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Dabrafenib/trametinib – Addendum to Commissions A15-39 and A15-40[1]

Addendum

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[1] Translation of addendum A16-05 *Dabrafenib/Trametinib – Addendum zu den Aufträgen A15-39 und A15-40* (Version 1.0; Status: 24 February 2016). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
BRAF	rapidly accelerated fibrosarcoma – isoform B (serine/threonine-protein kinase B-Raf)
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
VAS	visual analogue scale

1 Background

On 9 February 2016, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for the commissions A15-39 (Dabrafenib [new therapeutic indication] – Benefit assessment according to §35a Social Code Book V) [1] and A15-40 (Trametinib – Benefit assessment according to §35a Social Code Book V) [2].

In its written comments on these dossier assessments [3,4], the pharmaceutical company (hereinafter referred to as "the company") sent supplementary information, which went beyond the information provided in the dossiers on dabrafenib and trametinib [5,6], to prove the added benefit. In particular, these were results of a sensitivity analysis on the European Quality of Life-5 Dimensions (EQ-5D), subgroup analyses on patient-relevant outcomes and results on adverse events for the second data cut-off on 13 March 2015. The G-BA's commission comprised the assessment of the data presented by the company and particularly the question of the effect modification by sex.

The information subsequently submitted referred to the COMBI-v study, in which the combination of dabrafenib and trametinib was compared with vemurafenib. This study was used both for the assessment of the new therapeutic indication of dabrafenib (dossier assessment A15-39 [1]) and the assessment of trametinib (dossier assessment A15-40 [2]). The present addendum therefore refers to these 2 dossier assessments (in each case to the comparison of the combination of dabrafenib and trametinib with vemurafenib).

The responsibility for the present assessment and the results of the assessment lies exclusively with IQWiG. The assessment is forwarded to the G-BA. The G-BA decides on the added benefit.

2 Assessment of the newly submitted data

2.1 Sensitivity analysis on the EQ-5D

The company's dossier contained no evaluable data for the health status recorded with the visual analogue scale (VAS) of the EQ-5D because the company used the lower limit of the range of 7 to 10 points described in the literature as threshold value for the responder analysis and did not supplement this decision at least with a sensitivity analysis investigating the robustness of the result. With the comment, the company presented a sensitivity analysis with a threshold value of 10 points. Table 1 shows the results of both analyses. The risk of bias of these analyses was high because, in the present case, the VAS of the EQ-5D was a patient-reported outcome in an open-label study and because there were potentially informative censorings due to the different observation periods.

Table 1: Results (morbidity: time to deterioration) – RCT, direct comparison: dabrafenib + trametinib vs. vemurafenib

Study **Outcome**	**Dabrafenib + trametinib**		**Vemurafenib**		**Dabrafenib + trametinib vs. vemurafenib**	
	N	**Median (months) [95% CI]** **Patients with event n (%)**	**N**	**Median (months) [95% CI]** **Patients with event n (%)**	**HR [95% CI][a]**	**p-value[b]**
COMBI-v						
Health status (EQ-5D VAS)[c]						
Response criterion 7 points[d]	352	11.4 [9.5; NC] 147 (42)	352	5.6 [5.4; 7.4] 180 (51)	0.63 [0.50; 0.78]	< 0.001
Response criterion 10 points[e]	352	12.9 [11.0; NC] 137 (39)	352	6.5 [5.6; 8.3] 172 (49)	0.62 [0.49; 0.77]	< 0.001

a: Estimation using a Cox regression model without adjustment for further covariables.
b: Calculated using the Wald chi-square test.
c: Results of the first data cut-off on 17 April 2014.
d: A decrease in score by at least 7 points compared with baseline was considered as deterioration.
e: A decrease in score by at least 10 points compared with baseline was considered as deterioration.
CI: confidence interval; EQ-5D: European Quality of Life-5 Dimensions; HR: hazard ratio; N: number of analysed patients; NC: not calculable; RCT: randomized controlled trial; VAS: visual analogue scale; vs.: versus

There was a statistically significant advantage of the combination of dabrafenib and trametinib in comparison with vemurafenib with both response criteria. For the outcome, no effect modification was shown for the characteristic "sex"; no subgroup analyses on other characteristics were available.

This resulted in a hint of an added benefit of the combination of dabrafenib and trametinib in comparison with vemurafenib. The extent of added benefit was assessed as "considerable".

2.2 Subgroup analyses on patient-relevant outcomes

In its dossiers on dabrafenib (new therapeutic indication) [5] and trametinib [6], the company submitted only subgroup analyses for the outcome "overall survival". Subgroup analyses on the other patient-relevant outcomes were missing.

There was proof of an effect modification by sex for the outcome "overall survival". The results showed a statistically significant advantage of the combination of dabrafenib and trametinib in comparison with vemurafenib for overall survival in women, but not in men. Since there were no subgroup analyses for the further patient-relevant outcomes, it remained unclear whether there was an effect modification by sex (or another subgroup characteristic) for the other outcomes or not. In the overall consideration of the results, the added benefit for men was therefore non-quantifiable.

