IQWiG Reports – Commission No. A19-61

Pembrolizumab (non-squamous NSCLC, combination therapy) –

Addendum to Commission A19-30[1]

Addendum

Commission: A19-61
Version: 1.0
Status: 20 August 2019

[1] Translation of addendum A19-61 *Drug (Pembrolizumab) – Addendum zum Auftrag A19-30* (Version 1.0; Status: 5 August 2019). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

Publishing details

Publisher:
Institute for Quality and Efficiency in Health Care

Topic:
Pembrolizumab (non-squamous NSCLC, combination therapy) – Addendum to Commission A19-30

Commissioning agency:
Federal Joint Committee

Commission awarded on:
5 August 2019

Internal Commission No.:
A19-61

Address of publisher:
Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Im Mediapark 8
50670 Köln
Germany

Phone: +49 221 35685-0
Fax: +49 221 35685-1
E-mail: berichte@iqwig.de
Internet: www.iqwig.de

IQWiG employees involved in the addendum:

- Ulrike Seay
- Lars Beckmann
- Petra Kohlepp
- Beate Wieseler

Keywords: pembrolizumab, pemetrexed, carboplatin, cisplatin, carcinoma – non-small-cell lung, benefit assessment, NCT02039674, NCT02578680, NCT02142738, NCT02220894

Table of contents

List of tables

Page

List of figures

Page

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
ALK	anaplastic lymphoma kinase
CTCAE	Common Terminology Criteria for Adverse Events
EGFR	epidermal growth factor receptor
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
ITT	intention to treat
MedDRA	Medical Dictionary for Regulatory Activities
NSCLC	non-small cell lung cancer
PD-L1	Programmed Cell Death-Ligand 1
PT	preferred term
RCT	randomized controlled trial
SOC	system organ class
TPS	tumour proportion score

1 Background

On 5 August 2019, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A19-30 (Pembrolizumab – Benefit assessment according to §35a Social Code Book V) [1].

In Module 4 B [2] and Module 4 C [3] of its dossier on pembrolizumab, the pharmaceutical company (hereinafter referred to as "the company") presented contradictory data for the operationalization of the outcome "overall survival". In Module 4 C [3] on squamous non-small cell lung cancer (NSCLC), the company stated that patients who had switched from the control arm to monotherapy with pembrolizumab in KEYNOTE 407 and KEYNOTE 042 were censored in the statistical analyses at the time point of the treatment switch. Such analysis could not be meaningfully interpreted. The company did not provide this information in Module 4 B [2] on non-squamous NSCLC, but it neither stated that the patients who had switched to monotherapy with pembrolizumab had not been censored. Due to these contradictory data, the results on "overall survival" presented by the company were not usable in the dossier assessment.

With its comment [4], the company clarified that the information in Module 4 C was an editorial mistake. The analyses on the outcome "overall survival" were intention to treat (ITT) analyses with censoring at the time point of the last observation both in squamous NSCLC (Module 4 C) and in non-squamous NSCLC (Module 4 B).

The G-BA commissioned IQWiG with the assessment of the analyses on the outcome "overall survival" in the company's dossier.

The responsibility for the present assessment and the assessment result lies exclusively with IQWiG. The assessment is forwarded to the G-BA. The G-BA decides on the added benefit.

2 Assessment

The aim of dossier assessment A19-30 [1] was to assess the added benefit of pembrolizumab in combination with pemetrexed and platinum-based chemotherapy as first-line treatment in comparison with the appropriate comparator therapy (ACT) in adult patients with metastatic non-squamous NSCLC without epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK)-positive tumour mutations. This resulted in 2 research questions:

- Research question 1: Benefit assessment in adults with a Programmed Cell Death-Ligand 1 (PD-L1) expression < 50% in comparison with platinum-based chemotherapy
- Research question 2: Benefit assessment in adults with a PD-L1 expression ≥ 50% in comparison with pembrolizumab monotherapy

In its dossier, the company presented two randomized controlled trials (RCTs) for direct comparison for research question 1 and an adjusted indirect comparison according to Bucher [5] with a total of 4 RCTs for research question 2. The studies presented are relevant for the benefit assessment for both research questions. In dossier assessment A19-30, however, complete benefit assessment with subsequent balancing of positive and negative effects was impossible for both research questions because of the unclear operationalization of the outcome "overall survival". Detailed reasons can be found in dossier assessment A19-30 [1].

With its comment [4], the company clarified that the analyses presented on the outcome "overall survival" were adequate ITT analyses. Complete assessment of the company's analyses is thus possible.

Assessment of the outcome "overall survival" for research question 1 is found in Section 2.1 (assessment of the other outcomes of the presented RCTs was already conducted in the dossier assessment [1]). Section 2.2 comprises the assessment of the indirect comparison for research question 2.

2.1 Research question 1: PD-L1 expression < 50%

For research question 1, the company presented the two RCTs KEYNOTE 021G and KEYNOTE 189 in its dossier. Dossier assessment A19-30 [1] provides a detailed description of the characteristics of the two studies, the risk of bias as well as the presentation of the results for all outcomes with the exception of the outcome "overall survival". The results on the outcome "overall survival" are presented in the following Section 2.1.1.

2.1.1 Results

The Kaplan-Meier curves on the outcome "overall survival" are presented in Appendix A.1. Kaplan-Meier curves for subgroup results on the outcome "overall survival" are not included in the company's dossier.

Results on the outcome "overall survival"

Table 1 shows the results on the outcome “overall survival”.

Table 1: Results (mortality, time to event) – RCT, direct comparison: pembrolizumab + platinum-based chemotherapy[a] vs. platinum-based chemotherapy[a]

Outcome category Outcome Study	Pembrolizumab + platinum-based chemotherapy[a]		Platinum-based chemotherapy[a]		Pembrolizumab + platinum-based chemotherapy[a] vs. platinum-based chemotherapy[a]
	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 (%)	HR [95% CI]; p-value
Mortality					
Overall survival					
021G[b]	20	NA [11.1; NC] 6 (30.0)	20	14.9 [7.2; NC] 12 (60.0)	0.41 [0.15; 1.09]; 0.073[c]
189[d]	162	NA [14.4; NC] 54 (33.3)	88	12.1 [8.6; NC] 46 (52.3)	0.58 [0.39; 0.86]; 0.008[e]
Total					0.55 [0.38; 0.77]; 0.001[f]

a: Consisting of either cisplatin or carboplatin in combination with pemetrexed.
b: Data cut-off: 31 May 2017.
c: HR and CI: Cox proportional hazards model with treatment as covariate, stratified by PD-L1 status, platinum-based chemotherapy and smoking status; two-sided p-value (Wald test).
d: Data cut-off: 8 November 2017.
e: HR and CI: Cox proportional hazards model with treatment as covariate; 2-sided p-value (Wald test).
f: HR and CI: on the basis of a common data pool of the studies KEYNOTE 021G and KEYNOTE 189 Cox proportional hazards model with treatment, PD-L1 status, platinum-based chemotherapy and smoking status as covariates, additionally stratified by study; 2-sided p-value (Wald test).
CI: confidence interval; HR: hazard ratio; N: number of analysed patients; n: number of patients with event; NA: not achieved; NC: not calculable; PD-L1: programmed cell death ligand 1; RCT: randomized controlled trial; vs.: versus

The risk of bias of the results on the outcome “overall survival” was rated as low. Thus, at most proofs, e.g. of an added benefit, can be derived on the basis of the meta-analysis of the two studies KEYNOTE 021G and KEYNOTE 189.

Mortality

Overall survival

The meta-analysis of the KEYNOTE 021G and KEYNOTE 189 studies showed a statistically significant difference between the treatment groups in favour of pembrolizumab + platinum-based chemotherapy for the outcome “overall survival”. However, there is an effect modification by the characteristic “sex”. This resulted in proof of added benefit of pembrolizumab + platinum-based chemotherapy in comparison with platinum-based

chemotherapy for women. For men, this resulted in no hint of an added benefit of pembrolizumab + platinum-based chemotherapy; an added benefit is therefore not proven.

This concurs with the assessment of the company, insofar as it also derived proof of an added benefit. However, it does not consider the effect modification by the characteristic "sex".

Subgroup results for the outcome "overall survival"

Table 2 shows the subgroup results for the outcome "all-cause mortality".

Table 2: Subgroups (mortality, time to event) – RCT, direct comparison: pembrolizumab + platinum-based chemotherapy[a] vs. platinum-based chemotherapy[a]

Outcome Characteristic Study Subgroup	Pembrolizumab + platinum-based chemotherapy[a]		Platinum-based chemotherapy[a]		Pembrolizumab + platinum-based chemotherapy[a] vs. platinum-based chemotherapy[a]	
	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 (%)	HR [95% CI]	p-value[b]
Overall survival						
Sex						
021G[c]						
Men	11	NA [1.8; NC] 5 (45.5)	6	10.6 [2.0; NC] 5 (83.3)	0.48 [0.14; 1.66][d]	0.244
Women	9	NA [6.5; NC] 1 (11.1)	14	20.9 [3.3; NC] 7 (50.0)	0.17 [0.02; 1.40][d]	0.100
189[e]						
Men	103	NA [12.6; NC] 39 (37.9)	49	12.9 [8.1; NC] 23 (46.9)	0.78 [0.46; 1.32][f]	0.354
Women	59	NA 15 (25.4)	39	10.6 [7.2; NC] 23 (59.0)	0.37 [0.19; 0.74][f]	0.005
Total					Interaction:	0.035[g]
Men					0.73 [0.45; 1.18][h]	0.200
Women					0.31 [0.17; 0.59][h]	< 0.001

a: Consisting of either cisplatin or carboplatin in combination with pemetrexed.
b: 2-sided p-value (Wald test).
c: Data cut-off 31 May 2017.
d: Cox proportional hazards model with treatment as covariate.
e: Data cut-off: 8 November 2018.
f: Cox proportional hazards model with treatment as covariate, stratified by PD-L1 status, platinum-based chemotherapy and smoking status.
g: p-value from Q test for heterogeneity.
h: On the basis of a common data pool of the studies KEYNOTE 021G and KEYNOTE 189 Cox proportional hazards model with treatment, PD-L1 status, platinum-based chemotherapy and smoking status as covariates, additionally stratified by study.

