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Addendum

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List of abbreviations

Abbreviation	Meaning
AE	adverse event
BRAF	rapidly accelerated fibrosarcoma – isoform B (serine/threonine-protein kinase B-Raf)
BRAF V600 wt	BRAF V600 wild type
CTCAE	Common Terminology Criteria for Adverse Events
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HR	hazard ratio
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)

1 Background

On 21 December 2015, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A15-33 (Pembrolizumab – Benefit assessment according to §35a Social Code Book (SGB) V [1]).

In its written comments [2], the pharmaceutical company (hereinafter referred to as "the company") submitted supplementary information, which went beyond the information provided in the dossier, to prove the added benefit. This information concerned analyses on immune-related adverse events (AEs) of the KEYNOTE 006 study on the comparison of pembrolizumab and ipilimumab for research questions 1 and 2 in dossier assessment A15-33. Research question 1 comprises pretreated patients, research question 2 treatment-naive patients with BRAF V600 wild type (wt) tumour (BRAF: serine/threonine-protein kinase B-Raf [rapidly accelerated fibrosarcoma – isoform B]). In the dossier, the analyses were only available for the total population of the KEYNOTE 006 study [3-5], which in its totality was not relevant for the dossier assessment. The G-BA commissioned IQWiG with the assessment of the additional analyses on AEs (research questions 1 and 2) presented by the company in its written comments. Moreover, the G-BA commissioned IQWiG with the assessment of the data of the KEYNOTE 006 study for treatment-naive patients with BRAF V600 mutated tumour (research question 3) available in the dossier.

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

2 Assessment

2.1 Overview of the data relevant for the addendum

Immune-related adverse events

In its written comments, the company presented results on immune-related AEs and immune-related severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3) of the KEYNOTE 006 study on the comparison of pembrolizumab and ipilimumab, each for the subpopulations of pretreated patients and of treatment-naive patients with BRAF V600 wild type tumour. The company presented no results on immune-related serious AEs (SAEs), although these were analysed for the total population in the clinical study report.

Immune-related AEs are generally relevant for the present research question due to the comparison of immunotherapies and were therefore considered separately as specific AEs. The operationalization of the immune-related AEs was planned a priori in the KEYNOTE 006 study and was considered adequate. Immune-related AEs were evaluated by the investigator and were defined as AEs with unknown aetiology with a temporal association with treatment and consistent with an immunological response. Immunological, serological and histological data (biopsy) were to be used to support the diagnosis of an immune-related event.

Data on the comparison of pembrolizumab with ipilimumab in treatment-naive patients with BRAF V600 mutated tumour

Module 4 of the dossier on pembrolizumab contained data from subgroup analyses of the KEYNOTE 006 study for the comparison of pembrolizumab with ipilimumab in treatment-naive patients with BRAF V600 mutated tumour.

The company conducted no information retrieval in the dossier for the comparison of pembrolizumab with ipilimumab in these patients. However, a check of the company's study list provided no indication that further studies on this comparison in treatment-naive patients with BRAF V600 mutated tumour exist.

Importance of the data of the total population of the KEYNOTE 006 study

Due to the research questions of the benefit assessment of pembrolizumab formulated in Section 2.2 of dossier assessment A15-33, 3 different patient populations were considered, i.e. pretreated patients and treatment-naive patients with BRAF V600 wt tumour or with BRAF V600 mutated tumour. In dossier assessment A15-33, a subpopulation of the KEYNOTE 006 study on the comparison of pembrolizumab with ipilimumab was used both for treatment-naive patients with BRAF V600 wt tumour and for a part of the pretreated patients. As described above, the G-BA commission for the present addendum also included the assessment of pembrolizumab in comparison with ipilimumab in patients with BRAF V600 mutated tumour, for which there was also a subpopulation of the KEYNOTE 006 study. Overall, the 3 described subpopulations of this study comprised the entire study population.

The subpopulations were considered separately in the benefit assessment and separate conclusions on the added benefit were derived because these were basically different patient populations. However, it can be adequate in certain cases to transfer the results of the total population to the respective subpopulation if the result of this subpopulation, in contrast to the total population, is not statistically significant, and if this difference in statistical significance is not caused by the presence of different effects in the total population and in the subpopulation, but only by the loss of statistical power resulting from the smaller number of patients. The latter has to be present with sufficient certainty, however.

In contrast to the commonly used investigations of heterogeneity in meta-analyses, this is an equivalence testing in the narrower sense. A non-significant interaction test of $\alpha = 0.2$ alone is insufficient for deriving a conclusion about the equivalence of effects, justified by the statement that conclusions on a subpopulation are drawn on the basis of results of the total study population. Hence, despite a non-significant interaction test, situations can arise in which relevantly different effects exist between subpopulations.

For the present addendum, simulations were therefore used to check whether the statistically significant result in overall survival in the total population of the KEYNOTE 006 study can be transferred to the respective subpopulation of pretreated patients and of treatment-naive patients with BRAF V600 mutated tumour. For this purpose, it was checked in the simulation how likely it is to obtain the respective result if in truth there is no effect or an opposing effect in the subpopulation of interest.

If the results can be transferred, the result of the total population can be used for the conclusion on whether an added benefit can be derived for an outcome. In this case, the extent of the added benefit is non-quantifiable, but at most as large as the extent for the total population.

