IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Vismodegib – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 12 May 2016). 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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[3] Table numbers start with “2” as numbering follows that of the full dossier assessment.

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
BCC	basal cell carcinoma
BSC	best supportive care
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
ORR	objective response rate
RCT	randomized controlled trial
SAE	serious adverse event
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 vismodegib. The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as "the company"). The dossier was sent to IQWiG on 16 February 2016.

The company submitted a first dossier of the drug to be evaluated on 5 August 2013 for the early benefit assessment. In this procedure, by decision of 6 February 2014, the G-BA limited its decision until 15 February 2016.

Research question

The aim of the present report was to assess the added benefit of vismodegib in comparison with best supportive care (BSC) as appropriate comparator therapy (ACT) in patients with locally advanced or symptomatic metastatic basal cell carcinoma (BCC).

The G-BA specified for patients with symptomatic metastatic BCC that surgery or radiotherapy may be part of BSC. This was not the case for patients with locally advanced BCC inappropriate for surgery or radiotherapy. The company initially followed the ACT specified by the G-BA, but restricted this for patients with symptomatic metastatic BCC in such a way that neither surgery nor radiotherapy was indicated for them. It also restricted the options to be understood by the G-BA as BSC in the present therapeutic indication. The approach of the company was not followed. The ACT specified by the G-BA was used for the present benefit assessment. In the present report, the term "BSC" is used in the sense of what the G-BA included in BSC in the present therapeutic indication (e.g. photodynamic therapy).

The research questions presented in Table 2 resulted from the different treatment situations of patients with symptomatic metastatic BCC and patients with locally advanced BCC.

Table 2: Research questions of the benefit assessment of vismodegib

Research question	Subindication	Appropriate comparator therapy[a]
1	Adult patients with symptomatic metastatic BCC	BSC, if applicable including surgery or radiotherapy
2	Adult patients with locally advanced BCC inappropriate for surgery or radiotherapy	BSC

a: Presentation of the respective ACT specified by the G-BA.
ACT: appropriate comparator therapy; BCC: basal cell carcinoma; BSC: best supportive care; G-BA: Federal Joint Committee

The research questions deviated from the company's approach, which did not explicitly formulate 2 research questions, but derived its conclusions on the added benefit separately for the respective populations and presented study results separately for each population.

The assessment was conducted based on patient-relevant outcomes and on the data provided by the company in the dossier.

Results

As already in dossier assessment of vismodegib A13-27, no randomized controlled trials (RCTs) or non-RCTs were available for the assessment of the added benefit of vismodegib, neither for research question 1 nor for research question 2.

Irrespective of this, the study pool of the company on the historical comparison of vismodegib with the ACT was incomplete. A simplified search already identified one relevant study and 2 potentially relevant studies on BSC for the present dossier assessment.

Research question 1: patients with symptomatic metastatic basal cell carcinoma

The company included 4 one-arm intervention studies for the assessment of the added benefit in symptomatic metastatic BCC. Besides these 4 studies, the company also presented an extension study and an analysis of pooled data on adverse events (AEs).

It was already determined in the first assessment of vismodegib that patients with symptomatic metastatic BCC could not be delineated from patients with asymptomatic metastatic BCC in the 4 intervention studies. The company presented no data that differed from its first dossier, and argued in a comparable way to the first dossier. Hence the data on symptomatic metastatic BCC presented by the company remained not usable.

In its dossier, the company presented no suitable data on the comparison of vismodegib with BSC for patients with symptomatic metastatic BCC. Hence there was no hint of an added benefit of vismodegib in comparison with BSC. An added benefit of vismodegib for patients with symptomatic metastatic BCC is therefore not proven.

Research question 2: patients with locally advanced basal cell carcinoma

The company included 4 one-arm studies on vismodegib, which it had already included in its first dossier, in its assessment. Already in the first assessment of vismodegib, these studies were considered principally relevant for the benefit assessment of the research question on patients with locally advanced BCC regarding their populations and the administration of vismodegib. Apart from this, the company presented 3 one-arm observational studies, 1 extension study and an analysis of the pooled AE data.

