IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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

Extract

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[2] Due to legal data protection regulations, employees have the right not to be named.

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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
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
OS	overall survival
RCT	randomized controlled trial
RECIST	Response Evaluation Criteria in Solid Tumours
SGB	*Sozialgesetzbuch* (Social Code Book)
SPC	Summary of Product Characteristics

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 abbreviated to "the company"). The dossier was sent to IQWiG on 5 August 2013.

Research question

The objective of this report is to assess the added benefit of vismodegib in patients with

- symptomatic metastatic basal cell carcinoma (BCC)
- locally advanced BCC inappropriate for surgery or radiotherapy

The assessment was conducted in comparison with the appropriate comparator therapy (ACT). The G-BA specified the ACT as follows:

Table 2: Patient groups and ACTs for vismodegib

Patient group	ACT
Patients with symptomatic metastatic BCC inappropriate for surgery	Radiotherapy
Patients with symptomatic metastatic BCC inappropriate for radiotherapy	Surgery
Patients with symptomatic metastatic BCC inappropriate for surgery or radiotherapy	Best supportive care[a]
Patients with locally advanced BCC inappropriate for surgery or radiotherapy	Best supportive care[a]
a: 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; BCC: basal cell carcinoma	

The company deviated from the G-BA's specification in so far as it considered best supportive care (BSC) to be the only ACT for all patients with locally advanced BCC or symptomatic metastatic BCC. This was justified with the merely palliative effect of surgery and radiotherapy in the subindication "symptomatic metastatic BCC".

This approach was not accepted. Since BSC is defined as palliative treatment and, moreover, can be individually optimized, there is no reason why different palliative approaches cannot be defined for different patient groups for whom different optimum treatments may be indicated. The company did not present any data for the ACT "radiotherapy" specified by the G-BA for patients with symptomatic metastatic BCC inappropriate for surgery, or for the

ACT "surgery" specified for patients with symptomatic metastatic BCC inappropriate for radiotherapy.

The assessment was based on patient-relevant outcomes.

Results

There were no evaluable data for the present benefit assessment. This deviated from the company's approach, which based its assessment of the added benefit on 4 one-arm studies. Due to the one-arm design of the study, conclusions on added benefit would only be possible if there were dramatic effects regarding patient-relevant outcomes. Apart from the general suitability of the studies on vismodegib, sufficient data on the ACT regarding these outcomes are also necessary, which allow an estimation of the effect size, to derive a dramatic effect. Finally, the effect estimated on the basis of the available data has to be so large that it can be excluded that it is solely caused by systematic bias.

At least for the population of patients with locally advanced BCC, the studies on vismodegib met the inclusion criteria for this benefit assessment regarding the patient population and the intervention. This did not apply to patients with symptomatic metastatic BCC because, on the basis of the available information, patients with symptomatic metastatic disease could not be clearly delimited from patients with asymptomatic metastatic disease. According to the Summary of Product Characteristics (SPC), vismodegib is only approved for patients with symptomatic metastatic BCC.

Apart from studies on vismodegib, sufficient data on the ACT are also necessary. The company therefore aimed at a comparison with a historical control, but only identified individual case studies, which it did not combine to a cohort. Since the effect of BSC interventions regarding patient-relevant outcomes in the study populations investigated was not presented in the dossier, the results from the studies on vismodegib did not allow to draw conclusions on the added benefit due to the one-arm design of the study and the missing data on the ACT.

This deviates from the company’s assessment, which derived an added benefit that was "non-quantifiable", but at least "considerable". This was based on the assumption that spontaneous remissions are not to be expected in the present therapeutic indication, and that therefore every tumour response in the studies, i.e. improvement of the disease, could be attributed to vismodegib. This was not accepted because the assumption that no improvement can occur under BSC is only based on the fact that the company did not identify any contrary data. However, lack of evidence is no sufficient proof of this assumption.

The outcomes "overall survival (OS)", "health-related quality of life" and "adverse events (AEs)" and their operationalizations were assessed as patient-relevant. This assessment deviates from that of the company, which mainly based its conclusions on the added benefit of vismodegib on the outcome "objective response rate (ORR)", which it regarded as patient-relevant in addition to the outcomes mentioned above. In the ERIVANCE study, the ORR for

the subindication "locally advanced BCC" was operationalized as composite outcome with the response being assessed on the basis of the components "external tumour dimensions", "ulceration" and "new lesions" and using imaging techniques according to the Response Evaluation Criteria in Solid Tumours (RECIST).

