Gemeinsamer Bundesausschuss

Resolution

of the Federal Joint Committee on an Amendment of the Pharmaceuticals Directive:

Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V:

Pembrolizumab (new therapeutic indication: oesophageal or gastroesophageal junction adenocarcinoma, PD-L1 expression ≥ 10 (CPS), first-line, combination with platinum and fluoropyrimidine-based chemotherapy)

of 5 May 2022

At its session on 5 May 2022, the Federal Joint Committee (G-BA) resolved to amend the 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 by the publication of the resolution of D Month YYYY (Federal Gazette, BAnz AT DD.MM.YYYY BX), as follows:

I. **In Annex XII, the following information shall be added after No. 4 to the information on the benefit assessment of pembrolizumab in accordance with the resolution of 16 September 2021 for the therapeutic indication "...as monotherapy for the first-line treatment of c microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer in adults.":**

Pembrolizumab

Resolution of: 5 May 2022
Entry into force on: 5 May 2022
Federal Gazette, BAnz AT DD. MM YYYY Bx

New therapeutic indication (according to the marketing authorisation of 24 June 2021):

KEYTRUDA, in combination with platinum and fluoropyrimidine-based chemotherapy, is indicated for the first-line treatment of locally advanced unresectable or metastatic carcinoma of the oesophagus or HER2-negative gastroesophageal junction adenocarcinoma, in adults whose tumours express PD-L1 with a CPS ≥ 10.

Therapeutic indication of the resolution (resolution of 5 May 2022):

See new therapeutic indication according to marketing authorisation.

1. Additional benefit of the medicinal product in relation to the appropriate comparator therapy

a) Adults with locally advanced or metastatic squamous cell carcinoma of the oesophagus which cannot be treated curatively and whose tumours express PD-L1 (Combined Positive Score (CPS) ≥ 10); first-line therapy

Appropriate comparator therapy:

- Cisplatin in combination with 5-fluorouracil

Extent and probability of the additional benefit of Pembrolizumab in combination with cisplatin and 5-fluorouracil compared with cisplatin in combination with 5-fluorouracil:

Indication of a considerable additional benefit

b1) Adults with locally advanced or metastatic HER2-negative adenocarcinoma of the oesophagus or of the gastroesophageal junction which cannot be treated curatively and whose tumours express PD-L1 (Combined Positive Score (CPS) ≥ 10); first-line therapy

Appropriate comparator therapy:

- Therapy according to doctor's instructions

Extent and probability of the additional benefit of Pembrolizumab in combination with cisplatin and 5-fluorouracil or capecitabine compared with the appropriate comparator therapy:

An additional benefit is not proven.

b2) Adults with locally advanced or metastatic HER2-positive adenocarcinoma of the oesophagus which cannot be treated curatively and whose tumours express PD-L1 (Combined Positive Score (CPS) ≥ 10); first-line therapy

Appropriate comparator therapy:

- HER2-targeted therapy according to doctor's instructions

Extent and probability of the additional benefit of Pembrolizumab in combination with platinum and fluoropyrimidine-based chemotherapy compared with the appropriate comparator therapy:

An additional benefit is not proven.

Study results according to endpoints:[1]

a) Adults with locally advanced or metastatic squamous cell carcinoma of the oesophagus which cannot be treated curatively and whose tumours express PD-L1 (Combined Positive Score (CPS) ≥ 10); first-line therapy

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↑↑	Advantage in overall survival
Morbidity	↑↑	Advantages in the symptom scales of dyspnoea, choking and pain
Health-related quality of life	↔	No relevant differences for the benefit assessment
Side effects	↔	No relevant differences for the benefit assessment, in detail, mostly advantages in the specific AEs

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

KEYNOTE 590:

Comparison: Pembrolizumab + cisplatin + 5-fluorouracil vs placebo + cisplatin + 5-fluorouracil

Study design: RCT, double-blind, ongoing

Data cut-off: 2 July 2020

Relevant sub-population: Patients with squamous cell carcinoma of the oesophagus whose tumours express PD-L1 (CPS ≥ 10)

[1] Data from the dossier assessment of the IQWiG (A21-144) and from the addendum (A22-37), unless otherwise indicated.

Mortality

Endpoint	Pembrolizumab + cisplatin + 5-fluorouracil		Placebo + cisplatin + 5-fluorouracil		Intervention vs control
	N	Median survival time in months [95% CI] *Patients with event n (%)*	N	Median survival time in months [95% CI] *Patients with event n (%)*	Hazard ratio [95% CI] p value[a] Absolute difference (AD)[b]
Overall survival					
	143	13.9 [11.1; 17.7] 94 (65.7)	143	8.8 [7.8; 10.5] 121 (84.6)	0.57 [0.43; 0.75] < 0.001 AD = + 5.1 months

Morbidity

Endpoint	Pembrolizumab + cisplatin + 5-fluorouracil		Placebo + cisplatin + 5-fluorouracil		Intervention vs control
	N	Median time to event in months [95% CI] *Patients with event n (%)*	N	Median time to event in months [95% CI] *Patients with event n (%)*	Hazard ratio [95% CI] p value[a] Absolute difference (AD)[b]
Progression-free survival (PFS)[c]					
	143	7.3 [6.2; 8.2] 109 (76.2)	143	5.4 [4.2; 6.0] 127 (88.8)	0.53 [0.40; 0.69] < 0.001 AD: + 1.9 months
Symptomatology (EORTC QLQ-C30)[d]					
Fatigue					
	138	1.7 [1.0; 2.6] 97 (70.3)	136	1.4 [1.3; 2.1] 100 (73.5)	0.87 [0.65; 1.15] 0.318
Nausea and vomiting					
	138	3.1 [2.1; 4.2] 83 (60.1)	136	2.2 [1.8; 3.1] 84 (61.8)	0.79 [0.58; 1.08] 0.140

