IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

IQWiG Reports – Commission No. A13-35

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

Extract

[1] Translation of Sections 2.1 to 2.6 of the dossier assessment "Dabrafenib – Nutzenbewertung gemäß § 35a SGB V" (Version 1.0; Status: 23 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.

Publishing details

Publisher:
Institute for Quality and Efficiency in Health Care

Topic:
Dabrafenib – Benefit assessment according to § 35a Social Code Book V

Commissioning agency:
Federal Joint Committee

Commission awarded on:
24 September 2013

Internal Commission No.:
A13-35

Address of publisher:
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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
CTCAE	Common Terminology Criteria for Adverse Events
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
EQ-5D	European Quality of Life-5 Dimensions
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
MAPK	mitogen-activated protein kinase
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed-effects model repeated measures
PFS	progression-free survival
RCT	randomized controlled trial
SGB	*Sozialgesetzbuch* (Social Code Book)
SOC	System Organ Class
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 dabrafenib. The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter abbreviated to "the company"). The dossier was sent to IQWiG on 24 September 2013.

Research question

The aim of this report was to assess the added benefit of dabrafenib in adult patients with BRAF V600 mutation-positive unresectable or metastatic melanoma. The benefit assessment was conducted in comparison with the appropriate comparator therapy (ACT) dacarbazine specified by the G-BA.

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

Results

One relevant study (BREAK-3) was available for the benefit assessment. BREAK-3 is an ongoing, randomized, open-label, multicentre, active-controlled approval study of dabrafenib. Adult patients with histologically confirmed advanced melanoma (unresectable stage III) or metastatic melanoma (stage IV) and proven BRAF V600E mutation were enrolled. The patients were stratified according to disease stage (III, IVM1a, IVM1b versus IVM1c) and randomized in a ratio of 3:1 to receive dabrafenib or dacarbazine.

The study treatment according to the protocol was continued until progression occurred. If progression occurred, the patients discontinued treatment with the study medication. Patients in the dacarbazine arm then had the option to switch to treatment with dabrafenib (crossover phase). Patients in the dabrafenib arm and those patients in the dacarbazine arm who did not switch to the crossover phase could receive other treatments for their melanoma. The data of all patients were included in the analysis of overall survival also after treatment switching or crossover.

During the further course of the study, an amendment to the study protocol allowed patients in the dabrafenib arm to continue treatment with dabrafenib after progression was diagnosed radiologically, if, in the investigator's opinion, continued treatment posed a possible clinical advantage for the patients (Amendment 5 from 14 November 2011). No justification of this amendment could be inferred from the study documents. According to Amendment 6 (20 April 2012), patients in the dacarbazine arm, at the investigator's discretion, could already switch to treatment with dabrafenib before disease progression occurred. The justification

provided for this approach was that the prespecified primary analysis of progression-free survival (PFS) showed an advantage of dabrafenib.

The risk of bias at study level was rated as high for the study BREAK-3. This was largely due to the fact that, from the start of the study, patients in the dacarbazine arm had the option to switch to treatment with dabrafenib after disease progression. This crossover can have an important influence on the effect estimates of all patient-relevant outcomes investigated. Accordingly, all outcomes considered for the study BREAK-3 were rated as potentially highly biased.

Mortality (overall survival)

Over the entire observation period, treatment with dabrafenib produced no statistically significant prolongation in overall survival in comparison with treatment with dacarbazine. Hence an added benefit of dabrafenib in comparison with the ACT is not proven for this outcome.

The company included, among other things, the findings of the investigation it had conducted on the validation of the outcome "PFS" as surrogate for overall survival in the assessment of the added benefit for the outcome "overall survival". However, the documents presented by the company did not prove the validity of PFS as surrogate for overall survival. On the one hand, there was no specific consideration of the studies with targeted treatment or investigation of the influence of different types of treatment on the results of the validation. On the other hand, the variability of the corresponding estimates in the modelling of the relation of the effects of PFS and overall survival remains unconsidered in the simple linear model chosen by the company.

If the validation approach chosen by the company was limited to the subset of studies with targeted treatment (for the MAPK signalling cascade), no effect on overall survival could be predicted assuming a PFS greater than 0.48 (hazard ratio, corresponding to a surrogate threshold effect) (Institute's calculation). Even using the unsuitable approach of simple linear regression, no statistically significant effect of dabrafenib compared with dacarbazine regarding overall survival could therefore be derived from the effect for PFS (0.35 [0.20; 0.61]) found in the BREAK-3 study.

Overall, PFS is not validated as surrogate for overall survival on the basis of the data presented by the company.

Morbidity (symptoms)

Aspects of morbidity were recorded in the study BREAK-3 using the symptom scales of the disease-specific questionnaire European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30). The group comparison of the continuous data showed for EORTC QLQ-C30 a statistically significant effect in favour of dabrafenib regarding the symptom subscale "nausea and vomiting". There were no

statistically significant differences in comparison with dacarbazine in any of the other symptom subscales.

An analysis of the effect size on the subscale "nausea and vomiting" on the basis of Hedges' g showed that an irrelevant effect could not be excluded for nausea and vomiting because the 95% confidence interval was not fully below the irrelevance threshold of −0.2.

Summarizing the results on morbidity (symptoms), there is not proof of an added benefit of dabrafenib compared with the ACT.

Health-related quality of life
(disease-specific instrument EORTC-QLQ-C30 and generic instrument EQ-5D)

The analysis considered showed no statistically significant difference between dabrafenib and dacarbazine for any of the subscales on quality of life (functional scales) of the questionnaire EORTC QLQ-C30.

No evaluable results were available for health-related quality of life measured with the generic instrument European Quality of Life-5 Dimensions (EQ-5D).

Overall, there is no proof of added benefit of dabrafenib compared with the ACT for health-related quality of life (disease-specific instrument EORTC QLQ-C30 or generic instrument EQ-5D).

Adverse events

The company's dossier mostly contained no valid data for the assessment of adverse events, which could be included in the benefit assessment. The company presented the results on adverse events on the basis of the naive proportions (proportion of patients with at least one event). However, these results did not constitute an adequate analysis because the treatment durations differed considerably between the 2 treatment arms (median treatment duration 4.9 months in the dabrafenib arm, and 2.8 months in the dacarbazine arm). Due to the differences in treatment duration, more adverse events could occur in the dabrafenib group than in the comparator group. This constituted a bias to the disadvantage of dabrafenib.

Therefore the analysis of the incidence density on the basis of the Institute's calculations was used for this benefit assessment, but only in case of rare events. The incidence density ratio was calculated as related effect measure. For non-rare events, only a qualitative interpretation could be conducted on the basis of the data presented in the dossier.

Regarding the outcomes "serious adverse events" and "severe adverse events" (Common Terminology Criteria for Adverse Events [CTCAE] Grade ≥ 3), there was no statistically significant difference between the treatment arms on the basis of the naive proportions. It could only be concluded for these outcomes that the data presented showed no greater harm despite the bias to the disadvantage of dabrafenib. Hence greater or lesser harm from dabrafenib than from dacarbazine is not proven for these outcomes.

Results were available for discontinuations due to adverse events, on the basis of which the Institute could calculate the incidence density ratio. There was no statistically significant difference between dabrafenib and dacarbazine.

Considering common adverse events, there was a statistically significant difference in favour of dabrafenib compared with dacarbazine on the level of the System Organ Classes "blood and lymphatic system disorders" and "gastrointestinal disorders". Under consideration of the known direction of the bias it could be assumed that the statistically significant effect in favour of dabrafenib would remain if the bias was eliminated. This results in a hint of lesser harm from dabrafenib compared with dacarbazine for the adverse events "blood and lymphatic system disorders" and "gastrointestinal disorders".