CI: confidence interval; HR: hazard ratio; N: number of analysed patients; n: number of patients with event; NA: not achieved; NC: not calculable; PD-L1: programmed cell death ligand 1; RCT: randomized controlled trial; vs.: versus

Mortality

Overall survival

For the outcome "overall survival", there is an effect modification by the characteristic "sex" based on the meta-analysis of the studies KEYNOTE 021G and KEYNOTE 189. For men, there

was no difference between the treatment groups. This resulted in no hint of an added benefit of pembrolizumab + platinum-based chemotherapy; an added benefit is therefore not proven. The meta-analysis of the studies KEYNOTE 021G and KEYNOTE 189 showed a statistically significant difference in favour of pembrolizumab + platinum-based chemotherapy for women. This resulted in proof of added benefit of pembrolizumab + platinum-based chemotherapy in comparison with platinum-based chemotherapy for women.

The company presented the results for the effect modification by the characteristic “sex” in its dossier, however, it did not use them for the derivation of the added benefit.

Further subgroup results

Dossier assessment A19-30 presents further subgroup results [1]. These are effect modifications by the characteristics “age”, “smoking status” and “PD-L1 expression”. They relate to the outcomes “dyspnoea”, “fatigue”, “insomnia”, “pain (arm/shoulder)”, and severe AEs (Common Terminology Criteria for Adverse Events [CTCAE grade ≥ 3]). Except for the outcome “severe AEs (CTCAE grade ≥ 3)”, the results are only available for KEYNOTE 189. In the overall consideration, the subgroup results presented in dossier assessment A19-30 cannot be interpreted meaningfully and are therefore not considered further.

2.1.2 Probability and extent of added benefit

Probability and extent of the added benefit at outcome level for the outcome "overall survival” are presented below. The various outcome categories and the effect sizes were taken into account. The methods used for this purpose are explained in the *General Methods* of IQWiG [6]. Probability and extent of the further outcomes of the studies KEYNOTE 021G and KEYNOTE 189 are included in the dossier assessment [1].

The approach for deriving an overall conclusion on the added benefit based on the aggregation of conclusions derived at outcome level from the dossier assessment and the addendum is a proposal by IQWiG. The G-BA decides on the added benefit.

Assessment of the added benefit at outcome level

The extent of each added benefit at outcome level for the outcome “overall survival” was estimated from the results presented in Section 2.1.1 (see Table 3).

Table 3: Extent of added benefit at outcome level: pembrolizumab + platinum-based chemotherapy[a] vs. platinum-based chemotherapy[a]

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Pembrolizumab + platinum-based chemotherapy[a] vs. platinum-based chemotherapy[a]** **Median time to event (months)** **Effect estimation [95% CI]; p-value** **Probability[b]**	**Derivation of extent[c]**
Mortality		
Overall survival		
Sex		
Men	Median: NA vs. 10.6-12.9 HR: 0.73 [0.45; 1.18] p = 0.200	Lesser benefit/added benefit not proven
Women	Median: NA vs. 10.6-20.9 HR: 0.31 [0.17; 0.59] p < 0.001 Probability: "proof"	Outcome category: all-cause mortality CI_u < 0.85 Added benefit, extent: “major”

a: Consisting of either cisplatin or carboplatin in combination with pemetrexed.
b: Probability provided if there is a statistically significant and relevant effect.
c: Depending on the outcome category, estimations of effect size are made with different limits based on the CI_u.
CI: confidence interval; CI_u: upper limit of confidence interval; NA: not achieved; vs.: versus

Overall conclusion on added benefit

Table 4 summarizes the results of the dossier assessment [[1] and the addendum considered in the overall conclusion on the extent of added benefit.

Table 4: Positive and negative effects from the assessment of pembrolizumab + platinum-based chemotherapy[a] vs. platinum-based chemotherapy[a]

Positive effects	**Negative effects**
Mortality ▪ Overall survival ▫ Sex (women): proof of added benefit – extent: "major"	–
Serious/severe side effects ▪ Severe AEs (CTCAE grade ≥ 3): indication of lesser harm – extent: "minor"	–

a: Consisting of either cisplatin or carboplatin in combination with pemetrexed.
AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; vs.: versus

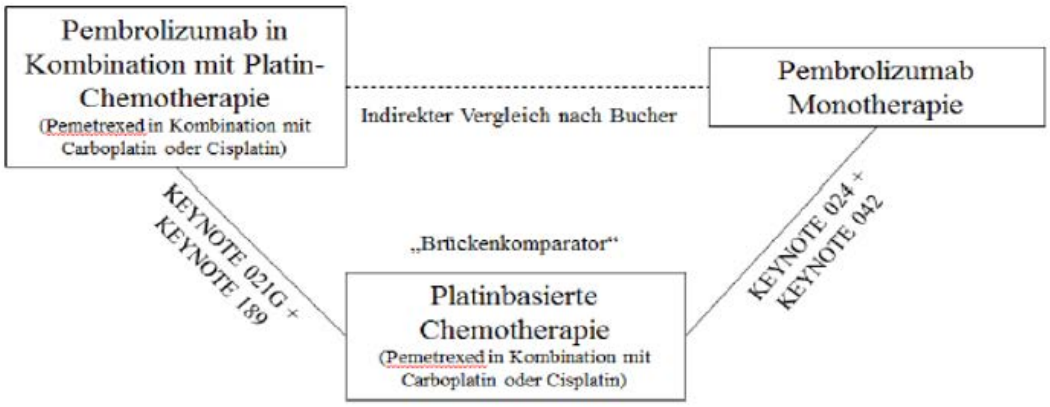
The overall consideration showed two positive effects for women, one of which with the extent "major". One positive effect with the extent "minor" was shown for men. These positive effects are not offset by negative effects.

In summary, this resulted in proof of an added benefit with the extent "major" for pembrolizumab in combination with pemetrexed and platinum-based chemotherapy in comparison with cisplatin or carboplatin, each in combination with pemetrexed, for women with metastatic non-squamous NSCLC without EGFR or ALK-positive tumour mutations with a PD-L1 expression of < 50 %.

For men with metastatic non-squamous NSCLC without EGFR or ALK-positive tumour mutations and with a PD-L1 expression of < 50%, this results in an indication of an added benefit with the extent "minor" for pembrolizumab in combination with pemetrexed and platinum-based chemotherapy versus cisplatin or carboplatin, each in combination with pemetrexed.

2.2 Research question 2: PD-L1 expression ≥ 50%

For research question 2, the company presented and adjusted indirect comparison according to Bucher [5] in its dossier. The study pool comprises the RCTs KEYNOTE 021G and KEYNOTE 189 for the intervention and the RCTs KEYNOTE 024 and KEYNOTE 042 for the comparator therapy. Figure 1 shows a schematic representation of the indirect comparison.



Pembrolizumab in Kombination mit… = Pembrolizumab in combination with platinum-based chemotherapy (Pemetrexed in combination with carboplatin or cisplatin); Indirekter Vergleich nach Bucher = indirect comparison according to Bucher: Pembrolizumab Monotherapie = pembrolizumab monotherapy; Brückenkomparator = common comparator; Platinbasierte Chemotherapie = platinum-based chemotherapy

Figure 1: Study pool for the indirect comparison between pembrolizumab + platinum-based chemotherapy and the ACT pembrolizumab monotherapy

Dossier assessment A19-30 [1] provides a detailed description of the characteristics of the four studies as well as of the risk of bias for all outcomes with the exception of the outcome "overall survival". The following sections present the results of the indirect comparison.

2.2.1 Results

2.2.1.1 Results based on the relevant subpopulation

The company's dossier does not include usable analyses for the adjusted indirect comparison for all patient-relevant outcomes. Usable analyses in the categories "morbidity" and "health-related quality of life", for instance, are completely missing. In the category "side effects", the selection of specific AEs is not possible (for detailed reasons please see dossier assessment A19-30 [1]).

Table 5 summarizes the results on the comparison of pembrolizumab + platinum-based chemotherapy in patients with metastatic non-squamous NSCLC and PD-L1 expression ≥ 50% with pembrolizumab. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier.

The Kaplan-Meier curves on the outcome "overall survival" can be found in Appendix A.2

At the level of system organ classes (SOC) according to the Medical Dictionary for Regulatory Activities (MedDRA), the company presented effect estimations from event time analyses for the relevant subpopulation on all AEs, severe AEs (CTCAE degree ≥ 3), discontinuation due to AEs and immune-related AEs (only KEYNOTE 189). At the level of the preferred term (PT) according to MedDRA, there are no results from event time analyses for the relevant subpopulation. For PTs, event rates are only presented if the corresponding SOC shows a statistically significant difference between the treatment arms in the corresponding event time analysis and if certain threshold values for the frequencies are reached. Therefore, results on common side effects are only presented at SOC level in Appendix B. Presentation of the common PTs is omitted due to incompleteness (see dossier assessment A19-30 [1]).

