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Addendum

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
BRAF	rapidly accelerated fibrosarcoma – isoform B
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
SGB	Sozialgesetzbuch (Social Code Book)

1 Background

On 26 April 2016, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct a supplementary assessment for Commission A15-52 (Cobimetinib – Benefit assessment according to §35a Social Code Book (SGB) V [1]).

In its written comments to the dossier assessment [2-4], the pharmaceutical company (hereinafter referred to as "the company") sent supplementary information, which went beyond the information provided in the dossier on cobimetinib [5], to prove the added benefit. In particular, it submitted results on the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) and on adverse events (AEs). The G-BA's commission comprised the assessment of the data presented by the company.

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

2 Data subsequently submitted

From the company's comments, the following analyses were considered for the present addendum:

- responder analyses for the EORTC QLQ-C30 for the third data cut-off (16 January 2015)
- survival time analyses for the outcome "neoplasms benign, malignant and unspecified (incl cysts and polyps)" for the second data cut-off (19 September 2014)
- results on overall survival for the fourth data cut-off (28 August 2015) and survival time analyses for AEs for the fifth data cut-off (30 September 2015)

The responder analyses for the EORTC QLQ-C30 and the survival time analysis for the outcome "neoplasms benign, malignant and unspecified (incl cysts and polyps)" were used as supplementary information to the analyses already included in the dossier assessment for the balancing of the effects for the overall conclusion on the added benefit. The recording of data on the EORTC QLQ-C30 was stopped shortly after the third data cut-off; results on morbidity and health-related quality of life were therefore not available for later data cut-offs.

The information on overall survival for the fourth data cut-off and on AEs for the fifth data cut-off were used to examine whether the overall conclusion on the added benefit based on the data cut-offs comprising all outcomes was called into question by these data.

3 Results on added benefit

3.1 Risk of bias

Table 1 shows the risk of bias for the relevant outcomes. Deviating from the dossier assessment, the risk of bias for the EORTC QLQ-C30 and for the AE "neoplasms benign, malignant and unspecified (incl cysts and polyps)" was assessed on the basis of the analyses subsequently submitted.

Table 1: Risk of bias at study and outcome level – RCT, direct comparison: cobimetinib + vemurafenib vs. vemurafenib

Study	Outcomes								
	Study level	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)	Specific AEs[a]
coBRIM	L	L	H[b, c]	H[b]	H[b, c]	H[c]	H[c]	H[c]	H[c]

a: Contains the following events (MedDRA coding): alopecia (PT), hyperkeratosis (PT), photosensitivity reaction (PT), diarrhoea (PT), nausea (PT), vomiting (PT), serous retinopathy/retinal detachment (AEGT), neoplasms benign, malignant and unspecified (incl cysts and polyps) (SOC).
b: Proportion of missing values in the analysis > 10%.
c: Different observation periods with potentially informative censoring.
AE: adverse event; AEGT: Adverse Event Grouped Terms; 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; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

No deviating assessment of the risk of bias resulted from the analyses subsequently submitted by the company in comparison with dossier assessment A15-52. The risk of bias for all outcomes, except for the outcome "overall survival", was rated as high.

3.2 Results

Table 2 and Table 3 summarize the results of the responder analyses for the outcomes on morbidity (symptoms) and health-related quality of life subsequently submitted by the company. The result for the specific AE "neoplasms benign, malignant and unspecified (incl cysts and polyps)" is presented in Table 4. The Kaplan-Meier curves on these outcomes were not available. The results for the outcomes "overall survival", "health status" and further outcomes of the category "side effects" can be found in dossier assessment A15-52 [1].

