Dokumentvorlage, Version vom 16.12.2021

Durvalumab (IMFINZI®)

AstraZeneca GmbH

Modul 4A – Anhang 4-G

Durvalumab in Kombination mit einer platinbasierten Chemotherapie zur neoadjuvanten Behandlung gefolgt von Durvalumab als Monotherapie zur adjuvanten Behandlung des resezierbaren nicht-kleinzelligen Lungenkarzinoms (NSCLC) mit hohem Rezidivrisiko und ohne EGFR-Mutationen oder ALK-Translokationen

Stand: 25.07.2025

Anhang 4-G: Ergänzende Unterlagen

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Anhang 4-G1: Patientendisposition

Table 3.1 AEGEAN ITC (Global): Subject disposition
Cisplatin subgroup, Modified ITT analysis set, DCO 10MAY2024

	Number (%) of subjects		
	Durvalumab + SoC (N=100)	Placebo + SoC (N=96)	Total (N=196)
Subjects enrolled [a]			196
Subjects randomized	100 (100)	96 (100)	196 (100)
Subjects who were not randomized			0
Intent-to-treat analysis set [b]	100 (100)	96 (100)	196 (100)
Modified intent-to-treat analysis set [c]	100 (100)	96 (100)	196 (100)
Subjects who received treatment in the neoadjuvant period	100 (100)	95 (99,0)	195 (99,5)
Subjects who did not receive treatment in the neoadjuvant period	0	1 (1,0)	1 (0,5)
Subjects who underwent surgery [d]	88 (88,0)	77 (80,2)	165 (84,2)
Subjects who completed surgery [d]	84 (84,0)	71 (74,0)	155 (79,1)
Subjects who received treatment in the adjuvant period [e]	74 (74,0)	63 (65,6)	137 (69,9)
Subjects who had post-operative radiation therapy	9 (9,0)	8 (8,3)	17 (8,7)
Subjects ongoing neoadjuvant durvalumab / placebo at data cut-off [f]	0	0	0
Subjects who received 4 cycles of neoadjuvant durvalumab / placebo [f]	89 (89,0)	82 (86,3)	171 (87,7)
Subjects who discontinued neoadjuvant durvalumab / placebo [f]	11 (11,0)	13 (13,7)	24 (12,3)
Subject decision	0	1 (1,1)	1 (0,5)
Adverse event	5 (5,0)	4 (4,2)	9 (4,6)
Development of study specific discontinuation criteria [g]	0	1 (1,1)	1 (0,5)
Clinical progression	0	1 (1,1)	1 (0,5)
Radiological progression according to RECIST 1,1	0	1 (1,1)	1 (0,5)
Death	0	1 (1,1)	1 (0,5)
Other [k]	6 (6,0)	4 (4,2)	10 (5,1)

[a] Signed informed consent received. [b] All randomized subjects. [c] Randomized subjects without known EGFRm/ALK translocation Percentages calculated from number of subjects randomized with the exception of rows with footnote [f]. [d] Excludes surgery done outside study. [e] Includes 4 subjects who did not complete surgery. [f] Percentages calculated from number of subjects who received treatment. [g] Includes subjects who completed neoadjuvant treatment but received < 4 cycles. [h] Subjects may have discontinued one non-platinum partner but still received 4 cycles of 2 SoCs. Reasons for discontinuation of SoC are not mutually exclusive for subjects discontinuing multiple SoC components. Subjects counted once per category. Does not include cisplatin discontinuation for subjects switching to carboplatin as allowed by the protocol. [i] May include subjects who never received study treatment. [j] Obtained from public records. [k] Includes investigator decision. Subject randomized to Placebo + SoC, but received Durva in error is reported as Placebo + SoC in this table. SoC = Standard of Care.
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Table 3.1 AEGEAN ITC (Global): Subject disposition
Cisplatin subgroup, Modified ITT analysis set, DCO 10MAY2024

	Number (%) of subjects		
	Durvalumab + SoC (N=100)	Placebo + SoC (N=96)	Total (N=196)
Subjects ongoing any SoC at data cut-off [f]	0	0	0
Subjects who received 4 cycles of two SoCs [f]	84 (84,0)	80 (84,2)	164 (84,1)
Subjects who discontinued at least one SoC [f][h]	17 (17,0)	15 (15,8)	32 (16,4)
Subject decision	1 (1,0)	1 (1,1)	2 (1,0)
Adverse event	9 (9,0)	6 (6,3)	15 (7,7)
Radiological progression according to RECIST 1,1	0	1 (1,1)	1 (0,5)
Death	0	1 (1,1)	1 (0,5)
Other [k]	6 (6,0)	4 (4,2)	10 (5,1)
Development of study specific discontinuation criteria [g]	1 (1,0)	1 (1,1)	2 (1,0)
Clinical progression	0	1 (1,1)	1 (0,5)
Subjects who switched platinum agent [f]	15 (15,0)	7 (7,4)	22 (11,3)
Subjects who underwent surgery	88 (88,0)	77 (80,2)	165 (84,2)
Subjects who did not undergo surgery	12 (12,0)	19 (19,8)	31 (15,8)
Subject decision	3 (3,0)	8 (8,3)	11 (5,6)
Unfit for surgery	1 (1,0)	0	1 (0,5)
Investigator decision	2 (2,0)	1 (1,0)	3 (1,5)
Surgical resection with curative intent that was performed outside the protocol	0	2 (2,1)	2 (1,0)
Other	1 (1,0)	0	1 (0,5)
Missing	0	1 (1,0)	1 (0,5)
Adverse event	0	1 (1,0)	1 (0,5)
Disease progression	4 (4,0)	6 (6,3)	10 (5,1)
Death	1 (1,0)	0	1 (0,5)

[a] Signed informed consent received. [b] All randomized subjects. [c] Randomized subjects without known EGFRm/ALK translocation Percentages calculated from number of subjects randomized with the exception of rows with footnote [f]. [d] Excludes surgery done outside study. [e] Includes 4 subjects who did not complete surgery. [f] Percentages calculated from number of subjects who received treatment. [g] Includes subjects who completed neoadjuvant treatment but received < 4 cycles. [h] Subjects may have discontinued one non-platinum partner but still received 4 cycles of 2 SoCs. Reasons for discontinuation of SoC are not mutually exclusive for subjects discontinuing multiple SoC components. Subjects counted once per category. Does not include cisplatin discontinuation for subjects switching to carboplatin as allowed by the protocol. [i] May include subjects who never received study treatment. [j] Obtained from public records. [k] Includes investigator decision. Subject randomized to Placebo + SoC, but received Durva in error is reported as Placebo + SoC in this table. SoC = Standard of Care.
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Table 3.1 AEGEAN ITC (Global): Subject disposition
Cisplatin subgroup, Modified ITT analysis set, DCO 10MAY2024

	Number (%) of subjects		
	Durvalumab + SoC (N=100)	Placebo + SoC (N=96)	Total (N=196)
Subjects who did not complete surgery	4 (4,0)	6 (6,3)	10 (5,1)
Tumor progression discovered upon attempting surgery	2 (2,0)	2 (2,1)	4 (2,0)
Tumor progression with malignant pleura pleuracarcinosis	1 (1,0)	0	1 (0,5)
Patient not sufficiently fit to tolerate completion of surgery	1 (1,0)	0	1 (0,5)
Other	0	4 (4,2)	4 (2,0)
Subjects who completed surgery, but did not receive treatment in the adjuvant period [d]	10 (10,0)	10 (10,4)	20 (10,2)
Disease progression	3 (3,0)	4 (4,2)	7 (3,6)
Subject decision	1 (1,0)	2 (2,1)	3 (1,5)
Other [k]	0	1 (1,0)	1 (0,5)
Adverse event	6 (6,0)	3 (3,1)	9 (4,6)
Subjects ongoing adjuvant durvalumab / placebo at data cut-off [f]	0	0	0
Subjects who received 12 cycles of adjuvant durvalumab / placebo [f]	51 (51,0)	39 (41,1)	90 (46,2)
Subjects who discontinued adjuvant durvalumab / placebo [f]	23 (23,0)	24 (25,3)	47 (24,1)
Subject decision	1 (1,0)	1 (1,1)	2 (1,0)
Adverse event	6 (6,0)	5 (5,3)	11 (5,6)
Clinical progression	4 (4,0)	3 (3,2)	7 (3,6)
Radiological progression according to RECIST 1,1	12 (12,0)	15 (15,8)	27 (13,8)
Subjects continuing study off treatment [i] at data cut-off	70 (70,0)	59 (61,5)	129 (65,8)
Subjects who terminated study [i]	30 (30,0)	37 (38,5)	67 (34,2)
Death	25 (25,0)	36 (37,5)	61 (31,1)
Withdrawal by subject	5 (5,0)	1 (1,0)	6 (3,1)
Subjects who died after terminating study [j]	0	0	0

