

IQWiG Reports - Commission No. A12-08

Vemurafenib –

Benefit assessment according to § 35a Social Code Book V¹

Extract

¹ Translation of Sections 2.1 to 2.6 of the dossier assessment (“Vemurafenib – Nutzenbewertung gemäß § 35a SGB V” (Version 1.0; Status: 13.06.2012). In the present extract, references to Sections 2.7 onwards relate to the full version of the assessment report (hereinafter called the “full dossier assessment”). 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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Institute for Quality and Efficiency in Health Care
Im Mediapark 8 (KölnTurm)
50670 Cologne
Germany

Tel.: +49 (0)221 – 35685-0

Fax: +49 (0)221 – 35685-1

E-Mail: berichte@iqwig.de

Internet: www.iqwig.de

Medical and scientific advice:

- Thomas Tüting, Department of Dermatology, Bonn University Hospital, Germany

IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, he was not involved in the actual preparation of the dossier assessment. Individual sections and conclusions in the dossier assessment therefore do not necessarily reflect his opinion.

IQWiG employees involved in the dossier assessment:²

- Anette Minarzyk
- Anne Catharina Brockhaus
- Miriam Höffken
- Michaela Florina Kerekes
- Regine Potthast
- Frank Sandmann
- Sibylle Sturtz
- Siw Waffenschmidt
- Beate Wieseler

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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 in this extract start with “2”, as numbers follow the numbering in the full dossier assessment.

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
AJCC	American Joint Committee on Cancer
BRAF	serine/threonine-protein kinase B-Raf (rapidly accelerated fibrosarcoma – isoform B)
CTCAE	Common Terminology Criteria for Adverse Events
ECOG	Eastern Cooperative Oncology Group
FACT-M	Functional Assessment of Cancer Therapy-Melanoma
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
LDH	lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
VAS	visual analogue scale

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 assessment was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as “the company”). The dossier was sent to IQWiG on 21.02.2012.

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 carried out with respect to patient-relevant outcomes. Only randomized controlled trials (RCTs) with a direct comparator were included in the assessment.

Results

One relevant study was considered in the benefit assessment (BRIM3). This was an open-label RCT with an active control. Vemurafenib was administered in the form of film-coated tablets (dosage 960 mg twice daily); dacarbazine was administered intravenously (dosage 1000 mg/m² body surface area) in 3-week cycles.

The risk of bias at study level was rated as low, but as high for all outcomes except adverse events.

Mortality

Over the entire observation period, treatment with vemurafenib produced a statistically significant prolongation in overall survival in comparison with treatment with dacarbazine. There is thus an indication of an added benefit of vemurafenib versus dacarbazine for overall survival.

Morbidity

“Pain” was the only outcome recorded in the study in relation to morbidity. There was no statistically significant difference in pain scores under treatment with vemurafenib or dacarbazine. Hence an added benefit of vemurafenib for the outcome “pain” is not proven.

Health-related quality of life

A statistically significant difference between the treatment groups was found for only 2 of the 5 subscales in the Functional Assessment of Cancer Therapy – Melanoma (FACT-M) questionnaire used by the company, namely for “physical well-being” – where the difference was in favour of vemurafenib – and for “emotional well-being” – where it was to its

disadvantage. The assessment of the relevance of the effects (based on standardized mean differences) showed that an irrelevant effect could not be definitively excluded in either case. Due to the lack of validity of the overall score, the results of this score could not be used. An added benefit or lesser harm from vemurafenib in comparison with dacarbazine for the outcome “health-related quality of life” is therefore not proven.

Adverse events

The overall rate of adverse events in patients in the vemurafenib arm was higher than in those in the dacarbazine arm. The difference was statistically significant. Despite this difference, because of the marginal effect size, greater harm from vemurafenib than from dacarbazine is not proven.

The overall rates of severe adverse events (Common Terminology Criteria for Adverse Events (CTCAE) Grade ≥ 3) and of serious adverse events (SAE) were higher in patients in the vemurafenib arm than in those in the dacarbazine arm. The difference was statistically significant in each case. For these outcomes there is therefore an indication of greater harm from vemurafenib than from dacarbazine.

There was no statistically significant difference between the vemurafenib and dacarbazine groups in the proportion of patients with adverse events that led to treatment discontinuation. Greater or lesser harm from vemurafenib than from dacarbazine is thus not proven for this outcome.

In summary, there is an indication of greater harm from vemurafenib than from dacarbazine for the outcome “adverse events”.

Extent and probability of added benefit, patient groups with therapeutically important added benefit⁴

On the basis of the results presented, the extent and probability of the added benefit of the drug vemurafenib versus the ACT is assessed as follows:

In the overall assessment, positive and negative results of equal certainty (indications) remain. On the positive side, the extent “major” is reached for overall survival. On the negative side, the extent “major” is also reached for the overall rates of severe and serious adverse events.

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 data not interpretable)., (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].

Due to the substantial risk of harm from severe and serious adverse events, the Institute decided to downgrade the added benefit of vemurafenib versus the ACT from “major” to “considerable”. This does not affect the certainty of results.

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

The approach for deriving an overall conclusion concerning the added benefit is a proposal from IQWiG. The decision regarding added benefit is made by the G-BA.

