Resolution

Gemeinsamer Bundesausschuss

of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL): Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients According to Section 35a SGB V Ribociclib (Reassessment after the Deadline (Breast Cancer, HR+, HER2-, Combination with Fulvestrant))

of 20 August 2020

At its session on 20 August 2020, the Federal Joint Committee (G-BA) resolved to amend the Directive on the Prescription of Medicinal Products in SHI-accredited Medical Care (Pharmaceuticals Directive, AM-RL) in the version dated 18 December 2008/22 January 2009 (Federal Gazette, BAnz. No. 49a of 31 March 2009), as last amended on DD Month YYYY (Federal Gazette, BAnz AT DD MM YYYY BX), as follows:

I. With the repeal of the limitation for patient groups a1) and b1), the findings set out in Annex XII for the active ingredient ribociclib as amended by the resolution of 4 July 2019 (BAnz AT 26 August 2019 B7) shall remain part of the Pharmaceuticals Directive in accordance with the following amendments:

1. The information for ribociclib on the date and entry into force of the resolutions is adopted as follows:

“1st resolution of: 4 July 2019

Entry into force on: 4 July 2019

Federal Gazette, BAnz AT 26 August 2019 B7

2nd resolution of: 20 August 2020

Entry into force on: 20 August 2020

Federal Gazette, BAnz AT DD MM YYYY Bx”

2. The following findings are added to the findings under "Approved therapeutic indication (according to the marketing authorisation of 17 December 2018)":

"Indication:

The resolution of 20 August 2020 relates exclusively to the assessment of the additional benefit of ribociclib in combination with fulvestrant in the sub-populations: a1) post-menopausal patients who have not yet received initial endocrine therapy and b1) post-menopausal patients with previous endocrine therapy".

3. The findings under "1. Additional benefit of the medicinal product in relation to fulvestrant" for the patient populations "a1)" and "b1)" are formulated as follows

"a1) Post-menopausal women with hormone receptor (HR)-positive, HER2-negative locally advanced or metastatic breast cancer who have not yet received initial endocrine therapy:

Appropriate comparator therapy:

Anastrozole or letrozole or fulvestrant or possibly tamoxifen if aromatase inhibitors are not suitable

The extent and probability of additional benefit of ribociclib in combination with fulvestrant compared with fulvestrant:

Indication of a minor additional benefit

b1) Post-menopausal women with hormone receptor (HR)-positive, HER2-negative locally advanced or metastatic breast cancer with previous endocrine therapy:

Appropriate comparator therapy:

Another endocrine therapy depending on the previous therapy with:

- tamoxifen or
- anastrozole or
- fulvestrant; only for patients with relapse or progress after anti-oestrogen treatment or
- letrozole; only for patients with relapse or progress after anti-oestrogen treatment or
- exemestane; only for patients with progress after anti-oestrogen treatment or
- everolimus in combination with exemestane; only for patients without symptomatic visceral metastasis after progression after a non-steroidal aromatase inhibitor.

The extent and probability of additional benefit of ribociclib in combination with fulvestrant compared with fulvestrant:

Hint for a minor additional benefit

Study results according to endpoints:[1]

a1) Post-menopausal women with hormone receptor (HR)-positive, HER2-negative locally advanced or metastatic breast cancer who have not yet received initial endocrine therapy:

MONALEESA-3 study: Ribociclib + fulvestrant vs placebo + fulvestrant

Study design: randomised, double-blind, two-armed

Relevant sub-population: Post-menopausal patients with initial endocrine therapy (80.5% of the study population)

Mortality

Endpoint	**Ribociclib + fulvestrant**		**Fulvestrant**		Intervention vs control
	N	Median time to event in months [95% CI][b] *Patients with event n (%)*	N	Median time to event in months [95% CI][b] *Patients with event n (%)*	Hazard Ratio [95% CI][c] p value[d] Absolute difference (AD)[a]
Overall survival					
	374	n.a. [42.48; n.c.] 123 (32.9)	198	40.0 [37.42; 45.08] 89 (44.9)	0.71 [0.54; 0.94] 0.015

Morbidity

Endpoint	**Ribociclib + fulvestrant**		**Fulvestrant**		Intervention vs control
	N	Median time to event in months [95% CI][b] *Patients with event n (%)*	N	Median time to event in months [95% CI][b] *Patients with event n (%)*	Hazard Ratio [95% CI][c] p value[d] Absolute difference (AD)[a]
Progression-free survival (PFS)[e]					
	374	21.9 [18.6; 27.0] 214 (57.2)	198	12.9 [11.0; 16.6] 158 (79.8)	0.60 [0.49; 0.74] < 0.001 AD: +9 months

[1] Data from the dossier assessment of the IQWiG (A20-21) and the addendum (A20-58) unless otherwise indicated.