[a] Signed informed consent received. [b] All randomized subjects. [c] Randomized subjects without known EGFRm/ALK translocation Percentages calculated from number of subjects randomized with the exception of rows with footnote [f]. [d] Excludes surgery done outside study. [e] Includes 4 subjects who did not complete surgery. [f] Percentages calculated from number of subjects who received treatment. [g] Includes subjects who completed neoadjuvant treatment but received < 4 cycles. [h] Subjects may have discontinued one non-platinum partner but still received 4 cycles of 2 SoCs. Reasons for discontinuation of SoC are not mutually exclusive for subjects discontinuing multiple SoC components. Subjects counted once per category. Does not include cisplatin discontinuation for subjects switching to carboplatin as allowed by the protocol. [i] May include subjects who never received study treatment. [j] Obtained from public records. [k] Includes investigator decision. Subject randomized to Placebo + SoC, but received Durva in error is reported as Placebo + SoC in this table. SoC = Standard of Care.
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Anhang 4-G2: Demografische Charakteristika

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Table 3.2 AEGEAN ITC (Global): Demographic characteristics
Cisplatin subgroup, Modified ITT analysis set, DCO 10MAY2024

Demographic characteristic		Durvalumab + SoC (N=100)	Placebo + SoC (N=96)	Total (N=196)
Age (years) [a]	Max	78	78	78
	Mean	62,6	62,0	62,3
	Median	64,0	62,5	63,0
	Min	40	40	40
	SD	7,39	8,20	7,79
	n	100	96	196
Age group (years) n (%) [a]	<50	4 (4,0)	8 (8,3)	12 (6,1)
	>=50 - <65	52 (52,0)	45 (46,9)	97 (49,5)
	>=65 - <75	41 (41,0)	40 (41,7)	81 (41,3)
	>=75	3 (3,0)	3 (3,1)	6 (3,1)
Sex n (%)	Female	30 (30,0)	26 (27,1)	56 (28,6)
	Male	70 (70,0)	70 (72,9)	140 (71,4)
Race n (%)	American Indian or Alaska Native	2 (2,0)	1 (1,0)	3 (1,5)
	Asian	32 (32,0)	41 (42,7)	73 (37,2)
	Black or African American	2 (2,0)	0	2 (1,0)
	Other	2 (2,0)	4 (4,2)	6 (3,1)
	White	62 (62,0)	50 (52,1)	112 (57,1)
Ethnic group n (%)	Hispanic or Latino	17 (17,0)	19 (19,8)	36 (18,4)
	Not Hispanic or Latino	83 (83,0)	77 (80,2)	160 (81,6)

[a] Age calculated using date of randomization.
Percentages are calculated based on the number of subjects in the analysis set, N.
Max = Maximum. Min = Minimum. N = Number of subjects in treatment group. n = Number of subjects in category or analysis.
SD = Standard deviation. SoC = Standard of Care.
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Table 3.2 AEGEAN ITC (Global): Demographic characteristics
Cisplatin subgroup, Modified ITT analysis set, DCO 10MAY2024

Demographic characteristic		Durvalumab + SoC (N=100)	Placebo + SoC (N=96)	Total (N=196)
Country n (%)	Argentina	1 (1,0)	5 (5,2)	6 (3,1)
	Austria	6 (6,0)	5 (5,2)	11 (5,6)
	Belgium	3 (3,0)	1 (1,0)	4 (2,0)
	Brazil	7 (7,0)	4 (4,2)	11 (5,6)
	Canada	1 (1,0)	0	1 (0,5)
	Chile	1 (1,0)	1 (1,0)	2 (1,0)
	China	8 (8,0)	8 (8,3)	16 (8,2)
	Costa Rica	2 (2,0)	0	2 (1,0)
	France	1 (1,0)	2 (2,1)	3 (1,5)
	Germany	5 (5,0)	1 (1,0)	6 (3,1)
	Hungary	7 (7,0)	7 (7,3)	14 (7,1)
	India	0	5 (5,2)	5 (2,6)
	Italy	6 (6,0)	7 (7,3)	13 (6,6)
	Japan	8 (8,0)	14 (14,6)	22 (11,2)
	Mexico	2 (2,0)	0	2 (1,0)
	Netherlands	0	1 (1,0)	1 (0,5)
	Peru	1 (1,0)	0	1 (0,5)
	Poland	2 (2,0)	0	2 (1,0)
	Russian Federation	5 (5,0)	2 (2,1)	7 (3,6)
	South Korea	8 (8,0)	7 (7,3)	15 (7,7)
	Spain	8 (8,0)	12 (12,5)	20 (10,2)
	Taiwan	5 (5,0)	3 (3,1)	8 (4,1)
	Thailand	1 (1,0)	0	1 (0,5)
	United States of America	10 (10,0)	6 (6,3)	16 (8,2)
	Vietnam	2 (2,0)	5 (5,2)	7 (3,6)

[a] Age calculated using date of randomization.
Percentages are calculated based on the number of subjects in the analysis set, N.
Max = Maximum. Min = Minimum. N = Number of subjects in treatment group. n = Number of subjects in category or analysis.
SD = Standard deviation. SoC = Standard of Care.
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Anhang 4-G3: Folgetherapien

Anhang 4-G3.1: Folgetherapien der AEGEAN-Studie

Table 3.5 AEGEAN ITC (Global): Subsequent anticancer therapies
Cisplatin subgroup, Modified ITT analysis set, DCO 10MAY2024

	Number (%) of subjects		
Anticancer therapy regimen [a]	Durvalumab + SoC (N=100)	Placebo + SoC (N=96)	Total (N=196)
Number of subjects with post-discontinuation anticancer therapy	19 (19,0)	34 (35,4)	53 (27,0)
Regimen category			
Systemic therapy	19 (19,0)	34 (35,4)	53 (27,0)
Cytotoxic chemotherapy	13 (13,0)	18 (18,8)	31 (15,8)
Single agent	3 (3,0)	3 (3,1)	6 (3,1)
Platinum doublet	9 (9,0)	13 (13,5)	22 (11,2)
Other combination	4 (4,0)	3 (3,1)	7 (3,6)
Immunotherapy	7 (7,0)	22 (22,9)	29 (14,8)
IO only	0	12 (12,5)	12 (6,1)
IO+chemo	7 (7,0)	9 (9,4)	16 (8,2)
IO+other	0	1 (1,0)	1 (0,5)
Targeted therapy	1 (1,0)	2 (2,1)	3 (1,5)
Radiotherapy	12 (12,0)	24 (25,0)	36 (18,4)
Concomitant chemoradiotherapy	6 (6,0)	7 (7,3)	13 (6,6)

[a] Therapies post discontinuation of study treatment. Regimen categories manually identified from preferred terms combined by regimen number and treatment start date. Treatment line i.e. 1st, 2nd, 3rd, >3rd subsequent therapy is based on a manually reviewed regimen number using treatment start date. Unknown includes treatments reported as a treatment line or missing data in the treatment status field on the CRF, without clear treatment intent. Treatment line is reported separately using Regimen Number. Subjects with therapies in more than one category are counted once in each of those categories. Percentages are calculated from number of subjects in the modified intent-to-treat in that treatment group.
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Table 3.5 AEGEAN ITC (Global): Subsequent anticancer therapies
Cisplatin subgroup, Modified ITT analysis set, DCO 10MAY2024

	Number (%) of subjects		
Anticancer therapy regimen [a]	Durvalumab + SoC (N=100)	Placebo + SoC (N=96)	Total (N=196)
1st subsequent therapy	19 (19,0)	34 (35,4)	53 (27,0)
Cytotoxic chemotherapy	11 (11,0)	13 (13,5)	24 (12,2)
Single agent	1 (1,0)	1 (1,0)	2 (1,0)
Carboplatin	0	1 (1,0)	1 (0,5)
Vinorelbine	1 (1,0)	0	1 (0,5)
Platinum doublet	8 (8,0)	10 (10,4)	18 (9,2)
Carboplatin + gemcitabine	0	2 (2,1)	2 (1,0)
Carboplatin + gemcitabine hydrochloride	1 (1,0)	0	1 (0,5)
Carboplatin + paclitaxel	4 (4,0)	5 (5,2)	9 (4,6)
Carboplatin + vinorelbine	1 (1,0)	1 (1,0)	2 (1,0)
Cisplatin + docetaxel	0	1 (1,0)	1 (0,5)
Cisplatin + gemcitabine	1 (1,0)	1 (1,0)	2 (1,0)
Cisplatin + vinorelbine	1 (1,0)	0	1 (0,5)
Other combination	2 (2,0)	2 (2,1)	4 (2,0)
Bevacizumab + carboplatin + docetaxel	1 (1,0)	0	1 (0,5)
Bevacizumab + carboplatin + paclitaxel	1 (1,0)	1 (1,0)	2 (1,0)
Cisplatin + gimeracil;oteracil potassium;tegafur	0	1 (1,0)	1 (0,5)
Immunotherapy	7 (7,0)	19 (19,8)	26 (13,3)
IO only	0	10 (10,4)	10 (5,1)
Atezolizumab	0	3 (3,1)	3 (1,5)
Cemiplimab	0	1 (1,0)	1 (0,5)
Nivolumab	0	4 (4,2)	4 (2,0)
Pembrolizumab	0	2 (2,1)	2 (1,0)
IO+chemo	7 (7,0)	8 (8,3)	15 (7,7)
Carboplatin + durvalumab + paclitaxel	1 (1,0)	0	1 (0,5)

