IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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Pembrolizumab (non-small cell lung cancer) –

Addendum to Commission A17-06[1]

Addendum

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[1] Translation of addendum A17-28 *Pembrolizumab (nicht kleinzelliges Lungenkarzinom) – Addendum zum Auftrag A17-06* (Version 1.0; Status: 30 June 2017). 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.

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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[2]:

- Simone Johner
- Christoph Schürmann
- Beate Wieseler

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[2] Due to legal data protection regulations, employees have the right not to be named.

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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)
NSCLC	non-small cell lung cancer
PD-L1	programmed cell death ligand 1
SAE	serious adverse events
SGB	Sozialgesetzbuch (Social Code Book)
TPS	tumour proportion score

1 Background

On 21 June 2017, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A17-06 (Pembrolizumab – Benefit assessment according to §35a Social Code Book V [1]).

In its dossier [2], the pharmaceutical (hereinafter referred to as "the company") presented results from the KEYNOTE 024 study [3,4] to prove the added benefit of pembrolizumab. A subpopulation of the KEYNOTE 024 study was used for the benefit assessment [1]. For this relevant subpopulation, the company's dossier did not contain any results on immune-related adverse events (AEs) and on further specific AEs.

After the oral hearing, the company presented further analyses on side effects for the relevant subpopulation of the KEYNOTE 024 study [5]. The G-BA commissioned IQWiG to assess these analyses.

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

2.1 Results on specific adverse events of the relevant subpopulation of the KEYNOTE 024 study

The company presented the KEYNOTE 024 study for the benefit assessment of pembrolizumab in comparison with the appropriate comparator therapy (ACT). This study was a randomized, open-label, active-controlled study on the comparison of pembrolizumab with a platinum-based combination chemotherapy. The study included 305 adult patients with metastatic non-small cell lung cancer (NSCLC) whose tumours express programmed cell death ligand 1 (PD-L1) (strongly positive PD-L1 expression: tumour proportion score [TPS] ≥ 50%). The patients should not have activating epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) mutations in their tumours.

In the KEYNOTE 024 study, treatment with carboplatin-based chemotherapies was not explicitly limited according to the criteria of the Pharmaceutical Directive for off-label use of carboplatin [6]. Because of this, only a subpopulation of the KEYNOTE 024 study was used for the benefit assessment A17-06. It was assumed for the subpopulation that the criteria of the Pharmaceutical Directive were fulfilled for the patients who were treated with carboplatin-based chemotherapy.

The original dossier compiled by the company did not contain any results on immune-related side effects and on further specific AEs for the relevant subpopulation of the KEYNOTE 024 study. After the oral hearing, the company presented analyses on immune-related AEs, serious AEs (SAEs) and severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3) of the relevant subpopulation.

2.1.1 Risk of bias

The risk of bias of the analyses subsequently submitted by the company on immune-related AEs, SAEs and severe AEs (CTCAE grade ≥ 3) is to be regarded as high because of the large proportions of observations with potentially informative censoring (see dossier assessment A17-06 for a detailed description).

2.1.2 Results

The data subsequently submitted by the company on immune-related AEs, SAEs and severe AEs (CTCAE grade ≥ 3) are presented in the following Table 1.

Table 1: Results (side effects) – RCT, direct comparison: pembrolizumab vs. cisplatin- or carboplatin-based chemotherapy (relevant subpopulation)

Study Outcome category Outcome	Pembrolizumab		Platinum-based chemotherapy[a]		Pembrolizumab vs. platinum-based chemotherapy
	N	Median survival time in months [95% CI] Patients with event n (%)	N	Median survival time in months [95% CI] Patients with event n (%)	HR [95% CI]; p-value[b]
KEYNOTE 024					
Side effects					
Specific AEs					
Immune-related AEs	109	NA [51.4; NC] 32 (29.4)	106	NA [NC; NC] 4 (3.8)	9.50 [3.32; 27.17][c]; < 0.001
Immune-related SAEs	109	NA [NC; NC] 11 (10.1)	106	NA [NC; NC] 1 (0.9)	13.29 [1.70; 103.71][d]; 0.014
Immune-related severe AEs (CTCAE grade ≥ 3)	109	NA [NC; NC] 9 (8.3)	106	NA [NC; NC] 1 (0.9)	9.21 [1.16; 73.01][e]; 0.036
Further specific AEs	No data available for the relevant subpopulation				

a: Before randomization, chemotherapy was chosen for the individual patient from the following combination chemotherapies: cisplatin + gemcitabine, cisplatin + pemetrexed, carboplatin + gemcitabine, carboplatin + pemetrexed, carboplatin + paclitaxel.
b: Effect, CI and p-value: Cox proportional hazards model stratified by geographical region (East Asia vs. not East Asia), ECOG Performance Status (0 vs. 1) and histology (squamous vs. non-squamous), p-value from Wald test.
c: Reversed direction of effect to enable use of limits to derive the extent of the added benefit: HR: 0.11 [0.04; 0.30].
d: Reversed direction of effect to enable use of limits to derive the extent of the added benefit: HR: 0.08 [0.01; 0.59].
e: Reversed direction of effect to enable use of limits to derive the extent of the added benefit: HR: 0.11 [0.01; 0.86].
AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; ECOG: Eastern Cooperative Oncology Group; HR: hazard ratio; N: number of analysed patients; n: number of patients with (at least 1) event; NA: not achieved; NC: not calculable; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus

Due to the high risk of bias, at most hints can be derived for the outcomes presented on the basis of the available data.