Table 5: Results (mortality, side effects, time to event) – indirect comparison: pembrolizumab + platinum-based chemotherapy[a] vs. platinum-based chemotherapy[a]

Outcome category Outcome Comparison Study	Pembrolizumab + platinum-based chemotherapy[a] (Int) or pembrolizumab (ACT)		Platinum-based chemotherapy[a]		Group difference
	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 (%)	HR [95% CI]; p-value
Mortality					
All-cause mortality					
Intervention vs. common comparator					
021G[b]	10	NA [10.7; NC] 2 (20.0)	10	19.0 [2.4; NC] 6 (60.0)	0.30 [0.06; 1.48]; 0.140[c]
189[d]	85	NA 18 (21.2)	40	10.0 [7.1; NC] 21 (52.5)	0.33 [0.17; 0.62]; < 0.001[e]
Total					0.32 [0.18; 0.58]; ND[f]
ACT vs. common comparator					
024[g]	75	NA [13.4; NC] 22 (29.3)	74	12.6 [11.8; NC] 28 (37.8)	0.66 [0.38; 1.16]; 0.149[h]
042[i]	90	16.7 [13.4; 22.4] 54 (60.0)	86	16.4 [10.4; 19.1] 52 (60.5)	0.88 [0.60; 1.30]; 0.524[h]
Total					0.79 [0.58; 1.09]; ND[j]
Indirect comparison using common comparators[k]: **Pembrolizumab + platinum-based chemotherapy[a] vs. pembrolizumab**					0.40 [0.20; 0.79]; 0.008
Morbidity					
No usable data[m]					
Health-related quality of life					
No usable data[m]					

(continued)

Table 5: Results (mortality, side effects, time to event) – indirect comparison: pembrolizumab + platinum-based chemotherapy[a] vs. pembrolizumab (continued)

Outcome category Outcome Comparison Study	Pembrolizumab + platinum-based chemotherapy[a] (Int) or pembrolizumab (ACT)		Platinum-based chemotherapy[a]		Group difference
	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 (%)	HR [95% CI]; p-value
Side effects					
AEs					
Intervention vs. common comparator					
021G[b]	10	0.1 [0.1; 0.3][l] 10 (100.0)	10	0.1 [0.1; 0.4][l] 10 (100.0)	–
189[d]	84	0.1 [0.1; 0.2][l] 84 (100.0)	38	0.1 [0.1; 0.2][l] 38 (100.0)	–
ACT vs. common comparator					
024[g]	75	0.2 [0.1; 0.3][l] 71 (94.7)	73	0.1 [0.1; 0.2][l] 69 (94.5)	–
042[i]	90	0.4 [0.3; 0.7][l] 89 (98.9)	79	0.2 [0.1; 0.2][l] 79 (100.0)	–
SAEs	No usable data[m]				
Severe AEs (CTCAE grade ≥ 3)					
Intervention vs. common comparator					
021G[b]	10	11.4 [0.1; NC][l] 5 (50.0)	10	1.1 [0.1; NC][l] 7 (70.0)	0.31 [0.09; 1.10]; 0.070[c]
189[d]	84	3.4 [2.6; 4.9][l] 65 (77.4)	38	4.0 [1.9; 16.6][l] 21 (55.3)	1.38 [0.84; 2.26]; 0.200[c]
Total					1.14 [0.73; 1.77]; ND[n]
ACT vs. common comparator					
024[g]	75	10.0 [3.4; NC][l] 37 (49.3)	73	1.5 [1.2; 3.7][l] 46 (63.0)	0.63 [0.41; 0.98]; 0.039[c]
042[i]	90	7.3 [3.8; 12.6][l] 51 (56.7)	79	4.6 [2.8; 9.0][l] 46 (58.2)	0.86 [0.58; 1.29]; 0.476[c]
Total					0.75 [0.56; 1.00]; ND[n]
Indirect comparison using common comparators[k]:					
Pembrolizumab + platinum-based chemotherapy[a] vs. pembrolizumab					1.52 [0.89; 2.58]; 0.124

(continued)

Table 5: Results (mortality, side effects, time to event) – indirect comparison: pembrolizumab + platinum-based chemotherapy[a] vs. pembrolizumab (continued)

Outcome category Outcome Comparison Study	Pembrolizumab + platinum-based chemotherapy[a] (Int) or pembrolizumab (ACT)		Platinum-based chemotherapy[a]		Group difference
	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 (%)	HR [95% CI]; p-value
Discontinuation due to AEs					
Intervention vs. common comparator					
021G[b]	10	NA [7.4; NC][l] 2 (20.0)	10	11.7 [5.6; NC][l] 2 (20.0)	0.27 [0.02; 2.99]; 0.286[c]
189[d]	84	17.1 [12.1; 19.2][l] 30 (35.7)	38	19.7 [NC][l] 4 (10.5)	3.07 [0.93; 10.15]; 0.066[c]
Total					2.00 [0.77; 5.21]; ND[n]
ACT vs. common comparator					
024[g]	75	NA 10 (13.3)	73	NA 15 (20.5)	0.61 [0.27; 1.35]; 0.222[c]
042[i]	90	NA [18.4; NC][l] 17 (18.9)	79	NA [17.4; NC][l] 13 (16.5)	1.05 [0.51; 2.17]; 0.898[c]
Total					0.82 [0.48; 1.39]; ND[n]
Indirect comparison using common comparators[k]:					
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: Data cut-off: 31 May 2017.
c Cox proportional hazards model with treatment as covariate; 2-sided p-value (Wald test).
d: Data cut-off: 8 November 2017.
c: Cox proportional hazards model with treatment as covariate, stratified by PD-L1 status (≥ 1% vs. < 1%), platinum-based chemotherapy (cisplatin vs. carboplatin) and smoking status (never vs. former/active), 2-sided p-value (Wald test).
f: Cox proportional hazards model with treatment, platinum-based chemotherapy (cisplatin vs. carboplatin) and smoking status (never vs. former/active) as covariate, stratified by study.
g: Data cut-off: 9 May 2016.
h: Cox proportional hazards model with treatment as covariate, stratified by geographical region (East Asia vs. not East Asia) and Eastern Cooperative Oncology Group Performance Status [ECOG PS] (0 vs. 1); 2-sided p-value (Wald test).
i: Data cut-off: 26 February 2018.
j: Cox proportional hazards model with treatment as covariate, geographical region (East Asia vs. not East Asia) and ECOG PS (0 vs. 1) as covariate, stratified by study.
k: Indirect comparison according to Bucher [5]
l: Institute's calculation.
m: No usable analyses available for the relevant subpopulation. For reasons, see [1].
n: Cox proportional hazards model with treatment as covariate, stratified by study.

(continued)

Table 5: Results (mortality, side effects, time to event) – indirect comparison: pembrolizumab + platinum-based chemotherapy[a] vs. pembrolizumab (continued)

ACT: appropriate comparator therapy; AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; ECOG PS: Eastern Cooperative Oncology Group Performance Status; HR: hazard ratio; Int: intervention; N: number of analysed patients; n: number of patients with (at least one) event; NA: not achieved; NC: not calculable; ND: no data; PD-L1: programmed cell death ligand 1; SAE: serious adverse event; vs.: versus

The bias for the results of the outcome "overall survival" was rated as potentially low. The risk of bias for the results on "side effects" was rated as high (for reasons, see dossier assessment A19-30 [1]).

Results of adjusted indirect comparisons have a low certainty of results per se. Only adjusted indirect comparisons of particularly high methodological quality that were based on a sufficient number of studies with a low risk of bias and included a valid check of the assumption of homogeneity and consistency can be considered as having a moderate certainty of results. In the present case, consistency could not be checked. Therefore, at most hints can be derived.

Mortality

Overall survival

The adjusted indirect comparison showed a statistically significant difference between the treatment groups in favour of pembrolizumab + platinum-based chemotherapy for the outcome "overall survival". However, there is an effect modification by the characteristic "sex". This resulted in a hint of an added benefit of pembrolizumab + platinum-based chemotherapy in comparison with pembrolizumab for women. For men, this resulted in no hint of an added benefit of pembrolizumab + platinum-based chemotherapy; an added benefit is therefore not proven.

This assessment deviates from that of the company. The company derived an indication of an added benefit and did not consider the effect modification by the characteristic "sex".

Morbidity

There are no usable data in the category "morbidity" (see dossier assessment A19-30 [1]). This resulted in no hint of an added benefit of pembrolizumab + platinum-based chemotherapy; an added benefit is therefore not proven.

This deviates from the company's assessment, which derived a hint of an added benefit for the category "morbidity".

Health-related quality of life

There are no usable data in the category "health-related quality of life" (see dossier assessment A19-30 [1]). This resulted in no hint of an added benefit of pembrolizumab + platinum-based chemotherapy; an added benefit is therefore not proven.

This concurs with the company's assessment.

Side effects

Severe AEs (CTCAE grade ≥ 3)

The adjusted indirect comparison showed no statistically significant difference between the treatment groups for the outcome "severe AEs (CTCAE grade ≥ 3)". However, there is an effect modification by the characteristic "sex". Hence, there was no hint of greater or lesser harm from pembrolizumab + platinum-based chemotherapy in women, greater or lesser harm is therefore not proven. For men, this resulted in a hint of greater harm from pembrolizumab + platinum-based chemotherapy in comparison with pembrolizumab.

This deviates from the assessment of the company, which considered an added benefit as not proven for side effects in general.

Discontinuation due to AEs

The adjusted indirect comparison showed no statistically significant difference between the treatment groups for the outcome "discontinuation due to AEs". This resulted in no hint of greater or lesser harm from pembrolizumab + platinum-based chemotherapy; an added benefit is therefore not proven.

This concurs with the company's assessment.

2.2.1.2 Subgroups and other effect modifiers

The following potential effect modifiers were considered in the present assessment:

- age (< 65 years; ≥ 65 years)
- sex (men, women)
- ethnicity (white, non-white)
- smoking status (never, former and active)
- brain metastases (yes, no)
- PD-L1 expression (TPS < 1%, TPS ≥ 1%)
- Platinum component of the chemotherapy (cisplatin, carboplatin)

Interaction tests were performed when at least 10 patients per subgroup were included in the analysis. For binary data, there must be 10 events in at least 1 subgroup.

Only results with an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05) are presented. In addition, subgroup results are only presented if there is a statistically significant and relevant effect in at least one subgroup.

Table 6 summarizes the subgroup results of pembrolizumab + platinum-based chemotherapy in comparison with pemprolizumab.

