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Vismodegib (basal cell carcinoma) –

Addendum to Commission A16-09[1]

Addendum

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List of abbreviations

Abbreviation	Meaning
CR	CR
CSR	clinical study report
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
IRF	Independent Review Facility
laBCC	locally advanced basal cell carcinoma
ORR	objective response rate
PD	progressive disease
PR	partial response
SD	stable disease
SGB	Sozialgesetzbuch (Social Code Book)

1 Background

On 6 July 2016, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct a supplementary assessment for Commission A16-09 (Vismodegib – Benefit assessment according to §35a Social Code Book (SGB) V [1]).

The drug vismodegib was approved in 2013. In its decision on the first benefit assessment of vismodegib from 6 February 2014, the G-BA had stated that the pharmaceutical company (hereinafter referred to as "the company") had provided no flawless documentation on the operationalization of the outcome "objective response rate (ORR)" on the approval study ERIVANCE that would allow a reliable assessment of the response of individual lesions (such as number, size, and location of the lesions), of the patients and the long-time duration of response [2]. According to the decision, these data had to be presented on expiry of the limitation period [2]. However, the company had provided no information that would allow such an assessment in its dossier or in the written comments [1,3,4]. Following the oral hearing, the company sent additional information to prove the added benefit, which went beyond the information in the dossier and its written comments on the dossier assessment [5]. To be able to decide on the added benefit, the G-BA therefore requires further analyses. The G-BA's commission comprised the assessment of the individual components of the composite outcome "ORR" of the ERIVANCE study; the operationalization of the ORR was also to be checked and assessed.

The responsibility for the present assessment and the results of the assessment lies exclusively with IQWiG. The assessment is forwarded to the G-BA. The G-BA decides on the added benefit.

2 Assessment

After the oral hearing on vismodegib, the company subsequently submitted the following information for patients with locally advanced basal cell carcinoma (laBCC) [5]:

- information on the individual assessment of the ORR by the Independent Review Facility (IRF), which comprised the categorization and the time point of response, information on lesion size, information on ulcerations, and additional information on the ORR categorization
- case studies
- image documentations (course from the start of the study until the end of treatment for each target lesion)

The information on the ORR was restricted to the first confirmatory data cut-off from 26 November 2010. The company did not present ORR information on the subsequent data cut-offs.

The information on the ORR was presented both at the patient level (overall assessment across all target lesions per patient) and at the level of the lesion. The information at the level of the lesion was incomplete, however. On the one hand, the company presented this information only for patients with partial response (PR) or complete response (CR). This was of no importance for the assessment of the relevance of the patients rated as responders (PR or CR), but prevented a comprehensive assessment of the response at lesion level for the total study population. On the other, the company presented information on lesion size for individual lesions, but not on ulceration. This complicated not only the assessment of the ORR at lesion level, but also the assessment of the relevance of response at patient level. It remained unclear for patients with more than one target lesion whether one or several target lesions were ulcerated. This concerned 11 of the 22 patients with clinical response (see below for information on clinical response).

In view of the incomplete provision of the data, the assessment below is restricted mostly to the patient level and to the first data cut-off.

Assessment of the operationalization of the ORR: clinical/radiographic response

Besides clinical characteristics (visible tumour expansion, ulcerations, occurrence of new lesions), radiographic information was also used for the assessment of the response. The data subsequently submitted by the company showed that, for 5 of the 27 patients assessed as responders by the IRF, response was determined on the basis of radiographic criteria. This applied to 4 patients with PR and to one patient with CR according to the assessment of the IRF. Hence 22 patients with clinical response remained, 12 with CR and 10 with PR. The corresponding assessments of the investigators were unclear because the company presented no information at patient or lesion level.

Characteristics of individual clinical response

The lesions included in the ERIVANCE study differed notably in size and degree of ulceration. For further characterization of the individual clinical response, the patients were allocated to 2 categories regarding the baseline status:

- 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

An additional categorization based on the degree of ulceration was not possible because the corresponding information at lesion level was lacking. In at least 56 of the 63 patients at least one target lesion was ulcerated (this remained unclear for 5 patients).

The following Table 1 characterizes the patients with laBCC in the ERIVANCE study based on the two categories of target lesion extension mentioned above.

