IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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Pembrolizumab – Benefit assessment according to §35a Social Code Book V[1]

Extract

[1] Translation of Sections 2.1 to 2.6 of the dossier assessment *Pembrolizumab – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 12 November 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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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
BRAF	serine/threonine-protein kinase B-Raf (rapidly accelerated fibrosarcoma – isoform B)
BRAF V600 mut	BRAF V600 mutant
BRAF V600 wt	BRAF V600 wild type
BW	body weight
CTLA	cytotoxic T-lymphocyte-associated antigen
CTCAE	Common Terminology Criteria for Adverse Events
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EMA	European Medicines Agency
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
FDA	Food and Drug Administration
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
MEK	mitogen-activated extracellular signal-regulated kinase
MTIC	monomethyl triazenoimidazole carboxamide
PD	programmed cell death 1
PD-L1, PD-L2	programmed cell death ligand 1, programmed cell death ligand 2
PFS	progression-free survival
PT	Preferred Term
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
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 pembrolizumab. 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 17 August 2015.

Research question

The aim of this report was to assess the added benefit of pembrolizumab compared with the appropriate comparator therapy (ACT) in adult patients with advanced (unresectable or metastatic) melanoma.

For the benefit assessment, the following 3 research questions result from the G-BA's specification on the ACT.

Table 2: Research questions of the benefit assessment of pembrolizumab

Research question	Therapeutic indication	ACT[a]
1	Pretreated patients	Individual treatment specified by the treating physician under consideration of the approval status and the respective prior therapy
2	Treatment-naive patients with BRAF V600 mutation-negative tumour[b]	Dacarbazine or **ipilimumab**
3	Treatment-naive patients with BRAF V600 mutation-positive tumour[c]	Vemurafenib

a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the choice of the company is printed in bold.
b: Hereinafter referred to as "patients with BRAF V600 wild type (wt) tumour".
c: Hereinafter referred to as "patients with BRAF V600 mutant (mut) tumour".
ACT: appropriate comparator therapy; BRAF: serine/threonine-protein kinase B-Raf (rapidly accelerated fibrosarcoma – isoform B); G-BA: Federal Joint Committee

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

Results

Research question 1: pretreated patients

Research question 1 concerns the comparison of pembrolizumab with the ACT (individual treatment specified by the treating physician) in pretreated patients.

The company presented one randomized controlled trial (RCT), the study KEYNOTE 002, on the comparison of pembrolizumab with individual chemotherapy of the investigator's choice in pretreated patients. Due to the use of partly unapproved chemotherapeutic regimens in the comparator arm, only a subpopulation of the study was relevant, namely the one for which, before randomization, dacarbazine was specified as chemotherapy in case of allocation to the chemotherapy arm. The company only presented results of the total study population in the dossier. Hence there were no evaluable data for the derivation of an added benefit of pembrolizumab for the relevant subpopulation of pretreated patients for whom dacarbazine is the individually optimized treatment.

In addition, a subpopulation of the RCT KEYNOTE 006 was additionally relevant for the present research question.

KEYNOTE 006

Study characteristics

The KEYNOTE 006 study was a multicentre, randomized, active-controlled, open-label phase 3 study for the approval of pembrolizumab. The study had 3 treatment arms: pembrolizumab administered at a dosage of 10 mg/kg body weight (BW) every 3 weeks or every 2 weeks, and ipilimumab at a dosage of 3 mg/kg BW every 3 weeks for 4 treatment cycles as comparator arm.

