Resolution

Gemeinsamer Bundesausschuss

of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL): Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients According to Section 35a SGB V Pembrolizumab (new therapeutic indication: non-small cell lung carcinoma, non-squamous, first line, combination with pemetrexed and platinum chemotherapy)

of 19 September 2019

At its session on 19 September 2019, the Federal Joint Committee (G-BA) resolved to amend the Directive on the Prescription of Medicinal Products in SHI-accredited Medical Care (Pharmaceuticals Directive, AM-RL) in the version dated 18 December 2008/22 January 2009 (Federal Gazette, BAnz. No. 49a of 31 March 2009), as last amended on DD Month YYYY (Federal Gazette, BAnz AT DD MM YYYY BX), as follows:

I. 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 4 April 2019:

Pembrolizumab

Resolution of: 19 September 2019
Entry into force on: 19 September 2019
Federal Gazette, BAnz AT DD MM YYYY Bx

New therapeutic indication (according to the marketing authorisation of 4 September 2018):

KEYTRUDA, in combination with pemetrexed and platinum chemotherapy, is indicated for the first-line treatment of metastatic non-squamous NSCLC in adults whose tumours have no EGFR or ALK positive mutations.

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

a) Adult patients with first-line treatment of metastatic squamous NSCLC without EGFR or ALK positive tumour mutations whose tumours express PD-L1 with a < 50% tumour proportion score (TPS[1]):

Appropriate comparator therapy:

- Cisplatin in combination with a third-generation cytostatic agent (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed)

  or

- Carboplatin in combination with a third-generation cytostatic agent (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed; *cf* Annex VI to Section K of the Pharmaceuticals Directive)

  or

- Carboplatin in combination with nab-paclitaxel

Extent and probability of additional benefit of pembrolizumab in combination with pemetrexed and platinum chemotherapy versus pemetrexed plus platinum chemotherapy:

Hint for a non-quantifiable additional benefit

b) Adult patients with first-line treatment of metastatic squamous NSCLC without EGFR or ALK positive tumour mutations whose tumours express PD-L1 with a ≥ 50% tumour proportion score (TPS[1]):

Appropriate comparator therapy:
Pembrolizumab as monotherapy

Extent and probability of additional benefit of pembrolizumab in combination with pemetrexed and platinum chemotherapy versus pembrolizumab as monotherapy:

Hint for a non-quantifiable additional benefit

[1] TPS: Tumour Proportion Score

Study results according to endpoints:[2]

a) Adult patients with first-line treatment of metastatic squamous NSCLC without EGFR or ALK positive tumour mutations whose tumours express PD-L1 with a < 50% tumour proportion score (TPS[1]):

KEYNOTE 021G study: Pembrolizumab in combination with pemetrexed and carboplatin vs pemetrexed and carboplatin (data cut-off: 31 May 2017)

KEYNOTE 189 study: Pembrolizumab in combination with pemetrexed and carboplatin or cisplatin vs pemetrexed and carboplatin or cisplatin (data cut-off: 8 November 2017)

Relevant TPC (Treatment of Physician's Choice) sub-population in each case with PD-L1 expression of < 50% (TPS)[1,3]

Mortality

Endpoint Study	Pembrolizumab + platinum-based chemotherapy[a]		Platinum-based chemotherapy[a]		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 (%)*	Effect estimate [95% CI] p value[b] Absolute difference (AD)[c]
Overall survival					
021G	20	n.a. [11.1; n.c.] 6 (30.0)	20	14.9 [7.2; n.c.] 12 (60.0)	0.41 [0.15; 1.09] 0.073[b]
189	162	n.a. [14.4; n.c.] 54 (33.3)	88	12.1 [8.6; n.c.] 46 (52.3)	0.58 [0.39; 0.86] 0.008[f]
Total					*0.55* *[0.38; 0.77]* *0.001*[m]
Sub-groups according to sex					
021G					
Men	*11*	*n.a. [1,8; n.c.]* *5 (45.5)*	*6*	*10.6 [2.0; n.c.]* *5 (83.3)*	*0.48 [0.14; 1.66]*[h] *0.244*
Women	*9*	*n.a. [6,5; n.c.]* *1 (11.1)*	*14*	*20.9 [3.3; n.c.]* *7 (50.0)*	*0,17 [0,02; 1,40]*[h] *0.100*
189					
Men	*103*	*n.a. [12,6; n.c.]* *39 (37.9)*	*49*	*12.9 [8.1; n.c.]* *23 (46.9)*	*0.78 [0.46; 1.32]*[i] *0354*

[2] Data from the dossier evaluation of the IQWiG (A19-30) and the addendum (A19-61) unless otherwise indicated.