Table 1: Patients with laBCC in the ERIVANCE study – characteristics of the patients according to lesion size

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**
ERIVANCE, data cut-off: 26 November 2010			
All categories			
Number of patients	63[c]	41[e] (65%)	22 (35%)
Number of lesions	116[c]	72	44
Category 1			
Number of patients	24	18[d] (75%)	6 (25%)
Number of lesions	42	32	10
Category 2			
Number of patients	34	18[d] (53%)	16 (47%)
Number of lesions	67	33	34

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: For 5 of the 63 patients with a total of 7 lesions, no sufficient information was available for categorization. This only concerned patients without clinical response because no information on lesion size at lesion level was presented for them.
d: The IRF determined response based on radiographic criteria for 5 of the 41 patients without clinical response. This concerned 3 patients in category 1 and 2 patients in category 2.
IRF: Independent Review Facility; 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

As described above, clinical response was determined in about one third of the patients (22 of 63). The patients with larger lesions (category 1) responded less frequently (1 in 4 patients) than those with smaller lesions (category 2, about 1 in 2 patients).

Based on the criteria used in the ERIVANCE study, individual response for these 22 patients was allocated to 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)

Table 2 contains the information on the allocation of CR or PR by the IRF, on the grades of individual clinical response, and on lesion size at the start of the study and at the time point of response for patients with clinical response.

Table 2: Patients with laBCC in the ERIVANCE study – characteristics of the clinical response according to lesion size

Study Lesion size[a]	Type of clinical response	Rating according to the IRF	Course of the lesion size (mean)
ERIVANCE, data cut-off: 26 November 2010			
Category 1 (N = 6; N_L = 10; minimum[b] lesion size: 52 mm; maximum lesion size: 250 mm)			
	grade 1: n=1 grade 2: n=0 grade 3: n=5	CR: n=4 PR: n=2	Patient level[c]: *start of the study: 137 mm* *at response: 67 mm* *reduction: 51%* Lesion level: *start of the study: 82 mm* *at response: 40 mm* *reduction: 51%*
Category 2 (N = 16; N_L = 34; minimum lesion size: 7 mm; maximum lesion size: 44 mm)			
	grade 1: n=3 grade 2: n=7 grade 3: n=6	CR: n=8 PR: n=8	Patient level[c]: *start of the study: 48 mm* *at response: 23 mm* *reduction: 52%* Lesion level: *start of the study: 23 mm* *at response: 11 mm* *reduction: 52%*

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; additional target lesions were partly smaller than 50 mm; the smallest target lesion for patients in category 1 was 7 mm.
c: Mean of the sum of the lesion sizes (sum of the target lesions per patient).
CR: complete response according to IRF assessment; IRF: Independent Review Facility; 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; PR: partial response according to the IRF assessment

In patients with clinical response, the lesion size was reduced by a mean value of about 50% in both lesion size categories. Complete resolution of lesions including ulcerations (grade 1) was determined in 4 patients (6%), of which one patient had a large lesion and 3 patients had smaller lesions. In half of the cases, the clinical response was based on a notable reduction in lesion size without resolution of the ulceration(s) or on resolution of the ulceration(s) without notable reduction in lesion size (grade 3).

Duration of response

In the ERIVANCE study, the response was operationalized as “best confirmed response”. The maximum of the 4 categories CR, PR, stable disease (SD), and progressive disease (PD) at an individual level was used for this purpose. This means that patients in whom PR was initially determined, were also counted as PR in the ORR analysis if the disease progressed in the further course.

In the data subsequently submitted after the oral hearing, the company provided no information on the ORR that went beyond the first data cut-off. It could be seen in the image documentation used by the IRF for the determination of response that such analyses are possible and should also be available: In the data cut-off presented by the company, the response (best confirmed response) was determined after a median period of time of 24 weeks in patients with clinical response. The image documentation, in contrast, comprised a median period of time of 96 weeks. The analyses on the ORR at fixed dates of analysis (e.g. 1 and 2 years after the start of the treatment) would be meaningful for the analyses on the duration of response. Such analyses were not available, however.

Since, according to the analyses described above, more than 80% of the ORR events (22 of 27) constituted a clinical response, the analyses on the duration of the ORR at the first data cut-off available in the clinical study report (CSR) of the ERIVANCE study could be used as an approximation [6]. The following Figure 1 shows the corresponding Kaplan-Meier curve. Besides the laBCC patients of interest (solid line), it also shows the patients with metastatic disease, which are not relevant for the present assessment.