This consideration was conducted in the present addendum for the outcome “overall survival”. A corresponding consideration is also conceivable for the remaining patient-relevant outcomes of the KEYNOTE 006 study in which statistically significant results were shown in the total population, but not in the relevant subpopulations. This was not conducted in the present addendum, however, because these results cannot influence the respective overall conclusion on the added benefit because of the results on the remaining outcomes in the subpopulations. For the population of pretreated patients (research question 1), the consideration of the results of the total population of the KEYNOTE 006 study on overall survival also had no effects on the summarizing conclusion on the added benefit because an added benefit with the same extent and greater probability was already derived for other outcomes. For research question 2 (treatment-naive patients with BRAF V600 wt tumour), no consideration of the results of the total population for the outcome “overall survival” was required because a statistically significant advantage of pembrolizumab over ipilimumab had already been shown for this outcome at the level of the subpopulation.

Structure of the following sections

The assessment of the present addendum is structured as follows. The updated assessment of research questions 1 (pretreated patients) and 2 (treatment-naive patients with BRAF V600 wild type tumour) under consideration of the analyses on immune-related AEs subsequently submitted by the company in the comment and of the consideration of the total population of the KEYNOTE 006 study for the outcome "overall survival" is conducted in Sections 2.2 and 2.3. Section 2.4 contains the assessment of pembrolizumab in comparison with ipilimumab in treatment-naive patients with BRAF V600 mutated tumour.

2.2 Research question 1: pretreated patients

Research question 1 concerns pretreated patients. For this population, the G-BA specified individual treatment chosen by the treating physician under consideration of the approval status and the respective prior therapy. The assessment was based on results of the KEYNOTE 006 study on the comparison of pembrolizumab with ipilimumab. Based on this study, conclusions on pretreated patients for whom ipilimumab is the individual treatment are possible.

2.2.1 Risk of bias

The analyses on immune-related AEs and immune-related severe AEs (CTCAE ≥ 3) subsequently submitted by the company have a high risk of bias. On the one hand, this is caused by potentially informative censoring as was the case for the other AE outcomes considered in dossier assessment A15-33. On the other, selective reporting cannot be excluded due to the lack of results on immune-related SAEs.

2.2.2 Results

Table 1 shows the results on overall survival for the subpopulation of pretreated patients and for the total population of the KEYNOTE 006 study as well as the results on immune-related AEs for the relevant subpopulation.

Table 1: Results on mortality and AEs – RCT, direct comparison, pretreated patients: pembrolizumab vs. ipilimumab

Study Outcome category Outcome	Pembrolizumab N	Pembrolizumab Median time in months M [95% CI] Patients with event n (%)	Ipilimumab N	Ipilimumab Median time in months M [95% CI] Patients with event n (%)	Pembrolizumab vs. ipilimumab HR [95% CI][a]; p-value[a]
KEYNOTE 006					
Mortality					
Overall survival					
Subpopulation: pretreated patients	91	NC [12.7; NC] ND	97	14.0 [10.9; NC] ND	0.69 [0.44; 1.09]; 0.112
Total population	277	NC ND	278	NC [13.9; NC] ND	0.69 [0.52; 0.91] 0.008
Adverse events					
Immune-related AEs	91	8.7 [5.8; NC] ND	88	NC [2.6; NC] ND	0.72 [0.42; 1.22]; 0.223
Immune-related SAEs	No results available				
Immune-related severe AEs (CTCAE grade ≥ 3)	91	NC 5 (5.5)	88	NC 11 (12.5)	0.25 [0.07; 0.90]; 0.035

a: HR, CI and p-value result from a Cox proportional hazards model adjusted for ECOG PS (0 vs. 1), PD-L1 expression (positive vs. negative) and pretreatment with systemic therapy (yes vs. no).

AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; ECOG PS: Eastern Cooperative Oncology Group Performance Status; HR: hazard ratio; M: months; N: number of analysed patients; n: number of patients with (at least one) event; NC: not calculable; ND: no data; PD-L1: programmed cell death ligand 1; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus

Overall survival

Based on the results of the relevant subpopulation of pretreated patients, no statistically significant difference was shown between the treatment groups. However, statistically significantly longer survival under pembrolizumab than under ipilimumab was shown for the total population of the KEYNOTE 006 study.

The simulations showed that the statistically significant effect of the total study population is transferable to the subpopulation of pretreated patients. For illustration, Figure 1 shows a meta-analysis of the 3 subpopulations of the KEYNOTE 006 study assessed in this addendum. Overall it can be seen that all the effect estimates are of a very similar magnitude.

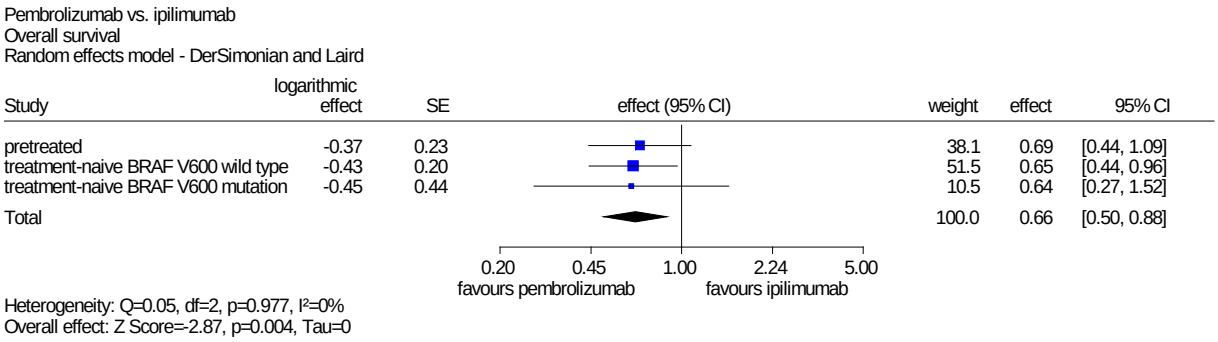

Figure 1: Meta-analysis with random effects according to DerSimonian and Laird on overall survival across the 3 subpopulations of the KEYNOTE 006 study; effect estimate: hazard ratio (HR)