Table 2: Results (morbidity: time to deterioration of symptoms) – RCT, direct comparison: cobimetinib + vemurafenib vs. vemurafenib (third data cut-off from 16 January 2015)

Study Outcome Subscale	Cobimetinib + vemurafenib N	Cobimetinib + vemurafenib Median time to event (months) [95% CI] Patients with event n (%)	Vemurafenib N	Vemurafenib Median time to event (months) [95% CI] Patients with event n (%)	Cobimetinib + vemurafenib vs. vemurafenib HR[a] [95% CI]; p-value[b]
coBRIM[c]					
EORTC QLQ-C30 symptom scales – time to deterioration of symptoms[d]					
Dyspnoea	206	ND 104 (50.5)	204	ND 81 (39.7)	1.14 [0.85; 1.53]; 0.359
Fatigue	206	ND 147 (71.4)	204	ND 155 (76.0)	0.74 [0.59; 0.93]; 0.011
Insomnia	206	ND 87 (42.2)	204	ND 106 (52.0)	0.61 [0.46; 0.82]; < 0.001
Pain	206	ND 120 (58.3)	204	ND 145 (71.1)	0.60 [0.47; 0.77]; < 0.001
Appetite loss	206	ND 114 (55.3)	204	ND 113 (55.4)	0.88 [0.68; 1.15]; 0.357
Diarrhoea	206	ND 148 (71.8)	204	ND 101 (50.0)	1.94 [1.51; 2.50]; < 0.001
Nausea and vomiting	206	ND 120 (58.3)	204	ND 111 (54.4)	1.08 [0.83; 1.40]; 0.561
Constipation	206	ND 80 (38.8)	204	ND 76 (37.3)	0.93 [0.68; 1.28]; 0.654

a: Stratified by geographical region and metastasis stage.
b: Log-rank test.
c: Results of the third data cut-off from 16 January 2015.
d: Time to increase in score by at least 10 points versus the baseline value.
CI: confidence interval; EORTC: European Organisation for Research and Treatment of Cancer; HR: hazard ratio; n: number of patients with (at least one) event; N: number of analysed patients; ND: no data; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; vs.: versus

Table 3: Results (time to deterioration of health-related quality of life) – RCT, direct comparison: cobimetinib + vemurafenib vs. vemurafenib (third data cut-off from 16 January 2015)

Study Outcome Subscale	Cobimetinib + vemurafenib N	Cobimetinib + vemurafenib Median time to event (months) [95% CI] Patients with event n (%)	Vemurafenib N	Vemurafenib Median time to event (months) [95% CI] Patients with event n (%)	Cobimetinib + vemurafenib vs. vemurafenib HR[a] [95% CI]; p-value[b]
coBRIM[c]					
EORTC QLQ-C30 functional scales – time to deterioration of health-related quality of life[d]					
Global health status	206	ND 125 (60.7)	204	ND 133 (65.2)	0.78 [0.61; 1.00]; 0.047
Physical functioning	206	ND 108 (52.4)	204	ND 119 (58.3)	0.70 [0.54; 0.91]; 0.009
Role functioning	206	ND 146 (70.9)	204	ND 138 (67.6)	0.94 [0.75; 1.19]; 0.627
Emotional functioning	206	ND 102 (49.5)	204	ND 96 (47.1)	0.91 [0.69; 1.21]; 0.518
Cognitive functioning	206	ND 117 (56.8)	204	ND 119 (58.3)	0.84 [0.65; 1.08]; 0.174
Social functioning	206	ND 131 (63.6)	204	ND 132 (64.7)	0.81 [0.63; 1.03]; 0.084

a: Stratified by geographical region and metastasis stage.
b: Log-rank test.
c: Results of the third data cut-off from 16 January 2015.
d: Time to decrease in score by at least 10 points versus the baseline value.
CI: confidence interval; EORTC: European Organisation for Research and Treatment of Cancer; HR: hazard ratio; n: number of patients with (at least one) event; N: number of analysed patients; ND: no data; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; vs.: versus

Table 4: Results (neoplasms benign, malignant and unspecified [incl cysts and polyps]: time to first event) – RCT, direct comparison: cobimetinib + vemurafenib vs. vemurafenib (second data cut-off from 19 September 2014)

Study Outcome	Cobimetinib + vemurafenib		Vemurafenib		Cobimetinib + vemurafenib vs. vemurafenib
	N	Median time to event (months) [95% CI] Patients with event n (%)	N	Median time to event (months) [95% CI] Patients with event n (%)	HR [95% CI]; p-value[a]
coBRIM[b]					
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	247	ND 60 (24.3)	246	ND 107 (43.5)	0.41 [0.30; 0.56]; < 0.001

a: Log-rank test.
b: Results of the second data cut-off from 19 September 2014.
CI: confidence interval; HR: hazard ratio; n: number of patients with (at least one) event; N: number of analysed patients; RCT: randomized controlled trial; vs.: versus

Morbidity

Symptoms

A statistically significant difference in favour of cobimetinib in combination with vemurafenib was shown for each of the outcomes **"insomnia"** and **"pain"**. There was a hint of an added benefit of cobimetinib in combination with vemurafenib compared with the appropriate comparator therapy (ACT) for both outcomes.