The dosage of pembrolizumab (10 mg/kg BW every 3 weeks or every 2 weeks) was not in compliance with the approval. A dosage of 2 mg/kg BW every 3 weeks is approved. However, an analysis of the data of the studies KEYNOTE 001 and KEYNOTE 002 conducted by the Institute produced no relevant differences between the 2 dosages regarding efficacy and harm outcomes. The European Medicines Agency (EMA) also assumes that there is no difference in efficacy or safety between 2 mg/kg BW and 10 mg/kg BW every 3 weeks. It is therefore assumed that the results of a treatment regimen with 10 mg/kg BW every 3 weeks are transferable to a treatment regimen with 2 mg/kg BW every 3 weeks. The KEYNOTE 006 study was therefore used for the present benefit assessment although the dosage did not comply with the approval. However, this caused uncertainty regarding the interpretability of the study results for answering the research question of the benefit assessment.

Patients with advanced (unresectable or metastatic) melanoma were enrolled in the study. The patients had received previous systemic treatment for their advanced melanoma or were treatment-naive. 277 patients were allocated to the pembrolizumab arm (10 mg/kg BW every 3 weeks) relevant for the present benefit assessment; 278 patients were allocated to the ipilimumab arm.

The subpopulation of the KEYNOTE 006 study relevant for research question 1 consisted of the pretreated patients. 91 of 277 patients (32.9%) in the relevant pembrolizumab arm (10 mg/kg BW every 3 weeks), and 97 of 278 patients (34.9%) in the ipilimumab arm had

already been pretreated with systemic treatment for their advanced melanoma. One patient in the pembrolizumab arm had already received 2 previous systemic treatments.

Due to the type of pretreatment of the patients it can be assumed for the KEYNOTE 006 study that, at the time point of the study, ipilimumab actually represented a comprehensible implementation of the ACT in the sense of individual treatment specified by the physician.

Risk of bias

The risk of bias at study level was rated as low for the KEYNOTE 006 study. The risk of bias at outcome level was rated as high for all outcomes except overall survival.

Results

Mortality

There was no statistically significant difference between the treatment arms for the outcome "overall survival". This resulted in no hint of an added benefit of pembrolizumab in comparison with individual treatment (ipilimumab); an added benefit is therefore not proven.

Morbidity (symptoms)

Aspects of symptoms were recorded using the symptom scales of the disease-specific instrument European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30). The time to deterioration by at least 10 points was considered.

No statistically significant difference between the treatment arms was shown for any of the symptoms considered. This resulted in no hint of an added benefit of pembrolizumab in comparison with individual treatment with ipilimumab; an added benefit is therefore not proven.

Morbidity (health status)

No statistically significant difference between the treatment groups was shown for health status (European Quality of Life-5 Dimensions [EQ-5D] visual analogue scale [VAS]). This resulted in no hint of an added benefit of pembrolizumab in comparison with individual treatment with ipilimumab; an added benefit is therefore not proven.

Health-related quality of life

Aspects of health-related quality of life were recorded with the functional scales and with the scale for the recording of the global health status/quality of life 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 arms was shown in health-related quality of life for any of the domains considered. This resulted in no hint of an added benefit

of pembrolizumab in comparison with individual treatment with ipilimumab; an added benefit is therefore not proven.

Adverse events

As described above, the higher dosage of pembrolizumab in the KEYNOTE 006 study in comparison with the approval resulted in an increased uncertainty. However, it is assumed for the outcomes on adverse events (AEs) that the effect of the increased dosage on the treatment effect was to the disadvantage of pembrolizumab. The further aspects resulting in a high risk of bias in these outcomes did not raise general doubts about this direction of the bias. Hence in this case, the certainty of results for the outcomes on AEs in effects in favour of pembrolizumab was not downgraded.

There was a statistically significant difference in favour of pembrolizumab for the outcome "serious AEs (SAEs)". This resulted in an indication of lesser harm from pembrolizumab in comparison with individual treatment with ipilimumab.

A statistically significant difference in favour of pembrolizumab was shown for the outcome "severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3)". This resulted in an indication of lesser harm from pembrolizumab in comparison with individual treatment with ipilimumab.

A statistically significant difference in favour of pembrolizumab was shown for the outcome "discontinuation due to AEs". This resulted in an indication of lesser harm from pembrolizumab in comparison with individual treatment with ipilimumab.

