)	1.75	[1.52; 2.02]	<.001
No	29 / 79 (36.7)	15 / 83 (18.1)	2.03	[1.18; 3.49]	0.010
Prior adjuvant chemotherapy					
Interaction test	**p = 0.757**				
Yes	203 / 513 (39.6)	108 / 488 (22.1)	1.79	[1.47; 2.18]	<.001
No	213 / 595 (35.8)	119 / 582 (20.4)	1.75	[1.44; 2.12]	<.001
Prior neoadjuvant chemotherapy					
Interaction test	**p = 0.869**				
Yes	194 / 546 (35.5)	108 / 538 (20.1)	1.77	[1.44; 2.17]	<.001
No	222 / 562 (39.5)	119 / 532 (22.4)	1.77	[1.46; 2.13]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Prior endocrine therapy					
Interaction test	**p = 0.831**				
Yes	318 / 853 (37.3)	164 / 789 (20.8)	1.79	[1.53; 2.11]	<.001
No	98 / 255 (38.4)	63 / 281 (22.4)	1.71	[1.31; 2.24]	<.001
Prior mastectomy					
Interaction test	**p = 0.636**				
Yes	298 / 769 (38.8)	168 / 745 (22.6)	1.72	[1.46; 2.02]	<.001
No	118 / 339 (34.8)	59 / 325 (18.2)	1.92	[1.46; 2.52]	<.001
Prior radiotherapy					
Interaction test	**p = 0.355**				
Yes	381 / 1011 (37.7)	206 / 987 (20.9)	1.81	[1.56; 2.09]	<.001
No	35 / 97 (36.1)	21 / 83 (25.3)	1.43	[0.91; 2.25]	0.126

N: Number of patients
n: Number of patients with event
CI: Confidence interval
RR: Relative risk
ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
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Analysis method for interaction test:
p-value from logistic regression model.
logit(proportion) = treatment + subgroup factor + treatment * subgroup factor

Analysis method for within subgroup analysis:
RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm.
ET was the reference group for treatment group comparison.

Table 5-3.2.55 PT alopecia: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	ET (N = 1070)	RR	[95% CI]	p-value
Alopecia					
	n / N (%)	n / N (%)			
Region					
Interaction test	**p = 0.023**				
NA/WE/O	118 / 640 (18.4)	29 / 627 (4.6)	3.99	[2.70; 5.89]	<.001
ROW	37 / 468 (7.9)	18 / 443 (4.1)	1.95	[1.12; 3.37]	0.017
Geographical region					
Interaction test	**p = 0.026**				
Europe	83 / 654 (12.7)	25 / 638 (3.9)	3.24	[2.10; 5.00]	<.001
North America/Australia	48 / 213 (22.5)	7 / 194 (3.6)	6.25	[2.90; 13.47]	<.001
Asia	19 / 178 (10.7)	13 / 168 (7.7)	1.38	[0.70; 2.70]	0.349
Latin America	5 / 63 (7.9)	2 / 70 (2.9)	2.78	[0.56; 13.82]	0.212
Age group 1 at randomization					
Interaction test	**p = 0.158**				
<45	78 / 549 (14.2)	17 / 496 (3.4)	4.15	[2.49; 6.91]	<.001
45 to 54	76 / 539 (14.1)	30 / 546 (5.5)	2.57	[1.71; 3.85]	<.001
55 to 64	1 / 20 (5.0)	0 / 28 (0.0)	4.14	[0.18; 96.77]	0.377
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)					
Interaction test	**p = 0.179**				
<Median	78 / 549 (14.2)	17 / 496 (3.4)	4.15	[2.49; 6.91]	<.001
≥Median	77 / 559 (13.8)	30 / 574 (5.2)	2.64	[1.76; 3.95]	<.001
Race					
Interaction test	**p = 0.066**				
Asian	30 / 211 (14.2)	14 / 186 (7.5)	1.89	[1.03; 3.45]	0.039
Non-Asian	116 / 840 (13.8)	30 / 827 (3.6)	3.81	[2.58; 5.62]	<.001
BMI at screening					
Interaction test	**p = 0.914**				
≥25	65 / 551 (11.8)	19 / 523 (3.6)	3.25	[1.98; 5.34]	<.001
<25	86 / 542 (15.9)	28 / 535 (5.2)	3.03	[2.01; 4.57]	<.001
AJCC Anatomic Stage Group					
Interaction test	**p = 0.861**				
Group I/II	68 / 417 (16.3)	21 / 418 (5.0)	3.25	[2.03; 5.19]	<.001
Group III	87 / 691 (12.6)	26 / 652 (4.0)	3.16	[2.06; 4.83]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Anatomic stages					
Interaction test	**p = 0.641**				
IA/IB/IIA	37 / 171 (21.6)	13 / 198 (6.6)	3.30	[1.81; 5.99]	<.001
IIB	31 / 246 (12.6)	8 / 220 (3.6)	3.47	[1.63; 7.38]	0.001
IIIA	54 / 451 (12.0)	12 / 393 (3.1)	3.92	[2.13; 7.22]	<.001
IIIB	6 / 67 (9.0)	4 / 59 (6.8)	1.32	[0.39; 4.46]	0.654
IIIC	27 / 173 (15.6)	10 / 200 (5.0)	3.12	[1.56; 6.26]	0.001
Nodal status					
Interaction test	**p = 0.864**				
N0	16 / 91 (17.6)	6 / 117 (5.1)	3.43	[1.40; 8.41]	0.007
N1-N3	139 / 1017 (13.7)	40 / 950 (4.2)	3.25	[2.31; 4.56]	<.001
Histological grade at time of surgery					
Interaction test	**p = 0.685**				
Grade 1	16 / 110 (14.5)	4 / 100 (4.0)	3.64	[1.26; 10.51]	0.017
Grade 2	83 / 604 (13.7)	22 / 601 (3.7)	3.75	[2.38; 5.92]	<.001
Grade 3	45 / 297 (15.2)	15 / 266 (5.6)	2.69	[1.53; 4.71]	<.001
Histological subtype					
Interaction test	**p = 0.178**				
Ductal	131 / 863 (15.2)	35 / 835 (4.2)	3.62	[2.53; 5.19]	<.001
Lobular	17 / 172 (9.9)	10 / 169 (5.9)	1.67	[0.79; 3.54]	0.181
Other	7 / 73 (9.6)	2 / 66 (3.0)	3.16	[0.68; 14.70]	0.142
Ki67 status from surgical specimen					
Interaction test	**p = 0.810**				
Ki67≤20	76 / 527 (14.4)	26 / 552 (4.7)	3.06	[1.99; 4.70]	<.001
Ki67>20	45 / 422 (10.7)	14 / 378 (3.7)	2.88	[1.61; 5.16]	<.001
Type of NSAI					
Interaction test	**p = 0.523**				
Letrozole	114 / 809 (14.1)	32 / 773 (4.1)	3.40	[2.33; 4.98]	<.001
Anastrozole	41 / 299 (13.7)	15 / 297 (5.1)	2.72	[1.54; 4.80]	<.001
Prior neo/adjuvant chemotherapy					
Interaction test	**p = 0.277**				
Yes	142 / 1029 (13.8)	45 / 987 (4.6)	3.03	[2.19; 4.18]	<.001
No	13 / 79 (16.5)	2 / 83 (2.4)	6.83	[1.59; 29.30]	0.010
Prior adjuvant chemotherapy					
Interaction test	**p = 0.214**				
Yes	71 / 513 (13.8)	26 / 488 (5.3)	2.60	[1.69; 4.00]	<.001
No	84 / 595 (14.1)	21 / 582 (3.6)	3.91	[2.46; 6.22]	<.001
Prior neoadjuvant chemotherapy					
Interaction test	**p = 0.367**				
Yes	73 / 546 (13.4)	19 / 538 (3.5)	3.79	[2.32; 6.18]	<.001
No	82 / 562 (14.6)	28 / 532 (5.3)	2.77	[1.84; 4.19]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Prior endocrine therapy					
Interaction test	**p = 0.475**				
Yes	128 / 853 (15.0)	40 / 789 (5.1)	2.96	[2.10; 4.17]	<.001
No	27 / 255 (10.6)	7 / 281 (2.5)	4.25	[1.88; 9.59]	<.001
Prior mastectomy					
Interaction test	**p = 0.603**				
Yes	108 / 769 (14.0)	31 / 745 (4.2)	3.38	[2.29; 4.97]	<.001
No	47 / 339 (13.9)	16 / 325 (4.9)	2.82	[1.63; 4.86]	<.001
Prior radiotherapy					
Interaction test	**p = 0.950**				
Yes	144 / 1011 (14.2)	44 / 987 (4.5)	3.20	[2.31; 4.43]	<.001
No	11 / 97 (11.3)	3 / 83 (3.6)	3.14	[0.91; 10.87]	0.071

N: Number of patients
n: Number of patients with event
CI: Confidence interval
RR: Relative risk
ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
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Analysis method for interaction test:
p-value from logistic regression model.
logit(proportion) = treatment + subgroup factor + treatment * subgroup factor

Analysis method for within subgroup analysis:
RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm.
ET was the reference group for treatment group comparison.

Table 5-3.2.56 PT rash: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	ET (N = 1070)	RR	[95% CI]	p-value
Rash					
	n / N (%)	n / N (%)			
Region					
Interaction test	**p = 0.381**				
NA/WE/O	77 / 640 (12.0)	23 / 627 (3.7)	3.28	[2.09; 5.16]	<.001
ROW	22 / 468 (4.7)	9 / 443 (2.0)	2.31	[1.08; 4.97]	0.032
Geographical region					
Interaction test	**p = 0.530**				
Europe	49 / 654 (7.5)	16 / 638 (2.5)	2.99	[1.72; 5.20]	<.001
North America/Australia	34 / 213 (16.0)	9 / 194 (4.6)	3.44	[1.69; 6.99]	<.001
Asia	14 / 178 (7.9)	7 / 168 (4.2)	1.89	[0.78; 4.56]	0.158
Latin America	2 / 63 (3.2)	0 / 70 (0.0)	5.55	[0.27; >99.99]	0.266
Age group 1 at randomization					
Interaction test	**p = 0.827**				
<45	43 / 549 (7.8)	11 / 496 (2.2)	3.53	[1.84; 6.77]	<.001
45 to 54	56 / 539 (10.4)	18 / 546 (3.3)	3.15	[1.88; 5.29]	<.001
55 to 64	0 / 20 (0.0)	3 / 28 (10.7)	0.20	[0.01; 3.62]	0.274
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)					
Interaction test	**p = 0.571**				
<Median	43 / 549 (7.8)	11 / 496 (2.2)	3.53	[1.84; 6.77]	<.001
≥Median	56 / 559 (10.0)	21 / 574 (3.7)	2.74	[1.68; 4.46]	<.001
Race					
Interaction test	**p = 0.904**				
Asian	24 / 211 (11.4)	8 / 186 (4.3)	2.64	[1.22; 5.74]	0.014
Non-Asian	67 / 840 (8.0)	23 / 827 (2.8)	2.87	[1.80; 4.56]	<.001
BMI at screening					
Interaction test	**p = 0.224**				
≥25	54 / 551 (9.8)	13 / 523 (2.5)	3.94	[2.18; 7.14]	<.001
<25	44 / 542 (8.1)	18 / 535 (3.4)	2.41	[1.41; 4.12]	0.001
AJCC Anatomic Stage Group					
Interaction test	**p = 0.879**				
Group I/II	43 / 417 (10.3)	15 / 418 (3.6)	2.87	[1.62; 5.09]	<.001
Group III	56 / 691 (8.1)	17 / 652 (2.6)	3.11	[1.83; 5.29]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Anatomic stages					
Interaction test	**p = 0.341**				
IA/IB/IIA	10 / 171 (5.8)	7 / 198 (3.5)	1.65	[0.64; 4.25]	0.296
IIB	33 / 246 (13.4)	8 / 220 (3.6)	3.69	[1.74; 7.81]	<.001
IIIA	40 / 451 (8.9)	14 / 393 (3.6)	2.49	[1.38; 4.51]	0.003
IIIB	1 / 67 (1.5)	0 / 59 (0.0)	2.65	[0.11; 63.76]	0.549
IIIC	15 / 173 (8.7)	3 / 200 (1.5)	5.78	[1.70; 19.63]	0.005
Nodal status					
Interaction test	**p = 0.466**				
N0	6 / 91 (6.6)	4 / 117 (3.4)	1.93	[0.56; 6.63]	0.297
N1-N3	93 / 1017 (9.1)	28 / 950 (2.9)	3.10	[2.05; 4.69]	<.001
Histological grade at time of surgery					
Interaction test	**p = 0.669**				
Grade 1	8 / 110 (7.3)	4 / 100 (4.0)	1.82	[0.56; 5.85]	0.316
Grade 2	53 / 604 (8.8)	17 / 601 (2.8)	3.10	[1.82; 5.29]	<.001
Grade 3	33 / 297 (11.1)	9 / 266 (3.4)	3.28	[1.60; 6.73]	0.001
Histological subtype					
Interaction test	**p = 0.613**				
Ductal	75 / 863 (8.7)	24 / 835 (2.9)	3.02	[1.93; 4.74]	<.001
Lobular	19 / 172 (11.0)	8 / 169 (4.7)	2.33	[1.05; 5.18]	0.037
Other	5 / 73 (6.8)	0 / 66 (0.0)	9.96	[0.56; >99.99]	0.117
Ki67 status from surgical specimen					
Interaction test	**p = 0.627**				
Ki67≤20	45 / 527 (8.5)	15 / 552 (2.7)	3.14	[1.77; 5.57]	<.001
Ki67>20	34 / 422 (8.1)	12 / 378 (3.2)	2.54	[1.33; 4.83]	0.005
Type of NSAI					
Interaction test	**p = 0.559**				
Letrozole	64 / 809 (7.9)	22 / 773 (2.8)	2.78	[1.73; 4.47]	<.001
Anastrozole	35 / 299 (11.7)	10 / 297 (3.4)	3.48	[1.75; 6.89]	<.001
Prior neo/adjuvant chemotherapy					
Interaction test	**p = 0.643**				
Yes	91 / 1029 (8.8)	30 / 987 (3.0)	2.91	[1.94; 4.35]	<.001
No	8 / 79 (10.1)	2 / 83 (2.4)	4.20	[0.92; 19.19]	0.064
Prior adjuvant chemotherapy					
Interaction test	**p = 0.908**				
Yes	51 / 513 (9.9)	16 / 488 (3.3)	3.03	[1.75; 5.24]	<.001
No	48 / 595 (8.1)	16 / 582 (2.7)	2.93	[1.69; 5.11]	<.001
Prior neoadjuvant chemotherapy					
Interaction test	**p = 0.618**				
Yes	41 / 546 (7.5)	15 / 538 (2.8)	2.69	[1.51; 4.81]	<.001
No	58 / 562 (10.3)	17 / 532 (3.2)	3.23	[1.91; 5.47]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Prior endocrine therapy					
Interaction test	**p = 0.962**				
Yes	75 / 853 (8.8)	23 / 789 (2.9)	3.02	[1.91; 4.76]	<.001
No	24 / 255 (9.4)	9 / 281 (3.2)	2.94	[1.39; 6.20]	0.005
Prior mastectomy					
Interaction test	**p = 0.645**				
Yes	69 / 769 (9.0)	21 / 745 (2.8)	3.18	[1.97; 5.13]	<.001
No	30 / 339 (8.8)	11 / 325 (3.4)	2.61	[1.33; 5.13]	0.005
Prior radiotherapy					
Interaction test	**p = 0.568**				
Yes	85 / 1011 (8.4)	29 / 987 (2.9)	2.86	[1.89; 4.32]	<.001
No	14 / 97 (14.4)	3 / 83 (3.6)	3.99	[1.19; 13.42]	0.025

N: Number of patients
n: Number of patients with event
CI: Confidence interval
RR: Relative risk
ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
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Analysis method for interaction test:
p-value from logistic regression model.
logit(proportion) = treatment + subgroup factor + treatment * subgroup factor

Analysis method for within subgroup analysis:
RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm.
ET was the reference group for treatment group comparison.

Table 5-3.2.57 PT pruritus: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	ET (N = 1070)	RR	[95% CI]	p-value
Pruritus					
	n / N (%)	n / N (%)			
Region					
Interaction test	**p = 0.758**				
NA/WE/O	48 / 640 (7.5)	23 / 627 (3.7)	2.04	[1.26; 3.32]	0.004
ROW	32 / 468 (6.8)	13 / 443 (2.9)	2.33	[1.24; 4.38]	0.009
Geographical region					
Interaction test	**p = 0.523**				
Europe	31 / 654 (4.7)	16 / 638 (2.5)	1.89	[1.04; 3.42]	0.035
North America/Australia	20 / 213 (9.4)	7 / 194 (3.6)	2.60	[1.13; 6.02]	0.025
Asia	22 / 178 (12.4)	12 / 168 (7.1)	1.73	[0.88; 3.38]	0.109
Latin America	7 / 63 (11.1)	1 / 70 (1.4)	7.78	[0.98; 61.48]	0.052
Age group 1 at randomization					
Interaction test	**p = 0.451**				
<45	36 / 549 (6.6)	18 / 496 (3.6)	1.81	[1.04; 3.14]	0.036
45 to 54	43 / 539 (8.0)	18 / 546 (3.3)	2.42	[1.41; 4.14]	0.001
55 to 64	1 / 20 (5.0)	0 / 28 (0.0)	4.14	[0.18; 96.77]	0.377
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)					
Interaction test	**p = 0.398**				
<Median	36 / 549 (6.6)	18 / 496 (3.6)	1.81	[1.04; 3.14]	0.036
≥Median	44 / 559 (7.9)	18 / 574 (3.1)	2.51	[1.47; 4.29]	<.001
Race					
Interaction test	**p = 0.242**				
Asian	23 / 211 (10.9)	14 / 186 (7.5)	1.45	[0.77; 2.73]	0.253
Non-Asian	54 / 840 (6.4)	22 / 827 (2.7)	2.42	[1.49; 3.93]	<.001
BMI at screening					
Interaction test	**p = 0.499**				
≥25	39 / 551 (7.1)	19 / 523 (3.6)	1.95	[1.14; 3.33]	0.015
<25	39 / 542 (7.2)	15 / 535 (2.8)	2.57	[1.43; 4.60]	0.002
AJCC Anatomic Stage Group					
Interaction test	**p = 0.656**				
Group I/II	29 / 417 (7.0)	12 / 418 (2.9)	2.42	[1.25; 4.68]	0.008
Group III	51 / 691 (7.4)	24 / 652 (3.7)	2.01	[1.25; 3.22]	0.004

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Anatomic stages					
Interaction test	**p = 0.744**				
IA/IB/IIA	9 / 171 (5.3)	4 / 198 (2.0)	2.61	[0.82; 8.31]	0.106
IIB	20 / 246 (8.1)	8 / 220 (3.6)	2.24	[1.01; 4.97]	0.049
IIIA	33 / 451 (7.3)	17 / 393 (4.3)	1.69	[0.96; 2.99]	0.070
IIIB	3 / 67 (4.5)	2 / 59 (3.4)	1.32	[0.23; 7.64]	0.756
IIIC	15 / 173 (8.7)	5 / 200 (2.5)	3.47	[1.29; 9.35]	0.014
Nodal status					
Interaction test	**p = 0.435**				
N0	4 / 91 (4.4)	1 / 117 (0.9)	5.14	[0.58; 45.23]	0.140
N1-N3	76 / 1017 (7.5)	34 / 950 (3.6)	2.09	[1.41; 3.10]	<.001
Histological grade at time of surgery					
Interaction test	**p = 0.708**				
Grade 1	6 / 110 (5.5)	4 / 100 (4.0)	1.36	[0.40; 4.69]	0.623
Grade 2	44 / 604 (7.3)	20 / 601 (3.3)	2.19	[1.31; 3.67]	0.003
Grade 3	25 / 297 (8.4)	9 / 266 (3.4)	2.49	[1.18; 5.23]	0.016
Histological subtype					
Interaction test	**p = 0.662**				
Ductal	56 / 863 (6.5)	28 / 835 (3.4)	1.94	[1.24; 3.02]	0.004
Lobular	17 / 172 (9.9)	6 / 169 (3.6)	2.78	[1.12; 6.89]	0.027
Other	7 / 73 (9.6)	2 / 66 (3.0)	3.16	[0.68; 14.70]	0.142
Ki67 status from surgical specimen					
Interaction test	**p = 0.597**				
Ki67≤20	42 / 527 (8.0)	19 / 552 (3.4)	2.32	[1.36; 3.93]	0.002
Ki67>20	27 / 422 (6.4)	8 / 378 (2.1)	3.02	[1.39; 6.57]	0.005
Type of NSAI					
Interaction test	**p = 0.743**				
Letrozole	54 / 809 (6.7)	25 / 773 (3.2)	2.06	[1.30; 3.28]	0.002
Anastrozole	26 / 299 (8.7)	11 / 297 (3.7)	2.35	[1.18; 4.66]	0.015
Prior neo/adjuvant chemotherapy					
Interaction test	**N.E.**				
Yes	78 / 1029 (7.6)	36 / 987 (3.6)	2.08	[1.41; 3.05]	<.001
No	2 / 79 (2.5)	0 / 83 (0.0)	5.25	[0.26; >99.99]	0.282
Prior adjuvant chemotherapy					
Interaction test	**p = 0.004**				
Yes	50 / 513 (9.7)	12 / 488 (2.5)	3.96	[2.14; 7.35]	<.001
No	30 / 595 (5.0)	24 / 582 (4.1)	1.22	[0.72; 2.07]	0.452
Prior neoadjuvant chemotherapy					
Interaction test	**p = 0.002**				
Yes	30 / 546 (5.5)	25 / 538 (4.6)	1.18	[0.70; 1.98]	0.525
No	50 / 562 (8.9)	11 / 532 (2.1)	4.30	[2.26; 8.18]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Prior endocrine therapy					
Interaction test	**p = 0.940**				
Yes	61 / 853 (7.2)	26 / 789 (3.3)	2.17	[1.39; 3.40]	<.001
No	19 / 255 (7.5)	10 / 281 (3.6)	2.09	[0.99; 4.42]	0.052
Prior mastectomy					
Interaction test	**p = 0.326**				
Yes	55 / 769 (7.2)	28 / 745 (3.8)	1.90	[1.22; 2.97]	0.004
No	25 / 339 (7.4)	8 / 325 (2.5)	3.00	[1.37; 6.55]	0.006
Prior radiotherapy					
Interaction test	**p = 0.766**				
Yes	76 / 1011 (7.5)	34 / 987 (3.4)	2.18	[1.47; 3.24]	<.001
No	4 / 97 (4.1)	2 / 83 (2.4)	1.71	[0.32; 9.11]	0.529

N: Number of patients
n: Number of patients with event
N.E.: Not estimable
CI: Confidence interval
RR: Relative risk
ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
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Analysis method for interaction test:
p-value from logistic regression model.
logit(proportion) = treatment + subgroup factor + treatment * subgroup factor

Analysis method for within subgroup analysis:
RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm.
ET was the reference group for treatment group comparison.

Table 5-3.2.58 PT dry skin: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	ET (N = 1070)	RR	[95% CI]	p-value
Dry skin					
	n / N (%)	n / N (%)			
Region					
Interaction test	**p = 0.792**				
NA/WE/O	36 / 640 (5.6)	12 / 627 (1.9)	2.94	[1.54; 5.60]	0.001
ROW	8 / 468 (1.7)	2 / 443 (0.5)	3.79	[0.81; 17.73]	0.091
Geographical region					
Interaction test	**p = 0.673**				
Europe	31 / 654 (4.7)	12 / 638 (1.9)	2.52	[1.31; 4.86]	0.006
North America/Australia	8 / 213 (3.8)	2 / 194 (1.0)	3.64	[0.78; 16.95]	0.099
Asia	4 / 178 (2.2)	0 / 168 (0.0)	8.50	[0.46; >99.99]	0.150
Latin America	1 / 63 (1.6)	0 / 70 (0.0)	3.33	[0.14; 80.25]	0.459
Age group 1 at randomization					
Interaction test	**p = 0.256**				
<45	21 / 549 (3.8)	4 / 496 (0.8)	4.74	[1.64; 13.72]	0.004
45 to 54	22 / 539 (4.1)	10 / 546 (1.8)	2.23	[1.07; 4.66]	0.033
55 to 64	1 / 20 (5.0)	0 / 28 (0.0)	4.14	[0.18; 96.77]	0.377
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)					
Interaction test	**p = 0.293**				
<Median	21 / 549 (3.8)	4 / 496 (0.8)	4.74	[1.64; 13.72]	0.004
≥Median	23 / 559 (4.1)	10 / 574 (1.7)	2.36	[1.13; 4.92]	0.022
Race					
Interaction test	**N.E.**				
Asian	5 / 211 (2.4)	0 / 186 (0.0)	9.70	[0.54; >99.99]	0.123
Non-Asian	32 / 840 (3.8)	13 / 827 (1.6)	2.42	[1.28; 4.58]	0.006
BMI at screening					
Interaction test	**p = 0.633**				
≥25	24 / 551 (4.4)	6 / 523 (1.1)	3.80	[1.56; 9.21]	0.003
<25	20 / 542 (3.7)	7 / 535 (1.3)	2.82	[1.20; 6.61]	0.017
AJCC Anatomic Stage Group					
Interaction test	**p = 0.614**				
Group I/II	15 / 417 (3.6)	6 / 418 (1.4)	2.51	[0.98; 6.40]	0.055
Group III	29 / 691 (4.2)	8 / 652 (1.2)	3.42	[1.58; 7.43]	0.002

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Anatomic stages					
Interaction test	**p = 0.632**				
IA/IB/IIA	5 / 171 (2.9)	1 / 198 (0.5)	5.79	[0.68; 49.07]	0.107
IIB	10 / 246 (4.1)	5 / 220 (2.3)	1.79	[0.62; 5.15]	0.281
IIIA	21 / 451 (4.7)	8 / 393 (2.0)	2.29	[1.02; 5.11]	0.043
IIIB	4 / 67 (6.0)	0 / 59 (0.0)	7.94	[0.44; >99.99]	0.162
IIIC	4 / 173 (2.3)	0 / 200 (0.0)	10.40	[0.56; >99.99]	0.115
Nodal status					
Interaction test	**N.E.**				
N0	0 / 91 (0.0)	0 / 117 (0.0)	N.E.	N.E.	N.E.
N1-N3	44 / 1017 (4.3)	14 / 950 (1.5)	2.94	[1.62; 5.32]	<.001
Histological grade at time of surgery					
Interaction test	**p = 0.673**				
Grade 1	4 / 110 (3.6)	1 / 100 (1.0)	3.64	[0.41; 31.99]	0.245
Grade 2	25 / 604 (4.1)	7 / 601 (1.2)	3.55	[1.55; 8.15]	0.003
Grade 3	11 / 297 (3.7)	5 / 266 (1.9)	1.97	[0.69; 5.60]	0.203
Histological subtype					
Interaction test	**p = 0.899**				
Ductal	35 / 863 (4.1)	11 / 835 (1.3)	3.08	[1.57; 6.02]	0.001
Lobular	7 / 172 (4.1)	2 / 169 (1.2)	3.44	[0.72; 16.32]	0.120
Other	2 / 73 (2.7)	1 / 66 (1.5)	1.81	[0.17; 19.48]	0.625
Ki67 status from surgical specimen					
Interaction test	**p = 0.588**				
Ki67≤20	28 / 527 (5.3)	6 / 552 (1.1)	4.89	[2.04; 11.71]	<.001
Ki67>20	15 / 422 (3.6)	4 / 378 (1.1)	3.36	[1.12; 10.03]	0.030
Type of NSAI					
Interaction test	**p = 0.494**				
Letrozole	30 / 809 (3.7)	8 / 773 (1.0)	3.58	[1.65; 7.77]	0.001
Anastrozole	14 / 299 (4.7)	6 / 297 (2.0)	2.32	[0.90; 5.95]	0.081
Prior neo/adjuvant chemotherapy					
Interaction test	**p = 0.974**				
Yes	41 / 1029 (4.0)	13 / 987 (1.3)	3.03	[1.63; 5.61]	<.001
No	3 / 79 (3.8)	1 / 83 (1.2)	3.15	[0.33; 29.67]	0.316
Prior adjuvant chemotherapy					
Interaction test	**p = 0.848**				
Yes	21 / 513 (4.1)	7 / 488 (1.4)	2.85	[1.22; 6.65]	0.015
No	23 / 595 (3.9)	7 / 582 (1.2)	3.21	[1.39; 7.43]	0.006
Prior neoadjuvant chemotherapy					
Interaction test	**p = 0.703**				
Yes	21 / 546 (3.8)	6 / 538 (1.1)	3.45	[1.40; 8.48]	0.007
No	23 / 562 (4.1)	8 / 532 (1.5)	2.72	[1.23; 6.03]	0.014

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Prior endocrine therapy					
Interaction test	**p = 0.115**				
Yes	36 / 853 (4.2)	8 / 789 (1.0)	4.16	[1.95; 8.90]	<.001
No	8 / 255 (3.1)	6 / 281 (2.1)	1.47	[0.52; 4.18]	0.470
Prior mastectomy					
Interaction test	**p = 0.607**				
Yes	37 / 769 (4.8)	11 / 745 (1.5)	3.26	[1.67; 6.34]	<.001
No	7 / 339 (2.1)	3 / 325 (0.9)	2.24	[0.58; 8.58]	0.240
Prior radiotherapy					
Interaction test	**p = 0.351**				
Yes	43 / 1011 (4.3)	13 / 987 (1.3)	3.23	[1.75; 5.97]	<.001
No	1 / 97 (1.0)	1 / 83 (1.2)	0.86	[0.05; 13.47]	0.912

N: Number of patients
n: Number of patients with event
N.E.: Not estimable
CI: Confidence interval
RR: Relative risk
ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
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Analysis method for interaction test:
p-value from logistic regression model.
logit(proportion) = treatment + subgroup factor + treatment * subgroup factor

Analysis method for within subgroup analysis:
RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm.
ET was the reference group for treatment group comparison.

Table 5-3.2.59 PT madarosis: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	ET (N = 1070)	RR	[95% CI]	p-value
Madarosis					
	n / N (%)	n / N (%)			
Region					
Interaction test	**p = 0.428**				
NA/WE/O	12 / 640 (1.9)	2 / 627 (0.3)	5.88	[1.32; 26.16]	0.020
ROW	2 / 468 (0.4)	1 / 443 (0.2)	1.89	[0.17; 20.80]	0.602
Geographical region					
The subgroup analysis is not presented as all subgroups have less than 10 events.					
Age group 1 at randomization					
Interaction test	**p = 0.874**				
<45	9 / 549 (1.6)	2 / 496 (0.4)	4.07	[0.88; 18.73]	0.072
45 to 54	5 / 539 (0.9)	1 / 546 (0.2)	5.06	[0.59; 43.21]	0.138
55 to 64	0 / 20 (0.0)	0 / 28 (0.0)	N.E.	N.E.	N.E.
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)					
Interaction test	**p = 0.866**				
<Median	9 / 549 (1.6)	2 / 496 (0.4)	4.07	[0.88; 18.73]	0.072
≥Median	5 / 559 (0.9)	1 / 574 (0.2)	5.13	[0.60; 43.81]	0.135
Race					
Interaction test	**N.E.**				
Asian	2 / 211 (0.9)	0 / 186 (0.0)	4.41	[0.21; 91.28]	0.337
Non-Asian	11 / 840 (1.3)	3 / 827 (0.4)	3.61	[1.01; 12.89]	0.048
BMI at screening					
Interaction test	**p = 0.324**				
≥25	5 / 551 (0.9)	2 / 523 (0.4)	2.37	[0.46; 12.18]	0.300
<25	9 / 542 (1.7)	1 / 535 (0.2)	8.88	[1.13; 69.88]	0.038
AJCC Anatomic Stage Group					
The subgroup analysis is not presented as all subgroups have less than 10 events.					
Anatomic stages					
The subgroup analysis is not presented as all subgroups have less than 10 events.					

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Nodal status					
Interaction test	**N.E.**				
N0	2 / 91 (2.2)	0 / 117 (0.0)	6.41	[0.31; >99.99]	0.228
N1-N3	12 / 1017 (1.2)	3 / 950 (0.3)	3.74	[1.06; 13.20]	0.041
Histological grade at time of surgery					
Interaction test	**N.E.**				
Grade 1	0 / 110 (0.0)	0 / 100 (0.0)	N.E.	N.E.	N.E.
Grade 2	11 / 604 (1.8)	2 / 601 (0.3)	5.47	[1.22; 24.59]	0.027
Grade 3	2 / 297 (0.7)	0 / 266 (0.0)	4.48	[0.22; 92.89]	0.332
Histological subtype					
Interaction test	**p = 0.452**				
Ductal	12 / 863 (1.4)	2 / 835 (0.2)	5.81	[1.30; 25.86]	0.021
Lobular	2 / 172 (1.2)	1 / 169 (0.6)	1.97	[0.18; 21.47]	0.580
Other	0 / 73 (0.0)	0 / 66 (0.0)	N.E.	N.E.	N.E.
Ki67 status from surgical specimen					
The subgroup analysis is not presented as all subgroups have less than 10 events.					
Type of NSAI					
Interaction test	**p = 0.248**				
Letrozole	10 / 809 (1.2)	1 / 773 (0.1)	9.56	[1.23; 74.46]	0.031
Anastrozole	4 / 299 (1.3)	2 / 297 (0.7)	1.99	[0.37; 10.76]	0.426
Prior neo/adjuvant chemotherapy					
Interaction test	**N.E.**				
Yes	14 / 1029 (1.4)	3 / 987 (0.3)	4.48	[1.29; 15.53]	0.018
No	0 / 79 (0.0)	0 / 83 (0.0)	N.E.	N.E.	N.E.
Prior adjuvant chemotherapy					
Interaction test	**p = 0.925**				
Yes	9 / 513 (1.8)	2 / 488 (0.4)	4.28	[0.93; 19.71]	0.062
No	5 / 595 (0.8)	1 / 582 (0.2)	4.89	[0.57; 41.73]	0.147
Prior neoadjuvant chemotherapy					
Interaction test	**p = 0.917**				
Yes	5 / 546 (0.9)	1 / 538 (0.2)	4.93	[0.58; 42.03]	0.145
No	9 / 562 (1.6)	2 / 532 (0.4)	4.26	[0.92; 19.62]	0.063
Prior endocrine therapy					
Interaction test	**N.E.**				
Yes	12 / 853 (1.4)	3 / 789 (0.4)	3.70	[1.05; 13.06]	0.042
No	2 / 255 (0.8)	0 / 281 (0.0)	5.51	[0.27; >99.99]	0.270
Prior mastectomy					
Interaction test	**N.E.**				
Yes	9 / 769 (1.2)	3 / 745 (0.4)	2.91	[0.79; 10.69]	0.108
No	5 / 339 (1.5)	0 / 325 (0.0)	10.55	[0.59; >99.99]	0.110

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Prior radiotherapy					
Interaction test	**N.E.**				
Yes	12 / 1011 (1.2)	3 / 987 (0.3)	3.91	[1.11; 13.80]	0.034
No	2 / 97 (2.1)	0 / 83 (0.0)	4.29	[0.21; 88.03]	0.345

N: Number of patients
n: Number of patients with event
N.E.: Not estimable
CI: Confidence interval
RR: Relative risk
ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
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Analysis method for interaction test:
p-value from logistic regression model.
logit(proportion) = treatment + subgroup factor + treatment * subgroup factor

Analysis method for within subgroup analysis:
RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm.
ET was the reference group for treatment group comparison.

Table 5-3.2.60 PT rash maculo-papular: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Rash maculo-papular					
	n / N (%)	**n / N (%)**			
Region					
Interaction test	**N.E.**				
NA/WE/O	12 / 640 (1.9)	3 / 627 (0.5)	3.92	[1.11; 13.82]	0.034
ROW	0 / 468 (0.0)	0 / 443 (0.0)	N.E.	N.E.	N.E.
Geographical region					
Interaction test	**p = 0.974**				
Europe	4 / 654 (0.6)	1 / 638 (0.2)	3.90	[0.44; 34.82]	0.223
North America/Australia	8 / 213 (3.8)	2 / 194 (1.0)	3.64	[0.78; 16.95]	0.099
Asia	0 / 178 (0.0)	0 / 168 (0.0)	N.E.	N.E.	N.E.
Latin America	0 / 63 (0.0)	0 / 70 (0.0)	N.E.	N.E.	N.E.
Age group 1 at randomization					
The subgroup analysis is not presented as all subgroups have less than 10 events.					
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)					
Interaction test	**p = 0.922**				
<Median	4 / 549 (0.7)	1 / 496 (0.2)	3.61	[0.41; 32.22]	0.250
≥Median	8 / 559 (1.4)	2 / 574 (0.3)	4.11	[0.88; 19.26]	0.073
Race					
Interaction test	**N.E.**				
Asian	0 / 211 (0.0)	0 / 186 (0.0)	N.E.	N.E.	N.E.
Non-Asian	11 / 840 (1.3)	3 / 827 (0.4)	3.61	[1.01; 12.89]	0.048
BMI at screening					
Interaction test	**p = 0.855**				
≥25	8 / 551 (1.5)	2 / 523 (0.4)	3.80	[0.81; 17.80]	0.091
<25	3 / 542 (0.6)	1 / 535 (0.2)	2.96	[0.31; 28.38]	0.346
AJCC Anatomic Stage Group					
The subgroup analysis is not presented as all subgroups have less than 10 events.					
Anatomic stages					
The subgroup analysis is not presented as all subgroups have less than 10 events.					

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Nodal status					
Interaction test	**N.E.**				
N0	2 / 91 (2.2)	0 / 117 (0.0)	6.41	[0.31; >99.99]	0.228
N1-N3	10 / 1017 (1.0)	3 / 950 (0.3)	3.11	[0.86; 11.28]	0.084
Histological grade at time of surgery					
The subgroup analysis is not presented as all subgroups have less than 10 events.					
Histological subtype					
Interaction test	**N.E.**				
Ductal	9 / 863 (1.0)	3 / 835 (0.4)	2.90	[0.79; 10.68]	0.109
Lobular	1 / 172 (0.6)	0 / 169 (0.0)	2.95	[0.12; 71.86]	0.507
Other	2 / 73 (2.7)	0 / 66 (0.0)	4.53	[0.22; 92.61]	0.327
Ki67 status from surgical specimen					
The subgroup analysis is not presented as all subgroups have less than 10 events.					
Type of NSAI					
The subgroup analysis is not presented as all subgroups have less than 10 events.					
Prior neo/adjuvant chemotherapy					
Interaction test	**N.E.**				
Yes	11 / 1029 (1.1)	3 / 987 (0.3)	3.52	[0.98; 12.57]	0.053
No	1 / 79 (1.3)	0 / 83 (0.0)	3.15	[0.13; 76.20]	0.480
Prior adjuvant chemotherapy					
Interaction test	**N.E.**				
Yes	5 / 513 (1.0)	0 / 488 (0.0)	10.46	[0.58; >99.99]	0.112
No	7 / 595 (1.2)	3 / 582 (0.5)	2.28	[0.59; 8.78]	0.230
Prior neoadjuvant chemotherapy					
The subgroup analysis is not presented as all subgroups have less than 10 events.					
Prior endocrine therapy					
Interaction test	**N.E.**				
Yes	9 / 853 (1.1)	3 / 789 (0.4)	2.77	[0.75; 10.21]	0.125
No	3 / 255 (1.2)	0 / 281 (0.0)	7.71	[0.40; >99.99]	0.176
Prior mastectomy					
Interaction test	**N.E.**				
Yes	10 / 769 (1.3)	3 / 745 (0.4)	3.23	[0.89; 11.69]	0.074
No	2 / 339 (0.6)	0 / 325 (0.0)	4.79	[0.23; 99.48]	0.311

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Prior radiotherapy					
Interaction test	**N.E.**				
Yes	11 / 1011 (1.1)	3 / 987 (0.3)	3.58	[1.00; 12.79]	0.050
No	1 / 97 (1.0)	0 / 83 (0.0)	2.57	[0.11; 62.29]	0.561

N: Number of patients
n: Number of patients with event
N.E.: Not estimable
CI: Confidence interval
RR: Relative risk
ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
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Analysis method for interaction test:
p-value from logistic regression model.
logit(proportion) = treatment + subgroup factor + treatment * subgroup factor

Analysis method for within subgroup analysis:
RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm.
ET was the reference group for treatment group comparison.

Table 5-3.2.61 SOC respiratory, thoracic and mediastinal disorders: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	ET (N = 1070)	RR	[95% CI]	p-value
Respiratory, thoracic and mediastinal disorders					
	n / N (%)	n / N (%)			
Region					
Interaction test	**p = 0.685**				
NA/WE/O	232 / 640 (36.3)	129 / 627 (20.6)	1.76	[1.46; 2.12]	<.001
ROW	107 / 468 (22.9)	57 / 443 (12.9)	1.78	[1.32; 2.38]	<.001
Geographical region					
Interaction test	**p = 0.523**				
Europe	165 / 654 (25.2)	87 / 638 (13.6)	1.85	[1.46; 2.34]	<.001
North America/Australia	103 / 213 (48.4)	53 / 194 (27.3)	1.77	[1.35; 2.31]	<.001
Asia	63 / 178 (35.4)	38 / 168 (22.6)	1.56	[1.11; 2.20]	0.011
Latin America	8 / 63 (12.7)	8 / 70 (11.4)	1.11	[0.44; 2.79]	0.822
Age group 1 at randomization					
Interaction test	**p = 0.743**				
<45	161 / 549 (29.3)	80 / 496 (16.1)	1.82	[1.43; 2.31]	<.001
45 to 54	172 / 539 (31.9)	99 / 546 (18.1)	1.76	[1.42; 2.19]	<.001
55 to 64	6 / 20 (30.0)	7 / 28 (25.0)	1.20	[0.47; 3.03]	0.700
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)					
Interaction test	**p = 0.829**				
<Median	161 / 549 (29.3)	80 / 496 (16.1)	1.82	[1.43; 2.31]	<.001
≥Median	178 / 559 (31.8)	106 / 574 (18.5)	1.72	[1.40; 2.13]	<.001
Race					
Interaction test	**p = 0.894**				
Asian	81 / 211 (38.4)	43 / 186 (23.1)	1.66	[1.21; 2.27]	0.001
Non-Asian	236 / 840 (28.1)	135 / 827 (16.3)	1.72	[1.43; 2.08]	<.001
BMI at screening					
Interaction test	**p = 0.559**				
≥25	176 / 551 (31.9)	92 / 523 (17.6)	1.82	[1.45; 2.27]	<.001
<25	156 / 542 (28.8)	92 / 535 (17.2)	1.67	[1.33; 2.10]	<.001
AJCC Anatomic Stage Group					
Interaction test	**p = 0.272**				
Group I/II	118 / 417 (28.3)	58 / 418 (13.9)	2.04	[1.54; 2.71]	<.001
Group III	221 / 691 (32.0)	128 / 652 (19.6)	1.63	[1.35; 1.97]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Anatomic stages					
Interaction test	**p = 0.249**				
IA/IB/IIA	43 / 171 (25.1)	21 / 198 (10.6)	2.37	[1.47; 3.83]	<.001
IIB	75 / 246 (30.5)	37 / 220 (16.8)	1.81	[1.28; 2.57]	<.001
IIIA	141 / 451 (31.3)	84 / 393 (21.4)	1.46	[1.16; 1.85]	0.001
IIIB	18 / 67 (26.9)	4 / 59 (6.8)	3.96	[1.42; 11.05]	0.008
IIIC	62 / 173 (35.8)	40 / 200 (20.0)	1.79	[1.27; 2.52]	<.001
Nodal status					
Interaction test	**p = 0.119**				
N0	24 / 91 (26.4)	10 / 117 (8.5)	3.09	[1.56; 6.12]	0.001
N1-N3	315 / 1017 (31.0)	175 / 950 (18.4)	1.68	[1.43; 1.98]	<.001
Histological grade at time of surgery					
Interaction test	**p = 0.986**				
Grade 1	25 / 110 (22.7)	12 / 100 (12.0)	1.89	[1.01; 3.57]	0.048
Grade 2	193 / 604 (32.0)	102 / 601 (17.0)	1.88	[1.52; 2.33]	<.001
Grade 3	108 / 297 (36.4)	54 / 266 (20.3)	1.79	[1.35; 2.37]	<.001
Histological subtype					
Interaction test	**p = 0.574**				
Ductal	271 / 863 (31.4)	149 / 835 (17.8)	1.76	[1.48; 2.10]	<.001
Lobular	49 / 172 (28.5)	24 / 169 (14.2)	2.01	[1.29; 3.11]	0.002
Other	19 / 73 (26.0)	13 / 66 (19.7)	1.32	[0.71; 2.46]	0.380
Ki67 status from surgical specimen					
Interaction test	**p = 0.713**				
Ki67≤20	150 / 527 (28.5)	88 / 552 (15.9)	1.79	[1.41; 2.26]	<.001
Ki67>20	119 / 422 (28.2)	64 / 378 (16.9)	1.67	[1.27; 2.18]	<.001
Type of NSAI					
Interaction test	**p = 0.847**				
Letrozole	233 / 809 (28.8)	126 / 773 (16.3)	1.77	[1.46; 2.14]	<.001
Anastrozole	106 / 299 (35.5)	60 / 297 (20.2)	1.75	[1.34; 2.31]	<.001
Prior neo/adjuvant chemotherapy					
Interaction test	**p = 0.049**				
Yes	322 / 1029 (31.3)	183 / 987 (18.5)	1.69	[1.44; 1.98]	<.001
No	17 / 79 (21.5)	3 / 83 (3.6)	5.95	[1.81; 19.53]	0.003
Prior adjuvant chemotherapy					
Interaction test	**p = 0.264**				
Yes	180 / 513 (35.1)	91 / 488 (18.6)	1.88	[1.51; 2.34]	<.001
No	159 / 595 (26.7)	95 / 582 (16.3)	1.64	[1.30; 2.05]	<.001
Prior neoadjuvant chemotherapy					
Interaction test	**p = 0.016**				
Yes	149 / 546 (27.3)	101 / 538 (18.8)	1.45	[1.16; 1.82]	<.001
No	190 / 562 (33.8)	85 / 532 (16.0)	2.12	[1.69; 2.65]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Prior endocrine therapy					
Interaction test	**p = 0.452**				
Yes	260 / 853 (30.5)	131 / 789 (16.6)	1.84	[1.52; 2.21]	<.001
No	79 / 255 (31.0)	55 / 281 (19.6)	1.58	[1.17; 2.14]	0.003
Prior mastectomy					
Interaction test	**p = 0.033**				
Yes	234 / 769 (30.4)	144 / 745 (19.3)	1.57	[1.31; 1.89]	<.001
No	105 / 339 (31.0)	42 / 325 (12.9)	2.40	[1.73; 3.31]	<.001
Prior radiotherapy					
Interaction test	**p = 0.913**				
Yes	318 / 1011 (31.5)	176 / 987 (17.8)	1.76	[1.50; 2.07]	<.001
No	21 / 97 (21.6)	10 / 83 (12.0)	1.80	[0.90; 3.60]	0.098

N: Number of patients
n: Number of patients with event
CI: Confidence interval
RR: Relative risk
ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
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Analysis method for interaction test:
p-value from logistic regression model.
logit(proportion) = treatment + subgroup factor + treatment * subgroup factor

Analysis method for within subgroup analysis:
RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm.
ET was the reference group for treatment group comparison.