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 carried out with respect to patient-relevant outcomes. Only RCTs with a direct comparator were included in the assessment.

The company used the ACT specified by the G-BA. The research question of this report corresponds to that of the company.

The company deviated from the Institute’s approach by adding a subordinate research question in its dossier. This arose during the company’s assessment of the study included in the benefit assessment and aimed to reduce the uncertainty of this study with regard to the outcome “overall survival”. To answer this subordinate question, the company did not restrict the type of study. The Institute does not concur with this approach.

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 data:

- Studies of vemurafenib completed by the company up to 15.12.2011 (study list of the company).
- Results of a search for studies of vemurafenib in trial registries (last search 15.12.2011, searches by the company).
- The Institute’s own searches for studies of vemurafenib in trial registries to check the search results of the company up to 15.03.2012. The check produced no deviations from the study pool presented in the company’s dossier.

The resulting study pool corresponded to that used by the company.

Further information about 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.

2.3.1 Included studies

The approval study BRIM3 listed in Table 2 was included in the benefit assessment.

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			

The study pool for the benefit assessment of vemurafenib corresponded to that of the company.

Study BRIM3 is 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; 30.12.2010). 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”. The analyses of this follow-up observation are referred to in this benefit assessment as the second data cut-off (31.03.2011) and third data cut-off (03.10.2011).

For this assessment, the Institute used the results of the 3 data cut-offs for the outcome “overall survival”. The possible bias in results through the switch of patients from the allocated study medication to another melanoma treatment is lowest for the first data cut-off. The hazard ratio of this point in time therefore shows the least biased effect of vemurafenib. However, because of the short observation time and the associated high censoring rates, the data have a limited certainty of results in respect of more sustainable treatment effects. For example, only 119 patients were still under observation at the first data cut-off at Month 6. In order to obtain more reliable conclusions, the second and third data cut-offs were therefore also considered. However, due to disease progression, the proportions of patients at these points in time who had switched to different melanoma treatments had risen further in comparison with the first data cut-off and were comparatively higher in the dacarbazine arm. In addition, more treatment switches occurred due to the cross-over possibility for patients in the dacarbazine arm into the vemurafenib arm. Overall, this led to a higher number of

treatment switches in the dacarbazine arm than in the vemurafenib arm during the course of the 3 data cut-offs. Nevertheless, the influence of treatment switching is estimated to be conservative, as this tends to lead to an underestimation of the effect of vemurafenib. The company presented results for the second and third data cut-offs with and without censoring of patients who switched into the vemurafenib arm. The Institute included both the censored and the uncensored results in its assessment.

This largely corresponded to the company's approach. The company rated the results of the first data cut-off as a valid estimator of the treatment effect of vemurafenib. The results of the second and third data cut-offs on median overall survival (with and without censoring) were described by the company as a cautious approximation to the actual values (see Section 2.7.2.1 of the full dossier assessment). However, in its comments on the description of the extent of the added benefit, the company referred solely to the first and third data cut-offs.

In its dossier, the company also presented data from the single-arm Phase II study BRIM2 (NP22657). This was used by the company to investigate whether the results of this study could minimize the uncertainty of the estimation of median survival for vemurafenib from the BRIM3 study. This study will not be further considered here because, due to the lack of a control arm, it is not suitable for assessing the added benefit of vemurafenib versus the ACT (dacarbazine).

Section 2.6 contains a list of data sources cited by the company for the included study and other data sources used by the Institute.

Further information about the results of information retrieval and the study pool derived from it can be found in Module 4, Sections 4.3.1.1 and 4.3.2.1.1 of the dossier and in Sections 2.7.2.3.1 and 2.7.2.3.1 of the full dossier assessment.

2.3.2 Study characteristics

Characteristics of the study and the interventions

Table 3 and Table 4 describe the studies used for the benefit assessment.

Study BRIM3 is an open-label, multicentre Phase III RCT with an active control and 2 treatment arms. Adult patients with histologically confirmed, metastatic melanoma (unresectable Stage IIIc or Stage IV) and proven BRAF V600 mutation were enrolled. According to the inclusion criteria of the study, patients were not to have been previously treated with systemic anti-cancer drugs for the treatment of advanced melanoma.

Patients were randomized 1:1 and allocated to treatment with vemurafenib (337 patients) or dacarbazine (338 patients). The study treatments were administered in a regimen that corresponded to the description in the summaries of product characteristics [3-5]. Vemurafenib was administered as film-coated tablets at a dosage of 960 mg twice daily. Treatment with dacarbazine consisted of the intravenous administration of a dosage of 1000 mg/m² body surface area in 3-week cycles.

Patients in both treatment arms were allowed to receive additional concomitant medication, restricted only with respect to other melanoma treatments.

Overall survival was recorded as the relevant primary outcome of the study. Relevant secondary outcomes were pain, health-related quality of life and adverse events.

Characteristics of the study population

Table 5 shows the characteristics of patients in the studies included in the assessment.