Table 6: Subgroups (mortality, side effects, time to event) – indirect comparison: pembrolizumab + platinum-based chemotherapy[a] vs. pembrolizumab

Outcome Characteristic Comparison Study Subgroup	Pembrolizumab + platinum-based chemotherapy[a] (Int) or pembrolizumab (ACT)		Platinum-based chemotherapy[a]		Group difference	
	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 (%)	HR [95% CI]	p-value
Overall survival						
Sex						
Intervention vs. common comparator						
021G[b]						
Men	2	ND 1 (50.0)	7	ND 5 (71.4)	ND	ND
Women	8	ND 1 (12.5)	3	ND 1 (33.3)	ND	ND
189[c]						
Men	58	NA 15 (25.9)	18	NA [7.8; NC] 7 (38.9)	0.73 [0.29; 1.79][d]	0.490[e]
Women	27	NA 3 (11.1)	22	8.0 [4.3; NC] 14 (63.6)	0.08 [0.02; 0.34][d]	< 0.001[e]
Total						
Men					0.68 [0.30; 1.56][f]	ND
Women					0.12 [0.04; 0.37][f]	N D
ACT vs. common comparator						
024[g]						
Men	43	NA [11.04; NC] 13 (30.2)	47	12.62 [6.01; NC] 22 (46.8)	0.48 [0.23; 0.96][h]	0.038[e]
Women	32	NA 9 (28.1)	27	NA [11.83; NC] 6 (22.2)	1.33 [0.45; 3.92][h]	0.607[e]
042[i]						
Men	56	11.7 [8.0; 14.8] 41 (73.2)	47	6.6 [5.5; 8.8] 39 (83.0)	0.60 [0.38; 0.96][h]	0.032[e]
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][h]	0.292[e]
Total						
Men					0.58 [0.39; 0.88][f]	ND
Women					1.27 [0.77; 2.11][f]	ND

(continued)

Table 6: Subgroups (mortality, side effects, time to event) – indirect comparison: pembrolizumab + platinum-based chemotherapy[a] vs. pembrolizumab (continued)

Outcome Characteristic Comparison Study Subgroup	Pembrolizumab + platinum-based chemotherapy[a] (Int) or pembrolizumab (ACT)		Platinum-based chemotherapy[a]		Group difference	
	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 (%)	HR [95% CI]	p-value
Indirect comparison using common comparators[j]						
Pembrolizumab + platinum-based chemotherapy[a] vs. pembrolizumab					Interaction:	0.001
Men					1.16 [0.46; 2.94]	0.754[k]
Women					0.09 [0.03; 0.32]	< 0.001[k]
Severe AEs (CTCAE grade ≥ 3)						
Sex						
Intervention vs. common comparator						
021G[b]						
Men	2	NA 1 (50.0)	7	NA 5 (71.4)	NC	NC
Women	8	NA 4 (50.0)	3	NA 2 (66.7)	NC	NC
189[c]						
Men	57	3.0 [1.8; 4.4][l] 44 (77.2)	18	16.6 [1.4; 16.6][l] 9 (50.0)	1.90 [0.92; 3.89][m]	0.081[e]
Women	27	4.9 [1.7; 8.6][l] 21 (77.8)	20	4.0 [1.1; NC][l] 12 (60.0)	0.84 [0.40; 1.77][m]	0.654[e]
Total						
Men					1.55 [0.83; 2.90][n]	N D
Women					0.75 [0.37; 1.50][n]	N D

(continued)

Table 6: Subgroups (mortality, side effects, time to event) – indirect comparison: pembrolizumab + platinum-based chemotherapy[a] vs. pembrolizumab (continued)

Outcome Characteristic Comparison Study Subgroup	Pembrolizumab + platinum-based chemotherapy[a] (Int) or pembrolizumab (ACT)		Platinum-based chemotherapy[a]		Group difference	
	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 (%)	HR [95% CI]	p-value
ACT vs. common comparator						
024[g]						
Men	43	6.2 [1.2; NC][l] 24 (55.8)	47	1.3 [1.0; 1.5][l] 35 (74.5)	0.51 [0.30; 0.87][m]	0.013[e]
Women	32	NA [3.4; NC][l] 13 (40.6)	26	NA [2.1; NC][l] 11 (42.3)	1.03 [0.46; 2.31][m]	0.940[e]
042[i]						
Men	56	11.6 [3.6; 26.2][l] 30 (53.6)	43	3.9 [2.2; NC][l] 25 (58.1)	0.75 [0.44; 1.28][m]	0.285[e]
Women	34	5.5 [2.0; 11.4][l] 21 (61.8)	36	6.2 [2.3; 15.8][l] 21 (58.3)	1.14 [0.62; 2.10][m]	0.662[e]
Total						
Men					0.61 [0.42; 0.89][n]	N D
Women					1.10 [0.68; 1.79][n]	N D
Indirect comparison using common comparators[j]						
Pembrolizumab + platinum-based chemotherapy[a] vs. pembrolizumab					Interaction:	0.021
Men					2.53 [1.22; 5.23]	0.012[k]
Women					0.68 [0.29; 1.58]	0.373[k]

(continued)

Table 6: Subgroups (mortality, side effects, time to event) – indirect comparison: pembrolizumab + platinum-based chemotherapy[a] vs. pembrolizumab (continued)

Outcome Characteristic Comparison Study Subgroup	Pembrolizumab + platinum-based chemotherapy[a] (Int) or pembrolizumab (ACT)		Platinum-based chemotherapy[a]		Group difference	
	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 (%)	HR [95% CI]	p-value
Severe AEs (CTCAE grade ≥ 3)						
Brain metastases at the start of the study						
Intervention vs. common comparator						
021G[b]						
Yes	2	NA 2 (100)	0	–	NC	NC
No	8	NA 3 (37.5)	10	NA 7 (70.0)	NC	NC
189[c]						
Yes	13	3.0 [0.1; 4.8][l] 10 (76.9)	8	NA [0.6; NC][l] 3 (37.5)	2.90 [0.79; 10.59][m]	0.107[e]
No	71	3.7 [2.5; 6.5][l] 55 (77.5)	30	3.9 [1.8; 16.6][l] 18 (60.0)	1.12 [0.66; 1.92][m]	0.671[e]
Total						
Yes					2.90 [0.79; 10.59][n]	ND
No					0.92 [0.57; 1.49][n]	N D
ACT vs. common comparator						
024[g]						
Yes	8	NA [1.4; NC][l] 3 (37.5)	5	1.1 [0.2; NC][l] 3 (60.0)	0.31 [0.06; 1.60][m]	0.161[e]
No	67	10.0 [3.4; NC][l] 34 (50.7)	68	2.0 [1.3; 3.9][l] 43 (63.2)	0.66 [0.42; 1.04][m]	0.073[e]
042[i]						
Yes	7	16.5 [2.1; NC][l] 2 (28.6)	6	2.0 [0.1; NC][l] 5 (83.3)	0.10 [0.01; 0.91][m]	0.041[e]
No	83	5.5 [3.6; 11.4][l] 49 (59.0)	73	4.9 [3.0; 15.8][l] 41 (56.2)	0.99 [0.66; 1.51][m]	0.978[e]
Total						
Yes					0.20 [0.06; 0.68][n]	N D
No					0.82 [0.61; 1.12][n]	N D

(continued)

Table 6: Subgroups (mortality, side effects, time to event) – indirect comparison: pembrolizumab + platinum-based chemotherapy[a] vs. pembrolizumab (continued)

Outcome Characteristic Comparison Study Subgroup	Pembrolizumab + platinum-based chemotherapy[a] (Int) or pembrolizumab (ACT)		Platinum-based chemotherapy[a]		Group difference	
	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 (%)	HR [95% CI]	p-value
Indirect comparison using common comparators[j]						
Pembrolizumab + platinum-based chemotherapy[a] vs. pembrolizumab					Interaction:	0.007
Yes					14.73 [2.46; 88.03]	0.003[k]
No					1.12 [0.63; 1.98]	0.698[k]

a: Consisting of either cisplatin or carboplatin in combination with pemetrexed.
b: Data cut-off: 31 May 2017.
c: Data cut-off: 8 November 2017.
d: Cox proportional hazards model stratified by PD-L1 status (≥ 1 % vs. < 1%), platinum-based chemotherapy (cisplatin vs. carboplatin) and smoking status (never vs. former/active).
e: 2-sided p-value (Wald test).
f: Cox proportional hazards model with treatment, platinum-based chemotherapy (cisplatin vs. carboplatin) and smoking status (never vs. former/active) as covariate, stratified by study.
g: Data cut-off: 9 May 2016.
h: Cox proportional hazards model with treatment, geographical region (East Asia vs. not East Asia) and ECOG PS (0 vs. 1) as covariate, stratified by study.
i: Data cut-off: 26 February 2018.
j: Indirect comparison according to Bucher [5].
k: Institute's calculation; asymptotic.
l: Institute's calculation.
m: Cox proportional hazards model with treatment as covariate.
n: Cox proportional hazards model with treatment as covariate, stratified by study.
ACT: appropriate comparator therapy; AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; ECOG PS: Eastern Cooperative Oncology Group Performance Status; HR: hazard ratio; Int: intervention; N: number of analysed patients; n: number of patients with (at least one) event; NA: not achieved; NC: not calculable; ND: no data; PD-L1: programmed cell death ligand 1; SAE: serious adverse event; vs.: versus

Mortality

Overall survival

Based on the adjusted indirect comparison, there was an effect modification by the characteristic "sex" for the outcome "overall survival". For men, there was no difference between the treatment groups. This resulted in no hint of an added benefit of pembrolizumab + platinum-based chemotherapy; an added benefit is therefore not proven. For women, the adjusted indirect comparison showed a statistically significant difference in favour of pembrolizumab + platinum-based chemotherapy. This resulted in a hint of an added benefit of pembrolizumab + platinum-based chemotherapy in comparison with pembrolizumab for women.

The company presented the results for the effect modification by the characteristic "sex" in its dossier, however, it did not use them for the derivation of the added benefit.

Side effects

Severe AEs (CTCAE grade ≥ 3)

There are two effect modifications for the outcome "severe AEs (CTCAE grade ≥ 3) based on the adjusted indirect comparison: both by the characteristic "sex" and by the characteristic "brain metastases".

A statistically significant difference in favour of pembrolizumab + platinum-based chemotherapy was shown for the characteristic "brain metastases at the start of the study" for the outcome "severe AEs (CTCAE grade ≥ 3)" in patients with brain metastases at the start of the study. No difference between the treatment groups was shown for patients without brain metastases at the start of the study. Since separate conclusions on the added benefit were required for men and women due to the effect modification on "overall survival" by the characteristic "sex", the characteristic "brain metastases at the start of the study" was not further considered.