The increased dosage of pembrolizumab in the KEYNOTE 006 study resulted in a reduced certainty of conclusions regarding the results for the outcome "overall survival" (see dossier assessment A15-33 [1]). It cannot be assessed whether the effect of the increased dosage was in favour or to the disadvantage of pembrolizumab. In summary, there is therefore a hint of an added benefit of pembrolizumab in comparison with ipilimumab regarding overall survival for pretreated patients.

Immune-related AEs

No statistically significant difference was shown between the treatment groups for the outcome "immune-related AEs". Hence there was no hint of lesser or greater harm of pembrolizumab in comparison with ipilimumab; greater or lesser harm is therefore not proven.

However, a statistically significant difference was shown in favour of pembrolizumab for the outcome "immune-related severe AEs (CTCAE ≥ 3)". There was an outcome-specific high risk of bias for this outcome. This resulted in a hint of lesser harm from pembrolizumab in comparison with ipilimumab.

2.2.3 Extent and probability of added benefit

2.2.3.1 Assessment of added benefit at outcome level

Based on the data presented in Section 2.3.2 of dossier assessment A15-33 and Section 2.2.2 of the present addendum, the extent of the added benefit was assessed at outcome level.

Table 2: Extent of added benefit at outcome level: pembrolizumab vs. ipilimumab (pretreated patients)

Outcome category **Outcome**	**Pembrolizumab vs. ipilimumab** **Median time to event or mean change** **Effect estimate [95% CI]** **p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality		
Overall survival	Pretreated patients: median: NC vs. 14.0 months HR 0.69 [0.44; 1.09] p = 0.112 Total population: median: NC vs. NC HR 0.69 [0.52; 0.91]; p = 0.008 probability: "hint"	Outcome category: mortality added benefit, extent: "non-quantifiable", at most "considerable"
Morbidity		
See dossier assessment A15-33	No statistically significant results	Lesser benefit/added benefit not proven
Health-related quality of life		
See dossier assessment A15-33	No statistically significant results	Lesser benefit/added benefit not proven
Adverse events		
SAEs	Median: 16.7 vs. NC months HR 0.54 [0.30; 0.98] p = 0.043 probability: "indication"	Outcome category: serious/severe AEs $0.90 \leq CI_u < 1.00$ lesser harm, extent: "minor"
Severe AEs (CTCAE grade ≥ 3)	Median: 16.7 vs. NC months HR 0.46 [0.24; 0.87] p = 0.017 probability: "indication"	Outcome category: serious/severe AEs $0.75 \leq CI_u < 0.90$ lesser harm, extent: "considerable"
Discontinuation due to AEs	Median: NC vs. NC HR 0.28 [0.09; 0.88] p = 0.029 probability: "indication"	Outcome category: serious/severe AEs $0.75 \leq CI_u < 0.90$ lesser harm, extent: "considerable"
Immune-related AEs	Median: 8.7 vs. NC HR 0.72 [0.42; 1.22]; p = 0.223	Lesser/greater harm not proven
Immune-related SAEs	No results available	Lesser/greater harm not proven
Immune-related severe AEs (CTCAE ≥ 3)	Median: NC vs. NC HR 0.25 [0.07; 0.90]; p = 0.035 probability: "hint"	Outcome category: serious/severe AEs $0.75 \leq CI_u < 0.90$ lesser harm, extent: "minor"

(continued)

Table 2: Extent of added benefit at outcome level: pembrolizumab vs. ipilimumab (pretreated patients) (continued)

a: Probability provided if statistically significant differences were present that were more than marginal. b: Estimations of effect size are made depending on the outcome category with different limits based on the CI_u. AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30; HR: hazard ratio; NC: not calculable; SAE: serious adverse event; vs.: versus

2.2.3.2 Overall conclusion on added benefit

Table 3 summarizes the results that were considered in the overall conclusion on the extent of added benefit.

Table 3: Positive and negative effects from the assessment of pembrolizumab in comparison with ipilimumab (pretreated patients)

Positive effects	**Negative effects**
Hint of an added benefit – extent: "non-quantifiable", at most "considerable" (mortality: overall survival)	-
Indication of lesser harm – extent: "minor" (serious/severe AEs: SAEs)	
Indication of lesser harm – extent: "considerable" (serious/severe AEs: severe AEs [CTCAE grade ≥ 3])	
Indication of lesser harm – extent: "considerable" (serious/severe AEs: discontinuation due to AEs)	
Hint of lesser harm – extent: "minor" (serious/severe AEs: immune-related severe AEs [CTCAE grade ≥ 3])	
AE: adverse event; CTCAE: Common Terminology Criteria of Adverse Events; SAE: serious adverse event	

Overall, only positive effects remain. In comparison with dossier assessment A15-33, a positive effect regarding overall survival and in the category "serious/severe AEs" was added in each case. None of these 2 effects had a probability or an extent that was greater than the one of the overall conclusion on pretreated patients in dossier assessment A15-33. Hence the present addendum produced no change in the overall conclusion for pretreated patients.

