IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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Dabrafenib (new therapeutic indication) – 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 (neues Anwendungsgebiet) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 28 December 2015). 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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Table of contents

List of tables[3]

Page

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

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
BRAF	rapidly accelerated fibrosarcoma – isoform B (serine/threonine-protein kinase B-Raf)
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
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
PFS	progression-free survival
QLQ-C30	Quality of Life Questionnaire - Core 30
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SOC	System Organ Class
SPC	Summary of Product Characteristics
TI	therapeutic indication
VAS	visual analogue scale

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug dabrafenib (new therapeutic indication). The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as "the company"). The dossier was sent to IQWiG on 18 September 2015.

Research question

The aim of this report was to assess the added benefit of dabrafenib and trametinib combination therapy compared with the appropriate comparator therapy (ACT) vemurafenib in adult patients with unresectable or metastatic melanoma with a rapidly accelerated fibrosarcoma – isoform B (serine/threonine-protein kinase B-Raf) (BRAF) V600 mutation. In its choice of the ACT, the company followed the G-BA's specification.

The assessment was conducted based on patient-relevant outcomes and on the data provided by the company in the dossier.

Results

Study pool and study characteristics

The study COMBI-v was included in the benefit assessment. This study was a randomized, open-label, multicentre, active-controlled study on the comparison of dabrafenib and trametinib combination therapy with vemurafenib. Adult patients with histologically confirmed unresectable (stage IIIc) or metastatic (stage IV) melanoma and confirmed BRAF V600E or BRAF V600K mutation who had no prior systemic anti-cancer treatment for the treatment of the advanced melanoma were included in the study. 704 patients were randomized in a ratio of 1:1, 352 patients to the combination arm (dabrafenib + trametinib) and 352 patients to the vemurafenib arm.

Overall survival was the primary outcome of the study. Further patient-relevant outcomes were disease-related symptoms, health status, health-related quality of life and adverse events (AEs).

An interim analysis after 70% of the expected events was planned in the study (202 of 288 deaths). The analysis was conducted after 222 deaths had actually occurred. Based on the results of the interim analysis, in which the prespecified stopping boundary was crossed due to extraordinary efficacy, the study was stopped on 14 July 2014. Patients in the vemurafenib arm were then allowed to cross over to the combination arm. The interim analysis constituted the final confirmatory analysis on overall survival (first data cut-off). The patients were followed up also after the first data cut-off regarding overall survival, but not for further

outcomes, however. A second data cut-off for the outcome "overall survival" was conducted on 13 March 2015. In the present benefit assessment, both data cut-offs were used for the assessment of the added benefit for the outcome "overall survival".

Risk of bias

The risk of bias at study level for the COMBI-v study was rated as low.

The risk of bias for the outcome "overall survival" was rated as low for the first data cut-off, whereas the second data cut-off was rated as having a high risk of bias. The allowed treatment switching from the vemurafenib arm to the combination arm after the first data cut-off was decisive for the high risk of bias. In the present situation (evidence of a survival advantage of the combination therapy), this resulted in potential bias of the results to the disadvantage of the combination therapy. Hence, rather an underestimation of the survival advantage of dabrafenib and trametinib combination therapy is assumed. The increased risk of bias for the second data cut-off therefore did not lead to a downgrading of the certainty of results for this outcome.

The risk of bias for the outcomes in the categories "morbidity" and "health-related quality of life" was rated as high because of the open-label study design and the great differences in observation periods in the 2 treatment arms with potential informative censoring. The risk of bias for the outcome "health status" was not assessed because no evaluable data were available. There was also a high risk of bias for the outcomes regarding AEs, which resulted in a downgrading of the certainty of results only in the outcomes with subjective components. This concerns all outcomes from the area of AEs except serious adverse events (SAEs) and severe AEs CTCAE grade ≥ 3.

Results

Mortality

Dabrafenib and trametinib combination therapy resulted in a statistically significant prolongation of overall survival in comparison with vemurafenib.

There was proof of an effect modification for the characteristic "sex" for this outcome in both data cut-offs, however. This resulted in an indication of an added benefit of dabrafenib and trametinib combination therapy compared with the ACT vemurafenib for women. For men, there was no hint of an added benefit; an added benefit is therefore not proven for this patient group.

Morbidity

- Symptoms (time to deterioration)

The morbidity of the patients was recorded with the symptom scales of the cancer-specific questionnaire European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 (EORTC QLQ-C30).

A statistically significant difference in favour of dabrafenib and trametinib combination therapy was shown for the time to deterioration for each of the following outcomes: pain, insomnia, appetite loss and diarrhoea. This resulted in a hint of an added benefit of dabrafenib and trametinib combination therapy compared with the ACT vemurafenib for each of these outcomes.

A statistically significant difference in favour of dabrafenib and trametinib combination therapy was also shown for the time to deterioration for the outcome "nausea and vomiting". The extent of the effect in this non-serious/non-severe outcome was no more than marginal, however. Hence there was no hint of an added benefit for this outcome; an added benefit is therefore not proven for this outcome.

No statistically significant difference was shown between the treatment groups for the time to deterioration for each of the outcomes "fatigue" and "dyspnoea". An added benefit for these outcomes is therefore not proven.

A statistically significant difference in favour of vemurafenib was shown for the time to deterioration for the outcome "constipation". The extent of the effect in this non-serious/non-severe outcome was no more than marginal, however. Hence there was no hint of lesser benefit or added benefit for this outcome; an added benefit is therefore not proven for this outcome.

- Health status (EQ-5D VAS)

The dossier contained no evaluable data for the outcome "health status" measured with the visual analogue scale (VAS) of the European Quality of Life-5 Dimensions (EQ-5D). Hence there was no hint of an added benefit for this outcome; an added benefit is therefore not proven for this outcome.

Health-related quality of life

- Functional scales (time to deterioration)

Aspects of health-related quality of life were recorded using the functional scales of the cancer-specific questionnaire EORTC QLQ-C30.

A statistically significant advantage in favour of dabrafenib and trametinib combination therapy was shown for all 6 functional scales investigated (global health status, physical functioning, role functioning, emotional functioning, cognitive functioning and social functioning). This resulted in a hint of an added benefit of dabrafenib and trametinib combination therapy compared with the ACT vemurafenib for the outcome "health-related quality of life".

Adverse events

- Serious adverse events

No statistically significant difference between the treatment groups was shown for the outcome "SAEs (time to first event)". Hence there was no hint of greater or lesser harm of dabrafenib and trametinib combination therapy compared with the ACT vemurafenib; greater or lesser harm is therefore not proven.

- Discontinuation due to adverse events

No statistically significant difference between the treatment groups was shown for the outcome "discontinuation due to AEs (time to first event)". Hence there was no hint of greater or lesser harm of dabrafenib and trametinib combination therapy compared with the ACT vemurafenib; greater or lesser harm is therefore not proven.

- Adverse events CTCAE grade ≥ 3

A statistically significant difference in favour of dabrafenib and trametinib combination therapy was shown for the outcome "AEs CTCAE grade ≥ 3 (time to first event)". This resulted in an indication of lesser harm of dabrafenib and trametinib combination therapy compared with the ACT vemurafenib for this outcome.

The company presented subgroup analyses based on naive proportions as additional information for this outcome. These analyses are at most suitable for drawing qualitative conclusions because of the possible bias caused by the differences in observation periods in the 2 treatment arms. A statistically significant advantage in favour of dabrafenib and trametinib combination therapy was shown for men for the outcome "AEs CTCAE grade ≥ 3", whereas for women the result was not statistically significant. Due to the known direction of bias to the disadvantage of the combination therapy, an indication of lesser harm from dabrafenib and trametinib combination therapy than from vemurafenib can therefore be derived for men. For women, only greater harm from dabrafenib and trametinib combination therapy can be excluded.

- Specific adverse events (time to first event)

A statistically significant difference in favour of dabrafenib and trametinib combination therapy was shown for each of the following outcomes: "skin and subcutaneous tissue disorders", "musculoskeletal and connective tissue disorders" and "neoplasms benign, malignant and unspecified". This resulted in a hint of lesser harm of dabrafenib and trametinib combination therapy compared with the ACT vemurafenib for each of these outcomes.

A statistically significant difference to the disadvantage of dabrafenib and trametinib combination therapy was shown for the outcome "respiratory, thoracic and mediastinal disorders". The extent of the effect in this non-serious/non-severe outcome was no more than marginal, however; greater or lesser harm is therefore not proven.

- Further specific adverse events (fever and chills)

No suitable analyses (survival time analyses) were available for the specific AEs "fever" and "chills" so that only a qualitative interpretation based on the naive proportions was conducted. The events "fever" and "chills" occurred in notably more patients in the combination arm than in the vemurafenib arm. The median observation period in the combination arm was also notably longer than in the vemurafenib arm (10 months versus 6 months); however, the difference between the 2 treatment arms appeared to be so large that it cannot be completely explained by the differences in observation periods. Greater harm from dabrafenib and trametinib combination therapy cannot be completely excluded.

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 dabrafenib and trametinib combination therapy in comparison with the ACT are assessed as follows.