[a] Therapies post discontinuation of study treatment. Regimen categories manually identified from preferred terms combined by regimen number and treatment start date. Treatment line i.e. 1st, 2nd, 3rd, >3rd subsequent therapy is based on a manually reviewed regimen number using treatment start date. Unknown includes treatments reported as a treatment line or missing data in the treatment status field on the CRF, without clear treatment intent. Treatment line is reported separately using Regimen Number. Subjects with therapies in more than one category are counted once in each of those categories. Percentages are calculated from number of subjects in the modified intent-to-treat in that treatment group.
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Table 3.5 AEGEAN ITC (Global): Subsequent anticancer therapies
Cisplatin subgroup, Modified ITT analysis set, DCO 10MAY2024

Anticancer therapy regimen [a]	Number (%) of subjects		
	Durvalumab + SoC (N=100)	Placebo + SoC (N=96)	Total (N=196)
Carboplatin + ipilimumab + nivolumab	0	1 (1,0)	1 (0,5)
Carboplatin + ipilimumab + nivolumab + paclitaxel	1 (1,0)	0	1 (0,5)
Carboplatin + paclitaxel + pembrolizumab	1 (1,0)	3 (3,1)	4 (2,0)
Carboplatin + paclitaxel nanoparticle albumin-bound + pembrolizumab	1 (1,0)	0	1 (0,5)
Carboplatin + pembrolizumab + pemetrexed	2 (2,0)	2 (2,1)	4 (2,0)
Cisplatin + pembrolizumab + pemetrexed disodium	0	1 (1,0)	1 (0,5)
Nedaplatin + paclitaxel + tislelizumab	0	1 (1,0)	1 (0,5)
Pembrolizumab + pemetrexed	1 (1,0)	0	1 (0,5)
IO+other	0	1 (1,0)	1 (0,5)
Atezolizumab + bevacizumab + carboplatin + paclitaxel	0	1 (1,0)	1 (0,5)
Targeted therapy	1 (1,0)	2 (2,1)	3 (1,5)
Alectinib	0	1 (1,0)	1 (0,5)
Datopotamab deruxtecan	1 (1,0)	0	1 (0,5)
Tepotinib	0	1 (1,0)	1 (0,5)

[a] Therapies post discontinuation of study treatment. Regimen categories manually identified from preferred terms combined by regimen number and treatment start date. Treatment line i.e. 1st, 2nd, 3rd, >3rd subsequent therapy is based on a manually reviewed regimen number using treatment start date. Unknown includes treatments reported as a treatment line or missing data in the treatment status field on the CRF, without clear treatment intent. Treatment line is reported separately using Regimen Number. Subjects with therapies in more than one category are counted once in each of those categories. Percentages are calculated from number of subjects in the modified intent-to-treat in that treatment group.
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Table 3.5 AEGEAN ITC (Global): Subsequent anticancer therapies
Cisplatin subgroup, Modified ITT analysis set, DCO 10MAY2024

Anticancer therapy regimen [a]	Number (%) of subjects		
	Durvalumab + SoC (N=100)	Placebo + SoC (N=96)	Total (N=196)
2nd subsequent therapy	4 (4,0)	9 (9,4)	13 (6,6)
Cytotoxic chemotherapy	4 (4,0)	5 (5,2)	9 (4,6)
Single agent	1 (1,0)	2 (2,1)	3 (1,5)
Docetaxel	1 (1,0)	0	1 (0,5)
Gemcitabine	0	1 (1,0)	1 (0,5)
Paclitaxel	0	1 (1,0)	1 (0,5)
Platinum doublet	1 (1,0)	2 (2,1)	3 (1,5)
Carboplatin + paclitaxel	1 (1,0)	1 (1,0)	2 (1,0)
Cisplatin + etoposide	0	1 (1,0)	1 (0,5)
Other combination	2 (2,0)	1 (1,0)	3 (1,5)
Docetaxel + nintedanib	2 (2,0)	0	2 (1,0)
Docetaxel + nintedanib esilate	0	1 (1,0)	1 (0,5)
Immunotherapy	0	3 (3,1)	3 (1,5)
IO only	0	2 (2,1)	2 (1,0)
Nivolumab	0	1 (1,0)	1 (0,5)
Pembrolizumab	0	1 (1,0)	1 (0,5)
IO+chemo	0	1 (1,0)	1 (0,5)
Carboplatin + paclitaxel + pembrolizumab	0	1 (1,0)	1 (0,5)
Targeted therapy	0	1 (1,0)	1 (0,5)
Capmatinib	0	1 (1,0)	1 (0,5)

[a] Therapies post discontinuation of study treatment. Regimen categories manually identified from preferred terms combined by regimen number and treatment start date. Treatment line i.e. 1st, 2nd, 3rd, >3rd subsequent therapy is based on a manually reviewed regimen number using treatment start date. Unknown includes treatments reported as a treatment line or missing data in the treatment status field on the CRF, without clear treatment intent. Treatment line is reported separately using Regimen Number. Subjects with therapies in more than one category are counted once in each of those categories. Percentages are calculated from number of subjects in the modified intent-to-treat in that treatment group.
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Table 3.5 AEGEAN ITC (Global): Subsequent anticancer therapies
Cisplatin subgroup, Modified ITT analysis set, DCO 10MAY2024

	Number (%) of subjects		
Anticancer therapy regimen [a]	Durvalumab + SoC (N=100)	Placebo + SoC (N=96)	Total (N=196)
>=3rd subsequent therapy	2 (2,0)	2 (2,1)	4 (2,0)
Cytotoxic chemotherapy	2 (2,0)	2 (2,1)	4 (2,0)
Single agent	1 (1,0)	1 (1,0)	2 (1,0)
Docetaxel	1 (1,0)	0	1 (0,5)
Vinorelbine tartrate	0	1 (1,0)	1 (0,5)
Platinum doublet	1 (1,0)	1 (1,0)	2 (1,0)
Carboplatin + gemcitabine hydrochloride	1 (1,0)	0	1 (0,5)
Carboplatin + pemetrexed disodium	0	1 (1,0)	1 (0,5)

[a] Therapies post discontinuation of study treatment. Regimen categories manually identified from preferred terms combined by regimen number and treatment start date. Treatment line i.e. 1st, 2nd, 3rd, >3rd subsequent therapy is based on a manually reviewed regimen number using treatment start date. Unknown includes treatments reported as a treatment line or missing data in the treatment status field on the CRF, without clear treatment intent. Treatment line is reported separately using Regimen Number. Subjects with therapies in more than one category are counted once in each of those categories. Percentages are calculated from number of subjects in the modified intent-to-treat in that treatment group.
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Table 3.5 AEGEAN ITC (Global): Subsequent anticancer therapies
Cisplatin subgroup, Modified ITT analysis set, DCO 10MAY2024

Anticancer therapy regimen [a]	Number (%) of subjects: Durvalumab + SoC (N=100)	Placebo + SoC (N=96)	Total (N=196)
Treatment Status (Intent)			
Neoadjuvant	2 (2,0)	3 (3,1)	5 (2,6)
Adjuvant	2 (2,0)	4 (4,2)	6 (3,1)
Definitive	2 (2,0)	1 (1,0)	3 (1,5)
Maintenance	2 (2,0)	0	2 (1,0)
Palliative	13 (13,0)	27 (28,1)	40 (20,4)
Not applicable	1 (1,0)	0	1 (0,5)

[a] Therapies post discontinuation of study treatment. Regimen categories manually identified from preferred terms combined by regimen number and treatment start date. Treatment line i.e. 1st, 2nd, 3rd, >3rd subsequent therapy is based on a manually reviewed regimen number using treatment start date. Unknown includes treatments reported as a treatment line or missing data in the treatment status field on the CRF, without clear treatment intent. Treatment line is reported separately using Regimen Number. Subjects with therapies in more than one category are counted once in each of those categories. Percentages are calculated from number of subjects in the modified intent-to-treat in that treatment group.
root/cdar/d419/d9106c00001/ar/pay_germany/tlf/prod/program/b_subtherapy_itc.sas gb_subtherapy_itca 08MAY2025:09:00

Anhang 4-G3.2: Folgetherapien der KEYNOTE 671-Studie (Quelle: Modul 4 des Pembrolizumab-Dossiers (2))

Dossier zur Nutzenbewertung – Modul 4 A Stand: 19.04.2024
Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Tabelle 4-38: Übersicht der ersten onkologischen Folgetherapien in der Studie KEYNOTE 671