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Pain					
	138	6.6 [4.1; 8.4] 71 (51.4)	136	3.2 [2.4; 3.8] 87 (64.0)	0.60 [0.44; 0.84] 0.002 AD: + 3.4 months
Dyspnoea					
	138	25.3 [7,2; n.c.] 49 (35,5)	136	3.7 [2.9; 5.8] 71 (52.2)	0.50 [0.35; 0.74] < 0.001 AD: + 21.6 months
Insomnia					
	138	4.5 [3.0; 25.3] 67 (48.6)	136	4.9 [3.7; 7.4] 61 (44.9)	1.01 [0.71; 1.43] 0.969
Appetite loss					
	138	3.5 [2.7; 4.9] 81 (58.7)	136	2.9 [2.1; 3.7] 81 (59.6)	0.81 [0.59; 1.12] 0.202
Constipation					
	138	5.2 [3,8; n.c.] 60 (43,5)	136	4.4 [3.0; 7.1] 67 (49.3)	0.81 [0.57; 1.15] 0.228
Diarrhoea					
	138	12.2 [3,3; n.c.] 57 (41,3)	136	n.a. [5,7; n.c.] 43 (31,6)	1.23 [0.83; 1.84] 0.308
Symptomatology (EORTC QLQ-OES18)[d]					
Eating					
	137	7.2 [3.9; 11.2] 67 (48.9)	133	3.5 [2.9; 5.5] 69 (51.9)	0.75 [0.53; 1.06] 0.103
Reflux[e]					
	137	7.6 [4,2; n.c.] 62 (45,3)	133	5.0 [3.4; 8.4] 63 (47.4)	0.89 [0.62; 1.27] 0.506
Pain					
	137	5.2 [3.5; 12.3] 66 (48.2)	133	4.6 [2.9; 5.8] 66 (49.6)	0.79 [0.56; 1.13] 0.195

(continuation)

Saliva swallowing					
	137	25.8 [4,9; n.c.] 53 (38,7)	133	5.5 [4,0; n.c.] 59 (44,4)	0.72 [0.49; 1.06] 0.093
Choking					
	137	12.3 [8,9; n.c.] 46 (33,6)	133	5.5 [3.9; 10.1] 56 (42.1)	0.53 [0.35; 0.80] 0.003 AD: + 6.8 months
Dry mouth					
	137	4.0 [2.1; 8.1] 74 (54.0)	133	3.0 [2.3; 6.7] 69 (51.9)	1.03 [0.74; 1.44] 0.846
Sense of taste					
	137	4.0 [2.4; 10.2] 70 (51.1)	133	4.2 [3.0; 5.5] 63 (47.4)	1.07 [0.76; 1.51] 0.686
Cough					
	137	n.a. [8.6; n.c.] 45 (32.8)	133	7.8 [5,3; n.c.] 49 (36,8)	0.73 [0.48; 1.10] 0.131
Speaking					
	137	25.3 [11,1; n.c.] 45 (32,8)	133	10.1 [5,5; n.c.] 46 (34,6)	0.83 [0.54; 1.26] 0.384
Dysphagia[e]					
	137	2.8 [1.6; 3.8] 79 (57.7)	133	3.0 [2.3; 3.7] 81 (60.9)	0.92 [0.67; 1.26] 0.593
Health status (EQ-5D VAS) time to first deterioration[e]					
≥ 7 points					
	139	2.7 [2.0; 3.5] 96 (69.1)	134	2.8 [2.1; 3.5] 88 (65.7)	1.08 [0.80; 1.44] 0.626
≥ 10 points					
	139	2.8 [2.1; 3.9] 93 (66.9)	134	2.9 [2.2; 3.6] 85 (63.4)	1.03 [0.76; 1.38] 0.857

(continuation)

Health-related quality of life

Endpoint	**Pembrolizumab + cisplatin + 5-fluorouracil**		**Placebo + cisplatin + 5-fluorouracil**		Intervention vs control
	N	Median time to event in months [95% CI] *Patients with event n (%)*	N	Median time to event in months [95% CI] *Patients with event n (%)*	Hazard ratio [95% CI] p value[a] Absolute difference (AD)[b]
Quality of life EORTC QLQ-C30[f]					
Global health status					
	138	3.2 [2.1; 4.2] 82 (59.4)	136	3.4 [2.1; 3.7] 81 (59.6)	0.97 [0.72; 1.33] 0.868
Physical functioning					
	138	3.6 [2.8; 4.4] 83 (60.1)	136	2.9 [2.5; 3.6] 82 (60.3)	0.89 [0.65; 1.22] 0.474
Role functioning					
	138	2.4 [1.4; 3.6] 89 (64.5)	136	2.3 [2.1; 3.0] 85 (62.5)	1.03 [0.76; 1.39] 0.868
Emotional functioning					
	138	11.8 [7,2; n.c.] 53 (38,4)	136	5.5 [3.7; 8.4] 63 (46.3)	0.68 [0.47; 0.99] 0.045 AD: + 6.3 months
Cognitive functioning					
	138	3.3 [2.7; 4.6] 79 (57.2)	136	3.7 [2.8; 4.9] 78 (57.4)	0.92 [0.67; 1.27] 0.609
Social functioning					
	138	4.4 [3.0; 5.7] 76 (55.1)	136	3.2 [2.3; 5.2] 72 (52.9)	0.84 [0.61; 1.17] 0.312

(continuation)