Endpoint	Ribociclib + fulvestrant		Fulvestrant		Intervention vs control
	N	Median time to event in months [95% CI][b] *Patients with event n (%)*	N	Median time to event in months [95% CI][b] *Patients with event n (%)*	Hazard Ratio [95% CI][c] p value[d] Absolute difference (AD)[a]
Time to first subsequent chemotherapy[e]					
	374	36.1 [29.11; n.a.] 180 (48.1)	198	23.9 [19.91; 28.19] 127 (64.1)	0.68 [0.54; 0.86] < 0.001 AD: +12.2 months
Symptomatology – time until permanent deterioration [f,g]					
Symptom scales of the EORTC QLQ-C30					
Fatigue	374	38.8 [35.81; n.c.] 108 (28.9)	198	36.0 [28.42; n.c.] 57 (28.8)	0.89 [0.64; 1.22] 0.467
Nausea/vomiting	374	n.a. 12 (3.2)	198	n.a. 4 (2.0)	1.34 [0.43; 4.18] 0.610
Pain	374	41.9 [39.82; n.c.] 79 (21.1)	198	n.a. 31 (15.7)	1.19 [0.79; 1.81] 0.409
Dyspnoea	374	n.a. 20 (5.3)	198	41.4 [38.90; n.c.] 13 (6.6)	0.70 [0.35; 1.41] 0.313
Insomnia	374	n.a. 32 (8.6)	198	n.a. [38.90; n.c.] 14 (7.1)	1.02 [0.55; 1.92] 0.940
Loss of appetite	374	n.a. 23 (6.1)	198	n.a. 5 (2.5)	2.20 [0.83; 5.79] 0.103
Constipation	374	n.a. 17 (4.5)	198	n.a. 6 (3.0)	1.40 [0.55; 3.56] 0.479
Diarrhoea	374	n.a. 6 (1.6)	198	n.a. 0 (0)	-[h]; 0.082

Endpoint	Ribociclib + fulvestrant		Fulvestrant		Intervention vs control
	N	Median time to event in months [95% CI][b] *Patients with event n (%)*	N	Median time to event in months [95% CI][b] *Patients with event n (%)*	Hazard Ratio [95% CI][c] p value[d] Absolute difference (AD)[a]
Health status					
EQ-5D VAS (time until deterioration by ≥ 7 points)[k]					
	374	35.8 [30.39; 41.43] 127 (34)	198	34.9 [27.60; 38.90] 62 (31.3)	0.94 [0.69; 1.27] 0.683
EQ-5D VAS (time until deterioration by ≥ 10 points)[k]					
	374	35.9 [31.05; 41.43] 121 (32.4)	198	34.9 [27.63; 38.90] 60 (30.3)	0.91 [0.67; 1.25] 0.574
EQ-5D VAS (mean change during the course of the study)[l]					
		Values at start of study MV (SD)	**Mean change during the course of the study [95% CI]**	**Values at start of study MV (SD)**	**Mean change during the course of the study [95% CI]**	**MD [95% CI] p value**
	330	no data available	no data available	174	no data available	no data available	−1.44 [−4.15; 1.28] 0.299
Pain (BPI-SF)[m]						
Worst pain (Item 3)	329	3.3 (2.9)	no data available	172	2.7 (2.8)	no data available	−0.16 [−0.53; 0.22] 0.405
Impairment because of pain (Items 9 a–g)	329	2.2 (2.4)	no data available	172	1.8 (2.4)	no data available	0.01 [−0.30; 0.33] 0.936
presented additionally: Pain intensity (Item 3–6)	*329*	*2.5 (2.2)*	*no data available*	*172*	*2.1 (2.1)*	*no data available*	*−0.09 [−0.39; 0.20] 0.526*