Table 5-3.2.62 PT cough: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	ET (N = 1070)	RR	[95% CI]	p-value
Cough					
	n / N (%)	n / N (%)			
Region					
Interaction test	**p = 0.749**				
NA/WE/O	117 / 640 (18.3)	63 / 627 (10.0)	1.82	[1.37; 2.42]	<.001
ROW	53 / 468 (11.3)	29 / 443 (6.5)	1.73	[1.12; 2.67]	0.013
Geographical region					
Interaction test	**p = 0.882**				
Europe	78 / 654 (11.9)	40 / 638 (6.3)	1.90	[1.32; 2.74]	<.001
North America/Australia	53 / 213 (24.9)	28 / 194 (14.4)	1.72	[1.14; 2.61]	0.010
Asia	35 / 178 (19.7)	20 / 168 (11.9)	1.65	[0.99; 2.74]	0.053
Latin America	4 / 63 (6.3)	4 / 70 (5.7)	1.11	[0.29; 4.26]	0.878
Age group 1 at randomization					
Interaction test	**p = 0.043**				
<45	81 / 549 (14.8)	31 / 496 (6.3)	2.36	[1.59; 3.51]	<.001
45 to 54	88 / 539 (16.3)	55 / 546 (10.1)	1.62	[1.18; 2.22]	0.003
55 to 64	1 / 20 (5.0)	6 / 28 (21.4)	0.23	[0.03; 1.79]	0.162
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)					
Interaction test	**p = 0.085**				
<Median	81 / 549 (14.8)	31 / 496 (6.3)	2.36	[1.59; 3.51]	<.001
≥Median	89 / 559 (15.9)	61 / 574 (10.6)	1.50	[1.11; 2.03]	0.009
Race					
Interaction test	**p = 0.399**				
Asian	49 / 211 (23.2)	22 / 186 (11.8)	1.96	[1.24; 3.12]	0.004
Non-Asian	112 / 840 (13.3)	68 / 827 (8.2)	1.62	[1.22; 2.16]	<.001
BMI at screening					
Interaction test	**p = 0.349**				
≥25	85 / 551 (15.4)	52 / 523 (9.9)	1.55	[1.12; 2.14]	0.008
<25	80 / 542 (14.8)	40 / 535 (7.5)	1.97	[1.38; 2.83]	<.001
AJCC Anatomic Stage Group					
Interaction test	**p = 0.185**				
Group I/II	63 / 417 (15.1)	28 / 418 (6.7)	2.26	[1.48; 3.45]	<.001
Group III	107 / 691 (15.5)	64 / 652 (9.8)	1.58	[1.18; 2.11]	0.002

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Anatomic stages					
Interaction test	**p = 0.472**				
IA/IB/IIA	24 / 171 (14.0)	10 / 198 (5.1)	2.78	[1.37; 5.65]	0.005
IIB	39 / 246 (15.9)	18 / 220 (8.2)	1.94	[1.14; 3.29]	0.014
IIIA	78 / 451 (17.3)	39 / 393 (9.9)	1.74	[1.22; 2.50]	0.002
IIIB	5 / 67 (7.5)	2 / 59 (3.4)	2.20	[0.44; 10.93]	0.334
IIIC	24 / 173 (13.9)	23 / 200 (11.5)	1.21	[0.71; 2.06]	0.492
Nodal status					
Interaction test	**p = 0.082**				
N0	14 / 91 (15.4)	4 / 117 (3.4)	4.50	[1.53; 13.21]	0.006
N1-N3	156 / 1017 (15.3)	87 / 950 (9.2)	1.67	[1.31; 2.14]	<.001
Histological grade at time of surgery					
Interaction test	**p = 0.920**				
Grade 1	14 / 110 (12.7)	6 / 100 (6.0)	2.12	[0.85; 5.31]	0.108
Grade 2	101 / 604 (16.7)	50 / 601 (8.3)	2.01	[1.46; 2.77]	<.001
Grade 3	52 / 297 (17.5)	26 / 266 (9.8)	1.79	[1.15; 2.78]	0.010
Histological subtype					
Interaction test	**p = 0.498**				
Ductal	136 / 863 (15.8)	72 / 835 (8.6)	1.83	[1.40; 2.39]	<.001
Lobular	26 / 172 (15.1)	13 / 169 (7.7)	1.97	[1.05; 3.69]	0.036
Other	8 / 73 (11.0)	7 / 66 (10.6)	1.03	[0.40; 2.69]	0.947
Ki67 status from surgical specimen					
Interaction test	**p = 0.822**				
Ki67≤20	75 / 527 (14.2)	46 / 552 (8.3)	1.71	[1.21; 2.42]	0.003
Ki67>20	54 / 422 (12.8)	30 / 378 (7.9)	1.61	[1.05; 2.46]	0.027
Type of NSAI					
Interaction test	**p = 0.709**				
Letrozole	120 / 809 (14.8)	62 / 773 (8.0)	1.85	[1.38; 2.47]	<.001
Anastrozole	50 / 299 (16.7)	30 / 297 (10.1)	1.66	[1.08; 2.53]	0.020
Prior neo/adjuvant chemotherapy					
Interaction test	**p = 0.202**				
Yes	161 / 1029 (15.6)	90 / 987 (9.1)	1.72	[1.35; 2.19]	<.001
No	9 / 79 (11.4)	2 / 83 (2.4)	4.73	[1.05; 21.21]	0.042
Prior adjuvant chemotherapy					
Interaction test	**p = 0.566**				
Yes	93 / 513 (18.1)	47 / 488 (9.6)	1.88	[1.36; 2.61]	<.001
No	77 / 595 (12.9)	45 / 582 (7.7)	1.67	[1.18; 2.37]	0.004
Prior neoadjuvant chemotherapy					
Interaction test	**p = 0.135**				
Yes	72 / 546 (13.2)	48 / 538 (8.9)	1.48	[1.05; 2.09]	0.027
No	98 / 562 (17.4)	44 / 532 (8.3)	2.11	[1.51; 2.95]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Prior endocrine therapy					
Interaction test	**p = 0.261**				
Yes	134 / 853 (15.7)	64 / 789 (8.1)	1.94	[1.46; 2.57]	<.001
No	36 / 255 (14.1)	28 / 281 (10.0)	1.42	[0.89; 2.25]	0.141
Prior mastectomy					
Interaction test	**p = 0.344**				
Yes	118 / 769 (15.3)	69 / 745 (9.3)	1.66	[1.25; 2.19]	<.001
No	52 / 339 (15.3)	23 / 325 (7.1)	2.17	[1.36; 3.46]	0.001
Prior radiotherapy					
Interaction test	**p = 0.466**				
Yes	161 / 1011 (15.9)	86 / 987 (8.7)	1.83	[1.43; 2.34]	<.001
No	9 / 97 (9.3)	6 / 83 (7.2)	1.28	[0.48; 3.46]	0.621

N: Number of patients
n: Number of patients with event
CI: Confidence interval
RR: Relative risk
ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
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Analysis method for interaction test:
p-value from logistic regression model.
logit(proportion) = treatment + subgroup factor + treatment * subgroup factor

Analysis method for within subgroup analysis:
RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm.
ET was the reference group for treatment group comparison.

Table 5-3.2.63 PT oropharyngeal pain: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	ET (N = 1070)	RR	[95% CI]	p-value
Oropharyngeal pain					
	n / N (%)	n / N (%)			
Region					
Interaction test	**p = 0.061**				
NA/WE/O	65 / 640 (10.2)	27 / 627 (4.3)	2.36	[1.53; 3.64]	<.001
ROW	27 / 468 (5.8)	21 / 443 (4.7)	1.22	[0.70; 2.12]	0.488
Geographical region					
Interaction test	**p = 0.309**				
Europe	28 / 654 (4.3)	14 / 638 (2.2)	1.95	[1.04; 3.67]	0.038
North America/Australia	44 / 213 (20.7)	17 / 194 (8.8)	2.36	[1.39; 3.98]	0.001
Asia	19 / 178 (10.7)	16 / 168 (9.5)	1.12	[0.60; 2.11]	0.723
Latin America	1 / 63 (1.6)	1 / 70 (1.4)	1.11	[0.07; 17.40]	0.940
Age group 1 at randomization					
Interaction test	**p = 0.075**				
<45	53 / 549 (9.7)	18 / 496 (3.6)	2.66	[1.58; 4.48]	<.001
45 to 54	39 / 539 (7.2)	28 / 546 (5.1)	1.41	[0.88; 2.26]	0.152
55 to 64	0 / 20 (0.0)	2 / 28 (7.1)	0.28	[0.01; 5.46]	0.398
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)					
Interaction test	**p = 0.050**				
<Median	53 / 549 (9.7)	18 / 496 (3.6)	2.66	[1.58; 4.48]	<.001
≥Median	39 / 559 (7.0)	30 / 574 (5.2)	1.33	[0.84; 2.12]	0.220
Race					
Interaction test	**p = 0.217**				
Asian	25 / 211 (11.8)	17 / 186 (9.1)	1.30	[0.72; 2.32]	0.384
Non-Asian	66 / 840 (7.9)	31 / 827 (3.7)	2.10	[1.38; 3.18]	<.001
BMI at screening					
Interaction test	**p = 0.120**				
≥25	50 / 551 (9.1)	20 / 523 (3.8)	2.37	[1.43; 3.93]	<.001
<25	39 / 542 (7.2)	28 / 535 (5.2)	1.37	[0.86; 2.20]	0.185
AJCC Anatomic Stage Group					
Interaction test	**p = 0.085**				
Group I/II	35 / 417 (8.4)	12 / 418 (2.9)	2.92	[1.54; 5.55]	0.001
Group III	57 / 691 (8.2)	36 / 652 (5.5)	1.49	[1.00; 2.24]	0.051

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Anatomic stages					
Interaction test	**p = 0.180**				
IA/IB/IIA	15 / 171 (8.8)	3 / 198 (1.5)	5.79	[1.70; 19.66]	0.005
IIB	20 / 246 (8.1)	9 / 220 (4.1)	1.99	[0.92; 4.27]	0.079
IIIA	36 / 451 (8.0)	25 / 393 (6.4)	1.25	[0.77; 2.05]	0.366
IIIB	5 / 67 (7.5)	1 / 59 (1.7)	4.40	[0.53; 36.62]	0.170
IIIC	16 / 173 (9.2)	10 / 200 (5.0)	1.85	[0.86; 3.97]	0.114
Nodal status					
Interaction test	**p = 0.232**				
N0	9 / 91 (9.9)	3 / 117 (2.6)	3.86	[1.08; 13.84]	0.038
N1-N3	83 / 1017 (8.2)	45 / 950 (4.7)	1.72	[1.21; 2.45]	0.002
Histological grade at time of surgery					
Interaction test	**p = 0.793**				
Grade 1	4 / 110 (3.6)	3 / 100 (3.0)	1.21	[0.28; 5.28]	0.798
Grade 2	45 / 604 (7.5)	22 / 601 (3.7)	2.04	[1.24; 3.35]	0.005
Grade 3	39 / 297 (13.1)	18 / 266 (6.8)	1.94	[1.14; 3.31]	0.015
Histological subtype					
Interaction test	**p = 0.147**				
Ductal	79 / 863 (9.2)	36 / 835 (4.3)	2.12	[1.45; 3.11]	<.001
Lobular	11 / 172 (6.4)	8 / 169 (4.7)	1.35	[0.56; 3.28]	0.506
Other	2 / 73 (2.7)	4 / 66 (6.1)	0.45	[0.09; 2.39]	0.350
Ki67 status from surgical specimen					
Interaction test	**p = 0.002**				
Ki67≤20	25 / 527 (4.7)	27 / 552 (4.9)	0.97	[0.57; 1.65]	0.910
Ki67>20	42 / 422 (10.0)	10 / 378 (2.6)	3.76	[1.91; 7.39]	<.001
Type of NSAI					
Interaction test	**p = 0.202**				
Letrozole	51 / 809 (6.3)	31 / 773 (4.0)	1.57	[1.02; 2.43]	0.042
Anastrozole	41 / 299 (13.7)	17 / 297 (5.7)	2.40	[1.39; 4.12]	0.002
Prior neo/adjuvant chemotherapy					
Interaction test	**p = 0.328**				
Yes	87 / 1029 (8.5)	47 / 987 (4.8)	1.78	[1.26; 2.50]	0.001
No	5 / 79 (6.3)	1 / 83 (1.2)	5.25	[0.63; 43.98]	0.126
Prior adjuvant chemotherapy					
Interaction test	**p = 0.967**				
Yes	48 / 513 (9.4)	25 / 488 (5.1)	1.83	[1.14; 2.91]	0.012
No	44 / 595 (7.4)	23 / 582 (4.0)	1.87	[1.15; 3.06]	0.012
Prior neoadjuvant chemotherapy					
Interaction test	**p = 0.770**				
Yes	41 / 546 (7.5)	23 / 538 (4.3)	1.76	[1.07; 2.89]	0.026
No	51 / 562 (9.1)	25 / 532 (4.7)	1.93	[1.21; 3.07]	0.005

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Prior endocrine therapy					
Interaction test	**p = 0.622**				
Yes	70 / 853 (8.2)	33 / 789 (4.2)	1.96	[1.31; 2.93]	0.001
No	22 / 255 (8.6)	15 / 281 (5.3)	1.62	[0.86; 3.05]	0.138
Prior mastectomy					
Interaction test	**p = 0.084**				
Yes	62 / 769 (8.1)	39 / 745 (5.2)	1.54	[1.05; 2.27]	0.029
No	30 / 339 (8.8)	9 / 325 (2.8)	3.20	[1.54; 6.63]	0.002
Prior radiotherapy					
Interaction test	**p = 0.197**				
Yes	84 / 1011 (8.3)	47 / 987 (4.8)	1.74	[1.23; 2.47]	0.002
No	8 / 97 (8.2)	1 / 83 (1.2)	6.85	[0.87; 53.61]	0.067

N: Number of patients
n: Number of patients with event
CI: Confidence interval
RR: Relative risk
ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
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Analysis method for interaction test:
p-value from logistic regression model.
logit(proportion) = treatment + subgroup factor + treatment * subgroup factor

Analysis method for within subgroup analysis:
RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm.
ET was the reference group for treatment group comparison.

Table 5-3.2.64 PT rhinorrhoea: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	ET (N = 1070)	RR	[95% CI]	p-value
Rhinorrhoea					
	n / N (%)	n / N (%)			
Region					
Interaction test	**p = 0.653**				
NA/WE/O	29 / 640 (4.5)	9 / 627 (1.4)	3.16	[1.51; 6.61]	0.002
ROW	10 / 468 (2.1)	2 / 443 (0.5)	4.73	[1.04; 21.48]	0.044
Geographical region					
Interaction test	**p = 0.754**				
Europe	25 / 654 (3.8)	8 / 638 (1.3)	3.05	[1.39; 6.71]	0.006
North America/Australia	7 / 213 (3.3)	1 / 194 (0.5)	6.38	[0.79; 51.35]	0.082
Asia	5 / 178 (2.8)	2 / 168 (1.2)	2.36	[0.46; 12.00]	0.301
Latin America	2 / 63 (3.2)	0 / 70 (0.0)	5.55	[0.27; >99.99]	0.266
Age group 1 at randomization					
Interaction test	**p = 0.313**				
<45	22 / 549 (4.0)	4 / 496 (0.8)	4.97	[1.72; 14.32]	0.003
45 to 54	17 / 539 (3.2)	7 / 546 (1.3)	2.46	[1.03; 5.88]	0.043
55 to 64	0 / 20 (0.0)	0 / 28 (0.0)	N.E.	N.E.	N.E.
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)					
Interaction test	**p = 0.322**				
<Median	22 / 549 (4.0)	4 / 496 (0.8)	4.97	[1.72; 14.32]	0.003
≥Median	17 / 559 (3.0)	7 / 574 (1.2)	2.49	[1.04; 5.97]	0.040
Race					
Interaction test	**p = 0.695**				
Asian	9 / 211 (4.3)	2 / 186 (1.1)	3.97	[0.87; 18.13]	0.075
Non-Asian	26 / 840 (3.1)	9 / 827 (1.1)	2.84	[1.34; 6.03]	0.006
BMI at screening					
Interaction test	**p = 0.114**				
≥25	17 / 551 (3.1)	8 / 523 (1.5)	2.02	[0.88; 4.63]	0.098
<25	20 / 542 (3.7)	3 / 535 (0.6)	6.58	[1.97; 22.01]	0.002
AJCC Anatomic Stage Group					
Interaction test	**p = 0.161**				
Group I/II	12 / 417 (2.9)	1 / 418 (0.2)	12.03	[1.57; 92.09]	0.017
Group III	27 / 691 (3.9)	10 / 652 (1.5)	2.55	[1.24; 5.22]	0.011

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Anatomic stages					
Interaction test	**p = 0.208**				
IA/IB/IIA	3 / 171 (1.8)	0 / 198 (0.0)	8.10	[0.42; >99.99]	0.165
IIB	9 / 246 (3.7)	1 / 220 (0.5)	8.05	[1.03; 63.02]	0.047
IIIA	17 / 451 (3.8)	9 / 393 (2.3)	1.65	[0.74; 3.65]	0.220
IIIB	4 / 67 (6.0)	0 / 59 (0.0)	7.94	[0.44; >99.99]	0.162
IIIC	6 / 173 (3.5)	1 / 200 (0.5)	6.94	[0.84; 57.05]	0.072
Nodal status					
Interaction test	**N.E.**				
N0	3 / 91 (3.3)	0 / 117 (0.0)	8.98	[0.47; >99.99]	0.145
N1-N3	36 / 1017 (3.5)	11 / 950 (1.2)	3.06	[1.57; 5.97]	0.001
Histological grade at time of surgery					
Interaction test	**p = 0.743**				
Grade 1	4 / 110 (3.6)	0 / 100 (0.0)	8.19	[0.45; >99.99]	0.157
Grade 2	29 / 604 (4.8)	8 / 601 (1.3)	3.61	[1.66; 7.83]	0.001
Grade 3	6 / 297 (2.0)	1 / 266 (0.4)	5.37	[0.65; 44.35]	0.118
Histological subtype					
Interaction test	**p = 0.111**				
Ductal	33 / 863 (3.8)	6 / 835 (0.7)	5.32	[2.24; 12.63]	<.001
Lobular	4 / 172 (2.3)	4 / 169 (2.4)	0.98	[0.25; 3.86]	0.980
Other	2 / 73 (2.7)	1 / 66 (1.5)	1.81	[0.17; 19.48]	0.625
Ki67 status from surgical specimen					
Interaction test	**p = 0.374**				
Ki67≤20	21 / 527 (4.0)	6 / 552 (1.1)	3.67	[1.49; 9.01]	0.005
Ki67>20	11 / 422 (2.6)	5 / 378 (1.3)	1.97	[0.69; 5.62]	0.205
Type of NSAI					
Interaction test	**p = 0.472**				
Letrozole	32 / 809 (4.0)	10 / 773 (1.3)	3.06	[1.51; 6.18]	0.002
Anastrozole	7 / 299 (2.3)	1 / 297 (0.3)	6.95	[0.86; 56.17]	0.069
Prior neo/adjuvant chemotherapy					
Interaction test	**N.E.**				
Yes	39 / 1029 (3.8)	11 / 987 (1.1)	3.40	[1.75; 6.60]	<.001
No	0 / 79 (0.0)	0 / 83 (0.0)	N.E.	N.E.	N.E.
Prior adjuvant chemotherapy					
Interaction test	**p = 0.537**				
Yes	22 / 513 (4.3)	5 / 488 (1.0)	4.19	[1.60; 10.97]	0.004
No	17 / 595 (2.9)	6 / 582 (1.0)	2.77	[1.10; 6.98]	0.031
Prior neoadjuvant chemotherapy					
Interaction test	**p = 0.335**				
Yes	18 / 546 (3.3)	7 / 538 (1.3)	2.53	[1.07; 6.02]	0.035
No	21 / 562 (3.7)	4 / 532 (0.8)	4.97	[1.72; 14.38]	0.003

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Prior endocrine therapy					
Interaction test	**p = 0.796**				
Yes	31 / 853 (3.6)	8 / 789 (1.0)	3.58	[1.66; 7.75]	0.001
No	8 / 255 (3.1)	3 / 281 (1.1)	2.94	[0.79; 10.96]	0.108
Prior mastectomy					
Interaction test	**p = 0.190**				
Yes	32 / 769 (4.2)	7 / 745 (0.9)	4.43	[1.97; 9.97]	<.001
No	7 / 339 (2.1)	4 / 325 (1.2)	1.68	[0.50; 5.68]	0.405
Prior radiotherapy					
Interaction test	**N.E.**				
Yes	37 / 1011 (3.7)	11 / 987 (1.1)	3.28	[1.68; 6.40]	<.001
No	2 / 97 (2.1)	0 / 83 (0.0)	4.29	[0.21; 88.03]	0.345

N: Number of patients
n: Number of patients with event
N.E.: Not estimable
CI: Confidence interval
RR: Relative risk
ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
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Analysis method for interaction test:
p-value from logistic regression model.
logit(proportion) = treatment + subgroup factor + treatment * subgroup factor

Analysis method for within subgroup analysis:
RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm.
ET was the reference group for treatment group comparison.

Table 5-3.2.65 PT nasal congestion: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Nasal congestion					
	n / N (%)	**n / N (%)**			
Region					
Interaction test	**p = 0.871**				
NA/WE/O	28 / 640 (4.4)	12 / 627 (1.9)	2.29	[1.17; 4.45]	0.015
ROW	3 / 468 (0.6)	1 / 443 (0.2)	2.84	[0.30; 27.20]	0.365
Geographical region					
Interaction test	**p = 0.959**				
Europe	9 / 654 (1.4)	4 / 638 (0.6)	2.19	[0.68; 7.09]	0.189
North America/Australia	20 / 213 (9.4)	9 / 194 (4.6)	2.02	[0.94; 4.34]	0.070
Asia	2 / 178 (1.1)	0 / 168 (0.0)	4.72	[0.23; 97.61]	0.315
Latin America	0 / 63 (0.0)	0 / 70 (0.0)	N.E.	N.E.	N.E.
Age group 1 at randomization					
Interaction test	**p = 0.183**				
<45	20 / 549 (3.6)	4 / 496 (0.8)	4.52	[1.55; 13.13]	0.006
45 to 54	10 / 539 (1.9)	7 / 546 (1.3)	1.45	[0.55; 3.77]	0.450
55 to 64	1 / 20 (5.0)	2 / 28 (7.1)	0.70	[0.07; 7.20]	0.764
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)					
Interaction test	**p = 0.067**				
<Median	20 / 549 (3.6)	4 / 496 (0.8)	4.52	[1.55; 13.13]	0.006
≥Median	11 / 559 (2.0)	9 / 574 (1.6)	1.26	[0.52; 3.01]	0.610
Race					
Interaction test	**N.E.**				
Asian	5 / 211 (2.4)	0 / 186 (0.0)	9.70	[0.54; >99.99]	0.123
Non-Asian	25 / 840 (3.0)	13 / 827 (1.6)	1.89	[0.98; 3.68]	0.059
BMI at screening					
Interaction test	**p = 0.791**				
≥25	18 / 551 (3.3)	8 / 523 (1.5)	2.14	[0.94; 4.87]	0.071
<25	13 / 542 (2.4)	5 / 535 (0.9)	2.57	[0.92; 7.15]	0.071
AJCC Anatomic Stage Group					
Interaction test	**p = 0.700**				
Group I/II	11 / 417 (2.6)	4 / 418 (1.0)	2.76	[0.88; 8.59]	0.080
Group III	20 / 691 (2.9)	9 / 652 (1.4)	2.10	[0.96; 4.57]	0.063

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Anatomic stages					
Interaction test	**p = 0.955**				
IA/IB/IIA	2 / 171 (1.2)	1 / 198 (0.5)	2.32	[0.21; 25.32]	0.491
IIB	9 / 246 (3.7)	3 / 220 (1.4)	2.68	[0.74; 9.78]	0.135
IIIA	15 / 451 (3.3)	7 / 393 (1.8)	1.87	[0.77; 4.53]	0.168
IIIB	0 / 67 (0.0)	0 / 59 (0.0)	N.E.	N.E.	N.E.
IIIC	5 / 173 (2.9)	2 / 200 (1.0)	2.89	[0.57; 14.71]	0.201
Nodal status					
Interaction test	**p = 0.675**				
N0	1 / 91 (1.1)	1 / 117 (0.9)	1.29	[0.08; 20.28]	0.858
N1-N3	30 / 1017 (2.9)	12 / 950 (1.3)	2.34	[1.20; 4.53]	0.012
Histological grade at time of surgery					
Interaction test	**p = 0.841**				
Grade 1	1 / 110 (0.9)	0 / 100 (0.0)	2.73	[0.11; 66.25]	0.537
Grade 2	21 / 604 (3.5)	9 / 601 (1.5)	2.32	[1.07; 5.03]	0.033
Grade 3	9 / 297 (3.0)	4 / 266 (1.5)	2.02	[0.63; 6.47]	0.239
Histological subtype					
Interaction test	**p = 0.284**				
Ductal	26 / 863 (3.0)	8 / 835 (1.0)	3.14	[1.43; 6.91]	0.004
Lobular	4 / 172 (2.3)	4 / 169 (2.4)	0.98	[0.25; 3.86]	0.980
Other	1 / 73 (1.4)	1 / 66 (1.5)	0.90	[0.06; 14.17]	0.943
Ki67 status from surgical specimen					
Interaction test	**p = 0.644**				
Ki67≤20	11 / 527 (2.1)	5 / 552 (0.9)	2.30	[0.81; 6.59]	0.119
Ki67>20	9 / 422 (2.1)	5 / 378 (1.3)	1.61	[0.55; 4.77]	0.388
Type of NSAI					
Interaction test	**p = 0.064**				
Letrozole	17 / 809 (2.1)	11 / 773 (1.4)	1.48	[0.70; 3.13]	0.310
Anastrozole	14 / 299 (4.7)	2 / 297 (0.7)	6.95	[1.59; 30.33]	0.010
Prior neo/adjuvant chemotherapy					
Interaction test	**N.E.**				
Yes	31 / 1029 (3.0)	13 / 987 (1.3)	2.29	[1.20; 4.35]	0.012
No	0 / 79 (0.0)	0 / 83 (0.0)	N.E.	N.E.	N.E.
Prior adjuvant chemotherapy					
Interaction test	**p = 0.488**				
Yes	18 / 513 (3.5)	6 / 488 (1.2)	2.85	[1.14; 7.13]	0.025
No	13 / 595 (2.2)	7 / 582 (1.2)	1.82	[0.73; 4.52]	0.199
Prior neoadjuvant chemotherapy					
Interaction test	**p = 0.259**				
Yes	13 / 546 (2.4)	8 / 538 (1.5)	1.60	[0.67; 3.83]	0.290
No	18 / 562 (3.2)	5 / 532 (0.9)	3.41	[1.27; 9.11]	0.015

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Prior endocrine therapy					
Interaction test	**p = 0.852**				
Yes	24 / 853 (2.8)	10 / 789 (1.3)	2.22	[1.07; 4.61]	0.033
No	7 / 255 (2.7)	3 / 281 (1.1)	2.57	[0.67; 9.84]	0.168
Prior mastectomy					
Interaction test	**p = 0.061**				
Yes	27 / 769 (3.5)	8 / 745 (1.1)	3.27	[1.50; 7.15]	0.003
No	4 / 339 (1.2)	5 / 325 (1.5)	0.77	[0.21; 2.83]	0.690
Prior radiotherapy					
Interaction test	**p = 0.295**				
Yes	29 / 1011 (2.9)	11 / 987 (1.1)	2.57	[1.29; 5.12]	0.007
No	2 / 97 (2.1)	2 / 83 (2.4)	0.86	[0.12; 5.94]	0.875

N: Number of patients
n: Number of patients with event
N.E.: Not estimable
CI: Confidence interval
RR: Relative risk
ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
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Analysis method for interaction test:
p-value from logistic regression model.
logit(proportion) = treatment + subgroup factor + treatment * subgroup factor

Analysis method for within subgroup analysis:
RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm.
ET was the reference group for treatment group comparison.

Table 5-3.2.66 PT productive cough: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	ET (N = 1070)	RR	[95% CI]	p-value
Productive cough					
	n / N (%)	n / N (%)			
Region					
Interaction test	**p = 0.584**				
NA/WE/O	13 / 640 (2.0)	7 / 627 (1.1)	1.82	[0.73; 4.53]	0.198
ROW	9 / 468 (1.9)	3 / 443 (0.7)	2.84	[0.77; 10.42]	0.116
Geographical region					
Interaction test	**p = 0.241**				
Europe	6 / 654 (0.9)	6 / 638 (0.9)	0.98	[0.32; 3.01]	0.966
North America/Australia	7 / 213 (3.3)	1 / 194 (0.5)	6.38	[0.79; 51.35]	0.082
Asia	8 / 178 (4.5)	3 / 168 (1.8)	2.52	[0.68; 9.33]	0.167
Latin America	1 / 63 (1.6)	0 / 70 (0.0)	3.33	[0.14; 80.25]	0.459
Age group 1 at randomization					
Interaction test	**p = 0.382**				
<45	6 / 549 (1.1)	4 / 496 (0.8)	1.36	[0.38; 4.77]	0.636
45 to 54	16 / 539 (3.0)	6 / 546 (1.1)	2.70	[1.07; 6.85]	0.036
55 to 64	0 / 20 (0.0)	0 / 28 (0.0)	N.E.	N.E.	N.E.
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)					
Interaction test	**p = 0.374**				
<Median	6 / 549 (1.1)	4 / 496 (0.8)	1.36	[0.38; 4.77]	0.636
≥Median	16 / 559 (2.9)	6 / 574 (1.0)	2.74	[1.08; 6.95]	0.034
Race					
Interaction test	**p = 0.817**				
Asian	8 / 211 (3.8)	3 / 186 (1.6)	2.35	[0.63; 8.73]	0.202
Non-Asian	14 / 840 (1.7)	7 / 827 (0.8)	1.97	[0.80; 4.85]	0.141
BMI at screening					
Interaction test	**p = 0.744**				
≥25	12 / 551 (2.2)	5 / 523 (1.0)	2.28	[0.81; 6.42]	0.119
<25	9 / 542 (1.7)	5 / 535 (0.9)	1.78	[0.60; 5.27]	0.300
AJCC Anatomic Stage Group					
Interaction test	**p = 0.379**				
Group I/II	5 / 417 (1.2)	1 / 418 (0.2)	5.01	[0.59; 42.72]	0.140
Group III	17 / 691 (2.5)	9 / 652 (1.4)	1.78	[0.80; 3.97]	0.157

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Anatomic stages					
Interaction test	**p = 0.606**				
IA/IB/IIA	2 / 171 (1.2)	0 / 198 (0.0)	5.78	[0.28; >99.99]	0.256
IIB	3 / 246 (1.2)	1 / 220 (0.5)	2.68	[0.28; 25.60]	0.391
IIIA	8 / 451 (1.8)	6 / 393 (1.5)	1.16	[0.41; 3.32]	0.779
IIIB	2 / 67 (3.0)	1 / 59 (1.7)	1.76	[0.16; 18.93]	0.640
IIIC	7 / 173 (4.0)	2 / 200 (1.0)	4.05	[0.85; 19.22]	0.079
Nodal status					
Interaction test	**N.E.**				
N0	2 / 91 (2.2)	0 / 117 (0.0)	6.41	[0.31; >99.99]	0.228
N1-N3	20 / 1017 (2.0)	10 / 950 (1.1)	1.87	[0.88; 3.97]	0.104
Histological grade at time of surgery					
Interaction test	**p = 0.511**				
Grade 1	3 / 110 (2.7)	0 / 100 (0.0)	6.37	[0.33; >99.99]	0.219
Grade 2	12 / 604 (2.0)	7 / 601 (1.2)	1.71	[0.68; 4.30]	0.258
Grade 3	7 / 297 (2.4)	2 / 266 (0.8)	3.13	[0.66; 14.96]	0.152
Histological subtype					
Interaction test	**p = 0.970**				
Ductal	15 / 863 (1.7)	7 / 835 (0.8)	2.07	[0.85; 5.06]	0.109
Lobular	4 / 172 (2.3)	2 / 169 (1.2)	1.97	[0.36; 10.59]	0.432
Other	3 / 73 (4.1)	1 / 66 (1.5)	2.71	[0.29; 25.44]	0.382
Ki67 status from surgical specimen					
Interaction test	**p = 0.210**				
Ki67≤20	12 / 527 (2.3)	3 / 552 (0.5)	4.19	[1.19; 14.76]	0.026
Ki67>20	6 / 422 (1.4)	4 / 378 (1.1)	1.34	[0.38; 4.73]	0.645
Type of NSAI					
Interaction test	**p = 0.480**				
Letrozole	18 / 809 (2.2)	7 / 773 (0.9)	2.46	[1.03; 5.85]	0.042
Anastrozole	4 / 299 (1.3)	3 / 297 (1.0)	1.32	[0.30; 5.87]	0.711
Prior neo/adjuvant chemotherapy					
Interaction test	**N.E.**				
Yes	21 / 1029 (2.0)	10 / 987 (1.0)	2.01	[0.95; 4.26]	0.067
No	1 / 79 (1.3)	0 / 83 (0.0)	3.15	[0.13; 76.20]	0.480
Prior adjuvant chemotherapy					
Interaction test	**p = 0.668**				
Yes	15 / 513 (2.9)	6 / 488 (1.2)	2.38	[0.93; 6.08]	0.070
No	7 / 595 (1.2)	4 / 582 (0.7)	1.71	[0.50; 5.82]	0.389
Prior neoadjuvant chemotherapy					
Interaction test	**p = 0.091**				
Yes	6 / 546 (1.1)	6 / 538 (1.1)	0.99	[0.32; 3.04]	0.979
No	16 / 562 (2.8)	4 / 532 (0.8)	3.79	[1.27; 11.25]	0.017

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Prior endocrine therapy					
Interaction test	**p = 0.227**				
Yes	16 / 853 (1.9)	9 / 789 (1.1)	1.64	[0.73; 3.70]	0.229
No	6 / 255 (2.4)	1 / 281 (0.4)	6.61	[0.80; 54.55]	0.079
Prior mastectomy					
Interaction test	**p = 0.648**				
Yes	17 / 769 (2.2)	7 / 745 (0.9)	2.35	[0.98; 5.64]	0.055
No	5 / 339 (1.5)	3 / 325 (0.9)	1.60	[0.38; 6.63]	0.519
Prior radiotherapy					
Interaction test	**N.E.**				
Yes	21 / 1011 (2.1)	10 / 987 (1.0)	2.05	[0.97; 4.33]	0.060
No	1 / 97 (1.0)	0 / 83 (0.0)	2.57	[0.11; 62.29]	0.561

N: Number of patients
n: Number of patients with event
N.E.: Not estimable
CI: Confidence interval
RR: Relative risk
ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
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Analysis method for interaction test:
p-value from logistic regression model.
logit(proportion) = treatment + subgroup factor + treatment * subgroup factor

Analysis method for within subgroup analysis:
RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm.
ET was the reference group for treatment group comparison.

Table 5-3.2.67 PT dysphonia: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	ET (N = 1070)	RR	[95% CI]	p-value
Dysphonia					
	n / N (%)	n / N (%)			
Region					
Interaction test	**p = 0.329**				
NA/WE/O	13 / 640 (2.0)	3 / 627 (0.5)	4.25	[1.22; 14.83]	0.023
ROW	1 / 468 (0.2)	1 / 443 (0.2)	0.95	[0.06; 15.09]	0.969
Geographical region					
Interaction test	**p = 0.864**				
Europe	9 / 654 (1.4)	3 / 638 (0.5)	2.93	[0.80; 10.76]	0.106
North America/Australia	4 / 213 (1.9)	1 / 194 (0.5)	3.64	[0.41; 32.31]	0.246
Asia	1 / 178 (0.6)	0 / 168 (0.0)	2.83	[0.12; 69.05]	0.523
Latin America	0 / 63 (0.0)	0 / 70 (0.0)	N.E.	N.E.	N.E.
Age group 1 at randomization					
Interaction test	**p = 0.830**				
<45	6 / 549 (1.1)	1 / 496 (0.2)	5.42	[0.65; 44.87]	0.117
45 to 54	8 / 539 (1.5)	2 / 546 (0.4)	4.05	[0.86; 18.99]	0.076
55 to 64	0 / 20 (0.0)	1 / 28 (3.6)	0.46	[0.02; 10.75]	0.629
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)					
Interaction test	**p = 0.593**				
<Median	6 / 549 (1.1)	1 / 496 (0.2)	5.42	[0.65; 44.87]	0.117
≥Median	8 / 559 (1.4)	3 / 574 (0.5)	2.74	[0.73; 10.27]	0.135
Race					
Interaction test	**N.E.**				
Asian	2 / 211 (0.9)	0 / 186 (0.0)	4.41	[0.21; 91.28]	0.337
Non-Asian	8 / 840 (1.0)	4 / 827 (0.5)	1.97	[0.60; 6.51]	0.267
BMI at screening					
Interaction test	**p = 0.197**				
≥25	9 / 551 (1.6)	1 / 523 (0.2)	8.54	[1.09; 67.19]	0.042
<25	5 / 542 (0.9)	3 / 535 (0.6)	1.65	[0.40; 6.85]	0.494
AJCC Anatomic Stage Group					
Interaction test	**N.E.**				
Group I/II	4 / 417 (1.0)	0 / 418 (0.0)	9.02	[0.49; >99.99]	0.140
Group III	10 / 691 (1.4)	4 / 652 (0.6)	2.36	[0.74; 7.48]	0.145
Anatomic stages					
The subgroup analysis is not presented as all subgroups have less than 10 events.					

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Nodal status					
Interaction test	**N.E.**				
N0	0 / 91 (0.0)	0 / 117 (0.0)	N.E.	N.E.	N.E.
N1-N3	14 / 1017 (1.4)	4 / 950 (0.4)	3.27	[1.08; 9.90]	0.036
Histological grade at time of surgery					
Interaction test	**N.E.**				
Grade 1	0 / 110 (0.0)	0 / 100 (0.0)	N.E.	N.E.	N.E.
Grade 2	10 / 604 (1.7)	4 / 601 (0.7)	2.49	[0.78; 7.89]	0.122
Grade 3	4 / 297 (1.3)	0 / 266 (0.0)	8.06	[0.44; >99.99]	0.161
Histological subtype					
Interaction test	**p = 0.352**				
Ductal	9 / 863 (1.0)	1 / 835 (0.1)	8.71	[1.11; 68.58]	0.040
Lobular	5 / 172 (2.9)	2 / 169 (1.2)	2.46	[0.48; 12.49]	0.279
Other	0 / 73 (0.0)	1 / 66 (1.5)	0.30	[0.01; 7.28]	0.461
Ki67 status from surgical specimen					
The subgroup analysis is not presented as all subgroups have less than 10 events.					
Type of NSAI					
Interaction test	**p = 0.289**				
Letrozole	11 / 809 (1.4)	2 / 773 (0.3)	5.26	[1.17; 23.63]	0.031
Anastrozole	3 / 299 (1.0)	2 / 297 (0.7)	1.49	[0.25; 8.85]	0.661
Prior neo/adjuvant chemotherapy					
Interaction test	**N.E.**				
Yes	14 / 1029 (1.4)	4 / 987 (0.4)	3.36	[1.11; 10.16]	0.032
No	0 / 79 (0.0)	0 / 83 (0.0)	N.E.	N.E.	N.E.
Prior adjuvant chemotherapy					
Interaction test	**p = 0.623**				
Yes	12 / 513 (2.3)	3 / 488 (0.6)	3.81	[1.08; 13.40]	0.038
No	2 / 595 (0.3)	1 / 582 (0.2)	1.96	[0.18; 21.52]	0.583
Prior neoadjuvant chemotherapy					
Interaction test	**p = 0.897**				
Yes	3 / 546 (0.5)	1 / 538 (0.2)	2.96	[0.31; 28.33]	0.347
No	11 / 562 (2.0)	3 / 532 (0.6)	3.47	[0.97; 12.37]	0.055
Prior endocrine therapy					
Interaction test	**p = 0.096**				
Yes	13 / 853 (1.5)	2 / 789 (0.3)	6.01	[1.36; 26.56]	0.018
No	1 / 255 (0.4)	2 / 281 (0.7)	0.55	[0.05; 6.04]	0.626
Prior mastectomy					
Interaction test	**p = 0.338**				
Yes	13 / 769 (1.7)	3 / 745 (0.4)	4.20	[1.20; 14.67]	0.025
No	1 / 339 (0.3)	1 / 325 (0.3)	0.96	[0.06; 15.26]	0.976

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Prior radiotherapy					
Interaction test	**N.E.**				
Yes	13 / 1011 (1.3)	4 / 987 (0.4)	3.17	[1.04; 9.70]	0.043
No	1 / 97 (1.0)	0 / 83 (0.0)	2.57	[0.11; 62.29]	0.561

N: Number of patients
n: Number of patients with event
N.E.: Not estimable
CI: Confidence interval
RR: Relative risk
ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
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Analysis method for interaction test:
p-value from logistic regression model.
logit(proportion) = treatment + subgroup factor + treatment * subgroup factor

Analysis method for within subgroup analysis:
RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm.
ET was the reference group for treatment group comparison.

Table 5-3.2.68 PT mood altered: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	ET (N = 1070)	RR	[95% CI]	p-value
Mood altered					
	n / N (%)	n / N (%)			
Region					
Interaction test	**p = 0.692**				
NA/WE/O	4 / 640 (0.6)	10 / 627 (1.6)	0.39	[0.12; 1.24]	0.112
ROW	1 / 468 (0.2)	4 / 443 (0.9)	0.24	[0.03; 2.11]	0.197
Geographical region					
The subgroup analysis is not presented as all subgroups have less than 10 events.					
Age group 1 at randomization					
Interaction test	**N.E.**				
<45	5 / 549 (0.9)	8 / 496 (1.6)	0.56	[0.19; 1.71]	0.313
45 to 54	0 / 539 (0.0)	6 / 546 (1.1)	0.08	[<0.01; 1.38]	0.082
55 to 64	0 / 20 (0.0)	0 / 28 (0.0)	N.E.	N.E.	N.E.
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)					
Interaction test	**N.E.**				
<Median	5 / 549 (0.9)	8 / 496 (1.6)	0.56	[0.19; 1.71]	0.313
≥Median	0 / 559 (0.0)	6 / 574 (1.0)	0.08	[<0.01; 1.40]	0.083
Race					
Interaction test	**p = 0.585**				
Asian	1 / 211 (0.5)	4 / 186 (2.2)	0.22	[0.02; 1.95]	0.174
Non-Asian	4 / 840 (0.5)	9 / 827 (1.1)	0.44	[0.14; 1.42]	0.168
BMI at screening					
Interaction test	**p = 0.488**				
≥25	2 / 551 (0.4)	8 / 523 (1.5)	0.24	[0.05; 1.11]	0.068
<25	3 / 542 (0.6)	6 / 535 (1.1)	0.49	[0.12; 1.96]	0.316
AJCC Anatomic Stage Group					
Interaction test	**p = 0.819**				
Group I/II	2 / 417 (0.5)	5 / 418 (1.2)	0.40	[0.08; 2.06]	0.273
Group III	3 / 691 (0.4)	9 / 652 (1.4)	0.31	[0.09; 1.16]	0.082
Anatomic stages					
The subgroup analysis is not presented as all subgroups have less than 10 events.					
Nodal status					
Interaction test	**N.E.**				
N0	0 / 91 (0.0)	1 / 117 (0.9)	0.43	[0.02; 10.37]	0.602
N1-N3	5 / 1017 (0.5)	13 / 950 (1.4)	0.36	[0.13; 1.00]	0.051

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Histological grade at time of surgery					
The subgroup analysis is not presented as all subgroups have less than 10 events.					
Histological subtype					
Interaction test	**N.E.**				
Ductal	5 / 863 (0.6)	10 / 835 (1.2)	0.48	[0.17; 1.41]	0.183
Lobular	0 / 172 (0.0)	2 / 169 (1.2)	0.20	[<0.01; 4.06]	0.292
Other	0 / 73 (0.0)	2 / 66 (3.0)	0.18	[<0.01; 3.70]	0.267
Ki67 status from surgical specimen					
The subgroup analysis is not presented as all subgroups have less than 10 events.					
Type of NSAI					
Interaction test	**p = 0.421**				
Letrozole	4 / 809 (0.5)	13 / 773 (1.7)	0.29	[0.10; 0.90]	0.032
Anastrozole	1 / 299 (0.3)	1 / 297 (0.3)	0.99	[0.06; 15.81]	0.996
Prior neo/adjuvant chemotherapy					
Interaction test	**N.E.**				
Yes	5 / 1029 (0.5)	14 / 987 (1.4)	0.34	[0.12; 0.95]	0.039
No	0 / 79 (0.0)	0 / 83 (0.0)	N.E.	N.E.	N.E.
Prior adjuvant chemotherapy					
Interaction test	**p = 0.681**				
Yes	2 / 513 (0.4)	7 / 488 (1.4)	0.27	[0.06; 1.30]	0.103
No	3 / 595 (0.5)	7 / 582 (1.2)	0.42	[0.11; 1.61]	0.206
Prior neoadjuvant chemotherapy					
Interaction test	**p = 0.883**				
Yes	3 / 546 (0.5)	8 / 538 (1.5)	0.37	[0.10; 1.39]	0.140
No	2 / 562 (0.4)	6 / 532 (1.1)	0.32	[0.06; 1.56]	0.157
Prior endocrine therapy					
Interaction test	**N.E.**				
Yes	5 / 853 (0.6)	11 / 789 (1.4)	0.42	[0.15; 1.20]	0.107
No	0 / 255 (0.0)	3 / 281 (1.1)	0.16	[<0.01; 3.03]	0.221
Prior mastectomy					
Interaction test	**p = 0.704**				
Yes	4 / 769 (0.5)	10 / 745 (1.3)	0.39	[0.12; 1.23]	0.108
No	1 / 339 (0.3)	4 / 325 (1.2)	0.24	[0.03; 2.13]	0.200

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Prior radiotherapy					
Interaction test	**N.E.**				
Yes	5 / 1011 (0.5)	14 / 987 (1.4)	0.35	[0.13; 0.96]	0.042
No	0 / 97 (0.0)	0 / 83 (0.0)	N.E.	N.E.	N.E.

N: Number of patients
n: Number of patients with event
N.E.: Not estimable
CI: Confidence interval
RR: Relative risk
ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
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Analysis method for interaction test:
p-value from logistic regression model.
logit(proportion) = treatment + subgroup factor + treatment * subgroup factor

Analysis method for within subgroup analysis:
RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm.
ET was the reference group for treatment group comparison.