There were no relevant differences between the treatment arms for the characteristics of age, sex, Eastern Cooperative Oncology Group (ECOG) performance status, American Joint Committee on Cancer (AJCC) classification of lymph node involvement or metastases [6], lactate dehydrogenase (LDH) status, number of metastases or time since diagnosis. The mean age of patients was about 54 years and the metastatic disease had been diagnosed for a median of 3 months. About 44% of patients were women. The vast majority (95%) of patients enrolled in the study had tumour Stage IV (M1a to M1c metastasis). The disease was in the most advanced stage of metastasis (M1c) in about 65% of the enrolled patients and in Stage M1b in another 19%. LDH levels were elevated in 42% of the study population. The proportion of study discontinuations in the dacarbazine arm was almost twice as high as that in the vemurafenib arm. The most frequently cited reason for treatment discontinuation was disease progression.

Table 3: Characteristics of the included studies – RCT, direct comparison of vemurafenib and dacarbazine

Study	Study design	Population	Interventions (number of randomized patients)	Duration of study	Location and period of study	Primary outcome; secondary outcomes ^a
BRIM3	RCT, open-label, parallel	Adult (≥ 18 years) patients not previously treated with systemic anti-cancer therapies, with histologically confirmed metastatic melanoma (unresectable Stage IIIC or Stage IV) and proven BRAF V600 mutation	Vemurafenib (N = 337) dacarbazine (N = 338)	Treatment planned until death, discontinuation or toxicity Interim analysis planned after 50% of the expected events (deaths) reached ^b (98 out of 196 deaths) (Data analysis at 31.12.2010) Planned follow-up: until death or discontinuation further data analyses at 31.03.2011 and 03.10.2011	104 centres in Australia, Germany, France, Italy, Israel, Canada, New Zealand, the Netherlands, Sweden, Switzerland, Great Britain, USA 1/2010 – 12/2010 (Enrolment of first patient until clinical cut-off)	Primary outcomes: overall survival, progression-free survival Secondary outcomes: pain, health-related quality of life, adverse events
<p>a: Primary outcomes contain information without consideration of its relevance for this benefit assessment. Secondary outcomes contain exclusively information on the relevant available outcomes for this benefit assessment.</p> <p>b: The analysis was originally planned as an interim analysis and due to the efficacy of vemurafenib was carried out as the main analysis.</p> <p>BRAF: gene “rapidly accelerated fibrosarcoma isoform B”; N: number of randomized patients; RCT: randomized controlled trial</p>						

Table 4: Characteristics of the interventions – RCT, direct comparison of vemurafenib and dacarbazine

Study	Intervention	Control	Concomitant therapy
BRIM3	4 film-coated tablets (equivalent to 960 mg) morning and evening (corresponds to a total daily dose of 1920 mg)	1000 mg/m ² body surface area as 60-minute infusion every 3 weeks	Apart from other anti-cancer treatments, concomitant therapies were permitted. Limited-field radiotherapy for palliative treatment of pain from pre-existing bone metastases was also explicitly allowed.
RCT: randomized controlled trial			

Characteristics of the study population

Table 5: Characteristics of the study populations – RCT, direct comparison of vemurafenib and dacarbazine

Study Group	N	Age (years)	Sex	ECOG status		Classification of lymph node involvement and metastases at randomization			Number of metastases		Elevated LDH level at start of study	Time since diagnosis [months]	Treatment discontinuations ^{a,b} (cut-off 30.12.2010)	
		mean (SD)	f/m [%]	n (%)		n (%)			n (%)		n (%)	median (min-max)	n (%)	
		0	1	Unresectable Stage IIC	M1a	M1b	M1c	< 3	≥ 3					
BRIM3														
Vemurafenib	337	55 (14)	41 / 59	229 (68)	108 (32)	20 (6)	34 (10)	62 (18)	221 (66)	185 (56)	145 (44)	142 (42)	3.0 (0–109)	113 (33.6)
Dacarbazine	338	53 (14)	46 / 54	230 (68)	108 (32)	13 (4)	40 (12)	65 (19)	220 (65)	181 (55)	149 (45)	142 (42)	3.0 (0–184)	206 (71.3)
<p>a: Data without patients who discontinued prior to the first treatment of the study. The percentages are based on all patients who received one treatment (336 patients in the vemurafenib arm and 289 patients in the dacarbazine arm).</p> <p>b: The commonest reason for discontinuation was progression of the disease (vemurafenib 26%, dacarbazine 58% of patients, in each case relative to the number of patients who had received one treatment). Other reasons reported were death, adverse events, refusal of treatment, withdrawal of consent and protocol violation.</p> <p>ECOG: Eastern Cooperative Oncology Group, f: female; LDH: lactate dehydrogenase; m: male; max: maximum; min: minimum, n: number of patients in the category; N: number of randomized patients; RCT: randomized controlled trial; SD: standard deviation</p>														

Risk of bias at study level

Table 6 shows the risk of bias at study level. This was rated as low for Study BRIM3. This concurs with the assessment of the company.

Table 6: Risk of bias at study level - RCT, direct comparison of vemurafenib and dacarbazine

Study	Adequate randomization sequence generation	Allocation concealment	Blinding		Selective outcome reporting	Other sources of bias	Risk of bias at study level
			Patient	Treating persons			
BRIM3	yes	yes	no	no	no	no	low
RCT: randomized controlled trial							

Further information about the study design, study populations and risk of bias at study level can be found in Module 4, Sections 4.3.1.2.1, 4.3.1.2.2 and 4.3.2.1.2 of the dossier and in Sections 2.7.2.4.1 and 2.7.2.4.2 of the full dossier assessment.