A statistically significant difference to the disadvantage of cobimetinib in combination with vemurafenib was shown for the outcome **"diarrhoea"**. There was a hint of lesser benefit of cobimetinib in combination with vemurafenib compared with the ACT for "diarrhoea".

A statistically significant difference in favour of cobimetinib in combination with vemurafenib was shown for the outcome **"fatigue"**. The extent of the effect in this outcome of the category of non-serious/non-severe symptoms/late complications was no more than marginal, however; an added benefit of cobimetinib in combination with vemurafenib for fatigue is therefore not proven.

No statistically significant difference between the treatment arms was shown for any of the outcomes **"dyspnoea", "appetite loss", "nausea and vomiting"**, and **"constipation"**. This resulted in no hint of an added benefit of cobimetinib in combination with vemurafenib in comparison with the ACT; an added benefit is therefore not proven for these outcomes.

Health-related quality of life

A statistically significant difference in favour of cobimetinib in combination with vemurafenib was shown for each of the outcomes **"global health status"** and **"physical functioning"**. In addition, there was proof of an effect modification by the characteristic "age" for both outcomes (see Section 3.3). The results for patients under the age of 65 years and for older patients were therefore interpreted separately. For both outcomes, this resulted in a hint of an added benefit for patients under the age of 65 years; for older patients, there was no hint of an added benefit of cobimetinib in combination with vemurafenib in comparison with the ACT; an added benefit is therefore not proven for this subgroup.

There was no statistically significant difference between the treatment arms for the outcomes **"role functioning", "emotional functioning", "cognitive functioning"** and **"social functioning"**. This resulted in no hint of an added benefit of cobimetinib in combination with vemurafenib in comparison with the ACT; an added benefit is therefore not proven for these outcomes.

Side effects

Specific adverse event "neoplasms benign, malignant and unspecified (incl cysts and polyps)"

A statistically significant difference in favour of cobimetinib in combination with vemurafenib was shown for the outcome "neoplasms benign, malignant and unspecified (incl cysts and polyps)". Despite the high risk of bias, there was an indication of lesser harm of cobimetinib in combination with vemurafenib for this outcome. The certainty of results was not downgraded because notably more events occurred in the vemurafenib arm, which had a shorter observation period, and it was therefore not assumed that the observed direction and size of effect was caused by bias alone.

3.3 Subgroups and other effect modifiers

Due to the different observation periods and informative censoring, there was a high risk for the responder analyses on symptoms and health-related quality of life, which might have a different extent in the subgroups. Only the analyses for which there was proof of an interaction ($p < 0.05$) were included in the assessment because of this uncertainty. Hereinafter, only the results on the subgroup analyses subsequently submitted by the company are presented for which there were, in addition, statistically significant and relevant results in at least one subgroup.

Table 5: Subgroups (time to deterioration of health-related quality of life: EORTC QLQ-C30 functional scales) – RCT, direct comparison: cobimetinib + vemurafenib vs. vemurafenib (third data cut-off from 16 January 2015)