In summary, there is an indication of considerable added benefit of pembrolizumab in comparison with the ACT ipilimumab for patients with advanced (unresectable or metastatic) melanoma who are pretreated and for whom ipilimumab represents the ACT in the sense of individual treatment.

2.3 Research question 2: treatment-naive patients with BRAF V600 wt tumour

Research question 2 refers to treatment-naive patients with BRAF V600 wt tumour. The G-BA specified dacarbazine and ipilimumab as ACT for this research question. In the dossier, the company derived the added benefit in comparison with ipilimumab.

2.3.1 Risk of bias

The analyses on immune-related AEs and immune-related severe AEs (CTCAE ≥ 3) subsequently submitted by the company have a high risk of bias. On the one hand, this is caused by potentially informative censoring as was the case for the other AE outcomes considered in dossier assessment A15-33. On the other, selective reporting cannot be excluded due to the lack of results on immune-related SAEs.

2.3.2 Results

Table 4 presents the results for the subpopulation of treatment-naive patients with BRAF V600 wt tumour on immune-related AEs.

Table 4: Results on AEs – RCT, direct comparison, treatment-naive patients with BRAF V600 wt tumour: pembrolizumab vs. ipilimumab

Study Outcome category Outcome	Pembrolizumab N	Pembrolizumab Median time in months M [95% CI] Patients with event n (%)	Ipilimumab N	Ipilimumab Median time in months M [95% CI] Patients with event n (%)	Pembrolizumab vs. ipilimumab HR [95% CI][a]; p-value[a]
KEYNOTE 006					
Adverse events					
Immune-related AEs	135	7.1 [5.3; 15.2] 60 (44.4)	122	2.5 [1.5; NC] 58 (47.5)	0.48 [0.32; 0.74]; < 0.001
Immune-related SAEs	No results available				
Immune-related severe AEs (CTCAE grade ≥ 3)	135	NC 16 (11.9)	46	NC 17 (13.9)	0.35 [0.14; 0.89]; 0.027

a: HR, CI and p-value result from a Cox proportional hazards model adjusted for ECOG PS (0 vs. 1), PD-L1 expression (positive vs. negative) and pretreatment with systemic therapy (yes vs. no).

AE: adverse event; BRAF: serine/threonine-protein kinase B-Raf (rapidly accelerated fibrosarcoma – isoform B); CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; ECOG PS: Eastern Cooperative Oncology Group Performance Status; HR: hazard ratio; M: months; N: number of analysed patients; n: number of patients with (at least one) event; NC: not calculable; PD-L1: programmed cell death ligand 1; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus; wt: wild type

Immune-related AEs

A statistically significant difference in favour of pembrolizumab in comparison with ipilimumab was shown for each of the outcomes “immune-related AEs” and “immune-related

severe AEs (CTCAE ≥ 3)". There was an outcome-specific high risk of bias for both outcomes. In each case, this resulted in a hint of lesser harm from pembrolizumab in comparison with ipilimumab.

2.3.3 Extent and probability of added benefit

2.3.3.1 Assessment of added benefit at outcome level

Based on the data presented in Section 2.4.2 of dossier assessment A15-33 and Section 2.3.2 of the present addendum, the extent of the added benefit was assessed at outcome level.

Table 5: Extent of added benefit at outcome level: pembrolizumab vs. ipilimumab (treatment-naive patients with BRAF V600 wt tumour)

Outcome category **Outcome**	**Pembrolizumab vs. ipilimumab** **Median time to event or mean change** **Effect estimate [95% CI]** **p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality		
Overall survival	Median: NC vs. 15.4 months HR 0.65 [0.44; 0.96] p = 0.032 probability: "hint"	Outcome category: mortality $0.95 \leq CI_u < 1.00$ added benefit, extent: "minor"
Morbidity		
See dossier assessment A15-33	No statistically significant effects or marginal effects	Lesser benefit/added benefit not proven
Health-related quality of life		
EORTC QLQ-C30 functional scales – time to deterioration by at least 10 points		
Social functioning	Median: 85.0 vs. 44.0 days HR: 0.68 [0.48; 0.95] p = 0.023 probability: "hint"	Outcome category: quality of life $0.90 \leq CI_u < 1.00$ added benefit, extent: "minor"
See dossier assessment A15-33 for remaining scales	No statistically significant effects	Lesser benefit/added benefit not proven
Adverse events		
SAEs; severe AEs (CTCAE grade ≥ 3); discontinuation due to AEs, see dossier assessment A15-33	No statistically significant effects	Greater/lesser harm not proven
Immune-related AEs	Median: 7.1 vs. 2.5 HR 0.48 [0.32; 0.74] p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe AEs $CI_u < 0.80$ lesser harm, extent: "considerable"
Immune-related SAEs	No results available	Greater/lesser harm not proven
Immune-related severe AEs (CTCAE ≥ 3)	Median: NC vs. NC HR 0.35 [0.14; 0.89]; p = 0.027 probability: "hint"	Outcome category: serious/severe AEs $0.75 \leq CI_u < 0.90$ lesser harm, extent: "considerable"

a: Probability provided if statistically significant differences were present that were more than marginal.
b: Estimations of effect size are made depending on the outcome category with different limits based on the CIu.