Health-related quality of life

Endpoint	Ribociclib + fulvestrant		Fulvestrant		Intervention vs control
	N	Median time to event in months [95% CI][b] *Patients with event n (%)*	N	Median time to event in months [95% CI][b] *Patients with event n (%)*	Hazard Ratio [95% CI][c] p value[d] Absolute difference (AD)[a]
Health-related quality of life – time until permanent deterioration[g, i]					
General health status and functional scales of the EORTC QLQ-C30					
Global health status	374	35.9 [30.42; 42.35] 124 (33.2)	198	33.4 [24.87; 35.98] 63 (31.8)	0.90 [0.67; 1.23] 0.509
Physical function	374	38.7 [34.60; n.c.] 107 (28.6)	198	35.9 [27.63; n.c.] 57 (28.8)	0.84 [0.61; 1.17] 0.305
Role function	374	37.7 [33.08; 41.43] 122 (32.6)	198	35.9 [30.62; n.c.] 48 (24.2)	1.18 [0.84; 1.65] 0.334
Emotional function	374	38.2 [35.91; 41.86] 109 (29.1)	198	33.1 [27.66; 41.72] 58 (29.3)	0.81 [0.59; 1.12] 0.197
Cognitive function	374	39.6 [33.91; n.c.] 114 (30.5)	198	36.1 [34.89; n.c.] 51 (25.8)	1.10 [0.79; 1.54] 0.571
Social function	374	41.4 [35.91; n.c.] 99 (26.5)	198	38.8 [34.89; n.c.] 40 (20.2)	1.15 [0.80; 1.66] 0.457

Side effects

Endpoint	Ribociclib + fulvestrant		Fulvestrant		Intervention vs control
	N	Median time to event in months [95% CI][b] *Patients with event n (%)*	N	Median time to event in months [95% CI][b] *Patients with event n (%)*	Hazard Ratio [95% CI][c] p value[d] Absolute difference (AD)[a]
Adverse events in total (presented additionally)					
	374	0.3 [0.16; 0.30] 369 (98.9)	198	0.4 [0.33; 0.49] 190 (96.0)	-
Serious adverse events (SAE)					
	374	44.2 [36.24; n.c.] 122 (32.7)	198	n.a. 41 (20.7)	1.50 [1.05; 2.14] 0.024
Severe adverse events (CTCAE grade 3 or 4)					
	374	1.9 [1.12; 1.97] 305 (81.8)	198	28.1 [21.85; n.c.] 72 (36.4)	3.90 [3.01; 5.05] < 0.001 AD: - 26.2 months
Therapy discontinuation because of adverse events[j]					
	374	n.a. 58 (15.5)	198	n.a. 13 (6.6)	2.39 [1.31; 4.36] 0.003
Specific adverse events					
Blood and lymphatic system disorders SOC CTCAE grade 3–4)	373	15.7 [10.15; 34.07] 180 (48.3)	198	n.a. 6 (3.0)	21.28 [9.43; 48.02]; < 0.001
Contained therein: Neutropoenia (PT, CTCAE grade 3–4)	373	20.1 [11.99; n.c.] 171 (45.8)	198	n.a. 2 (1.0)	59.73 [14.82; 240.85] < 0.001
Examinations (SOC, CTCAE grade 3–4)	373	n.a. [34.04; n.c.] 136 (36.5)	198	n.a. 13 (6.6)	6.36 [3.60; 11.23] < 0.001
Eye disorders (SOC, AE)	373	n.a. 86 (23.1)	198	n.a. 20 (10.1)	2.29 [1.41; 3.73] < 0.001
Endpoint	**Ribociclib + fulvestrant**		**Fulvestrant**		Intervention vs control

	N	Median time to event in months [95% CI][b] *Patients with event n (%)*	N	Median time to event in months [95% CI][b] *Patients with event n (%)*	Hazard Ratio [95% CI][c] p value[d] Absolute difference (AD)[a]
Skin and subcutaneous tissue disorders (SOC, AE)	373	5.1 [3.91; 8.25] 223 (59.8)	198	n.a. [31.61; n.c.] 58 (28.3)	2.81 [2.09; 3.77] < 0.001