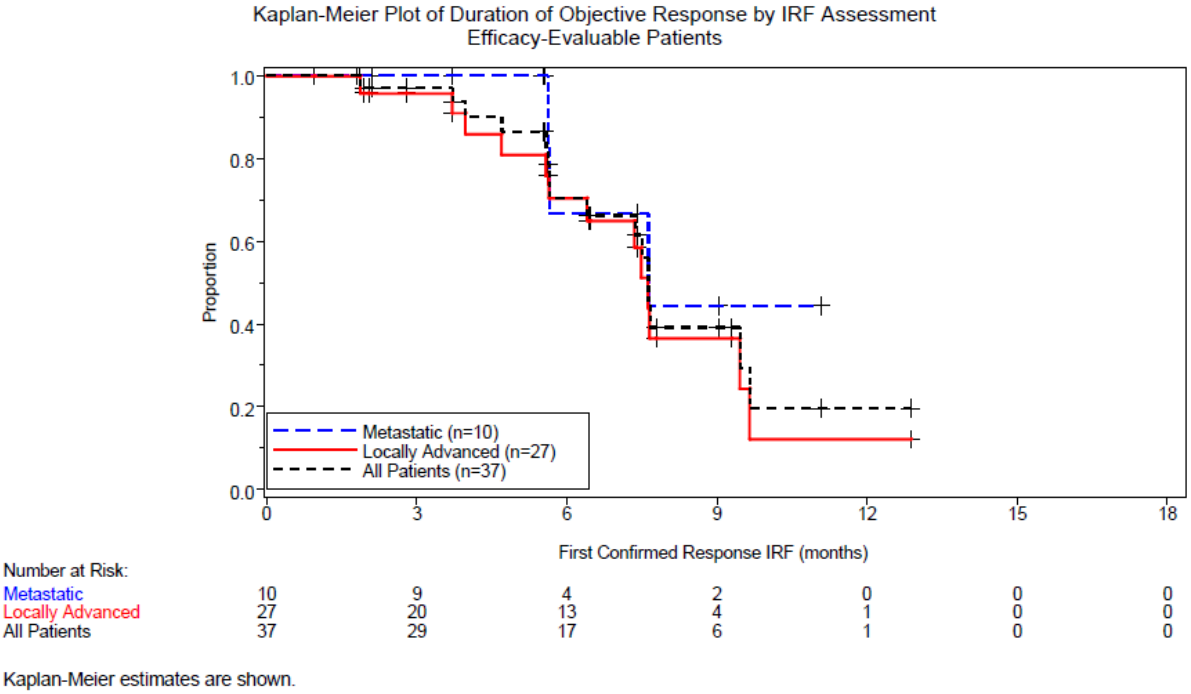

Figure 1: Kaplan-Meier curve on the duration of response in the ERIVANCE study

At the time point of the first data cut-off, the disease had advanced again in 13 of the 27 patients with response, of which 1 patient had died [6]. The median duration until progression of the disease was 7.6 months (95% confidence interval: [5.7; 9.7]) [6].

Summary

It could be inferred from the analyses subsequently submitted by the company that the majority (about 80%) of the cases assessed as responses by the IRF constituted a clinical response, whereas the response was not a clinical response, but a radiographic response in about 20%. Overall, vismodegib led to a clinical response in about 35% of the patients with laBCC.

Patients with larger lesions (at least one lesion larger than 50 mm) had fewer clinical responses (1 in 4 patients) than those with smaller lesions (about 1 in 2 patients). In case of clinical response, the mean reduction in lesion size was about 50%. Complete resolution of lesions including ulcerations was achieved in only few cases (4 patients [6%]), of which one patient had a large lesion and 3 patients had smaller lesions. In half of the cases, the clinical response was based on a notable reduction in lesion size without resolution of the ulceration(s) or on resolution of the ulceration(s) without notable reduction in lesion size. After the response, the disease progressed after a median time period of about 8 months.

The assessment was complicated because the company again provided incomplete data. On the one hand, a large proportion of the data at lesion level was missing, on the other, the company only subsequently submitted detailed data on the first data cut-off, but not on later data cut-offs.

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