This approach of the company for the derivation of the added benefit of vismodegib was inadequate for several reasons:

- Firstly, the company stated that it had identified no studies on BSC. As described above, a simplified search already identified one relevant study (Horn 2003) and 2 potentially relevant studies on BSC.
- Secondly, the presentation of the results on the outcome "objective response rate (ORR)" in the dossier was inadequate. The company showed no data on the individual components of the composite outcome "ORR". Information on size, number and location of the locally advanced BCC lesions that would allow an assessment of the patient relevance, particularly of partial response, was also lacking.
- Thirdly, the Horn 2003 study did not support the company's assumption of lacking response under BSC because high rates of complete response were achieved in this study. The rate of complete response in the investigated lesions in the Horn 2003 study 3 months after treatment was 77% (81 of 105 observed lesions), at the level of the patients 75% (62 of 83 patients). After 24 months, with imputation of missing values by "no response" (worst case analysis), 50% of the 108 lesions originally included still showed complete response. The pivotal approval study of vismodegib, ERIVANCE, showed response rates from 21% (13 of 63 patients with complete response) to about 43% (27 of 63 patients with complete or partial response). Hence, even if the analysis of the ORR data had been adequate, there would have been no superiority of vismodegib versus the ACT.
- Fourthly, the company stated that the occurrence of AEs under BSC was unknown. It was reported in the Horn 2003 study, however, that no serious AEs (SAEs) and 5 deaths (5% of the treated patients) had occurred. In the ERIVANCE study, about 40% of the patients had an SAE at the data cut-off on 30 May 2013. According to the company, 16 deaths occurred in the course of the study (23%). The SAE rate could therefore be higher under vismodegib than under BSC.

Overall, the company's data for patients with locally advanced BCC resulted in no hint of an added benefit of vismodegib in comparison with the ACT. An added benefit of vismodegib for patients with locally advanced BCC is therefore not proven.

Extent and probability of added benefit, patient groups with therapeutically important added benefit[4]

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

[4] 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, no added benefit, or less benefit). For further details see [1,2].

Table 3: Vismodegib – extent and probability of added benefit

Subindication	Appropriate comparator therapy[a]	Extent and probability of added benefit
Adult patients with symptomatic metastatic BCC	BSC, if applicable including surgery or radiotherapy	Added benefit not proven
Adult patients with locally advanced BCC inappropriate for surgery or radiotherapy	BSC	Added benefit not proven
a: Presentation of the respective ACT specified by the G-BA. ACT: appropriate comparator therapy; BCC: basal cell carcinoma; BSC: best supportive care; G-BA: Federal Joint Committee		

The G-BA decides on the added benefit.

2.2 Research question

The aim of the present report was to assess the added benefit of vismodegib in comparison with BSC as ACT in patients with locally advanced or symptomatic metastatic BCC.

The G-BA specified for patients with symptomatic metastatic BCC that surgery or radiotherapy may be part of BSC. This was not the case for patients with locally advanced BCC inappropriate for surgery or radiotherapy. The company initially followed the ACT specified by the G-BA, but restricted this for patients with symptomatic metastatic BCC in such a way that neither surgery nor radiotherapy was indicated for them. It also restricted the options to be understood by the G-BA as BSC in the present therapeutic indication. The approach of the company was not followed. The ACT specified by the G-BA was used for the present benefit assessment. In the present report, the term “BSC” is used in the sense of what the G-BA included in BSC in the present therapeutic indication (e.g. surgery, radiotherapy or photodynamic therapy, see [4]).

The research questions presented in Table 4 resulted from the different treatment situations of patients with symptomatic metastatic BCC and patients with locally advanced BCC.

Table 4: Research questions of the benefit assessment of vismodegib

Research question	Subindication	Appropriate comparator therapy[a]
1	Adult patients with symptomatic metastatic BCC	BSC, if applicable including surgery or radiotherapy
2	Adult patients with locally advanced BCC inappropriate for surgery or radiotherapy	BSC
a: Presentation of the respective ACT specified by the G-BA. ACT: appropriate comparator therapy; BCC: basal cell carcinoma; BSC: best supportive care; G-BA: Federal Joint Committee		

The research questions deviated from the company's approach, which did not explicitly formulate 2 research questions, but derived its conclusions on the added benefit separately for the respective populations and presented study results separately for each population.

