IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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

Extract

[1] Translation of Sections 2.1 to 2.6 of the dossier assessment "Vemurafenib – Nutzenbewertung gemäß § 35a SGB V" (Version 1.0; Status: 11 December 2013). 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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The dossier assessment was prepared under consideration of external medical and scientific expertise. For this assessment, IQWiG used information that it had received in the framework of the first assessment of vemurafenib (Commission A12-08). The responsibility for the contents of the dossier assessment lies solely with IQWiG.

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Table of contents

List of tables[3]

Page

[3] Table numbers start with "2" as numbering follows that of the full dossier assessment.

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
BRAF	serine/threonine-protein kinase B-Raf (rapidly accelerated fibrosarcoma – isoform B)
CTCAE	Common Terminology Criteria for Adverse Events
G-BA	*Gemeinsamer Bundesausschuss* (Federal Joint Committee)
IQWiG	*Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen* (Institute for Quality and Efficiency in Health Care)
MedDRA	Medical Dictionary for Regulatory Activities
RCT	randomized controlled trial
SGB	*Sozialgesetzbuch* (Social Code Book)
SOC	System Organ Class

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 vemurafenib. The pharmaceutical company (hereinafter abbreviated to "the company") submitted a first dossier of vemurafenib for the early benefit assessment on 21 February 2012. In this procedure, the G-BA limited its decision until 6 September 2013. The present assessment was based on a new dossier compiled by the company. This dossier was sent to IQWiG on 5 September 2013.

Research question

The aim of this report is to assess the added benefit of vemurafenib versus dacarbazine as appropriate comparator therapy (ACT) in the treatment of adult patients with BRAF V600 mutation-positive, unresectable or metastatic melanoma.

The assessment was based on patient-relevant outcomes. Direct comparative randomized controlled trials (RCTs) were included in the assessment.

In the assessment of vemurafenib from 13 June 2012 (A12-08), overall, there was an indication of considerable added benefit of vemurafenib versus the ACT dacarbazine.

Based on the assessment from 13 June 2012, the G-BA made a decision that was limited to 1 year. At the expiry of that period, the company submitted a new dossier. Accordingly, the specific research question for the present assessment was to what extent new data and findings were presented in the available dossier, and what influence these have on the assessment of the added benefit of vemurafenib from 13 June 2012.

Results

Besides the approval study BRIM3 already included in the assessment from 13 June 2012, the company included no further RCTs with the drug to be assessed in its assessment. The study pool for the present benefit assessment was therefore unchanged in comparison with the assessment of vemurafenib from 13 June 2012.

The study BRIM3 was an RCT comparing vemurafenib and dacarbazine. On the basis of the results on median overall survival in an initial interim analysis, the study was discontinued prematurely after running for one year (hereinafter described as the first data cut-off; 30 December 2010). Prior to this point, patients with progression could change to a different melanoma treatment, but not from dacarbazine to vemurafenib. After the first data cut-off, patients in the dacarbazine arm also had the opportunity to cross over to the vemurafenib arm. Patients continued to be observed after the first data cut-off for the patient-relevant outcome "overall survival". For the assessment of vemurafenib from 13 June 2012, the company

presented analyses of 2 subsequent observations (second data cut-off on 31 March 2011 and third data cut-off on 3 October 2011).

New data from RCT on the drug to be assessed

In comparison with the dossier on the assessment of vemurafenib from 17 February 2012, the company submitted results on additional data cut-offs of the study BRIM3 as new findings in the dossier from 2 September 2013. For the outcome "overall survival", this concerns the fourth and fifth data cut-off (on 1 February 2012 and on 20 December 2012 respectively), and for the outcome "adverse events", exclusively the fourth data cut-off. Moreover, the company presented subgroup analyses based on subsequent sequencing of the BRAF status of patients from the study BRIM3.

Overall survival and adverse events

Due to the patient flows during the study and the resulting more pronounced mixing of treatments in the 2 treatment arms, the risk of bias increased with each data cut-off. Hence the analyses on the first data cut-off represented the analyses with the least bias. The additional analyses presented on the outcome "overall survival" (fourth and fifth data cut-off) and on adverse events (fourth data cut-off) were therefore not considered further in the present benefit assessment.