[a] Absolute difference (AD) given only in the case of a statistically significant difference; own calculation
[b] Median time to event and associated 95% CI were estimated using the Kaplan-Meier method
[c] Effect and CI: Cox proportional hazard model, stratified by the presence of liver and/or lung metastases in accordance with IRT
[d] p value: Log-rank test, stratified by the presence of liver and/or lung metastases in accordance with IRT
[e] Information from the dossier of the pharmaceutical company
[f] An increase of the respective score by at least 10 points was considered clinically relevant deterioration, even if this applied to all subsequent values or if the deterioration occurred at the last time the patient was surveyed.
[g] Deaths were not counted as deterioration.
[h] Effect estimation cannot be interpreted meaningfully
[f] A decrease of the respective score by at least 10 points was considered clinically relevant deterioration, even if this applied to all subsequent values or if the deterioration occurred at the last time the patient was surveyed.
j Termination of therapy with ribociclib or placebo; termination of only fulvestrant treatment was not permitted in the study.
[k] A decrease of the score by 7 points or 10 points compared with baseline was considered a deterioration
[l] A positive effect estimate indicates an advantage for ribociclib.
[m] Higher values are equivalent to a worse condition or a worse state of health of the patient; a negative effect estimate indicates an advantage for ribociclib.

Abbreviations used:
AD = absolute difference; BPI_SF: Brief Pain Inventory – Short Form; CTCAE = Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Cancer-30; EQ-5D: European Quality of Life Questionnaire - 5 Dimensions; HR = hazard ratio; IRT: Interactive Response Technology; CI = confidence interval; MD = mean difference; MV = mean value; N = number of patients assessed; n = number of patients with (at least one) event; n.c. = not calculable; n.a. = not achieved; PT = preferred term; RCT = randomised controlled trial; SD = standard deviation; SOC = system organ class; SAE = serious adverse event; AE = adverse event; VAS = visual analogue scale; vs = versus

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ Risk of bias	Summary
Mortality	↑↑	Advantage in overall survival
Morbidity	↔	No differences relevant for the benefit assessment
Health-related quality of life	↔	No differences relevant for the benefit assessment
Side effects	↓↓	Detriments in the endpoints serious adverse events (SAE), severe AE (CTCAE grade 3–4), and therapy discontinuation because of AE as well as in detail for specific AE
Explanations: ↑: statistically significant and relevant positive effect with low/unclear reliability of data ↓: statistically significant and relevant negative effect with low/unclear reliability of data ↑↑: statistically significant and relevant positive effect with high reliability of data ↓↓: statistically significant and relevant negative effect with high reliability of data ↔: no statistically significant or relevant difference ∅: There are no usable data for the benefit assessment. n.a.: not assessable		

b1) Post-menopausal women with hormone receptor (HR)-positive, HER2-negative locally advanced or metastatic breast cancer with previous endocrine therapy:

MONALEESA-3 study: Ribociclib + fulvestrant vs placebo + fulvestrant

Study design: randomised, double-blind, two-armed

Relevant sub-population: Post-menopausal patients with previous endocrine therapy (19.5% of the study population)

Mortality

Endpoint	**Ribociclib + fulvestrant**		**Fulvestrant**		Intervention vs control
	N	Median time to event in months [95% CI][b] *Patients with event n (%)*	N	Median time to event in months [95% CI][b] *Patients with event n (%)*	Hazard Ratio [95% CI][c] p value[d] Absolute difference (AD)[a]
Overall survival					
Sub-population b1	100	n.a. [32.89; n.c.] 42 (42.0)	39	35.4 [20.50; n.c.] 18 (46.2)	0.70 [0.40; 1.24] 0.226
Total population[2]	484	n.a. [42.5; n.a.] 167 (34.5)	242	40 [37.0; n.a.] 108 (44.6)	0.72 [0.57; 0.92] 0.009

Morbidity

Endpoint	**Ribociclib + fulvestrant**		**Fulvestrant**		Intervention vs control
	N	Median time to event in months [95% CI][b] *Patients with event n (%)*	N	Median time to event in months [95% CI][b] *Patients with event n (%)*	Hazard Ratio [95% CI][c] p value[d] Absolute difference (AD)[a]
Progression-free survival (PFS)[e]					
	100	18.8 [12.5; 23.4] 65 (65)	39	9.5 [3.76; 14.7] 32 (82.1)	0.49 [0.31; 0.75] 0.001 AD: + 9.3 months
Endpoint	**Ribociclib + fulvestrant**		**Fulvestrant**		Intervention vs control

[2] The overall survival in the total population is used to assess overall survival in sub-population b1.