Side effects

Specific adverse events

Immune-related adverse events, serious adverse events, severe adverse events (CTCAE grade ≥ 3)

Statistically significant differences to the disadvantage of pembrolizumab versus cisplatin- or carboplatin-based chemotherapy were shown for each of the outcomes "immune-related AEs", "immune-related SAEs" and "immune-related severe AEs" (CTCAE grade ≥ 3). This resulted in a hint of greater harm of pembrolizumab in comparison with a cisplatin- or carboplatin-based chemotherapy for all 3 outcomes.

For the outcome "immune-related AEs" (category of non-serious side effects), the extent of the greater harm was estimated to be "considerable" using the upper confidence interval of 0.30 (reversed direction of effect). For serious side effects, immune-related SAEs and severe AEs (CTCAE grade ≥ 3), there was greater harm of major or considerable extent (upper limits of confidence interval of 0.59 [reversed direction of effect, immune-related SAEs] and 0.86 [reversed direction of effect, immune-related severe AEs]).

Further specific adverse events

For further specific AEs, the company still did not present any data for the relevant subpopulation.

2.1.3 Overall conclusion on added benefit

Due to the data subsequently submitted, results on immune-related side effects for the relevant subpopulation were now available in comparison with dossier assessment A17-06.

Under consideration of the present addendum and of dossier assessment A17-06, Table 2 summarizes the results that were considered in the overall conclusion on the extent of added benefit.

Table 2: Positive and negative effects from the assessment of pembrolizumab in comparison with a cisplatin- or carboplatin-based chemotherapy (relevant subpopulation)

Positive effects	**Negative effects**
Mortality ▫ overall survival: indication of an added benefit – extent: "considerable"	–
Non-serious/non-severe symptoms/late complications ▫ symptoms: hint of an added benefit – extent: "considerable" (including nausea and vomiting, constipation, alopecia, dysphagia, sore mouth, peripheral neuropathy) ▫ symptoms: hint of an added benefit – extent: "minor" (including dyspnoea, appetite loss)	–
Health-related quality of life ▫ hint of an added benefit – extent: "major" (including physical functioning, social functioning) ▫ hint of an added benefit – extent: "considerable" (role functioning)	–
Serious/severe side effects ▫ severe AEs (CTCAE grade ≥ 3): hint of lesser harm – extent: "major"	Serious/severe side effects ▫ specific AEs: hint of greater harm – extent "considerable" (immune-related severe AEs [CTCAE grade ≥ 3]) ▫ specific AEs: hint of greater harm – extent "major" (immune-related SAEs)
	Non-serious/non-severe side effects ▫ specific AEs: hint of greater harm – extent "considerable" (immune-related AEs)
For further specific AEs, no results are available in the relevant subpopulation.	
AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; SAE: serious adverse event	

Overall, there are positive and negative effects.

On the positive side, there is an indication of a considerable added benefit for the outcome "overall survival". Regarding symptoms, there is a hint of a considerable added benefit in 6 outcomes (e.g. nausea and vomiting, dysphagia) and a hint of a minor added benefit for 2 outcomes (dyspnoea, appetite loss). For the outcome "severe AEs" (CTCAE grade ≥ 3), there is a hint of lesser harm with the extent "major". Finally, there is a hint of an added benefit for 3 dimensions of health-related quality of life (extent "considerable" to "major"). On the side of negative effects, the positive effects are accompanied by hints of greater harm (extent "considerable" to "major") for specific AEs (immune-related AEs, SAEs and severe AEs [CTCAE grade ≥ 3]). The negative effects in immune-related side effects do not raise doubts about the positive effects, however.

Since the role of the effect modification by the characteristic "sex" in the relevant subpopulation still remains unclear and there are additional principal uncertainties regarding

the choice of the relevant subpopulation (see dossier assessment A17-06 for a detailed description), the certainty of conclusions on the basis of available data is limited.

In summary, there is a hint of a considerable added benefit of pembrolizumab in comparison with the ACT cisplatin- or carboplatin-based chemotherapy for patients with first-line treatment of metastatic NSCLC with PD-L1 expressing tumours (TPS $\geq$ 50%) without activating EGFR or ALK mutations.

The result of dossier assessment A17-06 therefore remains unchanged.

The approach for deriving an overall conclusion on added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

3 References

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