IQWiG Reports – Commission No. A19-62

Pembrolizumab (squamous NSCLC, combination therapy 1) –

Addendum to Commission A19-31[1]

Addendum

Commission: A19-62
Version: 1.0
Status: 20 August 2019

[1] Translation of addendum A19-62 *Pembrolizumab (plattenepitheliales NSCLC) – Addendum zum Auftrag A19-31* (Version 1.0; Status: 20 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 (squamous NSCLC, combination therapy 1) – Addendum to Commission A19-31

Commissioning agency:
Federal Joint Committee

Commission awarded on:
5 August 2019

Internal Commission No.:
A19-62

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
- Sabine Ostlender
- Beate Wieseler

Keywords: pembrolizumab, carboplatin, paclitaxel, albumin-bound paclitaxel, carcinoma – non-small-cell lung, benefit assessment, NCT02220894, NCT02775435

Table of contents

List of tables

Page

List of figures

Page

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
CTCAE	Common Terminology Criteria for Adverse Events
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
NSCLC	non-small cell lung cancer
PD-L1	programmed cell death ligand 1
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)

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 A19-31 (Pembrolizumab – Benefit assessment according to §35a Social Code Book V) [1].

When describing the operationalization of the outcome "overall survival" in the studies KEYNOTE 407 and KEYNOTE 042 in its dossier [2], the company stated that patients who had switched from the control arm to monotherapy with pembrolizumab were censored in the statistical analyses at the time point of the treatment switch. However, in connection with the intention to treat (ITT) analyses, the result tables indicate that the observation was censored at the time point of the data cut-off. Due to these contradictory data, the results on the outcome "overall survival" presented by the company was not usable in the dossier assessment.

With its comments [3], the company clarified that the information stating that patients who had switched from the control arm to monotherapy with pembrolizumab were censored at the time point of the treatment switch in the statistical analyses was an editorial mistake. The analyses of the outcome "overall survival" were ITT analyses with a censoring at the time point of the last observation.

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 A19-31 [1] was to assess the added benefit of pembrolizumab in combination with carboplatin and either paclitaxel or nab-paclitaxel in comparison with the appropriate comparator therapy (ACT) for the first-line treatment of adults with metastatic squamous non-small cell lung cancer (NSCLC). 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 one randomized controlled trial (RCT) for research question 1, and an adjusted indirect comparison according to Bucher [4] on the basis of two RCTs for research question 2. For the benefit assessment, the presented studies are relevant for both research questions. In dossier assessment A19-31, 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 A19-31 [1].

With its comments [3], the company clarified that the analyses presented on the outcome "overall survival" were adequate ITT analyses. Complete assessment of the analyses presented by the company is thus possible.

Assessment of the outcome "overall survival" for research question 1 can be found in Section 2.1 (assessment of the other outcomes of the presented RCT 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%

In its dossier, the company presented the RCT KEYNOTE 407 for research question 1. Dossier assessment A19-31 [1] includes a detailed description of the study characteristics, 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 hereinafter.

2.1.1 Results

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

Results on the outcome "overall survival"

Table 1 shows the results on the outcome "overall survival".

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

Study Outcome category Outcome	Pembrolizumab + carboplatin-based chemotherapy[a]		Carboplatin-based chemotherapy[a]		Pembrolizumab + carboplatin-based chemotherapy[a] vs. carboplatin-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
KEYNOTE 407[b]					
Mortality					
Overall survival[c]	157	14.4 [13.2; NC] 47 (29.9)	153	11.1 [8.9; 13.8] 68 (44.4)	0.56 [0.38; 0.82]; 0.003[d, e]

a: In combination with either paclitaxel or nab-paclitaxel.
b: Data cut-off: 3 April 2018.
c: Patients are censored at the time point of the data cut-off.
d: Cox proportional hazards model with treatment as covariate, stratified by PD-L1 expression (TPS < 1% vs. ≥ 1%), taxane chemotherapy (paclitaxel vs. nab-paclitaxel) and region (East Asia vs. not East Asia).
e: 2-sided p-value (Wald test).
CI: confidence interval; HR: hazard ratio; n: number of patients with event; N: number of analyzed patients of the TPC survey population with PD-L1 TPS < 50%; NC: not calculated; PD-L1: programmed cell death ligand 1; RCT: randomized controlled trial; TPC: treatment of physician's choice; TPS: Tumour Proportion Score; vs.: versus