AE: adverse event; BRAF: serine/threonine-protein kinase B-Raf (rapidly accelerated fibrosarcoma – isoform B); CI: confidence interval; CIu: upper limit of confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30; HR: hazard ratio; NC: not calculable; SAE: serious adverse event; vs.: versus; wt: wild type

2.3.3.2 Overall conclusion on added benefit

Table 6 summarizes the results that were considered in the overall conclusion on the extent of added benefit.

Table 6: Positive and negative effects from the assessment of pembrolizumab in comparison with ipilimumab (treatment-naive patients with BRAF V600 wt tumour)

Positive effects	**Negative effects**
Hint of an added benefit – extent: "minor" (mortality: overall survival)	-
Hint of an added benefit – extent: "minor" (health-related quality of life: social functioning)	
Hint of lesser harm – extent: "considerable" (non-serious/non-severe AEs: immune-related AEs)	
Hint of lesser harm – extent: "considerable" (serious/severe AEs: immune-related AEs)	
AE: adverse event; BRAF: serine/threonine-protein kinase B-Raf (rapidly accelerated fibrosarcoma – isoform B); wt.: wild type	

Overall, only positive effects of the same probability but with different extent remain.

There was a hint of a minor added benefit in each of the outcome categories "mortality" and "health-related quality of life", and a hint of considerable added benefit in the outcome categories "serious/severe AEs" and "non-serious/non-severe AEs".

In summary, there is a hint of a considerable added benefit of pembrolizumab in comparison with the ACT ipilimumab for patients with advanced (unresectable or metastatic) melanoma who are treatment-naive and whose tumour has no BRAF V600 mutation.

2.4 Comparison of pembrolizumab with ipilimumab in treatment-naive patients with BRAF V600 mutated tumour

2.4.1 Outcomes included and their risk of bias

The outcomes included concurred with the ones considered for research question 1 and research question 2 of dossier assessment A15-33 [1]. In addition, immune-related AEs (AEs, SAEs and severe AEs [CTCAE grade ≥ 3]) were included as relevant outcomes.

The risk of bias at outcome level is described in Section 2.3.2.2 of dossier assessment A15-33. The risk of bias was rated as high for all outcomes included except overall survival; the risk of bias for the outcome "overall survival" was rated as low.

2.4.2 Results

Table 7 to Table 11 summarize the results on the comparison of pembrolizumab with ipilimumab in treatment-naive patients with advanced (unresectable or metastatic) melanoma with BRAF V600 mutated tumour.

Table 7: Results on overall survival – RCT, direct comparison, treatment-naive patients with BRAF V600 mutated tumour: pembrolizumab vs. ipilimumab

Study **Outcome category** **Outcome**	**Pembrolizumab** **N**	**Pembrolizumab** **Median survival time in months M [95% CI]** **Patients with event n (%)**	**Ipilimumab** **N**	**Ipilimumab** **Median survival time in months M [95% CI]** **Patients with event n (%)**	**Pembrolizumab vs. ipilimumab** **HR [95% CI][a]; p-value[a]**
KEYNOTE 006					
Mortality					
Overall survival					
Subpopulation: treatment-naive patients with BRAF mut tumour	48	NC ND	47	NC [14.2; NC] ND	0.64 [0.27; 1.53]; 0.317
Total population	277	NC ND	278	NC [13.9; NC] ND	0.69 [0.52; 0.91] 0.008

a: HR, CI and p-value result from a Cox proportional hazards model adjusted for ECOG PS (0 vs. 1), PD-L1 expression (positive vs. negative) and pretreatment with systemic therapy (yes vs. no).

BRAF: serine/threonine-protein kinase B-Raf (rapidly accelerated fibrosarcoma – isoform B); CI: confidence interval; ECOG PS: Eastern Cooperative Oncology Group Performance Status; HR: hazard ratio; M: months; N: number of analysed patients; n: number of patients with (at least one) event; NC: not calculable; ND: no data; PD-L1: programmed cell death ligand 1; RCT: randomized controlled trial; vs.: versus

Table 8: Results on morbidity (symptoms), time to deterioration – RCT, direct comparison, treatment-naive patients with BRAF V600 mutated tumour: pembrolizumab vs. ipilimumab

Study Outcome category	Pembrolizumab		Ipilimumab		Pembrolizumab vs. ipilimumab
Outcome	**N**	**Median time in days D [95% CI] Patients with event n (%)**	**N**	**Median time in days D [95% CI] Patients with event n (%)**	**HR [95% CI][a]; p-value[a]**
KEYNOTE 006					
Morbidity (symptoms)					
EORTC QLQ-C30 symptom scales – time to deterioration of symptoms[b, c]					
Dyspnoea	48	NC [84; NC] ND	45	90 [64; NC] ND	0.90 [0.47; 1.74]; 0.757
Fatigue	48	43 [23; 86] ND	45	42 [22; 84] ND	0.84 [0.50; 1.42]; 0.522
Insomnia	48	86 [43; NC] ND	45	NC [41; NC] ND	0.82 [0.45; 1.53]; 0.542
Pain	48	87 [43; NC] ND	45	43 [23; 85] ND	0.53 [0.30; 0.94]; 0.031
Appetite loss	48	86 [84; NC] ND	45	90 [42; NC] ND	0.70 [0.37; 1.31]; 0.258
Diarrhoea	48	NC [85; NC] ND	45	84 [42; NC] ND	0.51 [0.26; 0.99]; 0.046
Nausea and vomiting	48	NC [84; NC] ND	45	84 [42; NC] ND	0.60 [0.33; 1.09]; 0.094
Constipation	48	NC [84; NC] ND	45	84 [42; NC] ND	0.71 [0.39; 1.32]; 0.284