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

Research question 2 concerns the comparison of pembrolizumab with the ACT (dacarbazine or ipilimumab) in treatment-naive patients with BRAF V600 wild type (wt) tumour. Following the company, the comparison of pembrolizumab versus ipilimumab was used to derive the added benefit.

The direct comparative KEYNOTE 006 study was also included in the assessment.

Of the patients who had not yet received any systemic treatment of their advanced melanoma, 135 of 185 patients (73.0%) in the pembrolizumab arm had a tumour without BRAF V600 mutation (BRAF V600 wt); and 134 of 181 patients (74.0%) in the ipilimumab arm had a BRAF V600 wt tumour. These patients represented the relevant subpopulation of research question 2.

The risk of bias at study level was rated as low for the KEYNOTE 006 study. The risk of bias at outcome level was rated as high for all outcomes except overall survival.

Results

Mortality

A statistically significant difference in favour of pembrolizumab was shown for the outcome "overall survival". The risk of bias was rated as low. However, the increased dosage of pembrolizumab in the KEYNOTE 006 study resulted in a reduced certainty of conclusions regarding the outcome "overall survival". It cannot be assessed whether the effect of the increased dosage was in favour or to the disadvantage of pembrolizumab. This resulted in a hint of an added benefit of pembrolizumab in comparison with ipilimumab.

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 the outcomes "fatigue" and "nausea and vomiting". The extent of the effect in these non-serious/non-severe outcomes was no more than marginal.

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

Morbidity (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.

A statistically significant difference in favour of pembrolizumab was shown for the outcome "social functioning". The risk of bias for this outcome was rated as high. This resulted in a hint of an added benefit of pembrolizumab in comparison with ipilimumab.

No statistically significant difference between the treatment arms was shown for any of the remaining outcomes "global health status/quality of life", "emotional functioning", "cognitive functioning", "physical functioning" and "role 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 arms was shown for the outcomes "SAEs", "severe AEs (CTCAE grade ≥ 3)" and "discontinuation due to AEs". Hence there was no hint of greater or lesser harm of pembrolizumab in comparison with ipilimumab for these outcomes; an added benefit is therefore not proven.

Research question 3: treatment-naive patients with BRAF V600 mut tumour

Research question 3 concerns the comparison of pembrolizumab with the ACT (vemurafenib) in treatment-naive patients with BRAF V600 mut tumour.

No study was included in the assessment. There were no data for the assessment of the added benefit of pembrolizumab for treatment-naive patients with BRAF V600 mut tumour. The added benefit of pembrolizumab versus the ACT vemurafenib is therefore not proven for these patients.

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 the drug pembrolizumab versus the ACT is assessed as follows:

Research question 1: pretreated patients

Overall, 3 positive effects of the same probability with different extent remain in the category "serious/severe AEs".

There was an indication of lesser harm from pembrolizumab with the extent "minor" for the outcome "SAEs". For the outcomes "severe AEs (CTCAE grade ≥ 3)" and "discontinuation due to AEs", there was an indication of lesser harm from pembrolizumab with the extent "considerable". The results on the other outcome categories also have to be considered for balancing the benefit and harm. These did not raise doubts about the advantage of pembrolizumab resulting from the adverse events.

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.

[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].

The added benefit is not proven for patients who are pretreated, but for whom ipilimumab does not represent individual treatment in the sense of the ACT.

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

Overall, 2 positive effects of the same probability and the same extent remain.

There was a hint of a minor added benefit in the category "mortality" for the outcome "overall survival". There was also a hint of a minor added benefit in the category "health-related quality of life" for the outcome "social functioning".

In summary, there is a hint of a minor 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.

Research question 3: treatment-naive patients with BRAF V600 mut tumour

Since no data were available, there was no proof of added benefit of pembrolizumab in comparison with the ACT vemurafenib specified by the G-BA for treatment-naive patients with a BRAF V600 mut tumour. Hence there are also no patient groups for whom a therapeutically important added benefit can be derived.