There was a statistically significant difference to the disadvantage of dabrafenib for the remaining System Organ Classes (SOCs) (skin and subcutaneous tissue disorders, musculoskeletal and connective tissue disorders, general disorders and administration site conditions, nervous system disorders, and neoplasms benign, malignant and unspecified). Under consideration of the known direction of the bias it could not be excluded that the statistically significant effect to the disadvantage of dabrafenib would still remain if the bias was eliminated. It could also not be excluded that the differences observed were caused by the bias. Overall, greater harm from dabrafenib is not excluded for these outcomes.

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 dabrafenib compared with the ACT is assessed as follows:

The data presented by the company did not result in an added benefit of dabrafenib regarding overall survival, morbidity (symptoms), health-related quality of life and discontinuations due to adverse events. Only a qualitative interpretation of the results on further outcomes regarding harm could be conducted because, overall, no valid results were available.

On the basis of the available results, positive effects (in each case "hint") remain for dabrafenib in the qualitative assessment of the outcome category "non-serious/non-severe adverse events" (blood and lymphatic system disorders, gastrointestinal disorders). The extent of added benefit is "considerable" for the outcome "blood and lymphatic system disorders", and "non-quantifiable" for the outcome "gastrointestinal disorders".

[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].

There was a statistically significant difference to the disadvantage of dabrafenib for the remaining SOCs (skin and subcutaneous tissue disorders, musculoskeletal and connective tissue disorders, general disorders and administration site conditions, nervous system disorders, and neoplasms benign, malignant and unspecified). Under consideration of the known direction of the bias it could not be excluded that the statistically significant effect to the disadvantage of dabrafenib would still remain if the bias was eliminated. It could also not be excluded that the differences observed were caused by the bias. Overall, greater harm from dabrafenib is not excluded for these outcomes.

The lack of effects regarding benefit and the uncertainty described regarding harm lead to the assessment that, overall, no proof of added benefit of dabrafenib compared with the ACT dacarbazine can be derived in the monotherapy of unresectable or metastatic melanoma in adult patients.

The approach for deriving an overall conclusion on added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

2.2 Research question

The aim of this report was to assess the added benefit of dabrafenib in adult patients with BRAF V600 mutation-positive unresectable or metastatic melanoma. The benefit assessment was conducted in comparison with the ACT dacarbazine specified by the G-BA.

The company concurred with the ACT specified by the G-BA. However, it additionally presented the results of an indirect comparison with another drug from the substance class of BRAF inhibitors (vemurafenib) because it regarded this drug to be a new standard for the therapeutic indication to be assessed, and considered the presentation of the comparison to be necessary for a comprehensive benefit assessment of dabrafenib. This expansion of the research question was not accepted in the benefit assessment.

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

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 dabrafenib (studies completed up to 15 July 2013)
  - search in trial registries for studies on dabrafenib (last search on 15 July 2013)
- The Institute's own search to check the completeness of the study pool:
  - search in trial registries for studies on dabrafenib (last search on 2 October 2013)

This check produced no deviations from the study pool presented in the dossier.

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.

2.3.1 Studies included

The study BREAK-3 (BRF113683) listed in Table 2 was included in the benefit assessment.

Table 2: Study pool – RCT, direct comparison: dabrafenib vs. 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)
BREAK-3 (BRF113683)	Yes	Yes	No
a: Study for which the company was sponsor, or in which the company was otherwise financially involved. RCT: randomized controlled trial; vs.: versus			

Additionally, the company presented data on 2 further investigations in the dossier. On the one hand, this was an indirect comparison of dabrafenib with vemurafenib, another drug from the substance class of BRAF inhibitors. On the other hand, the company presented results from the single-arm phase II cohort study BREAK-MB in patients with brain metastases. The company presented both studies additionally as supplemental evidence for dabrafenib in the present therapeutic indication, but did not use them primarily for deriving the added benefit versus the ACT (dacarbazine).

These investigations were not included in the present benefit assessment because they were unsuitable for assessing an added benefit of dabrafenib in comparison with the ACT specified by the G-BA (see Section 2.7.2.3.2 of the full dossier assessment).

Section 2.6 contains a reference list for the studies included.

Further information on the results of the information retrieval and the study pool derived from it can be found in Module 4, Section 4.3.1.1 of the dossier and in Sections 2.7.2.3.1 and 2.7.2.3.2 of the full dossier assessment.

2.3.2 Study characteristics

Characteristics of the study and of the interventions

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

Table 3: Characteristics of the studies included – RCT, direct comparison: dabrafenib vs. dacarbazine

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
BREAK-3 (BRF113683)	RCT, phase III, open-label, 3:1 randomized, multicentre, crossover[b]	▪ Adult patients (≥ 18 years) with histologically confirmed advanced melanoma (unresectable stage III) or metastatic melanoma (stage IV) and proven BRAF V600E mutation ▪ ECOG performance status 0-1 ▪ No prior anticancer treatment for advanced/ metastatic melanoma (except IL-2), prior surgery and radiotherapy were permitted	Dabrafenib (N = 187) Dacarbazine (N = 63)	▪ No defined time of study duration ▪ Recruitment completed ▪ Primary analysis at occurrence of 102 PFS events and enrolment of all patients. Data analysis of the primary analysis: 19 Dec 2011 ▪ Further data analyses on 25 Jun 2012 and 18 Dec 2012 ▪ Follow-up of all randomized patients and final analysis when 70% of the patients have died or are lost to follow-up	70 centres in Australia, Germany, France, Ireland, Italy, Canada, The Netherlands, Poland, Russian Federation, Spain, Hungary, USA 12/2010 – 09/2011 (period of randomization)	Primary outcome: PFS Secondary outcomes: overall survival, symptoms, health-related quality of life, adverse events

a: Primary outcomes contain information without consideration of its relevance for the present benefit assessment. Secondary outcomes contain exclusively information on relevant available outcomes for the present benefit assessment.
b: Crossover allowed patients in the dacarbazine treatment arm with confirmed radiologic disease progression to switch to a treatment with dabrafenib. During the further course of the study, an amendment to the study protocol allowed patients in the dabrafenib arm to continue treatment with dabrafenib after progression was diagnosed radiologically, if, in the investigator's opinion, continued treatment posed a possible clinical advantage for the patients (Amendment 5 from 14 November 2011). According to Amendment 6 (20 April 2012), patients in the dacarbazine arm, at the investigator's discretion, could already switch to treatment with dabrafenib before disease progression occurred.

BRAF: gene "rapidly accelerated fibrosarcoma isoform B"; ECOG: Eastern Cooperative Oncology Group; IL-2: interleukin 2; N: number of randomized patients; PFS: progression-free survival; RCT: randomized controlled trial; vs.: versus

Table 4: Characteristics of the interventions – RCT, direct comparison: dabrafenib vs. dacarbazine

Study	Dabrafenib	Dacarbazine	Concomitant medication
BREAK-3 (BRF113683)	150 mg orally twice a day every 12 hours Treatment planned until disease progression, death, discontinuation or intolerable toxicity	1000 mg/m^2 IV every 3 weeks	During the study, patients could receive concomitant treatments (supportive care) including antibiotics, antiemetics, drugs for diarrhoea and analgesics Other anticancer treatments were not allowed
IV: intravenous; RCT: randomized controlled trial; vs.: versus			

The study BREAK-3 is an ongoing, randomized, open-label, multicentre, active-controlled approval study. Adult patients with histologically confirmed advanced melanoma (unresectable stage III) or metastatic melanoma (stage IV) and proven BRAF V600E mutation were enrolled. The disease stages considered in the study fully concurred with the specifications in the Summary of Product Characteristics (SPC) of dabrafenib (unresectable or metastatic melanoma) [3].