Subgroup analyses on the characteristic "BRAF V600 mutation status"

For the assessment from 13 June 2012, the subgroup analyses for the factor "BRAF V600 mutation status" were not considered because a total of only about one third of the study population was tested for the exact BRAF V600 mutation type. Moreover, the somatic mutation was successfully determined in only about half of the patients classified as "non-BRAF V600E".

According to the study documents, the BRAF mutation status remained unclear in 14 patients despite subsequent sequencing because no valid sequencing results were available. In its subgroup analyses, the company categorized these patients as a whole into the group of patients with non-BRAF V600E. This approach of the company was not accepted. If all of these patients would have been BRAF V600E-positive, the proportion of patients wrongly assumed to be non-BRAF V600E would have been over 20% in the dacarbazine arm. Because this could not be excluded, the results of the subgroup analyses on BRAF V600 mutation status were not included in the present benefit assessment.

Historical comparison of vemurafenib and dacarbazine

In addition to the new findings from the study BRIM3, the company described in the dossier a historical comparison of survival rates under dacarbazine from published studies with survival rates under dacarbazine in the study BRIM3. It then related the results of this comparison to the survival rates under vemurafenib in the study BRIM3. Ultimately, this comparison could not add any new findings to the question of the added benefit of vemurafenib versus

dacarbazine because no new data were presented on vemurafenib that went beyond the results of the study BRIM3. Instead, the result can be interpreted to mean that the patients in the BRIM3 study evidently had a better prognosis than the patients in the older studies. This situation, in principle, makes a historical comparison futile and therefore unsuitable to prove the added benefit.

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

In comparison with the dossier on the assessment of vemurafenib from 17 February 2012, the company submitted no new evaluable data in the dossier from 2 September 2013. Hence the data submitted have no influence on the assessment of the added benefit from 13 June 2012.

Therefore, an indication of a considerable added benefit of vemurafenib versus the ACT (dacarbazine) remains for adult patients with BRAF V600 mutation-positive, unresectable or metastatic melanoma.

The approach for deriving an overall conclusion on added benefit is a proposal by IQWiG. 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 aim of this report is to assess the added benefit of vemurafenib versus dacarbazine as ACT in the treatment of adult patients with BRAF V600 mutation-positive, unresectable or metastatic melanoma.

The assessment was based on patient-relevant outcomes. Direct comparative RCTs were included in the assessment.

In the assessment of vemurafenib from 13 June 2012 (A12-08 [3]), overall, the balancing of positive and negative results resulted in an indication of considerable added benefit of vemurafenib versus the ACT dacarbazine.

Based on the assessment from 13 June 2012, the G-BA made a decision that was limited to 1 year. At the expiry of that period, the company submitted a new dossier. Accordingly, the specific research question for the present assessment was to what extent new data and findings were presented in the new dossier, and what influence these have on the assessment of the added benefit of vemurafenib from 13 June 2012.

Further information on the research question can be found in Module 3, Section 3.1 and in Module 4, Section 4.2.1 of 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 list on vemurafenib (studies completed up to 17 June 2013)
- bibliographical literature search on vemurafenib (last search on 11 June 2013)
- search in trial registries for studies on vemurafenib (last search on 11 June 2013)
- bibliographical literature search on the ACT (last search on 14 February 2013)

The Institute's own search to check the completeness of the study pool:

- search in trial registries for studies on vemurafenib (last search on 27 September 2013)

This check produced no deviations from the study pool presented in the present dossier and in the dossier for the assessment from 13 June 2012.

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 Section 2.7.1 of the full dossier assessment.

2.3.1 Studies included

Besides the approval study BRIM3 already included in the assessment from 13 June 2012, the company included no further RCTs with the drug to be assessed in its assessment. The study pool for the present benefit assessment was therefore unchanged in comparison with the assessment of vemurafenib from 13 June 2012 (Table 2).