The assessment was conducted based on patient-relevant outcomes and on the data provided by the company in the dossier.

2.3 Research question 1: patients with symptomatic metastatic basal cell carcinoma

2.3.1 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 list on vismodegib (status: 20 December 2015)
- bibliographical literature search on vismodegib (last search on 23 November 2015)
- search in trial registries for studies on vismodegib (last search on 16 November 2015)
- bibliographical literature search on the ACT (last search on 23 November 2015)
- search in trial registries for studies on the ACT (last search on 19 November 2015)

To check the completeness of the study pool:

- search in trial registries for studies on vismodegib (last search on 2 March 2016)
- bibliographical literature search on vismodegib (last search on 21 March 2016)
- simplified search on whether a relevant amount of data from studies on the ACT was not considered by the company for the historical comparison (last search on 31 March 2016)

The company's search on studies with BSC was unsuitable to ensure the completeness of the search results. In addition, the company inadequately restricted the ACT by excluding surgery, radiotherapy and further options, which, according to the G-BA, were to be included in BSC in the present therapeutic indication, and for the therapeutic indication of approved drugs. A simplified search already identified one relevant study for the study pool of research question 2, which the company had not found in its search for studies with BSC (see Section 2.4.1). Since the company conducted a search for the total therapeutic indication, the completeness of the study pool for research question 1 was also put into question. This had no consequence for the benefit assessment, however, because the company provided no relevant evidence also for research question 1.

As already in dossier assessment of vismodegib A13-27 [3], no RCTs or non-RCTs were available for the assessment of the added benefit of vismodegib. The company included the one-arm intervention studies SHH4476g (ERIVANCE, pivotal approval study) [5], MO25616 (STEVIE) [6], SHH4811g (US-EAP) [7] and the phase 1 study SHH3925g [8] for the

assessment of the added benefit in symptomatic metastatic BCC. Besides these 4 studies, the company also presented an extension study ("for reasons of completeness") and an analysis of pooled data on AEs. Patients with metastatic BCC were investigated in these 2 studies (see Section 2.6.2.3.2 of the full dossier assessment). However, patients with asymptomatic metastatic BCC were not delineated from patients with symptomatic metastatic BCC.

It was already determined in the first assessment of vismodegib that patients with symptomatic metastatic BCC could not be delineated from patients with asymptomatic metastatic BCC in the 4 intervention studies. See dossier assessment A13-27 [3] for a detailed description. The company presented no data that differed from its first dossier, and argued in a comparable way to the first dossier. Hence the data on symptomatic metastatic BCC presented by the company remained not usable.

This approach deviated from that of the company, which used the studies mentioned above for its benefit assessment of vismodegib in patients with symptomatic metastatic BCC.

2.3.2 Results on added benefit

In its dossier, the company presented no suitable data on the comparison of vismodegib with BSC for research question 1 (patients with symptomatic metastatic BCC). Hence there was no hint of an added benefit of vismodegib in comparison with BSC. An added benefit of vismodegib for patients with symptomatic metastatic BCC is therefore not proven.

2.3.3 Extent and probability of added benefit

The company presented no suitable data for the assessment of the added benefit of vismodegib in adult patients with symptomatic metastatic BCC. Hence an added benefit of vismodegib is not proven for these patients.

This deviates from the company's approach, which claimed a hint of considerable added benefit of vismodegib on the basis of the data presented by the company.

2.3.4 List of included studies

Not applicable as no studies were included in the benefit assessment.

2.4 Research question 2: patients with locally advanced basal cell carcinoma

2.4.1 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 list on vismodegib (status: 20 December 2015)
- bibliographical literature search on vismodegib (last search on 23 November 2015)
- search in trial registries for studies on vismodegib (last search on 16 November 2015)

- bibliographical literature search on the ACT (last search on 23 November 2015)
- search in trial registries for studies on the ACT (last search on 19 November 2015)

To check the completeness of the study pool:

- search in trial registries for studies on vismodegib (last search on 2 March 2016)
- bibliographical literature search on vismodegib (last search on 21 March 2016)
- simplified search on whether a relevant amount of data from studies on the ACT was not considered by the company for the historical comparison (last search on 31 March 2016)

The company's search on studies with BSC was unsuitable to ensure the completeness of the search results. In addition, the company inadequately restricted the ACT by excluding methods, which, according to the G-BA, were to be included in BSC in the present therapeutic indication (such as photodynamic therapy), and for the therapeutic indication locally advanced BCC of approved drugs. A simplified search on studies with BSC in the therapeutic indication of vismodegib already identified the study Horn 2003 [9]. This study was relevant because it considered patients with locally advanced BCC treated with photodynamic therapy. Hence the study pool of the company was incomplete.