According to the inclusion criteria of the study, patients were not allowed to be pretreated with anticancer drugs for the treatment of advanced or metastatic melanoma (except interleukin 2). Patients with ocular melanoma or primary mucosal melanoma as well as patients with active metastases of the central nervous system were excluded from study participation.

The patients were stratified according to disease stage (III, IVM1a, IVM1b versus IVM1c) and randomly assigned in a ratio of 3:1 to receive dabrafenib or dacarbazine. A total of 250 patients were randomized (187 patients to the dabrafenib arm, and 63 patients to the dacarbazine arm).

The drugs used in the study – dabrafenib or dacarbazine – were administered in a regimen that corresponded to the description in the SPCs [3-5]. Dabrafenib was administered at a dosage of 150 mg twice a day. Treatment with dacarbazine consisted of the intravenous administration of dacarbazine in a dosage of 1000 mg/m^2 body surface area on day 1 of the 3-week cycle. In addition to the study medication, patients in both treatment arms could receive supportive concomitant medication (supportive care).

The primary outcome recorded in the study BREAK-3 was PFS. If progression occurred (i.e. after occurrence of the event of the primary outcome), the patients discontinued treatment with the study medication (randomized treatment phase). Patients in the dacarbazine arm then had the option to switch to treatment with dabrafenib (crossover phase). Patients in the dabrafenib arm and those patients in the dacarbazine arm who did not switch to the crossover

phase could receive other treatments for their melanoma. The data of all patients were included in the analysis of overall survival also after switching treatment or crossover.

During the further course of the study, an amendment to the study protocol allowed patients in the dabrafenib arm to continue treatment with dabrafenib after progression was diagnosed radiologically, if, in the investigator's opinion, continued treatment posed a possible clinical advantage for the patients (Amendment 5 from 14 November 2011). No justification of this amendment could be inferred from the study documents. According to Amendment 6 (20 April 2012), patients in the dacarbazine arm, at the investigator's discretion, could already switch to treatment with dabrafenib before disease progression occurred. The justification provided for this approach was that the prespecified primary analysis of the PFS showed an advantage of dabrafenib. It was unclear how many patients in the dabrafenib arm continued their treatment with dabrafenib, and how many patients in the dacarbazine arm switched to treatment with dabrafenib before disease progression occurred.

At the time of this benefit assessment, observation of the patients in the study was not yet completed. The analysis of the primary outcome "PFS" was planned for the point in time at which 102 patients had shown progression of the disease or had died. This primary data cut-off was conducted for all outcomes on 19 December 2011 (hereinafter referred to as "first data cut-off"). At this point in time, approximately 17% of all deaths had occurred that were envisaged for the final analysis of the outcome "overall survival" (the final analysis of overall survival was to be conducted when 70% of the patients included had died or were lost to follow-up). At the time of the first data cut-off, 28 patients of the dacarbazine arm (44%) already used the crossover option.

At the request of the European Medicines Agency (EMA), additional analyses of further follow-up observations were conducted in the course of the approval procedure. In the present benefit assessment, these analyses are referred to as second data cut-off (25 June 2012) and third data cut-off (18 December 2012).

All 3 data cut-offs were used for the present benefit assessment if sufficient data were available.

Characteristics of the study population

Table 5 shows the characteristics of the patients in the study included.

Table 5: Characteristics of the study populations – RCT, direct comparison: dabrafenib vs. dacarbazine

Study **Characteristics** **Category**	**Dabrafenib** **N = 187**	**Dacarbazine** **N = 63**
Study BREAK-3 (BRF113683)		
Age [years], mean (SD)	53.5 (13.8)	51.6 (14.2)
Sex [f/m], %	40/60	41/59
ECOG status[a], n (%)		
0	124 (66)	44 (70)
1	62 (33)	16 (25)
Unknown	1 (< 1)	3 (5)
Tumour stage[a,b,c], n (%)		
III	7 (4)	4 (6)
IV	180 (96)	59 (94)
TNM classification: Distant metastases [a,c], n (%)		
Unresectable Stage III[d]	6 (3)	1 (2)
M1a	23 (12)	10 (16)
M1b	34 (18)	12 (19)
M1c	124 (66)	40 (63)
Extent of metastases (number of locations), n (%)		
< 3	94 (50)	35 (56)
≥ 3	93 (50)	28 (44)
Type of disease[a], n (%)		
Non-visceral	50 (27)	20 (32)
Visceral	22 (12)	8 (13)
Visceral and non-visceral	115 (61)	35 (56)
Elevated LDH level[a], n (%)	67 (36)	19 (30)
Treatment discontinuations[e] (data cut-off 19 Dec 2011), n (%)	80 (43)	46 (73)

a: Different points in time of the assessment of the characteristics (at the start of the study or at screening) were used in the study documents when describing the characteristics of the study population. These points in time are not presented because no differences with regards to content result from them.
b: Staging of the melanoma according to the AJCC.
c: Discrepancies between the information on disease stage (staging of the AJCC) and the classification of distant metastases were pointed out in the study documents. However, these were not relevant for the present benefit assessment.
d: Equivalent to the classification of distant metastases M0 (no distant metastases).
e: Disease progression was cited as the most common reason for discontinuation (dabrafenib 35%, dacarbazine 68%). Further reasons reported were adverse events, treatment discontinuation at the investigator's discretion, and decision by the patient.

AJCC: American Joint Committee on Cancer; ECOG: Eastern Cooperative Oncology Group, f: female; LDH: lactate dehydrogenase; m: male; n: number of patients in the category; N: number of randomized patients; RCT: randomized controlled trial; SD: standard deviation; TNM: tumour node metastasis; vs.: versus

There were no important differences between the treatment groups with regards to the following characteristics: age, sex, Eastern Cooperative Oncology Group (ECOG) performance status, tumour stage, extent of metastases, type of disease (visceral or non-visceral metastases) and lactate dehydrogenase (LDH) status. The patients were just over 50 years of age, about 40% of the patients were women. 99% of the patients in the study population were of white/European origin (data not presented in Table 5). The disease was in the most advanced stage of metastasis (M1c) in about 66% of the enrolled patients. The proportion of study discontinuations in the dacarbazine arm was more than 1.5 times as high as the one in the dabrafenib arm. The most frequently cited reason for treatment discontinuation was disease progression.

Risk of bias at study level

Table 6 shows the risk of bias at study level.

Table 6: Risk of bias at study level – RCT, direct comparison: dabrafenib vs. dacarbazine

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patient	Treating staff			
BRF113683 (BREAK-3)	Unclear[a]	Yes	No	No	Yes	No[b]	High

a: Due to imprecise description of the random sequence generation in the study documents.
b: High proportion of patients in the dacarbazine arm who changed to the dabrafenib arm after disease progression (crossover patients): 44% of the patients at the first data cut-off on 19 December 2011; this proportion increased during the 2 subsequent data cut-offs.
RCT: randomized controlled trial; vs.: versus

The risk of bias at study level in the BREAK-3 study was rated as high.

The random sequence generation was rated as unclear because of the imprecise description in the study documents. However, this did not result in rating the risk of bias at study level as high because allocation concealment in the study was conducted adequately.

The high risk of bias was largely due to the fact that, from the start of the study, patients in the dacarbazine arm had the option to switch to treatment with dabrafenib after disease progression. 44% of the patients in the dacarbazine arm had already chosen this option at the time of the primary analysis (first data cut-off). This crossover from patients of the dacarbazine arm to treatment with dabrafenib can have an important influence on the effect estimates of all patient-relevant outcomes investigated.