Table 5-3.2.69 SOC metabolism and nutrition disorders: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	ET (N = 1070)	RR	[95% CI]	p-value
Metabolism and nutrition disorders					
	n / N (%)	n / N (%)			
Region					
Interaction test	**p = 0.168**				
NA/WE/O	163 / 640 (25.5)	85 / 627 (13.6)	1.88	[1.48; 2.38]	<.001
ROW	145 / 468 (31.0)	58 / 443 (13.1)	2.37	[1.80; 3.12]	<.001
Geographical region					
Interaction test	**p = 0.846**				
Europe	161 / 654 (24.6)	79 / 638 (12.4)	1.99	[1.55; 2.54]	<.001
North America/Australia	65 / 213 (30.5)	28 / 194 (14.4)	2.11	[1.42; 3.15]	<.001
Asia	63 / 178 (35.4)	28 / 168 (16.7)	2.12	[1.43; 3.14]	<.001
Latin America	19 / 63 (30.2)	8 / 70 (11.4)	2.64	[1.24; 5.60]	0.012
Age group 1 at randomization					
Interaction test	**p = 0.496**				
<45	151 / 549 (27.5)	57 / 496 (11.5)	2.39	[1.81; 3.17]	<.001
45 to 54	149 / 539 (27.6)	80 / 546 (14.7)	1.89	[1.48; 2.41]	<.001
55 to 64	8 / 20 (40.0)	6 / 28 (21.4)	1.87	[0.77; 4.54]	0.169
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)					
Interaction test	**p = 0.223**				
<Median	151 / 549 (27.5)	57 / 496 (11.5)	2.39	[1.81; 3.17]	<.001
≥Median	157 / 559 (28.1)	86 / 574 (15.0)	1.87	[1.48; 2.37]	<.001
Race					
Interaction test	**p = 0.690**				
Asian	72 / 211 (34.1)	30 / 186 (16.1)	2.12	[1.45; 3.09]	<.001
Non-Asian	218 / 840 (26.0)	105 / 827 (12.7)	2.04	[1.65; 2.53]	<.001
BMI at screening					
Interaction test	**p = 0.226**				
≥25	175 / 551 (31.8)	90 / 523 (17.2)	1.85	[1.47; 2.31]	<.001
<25	129 / 542 (23.8)	51 / 535 (9.5)	2.50	[1.85; 3.37]	<.001
AJCC Anatomic Stage Group					
Interaction test	**p = 0.974**				
Group I/II	114 / 417 (27.3)	55 / 418 (13.2)	2.08	[1.55; 2.78]	<.001
Group III	194 / 691 (28.1)	88 / 652 (13.5)	2.08	[1.66; 2.61]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Anatomic stages					
Interaction test	**p = 0.973**				
IA/IB/IIA	53 / 171 (31.0)	27 / 198 (13.6)	2.27	[1.50; 3.44]	<.001
IIB	61 / 246 (24.8)	28 / 220 (12.7)	1.95	[1.29; 2.93]	0.001
IIIA	122 / 451 (27.1)	49 / 393 (12.5)	2.17	[1.60; 2.94]	<.001
IIIB	18 / 67 (26.9)	7 / 59 (11.9)	2.26	[1.02; 5.04]	0.045
IIIC	54 / 173 (31.2)	32 / 200 (16.0)	1.95	[1.32; 2.87]	<.001
Nodal status					
Interaction test	**p = 0.490**				
N0	33 / 91 (36.3)	18 / 117 (15.4)	2.36	[1.42; 3.90]	<.001
N1-N3	275 / 1017 (27.0)	125 / 950 (13.2)	2.06	[1.70; 2.49]	<.001
Histological grade at time of surgery					
Interaction test	**p = 0.549**				
Grade 1	31 / 110 (28.2)	17 / 100 (17.0)	1.66	[0.98; 2.80]	0.060
Grade 2	170 / 604 (28.1)	75 / 601 (12.5)	2.26	[1.76; 2.89]	<.001
Grade 3	85 / 297 (28.6)	40 / 266 (15.0)	1.90	[1.36; 2.67]	<.001
Histological subtype					
Interaction test	**p = 0.442**				
Ductal	240 / 863 (27.8)	117 / 835 (14.0)	1.98	[1.63; 2.42]	<.001
Lobular	39 / 172 (22.7)	17 / 169 (10.1)	2.25	[1.33; 3.82]	0.003
Other	29 / 73 (39.7)	9 / 66 (13.6)	2.91	[1.49; 5.69]	0.002
Ki67 status from surgical specimen					
Interaction test	**p = 0.341**				
Ki67≤20	149 / 527 (28.3)	66 / 552 (12.0)	2.36	[1.82; 3.08]	<.001
Ki67>20	115 / 422 (27.3)	53 / 378 (14.0)	1.94	[1.45; 2.61]	<.001
Type of NSAI					
Interaction test	**p = 0.195**				
Letrozole	217 / 809 (26.8)	107 / 773 (13.8)	1.94	[1.57; 2.39]	<.001
Anastrozole	91 / 299 (30.4)	36 / 297 (12.1)	2.51	[1.77; 3.57]	<.001
Prior neo/adjuvant chemotherapy					
Interaction test	**p = 0.764**				
Yes	286 / 1029 (27.8)	133 / 987 (13.5)	2.06	[1.71; 2.48]	<.001
No	22 / 79 (27.8)	10 / 83 (12.0)	2.31	[1.17; 4.57]	0.016
Prior adjuvant chemotherapy					
Interaction test	**p = 0.809**				
Yes	141 / 513 (27.5)	66 / 488 (13.5)	2.03	[1.56; 2.65]	<.001
No	167 / 595 (28.1)	77 / 582 (13.2)	2.12	[1.66; 2.71]	<.001
Prior neoadjuvant chemotherapy					
Interaction test	**p = 0.857**				
Yes	156 / 546 (28.6)	73 / 538 (13.6)	2.11	[1.64; 2.71]	<.001
No	152 / 562 (27.0)	70 / 532 (13.2)	2.06	[1.59; 2.66]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Prior endocrine therapy					
Interaction test	**p = 0.595**				
Yes	241 / 853 (28.3)	111 / 789 (14.1)	2.01	[1.64; 2.46]	<.001
No	67 / 255 (26.3)	32 / 281 (11.4)	2.31	[1.57; 3.39]	<.001
Prior mastectomy					
Interaction test	**p = 0.859**				
Yes	213 / 769 (27.7)	98 / 745 (13.2)	2.11	[1.69; 2.62]	<.001
No	95 / 339 (28.0)	45 / 325 (13.8)	2.02	[1.47; 2.79]	<.001
Prior radiotherapy					
Interaction test	**p = 0.064**				
Yes	285 / 1011 (28.2)	127 / 987 (12.9)	2.19	[1.81; 2.65]	<.001
No	23 / 97 (23.7)	16 / 83 (19.3)	1.23	[0.70; 2.17]	0.474

N: Number of patients
n: Number of patients with event
CI: Confidence interval
RR: Relative risk
ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
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Analysis method for interaction test:
p-value from logistic regression model.
logit(proportion) = treatment + subgroup factor + treatment * subgroup factor

Analysis method for within subgroup analysis:
RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm.
ET was the reference group for treatment group comparison.

Table 5-3.2.70 PT hypokalaemia: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	ET (N = 1070)	RR	[95% CI]	p-value
Hypokalaemia					
	n / N (%)	n / N (%)			
Region					
Interaction test	**p = 0.475**				
NA/WE/O	28 / 640 (4.4)	8 / 627 (1.3)	3.43	[1.58; 7.46]	0.002
ROW	28 / 468 (6.0)	5 / 443 (1.1)	5.30	[2.07; 13.61]	<.001
Geographical region					
Interaction test	**p = 0.553**				
Europe	23 / 654 (3.5)	7 / 638 (1.1)	3.21	[1.39; 7.42]	0.007
North America/Australia	12 / 213 (5.6)	4 / 194 (2.1)	2.73	[0.90; 8.33]	0.077
Asia	15 / 178 (8.4)	2 / 168 (1.2)	7.08	[1.64; 30.49]	0.009
Latin America	6 / 63 (9.5)	0 / 70 (0.0)	14.42	[0.83; >99.99]	0.067
Age group 1 at randomization					
Interaction test	**p = 0.514**				
<45	24 / 549 (4.4)	4 / 496 (0.8)	5.42	[1.89; 15.51]	0.002
45 to 54	31 / 539 (5.8)	9 / 546 (1.6)	3.49	[1.68; 7.26]	<.001
55 to 64	1 / 20 (5.0)	0 / 28 (0.0)	4.14	[0.18; 96.77]	0.377
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)					
Interaction test	**p = 0.559**				
<Median	24 / 549 (4.4)	4 / 496 (0.8)	5.42	[1.89; 15.51]	0.002
≥Median	32 / 559 (5.7)	9 / 574 (1.6)	3.65	[1.76; 7.58]	<.001
Race					
Interaction test	**p = 0.286**				
Asian	17 / 211 (8.1)	2 / 186 (1.1)	7.49	[1.75; 32.00]	0.007
Non-Asian	36 / 840 (4.3)	11 / 827 (1.3)	3.22	[1.65; 6.29]	<.001
BMI at screening					
Interaction test	**p = 0.717**				
≥25	36 / 551 (6.5)	9 / 523 (1.7)	3.80	[1.85; 7.80]	<.001
<25	20 / 542 (3.7)	4 / 535 (0.7)	4.94	[1.70; 14.34]	0.003
AJCC Anatomic Stage Group					
Interaction test	**p = 0.719**				
Group I/II	26 / 417 (6.2)	7 / 418 (1.7)	3.72	[1.63; 8.48]	0.002
Group III	30 / 691 (4.3)	6 / 652 (0.9)	4.72	[1.98; 11.26]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Anatomic stages					
Interaction test	**p = 0.687**				
IA/IB/IIA	12 / 171 (7.0)	5 / 198 (2.5)	2.78	[1.00; 7.73]	0.050
IIB	14 / 246 (5.7)	2 / 220 (0.9)	6.26	[1.44; 27.24]	0.014
IIIA	20 / 451 (4.4)	3 / 393 (0.8)	5.81	[1.74; 19.40]	0.004
IIIB	3 / 67 (4.5)	0 / 59 (0.0)	6.18	[0.33; >99.99]	0.225
IIIC	7 / 173 (4.0)	3 / 200 (1.5)	2.70	[0.71; 10.27]	0.146
Nodal status					
Interaction test	**p = 0.757**				
N0	8 / 91 (8.8)	3 / 117 (2.6)	3.43	[0.94; 12.56]	0.063
N1-N3	48 / 1017 (4.7)	10 / 950 (1.1)	4.48	[2.28; 8.81]	<.001
Histological grade at time of surgery					
Interaction test	**p = 0.709**				
Grade 1	5 / 110 (4.5)	2 / 100 (2.0)	2.27	[0.45; 11.45]	0.320
Grade 2	34 / 604 (5.6)	7 / 601 (1.2)	4.83	[2.16; 10.82]	<.001
Grade 3	17 / 297 (5.7)	4 / 266 (1.5)	3.81	[1.30; 11.17]	0.015
Histological subtype					
Interaction test	**p = 0.266**				
Ductal	36 / 863 (4.2)	12 / 835 (1.4)	2.90	[1.52; 5.54]	0.001
Lobular	10 / 172 (5.8)	0 / 169 (0.0)	20.64	[1.22; >99.99]	0.036
Other	10 / 73 (13.7)	1 / 66 (1.5)	9.04	[1.19; 68.74]	0.033
Ki67 status from surgical specimen					
Interaction test	**p = 0.371**				
Ki67≤20	30 / 527 (5.7)	5 / 552 (0.9)	6.28	[2.46; 16.08]	<.001
Ki67>20	19 / 422 (4.5)	5 / 378 (1.3)	3.40	[1.28; 9.03]	0.014
Type of NSAI					
Interaction test	**p = 0.743**				
Letrozole	41 / 809 (5.1)	10 / 773 (1.3)	3.92	[1.98; 7.77]	<.001
Anastrozole	15 / 299 (5.0)	3 / 297 (1.0)	4.97	[1.45; 16.98]	0.011
Prior neo/adjuvant chemotherapy					
Interaction test	**p = 0.208**				
Yes	51 / 1029 (5.0)	10 / 987 (1.0)	4.89	[2.50; 9.58]	<.001
No	5 / 79 (6.3)	3 / 83 (3.6)	1.75	[0.43; 7.09]	0.432
Prior adjuvant chemotherapy					
Interaction test	**p = 0.908**				
Yes	23 / 513 (4.5)	5 / 488 (1.0)	4.38	[1.68; 11.42]	0.003
No	33 / 595 (5.5)	8 / 582 (1.4)	4.03	[1.88; 8.66]	<.001
Prior neoadjuvant chemotherapy					
Interaction test	**p = 0.496**				
Yes	31 / 546 (5.7)	6 / 538 (1.1)	5.09	[2.14; 12.10]	<.001
No	25 / 562 (4.4)	7 / 532 (1.3)	3.38	[1.47; 7.75]	0.004

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Prior endocrine therapy					
Interaction test	**p = 0.430**				
Yes	39 / 853 (4.6)	10 / 789 (1.3)	3.61	[1.81; 7.18]	<.001
No	17 / 255 (6.7)	3 / 281 (1.1)	6.24	[1.85; 21.06]	0.003
Prior mastectomy					
Interaction test	**p = 0.084**				
Yes	40 / 769 (5.2)	6 / 745 (0.8)	6.46	[2.75; 15.14]	<.001
No	16 / 339 (4.7)	7 / 325 (2.2)	2.19	[0.91; 5.26]	0.079
Prior radiotherapy					
Interaction test	**p = 0.084**				
Yes	49 / 1011 (4.8)	9 / 987 (0.9)	5.32	[2.63; 10.76]	<.001
No	7 / 97 (7.2)	4 / 83 (4.8)	1.50	[0.45; 4.94]	0.507

N: Number of patients
n: Number of patients with event
CI: Confidence interval
RR: Relative risk
ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
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Analysis method for interaction test:
p-value from logistic regression model.
logit(proportion) = treatment + subgroup factor + treatment * subgroup factor

Analysis method for within subgroup analysis:
RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm.
ET was the reference group for treatment group comparison.

Table 5-3.2.71 PT hypocalcaemia: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	ET (N = 1070)	RR	[95% CI]	p-value
Hypocalcaemia					
	n / N (%)	n / N (%)			
Region					
Interaction test	**p = 0.191**				
NA/WE/O	25 / 640 (3.9)	1 / 627 (0.2)	24.49	[3.33; >99.99]	0.002
ROW	29 / 468 (6.2)	5 / 443 (1.1)	5.49	[2.14; 14.06]	<.001
Geographical region					
Interaction test	**p = 0.290**				
Europe	23 / 654 (3.5)	2 / 638 (0.3)	11.22	[2.66; 47.39]	0.001
North America/Australia	8 / 213 (3.8)	0 / 194 (0.0)	15.49	[0.90; >99.99]	0.059
Asia	17 / 178 (9.6)	4 / 168 (2.4)	4.01	[1.38; 11.68]	0.011
Latin America	6 / 63 (9.5)	0 / 70 (0.0)	14.42	[0.83; >99.99]	0.067
Age group 1 at randomization					
Interaction test	**p = 0.923**				
<45	29 / 549 (5.3)	3 / 496 (0.6)	8.73	[2.68; 28.49]	<.001
45 to 54	24 / 539 (4.5)	3 / 546 (0.5)	8.10	[2.45; 26.75]	<.001
55 to 64	1 / 20 (5.0)	0 / 28 (0.0)	4.14	[0.18; 96.77]	0.377
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)					
Interaction test	**p = 0.974**				
<Median	29 / 549 (5.3)	3 / 496 (0.6)	8.73	[2.68; 28.49]	<.001
≥Median	25 / 559 (4.5)	3 / 574 (0.5)	8.56	[2.60; 28.18]	<.001
Race					
Interaction test	**p = 0.259**				
Asian	21 / 211 (10.0)	4 / 186 (2.2)	4.63	[1.62; 13.24]	0.004
Non-Asian	28 / 840 (3.3)	2 / 827 (0.2)	13.78	[3.29; 57.67]	<.001
BMI at screening					
Interaction test	**p = 0.224**				
≥25	24 / 551 (4.4)	1 / 523 (0.2)	22.78	[3.09; >99.99]	0.002
<25	29 / 542 (5.4)	5 / 535 (0.9)	5.73	[2.23; 14.68]	<.001
AJCC Anatomic Stage Group					
Interaction test	**N.E.**				
Group I/II	17 / 417 (4.1)	0 / 418 (0.0)	35.08	[2.12; >99.99]	0.013
Group III	37 / 691 (5.4)	6 / 652 (0.9)	5.82	[2.47; 13.69]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Anatomic stages					
Interaction test	**p = 0.472**				
IA/IB/IIA	9 / 171 (5.3)	0 / 198 (0.0)	21.98	[1.29; >99.99]	0.033
IIB	8 / 246 (3.3)	0 / 220 (0.0)	15.21	[0.88; >99.99]	0.061
IIIA	21 / 451 (4.7)	4 / 393 (1.0)	4.57	[1.58; 13.21]	0.005
IIIB	3 / 67 (4.5)	1 / 59 (1.7)	2.64	[0.28; 24.72]	0.394
IIIC	13 / 173 (7.5)	1 / 200 (0.5)	15.03	[1.99; >99.99]	0.009
Nodal status					
Interaction test	**N.E.**				
N0	3 / 91 (3.3)	0 / 117 (0.0)	8.98	[0.47; >99.99]	0.145
N1-N3	51 / 1017 (5.0)	6 / 950 (0.6)	7.94	[3.42; 18.42]	<.001
Histological grade at time of surgery					
Interaction test	**p = 0.640**				
Grade 1	7 / 110 (6.4)	1 / 100 (1.0)	6.36	[0.80; 50.82]	0.081
Grade 2	33 / 604 (5.5)	3 / 601 (0.5)	10.95	[3.38; 35.50]	<.001
Grade 3	10 / 297 (3.4)	2 / 266 (0.8)	4.48	[0.99; 20.25]	0.052
Histological subtype					
Interaction test	**p = 0.534**				
Ductal	45 / 863 (5.2)	4 / 835 (0.5)	10.88	[3.93; 30.13]	<.001
Lobular	3 / 172 (1.7)	1 / 169 (0.6)	2.95	[0.31; 28.06]	0.347
Other	6 / 73 (8.2)	1 / 66 (1.5)	5.42	[0.67; 43.89]	0.113
Ki67 status from surgical specimen					
Interaction test	**p = 0.370**				
Ki67≤20	26 / 527 (4.9)	5 / 552 (0.9)	5.45	[2.11; 14.08]	<.001
Ki67>20	17 / 422 (4.0)	1 / 378 (0.3)	15.23	[2.04; >99.99]	0.008
Type of NSAI					
Interaction test	**p = 0.970**				
Letrozole	37 / 809 (4.6)	4 / 773 (0.5)	8.84	[3.17; 24.68]	<.001
Anastrozole	17 / 299 (5.7)	2 / 297 (0.7)	8.44	[1.97; 36.22]	0.004
Prior neo/adjuvant chemotherapy					
Interaction test	**N.E.**				
Yes	51 / 1029 (5.0)	6 / 987 (0.6)	8.15	[3.51; 18.91]	<.001
No	3 / 79 (3.8)	0 / 83 (0.0)	7.35	[0.39; >99.99]	0.185
Prior adjuvant chemotherapy					
Interaction test	**p = 0.098**				
Yes	24 / 513 (4.7)	5 / 488 (1.0)	4.57	[1.76; 11.87]	0.002
No	30 / 595 (5.0)	1 / 582 (0.2)	29.34	[4.01; >99.99]	<.001
Prior neoadjuvant chemotherapy					
Interaction test	**p = 0.327**				
Yes	29 / 546 (5.3)	2 / 538 (0.4)	14.29	[3.43; 59.58]	<.001
No	25 / 562 (4.4)	4 / 532 (0.8)	5.92	[2.07; 16.89]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Prior endocrine therapy					
Interaction test	**p = 0.717**				
Yes	43 / 853 (5.0)	5 / 789 (0.6)	7.95	[3.17; 19.98]	<.001
No	11 / 255 (4.3)	1 / 281 (0.4)	12.12	[1.58; 93.23]	0.017
Prior mastectomy					
Interaction test	**p = 0.377**				
Yes	35 / 769 (4.6)	5 / 745 (0.7)	6.78	[2.67; 17.22]	<.001
No	19 / 339 (5.6)	1 / 325 (0.3)	18.22	[2.45; >99.99]	0.005
Prior radiotherapy					
Interaction test	**N.E.**				
Yes	52 / 1011 (5.1)	6 / 987 (0.6)	8.46	[3.65; 19.61]	<.001
No	2 / 97 (2.1)	0 / 83 (0.0)	4.29	[0.21; 88.03]	0.345

N: Number of patients
n: Number of patients with event
N.E.: Not estimable
CI: Confidence interval
RR: Relative risk
ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
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Analysis method for interaction test:
p-value from logistic regression model.
logit(proportion) = treatment + subgroup factor + treatment * subgroup factor

Analysis method for within subgroup analysis:
RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm.
ET was the reference group for treatment group comparison.

Table 5-3.2.72 PT decreased appetite: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	ET (N = 1070)	RR	[95% CI]	p-value
Decreased appetite					
	n / N (%)	n / N (%)			
Region					
Interaction test	**p = 0.470**				
NA/WE/O	37 / 640 (5.8)	11 / 627 (1.8)	3.30	[1.70; 6.40]	<.001
ROW	13 / 468 (2.8)	2 / 443 (0.5)	6.15	[1.40; 27.11]	0.016
Geographical region					
Interaction test	**p = 0.213**				
Europe	24 / 654 (3.7)	10 / 638 (1.6)	2.34	[1.13; 4.86]	0.022
North America/Australia	18 / 213 (8.5)	2 / 194 (1.0)	8.20	[1.93; 34.87]	0.004
Asia	8 / 178 (4.5)	1 / 168 (0.6)	7.55	[0.95; 59.73]	0.055
Latin America	0 / 63 (0.0)	0 / 70 (0.0)	N.E.	N.E.	N.E.
Age group 1 at randomization					
Interaction test	**p = 0.373**				
<45	27 / 549 (4.9)	5 / 496 (1.0)	4.88	[1.89; 12.57]	0.001
45 to 54	22 / 539 (4.1)	8 / 546 (1.5)	2.79	[1.25; 6.20]	0.012
55 to 64	1 / 20 (5.0)	0 / 28 (0.0)	4.14	[0.18; 96.77]	0.377
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)					
Interaction test	**p = 0.423**				
<Median	27 / 549 (4.9)	5 / 496 (1.0)	4.88	[1.89; 12.57]	0.001
≥Median	23 / 559 (4.1)	8 / 574 (1.4)	2.95	[1.33; 6.54]	0.008
Race					
Interaction test	**p = 0.484**				
Asian	9 / 211 (4.3)	1 / 186 (0.5)	7.93	[1.01; 62.03]	0.048
Non-Asian	37 / 840 (4.4)	10 / 827 (1.2)	3.64	[1.82; 7.28]	<.001
BMI at screening					
Interaction test	**p = 0.185**				
≥25	21 / 551 (3.8)	8 / 523 (1.5)	2.49	[1.11; 5.58]	0.026
<25	29 / 542 (5.4)	5 / 535 (0.9)	5.73	[2.23; 14.68]	<.001
AJCC Anatomic Stage Group					
Interaction test	**p = 0.226**				
Group I/II	17 / 417 (4.1)	7 / 418 (1.7)	2.43	[1.02; 5.81]	0.045
Group III	33 / 691 (4.8)	6 / 652 (0.9)	5.19	[2.19; 12.30]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Anatomic stages					
Interaction test	**p = 0.613**				
IA/IB/IIA	6 / 171 (3.5)	3 / 198 (1.5)	2.32	[0.59; 9.12]	0.230
IIB	11 / 246 (4.5)	4 / 220 (1.8)	2.46	[0.79; 7.61]	0.119
IIIA	22 / 451 (4.9)	2 / 393 (0.5)	9.59	[2.27; 40.51]	0.002
IIIB	3 / 67 (4.5)	1 / 59 (1.7)	2.64	[0.28; 24.72]	0.394
IIIC	8 / 173 (4.6)	3 / 200 (1.5)	3.08	[0.83; 11.44]	0.092
Nodal status					
Interaction test	**p = 0.955**				
N0	6 / 91 (6.6)	2 / 117 (1.7)	3.86	[0.80; 18.66]	0.093
N1-N3	44 / 1017 (4.3)	11 / 950 (1.2)	3.74	[1.94; 7.19]	<.001
Histological grade at time of surgery					
Interaction test	**p = 0.225**				
Grade 1	5 / 110 (4.5)	3 / 100 (3.0)	1.52	[0.37; 6.18]	0.562
Grade 2	31 / 604 (5.1)	6 / 601 (1.0)	5.14	[2.16; 12.23]	<.001
Grade 3	12 / 297 (4.0)	1 / 266 (0.4)	10.75	[1.41; 82.10]	0.022
Histological subtype					
Interaction test	**N.E.**				
Ductal	39 / 863 (4.5)	13 / 835 (1.6)	2.90	[1.56; 5.40]	<.001
Lobular	7 / 172 (4.1)	0 / 169 (0.0)	14.74	[0.85; >99.99]	0.065
Other	4 / 73 (5.5)	0 / 66 (0.0)	8.15	[0.45; >99.99]	0.157
Ki67 status from surgical specimen					
Interaction test	**p = 0.262**				
Ki67≤20	23 / 527 (4.4)	5 / 552 (0.9)	4.82	[1.85; 12.58]	0.001
Ki67>20	15 / 422 (3.6)	6 / 378 (1.6)	2.24	[0.88; 5.71]	0.092
Type of NSAI					
Interaction test	**p = 0.467**				
Letrozole	33 / 809 (4.1)	7 / 773 (0.9)	4.50	[2.00; 10.12]	<.001
Anastrozole	17 / 299 (5.7)	6 / 297 (2.0)	2.81	[1.13; 7.04]	0.027
Prior neo/adjuvant chemotherapy					
Interaction test	**p = 0.880**				
Yes	47 / 1029 (4.6)	12 / 987 (1.2)	3.76	[2.01; 7.04]	<.001
No	3 / 79 (3.8)	1 / 83 (1.2)	3.15	[0.33; 29.67]	0.316
Prior adjuvant chemotherapy					
Interaction test	**p = 0.334**				
Yes	27 / 513 (5.3)	5 / 488 (1.0)	5.14	[1.99; 13.23]	<.001
No	23 / 595 (3.9)	8 / 582 (1.4)	2.81	[1.27; 6.24]	0.011
Prior neoadjuvant chemotherapy					
Interaction test	**p = 0.394**				
Yes	20 / 546 (3.7)	7 / 538 (1.3)	2.82	[1.20; 6.60]	0.017
No	30 / 562 (5.3)	6 / 532 (1.1)	4.73	[1.99; 11.28]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Prior endocrine therapy					
Interaction test	**p = 0.701**				
Yes	42 / 853 (4.9)	10 / 789 (1.3)	3.88	[1.96; 7.69]	<.001
No	8 / 255 (3.1)	3 / 281 (1.1)	2.94	[0.79; 10.96]	0.108
Prior mastectomy					
Interaction test	**p = 0.634**				
Yes	35 / 769 (4.6)	10 / 745 (1.3)	3.39	[1.69; 6.80]	<.001
No	15 / 339 (4.4)	3 / 325 (0.9)	4.79	[1.40; 16.40]	0.013
Prior radiotherapy					
Interaction test	**p = 0.220**				
Yes	47 / 1011 (4.6)	11 / 987 (1.1)	4.17	[2.18; 7.99]	<.001
No	3 / 97 (3.1)	2 / 83 (2.4)	1.28	[0.22; 7.50]	0.782

N: Number of patients
n: Number of patients with event
N.E.: Not estimable
CI: Confidence interval
RR: Relative risk
ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
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Analysis method for interaction test:
p-value from logistic regression model.
logit(proportion) = treatment + subgroup factor + treatment * subgroup factor

Analysis method for within subgroup analysis:
RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm.
ET was the reference group for treatment group comparison.

Table 5-3.2.73 PT hypomagnesaemia: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	ET (N = 1070)	RR	[95% CI]	p-value
Hypomagnesaemia					
	n / N (%)	n / N (%)			
Region					
Interaction test	**p = 0.468**				
NA/WE/O	14 / 640 (2.2)	4 / 627 (0.6)	3.43	[1.13; 10.36]	0.029
ROW	35 / 468 (7.5)	6 / 443 (1.4)	5.52	[2.35; 13.00]	<.001
Geographical region					
Interaction test	**p = 0.934**				
Europe	36 / 654 (5.5)	9 / 638 (1.4)	3.90	[1.90; 8.03]	<.001
North America/Australia	4 / 213 (1.9)	1 / 194 (0.5)	3.64	[0.41; 32.31]	0.246
Asia	5 / 178 (2.8)	0 / 168 (0.0)	10.39	[0.58; >99.99]	0.112
Latin America	4 / 63 (6.3)	0 / 70 (0.0)	9.98	[0.55; >99.99]	0.120
Age group 1 at randomization					
Interaction test	**p = 0.922**				
<45	21 / 549 (3.8)	4 / 496 (0.8)	4.74	[1.64; 13.72]	0.004
45 to 54	26 / 539 (4.8)	6 / 546 (1.1)	4.39	[1.82; 10.58]	<.001
55 to 64	2 / 20 (10.0)	0 / 28 (0.0)	6.90	[0.35; >99.99]	0.204
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)					
Interaction test	**p = 0.977**				
<Median	21 / 549 (3.8)	4 / 496 (0.8)	4.74	[1.64; 13.72]	0.004
≥Median	28 / 559 (5.0)	6 / 574 (1.0)	4.79	[2.00; 11.48]	<.001
Race					
Interaction test	**N.E.**				
Asian	5 / 211 (2.4)	0 / 186 (0.0)	9.70	[0.54; >99.99]	0.123
Non-Asian	44 / 840 (5.2)	9 / 827 (1.1)	4.81	[2.37; 9.80]	<.001
BMI at screening					
Interaction test	**p = 0.725**				
≥25	31 / 551 (5.6)	7 / 523 (1.3)	4.20	[1.87; 9.46]	<.001
<25	17 / 542 (3.1)	3 / 535 (0.6)	5.59	[1.65; 18.98]	0.006
AJCC Anatomic Stage Group					
Interaction test	**p = 0.521**				
Group I/II	23 / 417 (5.5)	6 / 418 (1.4)	3.84	[1.58; 9.34]	0.003
Group III	26 / 691 (3.8)	4 / 652 (0.6)	6.13	[2.15; 17.48]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Anatomic stages					
Interaction test	**p = 0.364**				
IA/IB/IIA	11 / 171 (6.4)	1 / 198 (0.5)	12.74	[1.66; 97.65]	0.014
IIB	12 / 246 (4.9)	5 / 220 (2.3)	2.15	[0.77; 6.00]	0.145
IIIA	16 / 451 (3.5)	2 / 393 (0.5)	6.97	[1.61; 30.13]	0.009
IIIB	4 / 67 (6.0)	0 / 59 (0.0)	7.94	[0.44; >99.99]	0.162
IIIC	6 / 173 (3.5)	2 / 200 (1.0)	3.47	[0.71; 16.96]	0.125
Nodal status					
Interaction test	**p = 0.618**				
N0	5 / 91 (5.5)	2 / 117 (1.7)	3.21	[0.64; 16.19]	0.157
N1-N3	44 / 1017 (4.3)	8 / 950 (0.8)	5.14	[2.43; 10.86]	<.001
Histological grade at time of surgery					
Interaction test	**p = 0.916**				
Grade 1	10 / 110 (9.1)	0 / 100 (0.0)	19.11	[1.13; >99.99]	0.041
Grade 2	25 / 604 (4.1)	7 / 601 (1.2)	3.55	[1.55; 8.15]	0.003
Grade 3	11 / 297 (3.7)	3 / 266 (1.1)	3.28	[0.93; 11.65]	0.066
Histological subtype					
Interaction test	**p = 0.466**				
Ductal	42 / 863 (4.9)	9 / 835 (1.1)	4.52	[2.21; 9.22]	<.001
Lobular	5 / 172 (2.9)	0 / 169 (0.0)	10.81	[0.60; >99.99]	0.106
Other	2 / 73 (2.7)	1 / 66 (1.5)	1.81	[0.17; 19.48]	0.625
Ki67 status from surgical specimen					
Interaction test	**p = 0.783**				
Ki67≤20	24 / 527 (4.6)	5 / 552 (0.9)	5.03	[1.93; 13.08]	<.001
Ki67>20	23 / 422 (5.5)	5 / 378 (1.3)	4.12	[1.58; 10.73]	0.004
Type of NSAI					
Interaction test	**p = 0.316**				
Letrozole	37 / 809 (4.6)	9 / 773 (1.2)	3.93	[1.91; 8.08]	<.001
Anastrozole	12 / 299 (4.0)	1 / 297 (0.3)	11.92	[1.56; 91.09]	0.017
Prior neo/adjuvant chemotherapy					
Interaction test	**p = 0.760**				
Yes	43 / 1029 (4.2)	9 / 987 (0.9)	4.58	[2.25; 9.35]	<.001
No	6 / 79 (7.6)	1 / 83 (1.2)	6.30	[0.78; 51.19]	0.085
Prior adjuvant chemotherapy					
Interaction test	**p = 0.926**				
Yes	24 / 513 (4.7)	5 / 488 (1.0)	4.57	[1.76; 11.87]	0.002
No	25 / 595 (4.2)	5 / 582 (0.9)	4.89	[1.89; 12.69]	0.001
Prior neoadjuvant chemotherapy					
Interaction test	**p = 0.833**				
Yes	21 / 546 (3.8)	4 / 538 (0.7)	5.17	[1.79; 14.97]	0.002
No	28 / 562 (5.0)	6 / 532 (1.1)	4.42	[1.84; 10.58]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Prior endocrine therapy					
Interaction test	**p = 0.434**				
Yes	40 / 853 (4.7)	9 / 789 (1.1)	4.11	[2.01; 8.42]	<.001
No	9 / 255 (3.5)	1 / 281 (0.4)	9.92	[1.27; 77.74]	0.029
Prior mastectomy					
Interaction test	**p = 0.877**				
Yes	33 / 769 (4.3)	7 / 745 (0.9)	4.57	[2.03; 10.26]	<.001
No	16 / 339 (4.7)	3 / 325 (0.9)	5.11	[1.50; 17.38]	0.009
Prior radiotherapy					
Interaction test	**N.E.**				
Yes	44 / 1011 (4.4)	10 / 987 (1.0)	4.30	[2.17; 8.49]	<.001
No	5 / 97 (5.2)	0 / 83 (0.0)	9.43	[0.53; >99.99]	0.127

N: Number of patients
n: Number of patients with event
N.E.: Not estimable
CI: Confidence interval
RR: Relative risk
ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
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Analysis method for interaction test:
p-value from logistic regression model.
logit(proportion) = treatment + subgroup factor + treatment * subgroup factor

Analysis method for within subgroup analysis:
RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm.
ET was the reference group for treatment group comparison.

Table 5-3.2.74 PT hyperkalaemia: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	ET (N = 1070)	RR	[95% CI]	p-value
Hyperkalaemia					
	n / N (%)	n / N (%)			
Region					
Interaction test	**p = 0.951**				
NA/WE/O	18 / 640 (2.8)	6 / 627 (1.0)	2.94	[1.17; 7.36]	0.021
ROW	13 / 468 (2.8)	4 / 443 (0.9)	3.08	[1.01; 9.36]	0.048
Geographical region					
Interaction test	**p = 0.252**				
Europe	16 / 654 (2.4)	3 / 638 (0.5)	5.20	[1.52; 17.77]	0.008
North America/Australia	7 / 213 (3.3)	5 / 194 (2.6)	1.28	[0.41; 3.95]	0.674
Asia	4 / 178 (2.2)	2 / 168 (1.2)	1.89	[0.35; 10.17]	0.460
Latin America	4 / 63 (6.3)	0 / 70 (0.0)	9.98	[0.55; >99.99]	0.120
Age group 1 at randomization					
Interaction test	**p = 0.849**				
<45	15 / 549 (2.7)	4 / 496 (0.8)	3.39	[1.13; 10.14]	0.029
45 to 54	15 / 539 (2.8)	5 / 546 (0.9)	3.04	[1.11; 8.30]	0.030
55 to 64	1 / 20 (5.0)	1 / 28 (3.6)	1.40	[0.09; 21.08]	0.808
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)					
Interaction test	**p = 0.774**				
<Median	15 / 549 (2.7)	4 / 496 (0.8)	3.39	[1.13; 10.14]	0.029
≥Median	16 / 559 (2.9)	6 / 574 (1.0)	2.74	[1.08; 6.95]	0.034
Race					
Interaction test	**p = 0.906**				
Asian	5 / 211 (2.4)	2 / 186 (1.1)	2.20	[0.43; 11.22]	0.341
Non-Asian	20 / 840 (2.4)	8 / 827 (1.0)	2.46	[1.09; 5.56]	0.030
BMI at screening					
Interaction test	**p = 0.023**				
≥25	20 / 551 (3.6)	2 / 523 (0.4)	9.49	[2.23; 40.41]	0.002
<25	9 / 542 (1.7)	7 / 535 (1.3)	1.27	[0.48; 3.38]	0.634
AJCC Anatomic Stage Group					
Interaction test	**p = 0.047**				
Group I/II	15 / 417 (3.6)	1 / 418 (0.2)	15.04	[2.00; >99.99]	0.009
Group III	16 / 691 (2.3)	9 / 652 (1.4)	1.68	[0.75; 3.77]	0.210

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Anatomic stages					
Interaction test	**p = 0.220**				
IA/IB/IIA	5 / 171 (2.9)	0 / 198 (0.0)	12.73	[0.71; >99.99]	0.084
IIB	10 / 246 (4.1)	1 / 220 (0.5)	8.94	[1.15; 69.30]	0.036
IIIA	10 / 451 (2.2)	7 / 393 (1.8)	1.24	[0.48; 3.24]	0.654
IIIB	2 / 67 (3.0)	0 / 59 (0.0)	4.41	[0.22; 90.08]	0.335
IIIC	4 / 173 (2.3)	2 / 200 (1.0)	2.31	[0.43; 12.47]	0.330
Nodal status					
Interaction test	**N.E.**				
N0	4 / 91 (4.4)	0 / 117 (0.0)	11.54	[0.63; >99.99]	0.099
N1-N3	27 / 1017 (2.7)	10 / 950 (1.1)	2.52	[1.23; 5.18]	0.012
Histological grade at time of surgery					
Interaction test	**p = 0.466**				
Grade 1	2 / 110 (1.8)	2 / 100 (2.0)	0.91	[0.13; 6.33]	0.923
Grade 2	19 / 604 (3.1)	6 / 601 (1.0)	3.15	[1.27; 7.83]	0.014
Grade 3	5 / 297 (1.7)	1 / 266 (0.4)	4.48	[0.53; 38.09]	0.170
Histological subtype					
Interaction test	**p = 0.966**				
Ductal	24 / 863 (2.8)	8 / 835 (1.0)	2.90	[1.31; 6.42]	0.009
Lobular	4 / 172 (2.3)	1 / 169 (0.6)	3.93	[0.44; 34.80]	0.219
Other	3 / 73 (4.1)	1 / 66 (1.5)	2.71	[0.29; 25.44]	0.382
Ki67 status from surgical specimen					
Interaction test	**p = 0.226**				
Ki67≤20	14 / 527 (2.7)	6 / 552 (1.1)	2.44	[0.95; 6.31]	0.065
Ki67>20	11 / 422 (2.6)	1 / 378 (0.3)	9.85	[1.28; 75.96]	0.028
Type of NSAI					
Interaction test	**p = 0.845**				
Letrozole	20 / 809 (2.5)	6 / 773 (0.8)	3.19	[1.29; 7.89]	0.012
Anastrozole	11 / 299 (3.7)	4 / 297 (1.3)	2.73	[0.88; 8.48]	0.082
Prior neo/adjuvant chemotherapy					
Interaction test	**N.E.**				
Yes	28 / 1029 (2.7)	10 / 987 (1.0)	2.69	[1.31; 5.50]	0.007
No	3 / 79 (3.8)	0 / 83 (0.0)	7.35	[0.39; >99.99]	0.185
Prior adjuvant chemotherapy					
Interaction test	**p = 0.236**				
Yes	13 / 513 (2.5)	2 / 488 (0.4)	6.18	[1.40; 27.26]	0.016
No	18 / 595 (3.0)	8 / 582 (1.4)	2.20	[0.96; 5.02]	0.061
Prior neoadjuvant chemotherapy					
Interaction test	**p = 0.139**				
Yes	16 / 546 (2.9)	8 / 538 (1.5)	1.97	[0.85; 4.57]	0.114
No	15 / 562 (2.7)	2 / 532 (0.4)	7.10	[1.63; 30.90]	0.009

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Prior endocrine therapy					
Interaction test	**p = 0.886**				
Yes	25 / 853 (2.9)	8 / 789 (1.0)	2.89	[1.31; 6.37]	0.008
No	6 / 255 (2.4)	2 / 281 (0.7)	3.31	[0.67; 16.23]	0.141
Prior mastectomy					
Interaction test	**p = 0.939**				
Yes	19 / 769 (2.5)	6 / 745 (0.8)	3.07	[1.23; 7.64]	0.016
No	12 / 339 (3.5)	4 / 325 (1.2)	2.88	[0.94; 8.83]	0.065
Prior radiotherapy					
Interaction test	**N.E.**				
Yes	29 / 1011 (2.9)	10 / 987 (1.0)	2.83	[1.39; 5.78]	0.004
No	2 / 97 (2.1)	0 / 83 (0.0)	4.29	[0.21; 88.03]	0.345

N: Number of patients
n: Number of patients with event
N.E.: Not estimable
CI: Confidence interval
RR: Relative risk
ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
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Analysis method for interaction test:
p-value from logistic regression model.
logit(proportion) = treatment + subgroup factor + treatment * subgroup factor

Analysis method for within subgroup analysis:
RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm.
ET was the reference group for treatment group comparison.

Table 5-3.2.75 PT hypercalcaemia: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	ET (N = 1070)	RR	[95% CI]	p-value
Hypercalcaemia					
	n / N (%)	n / N (%)			
Region					
Interaction test	**p = 0.855**				
NA/WE/O	11 / 640 (1.7)	5 / 627 (0.8)	2.16	[0.75; 6.17]	0.152
ROW	8 / 468 (1.7)	3 / 443 (0.7)	2.52	[0.67; 9.45]	0.169
Geographical region					
Interaction test	**p = 0.542**				
Europe	9 / 654 (1.4)	6 / 638 (0.9)	1.46	[0.52; 4.09]	0.468
North America/Australia	6 / 213 (2.8)	1 / 194 (0.5)	5.46	[0.66; 44.99]	0.114
Asia	2 / 178 (1.1)	1 / 168 (0.6)	1.89	[0.17; 20.63]	0.603
Latin America	2 / 63 (3.2)	0 / 70 (0.0)	5.55	[0.27; >99.99]	0.266
Age group 1 at randomization					
Interaction test	**N.E.**				
<45	11 / 549 (2.0)	0 / 496 (0.0)	20.78	[1.23; >99.99]	0.036
45 to 54	8 / 539 (1.5)	7 / 546 (1.3)	1.16	[0.42; 3.17]	0.776
55 to 64	0 / 20 (0.0)	1 / 28 (3.6)	0.46	[0.02; 10.75]	0.629
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)					
Interaction test	**N.E.**				
<Median	11 / 549 (2.0)	0 / 496 (0.0)	20.78	[1.23; >99.99]	0.036
≥Median	8 / 559 (1.4)	8 / 574 (1.4)	1.03	[0.39; 2.72]	0.957
Race					
Interaction test	**p = 0.848**				
Asian	2 / 211 (0.9)	1 / 186 (0.5)	1.76	[0.16; 19.29]	0.642
Non-Asian	16 / 840 (1.9)	7 / 827 (0.8)	2.25	[0.93; 5.44]	0.072
BMI at screening					
Interaction test	**p = 0.529**				
≥25	12 / 551 (2.2)	6 / 523 (1.1)	1.90	[0.72; 5.02]	0.196
<25	7 / 542 (1.3)	2 / 535 (0.4)	3.45	[0.72; 16.55]	0.121
AJCC Anatomic Stage Group					
Interaction test	**p = 0.816**				
Group I/II	6 / 417 (1.4)	3 / 418 (0.7)	2.00	[0.50; 7.96]	0.323
Group III	13 / 691 (1.9)	5 / 652 (0.8)	2.45	[0.88; 6.84]	0.086

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Anatomic stages					
Interaction test	**p = 0.996**				
IA/IB/IIA	4 / 171 (2.3)	2 / 198 (1.0)	2.32	[0.43; 12.49]	0.329
IIB	2 / 246 (0.8)	1 / 220 (0.5)	1.79	[0.16; 19.59]	0.634
IIIA	7 / 451 (1.6)	3 / 393 (0.8)	2.03	[0.53; 7.81]	0.301
IIIB	3 / 67 (4.5)	0 / 59 (0.0)	6.18	[0.33; >99.99]	0.225
IIIC	3 / 173 (1.7)	2 / 200 (1.0)	1.73	[0.29; 10.26]	0.544
Nodal status					
Interaction test	**p = 0.627**				
N0	3 / 91 (3.3)	1 / 117 (0.9)	3.86	[0.41; 36.47]	0.239
N1-N3	16 / 1017 (1.6)	7 / 950 (0.7)	2.14	[0.88; 5.17]	0.093
Histological grade at time of surgery					
Interaction test	**p = 0.714**				
Grade 1	0 / 110 (0.0)	1 / 100 (1.0)	0.30	[0.01; 7.36]	0.463
Grade 2	9 / 604 (1.5)	3 / 601 (0.5)	2.99	[0.81; 10.97]	0.100
Grade 3	7 / 297 (2.4)	3 / 266 (1.1)	2.09	[0.55; 8.00]	0.282
Histological subtype					
Interaction test	**N.E.**				
Ductal	18 / 863 (2.1)	7 / 835 (0.8)	2.49	[1.04; 5.93]	0.040
Lobular	0 / 172 (0.0)	1 / 169 (0.6)	0.33	[0.01; 7.98]	0.493
Other	1 / 73 (1.4)	0 / 66 (0.0)	2.72	[0.11; 65.54]	0.538
Ki67 status from surgical specimen					
Interaction test	**p = 0.396**				
Ki67≤20	8 / 527 (1.5)	2 / 552 (0.4)	4.19	[0.89; 19.64]	0.069
Ki67>20	8 / 422 (1.9)	4 / 378 (1.1)	1.79	[0.54; 5.90]	0.338
Type of NSAI					
Interaction test	**p = 0.264**				
Letrozole	10 / 809 (1.2)	6 / 773 (0.8)	1.59	[0.58; 4.36]	0.365
Anastrozole	9 / 299 (3.0)	2 / 297 (0.7)	4.47	[0.97; 20.51]	0.054
Prior neo/adjuvant chemotherapy					
Interaction test	**N.E.**				
Yes	17 / 1029 (1.7)	8 / 987 (0.8)	2.04	[0.88; 4.70]	0.095
No	2 / 79 (2.5)	0 / 83 (0.0)	5.25	[0.26; >99.99]	0.282
Prior adjuvant chemotherapy					
Interaction test	**p = 0.123**				
Yes	8 / 513 (1.6)	6 / 488 (1.2)	1.27	[0.44; 3.63]	0.658
No	11 / 595 (1.8)	2 / 582 (0.3)	5.38	[1.20; 24.17]	0.028
Prior neoadjuvant chemotherapy					
Interaction test	**p = 0.183**				
Yes	10 / 546 (1.8)	2 / 538 (0.4)	4.93	[1.08; 22.38]	0.039
No	9 / 562 (1.6)	6 / 532 (1.1)	1.42	[0.51; 3.96]	0.503

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Prior endocrine therapy					
Interaction test	**p = 0.984**				
Yes	17 / 853 (2.0)	7 / 789 (0.9)	2.25	[0.94; 5.39]	0.070
No	2 / 255 (0.8)	1 / 281 (0.4)	2.20	[0.20; 24.16]	0.518
Prior mastectomy					
Interaction test	**p = 0.558**				
Yes	12 / 769 (1.6)	6 / 745 (0.8)	1.94	[0.73; 5.14]	0.184
No	7 / 339 (2.1)	2 / 325 (0.6)	3.36	[0.70; 16.03]	0.129
Prior radiotherapy					
Interaction test	**N.E.**				
Yes	19 / 1011 (1.9)	8 / 987 (0.8)	2.32	[1.02; 5.27]	0.045
No	0 / 97 (0.0)	0 / 83 (0.0)	N.E.	N.E.	N.E.