In addition, the company conducted a search on evidence on spontaneous remissions in advanced BCC and an enquiry among the centres on spontaneous remissions. Both were not relevant for the present benefit assessment (see Section 2.6.2.3.1 of the full dossier assessment).

Evidence provided by the company

As was the case for the first assessment of vismodegib, no RCTs and non-RCTs for the assessment of the added benefit of vismodegib in comparison with the ACT were available for research question 2. The company included 4 one-arm studies on vismodegib, which it had already included in its first dossier, in its assessment [10]. These were the studies ERIVANCE, STEVIE, US-EAP and the phase I study SHH3925g. Already in the first assessment of vismodegib, these studies were considered principally relevant for the benefit assessment of the research question on patients with locally advanced BCC regarding their populations and the administration of vismodegib [3]. See this assessment for a detailed description of these studies.

The company presented updated data from the studies ERIVANCE and STEVIE in its new dossier. For the ERIVANCE study, this was the update of the final confirmatory analysis on 26 November 2010 after 30 months ("30-month update", data cut-off: 30 May 2013). For the STEVIE study, these were the study results on the basis of 500 included patients versus 300 patients in the first dossier (date: 6 November 2013). The presentation of these data was a condition of the G-BA's limitation for the new assessment of the drug [11] (see Section 2.5).

The company presented further evidence besides the 4 intervention studies. These included 3 one-arm observational studies, 1 extension study ("for reasons of completeness") and an analysis of the pooled AE data. The presentation of this pooled analysis was also a condition of the G-BA's limitation. See Section 2.6.2.3.2 of the full dossier assessment for further details on the evidence newly provided by the company.

The company identified no studies on the ACT BSC in patients with locally advanced BCC.

Assessment of the evidence and the arguments presented by the company

This approach of the company for the derivation of the added benefit of vismodegib was not followed for several reasons. Firstly, the company stated that it had identified no studies on BSC. In the present dossier assessment, a simplified search identified one relevant study (Horn 2003) and 2 potentially relevant studies on BSC, however. Hence the company's study pool for the benefit assessment was incomplete. Secondly, the presentation of the results on the outcome "ORR" in the dossier was inadequate. The company showed no data on the individual components of the composite outcome "ORR". Information on size, number and location of the locally advanced BCC lesions that would allow an assessment of the patient relevance, particularly of partial response, was also lacking. Thirdly, the Horn 2003 study did not support the company's assumption of lacking response under BSC because high rates of complete response were achieved in this study. Fourthly, results on SAEs were reported in the Horn 2003 study; the company stated however that the occurrence of AEs under BSC was unknown. The SAE rate could therefore be higher under vismodegib than under BSC.

The company's arguments for the derivation of the added benefit concurred with those of the first dossier on vismodegib. They were based on the same assumptions as the ones already stated by the company in the first dossier: Since there was "no proof" of spontaneous remissions and the ORR under BSC treatment was 0%, a change in the studies presented by the company must be caused by vismodegib. In addition, according to the company, the data on AEs provided "no new findings" in comparison with the first benefit assessment procedure. The company stated the result under BSC treatment for the outcomes "overall survival", "duration of response", "health-related quality of life" and "AEs" as "unknown".

The company conducted a supplementary analysis under the assumption of a "hypothetical BSC arm". Under different assumptions, it calculated how large the response rate under BSC in a comparative study could be in order to have a treatment effect of vismodegib that was still statistically significant. According to these calculations, the response rate under BSC had to be above 25% in locally advanced BCC in order to have no statistically significant advantage of vismodegib in comparison with BSC. According to the company, this was overall very unlikely.

Since the company assumed a lack of response under BSC, it also searched for evidence on spontaneous remissions for the newly presented dossier, but identified none. It therefore assumed that no spontaneous remission existed.