This deviates from the company’s assessment, which derived a low risk of bias at study level.

Further information on study design, study populations and the risk of bias at study level can be found in Module 4, Sections 4.2.5.2, 4.3.1.2.1, 4.3.1.2.2, 4.3.2.1.2 and 4.5.4, and in Appendix 4-G 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 on added benefit

The following patient-relevant outcomes were considered in this assessment (for reasons, see Section 2.7.2.4.3 of the full dossier assessment):

- Mortality: overall survival
- Morbidity: symptoms (recorded with the symptom scales of the disease-specific instrument EORTC QLQ-C30)
- Health-related quality of life (recorded with the scales on quality of life of the disease-specific instrument EORTC QLQ-C30 and using the generic instrument EQ-5D)
- Adverse events
  - serious adverse events
  - severe adverse event (CTCAE Grade ≥ 3)
  - adverse events that led to treatment discontinuation
  - common adverse events

The choice of patient-relevant outcomes deviated from that of the company, which used further outcomes in the dossier (Module 4) (see Section 2.7.2.4.3 of the full dossier assessment). Particularly the outcomes “PFS” and “tumour response” (“overall response rate”, “duration of response” and “time to response”) were not used for the present benefit assessment because these outcomes were only recorded using imaging techniques. The validity of a surrogate characteristic of both outcomes was also not sufficiently proven. See Sections 2.7.2.4.3 and 2.7.2.9.4 of the full dossier assessment for more details on the choice of outcomes and the assessment of the company’s rationale on the use of surrogate outcomes.

In addition, the company categorized the disease-specific instrument EORTC QLQ-C30 completely as health-related quality of life and therefore did not draw any conclusions on morbidity (symptoms). This approach was not accepted in the present benefit assessment; instead, the results of the EORTC QLQ-C30 on symptoms were categorized as morbidity.

Table 7 shows for which patient-relevant outcomes data were available in the study included.

Table 7: Matrix of outcomes – RCT, direct comparison: dabrafenib vs. dacarbazine

Study	Outcomes							
	Overall survival[a,b,c]	Morbidity (symptoms)[a,b,d]	Health-related quality of life (disease-specific instrument)[a,b,e]	Health-related quality of life (generic instrument EQ-5D)[a,b]	Serious adverse events[a]	Discontinuation due to adverse events[a]	Severe adverse events (CTCAE Grade ≥ 3)[a]	Common adverse events[a,f]
BRF113683 (BREAK-3)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

a: First data cut-off on 19 December 2011.
b: Second data cut-off on 25 June 2012.
c: Third data cut-off on 18 December 2012.
d: Recorded with the symptom scales of the disease-specific instrument EORTC QLQ-C30.
e: Recorded with the scales on health-related quality of life of the disease-specific instrument EORTC QLQ-C30.
f: Individual System Organ Classes according to the Medical Dictionary for Regulatory Activities were considered: skin and subcutaneous tissue disorders, gastrointestinal disorders, musculoskeletal and connective tissue disorders, nervous system disorders, neoplasms benign, malignant and unspecified, blood and lymphatic system disorders, general disorders and administration site conditions.

CTCAE: Common Terminology Criteria for Adverse Events, EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EQ-5D: European Quality of Life-5 Dimensions; RCT: randomized controlled trial; vs.: versus

For the study BREAK-3, the company presented data for the first date of analysis for the outcome "all-cause mortality" and the outcomes regarding harm. For overall survival, additional data were available after the second and third data cut-off.

For symptoms and health-related quality of life, the company exclusively presented results on the second data cut-off in Module 4 without justifying this. The analyses on the first data cut-off (change between start of the study and week 15) suitable for the benefit assessment were only very rudimentarily available in the study documents and could therefore not be used for the assessment. It could not be assumed on the basis of the study documents, however, that there were relevant differences in results between the analysis dates. At the first data cut-off, all patients were randomized and in observation for at least 15 weeks. Overall, no new patients were included in the analysis of quality of life at the second data cut-off. Hence the results of the second data cut-off were considered to be sufficiently valid. Due to this data constellation, solely the analysis of the second data cut-off was used for the assessment.

Table 8 shows the risk of bias for these outcomes.

Table 8: Risk of bias at study and outcome level – RCT, direct comparison: dabrafenib vs. dacarbazine

Study	Study level	Outcomes							
		Overall survival	Morbidity (symptoms)[b]	Health-related quality of life (disease-specific instrument)[d]	Health-related quality of life (generic instrument EQ-5D)	Serious adverse events	Discontinuation due to adverse events	Severe adverse events (CTCAE Grade ≥ 3)	Common adverse events[h]
BRF113683 (BREAK-3)	High	High[a]	High[a,c]	High[a,c]	–[e]	–[f]	High[g]	–[f]	–[f]

a: Due to the high proportion of patients in the dacarbazine arm who changed to the dabrafenib arm after disease progression (44% of the patients at the first data cut-off on 19 December 2011; this proportion increased during 2 subsequent data cut-offs).
b: Recorded with the symptom scales of the disease-specific instrument EORTC QLQ-C30.
c: Subjective outcome in open-label study.
d: Recorded with the scales on health-related quality of life of the disease-specific instrument EORTC QLQ-C30.
e: No evaluable data available (see Section 2.7.2.4.2 of the full dossier assessment).
f: Only qualitative interpretation of the results possible (see Section 2.4 and Section 2.7.2.4.2 of the full dossier assessment).
g: Due to the uncertainty of the approximation of the sum of the time under treatment for the sum of the time to event in the calculation of the IDR (see Section 2.7.2.4.2 of the full dossier assessment).
h: Individual System Organ Classes according to the Medical Dictionary for Regulatory Activities were considered: skin and subcutaneous tissue disorders, gastrointestinal disorders, musculoskeletal and connective tissue disorders, nervous system disorders, neoplasms benign, malignant and unspecified, blood and lymphatic system disorders, general disorders and administration site conditions.
CTCAE: Common Terminology Criteria for Adverse Events; EQ-5D: European Quality of Life-5 Dimensions; IDR: incidence density ratio; RCT: randomized controlled trial; vs.: versus

The risk of bias was rated as high for all outcomes for which evaluable results were presented in the dossier. The main reason for this rating is the high proportion of patients who switched from the dacarbazine arm to the dabrafenib arm (crossover patients). Treatment switching can have an important influence on the effect estimates of all outcomes investigated.

For the outcomes "morbidity" and "health-related quality of life" (measured using the disease-specific instrument EORTC QLQ-C30), the open-label study design additionally led to a high risk of bias.

Overall, the assessment of the risk of bias for the outcomes "all-cause mortality", "morbidity (symptoms)" and "health-related quality of life" (measured using the disease-specific instrument EORTC QLQ-C30) concurred with the company's assessment (high risk of bias).

No evaluable results were available for health-related quality of life measured using the generic instrument EQ-5D (see Section 2.7.2.4.3 of the full dossier assessment). Therefore no outcome-specific assessment of the risk of bias was conducted.

No outcome-specific assessment of the risk of bias for all outcomes regarding harm considered in the benefit assessment with the exception of discontinuations due to adverse events was conducted because the company presented no evaluable data. The decisive reason for this was the difference in treatment and observation duration in the 2 treatment arms of the study. Adverse events in the randomized treatment phase of the study were recorded up to the earliest occurrence of 1 of the following events: death, 28 days after the last dose of the study medication was taken due to disease progression, toxicity or study discontinuation. The median treatment duration in the dabrafenib and in the dacarbazine groups was 4.9 and 2.8 months. Due to the differences in treatment duration, more adverse events and treatment discontinuations due to an adverse event could occur in the dabrafenib group than in the comparator group. This constituted a bias to the disadvantage of dabrafenib. The company also pointed out this possible bias in the result section of the dossier, but did not present any adequate analyses addressing this problem.