a: HR, CI and p-value result from a Cox proportional hazards model adjusted for ECOG PS (0 vs. 1), PD-L1 expression (positive vs. negative) and pretreatment with systemic therapy (yes vs. no).
b: Presentation of deterioration by at least 10 points.
c: Imputation of missing values under the MNAR assumption using the pattern-mixture model.

BRAF: serine/threonine-protein kinase B-Raf (rapidly accelerated fibrosarcoma – isoform B); CI: confidence interval; D: days: ECOG PS: ECOG Performance Status; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer - Core 30; HR: hazard ratio; MNAR: missing not at random; N: number of analysed patients; n: number of patients with (at least one) event; NC: not calculable; ND: no data; PD-L1: programmed cell death ligand 1; RCT: randomized controlled trial; vs.: versus

Table 9: Results on morbidity (health status), mean change at week 12 – RCT, direct comparison, treatment-naive patients with BRAF V600 mutated tumour: pembrolizumab vs. ipilimumab

Study Outcome category	Pembrolizumab			Ipilimumab			Pembrolizumab vs. ipilimumab
Outcome	N	Baseline values mean (SD)	Change at week 12 mean (SD)	N	Baseline values mean (SD)	Change at week 12 mean (SD)	MD [95% CI]; p-value[a]
KEYNOTE 006							
Morbidity (health status)							
EQ-5D VAS[b, c]	47	69.5 (27.2)	-0.3 (22.3)	40	71.6 (22.8)	-6.6 (26.5)	5.14 [-5.74; 16.02]; 0.354

a: HR, CI and p-value result from a Cox proportional hazards model adjusted for ECOG PS (0 vs. 1), PD-L1 expression (positive vs. negative) and pretreatment with systemic therapy (yes vs. no).
b: Higher (increasing) values indicate better functionality; positive effects in the group comparison (pembrolizumab - ipilimumab) indicate an advantage of pembrolizumab.
c: Imputation of missing values under the MNAR assumption using the pattern-mixture model.

BRAF: serine/threonine-protein kinase B-Raf (rapidly accelerated fibrosarcoma – isoform B); CI: confidence interval; ECOG PS: Eastern Cooperative Oncology Group Performance Status; EQ-5D: European Quality of Life-5 Dimensions; MD: mean difference; MNAR: missing not at random; N: number of analysed patients; PD-L1: programmed cell death ligand 1; RCT: randomized controlled trial; SD: standard deviation; VAS: visual analogue scale; vs.: versus

Table 10: Results on health-related quality of life, time to deterioration – RCT, direct comparison, treatment-naive patients with BRAF V600 mutated tumour: pembrolizumab vs. ipilimumab

Study Outcome category Outcome	Pembrolizumab N	Pembrolizumab Median time in days D [95% CI] Patients with event n (%)	Ipilimumab N	Ipilimumab Median time in days D [95% CI] Patients with event n (%)	Pembrolizumab vs. ipilimumab HR [95% CI][a]; p-value[a]
KEYNOTE 006					
Health-related quality of life					
EORTC QLQ-C30 functional scales – time to deterioration of health-related quality of life[b, c]					
Global health status	48	NC [43; NC] ND	45	84 [41; 90] ND	0.57 [0.31; 1.05]; 0.071
Emotional functioning	48	113 [85; 113] ND	45	86 [43; 90] ND	0.56 [0.29; 1.12]; 0.100
Cognitive functioning	48	NC [43; NC] ND	45	90 [42; NC] ND	0.92 [0.49; 1.72]; 0.796
Physical functioning	48	NC [43; NC] ND	45	43 [25; NC] ND	0.61 [0.34; 1.10]; 0.097
Role functioning	48	84 [23; 113] ND	45	84 [43; NC] ND	1.09 [0.62; 1.93]; 0.759
Social functioning	48	86 [43; NC] ND	45	50 [41; NC] ND	0.69 [0.38; 1.23]; 0.206

a: HR, CI and p-value result from a Cox proportional hazards model adjusted for ECOG PS (0 vs. 1), PD-L1 expression (positive vs. negative) and pretreatment with systemic therapy (yes vs. no).
b: Presentation of deterioration by at least 10 points.
c: Imputation of missing values under the MNAR assumption using the pattern-mixture model.