N: Number of patients
n: Number of patients with event
N.E.: Not estimable
CI: Confidence interval
RR: Relative risk
ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
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Analysis method for interaction test:
p-value from logistic regression model.
logit(proportion) = treatment + subgroup factor + treatment * subgroup factor

Analysis method for within subgroup analysis:
RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm.
ET was the reference group for treatment group comparison.

Table 5-3.2.76 PT hyperphosphataemia: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	ET (N = 1070)	RR	[95% CI]	p-value
Hyperphosphataemia					
	n / N (%)	n / N (%)			
Region					
Interaction test	N.E.				
NA/WE/O	9 / 640 (1.4)	2 / 627 (0.3)	4.41	[0.96; 20.32]	0.057
ROW	3 / 468 (0.6)	0 / 443 (0.0)	6.63	[0.34; >99.99]	0.211
Geographical region					
The subgroup analysis is not presented as all subgroups have less than 10 events.					
Age group 1 at randomization					
Interaction test	N.E.				
<45	3 / 549 (0.5)	0 / 496 (0.0)	6.33	[0.33; >99.99]	0.222
45 to 54	8 / 539 (1.5)	2 / 546 (0.4)	4.05	[0.86; 18.99]	0.076
55 to 64	1 / 20 (5.0)	0 / 28 (0.0)	4.14	[0.18; 96.77]	0.377
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)					
Interaction test	N.E.				
<Median	3 / 549 (0.5)	0 / 496 (0.0)	6.33	[0.33; >99.99]	0.222
≥Median	9 / 559 (1.6)	2 / 574 (0.3)	4.62	[1.00; 21.29]	0.050
Race					
Interaction test	N.E.				
Asian	3 / 211 (1.4)	0 / 186 (0.0)	6.17	[0.32; >99.99]	0.228
Non-Asian	8 / 840 (1.0)	2 / 827 (0.2)	3.94	[0.84; 18.49]	0.082
BMI at screening					
Interaction test	N.E.				
≥25	8 / 551 (1.5)	2 / 523 (0.4)	3.80	[0.81; 17.80]	0.091
<25	4 / 542 (0.7)	0 / 535 (0.0)	8.88	[0.48; >99.99]	0.143
AJCC Anatomic Stage Group					
The subgroup analysis is not presented as all subgroups have less than 10 events.					
Anatomic stages					
The subgroup analysis is not presented as all subgroups have less than 10 events.					

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Nodal status					
Interaction test	**N.E.**				
N0	2 / 91 (2.2)	0 / 117 (0.0)	6.41	[0.31; >99.99]	0.228
N1-N3	10 / 1017 (1.0)	2 / 950 (0.2)	4.67	[1.03; 21.26]	0.046
Histological grade at time of surgery					
The subgroup analysis is not presented as all subgroups have less than 10 events.					
Histological subtype					
Interaction test	**p = 0.357**				
Ductal	9 / 863 (1.0)	1 / 835 (0.1)	8.71	[1.11; 68.58]	0.040
Lobular	2 / 172 (1.2)	1 / 169 (0.6)	1.97	[0.18; 21.47]	0.580
Other	1 / 73 (1.4)	0 / 66 (0.0)	2.72	[0.11; 65.54]	0.538
Ki67 status from surgical specimen					
The subgroup analysis is not presented as all subgroups have less than 10 events.					
Type of NSAI					
The subgroup analysis is not presented as all subgroups have less than 10 events.					
Prior neo/adjuvant chemotherapy					
Interaction test	**N.E.**				
Yes	11 / 1029 (1.1)	2 / 987 (0.2)	5.28	[1.17; 23.74]	0.030
No	1 / 79 (1.3)	0 / 83 (0.0)	3.15	[0.13; 76.20]	0.480
Prior adjuvant chemotherapy					
The subgroup analysis is not presented as all subgroups have less than 10 events.					
Prior neoadjuvant chemotherapy					
Interaction test	**N.E.**				
Yes	4 / 546 (0.7)	0 / 538 (0.0)	8.87	[0.48; >99.99]	0.143
No	8 / 562 (1.4)	2 / 532 (0.4)	3.79	[0.81; 17.75]	0.091
Prior endocrine therapy					
Interaction test	**N.E.**				
Yes	9 / 853 (1.1)	2 / 789 (0.3)	4.16	[0.90; 19.21]	0.068
No	3 / 255 (1.2)	0 / 281 (0.0)	7.71	[0.40; >99.99]	0.176
Prior mastectomy					
Interaction test	**p = 0.477**				
Yes	9 / 769 (1.2)	1 / 745 (0.1)	8.72	[1.11; 68.65]	0.040
No	3 / 339 (0.9)	1 / 325 (0.3)	2.88	[0.30; 27.51]	0.359

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Prior radiotherapy					
Interaction test	**N.E.**				
Yes	12 / 1011 (1.2)	1 / 987 (0.1)	11.72	[1.53; 89.93]	0.018
No	0 / 97 (0.0)	1 / 83 (1.2)	0.29	[0.01; 6.92]	0.441

N: Number of patients
n: Number of patients with event
N.E.: Not estimable
CI: Confidence interval
RR: Relative risk
ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
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Analysis method for interaction test:
p-value from logistic regression model.
logit(proportion) = treatment + subgroup factor + treatment * subgroup factor

Analysis method for within subgroup analysis:
RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm.
ET was the reference group for treatment group comparison.

Table 5-3.2.77 PT vulvovaginal dryness: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	ET (N = 1070)	RR	[95% CI]	p-value
Vulvovaginal dryness					
	n / N (%)	n / N (%)			
Region					
Interaction test	**p = 0.869**				
NA/WE/O	60 / 640 (9.4)	79 / 627 (12.6)	0.74	[0.54; 1.02]	0.068
ROW	7 / 468 (1.5)	10 / 443 (2.3)	0.66	[0.25; 1.73]	0.399
Geographical region					
Interaction test	**p = 0.448**				
Europe	35 / 654 (5.4)	52 / 638 (8.2)	0.66	[0.43; 0.99]	0.047
North America/Australia	28 / 213 (13.1)	27 / 194 (13.9)	0.94	[0.58; 1.54]	0.820
Asia	1 / 178 (0.6)	5 / 168 (3.0)	0.19	[0.02; 1.60]	0.126
Latin America	3 / 63 (4.8)	5 / 70 (7.1)	0.67	[0.17; 2.68]	0.568
Age group 1 at randomization					
Interaction test	**p = 0.533**				
<45	36 / 549 (6.6)	40 / 496 (8.1)	0.81	[0.53; 1.25]	0.350
45 to 54	31 / 539 (5.8)	47 / 546 (8.6)	0.67	[0.43; 1.03]	0.071
55 to 64	0 / 20 (0.0)	2 / 28 (7.1)	0.28	[0.01; 5.46]	0.398
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)					
Interaction test	**p = 0.476**				
<Median	36 / 549 (6.6)	40 / 496 (8.1)	0.81	[0.53; 1.25]	0.350
≥Median	31 / 559 (5.5)	49 / 574 (8.5)	0.65	[0.42; 1.00]	0.052
Race					
Interaction test	**p = 0.538**				
Asian	4 / 211 (1.9)	7 / 186 (3.8)	0.50	[0.15; 1.69]	0.268
Non-Asian	54 / 840 (6.4)	70 / 827 (8.5)	0.76	[0.54; 1.07]	0.115
BMI at screening					
Interaction test	**p = 0.717**				
≥25	30 / 551 (5.4)	38 / 523 (7.3)	0.75	[0.47; 1.19]	0.222
<25	34 / 542 (6.3)	50 / 535 (9.3)	0.67	[0.44; 1.02]	0.062
AJCC Anatomic Stage Group					
Interaction test	**p = 0.816**				
Group I/II	28 / 417 (6.7)	40 / 418 (9.6)	0.70	[0.44; 1.12]	0.134
Group III	39 / 691 (5.6)	49 / 652 (7.5)	0.75	[0.50; 1.13]	0.168

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Anatomic stages					
Interaction test	**p = 0.097**				
IA/IB/IIA	12 / 171 (7.0)	18 / 198 (9.1)	0.77	[0.38; 1.56]	0.469
IIB	16 / 246 (6.5)	22 / 220 (10.0)	0.65	[0.35; 1.21]	0.172
IIIA	29 / 451 (6.4)	30 / 393 (7.6)	0.84	[0.51; 1.38]	0.494
IIIB	6 / 67 (9.0)	1 / 59 (1.7)	5.28	[0.65; 42.63]	0.118
IIIC	4 / 173 (2.3)	18 / 200 (9.0)	0.26	[0.09; 0.74]	0.012
Nodal status					
Interaction test	**p = 0.309**				
N0	3 / 91 (3.3)	10 / 117 (8.5)	0.39	[0.11; 1.36]	0.139
N1-N3	64 / 1017 (6.3)	79 / 950 (8.3)	0.76	[0.55; 1.04]	0.085
Histological grade at time of surgery					
Interaction test	**p = 0.835**				
Grade 1	7 / 110 (6.4)	8 / 100 (8.0)	0.80	[0.30; 2.11]	0.646
Grade 2	34 / 604 (5.6)	45 / 601 (7.5)	0.75	[0.49; 1.16]	0.194
Grade 3	21 / 297 (7.1)	30 / 266 (11.3)	0.63	[0.37; 1.07]	0.086
Histological subtype					
Interaction test	**p = 0.753**				
Ductal	54 / 863 (6.3)	68 / 835 (8.1)	0.77	[0.54; 1.08]	0.134
Lobular	9 / 172 (5.2)	16 / 169 (9.5)	0.55	[0.25; 1.22]	0.141
Other	4 / 73 (5.5)	5 / 66 (7.6)	0.72	[0.20; 2.58]	0.618
Ki67 status from surgical specimen					
Interaction test	**p = 0.112**				
Ki67≤20	24 / 527 (4.6)	43 / 552 (7.8)	0.58	[0.36; 0.95]	0.030
Ki67>20	30 / 422 (7.1)	26 / 378 (6.9)	1.03	[0.62; 1.72]	0.898
Type of NSAI					
Interaction test	**p = 0.277**				
Letrozole	41 / 809 (5.1)	61 / 773 (7.9)	0.64	[0.44; 0.94]	0.024
Anastrozole	26 / 299 (8.7)	28 / 297 (9.4)	0.92	[0.55; 1.53]	0.756
Prior neo/adjuvant chemotherapy					
Interaction test	**p = 0.310**				
Yes	60 / 1029 (5.8)	83 / 987 (8.4)	0.69	[0.50; 0.96]	0.025
No	7 / 79 (8.9)	6 / 83 (7.2)	1.23	[0.43; 3.49]	0.703
Prior adjuvant chemotherapy					
Interaction test	**p = 0.900**				
Yes	32 / 513 (6.2)	41 / 488 (8.4)	0.74	[0.48; 1.16]	0.190
No	35 / 595 (5.9)	48 / 582 (8.2)	0.71	[0.47; 1.09]	0.115
Prior neoadjuvant chemotherapy					
Interaction test	**p = 0.425**				
Yes	29 / 546 (5.3)	45 / 538 (8.4)	0.64	[0.40; 1.00]	0.049
No	38 / 562 (6.8)	44 / 532 (8.3)	0.82	[0.54; 1.24]	0.344

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Prior endocrine therapy					
Interaction test	**p = 0.594**				
Yes	48 / 853 (5.6)	64 / 789 (8.1)	0.69	[0.48; 1.00]	0.047
No	19 / 255 (7.5)	25 / 281 (8.9)	0.84	[0.47; 1.48]	0.543
Prior mastectomy					
Interaction test	**p = 0.363**				
Yes	53 / 769 (6.9)	65 / 745 (8.7)	0.79	[0.56; 1.12]	0.185
No	14 / 339 (4.1)	24 / 325 (7.4)	0.56	[0.29; 1.06]	0.076
Prior radiotherapy					
Interaction test	**p = 0.780**				
Yes	62 / 1011 (6.1)	84 / 987 (8.5)	0.72	[0.53; 0.99]	0.042
No	5 / 97 (5.2)	5 / 83 (6.0)	0.86	[0.26; 2.85]	0.800

N: Number of patients
n: Number of patients with event
CI: Confidence interval
RR: Relative risk
ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
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Analysis method for interaction test:
p-value from logistic regression model.
logit(proportion) = treatment + subgroup factor + treatment * subgroup factor

Analysis method for within subgroup analysis:
RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm.
ET was the reference group for treatment group comparison.

Table 5-3.2.78 PT dyspareunia: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Dyspareunia					
	n / N (%)	**n / N (%)**			
Region					
Interaction test	**p = 0.399**				
NA/WE/O	5 / 640 (0.8)	18 / 627 (2.9)	0.27	[0.10; 0.73]	0.010
ROW	1 / 468 (0.2)	1 / 443 (0.2)	0.95	[0.06; 15.09]	0.969
Geographical region					
Interaction test	**p = 0.406**				
Europe	2 / 654 (0.3)	12 / 638 (1.9)	0.16	[0.04; 0.72]	0.017
North America/Australia	3 / 213 (1.4)	6 / 194 (3.1)	0.46	[0.12; 1.80]	0.261
Asia	0 / 178 (0.0)	0 / 168 (0.0)	N.E.	N.E.	N.E.
Latin America	1 / 63 (1.6)	1 / 70 (1.4)	1.11	[0.07; 17.40]	0.940
Age group 1 at randomization					
Interaction test	**p = 0.242**				
<45	5 / 549 (0.9)	10 / 496 (2.0)	0.45	[0.16; 1.31]	0.144
45 to 54	1 / 539 (0.2)	9 / 546 (1.6)	0.11	[0.01; 0.89]	0.038
55 to 64	0 / 20 (0.0)	0 / 28 (0.0)	N.E.	N.E.	N.E.
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)					
Interaction test	**p = 0.247**				
<Median	5 / 549 (0.9)	10 / 496 (2.0)	0.45	[0.16; 1.31]	0.144
≥Median	1 / 559 (0.2)	9 / 574 (1.6)	0.11	[0.01; 0.90]	0.039
Race					
Interaction test	**N.E.**				
Asian	0 / 211 (0.0)	0 / 186 (0.0)	N.E.	N.E.	N.E.
Non-Asian	6 / 840 (0.7)	18 / 827 (2.2)	0.33	[0.13; 0.82]	0.017
BMI at screening					
Interaction test	**p = 0.664**				
≥25	4 / 551 (0.7)	10 / 523 (1.9)	0.38	[0.12; 1.20]	0.100
<25	2 / 542 (0.4)	8 / 535 (1.5)	0.25	[0.05; 1.16]	0.076
AJCC Anatomic Stage Group					
Interaction test	**p = 0.587**				
Group I/II	2 / 417 (0.5)	9 / 418 (2.2)	0.22	[0.05; 1.02]	0.054
Group III	4 / 691 (0.6)	10 / 652 (1.5)	0.38	[0.12; 1.20]	0.098
Anatomic stages					
The subgroup analysis is not presented as all subgroups have less than 10 events.					

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Nodal status					
Interaction test	**N.E.**				
N0	0 / 91 (0.0)	2 / 117 (1.7)	0.26	[0.01; 5.28]	0.378
N1-N3	6 / 1017 (0.6)	17 / 950 (1.8)	0.33	[0.13; 0.83]	0.019
Histological grade at time of surgery					
Interaction test	**p = 0.402**				
Grade 1	2 / 110 (1.8)	2 / 100 (2.0)	0.91	[0.13; 6.33]	0.923
Grade 2	3 / 604 (0.5)	9 / 601 (1.5)	0.33	[0.09; 1.22]	0.097
Grade 3	0 / 297 (0.0)	8 / 266 (3.0)	0.05	[<0.01; 0.91]	0.043
Histological subtype					
Interaction test	**p = 0.632**				
Ductal	4 / 863 (0.5)	16 / 835 (1.9)	0.24	[0.08; 0.72]	0.011
Lobular	1 / 172 (0.6)	2 / 169 (1.2)	0.49	[0.04; 5.37]	0.560
Other	1 / 73 (1.4)	1 / 66 (1.5)	0.90	[0.06; 14.17]	0.943
Ki67 status from surgical specimen					
Interaction test	**p = 0.311**				
Ki67≤20	4 / 527 (0.8)	8 / 552 (1.4)	0.52	[0.16; 1.73]	0.288
Ki67>20	1 / 422 (0.2)	6 / 378 (1.6)	0.15	[0.02; 1.23]	0.078
Type of NSAI					
Interaction test	**p = 0.888**				
Letrozole	3 / 809 (0.4)	10 / 773 (1.3)	0.29	[0.08; 1.04]	0.057
Anastrozole	3 / 299 (1.0)	9 / 297 (3.0)	0.33	[0.09; 1.21]	0.095
Prior neo/adjuvant chemotherapy					
Interaction test	**N.E.**				
Yes	6 / 1029 (0.6)	18 / 987 (1.8)	0.32	[0.13; 0.80]	0.015
No	0 / 79 (0.0)	1 / 83 (1.2)	0.35	[0.01; 8.47]	0.518
Prior adjuvant chemotherapy					
Interaction test	**p = 0.397**				
Yes	2 / 513 (0.4)	10 / 488 (2.0)	0.19	[0.04; 0.86]	0.032
No	4 / 595 (0.7)	9 / 582 (1.5)	0.43	[0.13; 1.40]	0.164
Prior neoadjuvant chemotherapy					
Interaction test	**p = 0.391**				
Yes	4 / 546 (0.7)	9 / 538 (1.7)	0.44	[0.14; 1.41]	0.167
No	2 / 562 (0.4)	10 / 532 (1.9)	0.19	[0.04; 0.86]	0.031
Prior endocrine therapy					
Interaction test	**p = 0.449**				
Yes	5 / 853 (0.6)	12 / 789 (1.5)	0.39	[0.14; 1.09]	0.072
No	1 / 255 (0.4)	7 / 281 (2.5)	0.16	[0.02; 1.27]	0.083
Prior mastectomy					
Interaction test	**p = 0.628**				
Yes	5 / 769 (0.7)	14 / 745 (1.9)	0.35	[0.13; 0.96]	0.041
No	1 / 339 (0.3)	5 / 325 (1.5)	0.19	[0.02; 1.63]	0.131

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Prior radiotherapy					
Interaction test	**p = 0.442**				
Yes	5 / 1011 (0.5)	18 / 987 (1.8)	0.27	[0.10; 0.73]	0.010
No	1 / 97 (1.0)	1 / 83 (1.2)	0.86	[0.05; 13.47]	0.912

N: Number of patients
n: Number of patients with event
N.E.: Not estimable
CI: Confidence interval
RR: Relative risk
ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
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Analysis method for interaction test:
p-value from logistic regression model.
logit(proportion) = treatment + subgroup factor + treatment * subgroup factor

Analysis method for within subgroup analysis:
RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm.
ET was the reference group for treatment group comparison.

Table 5-3.2.79 SOC injury, poisoning and procedural complications: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	ET (N = 1070)	RR	[95% CI]	p-value
Injury, poisoning and procedural complications					
	n / N (%)	n / N (%)			
Region					
Interaction test	**p = 0.532**				
NA/WE/O	134 / 640 (20.9)	84 / 627 (13.4)	1.56	[1.22; 2.01]	<.001
ROW	50 / 468 (10.7)	34 / 443 (7.7)	1.39	[0.92; 2.11]	0.119
Geographical region					
Interaction test	**p = 0.356**				
Europe	93 / 654 (14.2)	62 / 638 (9.7)	1.46	[1.08; 1.98]	0.014
North America/Australia	66 / 213 (31.0)	37 / 194 (19.1)	1.62	[1.14; 2.31]	0.007
Asia	17 / 178 (9.6)	16 / 168 (9.5)	1.00	[0.52; 1.92]	0.993
Latin America	8 / 63 (12.7)	3 / 70 (4.3)	2.96	[0.82; 10.68]	0.097
Age group 1 at randomization					
Interaction test	**p = 0.147**				
<45	90 / 549 (16.4)	44 / 496 (8.9)	1.85	[1.32; 2.59]	<.001
45 to 54	93 / 539 (17.3)	70 / 546 (12.8)	1.35	[1.01; 1.79]	0.042
55 to 64	1 / 20 (5.0)	4 / 28 (14.3)	0.35	[0.04; 2.90]	0.331
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)					
Interaction test	**p = 0.132**				
<Median	90 / 549 (16.4)	44 / 496 (8.9)	1.85	[1.32; 2.59]	<.001
≥Median	94 / 559 (16.8)	74 / 574 (12.9)	1.30	[0.98; 1.73]	0.064
Race					
Interaction test	**p = 0.405**				
Asian	26 / 211 (12.3)	19 / 186 (10.2)	1.21	[0.69; 2.11]	0.510
Non-Asian	147 / 840 (17.5)	94 / 827 (11.4)	1.54	[1.21; 1.96]	<.001
BMI at screening					
Interaction test	**p = 0.404**				
≥25	102 / 551 (18.5)	69 / 523 (13.2)	1.40	[1.06; 1.86]	0.018
<25	79 / 542 (14.6)	45 / 535 (8.4)	1.73	[1.23; 2.45]	0.002
AJCC Anatomic Stage Group					
Interaction test	**p = 0.922**				
Group I/II	61 / 417 (14.6)	41 / 418 (9.8)	1.49	[1.03; 2.16]	0.035
Group III	123 / 691 (17.8)	77 / 652 (11.8)	1.51	[1.16; 1.96]	0.002

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Anatomic stages					
Interaction test	**p = 0.166**				
IA/IB/IIA	26 / 171 (15.2)	13 / 198 (6.6)	2.32	[1.23; 4.36]	0.009
IIB	35 / 246 (14.2)	28 / 220 (12.7)	1.12	[0.70; 1.78]	0.637
IIIA	77 / 451 (17.1)	53 / 393 (13.5)	1.27	[0.92; 1.75]	0.152
IIIB	10 / 67 (14.9)	5 / 59 (8.5)	1.76	[0.64; 4.86]	0.274
IIIC	36 / 173 (20.8)	19 / 200 (9.5)	2.19	[1.31; 3.67]	0.003
Nodal status					
Interaction test	**p = 0.138**				
N0	18 / 91 (19.8)	9 / 117 (7.7)	2.57	[1.21; 5.45]	0.014
N1-N3	166 / 1017 (16.3)	109 / 950 (11.5)	1.42	[1.14; 1.78]	0.002
Histological grade at time of surgery					
Interaction test	**p = 0.655**				
Grade 1	18 / 110 (16.4)	11 / 100 (11.0)	1.49	[0.74; 2.99]	0.266
Grade 2	94 / 604 (15.6)	68 / 601 (11.3)	1.38	[1.03; 1.84]	0.032
Grade 3	61 / 297 (20.5)	32 / 266 (12.0)	1.71	[1.15; 2.53]	0.008
Histological subtype					
Interaction test	**p = 0.371**				
Ductal	137 / 863 (15.9)	95 / 835 (11.4)	1.40	[1.09; 1.78]	0.007
Lobular	33 / 172 (19.2)	18 / 169 (10.7)	1.80	[1.06; 3.07]	0.031
Other	14 / 73 (19.2)	5 / 66 (7.6)	2.53	[0.96; 6.65]	0.059
Ki67 status from surgical specimen					
Interaction test	**p = 0.614**				
Ki67≤20	81 / 527 (15.4)	51 / 552 (9.2)	1.66	[1.20; 2.31]	0.002
Ki67>20	62 / 422 (14.7)	38 / 378 (10.1)	1.46	[1.00; 2.14]	0.050
Type of NSAI					
Interaction test	**p = 0.631**				
Letrozole	124 / 809 (15.3)	81 / 773 (10.5)	1.46	[1.13; 1.90]	0.004
Anastrozole	60 / 299 (20.1)	37 / 297 (12.5)	1.61	[1.10; 2.35]	0.013
Prior neo/adjuvant chemotherapy					
Interaction test	**p = 0.031**				
Yes	172 / 1029 (16.7)	117 / 987 (11.9)	1.41	[1.13; 1.75]	0.002
No	12 / 79 (15.2)	1 / 83 (1.2)	12.61	[1.68; 94.72]	0.014
Prior adjuvant chemotherapy					
Interaction test	**p = 0.925**				
Yes	86 / 513 (16.8)	55 / 488 (11.3)	1.49	[1.09; 2.04]	0.013
No	98 / 595 (16.5)	63 / 582 (10.8)	1.52	[1.13; 2.04]	0.005
Prior neoadjuvant chemotherapy					
Interaction test	**p = 0.240**				
Yes	89 / 546 (16.3)	66 / 538 (12.3)	1.33	[0.99; 1.79]	0.059
No	95 / 562 (16.9)	52 / 532 (9.8)	1.73	[1.26; 2.37]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Prior endocrine therapy					
Interaction test	**p = 0.964**				
Yes	142 / 853 (16.6)	87 / 789 (11.0)	1.51	[1.18; 1.94]	0.001
No	42 / 255 (16.5)	31 / 281 (11.0)	1.49	[0.97; 2.30]	0.069
Prior mastectomy					
Interaction test	**p = 0.662**				
Yes	131 / 769 (17.0)	87 / 745 (11.7)	1.46	[1.13; 1.88]	0.003
No	53 / 339 (15.6)	31 / 325 (9.5)	1.64	[1.08; 2.49]	0.020
Prior radiotherapy					
Interaction test	**p = 0.350**				
Yes	168 / 1011 (16.6)	112 / 987 (11.3)	1.46	[1.17; 1.83]	<.001
No	16 / 97 (16.5)	6 / 83 (7.2)	2.28	[0.94; 5.56]	0.070

N: Number of patients
n: Number of patients with event
CI: Confidence interval
RR: Relative risk
ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
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Analysis method for interaction test:
p-value from logistic regression model.
logit(proportion) = treatment + subgroup factor + treatment * subgroup factor

Analysis method for within subgroup analysis:
RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm.
ET was the reference group for treatment group comparison.

Table 5-3.2.80 SOC eye disorders: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	ET (N = 1070)	RR	[95% CI]	p-value
Eye disorders					
	n / N (%)	n / N (%)			
Region					
Interaction test	**p = 0.018**				
NA/WE/O	99 / 640 (15.5)	43 / 627 (6.9)	2.26	[1.60; 3.17]	<.001
ROW	35 / 468 (7.5)	29 / 443 (6.5)	1.14	[0.71; 1.84]	0.582
Geographical region					
Interaction test	**p = 0.228**				
Europe	78 / 654 (11.9)	44 / 638 (6.9)	1.73	[1.21; 2.46]	0.002
North America/Australia	39 / 213 (18.3)	13 / 194 (6.7)	2.73	[1.50; 4.96]	<.001
Asia	14 / 178 (7.9)	12 / 168 (7.1)	1.10	[0.52; 2.31]	0.799
Latin America	3 / 63 (4.8)	3 / 70 (4.3)	1.11	[0.23; 5.31]	0.895
Age group 1 at randomization					
Interaction test	**p = 0.525**				
<45	60 / 549 (10.9)	34 / 496 (6.9)	1.59	[1.07; 2.39]	0.023
45 to 54	71 / 539 (13.2)	38 / 546 (7.0)	1.89	[1.30; 2.76]	<.001
55 to 64	3 / 20 (15.0)	0 / 28 (0.0)	9.67	[0.53; >99.99]	0.126
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)					
Interaction test	**p = 0.405**				
<Median	60 / 549 (10.9)	34 / 496 (6.9)	1.59	[1.07; 2.39]	0.023
≥Median	74 / 559 (13.2)	38 / 574 (6.6)	2.00	[1.38; 2.90]	<.001
Race					
Interaction test	**p = 0.638**				
Asian	23 / 211 (10.9)	13 / 186 (7.0)	1.56	[0.81; 2.99]	0.181
Non-Asian	105 / 840 (12.5)	56 / 827 (6.8)	1.85	[1.35; 2.52]	<.001
BMI at screening					
Interaction test	**p = 0.413**				
≥25	68 / 551 (12.3)	31 / 523 (5.9)	2.08	[1.39; 3.13]	<.001
<25	65 / 542 (12.0)	39 / 535 (7.3)	1.65	[1.13; 2.40]	0.010
AJCC Anatomic Stage Group					
Interaction test	**p = 0.849**				
Group I/II	52 / 417 (12.5)	30 / 418 (7.2)	1.74	[1.13; 2.67]	0.011
Group III	82 / 691 (11.9)	42 / 652 (6.4)	1.84	[1.29; 2.63]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Anatomic stages					
Interaction test	**p = 0.011**				
IA/IB/IIA	14 / 171 (8.2)	20 / 198 (10.1)	0.81	[0.42; 1.56]	0.527
IIB	38 / 246 (15.4)	10 / 220 (4.5)	3.40	[1.73; 6.66]	<.001
IIIA	57 / 451 (12.6)	28 / 393 (7.1)	1.77	[1.15; 2.73]	0.009
IIIB	5 / 67 (7.5)	6 / 59 (10.2)	0.73	[0.24; 2.28]	0.593
IIIC	20 / 173 (11.6)	8 / 200 (4.0)	2.89	[1.31; 6.40]	0.009
Nodal status					
Interaction test	**p = 0.669**				
N0	8 / 91 (8.8)	7 / 117 (6.0)	1.47	[0.55; 3.90]	0.440
N1-N3	126 / 1017 (12.4)	65 / 950 (6.8)	1.81	[1.36; 2.41]	<.001
Histological grade at time of surgery					
Interaction test	**p = 0.891**				
Grade 1	16 / 110 (14.5)	8 / 100 (8.0)	1.82	[0.81; 4.06]	0.145
Grade 2	77 / 604 (12.7)	41 / 601 (6.8)	1.87	[1.30; 2.68]	<.001
Grade 3	34 / 297 (11.4)	19 / 266 (7.1)	1.60	[0.94; 2.74]	0.085
Histological subtype					
Interaction test	**p = 0.375**				
Ductal	106 / 863 (12.3)	53 / 835 (6.3)	1.94	[1.41; 2.65]	<.001
Lobular	18 / 172 (10.5)	15 / 169 (8.9)	1.18	[0.61; 2.26]	0.620
Other	10 / 73 (13.7)	4 / 66 (6.1)	2.26	[0.74; 6.86]	0.150
Ki67 status from surgical specimen					
Interaction test	**p = 0.584**				
Ki67≤20	55 / 527 (10.4)	35 / 552 (6.3)	1.65	[1.10; 2.47]	0.016
Ki67>20	54 / 422 (12.8)	25 / 378 (6.6)	1.93	[1.23; 3.04]	0.004
Type of NSAI					
Interaction test	**p = 0.498**				
Letrozole	87 / 809 (10.8)	49 / 773 (6.3)	1.70	[1.21; 2.37]	0.002
Anastrozole	47 / 299 (15.7)	23 / 297 (7.7)	2.03	[1.27; 3.25]	0.003
Prior neo/adjuvant chemotherapy					
Interaction test	**p = 0.096**				
Yes	128 / 1029 (12.4)	64 / 987 (6.5)	1.92	[1.44; 2.56]	<.001
No	6 / 79 (7.6)	8 / 83 (9.6)	0.79	[0.29; 2.17]	0.645
Prior adjuvant chemotherapy					
Interaction test	**p = 0.069**				
Yes	77 / 513 (15.0)	32 / 488 (6.6)	2.29	[1.54; 3.39]	<.001
No	57 / 595 (9.6)	40 / 582 (6.9)	1.39	[0.95; 2.05]	0.093
Prior neoadjuvant chemotherapy					
Interaction test	**p = 0.359**				
Yes	54 / 546 (9.9)	34 / 538 (6.3)	1.56	[1.04; 2.36]	0.033
No	80 / 562 (14.2)	38 / 532 (7.1)	1.99	[1.38; 2.88]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Prior endocrine therapy					
Interaction test	**p = 0.814**				
Yes	98 / 853 (11.5)	51 / 789 (6.5)	1.78	[1.29; 2.46]	<.001
No	36 / 255 (14.1)	21 / 281 (7.5)	1.89	[1.13; 3.15]	0.015
Prior mastectomy					
Interaction test	**p = 0.302**				
Yes	97 / 769 (12.6)	57 / 745 (7.7)	1.65	[1.21; 2.25]	0.002
No	37 / 339 (10.9)	15 / 325 (4.6)	2.36	[1.32; 4.22]	0.004
Prior radiotherapy					
Interaction test	**p = 0.617**				
Yes	117 / 1011 (11.6)	62 / 987 (6.3)	1.84	[1.37; 2.47]	<.001
No	17 / 97 (17.5)	10 / 83 (12.0)	1.45	[0.71; 3.00]	0.310

N: Number of patients
n: Number of patients with event
CI: Confidence interval
RR: Relative risk
ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
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Analysis method for interaction test:
p-value from logistic regression model.
logit(proportion) = treatment + subgroup factor + treatment * subgroup factor

Analysis method for within subgroup analysis:
RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm.
ET was the reference group for treatment group comparison.

Table 5-3.2.81 PT dry eye: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	ET (N = 1070)	RR	[95% CI]	p-value
Dry eye					
	n / N (%)	n / N (%)			
Region					
Interaction test	**p = 0.049**				
NA/WE/O	42 / 640 (6.6)	11 / 627 (1.8)	3.74	[1.94; 7.20]	<.001
ROW	5 / 468 (1.1)	5 / 443 (1.1)	0.95	[0.28; 3.25]	0.930
Geographical region					
Interaction test	**p = 0.568**				
Europe	26 / 654 (4.0)	7 / 638 (1.1)	3.62	[1.58; 8.29]	0.002
North America/Australia	16 / 213 (7.5)	4 / 194 (2.1)	3.64	[1.24; 10.71]	0.019
Asia	5 / 178 (2.8)	3 / 168 (1.8)	1.57	[0.38; 6.48]	0.531
Latin America	0 / 63 (0.0)	2 / 70 (2.9)	0.22	[0.01; 4.54]	0.328
Age group 1 at randomization					
Interaction test	**p = 0.587**				
<45	18 / 549 (3.3)	7 / 496 (1.4)	2.32	[0.98; 5.52]	0.056
45 to 54	28 / 539 (5.2)	9 / 546 (1.6)	3.15	[1.50; 6.62]	0.002
55 to 64	1 / 20 (5.0)	0 / 28 (0.0)	4.14	[0.18; 96.77]	0.377
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)					
Interaction test	**p = 0.530**				
<Median	18 / 549 (3.3)	7 / 496 (1.4)	2.32	[0.98; 5.52]	0.056
≥Median	29 / 559 (5.2)	9 / 574 (1.6)	3.31	[1.58; 6.93]	0.002
Race					
Interaction test	**p = 0.944**				
Asian	9 / 211 (4.3)	3 / 186 (1.6)	2.64	[0.73; 9.62]	0.140
Non-Asian	34 / 840 (4.0)	12 / 827 (1.5)	2.79	[1.45; 5.35]	0.002
BMI at screening					
Interaction test	**p = 0.248**				
≥25	21 / 551 (3.8)	4 / 523 (0.8)	4.98	[1.72; 14.42]	0.003
<25	26 / 542 (4.8)	11 / 535 (2.1)	2.33	[1.16; 4.67]	0.017
AJCC Anatomic Stage Group					
Interaction test	**p = 0.230**				
Group I/II	22 / 417 (5.3)	5 / 418 (1.2)	4.41	[1.69; 11.54]	0.002
Group III	25 / 691 (3.6)	11 / 652 (1.7)	2.14	[1.06; 4.32]	0.033

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Anatomic stages					
Interaction test	**p = 0.438**				
IA/IB/IIA	7 / 171 (4.1)	4 / 198 (2.0)	2.03	[0.60; 6.80]	0.253
IIB	15 / 246 (6.1)	1 / 220 (0.5)	13.41	[1.79; >99.99]	0.012
IIIA	19 / 451 (4.2)	9 / 393 (2.3)	1.84	[0.84; 4.02]	0.126
IIIB	2 / 67 (3.0)	1 / 59 (1.7)	1.76	[0.16; 18.93]	0.640
IIIC	4 / 173 (2.3)	1 / 200 (0.5)	4.62	[0.52; 40.98]	0.169
Nodal status					
Interaction test	**N.E.**				
N0	3 / 91 (3.3)	0 / 117 (0.0)	8.98	[0.47; >99.99]	0.145
N1-N3	44 / 1017 (4.3)	16 / 950 (1.7)	2.57	[1.46; 4.52]	0.001
Histological grade at time of surgery					
Interaction test	**p = 0.429**				
Grade 1	5 / 110 (4.5)	2 / 100 (2.0)	2.27	[0.45; 11.45]	0.320
Grade 2	28 / 604 (4.6)	13 / 601 (2.2)	2.14	[1.12; 4.10]	0.021
Grade 3	10 / 297 (3.4)	1 / 266 (0.4)	8.96	[1.15; 69.50]	0.036
Histological subtype					
Interaction test	**p = 0.896**				
Ductal	35 / 863 (4.1)	11 / 835 (1.3)	3.08	[1.57; 6.02]	0.001
Lobular	9 / 172 (5.2)	4 / 169 (2.4)	2.21	[0.69; 7.04]	0.180
Other	3 / 73 (4.1)	1 / 66 (1.5)	2.71	[0.29; 25.44]	0.382
Ki67 status from surgical specimen					
Interaction test	**p = 0.748**				
Ki67≤20	20 / 527 (3.8)	9 / 552 (1.6)	2.33	[1.07; 5.07]	0.033
Ki67>20	16 / 422 (3.8)	5 / 378 (1.3)	2.87	[1.06; 7.75]	0.038
Type of NSAI					
Interaction test	**p = 0.616**				
Letrozole	33 / 809 (4.1)	10 / 773 (1.3)	3.15	[1.56; 6.35]	0.001
Anastrozole	14 / 299 (4.7)	6 / 297 (2.0)	2.32	[0.90; 5.95]	0.081
Prior neo/adjuvant chemotherapy					
Interaction test	**p = 0.795**				
Yes	45 / 1029 (4.4)	15 / 987 (1.5)	2.88	[1.61; 5.13]	<.001
No	2 / 79 (2.5)	1 / 83 (1.2)	2.10	[0.19; 22.72]	0.541
Prior adjuvant chemotherapy					
Interaction test	**p = 0.135**				
Yes	28 / 513 (5.5)	6 / 488 (1.2)	4.44	[1.85; 10.63]	<.001
No	19 / 595 (3.2)	10 / 582 (1.7)	1.86	[0.87; 3.96]	0.109
Prior neoadjuvant chemotherapy					
Interaction test	**p = 0.230**				
Yes	18 / 546 (3.3)	9 / 538 (1.7)	1.97	[0.89; 4.35]	0.093
No	29 / 562 (5.2)	7 / 532 (1.3)	3.92	[1.73; 8.88]	0.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Prior endocrine therapy					
Interaction test	**p = 0.956**				
Yes	37 / 853 (4.3)	12 / 789 (1.5)	2.85	[1.50; 5.43]	0.001
No	10 / 255 (3.9)	4 / 281 (1.4)	2.75	[0.87; 8.68]	0.083
Prior mastectomy					
Interaction test	**p = 0.461**				
Yes	37 / 769 (4.8)	14 / 745 (1.9)	2.56	[1.40; 4.70]	0.002
No	10 / 339 (2.9)	2 / 325 (0.6)	4.79	[1.06; 21.71]	0.042
Prior radiotherapy					
Interaction test	**N.E.**				
Yes	40 / 1011 (4.0)	16 / 987 (1.6)	2.44	[1.38; 4.33]	0.002
No	7 / 97 (7.2)	0 / 83 (0.0)	12.86	[0.75; >99.99]	0.079

N: Number of patients
n: Number of patients with event
N.E.: Not estimable
CI: Confidence interval
RR: Relative risk
ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
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Analysis method for interaction test:
p-value from logistic regression model.
logit(proportion) = treatment + subgroup factor + treatment * subgroup factor

Analysis method for within subgroup analysis:
RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm.
ET was the reference group for treatment group comparison.

Table 5-3.2.82 PT lacrimation increased: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	ET (N = 1070)	RR	[95% CI]	p-value
Lacrimation increased					
	n / N (%)	n / N (%)			
Region					
Interaction test	**p = 0.731**				
NA/WE/O	14 / 640 (2.2)	2 / 627 (0.3)	6.86	[1.57; 30.05]	0.011
ROW	10 / 468 (2.1)	2 / 443 (0.5)	4.73	[1.04; 21.48]	0.044
Geographical region					
Interaction test	**p = 0.556**				
Europe	18 / 654 (2.8)	3 / 638 (0.5)	5.85	[1.73; 19.77]	0.004
North America/Australia	3 / 213 (1.4)	1 / 194 (0.5)	2.73	[0.29; 26.05]	0.382
Asia	2 / 178 (1.1)	0 / 168 (0.0)	4.72	[0.23; 97.61]	0.315
Latin America	1 / 63 (1.6)	0 / 70 (0.0)	3.33	[0.14; 80.25]	0.459
Age group 1 at randomization					
Interaction test	**p = 0.308**				
<45	13 / 549 (2.4)	1 / 496 (0.2)	11.74	[1.54; 89.46]	0.017
45 to 54	10 / 539 (1.9)	3 / 546 (0.5)	3.38	[0.93; 12.20]	0.063
55 to 64	1 / 20 (5.0)	0 / 28 (0.0)	4.14	[0.18; 96.77]	0.377
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)					
Interaction test	**p = 0.351**				
<Median	13 / 549 (2.4)	1 / 496 (0.2)	11.74	[1.54; 89.46]	0.017
≥Median	11 / 559 (2.0)	3 / 574 (0.5)	3.77	[1.06; 13.42]	0.041
Race					
Interaction test	**N.E.**				
Asian	2 / 211 (0.9)	0 / 186 (0.0)	4.41	[0.21; 91.28]	0.337
Non-Asian	22 / 840 (2.6)	4 / 827 (0.5)	5.41	[1.87; 15.65]	0.002
BMI at screening					
Interaction test	**p = 0.484**				
≥25	11 / 551 (2.0)	2 / 523 (0.4)	5.22	[1.16; 23.44]	0.031
<25	13 / 542 (2.4)	1 / 535 (0.2)	12.83	[1.68; 97.75]	0.014
AJCC Anatomic Stage Group					
Interaction test	**p = 0.678**				
Group I/II	9 / 417 (2.2)	2 / 418 (0.5)	4.51	[0.98; 20.75]	0.053
Group III	15 / 691 (2.2)	2 / 652 (0.3)	7.08	[1.62; 30.83]	0.009

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Anatomic stages					
Interaction test	**p = 0.408**				
IA/IB/IIA	3 / 171 (1.8)	2 / 198 (1.0)	1.74	[0.29; 10.27]	0.543
IIB	6 / 246 (2.4)	0 / 220 (0.0)	11.63	[0.66; >99.99]	0.094
IIIA	11 / 451 (2.4)	1 / 393 (0.3)	9.59	[1.24; 73.91]	0.030
IIIB	2 / 67 (3.0)	1 / 59 (1.7)	1.76	[0.16; 18.93]	0.640
IIIC	2 / 173 (1.2)	0 / 200 (0.0)	5.78	[0.28; >99.99]	0.257
Nodal status					
Interaction test	**p = 0.693**				
N0	3 / 91 (3.3)	1 / 117 (0.9)	3.86	[0.41; 36.47]	0.239
N1-N3	21 / 1017 (2.1)	3 / 950 (0.3)	6.54	[1.96; 21.85]	0.002
Histological grade at time of surgery					
Interaction test	**p = 0.679**				
Grade 1	2 / 110 (1.8)	0 / 100 (0.0)	4.55	[0.22; 93.64]	0.326
Grade 2	13 / 604 (2.2)	3 / 601 (0.5)	4.31	[1.23; 15.05]	0.022
Grade 3	8 / 297 (2.7)	1 / 266 (0.4)	7.16	[0.90; 56.91]	0.063
Histological subtype					
Interaction test	**p = 0.839**				
Ductal	15 / 863 (1.7)	3 / 835 (0.4)	4.84	[1.41; 16.65]	0.012
Lobular	5 / 172 (2.9)	0 / 169 (0.0)	10.81	[0.60; >99.99]	0.106
Other	4 / 73 (5.5)	1 / 66 (1.5)	3.62	[0.41; 31.54]	0.245
Ki67 status from surgical specimen					
Interaction test	**p = 0.624**				
Ki67≤20	10 / 527 (1.9)	2 / 552 (0.4)	5.24	[1.15; 23.79]	0.032
Ki67>20	11 / 422 (2.6)	1 / 378 (0.3)	9.85	[1.28; 75.96]	0.028
Type of NSAI					
Interaction test	**p = 0.955**				
Letrozole	12 / 809 (1.5)	2 / 773 (0.3)	5.73	[1.29; 25.53]	0.022
Anastrozole	12 / 299 (4.0)	2 / 297 (0.7)	5.96	[1.35; 26.40]	0.019
Prior neo/adjuvant chemotherapy					
Interaction test	**p = 0.205**				
Yes	23 / 1029 (2.2)	3 / 987 (0.3)	7.35	[2.22; 24.41]	0.001
No	1 / 79 (1.3)	1 / 83 (1.2)	1.05	[0.07; 16.51]	0.972
Prior adjuvant chemotherapy					
Interaction test	**p = 0.310**				
Yes	13 / 513 (2.5)	1 / 488 (0.2)	12.37	[1.62; 94.18]	0.015
No	11 / 595 (1.8)	3 / 582 (0.5)	3.59	[1.01; 12.79]	0.049
Prior neoadjuvant chemotherapy					
Interaction test	**p = 0.780**				
Yes	10 / 546 (1.8)	2 / 538 (0.4)	4.93	[1.08; 22.38]	0.039
No	14 / 562 (2.5)	2 / 532 (0.4)	6.63	[1.51; 29.02]	0.012

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Prior endocrine therapy					
Interaction test	**p = 0.405**				
Yes	18 / 853 (2.1)	2 / 789 (0.3)	8.32	[1.94; 35.76]	0.004
No	6 / 255 (2.4)	2 / 281 (0.7)	3.31	[0.67; 16.23]	0.141
Prior mastectomy					
Interaction test	**p = 0.372**				
Yes	12 / 769 (1.6)	1 / 745 (0.1)	11.63	[1.52; 89.18]	0.018
No	12 / 339 (3.5)	3 / 325 (0.9)	3.83	[1.09; 13.46]	0.036
Prior radiotherapy					
Interaction test	**N.E.**				
Yes	21 / 1011 (2.1)	4 / 987 (0.4)	5.13	[1.77; 14.88]	0.003
No	3 / 97 (3.1)	0 / 83 (0.0)	6.00	[0.31; >99.99]	0.234

N: Number of patients
n: Number of patients with event
N.E.: Not estimable
CI: Confidence interval
RR: Relative risk
ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
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Analysis method for interaction test:
p-value from logistic regression model.
logit(proportion) = treatment + subgroup factor + treatment * subgroup factor

Analysis method for within subgroup analysis:
RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm.
ET was the reference group for treatment group comparison.