[3] The relevant sub-population includes patients with PD-L1 expression < 50% and who were treated according to the results of the pharmaceutical company's TPC survey according to the criteria of the AM-RL for the off-label use of carboplatin (Annex VI to Section K).

Women	*59*	*n.a.* *15 (25.4)*	*39*	*10.6 [7.2; n.c.]* *23 (59.0)*	*0.37 [0.19; 0.74]*[i] *0.005*
Total					Interaction: 0.035 [k]
Men					*0.73 [0.45; 1.18]*[L] *0.200*
Women					*0.31 [0.17; 0.59]*[L] *< 0.001*

Morbidity

Endpoint Study	Pembrolizumab + platinum-based chemotherapy[a]		Platinum-based chemotherapy[a]		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 (%)*	Effect estimate [95% CI] p value [b] Absolute difference (AD)[c]
Progression-free survival (PFS)					
not reported					
Symptomology (EORTC QLQ-C30 symptom scales)[d]					
Dyspnoea					
021G	Endpoint not recorded				
189	161	7.4 [3.5; 19.5] 62 (38.5)	86	5.1 [2.8; 9.0] 38 (44.2)	0.88 [0.58; 1.35]; 0.564
Fatigue					
021G	Endpoint not recorded				
189	161	1.4 [1.1; 2.1] 88 (54.7)	86	1.4 [0.8; 1.6] 57 (66.3)	0.73 [0.52; 1.03]; 0.071
Insomnia					
021G	Endpoint not recorded				
189	161	n.a. [8.0; n.c.] 49 (30.4)	86	4.1 [2.6; n.c.] 34 (39.5)	0.71 [0.45; 1.12]; 0.140
Pain					
021G	Endpoint not recorded				
189	161	5.3 [2.5; 8.3] 71 (44.1)	86	2.6 [1.5; 5.3] 43 (50.0)	0.77 [0.52; 1.14]; 0.195
Loss of appetite					

021G	Endpoint not recorded				
189	161	7.2 [4.9; n.c.] 60 (37.3)	86	6.9 [2.8; n.c.] 33 (38.4)	1.02 [0.66; 1.58]; 0.917
Diarrhoea					
021G	Endpoint not recorded				
189	161	n.a. [5.2; n.c.] 49 (30.4)	86	11.3 [4.8; n.c.] 28 (32.6)	0.92 [0.57; 1.48]; 0.718
Nausea and vomiting					
021G	Endpoint not recorded				
189	161	2.1 [1.4; 4.9] 79 (49.1)	86	1.6 [1.4; 5.3] 46 (53.5)	0.94 [0.65; 1.37]; 0.748
Constipation					
021G	Endpoint not recorded				
189	161	9.7 [8.0; n.c.] 54 (33.5)	86	2.5 [1.6; 9.0] 42 (48.8)	0.59 [0.38; 0.90]; 0.013
Symptomology (EORTC QLQ-LC13 symptom scales)[d]					
Dyspnoea					
021G	Endpoint not recorded				
189	161	2.1 [1.4; 2.9] 92 (57.1)	86	2.6 [1.7; 3.7] 47 (54.7)	1.13 [0.78; 1.61]; 0.521
Pain (thorax)					
021G	Endpoint not recorded				
189	161	12.1 [8.0; 19.5] 46 (28.6)	86	11.8 [7.4; n.c.] 21 (24.4)	1.11 [0.65; 1.91]; 0.694
Pain (arm/shoulder)					
021G	Endpoint not recorded				
189	161	n.a. [11.1; n.c.] 40 (24.8)	86	n.a. [3.6; n.c.] 25 (29.1)	0.75 [0.45; 1.25]; 0.265
Pain (other)					
021G	Endpoint not recorded				
189	161	7.6 [4.3; n.c.] 60 (37.3)	86	3.0 [2.6; 8.6] 38 (44.2)	0.71 [0.46; 1.09]; 0.116
Coughing					

