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# Addendum to Commission A13-35 (dabrafenib)[1]

## Addendum

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

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**List of abbreviations**

| Abbreviation | Meaning |
|---|---|
| ACT | appropriate comparator therapy |
| ECOG PS | Eastern Cooperative Oncology Group Performance Status |
| 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 |
| PFS | progression-free survival |
| RECIST | Response Evaluation Criteria in Solid Tumours |
| RPSFTM | rank preserving structural failure time model |
| SGB | Sozialgesetzbuch (Social Code Book) |
| SPC | Summary of Product Characteristics |

## 1 Background

On 4 March 2014 the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct a supplementary assessment for Commission A13-35 (benefit assessment of dabrafenib [1]).

The company presented an indirect comparison of dabrafenib versus vemurafenib in its dossier from 19 September 2013 [2]. This comparison was not considered in the dossier assessment because, at the time point of the dossier assessment, vemurafenib was not the appropriate comparator therapy (ACT). The G-BA now commissioned IQWiG to assess the indirect comparison of dabrafenib versus vemurafenib.

The responsibility for the present assessment and its result lies solely with IQWiG. The assessment is forwarded to the G-BA. The G-BA decides on the added benefit.

In addition to the information provided in Modules 1 to 4, it was necessary to use information from Module 5 of the company's dossier for the present addendum. This was information on study methods and study results. The respective information was included in the present addendum.

# 2 Assessment

## 2.1 Selection of analyses for the benefit assessment

The assessment was conducted based on the indirect comparison of dabrafenib and vemurafenib presented by the company in its dossier from 19 September 2013 [2].

## 2.2 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the company's sources in the dossier:

- study list on dabrafenib (studies completed up to 15 July 2013)
- bibliographical literature search on dabrafenib + dacarbazine and vemurafenib + dacarbazine (last search on 9 September 2013)
- search in trial registries on dabrafenib + dacarbazine and vemurafenib + dacarbazine (last search on 10 September 2013)

For the indirect comparison, the company conducted the searches in bibliographical databases and trial registries that were required in accordance with the dossier templates. The company's search on the indirect comparison was suited to ensure the completeness of the search result.

No additional check of the completeness of the study pool presented by the company was performed because also no further relevant studies were identified in a comparison with the dossiers and the dossier assessments on dabrafenib [1] and vemurafenib [3].

The following studies were available for the indirect comparison of dabrafenib and vemurafenib:

Table 1: Study pool – RCT, indirect comparison: dabrafenib vs. vemurafenib

| **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) dabrafenib vs. dacarbazine | Yes | Yes | No |
| BRIM-3 (NO25026) vemurafenib vs. dacarbazine | No | No[b] | Yes |
| a: Study for which the company was sponsor, or in which the company was otherwise financially involved.<br>b: Study sponsored by the pharmaceutical company who holds the approval of vemurafenib.<br>RCT: randomized controlled trial; vs.: versus | | | |

## 2.3 Outcomes for the indirect comparison

The patient-relevant outcomes listed in Table 2 were available from the BREAK-3 study and the BRIM-3 study.

Table 2: Outcomes – RCT, indirect comparison: dabrafenib vs. vemurafenib

| | Overall survival | Symptoms | Health-related quality of life | Adverse events |
|---|---|---|---|---|
| BREAK-3 (BRF113683) dabrafenib vs. dacarbazine | Yes | Yes EORTC QLQ-C30 symptom scales | Yes EORTC QLQ-C30, EQ-5D[a] | Yes |
| BRIM-3 (NO25026) vemurafenib vs. dacarbazine | Yes | Yes VAS pain | Yes FACT-M | Yes |

a: No evaluable data available [1].
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; FACT-M: Functional Assessment of Cancer Therapy-Melanoma; RCT: randomized controlled trial; VAS: visual analogue scale; vs.: versus

Overall survival and adverse events were recorded in the 2 studies with comparable operationalizations and can therefore principally be used for the indirect comparison.

The outcomes on symptoms and health-related quality of life were measured with different instruments. The company therefore conducted no indirect comparison for these outcomes. This approach was accepted.

The company additionally used the outcomes “progression-free survival (PFS)” and “tumour response” for the indirect comparison in the dossier. Both outcomes were assessed using imaging techniques and based on the Response Evaluation Criteria in Solid Tumours (RECIST). PFS and tumour response were rated as surrogate outcomes of unclear validity in the present assessment (for reasons see dossier assessments of dabrafenib and vemurafenib [1,4]) and therefore not used.

## 2.4 Informative value of the indirect comparison

The informative value of the indirect comparison depends on the following factors:

- suitability of the statistical methods
- structural quality of the data included (similarity, homogeneity, consistency)
- risk of bias of the data included

The individual requirements are discussed in the following sections. The informative value of the indirect comparison of dabrafenib and vemurafenib is then summarized.