	N	Median time to event in months [95% CI][b] *Patients with event n (%)*	N	Median time to event in months [95% CI][b] *Patients with event n (%)*	Hazard Ratio [95% CI][c] p value[d] Absolute difference (AD)[a]
Time to first subsequent chemotherapy[e]					
	100	23.3 [16.23; 32.39] 60(60)	39	16.6 [7.82; 24.31] 29 (74.4)	0.60 [0.38; 0.95] 0.028 AD: + 6.7 months
Symptomatology – time until permanent deterioration[f,g]					
Symptom scales of the EORTC QLQ-C30					
Fatigue	100	38.7 [19.68; n.c.] 30 (30.0)	39	28.0 [9.20; n.c.] 9 (23.1)	0.90 [0.42; 1.93] 0.779
Nausea/vomiting	100	n.a. 1 (1.0)	39	n.a. 2 (5.1)	0.21 [0.02; 2.38] 0.165
Pain	100	n.a. [31.90; n.c.] 20 (20.0)	39	n.a. [12.98; n.c.] 9 (23.1)	0.61 [0.27; 1.36] 0.227
Dyspnoea	100	n.a. 3 (3.0)	39	35.9 [19.32; 35.91] 3 (7.7)	0.29 [0.06; 1.50] 0.120
Insomnia	100	n.a. 10 (10.0)	39	n.a. 4 (10.3)	0.80 [0.25; 2.62] 0.714
Loss of appetite	100	n.a. 3 (3.0)	39	n.a. 0 (0)	–; 0.357
Constipation	100	n.a. 3 (3.0)	39	n.a. 2 (5.1)	0.36 [0.05; 2.61] 0.291
Diarrhoea	100	n.a. 0 (0)	39	n.a. 0 (0)	-
Health status					
EQ-5D VAS (time until deterioration by ≥ 7 points)[k]					
	100	32.5 [14.75; n.a.] 34 (34)	39	22.9 [11.07; 38.67] 14 (35.9)	0.70 [0.37; 1.34] 0.282
Endpoint	**Ribociclib + fulvestrant**		**Fulvestrant**		Intervention vs control

	N	Median time to event in months [95% CI][b] *Patients with event n (%)*	N	Median time to event in months [95% CI][b] *Patients with event n (%)*	Hazard Ratio [95% CI][c] p value[d] Absolute difference (AD)[a]
EQ-5D VAS (time until deterioration by ≥ 10 points)[k]					
	100	33.1 [16.59; n.a.] 32 (32)	39	28 [11.07; 38.67] 13 (33.3)	0.69 [0.36; 1.35] 0.278
EQ-5D VAS (mean change during the course of the study)[l]					
		Values at start of study MV (SD)	**Mean change during the course of the study [95% CI]**	**Values at start of study MV (SD)**	**Mean change during the course of the study [95% CI]**	**MD [95% CI] p value**
No data available					
Pain (BPI-SF)[m]					
Worst pain (Item 3)	82	2.2 (2.4)	no data available	30	3.8 (2.7)	no data available	−0.77 [−1.62; 0.09] 0.080
Impairment because of pain (Items 9 a–g)	82	1.4 (2.0)	no data available	30	2.5 (2.1)	no data available	−0.58 [−1.24; 0.08] 0.086
presented additionally: Pain intensity (Item 3–6)	*82*	*1.8 (1.8)*	*no data available*	*30*	*3.1 (2.0)*	*no data available*	*−0.35 [−1.04; 0.33] 0.310*