For the characteristic "sex", there was no difference between the treatment groups for the outcome "severe AEs (CTCAE grade ≥ 3)" for women. This resulted in no hint of an added benefit of pembrolizumab + platinum-based chemotherapy; an added benefit is therefore not proven. For men, the adjusted indirect comparison showed a statistically significant difference to the disadvantage of pembrolizumab + platinum-based chemotherapy. This resulted in a hint of greater harm from pembrolizumab + platinum-based chemotherapy in comparison with pembrolizumab for men.

2.2.2 Probability and extent of added benefit

Probability and extent of the added benefit at outcome level are presented below. The various outcome categories and the effect sizes were taken into account. The methods used for this purpose are explained in the *General Methods* of IQWiG [6].

The approach for deriving an overall conclusion on the added benefit based on the aggregation of conclusions derived at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

2.2.2.1 Assessment of the added benefit at outcome level

The extent of the respective added benefit at outcome level was estimated from the results presented in Section 2.2.1 (see Table 7).

Table 7: Extent of added benefit at outcome level: pembrolizumab + platinum-based chemotherapy[a] vs. pembrolizumab

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Pembrolizumab + platinum-based chemotherapy[a] vs. pembrolizumab** **Median time to event (months)** **Effect estimation [95% CI]; p-value** **Probability[b]**	**Derivation of extent[c]**
Mortality		
Overall survival		
Sex		
Men	Median: NA vs. 11.7-NA HR: 1.16 [0.46; 2.94] p = 0.754	Lesser benefit/added benefit not proven
Women	Median: NA vs. 7.7-NA HR: 0.09 [0.03; 0.32] p < 0.001 Probability: "hint"	Outcome category: all-cause mortality $CI_u < 0.85$ Added benefit, extent: “major”
Morbidity		
No usable analyses		
Health-related quality of life		
No usable analyses		
Side effects		
Severe AEs (CTCAE grade ≥ 3)		
Sex		
Men	Median: 3.0-NA vs. 6.2-11.6 HR: 2.53 [1.22; 5.23] HR: 0.40 [0.19; 0.82][d] p = 0.012 Probability: "hint"	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ Greater harm, extent: "considerable"
Women	Median: 4.9-NA vs. 5.5-NA HR: 0.68 [0.29; 1.58] p = 373	Greater/lesser harm not proven
Discontinuation due to AEs	Median: NA-17.1 vs. NA 2.45 [0.82; 7.31]; 0.108 p = 0.108	Greater/lesser harm not proven

a: Consisting of either cisplatin or carboplatin in combination with pemetrexed.
b: Probability provided if there is a statistically significant and relevant effect.
c: Estimations of effect size are made depending on the outcome category with different limits based on the CI_u.
d: Institute's calculation, reversed direction of effect to enable use of limits to derive the extent of the added benefit.
AE: adverse event; CI: confidence interval; CI_u: upper limit of CI; CTCAE: Common Terminology Criteria for Adverse Events; HR: hazard ratio; NA: not achieved; vs.: versus

2.2.2.2 Overall conclusion on added benefit

Table 8 summarizes the results considered in the overall conclusion on the extent of added benefit.

Table 8: Positive and negative effects from the assessment of pembrolizumab + platinum-based chemotherapy[a] in comparison with pembrolizumab

Positive effects	Negative effects
Mortality ▪ Overall survival ▫ Sex (women): hint of an added benefit – extent: "major"	–
–	Serious/severe side effects ▪ Severe AEs (CTCAE grade ≥ 3) ▫ Sex (men): hint of greater harm – extent "considerable"
a: Consisting of either cisplatin or carboplatin in combination with pemetrexed. AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events	

The overall assessment showed a positive effect for women and a negative effect for men.

For women with metastatic non-squamous NSCLC without EGFR or ALK-positive tumour mutations with PD-L1 expression of ≥ 50 %, this resulted altogether in a hint of an added benefit with the extent “major” for pembrolizumab in combination with pemetrexed and platinum-based chemotherapy in comparison with pembrolizumab monotherapy.

For men with metastatic non-squamous NSCLC without EGFR or ALK-positive tumour mutations and PD-L1 expression of ≥ 50%, this results in a hint of lesser benefit of pembrolizumab in combination with pemetrexed and platinum-based chemotherapy versus pembrolizumab monotherapy.

2.3 Summary

Due to the subsequent assessment of the data presented by the company in its dossier, the statement on the added benefit of pembrolizumab in dossier assessment A19-30 changed for both research question 1 (adults with PD-L1 expression < 50%) and research question 2 (adults with PD-L1 expression ≥ 50%).

The following Table 9 shows the result of the benefit assessment of pembrolizumab under consideration of dossier assessment A19-30 and the present addendum.

Table 9: Pembrolizumab in combination with pemetrexed and platinum-based chemotherapy – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit[b]**
First-line treatment of metastatic non-squamous NSCLC without EFGR or ALK-positive tumour mutations in adults with PD-L1 expression < 50%[c]	▪ **Cisplatin in combination with a third-generation cytostatic agent** (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed) under consideration of the approval status *or* ▪ **carboplatin in combination with a third-generation cytostatic agent** (only for patients with increased risk of cisplatin-induced side effects within the framework of a combination therapy; see also Appendix VI to Section K of the Pharmaceutical Directive [7]) *or* ▪ carboplatin in combination with nab-paclitaxel	▪ **Women: proof of major added benefit** ▪ **Men: indication of minor added benefit**
First-line treatment of metastatic non-squamous NSCLC without EFGR or ALK-positive tumour mutations in adults with PD-L1 expression ≥ 50 %[c]	Pembrolizumab as monotherapy	▪ **Women: hint of major added benefit** ▪ **Men: hint of lesser benefit**

a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
b: Changes in comparison with dossier assessment A19-30 are printed in **bold**.
c: For the present therapeutic indication, it is assumed that patients have no medical indication for definitive local therapy.
ACT: appropriate comparator therapy; ALK: anaplastic lymphoma kinase; EGFR: epidermal growth factor receptor; G-BA: Federal Joint Committee; NSCLC: non-small cell lung cancer; PD-L1: programmed cell death ligand 1

The assessment described above deviates from that of the company, which derived proof of major added benefit for all patients with PD-L1 expression < 50%. Also for patients with PD-L1 expression ≥ 50%, it derived an indication of major added benefit. In both cases, it considered no effect modification by the characteristic “sex”.

The G-BA decides on the added benefit.

3 References

1. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Pembrolizumab (nicht plattenepitheliales NSCLC, Kombinationschemotherapie): Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung; Auftrag A19-30 [online]. 27.06.2019 [Accessed: 17.07.2019]. (IQWiG-Berichte; Volume 784). URL: https://www.iqwig.de/download/A19-30_Pembrolizumab_Nutzenbewertung-35a-SGB-V_V1-0.pdf.

2. MSD Sharp & Dohme. Pembrolizumab (KEYTRUDA): Dossier zur Nutzenbewertung gemäß § 35a SGB V [online]. 29.03.2019 [Accessed: 11.07.2019]. URL: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/452/#tab/dossier.

3. MSD Sharp & Dohme. Pembrolizumab (KEYTRUDA): Dossier zur Nutzenbewertung gemäß § 35a SGB V [online]. 29.03.2019 [Accessed: 11.07.2019]. URL: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/453/#tab/dossier.

4. MSD Sharp & Dohme. Stellungnahme zum IQWiG-Bericht Nr. 784: Pembrolizumab (nicht plattenepitheliales NSCLC, Kombinationschemotherapie); Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung; Auftrag A19-30. [Soon available under: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/452/#stellungnahmen im Dokument "Zusammenfassende Dokumentation"].

5. Bucher HC, Guyatt GH, Griffith LE, Walter SD. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. J Clin Epidemiol 1997; 50(6): 683-691.

6. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Allgemeine Methoden: Version 5.0. Köln: IQWiG; 2017. URL: https://www.iqwig.de/download/Allgemeine-Methoden_Version-5-0.pdf.

7. Gemeinsamer Bundesausschuss. Anlage VI zum Abschnitt K der Arzneimittel-Richtlinie: Verordnungsfähigkeit von zugelassenen Arzneimitteln in nicht zugelassenen Anwendungsgebieten (sog. Off-Label-Use) [online]. 05.01.2019 [Accessed: 25.02.2019]. URL: https://www.g-ba.de/downloads/83-691-518/AM-RL-VI-Off-label-2019-01-05.pdf.

Appendix A – Kaplan-Meier curves on "overall survival"

A.1 – Research question 1 (PD-L1 expression < 50%)