Side effects

Endpoint	Pembrolizumab + cisplatin + 5-fluorouracil		Placebo + cisplatin + 5-fluorouracil		Intervention vs control
	N	Median time to event in months [95% CI] *Patients with event n (%)*	N	Median time to event in months [95% CI] *Patients with event n (%)*	Hazard ratio [95% CI] p value[g]
Adverse events (presented additionally)					
	143	0.4 [0.3; 0.4] 143 (100.0)	140	0.4 [0.4; 0.6] 140 (100.0)	-
Serious adverse events (SAE)					
	143	35.6 [16.4; 62.1] 78 (54.5)	140	25.7 [16.7; 48.0] 79 (56.4)	0.87 [0.64; 1.20] 0.405
Severe adverse events (CTCAE grade ≥ 3)					
	143	4.4 [3.1; 6.3] 126 (88.1)	140	5.0 [3.3; 8.9] 119 (85.0)	1.01 [0.78; 1.30] 0.952
Therapy discontinuation due to adverse events					
	143	n.a. 36 (25.2)	140	n.a. [46,4; n.c.] 37 (26,4)	0.88 [0.55; 1.39] 0.571
Specific adverse events					
Immune-mediated SAEs (PT collection)[h]					
	143	n.a. 12 (8.4)	140	n.a. 2 (1.4)	5.36 [1.20; 24.00] 0.028
Immune-mediated severe AEs (PT collection)[h]					
	143	n.a. *12 (8.*4)	140	n.a. 3 (2.1)	3.30 [0.93; 11.77] 0.065

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Other specific AEs					
Musculoskeletal and connective tissue disorders (SOC, AEs)	143	n.a. [55.6; n.c.] 27 (18.9)	140	53.1 [34.1; n.c.] 44 (31.4)	0.41 [0.25; 0.67] < 0.001
General disorders and administration site conditions (SOC, SAEs)	143	n.a. 2 (1.4)	140	n.a. 15 (10.7)	0.11 [0.02; 0.47] 0.003
Thrombocytopenia (PT, severe AEs)	143	n.a. 3 (2.1)	140	n.a. 11 (7.9)	0.25 [0.07; 0.90] 0.033
Weight loss (PT, severe AEs)	143	n.a. 1 (0.7)	140	n.a. 9 (6.4)	0.07 [0.01; 0.58] 0.013

a. Hazard ratio and confidence interval from Cox proportional hazards model stratified by region (Asia vs rest of the world) and ECOG-PS (0 vs 1) with associated p value from two-sided Wald test
b. Indication of absolute difference (AD) only in case of statistically significant difference; own calculation
c. Data from the dossier of the pharmaceutical company (Module 4 A) of 12 November 2021
d. An increase in score by ≥ 10 points compared to baseline is considered a clinically relevant deterioration (scale range 0 to 100)
e. A decrease in the score by 7 or 10 points compared to the start of the study is considered a deterioration (scale range 0 to 100)
f. A decrease in score by ≥ 10 points compared to the start of the study is considered a clinically relevant deterioration (scale range 0 to 100)
g. Hazard ratio and confidence interval from Cox proportional hazards model, unstratified with associated p value from two-sided Wald test
h. Predefined list of PTs under continuous update (version 18)

Abbreviations used:
AD = absolute difference; CTCAE = Common Terminology Criteria for Adverse Events; ECOG-PS = Eastern Cooperative Oncology Group Performance Status; EQ-5D = European Quality of Life Questionnaire - 5 Dimensions; CI = confidence interval; N = number of patients evaluated; n = number of patients with (at least one) event; n.c. = not calculable; n.a. = not achieved; PT = preferred term QLQ-C30 = Quality of Life Questionnaire - Core 30; QLQ-OES18 = Quality of Life Questionnaire - Oesophageal Cancer 18 items; SOC = system organ class; AE = adverse event; VAS = visual analogue scale; vs = versus

b1) Adults with locally advanced or metastatic HER2-negative adenocarcinoma of the oesophagus or of the gastroesophageal junction which cannot be treated curatively and whose tumours express PD-L1 (Combined Positive Score (CPS) ≥ 10); first-line therapy

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↔	No relevant difference for the benefit assessment.
Morbidity	↔	No relevant differences for the benefit assessment.
Health-related quality of life	↔	No relevant differences for the benefit assessment.
Side effects	↓	Disadvantage in therapy discontinuations due to adverse events; in detail, a disadvantage in a 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		

KEYNOTE 590:

Comparison: Pembrolizumab + cisplatin + 5-fluorouracil vs placebo + cisplatin + 5-fluorouracil

Study design: RCT, double-blind, ongoing

Data cut-off: 2 July 2020

Relevant sub-population: Patients with adenocarcinoma of the oesophagus or of the gastroesophageal junction whose tumours express PD-L1 (CPS ≥ 10)

KEYNOTE 062:

Comparison: Pembrolizumab + cisplatin + 5-fluorouracil or capecitabine vs placebo + cisplatin + 5-fluorouracil or capecitabine vs pembrolizumab (monotherapy, not relevant for the assessment)

Study design: RCT, double-blind (for the relevant sub-population)

Data cut-off of 26 March 2019

Relevant sub-population: Patients with adenocarcinoma of the oesophagus or of the gastroesophageal junction whose tumours express PD-L1 (CPS ≥ 10)