Women

For women, there was an indication of major added benefit for the outcome "overall survival". The company presented no subgroup analyses for the outcomes in the categories "morbidity" and "health-related quality of life" so that it was unclear for them to what extent the effects in women differed from those in the total population. It cannot be assumed, however, that the notably positive effects in the total population turn into negative effects if only the subgroup of women is considered. Only subgroup analyses based on the naive proportions for the different overall rates of AEs were available for AEs. These can be interpreted in qualitative terms insofar as no greater harm from dabrafenib and trametinib combination therapy in women can be assumed. On a critical note on the balancing of the added benefit for women, no adequate subgroup results were available for a large proportion of the outcomes. However, based on the available data it can also not be assumed that the major survival advantage in women is to be questioned.

Overall, there is an indication of a major added benefit of dabrafenib and trametinib combination therapy compared with the ACT vemurafenib for women with unresectable or metastatic melanoma with a BRAF V600 mutation.

[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 to 3 cannot be drawn from the available data). 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). For further details see [1,2].

Men

Neither added benefit nor lesser benefit is proven for men for the outcome "overall survival". Analogous to the data situation for women, no adequate subgroup analyses were available for the outcomes in the categories "morbidity" and "health-related quality of life" so that it remains unclear to what extent the effects in men differ from those in the total population. It cannot be assumed, however, that the notably positive effects in the total population turn into negative effects if only the subgroup of men is considered. Only subgroup analyses based on the naive proportions were available for the different overall rates of AEs. Despite the potential bias to the disadvantage of the combination arm in the subgroup of men, a statistically significant advantage of dabrafenib and trametinib combination therapy was shown for the outcome "AEs CTCAE grade ≥ 3" so that an indication of lesser harm of the combination therapy could be derived. Due to the potential bias resulting from the different observation periods in both study arms, the extent is non-quantifiable, however. The results on the overall rates of SAEs and discontinuation due to AEs based on the naive proportions can be interpreted insofar as no greater harm from dabrafenib and trametinib combination therapy than from vemurafenib can be assumed for men.

Overall, there is an indication of a non-quantifiable added benefit of dabrafenib and trametinib combination therapy compared with the ACT vemurafenib for men with unresectable or metastatic melanoma with a BRAF V600 mutation.

Extent and probability of added benefit

Table 2 presents a summary of the extent and probability of the added benefit of dabrafenib and trametinib combination therapy.

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 a non-quantifiable 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 [3]. The study population of the included study for the assessment of the added benefit (only pretreated 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.

2.2 Research question

The aim of this report was to assess the added benefit of dabrafenib and trametinib combination therapy compared with the ACT vemurafenib in adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation. In its choice of the ACT, the company followed the G-BA's specification.

The assessment was conducted based on patient-relevant outcomes and on the data provided by the company in the dossier.

2.3 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study list on dabrafenib (status: 30 July 2015)
- bibliographical literature search on dabrafenib (last search on 14 July 2015)
- search in trial registries for studies on dabrafenib (last search on 7 July 2015)

To check the completeness of the study pool:

- search in trial registries for studies on dabrafenib (last search on 13 October 2015)

No additional relevant study was identified from the check.

2.3.1 Studies included

The study listed in Table 3 was included in the benefit assessment.

Table 3: Study pool – RCT, direct comparison: dabrafenib + trametinib 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)
COMBI-v (MEK116513)[b]	Yes	No[c]	Yes[c]

a: Study for which the company was sponsor, or in which the company was otherwise financially involved.
b: Hereinafter referred to as "COMBI-v".
c: The company (Novartis Pharma GmbH) obtained the rights to the drugs dabrafenib and trametinib from the sponsor of the study (GlaxoSmithKline).
RCT: randomized controlled trial; vs.: versus

The study pool for the benefit assessment of dabrafenib and trametinib combination therapy in comparison with vemurafenib consisted of the COMBI-v study and concurred with that of the company.

Section 2.6 contains a reference list for the studies included.

2.3.2 Study characteristics

Table 4 and Table 5 describe the studies used for the benefit assessment.

Table 4: Characteristics of the studies included – RCT, direct comparison: dabrafenib + trametinib vs. vemurafenib

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
COMBI-v	RCT, open-label, parallel	Treatment-naive[b] adult (≥ 18 years) patients with histologically confirmed unresectable (stage IIIc) or metastatic (stage IV) melanoma and confirmed BRAF V600E or BRAF V600K mutation	Dabrafenib + trametinib (N = 352) Vemurafenib (N = 352)	Treatment phase: treatment until disease progression[c], death, unacceptable toxicity or withdrawal of consent Planned follow-up: until death, withdrawal of consent or until all patients have been followed up for at least 5 years	163 centres in 28 countries in Africa, Asia, Australia and New Zealand, Europe, North and South America 6/2012–ongoing (follow-up for overall survival) First data cut-off: 17 April 2014[d, e]: planned after observation of 70% of the expected events (202 of 288 deaths)[f] Second data cut-off[g]: 13 March 2015	Primary: overall survival Secondary: disease-related symptoms, health status, health-related quality of life, AEs

a: Primary outcomes contain information without consideration of its relevance for this benefit assessment. Secondary outcomes contain exclusively information on the relevant available outcomes for this benefit assessment.
b: According to the inclusion criteria of the study, the patients were not allowed to have had prior systemic anti-cancer treatment for the treatment of the advanced melanoma (stage IIIc and IV). Prior systemic treatment in the adjuvant setting (line of treatment before the advanced stage) was allowed.
c: According to the study protocol (Amendment 3 from 22 October 2013), patients with only limited tumour progression who tolerated the treatment and who had benefitted from it before could continue treatment with the consent of the responsible Medical Monitor also after progression.
d: Based on the results of the interim analysis, in which the prespecified stopping boundary was crossed due to extraordinary efficacy, the study was stopped on 14 July 2014. The interim analysis therefore constituted the final confirmatory analysis on overall survival (the outcome "overall survival" was followed up, however).
e: According to the study protocol (Amendment 5 from 7 August 2014), patients in the vemurafenib arm were allowed to cross over to the combination arm after the premature ending of the study.
f: This analysis was conducted after 222 deaths had actually occurred.
g: Only data on overall survival and on the administration of alternative cancer treatments were recorded and analysed.
AE: adverse event; BRAF: rapidly accelerated fibrosarcoma – isoform B (serine/threonine-protein kinase B-Raf); N: number of randomized patients; RCT: randomized controlled trial; vs.: versus

Table 5: Characteristics of the interventions – RCT, direct comparison: dabrafenib + trametinib vs. vemurafenib

Study	Intervention	Comparison	Prior and concomitant medication
COMBI-v	Dabrafenib 150 mg twice daily, oral + trametinib 2 mg once daily, oral Dose adjustments and treatment discontinuations due to intolerance were allowed for both drugs[a]. Dose reductions below 75 mg dabrafenib twice daily[b] or below 1 mg trametinib once daily were not allowed.	Vemurafenib 960 mg twice daily, oral Dose adjustments and treatment discontinuations due to intolerance were allowed.	**Pretreatment[c]:** ▪ no prior systemic anti-cancer treatment (prior systemic treatment in the adjuvant setting was allowed[d]) ▪ no pretreatment with a BRAF inhibitor (e.g. dabrafenib) or a MEK inhibitor (e.g. trametinib) **Concomitant treatment:** all patients received concomitant supportive treatments (e.g. blood transfusion, antibiotics, antiemetics, analgesics) **Non-permitted concomitant treatment:** ▪ other systemic anti-cancer treatment including surgical removal of target lesions ▪ further investigational preparations ▪ antiretroviral therapy ▪ herbal agents (e.g. St. John's Wort) ▪ strong inhibitors or inducers of CYP3A or CYP2C8 (e.g. carbamazepine, ketoconazole, clarithromycin)

a: In case of dose reduction or treatment discontinuation of one substance, continued treatment with the other substance was possible.
b: According to the SPC of dabrafenib, further dose reduction to 50 mg twice daily is possible in combination with trametinib [3]. It is not assumed that this deviation had a relevant influence on the study results (see Section 2.7.2.3.2 of the full dossier assessment).
c: Prior treatment of advanced disease.
d: Fewer than 10% of the patients received systemic anti-cancer treatments.
BRAF: rapidly accelerated fibrosarcoma – isoform B (serine/threonine-protein kinase B-Raf); MEK: mitogen-activated extracellular signal-regulated kinase; RCT: randomized controlled trial; SPC: Summary of Product Characteristics; vs.: versus

Study design

The COMBI-v (MEK116513) study was a randomized, open-label, multicentre, active-controlled study on the comparison of dabrafenib and trametinib combination therapy with vemurafenib.

Adult patients with histologically confirmed unresectable (stage IIIc) or metastatic (stage IV) melanoma and confirmed BRAF V600E or BRAF V600K mutation were included in the study. The patients were not allowed to have received prior systemic anti-cancer treatment for the treatment of the advanced melanoma (stage IIIc or IV). Prior adjuvant (also systemic) treatment was allowed [4,5]. According to the Summary of Product Characteristics (SPC) [3], the administration of dabrafenib and trametinib combination therapy is approved for patients with unresectable or metastatic melanoma with a BRAF V600 mutation; there is no restriction

regarding pretreatment. The study population (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 (see Section 2.7.2.4.1 of the full dossier assessment).

704 patients were randomized in a ratio of 1:1, 352 patients to the combination arm (dabrafenib + trametinib) and 352 patients to the vemurafenib arm. Baseline lactate dehydrogenase (LDH) levels and BRAF V600 mutation status were stratification factors.

The drugs trametinib and vemurafenib used in the study were administered without relevant deviations from the SPCs [6,7]. Regarding the administration of dabrafenib, the dose reductions envisaged in the study due to AEs did not completely comply with the specifications in the SPC [3]. It appears unlikely, however, that the deviation had an important influence on the study results (see Section 2.7.2.3.2 of the full dossier assessment).