Table 5-3.2.83 PT vision blurred: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	ET (N = 1070)	RR	[95% CI]	p-value
Vision blurred					
	n / N (%)	n / N (%)			
Region					
Interaction test	**N.E.**				
NA/WE/O	21 / 640 (3.3)	4 / 627 (0.6)	5.14	[1.78; 14.90]	0.003
ROW	1 / 468 (0.2)	0 / 443 (0.0)	2.84	[0.12; 69.53]	0.522
Geographical region					
Interaction test	**p = 0.967**				
Europe	5 / 654 (0.8)	1 / 638 (0.2)	4.88	[0.57; 41.63]	0.147
North America/Australia	16 / 213 (7.5)	3 / 194 (1.5)	4.86	[1.44; 16.42]	0.011
Asia	1 / 178 (0.6)	0 / 168 (0.0)	2.83	[0.12; 69.05]	0.523
Latin America	0 / 63 (0.0)	0 / 70 (0.0)	N.E.	N.E.	N.E.
Age group 1 at randomization					
Interaction test	**p = 0.654**				
<45	9 / 549 (1.6)	2 / 496 (0.4)	4.07	[0.88; 18.73]	0.072
45 to 54	13 / 539 (2.4)	2 / 546 (0.4)	6.58	[1.49; 29.04]	0.013
55 to 64	0 / 20 (0.0)	0 / 28 (0.0)	N.E.	N.E.	N.E.
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)					
Interaction test	**p = 0.645**				
<Median	9 / 549 (1.6)	2 / 496 (0.4)	4.07	[0.88; 18.73]	0.072
≥Median	13 / 559 (2.3)	2 / 574 (0.3)	6.67	[1.51; 29.44]	0.012
Race					
Interaction test	**p = 0.720**				
Asian	4 / 211 (1.9)	1 / 186 (0.5)	3.53	[0.40; 31.27]	0.258
Non-Asian	17 / 840 (2.0)	3 / 827 (0.4)	5.58	[1.64; 18.97]	0.006
BMI at screening					
Interaction test	**p = 0.628**				
≥25	14 / 551 (2.5)	2 / 523 (0.4)	6.64	[1.52; 29.09]	0.012
<25	8 / 542 (1.5)	2 / 535 (0.4)	3.95	[0.84; 18.51]	0.081
AJCC Anatomic Stage Group					
Interaction test	**p = 0.915**				
Group I/II	10 / 417 (2.4)	2 / 418 (0.5)	5.01	[1.10; 22.74]	0.037
Group III	12 / 691 (1.7)	2 / 652 (0.3)	5.66	[1.27; 25.20]	0.023
Anatomic stages					
The subgroup analysis is not presented as all subgroups have less than 10 events.					

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Nodal status					
Interaction test	**p = 0.520**				
N0	2 / 91 (2.2)	1 / 117 (0.9)	2.57	[0.24; 27.92]	0.438
N1-N3	20 / 1017 (2.0)	3 / 950 (0.3)	6.23	[1.86; 20.89]	0.003
Histological grade at time of surgery					
Interaction test	**p = 0.223**				
Grade 1	3 / 110 (2.7)	0 / 100 (0.0)	6.37	[0.33; >99.99]	0.219
Grade 2	11 / 604 (1.8)	1 / 601 (0.2)	10.95	[1.42; 84.51]	0.022
Grade 3	8 / 297 (2.7)	3 / 266 (1.1)	2.39	[0.64; 8.91]	0.195
Histological subtype					
Interaction test	**p = 0.604**				
Ductal	18 / 863 (2.1)	3 / 835 (0.4)	5.81	[1.72; 19.64]	0.005
Lobular	3 / 172 (1.7)	1 / 169 (0.6)	2.95	[0.31; 28.06]	0.347
Other	1 / 73 (1.4)	0 / 66 (0.0)	2.72	[0.11; 65.54]	0.538
Ki67 status from surgical specimen					
The subgroup analysis is not presented as all subgroups have less than 10 events.					
Type of NSAI					
Interaction test	**p = 0.430**				
Letrozole	12 / 809 (1.5)	3 / 773 (0.4)	3.82	[1.08; 13.49]	0.037
Anastrozole	10 / 299 (3.3)	1 / 297 (0.3)	9.93	[1.28; 77.11]	0.028
Prior neo/adjuvant chemotherapy					
Interaction test	**p = 0.228**				
Yes	21 / 1029 (2.0)	3 / 987 (0.3)	6.71	[2.01; 22.44]	0.002
No	1 / 79 (1.3)	1 / 83 (1.2)	1.05	[0.07; 16.51]	0.972
Prior adjuvant chemotherapy					
Interaction test	**p = 0.381**				
Yes	16 / 513 (3.1)	2 / 488 (0.4)	7.61	[1.76; 32.92]	0.007
No	6 / 595 (1.0)	2 / 582 (0.3)	2.93	[0.59; 14.48]	0.186
Prior neoadjuvant chemotherapy					
Interaction test	**p = 0.935**				
Yes	5 / 546 (0.9)	1 / 538 (0.2)	4.93	[0.58; 42.03]	0.145
No	17 / 562 (3.0)	3 / 532 (0.6)	5.36	[1.58; 18.20]	0.007
Prior endocrine therapy					
Interaction test	**p = 0.969**				
Yes	17 / 853 (2.0)	3 / 789 (0.4)	5.24	[1.54; 17.82]	0.008
No	5 / 255 (2.0)	1 / 281 (0.4)	5.51	[0.65; 46.85]	0.118
Prior mastectomy					
Interaction test	**p = 0.557**				
Yes	19 / 769 (2.5)	3 / 745 (0.4)	6.14	[1.82; 20.65]	0.003
No	3 / 339 (0.9)	1 / 325 (0.3)	2.88	[0.30; 27.51]	0.359

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Prior radiotherapy					
Interaction test	**N.E.**				
Yes	18 / 1011 (1.8)	4 / 987 (0.4)	4.39	[1.49; 12.93]	0.007
No	4 / 97 (4.1)	0 / 83 (0.0)	7.71	[0.42; >99.99]	0.168

N: Number of patients
n: Number of patients with event
N.E.: Not estimable
CI: Confidence interval
RR: Relative risk
ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
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Analysis method for interaction test:
p-value from logistic regression model.
logit(proportion) = treatment + subgroup factor + treatment * subgroup factor

Analysis method for within subgroup analysis:
RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm.
ET was the reference group for treatment group comparison.

Table 5-3.2.84 PT palpitations: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	ET (N = 1070)	RR	[95% CI]	p-value
Palpitations					
	n / N (%)	n / N (%)			
Region					
Interaction test	**p = 0.880**				
NA/WE/O	33 / 640 (5.2)	13 / 627 (2.1)	2.49	[1.32; 4.68]	0.005
ROW	9 / 468 (1.9)	3 / 443 (0.7)	2.84	[0.77; 10.42]	0.116
Geographical region					
Interaction test	**p = 0.970**				
Europe	18 / 654 (2.8)	7 / 638 (1.1)	2.51	[1.05; 5.96]	0.037
North America/Australia	17 / 213 (8.0)	7 / 194 (3.6)	2.21	[0.94; 5.22]	0.070
Asia	6 / 178 (3.4)	2 / 168 (1.2)	2.83	[0.58; 13.83]	0.198
Latin America	1 / 63 (1.6)	0 / 70 (0.0)	3.33	[0.14; 80.25]	0.459
Age group 1 at randomization					
Interaction test	**p = 0.340**				
<45	19 / 549 (3.5)	9 / 496 (1.8)	1.91	[0.87; 4.18]	0.106
45 to 54	23 / 539 (4.3)	7 / 546 (1.3)	3.33	[1.44; 7.69]	0.005
55 to 64	0 / 20 (0.0)	0 / 28 (0.0)	N.E.	N.E.	N.E.
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)					
Interaction test	**p = 0.330**				
<Median	19 / 549 (3.5)	9 / 496 (1.8)	1.91	[0.87; 4.18]	0.106
≥Median	23 / 559 (4.1)	7 / 574 (1.2)	3.37	[1.46; 7.80]	0.004
Race					
Interaction test	**p = 0.542**				
Asian	9 / 211 (4.3)	4 / 186 (2.2)	1.98	[0.62; 6.33]	0.248
Non-Asian	31 / 840 (3.7)	10 / 827 (1.2)	3.05	[1.51; 6.18]	0.002
BMI at screening					
Interaction test	**p = 0.789**				
≥25	19 / 551 (3.4)	7 / 523 (1.3)	2.58	[1.09; 6.08]	0.031
<25	20 / 542 (3.7)	9 / 535 (1.7)	2.19	[1.01; 4.77]	0.048
AJCC Anatomic Stage Group					
Interaction test	**p = 0.454**				
Group I/II	17 / 417 (4.1)	5 / 418 (1.2)	3.41	[1.27; 9.15]	0.015
Group III	25 / 691 (3.6)	11 / 652 (1.7)	2.14	[1.06; 4.32]	0.033

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Anatomic stages					
Interaction test	**p = 0.373**				
IA/IB/IIA	4 / 171 (2.3)	1 / 198 (0.5)	4.63	[0.52; 41.04]	0.168
IIB	13 / 246 (5.3)	4 / 220 (1.8)	2.91	[0.96; 8.78]	0.059
IIIA	16 / 451 (3.5)	10 / 393 (2.5)	1.39	[0.64; 3.04]	0.403
IIIB	3 / 67 (4.5)	0 / 59 (0.0)	6.18	[0.33; >99.99]	0.225
IIIC	6 / 173 (3.5)	1 / 200 (0.5)	6.94	[0.84; 57.05]	0.072
Nodal status					
Interaction test	**p = 0.478**				
N0	2 / 91 (2.2)	2 / 117 (1.7)	1.29	[0.18; 8.95]	0.800
N1-N3	40 / 1017 (3.9)	14 / 950 (1.5)	2.67	[1.46; 4.87]	0.001
Histological grade at time of surgery					
Interaction test	**p = 0.252**				
Grade 1	2 / 110 (1.8)	2 / 100 (2.0)	0.91	[0.13; 6.33]	0.923
Grade 2	26 / 604 (4.3)	6 / 601 (1.0)	4.31	[1.79; 10.40]	0.001
Grade 3	13 / 297 (4.4)	6 / 266 (2.3)	1.94	[0.75; 5.03]	0.173
Histological subtype					
Interaction test	**p = 0.648**				
Ductal	33 / 863 (3.8)	11 / 835 (1.3)	2.90	[1.48; 5.70]	0.002
Lobular	8 / 172 (4.7)	4 / 169 (2.4)	1.97	[0.60; 6.40]	0.262
Other	1 / 73 (1.4)	1 / 66 (1.5)	0.90	[0.06; 14.17]	0.943
Ki67 status from surgical specimen					
Interaction test	**p = 0.438**				
Ki67≤20	13 / 527 (2.5)	4 / 552 (0.7)	3.40	[1.12; 10.37]	0.031
Ki67>20	15 / 422 (3.6)	7 / 378 (1.9)	1.92	[0.79; 4.66]	0.149
Type of NSAI					
Interaction test	**p = 0.821**				
Letrozole	28 / 809 (3.5)	11 / 773 (1.4)	2.43	[1.22; 4.85]	0.012
Anastrozole	14 / 299 (4.7)	5 / 297 (1.7)	2.78	[1.01; 7.62]	0.047
Prior neo/adjuvant chemotherapy					
Interaction test	**p = 0.870**				
Yes	40 / 1029 (3.9)	15 / 987 (1.5)	2.56	[1.42; 4.60]	0.002
No	2 / 79 (2.5)	1 / 83 (1.2)	2.10	[0.19; 22.72]	0.541
Prior adjuvant chemotherapy					
Interaction test	**p = 0.417**				
Yes	21 / 513 (4.1)	6 / 488 (1.2)	3.33	[1.36; 8.18]	0.009
No	21 / 595 (3.5)	10 / 582 (1.7)	2.05	[0.98; 4.32]	0.058
Prior neoadjuvant chemotherapy					
Interaction test	**p = 0.344**				
Yes	20 / 546 (3.7)	10 / 538 (1.9)	1.97	[0.93; 4.17]	0.076
No	22 / 562 (3.9)	6 / 532 (1.1)	3.47	[1.42; 8.49]	0.006

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Prior endocrine therapy					
Interaction test	**p = 0.915**				
Yes	31 / 853 (3.6)	11 / 789 (1.4)	2.61	[1.32; 5.15]	0.006
No	11 / 255 (4.3)	5 / 281 (1.8)	2.42	[0.85; 6.88]	0.096
Prior mastectomy					
Interaction test	**p = 0.747**				
Yes	33 / 769 (4.3)	12 / 745 (1.6)	2.66	[1.39; 5.12]	0.003
No	9 / 339 (2.7)	4 / 325 (1.2)	2.16	[0.67; 6.94]	0.197
Prior radiotherapy					
Interaction test	**p = 0.635**				
Yes	38 / 1011 (3.8)	14 / 987 (1.4)	2.65	[1.44; 4.86]	0.002
No	4 / 97 (4.1)	2 / 83 (2.4)	1.71	[0.32; 9.11]	0.529

N: Number of patients
n: Number of patients with event
N.E.: Not estimable
CI: Confidence interval
RR: Relative risk
ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
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Analysis method for interaction test:
p-value from logistic regression model.
logit(proportion) = treatment + subgroup factor + treatment * subgroup factor

Analysis method for within subgroup analysis:
RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm.
ET was the reference group for treatment group comparison.

Table 5-3.2.85 SOC renal and urinary disorders: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	ET (N = 1070)	RR	[95% CI]	p-value
Renal and urinary disorders					
	n / N (%)	n / N (%)			
Region					
Interaction test	**p = 0.025**				
NA/WE/O	57 / 640 (8.9)	26 / 627 (4.1)	2.15	[1.37; 3.37]	<.001
ROW	18 / 468 (3.8)	19 / 443 (4.3)	0.90	[0.48; 1.69]	0.735
Geographical region					
Interaction test	**p = 0.213**				
Europe	39 / 654 (6.0)	22 / 638 (3.4)	1.73	[1.04; 2.88]	0.036
North America/Australia	26 / 213 (12.2)	10 / 194 (5.2)	2.37	[1.17; 4.78]	0.016
Asia	6 / 178 (3.4)	7 / 168 (4.2)	0.81	[0.28; 2.36]	0.698
Latin America	4 / 63 (6.3)	6 / 70 (8.6)	0.74	[0.22; 2.51]	0.629
Age group 1 at randomization					
Interaction test	**p = 0.832**				
<45	42 / 549 (7.7)	22 / 496 (4.4)	1.72	[1.04; 2.85]	0.033
45 to 54	30 / 539 (5.6)	19 / 546 (3.5)	1.60	[0.91; 2.81]	0.102
55 to 64	3 / 20 (15.0)	4 / 28 (14.3)	1.05	[0.26; 4.18]	0.945
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)					
Interaction test	**p = 0.658**				
<Median	42 / 549 (7.7)	22 / 496 (4.4)	1.72	[1.04; 2.85]	0.033
≥Median	33 / 559 (5.9)	23 / 574 (4.0)	1.47	[0.88; 2.48]	0.144
Race					
Interaction test	**p = 0.229**				
Asian	8 / 211 (3.8)	8 / 186 (4.3)	0.88	[0.34; 2.30]	0.797
Non-Asian	59 / 840 (7.0)	35 / 827 (4.2)	1.66	[1.10; 2.49]	0.015
BMI at screening					
Interaction test	**p = 0.564**				
≥25	48 / 551 (8.7)	26 / 523 (5.0)	1.75	[1.10; 2.78]	0.017
<25	26 / 542 (4.8)	18 / 535 (3.4)	1.43	[0.79; 2.57]	0.238
AJCC Anatomic Stage Group					
Interaction test	**p = 0.098**				
Group I/II	29 / 417 (7.0)	25 / 418 (6.0)	1.16	[0.69; 1.95]	0.568
Group III	46 / 691 (6.7)	20 / 652 (3.1)	2.17	[1.30; 3.63]	0.003

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Anatomic stages					
Interaction test	**p = 0.174**				
IA/IB/IIA	11 / 171 (6.4)	15 / 198 (7.6)	0.85	[0.40; 1.80]	0.669
IIB	18 / 246 (7.3)	10 / 220 (4.5)	1.61	[0.76; 3.41]	0.214
IIIA	21 / 451 (4.7)	12 / 393 (3.1)	1.52	[0.76; 3.06]	0.235
IIIB	7 / 67 (10.4)	2 / 59 (3.4)	3.08	[0.67; 14.26]	0.150
IIIC	18 / 173 (10.4)	6 / 200 (3.0)	3.47	[1.41; 8.54]	0.007
Nodal status					
Interaction test	**p = 0.645**				
N0	7 / 91 (7.7)	7 / 117 (6.0)	1.29	[0.47; 3.53]	0.626
N1-N3	68 / 1017 (6.7)	38 / 950 (4.0)	1.67	[1.14; 2.46]	0.009
Histological grade at time of surgery					
Interaction test	**p = 0.673**				
Grade 1	7 / 110 (6.4)	5 / 100 (5.0)	1.27	[0.42; 3.88]	0.672
Grade 2	40 / 604 (6.6)	21 / 601 (3.5)	1.90	[1.13; 3.18]	0.015
Grade 3	18 / 297 (6.1)	12 / 266 (4.5)	1.34	[0.66; 2.74]	0.416
Histological subtype					
Interaction test	**p = 0.788**				
Ductal	56 / 863 (6.5)	36 / 835 (4.3)	1.51	[1.00; 2.26]	0.049
Lobular	13 / 172 (7.6)	6 / 169 (3.6)	2.13	[0.83; 5.47]	0.117
Other	6 / 73 (8.2)	3 / 66 (4.5)	1.81	[0.47; 6.94]	0.388
Ki67 status from surgical specimen					
Interaction test	**p = 0.515**				
Ki67≤20	29 / 527 (5.5)	24 / 552 (4.3)	1.27	[0.75; 2.14]	0.381
Ki67>20	31 / 422 (7.3)	17 / 378 (4.5)	1.63	[0.92; 2.90]	0.094
Type of NSAI					
Interaction test	**p = 0.993**				
Letrozole	54 / 809 (6.7)	32 / 773 (4.1)	1.61	[1.05; 2.47]	0.028
Anastrozole	21 / 299 (7.0)	13 / 297 (4.4)	1.60	[0.82; 3.14]	0.168
Prior neo/adjuvant chemotherapy					
Interaction test	**p = 0.377**				
Yes	71 / 1029 (6.9)	44 / 987 (4.5)	1.55	[1.07; 2.23]	0.019
No	4 / 79 (5.1)	1 / 83 (1.2)	4.20	[0.48; 36.79]	0.195
Prior adjuvant chemotherapy					
Interaction test	**p = 0.008**				
Yes	32 / 513 (6.2)	30 / 488 (6.1)	1.01	[0.63; 1.64]	0.953
No	43 / 595 (7.2)	15 / 582 (2.6)	2.80	[1.58; 4.99]	<.001
Prior neoadjuvant chemotherapy					
Interaction test	**p = 0.053**				
Yes	41 / 546 (7.5)	17 / 538 (3.2)	2.38	[1.37; 4.13]	0.002
No	34 / 562 (6.0)	28 / 532 (5.3)	1.15	[0.71; 1.87]	0.574

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Prior endocrine therapy					
Interaction test	**p = 0.794**				
Yes	56 / 853 (6.6)	31 / 789 (3.9)	1.67	[1.09; 2.56]	0.019
No	19 / 255 (7.5)	14 / 281 (5.0)	1.50	[0.77; 2.92]	0.238
Prior mastectomy					
Interaction test	**p = 0.111**				
Yes	58 / 769 (7.5)	29 / 745 (3.9)	1.94	[1.26; 2.99]	0.003
No	17 / 339 (5.0)	16 / 325 (4.9)	1.02	[0.52; 1.98]	0.957
Prior radiotherapy					
Interaction test	**p = 0.124**				
Yes	65 / 1011 (6.4)	35 / 987 (3.5)	1.81	[1.21; 2.71]	0.004
No	10 / 97 (10.3)	10 / 83 (12.0)	0.86	[0.37; 1.95]	0.712

N: Number of patients
n: Number of patients with event
CI: Confidence interval
RR: Relative risk
ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
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Analysis method for interaction test:
p-value from logistic regression model.
logit(proportion) = treatment + subgroup factor + treatment * subgroup factor

Analysis method for within subgroup analysis:
RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm.
ET was the reference group for treatment group comparison.

Table 5-3.2.86 SOC ear and labyrinth disorders: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	ET (N = 1070)	RR	[95% CI]	p-value
Ear and labyrinth disorders					
	n / N (%)	n / N (%)			
Region					
Interaction test	**p = 0.991**				
NA/WE/O	47 / 640 (7.3)	31 / 627 (4.9)	1.49	[0.96; 2.31]	0.078
ROW	16 / 468 (3.4)	10 / 443 (2.3)	1.51	[0.69; 3.30]	0.297
Geographical region					
Interaction test	**p = 0.652**				
Europe	35 / 654 (5.4)	25 / 638 (3.9)	1.37	[0.83; 2.26]	0.223
North America/Australia	21 / 213 (9.9)	10 / 194 (5.2)	1.91	[0.92; 3.96]	0.081
Asia	7 / 178 (3.9)	3 / 168 (1.8)	2.20	[0.58; 8.38]	0.247
Latin America	0 / 63 (0.0)	3 / 70 (4.3)	0.16	[<0.01; 3.01]	0.220
Age group 1 at randomization					
Interaction test	**p = 0.157**				
<45	30 / 549 (5.5)	13 / 496 (2.6)	2.08	[1.10; 3.95]	0.024
45 to 54	32 / 539 (5.9)	28 / 546 (5.1)	1.16	[0.71; 1.90]	0.560
55 to 64	1 / 20 (5.0)	0 / 28 (0.0)	4.14	[0.18; 96.77]	0.377
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)					
Interaction test	**p = 0.190**				
<Median	30 / 549 (5.5)	13 / 496 (2.6)	2.08	[1.10; 3.95]	0.024
≥Median	33 / 559 (5.9)	28 / 574 (4.9)	1.21	[0.74; 1.98]	0.445
Race					
Interaction test	**p = 0.191**				
Asian	13 / 211 (6.2)	4 / 186 (2.2)	2.86	[0.95; 8.63]	0.061
Non-Asian	49 / 840 (5.8)	37 / 827 (4.5)	1.30	[0.86; 1.98]	0.211
BMI at screening					
Interaction test	**p = 0.024**				
≥25	29 / 551 (5.3)	28 / 523 (5.4)	0.98	[0.59; 1.63]	0.947
<25	31 / 542 (5.7)	12 / 535 (2.2)	2.55	[1.32; 4.91]	0.005
AJCC Anatomic Stage Group					
Interaction test	**p = 0.395**				
Group I/II	26 / 417 (6.2)	21 / 418 (5.0)	1.24	[0.71; 2.17]	0.449
Group III	37 / 691 (5.4)	20 / 652 (3.1)	1.75	[1.02; 2.98]	0.041

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Anatomic stages					
Interaction test	**p = 0.637**				
IA/IB/IIA	6 / 171 (3.5)	8 / 198 (4.0)	0.87	[0.31; 2.45]	0.790
IIB	20 / 246 (8.1)	13 / 220 (5.9)	1.38	[0.70; 2.70]	0.354
IIIA	25 / 451 (5.5)	15 / 393 (3.8)	1.45	[0.78; 2.72]	0.242
IIIB	2 / 67 (3.0)	0 / 59 (0.0)	4.41	[0.22; 90.08]	0.335
IIIC	10 / 173 (5.8)	5 / 200 (2.5)	2.31	[0.81; 6.63]	0.119
Nodal status					
Interaction test	**p = 0.155**				
N0	1 / 91 (1.1)	4 / 117 (3.4)	0.32	[0.04; 2.83]	0.306
N1-N3	62 / 1017 (6.1)	37 / 950 (3.9)	1.57	[1.05; 2.33]	0.027
Histological grade at time of surgery					
Interaction test	**p = 0.541**				
Grade 1	8 / 110 (7.3)	2 / 100 (2.0)	3.64	[0.79; 16.72]	0.097
Grade 2	40 / 604 (6.6)	25 / 601 (4.2)	1.59	[0.98; 2.59]	0.061
Grade 3	14 / 297 (4.7)	9 / 266 (3.4)	1.39	[0.61; 3.17]	0.429
Histological subtype					
Interaction test	**p = 0.123**				
Ductal	52 / 863 (6.0)	30 / 835 (3.6)	1.68	[1.08; 2.60]	0.021
Lobular	10 / 172 (5.8)	6 / 169 (3.6)	1.64	[0.61; 4.41]	0.329
Other	1 / 73 (1.4)	5 / 66 (7.6)	0.18	[0.02; 1.51]	0.114
Ki67 status from surgical specimen					
Interaction test	**p = 0.224**				
Ki67≤20	29 / 527 (5.5)	19 / 552 (3.4)	1.60	[0.91; 2.82]	0.104
Ki67>20	19 / 422 (4.5)	18 / 378 (4.8)	0.95	[0.50; 1.77]	0.861
Type of NSAI					
Interaction test	**p = 0.530**				
Letrozole	40 / 809 (4.9)	28 / 773 (3.6)	1.37	[0.85; 2.19]	0.197
Anastrozole	23 / 299 (7.7)	13 / 297 (4.4)	1.76	[0.91; 3.40]	0.094
Prior neo/adjuvant chemotherapy					
Interaction test	**p = 0.205**				
Yes	61 / 1029 (5.9)	37 / 987 (3.7)	1.58	[1.06; 2.36]	0.024
No	2 / 79 (2.5)	4 / 83 (4.8)	0.53	[0.10; 2.79]	0.450
Prior adjuvant chemotherapy					
Interaction test	**p = 0.399**				
Yes	29 / 513 (5.7)	22 / 488 (4.5)	1.25	[0.73; 2.15]	0.412
No	34 / 595 (5.7)	19 / 582 (3.3)	1.75	[1.01; 3.03]	0.046
Prior neoadjuvant chemotherapy					
Interaction test	**p = 0.170**				
Yes	34 / 546 (6.2)	17 / 538 (3.2)	1.97	[1.11; 3.48]	0.020
No	29 / 562 (5.2)	24 / 532 (4.5)	1.14	[0.67; 1.94]	0.618

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Prior endocrine therapy					
Interaction test	**p = 0.489**				
Yes	45 / 853 (5.3)	25 / 789 (3.2)	1.66	[1.03; 2.69]	0.037
No	18 / 255 (7.1)	16 / 281 (5.7)	1.24	[0.65; 2.38]	0.518
Prior mastectomy					
Interaction test	**p = 0.715**				
Yes	42 / 769 (5.5)	26 / 745 (3.5)	1.56	[0.97; 2.53]	0.067
No	21 / 339 (6.2)	15 / 325 (4.6)	1.34	[0.70; 2.56]	0.371
Prior radiotherapy					
Interaction test	**p = 0.192**				
Yes	58 / 1011 (5.7)	35 / 987 (3.5)	1.62	[1.07; 2.44]	0.022
No	5 / 97 (5.2)	6 / 83 (7.2)	0.71	[0.23; 2.25]	0.564

N: Number of patients
n: Number of patients with event
CI: Confidence interval
RR: Relative risk
ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
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Analysis method for interaction test:
p-value from logistic regression model.
logit(proportion) = treatment + subgroup factor + treatment * subgroup factor

Analysis method for within subgroup analysis:
RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm.
ET was the reference group for treatment group comparison.

5-3.3 Subgroup analysis for grade ≥3 adverse events by SOC and PT

Table 5-3.3.1 SOC blood and lymphatic system disorders: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	ET (N = 1070)	RR	[95% CI]	p-value
Blood and lymphatic system disorders					
	n / N (%)	n / N (%)			
Region					
Interaction test	**p = 0.170**				
NA/WE/O	190 / 640 (29.7)	4 / 627 (0.6)	46.54	[17.39; >99.99]	<.001
ROW	158 / 468 (33.8)	8 / 443 (1.8)	18.69	[9.30; 37.58]	<.001
Geographical region					
Interaction test	**p = 0.144**				
Europe	253 / 654 (38.7)	7 / 638 (1.1)	35.26	[16.77; 74.12]	<.001
North America/Australia	51 / 213 (23.9)	1 / 194 (0.5)	46.45	[6.48; >99.99]	<.001
Asia	24 / 178 (13.5)	1 / 168 (0.6)	22.65	[3.10; >99.99]	0.002
Latin America	20 / 63 (31.7)	3 / 70 (4.3)	7.41	[2.31; 23.74]	<.001
Age group 1 at randomization					
Interaction test	**p = 0.345**				
<45	185 / 549 (33.7)	8 / 496 (1.6)	20.89	[10.40; 41.96]	<.001
45 to 54	158 / 539 (29.3)	4 / 546 (0.7)	40.01	[14.94; >99.99]	<.001
55 to 64	5 / 20 (25.0)	0 / 28 (0.0)	15.19	[0.89; >99.99]	0.060
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)					
Interaction test	**p = 0.311**				
<Median	185 / 549 (33.7)	8 / 496 (1.6)	20.89	[10.40; 41.96]	<.001
≥Median	163 / 559 (29.2)	4 / 574 (0.7)	41.84	[15.62; >99.99]	<.001
Race					
Interaction test	**p = 0.992**				
Asian	37 / 211 (17.5)	1 / 186 (0.5)	32.62	[4.52; >99.99]	<.001
Non-Asian	289 / 840 (34.4)	11 / 827 (1.3)	25.87	[14.28; 46.87]	<.001
BMI at screening					
Interaction test	**p = 0.932**				
≥25	137 / 551 (24.9)	4 / 523 (0.8)	32.51	[12.12; 87.23]	<.001
<25	207 / 542 (38.2)	8 / 535 (1.5)	25.54	[12.73; 51.23]	<.001
AJCC Anatomic Stage Group					
Interaction test	**p = 0.137**				
Group I/II	125 / 417 (30.0)	7 / 418 (1.7)	17.90	[8.46; 37.86]	<.001
Group III	223 / 691 (32.3)	5 / 652 (0.8)	42.08	[17.46; >99.99]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Anatomic stages					
Interaction test	**p = 0.098**				
IA/IB/IIA	57 / 171 (33.3)	2 / 198 (1.0)	33.00	[8.18; >99.99]	<.001
IIB	68 / 246 (27.6)	5 / 220 (2.3)	12.16	[5.00; 29.61]	<.001
IIIA	143 / 451 (31.7)	1 / 393 (0.3)	>99.99	[17.51; >99.99]	<.001
IIIB	28 / 67 (41.8)	3 / 59 (5.1)	8.22	[2.63; 25.65]	<.001
IIIC	52 / 173 (30.1)	1 / 200 (0.5)	60.12	[8.40; >99.99]	<.001
Nodal status					
Interaction test	**p = 0.018**				
N0	34 / 91 (37.4)	5 / 117 (4.3)	8.74	[3.56; 21.46]	<.001
N1-N3	314 / 1017 (30.9)	7 / 950 (0.7)	41.90	[19.92; 88.16]	<.001
Histological grade at time of surgery					
Interaction test	**p = 0.405**				
Grade 1	33 / 110 (30.0)	1 / 100 (1.0)	30.00	[4.18; >99.99]	<.001
Grade 2	198 / 604 (32.8)	5 / 601 (0.8)	39.40	[16.34; 95.03]	<.001
Grade 3	77 / 297 (25.9)	4 / 266 (1.5)	17.24	[6.40; 46.46]	<.001
Histological subtype					
Interaction test	**p = 0.407**				
Ductal	272 / 863 (31.5)	11 / 835 (1.3)	23.92	[13.19; 43.39]	<.001
Lobular	57 / 172 (33.1)	1 / 169 (0.6)	56.01	[7.84; >99.99]	<.001
Other	19 / 73 (26.0)	0 / 66 (0.0)	35.31	[2.17; >99.99]	0.012
Ki67 status from surgical specimen					
Interaction test	**p = 0.059**				
Ki67≤20	149 / 527 (28.3)	9 / 552 (1.6)	17.34	[8.94; 33.62]	<.001
Ki67>20	153 / 422 (36.3)	2 / 378 (0.5)	68.52	[17.10; >99.99]	<.001
Type of NSAI					
Interaction test	**p = 0.628**				
Letrozole	256 / 809 (31.6)	8 / 773 (1.0)	30.58	[15.23; 61.37]	<.001
Anastrozole	92 / 299 (30.8)	4 / 297 (1.3)	22.85	[8.51; 61.37]	<.001
Prior neo/adjuvant chemotherapy					
Interaction test	**p = 0.364**				
Yes	321 / 1029 (31.2)	10 / 987 (1.0)	30.79	[16.51; 57.42]	<.001
No	27 / 79 (34.2)	2 / 83 (2.4)	14.18	[3.49; 57.68]	<.001
Prior adjuvant chemotherapy					
Interaction test	**p = 0.387**				
Yes	141 / 513 (27.5)	3 / 488 (0.6)	44.71	[14.34; >99.99]	<.001
No	207 / 595 (34.8)	9 / 582 (1.5)	22.50	[11.66; 43.42]	<.001
Prior neoadjuvant chemotherapy					
Interaction test	**p = 0.932**				
Yes	188 / 546 (34.4)	7 / 538 (1.3)	26.46	[12.56; 55.74]	<.001
No	160 / 562 (28.5)	5 / 532 (0.9)	30.29	[12.54; 73.19]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Prior endocrine therapy					
Interaction test	**p = 0.740**				
Yes	261 / 853 (30.6)	9 / 789 (1.1)	26.82	[13.90; 51.76]	<.001
No	87 / 255 (34.1)	3 / 281 (1.1)	31.96	[10.24; 99.76]	<.001
Prior mastectomy					
Interaction test	**p = 0.498**				
Yes	254 / 769 (33.0)	10 / 745 (1.3)	24.61	[13.19; 45.92]	<.001
No	94 / 339 (27.7)	2 / 325 (0.6)	45.06	[11.20; >99.99]	<.001
Prior radiotherapy					
Interaction test	**p = 0.748**				
Yes	309 / 1011 (30.6)	11 / 987 (1.1)	27.42	[15.13; 49.72]	<.001
No	39 / 97 (40.2)	1 / 83 (1.2)	33.37	[4.69; >99.99]	<.001

N: Number of patients
n: Number of patients with event
CI: Confidence interval
RR: Relative risk
ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
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Analysis method for interaction test:
p-value from logistic regression model.
logit(proportion) = treatment + subgroup factor + treatment * subgroup factor

Analysis method for within subgroup analysis:
RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm.
ET was the reference group for treatment group comparison.

Table 5-3.3.2 PT neutropenia: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	ET (N = 1070)	RR	[95% CI]	p-value
Neutropenia					
	n / N (%)	n / N (%)			
Region					
Interaction test	**p = 0.079**				
NA/WE/O	183 / 640 (28.6)	2 / 627 (0.3)	89.64	[22.35; >99.99]	<.001
ROW	152 / 468 (32.5)	7 / 443 (1.6)	20.55	[9.74; 43.36]	<.001
Geographical region					
Interaction test	**p = 0.012**				
Europe	245 / 654 (37.5)	6 / 638 (0.9)	39.83	[17.85; 88.88]	<.001
North America/Australia	49 / 213 (23.0)	0 / 194 (0.0)	90.21	[5.60; >99.99]	0.001
Asia	23 / 178 (12.9)	0 / 168 (0.0)	44.37	[2.72; >99.99]	0.008
Latin America	18 / 63 (28.6)	3 / 70 (4.3)	6.67	[2.06; 21.56]	0.002
Age group 1 at randomization					
Interaction test	**p = 0.909**				
<45	181 / 549 (33.0)	5 / 496 (1.0)	32.71	[13.56; 78.87]	<.001
45 to 54	150 / 539 (27.8)	4 / 546 (0.7)	37.99	[14.17; >99.99]	<.001
55 to 64	4 / 20 (20.0)	0 / 28 (0.0)	12.43	[0.71; >99.99]	0.085
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)					
Interaction test	**p = 0.867**				
<Median	181 / 549 (33.0)	5 / 496 (1.0)	32.71	[13.56; 78.87]	<.001
≥Median	154 / 559 (27.5)	4 / 574 (0.7)	39.53	[14.75; >99.99]	<.001
Race					
Interaction test	**N.E.**				
Asian	36 / 211 (17.1)	0 / 186 (0.0)	64.39	[3.98; >99.99]	0.003
Non-Asian	278 / 840 (33.1)	9 / 827 (1.1)	30.41	[15.77; 58.65]	<.001
BMI at screening					
Interaction test	**p = 0.495**				
≥25	128 / 551 (23.2)	2 / 523 (0.4)	60.75	[15.11; >99.99]	<.001
<25	203 / 542 (37.5)	7 / 535 (1.3)	28.63	[13.60; 60.23]	<.001
AJCC Anatomic Stage Group					
Interaction test	**p = 0.265**				
Group I/II	121 / 417 (29.0)	5 / 418 (1.2)	24.26	[10.02; 58.72]	<.001
Group III	214 / 691 (31.0)	4 / 652 (0.6)	50.48	[18.88; >99.99]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Anatomic stages					
Interaction test	**p = 0.063**				
IA/IB/IIA	56 / 171 (32.7)	1 / 198 (0.5)	64.84	[9.07; >99.99]	<.001
IIB	65 / 246 (26.4)	4 / 220 (1.8)	14.53	[5.38; 39.23]	<.001
IIIA	139 / 451 (30.8)	1 / 393 (0.3)	>99.99	[17.02; >99.99]	<.001
IIIB	25 / 67 (37.3)	3 / 59 (5.1)	7.34	[2.33; 23.07]	<.001
IIIC	50 / 173 (28.9)	0 / 200 (0.0)	>99.99	[7.25; >99.99]	<.001
Nodal status					
Interaction test	**p = 0.030**				
N0	34 / 91 (37.4)	4 / 117 (3.4)	10.93	[4.02; 29.68]	<.001
N1-N3	301 / 1017 (29.6)	5 / 950 (0.5)	56.23	[23.34; >99.99]	<.001
Histological grade at time of surgery					
Interaction test	**p = 0.826**				
Grade 1	33 / 110 (30.0)	1 / 100 (1.0)	30.00	[4.18; >99.99]	<.001
Grade 2	190 / 604 (31.5)	4 / 601 (0.7)	47.26	[17.67; >99.99]	<.001
Grade 3	72 / 297 (24.2)	2 / 266 (0.8)	32.24	[7.99; >99.99]	<.001
Histological subtype					
Interaction test	**p = 0.583**				
Ductal	261 / 863 (30.2)	8 / 835 (1.0)	31.57	[15.72; 63.38]	<.001
Lobular	56 / 172 (32.6)	1 / 169 (0.6)	55.02	[7.70; >99.99]	<.001
Other	18 / 73 (24.7)	0 / 66 (0.0)	33.50	[2.06; >99.99]	0.014
Ki67 status from surgical specimen					
Interaction test	**p = 0.131**				
Ki67≤20	144 / 527 (27.3)	7 / 552 (1.3)	21.55	[10.19; 45.58]	<.001
Ki67>20	147 / 422 (34.8)	2 / 378 (0.5)	65.84	[16.42; >99.99]	<.001
Type of NSAI					
Interaction test	**p = 0.278**				
Letrozole	245 / 809 (30.3)	5 / 773 (0.6)	46.82	[19.42; >99.99]	<.001
Anastrozole	90 / 299 (30.1)	4 / 297 (1.3)	22.35	[8.32; 60.06]	<.001
Prior neo/adjuvant chemotherapy					
Interaction test	**p = 0.217**				
Yes	308 / 1029 (29.9)	7 / 987 (0.7)	42.20	[20.05; 88.82]	<.001
No	27 / 79 (34.2)	2 / 83 (2.4)	14.18	[3.49; 57.68]	<.001
Prior adjuvant chemotherapy					
Interaction test	**p = 0.356**				
Yes	136 / 513 (26.5)	2 / 488 (0.4)	64.69	[16.10; >99.99]	<.001
No	199 / 595 (33.4)	7 / 582 (1.2)	27.81	[13.20; 58.57]	<.001
Prior neoadjuvant chemotherapy					
Interaction test	**p = 0.951**				
Yes	180 / 546 (33.0)	5 / 538 (0.9)	35.47	[14.70; 85.57]	<.001
No	155 / 562 (27.6)	4 / 532 (0.8)	36.68	[13.69; 98.27]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Prior endocrine therapy					
Interaction test	**p = 0.757**				
Yes	253 / 853 (29.7)	6 / 789 (0.8)	39.00	[17.46; 87.13]	<.001
No	82 / 255 (32.2)	3 / 281 (1.1)	30.12	[9.64; 94.14]	<.001
Prior mastectomy					
Interaction test	**p = 0.352**				
Yes	245 / 769 (31.9)	8 / 745 (1.1)	29.67	[14.78; 59.56]	<.001
No	90 / 339 (26.5)	1 / 325 (0.3)	86.28	[12.09; >99.99]	<.001
Prior radiotherapy					
Interaction test	**N.E.**				
Yes	296 / 1011 (29.3)	9 / 987 (0.9)	32.11	[16.64; 61.96]	<.001
No	39 / 97 (40.2)	0 / 83 (0.0)	67.71	[4.23; >99.99]	0.003

N: Number of patients
n: Number of patients with event
N.E.: Not estimable
CI: Confidence interval
RR: Relative risk
ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
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Analysis method for interaction test:
p-value from logistic regression model.
logit(proportion) = treatment + subgroup factor + treatment * subgroup factor

Analysis method for within subgroup analysis:
RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm.
ET was the reference group for treatment group comparison.

Table 5-3.3.3 PT leukopenia: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	ET (N = 1070)	RR	[95% CI]	p-value
Leukopenia					
	n / N (%)	n / N (%)			
Region					
Interaction test	N.E.				
NA/WE/O	15 / 640 (2.3)	0 / 627 (0.0)	30.37	[1.82; >99.99]	0.017
ROW	23 / 468 (4.9)	1 / 443 (0.2)	21.77	[2.95; >99.99]	0.003
Geographical region					
Interaction test	N.E.				
Europe	32 / 654 (4.9)	1 / 638 (0.2)	31.22	[4.28; >99.99]	<.001
North America/Australia	3 / 213 (1.4)	0 / 194 (0.0)	6.38	[0.33; >99.99]	0.219
Asia	1 / 178 (0.6)	0 / 168 (0.0)	2.83	[0.12; 69.05]	0.523
Latin America	2 / 63 (3.2)	0 / 70 (0.0)	5.55	[0.27; >99.99]	0.266
Age group 1 at randomization					
Interaction test	N.E.				
<45	18 / 549 (3.3)	0 / 496 (0.0)	33.43	[2.02; >99.99]	0.014
45 to 54	20 / 539 (3.7)	1 / 546 (0.2)	20.26	[2.73; >99.99]	0.003
55 to 64	0 / 20 (0.0)	0 / 28 (0.0)	N.E.	N.E.	N.E.
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)					
Interaction test	N.E.				
<Median	18 / 549 (3.3)	0 / 496 (0.0)	33.43	[2.02; >99.99]	0.014
≥Median	20 / 559 (3.6)	1 / 574 (0.2)	20.54	[2.77; >99.99]	0.003
Race					
Interaction test	N.E.				
Asian	1 / 211 (0.5)	0 / 186 (0.0)	2.65	[0.11; 64.57]	0.550
Non-Asian	34 / 840 (4.0)	1 / 827 (0.1)	33.47	[4.59; >99.99]	<.001
BMI at screening					
Interaction test	N.E.				
≥25	14 / 551 (2.5)	0 / 523 (0.0)	27.53	[1.65; >99.99]	0.021
<25	24 / 542 (4.4)	1 / 535 (0.2)	23.69	[3.22; >99.99]	0.002
AJCC Anatomic Stage Group					
Interaction test	N.E.				
Group I/II	10 / 417 (2.4)	0 / 418 (0.0)	21.05	[1.24; >99.99]	0.035
Group III	28 / 691 (4.1)	1 / 652 (0.2)	26.42	[3.61; >99.99]	0.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Anatomic stages					
Interaction test	**N.E.**				
IA/IB/IIA	2 / 171 (1.2)	0 / 198 (0.0)	5.78	[0.28; >99.99]	0.256
IIB	8 / 246 (3.3)	0 / 220 (0.0)	15.21	[0.88; >99.99]	0.061
IIIA	21 / 451 (4.7)	0 / 393 (0.0)	37.48	[2.28; >99.99]	0.011
IIIB	6 / 67 (9.0)	1 / 59 (1.7)	5.28	[0.65; 42.63]	0.118
IIIC	1 / 173 (0.6)	0 / 200 (0.0)	3.47	[0.14; 84.52]	0.446
Nodal status					
Interaction test	**N.E.**				
N0	3 / 91 (3.3)	0 / 117 (0.0)	8.98	[0.47; >99.99]	0.145
N1-N3	35 / 1017 (3.4)	1 / 950 (0.1)	32.69	[4.49; >99.99]	<.001
Histological grade at time of surgery					
Interaction test	**N.E.**				
Grade 1	3 / 110 (2.7)	0 / 100 (0.0)	6.37	[0.33; >99.99]	0.219
Grade 2	26 / 604 (4.3)	1 / 601 (0.2)	25.87	[3.52; >99.99]	0.001
Grade 3	6 / 297 (2.0)	0 / 266 (0.0)	11.65	[0.66; >99.99]	0.094
Histological subtype					
Interaction test	**N.E.**				
Ductal	28 / 863 (3.2)	0 / 835 (0.0)	55.15	[3.37; >99.99]	0.005
Lobular	6 / 172 (3.5)	1 / 169 (0.6)	5.90	[0.72; 48.45]	0.099
Other	4 / 73 (5.5)	0 / 66 (0.0)	8.15	[0.45; >99.99]	0.157
Ki67 status from surgical specimen					
Interaction test	**N.E.**				
Ki67≤20	21 / 527 (4.0)	1 / 552 (0.2)	22.00	[2.97; >99.99]	0.002
Ki67>20	15 / 422 (3.6)	0 / 378 (0.0)	27.78	[1.67; >99.99]	0.021
Type of NSAI					
Interaction test	**N.E.**				
Letrozole	26 / 809 (3.2)	0 / 773 (0.0)	50.64	[3.09; >99.99]	0.006
Anastrozole	12 / 299 (4.0)	1 / 297 (0.3)	11.92	[1.56; 91.09]	0.017
Prior neo/adjuvant chemotherapy					
Interaction test	**N.E.**				
Yes	35 / 1029 (3.4)	1 / 987 (0.1)	33.57	[4.61; >99.99]	<.001
No	3 / 79 (3.8)	0 / 83 (0.0)	7.35	[0.39; >99.99]	0.185
Prior adjuvant chemotherapy					
Interaction test	**N.E.**				
Yes	11 / 513 (2.1)	0 / 488 (0.0)	21.88	[1.29; >99.99]	0.033
No	27 / 595 (4.5)	1 / 582 (0.2)	26.41	[3.60; >99.99]	0.001
Prior neoadjuvant chemotherapy					
Interaction test	**N.E.**				
Yes	26 / 546 (4.8)	1 / 538 (0.2)	25.62	[3.49; >99.99]	0.001
No	12 / 562 (2.1)	0 / 532 (0.0)	23.67	[1.40; >99.99]	0.028

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Prior endocrine therapy					
Interaction test	**N.E.**				
Yes	26 / 853 (3.0)	1 / 789 (0.1)	24.05	[3.27; >99.99]	0.002
No	12 / 255 (4.7)	0 / 281 (0.0)	27.54	[1.64; >99.99]	0.021
Prior mastectomy					
Interaction test	**N.E.**				
Yes	33 / 769 (4.3)	1 / 745 (0.1)	31.97	[4.38; >99.99]	<.001
No	5 / 339 (1.5)	0 / 325 (0.0)	10.55	[0.59; >99.99]	0.110
Prior radiotherapy					
Interaction test	**N.E.**				
Yes	34 / 1011 (3.4)	1 / 987 (0.1)	33.19	[4.55; >99.99]	<.001
No	4 / 97 (4.1)	0 / 83 (0.0)	7.71	[0.42; >99.99]	0.168

N: Number of patients
n: Number of patients with event
N.E.: Not estimable
CI: Confidence interval
RR: Relative risk
ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
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Analysis method for interaction test:
p-value from logistic regression model.
logit(proportion) = treatment + subgroup factor + treatment * subgroup factor

Analysis method for within subgroup analysis:
RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm.
ET was the reference group for treatment group comparison.