021G	Endpoint not recorded				
189	161	15.2 [5.4; 15.6] 53 (32.9)	86	11.5 [4.1; n.c.] 27 (31.4)	1.04 [0.65; 1.67]; 0.863
Haemoptysis					
021G	Endpoint not recorded				
189	161	n.a. 7 (4.3)	86	n.a. 7 (8.1)	0.45 [0.16; 1.31]; 0.144
Alopecia					
021G	Endpoint not recorded				
189	161	3.1 [2.1; n.c.] 67 (41.6)	86	11.3 [4.8; n.c.] 29 (33.7)	1.33 [0.85; 2.10]; 0.215
Dysphagia					
021G	Endpoint not recorded				
189	161	n.a. [11.5; n.c.] 31 (19.3)	86	11.8 [7.4; n.c.] 21 (24.4)	0.72 [0.41; 1.26]; 0.249
Mouth pain					
021G	Endpoint not recorded				
189	161	7.4 [3.1; n.c.] 60 (37.3)	86	n.a. [3.0; n.c.] 26 (30.2)	1.21 [0.75; 1.94]; 0.442
Peripheral neuropathy					
021G	Endpoint not recorded				
189	161	6.0 [3.2; 9.0] 65 (40.4)	86	5.1 [2.9; 11.5] 34 (39.5)	0.84 [0.55; 1.29]; 0.430
Health status (EQ-5D-VAS) – time until deterioration					
021G	Endpoint not recorded				
189					
Responder criterion 10 points	161	5.1 [2.8; 7.8] 71 (44.1)	86	2.6 [1.4; 4.8] 42 (48.8)	0.83 [0.56; 1.24] 0.363
Responder criterion 7 points	161	3.1 [2.1; 5.8] 78 (48.4)	86	2.1 [1.4; 4.5] 45 (52.3)	0.88 [0.60; 1.28] 0.502

Health-related quality of life

Endpoint Study	Pembrolizumab + platinum-based chemotherapy[a]		Platin-based chemotherapy[a]		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 (%)*	Effect estimate [95% CI] p value[b] Absolute difference (AD)[c]
EORTC QLQ-C30 functional scales[e]					
Global health status					
021G	Endpoint not recorded				
189	161	5.2 [2.3; 9.7] 70 (43.5)	86	4.1 [2.5; 7.0] 40 (46.5)	1.02 [0.68; 1.52]; 0.939
Emotional function					
021G	Endpoint not recorded				
189	161	17.7 [8.0; 17.7] 49 (30.4)	86	12.5 [3.6; n.c.] 30 (34.9)	0.87 [0.55; 1.38]; 0.555
Cognitive function					
021G	Endpoint not recorded				
189	161	5.5 [2.5; 7.4] 73 (45.3)	86	3.6 [2.2; 7.2] 39 (45.3)	0.95 [0.64; 1.42]; 0.809
Physical function					
021G	Endpoint not recorded				
189	161	5.2 [2.7; 7.8] 75 (46.6)	86	2.9 [2.1; 4.9] 45 (52.3)	0.84 [0.57; 1.23]; 0.369
Role function					
021G	Endpoint not recorded				
189	161	3.1 [1.7; 7.8] 74 (46.0)	86	2.7 [1.9; 5.0] 43 (50.0)	0.90 [0.62; 1.33]; 0.605
021G	Endpoint not recorded				
189	161	2.1 [1.6; 4.8] 87 (54.0)	86	1.9 [1.4; 3.4] 47 (54.7)	0.90 [0.63; 1.30]; 0.579

Side effects

Endpoint Study	Pembrolizumab + platinum-based chemotherapy[a]		Platinum-based chemotherapy[a]		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 (%)*	Effect estimate [95% CI] p value[b]
Total adverse events (presented additionally)					
021G	19	0.1 [0.1; 0.3] 19 (100.0)	19	0.1 [0.1; 0.3] 18 (94.7)	–
189	161	0.1 [0.1; 0.1] 161 (100.0)	87	0.1 [0.1; 0.1] 85 (97.7)	–
Serious adverse events (SAE)					
	No usable evaluations				
Adverse events (CTCAE grade 3 or 4)					
021G	19	8.2 [2.8; 17.1] 12 (63.2)	19	3.0 [0.7; n.c.] 10 (52.6)	0.68 [0.28; 1.65]; 0.398[f]
189	161	3.9 [2.8; 5.7] 96 (59.6)	87	3.4 [2.1; 4.1] 64 (73.6)	0.75 [0.54; 1.02]; 0.071[f]
Total					0.74 [0.55; 0.9957]; 0.047[g]
Therapy discontinuation because of adverse events					
021G	19	n.a. [11.8; n.c.] 3 (15.8)	19	n.a. [3.7; n.c.] 4 (21.1)	0.48 [0.10; 2.16]; 0.336[f]
189	161	16.3 [16.0; 17.9] 38 (23.6)	87	18.3 [n.c.] 13 (14.9)	1.21 [0.64; 2.28]; 0.561[f]
Total					1.05 [0.59; 1.87]; 0.859[g]
Specific adverse events					
immune-mediated AEs					