	Studie: KEYNOTE 671[a]	
Erste onkologische Folgetherapie	**Pembrolizumab + Chemotherapie[b] / Pembrolizumab N[c]= 397**	**Placebo + Chemotherapie[b] / Placebo N[c]= 400**
Erste onkologische Folgetherapie, n (%)		
Erste Folgetherapie war eine systemische Therapie[d]	77 (19,4)	144 (36,0)
Erste Folgetherapie war eine Radiotherapie	27 (6,8)	44 (11,0)
Erste Folgetherapie war eine systemische Therapie und Radiotherapie[e]	6 (1,5)	13 (3,3)
Verstorben, ohne eine Folgetherapie erhalten zu haben	61 (15,4)	45 (11,3)
Haben keine Folgetherapie erhalten	226 (56,9)	154 (38,5)

a: Datenschnitt: 10. Juli 2023
b: Cisplatin plus Gemcitabin (Plattenepithel) oder Cisplatin plus Pemetrexed (Nicht-Plattenepithel)
c: Anzahl der Patient:innen: Intention-To-Treat Population
d: Patienten mit onkologischer Folgetherapie einschließlich Immuntherapie, zytotoxischer Therapie, zielgerichteter Therapie oder anderer Therapie
e: Patient:innen die sowohl eine systemische Therapie als auch Radiotherapie erhalten haben, werden nur einmal in der kombinierten Kategorie gewertet

Tabelle 4-39: Übersicht der ersten onkologischen systemischen Folgetherapien in der Studie KEYNOTE 671

Studie: KEYNOTE 671[a]	**Patient:innen mit Ereignis n (%)**	
Therapieklasse[c] **Therapiebegriff[d]**	**Pembrolizumab + Chemotherapie[b] / Pembrolizumab (N[c]= 397)**	**Placebo + Chemotherapie[b] / Placebo (N[c]= 400)**
Patienten, die als erstes eine systemische Folgetherapie erhalten haben	83 (20,9)	157 (39,3)
Anaplastische Lymphom-Kinase (ALK)-Inhibitoren	7 (1,8)	2 (0,5)
Alectinib	4 (1,0)	1 (0,3)
Alectinib Hydrochlorid	1 (0,3)	1 (0,3)
Brigatinib	1 (0,3)	0 (0,0)
Ceritinib	1 (0,3)	0 (0,0)
Anthracycline und verwandte Substanzen	0 (0,0)	1 (0,3)
Doxorubicin	0 (0,0)	1 (0,3)
Antineoplastische Therapien	1 (0,3)	0 (0,0)
Antineoplastische Therapien	1 (0,3)	0 (0,0)
Epidermal Growth Factor Receptor (EGFR) Tyrosin Kinase Inhibitoren	9 (2,3)	20 (5,0)
Osimertinib	4 (1,0)	6 (1,5)
Osimertinib Mesilat	1 (0,3)	6 (1,5)
Icotinib Hydrochlorid	0 (0,0)	4 (1,0)
Afatinib	2 (0,5)	1 (0,3)
Furmonertinib Mesilat	1 (0,3)	1 (0,3)
Gefitinib	1 (0,3)	1 (0,3)
Afatinib Dimaleat	0 (0,0)	1 (0,3)
Erlotinib	0 (0,0)	1 (0,3)
Folsäure Analoga	9 (2,3)	21 (5,3)
Pemetrexed	9 (2,3)	20 (5,0)
Pemetrexed Dinatrium Heptahydrat	0 (0,0)	1 (0,3)
Prüfpräparat	0 (0,0)	1 (0,3)
Prüfpräparat	0 (0,0)	1 (0,3)
Mehrere	20 (5,0)	43 (10,8)
Paclitaxel	18 (4,5)	37 (9,3)
Bevacizumab	2 (0,5)	8 (2,0)
Astragalus Mongholicus Wurzel, Bärengalle, Cornus Officinalis Frucht, Curcuma Spp. Rhizom, Eleutherococcus Senticosus Wurzel mit Rhizom, Glycyrrhiza Spp. Wurzel mit Rhizom, Ligustrum Lucidum Frucht, Mylabris Spp., Panax Ginseng Wurzel mit Rhizom, Scutellaria Barbata Ganze Pflanze, Sparganium Stoloniferum Knolle	1 (0,3)	0 (0,0)

Dossier zur Nutzenbewertung – Modul 4 A Stand: 19.04.2024
Medizinischer Nutzen, medizinischer Zusatznutzen, Patientengruppen mit therap. bedeutsamem Zusatznutzen

Studie: KEYNOTE 671[a]	**Patient:innen mit Ereignis n (%)**	
Therapieklasse[c] **Therapiebegriff[d]**	**Pembrolizumab + Chemotherapie[b] / Pembrolizumab (N[c]= 397)**	**Placebo + Chemotherapie[b] / Placebo (N[c]= 400)**
Envafolimab	0 (0,0)	1 (0,3)
Antineoplastische Prüfpräparate	0 (0,0)	1 (0,3)
Magrolimab	1 (0,3)	0 (0,0)
Vibostolimab	0 (0,0)	1 (0,3)
Stickstoffsenf-Analoga	0 (0,0)	1 (0,3)
Cyclophosphamid	0 (0,0)	1 (0,3)
Alkylanzien	0 (0,0)	1 (0,3)
Lomustin	0 (0,0)	1 (0,3)
Andere antineoplastische Wirkstoffe	2 (0,5)	0 (0,0)
Sotorasib	2 (0,5)	0 (0,0)
Andere zytotoxische Antibiotika	0 (0,0)	1 (0,3)
Mitomycin	0 (0,0)	1 (0,3)
Weitere Medikamente, welche die Knochenstruktur und Mineralisierung beeinflussen	0 (0,0)	1 (0,3)
Denosumab	0 (0,0)	1 (0,3)
Weitere monoklonale Antikörper und Antikörper-Wirkstoff-Konjugate	1 (0,3)	6 (1,5)
Ipilimumab	0 (0,0)	5 (1,3)
Cadonilimab	1 (0,3)	0 (0,0)
Relatlimab	0 (0,0)	1 (0,3)
Weitere Proteinkinase Inhibitoren	1 (0,3)	1 (0,3)
Catequentinib hydrochloride	0 (0,0)	1 (0,3)
Tepotinib	1 (0,3)	0 (0,0)
Weitere Arzneimittel	1 (0,3)	2 (0,5)
Weitere Arzneimittel	1 (0,3)	2 (0,5)
PD-1/PDL-1 (Programmed Cell Death Protein 1/Programmed Cell Death Ligand 1) Inhibitoren	15 (3,8)	73 (18,3)
Pembrolizumab	9 (2,3)	37 (9,3)
Nivolumab	0 (0,0)	13 (3,3)
Atezolizumab	1 (0,3)	11 (2,8)
Durvalumab	3 (0,8)	5 (1,3)
Tislelizumab	1 (0,3)	4 (1,0)
Camrelizumab	1 (0,3)	1 (0,3)
Sintilimab	0 (0,0)	2 (0,5)
Platinverbindungen	42 (10,6)	82 (20,5)
Carboplatin	32 (8,1)	70 (17,5)
Cisplatin	9 (2,3)	12 (3,0)
Nedaplatin	1 (0,3)	1 (0,3)
Podophyllotoxin Derivate	3 (0,8)	9 (2,3)
Etoposid	3 (0,8)	9 (2,3)
Pyrimidin Analoga	10 (2,5)	8 (2,0)
Gemcitabin	7 (1,8)	6 (1,5)
Gemcitabin Hydrochlorid	1 (0,3)	1 (0,3)
Gimeracil; Oteracil Kalium; Tegafur	1 (0,3)	1 (0,3)
Tegafur-Uracil	1 (0,3)	0 (0,0)
Taxane	10 (2,5)	14 (3,5)
Docetaxel	9 (2,3)	5 (1,3)
nab-Paclitaxel	1 (0,3)	9 (2,3)
VEGF/VEGFR (Vascular Endothelial Growth Factor Receptor) Inhibitoren	2 (0,5)	2 (0,5)
Ramucirumab	2 (0,5)	2 (0,5)
Vinca-Alkaloide und Analoga	4 (1,0)	5 (1,3)
Vinorelbin	4 (1,0)	4 (1,0)
Vincristin	0 (0,0)	1 (0,3)

a: Datenschnitt: 10. Juli 2023

b: Cisplatin plus Gemcitabin (Plattenepithel) oder Cisplatin plus Pemetrexed (Nicht-Plattenepithel)

c: Eine bestimmte Therapieklasse erscheint nur dann, wenn das Inzidenzkriterium > 0% (nach Rundung) in einer oder mehreren der Spalten erfüllt ist. Ein:e Patient:in mit mehreren verabreichten systemischen Therapien einer Therapieklasse wird nur einmal zu dieser gerechnet

Studie: KEYNOTE 671[a]	**Patient:innen mit Ereignis n (%)**	
Therapieklasse[c] **Therapiebegriff[d]**	**Pembrolizumab + Chemotherapie[b] / Pembrolizumab (N[e]= 397)**	**Placebo + Chemotherapie[b] / Placebo (N[e]= 400)**
d: Jede:r Patient:in wird nur einmal in der Kategorie der systemischen Therapien, in denen er ein Ereignis hatte, gewertet e: Anzahl der Patient:innen: Intention-To-Treat Population		

Sofern die vorliegenden Studien bzw. Daten für eine Meta-Analyse medizinisch und methodisch geeignet sind, fassen Sie die Einzelergebnisse mithilfe von Meta-Analysen quantitativ zusammen und stellen Sie die Ergebnisse der Meta-Analysen (in der Regel als Forest-Plot) dar. Beschreiben Sie die Ergebnisse zusammenfassend. Begründen Sie, warum eine Meta-Analyse durchgeführt wurde bzw. warum eine Meta-Analyse nicht durchgeführt wurde bzw. warum einzelne Studien ggf. nicht in die Meta-Analyse einbezogen wurden. Machen Sie auch Angaben zur Übertragbarkeit der Studienergebnisse auf den deutschen Versorgungskontext.