In the company's opinion, the ORR in the operationalization of the ERIVANCE study is patient-relevant for patients with locally advanced BCC. This could not be accepted. The ORR was operationalized as composite outcome that incorporated several components for which patient relevance was not sufficiently justified. Data on health-related quality of life reported by patients and recording of the burden of symptoms during the treatment duration would have been adequate patient-relevant outcomes here.

In summary, an overall added benefit is not proven for patients with locally advanced BCC.

The company did not present any data for patients with symptomatic metastatic BCC inappropriate for surgery, or for patients with symptomatic metastatic BCC inappropriate for radiotherapy in comparison with the respective ACTs. For the reasons stated above, the data presented by the company could not be interpreted for patients with symptomatic metastatic BCC for whom BSC constituted the ACT. Hence the overall added benefit is not proven for patients with symptomatic metastatic BCC.

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

On the basis of the results presented, the extent and probability of the added benefit of the drug vismodegib compared with the ACT is assessed as follows:

The studies included by the company were unsuitable to derive an added benefit of vismodegib in comparison with the ACT. Hence an added benefit of vismodegib versus the respective ACT is neither proven for patients with locally advanced BCC inappropriate for surgery or radiotherapy nor for patients with symptomatic metastatic BCC. Hence there are no patient groups with therapeutically important added benefit.

This result deviates from the conclusions of the company, which claimed an indication of a non-quantifiable added benefit with an extent of at least "considerable" for patients with locally advanced BCC and for patients with symptomatic metastatic BCC.

The G-BA decides on the added benefit.

[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 1-3 cannot be drawn from the available data), see [1]. 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), see [2].

2.2 Research question

The benefit assessment of vismodegib was conducted in comparison with the ACT according to the approval [3] for the following therapeutic indication: adult patients with

- symptomatic metastatic BCC
- locally advanced BCC inappropriate for surgery or radiotherapy

The G-BA specified an ACT for each of the different patient groups. These are shown in Table 3.

Table 3: Patient groups and ACTs for vismodegib

Patient group	ACT specified by the G-BA
Patients with symptomatic metastatic BCC inappropriate for surgery	Radiotherapy
Patients with symptomatic metastatic BCC inappropriate for radiotherapy	Surgery
Patients with symptomatic metastatic BCC inappropriate for surgery or radiotherapy	Best supportive care[a]
Patients with locally advanced BCC inappropriate for surgery or radiotherapy	Best supportive care[a]
a: According to the G-BA's specification, 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; BCC: basal cell carcinoma; G-BA: Federal Joint Committee	

The company deviated from the G-BA's specification in so far as it regarded BSC to be the only ACT for all patients with locally advanced BCC or symptomatic metastatic BCC. This was justified with the merely palliative effect of surgery and radiotherapy in the subindication "symptomatic metastatic BCC".

This approach was not accepted. Since BSC is defined as palliative treatment and, moreover, can be individually optimized, there is no reason why different palliative approaches cannot be defined for different patient groups for whom different optimum treatments may be indicated.

Hence the assessment was conducted versus the ACT specified by the G-BA.

The assessment was conducted based on patient-relevant outcomes.

Further information about the research question can be found in Module 3, Section 3.1, and Module 4, Section 4.2.1 of the dossier, and in Sections 2.7.1 and 2.7.2.1 of the full dossier assessment.

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 list on vismodegib (studies completed up to 8 July 2013)
- bibliographical literature search on vismodegib (last search on 2 July 2013)
- search in trial registries for studies on vismodegib (last search on 1 July 2013)
- bibliographical literature search on the ACT (last search on 3 July 2013)
- search in trial registries for studies on the ACT (last search on 5 July 2013)

No studies suitable for deriving an added benefit in comparison with the ACT were identified from the steps of information retrieval mentioned. This deviated from the company's approach, which also did not identify any randomized controlled trials (RCTs) or non-RCTs with vismodegib in the therapeutic indication considered, but which based its assessment on 4 one-arm studies. These were the pivotal approval study SHH4476g (ERIVANCE [4,5]), which, for the company, was the basis for the assessment of the outcomes on benefit, and the studies MO25616 (STEVIE [6]), SHH4811g (US-EAP [7]) and SHH3925g (Phase I [8]), which the company considered only for the assessment of harm. Reasons why the studies were unsuitable to answer the research question of the present benefit assessment are given below.