Table 3 presents a summary of the extent and probability of the added benefit of pembrolizumab.

Table 3: Pembrolizumab – extent and probability of added benefit

Research question	**Therapeutic indication**	**ACT[a]**	**Subpopulation**	**Extent and probability of added benefit**
1	Pretreated patients	Individual treatment specified by the treating physician under consideration of the approval status and the respective prior therapy	Pretreated patients for whom ipilimumab is the adequate treatment	Indication of considerable added benefit
			Pretreated patients for whom ipilimumab is not the adequate treatment	Added benefit not proven
2	Treatment-naive patients with BRAF V600 wt tumour	Dacarbazine or **ipilimumab**	-	Hint of minor added benefit
3	Treatment-naive patients with BRAF V600 mut tumour	Vemurafenib	-	Added benefit not proven

a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the choice of the company is printed in bold.

ACT: appropriate comparator therapy; BRAF: serine/threonine-protein kinase B-Raf (rapidly accelerated fibrosarcoma – isoform B); BRAF V600 mut: BRAF V600 mutant; BRAF V600 wt: BRAF V600 wild type; G-BA: Federal Joint Committee

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 questions of the dossier assessment

The aim of this report was to assess the added benefit of pembrolizumab compared with the ACT in adult patients with advanced (unresectable or metastatic) melanoma.

For the benefit assessment, the following research questions result from the G-BA's specification on the ACT.

Table 4: Research questions of the benefit assessment of pembrolizumab

Research question	**Therapeutic indication**	**ACT**[a]
1	Pretreated patients	Individual treatment specified by the treating physician under consideration of the approval status and the respective prior therapy
2	Treatment-naive patients with BRAF V600 mutation-negative tumour[b]	Dacarbazine or **ipilimumab**
3	Treatment-naive patients with BRAF V600 mutation-positive tumour[c]	Vemurafenib
a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the choice of the company is printed in bold. b: Hereinafter referred to as "patients with BRAF V600 wild type (wt) tumour". c: Hereinafter referred to as "patients with BRAF V600 mutant (mut) tumour". ACT: appropriate comparator therapy; BRAF: serine/threonine-protein kinase B-Raf (rapidly accelerated fibrosarcoma – isoform B); G-BA: Federal Joint Committee		

The benefit assessment in the 3 research questions was conducted versus the ACTs specified by the G-BA.

The company also presented 3 research questions. In comparison with the G-BA specifications however, their formulations partly deviated and they were partly combined with one another. The company largely followed the G-BA regarding the ACT.

From the population of pretreated patients, the company only considered, in a separate research question, the patients who are already pretreated with ipilimumab and for whom, in the sense of the ACT (individual treatment specified by the physician), chemotherapy is an option. In Module 4 B of the dossier, the company considered patients who are pretreated, but have not yet received ipilimumab, together with treatment-naive patients with BRAF V600 wt tumour (BRAF: serine/threonine-protein kinase B-Raf [rapidly accelerated fibrosarcoma – isoform B]) and in comparison with the comparator therapy ipilimumab.

In the present benefit assessment, all pretreated patients, including the patients who have received a different pretreatment than ipilimumab, were allocated to research question 1

(pretreated patients). Treatment-naive patients with BRAF V600 wt tumour were considered under research question 2 in the present benefit assessment (see Section 2.7.1 of the full dossier assessment).

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

2.3 Research question 1: pretreated patients

2.3.1 Information retrieval and study pool (research question 1)

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

Sources of the company in the dossier:

- study lists on pembrolizumab (status: 1 June 2015)
- bibliographical literature search on pembrolizumab (last search on 18 May 2015)
- search in trial registries for studies on pembrolizumab (last search on 19 May 2015)

To check the completeness of the study pool:

- search in trial registries for studies on pembrolizumab (last search on 31 August 2015)

No additional relevant study was initially identified from the check.