The risk of bias for the outcome "overall survival" was rated as low; therefore, at most an indication, e.g. of an added benefit, can be derived.

Mortality

Overall survival

A statistically significant difference in favour of pembrolizumab + carboplatin-based chemotherapy was shown between the treatment groups for the outcome "overall survival". This resulted in an indication of an added benefit of pembrolizumab + carboplatin-based chemotherapy in comparison with carboplatin-based chemotherapy.

This concurs with the company's assessment.

Effect modifications

There are no effect modifications for the outcome "overall survival".

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. Outcome category and effect size were taken into account. The methods

used for this purpose are explained in the *General Methods* of IQWiG [5]. Probability and extent on the further outcomes of the KEYNOTE 407 study can be found 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 the added benefit at outcome level for the outcome "overall survival" was estimated from the results presented in Section 2.1.1 (see Table 2).

Table 2: Extent of added benefit at outcome level: pembrolizumab + carboplatin-based chemotherapy[a] vs. carboplatin-based chemotherapy[a]

Outcome category **Outcome**	**Pembrolizumab + carboplatin-based chemotherapy[a] vs. carboplatin-based chemotherapy[a]** **Median time to event (months)** **Effect estimation [95% CI]; p-value** **Probability[b]**	**Derivation of extent[c]**
Mortality		
Overall survival	Median: 14.4 vs. 11.1 HR: 0.56 [0.38; 0.82] p = 0.003 Probability: "indication"	Outcome category: all-cause mortality $CI_u < 0.85$ Added benefit, extent: "major"
a: In combination with either paclitaxel or nab-paclitaxel. 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; vs.: versus		

Overall conclusion on added benefit

Table 3 summarizes the results of the dossier assessment [1] and the addendum considered in the overall conclusion on the extent of added benefit.

Table 3: Positive and negative effects from the assessment of pembrolizumab + carboplatin-based chemotherapy[a] vs. carboplatin-based chemotherapy[a]

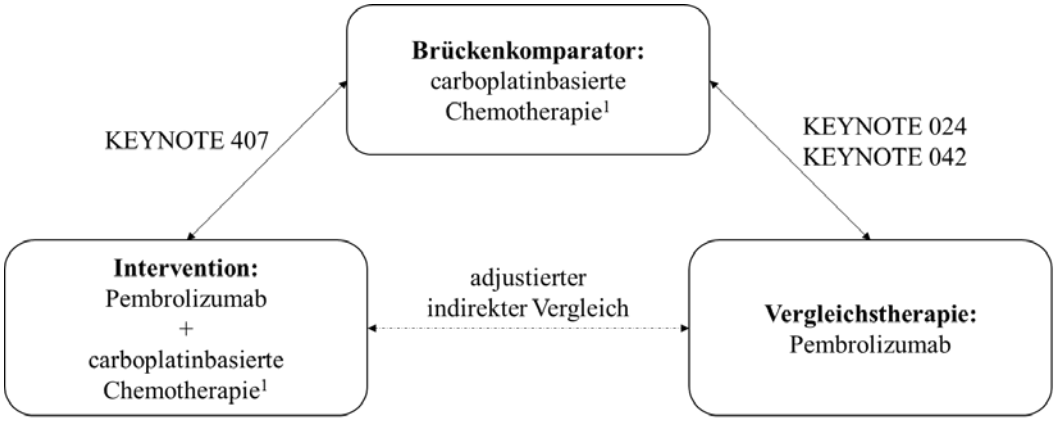
Positive effects[b]	**Negative effects[b]**
Mortality ▪ Overall survival Indication of major added benefit	–
Non-serious/non-severe symptoms/late complications ▪ Dysphagia: indication of an added benefit – extent: "minor"	–
Health-related quality of life ▪ Physical functioning: indication of an added benefit – extent: "minor"	–
Serious/severe side effects ▪ Severe AEs (CTCAE grade ≥ 3): hint of lesser harm – extent: "minor"	–
–	Non-serious/non-severe side effects ▪ Immune-related AEs: hint of greater harm - extent: "considerable"
a: In combination with either paclitaxel or nab-paclitaxel. b: The KEYNOTE 407 study included patients with an ECOG PS of 0 or 1. It remains unclear whether the observed effects can be transferred to patients with an ECOG PS of ≥ 2. AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; ECOG PS: Eastern Cooperative Oncology Group Performance Status	