Health-related quality of life

Endpoint	Ribociclib + fulvestrant		Fulvestrant		Intervention vs control
	N	Median time to event in months [95% CI][b] *Patients with event n (%)*	N	Median time to event in months [95% CI][b] *Patients with event n (%)*	Hazard Ratio [95% CI][c] p value[d] Absolute difference (AD)[a]
Health-related quality of life – time until permanent deterioration[g, i]					
General health status and functional scales of the EORTC QLQ-C30					
Global health status	100	n.a. [19.35; n.c.] 26 (26.0)	39	16.7 [11.83; 35.91] 15 (38.5)	0.53 [0.28; 1.02] 0.056
Physical function	100	38.7 [35.81; n.c.] 26 (26.0)	39	16.7 [13.90; n.c.] 12 (30.8)	0.52 [0.26; 1.07] 0.072
Role function	100	30.5 [22.01; 38.74] 31 (31.0)	39	24.9 [14.95; n.c.] 9 (23.1)	0.93 [0.43; 1.99] 0.873
Emotional function	100	n.a. [24.94; n.c.] 24 (24.0)	39	22.6 [9.23; 27.96] 15 (38.5)	0.46 [0.24; 0.88] 0.017
Cognitive function	100	35.9 [22.11; n.c.] 29 (29.0)	39	30.4 [14.78; n.c.] 7 (17.9)	1.15 [0.49; 2.65] 0.760
Social function	100	38.7 [30.92; n.c.] 26 (26.0)	39	16.7 [11.20; 27.96] 13 (33.3)	0.51 [0.26; 1.02] 0.054

Side effects

Endpoint	Ribociclib + fulvestrant		Fulvestrant		Intervention vs control
	N	Median time to event in months [95% CI][b] *Patients with event n (%)*	N	Median time to event in months [95% CI][b] *Patients with event n (%)*	Hazard Ratio [95% CI][c] p value[d] Absolute difference (AD)[a]
Adverse events in total (presented additionally)					
	100	0.3 [0.13; 0.49] 100 (100)	39	0.2 [0.07; 0.82] 37 (94.9)	-
Serious adverse events (SAE)					
	100	38.5 [22.28; n.c.] 36 (36.0)	39	n.a. 6 (15.4)	2.06 [0.86; 4.95] 0.099
Severe adverse events (CTCAE grade 3 or 4)					
	100	1.7 [0.95; 3.84] 81 (81.0)	39	n.a. [9.63; n.c.] 11 (28.2)	3.94 [2.08; 7.46] < 0.001
Therapy discontinuation because of adverse events					
	100	n.a. 24 (24.0)	39	n.a. 2 (5.1)	4.73 [1.11; 20.12] < 0.021
Specific adverse events					
Blood and lymphatic system disorders	100	15.7 [7.36; n.c.] 48 (48.0)	39	n.a. 2 (5.1)	11.74 [2.84; 48.47] < 0.001
Contained therein: Neutropoenia (PT, CTCAE grade 3–4)	100	n.a. [15.70; n.c.] 39 (39.0)	39	n.a. 0 (0)	-[h]; <0.001
Skin and subcutaneous tissue disorders (SOC, AE)	100	7.2 [4.44; 11.76] 56 (56.0)	39	n.a. [21.82; n.c.] 8 (20.5)	2.91 [1.38; 6.13] 0.003

[a] Absolute difference (AD) given only in the case of a statistically significant difference; own calculation
[b] Median time to event and associated 95% CI were estimated using the Kaplan-Meier method
[c] Effect and CI: Cox proportional hazard model, stratified by the presence of liver and/or lung metastases in accordance with IRT
[d] p value: Log-rank test, stratified by the presence of liver and/or lung metastases in accordance with IRT
[e] Information from the dossier of the pharmaceutical company

[f] An increase of the respective score by at least 10 points was considered clinically relevant deterioration, even if this applied to all subsequent values or if the deterioration occurred at the last time the patient was surveyed.
[g] Deaths were not counted as deterioration.
[h] Effect estimation cannot be interpreted meaningfully
[f] A decrease of the respective score by at least 10 points was considered clinically relevant deterioration, even if this applied to all subsequent values or if the deterioration occurred at the last time the patient was surveyed.
j Termination of therapy with ribociclib or placebo; termination of only fulvestrant treatment was not permitted in the study.
[k] A decrease of the score by 7 points or 10 points compared with baseline was considered a deterioration
[l] A positive effect estimate indicates an advantage for ribociclib.
[m] Higher values are equivalent to a worse condition or a worse state of health of the patient; a negative effect estimate indicates an advantage for ribociclib.