Study **Outcome**	**Cobimetinib + vemurafenib**		**Vemurafenib**		**Cobimetinib + vemurafenib vs. vemurafenib**	
Characteristic **Subgroup**	**N**	**Median time to event (months) [95% CI]** **Patients with event n (%)**	**N**	**Median time to event (months) [95% CI]** **Patients with event n (%)**	**HR [95% CI]**	**p-value**
coBRIM[a]						
Global health status						
Age						
< 65 years	154	ND 90 (58.4)	143	ND 97 (67.8)	0.66 [0.49; 0.88]	0.005
≥ 65 years	52	ND 35 (67.3)	61	ND 36 (59.0)	1.24 [0.78; 1.99]	0.373
					Interaction:	0.030[b]
Physical functioning						
Age						
< 65 years	154	ND 72 (46.8)	143	ND 83 (58.0)	0.58 [0.42; 0.80]	0.001
≥ 65 years	52	ND 36 (69.2)	61	ND 36 (59.0)	1.14 [0.72; 1.81]	0.577
					Interaction:	0.018[b]

a: Results of the third data cut-off from 16 January 2015.

b: Likelihood ratio test.

CI: confidence interval; EORTC: European Organisation for Research and Treatment of Cancer; HR: hazard ratio; n: number of patients with (at least one) event; N: number of analysed patients; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; vs.: versus

Health-related quality of life

There was proof of an effect modification by the characteristic "age" for each of the outcomes **"global health status"** and **"physical functioning"**. A statistically significant difference in favour of cobimetinib in combination with vemurafenib was shown for patients < 65 years. There was no statistically significant difference between the treatment groups in the group of patients ≥ 65 years.

This resulted in a hint of an added benefit of cobimetinib in combination with vemurafenib compared with the ACT for patients < 65 years for each of the outcomes "global health status" and "physical functioning". For patients ≥ 65 years, there was no hint of an added

benefit of cobimetinib in combination with vemurafenib in comparison with the ACT; an added benefit is therefore not proven for this subgroup.

3.4 Extent and probability of added benefit at outcome level

The derivation of extent and probability of added benefit at outcome level is shown below, taking into account the data on symptoms, health-related quality of life, and the outcome "neoplasms benign, malignant and unspecified (incl cysts and polyps)" subsequently submitted by the company. The methods used for this purpose are explained in the *General Methods* of IQWiG [6].

Table 6: Extent of added benefit at outcome level: cobimetinib + vemurafenib vs. vemurafenib

Outcome category **Outcome** **Effect modifier/subscale** **Subgroup**	**Cobimetinib + vemurafenib vs. vemurafenib** **Median time to event [months] or mean change** **Effect estimates [95% CI]; p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality (third data cut-off: 16 January 2015)		
Overall survival	Median: NA vs. 17.0 HR: 0.65 [0.49; 0.87]; p = 0.003 probability: "indication"	Outcome category: mortality $0.85 \leq CI_u < 0.95$ added benefit, extent: "considerable"
Morbidity (third data cut-off: 16 January 2015)		
EORTC QLQ-C30 symptom scales		
Dyspnoea	Median: ND vs. ND HR: 1.14 [0.85; 1.53]; p = 0.359	Lesser benefit/added benefit not proven
Fatigue	Median: ND vs. ND HR: 0.74 [0.59; 0.93]; p = 0.011	Lesser benefit/added benefit not proven
Insomnia	Median: ND vs. ND 0.61 [0.46; 0.82]; p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications $0.80 \leq CI_u < 0.90$ added benefit, extent: "minor"
Pain	Median: ND vs. ND HR: 0.60 [0.47; 0.77]; p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications $CI_u < 0.80$ added benefit, extent: "considerable"
Appetite loss	Median: ND vs. ND HR: 0.88 [0.68; 1.15]; p = 0.357	Lesser benefit/added benefit not proven
Diarrhoea	Median: ND vs. ND HR: 1.94 [1.51; 2.50]; p < 0.001 HR: 0.52 [0.40; 0.66][c] probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications lesser benefit, extent: "considerable"
Nausea and vomiting	Median: ND vs. ND HR: 1.08 [0.83; 1.40]; p = 0.561	Lesser benefit/added benefit not proven
Constipation	Median: ND vs. ND HR: 0.93 [0.68; 1.28]; p = 0.654	Lesser benefit/added benefit not proven
Health status		
EQ-5D VAS	Mean change: −0.5 vs. −3.6 MD: 3.14 [0.34; 5.94]; p = 0.028 Hedges' g: 0.22 [0.02; 0.41][d]	Lesser benefit/added benefit not proven