In the overall consideration, there are several indications and 1 hint of positive effects, which are offset by 1 hint of a negative effect. The positive effects are largely determined by the advantage in the outcome "overall survival". The negative effect of the non-serious/non-severe side effects is offset by a positive effect in the serious/severe side effects. Moreover, effect modifications by age, smoking status and PD-L1 expression are shown in various symptoms (pain, alopecia, dysphagia), social functioning and global health status. The results of these effect modifications are presented in dossier assessment A19-31 [1] and do not change the overall conclusion on added benefit.

Overall, this results in an indication of a major added benefit of pembrolizumab in combination with carboplatin and either paclitaxel or nab-paclitaxel in comparison with carboplatin in combination with either paclitaxel or nab-paclitaxel for the first-line treatment of patients with metastatic squamous NSCLC with a PD-L1 expression < 50%.

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

For research question 2, the company presented and adjusted indirect comparison according to Bucher [4] in its dossier. Figure 1 shows a schematic representation of the indirect comparison.



1: in combination with either paclitaxel or nab-paclitaxel; Brückenkomparator: common comparator; carboplatinbasierte Chemotherapie: carboplatin-based chemotherapy; adjustierter indirekter Vergleich: adjusted indirect comparison; Vergleichstherapie: comparator therapy

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

For the intervention, the study pool comprises the study KEYNOTE 407 and for the comparator therapy it includes the KEYNOTE 042 study. The study KEYNOTE 024 additionally presented in Figure 1 is not used for the benefit assessment (see dossier assessment A19-31 [1]).

A detailed description of the characteristics of the studies KEYNOTE 407 and KEYNOTE 042 can be found in dossier assessment A19-31 [1].

The results of the indirect comparison are presented in the following Section 2.2.1.

2.2.1 Results

The company's dossier does not include usable analyses for the adjusted indirect comparison for all patient-relevant outcomes. Analyses in the categories "morbidity" and "health-related quality of life", for instance, are completely missing, because outcomes of these categories were not recorded in the KEYNOTE 042 study. In the category "side effects", the selection of specific adverse events (AEs) is not possible (for detailed reasons please see dossier assessment A19-31 [1]).

Evaluable analyses were available only for the outcomes "overall survival", "discontinuation due to AEs" and "severe AEs Common Terminology Criteria for Adverse Events (CTCAE) grade ≥ 3".

Risk of bias

The bias for the results of the outcome "overall survival" was rated as potentially low. This concurs with the company's assessment.

There is a low risk of bias for the outcome "discontinuation due to AEs" in the KEYNOTE 407 study, but the certainty of results for this outcome is still limited (see dossier assessment A19-31

[1]). In the KEYNOTE 042 study, the risk of bias for the results of the outcome "discontinuation due to AEs" was rated as potentially high, because the study was unblinded.

The risk of bias for the results of the outcome "severe AEs (CTCAE grade ≥ 3)" was assessed as high for both studies, because information on the observation periods was missing.