BRAF: serine/threonine-protein kinase B-Raf (rapidly accelerated fibrosarcoma – isoform B); CI: confidence interval; D: days: ECOG PS: ECOG Performance Status; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer - Core 30; HR: hazard ratio; MNAR: missing not at random; N: number of analysed patients; n: number of patients with (at least one) event; NC: not calculable; ND: no data; PD-L1: programmed cell death ligand 1; RCT: randomized controlled trial; vs.: versus

Table 11: Results on AEs – RCT, direct comparison, treatment-naive patients with BRAF V600 mutated tumour: pembrolizumab vs. ipilimumab

Study Outcome category Outcome	Pembrolizumab N	Pembrolizumab Median time in months M [95% CI] Patients with event n (%)	Ipilimumab N	Ipilimumab Median time in months M [95% CI] Patients with event n (%)	Pembrolizumab vs. ipilimumab HR [95% CI][a]; p-value[a]
KEYNOTE 006					
Adverse events					
AEs (supplementary information)	48	0.5 [0.1; 0.7] ND	46	0.3 [0.1; 0.5] ND	–
SAEs	48	NC ND	46	NC ND	0.52 [0.22; 1.27]; 0.151
Severe AEs (CTCAE grade ≥ 3)	48	NC ND	46	NC ND	0.74 [0.29; 1.90]; 0.530
Discontinuation due to AEs	48	NC ND	46	NC ND	0.46 [0.11; 1.85]; 0.275
Immune-related AEs	No results available				
Immune-related SAEs	No results available				
Immune-related severe AEs (CTCAE grade ≥ 3)	No results available				

a: HR, CI and p-value result from a Cox proportional hazards model adjusted for ECOG PS (0 vs. 1), PD-L1 expression (positive vs. negative) and pretreatment with systemic therapy (yes vs. no).

AE: adverse event; BRAF: serine/threonine-protein kinase B-Raf (rapidly accelerated fibrosarcoma – isoform B); CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; ECOG PS: Eastern Cooperative Oncology Group Performance Status; HR: hazard ratio; M: months; N: number of analysed patients; n: number of patients with (at least one) event; NC: not calculable; ND: no data; PD-L1: programmed cell death ligand 1; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus

Mortality

Overall survival

Based on the results of the relevant subpopulation of treatment-naive patients with BRAF V600 mutated tumour, no statistically significant difference was shown between the treatment groups. However, statistically significantly longer survival under pembrolizumab than under ipilimumab was shown for the total population of the KEYNOTE 006 study.

The simulations showed that the statistically significant effect of the total study population is transferable to the subpopulation (see Figure 1 for illustration of the similarity of the effects).

The increased dosage of pembrolizumab in the KEYNOTE 006 study resulted in a reduced certainty of conclusions regarding the results for the outcome “overall survival” (see dossier assessment A15-33 [1]). It cannot be assessed whether the effect of the increased dosage was in favour or to the disadvantage of pembrolizumab. In summary, there is therefore a hint of an

added benefit of pembrolizumab in comparison with ipilimumab regarding overall survival for treatment-naive patients with BRAF V600 mutated tumour.

Morbidity

Symptoms

Aspects of symptoms were recorded using the symptom scales of the disease-specific questionnaire EORTC QLQ-C30. The time to deterioration by at least 10 points was considered.

A statistically significant difference in favour of pembrolizumab was shown for each of the outcomes “pain” and “diarrhoea”. The extent of the effect in these non-serious/non-severe outcomes was no more than marginal, however.

No statistically significant difference between the treatment arms was shown for any of the remaining outcomes “dyspnoea”, “fatigue”, “insomnia”, “appetite loss”, “nausea and vomiting” and “constipation”. Hence there was no hint of an added benefit of pembrolizumab in comparison with ipilimumab; an added benefit is therefore not proven.

Health status

There was no statistically significant difference between the treatment groups for health status (EQ-5D VAS). Hence there was no hint of an added benefit of pembrolizumab in comparison with ipilimumab; an added benefit is therefore not proven.

Health-related quality of life

Aspects of health-related quality of life were recorded using the functional scales of the disease-specific questionnaire EORTC QLQ-C30. The time to deterioration by at least 10 points was considered.

No statistically significant difference between the treatment groups was shown for any of the following outcomes: global health status/quality of life, emotional functioning, cognitive functioning, physical functioning, role functioning and social functioning. Hence there was no hint of an added benefit of pembrolizumab in comparison with ipilimumab for these outcomes; an added benefit is therefore not proven.

Adverse events

No statistically significant difference between the treatment groups was shown for any of the outcomes “SAEs”, “severe AEs (CTCAE grade ≥ 3)” and “discontinuation due to AEs”. Hence for these outcomes, there was no hint of greater or lesser harm from pembrolizumab in comparison with ipilimumab; greater or lesser harm is therefore not proven.

2.4.3 Extent and probability of added benefit

2.4.3.1 Assessment of added benefit at outcome level

Based on the data presented in Section 2.4.2, the extent of the added benefit was estimated at outcome level.

Table 12: Extent of added benefit at outcome level: pembrolizumab vs. ipilimumab (treatment-naive patients with BRAF V600 mutated tumour)