(continued)

Table 6: Extent of added benefit at outcome level: cobimetinib + vemurafenib vs. vemurafenib (continued)

Outcome category **Outcome** **Effect modifier/subscale** **Subgroup**	**Cobimetinib + vemurafenib vs. vemurafenib** **Median time to event [months] or mean change** **Effect estimates [95% CI]; p-value** **Probability**[a]	**Derivation of extent**[b]
Health-related quality of life (third data cut-off: 16 January 2015)		
EORTC QLQ-C30 functional scales		
Global health status		
Age		
< 65 years	Median: ND vs. ND HR: 0.66 [0.49; 0.88]; p = 0.005 probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications $0.80 \leq CI_u < 0.90$ added benefit, extent: "minor"
≥ 65 years	Median: ND vs. ND HR: 1.24 [0.78; 1.99]; p = 0.373	Lesser benefit/added benefit not proven
Physical functioning		
< 65 years	Median: ND vs. ND HR: 0.58 [0.42; 0.80]; p = 0.001 probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications $0.80 \leq CI_u < 0.90$ added benefit, extent: "minor"
≥ 65 years	Median: ND vs. ND HR: 1.14 [0.72; 1.81]; p = 0.577	Lesser benefit/added benefit not proven
Role functioning	Median: ND vs. ND HR: 0.94 [0.75; 1.19]; p = 0.627	Lesser benefit/added benefit not proven
Emotional functioning	Median: ND vs. ND HR: 0.91 [0.69; 1.21]; p = 0.518	Lesser benefit/added benefit not proven
Cognitive functioning	Median: ND vs. ND HR: 0.84 [0.65; 1.08]; p = 0.174	Lesser benefit/added benefit not proven
Social functioning	Median: ND vs. ND HR: 0.81 [0.63; 1.03]; p = 0.084	Lesser benefit/added benefit not proven
Side effects (second data cut-off: 19 September 2014)		
SAEs	Median: ND vs. ND HR: 1.27 [0.91; 1.75]; p = 0.154	Greater/lesser harm not proven
Discontinuation due to AEs	Median: ND vs. ND HR: 1.71 [0.99; 2.94]; p = 0.052	Greater/lesser harm not proven

(continued)

Table 6: Extent of added benefit at outcome level: cobimetinib + vemurafenib vs. vemurafenib (continued)

Outcome category **Outcome** **Effect modifier/subscale** **Subgroup**	**Cobimetinib + vemurafenib vs. vemurafenib** **Median time to event [months] or mean change** **Effect estimates [95% CI]; p-value** **Probability**[a]	**Derivation of extent**[b]
AEs CTCAE grade ≥ 3		
Metastasis stage[e]		
IIIc, M1a, M1b	Median: ND vs. ND HR: 1.76 [1.23; 2.53] HR: 0.57 [0.40; 0.81][c] p = 0.002 probability: "hint"	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ greater harm, extent: "considerable"
M1c	Median: ND vs. ND HR: 1.04 [0.78; 1.37]; p = 0.807	Greater/lesser harm not proven
Alopecia	Median: ND vs. ND HR: 0.41 [0.28; 0.61]; p < 0.001 probability: "indication"[f]	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ lesser harm, extent: "considerable"
Hyperkeratosis	Median: ND vs. ND HR: 0.28 [0.18; 0.44]; p < 0.001 probability: "indication"[f]	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ lesser harm, extent: "considerable"
Photosensitivity reaction		
Metastasis stage[e]		
IIIc, M1a, M1b	Median: ND vs. ND HR: 1.18 [0.71; 1.99]; p = 0.521	Greater/lesser harm not proven
M1c	Median: ND vs. ND HR: 2.81 [1.65; 4.76] HR: 0.36 [0.21; 0.61][c] p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ greater harm, extent: "considerable"
Diarrhoea	Median: ND vs. ND HR: 2.60 [1.97; 3.44] HR: 0.38 [0.29; 0.51][c] p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ greater harm, extent: "considerable"

(continued)

Table 6: Extent of added benefit at outcome level: cobimetinib + vemurafenib vs. vemurafenib (continued)

