IQWiG Reports – Commission No. A18-67

Pembrolizumab (head and neck squamous cell carcinoma) –

Benefit assessment according to §35a Social Code Book V[1]

Extract

[1] Translation of the executive summary of the dossier assessment *Pembrolizumab (Plattenepithelkarzinom des Kopf-Hals-Bereichs) – Nutzenbewertung gemäß § 35a SGB V* (Version 1,0; Status: 11 January 2019). Please note: This document was translated by an external translator and 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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Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SBG) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug pembrolizumab. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 2 October 2018.

Research question

The aim of this report was to assess the added benefit of pembrolizumab in comparison with individualized therapy upon the physician's discretion as the appropriate comparator therapy (ACT) in adult patients with recurrent or metastatic head and neck squamous cell carcinoma with programmed cell death ligand 1 (PD-L1) expressing tumours (tumour proportion score [TPS] ≥ 50%) and cancer progression during or after prior platinum-based therapy.

The G-BA's specification of the ACT resulted in one research question, which is presented in Table 2 below.

Table 2[2]: Research questions of the benefit assessment of pembrolizumab

Indication	ACT[a]
Adults with recurrent or metastatic head and neck squamous cell carcinoma with PD-L1 expressing tumours (TPS ≥ 50%) and cancer progression during or after prior platinum-based therapy[b]	Individualized therapy upon the physician's discretion (chemotherapy, primarily with methotrexate, radiotherapy, and/or surgery). Any drug therapy must be administered in accordance with approval.
a: Presentation of the ACT specified by the G-BA. b: It is assumed that surgical treatment or radiation therapy with a curative intent are not indicated. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; PD-L1: programmed cell death ligand 1; TPS: tumour proportion score	

The company identified individualized therapy upon the physician's discretion as the comparator therapy. In its further descriptions, the company stated that said therapy was represented by methotrexate, cetuximab, and docetaxel.

This benefit assessment was conducted using the appropriate comparator therapy (ACT) specified by the G-BA. In accordance with G-BA specifications, the approval status is to be taken into account for any drug therapies.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) were used for deriving any added benefit.

[2] Table numbers start with "2" as numbering follows that of the full dossier assessment.

Results

For the benefit assessment of pembrolizumab, the KEYNOTE 040 study was used. This is a randomized, open, controlled study comparing pembrolizumab with treatment upon the physician's discretion (choice between methotrexate, cetuximab, or docetaxel monotherapy).

The studies included adults with histologically or cytologically confirmed diagnosis of recurrent or metastatic head and neck squamous cell carcinoma (oral, oropharyngeal, hypopharyngeal, or laryngeal) and cancer progression during or after prior platinum-based therapy. These patients were to no longer be eligible for a curative treatment approach. In patients who received platinum-based therapy in the advanced or metastatic stage, tumour progression must have been identified at any time during or after this treatment. Patients after multimodal platinum-based therapy (e.g. in the locally advanced stage) were to have exhibited tumour progression or recurrence within 6 months after completion of therapy.

In total, 495 adults were randomly allocated in a 1:1 ratio to the intervention arm (pembrolizumab: N = 247) or the comparator arm (treatment upon the physician's discretion: N = 248). For all patients, the physician's selection of the treatment to be used in case of allocation to the comparator arm was made already prior to randomization. The latter was stratified by the Eastern Cooperative Oncology Group Performance Status (ECOG-PS) (0 versus 1), PD-L1 status (strongly positive TPS ≥ 50% versus not strongly positive TPS < 50%) and, for study participants with oropharyngeal cancer, additionally by human papilloma virus (HPV) status (positive versus negative).

The primary outcome of the study was overall survival. The patient-relevant secondary outcomes surveyed were morbidity, health-related quality of life, and adverse events (AEs).

Relevant subpopulation of the KEYNOTE 040 study

The KEYNOTE 040 study included adults with recurrent or metastatic head and neck squamous cell carcinoma, regardless of the PD-L1 expression of tumours. For these patients' treatment, physicians had a choice between 3 drug monotherapies (upon the physician's discretion): cetuximab, docetaxel, and methotrexate.

As part of the approval process, the use of pembrolizumab in the treatment of recurrent or metastatic head and neck squamous cell cancer with cancer progression during or after prior platinum-based therapy was limited to tumours expressing PD-L1 (TPS ≥ 50%). The 129 patients meeting these criteria make up approximately 26% of the total study population. On the basis of the approval, only this subpopulation (in this report referred to as **TPS subpopulation**) is indicated for treatment with pembrolizumab and must initially be taken into account.

In terms of the ACT, the G-BA specified individualized therapy upon the physician's discretion with consideration given to the approval. This therapy primarily comprises methotrexate from the group of chemotherapeutic agents, radiotherapy, and/or surgery. Among the 3 treatment

options available in the study, only methotrexate is approved as monotherapy for the aforementioned therapeutic indication. Accordingly, only patients with PD-L1-expressing tumours (TPS ≥ 50%) and for whom the investigator specified treatment with methotrexate before randomization (**methotrexate subpopulation**) are relevant for the benefit assessment. With 16 adults in the intervention arm and 21 adults in the comparator arm, this subpopulation comprises only 7.5% of the total study population.