Outcome category **Outcome**	**Pembrolizumab vs. ipilimumab** **Median time to event or mean change** **Effect estimate [95% CI]** **p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality		
Overall survival	Relevant subpopulation median: NC vs. NC HR 0.64 [0.27; 1.53]; p = 0.317 Total population: median: NC vs. NC HR 0.69 [0.52; 0.91] p = 0.008 probability: "hint"	Outcome category: mortality added benefit, extent: "non-quantifiable", at most "considerable"
Morbidity		
EORTC QLQ-C30 symptom scales – time to deterioration by at least 10 points		
Dyspnoea	Median: NC vs. 90 days HR 0.90 [0.47; 1.74] p = 0.757	Lesser benefit/added benefit not proven
Fatigue	Median: 43 vs. 42 days HR: 0.84 [0.50; 1.42] p = 0.522	Lesser benefit/added benefit not proven
Insomnia	Median: 86 vs. NC days HR 0.82 [0.45; 1.53] p = 0.542	Lesser benefit/added benefit not proven
Pain	Median: 87 vs. 43 days HR: 0.53 [0.30; 0.94] p = 0.031	Outcome category: non-serious/non-severe symptoms/late complications $0.90 \leq CI_u < 1.00$ lesser benefit/added benefit not proven[c]
Appetite loss	Median: 86 vs. 90 days HR: 0.70 [0.37; 1.31] p = 0.258	Lesser benefit/added benefit not proven
Diarrhoea	Median: NC vs. 84 days HR 0.51 [0.26; 0.99] p = 0.046	Outcome category: non-serious/non-severe symptoms/late complications $0.90 \leq CI_u < 1.00$ lesser benefit/added benefit not proven[c]

(continued)

Table 12: Extent of added benefit at outcome level: pembrolizumab vs. ipilimumab (treatment-naive patients with BRAF V600 mutated tumour) (continued)

Outcome category **Outcome**	**Pembrolizumab vs. ipilimumab** **Median time to event or mean change** **Effect estimate [95% CI]** **p-value** **Probability**[a]	**Derivation of extent**[b]
Nausea and vomiting	Median: NC vs. 84 days HR 0.60 [0.33; 1.09] p = 0.094	Lesser benefit/added benefit not proven
Constipation	Median: NC vs. 84 days HR 0.71 [0.39; 1.32] p = 0.284	Lesser benefit/added benefit not proven
Health status		
EQ-5D VAS	Mean change: -0.3 vs. -6.6 MD: 5.14 [-5.74; 16.02] p = 0.354	Lesser benefit/added benefit not proven
Health-related quality of life		
EORTC QLQ-C30 functional scales – time to deterioration by at least 10 points		
Global health status	Median: NC vs. 84 days HR 0.57 [0.31; 1.05] p = 0.071	Lesser benefit/added benefit not proven
Emotional functioning	Median: 113 vs. 86 days HR: 0.56 [0.29; 1.12] p = 0.100	Lesser benefit/added benefit not proven
Cognitive functioning	Median: NC vs. 90 days HR 0.92 [0.49; 1.72] p = 0.796	Lesser benefit/added benefit not proven
Physical functioning	Median: NC vs. 43 days HR 0.61 [0.34; 1.10] p = 0.097	Lesser benefit/added benefit not proven
Role functioning	Median: 84 vs. 84 days HR: 1.09 [0.62; 1.93] p = 0, 0.759	Lesser benefit/added benefit not proven
Social functioning	Median: 86 vs. 50 days HR: 0.69 [0.38; 1.23] p = 0.206	Lesser benefit/added benefit not proven

(continued)

Table 12: Extent of added benefit at outcome level: pembrolizumab vs. ipilimumab (treatment-naive patients with BRAF V600 mutated tumour) (continued)

Outcome category **Outcome**	**Pembrolizumab vs. ipilimumab** **Median time to event or mean change** **Effect estimate [95% CI]** **p-value** **Probability**[a]	**Derivation of extent**[b]
Adverse events		
SAEs	Median: NC vs. NC HR 0.52 [0.22; 1.27] p = 0.151	Greater/lesser harm not proven
Severe AEs (CTCAE grade ≥ 3)	Median: NC vs. NC HR 0.74 [0.29; 1.90] p = 0.530	Greater/lesser harm not proven
Discontinuation due to AEs	Median: NC vs. NC HR 0.46 [0.11; 1.85] p = 0.275	Greater/lesser harm not proven
Immune-related AEs	No results available	Greater/lesser harm not proven
Immune-related SAEs	No results available	Greater/lesser harm not proven
Immune-related severe AEs (CTCAE grade ≥ 3)	No results available	Greater/lesser harm not proven

a: Probability provided if statistically significant differences were present that were more than marginal.
b: Estimations of effect size are made depending on the outcome category with different limits based on the CI_u.
c: Lesser benefit or added benefit is not proven because the effect size was only marginal.

AE: adverse event; BRAF: serine/threonine-protein kinase B-Raf (rapidly accelerated fibrosarcoma – isoform B); CI: confidence interval; CI_u: upper limit of confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30; EQ-5D: European Quality of Life-5 Dimensions; HR: hazard ratio; MD: mean difference; NC: not calculable; ND: no data; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

2.4.3.2 Overall conclusion on added benefit

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

Table 13: Positive and negative effects from the assessment of pembrolizumab in comparison with ipilimumab (treatment-naive patients with BRAF V600 mutated tumour)

Positive effects	**Negative effects**
Hint of an added benefit – extent: “non-quantifiable”, at most “considerable” (mortality: overall survival)	-
BRAF: serine/threonine-protein kinase B-Raf (rapidly accelerated fibrosarcoma – isoform B)	

In the overall consideration, a positive effect in the outcome “overall survival” with the probability “hint” and the extent “non-quantifiable” (at most “considerable”) remains.

In summary, there is a hint of a non-quantifiable (at most “considerable”) added benefit of pembrolizumab in comparison with ipilimumab for patients with advanced (unresectable or metastatic) melanoma who are treatment-naive and whose tumour has BRAF V600 mutation.

3 References

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