In the case of rare events, the Institute performed its own calculations of the incidence density. This was only possible for the outcome “discontinuations due to adverse events”. For rare events, this analysis can serve as an approximation for the analysis of the time to an event. The risk of bias for this analysis was therefore rated as high.

The interpretation of the results on adverse events (naive proportions) depends on the direction of effect observed. In the case of a statistically significant advantage of dabrafenib with regards to adverse events, due to the known direction of the bias to the disadvantage of dabrafenib, it can be concluded that greater harm from dabrafenib is excluded. Moreover, it can be assumed that the statistically significant effect in favour of dabrafenib would remain if the bias was eliminated. In the case of differences that are not statistically significant between the treatment arms, it can only be concluded that the data presented showed no greater harm despite the bias to the disadvantage of dabrafenib. If the biased analysis shows a statistically significant disadvantage of dabrafenib, however, the effect would rather be overestimated, but it cannot be excluded that the true effect is in fact to the disadvantage of dabrafenib. Overall, the relative risks estimated on the basis of naive proportions were no adequate analysis.

Further information on the choice of outcomes and risk of bias at outcome level can be found in Module 4, Sections 4.2.5.2, 4.3.1.2.2, 4.3.1.3 and 4.5.4 of the dossier, and in Sections 2.7.2.4.2, 2.7.2.4.3 and 2.7.2.9.4 of the full dossier assessment.

Table 9, Table 10 and Table 11 summarize the results on the comparison of dabrafenib with dacarbazine in adult patients with unresectable or metastatic melanoma. The data from the company’s dossier were supplemented, where necessary, by the Institute’s own calculations. The Kaplan-Meier curves on the outcome “overall survival” can be found in Appendix B of the full dossier assessment.

Table 9: Results (survival time) – RCT, direct comparison: dabrafenib vs. dacarbazine

Study Outcome category	Dabrafenib		Dacarbazine		Dabrafenib vs. dacarbazine	
Outcome Data cut-off	N	Median survival time [95% CI] (months)	N	Median survival time [95% CI] (months)	HR[a] [95% CI]	p-value
BRF113683 (BREAK-3)						
Mortality						
Overall survival						
First data cut-off[b,c]						
19 Dec 2011	187	n.a. [n.a.; n.a.]	63	n.a. [n.a.; n.a.]	0.61 [0.25; 1.48]	n.d.
Second data cut-off[b,d]						
25 Jun 2012	187	n.a. [n.a.; n.a.]	63	n.a. [11.3; n.a.]	0.75 [0.44; 1.29]	n.d.
Third data cut-off[b,e]						
18 Dec 2012	187	18.2 [16.6; n.a]	63	15.6 [12.7; n.a]	0.76 [0.48; 1.21]	n.d.

a: Hazard ratio estimated using Pike estimator [6], adjusted according to disease stage at screening.
b: Patients were not censored at the time of treatment switching.
c: Number of crossover patients in the dacarbazine arm: n = 28 (44%).
d: Number of crossover patients in the dacarbazine arm: n = 35 (56%).
e: Number of crossover patients in the dacarbazine arm: n = 36 (57%) [7].
CI: confidence interval, HR: hazard ratio, N: number of analysed patients, n.a.: not achieved; n.d.: no data; RCT: randomized controlled trial; vs.: versus

Table 10: Results on morbidity (symptoms) and on health-related quality of life – RCT, direct comparison: dabrafenib vs. dacarbazine

Study Outcome category Instrument Scales	Dabrafenib			Dacarbazine			Dabrafenib vs. dacarbazine
	N[a]	Values at start of study mean (SD)	Change from start of study Mean (SE)	N[a]	Values at start of study mean (SD)	Change from start of study Mean (SE)	Mean difference[b] [95% CI]; p-value
BRF113683 (BREAK-3)							
Morbidity							
EORTC QLQ-C30 symptom scales[c] second data cut-off on 25 June 2012[d]							
Fatigue	131	27.34 (26.17)	0.83 (1.75)	18	25.19 (24.45)	7.02 (4.54)	–6.19 [–15.79; 3.41]; 0.205
Nausea and vomiting	132	7.17 (16.66)	–2.57 (0.97)	18	10.83 (20.31)	3.81 (2.59)	–6.38 [–11.84; –0.92] 0.022[e]
Pain	132	26.52 (30.83)	–3.16 (1.91)	18	22.22 (26.87)	−0.20 (5.02)	–2.96 [–13.56; 7.64]; 0.583
Dyspnoea	134	13.55 (22.15)	–0.98 (1.55)	18	10.56 (21.69)	7.20 (4.06)	–8.18 [–16.77; 0.41]; 0.062
Insomnia	133	28.57 (29.14)	–2.76 (2.40)	18	24.44 (31.21)	4.37 (6.34)	–7.13 [–20.51; 6.25]; 0.294
Appetite loss	134	15.39 (27.05)	–6.02 (1.47)	18	15.56 (25.65)	0.98 (3.89)	–7.00 [–15.21; 1.21]; 0.094
Constipation	131	8.80 (21.05)	–1.49 (1.18)	18	8.89 (22.01)	1.14 (3.02)	–2.63 [–9.04; 3.77]; 0.418
Diarrhoea	131	5.43 (12.34)	–2.24 (1.07)	18	8.33 (16.95)	0.27 (2.83)	–2.51 [–8.48; 3.46]; 0.407
Financial difficulties[f]	132	20.37 (31.59)	0.56 (1.89)	18	23.16 (29.85)	0.07 (4.94)	0.49 [–9.95; 10.92]; 0.927

(continued)

Table 10: Results on morbidity (symptoms) and on health-related quality of life – RCT, direct comparison: dabrafenib vs. dacarbazine (continued)

Study Outcome category	Dabrafenib			Dacarbazine			Dabrafenib vs. dacarbazine
Instrument Scales	N[a]	Values at start of study mean (SD)	Change from start of study Mean (SE)	N[a]	Values at start of study mean (SD)	Change from start of study Mean (SE)	Mean difference[b] [95% CI]; p-value
BRF113683 (BREAK-3)							
Health-related quality of life							
EORTC QLQ-C30[g] **second data cut-off on 25 June 2012[d]**							
Global health status/health-related quality of life	131	67.13 (22.66)	–0.13 (1.66)	17	67.64 (20.42)	4.84 (4.53)	–4.97 [–14.50; 4.57]; 0.305
Physical functioning	132	83.59 (19.71)	–1.33 (1.20)	18	86.22 (18.93)	–3.45 (3.12)	2.12 [–4.48; 8.72]; 0.527
Role functioning	133	75.09 (30.23)	–2.05 (1.83)	17	77.12 (30.62)	0.78 (4.95)	–2.84 [–13.26; 7.59]; 0.592
Emotional functioning	132	72.64 (22.39)	7.52 (1.46)	18	71.94 (20.58)	1.93 (3.92)	5.59 [–2.68; 13.85]; 0.184
Cognitive functioning	133	87.69 (17.82)	–1.59 (1.28)	17	88.98 (15.97)	–5.04 (3.47)	3.45 [–3.86; 10.76]; 0.352
Social functioning	130	75.98 (28.44)	1.64 (1.80)	18	75.42 (25.77)	1.07 (4.72)	0.571 [–9.40; 10.54]; 0.910
EQ-5D	No evaluable results available						