Table 5-3.3.4 SOC investigations: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	ET (N = 1070)	RR	[95% CI]	p-value
Investigations					
	n / N (%)	n / N (%)			
Region					
Interaction test	**p = 0.305**				
NA/WE/O	175 / 640 (27.3)	16 / 627 (2.6)	10.72	[6.50; 17.67]	<.001
ROW	160 / 468 (34.2)	22 / 443 (5.0)	6.88	[4.49; 10.54]	<.001
Geographical region					
Interaction test	**p = <.001**				
Europe	135 / 654 (20.6)	19 / 638 (3.0)	6.93	[4.34; 11.06]	<.001
North America/Australia	69 / 213 (32.4)	10 / 194 (5.2)	6.28	[3.33; 11.85]	<.001
Asia	119 / 178 (66.9)	5 / 168 (3.0)	22.46	[9.42; 53.59]	<.001
Latin America	12 / 63 (19.0)	4 / 70 (5.7)	3.33	[1.13; 9.81]	0.029
Age group 1 at randomization					
Interaction test	**p = 0.040**				
<45	170 / 549 (31.0)	21 / 496 (4.2)	7.31	[4.73; 11.32]	<.001
45 to 54	157 / 539 (29.1)	12 / 546 (2.2)	13.25	[7.46; 23.55]	<.001
55 to 64	8 / 20 (40.0)	5 / 28 (17.9)	2.24	[0.86; 5.84]	0.099
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)					
Interaction test	**p = 0.399**				
<Median	170 / 549 (31.0)	21 / 496 (4.2)	7.31	[4.73; 11.32]	<.001
≥Median	165 / 559 (29.5)	17 / 574 (3.0)	9.97	[6.13; 16.19]	<.001
Race					
Interaction test	**p = <.001**				
Asian	131 / 211 (62.1)	7 / 186 (3.8)	16.50	[7.92; 34.38]	<.001
Non-Asian	195 / 840 (23.2)	30 / 827 (3.6)	6.40	[4.41; 9.29]	<.001
BMI at screening					
Interaction test	**p = 0.069**				
≥25	133 / 551 (24.1)	19 / 523 (3.6)	6.64	[4.17; 10.58]	<.001
<25	196 / 542 (36.2)	18 / 535 (3.4)	10.75	[6.73; 17.16]	<.001
AJCC Anatomic Stage Group					
Interaction test	**p = 0.773**				
Group I/II	115 / 417 (27.6)	14 / 418 (3.3)	8.23	[4.81; 14.10]	<.001
Group III	220 / 691 (31.8)	24 / 652 (3.7)	8.65	[5.75; 13.00]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Anatomic stages					
Interaction test	**p = 0.743**				
IA/IB/IIA	46 / 171 (26.9)	8 / 198 (4.0)	6.66	[3.23; 13.71]	<.001
IIB	69 / 246 (28.0)	6 / 220 (2.7)	10.28	[4.56; 23.21]	<.001
IIIA	132 / 451 (29.3)	14 / 393 (3.6)	8.22	[4.82; 14.01]	<.001
IIIB	15 / 67 (22.4)	2 / 59 (3.4)	6.60	[1.58; 27.69]	0.010
IIIC	73 / 173 (42.2)	8 / 200 (4.0)	10.55	[5.23; 21.26]	<.001
Nodal status					
Interaction test	**p = 0.385**				
N0	25 / 91 (27.5)	2 / 117 (1.7)	16.07	[3.91; 66.09]	<.001
N1-N3	310 / 1017 (30.5)	36 / 950 (3.8)	8.04	[5.76; 11.23]	<.001
Histological grade at time of surgery					
Interaction test	**p = 0.459**				
Grade 1	31 / 110 (28.2)	1 / 100 (1.0)	28.18	[3.92; >99.99]	<.001
Grade 2	194 / 604 (32.1)	21 / 601 (3.5)	9.19	[5.94; 14.21]	<.001
Grade 3	92 / 297 (31.0)	11 / 266 (4.1)	7.49	[4.10; 13.69]	<.001
Histological subtype					
Interaction test	**p = 0.666**				
Ductal	254 / 863 (29.4)	31 / 835 (3.7)	7.93	[5.53; 11.37]	<.001
Lobular	54 / 172 (31.4)	5 / 169 (3.0)	10.61	[4.35; 25.87]	<.001
Other	27 / 73 (37.0)	2 / 66 (3.0)	12.21	[3.02; 49.36]	<.001
Ki67 status from surgical specimen					
Interaction test	**p = 0.164**				
Ki67≤20	189 / 527 (35.9)	19 / 552 (3.4)	10.42	[6.60; 16.44]	<.001
Ki67>20	103 / 422 (24.4)	13 / 378 (3.4)	7.10	[4.05; 12.42]	<.001
Type of NSAI					
Interaction test	**p = 0.302**				
Letrozole	254 / 809 (31.4)	26 / 773 (3.4)	9.33	[6.31; 13.81]	<.001
Anastrozole	81 / 299 (27.1)	12 / 297 (4.0)	6.70	[3.74; 12.03]	<.001
Prior neo/adjuvant chemotherapy					
Interaction test	**p = 0.766**				
Yes	314 / 1029 (30.5)	36 / 987 (3.6)	8.37	[5.99; 11.68]	<.001
No	21 / 79 (26.6)	2 / 83 (2.4)	11.03	[2.67; 45.52]	<.001
Prior adjuvant chemotherapy					
Interaction test	**p = 0.972**				
Yes	165 / 513 (32.2)	19 / 488 (3.9)	8.26	[5.22; 13.06]	<.001
No	170 / 595 (28.6)	19 / 582 (3.3)	8.75	[5.52; 13.87]	<.001
Prior neoadjuvant chemotherapy					
Interaction test	**p = 0.259**				
Yes	160 / 546 (29.3)	22 / 538 (4.1)	7.17	[4.66; 11.01]	<.001
No	175 / 562 (31.1)	16 / 532 (3.0)	10.35	[6.29; 17.04]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Prior endocrine therapy					
Interaction test	**p = 0.032**				
Yes	265 / 853 (31.1)	23 / 789 (2.9)	10.66	[7.04; 16.14]	<.001
No	70 / 255 (27.5)	15 / 281 (5.3)	5.14	[3.02; 8.75]	<.001
Prior mastectomy					
Interaction test	**p = 0.917**				
Yes	234 / 769 (30.4)	27 / 745 (3.6)	8.40	[5.71; 12.34]	<.001
No	101 / 339 (29.8)	11 / 325 (3.4)	8.80	[4.81; 16.09]	<.001
Prior radiotherapy					
Interaction test	**p = 0.028**				
Yes	311 / 1011 (30.8)	32 / 987 (3.2)	9.49	[6.67; 13.51]	<.001
No	24 / 97 (24.7)	6 / 83 (7.2)	3.42	[1.47; 7.97]	0.004

N: Number of patients
n: Number of patients with event
CI: Confidence interval
RR: Relative risk
ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
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Analysis method for interaction test:
p-value from logistic regression model.
logit(proportion) = treatment + subgroup factor + treatment * subgroup factor

Analysis method for within subgroup analysis:
RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm.
ET was the reference group for treatment group comparison.

Table 5-3.3.5 PT neutrophil count decreased: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	ET (N = 1070)	RR	[95% CI]	p-value
Neutrophil count decreased					
	n / N (%)	n / N (%)			
Region					
Interaction test	**N.E.**				
NA/WE/O	135 / 640 (21.1)	0 / 627 (0.0)	>99.99	[16.56; >99.99]	<.001
ROW	110 / 468 (23.5)	5 / 443 (1.1)	20.82	[8.58; 50.55]	<.001
Geographical region					
Interaction test	**p = 0.563**				
Europe	81 / 654 (12.4)	2 / 638 (0.3)	39.51	[9.76; >99.99]	<.001
North America/Australia	57 / 213 (26.8)	0 / 194 (0.0)	>99.99	[6.52; >99.99]	0.001
Asia	104 / 178 (58.4)	3 / 168 (1.8)	32.72	[10.59; >99.99]	<.001
Latin America	3 / 63 (4.8)	0 / 70 (0.0)	7.77	[0.41; >99.99]	0.172
Age group 1 at randomization					
Interaction test	**p = 0.235**				
<45	129 / 549 (23.5)	4 / 496 (0.8)	29.14	[10.85; 78.23]	<.001
45 to 54	113 / 539 (21.0)	1 / 546 (0.2)	>99.99	[16.04; >99.99]	<.001
55 to 64	3 / 20 (15.0)	0 / 28 (0.0)	9.67	[0.53; >99.99]	0.126
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)					
Interaction test	**p = 0.222**				
<Median	129 / 549 (23.5)	4 / 496 (0.8)	29.14	[10.85; 78.23]	<.001
≥Median	116 / 559 (20.8)	1 / 574 (0.2)	>99.99	[16.70; >99.99]	<.001
Race					
Interaction test	**p = 0.981**				
Asian	115 / 211 (54.5)	3 / 186 (1.6)	33.79	[10.92; >99.99]	<.001
Non-Asian	124 / 840 (14.8)	2 / 827 (0.2)	61.04	[15.15; >99.99]	<.001
BMI at screening					
Interaction test	**p = 0.606**				
≥25	85 / 551 (15.4)	1 / 523 (0.2)	80.68	[11.28; >99.99]	<.001
<25	155 / 542 (28.6)	4 / 535 (0.7)	38.25	[14.28; >99.99]	<.001
AJCC Anatomic Stage Group					
Interaction test	**p = 0.694**				
Group I/II	78 / 417 (18.7)	2 / 418 (0.5)	39.09	[9.67; >99.99]	<.001
Group III	167 / 691 (24.2)	3 / 652 (0.5)	52.52	[16.85; >99.99]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Anatomic stages					
Interaction test	**p = 0.487**				
IA/IB/IIA	30 / 171 (17.5)	0 / 198 (0.0)	70.58	[4.35; >99.99]	0.003
IIB	48 / 246 (19.5)	2 / 220 (0.9)	21.46	[5.28; 87.28]	<.001
IIIA	104 / 451 (23.1)	1 / 393 (0.3)	90.63	[12.71; >99.99]	<.001
IIIB	9 / 67 (13.4)	0 / 59 (0.0)	16.76	[1.00; >99.99]	0.050
IIIC	54 / 173 (31.2)	2 / 200 (1.0)	31.21	[7.72; >99.99]	<.001
Nodal status					
Interaction test	**N.E.**				
N0	17 / 91 (18.7)	0 / 117 (0.0)	44.89	[2.74; >99.99]	0.008
N1-N3	228 / 1017 (22.4)	5 / 950 (0.5)	42.60	[17.64; >99.99]	<.001
Histological grade at time of surgery					
Interaction test	**p = 0.376**				
Grade 1	26 / 110 (23.6)	0 / 100 (0.0)	48.23	[2.98; >99.99]	0.006
Grade 2	143 / 604 (23.7)	2 / 601 (0.3)	71.14	[17.70; >99.99]	<.001
Grade 3	66 / 297 (22.2)	2 / 266 (0.8)	29.56	[7.31; >99.99]	<.001
Histological subtype					
Interaction test	**p = 0.379**				
Ductal	191 / 863 (22.1)	4 / 835 (0.5)	46.20	[17.24; >99.99]	<.001
Lobular	36 / 172 (20.9)	0 / 169 (0.0)	71.73	[4.44; >99.99]	0.003
Other	18 / 73 (24.7)	1 / 66 (1.5)	16.27	[2.23; >99.99]	0.006
Ki67 status from surgical specimen					
Interaction test	**p = 0.463**				
Ki67≤20	148 / 527 (28.1)	3 / 552 (0.5)	51.67	[16.58; >99.99]	<.001
Ki67>20	68 / 422 (16.1)	2 / 378 (0.5)	30.45	[7.52; >99.99]	<.001
Type of NSAI					
Interaction test	**p = 0.854**				
Letrozole	187 / 809 (23.1)	4 / 773 (0.5)	44.67	[16.67; >99.99]	<.001
Anastrozole	58 / 299 (19.4)	1 / 297 (0.3)	57.61	[8.03; >99.99]	<.001
Prior neo/adjuvant chemotherapy					
Interaction test	**N.E.**				
Yes	236 / 1029 (22.9)	5 / 987 (0.5)	45.27	[18.75; >99.99]	<.001
No	9 / 79 (11.4)	0 / 83 (0.0)	19.95	[1.18; >99.99]	0.038
Prior adjuvant chemotherapy					
Interaction test	**p = 0.764**				
Yes	128 / 513 (25.0)	3 / 488 (0.6)	40.59	[13.01; >99.99]	<.001
No	117 / 595 (19.7)	2 / 582 (0.3)	57.22	[14.21; >99.99]	<.001
Prior neoadjuvant chemotherapy					
Interaction test	**p = 0.625**				
Yes	118 / 546 (21.6)	3 / 538 (0.6)	38.76	[12.40; >99.99]	<.001
No	127 / 562 (22.6)	2 / 532 (0.4)	60.11	[14.95; >99.99]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Prior endocrine therapy					
Interaction test	**p = 0.395**				
Yes	194 / 853 (22.7)	3 / 789 (0.4)	59.81	[19.20; >99.99]	<.001
No	51 / 255 (20.0)	2 / 281 (0.7)	28.10	[6.91; >99.99]	<.001
Prior mastectomy					
Interaction test	**p = 0.770**				
Yes	179 / 769 (23.3)	4 / 745 (0.5)	43.35	[16.18; >99.99]	<.001
No	66 / 339 (19.5)	1 / 325 (0.3)	63.27	[8.83; >99.99]	<.001
Prior radiotherapy					
Interaction test	**p = 0.003**				
Yes	234 / 1011 (23.1)	3 / 987 (0.3)	76.15	[24.47; >99.99]	<.001
No	11 / 97 (11.3)	2 / 83 (2.4)	4.71	[1.07; 20.63]	0.040

N: Number of patients
n: Number of patients with event
N.E.: Not estimable
CI: Confidence interval
RR: Relative risk
ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
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Analysis method for interaction test:
p-value from logistic regression model.
logit(proportion) = treatment + subgroup factor + treatment * subgroup factor

Analysis method for within subgroup analysis:
RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm.
ET was the reference group for treatment group comparison.

Table 5-3.3.6 PT alanine aminotransferase increased: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	ET (N = 1070)	RR	[95% CI]	p-value
Alanine aminotransferase increased					
	n / N (%)	n / N (%)			
Region					
Interaction test	**p = 0.796**				
NA/WE/O	33 / 640 (5.2)	6 / 627 (1.0)	5.39	[2.27; 12.77]	<.001
ROW	39 / 468 (8.3)	6 / 443 (1.4)	6.15	[2.63; 14.39]	<.001
Geographical region					
Interaction test	**p = 0.596**				
Europe	37 / 654 (5.7)	5 / 638 (0.8)	7.22	[2.86; 18.25]	<.001
North America/Australia	14 / 213 (6.6)	4 / 194 (2.1)	3.19	[1.07; 9.52]	0.038
Asia	13 / 178 (7.3)	1 / 168 (0.6)	12.27	[1.62; 92.77]	0.015
Latin America	8 / 63 (12.7)	2 / 70 (2.9)	4.44	[0.98; 20.15]	0.053
Age group 1 at randomization					
Interaction test	**p = 0.173**				
<45	31 / 549 (5.6)	8 / 496 (1.6)	3.50	[1.62; 7.54]	0.001
45 to 54	34 / 539 (6.3)	3 / 546 (0.5)	11.48	[3.55; 37.15]	<.001
55 to 64	7 / 20 (35.0)	1 / 28 (3.6)	9.80	[1.31; 73.52]	0.026
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)					
Interaction test	**p = 0.089**				
<Median	31 / 549 (5.6)	8 / 496 (1.6)	3.50	[1.62; 7.54]	0.001
≥Median	41 / 559 (7.3)	4 / 574 (0.7)	10.53	[3.80; 29.19]	<.001
Race					
Interaction test	**p = 0.565**				
Asian	15 / 211 (7.1)	3 / 186 (1.6)	4.41	[1.30; 14.99]	0.018
Non-Asian	55 / 840 (6.5)	8 / 827 (1.0)	6.77	[3.24; 14.12]	<.001
BMI at screening					
Interaction test	**p = 0.824**				
≥25	40 / 551 (7.3)	7 / 523 (1.3)	5.42	[2.45; 12.00]	<.001
<25	32 / 542 (5.9)	5 / 535 (0.9)	6.32	[2.48; 16.09]	<.001
AJCC Anatomic Stage Group					
Interaction test	**p = 0.354**				
Group I/II	33 / 417 (7.9)	4 / 418 (1.0)	8.27	[2.96; 23.14]	<.001
Group III	39 / 691 (5.6)	8 / 652 (1.2)	4.60	[2.17; 9.77]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Anatomic stages					
Interaction test	**p = 0.398**				
IA/IB/IIA	15 / 171 (8.8)	3 / 198 (1.5)	5.79	[1.70; 19.66]	0.005
IIB	18 / 246 (7.3)	1 / 220 (0.5)	16.10	[2.17; >99.99]	0.007
IIIA	22 / 451 (4.9)	6 / 393 (1.5)	3.20	[1.31; 7.80]	0.011
IIIB	2 / 67 (3.0)	0 / 59 (0.0)	4.41	[0.22; 90.08]	0.335
IIIC	15 / 173 (8.7)	2 / 200 (1.0)	8.67	[2.01; 37.38]	0.004
Nodal status					
Interaction test	**p = 0.551**				
N0	8 / 91 (8.8)	1 / 117 (0.9)	10.29	[1.31; 80.76]	0.027
N1-N3	64 / 1017 (6.3)	11 / 950 (1.2)	5.43	[2.88; 10.24]	<.001
Histological grade at time of surgery					
Interaction test	**p = 0.576**				
Grade 1	5 / 110 (4.5)	0 / 100 (0.0)	10.01	[0.56; >99.99]	0.117
Grade 2	40 / 604 (6.6)	6 / 601 (1.0)	6.63	[2.83; 15.53]	<.001
Grade 3	20 / 297 (6.7)	4 / 266 (1.5)	4.48	[1.55; 12.93]	0.006
Histological subtype					
Interaction test	**p = 0.983**				
Ductal	53 / 863 (6.1)	11 / 835 (1.3)	4.66	[2.45; 8.86]	<.001
Lobular	14 / 172 (8.1)	0 / 169 (0.0)	28.50	[1.71; >99.99]	0.020
Other	5 / 73 (6.8)	1 / 66 (1.5)	4.52	[0.54; 37.70]	0.163
Ki67 status from surgical specimen					
Interaction test	**p = 0.192**				
Ki67≤20	35 / 527 (6.6)	3 / 552 (0.5)	12.22	[3.78; 39.49]	<.001
Ki67>20	25 / 422 (5.9)	5 / 378 (1.3)	4.48	[1.73; 11.58]	0.002
Type of NSAI					
Interaction test	**p = 0.170**				
Letrozole	56 / 809 (6.9)	7 / 773 (0.9)	7.64	[3.51; 16.67]	<.001
Anastrozole	16 / 299 (5.4)	5 / 297 (1.7)	3.18	[1.18; 8.57]	0.022
Prior neo/adjuvant chemotherapy					
Interaction test	**p = 0.373**				
Yes	60 / 1029 (5.8)	11 / 987 (1.1)	5.23	[2.77; 9.89]	<.001
No	12 / 79 (15.2)	1 / 83 (1.2)	12.61	[1.68; 94.72]	0.014
Prior adjuvant chemotherapy					
Interaction test	**p = 0.614**				
Yes	31 / 513 (6.0)	6 / 488 (1.2)	4.91	[2.07; 11.68]	<.001
No	41 / 595 (6.9)	6 / 582 (1.0)	6.68	[2.86; 15.62]	<.001
Prior neoadjuvant chemotherapy					
Interaction test	**p = 0.400**				
Yes	32 / 546 (5.9)	7 / 538 (1.3)	4.50	[2.01; 10.12]	<.001
No	40 / 562 (7.1)	5 / 532 (0.9)	7.57	[3.01; 19.04]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Prior endocrine therapy					
Interaction test	**p = 0.718**				
Yes	53 / 853 (6.2)	9 / 789 (1.1)	5.45	[2.71; 10.97]	<.001
No	19 / 255 (7.5)	3 / 281 (1.1)	6.98	[2.09; 23.31]	0.002
Prior mastectomy					
Interaction test	**p = 0.898**				
Yes	41 / 769 (5.3)	7 / 745 (0.9)	5.67	[2.56; 12.57]	<.001
No	31 / 339 (9.1)	5 / 325 (1.5)	5.94	[2.34; 15.10]	<.001
Prior radiotherapy					
Interaction test	**p = 0.823**				
Yes	61 / 1011 (6.0)	10 / 987 (1.0)	5.96	[3.07; 11.56]	<.001
No	11 / 97 (11.3)	2 / 83 (2.4)	4.71	[1.07; 20.63]	0.040

N: Number of patients
n: Number of patients with event
CI: Confidence interval
RR: Relative risk
ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
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Analysis method for interaction test:
p-value from logistic regression model.
logit(proportion) = treatment + subgroup factor + treatment * subgroup factor

Analysis method for within subgroup analysis:
RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm.
ET was the reference group for treatment group comparison.

Table 5-3.3.7 PT white blood cell count decreased: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	ET (N = 1070)	RR	[95% CI]	p-value
White blood cell count decreased					
	n / N (%)	n / N (%)			
Region					
Interaction test	**p = 0.993**				
NA/WE/O	19 / 640 (3.0)	1 / 627 (0.2)	18.61	[2.50; >99.99]	0.004
ROW	37 / 468 (7.9)	2 / 443 (0.5)	17.51	[4.25; 72.23]	<.001
Geographical region					
Interaction test	**p = 0.539**				
Europe	14 / 654 (2.1)	1 / 638 (0.2)	13.66	[1.80; >99.99]	0.011
North America/Australia	8 / 213 (3.8)	1 / 194 (0.5)	7.29	[0.92; 57.73]	0.060
Asia	33 / 178 (18.5)	1 / 168 (0.6)	31.15	[4.31; >99.99]	<.001
Latin America	1 / 63 (1.6)	0 / 70 (0.0)	3.33	[0.14; 80.25]	0.459
Age group 1 at randomization					
Interaction test	**N.E.**				
<45	36 / 549 (6.6)	2 / 496 (0.4)	16.26	[3.94; 67.19]	<.001
45 to 54	20 / 539 (3.7)	0 / 546 (0.0)	41.53	[2.52; >99.99]	0.009
55 to 64	0 / 20 (0.0)	1 / 28 (3.6)	0.46	[0.02; 10.75]	0.629
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)					
Interaction test	**p = 0.872**				
<Median	36 / 549 (6.6)	2 / 496 (0.4)	16.26	[3.94; 67.19]	<.001
≥Median	20 / 559 (3.6)	1 / 574 (0.2)	20.54	[2.77; >99.99]	0.003
Race					
Interaction test	**p = 0.323**				
Asian	35 / 211 (16.6)	1 / 186 (0.5)	30.85	[4.27; >99.99]	<.001
Non-Asian	21 / 840 (2.5)	2 / 827 (0.2)	10.34	[2.43; 43.95]	0.002
BMI at screening					
Interaction test	**p = 0.898**				
≥25	17 / 551 (3.1)	1 / 523 (0.2)	16.14	[2.16; >99.99]	0.007
<25	37 / 542 (6.8)	2 / 535 (0.4)	18.26	[4.42; 75.39]	<.001
AJCC Anatomic Stage Group					
Interaction test	**p = 0.459**				
Group I/II	9 / 417 (2.2)	1 / 418 (0.2)	9.02	[1.15; 70.89]	0.037
Group III	47 / 691 (6.8)	2 / 652 (0.3)	22.17	[5.41; 90.92]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Anatomic stages					
Interaction test	**p = 0.897**				
IA/IB/IIA	1 / 171 (0.6)	0 / 198 (0.0)	3.47	[0.14; 84.65]	0.445
IIB	8 / 246 (3.3)	1 / 220 (0.5)	7.15	[0.90; 56.75]	0.063
IIIA	31 / 451 (6.9)	0 / 393 (0.0)	54.92	[3.37; >99.99]	0.005
IIIB	2 / 67 (3.0)	0 / 59 (0.0)	4.41	[0.22; 90.08]	0.335
IIIC	14 / 173 (8.1)	2 / 200 (1.0)	8.09	[1.87; 35.11]	0.005
Nodal status					
Interaction test	**N.E.**				
N0	3 / 91 (3.3)	0 / 117 (0.0)	8.98	[0.47; >99.99]	0.145
N1-N3	53 / 1017 (5.2)	3 / 950 (0.3)	16.50	[5.17; 52.63]	<.001
Histological grade at time of surgery					
Interaction test	**p = 0.507**				
Grade 1	3 / 110 (2.7)	0 / 100 (0.0)	6.37	[0.33; >99.99]	0.219
Grade 2	35 / 604 (5.8)	1 / 601 (0.2)	34.83	[4.79; >99.99]	<.001
Grade 3	15 / 297 (5.1)	1 / 266 (0.4)	13.43	[1.79; >99.99]	0.012
Histological subtype					
Interaction test	**N.E.**				
Ductal	40 / 863 (4.6)	3 / 835 (0.4)	12.90	[4.01; 41.54]	<.001
Lobular	10 / 172 (5.8)	0 / 169 (0.0)	20.64	[1.22; >99.99]	0.036
Other	6 / 73 (8.2)	0 / 66 (0.0)	11.77	[0.68; >99.99]	0.091
Ki67 status from surgical specimen					
Interaction test	**N.E.**				
Ki67≤20	34 / 527 (6.5)	0 / 552 (0.0)	72.27	[4.44; >99.99]	0.003
Ki67>20	17 / 422 (4.0)	3 / 378 (0.8)	5.08	[1.50; 17.18]	0.009
Type of NSAI					
Interaction test	**p = 0.999**				
Letrozole	38 / 809 (4.7)	2 / 773 (0.3)	18.15	[4.39; 74.99]	<.001
Anastrozole	18 / 299 (6.0)	1 / 297 (0.3)	17.88	[2.40; >99.99]	0.005
Prior neo/adjuvant chemotherapy					
Interaction test	**N.E.**				
Yes	56 / 1029 (5.4)	3 / 987 (0.3)	17.90	[5.62; 57.01]	<.001
No	0 / 79 (0.0)	0 / 83 (0.0)	N.E.	N.E.	N.E.
Prior adjuvant chemotherapy					
Interaction test	**p = 0.491**				
Yes	26 / 513 (5.1)	2 / 488 (0.4)	12.37	[2.95; 51.82]	<.001
No	30 / 595 (5.0)	1 / 582 (0.2)	29.34	[4.01; >99.99]	<.001
Prior neoadjuvant chemotherapy					
Interaction test	**p = 0.409**				
Yes	32 / 546 (5.9)	1 / 538 (0.2)	31.53	[4.32; >99.99]	<.001
No	24 / 562 (4.3)	2 / 532 (0.4)	11.36	[2.70; 47.83]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Prior endocrine therapy					
Interaction test	**N.E.**				
Yes	46 / 853 (5.4)	3 / 789 (0.4)	14.18	[4.43; 45.42]	<.001
No	10 / 255 (3.9)	0 / 281 (0.0)	23.13	[1.36; >99.99]	0.030
Prior mastectomy					
Interaction test	**p = 0.150**				
Yes	42 / 769 (5.5)	1 / 745 (0.1)	40.69	[5.61; >99.99]	<.001
No	14 / 339 (4.1)	2 / 325 (0.6)	6.71	[1.54; 29.30]	0.011
Prior radiotherapy					
Interaction test	**N.E.**				
Yes	56 / 1011 (5.5)	2 / 987 (0.2)	27.34	[6.69; >99.99]	<.001
No	0 / 97 (0.0)	1 / 83 (1.2)	0.29	[0.01; 6.92]	0.441

N: Number of patients
n: Number of patients with event
N.E.: Not estimable
CI: Confidence interval
RR: Relative risk
ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
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Analysis method for interaction test:
p-value from logistic regression model.
logit(proportion) = treatment + subgroup factor + treatment * subgroup factor

Analysis method for within subgroup analysis:
RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm.
ET was the reference group for treatment group comparison.

Table 5-3.3.8 PT aspartate aminotransferase increased: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	ET (N = 1070)	RR	[95% CI]	p-value
Aspartate aminotransferase increased					
	n / N (%)	n / N (%)			
Region					
Interaction test	**p = 0.119**				
NA/WE/O	19 / 640 (3.0)	1 / 627 (0.2)	18.61	[2.50; >99.99]	0.004
ROW	24 / 468 (5.1)	7 / 443 (1.6)	3.25	[1.41; 7.46]	0.006
Geographical region					
Interaction test	**p = 0.679**				
Europe	25 / 654 (3.8)	5 / 638 (0.8)	4.88	[1.88; 12.66]	0.001
North America/Australia	7 / 213 (3.3)	0 / 194 (0.0)	13.67	[0.79; >99.99]	0.073
Asia	7 / 178 (3.9)	1 / 168 (0.6)	6.61	[0.82; 53.13]	0.076
Latin America	4 / 63 (6.3)	2 / 70 (2.9)	2.22	[0.42; 11.72]	0.347
Age group 1 at randomization					
Interaction test	**p = 0.624**				
<45	17 / 549 (3.1)	4 / 496 (0.8)	3.84	[1.30; 11.33]	0.015
45 to 54	22 / 539 (4.1)	4 / 546 (0.7)	5.57	[1.93; 16.06]	0.001
55 to 64	4 / 20 (20.0)	0 / 28 (0.0)	12.43	[0.71; >99.99]	0.085
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)					
Interaction test	**p = 0.463**				
<Median	17 / 549 (3.1)	4 / 496 (0.8)	3.84	[1.30; 11.33]	0.015
≥Median	26 / 559 (4.7)	4 / 574 (0.7)	6.67	[2.34; 19.00]	<.001
Race					
Interaction test	**p = 0.757**				
Asian	9 / 211 (4.3)	1 / 186 (0.5)	7.93	[1.01; 62.03]	0.048
Non-Asian	34 / 840 (4.0)	6 / 827 (0.7)	5.58	[2.35; 13.22]	<.001
BMI at screening					
Interaction test	**p = 0.991**				
≥25	22 / 551 (4.0)	4 / 523 (0.8)	5.22	[1.81; 15.05]	0.002
<25	21 / 542 (3.9)	4 / 535 (0.7)	5.18	[1.79; 15.00]	0.002
AJCC Anatomic Stage Group					
Interaction test	**p = 0.851**				
Group I/II	17 / 417 (4.1)	3 / 418 (0.7)	5.68	[1.68; 19.24]	0.005
Group III	26 / 691 (3.8)	5 / 652 (0.8)	4.91	[1.90; 12.70]	0.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Anatomic stages					
Interaction test	**p = 0.572**				
IA/IB/IIA	6 / 171 (3.5)	2 / 198 (1.0)	3.47	[0.71; 16.99]	0.124
IIB	11 / 246 (4.5)	1 / 220 (0.5)	9.84	[1.28; 75.58]	0.028
IIIA	14 / 451 (3.1)	4 / 393 (1.0)	3.05	[1.01; 9.19]	0.048
IIIB	2 / 67 (3.0)	0 / 59 (0.0)	4.41	[0.22; 90.08]	0.335
IIIC	10 / 173 (5.8)	1 / 200 (0.5)	11.56	[1.49; 89.40]	0.019
Nodal status					
Interaction test	**p = 0.138**				
N0	2 / 91 (2.2)	2 / 117 (1.7)	1.29	[0.18; 8.95]	0.800
N1-N3	41 / 1017 (4.0)	6 / 950 (0.6)	6.38	[2.72; 14.97]	<.001
Histological grade at time of surgery					
Interaction test	**N.E.**				
Grade 1	3 / 110 (2.7)	0 / 100 (0.0)	6.37	[0.33; >99.99]	0.219
Grade 2	27 / 604 (4.5)	7 / 601 (1.2)	3.84	[1.68; 8.75]	0.001
Grade 3	11 / 297 (3.7)	0 / 266 (0.0)	20.61	[1.22; >99.99]	0.036
Histological subtype					
Interaction test	**p = 0.938**				
Ductal	29 / 863 (3.4)	6 / 835 (0.7)	4.68	[1.95; 11.21]	<.001
Lobular	10 / 172 (5.8)	2 / 169 (1.2)	4.91	[1.09; 22.09]	0.038
Other	4 / 73 (5.5)	0 / 66 (0.0)	8.15	[0.45; >99.99]	0.157
Ki67 status from surgical specimen					
Interaction test	**p = 0.747**				
Ki67≤20	22 / 527 (4.2)	5 / 552 (0.9)	4.61	[1.76; 12.08]	0.002
Ki67>20	12 / 422 (2.8)	3 / 378 (0.8)	3.58	[1.02; 12.60]	0.047
Type of NSAI					
Interaction test	**p = 0.336**				
Letrozole	34 / 809 (4.2)	5 / 773 (0.6)	6.50	[2.55; 16.53]	<.001
Anastrozole	9 / 299 (3.0)	3 / 297 (1.0)	2.98	[0.81; 10.90]	0.099
Prior neo/adjuvant chemotherapy					
Interaction test	**N.E.**				
Yes	33 / 1029 (3.2)	8 / 987 (0.8)	3.96	[1.84; 8.52]	<.001
No	10 / 79 (12.7)	0 / 83 (0.0)	22.05	[1.31; >99.99]	0.032
Prior adjuvant chemotherapy					
Interaction test	**p = 0.046**				
Yes	19 / 513 (3.7)	7 / 488 (1.4)	2.58	[1.10; 6.09]	0.030
No	24 / 595 (4.0)	1 / 582 (0.2)	23.48	[3.19; >99.99]	0.002
Prior neoadjuvant chemotherapy					
Interaction test	**p = 0.437**				
Yes	15 / 546 (2.7)	4 / 538 (0.7)	3.70	[1.23; 11.06]	0.019
No	28 / 562 (5.0)	4 / 532 (0.8)	6.63	[2.34; 18.76]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Prior endocrine therapy					
Interaction test	**p = 0.260**				
Yes	32 / 853 (3.8)	4 / 789 (0.5)	7.40	[2.63; 20.83]	<.001
No	11 / 255 (4.3)	4 / 281 (1.4)	3.03	[0.98; 9.40]	0.055
Prior mastectomy					
Interaction test	**p = 0.315**				
Yes	24 / 769 (3.1)	6 / 745 (0.8)	3.88	[1.59; 9.43]	0.003
No	19 / 339 (5.6)	2 / 325 (0.6)	9.11	[2.14; 38.79]	0.003
Prior radiotherapy					
Interaction test	**p = 0.863**				
Yes	38 / 1011 (3.8)	7 / 987 (0.7)	5.30	[2.38; 11.81]	<.001
No	5 / 97 (5.2)	1 / 83 (1.2)	4.28	[0.51; 35.89]	0.180

N: Number of patients
n: Number of patients with event
N.E.: Not estimable
CI: Confidence interval
RR: Relative risk
ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
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Analysis method for interaction test:
p-value from logistic regression model.
logit(proportion) = treatment + subgroup factor + treatment * subgroup factor

Analysis method for within subgroup analysis:
RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm.
ET was the reference group for treatment group comparison.

Table 5-3.3.9 SOC infections and infestations: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	ET (N = 1070)	RR	[95% CI]	p-value
Infections and infestations					
	n / N (%)	n / N (%)			
Region					
Interaction test	**p = 0.770**				
NA/WE/O	37 / 640 (5.8)	20 / 627 (3.2)	1.81	[1.06; 3.09]	0.029
ROW	20 / 468 (4.3)	9 / 443 (2.0)	2.10	[0.97; 4.57]	0.060
Geographical region					
Interaction test	**p = 0.815**				
Europe	25 / 654 (3.8)	14 / 638 (2.2)	1.74	[0.91; 3.32]	0.092
North America/Australia	22 / 213 (10.3)	9 / 194 (4.6)	2.23	[1.05; 4.72]	0.037
Asia	7 / 178 (3.9)	5 / 168 (3.0)	1.32	[0.43; 4.08]	0.628
Latin America	3 / 63 (4.8)	1 / 70 (1.4)	3.33	[0.36; 31.23]	0.292
Age group 1 at randomization					
Interaction test	**p = 0.591**				
<45	30 / 549 (5.5)	11 / 496 (2.2)	2.46	[1.25; 4.86]	0.009
45 to 54	26 / 539 (4.8)	17 / 546 (3.1)	1.55	[0.85; 2.82]	0.152
55 to 64	1 / 20 (5.0)	1 / 28 (3.6)	1.40	[0.09; 21.08]	0.808
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)					
Interaction test	**p = 0.305**				
<Median	30 / 549 (5.5)	11 / 496 (2.2)	2.46	[1.25; 4.86]	0.009
≥Median	27 / 559 (4.8)	18 / 574 (3.1)	1.54	[0.86; 2.76]	0.148
Race					
Interaction test	**p = 0.849**				
Asian	10 / 211 (4.7)	5 / 186 (2.7)	1.76	[0.61; 5.06]	0.292
Non-Asian	46 / 840 (5.5)	23 / 827 (2.8)	1.97	[1.20; 3.22]	0.007
BMI at screening					
Interaction test	**p = 0.953**				
≥25	33 / 551 (6.0)	17 / 523 (3.3)	1.84	[1.04; 3.27]	0.037
<25	22 / 542 (4.1)	12 / 535 (2.2)	1.81	[0.90; 3.62]	0.094
AJCC Anatomic Stage Group					
Interaction test	**p = 0.191**				
Group I/II	21 / 417 (5.0)	7 / 418 (1.7)	3.01	[1.29; 7.00]	0.011
Group III	36 / 691 (5.2)	22 / 652 (3.4)	1.54	[0.92; 2.60]	0.101

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Anatomic stages					
Interaction test	**p = 0.694**				
IA/IB/IIA	11 / 171 (6.4)	3 / 198 (1.5)	4.25	[1.20; 14.97]	0.025
IIB	10 / 246 (4.1)	4 / 220 (1.8)	2.24	[0.71; 7.03]	0.168
IIIA	22 / 451 (4.9)	12 / 393 (3.1)	1.60	[0.80; 3.19]	0.183
IIIB	4 / 67 (6.0)	2 / 59 (3.4)	1.76	[0.33; 9.27]	0.504
IIIC	10 / 173 (5.8)	8 / 200 (4.0)	1.45	[0.58; 3.58]	0.426
Nodal status					
Interaction test	**N.E.**				
N0	9 / 91 (9.9)	0 / 117 (0.0)	24.37	[1.44; >99.99]	0.027
N1-N3	48 / 1017 (4.7)	29 / 950 (3.1)	1.55	[0.98; 2.43]	0.059
Histological grade at time of surgery					
Interaction test	**p = 0.513**				
Grade 1	3 / 110 (2.7)	1 / 100 (1.0)	2.73	[0.29; 25.80]	0.381
Grade 2	39 / 604 (6.5)	17 / 601 (2.8)	2.28	[1.31; 3.99]	0.004
Grade 3	13 / 297 (4.4)	9 / 266 (3.4)	1.29	[0.56; 2.98]	0.545
Histological subtype					
Interaction test	**p = 0.348**				
Ductal	41 / 863 (4.8)	24 / 835 (2.9)	1.65	[1.01; 2.71]	0.046
Lobular	13 / 172 (7.6)	3 / 169 (1.8)	4.26	[1.24; 14.67]	0.022
Other	3 / 73 (4.1)	2 / 66 (3.0)	1.36	[0.23; 7.87]	0.734
Ki67 status from surgical specimen					
Interaction test	**p = 0.828**				
Ki67≤20	26 / 527 (4.9)	11 / 552 (2.0)	2.48	[1.24; 4.96]	0.011
Ki67>20	27 / 422 (6.4)	11 / 378 (2.9)	2.20	[1.11; 4.37]	0.025
Type of NSAI					
Interaction test	**p = 0.753**				
Letrozole	38 / 809 (4.7)	20 / 773 (2.6)	1.82	[1.07; 3.09]	0.028
Anastrozole	19 / 299 (6.4)	9 / 297 (3.0)	2.10	[0.96; 4.56]	0.062
Prior neo/adjuvant chemotherapy					
Interaction test	**p = 0.653**				
Yes	54 / 1029 (5.2)	28 / 987 (2.8)	1.85	[1.18; 2.90]	0.007
No	3 / 79 (3.8)	1 / 83 (1.2)	3.15	[0.33; 29.67]	0.316
Prior adjuvant chemotherapy					
Interaction test	**p = 0.210**				
Yes	24 / 513 (4.7)	8 / 488 (1.6)	2.85	[1.29; 6.29]	0.009
No	33 / 595 (5.5)	21 / 582 (3.6)	1.54	[0.90; 2.62]	0.115
Prior neoadjuvant chemotherapy					
Interaction test	**p = 0.291**				
Yes	32 / 546 (5.9)	20 / 538 (3.7)	1.58	[0.91; 2.72]	0.102
No	25 / 562 (4.4)	9 / 532 (1.7)	2.63	[1.24; 5.58]	0.012

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Prior endocrine therapy					
Interaction test	**p = 0.457**				
Yes	41 / 853 (4.8)	22 / 789 (2.8)	1.72	[1.04; 2.87]	0.036
No	16 / 255 (6.3)	7 / 281 (2.5)	2.52	[1.05; 6.02]	0.038
Prior mastectomy					
Interaction test	**p = 0.825**				
Yes	50 / 769 (6.5)	26 / 745 (3.5)	1.86	[1.17; 2.96]	0.008
No	7 / 339 (2.1)	3 / 325 (0.9)	2.24	[0.58; 8.58]	0.240
Prior radiotherapy					
Interaction test	**N.E.**				
Yes	50 / 1011 (4.9)	29 / 987 (2.9)	1.68	[1.07; 2.64]	0.023
No	7 / 97 (7.2)	0 / 83 (0.0)	12.86	[0.75; >99.99]	0.079

N: Number of patients
n: Number of patients with event
N.E.: Not estimable
CI: Confidence interval
RR: Relative risk
ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
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Analysis method for interaction test:
p-value from logistic regression model.
logit(proportion) = treatment + subgroup factor + treatment * subgroup factor

Analysis method for within subgroup analysis:
RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm.
ET was the reference group for treatment group comparison.

Table 5-3.3.10 SOC gastrointestinal disorders: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	ET (N = 1070)	RR	[95% CI]	p-value
Gastrointestinal disorders					
	n / N (%)	n / N (%)			
Region					
Interaction test	**p = 0.435**				
NA/WE/O	15 / 640 (2.3)	7 / 627 (1.1)	2.10	[0.86; 5.11]	0.103
ROW	9 / 468 (1.9)	2 / 443 (0.5)	4.26	[0.93; 19.61]	0.063
Geographical region					
Interaction test	**p = 0.749**				
Europe	15 / 654 (2.3)	6 / 638 (0.9)	2.44	[0.95; 6.25]	0.063
North America/Australia	7 / 213 (3.3)	2 / 194 (1.0)	3.19	[0.67; 15.16]	0.145
Asia	1 / 178 (0.6)	1 / 168 (0.6)	0.94	[0.06; 14.97]	0.967
Latin America	1 / 63 (1.6)	0 / 70 (0.0)	3.33	[0.14; 80.25]	0.459
Age group 1 at randomization					
Interaction test	**p = 0.160**				
<45	10 / 549 (1.8)	6 / 496 (1.2)	1.51	[0.55; 4.11]	0.425
45 to 54	14 / 539 (2.6)	3 / 546 (0.5)	4.73	[1.37; 16.36]	0.014
55 to 64	0 / 20 (0.0)	0 / 28 (0.0)	N.E.	N.E.	N.E.
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)					
Interaction test	**p = 0.155**				
<Median	10 / 549 (1.8)	6 / 496 (1.2)	1.51	[0.55; 4.11]	0.425
≥Median	14 / 559 (2.5)	3 / 574 (0.5)	4.79	[1.38; 16.58]	0.013
Race					
Interaction test	**p = 0.659**				
Asian	2 / 211 (0.9)	1 / 186 (0.5)	1.76	[0.16; 19.29]	0.642
Non-Asian	22 / 840 (2.6)	7 / 827 (0.8)	3.09	[1.33; 7.20]	0.009
BMI at screening					
Interaction test	**p = 0.505**				
≥25	14 / 551 (2.5)	4 / 523 (0.8)	3.32	[1.10; 10.03]	0.033
<25	10 / 542 (1.8)	5 / 535 (0.9)	1.97	[0.68; 5.74]	0.211
AJCC Anatomic Stage Group					
Interaction test	**p = 0.277**				
Group I/II	10 / 417 (2.4)	2 / 418 (0.5)	5.01	[1.10; 22.74]	0.037
Group III	14 / 691 (2.0)	7 / 652 (1.1)	1.89	[0.77; 4.65]	0.167

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Anatomic stages					
Interaction test	**p = 0.413**				
IA/IB/IIA	1 / 171 (0.6)	1 / 198 (0.5)	1.16	[0.07; 18.37]	0.917
IIB	9 / 246 (3.7)	1 / 220 (0.5)	8.05	[1.03; 63.02]	0.047
IIIA	8 / 451 (1.8)	6 / 393 (1.5)	1.16	[0.41; 3.32]	0.779
IIIB	4 / 67 (6.0)	0 / 59 (0.0)	7.94	[0.44; >99.99]	0.162
IIIC	2 / 173 (1.2)	1 / 200 (0.5)	2.31	[0.21; 25.28]	0.492
Nodal status					
Interaction test	**N.E.**				
N0	1 / 91 (1.1)	0 / 117 (0.0)	3.85	[0.16; 93.36]	0.408
N1-N3	23 / 1017 (2.3)	9 / 950 (0.9)	2.39	[1.11; 5.13]	0.026
Histological grade at time of surgery					
Interaction test	**p = 0.262**				
Grade 1	1 / 110 (0.9)	1 / 100 (1.0)	0.91	[0.06; 14.34]	0.946
Grade 2	12 / 604 (2.0)	2 / 601 (0.3)	5.97	[1.34; 26.56]	0.019
Grade 3	8 / 297 (2.7)	5 / 266 (1.9)	1.43	[0.47; 4.33]	0.523
Histological subtype					
Interaction test	**p = 0.060**				
Ductal	21 / 863 (2.4)	5 / 835 (0.6)	4.06	[1.54; 10.73]	0.005
Lobular	3 / 172 (1.7)	4 / 169 (2.4)	0.74	[0.17; 3.24]	0.686
Other	0 / 73 (0.0)	0 / 66 (0.0)	N.E.	N.E.	N.E.
Ki67 status from surgical specimen					
Interaction test	**p = 0.810**				
Ki67≤20	10 / 527 (1.9)	4 / 552 (0.7)	2.62	[0.83; 8.30]	0.102
Ki67>20	12 / 422 (2.8)	5 / 378 (1.3)	2.15	[0.76; 6.05]	0.147
Type of NSAI					
Interaction test	**p = 0.198**				
Letrozole	19 / 809 (2.3)	5 / 773 (0.6)	3.63	[1.36; 9.68]	0.010
Anastrozole	5 / 299 (1.7)	4 / 297 (1.3)	1.24	[0.34; 4.58]	0.745
Prior neo/adjuvant chemotherapy					
Interaction test	**p = 0.968**				
Yes	19 / 1029 (1.8)	7 / 987 (0.7)	2.60	[1.10; 6.17]	0.030
No	5 / 79 (6.3)	2 / 83 (2.4)	2.63	[0.52; 13.15]	0.240
Prior adjuvant chemotherapy					
Interaction test	**p = 0.526**				
Yes	8 / 513 (1.6)	4 / 488 (0.8)	1.90	[0.58; 6.28]	0.291
No	16 / 595 (2.7)	5 / 582 (0.9)	3.13	[1.15; 8.49]	0.025
Prior neoadjuvant chemotherapy					
Interaction test	**p = 0.489**				
Yes	11 / 546 (2.0)	3 / 538 (0.6)	3.61	[1.01; 12.88]	0.048
No	13 / 562 (2.3)	6 / 532 (1.1)	2.05	[0.79; 5.36]	0.143

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Prior endocrine therapy					
Interaction test	**p = 0.589**				
Yes	19 / 853 (2.2)	6 / 789 (0.8)	2.93	[1.18; 7.30]	0.021
No	5 / 255 (2.0)	3 / 281 (1.1)	1.84	[0.44; 7.61]	0.402
Prior mastectomy					
Interaction test	**p = 0.881**				
Yes	18 / 769 (2.3)	7 / 745 (0.9)	2.49	[1.05; 5.93]	0.039
No	6 / 339 (1.8)	2 / 325 (0.6)	2.88	[0.58; 14.15]	0.194
Prior radiotherapy					
Interaction test	**N.E.**				
Yes	18 / 1011 (1.8)	9 / 987 (0.9)	1.95	[0.88; 4.33]	0.099
No	6 / 97 (6.2)	0 / 83 (0.0)	11.14	[0.64; >99.99]	0.099

N: Number of patients
n: Number of patients with event
N.E.: Not estimable
CI: Confidence interval
RR: Relative risk
ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
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Analysis method for interaction test:
p-value from logistic regression model.
logit(proportion) = treatment + subgroup factor + treatment * subgroup factor

Analysis method for within subgroup analysis:
RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm.
ET was the reference group for treatment group comparison.