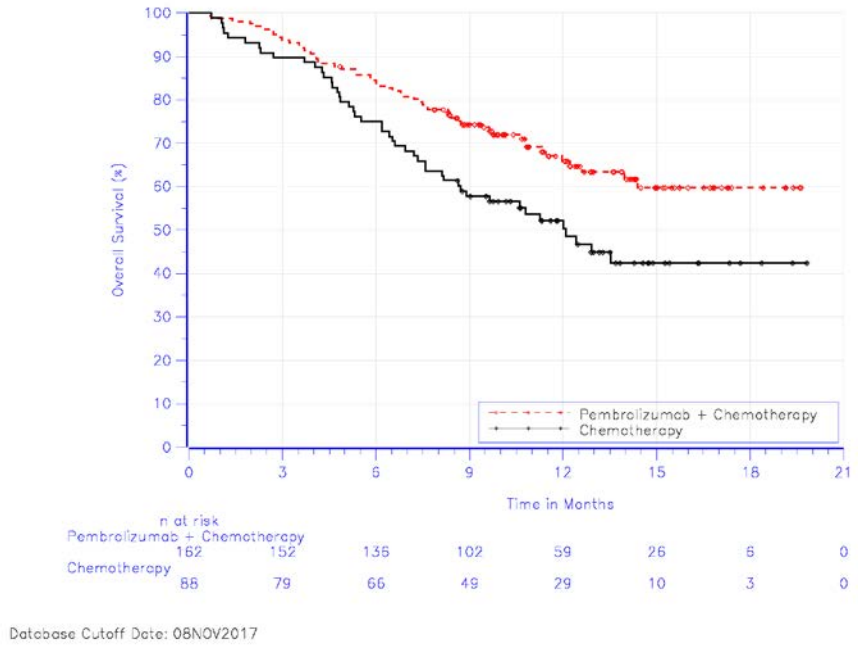


Figure 2: Kaplan-Meier curve on overall survival, study KEYNOTE 189

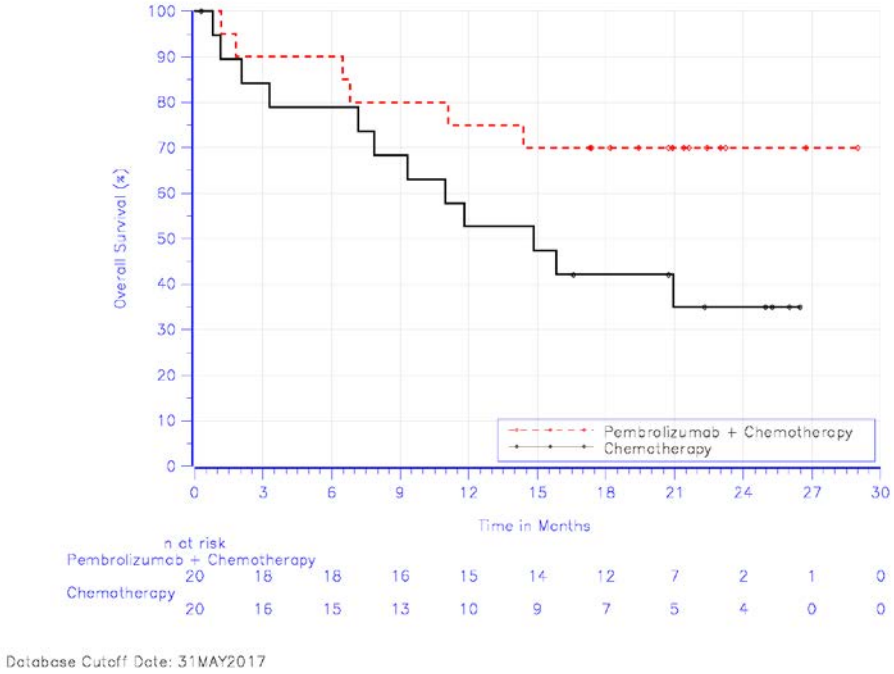


Figure 3: Kaplan-Meier curve on overall survival, study KEYNOTE 021G

A.2 – Research question 2 (PD-L1 expression ≥ 50%)

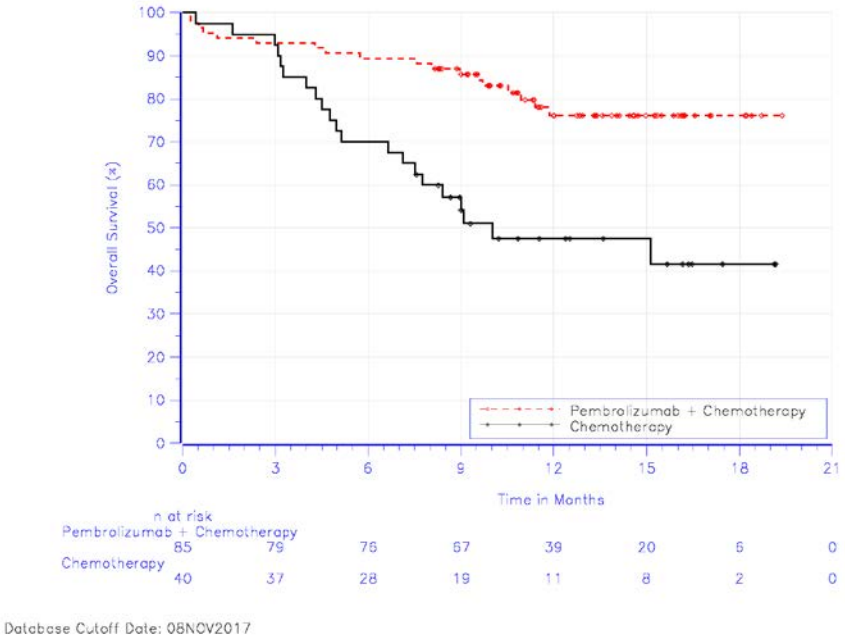


Figure 4: Kaplan-Meier curve on overall survival, study KEYNOTE 189

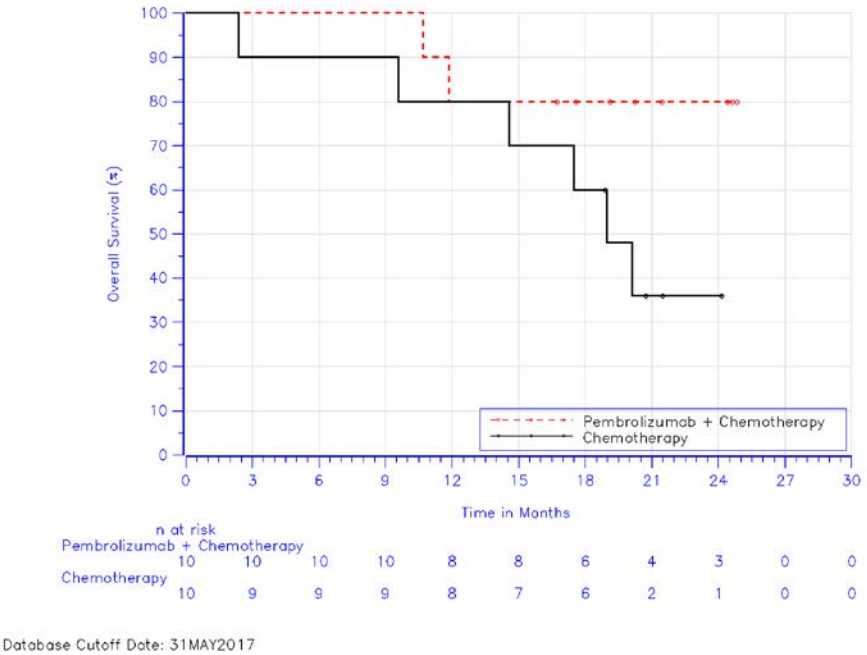


Figure 5: Kaplan-Meier curve on overall survival, study KEYNOTE 021

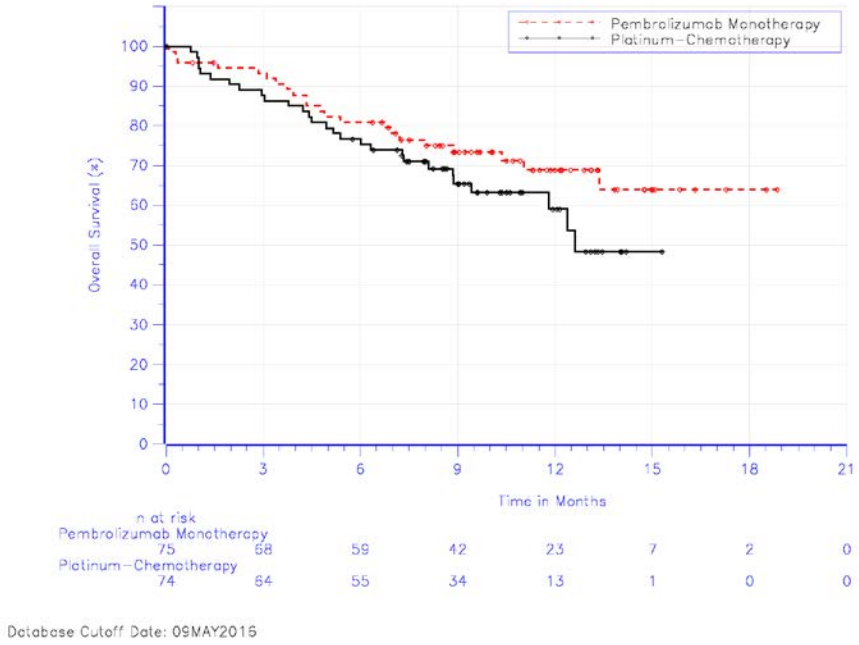


Figure 6: Kaplan-Meier curve on overall survival, study KEYNOTE 024

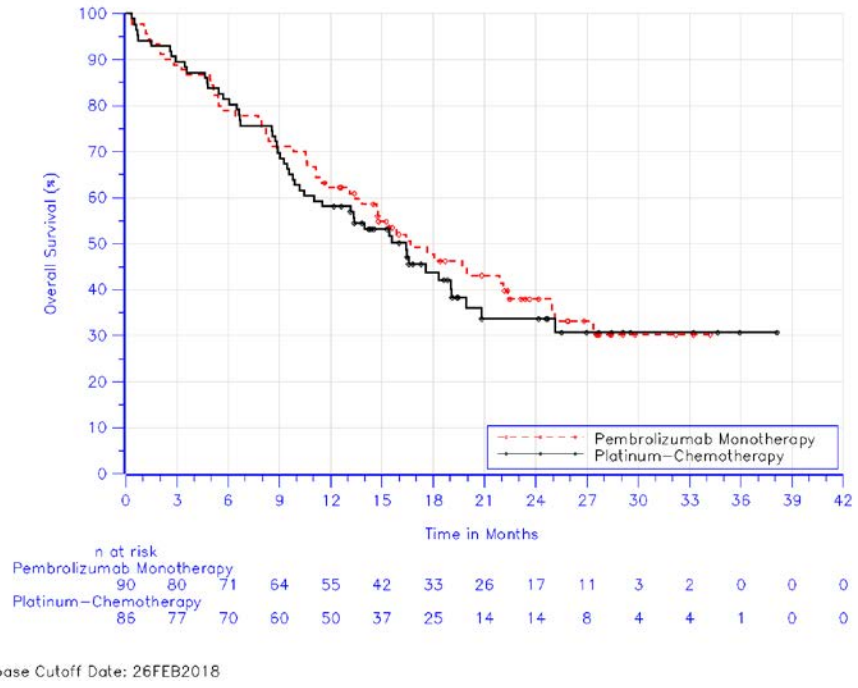


Figure 7: Kaplan-Meier curve on overall survival, study KEYNOTE 042

Appendix B – Results on side effects (research question 2)

At the level of SOC according to MedDRA, the company presented effect estimations from event time analyses for the relevant subpopulations on all AEs, severe AEs (CTCAE grade ≥ 3), discontinuation due to AEs and immune-related AEs (only KEYNOTE 189) . At the level of PT according to MedDRA, there are no results from event time analyses for the relevant subpopulation. For PTs, event rates are only presented if the corresponding SOC shows a statistically significant difference between the treatment arms in the corresponding event time analysis and certain threshold values for the frequencies are reached. Therefore, results on common side effects are only presented at SOC level. Presentation of the common PTs is omitted due to incompleteness (see dossier assessment A19-30 [1]).