021G	No usable evaluations				
189	161	n.a. 28 (17.4)	87	16.6 [n.c.] 9 (10.3)	1.46 [0.69; 3.11]; 0.320[f]
immune-mediated SAEs					
	No usable evaluations				
immune-mediated AEs (CTCAE grade ≥ 3)					
021G	No usable evaluations				
189	161	n.a. 12 (7.5)	87	n.a. 3 (3.4)	1.82 [0.51; 6.46]; 0.354[f]
other specific AEs					
	No usable evaluations				

a Consisting of either cisplatin or carboplatin in combination with pemetrexed

b HR and CI: Cox proportional hazard model with treatment as covariates, stratified by PD-L1 status, platinum chemotherapy, and smoker status; 2-sided p value (Wald test)

c Absolute difference (AD) given only in the case of a statistically significant difference; own calculation.

d Time to first deterioration; defined as an increase of the score by ≥ 10 points compared with baseline

e Time to first deterioration; defined as a decrease of the score by ≥ 10 points compared with baseline

f HR and CI: Cox proportional hazard model with treatment as covariates; 2-sided p value (Wald test)

g HR and CI: based on a common data pool of the KEYNOTE 021G and KEYNOTE 189 studies Cox proportional hazard model with treatment, PD-L1 status, platinum chemotherapy, and smoker status as covariates, additionally stratified by study; 2-sided p value (Wald test)

h Cox proportional hazard model with treatment as covariates

i Cox proportional hazard model with treatment as covariates, stratified according to PD-L1 status, platinum chemotherapy, and smoker status

k p-test from Q-test for heterogeneity

L Based on a common data pool of the KEYNOTE 021G and KEYNOTE 189 studies Cox proportional hazard model with treatment, PD-L1 status, platinum chemotherapy, and smoker status as covariates, additionally stratified by study

m HR and CI: based on a common data pool of the KEYNOTE 021G and KEYNOTE 189 studies Cox proportional hazard model with treatment, PD-L1 status, platinum chemotherapy, and smoker status as covariates, additionally stratified by study; 2-sided p value (Wald test)

Abbreviations used:

AD = absolute difference; CTCAE = Common Terminology Criteria for Adverse Events; EORTC = European Organization for Research and Treatment of Cancer; EQ-5D = Questionnaire on health-related quality of life (Euro QoL-5 Dimensions); HR = hazard ratio; 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; PD-L1: Programmed Cell Death-Ligand 1; QLQ-C30: Quality of Life Questionnaire – Cancer 30; QLQ-LC-13: Quality of Life Questionnaire – Lung Cancer 13; RCT: randomised controlled study; VAS: visual analogue scale; vs: versus

b) <u>Adult patients with first-line treatment of metastatic squamous NSCLC without EGFR or ALK positive tumour mutations whose tumours express PD-L1 with a ≥ 50% tumour proportion score (TPS[1]):</u>

Intervention vs bridge comparator:

KEYNOTE 021G study: Pembrolizumab in combination with pemetrexed and carboplatin vs pemetrexed and carboplatin (data cut-off: 31 May 2017)

KEYNOTE 189 study: Pembrolizumab in combination with pemetrexed and carboplatin or cisplatin vs pemetrexed and carboplatin or cisplatin (data cut-off: 8 November 2017)

Relevant TPC (Treatment of Physician's Choice) sub-population in each case with PD-L1 expression of ≥ 50% (TPS)[1,4]

Appropriate comparator therapy vs bridge comparator:

KEYNOTE 024 study: Pembrolizumab vs pemetrexed in combination with cisplatin or carboplatin (data cut-off: 9 May 2016)

KEYNOTE 042 study: Pembrolizumab vs carboplatin in combination with pemetrexed or paclitaxel (data cut-off: 26 February 2018)

Relevant TPC (Treatment of Physician's Choice) sub-population in each case with PD-L1 expression of ≥ 50% (TPS)[1,4]

Mortality

Endpoint Study	**Pembrolizumab + platinum-based chemotherapy[a] (intervention) or pembrolizumab (appropriate comparator therapy)**		**Platinum-based chemotherapy[a]**		**Group difference**
	N	Median survival time in months [95% CI] *Patients with event n (%)*	N	Median survival time in months [95% CI] *Patients with event n (%)*	Effect estimate [95% CI] p value
Overall survival					
Intervention vs bridge comparator					
021G	10	n.a. [10,7; n.c.] 2 (20.0)	10	19.0 [2.4; n.c.] 6 (60.0)	0.30 [0.06; 1.48] 0.140[b]
189	85	n.a. 18 (21.2)	40	10.0 [7.1; n.c.] 21 (52.5)	0.33 [0.17; 0.62] < 0.001[d]
Total					0.32 [0.18; 0.58] no data available [f]
Appropriate comparator therapy vs bridge comparator					
024	75	n.a.	73	n.a.	0.61

4 The relevant sub-population includes patients with PD-L1 expression ≥ 50% and who were treated according to the results of the pharmaceutical company's TPC survey according to the criteria of the AM-RL for the off-label use of carboplatin (Annex VI to Section K).