Mortality

Endpoint	**Pembrolizumab + cisplatin + 5-fluorouracil/ capecitabine**		**Placebo + cisplatin + 5-fluorouracil/ capecitabine**		Intervention vs control
	N	Median survival time in months [95% CI] *Patients with event n (%)*	N	Median survival time in months [95% CI] *Patients with event n (%)*	Hazard ratio [95% CI] p value
Overall survival					
KEYNOTE 590	43	12.1 [9.6; 18.7] 30 (69.8)	54	10.7 [8.2; 15.3] 44 (81.5)	0.83 [0.52; 1.34] 0.447[a]
KEYNOTE 062	30	11.8 [9.1; 17.2] 24 (80.0)	20	10.4 [6.5; 18.5] 16 (80.0)	0.95 [0.50; 1.78] 0.866[b]
Total[c]					0.87 [0.60; 1.27] 0.476

Morbidity

Endpoint	**Pembrolizumab + cisplatin + 5-fluorouracil/ capecitabine**		**Placebo + cisplatin + 5-fluorouracil/ capecitabine**		Intervention vs control
	N	Median time to event in months [95% CI] *Patients with event n (%)*	N	Median time to event in months [95% CI] *Patients with event n (%)*	Hazard ratio [95% CI] p value Absolute Difference (AD)[d]
Progression-free survival (PFS)[e]					
KEYNOTE 590	43	8.0 [6.0; 8.3] 31 (72.1)	54	6.0 [4.1; 6.2] 47 (87.0)	0.49 [0.30; 0.81] 0.006[f] AD: + 2.0 months
KEYNOTE 062	30	5.6 [4.4; 8.3] 26 (86.7)	20	6.3 [2.7; 9.9] 19 (95.0)	0.84 [0.46; 1.54] 0.579[b]

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Symptomatology (EORTC QLQ-C30) time to first deterioration[g]					
Fatigue					
KEYNOTE 590	41	1.6 [1.0; 4.3] 28 (68.3)	49	2.0 [1.0; 2.8] 34 (69.4)	0.88 [0.53; 1.46]; 0.627[a]
KEYNOTE 062	28	1.4 [1.0; 2.3] 24 (85.7)	20	0.8 [0.7; 3.0] 15 (75.0)	0.84 [0.44; 1.61] 0.597[b]
Total[c]					0.86 [0.58; 1.29] 0.475
Nausea and vomiting					
KEYNOTE 590	41	2.1 [1.4; 7.0] 26 (63.4)	49	2.3 [1.4; 4.1] 30 (61.2)	0.91 [0.53; 1.54] 0.712[a]
KEYNOTE 062	28	1.9 [0.8; 5.3] 19 (67.9)	20	1.4 [0.7; 1.6] 17 (85.0)	0.56 [0.29; 1.08] 0.085[b]
Total[c]					0.75 [0.50; 1.14] 0.174
Pain					
KEYNOTE 590	41	3.3 [2.4; 14.1] 25 (61.0)	49	4.1 [1,9; n.c.] 22 (44,9)	1.11 [0.62; 2.01] 0.723[a]
KEYNOTE 062	28	6.5 [2.4; 8.8] 16 (57.1)	20	3.3 [1.5; n.c.] 12 (60.0)	0.80 [0.38; 1.69] 0.551[b]
Total[c]					0.98 [0.62; 1.55] 0.929
Dyspnoea					
KEYNOTE 590	41	8.3 [3,2; n.c.] 19 (46,3)	49	5.1 [3.0; 12.0] 25 (51.0)	0.96 [0.51; 1.78] 0.887[a]
KEYNOTE 062	28	8.6 [4.4; n.c.] 12 (42.9)	20	2.6 [0.8; 6.0] 13 (65.0)	0.43 [0.19; 0.94] 0.035[b] AD = + 6.0 months
Total[c]					0.71 [0.43; 1.16] 0.169

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Insomnia					
KEYNOTE 590	41	n.a. [7.0; n.c.] 15 (36.6)	49	4.6 [2.8; 12.9] 24 (49.0)	0.65 [0.34; 1.26] 0.204[a]
KEYNOTE 062	28	n.a. [2.7; n.c.] 1 (39.3)	20	6.0 [0.7; n.c.] 10 (50.0)	0.64 [0.27; 1.52] 0.315[b]
Appetite loss					
KEYNOTE 590	41	2.7 [1.3; 14.9] 24 (58.5)	49	3.0 [1.4; 4.1] 30 (61.2)	0.83 [0.48; 1.44] 0.513[a]
KEYNOTE 062	28	5.8 [1.4; 10.2] 18 (64.3)	20	3.4 [1.5; 6.0] 13 (65.0)	0.65 [0.31; 1.37] 0.257[b]
Total[c]					0.76 [0.49; 1.18] 0.226
Constipation					
KEYNOTE 590	41	3.0 [1,4; n.c.] 22 (53,7)	49	3.5 [2,1; n.c.] 25 (51,0)	1.00 [0.56; 1.79] 0.993[a]
KEYNOTE 062	28	3.0 [1.4; n.c.] 15 (53.6)	20	3.2 [1.4; 6.1] 14 (70.0)	0.76 [0.36; 1.57] 0.454[b]
Total[c]					0.90 [0.57; 1.42] 0.651
Diarrhoea					
KEYNOTE 590	41	3.0 [1.3; 10.6] 24 (58.5)	49	4.1 [1,8; n.c.] 23 (46,9)	1.17 [0.65; 2.11] 0.591[a]
KEYNOTE 062	28	4.4 [1.4; n.c.] 15 (53.6)	20	n.a. [0.7; n.c.] 9 (45.0)	1.04 [0.45; 2.38] 0.924[b]
Total[c]					1.12 [0.70; 1.82] 0.631