Overall survival was the primary outcome of the study. Further patient-relevant outcomes were disease-related symptoms, health status, health-related quality of life and AEs.

Analyses on 2 data cut-offs were available for the outcome "overall survival" (17 April 2014 and 13 March 2015).

An interim analysis after 70% of the expected events was planned in the study (202 of 288 deaths). This analysis was conducted after 222 deaths had actually occurred. Based on the results of the interim analysis, in which the prespecified stopping boundary was crossed due to extraordinary efficacy, the study was stopped on 14 July 2014. The interim analysis therefore constituted the final confirmatory analysis on overall survival. Hereinafter, this is referred to as "first data cut-off". The patients were followed up also after the first data cut-off regarding overall survival, but not for further outcomes, however. At the time point of the first data cut-off, 20% of the patients in the combination arm and 43% of the patients in the vemurafenib arm had ended their study treatment due to progression and were receiving a different treatment of their melanoma. 174 patients (49%) in the combination arm and 89 patients (25%) in the vemurafenib arm were still treated with their originally assigned medication. With Amendment 5 of the study protocol from 7 August 2014, patients were allowed to switch treatments from the vemurafenib to the combination arm after the first data cut-off.

A second data cut-off for the outcome "overall survival" was conducted on 13 March 2015. This was not preplanned, but was required by the European Medicines Agency (EMA) [8] because it did not consider the data on overall survival based on the first data cut-off as final (see Section 2.7.2.4.3 of the full dossier assessment). At the time point of the second data cut-off, about 8% of the patients originally randomized to the vemurafenib arm had switched from the vemurafenib arm to the combination arm. 34% of the patients in the combination arm and 51% of the patients in the vemurafenib arm had ended their study treatment due to

progression and were receiving a different treatment of their melanoma. The results of the first and second data cut-off were used in the overall consideration for the assessment of overall survival (see Section 2.7.2.4.3 of the full dossier assessment).

The study is ongoing until all patients have been followed up for at least 5 years, have withdrawn their consent or have died. Treatment in both study arms is continued until disease progression, death, unacceptable toxicity or withdrawal of consent. According to Amendment 3 of the study protocol, patients with only limited tumour progression who tolerated the treatment and who had benefitted from it before could continue treatment with the consent of the responsible Medical Monitor also after progression, however. At the time point of the first data cut-off, 80 patients (23%) in the combination arm and 81 patients (23%) in the vemurafenib arm had been continuing their assigned treatment despite progression for at least 15 days [4].

Duration of follow-up

Table 6 shows the planned duration of follow-up of the patients for the individual outcomes.

Table 6: Planned duration of follow-up – RCT, direct comparison: dabrafenib + trametinib vs. vemurafenib

Study **Outcome category** **Outcome**	**Planned follow-up**
COMBI-v	
Overall survival	Until death, withdrawal of consent or until all patients have been followed up for at least 5 years
Morbidity	
EORTC QLQ-C30 (symptoms) and health status (EQ-5D VAS)	Every 8 weeks until week 56; then every 12 weeks until disease progression and 5 weeks after occurrence of disease progression
Health-related quality of life	
EORTC QLQ-C30 (functions)	Every 8 weeks until week 56; then every 12 weeks until disease progression and 5 weeks after occurrence of disease progression
Adverse events	Starting with the first administration of the study medication continuously until 30 days after the last treatment with the study medication
EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D: European Quality of Life-5 Dimensions; QLQ-C30: Quality of Life Questionnaire Core-30; RCT: randomized controlled trial; VAS: visual analogue scale; vs.: versus	

Of the outcomes included, only overall survival until death, withdrawal of consent and end of study were recorded. The results on the basis of 2 data cut-offs were available for this outcome. The recording of other data was conducted outcome-specific beyond the end of treatment: AEs were recorded until 30 days after the last treatment with the study medication, data on the outcomes “symptoms”, “health status” and “health-related quality of life” until

5 weeks after occurrence of disease progression. There was no follow-up of these outcomes beyond the first data cut-off.

Patient characteristics

Table 7 shows the characteristics of the patients in the study included.

Table 7: Characteristics of the study population – RCT, direct comparison: dabrafenib + trametinib vs. vemurafenib

Study Characteristics Category	Dabrafenib + trametinib N = 352	Vemurafenib N = 352
Study COMBI-v		
Age [years], mean (SD)	54 (14)	54 (14)
Sex [F/M], %	41/59	49/51
Baseline ECOG PS, n (%)		
0	248 (70)	248 (70)
1	102 (29)	104 (30)
Skin colour, (n, %)		
White/Caucasian/European origin	339 (96)	339 (96)
Other	13 (4)	13 (4)
BRAF mutation status, (n, %)		
V600E	312 (89)	317 (90)
V600K	34 (10)	34 (10)
V600E and V600K	5 (1)	1 (< 1)
Metastasis stage at screening, (n, %)		
M0	14 (4)	26 (7)
M1a	55 (16)	50 (14)
M1b	61 (17)	67 (19)
M1c	221 (63)	208 (59)
Unknown	0 (0)	1 (< 1)
Disease stage at screening[a], n (%)		
Stage IIIc	14 (4)	26 (7)
Stage IV	337 (96)	326 (93)
History of brain metastases, n (%)[b]	ND	ND
Baseline LDH, n (%)		
> ULN	118 (34)	114 (32)
≤ ULN	233 (66)	238 (68)
Visceral metastases at baseline, n (%)		
Yes	278 (79)	271 (77)
No	73 (21)	81 (23)
Extent of metastases (number of locations), n (%)		
< 3	177 (50)	201 (57)
≥ 3	174 (49)	151 (43)
Time since first diagnosis (months), median [min; max]	24.0 [0; 455]	28.0 [0; 349]
Study discontinuations (first data cut-off), n (%)	16 (5)[c]	28 (8)[c]
Treatment discontinuations (first data cut-off), n (%)	181 (52)[d]	260 (74)[d]

(continued)

Table 7: Characteristics of the study population – RCT, direct comparison: dabrafenib + trametinib vs. vemurafenib (continued)

a: According to AJCC classification [9].
b: Patients with brain metastases were included in the study only under certain conditions. According to the available study documents, fewer than 20 patients in the study had a history of brain metastases.
c: The most common reason for discontinuation was withdrawal of consent.
d: The most common reason for discontinuation stated was progression of the disease, including death after progression.
AJCC: American Joint Committee on Cancer; BRAF: serine/threonine-protein kinase B-Raf (rapidly accelerated fibrosarcoma – isoform B); 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; ULN: upper limit of normal; vs.: versus

The characteristics of the COMBI-v study were mostly balanced between the study arms. The mean age was 54 years. Somewhat fewer women than men were included in the combination arm (41% versus 59%), whereas the proportion in the vemurafenib arm was balanced (about 50% each). Almost all patients were white, Caucasian or of European origin (96% in both study arms).

About 2 thirds of the patients had normal LDH levels. A large proportion of the patients had a baseline Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 (70% in both study arms). Most patients had tumour stage IV (about 96% and 93%); the metastasis stage was mainly M1C (63% and 59%). About 78% of the patients already had visceral metastases at baseline. Whereas the proportion of patients with < 3 and ≥ 3 lesions in the combination arm was balanced (about 50% each), more patients had < 3 lesions in the vemurafenib arm (57%; 43% with ≥ 3 locations).

Patients with brain metastases were included in the study only under certain conditions, e.g. if all known lesions had been successfully treated with surgery or stereotactic radiotherapy [5]. A check performed by the company at the EMA's request found that fewer than 20 patients in the study had a history of brain metastases [8].

Table 8: Information on the course of the study – RCT, direct comparison: dabrafenib + trametinib vs. vemurafenib

Study **Duration of the study phase** **Outcome category** **Data cut-off**	**Dabrafenib + trametinib** **N = 352**	**Vemurafenib** **N = 352**
COMBI-v		
Treatment duration [months]		
First data cut-off (17 April 2014)		
Median [min; max]	10 [0; 21][a]	6 [0; 18][a]
Observation period [months]		
Overall survival		
First data cut-off (17 April 2014)		
Median [min; max]	11 [0; 21]	10 [0; 20]
Second data cut-off (13 March 2015)		
Median [min; max]	19 [0; 30][a]	15 [0; 29][a]
Morbidity, health-related quality of life, adverse events		
Median [min; max]	ND	ND

a: Information was only available for the safety population (350 patients with dabrafenib + trametinib and 349 patients with vemurafenib) and not for the ITT population.
ITT: intention to treat; max: maximum; min: minimum; N: number of randomized patients; ND: no data; RCT: randomized controlled trial; vs.: versus

The treatment duration of the population in the COMBI-v study differed between the 2 treatment arms. With a median of 10 months, patients in the combination arm were treated notably longer than in the vemurafenib arm (6 months), whereas the difference in the median observation period for overall survival was not as pronounced for the available data cut-offs (first data cut-off: 11 versus 10 months; second data cut-off: 19 versus 15 months).

No information was available on the actual observation period for the outcomes from the areas of morbidity, health-related quality of life and AEs. The observation period can differ between the individual outcomes because of the different criteria for follow-up (see Table 6). The observation period for AEs can be estimated on the basis of the data on median treatment duration because AEs were predefined to be recorded up to 30 days (about one month) after the last study medication. Under the assumption that all patients exhausted the specified follow-up period, the resulting median observation period was approximately 11 months in the combination arm versus approximately 7 months in the vemurafenib arm.