Table 5-3.3.11 SOC general disorders and administration site conditions: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	ET (N = 1070)	RR	[95% CI]	p-value
General disorders and administration site conditions					
	n / N (%)	n / N (%)			
Region					
Interaction test	**p = 0.462**				
NA/WE/O	21 / 640 (3.3)	7 / 627 (1.1)	2.94	[1.26; 6.86]	0.013
ROW	3 / 468 (0.6)	2 / 443 (0.5)	1.42	[0.24; 8.46]	0.700
Geographical region					
Interaction test	**p = 0.342**				
Europe	18 / 654 (2.8)	5 / 638 (0.8)	3.51	[1.31; 9.40]	0.012
North America/Australia	5 / 213 (2.3)	3 / 194 (1.5)	1.52	[0.37; 6.27]	0.564
Asia	1 / 178 (0.6)	0 / 168 (0.0)	2.83	[0.12; 69.05]	0.523
Latin America	0 / 63 (0.0)	1 / 70 (1.4)	0.37	[0.02; 8.92]	0.540
Age group 1 at randomization					
Interaction test	**p = 0.098**				
<45	12 / 549 (2.2)	6 / 496 (1.2)	1.81	[0.68; 4.78]	0.233
45 to 54	12 / 539 (2.2)	1 / 546 (0.2)	12.16	[1.59; 93.16]	0.016
55 to 64	0 / 20 (0.0)	2 / 28 (7.1)	0.28	[0.01; 5.46]	0.398
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)					
Interaction test	**p = 0.313**				
<Median	12 / 549 (2.2)	6 / 496 (1.2)	1.81	[0.68; 4.78]	0.233
≥Median	12 / 559 (2.1)	3 / 574 (0.5)	4.11	[1.17; 14.48]	0.028
Race					
Interaction test	**p = 0.823**				
Asian	2 / 211 (0.9)	1 / 186 (0.5)	1.76	[0.16; 19.29]	0.642
Non-Asian	19 / 840 (2.3)	8 / 827 (1.0)	2.34	[1.03; 5.31]	0.042
BMI at screening					
Interaction test	**p = 0.189**				
≥25	10 / 551 (1.8)	6 / 523 (1.1)	1.58	[0.58; 4.32]	0.371
<25	14 / 542 (2.6)	3 / 535 (0.6)	4.61	[1.33; 15.94]	0.016
AJCC Anatomic Stage Group					
Interaction test	**p = 0.944**				
Group I/II	8 / 417 (1.9)	3 / 418 (0.7)	2.67	[0.71; 10.01]	0.144
Group III	16 / 691 (2.3)	6 / 652 (0.9)	2.52	[0.99; 6.39]	0.052

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Anatomic stages					
Interaction test	**p = 0.379**				
IA/IB/IIA	2 / 171 (1.2)	1 / 198 (0.5)	2.32	[0.21; 25.32]	0.491
IIB	6 / 246 (2.4)	2 / 220 (0.9)	2.68	[0.55; 13.16]	0.224
IIIA	13 / 451 (2.9)	3 / 393 (0.8)	3.78	[1.08; 13.15]	0.037
IIIB	2 / 67 (3.0)	0 / 59 (0.0)	4.41	[0.22; 90.08]	0.335
IIIC	1 / 173 (0.6)	3 / 200 (1.5)	0.39	[0.04; 3.67]	0.407
Nodal status					
Interaction test	**p = 0.613**				
N0	1 / 91 (1.1)	1 / 117 (0.9)	1.29	[0.08; 20.28]	0.858
N1-N3	23 / 1017 (2.3)	8 / 950 (0.8)	2.69	[1.21; 5.97]	0.015
Histological grade at time of surgery					
Interaction test	**p = 0.968**				
Grade 1	2 / 110 (1.8)	0 / 100 (0.0)	4.55	[0.22; 93.64]	0.326
Grade 2	14 / 604 (2.3)	5 / 601 (0.8)	2.79	[1.01; 7.69]	0.048
Grade 3	6 / 297 (2.0)	2 / 266 (0.8)	2.69	[0.55; 13.20]	0.224
Histological subtype					
Interaction test	**p = 0.743**				
Ductal	20 / 863 (2.3)	7 / 835 (0.8)	2.76	[1.18; 6.50]	0.020
Lobular	3 / 172 (1.7)	1 / 169 (0.6)	2.95	[0.31; 28.06]	0.347
Other	1 / 73 (1.4)	1 / 66 (1.5)	0.90	[0.06; 14.17]	0.943
Ki67 status from surgical specimen					
Interaction test	**p = 0.226**				
Ki67≤20	9 / 527 (1.7)	5 / 552 (0.9)	1.89	[0.64; 5.59]	0.253
Ki67>20	13 / 422 (3.1)	2 / 378 (0.5)	5.82	[1.32; 25.63]	0.020
Type of NSAI					
Interaction test	**p = 0.781**				
Letrozole	15 / 809 (1.9)	6 / 773 (0.8)	2.39	[0.93; 6.12]	0.070
Anastrozole	9 / 299 (3.0)	3 / 297 (1.0)	2.98	[0.81; 10.90]	0.099
Prior neo/adjuvant chemotherapy					
Interaction test	**N.E.**				
Yes	23 / 1029 (2.2)	9 / 987 (0.9)	2.45	[1.14; 5.27]	0.022
No	1 / 79 (1.3)	0 / 83 (0.0)	3.15	[0.13; 76.20]	0.480
Prior adjuvant chemotherapy					
Interaction test	**p = 0.972**				
Yes	11 / 513 (2.1)	4 / 488 (0.8)	2.62	[0.84; 8.16]	0.098
No	13 / 595 (2.2)	5 / 582 (0.9)	2.54	[0.91; 7.09]	0.074
Prior neoadjuvant chemotherapy					
Interaction test	**p = 0.816**				
Yes	12 / 546 (2.2)	5 / 538 (0.9)	2.36	[0.84; 6.67]	0.104
No	12 / 562 (2.1)	4 / 532 (0.8)	2.84	[0.92; 8.75]	0.069

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Prior endocrine therapy					
Interaction test	**p = 0.414**				
Yes	16 / 853 (1.9)	7 / 789 (0.9)	2.11	[0.87; 5.11]	0.097
No	8 / 255 (3.1)	2 / 281 (0.7)	4.41	[0.94; 20.56]	0.059
Prior mastectomy					
Interaction test	**p = 0.545**				
Yes	16 / 769 (2.1)	7 / 745 (0.9)	2.21	[0.92; 5.35]	0.077
No	8 / 339 (2.4)	2 / 325 (0.6)	3.83	[0.82; 17.92]	0.088
Prior radiotherapy					
Interaction test	**N.E.**				
Yes	21 / 1011 (2.1)	9 / 987 (0.9)	2.28	[1.05; 4.95]	0.038
No	3 / 97 (3.1)	0 / 83 (0.0)	6.00	[0.31; >99.99]	0.234

N: Number of patients
n: Number of patients with event
N.E.: Not estimable
CI: Confidence interval
RR: Relative risk
ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
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Analysis method for interaction test:
p-value from logistic regression model.
logit(proportion) = treatment + subgroup factor + treatment * subgroup factor

Analysis method for within subgroup analysis:
RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm.
ET was the reference group for treatment group comparison.

5-3.4 Subgroup analysis for serious adverse events by SOC and PT

Table 5-3.4.1 SOC infections and infestations: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	ET (N = 1070)	RR	[95% CI]	p-value
Infections and infestations					
	n / N (%)	n / N (%)			
Region					
Interaction test	**p = 0.658**				
NA/WE/O	28 / 640 (4.4)	15 / 627 (2.4)	1.83	[0.99; 3.39]	0.055
ROW	22 / 468 (4.7)	14 / 443 (3.2)	1.49	[0.77; 2.87]	0.236
Geographical region					
Interaction test	**p = 0.592**				
Europe	26 / 654 (4.0)	13 / 638 (2.0)	1.95	[1.01; 3.76]	0.046
North America/Australia	13 / 213 (6.1)	7 / 194 (3.6)	1.69	[0.69; 4.15]	0.251
Asia	8 / 178 (4.5)	8 / 168 (4.8)	0.94	[0.36; 2.46]	0.906
Latin America	3 / 63 (4.8)	1 / 70 (1.4)	3.33	[0.36; 31.23]	0.292
Age group 1 at randomization					
Interaction test	**p = 0.562**				
<45	25 / 549 (4.6)	10 / 496 (2.0)	2.26	[1.10; 4.66]	0.027
45 to 54	24 / 539 (4.5)	18 / 546 (3.3)	1.35	[0.74; 2.46]	0.326
55 to 64	1 / 20 (5.0)	1 / 28 (3.6)	1.40	[0.09; 21.08]	0.808
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)					
Interaction test	**p = 0.281**				
<Median	25 / 549 (4.6)	10 / 496 (2.0)	2.26	[1.10; 4.66]	0.027
≥Median	25 / 559 (4.5)	19 / 574 (3.3)	1.35	[0.75; 2.43]	0.313
Race					
Interaction test	**p = 0.212**				
Asian	9 / 211 (4.3)	8 / 186 (4.3)	0.99	[0.39; 2.52]	0.986
Non-Asian	40 / 840 (4.8)	20 / 827 (2.4)	1.97	[1.16; 3.34]	0.012
BMI at screening					
Interaction test	**p = 0.516**				
≥25	31 / 551 (5.6)	16 / 523 (3.1)	1.84	[1.02; 3.32]	0.043
<25	18 / 542 (3.3)	13 / 535 (2.4)	1.37	[0.68; 2.76]	0.384
AJCC Anatomic Stage Group					
Interaction test	**p = 0.286**				
Group I/II	19 / 417 (4.6)	8 / 418 (1.9)	2.38	[1.05; 5.38]	0.037
Group III	31 / 691 (4.5)	21 / 652 (3.2)	1.39	[0.81; 2.40]	0.232

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Anatomic stages					
Interaction test	**p = 0.842**				
IA/IB/IIA	8 / 171 (4.7)	4 / 198 (2.0)	2.32	[0.71; 7.56]	0.164
IIB	11 / 246 (4.5)	4 / 220 (1.8)	2.46	[0.79; 7.61]	0.119
IIIA	17 / 451 (3.8)	12 / 393 (3.1)	1.23	[0.60; 2.55]	0.570
IIIB	4 / 67 (6.0)	2 / 59 (3.4)	1.76	[0.33; 9.27]	0.504
IIIC	10 / 173 (5.8)	7 / 200 (3.5)	1.65	[0.64; 4.25]	0.298
Nodal status					
Interaction test	**p = 0.060**				
N0	8 / 91 (8.8)	1 / 117 (0.9)	10.29	[1.31; 80.76]	0.027
N1-N3	42 / 1017 (4.1)	28 / 950 (2.9)	1.40	[0.88; 2.24]	0.159
Histological grade at time of surgery					
Interaction test	**p = 0.861**				
Grade 1	3 / 110 (2.7)	2 / 100 (2.0)	1.36	[0.23; 7.99]	0.731
Grade 2	32 / 604 (5.3)	17 / 601 (2.8)	1.87	[1.05; 3.34]	0.033
Grade 3	13 / 297 (4.4)	8 / 266 (3.0)	1.46	[0.61; 3.46]	0.395
Histological subtype					
Interaction test	**p = 0.665**				
Ductal	37 / 863 (4.3)	24 / 835 (2.9)	1.49	[0.90; 2.47]	0.121
Lobular	10 / 172 (5.8)	4 / 169 (2.4)	2.46	[0.79; 7.68]	0.122
Other	3 / 73 (4.1)	1 / 66 (1.5)	2.71	[0.29; 25.44]	0.382
Ki67 status from surgical specimen					
Interaction test	**p = 0.950**				
Ki67≤20	24 / 527 (4.6)	12 / 552 (2.2)	2.09	[1.06; 4.15]	0.034
Ki67>20	24 / 422 (5.7)	10 / 378 (2.6)	2.15	[1.04; 4.44]	0.038
Type of NSAI					
Interaction test	**p = 0.989**				
Letrozole	35 / 809 (4.3)	20 / 773 (2.6)	1.67	[0.97; 2.87]	0.062
Anastrozole	15 / 299 (5.0)	9 / 297 (3.0)	1.66	[0.74; 3.72]	0.223
Prior neo/adjuvant chemotherapy					
Interaction test	**p = 0.568**				
Yes	47 / 1029 (4.6)	28 / 987 (2.8)	1.61	[1.02; 2.55]	0.042
No	3 / 79 (3.8)	1 / 83 (1.2)	3.15	[0.33; 29.67]	0.316
Prior adjuvant chemotherapy					
Interaction test	**p = 0.548**				
Yes	21 / 513 (4.1)	10 / 488 (2.0)	2.00	[0.95; 4.20]	0.068
No	29 / 595 (4.9)	19 / 582 (3.3)	1.49	[0.85; 2.63]	0.166
Prior neoadjuvant chemotherapy					
Interaction test	**p = 0.541**				
Yes	27 / 546 (4.9)	18 / 538 (3.3)	1.48	[0.82; 2.65]	0.190
No	23 / 562 (4.1)	11 / 532 (2.1)	1.98	[0.97; 4.02]	0.059

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Prior endocrine therapy					
Interaction test	**p = 0.945**				
Yes	36 / 853 (4.2)	20 / 789 (2.5)	1.66	[0.97; 2.85]	0.063
No	14 / 255 (5.5)	9 / 281 (3.2)	1.71	[0.75; 3.89]	0.198
Prior mastectomy					
Interaction test	**p = 0.581**				
Yes	45 / 769 (5.9)	25 / 745 (3.4)	1.74	[1.08; 2.81]	0.023
No	5 / 339 (1.5)	4 / 325 (1.2)	1.20	[0.32; 4.42]	0.786
Prior radiotherapy					
Interaction test	**p = 0.145**				
Yes	42 / 1011 (4.2)	28 / 987 (2.8)	1.46	[0.92; 2.34]	0.112
No	8 / 97 (8.2)	1 / 83 (1.2)	6.85	[0.87; 53.61]	0.067

N: Number of patients
n: Number of patients with event
CI: Confidence interval
RR: Relative risk
ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
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Analysis method for interaction test:
p-value from logistic regression model.
logit(proportion) = treatment + subgroup factor + treatment * subgroup factor

Analysis method for within subgroup analysis:
RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm.
ET was the reference group for treatment group comparison.

Table 5-3.4.2 SOC reproductive system and breast disorders: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	ET (N = 1070)	RR	[95% CI]	p-value
Reproductive system and breast disorders					
	n / N (%)	n / N (%)			
Region					
Interaction test	**p = 0.484**				
NA/WE/O	3 / 640 (0.5)	2 / 627 (0.3)	1.47	[0.25; 8.76]	0.673
ROW	13 / 468 (2.8)	4 / 443 (0.9)	3.08	[1.01; 9.36]	0.048
Geographical region					
Interaction test	**p = 0.325**				
Europe	13 / 654 (2.0)	3 / 638 (0.5)	4.23	[1.21; 14.76]	0.024
North America/Australia	0 / 213 (0.0)	1 / 194 (0.5)	0.30	[0.01; 7.41]	0.465
Asia	3 / 178 (1.7)	2 / 168 (1.2)	1.42	[0.24; 8.37]	0.701
Latin America	0 / 63 (0.0)	0 / 70 (0.0)	N.E.	N.E.	N.E.
Age group 1 at randomization					
Interaction test	**p = 0.060**				
<45	11 / 549 (2.0)	1 / 496 (0.2)	9.94	[1.29; 76.70]	0.028
45 to 54	5 / 539 (0.9)	5 / 546 (0.9)	1.01	[0.29; 3.48]	0.984
55 to 64	0 / 20 (0.0)	0 / 28 (0.0)	N.E.	N.E.	N.E.
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)					
Interaction test	**p = 0.062**				
<Median	11 / 549 (2.0)	1 / 496 (0.2)	9.94	[1.29; 76.70]	0.028
≥Median	5 / 559 (0.9)	5 / 574 (0.9)	1.03	[0.30; 3.53]	0.966
Race					
Interaction test	**p = 0.411**				
Asian	3 / 211 (1.4)	2 / 186 (1.1)	1.32	[0.22; 7.83]	0.758
Non-Asian	13 / 840 (1.5)	4 / 827 (0.5)	3.20	[1.05; 9.77]	0.041
BMI at screening					
Interaction test	**p = 0.274**				
≥25	7 / 551 (1.3)	1 / 523 (0.2)	6.64	[0.82; 53.82]	0.076
<25	9 / 542 (1.7)	5 / 535 (0.9)	1.78	[0.60; 5.27]	0.300
AJCC Anatomic Stage Group					
Interaction test	**p = 0.614**				
Group I/II	7 / 417 (1.7)	2 / 418 (0.5)	3.51	[0.73; 16.79]	0.116
Group III	9 / 691 (1.3)	4 / 652 (0.6)	2.12	[0.66; 6.86]	0.208
Anatomic stages					
The subgroup analysis is not presented as all subgroups have less than 10 events.					

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Nodal status					
Interaction test	**N.E.**				
N0	0 / 91 (0.0)	0 / 117 (0.0)	N.E.	N.E.	N.E.
N1-N3	16 / 1017 (1.6)	6 / 950 (0.6)	2.49	[0.98; 6.34]	0.055
Histological grade at time of surgery					
Interaction test	**p = 0.278**				
Grade 1	1 / 110 (0.9)	2 / 100 (2.0)	0.45	[0.04; 4.94]	0.517
Grade 2	8 / 604 (1.3)	4 / 601 (0.7)	1.99	[0.60; 6.57]	0.259
Grade 3	5 / 297 (1.7)	0 / 266 (0.0)	9.86	[0.55; >99.99]	0.121
Histological subtype					
Interaction test	**p = 0.953**				
Ductal	11 / 863 (1.3)	4 / 835 (0.5)	2.66	[0.85; 8.32]	0.093
Lobular	3 / 172 (1.7)	1 / 169 (0.6)	2.95	[0.31; 28.06]	0.347
Other	2 / 73 (2.7)	1 / 66 (1.5)	1.81	[0.17; 19.48]	0.625
Ki67 status from surgical specimen					
Interaction test	**p = 0.987**				
Ki67≤20	7 / 527 (1.3)	2 / 552 (0.4)	3.67	[0.77; 17.57]	0.104
Ki67>20	8 / 422 (1.9)	2 / 378 (0.5)	3.58	[0.77; 16.77]	0.105
Type of NSAI					
Interaction test	**p = 0.822**				
Letrozole	10 / 809 (1.2)	4 / 773 (0.5)	2.39	[0.75; 7.58]	0.140
Anastrozole	6 / 299 (2.0)	2 / 297 (0.7)	2.98	[0.61; 14.65]	0.179
Prior neo/adjuvant chemotherapy					
Interaction test	**N.E.**				
Yes	14 / 1029 (1.4)	6 / 987 (0.6)	2.24	[0.86; 5.80]	0.097
No	2 / 79 (2.5)	0 / 83 (0.0)	5.25	[0.26; >99.99]	0.282
Prior adjuvant chemotherapy					
Interaction test	**p = 0.680**				
Yes	7 / 513 (1.4)	2 / 488 (0.4)	3.33	[0.70; 15.95]	0.132
No	9 / 595 (1.5)	4 / 582 (0.7)	2.20	[0.68; 7.11]	0.187
Prior neoadjuvant chemotherapy					
Interaction test	**p = 0.513**				
Yes	8 / 546 (1.5)	4 / 538 (0.7)	1.97	[0.60; 6.51]	0.266
No	8 / 562 (1.4)	2 / 532 (0.4)	3.79	[0.81; 17.75]	0.091
Prior endocrine therapy					
Interaction test	**N.E.**				
Yes	11 / 853 (1.3)	6 / 789 (0.8)	1.70	[0.63; 4.56]	0.296
No	5 / 255 (2.0)	0 / 281 (0.0)	12.12	[0.67; >99.99]	0.091
Prior mastectomy					
Interaction test	**p = 0.457**				
Yes	15 / 769 (2.0)	5 / 745 (0.7)	2.91	[1.06; 7.96]	0.038
No	1 / 339 (0.3)	1 / 325 (0.3)	0.96	[0.06; 15.26]	0.976

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Prior radiotherapy					
Interaction test	**N.E.**				
Yes	13 / 1011 (1.3)	6 / 987 (0.6)	2.12	[0.81; 5.54]	0.127
No	3 / 97 (3.1)	0 / 83 (0.0)	6.00	[0.31; >99.99]	0.234

N: Number of patients
n: Number of patients with event
N.E.: Not estimable
CI: Confidence interval
RR: Relative risk
ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
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Analysis method for interaction test:
p-value from logistic regression model.
logit(proportion) = treatment + subgroup factor + treatment * subgroup factor

Analysis method for within subgroup analysis:
RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm.
ET was the reference group for treatment group comparison.

5-3.5 Subgroup analysis for adverse events of special interest

Table 5-3.5.1 Hepatobiliary toxicity: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	ET (N = 1070)	RR	[95% CI]	p-value
Hepatobiliary toxicity					
	n / N (%)	n / N (%)			
Region					
Interaction test	**p = 0.548**				
NA/WE/O	117 / 640 (18.3)	56 / 627 (8.9)	2.05	[1.52; 2.76]	<.001
ROW	153 / 468 (32.7)	69 / 443 (15.6)	2.10	[1.63; 2.70]	<.001
Geographical region					
Interaction test	**p = 0.979**				
Europe	151 / 654 (23.1)	70 / 638 (11.0)	2.10	[1.62; 2.73]	<.001
North America/Australia	47 / 213 (22.1)	21 / 194 (10.8)	2.04	[1.27; 3.28]	0.003
Asia	53 / 178 (29.8)	25 / 168 (14.9)	2.00	[1.31; 3.06]	0.001
Latin America	19 / 63 (30.2)	9 / 70 (12.9)	2.35	[1.15; 4.80]	0.020
Age group 1 at randomization					
Interaction test	**p = 0.402**				
<45	133 / 549 (24.2)	52 / 496 (10.5)	2.31	[1.72; 3.11]	<.001
45 to 54	127 / 539 (23.6)	68 / 546 (12.5)	1.89	[1.45; 2.48]	<.001
55 to 64	10 / 20 (50.0)	5 / 28 (17.9)	2.80	[1.13; 6.94]	0.026
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)					
Interaction test	**p = 0.394**				
<Median	133 / 549 (24.2)	52 / 496 (10.5)	2.31	[1.72; 3.11]	<.001
≥Median	137 / 559 (24.5)	73 / 574 (12.7)	1.93	[1.49; 2.50]	<.001
Race					
Interaction test	**p = 0.453**				
Asian	58 / 211 (27.5)	29 / 186 (15.6)	1.76	[1.18; 2.63]	0.005
Non-Asian	205 / 840 (24.4)	93 / 827 (11.2)	2.17	[1.73; 2.72]	<.001
BMI at screening					
Interaction test	**p = 0.451**				
≥25	159 / 551 (28.9)	70 / 523 (13.4)	2.16	[1.67; 2.78]	<.001
<25	107 / 542 (19.7)	54 / 535 (10.1)	1.96	[1.44; 2.65]	<.001
AJCC Anatomic Stage Group					
Interaction test	**p = 0.379**				
Group I/II	103 / 417 (24.7)	44 / 418 (10.5)	2.35	[1.69; 3.25]	<.001
Group III	167 / 691 (24.2)	81 / 652 (12.4)	1.95	[1.53; 2.48]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Anatomic stages					
Interaction test	**p = 0.011**				
IA/IB/IIA	45 / 171 (26.3)	19 / 198 (9.6)	2.74	[1.67; 4.50]	<.001
IIB	58 / 246 (23.6)	25 / 220 (11.4)	2.07	[1.35; 3.20]	<.001
IIIA	96 / 451 (21.3)	59 / 393 (15.0)	1.42	[1.06; 1.90]	0.020
IIIB	21 / 67 (31.3)	6 / 59 (10.2)	3.08	[1.33; 7.12]	0.008
IIIC	50 / 173 (28.9)	16 / 200 (8.0)	3.61	[2.14; 6.11]	<.001
Nodal status					
Interaction test	**p = 0.046**				
N0	28 / 91 (30.8)	9 / 117 (7.7)	4.00	[1.99; 8.05]	<.001
N1-N3	242 / 1017 (23.8)	116 / 950 (12.2)	1.95	[1.59; 2.39]	<.001
Histological grade at time of surgery					
Interaction test	**p = 0.315**				
Grade 1	22 / 110 (20.0)	13 / 100 (13.0)	1.54	[0.82; 2.89]	0.180
Grade 2	144 / 604 (23.8)	62 / 601 (10.3)	2.31	[1.75; 3.04]	<.001
Grade 3	78 / 297 (26.3)	41 / 266 (15.4)	1.70	[1.21; 2.39]	0.002
Histological subtype					
Interaction test	**p = 0.113**				
Ductal	201 / 863 (23.3)	102 / 835 (12.2)	1.91	[1.53; 2.37]	<.001
Lobular	50 / 172 (29.1)	14 / 169 (8.3)	3.51	[2.02; 6.10]	<.001
Other	19 / 73 (26.0)	9 / 66 (13.6)	1.91	[0.93; 3.92]	0.078
Ki67 status from surgical specimen					
Interaction test	**p = 0.725**				
Ki67≤20	125 / 527 (23.7)	63 / 552 (11.4)	2.08	[1.57; 2.75]	<.001
Ki67>20	111 / 422 (26.3)	45 / 378 (11.9)	2.21	[1.61; 3.03]	<.001
Type of NSAI					
Interaction test	**p = 0.679**				
Letrozole	211 / 809 (26.1)	100 / 773 (12.9)	2.02	[1.62; 2.50]	<.001
Anastrozole	59 / 299 (19.7)	25 / 297 (8.4)	2.34	[1.51; 3.64]	<.001
Prior neo/adjuvant chemotherapy					
Interaction test	**p = 0.421**				
Yes	243 / 1029 (23.6)	107 / 987 (10.8)	2.18	[1.77; 2.69]	<.001
No	27 / 79 (34.2)	18 / 83 (21.7)	1.58	[0.95; 2.63]	0.081
Prior adjuvant chemotherapy					
Interaction test	**p = 0.066**				
Yes	114 / 513 (22.2)	63 / 488 (12.9)	1.72	[1.30; 2.28]	<.001
No	156 / 595 (26.2)	62 / 582 (10.7)	2.46	[1.88; 3.23]	<.001
Prior neoadjuvant chemotherapy					
Interaction test	**p = 0.018**				
Yes	138 / 546 (25.3)	50 / 538 (9.3)	2.72	[2.01; 3.67]	<.001
No	132 / 562 (23.5)	75 / 532 (14.1)	1.67	[1.29; 2.16]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Prior endocrine therapy					
Interaction test	**p = 0.793**				
Yes	192 / 853 (22.5)	81 / 789 (10.3)	2.19	[1.72; 2.79]	<.001
No	78 / 255 (30.6)	44 / 281 (15.7)	1.95	[1.41; 2.71]	<.001
Prior mastectomy					
Interaction test	**p = 0.439**				
Yes	192 / 769 (25.0)	94 / 745 (12.6)	1.98	[1.58; 2.48]	<.001
No	78 / 339 (23.0)	31 / 325 (9.5)	2.41	[1.64; 3.55]	<.001
Prior radiotherapy					
Interaction test	**p = 0.408**				
Yes	229 / 1011 (22.7)	102 / 987 (10.3)	2.19	[1.77; 2.72]	<.001
No	41 / 97 (42.3)	23 / 83 (27.7)	1.53	[1.00; 2.32]	0.048

N: Number of patients
n: Number of patients with event
CI: Confidence interval
RR: Relative risk
ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
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Analysis method for interaction test:
p-value from logistic regression model.
logit(proportion) = treatment + subgroup factor + treatment * subgroup factor

Analysis method for within subgroup analysis:
RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm.
ET was the reference group for treatment group comparison.

Table 5-3.5.2 ILD Pneumonitis: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	ET (N = 1070)	RR	[95% CI]	p-value
ILD Pneumonitis					
	n / N (%)	n / N (%)			
Region					
Interaction test	**p = 0.674**				
NA/WE/O	8 / 640 (1.3)	2 / 627 (0.3)	3.92	[0.84; 18.38]	0.083
ROW	8 / 468 (1.7)	3 / 443 (0.7)	2.52	[0.67; 9.45]	0.169
Geographical region					
The subgroup analysis is not presented as all subgroups have less than 10 events.					
Age group 1 at randomization					
Interaction test	**p = 0.114**				
<45	5 / 549 (0.9)	3 / 496 (0.6)	1.51	[0.36; 6.27]	0.574
45 to 54	11 / 539 (2.0)	1 / 546 (0.2)	11.14	[1.44; 86.01]	0.021
55 to 64	0 / 20 (0.0)	1 / 28 (3.6)	0.46	[0.02; 10.75]	0.629
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)					
Interaction test	**p = 0.209**				
<Median	5 / 549 (0.9)	3 / 496 (0.6)	1.51	[0.36; 6.27]	0.574
≥Median	11 / 559 (2.0)	2 / 574 (0.3)	5.65	[1.26; 25.36]	0.024
Race					
Interaction test	**p = 0.646**				
Asian	5 / 211 (2.4)	2 / 186 (1.1)	2.20	[0.43; 11.22]	0.341
Non-Asian	11 / 840 (1.3)	3 / 827 (0.4)	3.61	[1.01; 12.89]	0.048
BMI at screening					
Interaction test	**p = 0.855**				
≥25	9 / 551 (1.6)	3 / 523 (0.6)	2.85	[0.78; 10.46]	0.115
<25	7 / 542 (1.3)	2 / 535 (0.4)	3.45	[0.72; 16.55]	0.121
AJCC Anatomic Stage Group					
Interaction test	**N.E.**				
Group I/II	2 / 417 (0.5)	0 / 418 (0.0)	5.01	[0.24; >99.99]	0.298
Group III	14 / 691 (2.0)	5 / 652 (0.8)	2.64	[0.96; 7.29]	0.061
Anatomic stages					
Interaction test	**N.E.**				
IA/IB/IIA	1 / 171 (0.6)	0 / 198 (0.0)	3.47	[0.14; 84.65]	0.445
IIB	1 / 246 (0.4)	0 / 220 (0.0)	2.68	[0.11; 65.55]	0.545
IIIA	6 / 451 (1.3)	5 / 393 (1.3)	1.05	[0.32; 3.40]	0.941
IIIB	2 / 67 (3.0)	0 / 59 (0.0)	4.41	[0.22; 90.08]	0.335
IIIC	6 / 173 (3.5)	0 / 200 (0.0)	15.02	[0.85; >99.99]	0.064

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Nodal status					
Interaction test	**N.E.**				
N0	1 / 91 (1.1)	0 / 117 (0.0)	3.85	[0.16; 93.36]	0.408
N1-N3	15 / 1017 (1.5)	5 / 950 (0.5)	2.80	[1.02; 7.68]	0.045
Histological grade at time of surgery					
Interaction test	**p = 0.923**				
Grade 1	0 / 110 (0.0)	0 / 100 (0.0)	N.E.	N.E.	N.E.
Grade 2	9 / 604 (1.5)	3 / 601 (0.5)	2.99	[0.81; 10.97]	0.100
Grade 3	6 / 297 (2.0)	2 / 266 (0.8)	2.69	[0.55; 13.20]	0.224
Histological subtype					
Interaction test	**p = 0.909**				
Ductal	11 / 863 (1.3)	3 / 835 (0.4)	3.55	[0.99; 12.67]	0.051
Lobular	2 / 172 (1.2)	1 / 169 (0.6)	1.97	[0.18; 21.47]	0.580
Other	3 / 73 (4.1)	1 / 66 (1.5)	2.71	[0.29; 25.44]	0.382
Ki67 status from surgical specimen					
Interaction test	**p = 0.642**				
Ki67≤20	4 / 527 (0.8)	2 / 552 (0.4)	2.09	[0.39; 11.39]	0.392
Ki67>20	8 / 422 (1.9)	2 / 378 (0.5)	3.58	[0.77; 16.77]	0.105
Type of NSAI					
Interaction test	**N.E.**				
Letrozole	9 / 809 (1.1)	5 / 773 (0.6)	1.72	[0.58; 5.11]	0.329
Anastrozole	7 / 299 (2.3)	0 / 297 (0.0)	14.90	[0.85; >99.99]	0.064
Prior neo/adjuvant chemotherapy					
Interaction test	**N.E.**				
Yes	15 / 1029 (1.5)	5 / 987 (0.5)	2.88	[1.05; 7.89]	0.040
No	1 / 79 (1.3)	0 / 83 (0.0)	3.15	[0.13; 76.20]	0.480
Prior adjuvant chemotherapy					
Interaction test	**p = 0.393**				
Yes	10 / 513 (1.9)	2 / 488 (0.4)	4.76	[1.05; 21.60]	0.043
No	6 / 595 (1.0)	3 / 582 (0.5)	1.96	[0.49; 7.79]	0.341
Prior neoadjuvant chemotherapy					
Interaction test	**p = 0.400**				
Yes	6 / 546 (1.1)	3 / 538 (0.6)	1.97	[0.50; 7.84]	0.336
No	10 / 562 (1.8)	2 / 532 (0.4)	4.73	[1.04; 21.50]	0.044
Prior endocrine therapy					
Interaction test	**p = 0.836**				
Yes	8 / 853 (0.9)	2 / 789 (0.3)	3.70	[0.79; 17.37]	0.097
No	8 / 255 (3.1)	3 / 281 (1.1)	2.94	[0.79; 10.96]	0.108
Prior mastectomy					
Interaction test	**p = 0.480**				
Yes	10 / 769 (1.3)	4 / 745 (0.5)	2.42	[0.76; 7.69]	0.133
No	6 / 339 (1.8)	1 / 325 (0.3)	5.75	[0.70; 47.52]	0.104

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Prior radiotherapy					
Interaction test	**N.E.**				
Yes	15 / 1011 (1.5)	5 / 987 (0.5)	2.93	[1.07; 8.03]	0.037
No	1 / 97 (1.0)	0 / 83 (0.0)	2.57	[0.11; 62.29]	0.561

N: Number of patients
n: Number of patients with event
N.E.: Not estimable
CI: Confidence interval
RR: Relative risk
ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
.....

Analysis method for interaction test:
p-value from logistic regression model.
logit(proportion) = treatment + subgroup factor + treatment * subgroup factor

Analysis method for within subgroup analysis:
RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm.
ET was the reference group for treatment group comparison.

Table 5-3.5.3 Infections: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	ET (N = 1070)	RR	[95% CI]	p-value
Infections					
	n / N (%)	n / N (%)			
Region					
Interaction test	**p = 0.013**				
NA/WE/O	364 / 640 (56.9)	247 / 627 (39.4)	1.44	[1.28; 1.62]	<.001
ROW	217 / 468 (46.4)	176 / 443 (39.7)	1.17	[1.00; 1.36]	0.044
Geographical region					
Interaction test	**p = 0.015**				
Europe	310 / 654 (47.4)	243 / 638 (38.1)	1.24	[1.10; 1.41]	<.001
North America/Australia	138 / 213 (64.8)	74 / 194 (38.1)	1.70	[1.38; 2.08]	<.001
Asia	103 / 178 (57.9)	75 / 168 (44.6)	1.30	[1.05; 1.60]	0.015
Latin America	30 / 63 (47.6)	31 / 70 (44.3)	1.08	[0.74; 1.56]	0.700
Age group 1 at randomization					
Interaction test	**p = 0.069**				
<45	293 / 549 (53.4)	182 / 496 (36.7)	1.45	[1.27; 1.67]	<.001
45 to 54	282 / 539 (52.3)	229 / 546 (41.9)	1.25	[1.10; 1.42]	<.001
55 to 64	6 / 20 (30.0)	12 / 28 (42.9)	0.70	[0.32; 1.55]	0.379
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)					
Interaction test	**p = 0.089**				
<Median	293 / 549 (53.4)	182 / 496 (36.7)	1.45	[1.27; 1.67]	<.001
≥Median	288 / 559 (51.5)	241 / 574 (42.0)	1.23	[1.08; 1.39]	0.001
Race					
Interaction test	**p = 0.841**				
Asian	121 / 211 (57.3)	82 / 186 (44.1)	1.30	[1.07; 1.59]	0.010
Non-Asian	427 / 840 (50.8)	321 / 827 (38.8)	1.31	[1.18; 1.46]	<.001
BMI at screening					
Interaction test	**p = 0.492**				
≥25	286 / 551 (51.9)	213 / 523 (40.7)	1.27	[1.12; 1.45]	<.001
<25	285 / 542 (52.6)	206 / 535 (38.5)	1.37	[1.19; 1.56]	<.001
AJCC Anatomic Stage Group					
Interaction test	**p = 0.314**				
Group I/II	214 / 417 (51.3)	150 / 418 (35.9)	1.43	[1.22; 1.68]	<.001
Group III	367 / 691 (53.1)	273 / 652 (41.9)	1.27	[1.13; 1.42]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Anatomic stages					
Interaction test	**p = 0.134**				
IA/IB/IIA	82 / 171 (48.0)	62 / 198 (31.3)	1.53	[1.18; 1.98]	0.001
IIB	132 / 246 (53.7)	88 / 220 (40.0)	1.34	[1.10; 1.64]	0.004
IIIA	228 / 451 (50.6)	174 / 393 (44.3)	1.14	[0.99; 1.32]	0.070
IIIB	36 / 67 (53.7)	21 / 59 (35.6)	1.51	[1.00; 2.27]	0.048
IIIC	103 / 173 (59.5)	78 / 200 (39.0)	1.53	[1.23; 1.89]	<.001
Nodal status					
Interaction test	**p = 0.205**				
N0	44 / 91 (48.4)	33 / 117 (28.2)	1.71	[1.20; 2.45]	0.003
N1-N3	537 / 1017 (52.8)	389 / 950 (40.9)	1.29	[1.17; 1.42]	<.001
Histological grade at time of surgery					
Interaction test	**p = 0.755**				
Grade 1	51 / 110 (46.4)	35 / 100 (35.0)	1.32	[0.95; 1.85]	0.099
Grade 2	327 / 604 (54.1)	244 / 601 (40.6)	1.33	[1.18; 1.51]	<.001
Grade 3	166 / 297 (55.9)	104 / 266 (39.1)	1.43	[1.19; 1.71]	<.001
Histological subtype					
Interaction test	**p = 0.448**				
Ductal	463 / 863 (53.7)	333 / 835 (39.9)	1.35	[1.21; 1.49]	<.001
Lobular	84 / 172 (48.8)	61 / 169 (36.1)	1.35	[1.05; 1.74]	0.019
Other	34 / 73 (46.6)	29 / 66 (43.9)	1.06	[0.73; 1.53]	0.756
Ki67 status from surgical specimen					
Interaction test	**p = 0.283**				
Ki67≤20	271 / 527 (51.4)	228 / 552 (41.3)	1.24	[1.09; 1.42]	<.001
Ki67>20	216 / 422 (51.2)	137 / 378 (36.2)	1.41	[1.20; 1.66]	<.001
Type of NSAI					
Interaction test	**p = 0.849**				
Letrozole	412 / 809 (50.9)	292 / 773 (37.8)	1.35	[1.20; 1.51]	<.001
Anastrozole	169 / 299 (56.5)	131 / 297 (44.1)	1.28	[1.09; 1.51]	0.003
Prior neo/adjuvant chemotherapy					
Interaction test	**p = 0.947**				
Yes	546 / 1029 (53.1)	396 / 987 (40.1)	1.32	[1.20; 1.45]	<.001
No	35 / 79 (44.3)	27 / 83 (32.5)	1.36	[0.92; 2.02]	0.127
Prior adjuvant chemotherapy					
Interaction test	**p = 0.648**				
Yes	282 / 513 (55.0)	210 / 488 (43.0)	1.28	[1.12; 1.45]	<.001
No	299 / 595 (50.3)	213 / 582 (36.6)	1.37	[1.20; 1.57]	<.001
Prior neoadjuvant chemotherapy					
Interaction test	**p = 0.739**				
Yes	282 / 546 (51.6)	205 / 538 (38.1)	1.36	[1.18; 1.55]	<.001
No	299 / 562 (53.2)	218 / 532 (41.0)	1.30	[1.14; 1.48]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Prior endocrine therapy					
Interaction test	**p = 0.811**				
Yes	446 / 853 (52.3)	313 / 789 (39.7)	1.32	[1.18; 1.47]	<.001
No	135 / 255 (52.9)	110 / 281 (39.1)	1.35	[1.12; 1.63]	0.001
Prior mastectomy					
Interaction test	**p = 0.916**				
Yes	417 / 769 (54.2)	306 / 745 (41.1)	1.32	[1.19; 1.47]	<.001
No	164 / 339 (48.4)	117 / 325 (36.0)	1.34	[1.12; 1.61]	0.001
Prior radiotherapy					
Interaction test	**p = 0.967**				
Yes	529 / 1011 (52.3)	389 / 987 (39.4)	1.33	[1.20; 1.46]	<.001
No	52 / 97 (53.6)	34 / 83 (41.0)	1.31	[0.95; 1.80]	0.097

N: Number of patients
n: Number of patients with event
CI: Confidence interval
RR: Relative risk
ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
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Analysis method for interaction test:
p-value from logistic regression model.
logit(proportion) = treatment + subgroup factor + treatment * subgroup factor

Analysis method for within subgroup analysis:
RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm.
ET was the reference group for treatment group comparison.

Table 5-3.5.4 Myelosuppression - Anaemia: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	ET (N = 1070)	RR	[95% CI]	p-value
Myelosuppression - Anaemia					
	n / N (%)	n / N (%)			
Region					
Interaction test	**p = 0.328**				
NA/WE/O	40 / 640 (6.3)	20 / 627 (3.2)	1.96	[1.16; 3.31]	0.012
ROW	45 / 468 (9.6)	15 / 443 (3.4)	2.84	[1.61; 5.02]	<.001
Geographical region					
Interaction test	**p = 0.837**				
Europe	45 / 654 (6.9)	23 / 638 (3.6)	1.91	[1.17; 3.12]	0.010
North America/Australia	17 / 213 (8.0)	6 / 194 (3.1)	2.58	[1.04; 6.41]	0.041
Asia	14 / 178 (7.9)	6 / 168 (3.6)	2.20	[0.87; 5.60]	0.097
Latin America	9 / 63 (14.3)	0 / 70 (0.0)	21.08	[1.25; >99.99]	0.034
Age group 1 at randomization					
Interaction test	**p = 0.716**				
<45	40 / 549 (7.3)	15 / 496 (3.0)	2.41	[1.35; 4.31]	0.003
45 to 54	41 / 539 (7.6)	20 / 546 (3.7)	2.08	[1.23; 3.50]	0.006
55 to 64	4 / 20 (20.0)	0 / 28 (0.0)	12.43	[0.71; >99.99]	0.085
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)					
Interaction test	**p = 0.926**				
<Median	40 / 549 (7.3)	15 / 496 (3.0)	2.41	[1.35; 4.31]	0.003
≥Median	45 / 559 (8.1)	20 / 574 (3.5)	2.31	[1.38; 3.86]	0.001
Race					
Interaction test	**p = 0.562**				
Asian	15 / 211 (7.1)	7 / 186 (3.8)	1.89	[0.79; 4.53]	0.154
Non-Asian	69 / 840 (8.2)	27 / 827 (3.3)	2.52	[1.63; 3.88]	<.001
BMI at screening					
Interaction test	**p = 0.097**				
≥25	45 / 551 (8.2)	12 / 523 (2.3)	3.56	[1.90; 6.65]	<.001
<25	40 / 542 (7.4)	22 / 535 (4.1)	1.79	[1.08; 2.98]	0.024
AJCC Anatomic Stage Group					
Interaction test	**p = 0.606**				
Group I/II	31 / 417 (7.4)	15 / 418 (3.6)	2.07	[1.14; 3.78]	0.018
Group III	54 / 691 (7.8)	20 / 652 (3.1)	2.55	[1.54; 4.21]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Anatomic stages					
Interaction test	**p = 0.681**				
IA/IB/IIA	14 / 171 (8.2)	7 / 198 (3.5)	2.32	[0.96; 5.61]	0.063
IIB	17 / 246 (6.9)	8 / 220 (3.6)	1.90	[0.84; 4.32]	0.125
IIIA	32 / 451 (7.1)	10 / 393 (2.5)	2.79	[1.39; 5.60]	0.004
IIIB	11 / 67 (16.4)	2 / 59 (3.4)	4.84	[1.12; 20.97]	0.035
IIIC	11 / 173 (6.4)	8 / 200 (4.0)	1.59	[0.65; 3.86]	0.306
Nodal status					
Interaction test	**p = 0.837**				
N0	10 / 91 (11.0)	5 / 117 (4.3)	2.57	[0.91; 7.26]	0.075
N1-N3	75 / 1017 (7.4)	30 / 950 (3.2)	2.34	[1.54; 3.53]	<.001
Histological grade at time of surgery					
Interaction test	**p = 0.187**				
Grade 1	6 / 110 (5.5)	2 / 100 (2.0)	2.73	[0.56; 13.20]	0.212
Grade 2	44 / 604 (7.3)	25 / 601 (4.2)	1.75	[1.09; 2.82]	0.022
Grade 3	29 / 297 (9.8)	6 / 266 (2.3)	4.33	[1.83; 10.26]	<.001
Histological subtype					
Interaction test	**p = 0.914**				
Ductal	67 / 863 (7.8)	27 / 835 (3.2)	2.40	[1.55; 3.72]	<.001
Lobular	12 / 172 (7.0)	6 / 169 (3.6)	1.97	[0.75; 5.12]	0.166
Other	6 / 73 (8.2)	2 / 66 (3.0)	2.71	[0.57; 12.98]	0.212
Ki67 status from surgical specimen					
Interaction test	**p = 0.027**				
Ki67≤20	40 / 527 (7.6)	24 / 552 (4.3)	1.75	[1.07; 2.85]	0.026
Ki67>20	39 / 422 (9.2)	7 / 378 (1.9)	4.99	[2.26; 11.02]	<.001
Type of NSAI					
Interaction test	**p = 0.247**				
Letrozole	60 / 809 (7.4)	28 / 773 (3.6)	2.05	[1.32; 3.17]	0.001
Anastrozole	25 / 299 (8.4)	7 / 297 (2.4)	3.55	[1.56; 8.08]	0.003
Prior neo/adjuvant chemotherapy					
Interaction test	**p = 0.165**				
Yes	77 / 1029 (7.5)	28 / 987 (2.8)	2.64	[1.73; 4.03]	<.001
No	8 / 79 (10.1)	7 / 83 (8.4)	1.20	[0.46; 3.16]	0.711
Prior adjuvant chemotherapy					
Interaction test	**p = 0.631**				
Yes	31 / 513 (6.0)	14 / 488 (2.9)	2.11	[1.13; 3.91]	0.018
No	54 / 595 (9.1)	21 / 582 (3.6)	2.52	[1.54; 4.11]	<.001
Prior neoadjuvant chemotherapy					
Interaction test	**p = 0.211**				
Yes	46 / 546 (8.4)	15 / 538 (2.8)	3.02	[1.71; 5.35]	<.001
No	39 / 562 (6.9)	20 / 532 (3.8)	1.85	[1.09; 3.12]	0.022

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Prior endocrine therapy					
Interaction test	**p = 0.348**				
Yes	57 / 853 (6.7)	25 / 789 (3.2)	2.11	[1.33; 3.34]	0.001
No	28 / 255 (11.0)	10 / 281 (3.6)	3.09	[1.53; 6.22]	0.002
Prior mastectomy					
Interaction test	**p = 0.300**				
Yes	60 / 769 (7.8)	28 / 745 (3.8)	2.08	[1.34; 3.21]	0.001
No	25 / 339 (7.4)	7 / 325 (2.2)	3.42	[1.50; 7.81]	0.003
Prior radiotherapy					
Interaction test	**p = 0.305**				
Yes	68 / 1011 (6.7)	31 / 987 (3.1)	2.14	[1.41; 3.24]	<.001
No	17 / 97 (17.5)	4 / 83 (4.8)	3.64	[1.27; 10.38]	0.016

N: Number of patients
n: Number of patients with event
CI: Confidence interval
RR: Relative risk
ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
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Analysis method for interaction test:
p-value from logistic regression model.
logit(proportion) = treatment + subgroup factor + treatment * subgroup factor

Analysis method for within subgroup analysis:
RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm.
ET was the reference group for treatment group comparison.