Outcome category **Outcome** **Effect modifier/subscale** **Subgroup**	**Cobimetinib + vemurafenib vs. vemurafenib** **Median time to event [months] or mean change** **Effect estimates [95% CI]; p-value** **Probability**[a]	**Derivation of extent**[b]
Nausea	Median: ND vs. ND HR: 1.80 [1.31; 2.47] HR: 0.56 [0.40; 0.76][c] p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe side effects CI_u < 0.80 greater harm, extent: "considerable"
Vomiting	Median: ND vs. ND HR: 2.03 [1.32; 3.13] HR: 0.49 [0.32; 0.76][c] p = 0.001 probability: "hint"	Outcome category: non-serious/non-severe side effects CI_u < 0.80 greater harm, extent: "considerable"
Serous retinopathy/retinal detachment	Median: ND vs. ND HR: 9.72 [4.45; 21.23] HR: 0.10 [0.05; 0.22][c] p < 0.001 probability: "hint"[g]	Outcome category: non-serious/non-severe side effects CI_u < 0.80 greater harm, extent: "considerable"
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Median: ND vs. ND HR: 0.41 [0.30; 0.56]; p < 0.001 probability: "indication"[f]	Outcome category: serious/severe side effects CI_u < 0.75, risk ≥ 5% lesser harm, extent: "major"

a: Probability provided if statistically significant differences were present.
b: Estimations of effect size are made depending on the outcome category with different limits based on the CI_u.
c: Institute's calculation, reversed direction of effect to enable use of limits to derive the extent of the added benefit.
d: Added benefit assumed with upper and lower CI limits < −0.2 and > 0.2.
e: According to AJCC classification [7].
f: Despite the longer observation period, the event was less frequent in the cobimetinib + vemurafenib arm than in the vemurafenib arm.
g: Due to the effect size, which cannot be explained by the different observation periods and the potentially informative censorings alone, a high certainty of results could be assumed for this result.

AE: adverse event; AJCC: American Joint Committee on Cancer; 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; MD: mean difference; NA: not achieved; ND: no data; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

3.5 Overall conclusion on added benefit

The analyses subsequently submitted by the company resulted in additional positive effects of cobimetinib in combination with vemurafenib for symptoms (insomnia) and – for patients < 65 years – for health-related quality of life (global health status and physical functioning) in comparison with dossier assessment A15-52. The positive effect in pain was shown by considering the responder analyses at the level of the total population. In addition, the extent of added benefit regarding the outcome "neoplasms benign, malignant and unspecified (incl cysts and polyps)" was quantified as "major". On the negative side, deviating from the dossier assessment, the greater harm of cobimetinib in combination with vemurafenib for the symptom "diarrhoea" recorded with the EORTC QLQ-C30 was quantified as "considerable".

Table 7 summarizes the results that were considered in the overall conclusion on the extent of added benefit.

Table 7: Positive and negative effects from the assessment of cobimetinib in combination with vemurafenib compared with vemurafenib

Positive effects	**Negative effects**
Mortality overall survival: indication of an added benefit – extent: “considerable”	
Non-serious/non-severe symptoms/late complications ▪ EORTC QLQ-C30 symptom scales: insomnia: hint of an added benefit – extent: “minor” ▪ EORTC QLQ-C30 symptom scales: pain: hint of an added benefit – extent: “considerable” ▪ EORTC QLQ-C30 functional scales: global health status ▫ < 65 years: hint of an added benefit – extent: “minor” ▪ EORTC QLQ-C30 functional scales: physical functioning: ▫ < 65 years: hint of an added benefit – extent: “minor”	Non-serious/non-severe symptoms/late complications ▪ EORTC QLQ-C30 symptom scales: diarrhoea: hint of lesser benefit, extent: “considerable”
Serious/severe side effects ▪ neoplasms benign, malignant and unspecified (incl cysts and polyps): indication of lesser harm – extent: “major”	Serious/severe side effects ▪ severe AEs (CTCAE grade ≥ 3) ▫ metastasis stage[a] (IIIc, M1a, M1b): hint of greater harm, extent: “considerable”
Non-serious/non-severe side effects ▪ alopecia: indication of lesser harm – extent: “considerable” ▪ hyperkeratosis: indication of lesser harm – extent: “considerable”	Non-serious/non-severe side effects ▪ photosensitivity reaction ▫ metastasis stage[a] (M1c): hint of greater harm – extent: “considerable” ▪ diarrhoea: hint of greater harm – extent: “considerable” ▪ nausea: hint of greater harm – extent: “considerable” ▪ vomiting: hint of greater harm – extent: “considerable” ▪ serous retinopathy/retinal detachment: indication of greater harm – extent: “considerable”
a: According to AJCC classification [7]. AE: adverse event; AJCC: American Joint Committee on Cancer; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; QLQ-C30: Quality of Life Questionnaire-Core 30	