Since the company had shown that also results from studies with a dose of 10 mg/kg BW pembrolizumab, which is not compliant with the approval, are transferable to the dose of 2 mg/kg BW pembrolizumab, which is compliant with the approval, the KEYNOTE 006 study presented by the company in its research question B was additionally identified for research question 1. More details on this can be found in Section 2.3.1.2 and in Section 2.7.3.4.1 of the full dossier assessment. No further relevant studies with a dose between 2 and 10 mg/kg BW pembrolizumab were identified.

2.3.1.1 Studies included

The studies listed in the following table were included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: pembrolizumab vs. individual treatment for pretreated patients

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
KEYNOTE 002	Yes	Yes	No
KEYNOTE 006	Yes	Yes	No
a: Study for which the company was sponsor, or in which the company was otherwise financially involved. RCT: randomized controlled trial; vs.: versus			

The study pool deviated from that of the company. In the present research question 1 (pretreated patients), the KEYNOTE 006 study was included in the assessment in addition to the KEYNOTE 002 study included by the company.

Section 2.3.4 contains a reference list for the studies included.

2.3.1.2 Study characteristics

Table 6 and Table 7 describe the studies used for the benefit assessment. Table 8 shows the planned duration of follow-up of the patients for the individual outcomes.

Table 6: Characteristics of the studies included – RCT, direct comparison, pretreated patients: pembrolizumab vs. individual treatment

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
KEYNOTE 002	RCT, open-label, parallel	Adult patients with advanced (unresectable or metastatic) melanoma with previous BRAF/MEK inhibitor therapy and/or chemotherapy and progression of their cancer disease under or after ipilimumab[b]	Pembrolizumab 2 mg/kg BW every 3 weeks (N = 180) pembrolizumab 10 mg/kg BW every 3 weeks (N = 181)[c] chemotherapy of physician's choice[d] (N = 179) Thereof subpopulation relevant for research question 1[e]: pembrolizumab 2 mg/kg BW every 3 weeks (n = ND) chemotherapy of physician's choice (n = 45)	Screening: 28 days prior to the start of treatment Treatment phase: until progression of the cancer disease, unacceptable toxicity, or complete response under pembrolizumab	73 centres in Argentina, Australia, France, Germany, Israel, Italy, Netherlands, Norway, Spain, Sweden, Switzerland, USA 11/2012–ongoing Data cut-off: 12 May 2014[f]	Primary: overall survival, progression-free survival Secondary: disease-related symptoms, health status, health-related quality of life, AEs

(continued)

Table 6: Characteristics of the studies included – RCT, direct comparison, pretreated patients: pembrolizumab vs. individual treatment (continued)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
KEYNOTE 006	RCT, open-label, parallel	Adult patients with advanced (unresectable or metastatic) melanoma who are untreated or pretreated with BRAF/MEK inhibitor therapy or chemotherapy	Pembrolizumab 10 mg/kg BW every 3 weeks (N = 277) pembrolizumab 10 mg/kg BW every 2 weeks (N = 279)[g] ipilimumab 3 mg/kg BW every 3 weeks (N = 278) Thereof subpopulation relevant for research question 1[h]: pembrolizumab 10 mg/kg BW every 3 weeks (n = 92) ipilimumab 3 mg/kg BW every 3 weeks (n = 97) subpopulation relevant for research question 2[i]: pembrolizumab 10 mg/kg BW every 3 weeks (n = 135) ipilimumab 3 mg/kg BW every 3 weeks (n = 134)	Screening: 28 days prior to the start of treatment Treatment phase: until progression, unacceptable toxicity, or complete response	87 centres in Australia, Austria, Belgium, Canada, Chile, Columbia, France, Germany, Israel, Netherlands, New Zealand, Norway, Spain, Sweden, United Kingdom, USA 8/2013–ongoing Data cut-offs: 3 September 2014[j] 3 March 2015[k]	Primary: overall survival, progression-free survival Secondary: disease-related symptoms, health status, health-related quality of life, AEs