2.4 Results concerning added benefit

The assessment covers the following patient-relevant outcomes (for more detailed reasoning, see Section 2.7.2.4.3 of the full dossier assessment):

- Mortality (overall survival)
- Morbidity (pain, assessed using a visual analogue scale for pain [VAS Pain])
- Health-related quality of life (assessed using the FACT-M questionnaire)
- Adverse events
 - Overall rate of adverse events
 - Overall rate of adverse events of CTCAE Grade ≥ 3
 - Overall rate of serious adverse events
 - Overall rate of adverse events that led to treatment discontinuation
 - Rates of common adverse events

The Institute chose different patient-relevant outcomes to those used by the company.

The deviation was that the company also named progression-free survival and tumour response as outcomes in its dossier. However, from the information given therein, the company did not include these two outcomes in its assessment of the added benefit of vemurafenib.

An explanation of the choice of patient-relevant outcomes can be found in Section 2.7.2.4.3 of the full dossier assessment.

Table 7 shows the outcomes for which data were available from the studies included in the assessment. Table 8 provides the risk of bias for these outcomes.

Table 7: Matrix of outcomes – RCT, direct comparison of vemurafenib and dacarbazine

Study	Outcomes							
	Overall survival	Health-related quality of life	Pain	Adverse events	Serious adverse events	Adverse events of CTCAE Grade ≥ 3	Adverse events that led to treatment discontinuation	Common adverse events ^a
BRIM3	yes	yes	yes	yes	yes	yes	yes	yes
<p>a: Individual system organ classes (SOCs coded according to MedDRA) were considered: “Gastrointestinal disorders”, “Skin and subcutaneous tissue disorders”, “Musculoskeletal and connective tissue disorders”, “Nervous system disorders”, “Neoplasms benign, malignant and unspecified”, “Metabolic and nutritional disorders”, “Blood and lymphatic system disorders”</p> <p>CTCAE: National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events; MedDRA: Medical Dictionary for Regulatory Activities; RCT: randomized controlled trial; SOC: system organ class</p>								

Table 8: Risk of bias at study and outcome levels – RCT, direct comparison of vemurafenib and dacarbazine

Study	Outcomes								
	Study level	Overall survival	Health-related quality of life	Pain	Adverse events	Serious adverse events	Adverse events of CTCAE Grade ≥ 3	Adverse events that led to treatment discontinuation	Common adverse events ^a
BRIM3	low	high ^b	high ^{b,c,d,e}	high ^{b,c,e,f}	low	low	low	low	low
<p>a: The risk of bias of individual system organ classes (SOCs coded according to MedDRA) were considered: “Gastrointestinal disorders”, “Skin and subcutaneous tissue disorders”, “Musculoskeletal and connective tissue disorders”, “Nervous system disorders”, “Neoplasms benign, malignant and unspecified”, “Metabolic and nutritional disorders”, “Blood and lymphatic system disorders”.</p> <p>b: Because of the proportion of patients in the analysis who received another melanoma treatment after prematurely discontinuing the study treatment, in open-label study design (see Section 2.7.2.4.2 of the full dossier assessment).</p> <p>c: Subjective outcome in an open-label study.</p> <p>d: Patients not considered in the analysis > 10%, apart from the subscales “physical well-being” and “social well-being”.</p> <p>e: Difference between the groups for the proportion of patients not considered in the analysis > 5 percentage points.</p> <p>f: Patients not considered in the analysis >10%.</p> <p>AE: adverse event; CTCAE: National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events; MedDRA: Medical Dictionary for Regulatory Activities; RCT: randomized controlled trial; SOC: system organ class</p>									

Contrary to the company’s assessment, the risk of bias for the outcome “overall survival” was rated as high for all 3 data cut-offs. Inspection of the study data showed that the proportion of patients who discontinued the study treatment due to progression and received another melanoma treatment was relevantly higher in the dacarbazine arm than in the vemurafenib arm. These patients were included in the analysis of overall survival. However, this does not lead to a downgrading of the certainty of results of the conclusions regarding added benefit for this outcome, because after inspection of the actual data on these other melanoma treatments, an overestimation of the effect of vemurafenib appears unlikely (see Section 2.7.2.4.2 of the full dossier assessment).

The risk of bias for the outcomes “health-related quality of life” and “pain” was rated as high, since these are subjective outcomes in an open-label study design. In addition, the analysis of data included only those patients for whom a value was recorded at the start of the study and

under treatment. The difference between the groups with regard to the proportion of patients not considered in the analysis was greater than 5 percentage points. In the FACT-M subscales (with the exception of the subscale “physical well-being”) and for the outcome “pain”, a total of more than 10% of patients were not considered in the analysis. The rating of the risk of bias as high for both outcomes concurs with the company’s assessment.

The risk of bias for the outcomes “AEs”, “AEs of CTCAE Grade ≥ 3 ”, “SAEs”, “AEs that led to treatment discontinuation”, and “common AEs” was rated as low. This concurs with the assessment of the company, which admittedly did not carry out an assessment at outcome level, but for adverse events as a whole.

Further information about the choice of outcome and risk of bias at outcome level can be found in Module 4, Sections 4.3.1.2.2, 4.3.1.3 and 4.3.2.1.3 of the dossier and in Sections 2.7.2.4.2 and 2.7.2.4.3 of the full dossier assessment.