As described above, the company did not identify the one-arm study Horn 2003 with its search for studies with BSC. The study fulfilled the inclusion criteria of the present benefit assessment. The intervention in this study was photodynamic therapy. Adult patients with at least one BCC lesion that was rated as difficult to treat were included in the Horn 2003 study. The authors' definition of difficult to treat concurs with the definition of locally advanced BCC. This study was therefore rated to be a relevant study for the ACT.

As an approximation of whether the company's approach and assumptions on results under BSC were justified, the inclusion criteria related to locally advanced BCC, the operationalizations of the outcome "ORR" and the results on this outcome and on SAEs as well as deaths from the studies ERIVANCE and Horn 2003 are considered below. The company based its benefit assessment mainly on the ERIVANCE study.

Presentation of the studies ERIVANCE and Horn 2003

Table 5 shows the inclusion criteria related to locally advanced BCC and the operationalizations of complete response of the studies ERIVANCE and Horn 2003.

Table 5: Inclusion criteria related to locally advanced BCC and operationalization of complete response in the studies ERIVANCE and Horn 2003

Study ERIVANCE	**Study Horn 2003**
Inclusion criteria related to locally advanced BCC	
▪ At least 1 histologically confirmed lesion ≥ 10 mm rated as inoperable or for which surgery was contraindicated[a] ▪ Reasons for medical contraindication for surgery included: ▫ recurrence after 2 or more operations on the same location and curative resection deemed to be unlikely ▫ presumed substantial morbidity and/or deformity resulting from surgery ▫ other reasons that had to be clarified before inclusion of the patient in the study ▪ Patients were pretreated with radiotherapy if radiotherapy was not contraindicated or inappropriate[b]; disease progression after treatment	▪ At least 1 clinically and histologically documented BCC (superficial or nodular) rated as "difficult to treat" in relation to ▫ possible complications (e.g. scarring from restorative surgery, functional impairment of eyelid or lips, postoperative infections) ▫ poor cosmetic outcome ▫ disfigurement or recurrence after conventional treatment "Difficult to treat" was defined as: ▪ location in the centre of the face (nose, nasolabial, eye area) and on the ear ▪ large extension (diameter: > 20 mm on extremities, > 30 mm on body or neck, or > 15 mm on the face) ▪ recurrence after 2 prior treatments within one year ▪ location in skin area severely damaged by sun radiation, where surgery or radiotherapy was inappropriate due to the risk of frequent recurrences and occurrence of new lesions
Operationalization of complete response	
Assessment every 8 weeks and at the last study visit: Overall response is a composite outcome of: ▫ clinical response[c] and no progression according to RECIST, or ▫ clinically stable disease and complete or partial response according to RECIST Definitions of complete response: ▪ clinically complete response: ▫ complete resolution of all target lesions ▫ reepithelization of the total ulcerated area of the target lesions ▫ no new lesions ▫ histological confirmation of the complete response ▪ radiographic assessment with RECIST: resolution of all target and non-target lesions	Assessment 3 months after the first treatment cycle with PDT: ▪ lesions in complete clinical remission (assessment at the level of the individual lesion) ▪ histological confirmation of response, in case of positive histology repeated treatment and reassessment after 3 months
a: In the opinion of a dermatologic, oral and maxillofacial, or plastic Mohs surgeon. b: E.g. in case of hypersensitivity to radiotherapy due to a genetic condition such as Gorlin syndrome, due to the location or the cumulative radiation dose from previous treatments. c: Clinical response may comprise complete and partial response. BCC: basal cell carcinoma; PDT: photodynamic therapy; RECIST: Response Evaluation Criteria in Solid Tumours	

Overall, the inclusion criteria for locally advanced BCC were comparable in the studies ERIVANCE and Horn 2003. It was clear from the criteria for "difficult-to-treat" lesions in the Horn 2003 study that the lesions included in this study were to be considered as locally advanced BCC. It could be assumed that the lesions to be included were inappropriate for surgical treatment or radiotherapy. Comparing the criteria of both studies it became clear that the size of the lesions to be included in Horn 2003 (at least 15 mm, different depending on skin area) was even above the minimum size required in the ERIVANCE study (10 mm). This was important in so far as the size and location of the BCC lesions are decisive for the assessment of patient relevance of the treatment success (see below, under the heading "Company's presentation of the results on response was inadequate").