For the outcomes from the areas of morbidity and health-related quality of life, which were recorded for at most 5 weeks after occurrence of disease progression, the observation period

can be estimated considering the data on progression-free survival (PFS). According to the clinical study report (CSR), the median PFS was 11.4 months in the combination arm and 7.3 months in the vemurafenib arm [4]. Under the assumption that all patients exhausted the specified follow-up period, the resulting median observation period was approximately 12.6 months in the combination arm versus approximately 8.5 months in the vemurafenib arm.

Overall, a notably longer observation period can be assumed for the combination arm in comparison with the vemurafenib arm for all outcomes (except all-cause mortality).

Table 9 shows the risk of bias at study level.

Table 9: Risk of bias at study level – RCT, direct comparison: dabrafenib + trametinib vs. vemurafenib

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			
COMBI-v	Yes	Yes	No	No	Yes	Yes	Low
RCT: randomized controlled trial; vs.: versus							

The risk of bias at study level for the COMBI-v study was rated as low. This concurs with the company's assessment.

Restrictions resulting from the open-label study design and the different observation periods in the 2 treatment arms are described in Section 2.4.2 for the outcome-specific risk of bias.

2.4 Results on added benefit

2.4.1 Outcomes included

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

- Mortality
  - Overall survival
- Morbidity
  - symptoms measured with the symptom scales of the EORTC QLQ-C30
  - health status measured with the EQ-5D VAS
- Health-related quality of life
  - measured with the functional scales of the EORTC QLQ-C30 questionnaire
- Adverse events
  - SAEs
  - discontinuation due to AEs
  - severe AEs (CTCAE grade ≥ 3)
  - if applicable, further specific AEs

The choice of patient-relevant outcomes deviated from that of the company, which used further outcomes in the dossier (Module 4 A) (see Section 2.7.2.4.3 of the full dossier assessment).

Table 10 shows for which outcomes data were available in the study included.

Table 10: Matrix of outcomes – RCT, direct comparison: dabrafenib + trametinib vs. vemurafenib

Study	Outcomes										
	Overall survival	Symptoms (EORTC QLQ-C30)[a]	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30)[b]	SAEs	Discontinuation due to AEs	Severe AEs (CTCAE grade ≥ 3)	Skin and subcutaneous tissue disorders (SOC)	Musculoskeletal and connective tissue disorders (SOC)	Respiratory, thoracic and mediastinal disorders (SOC)	Neoplasms benign, malignant and unspecified (including cysts and polyps) (SOC)
COMBI-v	Yes	Yes	No[c]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

a: Measured with the symptom scales of the EORTC QLQ-C30 version 3.0.
b: Measured with the functional scales of the EORTC QLQ-C30 version 3.0.
c: No evaluable data available; for reasons, see Section 2.7.2.4.3 of the full dossier assessment.
AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D: European Quality of Life-5 Dimensions; QLQ-C30: Quality of Life Questionnaire Core-30; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale; vs.: versus

2.4.2 Risk of bias

Table 11 shows the risk of bias for the relevant outcomes.

Table 11: Risk of bias at study and outcome level – RCT, direct comparison: dabrafenib + trametinib vs. vemurafenib

Study	Study level	Outcomes										
		Overall survival	Symptoms (EORTC QLQ-C30)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30)	SAEs	Discontinuation due to AEs	Severe AEs (CTCAE grade ≥ 3)	Skin and subcutaneous tissue disorders	Musculoskeletal and connective tissue disorders	Respiratory, thoracic and mediastinal disorders	Neoplasms benign, malignant and unspecified (including cysts and polyps)
COMBI-v	L	L/H[a]	H[b]	-[c]	H[b]	H[d, e]	H[d, f]	H[d, e]	H[d, f]	H[d, f]	H[d, f]	H[d, f]

a: The risk of bias of the results of the first data cut-off is rated as low. In the second data cut-off, a potentially biasing influence of the treatment switch from the vemurafenib arm to the combination arm allowed after the interim analysis (8% of the patients) cannot be excluded. However, potential bias of the results to the disadvantage of the combination therapy and hence rather an underestimation of the survival advantage of dabrafenib and trametinib combination therapy can be assumed. The increased risk of bias therefore did not lead to a downgrading of the certainty of results for this outcome.
b: Patient-reported outcome in open-label study; great differences in observation periods with potential informative censoring.
c: No evaluable data available (see Section 2.7.2.4.3 of the full dossier assessment).
d: Difference in the median treatment duration (and the resulting observation period) between the intervention arm (10.0 months) and the comparator arm (6.0 months).
e: Bias to the disadvantage of the intervention arm because more AEs can occur in a longer treatment period. The increased risk of bias therefore did not lead to a downgrading of the certainty of results for this outcome.
f: These were mainly non-serious events, the documentation of which as AEs has subjective components. Hence in the open-label study design, this leads to a high risk of bias.
AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D: European Quality of Life-5 Dimensions; H: high; L: low; QLQ-C30: Quality of Life Questionnaire Core-30; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

The risk of bias at study level was rated as low. This concurs with the company's assessment.

The risk of bias for the outcome "overall survival" was rated as low for the first data cut-off, whereas the second data cut-off was rated as having a high risk of bias. The allowed treatment switching from the vemurafenib arm to the combination arm after the first data cut-off, which was performed by 8% of the randomized patients in the vemurafenib arm, was decisive for this. In the present situation, this resulted in potential bias of the results to the disadvantage of the combination therapy and hence rather an underestimation of the survival advantage of

dabrafenib and trametinib combination therapy can be assumed. The increased risk of bias for the second data cut-off therefore did not lead to a downgrading of the certainty of results for this outcome.

This partly deviates from the company's assessment. The company considered the risk of bias jointly for both data cut-offs and overall derived a high risk of bias, but did not downgrade the certainty of results due to the known direction of the bias. The company's approach to rate the risk of bias for the first data cut-off as high because already different numbers of patients in both treatment arms had received subsequent therapy after occurrence of progression was not followed because the subsequent therapies are to be considered as part of a therapeutic strategy for the treatment of the patients (see Section 2.7.2.4.2 of the full dossier assessment).

The risk of bias for the outcomes in the categories "morbidity" and "health-related quality of life" was rated as high because of the open-label study design and the great differences in observation periods with potential informative censoring. This concurs with the company's assessment, which assumed a high risk of bias for these outcomes. The company's assessment that a high certainty of results can still be assumed for these outcomes because the observed effects correlate with the effects of objectively recorded outcomes (e.g. PFS, AEs) regarding both direction and size was not followed, however (see Section 2.7.2.4.2 of the full dossier assessment). The results for the outcome "health status" (EQ-5D VAS) were overall considered to be not evaluable because they were subject to great uncertainty (see Section 2.7.2.4.3 of the full dossier assessment). The risk of bias was therefore not assessed.

There was also a high risk of bias for the outcomes regarding AEs, which resulted in a downgrading of the certainty of results only in the outcomes with subjective components. This concerns all outcomes from the area of AEs except SAEs and severe AEs CTCAE grade ≥ 3. This approach partially deviates from that of the company. The company also assumed a high risk of bias for all outcomes on AEs. However, it did not downgrade the certainty of results for outcomes for which an advantage in favour of the combination therapy was shown already on the basis of the naive proportions despite the longer observation period in the combination arm (see Section 2.7.2.4.2 of the full dossier assessment).

2.4.3 Results

The following tables summarize the results on the comparison of dabrafenib and trametinib combination therapy with vemurafenib in adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation. The Kaplan-Meier curves on the outcomes included are presented in Appendix A of the full dossier assessment.

Table 12: Results (mortality) – RCT, direct comparison: dabrafenib + trametinib vs. vemurafenib

Study Outcome	Dabrafenib + trametinib		Vemurafenib		Dabrafenib + trametinib vs. vemurafenib	
	N	Median survival time in months [95% CI] Patients with event n (%)	N	Median survival time in months [95% CI] Patients with event n (%)	HR [95% CI][a]	p-value[b]
COMBI-v						
Overall survival						
First data cut-off (17 April 2014)	352	NA [18.3; NA] 100 (28)	352	17.2 [16.4; NA] 122 (35)	0.69 [0.53; 0.89]	0.005
Second data cut-off[c] (13 March 2015)	352	25.6 [22.6; NA] 155 (44)	352	18.0 [15.6; 20.7] 194 (55)	0.66 [0.53; 0.81]	< 0.001

a: Calculated with the Pike method [10], adjusted for baseline LDH level and BRAF V600 mutation status.
b: Calculation of the p-value using a log-rank test stratified by baseline LDH value and BRAF V600 mutation status.
c: This data cut-off was not predefined, but was additionally requested by the regulatory authority [8].
BRAF: serine/threonine-protein kinase B-Raf (rapidly accelerated fibrosarcoma – isoform B); CI: confidence interval; HR: hazard ratio; LDH: lactate dehydrogenase; N: number of analysed patients; n: number of patients with event; NA: not achieved; RCT: randomized controlled trial; vs.: versus

Table 13: Results (morbidity: time to deterioration) – RCT, direct comparison: dabrafenib + trametinib vs. vemurafenib