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Symptomatology (EORTC QLQ-OES18)[g]					
Eating					
KEYNOTE 590	41	5.3 [3.2; n.c.] 21 (51.2)	47	4.4 [3,0; n.c.] 23 (48,9)	0.88 [0.48; 1.60] 0.669[a]
KEYNOTE 062	*Instrument not assessed*				
Reflux					
KEYNOTE 590	41	12.7 [2,3; n.c.] 18 (43,9)	47	2.6 [1.4; 10.2] 28 (59.6)	0.50 [0.27; 0.92] 0.026[a] AD: + 10.1 months
KEYNOTE 062	*Instrument not assessed*				
Pain					
KEYNOTE 590	41	3.9 [2.9; 14.9] 22 (53.7)	47	4.4 [3.1; 8.0] 27 (57.4)	0.94 [0.53; 1.66] 0.827[a]
KEYNOTE 062	*Instrument not assessed*				
Saliva swallowing					
KEYNOTE 590	41	8.3 [2,8; n.c.] 19 (46,3)	47	5.1 [2,6; n.c.] 21 (44,7)	0.93 [0.50; 1.75] 0.823[a]
KEYNOTE 062	*Instrument not assessed*				
Choking					
KEYNOTE 590	41	5.6 [2,6; n.c.] 20 (48,8)	47	12.2 [4,2; n.c.] 16 (34,0)	1.71 [0.86; 3.41] 0.124[a]
KEYNOTE 062	*Instrument not assessed*				
Dry mouth					
KEYNOTE 590	41	1.7 [1.4; 3.5] 28 (68.3)	47	3.4 [1,6; n.c.] 23 (48,9)	1.81 [1.00; 3.27] 0.048[a] AD: - 1.7 months
KEYNOTE 062	*Instrument not assessed*				
Sense of taste					
KEYNOTE 590	41	1.4 [1.3; 3.0] 28 (68.3)	47	2.0 [1.4; 2.8] 35 (74.5)	0.87 [0.52; 1.44] 0.576[a]
KEYNOTE 062	*Instrument not assessed*				

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Cough					
KEYNOTE 590	41	4.7 [2,7; n.c.] 19 (46,3)	47	7.7 [4,2; n.c.] 19 (40,4)	1.32 [0.70; 2.52] 0.393[a]
KEYNOTE 062	*Instrument not assessed*				
Speaking					
KEYNOTE 590	41	24.3 [2,8; n.c.] 15 (36,6)	47	n.a. [4,7; n.c.] 13 (27,7)	1.33 [0.62; 2.84] 0.461[a]
KEYNOTE 062	*Instrument not assessed*				
Dysphagia					
KEYNOTE 590	41	3.7 [1,6; n.c.] 22 (53,7)	47	3.5 [2,1; n.c.] 24 (51,1)	0.98 [0.55; 1.76] 0.942[a]
KEYNOTE 062	*Instrument not assessed*				
Health status (EQ-5D VAS) time to first deterioration[h]					
≥ 7 points					
KEYNOTE 590	41	4.8 [3.2; 9.3] 24 (58.5)	49	4.5 [2.8; 8.1] 27 (55.1)	0.83 [0.47; 1.48] 0.529[a]
KEYNOTE 062	29	2.3 [1.0; 8.3] 21 (72.4)	20	2.8 [0.8; 6.1] 14 (70.0)	1.02 [0.51; 2.00] 0.966[b]
Total[c]					0.90 [0.58; 1.40] 0.652
≥ 10 points					
KEYNOTE 590	41	7.8 [3.6; 13.8] 22 (53.7)	49	4.9 [3.0; 8.1] 27 (55.1)	0.78 [0.43; 1.41] 0.410[a]
KEYNOTE 062	29	2.4 [1.4; 8.3] 21 (72.4)	20	3.0 [1.9; n.c.] 11 (55.0)	1.38 [0.66; 2.87] 0.387[b]
Total[c]					0.98 [0.62; 1.55] 0.922

(continuation)

Health-related quality of life

Endpoint	**Pembrolizumab + cisplatin + 5-fluorouracil/ capecitabine**		**Placebo + cisplatin + 5-fluorouracil/ capecitabine**		Intervention vs control
	N	Median time to event in months [95% CI] *Patients with event n (%)*	N	Median time to event in months [95% CI] *Patients with event n (%)*	Hazard ratio [95% CI] p value Absolute Difference (AD)[d]
EORTC QLQ-C30 time to first deterioration[i]					
Global health status					
KEYNOTE 590	41	3.7 [1.6; 7.8] 24 (58.5)	49	5.6 [4.1; 12.2] 24 (49.0)	1.14 [0.63; 2.04] 0.665[a]
KEYNOTE 062	28	8.3 [2.4; 10.2] 16 (57.1)	20	2.4 [1.4; 7.4] 13 (65.0)	0.59 [0.28; 1.26] 0.176[b]
Total[c]					0.89 [0.56; 1.41] 0.616
Physical functioning					
KEYNOTE 590	41	4.1 [1.4; 10.9] 25 (61.0)	49	3.7 [2.8; 8.0] 29 (59.2)	1.16 [0.66; 2.02] 0.608[a]
KEYNOTE 062	28	4.2 [1.4; 5.9] 21 (75.0)	20	1.4 [0.8; 2.2] 15 (75.0)	0.60 [0.31; 1.17] 0.136[b]
Total[c]					0.88 [0.58; 1.35] 0.566
Role functioning					
KEYNOTE 590	41	3.0 [1.2; 5.5] 28 (68.3)	49	2.8 [1.2; 8.0] 29 (59.2)	1.05 [0.61; 1.81] 0.847[a]
KEYNOTE 062	28	2.1 [1.4; 5.1] 23 (82.1)	20	2.2 [0.7; n.c.] 13 (65.0)	1.10 [0.56; 2.17] 0.785[b]
Total[c]					1.07 [0.70; 1.63] 0.757