Da nur eine RCT zum zbAM im Anwendungsgebiet vorliegt, wurde keine Meta-Analyse durchgeführt.

Anhang 4-G4: Definition der UESI

Anhang 4-G4.1: Liste der PTs der AEGEAN-Studie

Study Code: D9106C00001 Phase III
IA2 - Data Cut-off: 2024-05-10
Table 14.3.6.1.1.IA2 Adverse events of special or possible interest - list of preferred terms (Safety analysis set)

Specific adverse event of interest: Category	Specific adverse event of interest: Sub-category	AE Type	MedDRA Preferred term
Adrenal insufficiency	Adrenal insufficiency	AESI	^Addison's disease
			Adrenal insufficiency
			^Adrenocortical insufficiency acute
			^Immune-mediated adrenal insufficiency
			^Primary adrenal insufficiency
		AEPI	^Blood corticotrophin increased
			^Glucocorticoid deficiency
			^Secondary adrenocortical insufficiency
			^Tertiary adrenal insufficiency
Dermatitis/Rash	Dermatitis	AESI	^AGEP-DRESS overlap
			^Autoimmune blistering disease
			^Autoimmune dermatitis
			^Bullous haemorrhagic dermatosis
			Dermatitis
			^Dermatitis bullous
			^Dermatitis exfoliative

Specific adverse events of special interest or possible interest may either be grouped MedDRA preferred terms or individual MedDRA preferred terms.
AESI = Adverse event of special interest. AEPI = Adverse event of possible interest.
^ = MedDRA Preferred term searched for but not present in the study.
MedDRA version 26.1. AESI version 19.1.

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Table 14.3.6.1.1.IA2 Adverse events of special or possible interest - list of preferred terms (Safety analysis set)

Specific adverse event of interest: Category	Specific adverse event of interest: Sub-category	AE Type	MedDRA Preferred term
Dermatitis/Rash	Dermatitis	AESI	^Dermatitis exfoliative generalised
			Dermatitis psoriasiform
			Eczema
			^Eczema nummular
			^Eczema vesicular
			^Erythema multiforme
			^Immune-mediated dermatitis
			^Mucous membrane pemphigoid
			^Ocular pemphigoid
			Pemphigoid
			^Pemphigus
			^Periorbital dermatitis
			^Pityriasis lichenoides et varioliformis acuta
			^Pityriasis rosea
			^Pityriasis rubra pilaris
			Psoriasis
			^Pustular psoriasis

Specific adverse events of special interest or possible interest may either be grouped MedDRA preferred terms or individual MedDRA preferred terms.
AESI = Adverse event of special interest. AEPI = Adverse event of possible interest.
^ = MedDRA Preferred term searched for but not present in the study.
MedDRA version 26.1. AESI version 19.1.

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Study Code: D9106C00001 Phase III
IA2 - Data Cut-off: 2024-05-10
Table 14.3.6.1.1.IA2 Adverse events of special or possible interest - list of preferred terms (Safety analysis set)

Specific adverse event of interest: Category	Specific adverse event of interest: Sub-category	AE Type	MedDRA Preferred term
Dermatitis/Rash	Dermatitis	AESI	^SJS-TEN overlap
			Seborrhoeic dermatitis
			^Stevens-Johnson syndrome
			^Toxic epidermal necrolysis
			^Toxic skin eruption
			Urticarial dermatitis
		AEPI	Dermatosis
			^Dermo-hypodermitis
			Erythema
			Pruritus
			^Severe cutaneous adverse reaction
			Skin exfoliation
			^Skin necrosis
			Skin toxicity
			Superficial inflammatory dermatosis
	Rash	AESI	^Exfoliative rash
			^Lichen planopilaris

Specific adverse events of special interest or possible interest may either be grouped MedDRA preferred terms or individual MedDRA preferred terms.
AESI = Adverse event of special interest. AEPI = Adverse event of possible interest.
^ = MedDRA Preferred term searched for but not present in the study.
MedDRA version 26.1. AESI version 19.1.

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Study Code: D9106C00001 Phase III Page 4 of 23
IA2 - Data Cut-off: 2024-05-10
Table 14.3.6.1.1.IA2 Adverse events of special or possible interest - list of preferred terms (Safety analysis set)

Specific adverse event of interest: Category	Specific adverse event of interest: Sub-category	AE Type	MedDRA Preferred term
Dermatitis/Rash	Rash	AESI	^Lichen planus
			^Lichen planus pemphigoides
			^Oral lichen planus
			Rash
			Rash erythematous
			^Rash follicular
			Rash macular
			Rash maculo-papular
			^Rash maculovesicular
			^Rash morbilliform
			Rash papular
			^Rash papulosquamous
			Rash pruritic
			Rash pustular
			^Rash vesicular
			^Vasculitic rash
		AEPI	Dermatitis acneiform

Specific adverse events of special interest or possible interest may either be grouped MedDRA preferred terms or individual MedDRA preferred terms.
AESI = Adverse event of special interest. AEPI = Adverse event of possible interest.
^ = MedDRA Preferred term searched for but not present in the study.
MedDRA version 26.1. AESI version 19.1.

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Table 14.3.6.1.1.IA2 Adverse events of special or possible interest - list of preferred terms (Safety analysis set)

Specific adverse event of interest: Category	Specific adverse event of interest: Sub-category	AE Type	MedDRA Preferred term
Dermatitis/Rash	Rash	AEPI	^Heliotrope rash
			^Mucocutaneous rash
			^Nodular rash
			^Oral lichenoid reaction
Diarrhoea/Colitis	Colitis	AESI	^Autoimmune colitis
			^Autoimmune enteropathy
			Colitis
			^Colitis ulcerative
			Enteritis
			^Enterocolitis
			^Immune-mediated enterocolitis
		AEPI	^Acute haemorrhagic ulcerative colitis
			^Colitis erosive
			^Colitis microscopic
			^Enterocolitis haemorrhagic
			^Microscopic enteritis

Specific adverse events of special interest or possible interest may either be grouped MedDRA preferred terms or individual MedDRA preferred terms.
AESI = Adverse event of special interest. AEPI = Adverse event of possible interest.
^ = MedDRA Preferred term searched for but not present in the study.
MedDRA version 26.1. AESI version 19.1.

Program: S:\AZ\Durvalumab\AEGEAN\IA2\Prog\Output\aesi4.sas Executed : 2024-07-09T122719

Table 14.3.6.1.1.IA2 Adverse events of special or possible interest - list of preferred terms (Safety analysis set)

Specific adverse event of interest: Category	Specific adverse event of interest: Sub-category	AE Type	MedDRA Preferred term
Diarrhoea/Colitis	Colitis	AEPI	^Necrotising colitis
			Proctitis
			^Proctitis haemorrhagic
	Diarrhoea	AESI	Diarrhoea
		AEPI	^Diarrhoea haemorrhagic
			^Frequent bowel movements
			Gastroenteritis
Guillain-Barre syndrome	Guillain-Barre syndrome	AESI	^Acute motor axonal neuropathy
			^Acute motor-sensory axonal neuropathy
			^Acute polyneuropathy
			^Autoimmune neuropathy
			^Axonal and demyelinating polyneuropathy
			^Demyelinating polyneuropathy
			^Guillain-Barre syndrome
			^Immune-mediated neuropathy
			^Miller Fisher syndrome

Specific adverse events of special interest or possible interest may either be grouped MedDRA preferred terms or individual MedDRA preferred terms.
AESI = Adverse event of special interest. AEPI = Adverse event of possible interest.
^ = MedDRA Preferred term searched for but not present in the study.
MedDRA version 26.1. AESI version 19.1.

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IA2 - Data Cut-off: 2024-05-10
Table 14.3.6.1.1.IA2 Adverse events of special or possible interest - list of preferred terms (Safety analysis set)

Specific adverse event of interest: Category	Specific adverse event of interest: Sub-category	AE Type	MedDRA Preferred term
Guillain-Barre syndrome	Guillain-Barre syndrome	AESI	^Subacute inflammatory demyelinating polyneuropathy
		AEPI	^Demyelination
Hepatic events	Hepatic events	AESI	Autoimmune hepatitis
			Drug-induced liver injury
			^Hepatic lymphocytic infiltration
			Hepatitis
			^Hepatitis acute
			^Hepatitis fulminant
			Immune-mediated hepatitis
		AEPI	^Acute hepatic failure
			Alanine aminotransferase increased
			Aspartate aminotransferase increased
			Blood bilirubin increased
			Blood bilirubin unconjugated increased
			Hepatic cytolysis
			^Hepatic enzyme abnormal

Specific adverse events of special interest or possible interest may either be grouped MedDRA preferred terms or individual MedDRA preferred terms.
AESI = Adverse event of special interest. AEPI = Adverse event of possible interest.
^ = MedDRA Preferred term searched for but not present in the study.
MedDRA version 26.1. AESI version 19.1.