		10 (13.3)		15 (20.5)	[0.27; 1.35] 0.222[e]
042	90	n.a. [18.4; n.c.] 17 (18.9)	79	n.a. [17.4; n.c.] 13 (16.5)	1.05 [0.51; 2.17] 0.898[e]
Total					0.79 [0.58; 1.09] no data available [g]
Indirect comparison via bridge comparators (according to Bucher): Pembrolizumab + platinum-based chemotherapy[a] vs pembrolizumab					0.40 [0.20; 0.79] 0.008
Sub-groups according to sex					
Intervention vs bridge comparator					
021G					
Men	*2*	*no data available* *1 (50.0)*	*7*	*no data available* *5 (71.4)*	*no data available*
Women	*8*	*no data available* *1 (12.5)*	*3*	*no data available* *1 (33.3)*	*no data available*
189					
Men	*58*	*n.a.* *5 (25.9)*	*18*	*n.a.* *[7.8; n.c.] [h]* *7 (38.9)*	*0.73* *[0.29; 1.79] [i]* *p = 0.490*
Women	*27*	*n.a.* *3 (11.1)*	*22*	*8.0* *[4.3; n.c.] [h]* *14 (63.6)*	*0.08* *[0.02; 0.34] [i]* *p < 0.001*
Total					
Men					*0.68* *[0.30; 1.56] [f]* *no data available*
Women					*0.12* *[0.04; 0.37] [f]* *no data available*
Appropriate comparator therapy vs bridge comparator					
024					
Men	*43*	*n.a.* *[11.04; n.c.]* *13 (30.2)*	*47*	*12.62* *[6.01; n.c.]* *22 (46.8)*	*0.48* *[0.23; 0.96] [g]* *p = 0.038] [i]*
Women	*32*	*n.a.* *9 (28.1)*	*27*	*n.a.* *[11.83; n.c.]* *6 (22.2)*	*1.33* *[0.45; 3.92] [g]* *p = 0.607] [i]*
042					
Men	*56*	*11.7*	*47*	*6.6*	*0.60* *[0.38; 0.96] [g]*

		[8.0; 14.8] *41 (73.2)*		*[5.5; 8.8]* *39 (83.0)*	*p = 0.032]* [i]
Women	*34*	*7.7* *[2.5; 10.0]* *30 (88.2)*	*39*	*8.5* *[5.4; 11.3]* *29 (74.4)*	*1.33* *[0.79; 2.24]* [g] *p = 0.292* [i]
Total					
Men					*0.58* *[0.39; 0.88]* [f] *no data available*
Women					*1.27* *[0.77; 2.11]* [f] *no data available*
Indirect comparison via bridge comparators (according to Bucher)					
Pembrolizumab + platinum-based chemotherapy [a] ***vs pembrolizumab***					*Interaction:* *p = 0.001*
Men					*1.16* *[0.46; 2.94]* *p = 0.754*
Women					*0.09* *[0.03; 0.32]* *p < 0.001*

Morbidity and health-related quality of life

Endpoint Study	**Pembrolizumab + platinum-based chemotherapy**[a] **(intervention) or pembrolizumab (appropriate comparator therapy)**		**Platinum-based chemotherapy**[a]		**Group difference**
	N	Median survival time in months [95% CI] *Patients with event n (%)*	N	Median survival time in months [95% CI] *Patients with event n (%)*	Effect estimate [95% CI] p value
Morbidity					
No usable data					
Health-related quality of life					
No usable data					

Side effects

Endpoint Study	**Pembrolizumab + platinum-based chemotherapy[a] (intervention) or pembrolizumab (appropriate comparator therapy)**		**Platinum-based chemotherapy[a]**		**Group difference**
	N	Median survival time in months [95% CI] *Patients with event n (%)*	N	Median survival time in months [95% CI] *Patients with event n (%)*	Effect estimate [95% CI] p value
AEs					
Intervention vs bridge comparator					
021G	10	0.1 [0.1; 0.3] 10 (100.0)	10	0.1 [0.1; 0.4] 10 (100.0)	-
189	84	0.1 [0.1; 0.2] 84 (100.0)	38	0.1 [0.1; 0.2] 38 (100.0)	-
Appropriate comparator therapy vs bridge comparator					
024	75	0.2 [0.1; 0.3] 71 (94.7)	73	0.1 [0.1; 0.2] 69 (94.5)	-
042	90	0.4 [0.3; 0.7] 89 (98.9)	79	0.2 [0.1; 0.2] 79 (100.0)	-
SAEs					
No usable data					
Adverse events (CTCAE grade ≥ 3)					
Intervention vs bridge comparator					
021G	10	11.4 [0.1; n.c.] 5 (50.0)	10	1.1 [0.1; n.c.] 7 (70.0)	0.31 [0.09; 1.10] p = 0.070[b]
189	84	3.4 [2.6; 4.9] 65 (77.4)	38	4.0 [1.9; 16.6] 21 (55.3)	1.38 [0.84; 2.26] p = 0.200[b]
Total					1.14 [0.73; 1.77] no data available[c]
Appropriate comparator therapy vs bridge comparator					
024	75	10.0 [3.4; n.c.] 37 (49.3)	73	1.5 [1.2; 3.7] 46 (63.0)	0.63 [0.41; 0.98] p = 0.039[b]