(continuation)

Emotional functioning					
KEYNOTE 590	41	3.3 [1.6; 14.1] 24 (58.5)	49	8.0 [4.2; 17.1] 22 (44.9)	1.34 [0.73; 2.44] 0.342[a]
KEYNOTE 062	28	5.9 [1.4; n.c.] 15 (53.6)	20	6.1 [1.4; n.c.] 8 (40.0)	1.21 [0.51; 2.85] 0.670[b]
Total[c]					1.30 [0.79; 2.12] 0.304
Cognitive functioning					
KEYNOTE 590	41	2.8 [1.6; 4.3] 27 (65.9)	49	3.7 [2.3; 5.3] 31 (63.3)	0.94 [0.55; 1.61] 0.832[a]
KEYNOTE 062	28	3.4 [1.4; 9.7] 17 (60.7)	20	1.5 [0.7; n.c.] 12 (60.0)	0.75 [0.35; 1.57] 0.442[b]
Total[c]					0.87 [0.56; 1.35] 0.535
Social functioning					
KEYNOTE 590	41	3.2 [1.6; 7.1] 25 (61.0)	49	3.7 [1.6; 4.2] 28 (57.1)	0.94 [0.54; 1.62] 0.811[a]
KEYNOTE 062	28	4.4 [1.6; n.c.] 16 (57.1)	20	1.9 [1.0; 4.7] 15 (75.0)	0.62 [0.31; 1.27] 0.191[b]
Total[c]					0.80 [0.52; 1.24] 0.322

(continuation)

Side effects

Endpoint	**Pembrolizumab + cisplatin + 5-fluorouracil/ capecitabine**		**Placebo + cisplatin + 5-fluorouracil/ capecitabine**		Intervention vs control
	N	Median time to event in months [95% CI] *Patients with event n (%)*	N	Median time to event in months [95% CI] *Patients with event n (%)*	Effect estimator [95% CI] p value Absolute Difference (AD)[d]
Adverse events (presented additionally)					
KEYNOTE 590	42	0.4 [0.3; 0.4] 42 (100.0)	53	0.3 [0.3; 0.7] 52 (98.1)	–
KEYNOTE 062	30	0.3 [0.3; 0.6] 30 (100.0)	20	0.6 [0.1; 1.0] 19 (95.0)	–
Serious adverse events (SAE)					
KEYNOTE 590	42	15.6 [8.0; 27.9] 28 (66.7)	53	31.1 [17.1; 60.3] 30 (56.6)	1.34 [0.80; 2.26] 0.266[b]
KEYNOTE 062	30	11.6 [2.1; n.c.] 19 (63.3)	20	36.7 [5.6; n.c.] 9 (45.0)	1.64 [0.74; 3.64] 0.220[b]
Total[c]					1.42 [0.92; 2.20] 0.112
Severe adverse events (CTCAE grade ≥ 3)					
KEYNOTE 590	42	4.7 [2.4; 7.4] 37 (88.1)	53	6.3 [3.9; 11.6] 44 (83.0)	1.14 [0.73; 1.77] 0.567[b]
KEYNOTE 062	30	5.4 [3.0; 9.0] 26 (86.7)	20	5.6 [1.1; 29.4] 15 (75.0)	1.31 [0.69; 2.49] 0.407[b]
Total[c]					1.19 [0.83; 1.72] 0.344

(continuation)

Therapy discontinuation due to adverse events					
KEYNOTE 590	42	n.a. 10 (23.8)	53	n.a. 3 (5.7)	4.35 [1.20; 15.82] 0.025[b]
KEYNOTE 062	30	n.a. [20,0; n.c.] 11 (36,7)	20	n.a. [21,1; n.c.] 4 (20,0)	1.83 [0.58; 5.74] 0.303[b]
Total[c]					2.68 [1.14; 6.32] 0.024
Specific adverse events					
Immune-mediated SAEs (PT collection)[j]					
KEYNOTE 590	42	n.a. 3 (7.1)	53	n.a. 1 (1.9)	3.88 [0.40; 37.33] 0.240[b]
KEYNOTE 062	30	n.a. 2 (6.7)	20	n.a. 1 (5.0)	1.19 [0.11; 13.20] 0.886[b]
Total[c]					2.22 [0.43; 11.51] 0.343
Immune-mediated severe AEs (PT collection)[j]					
KEYNOTE 590	42	n.a. 3 (7.1)	53	n.a. 1 (1.9)	3.59 [0.37; 34.57] 0.268[b]
KEYNOTE 062	30	n.a. 2 (6.7)	20	n.a. 1 (5.0)	1.03 [0.09; 11.48] 0.981[b]
Total[c]					2.00 [0.38; 10.50] 0.411
Endocrine disorders (AE, SAE)[k]					
KEYNOTE 590	42	n.a. 8 (19.0)	53	n.a. 2 (3.8)	RR: 5.05 [1.13; 22.52] 0.034[l,m]
KEYNOTE 062	30	n.a. 5 (16.7)	20	n.a. 0 (0)	RR: 7.45 [0.43; 127.74] 0.062[l,n]
Total[o]					RR: 5.65 [1.48; 21.58] 0.011