### 2.4.1 Suitability of the statistical methods

The company presented an adjusted indirect comparison according to Bucher [5]. The statistical methods are principally suitable.

### 2.4.2 Structural quality of the data included

**Evaluation of similarity**

It was checked for the present addendum whether the studies were sufficiently comparable with regard to the patient population included and the common comparator.

The BREAK-3 study and the BRIM-3 study are active-controlled, open-label, multicentre phase 3 RCTs with 2 treatment arms. The BREAK-3 study was already presented by the company for the comparison with dacarbazine and assessed in the dossier assessment A13-35 [1]. The BRIM-3 study was used for the assessment of the added benefit of vemurafenib [3,4]. Detailed characteristics of the studies included can be found in the dossier assessments on dabrafenib and vemurafenib [1,3,4].

Both studies were approval studies for dabrafenib (BREAK-3) and vemurafenib (BRIM-3), each in comparison with dacarbazine. Adult patients with histologically confirmed advanced melanoma (stage III in the BREAK-3 study and exclusively stage IIIc in the BRIM-3 study) or metastatic melanoma (stage IV) and proven BRAF V600 mutation were enrolled. Only patients with BRAF V600E mutation were eligible for participation in the BREAK-3 study, whereas the inclusion criteria of the BRIM-3 study had no limitations with regard to the type of BRAF V600 mutation. However, also in the BRIM-3 study approximately 90% of the patients had BRAF V600E mutation.

The comparator intervention dacarbazine used in the studies was administered according to a treatment regimen that corresponded to the description in the Summary of Product Characteristics (SPC) [6,7]. Dacarbazine was administered intravenously in a dosage of 1000 mg/m$^2$ body surface area on day 1 of the 3-week cycle in both studies. Treatment with the study medications was continued until disease progression, death or study discontinuation.

Overall, the BRIM-3 study and the BREAK-3 study were comparable with respect to inclusion criteria and the treatment regimen of the comparator intervention (dacarbazine).

***Study populations included***

Table 3 shows the characteristics of patients in the studies included in the assessment.

Table 3: Characteristics of the study populations – RCT, indirect comparison: dabrafenib vs. vemurafenib

| **Study** | **BREAK-3 (BRF113683)[a]** | | **BRIM-3 (NO25026)** | |
|---|---|---|---|---|
| **Characteristics category** | **Dabrafenib N = 187** | **Dacarbazine N = 63** | **Vemurafenib N = 337** | **Dacarbazine N = 338** |
| Age [years], mean (SD) | 53.5 (13.8) | 51.6 (14.2) | 55 (14) | 53 (14) |
| Sex [F/M], % | 40/60 | 41/59 | 41/59 | 46/54 |
| ECOG status, n (%) | | | | |
| 0 | 124 (66) | 44 (70) | 229 (68) | 230 (68) |
| 1 | 62 (33) | 16 (25) | 108 (32) | 108 (32) |
| unknown | 1 (< 1) | 3 (5) | 0 (0) | 0 (0) |
| Tumour stage[b,c], n (%) | | | | |
| III[d] | 7 (4) | 4 (6) | 20 (6) | 13 (4) |
| IV | 180 (96) | 59 (94) | 317 (94) | 325 (96) |
| TNM classification: distant metastases[b], n (%) | | | | |
| unresectable stage III[c,d,e] | 6 (3) | 1 (2) | 20 (6) | 13 (4) |
| M1a | 23 (12) | 10 (16) | 34 (10) | 40 (12) |
| M1b | 34 (18) | 12 (19) | 62 (18) | 65 (19) |
| M1c | 124 (66) | 40 (63) | 221 (66) | 220 (65) |
| Extent of metastases (number of locations), n (%) | | | | |
| < 3 | 94 (50) | 35 (56) | 185 (56) | 181 (55) |
| ≥ 3 | 93 (50) | 28 (44) | 145 (44) | 149 (45) |
| Type of disease, n (%) | | | | |
| non-visceral | 50 (27) | 20 (32) | ND | ND |
| visceral | 22 (12) | 8 (13) | ND | ND |
| visceral and non-visceral | 115 (61) | 35 (56) | ND | ND |
| Elevated LDH level, n (%) | 67 (36) | 19 (30) | 142 (42) | 142 (42) |
| BRAF mutation status | | | | |
| BRAF V600E | 187 (100) | 63 (100) | 295 (88) | 303 (90) |
| BRAF V600 non-E | 0 (0) | 0 (0) | 34 (10) | 27 (8) |
| unclear | 0 (0) | 0 (0) | 7 (2)[f] | 7 (2)[f] |
| Time since first diagnosis [months], median (min-max) | 25.4 (1-358) | 24.1 (1-339) | ND | ND |
| Time since diagnosis of the metastatic stage [months], median (min-max) | ND | ND | 3.0 (0-109) | 3.0 (0-184) |
| Treatment discontinuations, n (%) | 80 (43)[g] | 46 (73)[g] | 113 (33.6)[h] | 206 (71.3)[h] |