Table 9, Table 10 and Table 11 summarize the results on the comparison of vemurafenib and dacarbazine. Where necessary, the data from the company's dossier were supplemented by the Institute's own calculations.

Table 9: Results on overall survival – RCT, direct comparison of vemurafenib and dacarbazine (BRIM3 study)

Outcome	Vemurafenib		Dacarbazine		Vemurafenib vs. dacarbazine		
	Date of data cut-off	N	KM [95% CI] [months]	N	KM [95% CI] [months]	HR [95% CI]	p-value
Overall survival – first data cut-off							
30.12.2010	336 ^b	9.23	336 ^b	7.75 [6.28; 10.28]	0.37 [0.26; 0.55]	< 0.001	
Without censoring of patients who switched treatment ^a		[8.05; not reached]					
Overall survival – second data cut-off							
31.03.2011	337	not reached	338	8.80 [7.33; 10.28]	0.47 [0.35; 0.62]	< 0.001	
Without censoring of cross-over patients ^c		[9.59; not reached]					
31.03.2011	337	not reached	338	7.89 [7.26; 9.63]	0.44 [0.33; 0.59]	< 0.001	
With censoring of cross-over patients ^c		[9.59; not reached]					
Overall survival – third data cut-off							
03.10.2011	337	13.2 [12; 15]	338	9.9 [9.1; 12.2]	0.67 [0.54; 0.84]	< 0.001	
Without censoring of cross-over patients ^c							
03.10.2011	337	13.2 [12; 15]	338	9.6 [7.9; 11.8]	0.62 [0.49; 0.77]	< 0.001	
With censoring of cross-over patients ^c							
<p>a: It was already possible to switch to an alternative melanoma treatment because of disease progression before the first data cut-off. According to the information in the submitted documents, no sensitivity analysis with censoring of the patients who switched treatment was performed because the results were adequately robust.</p> <p>b: For the first data cut-off on 30.12.2010, 336 patients in both treatment arms who had been randomized at least 2 weeks before the data cut-off were analysed. For the following analyses, all patients were considered.</p> <p>c: Switching patients from the dacarbazine arm into the vemurafenib arm (cross-over) was permitted after the first data cut-off.</p> <p>CI: confidence interval; HR: hazard ratio; KM: Kaplan-Meier estimator of median survival; N: number of randomized patients; RCT: randomized controlled trial; vs.: versus</p>							

Table 10: Results on morbidity and health-related quality of life (continuous outcomes) – RCT, direct comparison of vemurafenib and dacarbazine (BRIM3 study)

Outcome Instrument Subscale	Vemurafenib		Dacarbazine		Vemurafenib vs. dacarbazine	
	Score at start of study		Score at start of study		Group difference effect ^a [SE]	p-value
	N	mean (SE)	N	mean (SE)		
Morbidity						
VAS pain ^b	319	2.2 (0.1)	264	2.4 (0.2)	-0.39 (0.33) ^c	0.235
Health-related quality of life						
FACT-M ^d						
Physical well-being	327	22.1 (0.32)	285	21.8 (0.37)	2.32 (0.80) ^e	0.004
Emotional well-being	319	17.1 (0.24)	277	15.3 (0.30)	-1.38 (0.48) ^e	0.004
Functional well-being	320	17.3 (0.35)	278	16.7 (0.41)	0.57 (0.68) ^e	0.403
Social well-being	325	22.9 (0.29)	283	22.8 (0.25)	0.07 (0.59) ^e	0.906
Melanoma symptoms, additional concerns	325	51.1 (0.49)	282	50.4 (0.56)	1.56 (1.08) ^e	0.148
<p>a: The changes between the treatment arms from the start of the study were compared using a repeated measures analysis with the factors “treatment”, “visit” and “treatment/visit” interaction for the VAS pain and for all FACT-M subscales. Since in the dacarbazine arm only a few patients were available for assessment after the 6th cycle (12 patients at Cycle 9), the model contained only the assessments up to Cycle 6. The repeated measures analysis was based on other patient numbers (a total of 558 patients for FACT-M and 553 for VAS pain in both groups) than the cases observed after 6 cycles.</p> <p>b: The scale was divided into 10 steps from 0 (no pain) to 10 (greatest possible pain).</p> <p>c: Group difference of VAS pain scores for the treatment period from the start of the study to Cycle 6.</p> <p>d: A positive change denotes improvement. Positive effects denote a better quality of life for the vemurafenib group than for the dacarbazine group, negative effects a worse quality of life for the vemurafenib group than for the dacarbazine group.</p> <p>e: Group difference of changes over the treatment period from start of study to Cycle 6.</p>						
FACT-M: Functional Assessment of Cancer Therapy-Melanoma; N: number of analysed patients; SE: standard error; VAS: visual analogue scale; vs.: versus						

Table 11: Results on adverse events – RCT, direct comparison of vemurafenib and dacarbazine (BRIM3 study)