Program: S:\AZ\Durvalumab\AEGEAN\IA2\Prog\Output\aesi4.sas Executed : 2024-07-09T122719

Table 14.3.6.1.1.IA2 Adverse events of special or possible interest - list of preferred terms (Safety analysis set)

Specific adverse event of interest: Category	Specific adverse event of interest: Sub-category	AE Type	MedDRA Preferred term
Hepatic events	Hepatic events	AEPI	Hepatic enzyme increased
			Hepatic failure
			Hepatic function abnormal
			^Hepatitis toxic
			^Hepatocellular injury
			^Hepatotoxicity
			Hyperbilirubinaemia
			Hypertransaminasaemia
			^Immune-mediated hepatic disorder
			^Jaundice
			^Jaundice hepatocellular
			^Liver function test increased
			^Mitochondrial aspartate aminotransferase increased
			^Subacute hepatic failure
			^Transaminases abnormal
			Transaminases increased
			^Yellow skin

Specific adverse events of special interest or possible interest may either be grouped MedDRA preferred terms or individual MedDRA preferred terms.
AESI = Adverse event of special interest. AEPI = Adverse event of possible interest.
^ = MedDRA Preferred term searched for but not present in the study.
MedDRA version 26.1. AESI version 19.1.

Program: S:\AZ\Durvalumab\AEGEAN\IA2\Prog\Output\aesi4.sas Executed : 2024-07-09T122719

Table 14.3.6.1.1.IA2 Adverse events of special or possible interest - list of preferred terms (Safety analysis set)

Specific adverse event of interest: Category	Specific adverse event of interest: Sub-category	AE Type	MedDRA Preferred term
Hyperthyroid events	Hyperthyroid events	AESI	Graves' disease
			Hyperthyroidism
			Immune-mediated hyperthyroidism
			^Primary hyperthyroidism
			^Thyrotoxic crisis
		AEPI	Blood thyroid stimulating hormone decreased
			^Secondary hyperthyroidism
			^Thyroxine free increased
			^Thyroxine increased
			^Toxic goitre
			^Toxic nodular goitre
			^Tri-iodothyronine free increased
			Tri-iodothyronine increased
Hypophysitis	Hypophysitis	AESI	^Adrenocorticotropic hormone deficiency
			^Diabetes insipidus
			Hypophysitis

Specific adverse events of special interest or possible interest may either be grouped MedDRA preferred terms or individual MedDRA preferred terms.
AESI = Adverse event of special interest. AEPI = Adverse event of possible interest.
^ = MedDRA Preferred term searched for but not present in the study.
MedDRA version 26.1. AESI version 19.1.

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IA2 - Data Cut-off: 2024-05-10
Table 14.3.6.1.1.IA2 Adverse events of special or possible interest - list of preferred terms (Safety analysis set)

Specific adverse event of interest: Category	Specific adverse event of interest: Sub-category	AE Type	MedDRA Preferred term
Hypophysitis	Hypophysitis	AESI	^Hypopituitarism
			^Hypothalamic pituitary adrenal axis suppression
			^Hypothalamo-pituitary disorder
			^Immune-mediated hypophysitis
			^Lymphocytic hypophysitis
		AEPI	^Pituitary scan abnormal
Hypothyroid events	Hypothyroid events	AESI	^Autoimmune hypothyroidism
			^Central hypothyroidism
			Hypothyroidism
			^Immune-mediated hypothyroidism
			Primary hypothyroidism
		AEPI	Blood thyroid stimulating hormone increased
			^Decompensated hypothyroidism
			^Myxoedema
			^Thyroxine decreased
			Thyroxine free decreased

Specific adverse events of special interest or possible interest may either be grouped MedDRA preferred terms or individual MedDRA preferred terms.
AESI = Adverse event of special interest. AEPI = Adverse event of possible interest.
^ = MedDRA Preferred term searched for but not present in the study.
MedDRA version 26.1. AESI version 19.1.

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Study Code: D9106C00001 Phase III Page 11 of 23
IA2 - Data Cut-off: 2024-05-10
Table 14.3.6.1.1.IA2 Adverse events of special or possible interest - list of preferred terms (Safety analysis set)

Specific adverse event of interest: Category	Specific adverse event of interest: Sub-category	AE Type	MedDRA Preferred term
Hypothyroid events	Hypothyroid events	AEPI	^Tri-iodothyronine decreased
			Tri-iodothyronine free decreased
Infusion/hypersensitivity reactions	Hypersensitivity/Anaphylactic reactions	AESI	^Allergy to immunoglobulin therapy
			Anaphylactic reaction
			^Anaphylactic shock
			^Anaphylactoid reaction
			^Anaphylactoid shock
			^Cross sensitivity reaction
			Drug eruption
			Drug hypersensitivity
			^Generalised bullous fixed drug eruption
			Hypersensitivity
			^Infusion related hypersensitivity reaction
			^Serum sickness
			^Serum sickness-like reaction
			^Systemic immune activation

Specific adverse events of special interest or possible interest may either be grouped MedDRA preferred terms or individual MedDRA preferred terms.
AESI = Adverse event of special interest. AEPI = Adverse event of possible interest.
^ = MedDRA Preferred term searched for but not present in the study.
MedDRA version 26.1. AESI version 19.1.

Program: S:\AZ\Durvalumab\AEGEAN\IA2\Prog\Output\aesi4.sas Executed : 2024-07-09T122719

Table 14.3.6.1.1.IA2 Adverse events of special or possible interest - list of preferred terms (Safety analysis set)

Specific adverse event of interest: Category	Specific adverse event of interest: Sub-category	AE Type	MedDRA Preferred term
Infusion/hypersensitivity reactions	Hypersensitivity/Anaphylactic reactions	AESI	Type I hypersensitivity
			^Type II hypersensitivity
			^Type III immune complex mediated reaction
			^Type IV hypersensitivity reaction
	Infusion related reaction	AESI	Infusion related reaction
			^Infusion site urticaria
			^Urticaria
Intestinal perforations	Intestinal perforations	AEPI	^Intestinal perforation
			^Intestinal ulcer perforation
			^Large intestinal ulcer perforation
			^Large intestine perforation
Myasthenia gravis	Myasthenia gravis	AESI	^Immune-mediated myasthenia gravis
			Myasthenia gravis
			^Myasthenia gravis crisis
			^Myasthenic syndrome
			^Ocular myasthenia

Specific adverse events of special interest or possible interest may either be grouped MedDRA preferred terms or individual MedDRA preferred terms.
AESI = Adverse event of special interest. AEPI = Adverse event of possible interest.
^ = MedDRA Preferred term searched for but not present in the study.
MedDRA version 26.1. AESI version 19.1.

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Table 14.3.6.1.1.IA2 Adverse events of special or possible interest - list of preferred terms (Safety analysis set)

Specific adverse event of interest: Category	Specific adverse event of interest: Sub-category	AE Type	MedDRA Preferred term
Myocarditis	Myocarditis	AESI	^Autoimmune myocarditis
			^Eosinophilic myocarditis
			^Giant cell myocarditis
			^Hypersensitivity myocarditis
			^Immune-mediated myocarditis
			Myocarditis
			^Myopericarditis
		AEPI	^Acute left ventricular failure
			^Acute right ventricular failure
			Cardiac failure acute
			Cardiogenic shock
			Cardiomyopathy
			^Cardiomyopathy acute
Myositis	Myositis	AESI	^Autoimmune myositis
			^Dermatomyositis
			^Immune-mediated myositis

Specific adverse events of special interest or possible interest may either be grouped MedDRA preferred terms or individual MedDRA preferred terms.
AESI = Adverse event of special interest. AEPI = Adverse event of possible interest.
^ = MedDRA Preferred term searched for but not present in the study.
MedDRA version 26.1. AESI version 19.1.

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Table 14.3.6.1.1.IA2 Adverse events of special or possible interest - list of preferred terms (Safety analysis set)

Specific adverse event of interest: Category	Specific adverse event of interest: Sub-category	AE Type	MedDRA Preferred term
Myositis	Myositis	AESI	Myositis
			^Necrotising myositis
			^Polymyositis
		AEPI	Blood creatine phosphokinase increased
			^Myositis-like syndrome
			^Rhabdomyolysis
Other rare/miscellaneous	Other rare/miscellaneous	AESI	^Alopecia areata
			^Autoimmune arthritis
			^Autoimmune haemolytic anaemia
			^Autoimmune pericarditis
			^Central nervous system vasculitis
			Cutaneous vasculitis
			Encephalitis
			Encephalitis autoimmune
			^Episcleritis
			^Evans syndrome

Specific adverse events of special interest or possible interest may either be grouped MedDRA preferred terms or individual MedDRA preferred terms.
AESI = Adverse event of special interest. AEPI = Adverse event of possible interest.
^ = MedDRA Preferred term searched for but not present in the study.
MedDRA version 26.1. AESI version 19.1.