(continued)

Table 3: Characteristics of the study populations – RCT, indirect comparison: dabrafenib vs. vemurafenib (continued)

a: Different time points 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 time points are not presented because no differences with regard 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 are pointed out in the study documents of the BREAK-3 study (BRF113683). However, these are not relevant for the present benefit assessment.
d: Exclusively patients in stage IIIc were included in the BRIM-3 study.
e: Equivalent to the classification of distant metastases M0 (no distant metastases).
f: Due to non-valid results of the sequencing of the somatic mutation [3].
g: Data cut-off on 19 December 2011. 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.
h: Data cut-off on 30 December 2010. Data without patients who discontinued the study prior to the first treatment. The percentages are based on all patients who received one treatment (336 patients in the vemurafenib arm and 289 patients in the dacarbazine arm). Disease progression was cited as the most common reason for discontinuation (vemurafenib 26%, dacarbazine 58%). Other reasons reported were death, adverse events, refusal of treatment, withdrawal of consent and protocol violation.

AJCC: American Joint Committee on Cancer; BRAF: rapidly accelerated fibrosarcoma isoform B gene ECOG: Eastern Cooperative Oncology Group, F: female; LDH: lactate dehydrogenase; M: male; max: maximum; min: minimum; N: number of randomized patients; n: number of patients in the category; ND: no data; RCT: randomized controlled trial; SD: standard deviation; TNM: tumour node metastasis; vs.: versus

There were no important differences between the treatment groups of both studies with regard to the following characteristics: age, sex, Eastern Cooperative Oncology Group Performance Status (ECOG PS), tumour stage and extent of metastases.

However, the populations differed with regard to the proportion of patients with increased lactate dehydrogenase (LDH) level, particularly in the dacarbazine arms (increased LDH level in 30% of the patients in the dacarbazine arm of the BREAK-3 study, and in 42% of the patients in the dacarbazine arm of the BRIM-3 study). Moreover, it was unclear whether the populations were comparable with respect to the time since the first diagnosis and since the diagnosis of the metastatic stage, because different data on this were analysed in the studies.

***Comparability of the common comparator dacarbazine***

Treatment with dacarbazine was continued in the BREAK-3 study and in the BRIM-3 study until disease progression, death or study discontinuation. Nonetheless, there were important differences with regard to treatment duration in the 2 studies.

At the first data cut-off, which was about 1 year after the start of the study in both studies, the median treatment duration with dacarbazine was 3.2 months in the BREAK-3 study, whereas it was 0.76 months in the BRIM-3 study. The criteria for treatment discontinuation defined in the study protocol were comparable in the 2 studies and could therefore not be the reason for the differences in treatment duration. The noticeable difference in treatment duration might be

explained partly by the possibly different course of patient recruitment (recruitment in the BREAK-3 study ended about 3 months before the first data cut-off, and in the BRIM-3 study only few days before). However, the company did not present any corresponding information.

But the different treatment durations can also be regarded as an indication that the patient populations of the studies were not comparable in their prognosis. The fact that the median duration of PFS was 2.7 months in the dacarbazine arm of the BREAK-3 study, whereas it was 1.6 months in the BRIM-3 study (comparable operationalization: assessment by the investigator) also indicates this.

***Summary on the comparability of the studies***

Regarding the comparability of the BREAK-3 study and the BRIM-3 study, there was an uncertainty because it could not be finally assessed whether the patients were sufficiently comparable in their prognosis. This is due to the following reasons:

- The proportion of patients with an increased LDH level is different in the dacarbazine arms of the 2 studies. At the same time, there were no data on the time since the first diagnosis or since the diagnosis of the metastatic stage.
- There was a considerable difference between the studies in the treatment duration with dacarbazine and in the duration of PFS under dacarbazine, which might have been caused by differences in the prognoses of the patients.

**Evaluation of homogeneity and consistency**

It was not possible to evaluate the assumption of homogeneity because only one study was available for each of the 2 pairwise comparisons of the indirect comparison. Because of this, the assumption of consistency could also not be evaluated (i.e. the study constellation necessary for this was not available in the study pool of the indirect comparison). It should be noted that while the impossibility to evaluate homogeneity and consistency of the results of the indirect comparison impaired the qualitative certainty of results of the indirect comparison, it was not the reason for the lack of informative value.

### 2.4.3 Risk of bias of the data included

The risk of bias of the results of the indirect comparison was largely determined by the design of the BREAK-3 study (early crossover to the test medication) and by the recording and the analysis of the adverse events (analysis of naive proportions in different observation periods) in the 2 studies included.