Outcome System organ class (SOC) ^a Preferred term (PT) ^b	Vemurafenib		Dacarbazine		Vemurafenib vs. dacarbazine	
	N	Patients with events n (%)	N	Patients with events n (%)	RR [95% CI] ^c	p-value ^d
AEs	336	326 (97)	282	253 (90)	1.08 [1.00; 1.13]	< 0.001
CTCAE Grade ≥3	336	168 (50)	282	86 (30)	1.64 [1.33; 2.01]	< 0.001
SAEs	336	110 (33)	282	45 (16)	2.05 [1.51; 2.79]	< 0.001
AEs that led to treatment discontinuation	336	19 (6)	282	12 (4)	1.33 [0.66; 2.69]	0.446
Common AEs						
Gastrointestinal disorders	336	213 (63)	282	182 (65)	0.98 [0.87; 1.11]	0.783
Nausea	336	101 (30)	282	115 (41)		
Diarrhoea	336	84 (25)	282	34 (12)		
Vomiting	336	50 (15)	282	67 (24)		
Constipation	336	32 (10)	282	65 (23)		
Skin and subcutaneous tissue disorders	336	302 (90)	282	53 (19)	4.78 [3.74; 6.11]	< 0.001
Rash	336	121 (36)	282	3 (1)		
Alopecia	336	117 (35)	282	6 (2)		
Photosensitivity reactions	336	101 (30)	282	10 (4)		
Pruritus	336	74 (22)	282	4 (1)		
Hyperkeratosis	336	67 (20)	282	0 (0)		
Musculoskeletal and connective tissue disorders	336	225 (67)	282	67 (24)	2.82 [2.26; 3.52]	< 0.001
Arthralgia	336	165 (49)	282	9 (3)		
Nervous system disorders	336	152 (45)	282	67 (24)	1.90 [1.50; 2.42]	< 0.001
Headache	336	72 (21)	282	26 (9)		
Neoplasms, benign, malignant and unspecified (including cysts and polyps)	336	144 (43)	282	25 (9)	4.83 [3.26; 7.17]	< 0.001
Skin papilloma	336	62 (18)	282	0 (0)		
Cutaneous squamous cell carcinoma	336	40 (12)	282	1 (< 1)		
Keratoacanthoma	336	27 (8)	282	0 (0)		
Seborrhoeic keratosis	336	24 (7)	282	3 (1)		
Metabolic and nutritional disorders	336	74 (22)	282	33 (12)	1.88 [1.29; 2.75]	< 0.001

(continued on next page)

Table 11: Results on adverse events – RCT, direct comparison of vemurafenib and dacarbazine (BRIM3 study) (continued)

Outcome System organ class (SOC) ^a Preferred term (PT) ^b	Vemurafenib		Dacarbazine		Vemurafenib vs. dacarbazine	
	N	Patients with events n (%)	N	Patients with events n (%)	RR [95% CI] ^c	p-value ^d
Blood and lymphatic system disorders	336	32 (10)	282	51 (18)	0.53 [0.35; 0.80]	0.002
Neutropenia	336	2 (< 1)	282	32 (11)		
Anaemia	336	17 (5)	282	15 (5)		
Thrombocytopenia	336	4 (1)	282	14 (5)		

a: According to MedDRA coding.
b: Only PTs that occurred in $\geq 20\%$ of patients in a group are shown. In the SOCs “Neoplasms, benign, malignant and unspecified” and “Blood and lymphatic system disorders”, all PTs with a frequency $\geq 5\%$ are shown.
c: Institute’s calculation.
d: Institute’s calculation, unconditional exact test (CSZ method according to [7]).
AE: adverse event; CSZ: convex, symmetry, z-score; CTC/AE: Common Terminology Criteria for Adverse Events; CI: confidence interval; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with event; N: number of patients in the safety population; PT: preferred term; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SOC: system organ class; vs.: versus

Only one study was available for the assessment of vemurafenib. In the Institute's view, the present study did not meet the particular requirements placed on the derivation of proof from a single study. Hence at most indications could be inferred from the data, provided that there were no other aspects that further weakened the informative value.

Overall survival

Over the entire observation period (in all 3 data cut-offs), treatment with vemurafenib produced a statistically significant prolongation in overall survival in comparison with treatment with dacarbazine. There is thus an indication of an added benefit of vemurafenib versus dacarbazine for overall survival. This concurs with the company's assessment.

Morbidity

“Pain” was the only outcome recorded in the study in relation to morbidity (in the sense of symptoms or complications caused by the disease). The analysis was based on the score on a visual analogue scale. There was no statistically significant difference in the pain score under treatment with vemurafenib and dacarbazine. An added benefit of vemurafenib for the outcome “pain” is thus not proven. This concurs with the company's assessment.

Health-related quality of life

A statistically significant difference between the treatment groups was found for only 2 of the 5 subscales in the FACT-M questionnaire used by the company, namely for “physical well-being” – where the difference was in favour of vemurafenib – and for “emotional well-being”

– where it was to its disadvantage. The assessment of the relevance of the effects (based on standardized mean differences) showed that an irrelevant effect could not be definitively excluded in either case. Due to the lack of validity of the overall score, the results of this score could not be used. An added benefit or lesser harm from vemurafenib in comparison with dacarbazine for the outcome “health-related quality of life” is therefore not proven. This concurs with the company's assessment.

Adverse events

The overall rate of adverse events in patients in the vemurafenib arm was higher than in those in the dacarbazine arm. The difference was statistically significant. Despite a statistically significant difference, because of the marginal effect size greater harm from vemurafenib than from dacarbazine is not proven.