This contradicts the company's assessment, which rated the risk of bias of the outcomes of the category "side effects" as sweepingly low.

Consequences for the assessment

In the present indirect comparison of the two studies KEYNOTE 407 and KEYNOTE 042, the bias of the results of the outcome "overall survival" was rated as potentially low, the bias for the outcomes "discontinuation due to AEs" and "severe AEs (CTCAE grade ≥ 3)" was rated as potentially high in both studies. In this data situation, the indirect comparison does not permit a final conclusion on the added benefit by balancing benefit and harm. This is explained below:

Results of adjusted indirect comparisons had a low certainty of results per se. If the adjusted indirect comparison includes outcomes with a high risk of bias between the intervention and the control treatment with the same comparator therapy (common comparator) and only one RCT each on one or both sides of the comparison, a hint of an added benefit or higher/lesser harm is regularly not derived for these outcomes.

Balancing of positive and negative effects is thus impossible in the present case. Thus, an effect could be described for "overall survival", but not for the AE-related outcomes. Overall, the data on the indirect comparison presented by the company are unsuitable to derive an added benefit of pembrolizumab in combination with carboplatin and either paclitaxel or nab-paclitaxel versus pembrolizumab in first-line treatment of metastatic squamous NSCLC with a PD-L1 expression ≥ 50% in adults. This resulted in no hint of an added benefit of pembrolizumab in combination with carboplatin and either paclitaxel or nab-paclitaxel in comparison with pembrolizumab; an added benefit is therefore not proven.

Irrespective of the considerations described above on the data situation in the indirect comparison, no statistically significant difference between the treatment groups was shown for the outcome "overall survival" (HR 1.06; 95% CI: [0.51; 2.22]; p = 0.872). This concurs with the company's assessment.

2.2.2 Probability and extent of added benefit

An added benefit is not proven, since the company presented no suitable data for the assessment of the added benefit of pembrolizumab in combination with carboplatin and either paclitaxel or nab-paclitaxel in comparison with pembrolizumab in first-line treatment of adults with metastatic squamous NSCLC with a PD-L1 expression ≥ 50%.

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 A19-31 for research question 1 (adults with PD-L1 expression < 50%) is changed.

The following Table 4 shows the result of the benefit assessment of pembrolizumab under consideration of dossier assessment A19-31 and the present addendum.

Table 4: Pembrolizumab in combination with carboplatin and either paclitaxel or nab-paclitaxel – Probability and extent of added benefit

Research question	**Subindication**	**ACT[a]**	**Probability and extent of added benefit[b]**
1	First-line treatment of metastatic squamous NSCLC in adults[c] with a PD-L1 expression < 50%	Cisplatin in combination with a third-generation cytostatic agent (vinorelbine or gemcitabine or docetaxel or paclitaxel) *or* **carboplatin in combination with a third-generation cytostatic agent** (vinorelbine or gemcitabine or docetaxel or **paclitaxel**; see also Appendix VI to Section K of the pharmaceutical directive) *or* **carboplatin in combination with nab-paclitaxel**	**Indication of major added benefit**
2	First-line treatment of metastatic squamous NSCLC in adults[c] with a PD-L1 expression ≥ 50%	Pembrolizumab as monotherapy	Added benefit not proven

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: It is assumed for the present therapeutic indication that the NSCLC patients have stage IV disease (staging according to IASLC and UICC, without medical indication for definitive local therapy.
ACT: appropriate comparator therapy;G-BA: Federal Joint Committee; IASLC: International Association for the Study of Lung Cancer; NSCLC: non-small cell lung cancer; PD-L1: programmed cell death ligand 1; UICC: Union for International Cancer Control

The assessment described above concurs with that of the company.

The G-BA decides on the added benefit.

3 References

The reference list contains citations provided by the company in which bibliographical information may be missing.

1. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Pembrolizumab (plattenepitheliales NSCLC, Kombinationschemotherapie): Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung; Auftrag A19-31 [online]. 27.06.2019 [Accessed: 17.07.2019]. (IQWiG-Berichte; Band 786). URL: https://www.iqwig.de/download/A19-31_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/453/#tab/dossier.

3. MSD Sharp & Dohme. Stellungnahme zum IQWiG-Bericht Nr. 786: Pembrolizumab (plattenepitheliales NSCLC, Kombinationschemotherapie); Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung; Auftrag A19-31. [Soon available under: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/453/#stellungnahmen im Dokument "Zusammenfassende Dokumentation"].

4. 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.

5. 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.

Appendix A – Kaplan-Meier curve on overall survival (research question 1)

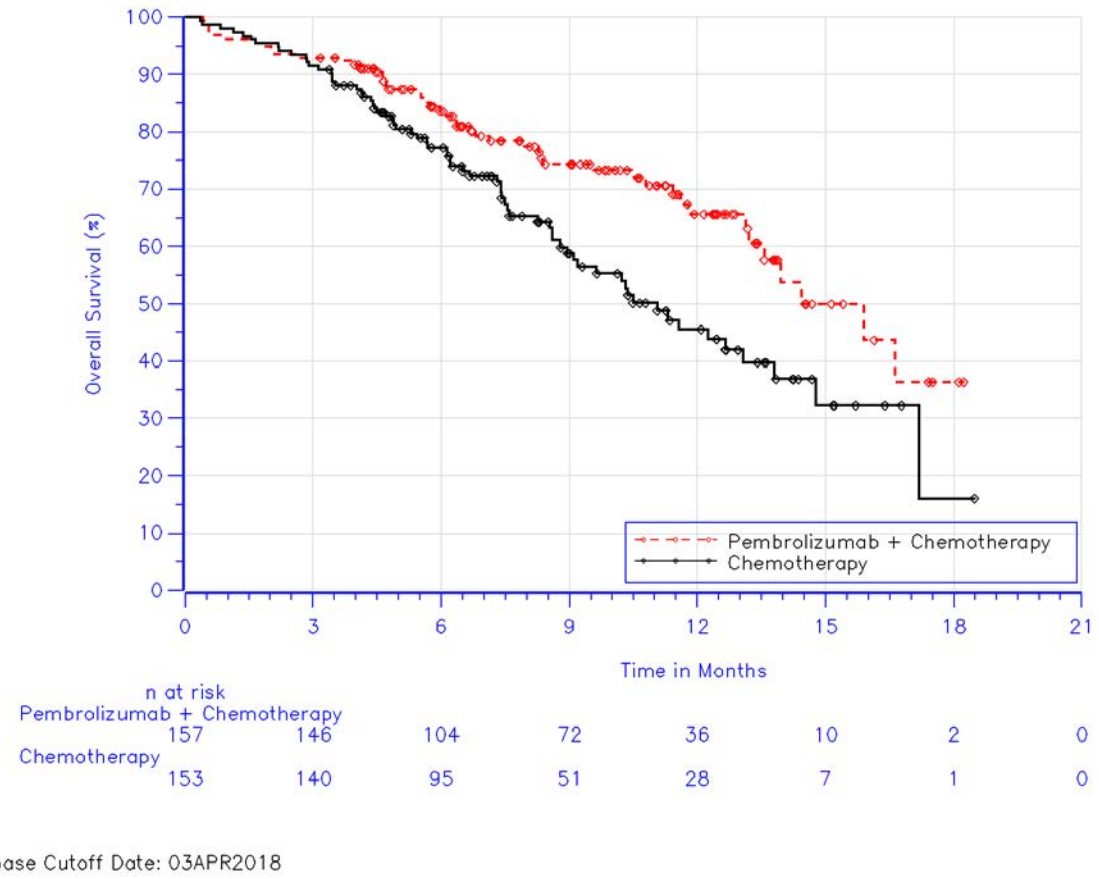


Figure 2: Kaplan-Meier curve on overall survival, KEYNOTE 407 study