Study Outcome	Dabrafenib + trametinib		Vemurafenib		Dabrafenib + trametinib vs. vemurafenib	
Subscale	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						
EORTC QLQ-C30 symptom scales – time to deterioration of symptoms[c, d]						
Fatigue	352	5.3 [3.7; 5.6] 209 (59)	352	3.7 [2.1; 5.6] 214 (61)	0.85 [0.71; 1.03]	0.104
Nausea and vomiting	352	15.6 [11.0; NA] 137 (39)	352	9.3 [7.4; NA] 148 (42)	0.78 [0.62; 0.99]	0.039
Pain	352	13.6 [9.4; NA] 140 (40)	352	5.8 [5.6; 7.7] 171 (49)	0.61 [0.49; 0.76]	< 0.001
Dyspnoea	352	NA [15.6; NA] 115 (33)	352	NA [9.6; NA] 121 (34)	0.84 [0.65; 1.08]	0.179
Insomnia	352	NA [15.7; NA] 105 (30)	352	8.3 [7.3; NA] 152 (43)	0.52 [0.40; 0.67]	< 0.001
Appetite loss	352	NA [NA; NA] 101 (29)	352	9.2 [5.6; NA] 154 (44)	0.48 [0.37; 0.62]	< 0.001
Constipation	352	NA [13.0; NA] 110 (31)	352	NA [NA; NA] 73 (21)	1.41 [1.05; 1.90]	0.023
Diarrhoea	352	18.5 [11.1; 18.5] 131 (37)	352	5.6 [4.3; 7.4] 181 (51)	0.51 [0.40; 0.64]	< 0.001
Health status (EQ-5D VAS)	No evaluable data[e]					

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: An increase in score by at least 10 points compared with baseline was considered as deterioration.
e: The uncertainty of the data presented by the company was too great (see Section 2.7.2.4.3 of the full dossier assessment).

CI: confidence interval; EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D: European Quality of Life-5 Dimensions; HR: hazard ratio; N: number of analysed patients; n: number of patients with event; NA: not achieved; QLQ-C30: Quality of Life Questionnaire Core-30 (general symptoms of cancer disease); RCT: randomized controlled trial; VAS: visual analogue scale; vs.: versus

Table 14: Results (health-related quality of life: time to deterioration) – RCT, direct comparison: dabrafenib + trametinib vs. vemurafenib

Study Outcome	Dabrafenib + trametinib		Vemurafenib		Dabrafenib + trametinib vs. vemurafenib	
Subscale	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						
EORTC QLQ-C30 functional scales – time to deterioration of health-related quality of life[c, d]						
Global health status	352	11.1 [8.8; NA] 151 (43)	352	5.6 [4.0; 7.4] 181 (51)	0.64 [0.51; 0.79]	< 0.001
Physical functioning	352	15.2 [10.2; NA] 133 (38)	352	7.4 [5.6; 11.0] 159 (45)	0.66 [0.53; 0.83]	< 0.001
Role functioning	352	9.2 [7.4; 12.45] 169 (48)	352	5.6 [3.8; 5.9] 191 (54)	0.69 [0.56; 0.85]	< 0.001
Emotional functioning	352	NA [15.7; NA] 103 (29)	352	13.3 [9.2; NA] 118 (34)	0.70 [0.54; 0.91]	0.008
Cognitive functioning	352	9.4 [7.5; NA] 155 (44)	352	7.4 [5.6; 9.3] 165 (47)	0.77 [0.62; 0.96]	0.020
Social functioning	352	12.3 [9.5; NA] 145 (41)	352	5.6 [4.6; 6.8] 191 (54)	0.59 [0.47; 0.73]	< 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 10 points compared with baseline was considered as deterioration.
CI: confidence interval; EORTC: European Organisation for Research and Treatment of Cancer; HR: hazard ratio; N: number of analysed patients; n: number of patients with event; NA: not achieved; QLQ-C30: Quality of Life Questionnaire Core-30 (general symptoms of cancer disease); RCT: randomized controlled trial; vs.: versus

Table 15: Results (AEs: time to first event) – 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						
Adverse events[c]						
AEs	350	0.3 [0.2; 0.4] 343 (98)	349	0.2 [0.1; 0.2] 345 (99)		
SAEs	350	NA [NA; NA] 131 (37)	349	NA [NA; NA] 122 (35)	1.03 [0.80; 1.32]	0.819
Discontinuation due to AEs	350	NA [NA; NA] 44 (13)	349	NA [NA; NA] 41 (12)	1.01 [0.66; 1.55]	0.957
AEs CTCAE grade ≥ 3	350	10.1 [6.2; 12.2] 186 (53)	349	2.7 [1.8; 3.6] 224 (64)	0.65 [0.53; 0.78]	< 0.001
Skin and subcutaneous tissue disorders	350	3.6 [2.5; 4.9] 220 (63)	349	0.3 [0.3; 0.3] 317 (91)	0.29 [0.24; 0.35]	< 0.001
Musculoskeletal and connective tissue disorders	350	10.0 [6.4; 14.7] 176 (50)	349	1.0 [0.7; 1.5] 248 (71)	0.48 [0.40; 0.59]	< 0.001
Respiratory, thoracic and mediastinal disorders	350	NA [NA; NA] 127 (36)	349	NA [NA; NA] 94 (27)	1.36 [1.04; 1.78]	0.023
Neoplasms benign, malignant and unspecified (including cysts and polyps)	350	NA [NA; NA] 34 (10)	349	NA [NA; NA] 148 (42)	0.17 [0.12; 0.24]	< 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.

AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; HR: hazard ratio; N: number of analysed patients; n: number of patients with event; NA: not achieved; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus

Table 16: Results (common AEs with potentially important differences between the treatment arms) – RCT, direct comparison: dabrafenib + trametinib vs. vemurafenib

Study Outcome category outcome[a]	Dabrafenib + trametinib N	 Patients with event n (%)	Vemurafenib N	 Patients with event n (%)
COMBI-v				
Specific adverse events[b]				
Fever (PT)[c]	350	184 (53)[d]	349	73 (21)[d]
Chills (PT)	350	110 (31)[e]	349	27 (8)[e]

a: Results of the first data cut-off on 17 April 2014.
b: The AEs presented can only be interpreted in qualitative terms because of the differences in treatment duration between the 2 study arms (10 vs. 6 months).
c: The CSR contained a further operationalization for fever under the term "pyrexia", which included the following PTs: fever, influenza like illness, body temperature increased and hyperthermia. The following results were shown: 200 patients (57%) in the combination arm and 89 patients (26%) in the vemurafenib arm.
d: Including 49 patients with SAEs (14%) in the combination arm and 6 patients with SAEs (2%) in the vemurafenib arm.
e: Including 13 patients (4%) in the combination arm and no patient in the vemurafenib arm with SAEs.
AE: adverse event; CSR: clinical study report; N: number of analysed patients; n: number of patients with (at least one) event; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus

Only one study with a low risk of bias (COMBI-v) was available for the assessment of dabrafenib and trametinib combination therapy in comparison with the ACT vemurafenib. The study COMBI-v 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.

This partly deviates from the company's assessment, which stated no concrete probability (proof, indication or hint), but only stated to be able to derive an added benefit with high certainty of results on the basis of the COMBI-v study.

Mortality

Overall survival

Dabrafenib and trametinib combination therapy resulted in a statistically significant prolongation of overall survival in comparison with vemurafenib.

For both data cut-offs, there was proof of an effect modification for the characteristic "sex" and indications of an effect modification by the characteristics "visceral metastases at baseline" and "disease stage at screening" for this outcome, however. Not all the subgroup results could be interpreted because data for the investigation of possible dependencies between the subgroup characteristics were missing. Since the interaction strength for the characteristic "sex" was higher than for other subgroups (proof), only the subgroup results for this characteristic were considered.

This resulted in an indication of an added benefit of dabrafenib and trametinib combination therapy compared with the ACT vemurafenib for women. For men, there was no hint of an added benefit; an added benefit is therefore not proven for this patient group.

This deviates from the company's assessment, which derived an added benefit with high certainty of results for the total population.

Morbidity

Symptom scales of the EORTC (time to deterioration)

The morbidity of the patients was recorded with the symptom scales of the cancer-specific questionnaire EORTC QLQ-C30.

A statistically significant difference in favour of dabrafenib and trametinib combination therapy was shown for the time to deterioration for each of the following outcomes: pain, insomnia, appetite loss and diarrhoea. This resulted in a hint of an added benefit of dabrafenib and trametinib combination therapy compared with the ACT vemurafenib for each of these outcomes.

A statistically significant difference in favour of dabrafenib and trametinib combination therapy was also shown for the time to deterioration for the outcome "nausea and vomiting". The extent of the effect in this non-serious/non-severe outcome was no more than marginal, however. Hence there was no hint of an added benefit for this outcome; an added benefit is therefore not proven for this outcome.

No statistically significant difference was shown between the treatment groups for the time to deterioration for each of the outcomes "fatigue" and "dyspnoea". An added benefit for these outcomes is therefore not proven.

A statistically significant difference in favour of vemurafenib was shown for the time to deterioration for the outcome "constipation". The extent of the effect in this non-serious/non-severe outcome was no more than marginal, however. Hence there was no hint of lesser benefit or added benefit for this outcome; an added benefit is therefore not proven for this outcome.

The assessment for the outcomes from the area of symptoms (time to deterioration) deviates from the company's assessment insofar as the company derived an added benefit across all scales. In addition, the company assumed a high certainty of results overall.