The overall rates of severe adverse events CTCAE Grade ≥ 3 and of SAE were higher in patients in the vemurafenib arm than in those in the dacarbazine arm. The difference was statistically significant in each case. For these outcomes there is therefore an indication of greater harm from vemurafenib than from dacarbazine.

There was no statistically significant difference between the vemurafenib and dacarbazine groups in the proportion of patients with adverse events that led to treatment discontinuation. Greater or lesser harm from vemurafenib than from dacarbazine is thus not proven for this outcome.

The proportion of patients with events from the system organ classes “Skin and subcutaneous tissue disorders”, “Musculoskeletal and connective tissue disorders”, “Nervous system disorders”, “Neoplasms, benign, malignant and unspecified”, and “Metabolic and nutritional disorders” was, in each case, higher in the vemurafenib arm than in the dacarbazine arm. In all cases, the difference between the treatment groups was statistically significant. The proportion of patients with events from the system organ class “Blood and lymphatic system disorders” was higher under dacarbazine than under vemurafenib. The difference was also statistically significant. “Gastrointestinal disorders” occurred in an overall comparable frequency in the two treatment groups, but nausea, vomiting and constipation were commoner under dacarbazine and diarrhoea was more frequent under vemurafenib.

In summary, there is an indication of greater harm from vemurafenib than from dacarbazine for the outcome “adverse events”.

The company presented the results on the various operational definitions of the complex “adverse events”, without specifically reaching a summarizing conclusion about this complex. The company assessed the adverse events overall as tolerable and readily treatable.

Subgroup analyses

Subgroup analyses for the outcomes “mortality” (overall survival), “morbidity” (pain), “health-related quality of life” and “adverse events at the level of overall rates of adverse events”, “severe adverse events”, “serious adverse events”, and “adverse events that led to treatment discontinuation” were considered for this benefit assessment.

For the outcome “overall survival” the company submitted subgroup analyses for all 3 data cut-offs on the factors of age, sex, ECOG performance status, classification of lymph node involvement and metastases, LDH, geographical region, BRAF mutation status, race and presence of brain metastases. The 3 latter factors were not considered further, because altogether only about one third of the study population were tested for the precise BRAF V600 mutation type and more than 99% of the enrolled patients were white and/or showed no brain metastases.

For the first data cut-off no interactions occurred between the investigated factors and the treatment effect; for the second and third data cut-offs, the heterogeneity test showed occasional p-values indicative of interactions. Since the interactions did not occur consistently in all data cut-offs and, even in the case of an interaction, marked effects on overall survival were observed in the individual subgroups, the Institute did not draw separate conclusions for subgroups (for details see Section 2.7.2.4.3 of the full dossier assessment). The subgroup analyses on the outcome “overall survival” are therefore not shown separately here.

The company did not present any subgroups analyses for the outcomes “morbidity” (pain) or “health-related quality of life”.

To describe adverse events, subgroup data were available for adverse events and severe adverse events of CTCAE Grade ≥ 3 (in each case overall and summary according to MedDRA system organ class and preferred term) for the factors of age, sex and BRAF mutation status. The interaction tests calculated by the Institute on the basis of the available data showed no interactions at the level of the overall rate of adverse events and the overall rate of severe adverse events between the factors of age and sex and the treatment effect. The BRAF V600 mutation status was not further considered by the Institute because altogether only about one third of the study population were tested for the precise BRAF V600 mutation type and a successful sequencing of the somatic mutation was only available for about half of the patients classified thereby as “non-BRAF V600E”. The subgroup analyses for the outcome “adverse events” are therefore not shown separately here.

Further information about the choice of outcome, risk of bias at outcome level and outcome results can be found in Module 4, Sections 4.3.1.2.2, 4.3.1.3 and 4.3.2.1.3 of the dossier and in Sections 2.7.2.4.2 and 2.7.2.4.3 of the full dossier assessment.

2.5 Extent and probability of added benefit

The derivation of extent and probability of added benefit of vemurafenib at outcome level is shown below, taking into account the various outcome categories and effect sizes. The methods used are explained in Appendix A of Benefit Assessment A11-02 [2].

The approach for deriving an overall conclusion regarding added benefit based on the aggregation of the conclusions derived at outcome level is a proposal from IQWiG. The decision regarding added benefit is made by the G-BA.

2.5.1 Evaluation of added benefit at outcome level

The data presented in Section 2.4 showed an indication of an added benefit of vemurafenib for overall survival. This is opposed by indications of greater harm.

An estimation of the extent of the added benefit from the data presented in Section 2.4 at the level of the individual outcomes is given in Table 12.