In the ERIVANCE study, ORR was operationalized as composite outcome. Complete and partial response as well as stable disease and progression were distinguished here. Information on the extension of the tumour, ulceration or reepithelization, occurrence of new lesions and radiographic response were included in the outcome. Complete response was present in case of complete histologically confirmed resolution of the target lesions if no new lesions occurred. This was largely comparable with the operationalization of the complete response in the Horn 2003 study.

Since both the patients with locally advanced BCC to be included and the operationalization of the outcome "complete response" were comparable in the studies ERIVANCE and Horn 2003, the results of both studies were considered to check the assumptions made by the company. Table 6 shows the results on objective complete and partial tumour response.

Table 6: Results on the outcome "response" in patients with locally advanced BCC in the studies ERIVANCE and Horn 2003

Outcome	**Study ERIVANCE**		**Study Horn 2003**	
	Data cut-off: 26 Nov 2010[a]	**Data cut-off: 29 Nov 2012[b]**	**3 months after treatment**	**24 months after treatment**
	Analysis of patients with histologically confirmed locally advanced BCC finding at the start of the study		***Analysis of locally advanced BCC findings (patients and lesions) with recording of outcomes***	
Complete response	**N = 63**	**N = 63**	**N = 83; N_L = 105**	**N = 65[c]; N_L = 71[d]**
	n (%)	**n (%)**	**n (%)**	**n (%)**
Number of patients	13 (21[e])	14 (22[e])	62 (75)[f]	51[g] (78[e])
Number of lesions	ND	ND	81 (77)[f]	54 (76[e])
			Analysis of locally advanced BCC findings (patients and lesions) with and without recording of outcomes	
			N = 85; N_L = 108	**N = 85; N_L = 108**
			n (%)	**n (%)**
Number of patients			62 (73[e])[f]	51 (60[e])
Number of lesions			81 (75)[f]	54 (50[e])
Partial response				
Number of patients	14 (22[e])	16 (25[e])	No data on events on partial response reported	
Number of lesions	ND	ND		

a: IRF assessment; final confirmatory data cut-off, about 21 months after the start of the study (start of the study: 10 February 2009).
b: IRF assessment; about 45 months after the start of the study ("24-month update"); no IRF-assessed results available for the 30-month data cut-off after the final confirmatory data cut-off ("30-month update", 30 May 2013); hence the values of the "24-month update" are used instead.
c: Institute's calculation: 68 patients with complete response after 12 months, less patients with locally advanced BCC who did not concur with the authors' inclusion criteria (n = 1) or who withdrew their consent for study participation (n = 2).
d: Institute's calculation; 80 lesions with complete response after 12 months less lesions that did not concur with the authors' inclusion criteria (n = 1), lesions of patients who did not present for the follow-up visit after 24 months (n = 6) or who withdrew their consent for study participation (n = 2).
e: Institute's calculation.
f: Histologically confirmed.
g: Institute's calculation: 68 patients with complete response after 12 months, less patients with BCC who did not concur with the authors' inclusion criteria (n = 1), who withdrew their consent for study participation (n = 2), who had recurrence until month 24 (n = 9) or who died (n = 5).

BCC: basal cell carcinoma; IRF: Independent Review Facility; N: number of patients in the analysis; N_L: Number of lesions in the analysis; n: number of patients/lesions with event; ND: no data

Company's presentation of the results on response was inadequate

In the ERIVANCE study, the outcome "ORR" was a composite outcome, which, among other aspects, included ulcerations, but also imaging (see Table 5). It was necessary to present the results on all individual components for the assessment of the patient relevance of the response rates. This allowed the corresponding interpretation of components that may be patient-relevant, such as symptomatic ulcerations. This was already commented on in detail in dossier assessment A13-27 on vismodegib.

The G-BA also noted the importance of the presentation of the individual components in its decision in the first benefit assessment procedure. According to this, a relevant reduction in externally visible tumours and tumour ulcerations up to complete remission is to be considered patient-relevant. For a reliable assessment of the response of individual lesions and the duration of response, the G-BA required a "flawless documentation of the operationalization of the outcome" of the ORR after limitation of the decision. Number, size, location and lesions were to be described in the documentation [11].

The company provided no data that allowed an assessment of the response on the basis of individual components. Its description in the dossier on the operationalization of the outcome "ORR" was more detailed, but did not differ in content from its first dossier. The only information found in its dossier on individual lesions was information on the percentages of the lesions in different skin areas at the population level at the start of the study as well as a subgroup analysis on the characteristic "number of lesions at the start of the study". This information does not allow an individual assessment of the relevance of the response, however. The company stated a response rate of 42.9% for the derivation of the added benefit of vismodegib (data cut-off of the ERIVANCE study: 26 May 2011). It can be assumed that the probability that the improvement is patient-relevant is higher in complete response than in partial response. For patients with partial response, no general conclusion can be drawn on the relevance of the response without information on the size and location of the lesions, however.

Instead of the presentation of the individual components of the outcome "ORR", the company wanted to support its description of the operationalization of the outcome with an analysis aimed to show that patient-relevant tumour response was recorded in the ERIVANCE study. According to the company, the tumour response was based on imaging techniques alone in only one of 38 patients with objective response. For the other 37 patients, the response was therefore reported based on "clinical tumour assessment".

The company's conclusions drawn from the analysis mentioned above were not comprehensible for several reasons. The company did not distinguish between complete and partial response. In addition, the company did not describe what was to be understood by "clinical tumour assessment". The analysis was therefore unsuitable for the assessment of the patient relevance of the response.

Assumption of a response rate of 0% under BSC not justified

The Horn 2003 study showed that noteworthy response rates can be observed under BSC, in this case photodynamic therapy. The rate of complete response in the investigated lesions 3 months after treatment was 77%, at the patient level 75%. After 24 months, with imputation of missing values by "no event" (worst case analysis), 50% of the lesions originally observed still showed complete response. These results showed that lesions can be treated partly up to complete response with photodynamic therapy. The response rates under photodynamic therapy in the Horn 2003 study were notably above the response rates of 0% and 25% assumed for BSC by the company.

Due to the data available from the Horn 2003 study, the question of spontaneous remission of locally advanced BCC can also be neglected.

Besides the Horn 2003 study, the simplified search conducted by the Institute also identified the studies Vinciullo 2005 [12] and Eibenschutz 2008 [13], in which also photodynamic therapy was used. At least part of the patients in these studies probably also had locally advanced BCC. In the Vinciullo 2005 study, patients with difficult-to-treat lesions, particularly in the facial area, were investigated; in the Eibenschutz 2008 study, patients with large lesions with a diameter of 4 cm or bigger. In the Eibenschutz 2008 study, 13 of 19 lesions included were in the centre of the face, on the ear or in severely sun-damaged skin areas. It was not clear from the study publications whether the patients or lesions considered were eligible for surgery or radiotherapy. The relevance of these 2 studies for the benefit assessment could therefore not be conclusively assessed. Subject to the uncertainties described, similar or even higher rates of complete response were described for both studies in comparison with the Horn 2003 study (Vinciullo 2005: 3 months: 90%; 24 months: 78%; Eibenschutz 2008: 6 months: 95%; 36 months: 53%; all data based on lesions, not on patients with lesions).

Even if the company had provided an adequate analysis of the ORR data, there would have been no superiority of vismodegib in comparison with the ACT because the identified data on BSC in patients with locally advanced BCC did not justify the underlying assumption made by the company on response under BSC.

Overall, the information provided by the company on ORR was not usable for the benefit assessment. Consequently, this also applied to the data presented by the company on duration of response because they were based on the same operationalization on response rate as the outcome "ORR" itself.

Harm of vismodegib in comparison with the ACT

The company's assumption that the occurrence of AEs under BSC was unknown and that therefore vismodegib and BSC could not be compared was not justified on the basis of the results from the Horn 2003 study. Table 7 shows the results on SAEs from the studies ERIVANCE and Horn 2003.

Table 7: Results on the outcome "SAEs and death" in patients with locally advanced BCC in the studies ERIVANCE and Horn 2003

Outcome	Study ERIVANCE		Study Horn 2003	
	Data cut-off: 26 Nov 2010[a]	Data cut-off: 30 May 2013[b]	3 months after treatment	24 months after treatment
	N = 71	N = 71	N = 94	N = 94
	n (%)	n (%)	n (%)	n (%)
SAEs				
Number of patients	19 (27)[c]	28 (39)[c]	0 (0)[d]	0 (0)[d]
Deaths				
Number of patients	9 (13)	16 (23)	ND	5 (5)

a: IRF assessment; final confirmatory data cut-off, about 21 months after the start of the study (start of the study: 10 February 2009).
b: 30 months after the data cut-off for the final confirmatory analysis ("30-month update").
c: 6 (26 November 2010) and 7 (30 May 2013) deaths from AEs are documented here; different information in the clinical study report.
d: Unclear whether only treatment-related SAEs are meant because no deaths were reported according to the information in the text; information on deaths from flow charts of the publication.
BCC: basal cell carcinoma; IRF: Independent Review Facility; N: number of all treated patients in the analyses; n: number of patients with event; ND: no data; SAE: serious adverse event

In the ERIVANCE study, about 40% of the patients had an SAE at the data cut-off on 30 May 2013. According to the company, 16 deaths occurred in the course of the study (23%). No SAEs and 5 deaths (5% of the treated patients) were reported in the Horn 2003 study, however [9].

The SAE rates of about 40% under vismodegib might therefore be higher than the rate of 0% under photodynamic therapy reported in the Horn 2003 study.

2.4.2 Results on added benefit

In its dossier, the company presented no suitable data for the assessment of the added benefit of vismodegib for patients with locally advanced BCC. This resulted in no hint of an added benefit of vismodegib in comparison with BSC; an added benefit is therefore not proven.

2.4.3 Extent and probability of added benefit

The company presented no suitable data for the assessment of the added benefit of vismodegib in adult patients with locally advanced BCC inappropriate for surgery or radiotherapy. Hence an added benefit of vismodegib is not proven for these patients.

This deviates from the company's approach, which claimed an indication of considerable added benefit of vismodegib on the basis of the data presented by the company.

2.4.4 List of included studies

Not applicable as no studies were included in the benefit assessment.

2.5 Extent and probability of added benefit – summary

Table 8 presents a summary of the extent and probability of the added benefit of vismodegib.

Table 8: Vismodegib – extent and probability of added benefit

Subindication	Appropriate comparator therapy[a]	Extent and probability of added benefit
Adult patients with symptomatic metastatic BCC	BSC, if applicable including surgery or radiotherapy	Added benefit not proven
Adult patients with locally advanced BCC inappropriate for surgery or radiotherapy	BSC	Added benefit not proven
a: Presentation of the respective ACT specified by the G-BA. ACT: appropriate comparator therapy; BCC: basal cell carcinoma; BSC: best supportive care; G-BA: Federal Joint Committee		

This deviates from the company's approach, which derived a hint of a considerable added benefit for patients with symptomatic metastatic BCC, and an indication of a considerable added benefit for patients with locally advanced BCC.

The G-BA decides on the added benefit.

Conditions of the G-BA for the new referral on the added benefit

The G-BA's justification on the first assessment of vismodegib included the following statement [11]:

1) *"Regarding the evidence to be provided, EMA requires, among other things, an update of the pooled safety population, a final analysis of the study SHH4476g (pivotal study), and an interim analysis of the study MO25616 with 500 patients with possible follow-up for one year. These data are to be submitted to the G-BA for a new referral.*
2) *"The pharmaceutical company provided no flawless documentation on the operationalization of the outcome "objective response rate" 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-term duration of response. These data are also to be submitted to the G-BA for a new referral."*

The company presented data on point 1 in its dossier. The company did not fulfil the condition of a flawless documentation on the operationalization of the outcome "ORR" (point 2). The presentation of results on the individual components of the composite outcome was missing, and there were no data on number, size and location of the lesions.

References for English extract

Please see full dossier assessment for full reference list.

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The full report (German version) is published under https://www.iqwig.de/de/projekte-ergebnisse/projekte/arzneimittelbewertung/a16-09-vismodegib-nutzenbewertung-gemaess-35a-sgb-v.7301.html.