Table 5-3.5.5 Myelosuppression - Leukopenia: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	ET (N = 1070)	RR	[95% CI]	p-value
Myelosuppression - Leukopenia					
	n / N (%)	n / N (%)			
Region					
Interaction test	**p = 0.366**				
NA/WE/O	108 / 640 (16.9)	31 / 627 (4.9)	3.41	[2.33; 5.01]	<.001
ROW	148 / 468 (31.6)	37 / 443 (8.4)	3.79	[2.71; 5.30]	<.001
Geographical region					
Interaction test	**p = 0.429**				
Europe	141 / 654 (21.6)	35 / 638 (5.5)	3.93	[2.76; 5.60]	<.001
North America/Australia	41 / 213 (19.2)	14 / 194 (7.2)	2.67	[1.50; 4.74]	<.001
Asia	65 / 178 (36.5)	15 / 168 (8.9)	4.09	[2.43; 6.88]	<.001
Latin America	9 / 63 (14.3)	4 / 70 (5.7)	2.50	[0.81; 7.72]	0.111
Age group 1 at randomization					
Interaction test	**p = 0.715**				
<45	134 / 549 (24.4)	37 / 496 (7.5)	3.27	[2.32; 4.61]	<.001
45 to 54	113 / 539 (21.0)	27 / 546 (4.9)	4.24	[2.83; 6.34]	<.001
55 to 64	9 / 20 (45.0)	4 / 28 (14.3)	3.15	[1.13; 8.81]	0.029
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)					
Interaction test	**p = 0.490**				
<Median	134 / 549 (24.4)	37 / 496 (7.5)	3.27	[2.32; 4.61]	<.001
≥Median	122 / 559 (21.8)	31 / 574 (5.4)	4.04	[2.77; 5.89]	<.001
Race					
Interaction test	**p = 0.599**				
Asian	70 / 211 (33.2)	16 / 186 (8.6)	3.86	[2.33; 6.40]	<.001
Non-Asian	176 / 840 (21.0)	47 / 827 (5.7)	3.69	[2.71; 5.01]	<.001
BMI at screening					
Interaction test	**p = 0.132**				
≥25	118 / 551 (21.4)	23 / 523 (4.4)	4.87	[3.17; 7.49]	<.001
<25	134 / 542 (24.7)	43 / 535 (8.0)	3.08	[2.23; 4.24]	<.001
AJCC Anatomic Stage Group					
Interaction test	**p = 0.476**				
Group I/II	82 / 417 (19.7)	25 / 418 (6.0)	3.29	[2.15; 5.04]	<.001
Group III	174 / 691 (25.2)	43 / 652 (6.6)	3.82	[2.78; 5.24]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Anatomic stages					
Interaction test	**p = 0.729**				
IA/IB/IIA	29 / 171 (17.0)	11 / 198 (5.6)	3.05	[1.57; 5.93]	<.001
IIB	53 / 246 (21.5)	14 / 220 (6.4)	3.39	[1.93; 5.93]	<.001
IIIA	110 / 451 (24.4)	28 / 393 (7.1)	3.42	[2.31; 5.07]	<.001
IIIB	18 / 67 (26.9)	5 / 59 (8.5)	3.17	[1.25; 8.01]	0.015
IIIC	46 / 173 (26.6)	10 / 200 (5.0)	5.32	[2.77; 10.22]	<.001
Nodal status					
Interaction test	**p = 0.610**				
N0	21 / 91 (23.1)	9 / 117 (7.7)	3.00	[1.44; 6.23]	0.003
N1-N3	235 / 1017 (23.1)	59 / 950 (6.2)	3.72	[2.84; 4.88]	<.001
Histological grade at time of surgery					
Interaction test	**p = 0.499**				
Grade 1	20 / 110 (18.2)	7 / 100 (7.0)	2.60	[1.15; 5.88]	0.022
Grade 2	145 / 604 (24.0)	40 / 601 (6.7)	3.61	[2.59; 5.02]	<.001
Grade 3	71 / 297 (23.9)	14 / 266 (5.3)	4.54	[2.62; 7.86]	<.001
Histological subtype					
Interaction test	**p = 0.632**				
Ductal	194 / 863 (22.5)	55 / 835 (6.6)	3.41	[2.57; 4.53]	<.001
Lobular	41 / 172 (23.8)	9 / 169 (5.3)	4.48	[2.25; 8.92]	<.001
Other	21 / 73 (28.8)	4 / 66 (6.1)	4.75	[1.72; 13.11]	0.003
Ki67 status from surgical specimen					
Interaction test	**p = 0.448**				
Ki67≤20	121 / 527 (23.0)	32 / 552 (5.8)	3.96	[2.73; 5.74]	<.001
Ki67>20	102 / 422 (24.2)	29 / 378 (7.7)	3.15	[2.14; 4.65]	<.001
Type of NSAI					
Interaction test	**p = 0.685**				
Letrozole	174 / 809 (21.5)	43 / 773 (5.6)	3.87	[2.81; 5.32]	<.001
Anastrozole	82 / 299 (27.4)	25 / 297 (8.4)	3.26	[2.14; 4.95]	<.001
Prior neo/adjuvant chemotherapy					
Interaction test	**p = 0.943**				
Yes	230 / 1029 (22.4)	60 / 987 (6.1)	3.68	[2.81; 4.82]	<.001
No	26 / 79 (32.9)	8 / 83 (9.6)	3.41	[1.65; 7.09]	<.001
Prior adjuvant chemotherapy					
Interaction test	**p = 0.237**				
Yes	108 / 513 (21.1)	33 / 488 (6.8)	3.11	[2.15; 4.51]	<.001
No	148 / 595 (24.9)	35 / 582 (6.0)	4.14	[2.91; 5.87]	<.001
Prior neoadjuvant chemotherapy					
Interaction test	**p = 0.650**				
Yes	132 / 546 (24.2)	34 / 538 (6.3)	3.83	[2.68; 5.47]	<.001
No	124 / 562 (22.1)	34 / 532 (6.4)	3.45	[2.41; 4.95]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Prior endocrine therapy					
Interaction test	**p = 0.506**				
Yes	188 / 853 (22.0)	44 / 789 (5.6)	3.95	[2.89; 5.41]	<.001
No	68 / 255 (26.7)	24 / 281 (8.5)	3.12	[2.02; 4.82]	<.001
Prior mastectomy					
Interaction test	**p = 0.785**				
Yes	189 / 769 (24.6)	52 / 745 (7.0)	3.52	[2.64; 4.71]	<.001
No	67 / 339 (19.8)	16 / 325 (4.9)	4.01	[2.38; 6.78]	<.001
Prior radiotherapy					
Interaction test	**p = 0.426**				
Yes	224 / 1011 (22.2)	62 / 987 (6.3)	3.53	[2.70; 4.61]	<.001
No	32 / 97 (33.0)	6 / 83 (7.2)	4.56	[2.01; 10.37]	<.001

N: Number of patients
n: Number of patients with event
CI: Confidence interval
RR: Relative risk
ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
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Analysis method for interaction test:
p-value from logistic regression model.
logit(proportion) = treatment + subgroup factor + treatment * subgroup factor

Analysis method for within subgroup analysis:
RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm.
ET was the reference group for treatment group comparison.

Table 5-3.5.6 Myelosuppression - Neutropenia: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	ET (N = 1070)	RR	[95% CI]	p-value
Myelosuppression - Neutropenia					
	n / N (%)	n / N (%)			
Region					
Interaction test	**p = 0.101**				
NA/WE/O	387 / 640 (60.5)	21 / 627 (3.3)	18.05	[11.80; 27.62]	<.001
ROW	352 / 468 (75.2)	45 / 443 (10.2)	7.40	[5.59; 9.81]	<.001
Geographical region					
Interaction test	**p = 0.489**				
Europe	425 / 654 (65.0)	38 / 638 (6.0)	10.91	[7.97; 14.93]	<.001
North America/Australia	133 / 213 (62.4)	7 / 194 (3.6)	17.31	[8.30; 36.08]	<.001
Asia	144 / 178 (80.9)	16 / 168 (9.5)	8.49	[5.30; 13.61]	<.001
Latin America	37 / 63 (58.7)	5 / 70 (7.1)	8.22	[3.45; 19.62]	<.001
Age group 1 at randomization					
Interaction test	**p = 0.961**				
<45	381 / 549 (69.4)	34 / 496 (6.9)	10.12	[7.28; 14.07]	<.001
45 to 54	346 / 539 (64.2)	31 / 546 (5.7)	11.31	[7.99; 16.01]	<.001
55 to 64	12 / 20 (60.0)	1 / 28 (3.6)	16.80	[2.37; >99.99]	0.005
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)					
Interaction test	**p = 0.939**				
<Median	381 / 549 (69.4)	34 / 496 (6.9)	10.12	[7.28; 14.07]	<.001
≥Median	358 / 559 (64.0)	32 / 574 (5.6)	11.49	[8.16; 16.18]	<.001
Race					
Interaction test	**p = 0.247**				
Asian	170 / 211 (80.6)	16 / 186 (8.6)	9.37	[5.84; 15.03]	<.001
Non-Asian	540 / 840 (64.3)	48 / 827 (5.8)	11.08	[8.38; 14.64]	<.001
BMI at screening					
Interaction test	**p = 0.501**				
≥25	321 / 551 (58.3)	24 / 523 (4.6)	12.70	[8.53; 18.88]	<.001
<25	407 / 542 (75.1)	42 / 535 (7.9)	9.57	[7.13; 12.84]	<.001
AJCC Anatomic Stage Group					
Interaction test	**p = 0.239**				
Group I/II	267 / 417 (64.0)	28 / 418 (6.7)	9.56	[6.64; 13.77]	<.001
Group III	472 / 691 (68.3)	38 / 652 (5.8)	11.72	[8.57; 16.02]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Anatomic stages					
Interaction test	**p = 0.275**				
IA/IB/IIA	110 / 171 (64.3)	10 / 198 (5.1)	12.74	[6.89; 23.54]	<.001
IIB	157 / 246 (63.8)	18 / 220 (8.2)	7.80	[4.96; 12.26]	<.001
IIIA	299 / 451 (66.3)	21 / 393 (5.3)	12.41	[8.14; 18.91]	<.001
IIIB	46 / 67 (68.7)	6 / 59 (10.2)	6.75	[3.11; 14.66]	<.001
IIIC	127 / 173 (73.4)	11 / 200 (5.5)	13.35	[7.46; 23.87]	<.001
Nodal status					
Interaction test	**p = 0.211**				
N0	63 / 91 (69.2)	12 / 117 (10.3)	6.75	[3.88; 11.74]	<.001
N1-N3	676 / 1017 (66.5)	54 / 950 (5.7)	11.69	[8.99; 15.21]	<.001
Histological grade at time of surgery					
Interaction test	**p = 0.997**				
Grade 1	77 / 110 (70.0)	7 / 100 (7.0)	10.00	[4.84; 20.64]	<.001
Grade 2	410 / 604 (67.9)	37 / 601 (6.2)	11.03	[8.03; 15.14]	<.001
Grade 3	190 / 297 (64.0)	14 / 266 (5.3)	12.15	[7.25; 20.38]	<.001
Histological subtype					
Interaction test	**p = 0.156**				
Ductal	580 / 863 (67.2)	55 / 835 (6.6)	10.20	[7.87; 13.23]	<.001
Lobular	113 / 172 (65.7)	5 / 169 (3.0)	22.21	[9.30; 53.01]	<.001
Other	46 / 73 (63.0)	6 / 66 (9.1)	6.93	[3.17; 15.16]	<.001
Ki67 status from surgical specimen					
Interaction test	**p = 0.848**				
Ki67≤20	361 / 527 (68.5)	37 / 552 (6.7)	10.22	[7.45; 14.03]	<.001
Ki67>20	285 / 422 (67.5)	23 / 378 (6.1)	11.10	[7.43; 16.58]	<.001
Type of NSAI					
Interaction test	**p = 0.250**				
Letrozole	543 / 809 (67.1)	44 / 773 (5.7)	11.79	[8.81; 15.77]	<.001
Anastrozole	196 / 299 (65.6)	22 / 297 (7.4)	8.85	[5.87; 13.34]	<.001
Prior neo/adjuvant chemotherapy					
Interaction test	**p = 0.553**				
Yes	685 / 1029 (66.6)	59 / 987 (6.0)	11.14	[8.66; 14.32]	<.001
No	54 / 79 (68.4)	7 / 83 (8.4)	8.10	[3.93; 16.73]	<.001
Prior adjuvant chemotherapy					
Interaction test	**p = 0.788**				
Yes	329 / 513 (64.1)	28 / 488 (5.7)	11.18	[7.76; 16.11]	<.001
No	410 / 595 (68.9)	38 / 582 (6.5)	10.55	[7.72; 14.42]	<.001
Prior neoadjuvant chemotherapy					
Interaction test	**p = 0.879**				
Yes	378 / 546 (69.2)	36 / 538 (6.7)	10.35	[7.51; 14.25]	<.001
No	361 / 562 (64.2)	30 / 532 (5.6)	11.39	[8.00; 16.21]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Prior endocrine therapy					
Interaction test	**p = 0.199**				
Yes	561 / 853 (65.8)	41 / 789 (5.2)	12.66	[9.36; 17.12]	<.001
No	178 / 255 (69.8)	25 / 281 (8.9)	7.85	[5.35; 11.50]	<.001
Prior mastectomy					
Interaction test	**p = 0.279**				
Yes	516 / 769 (67.1)	51 / 745 (6.8)	9.80	[7.49; 12.83]	<.001
No	223 / 339 (65.8)	15 / 325 (4.6)	14.25	[8.64; 23.50]	<.001
Prior radiotherapy					
Interaction test	**p = 0.048**				
Yes	672 / 1011 (66.5)	55 / 987 (5.6)	11.93	[9.19; 15.48]	<.001
No	67 / 97 (69.1)	11 / 83 (13.3)	5.21	[2.96; 9.18]	<.001

N: Number of patients
n: Number of patients with event
CI: Confidence interval
RR: Relative risk
ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
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Analysis method for interaction test:
p-value from logistic regression model.
logit(proportion) = treatment + subgroup factor + treatment * subgroup factor

Analysis method for within subgroup analysis:
RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm.
ET was the reference group for treatment group comparison.

Table 5-3.5.7 Myelosuppression - Thrombocytopenia: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	ET (N = 1070)	RR	[95% CI]	p-value
Myelosuppression - Thrombocytopenia					
	n / N (%)	n / N (%)			
Region					
Interaction test	**p = 0.640**				
NA/WE/O	23 / 640 (3.6)	9 / 627 (1.4)	2.50	[1.17; 5.37]	0.018
ROW	35 / 468 (7.5)	17 / 443 (3.8)	1.95	[1.11; 3.43]	0.021
Geographical region					
Interaction test	**p = 0.119**				
Europe	30 / 654 (4.6)	21 / 638 (3.3)	1.39	[0.81; 2.41]	0.234
North America/Australia	13 / 213 (6.1)	3 / 194 (1.5)	3.95	[1.14; 13.64]	0.030
Asia	12 / 178 (6.7)	1 / 168 (0.6)	11.33	[1.49; 86.16]	0.019
Latin America	3 / 63 (4.8)	1 / 70 (1.4)	3.33	[0.36; 31.23]	0.292
Age group 1 at randomization					
Interaction test	**p = 0.796**				
<45	33 / 549 (6.0)	12 / 496 (2.4)	2.48	[1.30; 4.76]	0.006
45 to 54	23 / 539 (4.3)	12 / 546 (2.2)	1.94	[0.98; 3.86]	0.059
55 to 64	2 / 20 (10.0)	2 / 28 (7.1)	1.40	[0.21; 9.12]	0.725
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)					
Interaction test	**p = 0.507**				
<Median	33 / 549 (6.0)	12 / 496 (2.4)	2.48	[1.30; 4.76]	0.006
≥Median	25 / 559 (4.5)	14 / 574 (2.4)	1.83	[0.96; 3.49]	0.065
Race					
Interaction test	**p = 0.064**				
Asian	14 / 211 (6.6)	1 / 186 (0.5)	12.34	[1.64; 92.95]	0.015
Non-Asian	43 / 840 (5.1)	24 / 827 (2.9)	1.76	[1.08; 2.88]	0.023
BMI at screening					
Interaction test	**p = 0.048**				
≥25	25 / 551 (4.5)	17 / 523 (3.3)	1.40	[0.76; 2.55]	0.279
<25	33 / 542 (6.1)	9 / 535 (1.7)	3.62	[1.75; 7.49]	<.001
AJCC Anatomic Stage Group					
Interaction test	**p = 0.361**				
Group I/II	22 / 417 (5.3)	13 / 418 (3.1)	1.70	[0.87; 3.32]	0.123
Group III	36 / 691 (5.2)	13 / 652 (2.0)	2.61	[1.40; 4.88]	0.003

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Anatomic stages					
Interaction test	**p = 0.667**				
IA/IB/IIA	7 / 171 (4.1)	7 / 198 (3.5)	1.16	[0.41; 3.24]	0.780
IIB	15 / 246 (6.1)	6 / 220 (2.7)	2.24	[0.88; 5.66]	0.090
IIIA	23 / 451 (5.1)	7 / 393 (1.8)	2.86	[1.24; 6.60]	0.014
IIIB	5 / 67 (7.5)	3 / 59 (5.1)	1.47	[0.37; 5.88]	0.588
IIIC	8 / 173 (4.6)	3 / 200 (1.5)	3.08	[0.83; 11.44]	0.092
Nodal status					
Interaction test	**p = 0.734**				
N0	7 / 91 (7.7)	5 / 117 (4.3)	1.80	[0.59; 5.49]	0.301
N1-N3	51 / 1017 (5.0)	21 / 950 (2.2)	2.27	[1.38; 3.74]	0.001
Histological grade at time of surgery					
Interaction test	**p = 0.167**				
Grade 1	5 / 110 (4.5)	6 / 100 (6.0)	0.76	[0.24; 2.41]	0.638
Grade 2	40 / 604 (6.6)	15 / 601 (2.5)	2.65	[1.48; 4.75]	0.001
Grade 3	11 / 297 (3.7)	5 / 266 (1.9)	1.97	[0.69; 5.60]	0.203
Histological subtype					
Interaction test	**p = 0.627**				
Ductal	49 / 863 (5.7)	22 / 835 (2.6)	2.16	[1.32; 3.53]	0.002
Lobular	4 / 172 (2.3)	3 / 169 (1.8)	1.31	[0.30; 5.77]	0.721
Other	5 / 73 (6.8)	1 / 66 (1.5)	4.52	[0.54; 37.70]	0.163
Ki67 status from surgical specimen					
Interaction test	**p = 0.887**				
Ki67≤20	30 / 527 (5.7)	16 / 552 (2.9)	1.96	[1.08; 3.56]	0.026
Ki67>20	19 / 422 (4.5)	8 / 378 (2.1)	2.13	[0.94; 4.80]	0.069
Type of NSAI					
Interaction test	**p = 0.323**				
Letrozole	39 / 809 (4.8)	20 / 773 (2.6)	1.86	[1.10; 3.17]	0.021
Anastrozole	19 / 299 (6.4)	6 / 297 (2.0)	3.15	[1.27; 7.77]	0.013
Prior neo/adjuvant chemotherapy					
Interaction test	**p = 0.138**				
Yes	51 / 1029 (5.0)	19 / 987 (1.9)	2.57	[1.53; 4.33]	<.001
No	7 / 79 (8.9)	7 / 83 (8.4)	1.05	[0.39; 2.86]	0.923
Prior adjuvant chemotherapy					
Interaction test	**p = 0.178**				
Yes	25 / 513 (4.9)	7 / 488 (1.4)	3.40	[1.48; 7.78]	0.004
No	33 / 595 (5.5)	19 / 582 (3.3)	1.70	[0.98; 2.95]	0.060
Prior neoadjuvant chemotherapy					
Interaction test	**p = 0.829**				
Yes	27 / 546 (4.9)	13 / 538 (2.4)	2.05	[1.07; 3.92]	0.031
No	31 / 562 (5.5)	13 / 532 (2.4)	2.26	[1.19; 4.27]	0.012

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Prior endocrine therapy					
Interaction test	**p = 0.008**				
Yes	37 / 853 (4.3)	7 / 789 (0.9)	4.89	[2.19; 10.90]	<.001
No	21 / 255 (8.2)	19 / 281 (6.8)	1.22	[0.67; 2.21]	0.517
Prior mastectomy					
Interaction test	**p = 0.498**				
Yes	46 / 769 (6.0)	19 / 745 (2.6)	2.35	[1.39; 3.96]	0.001
No	12 / 339 (3.5)	7 / 325 (2.2)	1.64	[0.66; 4.12]	0.290
Prior radiotherapy					
Interaction test	**p = 0.057**				
Yes	46 / 1011 (4.5)	16 / 987 (1.6)	2.81	[1.60; 4.92]	<.001
No	12 / 97 (12.4)	10 / 83 (12.0)	1.03	[0.47; 2.25]	0.947

N: Number of patients
n: Number of patients with event
CI: Confidence interval
RR: Relative risk
ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
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Analysis method for interaction test:
p-value from logistic regression model.
logit(proportion) = treatment + subgroup factor + treatment * subgroup factor

Analysis method for within subgroup analysis:
RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm.
ET was the reference group for treatment group comparison.

Table 5-3.5.8 QT interval prolongation: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	ET (N = 1070)	RR	[95% CI]	p-value
QT interval prolongation					
	n / N (%)	n / N (%)			
Region					
Interaction test	**p = 0.136**				
NA/WE/O	23 / 640 (3.6)	11 / 627 (1.8)	2.05	[1.01; 4.17]	0.048
ROW	44 / 468 (9.4)	10 / 443 (2.3)	4.16	[2.12; 8.17]	<.001
Geographical region					
Interaction test	**p = 0.609**				
Europe	36 / 654 (5.5)	12 / 638 (1.9)	2.93	[1.54; 5.57]	0.001
North America/Australia	8 / 213 (3.8)	4 / 194 (2.1)	1.82	[0.56; 5.95]	0.321
Asia	13 / 178 (7.3)	2 / 168 (1.2)	6.13	[1.41; 26.78]	0.016
Latin America	10 / 63 (15.9)	3 / 70 (4.3)	3.70	[1.07; 12.86]	0.039
Age group 1 at randomization					
Interaction test	**p = 0.407**				
<45	35 / 549 (6.4)	12 / 496 (2.4)	2.64	[1.38; 5.02]	0.003
45 to 54	32 / 539 (5.9)	8 / 546 (1.5)	4.05	[1.88; 8.71]	<.001
55 to 64	0 / 20 (0.0)	1 / 28 (3.6)	0.46	[0.02; 10.75]	0.629
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)					
Interaction test	**p = 0.522**				
<Median	35 / 549 (6.4)	12 / 496 (2.4)	2.64	[1.38; 5.02]	0.003
≥Median	32 / 559 (5.7)	9 / 574 (1.6)	3.65	[1.76; 7.58]	<.001
Race					
Interaction test	**p = 0.165**				
Asian	16 / 211 (7.6)	2 / 186 (1.1)	7.05	[1.64; 30.27]	0.009
Non-Asian	46 / 840 (5.5)	19 / 827 (2.3)	2.38	[1.41; 4.03]	0.001
BMI at screening					
Interaction test	**p = 0.889**				
≥25	33 / 551 (6.0)	10 / 523 (1.9)	3.13	[1.56; 6.29]	0.001
<25	34 / 542 (6.3)	10 / 535 (1.9)	3.36	[1.68; 6.72]	<.001
AJCC Anatomic Stage Group					
Interaction test	**p = 0.110**				
Group I/II	16 / 417 (3.8)	9 / 418 (2.2)	1.78	[0.80; 3.99]	0.160
Group III	51 / 691 (7.4)	12 / 652 (1.8)	4.01	[2.16; 7.45]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Anatomic stages					
Interaction test	**p = 0.411**				
IA/IB/IIA	8 / 171 (4.7)	5 / 198 (2.5)	1.85	[0.62; 5.56]	0.271
IIB	8 / 246 (3.3)	4 / 220 (1.8)	1.79	[0.55; 5.86]	0.337
IIIA	29 / 451 (6.4)	9 / 393 (2.3)	2.81	[1.35; 5.86]	0.006
IIIB	10 / 67 (14.9)	1 / 59 (1.7)	8.81	[1.16; 66.76]	0.035
IIIC	12 / 173 (6.9)	2 / 200 (1.0)	6.94	[1.57; 30.56]	0.010
Nodal status					
Interaction test	**p = 0.433**				
N0	6 / 91 (6.6)	4 / 117 (3.4)	1.93	[0.56; 6.63]	0.297
N1-N3	61 / 1017 (6.0)	17 / 950 (1.8)	3.35	[1.97; 5.70]	<.001
Histological grade at time of surgery					
Interaction test	**p = 0.523**				
Grade 1	9 / 110 (8.2)	2 / 100 (2.0)	4.09	[0.91; 18.48]	0.067
Grade 2	38 / 604 (6.3)	16 / 601 (2.7)	2.36	[1.33; 4.19]	0.003
Grade 3	16 / 297 (5.4)	3 / 266 (1.1)	4.78	[1.41; 16.21]	0.012
Histological subtype					
Interaction test	**p = 0.268**				
Ductal	52 / 863 (6.0)	16 / 835 (1.9)	3.14	[1.81; 5.46]	<.001
Lobular	8 / 172 (4.7)	5 / 169 (3.0)	1.57	[0.52; 4.71]	0.419
Other	7 / 73 (9.6)	0 / 66 (0.0)	13.58	[0.79; >99.99]	0.072
Ki67 status from surgical specimen					
Interaction test	**p = 0.452**				
Ki67≤20	33 / 527 (6.3)	13 / 552 (2.4)	2.66	[1.42; 5.00]	0.002
Ki67>20	27 / 422 (6.4)	6 / 378 (1.6)	4.03	[1.68; 9.66]	0.002
Type of NSAI					
Interaction test	**p = 0.236**				
Letrozole	53 / 809 (6.6)	19 / 773 (2.5)	2.67	[1.59; 4.46]	<.001
Anastrozole	14 / 299 (4.7)	2 / 297 (0.7)	6.95	[1.59; 30.33]	0.010
Prior neo/adjuvant chemotherapy					
Interaction test	**p = 0.736**				
Yes	65 / 1029 (6.3)	20 / 987 (2.0)	3.12	[1.90; 5.11]	<.001
No	2 / 79 (2.5)	1 / 83 (1.2)	2.10	[0.19; 22.72]	0.541
Prior adjuvant chemotherapy					
Interaction test	**p = 0.004**				
Yes	24 / 513 (4.7)	15 / 488 (3.1)	1.52	[0.81; 2.87]	0.193
No	43 / 595 (7.2)	6 / 582 (1.0)	7.01	[3.01; 16.34]	<.001
Prior neoadjuvant chemotherapy					
Interaction test	**p = 0.015**				
Yes	42 / 546 (7.7)	7 / 538 (1.3)	5.91	[2.68; 13.04]	<.001
No	25 / 562 (4.4)	14 / 532 (2.6)	1.69	[0.89; 3.22]	0.110

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Prior endocrine therapy					
Interaction test	**p = 0.874**				
Yes	52 / 853 (6.1)	16 / 789 (2.0)	3.01	[1.73; 5.22]	<.001
No	15 / 255 (5.9)	5 / 281 (1.8)	3.31	[1.22; 8.97]	0.019
Prior mastectomy					
Interaction test	**p = 0.460**				
Yes	42 / 769 (5.5)	15 / 745 (2.0)	2.71	[1.52; 4.85]	<.001
No	25 / 339 (7.4)	6 / 325 (1.8)	3.99	[1.66; 9.61]	0.002
Prior radiotherapy					
Interaction test	**p = 0.028**				
Yes	64 / 1011 (6.3)	17 / 987 (1.7)	3.68	[2.17; 6.23]	<.001
No	3 / 97 (3.1)	4 / 83 (4.8)	0.64	[0.15; 2.79]	0.554

N: Number of patients
n: Number of patients with event
CI: Confidence interval
RR: Relative risk
ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
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Analysis method for interaction test:
p-value from logistic regression model.
logit(proportion) = treatment + subgroup factor + treatment * subgroup factor

Analysis method for within subgroup analysis:
RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm.
ET was the reference group for treatment group comparison.

Table 5-3.5.9 Renal toxicity: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Renal toxicity					
	n / N (%)	**n / N (%)**			
Region					
Interaction test	**p = 0.022**				
NA/WE/O	21 / 640 (3.3)	2 / 627 (0.3)	10.29	[2.42; 43.69]	0.002
ROW	12 / 468 (2.6)	8 / 443 (1.8)	1.42	[0.59; 3.44]	0.438
Geographical region					
Interaction test	**p = 0.661**				
Europe	25 / 654 (3.8)	9 / 638 (1.4)	2.71	[1.27; 5.76]	0.010
North America/Australia	5 / 213 (2.3)	1 / 194 (0.5)	4.55	[0.54; 38.64]	0.165
Asia	3 / 178 (1.7)	0 / 168 (0.0)	6.61	[0.34; >99.99]	0.210
Latin America	0 / 63 (0.0)	0 / 70 (0.0)	N.E.	N.E.	N.E.
Age group 1 at randomization					
Interaction test	**p = 0.338**				
<45	13 / 549 (2.4)	2 / 496 (0.4)	5.87	[1.33; 25.89]	0.019
45 to 54	19 / 539 (3.5)	6 / 546 (1.1)	3.21	[1.29; 7.97]	0.012
55 to 64	1 / 20 (5.0)	2 / 28 (7.1)	0.70	[0.07; 7.20]	0.764
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)					
Interaction test	**p = 0.344**				
<Median	13 / 549 (2.4)	2 / 496 (0.4)	5.87	[1.33; 25.89]	0.019
≥Median	20 / 559 (3.6)	8 / 574 (1.4)	2.57	[1.14; 5.78]	0.023
Race					
Interaction test	**N.E.**				
Asian	4 / 211 (1.9)	0 / 186 (0.0)	7.94	[0.43; >99.99]	0.164
Non-Asian	27 / 840 (3.2)	10 / 827 (1.2)	2.66	[1.29; 5.46]	0.008
BMI at screening					
Interaction test	**p = 0.307**				
≥25	19 / 551 (3.4)	4 / 523 (0.8)	4.51	[1.54; 13.16]	0.006
<25	13 / 542 (2.4)	6 / 535 (1.1)	2.14	[0.82; 5.59]	0.121
AJCC Anatomic Stage Group					
Interaction test	**p = 0.487**				
Group I/II	10 / 417 (2.4)	2 / 418 (0.5)	5.01	[1.10; 22.74]	0.037
Group III	23 / 691 (3.3)	8 / 652 (1.2)	2.71	[1.22; 6.02]	0.014

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Anatomic stages					
Interaction test	**p = 0.746**				
IA/IB/IIA	4 / 171 (2.3)	1 / 198 (0.5)	4.63	[0.52; 41.04]	0.168
IIB	6 / 246 (2.4)	1 / 220 (0.5)	5.37	[0.65; 44.22]	0.118
IIIA	11 / 451 (2.4)	5 / 393 (1.3)	1.92	[0.67; 5.47]	0.224
IIIB	6 / 67 (9.0)	3 / 59 (5.1)	1.76	[0.46; 6.73]	0.408
IIIC	6 / 173 (3.5)	0 / 200 (0.0)	15.02	[0.85; >99.99]	0.064
Nodal status					
Interaction test	**N.E.**				
N0	3 / 91 (3.3)	0 / 117 (0.0)	8.98	[0.47; >99.99]	0.145
N1-N3	30 / 1017 (2.9)	10 / 950 (1.1)	2.80	[1.38; 5.70]	0.004
Histological grade at time of surgery					
Interaction test	**p = 0.072**				
Grade 1	3 / 110 (2.7)	2 / 100 (2.0)	1.36	[0.23; 7.99]	0.731
Grade 2	24 / 604 (4.0)	4 / 601 (0.7)	5.97	[2.08; 17.10]	<.001
Grade 3	4 / 297 (1.3)	4 / 266 (1.5)	0.90	[0.23; 3.55]	0.875
Histological subtype					
Interaction test	**p = 0.942**				
Ductal	23 / 863 (2.7)	7 / 835 (0.8)	3.18	[1.37; 7.37]	0.007
Lobular	9 / 172 (5.2)	3 / 169 (1.8)	2.95	[0.81; 10.70]	0.100
Other	1 / 73 (1.4)	0 / 66 (0.0)	2.72	[0.11; 65.54]	0.538
Ki67 status from surgical specimen					
Interaction test	**p = 0.589**				
Ki67≤20	17 / 527 (3.2)	7 / 552 (1.3)	2.54	[1.06; 6.08]	0.036
Ki67>20	13 / 422 (3.1)	3 / 378 (0.8)	3.88	[1.11; 13.52]	0.033
Type of NSAI					
Interaction test	**p = 0.263**				
Letrozole	24 / 809 (3.0)	9 / 773 (1.2)	2.55	[1.19; 5.45]	0.016
Anastrozole	9 / 299 (3.0)	1 / 297 (0.3)	8.94	[1.14; 70.12]	0.037
Prior neo/adjuvant chemotherapy					
Interaction test	**p = 0.608**				
Yes	29 / 1029 (2.8)	8 / 987 (0.8)	3.48	[1.60; 7.57]	0.002
No	4 / 79 (5.1)	2 / 83 (2.4)	2.10	[0.40; 11.15]	0.383
Prior adjuvant chemotherapy					
Interaction test	**p = 0.973**				
Yes	10 / 513 (1.9)	3 / 488 (0.6)	3.17	[0.88; 11.45]	0.078
No	23 / 595 (3.9)	7 / 582 (1.2)	3.21	[1.39; 7.43]	0.006
Prior neoadjuvant chemotherapy					
Interaction test	**p = 0.919**				
Yes	20 / 546 (3.7)	6 / 538 (1.1)	3.28	[1.33; 8.12]	0.010
No	13 / 562 (2.3)	4 / 532 (0.8)	3.08	[1.01; 9.38]	0.048

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Prior endocrine therapy					
Interaction test	**p = 0.199**				
Yes	25 / 853 (2.9)	5 / 789 (0.6)	4.62	[1.78; 12.02]	0.002
No	8 / 255 (3.1)	5 / 281 (1.8)	1.76	[0.58; 5.32]	0.314
Prior mastectomy					
Interaction test	**p = 0.283**				
Yes	24 / 769 (3.1)	9 / 745 (1.2)	2.58	[1.21; 5.52]	0.014
No	9 / 339 (2.7)	1 / 325 (0.3)	8.63	[1.10; 67.72]	0.040
Prior radiotherapy					
Interaction test	**p = 0.485**				
Yes	26 / 1011 (2.6)	7 / 987 (0.7)	3.63	[1.58; 8.32]	0.002
No	7 / 97 (7.2)	3 / 83 (3.6)	2.00	[0.53; 7.48]	0.305

N: Number of patients
n: Number of patients with event
N.E.: Not estimable
CI: Confidence interval
RR: Relative risk
ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
.....

Analysis method for interaction test:
p-value from logistic regression model.
logit(proportion) = treatment + subgroup factor + treatment * subgroup factor

Analysis method for within subgroup analysis:
RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm.
ET was the reference group for treatment group comparison.

Table 5-3.5.10 Reproductive toxicity: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	ET (N = 1070)	RR	[95% CI]	p-value
Reproductive toxicity					
	n / N (%)	n / N (%)			
Region The subgroup analysis is not presented as all subgroups have less than 10 events.					
Geographical region The subgroup analysis is not presented as all subgroups have less than 10 events.					
Age group 1 at randomization The subgroup analysis is not presented as all subgroups have less than 10 events.					
Age group 2 at randomization (median for subpopulation pre-menopausal female patients) The subgroup analysis is not presented as all subgroups have less than 10 events.					
Race The subgroup analysis is not presented as all subgroups have less than 10 events.					
BMI at screening The subgroup analysis is not presented as all subgroups have less than 10 events.					
AJCC Anatomic Stage Group The subgroup analysis is not presented as all subgroups have less than 10 events.					
Anatomic stages The subgroup analysis is not presented as all subgroups have less than 10 events.					

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	ET (N = 1070)	RR	[95% CI]	p-value
Nodal status					
The subgroup analysis is not presented as all subgroups have less than 10 events.					
Histological grade at time of surgery					
The subgroup analysis is not presented as all subgroups have less than 10 events.					
Histological subtype					
The subgroup analysis is not presented as all subgroups have less than 10 events.					
Ki67 status from surgical specimen					
The subgroup analysis is not presented as all subgroups have less than 10 events.					
Type of NSAI					
The subgroup analysis is not presented as all subgroups have less than 10 events.					
Prior neo/adjuvant chemotherapy					
The subgroup analysis is not presented as all subgroups have less than 10 events.					
Prior adjuvant chemotherapy					
The subgroup analysis is not presented as all subgroups have less than 10 events.					
Prior neoadjuvant chemotherapy					
The subgroup analysis is not presented as all subgroups have less than 10 events.					
Prior endocrine therapy					
The subgroup analysis is not presented as all subgroups have less than 10 events.					
Prior mastectomy					
The subgroup analysis is not presented as all subgroups have less than 10 events.					

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Prior radiotherapy					
The subgroup analysis is not presented as all subgroups have less than 10 events.					

N: Number of patients
n: Number of patients with event
CI: Confidence interval
RR: Relative risk
ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
.....

Analysis method for interaction test:
p-value from logistic regression model.
logit(proportion) = treatment + subgroup factor + treatment * subgroup factor

Analysis method for within subgroup analysis:
RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm.
ET was the reference group for treatment group comparison.

Table 5-3.5.11 Second Primary Malignancies: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	ET (N = 1070)	RR	[95% CI]	p-value
Second Primary Malignancies					
	n / N (%)	n / N (%)			
Region					
Interaction test	**p = 0.754**				
NA/WE/O	12 / 640 (1.9)	9 / 627 (1.4)	1.31	[0.55; 3.08]	0.541
ROW	9 / 468 (1.9)	8 / 443 (1.8)	1.06	[0.41; 2.74]	0.896
Geographical region					
Interaction test	**p = 0.961**				
Europe	11 / 654 (1.7)	9 / 638 (1.4)	1.19	[0.50; 2.86]	0.693
North America/Australia	5 / 213 (2.3)	4 / 194 (2.1)	1.14	[0.31; 4.18]	0.845
Asia	4 / 178 (2.2)	4 / 168 (2.4)	0.94	[0.24; 3.71]	0.934
Latin America	1 / 63 (1.6)	0 / 70 (0.0)	3.33	[0.14; 80.25]	0.459
Age group 1 at randomization					
Interaction test	**p = 0.483**				
<45	7 / 549 (1.3)	8 / 496 (1.6)	0.79	[0.29; 2.16]	0.647
45 to 54	12 / 539 (2.2)	8 / 546 (1.5)	1.52	[0.63; 3.69]	0.355
55 to 64	2 / 20 (10.0)	1 / 28 (3.6)	2.80	[0.27; 28.80]	0.387
Age group 2 at randomization (median for subpopulation pre-menopausal female patients)					
Interaction test	**p = 0.290**				
<Median	7 / 549 (1.3)	8 / 496 (1.6)	0.79	[0.29; 2.16]	0.647
≥Median	14 / 559 (2.5)	9 / 574 (1.6)	1.60	[0.70; 3.66]	0.268
Race					
Interaction test	**p = 0.511**				
Asian	5 / 211 (2.4)	5 / 186 (2.7)	0.88	[0.26; 3.00]	0.840
Non-Asian	16 / 840 (1.9)	11 / 827 (1.3)	1.43	[0.67; 3.07]	0.355
BMI at screening					
Interaction test	**p = 0.117**				
≥25	13 / 551 (2.4)	6 / 523 (1.1)	2.06	[0.79; 5.37]	0.141
<25	8 / 542 (1.5)	11 / 535 (2.1)	0.72	[0.29; 1.77]	0.472
AJCC Anatomic Stage Group					
Interaction test	**p = 0.718**				
Group I/II	6 / 417 (1.4)	6 / 418 (1.4)	1.00	[0.33; 3.08]	0.997
Group III	15 / 691 (2.2)	11 / 652 (1.7)	1.29	[0.60; 2.78]	0.521

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Anatomic stages					
Interaction test	**p = 0.183**				
IA/IB/IIA	1 / 171 (0.6)	4 / 198 (2.0)	0.29	[0.03; 2.57]	0.265
IIB	5 / 246 (2.0)	2 / 220 (0.9)	2.24	[0.44; 11.41]	0.333
IIIA	9 / 451 (2.0)	2 / 393 (0.5)	3.92	[0.85; 18.04]	0.079
IIIB	0 / 67 (0.0)	1 / 59 (1.7)	0.29	[0.01; 7.08]	0.451
IIIC	6 / 173 (3.5)	8 / 200 (4.0)	0.87	[0.31; 2.45]	0.788
Nodal status					
Interaction test	**p = 0.687**				
N0	2 / 91 (2.2)	3 / 117 (2.6)	0.86	[0.15; 5.02]	0.864
N1-N3	19 / 1017 (1.9)	14 / 950 (1.5)	1.27	[0.64; 2.51]	0.497
Histological grade at time of surgery					
Interaction test	**p = 0.610**				
Grade 1	2 / 110 (1.8)	1 / 100 (1.0)	1.82	[0.17; 19.75]	0.623
Grade 2	15 / 604 (2.5)	10 / 601 (1.7)	1.49	[0.68; 3.30]	0.322
Grade 3	4 / 297 (1.3)	5 / 266 (1.9)	0.72	[0.19; 2.64]	0.616
Histological subtype					
Interaction test	**p = 0.306**				
Ductal	13 / 863 (1.5)	14 / 835 (1.7)	0.90	[0.42; 1.90]	0.779
Lobular	7 / 172 (4.1)	2 / 169 (1.2)	3.44	[0.72; 16.32]	0.120
Other	1 / 73 (1.4)	1 / 66 (1.5)	0.90	[0.06; 14.17]	0.943
Ki67 status from surgical specimen					
Interaction test	**p = 0.964**				
Ki67≤20	13 / 527 (2.5)	11 / 552 (2.0)	1.24	[0.56; 2.74]	0.598
Ki67>20	4 / 422 (0.9)	3 / 378 (0.8)	1.19	[0.27; 5.30]	0.815
Type of NSAI					
Interaction test	**p = 0.771**				
Letrozole	17 / 809 (2.1)	13 / 773 (1.7)	1.25	[0.61; 2.56]	0.542
Anastrozole	4 / 299 (1.3)	4 / 297 (1.3)	0.99	[0.25; 3.93]	0.992
Prior neo/adjuvant chemotherapy					
Interaction test	**p = 0.819**				
Yes	17 / 1029 (1.7)	14 / 987 (1.4)	1.16	[0.58; 2.35]	0.670
No	4 / 79 (5.1)	3 / 83 (3.6)	1.40	[0.32; 6.06]	0.652
Prior adjuvant chemotherapy					
Interaction test	**p = 0.761**				
Yes	9 / 513 (1.8)	8 / 488 (1.6)	1.07	[0.42; 2.75]	0.888
No	12 / 595 (2.0)	9 / 582 (1.5)	1.30	[0.55; 3.07]	0.543
Prior neoadjuvant chemotherapy					
Interaction test	**p = 0.592**				
Yes	9 / 546 (1.6)	6 / 538 (1.1)	1.48	[0.53; 4.12]	0.455
No	12 / 562 (2.1)	11 / 532 (2.1)	1.03	[0.46; 2.32]	0.938

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1108)	**ET (N = 1070)**	**RR**	**[95% CI]**	**p-value**
Prior endocrine therapy					
Interaction test	**p = 0.205**				
Yes	18 / 853 (2.1)	11 / 789 (1.4)	1.51	[0.72; 3.18]	0.275
No	3 / 255 (1.2)	6 / 281 (2.1)	0.55	[0.14; 2.18]	0.396
Prior mastectomy					
Interaction test	**p = 0.942**				
Yes	15 / 769 (2.0)	12 / 745 (1.6)	1.21	[0.57; 2.57]	0.618
No	6 / 339 (1.8)	5 / 325 (1.5)	1.15	[0.35; 3.73]	0.815
Prior radiotherapy					
Interaction test	**p = 0.923**				
Yes	18 / 1011 (1.8)	15 / 987 (1.5)	1.17	[0.59; 2.31]	0.648
No	3 / 97 (3.1)	2 / 83 (2.4)	1.28	[0.22; 7.50]	0.782

N: Number of patients
n: Number of patients with event
CI: Confidence interval
RR: Relative risk
ET: Endocrine therapy (Anastrozole/Letrozole+Goserelin)
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Analysis method for interaction test:
p-value from logistic regression model.
logit(proportion) = treatment + subgroup factor + treatment * subgroup factor

Analysis method for within subgroup analysis:
RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm.
ET was the reference group for treatment group comparison.