Table 12: Vemurafenib versus dacarbazine – extent of added benefit at outcome level

	Effect estimator [95% CI]^a, quantile of time to event or proportion of events Vemurafenib vs. dacarbazine p-value Probability	Derivation of extent
Mortality		
Overall survival	<p>First data cut-off (30.12.2010) HR: 0.37 [0.26; 0.55] median 9.23 vs. 7.75 months</p> <p>Second data cut-off (31.03.2011) Without censoring of cross-over patients^b: HR: 0.47 [0.35; 0.62] median: not reached vs. 8.80 With censoring of cross-over patients^b: HR: 0.44 [0.33; 0.59] median: not reached vs. 7.89</p> <p>Third data cut-off (03.10.2011) Without censoring of cross-over patients^b: HR: 0.67 [0.54; 0.84] median: 13.2 vs. 9.9 With censoring of cross-over patients^b: HR: 0.62 [0.49; 0.77] median: 13.2 vs. 9.6</p> <p>p-value (for all data cut-offs) < 0.001 Probability: indication</p>	Outcome category: survival period CI ₀ < 0.85 Added benefit, extent: “major”
Morbidity		
VAS pain	No statistically significant difference	Added benefit not proven.
Health-related quality of life		
FACT-M	Statistically significant difference in 2 of the 5 subscales (“physical well-being” and “emotional well-being”); effect size not definitely above an irrelevance threshold; no overall score available	Added benefit not proven.

(continued on next page)

Table 12: Vemurafenib versus dacarbazine – extent of added benefit at outcome level (continued)

	Effect estimator [95% CI] ^a , quantile of time to event or proportion of events Vemurafenib vs. dacarbazine p-value Probability	Derivation of extent
Adverse events		
AEs	RR ^c 1.08 [1.04; 1.13] 97% vs. 90% RR ^d 0.92 [0.89; 0.97] p-value < 0.001 Probability: indication	Outcome category: non-serious/non-severe adverse events CI ₀ ≥ 0.90 Greater/lesser harm not proven.
AE of CTCAE Grade ≥ 3	RR ^c 1.64 [1.33; 2.01] 50% vs. 30% RR ^d : 0.61 [0.50; 0.75] p-value < 0.001 Probability: indication	Outcome category: serious/severe adverse events CI ₀ < 0.75 ^f Greater harm; extent: major
SAEs	RR ^c 2.05 [1.51; 2.79] 33% vs. 16% RR ^d : 0.49 [0.36; 0.66] p-value < 0.001 Probability: indication	Outcome category: serious/severe adverse events CI ₀ < 0.75 Greater harm; extent: major
AEs that led to treatment discontinuation	RR ^c 1.33 [0.66; 2.69] p-value = 0.446	Greater/lesser harm not proven.
<p>a: According to the inclusion criteria, patients with histologically confirmed metastatic melanoma (unresectable Stage IIIC or Stage IV) were enrolled in the study. According to the summary of product characteristics [3] vemurafenib is approved for patients with unresectable or metastatic melanoma, with no restriction of severity. Since this also includes patients of earlier stages (unresectable Stage I-IIIb, metastatic Stage IIIa, IIIb and metastatic but resectable Stage IIIC melanoma), the study population does not fully cover the therapeutic indication. It remains unclear whether the observed effects can be applied to these patients.</p> <p>b: Switching patients from the dacarbazine arm into the vemurafenib arm (cross-over) was permitted after the first data cut-off.</p> <p>c: Institute's calculation, proportion of events vemurafenib vs. dacarbazine.</p> <p>d: Institute's calculation, proportion of events dacarbazine vs. vemurafenib (direction of effect reversed to derive extent of added benefit).</p> <p>e: Greater harm not proven, because upper limit of confidence interval above the specified threshold of 0.90.</p> <p>f: The precise value is 0.7495.</p> <p>AEs: adverse events; CI: confidence interval; CI₀: upper limit of the CI; CTCAE: Common Terminology Criteria for Adverse Events; FACT-M: Functional Assessment of Cancer Therapy-Melanoma; HR: hazard ratio; KM: Kaplan-Meier estimator of median survival; RR: relative risk; SAEs: serious adverse events; VAS: visual analogue scale; vs.: versus</p>		

Table 12 shows that for the outcome “adverse events”, major harm is already present at the level of overall rates (both of severe and also of serious adverse events), and hence the maximum extent of harm is reached. Therefore no further estimation of the extent of added benefit or harm is made for the outcome “adverse events” at the level of the individual system organ classes.

2.5.2 Overall conclusion on added benefit

Table 13 summarizes the results considered in the overall conclusion on the extent of added benefit.

Table 13: Positive and negative effects from the assessment of vemurafenib versus dacarbazine

Positive effects	Negative effects
Indication of added benefit – extent: “major” (survival: overall mortality)	Indication of greater harm –extent: “major” (serious/severe adverse events – AE of CTCAE Grade \geq 3)
	Indication of greater harm –extent: “major” (serious/severe adverse events - SAE)
AE: adverse event; CTCAE: Common Terminology Criteria of Adverse Events; SAE: serious adverse event	

In the overall assessment, positive and negative results of equal certainty (indications) remain. On the positive side, the extent “major” was reached for overall survival. On the negative side, the extent “major” was also reached for the overall rate of severe as well as serious adverse events.

Due to the substantial risk of harm from severe and serious adverse events, the Institute decided to downgrade the added benefit of vemurafenib versus the ACT from “major” to “considerable”. This does not affect the certainty of results.

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

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

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Roche. A randomized, open-label, controlled, multicenter, phase III study in previously untreated patients with unresectable IIIC or stage IV melanoma with V600E BRAF mutation receiving RO5185426 or dacarbazine: study NO25026 - BRIM 3; clinical study report [unpublished]. 2011.

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Please see full dossier assessment for full reference list.

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The full report (German version) is published under www.iqwig.de.