**Overall survival**

The results on overall survival from the BREAK-3 study were highly biased with regard to the comparison of dabrafenib and dacarbazine. This was primarily due to the fact that, from the beginning of the study, patients in the dacarbazine arm had the option to switch to treatment with dabrafenib after progression occurred. The study showed no statistically

significant difference between dabrafenib and dacarbazine with regard to overall survival. Due to the bias caused by the crossover, the influence of dabrafenib on overall survival cannot be assessed on the basis of the BREAK-3 study. In the BRIM-3 study, in contrast, patients in the dacarbazine arm could cross over to treatment with vemurafenib only after the analysis of the first data cut-off. This analysis showed a statistically significant advantage of vemurafenib compared with dacarbazine. The company described in the dossier as a result of the different design of the 2 studies that the proportions of patients with crossover to the test medication were relevantly higher in the BREAK-3 study than in the BRIM-3 study at the time point of the different data cut-offs (first data cut-off: 44% versus 0%; second data cut-off: 56% versus 15%; third data cut-off: 59% versus 24%).

The sensitivity analyses on the crossover adjustment with statistical methods (rank preserving structural failure time model [RPSFTM]) in the BREAK-3 study presented by the company were not used for the benefit assessment because they were based on strong assumptions that were not justified by the company and the fulfilment of which cannot be checked with the available data (see also dossier assessment on dabrafenib [1]).

The results of the BREAK-3 study on overall survival are also of little informative value within the indirect comparison because of the early crossover. Hence overall, no reliable conclusions on overall survival under dabrafenib in comparison with vemurafenib can be drawn from the indirect comparison.

Regardless of the problems described, the company's analyses showed (with one exception) no statistically significant difference between dabrafenib and vemurafenib. The estimation of the effect on overall survival was of very low precision and is compatible both with an advantage and with a disadvantage of dabrafenib in comparison with vemurafenib.

An added benefit of dabrafenib compared with vemurafenib for overall survival is not proven.

**Adverse events**

The company's dossier contained no valid data for the assessment of adverse events, which could be included in the benefit assessment. The indirect comparison of the company was only based on analyses on the basis of the naive proportion of patients with at least one event. However, these results were not an adequate analysis because of the considerably different treatment durations in the arms of the 2 studies. The median treatment duration in the BREAK-3 study was 4.9 months in the dabrafenib arm and 2.8 months in the dacarbazine arm. In contrast, the median treatment duration in the BRIM-3 study was 3.1 months in the vemurafenib arm and 0.76 months in the dacarbazine arm.

As there were important differences in both studies between the treatment durations and therefore observation periods – particularly regarding the common comparator dacarbazine – the available data on adverse events can be so highly biased that only a qualitative assessment is reasonable. But also this qualitative assessment is only possible if the direction of the bias

can be clearly estimated. Because of the longer treatment periods in the intervention arms (dabrafenib or vemurafenib), the risks in these groups tend to be biased to the disadvantage of the interventions in both studies.

As the extent of the bias in the individual studies cannot be quantified, the direction of the bias cannot be estimated for the indirect comparison. In this case, the result cannot be interpreted. The available data are therefore unsuitable to draw conclusions on the comparison of adverse events under treatment with dabrafenib or vemurafenib.

Greater or lesser harm from dabrafenib in comparison with vemurafenib is not proven.

### 2.4.4 Summarizing assessment of the informative value of the indirect comparison

The informative value of the indirect comparison on the investigation of the added benefit of dabrafenib versus vemurafenib is limited for the following reasons:

- There is an uncertainty regarding the similarity of the 2 studies included. It is unclear whether the prognosis of the patient populations in the 2 studies is sufficiently comparable.
- The results on overall survival are biased particularly by the early crossover in the BREAK-3 study. Hence no reliable conclusions on overall survival under dabrafenib in comparison with vemurafenib can be drawn from the indirect comparison.
- The informative value of the indirect comparison of adverse events is limited because of the different observation periods within the studies. A direction of the bias for the indirect comparison cannot be estimated. The data are therefore not interpretable.

In summary, the informative value of the indirect comparison is so severely limited that no reliable conclusions on the comparison of dabrafenib and vemurafenib are possible. Thus, an added benefit of dabrafenib compared with vemurafenib is not proven.

## 2.5 Extent and probability of added benefit

The result of the assessment of the added benefit of dabrafenib in comparison with vemurafenib is shown in Table 4.

Table 4: Extent and probability of the added benefit of dabrafenib

| Therapeutic indication | Comparator therapy | Extent and probability of added benefit |
|---|---|---|
| Monotherapy in adult patients with BRAF V600 mutation-positive, unresectable or metastatic melanoma | Vemurafenib | Added benefit not proven |

No proof of added benefit of dabrafenib versus vemurafenib 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 G-BA decides on the added benefit.

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