Due to the one-arm design of the study, conclusions on added benefit would only be possible if there were dramatic effects regarding patient-relevant outcomes [1]. To derive a dramatic effect, the studies on vismodegib first have to be generally suitable to provide information on vismodegib with regards to the research question of the benefit assessment. Moreover, sufficient data on the ACT regarding these outcomes are also necessary, which allow an estimation of the effect size. Finally, the effect estimated on the basis of the available data has to be so large that it can be excluded that it is solely caused by systematic bias.

At least for the population of patients with locally advanced BCC, the studies on vismodegib met the inclusion criteria for this benefit assessment regarding the patient population and the intervention. This did not apply to patients with symptomatic metastatic BCC because patients with symptomatic metastatic disease could not be clearly delimited from patients with asymptomatic metastatic disease. According to the SPC, vismodegib is only approved for patients with symptomatic metastatic BCC [3]. Since the inclusion criteria of the studies only required metastatic BCC without consideration of the symptoms, and the company did not provide plausible delimitation of these subpopulations with metastatic BCC, these data on patients with metastatic BCC were not interpretable for the present research question (see Section 2.7.2.3.2 of the full dossier assessment).

Apart from studies on vismodegib, sufficient data on the ACT are also necessary. The company therefore aimed at a comparison with a historical control, but only identified

individual case studies. These cases were not combined to a cohort. Hence there was no control arm without vismodegib for the patient-relevant outcomes "OS", "health-related quality of life" and "AEs" recorded in the studies. However, since the effect of BSC interventions regarding these outcomes in the study populations investigated was unknown, the results from the studies on vismodegib did not allow to draw conclusions on the added benefit due to the one-arm design of the study and the missing data on the ACT. A dramatic effect of vismodegib compared with BSC could also not be derived for these outcomes. The company itself also stated that it did not deem a historical comparison feasible for these outcomes.

This deviates from the company's assessment, which derived an added benefit that was "non-quantifiable", but at least "considerable", particularly on the basis of the results on ORR. This was based on the assumption that spontaneous remissions are not to be expected in the present therapeutic indication, and that therefore every tumour response in the studies, i.e. improvement of the disease, could be attributed to vismodegib. The company therefore assumed a remission rate of 0% for BSC. Hence the remission rate observed in the ERIVANCE study would correspond to the treatment effect of vismodegib. This was not accepted because the assumption that no improvement can occur under BSC is only based on the fact that the company did not identify any corresponding data. However, lack of evidence is no sufficient proof of this assumption. Moreover, the patient relevance of the ORR was not sufficiently justified in the study.

With regards to the outcomes investigated in the studies, the outcome "OS", "health-related quality of life" and "AEs" including their operationalizations were assessed as patient-relevant. This assessment deviates from that of the company, which mainly based its conclusions on the added benefit of vismodegib on the outcome "ORR", which it regarded as patient-relevant in addition to the outcomes mentioned above. For the subindication "locally advanced BCC", the ORR was operationalized as composite outcome in the ERIVANCE study. First, the clinical response was assessed based on the components "external tumour dimensions", "ulceration" and "new lesions". In addition, tumour response was assessed according to RECIST using imaging techniques. The results of the 2 methods were then summarized using an algorithm on overall response. In the other 3 studies (STEVIE, US-EAP and Phase I), tumour response was defined solely using RECIST.

In the company's opinion, the ORR in the operationalization of the ERIVANCE study is patient-relevant for patients with locally advanced BCC (see Module 4, Section 4.2.5.2). This could not be accepted. It is comprehensible that the externally visible tumour and tumour ulceration are burdensome for the patients affected. It is questionable, however, whether this is adequately represented by the mere measurement of the change in dimension of the tumour or the ulceration. Tumour regression should rather manifest itself in a change of quality of life and of symptoms associated with the tumour. Consequently, data on health-related quality of life reported by patients and recording of the burden of symptoms during the treatment duration would be the actual patient-relevant outcomes. Only the degree of ulceration can

possibly be regarded as a directly patient-relevant component. But no separate results on the degree of ulceration were presented. It would be questionable, however, whether the results would have been sufficient to derive a dramatic effect.

In summary, an overall added benefit is not proven for patients with locally advanced BCC.

The company did not present any data for patients with symptomatic metastatic BCC inappropriate for surgery, or for patients with symptomatic metastatic BCC inappropriate for radiotherapy in comparison with the respective ACTs. For the reasons stated above, the data presented by the company could not be interpreted for patients with symptomatic metastatic BCC for whom BSC constituted the ACT. Hence the overall added benefit is not proven for patients with symptomatic metastatic BCC.

Further information on the inclusion criteria for studies in this benefit assessment and the methods of information retrieval can be found in Module 4, Sections 4.2.2 and 4.2.3 of the dossier, and in Sections 2.7.2.1 and 2.7.2.3 of the full dossier assessment.

2.4 Results on added benefit

There were no evaluable data for the research question of the benefit assessment. Hence there is no proof of added benefit of vismodegib versus the ACT specified by the G-BA.

This result deviates from that of the company, which derived an added benefit of vismodegib both for patients with locally advanced BCC and for patients with symptomatic metastatic BCC from the studies included by the company.

Further information on the choice of outcomes and on risk of bias at outcome level can be found in Module 4, Sections 4.2.5.2, 4.3.2.3.2.2 and 4.3.2.3.3 of the dossier.

2.5 Extent and probability of added benefit

The studies included by the company were not relevant for the assessment of the added benefit. Hence an added benefit of vismodegib versus the respective ACT is neither proven for patients with locally advanced BCC inappropriate for surgery or radiotherapy nor for patients with symptomatic metastatic BCC. Hence there are no patient groups with therapeutically important added benefit.

This result deviates from the conclusions of the company, which claimed an indication of a non-quantifiable added benefit with an extent of at least "considerable" for patients with locally advanced BCC and for patients with symptomatic metastatic BCC.

The G-BA decides on the added benefit.

Further information about the extent and probability of the added benefit can be found in Module 4, Section 4.4 of the dossier, and in Section 2.7.2.8 of the full dossier assessment.

2.6 List of included studies

Not applicable as the company did not present any studies in the dossier from which an added benefit versus the ACT specified by the G-BA could be derived.

References for English extract

Please see full dossier assessment for full reference list.

1. Institute for Quality and Efficiency in Health Care. General methods: version 4.0 [online]. 23 September 2011 [accessed: 29 August 2013]. URL: https://www.iqwig.de/download/General_Methods_4-0.pdf.

2. Institute for Quality and Efficiency in Health Care. Ticagrelor: benefit assessment according to § 35a Social Code Book V; extract; commission no. A11-02 [online]. 29 September 2011 [accessed: 5 May 2013]. URL: https://www.iqwig.de/download/A11-02_Extract_of_dossier_assessment_Ticagrelor.pdf.

3. Roche. Erivedge 150 mg Hartkapseln: Fachinformation [online]. July 2013 [accessed: 23 September 2013]. URL: http://www.fachinfo.de.

4. Genentech. A study evaluating the efficacy and safety of vismodegib (GDC-0449, Hedgehog pathway inhibitor) in patients with advanced basal cell carcinoma: full text view [online]. In: Clinicaltrials.gov. 1 March 2013 [accessed: 15 October 2013]. URL: http://www.clinicaltrials.gov/ct2/show/NCT00833417.

5. Sekulic A, Migden MR, Oro AE, Dirix L, Lewis KD, Hainsworth JD et al. Efficacy and safety of vismodegib in advanced basal-cell carcinoma. N Engl J Med 2012; 366(23): 2171-2179.

6. Hoffmann-La Roche. A study of vismodegib in patients with locally advanced or metastatic basal cell carcinoma: full text view [online]. In: Clinicaltrials.gov. 1 July 2013 [accessed: 15 October 2013]. URL: http://www.clinicaltrials.gov/ct2/show/NCT01367665.

7. Genentech. A study of vismodegib (GDC-0449) in patients with locally advanced or metastatic basal cell carcinoma: full text view [online]. In: Clinicaltrials.gov. 7 January 2013 [accessed: 16 October 2013]. URL: http://www.clinicaltrials.gov/ct2/show/NCT01160250.

8. Genentech. GDC-0449 in treating patients with locally advanced or metastatic solid tumors: full text view [online]. In: Clinicaltrials.gov. 4 May 2010 [accessed: 15 October 2013]. URL: http://www.clinicaltrials.gov/ct2/show/NCT00607724.

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