Health status

The dossier contained no evaluable data for the outcome "health status" measured with the EQ-5D VAS. Hence there was no hint of an added benefit for this outcome; an added benefit is therefore not proven for this outcome.

This deviates from the company's assessment, which derived an added benefit based on a high certainty of results.

Health-related quality of life

Functional scales of the EORTC (time to deterioration)

Aspects of health-related quality of life were recorded using the functional scales of the cancer-specific questionnaire EORTC QLQ-C30.

A statistically significant advantage in favour of dabrafenib and trametinib combination therapy was shown for all 6 functional scales investigated (global health status, physical functioning, role functioning, emotional functioning, cognitive functioning and social functioning). This resulted in a hint of an added benefit of dabrafenib and trametinib combination therapy compared with the ACT vemurafenib for the outcome "health-related quality of life".

This deviates from the company's assessment, which also derived an added benefit for all scales, but assumed a high certainty of results.

Adverse events

The AEs that most commonly occurred in the COMBI-v study (AEs, SAEs, discontinuation due to AEs, and AEs CTCAE grade ≥ 3) are presented in Appendix C (Table 26 to Table 29) of the full dossier assessment. Due to the different observation periods in the 2 study arms, the time-adjusted analyses in Table 15 were primarily used for the assessment.

Serious adverse events

No statistically significant difference between the treatment groups was shown for the outcome "SAEs (time to first event)". Hence there was no hint of greater or lesser harm of dabrafenib and trametinib combination therapy compared with the ACT vemurafenib; greater or lesser harm is therefore not proven.

This concurs with the company's assessment.

Discontinuation due to adverse events

No statistically significant difference between the treatment groups was shown for the outcome "discontinuation due to AEs (time to first event)". Hence there was no hint of greater or lesser harm of dabrafenib and trametinib combination therapy compared with the ACT vemurafenib; greater or lesser harm is therefore not proven.

This concurs with the company's assessment.

Adverse events CTCAE grade ≥ 3

A statistically significant difference in favour of dabrafenib and trametinib combination therapy was shown for the outcome "AEs CTCAE grade ≥ 3 (time to first event)". This

resulted in an indication of lesser harm of dabrafenib and trametinib combination therapy compared with the ACT vemurafenib for this outcome.

The assessment concurs with that of the company, which derived lesser harm assuming a high certainty of results.

Skin and subcutaneous tissue disorders

A statistically significant difference in favour of dabrafenib and trametinib combination therapy was shown for the outcome "skin and subcutaneous tissue disorders (time to first event)". This resulted in a hint of lesser harm of dabrafenib and trametinib combination therapy compared with the ACT vemurafenib for this outcome.

This partly deviates from the company's assessment, which also derived lesser harm, but assumed a high certainty of results for this outcome.

Musculoskeletal and connective tissue disorders

A statistically significant difference in favour of dabrafenib and trametinib combination therapy was shown for the outcome "musculoskeletal and connective tissue disorders (time to first event)". This resulted in a hint of lesser harm of dabrafenib and trametinib combination therapy compared with the ACT vemurafenib for this outcome.

This partly deviates from the company's assessment, which also derived lesser harm, but assumed a high certainty of results for this outcome.

Respiratory, thoracic and mediastinal disorders

A statistically significant difference to the disadvantage of dabrafenib and trametinib combination therapy was shown for the outcome "respiratory, thoracic and mediastinal disorders (time to first event)". The extent of the effect in this non-serious/non-severe outcome was no more than marginal, however; greater or lesser harm is therefore not proven.

This deviates from the company's assessment, which assumed a low certainty of results for this outcome and derived greater harm of the combination therapy.

Neoplasms benign, malignant and unspecified (including cysts and polyps)

A statistically significant difference in favour of dabrafenib and trametinib combination therapy was shown for the outcome "neoplasms benign, malignant and unspecified (time to first event)". This resulted in a hint of lesser harm of dabrafenib and trametinib combination therapy compared with the ACT vemurafenib for this outcome.

This partly deviates from the company's assessment, which also derived lesser harm, but assumed a high certainty of results for this outcome.

Further specific adverse events (fever and chills)

The overview of the most common AEs (Table 26 in Appendix C of the full dossier assessment) shows a potentially important difference between the treatment arms for fever and chills (further specific AEs with notable group difference are already contained in the analyses of the System Organ Classes (SOC) or in the EORTC QLQ-C30). Due to the different observation periods in the 2 treatment arms and the missing survival time analyses for these outcomes, only a qualitative interpretation was conducted on the basis of the naive proportions (see Section 2.7.2.4.3 of the full dossier assessment). The events "fever" and "chills" occurred in notably more patients in the combination arm than in the vemurafenib arm. This relation was shown in particular also at the level of SAEs. It is unclear to what extent the greater proportion of patients with these events in the combination arm was due to the longer observation periods. The difference between the 2 treatment arms appears to be so large that it cannot be fully explained by the different observation periods, however. Greater harm from dabrafenib and trametinib combination therapy cannot be completely excluded.

This deviates from the company's assessment, which did not present these events individually, but used the SOC "general disorders and administration site conditions (time to first event)", which contains the 2 AEs "fever" and "chills". The company derived no greater or lesser harm for this outcome.

2.4.4 Subgroups and other effect modifiers

The following subgroup characteristics were considered to be relevant for the present benefit assessment:

- age (< 65 years/≥ 65 years)
- sex (men/women)
- BRAF mutation status (V600E/V600K)
- disease stage at screening (IIIc, IVM1a, IVM1b/IVM1c)
- baseline LDH (> ULN/≤ ULN)
- visceral metastases at baseline (yes/no)
- geographical region (Western Europe/other)

Except for the subgroup on geographical region, which was generated post hoc for the benefit assessment, the subgroup characteristics and cut-off values mentioned were predefined in the COMBI-v study.

The company presented suitable subgroup analyses only for the outcome "overall survival" (for both data cut-offs). Since the treatment switch allowed after the first data cut-off led to an increased uncertainty of the subgroup results of the second data cut-off, the results of the first

data cut-off were decisive for the present assessment (see Section 2.7.2.4.2 of the full dossier assessment).

The company presented further subgroup analyses for a choice of further outcomes from the area of AEs relevant for the present benefit assessment (discontinuation due to AEs, SAEs and AEs CTCAE grade ≥ 3), but these were based on the naive proportions. These analyses are at most suitable for drawing qualitative conclusions because of the possible bias caused by the differences in observation periods in the 2 treatment arms. Furthermore, the analyses were limited to the 2 characteristics “age” and “sex”.

Subgroup analyses on the outcomes of the areas “morbidity” and “health-related quality of life” were missing completely.

The prerequisite for proof of differing effects is a statistically significant homogeneity and/or interaction test ($p < 0.05$). An indication of differing effects results from a p-value between 0.05 and 0.2. Due to the described uncertainty regarding the subgroup results of the second data cut-off, indications of effect modifications are only presented if they were already shown in the first data cut-off.

Table 17 shows the results of the subgroup analyses for subgroup characteristics for which at least an indication of an effect modification was provided in the first data cut-off. Where necessary, the data from the company’s dossier were supplemented by the Institute’s calculations.

Table 17: Subgroups (outcome "overall survival"): RCT, direct comparison: dabrafenib + trametinib vs. vemurafenib

Study Outcome	Dabrafenib + trametinib		Vemurafenib		Dabrafenib + trametinib vs. vemurafenib	
Characteristic Time point Subgroup	N	Median survival time in months [95% CI]	N	Median survival time in months [95% CI]	HR [95% CI][a]	p-value
COMBI-v						
Overall survival						
Sex						
First data cut-off (17 April 2014)						
Men	208	18.3 [16.0; NA]	180	16.8 [15.9; NA]	0.87 [0.62; 1.22]	0.420[b]
Women	144	NA [NA; NA]	172	17.2 [14.3; NA]	0.46 [0.30; 0.71]	< 0.001[b]
					Interaction:	0.034[c]
Second data cut-off (13 March 2015)						
Men	208	20.7 [16.3; NA]	180	19.2 [15.9; 21.9]	0.82 [0.62; 1.09]	0.168[b]
Women	144	NA [24.1; NA]	172	16.7 [14.3; 20.1]	0.48 [0.35; 0.67]	< 0.001[b]
					Interaction:	0.025[c]
Visceral metastases at baseline						
First data cut-off (17 April 2014)						
Yes	278	NA [18.3; NA]	271	15.9 [13.1; NA]	0.65 [0.49; 0.86]	0.003[b]
No	73	NA [16.8; NA]	81	NA [16.7; NA]	1.15 [0.56; 2.36]	0.703[b]
					Interaction:	0.150[c]
Disease stage at screening[d]						
First data cut-off (17 April 2014)						
IIIc, IVM1a, IVM1b	130	NA [NA; NA]	143	17.2 [16.7; NA]	0.40 [0.22; 0.72]	0.002[b]
IVM1c	221	17.5 [14.8; NA]	208	18.0 [10.7; NA]	0.77 [0.58; 1.04]	0.079[b]
					Interaction:	0.094[c]

a: Calculated with the Pike method [10].
b: Institute's calculation.
c: Calculated using the Wald chi-square test after corresponding extension of the Cox regression model by subgroup variable and interaction term treatment*subgroup variable.
d: According to AJCC classification [9].
AJCC: American Joint Committee on Cancer;; CI: confidence interval; HR: hazard ratio; N: number of analysed patients; NA: not achieved; RCT: randomized controlled trial; vs.: versus

Mortality

Overall survival

Both data cut-offs showed proof of an effect modification by the characteristic "sex" and indications of an effect modification by the characteristics "visceral metastases at baseline" and "disease stage at screening" for the outcome "overall survival". Not all the subgroup results could be interpreted because data for the investigation of possible dependencies

between the subgroup characteristics were missing. Since the interaction strength for the characteristic "sex" was higher than for other subgroups (proof), only the subgroup results for this characteristic were considered.