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IA2 - Data Cut-off: 2024-05-10
Table 14.3.6.1.1.IA2 Adverse events of special or possible interest - list of preferred terms (Safety analysis set)

Specific adverse event of interest: Category	Specific adverse event of interest: Sub-category	AE Type	MedDRA Preferred term
Other rare/miscellaneous	Other rare/miscellaneous	AESI	^Giant cell arteritis
			^Haemolytic anaemia
			^Haemophagocytic lymphohistiocytosis
			^Hypoparathyroidism
			^Immune thrombocytopenia
			^Immune-mediated arthritis
			^Immune-mediated cholestasis
			^Immune-mediated cystitis
			^Immune-mediated encephalitis
			^Immune-mediated encephalopathy
			^Immune-mediated myelitis
			^Immune-mediated optic neuritis
			^Immune-mediated pancytopenia
			^Immune-mediated pericarditis
			^Immune-mediated polyserositis
			^Immune-mediated scleritis
			^Immune-mediated uveitis

Specific adverse events of special interest or possible interest may either be grouped MedDRA preferred terms or individual MedDRA preferred terms.
AESI = Adverse event of special interest. AEPI = Adverse event of possible interest.
^ = MedDRA Preferred term searched for but not present in the study.
MedDRA version 26.1. AESI version 19.1.

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IA2 - Data Cut-off: 2024-05-10
Table 14.3.6.1.1.IA2 Adverse events of special or possible interest - list of preferred terms (Safety analysis set)

Specific adverse event of interest: Category	Specific adverse event of interest: Sub-category	AE Type	MedDRA Preferred term
Other rare/miscellaneous	Other rare/miscellaneous	AESI	^Iridocyclitis
			^Iritis
			^Keratitis
			^Loefgren syndrome
			^Lymphocytic oesophagitis
			^Meningitis aseptic
			^Meningitis noninfective
			^Noninfective encephalitis
			^Optic neuritis
			^Optic perineuritis
			Pericarditis
			^Polymyalgia rheumatica
			^Pulmonary vasculitis
			^Punctate keratitis
			^Renal vasculitis
			^Sarcoidosis
			^Sarcoidosis of lymph node

Specific adverse events of special interest or possible interest may either be grouped MedDRA preferred terms or individual MedDRA preferred terms.
AESI = Adverse event of special interest. AEPI = Adverse event of possible interest.
^ = MedDRA Preferred term searched for but not present in the study.
MedDRA version 26.1. AESI version 19.1.

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IA2 - Data Cut-off: 2024-05-10
Table 14.3.6.1.1.IA2 Adverse events of special or possible interest - list of preferred terms (Safety analysis set)

Specific adverse event of interest: Category	Specific adverse event of interest: Sub-category	AE Type	MedDRA Preferred term
Other rare/miscellaneous	Other rare/miscellaneous	AESI	^Scleritis
			Scleroderma
			^Subacute cutaneous lupus erythematosus
			^Urticarial vasculitis
			Uveitis
			Vasculitis
			^Vasculitis gastrointestinal
			Vitiligo
			^Warm autoimmune haemolytic anaemia
		AEPI	^Acute aseptic arthritis
			^Anti IFN gamma autoantibody syndrome
			^Anti-glomerular basement membrane disease
			Aplastic anaemia
			^Arteritis
			Arthralgia
			Arthritis
			^Autoimmune cholangitis

Specific adverse events of special interest or possible interest may either be grouped MedDRA preferred terms or individual MedDRA preferred terms.
AESI = Adverse event of special interest. AEPI = Adverse event of possible interest.
^ = MedDRA Preferred term searched for but not present in the study.
MedDRA version 26.1. AESI version 19.1.

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IA2 - Data Cut-off: 2024-05-10
Table 14.3.6.1.1.IA2 Adverse events of special or possible interest - list of preferred terms (Safety analysis set)

Specific adverse event of interest: Category	Specific adverse event of interest: Sub-category	AE Type	MedDRA Preferred term
Other rare/miscellaneous	Other rare/miscellaneous	AEPI	^Cholangitis sclerosing
			^Encephalitis allergic
			^Eosinophilic cholangitis
			^Eosinophilic cholecystitis
			^Faecal lactoferrin increased
			^Goodpasture's syndrome
			^Histiocytic necrotising lymphadenitis
			^Idiopathic pancreatitis
			^Immune effector cell-associated neurotoxicity syndrome
			^Immune-mediated cholangitis
			^Immune-mediated gastritis
			^Immune-mediated oesophagitis
			Musculoskeletal pain
			Papillitis
			^Pericarditis adhesive
			^Reactive capillary endothelial proliferation
			^Solid organ transplant rejection

Specific adverse events of special interest or possible interest may either be grouped MedDRA preferred terms or individual MedDRA preferred terms.
AESI = Adverse event of special interest. AEPI = Adverse event of possible interest.
^ = MedDRA Preferred term searched for but not present in the study.
MedDRA version 26.1. AESI version 19.1.

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Table 14.3.6.1.1.IA2 Adverse events of special or possible interest - list of preferred terms (Safety analysis set)

Specific adverse event of interest: Category	Specific adverse event of interest: Sub-category	AE Type	MedDRA Preferred term
Other rare/miscellaneous	Other rare/miscellaneous	AEPI	^Systemic inflammatory response syndrome
			^Vogt-Koyanagi-Harada disease
Pancreatic events	Pancreatic events	AESI	^Autoimmune pancreatitis
			Immune-mediated pancreatitis
			Pancreatitis
			Pancreatitis acute
			^Subacute pancreatitis
		AEPI	Amylase increased
			^Haemorrhagic necrotic pancreatitis
			Hyperamylasaemia
			Hyperlipasaemia
			Lipase increased
			^Pancreatitis haemorrhagic
			^Pancreatitis necrotising
			^Pancreatitis relapsing

Specific adverse events of special interest or possible interest may either be grouped MedDRA preferred terms or individual MedDRA preferred terms.
AESI = Adverse event of special interest. AEPI = Adverse event of possible interest.
^ = MedDRA Preferred term searched for but not present in the study.
MedDRA version 26.1. AESI version 19.1.

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IA2 - Data Cut-off: 2024-05-10
Table 14.3.6.1.1.IA2 Adverse events of special or possible interest - list of preferred terms (Safety analysis set)

Specific adverse event of interest: Category	Specific adverse event of interest: Sub-category	AE Type	MedDRA Preferred term
Pneumonitis	Pneumonitis	AESI	^Acute interstitial pneumonitis
			^Alveolitis
			Immune-mediated lung disease
			Interstitial lung disease
			Pneumonitis
		AEPI	^Diffuse alveolar damage
			^Hypersensitivity pneumonitis
			^Idiopathic interstitial pneumonia
			^Idiopathic pneumonia syndrome
			Lung opacity
			Organising pneumonia
			^Pleuroparenchymal fibroelastosis
			Pulmonary fibrosis
Renal events	Renal events	AESI	^Autoimmune nephritis
			^Glomerulonephritis
			^Glomerulonephritis acute

Specific adverse events of special interest or possible interest may either be grouped MedDRA preferred terms or individual MedDRA preferred terms.
AESI = Adverse event of special interest. AEPI = Adverse event of possible interest.
^ = MedDRA Preferred term searched for but not present in the study.
MedDRA version 26.1. AESI version 19.1.

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IA2 - Data Cut-off: 2024-05-10
Table 14.3.6.1.1.IA2 Adverse events of special or possible interest - list of preferred terms (Safety analysis set)

Specific adverse event of interest: Category	Specific adverse event of interest: Sub-category	AE Type	MedDRA Preferred term
Renal events	Renal events	AESI	^Glomerulonephritis chronic
			^Glomerulonephritis membranoproliferative
			^Glomerulonephritis membranous
			^Glomerulonephritis minimal lesion
			^Glomerulonephritis rapidly progressive
			^Immune-mediated nephritis
			^Mesangioproliferative glomerulonephritis
			Nephritis
			Tubulointerstitial nephritis
		AEPI	^Anti-LRP2 nephropathy
			Blood creatinine increased
			Blood urea increased
			^Creatinine renal clearance decreased
			^Focal segmental glomerulosclerosis
			^Glomerular filtration rate decreased
			^Glomerulonephritis proliferative
			^Hypercreatininaemia

Specific adverse events of special interest or possible interest may either be grouped MedDRA preferred terms or individual MedDRA preferred terms.
AESI = Adverse event of special interest. AEPI = Adverse event of possible interest.
^ = MedDRA Preferred term searched for but not present in the study.
MedDRA version 26.1. AESI version 19.1.

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Table 14.3.6.1.1.IA2 Adverse events of special or possible interest - list of preferred terms (Safety analysis set)

Specific adverse event of interest: Category	Specific adverse event of interest: Sub-category	AE Type	MedDRA Preferred term
Renal events	Renal events	AEPI	^Immune-mediated renal disorder
			^Nephritis allergic
			^Paraneoplastic glomerulonephritis
			^Renal tubular necrosis
Thyroiditis	Thyroiditis	AESI	Autoimmune thyroiditis
			^Immune-mediated thyroiditis
			Thyroiditis
			^Thyroiditis acute
			^Thyroiditis subacute
		AEPI	^Atrophic thyroiditis
			^Hashimoto's encephalopathy
			^Silent thyroiditis
			^Thyroid pain
			^Thyroiditis chronic
Type 1 diabetes mellitus	Type 1 diabetes mellitus	AESI	^Fulminant type 1 diabetes mellitus
			^Latent autoimmune diabetes in adults
			Type 1 diabetes mellitus

Specific adverse events of special interest or possible interest may either be grouped MedDRA preferred terms or individual MedDRA preferred terms.
AESI = Adverse event of special interest. AEPI = Adverse event of possible interest.
^ = MedDRA Preferred term searched for but not present in the study.
MedDRA version 26.1. AESI version 19.1.