(continued)

Table 6: Characteristics of the studies included – RCT, direct comparison, pretreated patients: pembrolizumab vs. individual treatment (continued)

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: Pretreatment with ipilimumab was defined as administration of at least 2 doses of ipilimumab 3 mg/kg BW and confirmed disease progression within 24 weeks.
c: The dosage was not in compliance with the approval. The transferability of the results of 10 mg/kg BW to 2 mg/kg BW was shown, however. Since there was a treatment arm with the approved dosage of 2 mg/kg BW, this arm was the primarily relevant treatment arm.
d: Chemotherapy with the active metabolite MTIC (dacarbazine, temozolomide), paclitaxel-based chemotherapy (paclitaxel, carboplatin + paclitaxel) or chemotherapy with carboplatin alone. Following a recommendation of the US regulatory authority FDA, carboplatin as monotherapy was removed in the framework of Amendment 01 of the study protocol on 22 April 2013. The study protocol specified paclitaxel-based chemotherapy as treatment alternative for patients with a history of treatment failure under chemotherapy with the active metabolite MTIC.
e: Pretreated patients for whom, before randomization, treatment with dacarbazine was specified in case of allocation to the comparator arm.
f: Interim analysis II: planned after 270 events in the PFS (“disease progression” or “death”).
g: The arm is not relevant for the assessment and is not shown in the next tables.
h: Pretreated patients.
i: Treatment-naive patients with BRAF V600 wt tumour
j: Interim analysis I: planned after a follow-up period of 6 months and about 260 events in the PFS.
k: Interim analysis II: planned after a follow-up period of at least 9 months and about 290 deaths. The study was ended prematurely at the time point of interim analysis II because the data showed superiority in overall survival under pembrolizumab vs. ipilimumab (criterion for study discontinuation defined a priori).

AE: adverse event; BRAF: serine/threonine-protein kinase B-Raf (rapidly accelerated fibrosarcoma – isoform B); BRAF V600 wt: BRAF V600 wild type; BW: body weight; FDA: Food and Drug Administration; MEK: mitogen-activated extracellular signal-regulated kinase; MTIC: monomethyl triazenoimidazole carboxamide; N: number of randomized patients; n: relevant subpopulation; ND: no data; PFS: progression-free survival; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus

Table 7: Characteristics of the interventions – RCT, direct comparison, pretreated patients: pembrolizumab vs. individual treatment

Study	Intervention	Comparison	Pre- and concomitant treatment
KEYNOTE 002	Pembrolizumab 2 mg/kg BW IV, every 3 weeks	Chemotherapy of physician's choice: ▪ dacarbazine 1000 mg/m^2 BSA IV, every 3 weeks or ▪ temozolomide 200 mg/m^2 BSA orally, once daily on day 1–5, every 28 days or ▪ paclitaxel 175 mg/m^2 BSA IV, every 3 weeks or ▪ carboplatin + paclitaxel, each IV, every 3 weeks ▫ cycle 1–4: carboplatin: AUC = 6 mg/mL/min and paclitaxel: 225 mg/m^2 BSA ▫ cycle 5–10: carboplatin AUC = 5 mg/mL/min (mandatory dose reduction for patients who have received none before) and paclitaxel: 175 mg/m^2 BSA	**Pretreatment[a]:** ▪ ipilimumab 3 mg/kg BW, at least 2 doses ▪ BRAF/MEK inhibitors in BRAF V600 mut patients ▪ further prior therapies allowed Concomitant treatment: ▪ medication necessary for the patient's wellbeing at the physician's discretion Not allowed during screening and treatment: ▪ antineoplastic systemic chemotherapy ▪ biologics ▪ immunotherapy including corticosteroids ▪ live vaccines Wash-out for patients switching treatment: 28-day wash-out phase between the last dose of chemotherapy and the first dose of pembrolizumab
KEYNOTE 006	Pembrolizumab: 10 mg/kg BW every 3 weeks for 30 min IV	Ipilimumab: 3 mg/kg BW every 3 weeks for 90 min IV up to 4 doses[b]	**Pretreatment[a]:** (only research question 1) ▪ systemic treatment except ipilimumab or other anti-CTLA-4 drugs, anti-PD-1, anti-PD-L1 or anti-PD-L2 drugs ▪ BRAF inhibitors Not allowed during screening and treatment: ▪ antineoplastic systemic chemotherapy ▪ biologics ▪ immunotherapy including corticosteroids ▪ radiotherapy ▪ live vaccines