(continued)

Table 10: Results on morbidity (symptoms) and on health-related quality of life – RCT, direct comparison: dabrafenib vs. dacarbazine (continued)

a: Number of patients in the analysis at the end of the study, the values at the start of the study (or at other points in time) may be based on other patient numbers.
b: Change between start of study and week 15; estimator from a model using repeated measures (MMRM) with the following variables: time, treatment, treatment-time interaction.
c: EORTC QLQ-C30 symptom scales, range 0-100; lower (decreasing) values mean fewer symptoms; negative values in the group comparison mean an advantage of dabrafenib.
d: The company did not present the analysis of the first data cut-off (19 Dec 2011). The company did not provide an explanation for this. The information on the first data cut-off was only rudimentarily available in the clinical study report.
e: SMD in the form of Hedges' g for assessment of the relevance of the statistically significant group difference: −0.57 [−1.07; −0.07] p = 0.024 (Institute's calculation). As the 95% CI for the SMD does not lie completely below the irrelevance threshold of −0.2, an irrelevant effect cannot be excluded.
f: Financial difficulties are part of the questionnaire, but are not considered to be part of morbidity (symptoms).
g: EORTC QLQ-C30 functional scales, range 0-100; higher (increasing) values mean better functionality; positive effects in the group comparison mean an advantage of dabrafenib.
CI: confidence interval; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (Version 3); EQ-5D: European Quality of Life-5 Dimensions; n.d.: no data; MMRM: mixed-effects model repeated measures; N: number of analysed patients; RCT: randomized controlled trial; SD: standard deviation; SE: standard error; SMD: standardized mean difference; VAS; visual analogue scale; vs.: versus

Table 11: Results on adverse events – RCT, direct comparison: dabrafenib vs. dacarbazine

Study Outcome	Dabrafenib		Dacarbazine		Dabrafenib vs. dacarbazine
	N	Patients with event n (n/1000 patient years)[a]	N	Patients with event n (n/1000 patient years)[b]	IDR [95% CI]; p-value
BRF113683 (BREAK-3)					
First data cut-off 19 Dec 2011					
SAEs	Only qualitative interpretation of results possible[c]				
Discontinuation due to AE	187	5 (63.6)[d]	59	2 (125.8)[d]	IDR 0.51 [0.10; 2.61] 0.416[e]
Severe AEs (CTCAE Grade ≥ 3)	Only qualitative interpretation of results possible[c]				
Common AEs[f]					
Skin and subcutaneous tissue disorders	Only qualitative interpretation of results possible[c]				
Blood and lymphatic system disorders	Only qualitative interpretation of results possible[c]				
Gastrointestinal disorders	Only qualitative interpretation of results possible[c]				
Musculoskeletal and connective tissue disorders	Only qualitative interpretation of results possible[c]				
General disorders and administration site conditions	Only qualitative interpretation of results possible[c]				
Nervous system disorders	Only qualitative interpretation of results possible[c]				
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Only qualitative interpretation of results possible[c]				

a: Mean treatment time with study medication in the dabrafenib arm: 5.0 months.
b: Mean treatment time with study medication in the dacarbazine arm: 3.2 months.
c: See Appendix A, Table 19, of the full dossier assessment for the presentation of the naive proportions of the patients with events.
d: Patients with event per 1000 patient years; Institute's calculation.
e: Institute's calculation of estimate, related confidence interval and p-value.
f: System organ classes coded according to the Medical Dictionary for Regulatory Activities.
AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; IDR: incidence density ratio; N: number of analysed patients; n: number of patients with event; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus

Only 1 study was available for the assessment of dabrafenib. The study BREAK-3 did not meet the particular requirements placed on the derivation of proof of an added benefit from a single study [1]. Hence, at most "indications" – e.g. of an added benefit – could be derived from the data.

Mortality (overall survival)

Over the entire observation period (in all 3 data cut-offs), treatment with dabrafenib produced no statistically significant prolongation in overall survival in comparison with treatment with

dacarbazine. Hence an added benefit of dabrafenib in comparison with the ACT is not proven for this outcome.

This deviates from the company's assessment, which derived a major added benefit for overall survival. The company's conclusions were based on a summary of different analyses (intention-to-treat analysis and analyses for the adjustment of the crossover effect). However, the crossover adjustments conducted by the company were not relevant for the benefit assessment because they were based on strong assumptions, the fulfilment of which cannot be checked with the available data (see Section 2.7.2.2 of the full dossier assessment). In addition, the results of these analyses presented by the company showed no statistically significant advantage of dabrafenib with regards to overall survival.

Moreover, the company derived the added benefit on the basis of the results on PFS as surrogate for overall survival. These were not used for the assessment of the added benefit of dabrafenib in the present benefit assessment because the validity of the surrogate characteristic was not shown (also not on the basis of the validity study presented by the company) (see Section 2.7.2.9.4 of the full dossier assessment).

Morbidity (symptoms)

Aspects of morbidity were recorded in the study BREAK-3 using the symptom scales of the disease-specific questionnaire EORTC QLQ-C30.

The group comparison of the continuous data (change between start of study and week 15, mixed-effects model repeated measures [MMRM]) for EORTC QLQ-C30 showed a statistically significant effect in favour of dabrafenib regarding the symptom subscale "nausea and vomiting". This result was also consistent with the direction of the effect regarding harm (SOC "gastrointestinal disorders" according to the Medical Dictionary for Regulatory Activities [MedDRA], see section on adverse events below). For all other symptom subscales (fatigue, pain, dyspnoea, insomnia, appetite loss, constipation and diarrhoea), there were no statistically significant differences in comparison with dacarbazine.

An analysis of the effect size on the subscale "nausea and vomiting" on the basis of Hedges' g (responder analyses with an empirically validated response criterion were not available) showed that an irrelevant effect could not be excluded for nausea and vomiting because the 95% confidence interval was not fully below the irrelevance threshold of −0.2 (see Table 10).

Summarizing the results on morbidity (symptoms), there is not proof of an added benefit of dabrafenib compared with the ACT.

This result deviates from the assessment of the company, which classified the entire EORTC QLQ-C30 questionnaire as the outcome "health-related quality of life". It did not draw any separate conclusions on the symptom scales and thus on morbidity.

Health-related quality of life: disease-specific instrument (EORTC-QLQ-C30) and generic instrument (EQ-5D)

EORTC QLQ-C30 is an instrument developed for cancer patients, which contains 6 subscales on quality of life. In the analysis considered (change between start of study and week 15, MMRM), there were no statistically significant differences between dabrafenib and dacarbazine in any of the subscales of the questionnaire.

No evaluable results were available for health-related quality of life measured with the generic instrument EQ-5D (see Section 2.7.2.4.3 of the full dossier assessment).

Overall, there is no proof of added benefit of dabrafenib compared with the ACT for health-related quality of life (disease-specific instrument EORTC QLQ-C30 or generic instrument EQ-5D).

This result deviates from the company's assessment, which used both instruments for the assessment of the added benefit. Due to a statistically significant effect of dabrafenib in a EORTC QLQ-C30 subscale on emotional functioning at earlier points in time (change at week 6 and week 12), the company overall derived a minor added benefit.

Adverse events

The company's dossier mostly contained no valid data for the assessment of adverse events, which could be included in the benefit assessment. The company presented the data on the basis of the naive proportions (proportion of patients with at least one event). However, these results did not constitute an adequate analysis because the treatment durations with the study medication differed considerably between the 2 treatment arms (median treatment duration 4.9 months in the dabrafenib arm, and 2.8 months in the dacarbazine arm) (see also Section 2.7.2.4.2 of the full dossier assessment).