Table 2: Study pool – RCT with the drug to be assessed, direct comparison of vemurafenib and dacarbazine

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
BRIM3 (NO25026)	Yes	Yes	No

a: Study for which the company was sponsor, or in which the company was otherwise financially involved.
RCT: randomized controlled trial

In the assessment of vemurafenib from 13 June 2012, the added benefit of vemurafenib was derived on the basis of the documents that were available at the time. For the present benefit assessment, it was investigated whether new relevant data on the study were available and, if so, what influence the analysis of these data has on the existing assessment of the added benefit of vemurafenib.

Study BRIM3 was an RCT comparing vemurafenib and dacarbazine. On the basis of the results on median overall survival in an initial interim analysis, the study was discontinued prematurely after running for one year (hereinafter described as the first data cut-off; 30 December 2010). Prior to this point, patients with progression could change to a different melanoma treatment, but not from dacarbazine to vemurafenib. After the first data cut-off, patients in the dacarbazine arm also had the opportunity to cross over to the vemurafenib arm. Patients continued to be observed after the first data cut-off for the patient-relevant outcome "overall survival". For the assessment of vemurafenib from 13 June 2012, the company presented analyses of 2 subsequent observations (second data cut-off on 31 March 2011 and third data cut-off on 3 October 2011).

Section 2.6 contains a reference list for the study included.

Further information about the result of information retrieval and the resulting study pool can be found in Module 4, Sections 4.3.1.1 and 4.3.2.1.1 of the dossier.

2.4 Results on added benefit

In comparison with the dossier on the assessment of vemurafenib from 17 February 2012, the company submitted results on the fourth and fifth data cut-off of the study BRIM3 (on 1 February 2012 and 20 December 2012 respectively) and subgroup analyses on the basis of

subsequent sequencing of the BRAF status of the patients from the study BRIM3 as new findings in the dossier from 2 September 2013.

In addition, the company described in the dossier a historical comparison of survival rates under dacarbazine from published studies with survival rates under dacarbazine in the study BRIM3. It then related the results of this comparison to the survival rates under vemurafenib in the study BRIM3.

2.4.1 New data from RCT on the drug to be assessed

In detail, the company presented the following additional results for the study BRIM3 in the dossier from 2 September 2013:

- Analyses on 2 additional subsequent observations for the patient-relevant outcome "overall survival": fourth data cut-off on 1 February 2012 and fifth data cut-off on 20 December 2012. Analyses with and without censoring of crossover patients were available for both data cut-offs.
- Analyses on the fourth data cut-off for the patient-relevant outcome "adverse events": Overall rate of adverse events, overall rate of adverse events with Common Terminology Criteria for Adverse Events (CTCAE) Grade ≥ 3, overall rate of serious adverse events, adverse events leading to treatment discontinuation, patient-relevant adverse events according to the Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC); besides the presentation of the results for both treatment arms, data on patients of the dacarbazine arm who changed to vemurafenib treatment after the first data cut-off (crossover) were also available.
- Subgroup analyses on the characteristic "BRAF V600 mutation status" were available for all 5 data cut-offs; starting from the second data cut-off, analyses with and without censoring of crossover patients were available; in comparison with the assessment from 13 June 2012, the subgroups included additional patients due to newly available sequencing results.

Additional results on the outcome "overall survival" (fourth and fifth data cut-off)

As explained in the assessment from 13 June 2012, the hazard ratio on the first data cut-off shows the least biased effect of vemurafenib. The reason is that the possible bias of the results caused by patients switching from the allocated study medication to a different treatment of melanoma – due to disease progression – was lowest at this point in time. Particularly, no patient crossover from the dacarbazine arm was yet included in the vemurafenib arm at the first data cut-off.

Each subsequent data cut-off increased the risk of bias because of the more pronounced mixing of treatments in the 2 treatment arms. This is due to the increasing number of patients who switched to another treatment of melanoma (particularly in the dacarbazine arm). In addition, the option of a crossover for patients from the dacarbazine arm to the vemurafenib

arm led to a comparably higher number of patients who switched treatment in the dacarbazine arm and to a particularly relevant bias of the comparison between dacarbazine and vemurafenib.

The results of the first 3 data cut-offs were used for the assessment from 13 June 2012. Since no new findings on the added benefit of vemurafenib compared with dacarbazine could be derived from the results of the fourth and fifth data cut-off with a comparably higher risk of bias, these 2 data cut-offs on overall survival that were additionally presented were not considered any further in the present benefit assessment.