The following tables present events for SOCs according MedDRA for the overall rates of "AEs", "SAEs" and "severe AEs (e.g. CTCAE grade ≥ 3), each on the basis of the following criteria:

- Overall rate AEs (irrespective of the severity grade): events that occurred in at least 10% of the patients in one study arm
- Overall rates severe AEs (e.g. CTCAE grade ≥ 3) and SAEs: events that occurred in at least 5% of the patients in one study arm
- in addition for all events irrespective of the severity grade: events that occurred in at least 10 patients and in at least 1% of the patients in one study arm

For the outcome "discontinuation due to adverse events", all events (SOCs) that resulted in discontinuation were presented".

Table 10: Common AEs (according to SOC) – RCT, direct comparison: pembrolizumab + carboplatin-based chemotherapy vs. carboplatin-based chemotherapy (study 021G[a])

SOC[b]	Patients with event n (%)	
	Pembrolizumab + carboplatin-based chemotherapy N = 10	**Carboplatin-based chemotherapy N = 10**
Overall rate AEs	10 (100.0)	10 (100.0)
Blood and lymphatic system disorders	6 (60.0)	7 (70.0)
Cardiac disorders	0 (0)	1 (10.0)
Ear and labyrinth disorders	2 (20.0)	0 (0)
Endocrine disorders	3 (30.0)	0 (0)
Eye disorders	5 (50.0)	4 (40.0)
Gastrointestinal disorders	10 (100.0)	10 (100.0)
General disorders and administration site conditions	8 (80.0)	6 (60.0)
Infections and infestations	8 (80.0)	4 (40.0)
Injury, poisoning and procedural complications	3 (30.0)	2 (20.0)
Investigations	6 (60.0)	6 (60.0)
Metabolism and nutrition disorders	8 (80.0)	6 (60.0)
Musculoskeletal and connective tissue disorders	6 (60.0)	6 (60.0)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	1 (10.0)	0 (0)
Nervous system disorders	8 (80.0)	5 (50.0)
Psychiatric disorders	4 (40.0)	2 (20.0)
Renal and urinary disorders	3 (30.0)	1 (10.0)
Reproductive system and breast disorders	2 (20.0)	0 (0)
Respiratory, thoracic and mediastinal disorders	5 (50.0)	7 (70.0)
Skin and subcutaneous tissue disorders	7 (70.0)	5 (50.0)
Vascular disorders	3 (30.0)	1 (10.0)

a: Data cut-off: 31 May 2017.
b: MedDRA version 19.0.
AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least one) event; N: number of analysed patients; RCT: randomized controlled trial; SOC: System Organ Class; vs.: versus

Table 11: Common AEs (CTCAE grade ≥ 3) (according to SOC); RCT, direct comparison: pembrolizumab + carboplatin-based chemotherapy vs. carboplatin-based chemotherapy (study 021G[a])

SOC[b]	Patients with event n (%)	
	Pembrolizumab + carboplatin-based chemotherapy N = 10	Carboplatin-based chemotherapy N = 10
Overall rate of severe AEs (CTCAE grade ≥ 3)	5 (50.0)	7 (70.0)
Blood and lymphatic system disorders	3 (30.0)	4 (40.0)
Gastrointestinal disorders	1 (10.0)	4 (40.0)
Infections and infestations	1 (10.0)	2 (20.0)
Investigations	2 (20.0)	1 (10.0)
Musculoskeletal and connective tissue disorders	0 (0)	1 (10.0)
Nervous system disorders	1 (10.0)	0 (0)
Renal and urinary disorders	1 (10.0)	0 (0)
Respiratory, thoracic and mediastinal disorders	0 (0)	2 (20.0)
Vascular disorders	1 (10.0)	0 (0)

a: Data cut-off: 31 May 2017.
b: MedDRA version 19.0.
AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least 1) event; N: number of analysed patients; RCT: randomized controlled trial; SOC: System Organ Class; vs.: versus

Table 12: Common AEs resulting in treatment discontinuation (according to SOC) – RCT, direct comparison: pembrolizumab + carboplatin-based chemotherapy vs. carboplatin-based chemotherapy (study 021Ga)

SOC[b]	Patients with event n (%)	
	Pembrolizumab + carboplatin-based chemotherapy N = 10	Carboplatin-based chemotherapy N = 10
Overall rate of AEs resulting in treatment discontinuation	2 (20.0)	2 (20.0)
Gastrointestinal disorders	0 (0)	1 (10.0)
Investigations	0 (0)	1 (10.0)
Musculoskeletal and connective tissue disorders	1 (10.0)	0 (0)
Renal and urinary disorders	1 (10.0)	0 (0)

a: Data cut-off: 31 May 2017.
b: MedDRA version 19.0.
AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least one) event; N: number of analysed patients; RCT: randomized controlled trial; SOC: System Organ Class; vs.: versus

Table 13: Common AEs (according to SOC) – RCT, direct comparison: pembrolizumab + platinum-based chemotherapya vs. platinum-based chemotherapya (study 189[b])

SOC[c]	Patients with event n (%)	
	Pembrolizumab + platinum-based chemotherapy[a] N = 84	Platinum-based chemotherapy[a] N = 38
Overall rate AEs	84 (100.0)	38 (100.0)
Blood and lymphatic system disorders	56 (66.7)	19 (50.0)
Cardiac disorders	7 (8.3)	4 (10.5)
Ear and labyrinth disorders	10 (11.9)	7 (18.4)
Endocrine disorders	10 (11.9)	3 (7.9)
Eye disorders	26 (31.0)	9 (23.7)
Gastrointestinal disorders	69 (82.1)	28 (73.7)
General disorders and administration site conditions	64 (76.2)	31 (81.6)
Infections and infestations	53 (63.1)	18 (47.4)
Injury, poisoning and procedural complications	14 (16.7)	3 (7.9)
Investigations	46 (54.8)	13 (34.2)
Metabolism and nutrition disorders	44 (52.4)	22 (57.9)
Musculoskeletal and connective tissue disorders	32 (38.1)	18 (47.4)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	3 (3.6)	5 (13.2)
Nervous system disorders	36 (42.9)	18 (47.4)
Psychiatric disorders	11 (13.1)	8 (21.1)
Renal and urinary disorders	16 (19.0)	3 (7.9)
Respiratory, thoracic and mediastinal disorders	50 (59.5)	27 (71.1)
Skin and subcutaneous tissue disorders	34 (40.5)	22 (57.9)
Vascular disorders	15 (17.9)	3 (7.9)

a: Consisting of either cisplatin or carboplatin in combination with pemetrexed.
b: Data cut-off: 8 November 2017.
c: MedDRA version 20.1.

AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least one) event; N: number of analysed patients; RCT: randomized controlled trial; SOC: System Organ Class; vs.: versus

Table 14: Common severe AEs (CTCAE grade ≥ 3) (according to SOC) – RCT, direct comparison: pembrolizumab + platinum-based chemotherapya vs. platinum-based chemotherapya (study 189[b])

SOC[c]	**Patients with event n (%)**	
	Pembrolizumab + platinum-based chemotherapy[a] N = 84	**Platinum-based chemotherapy[a] N = 38**
Overall rate of severe AEs (CTCAE grade ≥ 3)	65 (77.4)	21 (55.3)
Blood and lymphatic system disorders	28 (33.3)	8 (21.1)
Cardiac disorders	3 (3.6)	2 (5.3)
Gastrointestinal disorders	16 (19.0)	2 (5.3)
General disorders and administration site conditions	18 (21.4)	6 (15.8)
Infections and infestations	14 (16.7)	4 (10.5)
Injury, poisoning and procedural complications	6 (7.1)	0 (0)
Investigations	11 (13.1)	3 (7.9)
Metabolism and nutrition disorders	11 (13.1)	3 (7.9)
Musculoskeletal and connective tissue disorders	6 (7.1)	2 (5.3)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	2 (2.4)	2 (5.3)
Nervous system disorders	7 (8.3)	0 (0)
Renal and urinary disorders	5 (6.0)	0 (0)
Respiratory, thoracic and mediastinal disorders	11 (13.1)	6 (15.8)
Vascular disorders	3 (3.6)	2 (5.3)

a: Consisting of either cisplatin or carboplatin in combination with pemetrexed.
b: Data cut-off: 8 November 2017.
c: MedDRA version 20.1.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least 1) event; N: number of analysed patients; RCT: randomized controlled trial; SOC: System Organ Class; vs.: versus

Table 15: Common AEs resulting in treatment discontinuation (according to SOC) – RCT, direct comparison: pembrolizumab + platinum-based chemotherapya vs. platinum-based chemotherapya (study 189[b])

SOC[c]	**Patients with event n (%)**	
	Pembrolizumab + platinum-based chemotherapy[a] N = 84	**Platinum-based chemotherapy[a] N = 38**
Overall rate of AEs resulting in treatment discontinuation	30 (35.7)	4 (10.5)
Blood and lymphatic system disorders	3 (3.6)	1 (2.6)
Gastrointestinal disorders	3 (3.6)	0 (0)
General disorders and administration site conditions	2 (2.4)	1 (2.6)
Hepatobiliary disorders	2 (2.4)	0 (0)
Infections and infestations	2 (2.4)	0 (0)
Investigations	5 (6.0)	0 (0)
Musculoskeletal and connective tissue disorders	2 (2.4)	0 (0)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	0 (0)	1 (2.6)
Nervous system disorders	2 (2.4)	0 (0)
Renal and urinary disorders	4 (4.8)	0 (0)
Respiratory, thoracic and mediastinal disorders	5 (6.0)	1 (2.6)
Skin and subcutaneous tissue disorders	1 (1.2)	0 (0)

a: Consisting of either cisplatin or carboplatin in combination with pemetrexed.
b: Data cut-off: 8 November 2017.
c: MedDRA version 20.1.
AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least one) event; N: number of analysed patients; RCT: randomized controlled trial; SOC: System Organ Class; vs.: versus