Therefore the analysis of the incidence density on the basis of the Institute's calculations was used for this benefit assessment, but only in case of rare events. The incidence density ratio was calculated as related effect measure. For non-rare events, only a qualitative interpretation could be conducted on the basis of the data presented in the dossier.

Serious adverse events and severe adverse event (CTCAE Grade ≥ 3)

Regarding the outcomes "serious adverse events" and "severe adverse events" (CTCAE Grade ≥ 3), there was no statistically significant difference between the treatment arms on the basis of the naive proportions. It could only be concluded for these outcomes that the data presented showed no greater harm despite the bias to the disadvantage of dabrafenib. Hence greater or lesser harm from dabrafenib than from dacarbazine is not proven for these outcomes.

Treatment discontinuation due to adverse events

Results were available for the outcome "treatment discontinuation due to adverse events", on the basis of which the Institute could calculate the incidence density ratio. There was no statistically significant difference between dabrafenib and dacarbazine. Hence greater or lesser harm from dabrafenib than from dacarbazine is not proven for this outcome.

Common adverse events

For the SOCs "blood and lymphatic system disorders" and "gastrointestinal disorders", there was a statistically significant difference in favour of dabrafenib on the basis of the naive proportions. Under consideration of the known direction of the bias, a qualitative conclusion can be derived from these results that greater harm from dabrafenib compared with dacarbazine is excluded. Moreover, it can be assumed that the statistically significant effect in favour of dabrafenib would remain if the bias was eliminated. This resulted in a hint of lesser harm from dabrafenib compared with dacarbazine for these 2 outcomes.

There was a statistically significant difference to the disadvantage of dabrafenib for the remaining SOCs (skin and subcutaneous tissue disorders, musculoskeletal and connective tissue disorders, general disorders and administration site conditions, nervous system disorders, and neoplasms benign, malignant and unspecified). Under consideration of the known direction of the bias it could not be excluded that the statistically significant effect to the disadvantage of dabrafenib would still remain if the bias was eliminated. It could also not be excluded that the differences observed were caused by the bias. Overall, greater harm from dabrafenib is not excluded for these outcomes.

The company presented the results on the individual operationalizations of the complex "adverse events" using the naive proportions. Under consideration of the severity of the disease, it assessed the adverse events overall as tolerable and readily treatable.

Subgroup analyses

Subgroup analyses for the following characteristics were considered to be relevant for the present benefit assessment: age (< 65 years/≥ 65 years), sex (male/female), disease stage at the start of the study (unresectable III, IVM1a, IVM1b/IVM1c), ECOG status (0/1), LDH value at the start of the study (normal/increased) and presence of visceral disease at screening (yes/no).

For overall survival, the company presented subgroup analyses on all factors. For all other outcomes included, only results on the relevant subgroup characteristics "age", "sex" and "disease stage" were available. Overall, interaction tests showed no interactions between the factors mentioned above and the treatment effect. Hence the subgroup analyses are not considered further here.

Further information on the choice of outcomes, on risk of bias at outcome level, and on outcome results can be found in Module 4, Sections 4.2.5.2, 4.3.1.2.2, 4.3.1.3 and 4.5.4 of the dossier and in Sections 2.7.2.4.2, 2.7.2.4.3 and 2.7.2.9.4 of the full dossier assessment.

2.5 Extent and probability of added benefit

The derivation of extent and probability of added benefit of dabrafenib at outcome level is shown below, taking into account the various outcome categories and effect sizes. The methods used for this purpose are explained in the *General Methods* of the Institute [1].

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

2.5.1 Assessment of added benefit at outcome level

The data presented in Section 2.4 did not result in an added benefit of dabrafenib regarding overall survival, morbidity (symptoms), health-related quality of life and discontinuations due to adverse events.

Only a qualitative interpretation of the results on further outcomes regarding harm could be conducted because, overall, no valid results were available. For the outcomes “blood and lymphatic system disorders” and “gastrointestinal disorders”, this resulted in a hint of lesser harm. In contrast, it is unclear whether the statistically significant effects observed for the outcomes “skin and subcutaneous tissue disorders”, “musculoskeletal and connective tissue disorders”, “general disorders and administration site conditions”, “nervous system disorders”, and “neoplasms benign, malignant and unspecified” were in fact due to greater harm or caused by bias. Because of the uncertainty described with regards to the effects on adverse events, the harm cannot be adequately assessed.

The extent of the respective added benefit at outcome level was estimated from these results (see Table 12).

Table 12: Extent of added benefit at outcome level: dabrafenib vs. dacarbazine

Outcome category **Outcome**	**Dabrafenib vs. dacarbazine** **quantile of time to event or proportion of events/** **effect estimate [95%]** **p-value** **probability**[a]	**Derivation of extent**[b]
Mortality		
Overall survival	**First data cut-off (19 Dec 2011)** median: not achieved HR: 0.61 [0.25; 1.48] p-value = n.d. **Second data cut-off (19 Jun 2012)** median: not achieved HR: 0.75 [0.44; 1.29] p-value = n.d. **Third data cut-off (18 Dec 2012)** median: 18.2 vs. 15.6 HR: 0.76 [0.48; 1.21] p-value = n.d.	Added benefit not proven
Morbidity		
EORTC QLQ-C30: symptom scales		
Fatigue	MD: −6.19 [−15.79; 3.41] p = 0.205	Added benefit not proven
Nausea and vomiting	MD: −6.38 [−11.84; −0.92] p = 0.022 An irrelevant effect cannot be excluded: SMD: −0.57 [−1.07; −0.07]	
Pain	MD: –2.96 [–13.56; 7.64] p = 0.583	
Dyspnoea	MD: –8.18 [–16.77; 0.41] p = 0.062	
Insomnia	MD: –7.13 [–20.51; 6.25] p = 0.294	
Appetite loss	MD: –7.00 [–15.21; 1.21] p = 0.094	
Constipation	MD: –2.63 [–9.04; 3.77] p = 0.418	
Diarrhoea	MD: –2.51 [–8.48; 3.46] p = 0.407	

(continued)

Table 12: Extent of added benefit at outcome level: dabrafenib vs. dacarbazine (continued)

Outcome category **Outcome**	**Dabrafenib vs. dacarbazine** **quantile of time to event or proportion of events/** **effect estimates [95% CI]** **p-value** **probability**[a]	**Derivation of extent**[b]
Health-related quality of life		
EORTC QLQ-C30: functional scales		
Global health status/health-related quality of life	MD: –4.97 [–14.50; 4.57] p = 0.305	Added benefit not proven
Physical functioning	MD: 2.12 [–4.48; 8.72] p = 0.527	
Role functioning	MD: –2.84 [–13.26; 7.59] p = 0.592	
Emotional functioning	MD: 5.59 [–2.68; 13.85] p = 0.184	
Cognitive functioning	MD: 3.45 [–3.86; 10.76] p = 0.352	
Social functioning	MD: 0.571 [–9.40; 10.54] p = 0.910	
EQ-5D	No evaluable data available	
Adverse events		
Serious adverse events	Qualitative interpretation on the basis of the naive proportions of the patients with adverse events[c]	Greater/lesser harm not proven
Severe adverse events (CTCAE Grade ≥ 3)	Qualitative interpretation on the basis of the naive proportions of the patients with adverse events[c]	Greater/lesser harm not proven
Discontinuations due to adverse events	IDR: 0.51 [0.10; 2.61] p = 0.416	Greater/lesser harm not proven

(continued)

Table 12: Extent of added benefit at outcome level: dabrafenib vs. dacarbazine (continued)