A statistically significant effect in favour of dabrafenib and trametinib combination therapy for women was shown in both data cut-offs. Overall, this resulted in an indication of an added benefit of dabrafenib and trametinib combination therapy compared with the ACT for the outcome "overall survival" for women.

For men, there was no statistically significant difference between the treatment groups in both data cut-offs. As a result, there was no hint of an added benefit for men for the outcome "overall survival"; an added benefit is therefore not proven for men.

The assessment regarding the subgroup results for the outcome "overall survival" deviates from that of the company, which derived an added benefit for the total population. The company did not take into further consideration the results of the subgroup analyses it submitted because it considered them to provide an inconsistent and partly contradictory picture and could overall not be interpreted.

Subgroup results on further outcomes

The company presented no suitable subgroup analyses based on survival time analyses for further outcomes (see Section 2.7.2.2 of the full dossier assessment). This is considered critical particularly in the present case because a relevant effect modification was identified for the outcome "overall survival" by the characteristic "sex", which requires a separate conclusion on the added benefit for men and women.

In Module 4 A (Section 4.3.1.3.2 [11]) however, the company presented supplementary subgroup analyses for the outcomes "discontinuation due to AEs", "SAEs", and "AEs CTCAE grade ≥ 3" based on naive proportions for the subgroup characteristics "age" and "sex". These analyses at most allow drawing qualitative conclusions because of the possible bias caused by the differences in observation periods in the 2 treatment arms. No statistically significant effect was shown for men or for women for the outcomes "discontinuation due to AEs" and "SAEs" despite the notably longer observation period in the combination arm (data not shown). Due to the known direction of bias to the disadvantage of the combination therapy, greater harm of dabrafenib and trametinib combination therapy can therefore be excluded for these 2 outcomes for both sexes on the basis of the data presented.

A statistically significant advantage in favour of dabrafenib and trametinib combination therapy was shown for men for the outcome "AEs CTCAE grade ≥ 3" (RR [95% CI]: 0.81 [0.67; 0.97]), whereas for women the result was not statistically significant (RR [95% CI]: 0.87 [0.74; 1.03]). Due to the known direction of bias to the disadvantage of the combination therapy, an indication of lesser harm from dabrafenib and trametinib combination therapy

than from vemurafenib can therefore be derived for men. For women, only greater harm from dabrafenib and trametinib combination therapy can be excluded.

This assessment deviates from that of the company, which did not consider the subgroup analyses on AEs based on naive proportions, but only presented them as additional information.

2.5 Extent and probability of added benefit

The derivation of extent and probability of added benefit is presented below at outcome level, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the *General Methods* of IQWiG [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 resulted in indications and hints of an added benefit of dabrafenib and trametinib combination therapy in comparison with vemurafenib for the outcomes from the areas “mortality”, “morbidity”, “health-related quality of life” and “AEs”. There was proof of an effect modification by the subgroup characteristic “sex” for the outcome “overall survival”.

The extent of the respective added benefit at outcome level was estimated from these results (see Table 18).

Table 18: Extent of added benefit at outcome level: dabrafenib + trametinib vs. vemurafenib

Outcome category **Outcome** **Effect modifier/subscale** **Subgroup**	**Dabrafenib + trametinib vs. vemurafenib[a]** **Median time to event [months]** **Effect estimates [95% CI]; p-value** **Probability[b]**	**Derivation of extent[c]**
Mortality		
Overall survival		
Sex		
Men	First data cut-off 18.3 vs. 16.8 HR: 0.87 [0.62; 1.22]; p = 0.420	Lesser benefit/added benefit not proven
	Second data cut-off 20.7 vs. 19.2 HR: 0.82 [0.62; 1.09]; p = 0.168	
Women	First data cut-off NA vs. 17.2 HR: 0.46 [0.30; 0.71]; p < 0.001	Outcome category: mortality $CI_u < 0.85$ added benefit, extent: "major"
	Second data cut-off NA vs. 16.7 HR: 0.48 [0.35; 0.67]; p < 0.001	
	Summarizing assessment of the probability (first and second data cut-off): "indication"	

(continued)

Table 18: Extent of added benefit at outcome level: dabrafenib + trametinib vs. vemurafenib (continued)

Outcome category **Outcome** **Effect modifier/subscale** **Subgroup**	**Dabrafenib + trametinib vs. vemurafenib[a]** **Median time to event [months]** **Effect estimates [95% CI]; p-value** **Probability[b]**	**Derivation of extent[c]**
Morbidity		
EORTC QLQ-C30 symptom scales – time to deterioration of symptoms		
Fatigue	5.3 vs. 3.7 HR: 0.85 [0.71; 1.03]; p = 0.104	Lesser benefit/added benefit not proven
Nausea and vomiting	15.6 vs. 9.3 HR: 0.78 [0.62; 0.99]; p = 0.039 probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications $0.90 < CI_u$ Lesser benefit/added benefit not proven[d]
Pain	13.6 vs. 5.8 HR: 0.61 [0.49; 0.76]; p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications $CI_u < 0.80$ added benefit, extent: "considerable"
Dyspnoea	NA vs. NA HR: 0.84 [0.65; 1.08]; p = 0.179	Lesser benefit/added benefit not proven
Insomnia	NA vs. 8.3 HR: 0.52 [0.40; 0.67]; p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications $CI_u < 0.80$ added benefit, extent: "considerable"
Appetite loss	NA vs. 9.2 HR: 0.48 [0.37; 0.62]; p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications $CI_u < 0.80$ added benefit, extent: "considerable"
Constipation	NA vs. NA HR: 1.41 [1.05; 1.90] HR: 0.71 [0.53; 0.95][e]; p = 0.023 probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications $0.90 < CI_u$ Lesser benefit/added benefit not proven[d]
Diarrhoea	18.5 vs. 5.6 HR: 0.51 [0.40; 0.64]; p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications $CI_u < 0.80$ added benefit, extent: "considerable"
Health status (EQ-5D VAS)	No evaluable data	Lesser benefit/added benefit not proven

(continued)

Table 18: Extent of added benefit at outcome level: dabrafenib + trametinib vs. vemurafenib (continued)

Outcome category **Outcome** **Effect modifier/subscale** **Subgroup**	**Dabrafenib + trametinib vs. vemurafenib[a]** **Median time to event [months]** **Effect estimates [95% CI]; p-value** **Probability[b]**	**Derivation of extent[c]**
Health-related quality of life		
EORTC QLQ-C30 functional scales – time to deterioration of health-related quality of life		
Global health status	11.1 vs. 5.6 HR: 0.64 [0.51; 0.79]; p < 0.001 probability: "hint"	Outcome category: health-related quality of life $CI_u < 0.90$ added benefit, extent: "considerable"
Physical functioning	15.2 vs. 7.4 HR: 0.66 [0.53; 0.83]; p < 0.001 probability: "hint"	Outcome category: health-related quality of life $CI_u < 0.90$ added benefit, extent: "considerable"
Role functioning	9.2 vs. 5.6 HR: 0.69 [0.56; 0.85]; p < 0.001 probability: "hint"	Outcome category: health-related quality of life $CI_u < 0.90$ added benefit, extent: "considerable"
Emotional functioning	NA vs. 13.3 HR: 0.70 [0.54; 0.91]; p = 0.008 probability: "hint"	Outcome category: health-related quality of life $0.90 \leq CI_u < 1.00$ added benefit, extent: "minor"
Cognitive functioning	9.4 vs. 7.4 HR: 0.77 [0.62; 0.96]; p = 0.020 probability: "hint"	Outcome category: health-related quality of life $0.90 \leq CI_u < 1.00$ added benefit, extent: "minor"
Social functioning	12.3 vs. 5.6 HR: 0.59 [0.47; 0.73]; p < 0.001 probability: "hint"	Outcome category: health-related quality of life $CI_u < 0.75$, risk ≥ 5% added benefit, extent: "major"

(continued)

Table 18: Extent of added benefit at outcome level: dabrafenib + trametinib vs. vemurafenib (continued)

Outcome category **Outcome** **Effect modifier/subscale** **Subgroup**	**Dabrafenib + trametinib vs. vemurafenib[a]** **Median time to event [months]** **Effect estimates [95% CI]; p-value** **Probability[b]**	**Derivation of extent[c]**
Adverse events		
SAEs	NA vs. NA HR: 1.03 [0.80; 1.32]; p = 0.819	Greater/lesser harm not proven
Discontinuation due to AEs	NA vs. NA HR: 1.01 [0.66; 1.55]; p = 0.957	Greater/lesser harm not proven
AEs CTCAE grade ≥ 3	10.1 vs. 2.7 HR: 0.65 [0.53; 0.78]; p < 0.001 probability: "indication"	Outcome category: serious/severe AEs $CI_u < 0.90$ lesser harm, extent: "considerable"
Skin and subcutaneous tissue disorders	3.6 vs. 0.3 HR: 0.29 [0.24; 0.35]; p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe AEs[f] $CI_u < 0.80$ lesser harm, extent: "considerable"
Musculoskeletal and connective tissue disorders	10.0 vs. 1.0 HR: 0.48 [0.40; 0.59]; p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe AEs[f] $CI_u < 0.80$ lesser harm, extent: "considerable"
Respiratory, thoracic and mediastinal disorders	NA vs. NA HR: 1.36 [1.04; 1.78] HR: 0.74 [0.56; 0.96][e]; p = 0.023 probability: "hint"	Outcome category: non-serious/non-severe AEs[f] $0.90 < CI_u$ Greater/lesser harm not proven[d]
Neoplasms benign, malignant and unspecified (including cysts and polyps)	NA vs. NA HR: 0.17 [0.12; 0.24]; p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe AEs[f] $CI_u < 0.80$ lesser harm, extent: "considerable"