(continuation)

a. Hazard ratio and confidence interval from Cox proportional hazards model stratified by region (Asia vs rest of the world) and ECOG-PS (0 vs 1) with associated p value from two-sided Wald test
b. Hazard ratio and confidence interval from Cox proportional hazards model, unstratified with associated p value from two-sided Wald test
c. Fixed-effect meta-analysis (inverse variance method)
d. Indication of absolute difference (AD) only in case of statistically significant difference; own calculation
e. Data from the dossier of the pharmaceutical company (Module 4 A) of 12 November 2021
f. Hazard ratio and confidence interval from Cox proportional hazards model with treatment as covariate, stratified by region (Asia vs rest of the world) and ECOG-PS (0 vs 1) with associated p value from two-sided Wald test
g. An increase in score by ≥ 10 points compared to the start of the study is considered a clinically relevant deterioration (scale range 0 to 100)
h. A decrease in the score by 7 or 10 points compared to the start of the study is considered a deterioration (scale range 0 to 100)
i. A decrease in score by ≥ 10 points compared to the start of the study is considered a clinically relevant deterioration (scale range 0 to 100)
j. Predefined list of PTs under continuous update (version 18)
k. The main underlying events are hyperthyroidism (KEYNOTE 590 study) and hypothyroidism (KEYNOTE 062 study). No information is available on how many of these events were CTCAE grade 1 and thus, not symptomatic
l. Confidence interval (asymptomatic); p value (unconditional exact test; CSZ method according to Martín Andrés & Silva Mato, 1994)
m. KEYNOTE 590: HR 4.96 [1.05; 23.35], p value 0.043; the RR is used provisionally for the meta-analytic summary.
n. KEYNOTE 062: p value 0.091 (based on score test statistics)
o. Fixed-effect meta-analysis (Mantel-Haenszel method)

Abbreviations used:
AD = absolute difference; CTCAE = Common Terminology Criteria for Adverse Events; ECOG-PS = Eastern Cooperative Oncology Group Performance Status; EORTC = European Organisation for Research and Treatment of Cancer; EQ-5D = European Quality of Life Questionnaire - 5 Dimensions; CI = confidence interval; N = number of patients evaluated; n = number of patients with (at least one) event; n.c. = not calculable; n.a. = not achieved; PT = preferred term; QLQ-C30 = Quality of Life Questionnaire - Core 30; QLQ-OES18 = Quality of Life Questionnaire - Oesophageal Cancer 18 items; RR = relative risk; SOC = system organ class; AE = adverse event; VAS = visual analogue scale; vs = versus

b2) Adults with locally advanced or metastatic HER2-positive adenocarcinoma of the oesophagus which cannot be treated curatively and whose tumours express PD-L1 (Combined Positive Score (CPS) ≥ 10); first-line therapy

No data are available to allow an assessment of the additional benefit.

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	∅	No data available.
Morbidity	∅	No data available.
Health-related quality of life	∅	No data available.
Side effects	∅	No data available.

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

2. Number of patients or demarcation of patient groups eligible for treatment

a) Adults with locally advanced or metastatic squamous cell carcinoma of the oesophagus which cannot be treated curatively and whose tumours express PD-L1 (Combined Positive Score (CPS) ≥ 10); first-line therapy

approx. 170 – 280 patients

b1) Adults with locally advanced or metastatic HER2-negative adenocarcinoma of the oesophagus or of the gastroesophageal junction which cannot be treated curatively and whose tumours express PD-L1 (Combined Positive Score (CPS) ≥ 10); first-line therapy

approx. 345 – 475 patients

b2) Adults with locally advanced or metastatic HER2-positive adenocarcinoma of the oesophagus which cannot be treated curatively and whose tumours express PD-L1 (Combined Positive Score (CPS) ≥ 10); first-line therapy

approx. 20 – 50 patients

3. Requirements for a quality-assured application

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 Keytruda (active ingredient: pembrolizumab) at the following publicly accessible link (last access: 16 February 2022):

https://www.ema.europa.eu/en/documents/product-information/keytruda-epar-product-information_en.pdf

Treatment with pembrolizumab should only be initiated and monitored by specialists in internal medicine, haematology and oncology as well as specialists in internal medicine and gastroenterology and other specialists participating in the Oncology Agreement, all of whom are experienced in the treatment of patients with oesophageal cancer.

In accordance with the EMA requirements regarding additional risk minimisation measures, the pharmaceutical company must provide training material that contains information for medical professionals and patients. The training material contains, in particular, instructions on the management of immune-mediated side effects potentially occurring with pembrolizumab as well as on infusion-related reactions.

4. Treatment costs

a) Adults with locally advanced or metastatic squamous cell carcinoma of the oesophagus which cannot be treated curatively and whose tumours express PD-L1 (Combined Positive Score (CPS) ≥ 10); first-line therapy

Annual treatment costs:

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Pembrolizumab in combination with cisplatin and 5-fluorouracil	
Pembrolizumab	€ 99,714.53
Cisplatin	€ 2,284.10
5-fluorouracil	€ 2,514.30
Total	€ 104,512.93
Additionally required SHI services	€ 328.58 - € 421.62
Appropriate comparator therapy:	
Cisplatin in combination with 5-fluorouracil	
Cisplatin	€ 2,284.10
5-fluorouracil	€ 2,514.30
Total	€ 4,798.40
Additionally required SHI services	€ 328.58 - € 421.62

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 April 2022)

Other SHI services:

Designation of the therapy	Type of service	Costs/ unit	Number/ cycle	Number/ patient/ year	Costs/ patient/ year
Medicinal product to be assessed					
Pembrolizumab in combination with cisplatin and 5-fluorouracil					
Pembrolizumab	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 71	1	8.7 - 17.4	€ 617.70 - € 1,235.40
Cisplatin	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1	17.4	€ 1,409.40
5-fluorouracil	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	5	87	€ 7,047.00
Appropriate comparator therapy					
Cisplatin in combination with 5-fluorouracil					
Cisplatin	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1	17.4	€ 1,409.40
5-fluorouracil	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	5	87	€ 7,047.00

b1) Adults with locally advanced or metastatic HER2-negative adenocarcinoma of the oesophagus or of the gastroesophageal junction which cannot be treated curatively and whose tumours express PD-L1 (Combined Positive Score (CPS) ≥ 10); first-line therapy