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IA2 - Data Cut-off: 2024-05-10
Table 14.3.6.1.1.IA2 Adverse events of special or possible interest - list of preferred terms (Safety analysis set)

Specific adverse event of interest: Category	Specific adverse event of interest: Sub-category	AE Type	MedDRA Preferred term
Type 1 diabetes mellitus	Type 1 diabetes mellitus	AEPI	^Diabetic ketoacidosis
			^Diabetic ketoacidotic hyperglycaemic coma
			^Diabetic ketosis
			^Hyperglycaemic hyperosmolar nonketotic syndrome
			^Hyperglycaemic seizure
			^Hyperglycaemic unconsciousness
			^Ketosis-prone diabetes mellitus

Specific adverse events of special interest or possible interest may either be grouped MedDRA preferred terms or individual MedDRA preferred terms.
AESI = Adverse event of special interest. AEPI = Adverse event of possible interest.
^ = MedDRA Preferred term searched for but not present in the study.
MedDRA version 26.1. AESI version 19.1.

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Anhang 4-G4.2: Liste der PTs der KEYNOTE 671-Studie (Quelle: Modul 4 des Pembrolizumab-Dossiers (2))

Anhang 4-G6: Definition der Immunvermittelten unerwünschten Ereignisse (AEOSI)

Im Folgenden wird ergänzend zu Abschnitt 4.3.1.3.1.4.3. die Definition der Immunvermittelten unerwünschten Ereignisse (AEOSI) anhand der zugeordneten PT dargestellt.

Tabelle 4G-47: Definition der Immunvermittelten unerwünschten Ereignisse (AEOSI) anhand der zugeordneten PT in der Studie KEYNOTE 671

AEOSI	**Preferred Terms**	**Immune-mediated (Yes/No)**
Pneumonitis	Acute interstitial pneumonitis, Autoimmune lung disease, Interstitial lung disease, Pneumonitis, Idiopathic pneumonia syndrome, Organising pneumonia, Immune-mediated lung disease	Yes
Colitis	Colitis, Colitis microscopic, Enterocolitis, Enterocolitis haemorrhagic, Necrotising colitis, Colitis erosive, Autoimmune colitis, Immune-mediated enterocolitis	Yes
Hepatitis	Hepatitis, Immune-mediated hepatitis, Autoimmune hepatitis, Hepatitis acute, Hepatitis fulminant, Drug-induced liver injury	Yes
Nephritis	Nephritis, Autoimmune nephritis, Chronic autoimmune glomerulonephritis, Fibrillary glomerulonephritis, Focal segmental glomerulosclerosis, Glomerulonephritis, Glomerulonephritis acute, Glomerulonephritis membranoproliferative, Glomerulonephritis membranous, Glomerulonephritis minimal lesion, Glomerulonephritis proliferative, Glomerulonephritis rapidly progressive, Mesangioproliferative glomerulonephritis, Nephritis haemorrhagic, Tubulointerstitial nephritis, Nephrotic syndrome, Immune-mediated nephritis	Yes
Adrenal Insufficiency	Adrenal insufficiency, Adrenocortical insufficiency acute, Secondary adrenocortical insufficiency, Primary adrenal insufficiency, Addison's disease, Immune-mediated adrenal insufficiency	Yes

AEOSI	**Preferred Terms**	**Immune-mediated (Yes/No)**
Hypophysitis	Hypophysitis, Hypopituitarism, Lymphocytic hypophysitis, Immune-mediated hypophysitis	Yes
Hyperthyroidism	Hyperthyroidism, Thyrotoxic crisis, Immune-mediated hyperthyroidism, Graves' disease	Yes
Hypothyroidism	Hypothyroidism, Hypothyroidic goitre, Myxoedema, Myxoedema coma, Primary hypothyroidism, Autoimmune hypothyroidism, Immune-mediated hypothyroidism	Yes
Thyroiditis	Thyroid disorder, Thyroiditis, Autoimmune thyroiditis, Thyroiditis acute, Silent thyroiditis, Autoimmune thyroid disorder, Immune-mediated thyroiditis	Yes
Type 1 Diabetes Mellitus	Diabetic ketoacidosis, Diabetic ketoacidotic hyperglycaemic coma, Fulminant type 1 diabetes mellitus, Latent autoimmune diabetes in adults, Type 1 diabetes mellitus, Euglycaemic diabetic ketoacidosis, Diabetic ketosis, Ketosis-prone diabetes mellitus	Yes
Severe Skin Reactions Including Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN): or Severe Skin (continued): If grade 3 or higher:	Dermatitis bullous, Dermatitis exfoliative, Dermatitis exfoliative generalised, Epidermal necrosis, Erythema multiforme, Exfoliative rash, Pemphigoid, Mucous membrane pemphigoid, Pemphigus, Skin necrosis, Stevens-Johnson syndrome, Toxic epidermal necrolysis, Toxic skin eruption, SJS-TEN overlap, Lichen planus pemphigoides Rash, Rash erythematous, Rash maculo-papular, Rash pruritic, Rash pustular, Pruritus, Pruritus genital, Lichen planus, Oral lichen planus, Cutaneous vasculitis, Vasculitic rash	Yes Yes
Uveitis	Iritis, Uveitis, Cyclitis, Autoimmune uveitis, Iridocyclitis, Vogt-Koyanagi-Harada disease, Chorioretinitis, Choroiditis, Immune-mediated	Yes

AEOSI	**Preferred Terms**	**Immune-mediated (Yes/No)**
	uveitis, Choroidal effusion, Choroidal detachment, Serous retinal detachment	
Pancreatitis	Pancreatitis, Autoimmune pancreatitis, Pancreatitis acute, Pancreatitis haemorrhagic, Pancreatitis necrotising, Immune-mediated pancreatitis	Yes
Myositis	Myositis, Necrotising myositis, Polymyositis, Immune-mediated myositis, Rhabdomyolysis, Myopathy, Dermatomyositis, Autoimmune myositis	Yes
Guillain-Barre Syndrome	Demyelinating polyneuropathy, Guillain-Barre syndrome, Axonal neuropathy, Multifocal motor neuropathy, Polyneuropathy idiopathic progressive, Miller Fisher syndrome, Subacute inflammatory demyelinating polyneuropathy	Yes
Myocarditis	Myocarditis, Autoimmune myocarditis, Hypersensitivity myocarditis, Immune-mediated myocarditis	Yes
Encephalitis	Encephalitis, Encephalitis autoimmune, Limbic encephalitis, Noninfective encephalitis, Immune-mediated encephalitis	Yes
Sarcoidosis	Sarcoidosis, Cutaneous sarcoidosis, Ocular sarcoidosis, Pulmonary sarcoidosis, Sarcoidosis of lymph node	Yes
Infusion Reactions	Hypersensitivity, Drug hypersensitivity, Anaphylactic reaction, Anaphylactoid reaction, Cytokine release syndrome, Serum sickness, Serum sickness-like reaction, Infusion related reaction, Infusion related hypersensitivity reaction	No
Myasthenic Syndrome	Myasthenic syndrome, Myasthenia gravis, Myasthenia gravis crisis, Ocular myasthenia,	Yes

AEOSI	**Preferred Terms**	**Immune-mediated (Yes/No)**
	Immune-mediated myasthenia gravis	
Myelitis	Myelitis, Myelitis transverse, Acute necrotising myelitis, Immune-mediated myelitis	Yes
Vasculitis	Anti-neutrophil cytoplasmic antibody positive vasculitis, Aortitis, Arteritis, Arteritis coronary, Behcet's syndrome, Central nervous system vasculitis, Cerebral arteritis, Diffuse vasculitis, Eosinophilic granulomatosis with polyangiitis, Granulomatosis with polyangiitis, Haemorrhagic vasculitis, Hypersensitivity vasculitis, Microscopic polyangiitis, Ocular vasculitis, Polyarteritis nodosa, Pulmonary vasculitis, Renal arteritis, Renal vasculitis, Retinal vasculitis, Takayasu's arteritis, Giant cell arteritis, Vasculitis, Vasculitis gastrointestinal, Vasculitis necrotising	Yes
Cholangitis Sclerosing	Cholangitis sclerosing, Autoimmune cholangitis, Immune-mediated cholangitis	Yes
Hypoparathyroidism	Hypoparathyroidism, Primary hypoparathyroidism	Yes
Arthritis	Autoimmune arthritis, Immune-mediated arthritis	Yes
HLH	Haemophagocytic lymphohistiocytosis	Yes
Optic Neuritis	Optic neuritis, Immune-mediated optic neuritis	Yes
Gastritis	Gastritis, Gastritis erosive, Gastritis haemorrhagic, Haemorrhagic erosive gastritis, Immune-mediated gastritis, Ulcerative gastritis	Yes