Deviating from dossier assessment A15-52, the unchanged considerable negative effects were accompanied by additional positive effects, which were of major extent for neoplasms benign, malignant and unspecified. This changed the assessment of the added benefit in comparison with the dossier assessment. The additional positive effects resulted in the extent of the added benefit of cobimetinib in combination with vemurafenib being rated as “considerable”. Results of the fourth and fifth data cut-off (see Appendix A) did not change this assessment.

In summary, there is an indication of a considerable added benefit of cobimetinib in combination with vemurafenib compared with the ACT vemurafenib for patients with unresectable or metastatic melanoma with a rapidly accelerated fibrosarcoma – isoform B (BRAF) V600 mutation (see Table 8).

Table 8: Cobimetinib – extent and probability of added benefit

Therapeutic indication	**Appropriate comparator therapy**[a]	**Extent and probability of added benefit**
Adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation[b]	Vemurafenib	Indication of considerable added benefit
a: Presentation of the ACT specified by the G-BA. b: According to the SPC, the administration of cobimetinib in combination with vemurafenib is approved for patients with unresectable or metastatic melanoma with a BRAF V600 mutation – without restriction of pretreatment [8]. The study population of the included study for the assessment of the added benefit (only treatment-naive patients) therefore does not completely cover the therapeutic indication. It remains unclear whether the observed effects can be transferred to patients who have already had treatment for their advanced melanoma. ACT: appropriate comparator therapy; BRAF: rapidly accelerated fibrosarcoma – isoform B; 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.

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Appendix A – Supplementary presentation of the results of the fourth and fifth data cut-off

Table 9: Results (mortality) – RCT, direct comparison: cobimetinib + vemurafenib vs. vemurafenib (fourth data cut-off from 28 August 2015)

Study Outcome	Cobimetinib + vemurafenib		Vemurafenib		Cobimetinib + vemurafenib 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]
coBRIM					
Overall survival					
Fourth data cut-off (28 August 2015)	247	22.3 [20.3; NA] 114 (46.2)	248	17.4 [15.0; 19.8] 141 (56.9)	0.70 [0.55; 0.90]; 0.005

a: Results from a Cox proportional hazards model adjusted for geographical region and metastasis stage.
b: Log-rank test.
CI: confidence interval; HR: hazard ratio; N: number of analysed patients; n: number of patients with event; NA: not achieved; RCT: randomized controlled trial; vs.: versus