Table 16: Common immune-related AEs (according to SOC) – RCT, direct comparison: pembrolizumab + platinum-based chemotherapya vs. platinum-based chemotherapya (study 189[b])

SOC[c]	**Patients with event n (%)**	
	Pembrolizumab + platinum-based chemotherapy[a] N = 84	**Platinum-based chemotherapy[a] N = 38**
Overall rate of immune-related AEs	25 (29.8)	4 (10.5)
Endocrine disorders	9 (10.7)	2 (5.3)

a: Consisting of either cisplatin or carboplatin in combination with pemetrexed.
b: Data cut-off: 8 November 2017.
c: MedDRA version 20.1.
AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least one) event; N: number of analysed patients; RCT: randomized controlled trial; SOC: System Organ Class; vs.: versus

Table 17: Common AEs (according to SOC) – RCT, direct comparison: pembrolizumab vs. platinum-based chemotherapya (study 024[b])

SOC[c]	Patients with event n (%)	
	Pembrolizumab + platinum-based chemotherapy[a] N = 75	Platinum-based chemotherapy[a] N = 73
Overall rate AEs	71 (94.7)	69 (94.5)
Blood and lymphatic system disorders	15 (20.0)	47 (64.4)
Cardiac disorders	8 (10.7)	11 (15.1)
Endocrine disorders	9 (12.0)	3 (4.1)
Eye disorders	4 (5.3)	12 (16.4)
Gastrointestinal disorders	46 (61.3)	56 (76.7)
General disorders and administration site conditions	48 (64.0)	50 (68.5)
Infections and infestations	32 (42.7)	32 (43.8)
Injury, poisoning and procedural complications	11 (14.7)	4 (5.5)
Investigations	33 (44.0)	42 (57.5)
Metabolism and nutrition disorders	31 (41.3)	43 (58.9)
Musculoskeletal and connective tissue disorders	31 (41.3)	23 (31.5)
Nervous system disorders	23 (30.7)	28 (38.4)
Psychiatric disorders	12 (16.0)	11 (15.1)
Renal and urinary disorders	3 (4.0)	11 (15.1)
Respiratory, thoracic and mediastinal disorders	34 (45.3)	34 (46.6)
Skin and subcutaneous tissue disorders	35 (46.7)	15 (20.5)
Vascular disorders	5 (6.7)	8 (11.0)

a: Consisting of either cisplatin or carboplatin in combination with pemetrexed.
b: Data cut-off: 9 May 2016.
c: MedDRA version 19.0.
AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least one) event; N: number of analysed patients; RCT: randomized controlled trial; SOC: System Organ Class; vs.: versus

Table 18: Common severe AEs (CTCAE grade ≥ 3) (according to SOC) – RCT, direct comparison: pembrolizumab vs. platinum-based chemotherapya (study 024[b])

SOC[c]	**Patients with event n (%)**	
	Pembrolizumab + platinum-based chemotherapy[a] N = 75	**Platinum-based chemotherapy[a] N = 73**
Overall rate of severe AEs (CTCAE grade ≥ 3)	37 (49.3)	46 (63.0)
Blood and lymphatic system disorders	3 (4.0)	21 (28.8)
Cardiac disorders	3 (4.0)	6 (8.2)
Gastrointestinal disorders	3 (4.0)	6 (8.2)
General disorders and administration site conditions	5 (6.7)	8 (11.0)
Infections and infestations	12 (16.0)	15 (20.5)
Investigations	4 (5.3)	7 (9.6)
Metabolism and nutrition disorders	7 (9.3)	14 (19.2)
Respiratory, thoracic and mediastinal disorders	13 (17.3)	10 (13.7)
Skin and subcutaneous tissue disorders	4 (5.3)	0 (0)

a: Consisting of either cisplatin or carboplatin in combination with pemetrexed.
b: Data cut-off: 9 May 2016.
c: MedDRA version 19.0.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least 1) event; N: number of analysed patients; RCT: randomized controlled trial; SOC: System Organ Class; vs.: versus

Table 19: Common AEs resulting in treatment discontinuation (according to SOC) – RCT, direct comparison: pembrolizumab vs. platinum-based chemotherapya (study 024[b])

SOC[c]	**Patients with event n (%)**	
	Pembrolizumab + platinum-based chemotherapy[a] N = 75	**Platinum-based chemotherapy[a] N = 73**
Overall rate of AEs resulting in treatment discontinuation	10 (13.3)	15 (20.5)
Blood and lymphatic system disorders	0 (0)	1 (1.4)
Cardiac disorders	0 (0)	1 (1.4)
Ear and labyrinth disorders	0 (0)	1 (1.4)
Gastrointestinal disorders	1 (1.3)	1 (1.4)
General disorders and administration site conditions	2 (2.7)	4 (5.5)
Infections and infestations	1 (1.3)	1 (1.4)
Investigations	1 (1.3)	5 (6.8)
Nervous system disorders	1 (1.3)	3 (4.1)
Renal and urinary disorders	0 (0)	1 (1.4)
Respiratory, thoracic and mediastinal disorders	4 (5.3)	1 (1.4)

a: Consisting of either cisplatin or carboplatin in combination with pemetrexed.
b: Data cut-off: 9 May 2016.
c: MedDRA version 19.0.

AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least one) event; N: number of analysed patients; RCT: randomized controlled trial; SOC: System Organ Class; vs.: versus

Table 20: Common AEs (according to SOC) – RCT, direct comparison: pembrolizumab vs. platinum-based chemotherapya (study 042[b])

SOC[c]	Patients with event n (%)	
	Pembrolizumab + platinum-based chemotherapy[a] N = 90	Platinum-based chemotherapy[a] N = 79
Overall rate AEs	89 (98.9)	79 (100.0)
Blood and lymphatic system disorders	20 (22.2)	43 (54.4)
Cardiac disorders	9 (10.0)	5 (6.3)
Endocrine disorders	14 (15.6)	3 (3.8)
Eye disorders	6 (6.7)	8 (10.1)
Gastrointestinal disorders	36 (40.0)	51 (64.6)
General disorders and administration site conditions	39 (43.3)	32 (40.5)
Infections and infestations	42 (46.7)	35 (44.3)
Injury, poisoning and procedural complications	10 (11.1)	4 (5.1)
Investigations	21 (23.3)	31 (39.2)
Metabolism and nutrition disorders	22 (24.4)	34 (43.0)
Musculoskeletal and connective tissue disorders	22 (24.4)	23 (29.1)
Nervous system disorders	25 (27.8)	24 (30.4)
Psychiatric disorders	7 (7.8)	14 (17.7)
Renal and urinary disorders	10 (11.1)	4 (5.1)
Respiratory, thoracic and mediastinal disorders	57 (63.3)	33 (41.8)
Skin and subcutaneous tissue disorders	34 (37.8)	25 (31.6)
Vascular disorders	11 (12.2)	6 (7.6)

a: Consisting of either cisplatin or carboplatin in combination with pemetrexed.
b: Data cut-off: 26 February 2018.
c: MedDRA version 20.1.
AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least one) event; N: number of analysed patients; RCT: randomized controlled trial; SOC: System Organ Class; vs.: versus

Table 21: Common severe AEs (CTCAE grade ≥ 3) (according to SOC) – RCT, direct comparison: pembrolizumab vs. platinum-based chemotherapya (study 042[b])

SOC[c]	Patients with event n (%)	
	Pembrolizumab + platinum-based chemotherapy[a] N = 90	Platinum-based chemotherapy[a] N = 79
Overall rate of severe AEs (CTCAE grade ≥ 3)	51 (56.7)	46 (58.2)
Blood and lymphatic system disorders	5 (5.6)	24 (30.4)
Cardiac disorders	7 (7.8)	2 (2.5)
General disorders and administration site conditions	7 (7.8)	2 (2.5)
Infections and infestations	15 (16.7)	13 (16.5)
Investigations	4 (4.4)	9 (11.4)
Metabolism and nutrition disorders	4 (4.4)	7 (8.9)
Respiratory, thoracic and mediastinal disorders	18 (20.0)	3 (3.8)

a: Consisting of either cisplatin or carboplatin in combination with pemetrexed.
b: Data cut-off: 26 February 2018.
c: MedDRA version 20.1.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least 1) event; N: number of analysed patients; RCT: randomized controlled trial; SOC: System Organ Class; vs.: versus

Table 22: Common AEs resulting in treatment discontinuation (according to SOC) – RCT, direct comparison: pembrolizumab vs. platinum-based chemotherapya (study 042[b])

SOC[c]	**Patients with event n (%)**	
	Pembrolizumab + platinum-based chemotherapy[a] N = 90	**Platinum-based chemotherapy[a] N = 79**
Overall rate of AEs resulting in treatment discontinuation	17 (18.9)	13 (16.5)
Blood and lymphatic system disorders	0 (0)	1 (1.3)
Cardiac disorders	1 (1.1)	0 (0)
Gastrointestinal disorders	0 (0)	1 (1.3)
General disorders and administration site conditions	2 (2.2)	0 (0)
Hepatobiliary disorders	1 (1.1)	0 (0)
Infections and infestations	2 (2.2)	4 (5.1)
Investigations	1 (1.1)	0 (0)
Nervous system disorders	2 (2.2)	1 (1.3)
Renal and urinary disorders	1 (1.1)	1 (1.3)
Respiratory, thoracic and mediastinal disorders	7 (7.8)	2 (2.5)
Skin and subcutaneous tissue disorders	0 (0)	2 (2.5)
Vascular disorders	0 (0)	1 (1.3)

a: Consisting of either cisplatin or carboplatin in combination with pemetrexed.
b: Data cut-off: 26 February 2018.
c: MedDRA version 20.1.
AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least one) event; N: number of analysed patients; RCT: randomized controlled trial; SOC: System Organ Class; vs.: versus