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Cemiplimab (basal cell carcinoma) –

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

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Cemiplimab (Basalzellkarzinom) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 28 October 2021). 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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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
BSC	Best supportive Care
ECOG-PS	Eastern Cooperative Oncology Group Performance St
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HhI	hedgehog signal pathway inhibitor
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
laBCC	locally advanced basal cell carcinoma
mBCC	metastatic basal cell carcinoma
ORR	objective response rate
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) 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 cemiplimab. 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 21 July 2021.

Research question

The aim of this report was to assess the added benefit of cemiplimab in comparison with best supportive care (BSC) as appropriate comparator therapy (ACT) in adult patients with locally advanced basal cell carcinoma (laBCC) or metastatic basal cell carcinoma (mBCC) who were previously treated with a hedgehog signal pathway inhibitor (HhI) and show disease progression or intolerance to it during this treatment.

The research question presented in Table 2 resulted from the ACT specified by the G-BA.

Table 2: Research questions of the benefit assessment of cemiplimab

Therapeutic indication	**ACT[a]**
Adult patients with laBCC or mBCC who were previously treated with an HhI and show disease progression or intolerance to it during this treatment[b]	BSC[c]
a. Presentation of the ACT specified by the G-BA. b. The G-BA assumes that the therapeutic indication only comprised patients for whom neither radiotherapy nor surgery and local therapy were an option. c. According to the G-BA, best supportive care refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life. ACT: appropriate comparator therapy; BSC: best supportive care; G-BA: Federal Joint Committee; HhI: hedgehog signal pathway inhibitor; laBCC: locally advanced basal cell carcinoma; mBCC: metastatic basal cell carcinoma	

The company followed the specification of the ACT.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier.

Study pool and study design

Concurring with the company, the check of the completeness of the study pool produced no randomized controlled trial (RCT) on the comparison of cemiplimab versus BSC as ACT.

As the company identified no RCTs, it additionally conducted an information retrieval for further studies. For the intervention, it identified one single-arm study with cemiplimab (R2810-ONC-1620). The company was not able to identify studies on the comparator therapy.

The data from the R2810-ONC-1620 study presented by the company were unsuitable to draw conclusions on the added benefit of cemiplimab in comparison with the ACT. This is justified below.

Study R2810-ONC-1620

R2810-ONC-1620 is an ongoing, single-arm, open-label and multicentre phase 2 study with cemiplimab. It included adult patients with laBCC or mBCC who had been pretreated with at least 1 Hhl and who showed progression or intolerance to HhI during this therapy. In addition, patients had to have at least 1 measurable lesion with a diameter of at least 10 mm. For patients with laBCC, it was also defined that they had to have an unresectable tumour at enrolment and were not allowed to be eligible for radiotherapy. Only patients with a good general condition (Eastern Cooperative Oncology Group Performance Status [ECOG PS] of 0 or 1) were included in the study.

A total of 132 patients, 84 of which had laBCC and 48 had mBCC, had been included in the study by the data cut-off of 17 February 2020.

Treatment with cemiplimab was in compliance with the recommendations of the SPC.

Primary outcome of the study was the objective response rate (ORR), which was analysed by a central review committee separately for patients with laBCC and mBCC. Secondary outcomes were “overall survival” and outcomes of the outcome categories “morbidity”, “health-related quality of life” and “side effects”.

Results

Overall, the study R2810-ONC-1620 is not suitable for the present benefit assessment because it does not allow a comparison with the ACT. The company nevertheless used the study to derive the added benefit of cemiplimab, as in its view it represents the best available evidence.

The added benefit of cemiplimab derived by the company is ultimately based exclusively on results for the outcome “ORR”. Hereby, the company refers to the decision of the G-BA on the benefit assessment of vismodegib, according to which the outcome “ORR” in the therapeutic indication of laBCC was considered patient-relevant due to the good external visibility of tumour lesions and ulcerations if an adequate operationalization shows a relevant decrease in tumour size and tumour ulcerations. However, the analyses on ORR presented by the company are not suitable to present ORR as patient-relevant outcome:

- In Module 4 C of its dossier on ORR, the company did not present any analyses in a suitable operationalization, but only analyses of the composite response, which is composed of the clinical response (digital photography, if necessary also with

confirmation by biopsy) and the radiological response (CT or MRI). Through the use of radiological methods of measurement, non-patient-relevant operationalizations are thus also included in the ORR.

- The company's documents provide no or no adequately prepared analyses of the extent of the lesions, the degree of ulceration of individual lesions at baseline and their development during the course of therapy, as well as on the number and localisation of the lesions.

The approach used by the company to present the results is not comprehensible as corresponding analyses had already been requested in the benefit assessments of vismodegib and had been presented in the addendum on the second assessment of vismodegib.

In summary, there are no suitable data to assess the added benefit of cemiplimab compared to BSC in adult patients with laBCC or mBCC who have previously been treated with an HhI and who demonstrate disease progression or intolerance to it during this treatment. This resulted in no hint of an added benefit of cemiplimab in comparison with BSC; an added benefit is therefore not proven.

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

Based on the results presented, probability and extent of the added benefit of the drug cemiplimab in comparison with the ACT are assessed as follows:

Table 3 shows a summary of probability and extent of the added benefit of cemiplimab.

[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: Cemiplimab – probability and extent of added benefit

Therapeutic indication	ACT[a]	Probability and extent of added benefit
Adult patients with laBCC or mBCC who were previously treated with an HhI and show disease progression or intolerance to it during this treatment[b]	BSC[c]	Added benefit not proven

a. Presentation of the ACT specified by the G-BA.
b. The G-BA assumes that the therapeutic indication only comprised patients for whom neither radiotherapy nor surgery and local therapy were an option.
c. According to the G-BA, best supportive care refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.

ACT: appropriate comparator therapy; BSC: best supportive care; G-BA: Federal Joint Committee; HhI: hedgehog signal pathway inhibitor; laBCC: locally advanced basal cell carcinoma; mBCC: metastatic basal cell carcinoma

The G-BA decides on the added benefit.

2.2 Research question

The aim of this report was to assess the added benefit of cemiplimab in comparison with BSC as ACT in adult patients with laBCC or mBCC who were previously treated with an HhI and show disease progression or intolerance to it during this treatment.

The research question presented in Table 4 resulted from the ACT specified by the G-BA.

Table 4: Research question of the benefit assessment of cemiplimab

Therapeutic indication	ACT[a]
Adult patients with laBCC or mBCC who were previously treated with an HhI and show disease progression or intolerance to it during this treatment[b]	BSC[c]

a. Presentation of the ACT specified by the G-BA.
b. The G-BA assumes that the therapeutic indication only comprised patients for whom neither radiotherapy nor surgery and local therapy were an option.
c. According to the G-BA, best supportive care refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.

ACT: appropriate comparator therapy; BSC: best supportive care; G-BA: Federal Joint Committee; HhI: hedgehog signal pathway inhibitor; laBCC: locally advanced basal cell carcinoma; mBCC: metastatic basal cell carcinoma

The company followed the specification of the ACT.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier.

2.3 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study lists on cemiplimab (status: 3 June 2021)
- bibliographical literature search on cemiplimab (last search on 28 May 2021)
- search in trial registries/trial results databases for studies on cemiplimab (last search on 3 June 2021)
- search on the G-BA website for cemiplimab (last search on 3 June 2021)
- bibliographical literature search on the ACT (last search on 28 May 2021)
- search in trial registries/trial results databases for studies on the ACT (last search on 3 June 2021)
- search on the G-BA website for the ACT (last search on 3 June 2021)

To check the completeness of the study pool:

- search in trial registries for studies on cemiplimab (last search on 28 July 2021); for search strategies, see Appendix B of the full dossier assessment

Concurring with the company, the check of the completeness of the study pool produced no RCT on the comparison of cemiplimab versus BSC as ACT.

As the company identified no RCTs, it additionally conducted an information retrieval for further studies. For the intervention, it identified one single-arm study with cemiplimab (R2810-ONC-1620 [3-7]). The check of the completeness of the study pool identified no additional potentially relevant studies on cemiplimab. The company was not able to identify studies on the comparator therapy. The completeness of the study pool on the ACT was not checked.

The data from the R2810-ONC-1620 study presented by the company were unsuitable to draw conclusions on the added benefit of cemiplimab in comparison with the ACT. This is justified below.

Evidence provided by the company

Study R2810-ONC-1620

R2810-ONC-1620 is an ongoing, single-arm, open-label and multicentre phase 2 study with cemiplimab. It included adult patients with laBCC or mBCC who had been pretreated with at least 1 Hhl and who showed progression or intolerance to HhI during this therapy. In addition, patients had to have at least 1 measurable lesion with a diameter of at least 10 mm. For patients with laBCC, it was also defined that they had to have an unresectable tumour at enrolment and were not allowed to be eligible for radiotherapy. Only patients with a good general condition (ECOG PS of 0 or 1) were included in the study.

A total of 132 patients, 84 of which had laBCC and 48 had mBCC, had been included in the study by the data cut-off of 17 February 2020. 6 other patients with mBCC were included in the study by the data cut-off of 30 June 2020.

Cemiplimab was administered intravenously at a dose of 350 mg every 3 weeks for a maximum of 93 weeks or until disease progression, unacceptable toxicity, withdrawal of consent or until complete response. In the event of the occurrence of certain adverse events (AEs), dose adjustments were permitted in deviation from the information in the Summary of Product Characteristics (SPC) [8]. Overall, the dose was reduced in only 1 patient up to the data cut-off of 17 February 2020. Thus, treatment with cemiplimab was in compliance with the recommendations of the SPC [8].

Primary outcome of the study was the ORR, which was analysed by a central review committee separately for patients with laBCC and mBCC. Secondary outcomes were "overall survival" and outcomes of the outcome categories "morbidity", "health-related quality of life" and "side effects".

Further information on the R2810-ONC-1620 study can be found in Appendix A of the present benefit assessment.

Data cut-offs

For the R2810-ONC-1620 study, 2 data cut-offs were available in the company's dossier:

- First data cut-off of 17 February 2020: prespecified primary analysis of efficacy outcomes for all patients with laBCC (N = 84) 57 weeks after the start of treatment of the last enrolled study participant with laBCC; additional prespecified interim analysis of efficacy outcomes for those patients with mBCC who had completed at least 57 weeks of treatment or follow-up at the same time point (N = 28).
- Second data cut-off of 30 June 2020: non-prespecified analysis for both patient groups (IaBCC [N = 84] and mBCC [N = 54]).

For the derivation of the added benefit, the company considered the results of the first data cut-off (17 February 2020).

Overall, the study R2810-ONC-1620 is not suitable for the present benefit assessment because it does not allow a comparison with the ACT. The company nevertheless used the study to derive the added benefit of cemiplimab, as in its view it represents the best available evidence. The company's approach for the derivation of the added benefit on the basis of the study R2810-ONC-1620 is described and assessed below.

Approach of the company for the derivation of the added benefit

At first, the company provided a descriptive presentation of the results on several outcomes of the outcome categories "mortality", "morbidity", "health-related quality of life" and "side

effects" from the R2810-ONC-1620 study. For the derivation of the added benefit, the company used the outcomes "overall survival", "ORR", "disease control rate (DCR)", "progression-free survival (PFS)" and "side effects". The company stated that it would discuss these data both in the context of BSC as ACT and in the context of the results of the ERIVANCE study in the benefit assessment procedure for vismodegib in the therapeutic indication "basal cell carcinoma".

Overall, the company identified no studies on BSC. However, it assumes that spontaneous remission does not usually occur under BSC and therefore any response must be considered a patient-relevant improvement. In doing so, the company refers to statements from the procedure on vismodegib [9,10]. It transfers these statements to the disease stage of laBCC and mBCC after treatment with HhI, which is more advanced compared to vismodegib and for which cemiplimab is approved. Furthermore, it compares the results on the outcomes "ORR", "PFS", "overall survival" and "side effects" from the R2810-ONC-1620 study with those from the ERIVANCE study, which were presented in the benefit assessment procedure of vismodegib. The company stated that the data on vismodegib were not collected in the same therapeutic indication and that vismodegib was not the ACT in the present therapeutic indication. Nevertheless, the company came to the overall conclusion that the results on the efficacy and safety of cemiplimab are of a similar magnitude as those that led to the derivation of a minor added benefit or vismodegib by the G-BA.

The added benefit of cemiplimab derived by the company is ultimately based exclusively on results for the outcome "ORR". Therefore, the outcome "response" is discussed in more detail below.

Assessment of the approach of the company to the outcome "response"

Operationalization of the outcome "response" also using radiographic methods

The company considered the outcome "ORR" to be patient relevant. In doing so, it refers to the decision of the G-BA on the benefit assessment of vismodegib [11]. According to this, the outcome "ORR" in the therapeutic indication of laBCC was considered patient-relevant due to the good external visibility of tumour lesions and ulcerations if an adequate operationalization shows a relevant decrease in tumour size and tumour ulcerations. However, the company did not present a suitable operationalization in Module 4 C of its dossier.

In R2810-ONC-1620, response is operationalized as a composite outcome consisting of clinical response and radiological response. Complete or partial response as well as stable disease and progression were distinguished here. Only complete and partial response are included in the ORR. The documentation of the response was partly different for the patient groups laBCC and mBCC:

- In patients with laBCC, externally visible lesions should be documented using two-dimensional medical digital photographs according to the World Health Organisation (WHO) criteria for the assessment of externally visible tumours [12]. Here, information

on the extent of the tumour, the occurrence of new lesions and ulcerations of the target lesions are recorded. Moreover, imaging techniques such as computed tomography (CT) or magnetic resonance imaging (MRI) should be used unless the investigator judged that they did not provide substantial additional information.

- In patients with mBCC, tumour response was primarily determined on the basis of Version 1.1 of the Response Evaluation Criteria-In-Solid-Tumours (RECIST) criteria [13]. Information on the extent of the tumour, the occurrence of new lesions and the change of pathological lymph nodes is considered here. This information could be recorded in the study using imaging techniques such as CT or MRI. In patients with externally visible lesions, these could be documented as target lesions by means of digital photography. Moreover, recording exclusively based on digital photography was allowed for patients whose tumour response could not be measured on the basis of RECIST criteria.

For both patient groups, the ORR was determined by a central review committee. The assessment was based on a composite response, which consisted of the clinical response (digital photography, possibly also confirmed by biopsy) and the radiological response (CT or MRI), if both types of response were documented. In the remaining cases, assessment could be based on clinical or radiological response alone. Through the use of radiological methods of measurement, non-patient-relevant operationalizations are thus also included in the ORR for both patients with laBCC and patients with mBCC.

Overall, it can be assumed that, according to the outcome definition, radiological response was taken into account to a large extent in the outcome ORR for both patient groups. According to information in the study report, the composite response was the basis of assessment for all patients with laBCC (N = 84) at the data cut-off of 17 February 2020. For 28 patients with mBCC, for whom results were available at the first data cut-off, this was the case for 50% (N = 14); for 46% (N = 13) of the patients, an assessment was based solely on radiological imaging. Deviating from this, the company states in Module 4 C that the ORR for all patients (N = 112) was based on the criteria of the composite response.

Presentation of the results on "response" was inadequate

In Module 4 C of its dossier, the company only presented analyses of the composite response on ORR. Results of the individual components of the composite outcome, in particular of clinical response, are completely missing. Therefore, the analyses presented by the company are not suitable to present ORR as patient-relevant outcome. This is explained below.

In its decisions on vismodegib, the G-BA explained that the magnitude and the relevance of tumour response cannot be clearly inferred without knowledge of the individual components of the outcome "ORR" and information on the extent of the lesions and the grade of ulceration at the start of the study and during the study [11,14]. In Module 4 C, the company also states that, according to the G-BA, the presentation of results for all individual components was a

prerequisite for the patient relevance of the outcome "ORR". Nevertheless, it does not present corresponding analyses. Analyses on the clinical response depending on the size of the target lesion, as was used in the procedure on vismodegib, are not found in Module 4 C. Moreover, information on changes of ulcerations in the course of the study are lacking.

With regard to the localisation of the lesions, the company provides information in Module 4 C on the percentage distribution of lesions in different skin areas at population level at baseline. However, this information does not allow an individual assessment of the relevance of the response; for instance, also under consideration of the localisation of the tumour and the ulcerations.

Overall, the company's documents provide no or no adequately prepared analyses of the extent of the lesions, the degree of ulceration of individual lesions at baseline and their development during the course of therapy, as well as on the number and localisation of the lesions. However, the company could have conducted corresponding analyses on the basis of the photo documentation of patients at different points in time available in Module 5.

The approach used by the company to present the results is not comprehensible as corresponding analyses had already been requested in the benefit assessments of vismodegib and had been presented in the addendum on the second assessment of vismodegib [15-17].

The required presentation of results on response was also addressed in a more recent procedure in the therapeutic indication of basal cell carcinoma (sonidegib) [18,19]. However, in its dossier on cemiplimab, the company only presented aggregate data on the proportion of patients with ORR.

Transferability of the results on "response" to the present therapeutic indication

Taking into account the procedure on vismodegib, the company states that each response must be considered a patient-relevant improvement, as there is usually no spontaneous remission under BSC. In the company's opinion, this is also transferable to the more advanced clinical picture of laBCC and mBCC. However, the company presented no arguments that support this transferability.

2.4 Results on added benefit

There are no suitable data to assess the added benefit of cemiplimab compared to BSC in adult patients with laBCC or mBCC who have previously been treated with an HhI and who demonstrate disease progression or intolerance to it during this treatment. This resulted in no hint of an added benefit of cemiplimab in comparison with BSC; an added benefit is therefore not proven.

2.5 Probability and extent of added benefit

The result of the assessment of the added benefit of cemiplimab in comparison with the ACT is summarized in Table 5.

Table 5: Cemiplimab – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adult patients with laBCC or mBCC who were previously treated with an HhI and show disease progression or intolerance to it during this treatment[b]	BSC[c]	Added benefit not proven

a. Presentation of the ACT specified by the G-BA.
b. The G-BA assumes that the therapeutic indication only comprised patients for whom neither radiotherapy nor surgery and local therapy were an option.
c. According to the G-BA, best supportive care refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.

ACT: appropriate comparator therapy; BSC: best supportive care; G-BA: Federal Joint Committee; HhI: hedgehog signal pathway inhibitor; laBCC: locally advanced basal cell carcinoma; mBCC: metastatic basal cell carcinoma

The assessment described above deviates from that of the company, which derived a hint of minor added benefit based on the results on ORR of the single-arm study R2810-ONC-1620.

The G-BA decides on the added benefit.

References for English extract

Please see full dossier assessment for full reference list.

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

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