For the population investigated in the study, methotrexate is considered an adequate representation of the ACT specified by the G-BA (individualized therapy upon the physician's discretion).

All things considered, the above discussion shows that the KEYNOTE 040 study was not explicitly designed to investigate the research question of this benefit assessment. Due to the very low number of included patients in the methotrexate subpopulation, the results for this subpopulation of the study are very imprecise.

In deviation from the procedure described above, the company used a further subpopulation of the study in its assessment. In addition to the patients of the methotrexate subpopulation, the company included patients who, in its opinion, received cetuximab or docetaxel in justified cases. The company presented the results for the methotrexate subpopulation in the form of subgroup analyses on the attribute of treatment upon the physician's discretion.

Risk of bias

The risk of bias at study level is considered low. For the results of all outcomes with usable data, the risk of bias is considered high.

Results

Mortality

- Overall survival

This benefit assessment uses the results of the stratified Cox model, the model predefined for the total population in the study report. In the relevant methotrexate subpopulation, the result of this model shows no statistically significant difference between treatment groups.

Given the present data situation, the results of the TPS subpopulation are used to support the interpretation of results from the methotrexate subpopulation – due to the very small size of the relevant population and related low precision of the effect estimate. The TPS subpopulation's result for the outcome of overall survival shows a statistically significant difference in favour of pembrolizumab.

In this specific data constellation, the consistent effect direction and location of point estimates between the methotrexate and TPS subpopulations allows an overall qualitative conclusion of a hint of added benefit of pembrolizumab for the outcome of overall survival in the methotrexate subpopulation. However, the extent of this effect is not quantifiable.

This results in a hint of added benefit of pembrolizumab in comparison with methotrexate.

Morbidity

- Disease symptoms, as surveyed using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Cancer-30 (EORTC QLQ-C30) (symptom scales)

The outcome of disease symptoms is measured using the following symptom scales of EORTC QLQ-C30: fatigue, nausea and vomiting, pain, dyspnoea, insomnia, appetite loss, constipation, and diarrhoea. This benefit assessment uses the time until 1st deterioration, which is defined as an increase from baseline by at least 10 points.

For the outcome of the EORTC QLQ-C30 diarrhoea symptom scale, the company supplied no effect estimate; therefore, no conclusion can be drawn on added benefit for this outcome. For each of the other included EORTC QLQ-C30 symptom scales, no statistically significant difference between treatment groups was found. For each of the outcomes of fatigue, nausea and vomiting, pain, dyspnoea, insomnia, appetite loss, constipation, and diarrhoea, this results in no hint of added benefit of pembrolizumab in comparison with methotrexate; an added benefit is therefore not proven.

- Disease symptoms, as surveyed using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Head & Neck 35 (EORTC QLQ-C30) (symptom scales)

Disease symptoms were measured with the individual scales of the EORTC QLQ-C30 as well as with the following EORTC QLQ-H&N 35 symptom scales: pain, swallowing, sense, speech, tooth problems, difficulty in opening mouth, dry mouth, sticky saliva, coughing, and feeling ill. This benefit assessment uses the time until 1st deterioration, which is defined as an increase from baseline by at least 10 points.

None of the EORTC QLQ-H&N 35 symptom scales used revealed a statistically significant difference between treatment groups. Consequently, there is no hint of added benefit of pembrolizumab in comparison with methotrexate; an added benefit is therefore not proven.

- Health status as measured by the European Quality of Life-5 Dimensions (EQ-5D) visual analogue scale (VAS)

For the outcome of health status as measured by EQ-5D VAS, no usable data are available. For the outcome of health status, there was therefore no hint of an added benefit of pembrolizumab in comparison with methotrexate; an added benefit is therefore not proven.

Health-related quality of life

- EORTC QLQ-C30 (functional scales and general health status scale)

The outcome of health-related quality of life, as measured using the general health status scale and the functional scales of the EORTC QLQ-C30, comprises the following scales: general

health status, physical functioning, role functioning, emotional functioning, cognitive functioning, and social functioning. This benefit assessment uses the time until 1st deterioration, defined as a decrease from baseline by at least 10 points.

None of the included EORTC QLQ-C30 functional scales nor the general health status scale showed a statistically significant difference between treatment groups. Consequently, there is no hint of added benefit of pembrolizumab in comparison with methotrexate; an added benefit is therefore not proven.

- EORTC QLQ-H&N35 (functional scales)

The outcome of health-related quality of life, as measured by the EORTC QLQ-H&N35 functional scales, comprised the following scales: problems with social eating, problems with social contacts, and reduced sexuality. This benefit assessment uses the time until 1st deterioration, which is defined as an increase from baseline by at least 10 points.

None of the used EORTC QLQ-H&N 35 functional scales exhibited a statistically significant difference between treatment groups. Consequently, there is no hint of added benefit of pembrolizumab in comparison with methotrexate; an added benefit is therefore not proven.