042	90	7.3 [3.8; 12.6] 51 (56.7)	79	4.6 [2.8; 9.0] 46 (58.2)	0.86 [0.58; 1.29] p = 0.476[b]
Total					0.75 [0.56; 1.00] no data available[c]
Indirect comparison via bridge comparators (according to Bucher): Pembrolizumab + platinum-based chemotherapy[a] vs pembrolizumab					1.52 [0.89; 2.58] p = 0.124
Sub-groups according to sex					
Intervention vs bridge comparator					
021G					
Men	*2*	*n.a.* *1 (50.0)*	*7*	*n.a.* *5 (71.4)*	*n.c.*
Women	*8*	*n.a.* *4 (50.0)*	*3*	*n.a.* *2 (66.7)*	*n.c.*
189					
Men	*57*	*3.0* *[1.8; 4.4]* *44 (77.2)*	*18*	*16.6* *[1.4; 16.6]* *9 (50.0)*	*1.90* *[0.92; 3.89][k]* *p = 0.081[i]*
Women	*27*	*4.9* *[1.7; 8.6]* *21 (77.8)*	*20*	*4.0* *[1.1; n.c.]* *12 (60.0)*	*0.84* *[0.40; 1.77][k]* *p = 0.654[i]*
Total					
Men					*1.55* *[0.83; 2.90][c]* *no data available*
Women					*0.75* *[0.37; 1.50][c]* *no data available*
Appropriate comparator therapy vs bridge comparator					
024					
Men	*43*	*6.2* *[1.2; n.c.]* *24 (55.8)*	*47*	*1.3* *[1.0; 1.5]* *35 (74.5)*	*0.51* *[0.30; 0.87][k]* *p = 0.013[i]*
Women	*32*	*n.a.* *[3.4; n.c.]* *13 (40.6)*	*26*	*n.a.* *[2.1; n.c.]* *11 (42.3)*	*1.03* *[0.46; 2.31][k]* *p = 0.285[i]*
042					
Men	*56*	*11.6* *[3.6; 26.2]* *30 (53.6)*	*43*	*3.9* *[2.2; n.c.]* *25 (58.1)*	*0.75* *[0.44; 1.28][k]* *p = 0.940[i]*
Women	*34*	*5.5* *[2.0; 11.4]* *21 (61.8)*	*36*	*6.2* *[2.3; 15.8]* *21 (58.3)*	*1.14* *[0.62; 2.10][k]* *p = 0.662[i]*

Total					
Men					*0.61 [0.42; 0.89][c] no data available*
Women					*1.10 [0.68; 1.79][c] no data available*
Indirect comparison via bridge comparators (according to Bucher): Pembrolizumab + platinum-based chemotherapy[a] vs pembrolizumab					
					Interaction: p = 0.021
Men					*2.53 [1.22; 5.23] p = 0.012*
Women					*0.68 [0.29; 1.58] p = 0.373*
Discontinuation because of AE					
Intervention vs bridge comparator					
021G	*10*	*n.a. [7.4; n.c.] 2 (20.0)*	*10*	*11.7 [5.6; n.c.] 2 (20.0)*	*0.27 [0.02; 2.99] 0.286[b]*
189	*84*	*17.1 [12.1; 19.2] 30 (35.7)*	*38*	*19.7 [n.c.] 4 (10.5)*	*3.07 [0.93; 10.15] 0.066[b]*
Total					*2.00 [0.77; 5.21] no data available[c]*
Appropriate comparator therapy vs bridge comparator					
024	*75*	*n.a. 10 (13.3)*	*73*	*n.a. 15 (20.5)*	*0.61 [0.27; 1.35] 0.222[b]*
042	*90*	*n.a. [18.4; n.c.] 17 (18.9)*	*79*	*n.a. [17.4; n.c.] 13 (16.5)*	*1.05 [0.51; 2.17] 0.898[b]*
Total					*0.82 [0.48; 1.39] no data available[c]*
Indirect comparison via bridge comparators (according to Bucher): Pembrolizumab + platinum-based chemotherapy[a] vs pembrolizumab					*2.45 [0.82; 7.31] 0.108*