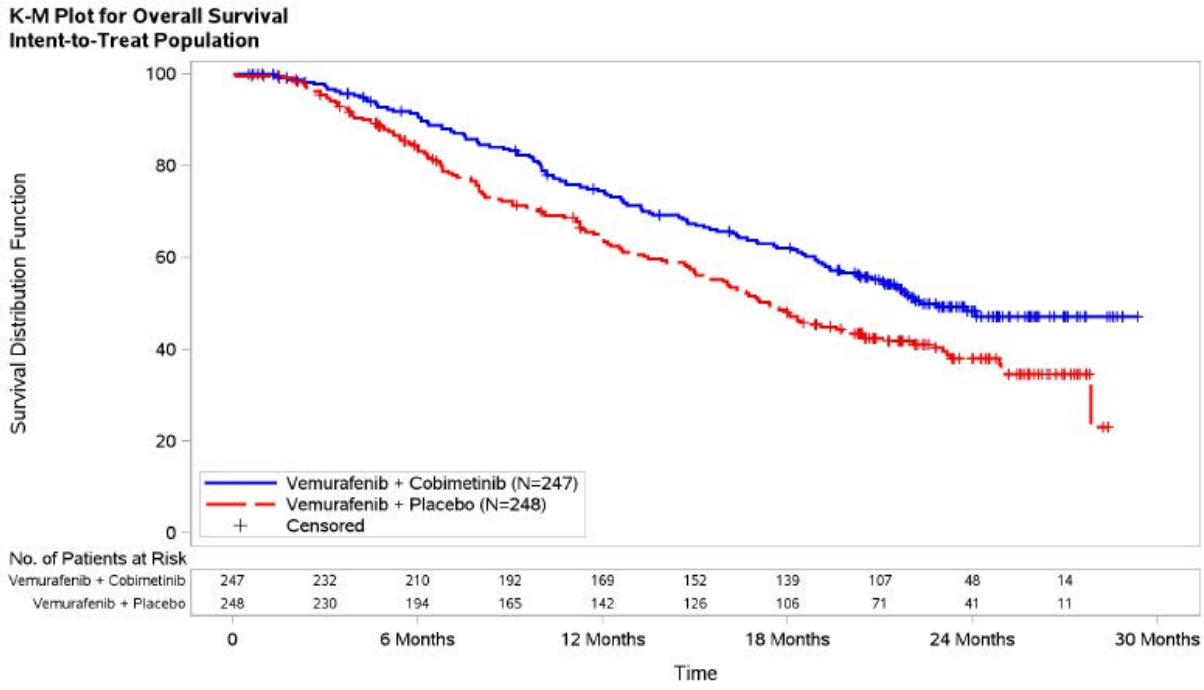

Figure 1: Kaplan-Meier curve for the outcome "overall survival" at the fourth data cut-off (28 August 2015)

Table 10: Results (side effects: time to first event) – RCT, direct comparison: cobimetinib + vemurafenib vs. vemurafenib (fifth data cut-off from 30 September 2015)

Study Outcome	Cobimetinib + vemurafenib		Vemurafenib		Cobimetinib + vemurafenib vs. vemurafenib
	N	Median time to event (months) [95% CI] Patients with event n (%)	N	Median time to event (months) [95% CI] Patients with event n (%)	HR [95% CI]; p-value[a]
coBRIM[b]					
AEs	247	ND 245 (99.2)	246	ND 241 (98.0)	–
SAEs	247	ND 92 (37.2)	246	ND 69 (28.0)	1.20 [0.88; 1.64]; 0.251
Discontinuation due to AEs	247	ND 41 (16.6)	246	ND 22 (8.9)	1.63 [0.97; 2.74]; 0.064
AEs CTCAE grade ≥ 3	247	ND 186 (75.3)	246	ND 151 (61.4)	1.32 [1.06; 1.64]; 0.011
Alopecia	247	ND 41 (16.6)	246	ND 75 (30.5)	0.42 [0.29; 0.62]; < 0.001
Hyperkeratosis	247	ND 25 (10.1)	246	ND 67 (27.2)	0.29 [0.18; 0.47]; < 0.001
Photosensitivity reaction	247	ND 84 (34.0)	246	ND 48 (19.5)	1.73 [1.21; 2.46]; 0.002
Diarrhoea	247	ND 150 (60.7)	246	ND 82 (33.3)	2.41 [1.84; 3.15]; < 0.001
Nausea	247	ND 105 (42.5)	246	ND 64 (26.0)	1.78 [1.31; 2.43]; < 0.001
Vomiting	247	ND 63 (25.5)	246	ND 34 (13.8)	1.88 [1.24; 2.85]; 0.003
Serous retinopathy/retinal detachment	247	ND 67 (27.1)	246	ND 9 (3.7)	8.07 [4.02; 16.19]; < 0.001
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	247	ND 67 (27.1)	246	ND 110 (44.7)	0.44 [0.32; 0.59]; < 0.001

a: Log-rank test.
b: Results of the fifth data cut-off from 30 September 2015.

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 (at least one) event; ND: no data; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus