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Cemiplimab (basal cell carcinoma 1) –

Addendum to Commission A21-97[1]

Addendum

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List of abbreviations

Abbreviation	Meaning
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HhI	hedgehog signal pathway inhibitor
ICR	independent central review
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
RECIST	Response Evaluation Criteria in Solid Tumours
SGB	Sozialgesetzbuch (Social Code Book)
WHO	World Health Organization

1 Background

On 7 December 2021, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A21-97 (Cemiplimab – Benefit assessment according to §35a Social Code Book V) [1].

For the benefit assessment of cemiplimab in 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 pharmaceutical company (hereinafter referred to as "the company") submitted the single-arm study R2810-ONC-1620 with cemiplimab in its dossier [2]. The company derived an added benefit of cemiplimab on the basis of the objective response rate (ORR). The analyses on ORR were based on the composite response, which includes the clinical and the radiological response. The company submitted no analyses exclusively on the clinical response.

With its comment, the company presented analyses on the clinical response for patients with laBCC [3].

To be able to decide on the added benefit, the G-BA needs further analyses in this procedure. Therefore, the G-BA commissioned IQWiG with the following assessment of the analyses submitted by the company in the commenting procedure under consideration of the information provided in the dossier:

- Operationalization of the outcome "ORR" (describe)
- Analyses on clinical response
- Analyses on changes of the tumour lesions

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

Operationalization of the outcome "ORR"

In the R2810-ONC-1620 study, ORR was defined as the proportion of patients with complete or partial response. In patients with laBCC, primarily the clinical response was documented according to the World Health Organization (WHO) criteria for the assessment of externally visible tumours by means of digital photography (two-dimensional measurement, sum of the products of the longest horizontal and vertical extensions of the target lesion[s] [4,5]). In this regard, the following assessment criteria are defined for each tumour response:

Complete response

- Externally visible tumour lesions
  - Disappearance of the target lesion(s) and non-target lesion(s) over a minimum period of 4 weeks
  - Confirmation by histological tumour biopsy for target lesion(s)
- Ulcerations (for lesions with intensive ulceration at baseline)
  - Re-epithelialization of the entire ulceration area of the target lesion(s) present at baseline over at least 4 weeks

Partial response

- Externally visible tumour lesions
  - ≥ 50% decrease in tumour size (sum of the products of largest longitudinal and vertical diameter) of the target lesion(s) over a period of at least 4 weeks
- Ulcerations
  - no criteria defined

In addition, deep tumour lesions were assessed with regard to the radiological response of the patients on the basis of Version 1.1 of the Response Evaluation Criteria in Solid Tumours (RECIST) criteria [6]. The clinical and radiological response was assessed by means of an independent central review (ICR).

In R2810-ONC-1620, the ORR is based on pre-specified analyses of the composite response, which includes the clinical and the radiological response. In Module 4 C, the company only presented analyses of the ORR on the basis of the composite response.

Analyses on the clinical response presented by the company with its comments

With its comments, the company subsequently presented 2 different analyses on the clinical response. On the one hand, the company presented analyses on the basis of the above operationalizations prespecified in the R2810-ONC-1620 study. On the other, it presented a

deviating operationalization that was used in the ERIVANCE study assessed in the procedure on vismodegib [7]. This is structured in 3 grades

- Grade 1: complete resolution of lesion(s) (100% reduction in visible dimension of lesion) and resolution of ulceration(s)
- Grade 2: notable, but incomplete reduction in lesion(s) (reduction in visible dimension of lesion by at least 30% and less than 100%) and resolution of ulceration(s)
- Grade 3: notable, but incomplete reduction in lesion(s) and persisting ulceration(s) or no/minor reduction in lesion size (reduction in visible dimension of lesion by less than 30%), but resolution of ulceration(s)

The results of both operationalizations are presented in the following section.

Results on the clinical response in patients with laBCC

At baseline, the lesions of the patients included in the R2810-ONC-1620 study with laBCC differed clearly. For further characterization of the individual clinical response, the patients were allocated to 2 categories regarding the baseline status in addition to the presentation of the total study population:

- Category 1: patients who had at least one target lesion that was larger than 50 mm (measurement of the longest diameter)
- Category 2: patients in whom all target lesions were no larger than 50 mm

The subsequent Table 1 shows the clinical response of patients with laBCC of the R2810-ONC-1620 study overall and for the two categories on the extent of target lesions mentioned above.