Outcome category **Outcome**	**Dabrafenib vs. dacarbazine** **quantile of time to event or proportion of events/** **effect estimates [95% CI]** **p-value** **probability**[a]	**Derivation of extent**[b]
Adverse events		
Common adverse events[d]		
Skin and subcutaneous tissue disorders	Qualitative interpretation on the basis of the naive proportions of the patients with adverse events[c]	–[e]
Blood and lymphatic system disorders	Qualitative interpretation on the basis of the naive proportions of the patients with adverse events[c] probability: "hint"	Outcome category: non-serious/non-severe adverse events lesser harm, extent: "considerable"
Gastrointestinal disorders	Qualitative interpretation on the basis of the naive proportions of the patients with adverse events[c] probability: "hint"	Outcome category: non-serious/non-severe adverse events lesser harm, extent: "non-quantifiable"
Musculoskeletal and connective tissue disorders	Qualitative interpretation on the basis of the naive proportions of the patients with adverse events[c]	–[e]
General disorders and administration site conditions	Qualitative interpretation on the basis of the naive proportions of the patients with adverse events[c]	–[e]
Nervous system disorders	Qualitative interpretation on the basis of the naive proportions of the patients with adverse events[c]	–[e]
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Qualitative interpretation on the basis of the naive proportions of the patients with adverse events[c]	–[e]

a: Probability provided if statistically significant differences were present.
b: Estimations of effect size are made depending on the outcome category with different limits based on the upper limit of the CI.
c: The naive proportions of the patients with events are presented in Appendix A, Table 19, of the full dossier assessment.
d: System organ classes coded according to the Medical Dictionary for Regulatory Activities.
e: Not evaluable because of the bias.

CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (Version 3); EQ-5D: European Quality of Life-5 Dimensions; HR: Hazard Ratio; IDR: incidence density ratio; MD: mean difference; n.d.: no data; RR: relative risk; SMD: standardized mean difference in form of Hedges' g; vs.: versus

2.5.2 Overall conclusion on added benefit

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

Table 13: Positive and negative effects from the assessment of dabrafenib compared with dacarbazine

Positive effects	**Negative effects**
Hint of lesser harm – extent: "considerable" (non-serious/non-severe adverse events: blood and lymphatic system disorders)	No adequate assessment of harm possible because of great uncertainty in the assessment of the effects for adverse events[a] Greater harm is not excluded
Hint of lesser harm – extent: "non-quantifiable" (non-serious/non-severe adverse events: gastrointestinal disorders)	
a: In relation to skin and subcutaneous tissue disorders, musculoskeletal and connective tissue disorders, general disorders and administration site conditions, nervous system disorders, and neoplasms benign, malignant and unspecified (including cysts and polyps).	

On the basis of the available results, positive effects (in each case "hint") remain for dabrafenib for the outcome category "non-serious/non-severe adverse events" (blood and lymphatic system disorders, gastrointestinal disorders). The extent of added benefit is "considerable" for the outcome "blood and lymphatic system disorders", and "non-quantifiable" for the outcome "gastrointestinal disorders". The outcome category "non-quantifiable" for the outcome "gastrointestinal disorders" expresses the uncertainty regarding the effect size.

With regards to negative effects and under consideration of the known direction of the bias it could not be excluded that the statistically significant effect to the disadvantage of dabrafenib would still remain if the bias was eliminated. It could also not be excluded that the differences observed were caused by the bias. Overall, greater harm from dabrafenib is not excluded for these outcomes. An adequate assessment of harm is therefore not possible.

The lack of effects regarding benefit and the uncertainty described regarding harm lead to the assessment that, overall, no proof of added benefit of dabrafenib compared with the ACT dacarbazine can be derived in the monotherapy of unresectable or metastatic melanoma in adult patients.

2.5.3 Extent and probability of added benefit – summary

The result of the assessment of the added benefit of dabrafenib in comparison with the ACT is shown in Table 14.

Table 14: Extent and probability of the added benefit of dabrafenib

Therapeutic indication	ACT specified by the G-BA	Extent and probability of added benefit
Monotherapy in adult patients with BRAF V600 mutation-positive, unresectable or metastatic melanoma	Dacarbazine	Added benefit not proven
ACT: appropriate comparator therapy; G-BA: Federal Joint Committee		

No proof of added benefit of dabrafenib versus the ACT (dacarbazine) for the treatment of adult patients with BRAF V600 mutation-positive, unresectable or metastatic melanoma could be derived from the data presented by the company.

The approach for deriving an overall conclusion on added benefit is a proposal by IQWiG. 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

GlaxoSmithKline. A phase III randomized, open-label study comparing GSK2118436 to dacarbazine (DTIC) in previously untreated subjects with BRAF mutation positive advanced (stage III) or metastatic (stage IV) melanoma: protocol summary [online]. In: GSK Clinical Study Register. 27 November 2013 [accessed: 5 December 2013]. URL: http://www.gsk-clinicalstudyregister.com/protocol_detail.jsp?protocolId=113683&studyId=8E5A30C9-58E9-4B81-B403-190608848BE0&compound=dabrafenib&type=Compound&letterrange=A-F.

GlaxoSmithKline. A phase III randomized, open-label study comparing GSK2118436 to DTIC in previously untreated subjects with BRAF mutation positive advanced (stage III) or metastatic (sage IV) melanoma [online]. In: EU Clinical Trials Register [accessed: 2 October 2013]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2009-015298-11.

GlaxoSmithKline. A study comparing GSK2118436 to dacarbazine (DTIC) in previously untreated subjects with BRAF mutation positive advanced (stage III) or metastatic (stage IV) melanoma: full text view [online]. In: Clinicaltrials.gov. 28 March 2013 [accessed: 2 October 2013]. URL: http://ClinicalTrials.gov/show/NCT01227889.

GlaxoSmithKline Group of Companies. A phase III randomized, open-label study comparing GSK2118436 to DTIC in previously untreated subjects with BRAF mutation positive advanced (stage III) or metastatic (stage IV) melanoma: study BRF113683; clinical protocol [unpublished]. 2010.

GlaxoSmithKline Group of Companies. A phase III randomized, open-label study comparing GSK2118436 to DTIC in previously untreated subjects with BRAF mutation positive advanced (stage III) or metastatic (stage IV) melanoma: study BRF113683; protocol amendment 01 [unpublished]. 2010.

GlaxoSmithKline Group of Companies. A phase III randomized, open-label study comparing GSK2118436 to DTIC in previously untreated subjects with BRAF mutation positive metastatic melanoma: study BRF113683; reporting and analysis plan [unpublished]. 2011.

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GlaxoSmithKline Group of Companies. A phase III randomized, open-label study comparing GSK2118436 to DTIC in previously untreated subjects with BRAF mutation positive advanced (stage III) or metastatic (stage IV) melanoma: study BRF113683; protocol amendment 06 [unpublished]. 2012.

GlaxoSmithKline Group of Companies. A phase III randomized, open-label study comparing GSK2118436 to DTIC in previously untreated subjects with BRAF mutation positive metastatic melanoma: BRF113683; additional analyses of endpoints and subgroups [unpublished]. 2013.

Hauschild A, Grob JJ, Demidov LV, Jouary T, Gutzmer R, Millward M et al. Dabrafenib in BRAF-mutated metastatic melanoma: a multicentre, open-label, phase 3 randomised controlled trial. Lancet 2012; 380(9839): 358-365.

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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 https://www.iqwig.de/de/projekte_ergebnisse/projekte/arzneimittelbewertung/a13_35_dabrafenib_nutzenbewertung_gemaess_35a_sgb_v_dossierbewertung.5344.html.