Adverse events

- Serious AEs (SAEs), severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade 3–4) and discontinuation due to AEs

For the outcomes of SAEs and severe AEs (CTCAE ≥ grade 3), no statistically significant difference between treatment groups was found. For the outcome of discontinuation due to AEs, the company did not deliver an effect estimate; in the pembrolizumab group, 1 treatment discontinuation due to AEs was documented, whereas in the methotrexate group, 4 patients discontinued treatment due to AEs. For each of the outcomes of SAEs, severe AEs (CTCAE grade ≥ 3), and discontinuation due to AEs, this resulted in no hint of greater or lesser harm of pembrolizumab in comparison with methotrexate; therefore, there is no proof of greater or lesser harm.

- Immune-mediated AEs

For the outcome of immune-mediated AEs, the relevant methotrexate subpopulation did not exhibit a statistically significant difference between treatment groups.

Given this data situation, the results in the TPS subpopulation were analysed to support interpretation of the methotrexate subpopulation's results due to the very small size of the relevant population and associated low precision of the effect estimate. The result for the outcome of immune-mediated AEs in the TPS subpopulation reveals a statistically significant difference to the disadvantage of pembrolizumab. Overall, the results of the methotrexate and TPS subpopulations show a hint of greater harm of pembrolizumab for the outcome of immune-mediated AEs. However, the extent of this effect is not quantifiable.

For the outcome of immune-mediated AEs, this results in a hint of greater harm of pembrolizumab in comparison with methotrexate.

- Immune-mediated SAEs and immune-mediated severe AEs (CTCAE grade ≥ 3)

In the relevant methotrexate subpopulation, a total of 3 severe immune-mediated AEs – all in the pembrolizumab arm – were documented. Severe immune-mediated AEs (CTCAE grade ≥ 3) did not occur. For each of the outcomes of immune-mediated severe AEs (CTCAE grade ≥ 3) and immune-mediated SAEs, there is no hint of greater or lesser harm of pembrolizumab in comparison with methotrexate; therefore, there is no proof of greater or lesser harm.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

On the basis of the results presented, the probability and extent of added benefit of the drug pembrolizumab in comparison with the ACT are assessed as follows:

Overall, the results of the relevant methotrexate subpopulation, taking into account the results of the TPS subpopulation, show both positive effects (overall survival) and negative effects (immune-mediated AEs) of pembrolizumab versus methotrexate. However, the extent of these effects is not quantifiable.

Particularly given the very small size of the relevant population, the results of the study are also very imprecise for further outcomes in the categories of morbidity, health-related quality of life, and adverse events. All things considered, however, potential disadvantages regarding any of these outcomes are not expected to put into question or offset the survival advantage associated with pembrolizumab.

In summary, for adults with recurrent or metastatic head and neck squamous cell cancer with PD-L1-expressing tumours (TPS ≥ 50%) and cancer progression during or after prior platinum-based therapy, there is a hint of non-quantifiable added benefit of pembrolizumab in comparison with the ACT of methotrexate.

No data are available on adults eligible for different individualized therapy upon the physician's discretion.

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) "proof", (2) "indication", (3) "hint", or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or less benefit). For further details see [1,2].

Table 3 presents a summary of the probability and extent of added benefit of pembrolizumab.

Table 3: Pembrolizumab – probability and extent of added benefit

Indication	**ACT[a]**	**Probability and extent of added benefit**
Adults with recurrent or metastatic head and neck squamous cell carcinoma with PD-L1-expressing tumours (TPS ≥ 50%) and cancer progression during or after prior platinum-based therapy[b]	Individualized therapy upon the physician's discretion (chemotherapy, primarily with methotrexate, radiotherapy, and/or surgery). Any drug therapy must be administered in accordance with approval.	Hint of non-quantifiable added benefit[c]
a: Presentation of the ACT specified by the G-BA. b: It is assumed that surgical treatment or radiation therapy with a curative intent are not indicated. c: In the relevant subpopulation of the KEYNOTE 040 study, pembrolizumab was investigated in comparison with methotrexate. Only patients with an ECOG-PS of 0 or 1 were included in the study. It remains unclear whether the observed effects are transferable to patients with an ECOG-PS ≥ 2. ACT: appropriate comparator therapy; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee; PD-L1: programmed cell death ligand 1; TPS: tumour proportion score		

The approach for deriving the overall conclusion on added benefit is a suggestion from IQWiG. The G-BA decides on the added benefit.

References for English extract

Please see full dossier assessment for full reference list.

1. Institute for Quality and Efficiency in Health Care. General methods: version 5.0 [online]. 10 July 2017 [Accessed: 4 June 2018]. URL: https://www.iqwig.de/download/General-Methods_Version-5-0.pdf.

2. Skipka G, Wieseler B, Kaiser T, Thomas S, Bender R, Windeler J et al. Methodological approach to determine minor, considerable, and major treatment effects in the early benefit assessment of new drugs. Biom J 2015; 58(1): 43-58

The full report (German version) is published under https://www.iqwig.de/en/projects-results/projects/drug-assessment/a18-67-pembrolizumab-head-and-neck-squamous-cell-carcinoma-benefit-assessment-according-to-35a-social-code-book-v.10756.html.