(continued)

Table 18: Extent of added benefit at outcome level: dabrafenib + trametinib vs. vemurafenib (continued)

a: 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 [3]. The study population of the included study for the assessment of the added benefit (only pretreated 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.
b: Probability given if statistically significant differences are present.
c: Estimations of effect size are made depending on the outcome category with different limits based on the CI_u.
d: Lesser benefit/added benefit or greater/lesser harm is not proven because the effect size was only marginal.
e: Institute's calculation, reversed direction of effect to enable use of limits to derive the extent of the added benefit.
f: The majority of AEs in the analysis were non-serious/non-severe.
AE: adverse event; BRAF: rapidly accelerated fibrosarcoma – isoform B (serine/threonine-protein kinase B-Raf); CI: confidence interval; CI_u: upper limit of confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D: European Quality of Life-5 Dimensions; HR: hazard ratio; NA: not achieved: QLQ-C30: questionnaire on quality of life; VAS: visual analogue scale; vs.: versus

2.5.2 Overall conclusion on added benefit

Table 19 summarizes the results that were considered in the overall conclusion on the extent of added benefit.

Table 19: Positive and negative effects from the assessment of dabrafenib + trametinib compared with vemurafenib[a]

Positive effects	Negative effects
Mortality ▪ Overall survival ▫ sex (men): lesser benefit/added benefit not proven ▫ sex (women): indication of an added benefit – extent: "major"	
Morbidity – non-serious/non-severe symptoms ▪ EORTC QLQ-C30 symptom scales (pain, insomnia, appetite loss, diarrhoea); hint of an added benefit; extent: "considerable"	
Health-related quality of life ▪ EORTC QLQ-C30 functional scales (global health status, physical functioning, role functioning, emotional functioning, cognitive functioning, social functioning); hint of an added benefit, extent: "considerable"	
Serious/severe adverse events ▪ AEs CTCAE grade ≥ 3; indication of lesser harm; extent: "considerable" Non-serious/non-severe AEs ▪ skin and subcutaneous tissue disorders; hint of lesser harm, extent: "considerable" ▪ musculoskeletal and connective tissue disorders; hint of lesser harm, extent: "considerable" ▪ neoplasms benign, malignant and unspecified (including cysts and polyps); hint of lesser harm, extent: "considerable"	
a: 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 [3]. The study population of the included study for the assessment of the added benefit (only pretreated 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. AE: adverse event; BRAF: rapidly accelerated fibrosarcoma – isoform B (serine/threonine-protein kinase B-Raf); CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; QLQ-C30: questionnaire on quality of life; SPC: Summary of Product Characteristics	

Since there was proof of an effect modification for the subgroup characteristic "sex" for the outcome "overall survival", the added benefit is presented separately for men and women.

Women

For women, there was an indication of major added benefit for the outcome "overall survival". The company presented no subgroup analyses for the outcomes in the categories "morbidity" and "health-related quality of life" so that it was unclear for them to what extent

the effects in women differed from those in the total population. It cannot be assumed, however, that the notably positive effects in the total population turn into negative effects if only the subgroup of women is considered. Only subgroup analyses based on the naive proportions for the different overall rates of AEs were available for AEs. These can be interpreted in qualitative terms insofar as no greater harm from dabrafenib and trametinib combination therapy in women can be assumed. On a critical note on the balancing of the added benefit for women, no adequate subgroup results were available for a large proportion of the outcomes. However, based on the available data it can also not be assumed that the major survival advantage in women is to be questioned.

Overall, there is an indication of a major added benefit of dabrafenib and trametinib combination therapy compared with the ACT vemurafenib for women with unresectable or metastatic melanoma with a BRAF V600 mutation.

Men

Neither added benefit nor lesser benefit is proven for men for the outcome "overall survival". Analogous to the data situation for women, no adequate subgroup analyses were available for the outcomes in the categories "morbidity" and "health-related quality of life" so that it remains unclear to what extent the effects in men differ from those in the total population. It cannot be assumed, however, that the notably positive effects in the total population turn into negative effects if only the subgroup of men is considered. Only subgroup analyses based on the naive proportions were available for the different overall rates of AEs. Despite the potential bias to the disadvantage of the combination arm in the subgroup of men, a statistically significant advantage of dabrafenib and trametinib combination therapy was shown for the outcome "AEs CTCAE grade ≥ 3" so that an indication of lesser harm of the combination therapy could be derived. Due to the potential bias resulting from the different observation periods in both study arms, the extent is non-quantifiable, however. The results on the overall rates of SAEs and discontinuation due to AEs based on the naive proportions can be interpreted insofar as no greater harm from dabrafenib and trametinib combination therapy than from vemurafenib can be assumed for men.

Overall, there is an indication of a non-quantifiable added benefit of dabrafenib and trametinib combination therapy compared with the ACT vemurafenib for men with unresectable or metastatic melanoma with a BRAF V600 mutation.

Summary

In summary, there is an indication of a major added benefit of dabrafenib and trametinib combination therapy compared with the ACT vemurafenib for women with unresectable or metastatic melanoma with a BRAF V600 mutation, and an indication of a non-quantifiable added benefit for men with unresectable or metastatic melanoma with a BRAF V600 mutation.

The result of the assessment of the added benefit of dabrafenib and trametinib combination therapy in comparison with the ACT is summarized in Table 20.

Table 20: 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 a non-quantifiable 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 [3]. The study population of the included study for the assessment of the added benefit (only pretreated 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

This deviates from the company's approach, which, postulating high certainty of results irrespective of sex, claimed a major added benefit for the total population.

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

2.6 List of included studies

COMBI-v

GlaxoSmithKline. Dabrafenib plus trametinib vs vemurafenib alone in unresectable or metastatic BRAF V600E/K cutaneous melanoma (COMBI-v): full text view [online]. In: ClinicalTrials.gov. 4 December 2014 [accessed: 18 November 2015]. URL: https://clinicaltrials.gov/show/NCT01597908.

GlaxoSmithKline. Dabrafenib plus trametinib vs vemurafenib alone in unresectable or metastatic BRAF V600E/K cutaneous melanoma (COMBI-v): study results [online]. In: ClinicalTrials.gov. 4 December 2014 [accessed: 18 November 2015]. URL: https://www.clinicaltrials.gov/ct2/show/results/NCT01597908.

GlaxoSmithKline. A Phase III, randomised, open-label study comparing the combination of the BRAF inhibitor dabrafenib and the MEK inhibitor trametinib to the BRAF inhibitor vemurafenib in subjects with unresectable (stage IIIc) or metastatic (stage IV) BRAF V600E/K mutation positive cutaneous melanoma: study MEK116513, clinical sudy report [unpublished]. 2015.

GlaxoSmithKline. A phase III, randomised, open-label study comparing the combination of the BRAF inhibitor, dabrafenib and the MEK inhibitor, trametinib to the BRAF inhibitor vemurafenib in subjects with unresectable (stage IIIc) or metastatic (stage IV) BRAF V600E/K mutation positive cutaneous melanoma [online]. In: EU Clinical Trials Register. [Accessed: 18 November 2015]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2011-006088-23.

GlaxoSmithKline Research and Development. A phase III, randomised, open-label study comparing the combination of the BRAF inhibitor, dabrafenib and the MEK inhibitor, trametinib to the BRAF inhibitor vemurafenib in subjects with unresectable (stage IIIc) or metastatic (stage IV) BRAF V600E/K mutation positive cutaneous melanoma [online]. In: PharmNet.Bund Klinische Prüfungen. [Accessed: 2 November 2015]. URL: http://www.pharmnet-bund.de/dynamic/de/klinische-pruefungen/index.htm.

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Please see full dossier assessment for full reference list.

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3. Novartis Pharma. Tafinlar 50 mg Hartkapseln, Tafinlar 75 mg Hartkapseln: Fachinformation [online]. August 2015 [accessed: 26 October 2015]. URL: http://www.fachinfo.de.

4. GlaxoSmithKline. A Phase III, randomised, open-label study comparing the combination of the BRAF inhibitor dabrafenib and the MEK inhibitor trametinib to the BRAF inhibitor vemurafenib in subjects with unresectable (stage IIIc) or metastatic (stage IV) BRAF V600E/K mutation positive cutaneous melanoma: study MEK116513, clinical sudy report [unpublished]. 2015.

5. GlaxoSmithKline. A Phase III, randomised, open-label study comparing the combination of the BRAF inhibitor dabrafenib and the MEK inhibitor trametinib to the BRAF inhibitor vemurafenib in subjects with unresectable (stage IIIc) or metastatic (stage IV) BRAF V600E/K mutation positive cutaneous melanoma: study MEK116513, protocol amendment 05 [unpublished]. 2014.

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