Abbreviations used:
AD = absolute difference; BPI_SF: Brief Pain Inventory – Short Form; CTCAE = Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Cancer-30; EQ-5D: European Quality of Life Questionnaire - 5 Dimensions; HR = hazard ratio; IRT: Interactive Response Technology; CI = confidence interval; MD = mean difference; MV = mean value; N = number of patients assessed; n = number of patients with (at least one) event; n.c. = not calculable; n.a. = not achieved; PT = preferred term; RCT = randomised controlled trial; SD = standard deviation; SOC = system organ class; SAE = serious adverse event; AE = adverse event; VAS = visual analogue scale; vs = versus

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ Risk of bias	Summary
Mortality	↑	Advantage in overall survival
Morbidity	↔	No differences relevant for the benefit assessment
Health-related quality of life	↑	Advantage in the functional scale emotional function
Side effects	↓↓	Detriments in the endpoints, severe AE (CTCAE grade 3–4) and therapy discontinuation because of AE as well as in detail for specific AE

Explanations:
↑: statistically significant and relevant positive effect with low/unclear reliability of data
↓: statistically significant and relevant negative effect with low/unclear reliability of data
↑↑: statistically significant and relevant positive effect with high reliability of data
↓↓: statistically significant and relevant negative effect with high reliability of data
↔: no statistically significant or relevant difference
∅: There are no usable data for the benefit assessment.
n.a.: not assessable

“

4. The findings under "2. Number of patients or demarcation of patient groups eligible for treatment" for patient population "a1)" and "b1)" are formulated as follows:

"a1) Post-menopausal women with hormone receptor (HR)-positive, HER2-negative locally advanced or metastatic breast cancer who have not yet received initial endocrine therapy:

- approx. 7,400–34,790 patients

b1) Post-menopausal women with hormone receptor (HR)-positive, HER2-negative locally advanced or metastatic breast cancer with previous endocrine therapy:

- approx. 5,470–24,900 patients"

5. The findings under "3. Requirements for a quality-assured application" are formulated as follows:

"The requirements in the product information are to be taken into account. The European Medicines Agency (EMA) provides the contents of the product information (summary of product characteristics, SmPC) for Kisqali® (active ingredient: ribociclib) at the following publicly accessible link (last access: 2 June 2020):

https://www.ema.europa.eu/documents/product-information/kisqali-epar-product-information_de.pdf

Treatment with ribociclib should only be initiated and monitored by specialists in internal medicine, haematology, and oncology, specialists in gynaecology and obstetrics, and specialists participating in the Oncology Agreement who are experienced in the treatment of patients with locally advanced or metastatic breast cancer.

6. Under “4. Treatment costs”, the findings on the annual treatment costs for patient populations “a1)” and “b1)” are formulated as follows:

“a1) Post-menopausal women with hormone receptor (HR)-positive, HER2-negative locally advanced or metastatic breast cancer who have not yet received initial endocrine therapy:

Designation of the therapy	Annual treatment costs/patient
Medicinal product to be assessed:	
Ribociclib	€ 28,917.11
plus fulvestrant	
Fulvestrant	€ 8,980.21
Total:	€ 37,897.32
Appropriate comparator therapy:	
Anastrozole	€ 183.96
Letrozole	€ 164.58
Exemestane	€ 412.78
Tamoxifen	€ 69.28

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 1 August 2020

Costs for additionally required SHI services: not applicable

b1) Post-menopausal women with hormone receptor (HR)-positive, HER2-negative locally advanced or metastatic breast cancer with previous endocrine therapy:

Designation of the therapy	Annual treatment costs/patient
Medicinal product to be assessed:	
Ribociclib	€ 28,917.11
plus fulvestrant	
Fulvestrant	€ 8,980.21
Total:	€ 37,897.32
Appropriate comparator therapy:	
Tamoxifen	€ 69.28
Anastrozole	€ 183.96
Fulvestrant	€ 8,990.75
Letrozole	€ 164.58
Exemestane	€ 412.78
Everolimus + exemestane	
Everolimus	€ 17,145.06
Exemestane	€ 412.78
Total:	€ 17,557.84

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 1 August 2020

Costs for additionally required SHI services: not applicable“

II. The resolution will enter into force with effect from the day of its publication on the internet on the website of the G-BA on 20 August 2020.

The justification to this resolution will be published on the website of the G-BA at www.g-ba.de.

Berlin, 20 August 2020

Federal Joint Committee
in accordance with Section 91 SGB V
The Chair

Prof. Hecken