Table 1: Patients with laBCC in the R2810-ONC-1620 study – Clinical response of the patients overall and by lesion size at baseline

Study lesion size[a]	Total study population N N_L	Patients without clinical response n (%)[b] N_L	Patients with clinical response n (%)[b] N_L
R2810-ONC-1620, data cut-off of 17 February 2020			
All categories			
Number of patients	81[c]	40 (49)	24 (30)
Number of lesions	109[c]	58	31
Category 1 (> 50 mm)			
Number of patients	31[d]	21 (68)	7 (23)
Number of lesions	47[d]	32	12
Category 2 (≤ 50 mm)			
Number of patients	39[e]	19 (49)	17 (44)
Number of lesions	51[e]	26	19

a. Category 1: patients with at least one target lesion larger than 50 mm (measurement of the longest diameter); category 2: patients in whom all target lesions were no larger than 50 mm.
b. Percentage refers to the total study population and the respective category.
c. Information missing for 3 patients; clinical response not evaluable for 20 lesions in 17 patients.
d. Category not determinable for 11 patients with 1 lesion each. Clinical response not evaluable for 3 lesions in 3 patients.
d. Category not determinable for 11 patients with 1 lesion each. Clinical response not evaluable for 6 lesions in 3 patients.

laBCC: locally advanced basal cell carcinoma; N: number of patients in the analysis; N_L: Number of lesions in the analysis; n: number of patients with event

Clinical response was determined in about one third of the patients (24 of 81). The patients with larger lesions (category 1) responded less frequently (approx. 1 in 4 patients) than those with smaller lesions (category 2, about 1 in 2 patients). Clinical response was not evaluable in 17 of 81 patients.

The individual response for these 24 patients was analysed by the company according to the operationalizations of the clinical response described in the previous section.

Table 2 shows the results on the clinical response and the lesion size at baseline and at the time of response for patients with laBCC from the R2810-ONC-2610 study.

Table 2: Patients with laBCC in the R2810-ONC-1620 study – Characteristics of the clinical response by lesion size

Study lsion size[a]	**Type of clinical response (operationalization in accordance with R2810-ONC-1620)**	**Type of clinical response (operationalization in accordance with ERIVANCE)**	**Course of the lesion size (mean)**
R2810-ONC-1620, data cut-off of 17 February 2020			
Category 1 (N = 7; N_L = 12; minimum lesion size: 54.4 mm[b]; maximum lesion size: 96.97 mm)			
	CR: n = 1	Grade 1: n = 1	Patient level[c]:
	PR: n = 6	Grade 2: n = 5	*Baseline: 96.4 mm*
		Grade 3: n = 1	*Upon response: 58.7 mm*
			Reduction: ≥ 39.1%
			Lesion level:
			Baseline: 56.3 mm
			Upon response: 34.3 mm
			Reduction: ≥ 39.1%
Category 2 (N = 17; N_L = 19; minimum lesion size: 8.56 mm; maximum lesion size: 46.39 mm)			
	CR: n = 8	Grade 1: n = 8	Patient level[c]:
	PR: n = 9	Grade 2: n = 7	*Baseline: 30.5 mm*
		Grade 3: n = 2	*Upon response: 10.7 mm*
			Reduction: ≥ 64.8%
			Lesion level:
			Baseline: 27.3 mm
			Upon response: 9.6 mm
			Reduction: ≥ 64.8%

a. Category 1: patients with at least one target lesion larger than 50 mm (measurement of the longest diameter); category 2: patients in whom all target lesions were no larger than 50 mm.
b. In category 1 provision of minimum lesion size for lesions > 50 mm; individual patients with additional target lesions < 50 mm; the smallest target lesion for patients in category 1 was 22.24 mm.
c. Mean of the sum of the lesion sizes (sum of the target lesions per patient).
CR: complete response; ICR: independent central review; laBCC: locally advanced basal cell carcinoma; N: number of patients in the analysis; N_L: Number of lesions in the analysis; n: number of patients with event

Complete resolution of lesions including ulcerations was seen in 9 patients (11%). The remaining 15 patients with clinical response had partial response (operationalization in accordance with R2810-ONC-1620) or response in accordance with grade 2 or grade 3 (operationalization in accordance with ERIVANCE). In patients with clinical response in category 1 (lesion size > 50 mm), the mean reduction in lesion size was about 39%, in patients with clinical response in category 2 (lesion size ≤ 50 mm) it was about 65%.

Summary

Overall, cemiplimab led to a clinical response in 24 patients (approx. 30%) with laBCC. Patients with larger lesions (at least one lesion larger than 50 mm) had fewer clinical responses

than those with smaller lesions. Complete resolution of lesions including ulcerations was achieved in only few cases (9 patients [11%]), of which one patient had a large lesion and 8 patients had smaller lesions. In case of clinical response, the mean reduction in lesion size was about 39% (category 1, > 50 mm) or 65% (category 2, ≤ 50 mm).

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