With its comment, the company presented subgroup analyses by sex for the further patient-relevant outcomes (except specific adverse events [AEs]). Subgroup analyses for these outcomes for the further subgroup characteristics (age, BRAF mutation status, disease stage, baseline lactate dehydrogenase [LDH], visceral metastases at baseline and geographical region) were still missing.

The different observation periods between the treatment arms had to be considered in the interpretation of the subgroup analyses of the COMBI-v study. Particularly in the first data cut-off, this difference was not pronounced in the analyses on overall survival (first data cut-off, median: 11 vs. 10 months, second data cut-off, median: 19 vs. 15 months). There was no information on the observation periods for the further patient-relevant outcomes. Median observation periods of 11 (dabrafenib/trametinib) versus 7 (vemurafenib) months for AEs and of 12.6 (dabrafenib/trametinib) versus 8.5 (vemurafenib) for morbidity and health-related quality of life could be inferred from the available information (see dossier assessments [1,2]). Due to the greater bias caused by different observation periods for the outcomes on morbidity and health-related quality of life as well as on AEs, only proof of an interaction was considered in the interpretation of the subgroup analyses for these outcomes.

The subgroup analyses presented showed no proof of an effect modification by sex for the further patient-relevant outcomes (symptoms and health-related quality of life measured with the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 [EORTC QLQ-C30], health status measured with the EQ-5D, severe and serious AEs, discontinuations due to AEs). It could not be assessed whether there was an effect modification by the other subgroup characteristics because there were still no subgroup analyses for these characteristics.

2.3 Results on adverse events at the second data cut-off

The COMBI-v study on the comparison of the combination of dabrafenib and trametinib with vemurafenib was ended after an interim analysis (first data cut-off on 17 April 2014) because the results exceeded the predefined stopping boundaries. According to the study documents, only overall survival and the anti-cancer treatment were to be recorded after the end of the study. No follow-up of further outcomes beyond the first data cut-off was planned. This planning of the study was also described in the dossier assessment.

A further data cut-off was conducted on 13 March 2015 to reanalyse overall survival. The results on overall survival for this data cut-off were presented in the dossier and considered in the dossier assessment. The company presented no further data for the second data cut-off. Due to the planning of the study, no further results were expected either. The analysis of the second data cut-off was therefore considered to be complete and was taken into account.

The company presented an analysis of AEs at the second data cut-off from 13 March 2015 in its comment on the dossier assessment. It did not describe why this analysis was available, which deviated from the planning of the study described in the study documents and in the dossier assessment. It also remained unclear why this analysis was not presented in the dossier (from 16 September 2015) as were the analyses on overall survival for the second data cut-off. Hence the analyses on the second data cut-off in the dossier were potentially incomplete.

Since the importance of the analyses of the AEs at the second data cut-off remained unclear from the documents presented, the analyses were not used for the assessment of the added benefit. Irrespective of this, the results showed no relevant deviations from the results of the first data cut-off.

3 Extent and probability of added benefit

The extent and probability of the added benefit of the combination of dabrafenib and trametinib in comparison with vemurafenib under consideration of the supplementary information are described below.

The available analyses on the EQ-5D resulted in a hint of an added benefit of the combination of dabrafenib and trametinib in comparison with vemurafenib. The extent of added benefit was assessed as "considerable".

The supplementary subgroup analyses by sex showed that there was no effect modification by sex for the patient-relevant outcomes except for the outcome "overall survival". The observed results therefore exist both for women and for men for the outcomes except for overall survival (for more details of the results see dossier assessments A15-39 and A15-40 [1,2] and Section 2 of the present addendum for the EQ-5D).

Hence for overall survival, there is an indication of a major added benefit for women. For men, there was no hint of an added benefit for overall survival; an added benefit is therefore not proven for this outcome. An indication (severe AEs) or hints (non-severe/non-serious symptoms and AEs) of a considerable added benefit were shown for the outcomes from the categories of morbidity, health-related quality of life and AEs. Overall, this resulted in an indication of a major added benefit of the combination of dabrafenib and trametinib in comparison with vemurafenib for women, and in an indication of considerable added benefit for men.

The result of the assessment of the added benefit of dabrafenib and trametinib combination therapy in comparison with the appropriate comparator therapy (ACT) is summarized in Table 2.

Table 2: Dabrafenib in combination with trametinib – extent and probability of added benefit

Intervention	**Therapeutic indication**	**ACT**[a]	**Subgroup**	**Extent and probability of added benefit**
Dabrafenib + trametinib	Adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation[b]	Vemurafenib	Women	Indication of major added benefit
			Men	Indication of considerable added benefit

a: Presentation of the appropriate comparator therapy specified by the G-BA.
b: According to the SPC, the administration of dabrafenib and trametinib combination therapy is approved for patients with unresectable or metastatic melanoma with a BRAF V600 mutation – without restriction of pretreatment [7]. The study population of the included study for the assessment of the added benefit (only treatment-naive patients) therefore does not completely cover the therapeutic indication. It remains unclear whether the observed effects can be transferred to patients who have already had treatment for their advanced melanoma.
ACT: appropriate comparator therapy; BRAF: rapidly accelerated fibrosarcoma – isoform B (serine/threonine-protein kinase B-Raf); G-BA: Federal Joint Committee; SPC: Summary of Product Characteristics

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

4 References

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