Additional results on the outcome "adverse events" (fourth data cut-off)

For the assessment from 13 June 2012, analyses on the overall rates of adverse events and severe, serious and frequent adverse events were available on the outcome "adverse events". These analyses referred to the first data cut-off.

In the present dossier, the company presented the overall rates mentioned in addition to the fourth data cut-off. As already explained for the outcome "overall survival", the risk of bias increased with each additional data cut-off due to the patient flows during the study and the resulting more pronounced mixing of the treatments in the 2 treatment arms. Hence the analyses on the first data cut-off represented the analyses with the least bias. The analyses on the outcome "adverse events" additionally presented were therefore not considered any further in the present benefit assessment.

Subgroup analyses on the characteristic "BRAF V600 mutation status"

For the assessment from 13 June 2012, the subgroup analyses for the factor "BRAF V600 mutation status" were not considered because a total of only about one third of the study population was tested for the exact BRAF V600 mutation type. Moreover, the somatic mutation was successfully sequenced in only about half of the patients classified as "non-BRAF V600E" [4].

Due to subsequent sequencing, sequencing results were available for 673 of the 675 (99.7%) randomized study participants for the present benefit assessment (no DNA material was available for 2 patients). However, it can be seen from the addendum of the clinical study report [4] that in 14 patients, the sequencing provided no valid results (status: "indeterminate" or "no sequence"). Hence the mutation status (BRAF V600E or non-BRAF V600E) was unclear for these patients. In its subgroup analyses, the company categorized the 14 patients as a whole into the group of patients with non-BRAF V600E. This approach was inadequate.

According to the study documents, the group of non-BRAF V600E patients included 7 patients with unclear mutation status in the vemurafenib arm (41 patients) and 7 patients with unclear mutation status in the dacarbazine arm (34 patients). It could not be excluded that all of these patients were BRAF V600E positive. In this case, the proportion of patients wrongly assumed by the company to have non-BRAF V600E would have been 20.6% (7 out of 34

patients) in the dacarbazine arm. It can therefore not be estimated to what extent the results of the subgroup analysis presented by the company adequately represent the influence of the mutation status on the effect of vemurafenib.

Hence the results of the subgroup analyses on the BRAF V600 mutation status were not considered further in the present benefit assessment.

2.4.2 Historical comparison of vemurafenib and dacarbazine

In addition to the new data from the study BRIM3, the company presented 2 historical comparisons:

- a historical comparison that relates the effects of dacarbazine on overall survival in the study NO25026 (BRIM3) to the effects of dacarbazine in published studies
- a historical comparison based on the first historical comparison that contrasts the effect of vemurafenib on overall survival in the study NO25026 (BRIM3) with the pooled published effects of dacarbazine

Using these historical comparisons, the company wanted to investigate whether the study BRIM3 showed the actual effects of dacarbazine. The company assessed the results for survival time observed in the study BRIM3 as surprisingly positive. Based on this, the effect of vemurafenib in the study BRIM3 was to be compared with the pooled historical results on survival under dacarbazine.

Ultimately, this comparison could not add any new findings to the question of the added benefit of vemurafenib versus dacarbazine because no new data were presented that went beyond the results of the study BRIM3. Instead, the result can be interpreted to mean that the patients in the BRIM3 study evidently had a better prognosis than the patients in the older studies. This situation, in principle, makes a historical comparison futile and therefore unsuitable to prove the added benefit (for detailed reasoning, see Section 2.7.2 of the full dossier assessment).

2.5 Extent and probability of added benefit

As described in Section 2.4, the dossier presented by the company contained no evaluable new data. Hence the data submitted have no influence on the assessment of the added benefit from 13 June 2012 [3].

Overall, there is still an indication of a considerable added benefit of vemurafenib versus the ACT dacarbazine for adult patients with BRAF V600 mutation-positive, unresectable or metastatic melanoma.

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

2.6 List of included studies

BRIM3

Chapman PB, Hauschild A, Robert C, Haanen JB, Ascierto P, Larkin J et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. N Engl J Med 2011; 364(26): 2507-2516.

European Medicines Agency. Zelboraf (previously Brafyte): vemurafenib; rapporteurs' day 150 joint response assessment report; overview [unpublished]. 2011.

European Medicines Agency. Zelboraf (vemurafenib): rapporteurs' day 150 joint response assessment report; clinical-assessment of the responses to the CHMP list of questions [unpublished]. 2011.

European Medicines Agency. Zelboraf (previously Brafyte): vemurafenib; rapporteurs' day 170 joint response assessment report; clinical-assessment of the responses to the CHMP list of questions [unpublished]. 2011.

European Medicines Agency. Zelboraf (previously Brafyte): vemurafenib; rapporteur and co-rapporteur updated day 170 joint response assessment report; overview [unpublished]. 2011.

European Medicines Agency. Zelboraf: European public assessment report [online]. 15 December 2011 [accessed: 12 November 2013]. URL: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002409/WC500124400.pdf.

Hoffmann-La Roche. A study of vemurafenib (RO5185426) in comparison with dacarbazine in previously untreated patients with metastatic melanoma (BRIM3): full text view [online]. In: Clinicaltrials.gov. 18 December 2012 [accessed: 12 November 2013]. URL: http://clinicaltrials.gov/ct2/show/NCT01006980.

Hoffmann-La Roche. BRIM 3: a randomized, open-label, controlled, multicenter, phase III study in previously untreated patients with unresectable stage IIIC or stage IV melanoma with V600E BRAF mutation receiving RO5185426 or dacarbazine; research report no. 1039652; study NO25026; clinical study report [unpublished]. 2011.

Hoffmann-La Roche. BRIM 3: a randomized, open-label, controlled, multicenter, phase III study in previously untreated patients with unresectable stage IIIC or stage IV melanoma with V600E BRAF mutation receiving RO5185426 or dacarbazine; research report number 1050908; study NO25026; clinical study report addendum no. 2 [unpublished]. 2012.

Hoffmann-La Roche. BRIM 3: a randomized, open-label, controlled, multicenter, phase III study in previously untreated patients with unresectable stage IIIC or stage IV melanoma with V600E BRAF mutation receiving RO5185426 or dacarbazine; research report number 1050643; study NO25026; clinical study report addendum no. 1050643 [unpublished]. 2012.

Hoffmann-La Roche. BRIM 3: a randomized, open-label, controlled, multicenter, phase III study in previously untreated patients with unresectable stage IIIC or stage IV melanoma with V600E BRAF mutation receiving RO5185426 or DTIC; study NO25026; clinical study report addendum number 1052726 [unpublished]. 2012.

Hoffmann-La Roche. BRIM 3: a randomized, open-label, controlled, multicenter, phase III study in previously untreated patients with unresectable stage IIIC or stage IV melanoma with V600E BRAF mutation receiving RO5185426 or dacarbazine; overall survival update; research report number 1055972; study NO25026; clinical study report update [unpublished]. 2013.

Roche Pharma. NO25026 (BRIM3): Subgruppenanalysen [unpublished]. 2013.

Roche Pharma. NO25026 (BRIM3): unerwünschte Ereignisse; Zusatzanalysen [unpublished]. 2013.

Su F, Viros A, Milagre C, Trunzer K, Bollag G, Spleiss O et al. RAS mutations in cutaneous squamous-cell carcinomas in patients treated with BRAF inhibitors. N Engl J Med 2012; 366(3): 207-215.

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: 5 May 2012]. 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 2012]. URL: https://www.iqwig.de/download/A11-02_Extract_of_dossier_assessment_Ticagrelor.pdf.

3. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Vemurafenib: Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung; Auftrag A12-08 [online]. 13 June 2012 [accessed: 12 November 2013]. (IQWiG-Berichte; Volume 133). URL: https://www.iqwig.de/download/A12-08_Vemurafenib_Nutzenbewertung_35a_SGB_V.pdf.

4. Hoffmann-La Roche. BRIM 3: a randomized, open-label, controlled, multicenter, phase III study in previously untreated patients with unresectable stage IIIC or stage IV melanoma with V600E BRAF mutation receiving RO5185426 or dacarbazine; research report number 1050908; study NO25026; clinical study report addendum no. 2 [unpublished]. 2012.

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