a Consisting of either cisplatin or carboplatin in combination with pemetrexed

b Cox proportional hazard model with treatment as covariates; 2-sided p value (Wald test)

c Cox proportional hazard model with treatment as covariates, stratified by study

d Cox proportional hazard model with treatment as covariates, stratified by PD-L1 status (≥ 1 vs < 1%), platinum chemotherapy (cisplatin vs carboplatin), and smoker status (never vs former/active); 2-sided p value (Wald test)

e	Cox proportional hazard model with treatment as covariates, stratified by geographical region (East Asia vs non-East Asia) and ECOG performance status (0 vs 1); 2-sided p value (Wald test)
f	Cox proportional hazard model with treatment, platinum chemotherapy (cisplatin vs carboplatin), and smoker status (never vs former/active) stratified by study
g	Cox proportional hazard model with treatment, geographical region (East Asia vs non-East Asia), and ECOG performance status (0 vs 1) stratified by study
d	Cox proportional hazard model stratified by PD-L1 status (≥ 1 vs < 1%), platinum chemotherapy (cisplatin vs carboplatin), and smoker status (never vs former/active)
i	2-sided p value (Wald test)
k	Cox proportional hazard model with treatment as covariates

Abbreviations used:

CTCAE = Common Terminology Criteria for Adverse Events; ECOG: Eastern Cooperative Oncology Group; HR = hazard ratio; 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; PD-L1: Programmed Cell Death-Ligand 1; RCT: randomised controlled study; SAE: serious AE, AE: adverse event; vs: versus

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

a) Adult patients with first-line treatment of metastatic squamous NSCLC without EGFR or ALK positive tumour mutations whose tumours express PD-L1 with a < 50% tumour proportion score (TPS[1]):

approx. 5,700 to 6,480 patients

b) Adult patients with first-line treatment of metastatic squamous NSCLC without EGFR or ALK positive tumour mutations with one patient whose tumour expressed PD-L1 with a ≥ 50% tumour proportion score (TPS[1]):

approx. 2320 to 2640 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: 10 July 2019):

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

Treatment with pembrolizumab should only be initiated and monitored by specialists in internal medicine, haematology, and oncology, specialists in internal medicine and pneumology, specialists in pulmonary medicine, and specialists participating in the Oncology Agreement who are experienced in the treatment of patients with non-small cell lung carcinoma.

According to the requirements for risk minimisation activities in the EPAR (European Public Assessment Report), the pharmaceutical company must provide the following information material on pembrolizumab:

- Training and information material for doctors/medical professionals

– Training and information material for the patient

In patients with NSCLC whose tumours show a high PD-L1 expression, the risk of side effects of a combination therapy compared with a monotherapy with pembrolizumab should be considered and the benefit-risk ratio of a combination therapy individually evaluated.

For women, the results show better therapeutic effects of pembrolizumab in combination with pemetrexed and platinum chemotherapy than men, especially for overall survival. This is evident from the sub-group evaluations by sex in the relevant sub-populations of the present benefit assessment. The better therapeutic effects for women are shown both compared with pemetrexed plus platinum chemotherapy (PD L1 expression < 50%, TPS) and to pembrolizumab as monotherapy (PD L1 expression ≥ 50%, TPS). This should be considered in the individual therapy decision.

4. Treatment costs

Annual treatment costs:

a) Adult patients with first-line treatment of metastatic squamous NSCLC without EGFR or ALK positive tumour mutations whose tumours express PD-L1 with a < 50% tumour proportion score (TPS[1]):

Designation of the therapy	Annual treatment costs/patient
Medicinal product to be assessed:	
Pembrolizumab plus pemetrexed plus carboplatin	
Pembrolizumab	103,757.46
Pemetrexed	€ 67,076.22
Carboplatin	€ 8,514.45
Total:	€ 179,348.13
Additionally required SHI services:	€ 123.61–169.71
Pembrolizumab plus pemetrexed plus cisplatin	
Pembrolizumab	103,757.46
Pemetrexed	€ 67,076.22
Cisplatin	€ 1,959.42
Total:	€ 172,793.10
Additionally required SHI services:	€ 448.03–585.03
Appropriate comparator therapy:	
Cisplatin plus docetaxel	
Cisplatin	€ 1,959.42
Docetaxel	€ 20,741.53
Total:	€ 22,700.95