Annual treatment costs:

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Pembrolizumab in combination with cisplatin and 5-fluorouracil	
Pembrolizumab	€ 99,714.53
Cisplatin	€ 2,284.10
5-fluorouracil	€ 2,514.30
Total	€ 104,512.93
Additionally required SHI services	€ 328.58 - € 421.62
Pembrolizumab in combination with cisplatin and capecitabine	
Pembrolizumab	€ 99,714.53
Cisplatin	€ 2,284.10
Capecitabine	€ 2,089.64
Total	€ 104,088.27
Additionally required SHI services	€ 328.58 - € 421.62
Appropriate comparator therapy:	
Therapy according to doctor's instructions - Cisplatin in combination with 5-fluorouracil[2]	
Cisplatin	€ 2,284.10
5-fluorouracil	€ 2,514.30
Total	€ 4,798.40
Additionally required SHI services	€ 328.58 - € 421.62
- Docetaxel in combination with cisplatin and 5-fluorouracil[2]	
Cisplatin	€ 2,015.79
Docetaxel	€ 13,742.35
5-fluorouracil	€ 2,312.46
Total	€ 18,070.60
Additionally required SHI services	€ 328.58 - € 421.62

[2] Costs are only shown for the active ingredients cisplatin, 5-fluorouracil and docetaxel. In addition to these, the following medicinal product combinations S-1 (tegafur/ gimeracil/ oteracil) + cisplatin, capecitabine + cisplatin, 5-fluorouracil + oxaliplatin + folinic acid [FLO and FOLFOX], capecitabine + oxaliplatin, infusional 5-fluorouracil + folinic acid + cisplatin [PLF], epirubicin + cisplatin + capecitabine [ECX], epirubicin + oxaliplatin + capecitabine [EOX], epirubicin + cisplatin + infusional 5-fluorouracil [ECF], 5-fluorouracil + oxaliplatin + epirubicin, infusional 5-fluorouracil + folinic acid + oxaliplatin + docetaxel [FLOT regimen] are also suitable comparators for the present benefit assessment in the context of a therapy according to doctor's instructions. These medicinal product combinations contain active ingredients that are not approved in the present therapeutic indication, and therefore, no costs are presented for these medicinal products.

Other SHI services:

Designation of the therapy	Type of service	Costs/ unit	Number/ cycle	Number/ Patient/ year	Costs/ patient/ year
Medicinal product to be assessed					
Pembrolizumab in combination with cisplatin and 5-fluorouracil					
Pembrolizumab	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 71	1	8.7 - 17.4	€ 617.70 - € 1,235.40
Cisplatin	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1	17.4	€ 1,409.40
5-fluorouracil	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	5	87	€ 7047.00
Pembrolizumab in combination with cisplatin and capecitabine					
Pembrolizumab	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 71	1	8.7 - 17.4	€ 617.70 - € 1,235.40
Cisplatin	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1	17.4	€ 1,409.40
Appropriate comparator therapy:					
Cisplatin in combination with 5-fluorouracil					
Cisplatin	Surcharge for production of a	€ 81	1	17.4	€ 1,409.40

	parenteral preparation containing cytostatic agents				
5-fluorouracil	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	5	87	€ 7047.00
Docetaxel in combination with cisplatin and 5-fluorouracil					
Cisplatin	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1	17.4	€ 1,409.40
Docetaxel	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1	17.4	€ 1,409.40
5-fluorouracil	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	5	87	€ 7,047.00

b2) Adults with locally advanced or metastatic HER2-positive adenocarcinoma of the oesophagus which cannot be treated curatively and whose tumours express PD-L1 (Combined Positive Score (CPS) ≥ 10); first-line therapy

Annual treatment costs:

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Pembrolizumab in combination with cisplatin and 5-fluorouracil	
Pembrolizumab	€ 99,714.53
Cisplatin	€ 2,284.10
5-fluorouracil	€ 2,514.30
Total	€ 104,512.93

Designation of the therapy	Annual treatment costs/ patient
Additionally required SHI services	€ 328.58 - € 421.62
Appropriate comparator therapy:	
HER2-targeted therapy according to doctor's instructions[3]	

Other SHI services:

Designation of the therapy	Type of service	Costs/ unit	Number/ cycle	Number/ patient/ year	Costs/ patient/ year
Medicinal product to be assessed					
Pembrolizumab in combination with cisplatin and 5-fluorouracil					
Pembrolizumab	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 71	1	8.7 - 17.4	€ 617.70 - € 1235.40
Cisplatin	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1	17.4	€ 1409.40
5-fluorouracil	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	5	87	€ 7047.00

[3] The medicinal product combinations trastuzumab + cisplatin + capecitabine and trastuzumab + cisplatin + 5-fluorouracil are suitable comparators for the present benefit assessment in the context of HER2-targeted therapy according to doctor's instructions. All medicinal therapies that represent a suitable comparator for the present benefit assessment in the context of HER2-targeted therapy according to a doctor's instructions are not approved in the present therapeutic indication, which is why no costs are presented for these medicinal products.

II. The resolution will enter into force on the day of its publication on the website of the G-BA on 5 May 2022.

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

Berlin, 5 May 2022

Federal Joint Committee (G-BA)
in accordance with Section 91 SGB V
The Chair

Prof. Hecken