Designation of the therapy	Annual treatment costs/patient
Additionally required SHI services:	€ 324.43–415.33
Cisplatin plus gemcitabine	
Cisplatin	€ 1,959.42–2,427.26
Gemcitabine	€ 7,999.18
Total:	€ 9,958.60–10,426.44
Additionally required SHI services:	€ 324.43–415.33
Cisplatin plus paclitaxel	
Cisplatin	€ 2,216.63
Paclitaxel	€ 20,269.78
Total:	€ 22,486.41
Additionally required SHI services:	€ 557.97–648.87
Cisplatin plus pemetrexed	
Cisplatin	€ 1,959.42
Pemetrexed	€ 67,076.22
Total:	€ 69,035.64
Additionally required SHI services:	€ 448.03–585.03
Cisplatin plus vinorelbine	
Cisplatin	€ 1,959.42–2,427.26
Vinorelbine	€ 4,890.22–6,096.88
Total:	€ 6,849.64–8,524.14
Additionally required SHI services:	€ 324.43–415.33
Carboplatin plus docetaxel	
Carboplatin	€ 8,514.45
Docetaxel	€ 20,741.53
Total:	€ 29,255.98
Carboplatin plus gemcitabine	
Carboplatin	€ 8,514.45
Gemcitabine	€ 7,999.18
Total:	€ 16,513.63
Carboplatin plus paclitaxel	
Carboplatin	€ 8,514.45
Paclitaxel	€ 20,269.78
Total:	€ 28,784.23

Designation of the therapy	Annual treatment costs/patient
Additionally required SHI services:	€ 233.55
Carboplatin plus pemtrexed	
Carboplatin	€ 8,514.45
Pemetrexed	€ 72,399.94
Total:	€ 80,914.39
Additionally required SHI services:	€ 123.61–169.71
Carboplatin plus vinorelbine	
Carboplatin	€ 8,514.45
Vinorelbine	€ 4,890.22–6,096.88
Total:	€ 13,404.67–14,611.33
Carboplatin plus nab-paclitaxel	
Carboplatin	€ 8,514.45
nab-paclitaxel	€ 41,219.22
Total:	€ 49,733.67

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 1 September 2019)

Other services covered by SHI funds:

Designation of the therapy	Type of service	Cost per unit	Number per cycle	Number per patient per year[5]	Cost per patient per year
Medicinal product to be assessed:					
Pembrolizumab	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 71	1	17	€ 1,207
Carboplatin	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1	17	€ 1,377
Cisplatin	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1	17	€ 1,377
Pemetrexed	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1	17	€ 1,377

[5] calculated and standardised for one year

Appropriate comparator therapy:					
Carboplatin	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1	17	€ 1,377
Cisplatin	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1	17	€ 1,377
Vinorelbine	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	2	34	€ 2,754
Gemcitabine	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	2	34	€ 2,754
Docetaxel	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1	17	€ 1,377
Paclitaxel	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1	17	€ 1,377
nab-paclitaxel	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1	51	€ 4,131
Pemetrexed	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1	17	€ 1,377

b) Adult patients with first-line treatment of metastatic squamous NSCLC without EGFR or ALK positive tumour mutations with one patient whose tumour expressed PD-L1 with a ≥ 50% tumour proportion score (TPS[1]):

Designation of the therapy	Annual treatment costs/patient
Medicinal product to be assessed:	
Pembrolizumab plus pemtrexed plus carboplatin	
Pembrolizumab	103,757.46
Pemetrexed	€ 67,076.22
Carboplatin	€ 8,514.45
Total:	€ 179,348.13
Additionally required SHI services:	€ 123.61–169.71
Pembrolizumab plus pemtrexed plus cisplatin	
Pembrolizumab	103,757.46

Designation of the therapy	Annual treatment costs/patient
Pemetrexed	€ 67,076.22
Cisplatin	€ 1,959.42
Total:	€ 172,793.10
Additionally required SHI services:	€ 448.03–585.03
Appropriate comparator therapy:	
Pembrolizumab	103,757.46

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 1 September 2019)

Other services covered by SHI funds:

Designation of the therapy	Type of service	Cost per unit	Number per cycle	Number per patient per year[6]	Cost per patient per year
Medicinal product to be assessed:					
Pembrolizumab	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 71	1	17	€ 1,207
Carboplatin	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1	17	€ 1,377
Cisplatin	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1	17	€ 1,377
Pemetrexed	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1	17	€ 1,377
Appropriate comparator therapy:					
Pembrolizumab	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 71	1	17	€ 1,207

6 calculated and standardised for one year

II. The resolution will enter into force on the day of its publication on the internet on the website of the G-BA on 19 September 2019.

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

Berlin, 19 September 2019

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

Prof Hecken