a: Prior treatment of advanced disease.
b: According to approval.

AUC: area under the curve; BRAF: serine/threonine-protein kinase B-Raf (rapidly accelerated fibrosarcoma – isoform B); BRAF V600 wt: BRAF V600 wild type; BSA: body surface area; BW: body weight; CTLA: cytotoxic T-lymphocyte-associated antigen; IV: intravenous; MEK: mitogen-activated extracellular signal-regulated kinase; PD-1: programmed cell death 1; PD-L1: programmed cell death ligand 1; PD-L2: programmed cell death ligand 2; RCT: randomized controlled trial; vs.: versus

Table 8: Planned duration of follow-up – RCT, direct comparison, pretreated patients: pembrolizumab vs. individual treatment

Study Outcome	Planned follow-up
KEYNOTE 002	
Overall survival	Every 3 months until death
Symptoms	Up to 30 days after the last dose of the study medication or before the start of a new antineoplastic treatment
Health-related quality of life	Up to 30 days after the last dose of the study medication or before the start of a new antineoplastic treatment
Adverse events	AEs: 30 days after the last dose of the study medication or before the start of a new antineoplastic treatment SAEs: 90 days after the last dose of the study medication or before the start of a new antineoplastic treatment
KEYNOTE 006	
Overall survival	Every 3 months until death or completion of the study by the sponsor
Symptoms	Recorded with the EORTC QLQ-C30 and the EQ-5D at treatment week 0, 3, 6, 12, 24 and 36. In case of treatment discontinuation, up to 30 days after the last dose of the study medication or at the start of a new antineoplastic treatment. For patients in the ipilimumab arm who had received all 4 doses, recording of morbidity with the EORTC QLQ-C30 and the EQ-5D was continued at study week 12, 24 and 36 or the end-of-study visit (after disease progression or unacceptable toxicity).
Health-related quality of life	Recorded with the EORTC QLQ-C30 at treatment week 0, 3, 6, 12, 24 and 36. In case of treatment discontinuation, up to 30 days after the last dose of the study medication or at the start of a new antineoplastic treatment. For patients in the ipilimumab arm who had received all 4 doses, recording of health-related quality of life with the EORTC QLQ-C30 was continued at study week 12, 24 and 36 or the end-of-study visit (after disease progression or unacceptable toxicity).
Adverse events	AEs: 30 days after the last dose of the study medication or before the start of a new antineoplastic treatment. For patients in the ipilimumab arm who had received all 4 doses, recording of AEs was continued every 3 weeks until progression or the start of a new antineoplastic treatment. SAEs: 90 days after the last dose of the study medication

AE: adverse event; 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; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus

Study KEYNOTE 002

The KEYNOTE 002 study was a multicentre, randomized, active-controlled, and, regarding the drugs, open-label phase 2 study for the approval of pembrolizumab. The study had 3 treatment arms: pembrolizumab in a dosage of 2 mg/kg BW and in a dosage of 10 mg/kg BW and individual chemotherapy of the investigator's choice. The treatment arm with pembrolizumab 2 mg/kg BW and the individual chemotherapy were relevant for the present benefit assessment. The transferability of the results of the dosage of 10 mg/kg BW, which is not compliant with the approval, to the approved dosage of 2 mg/kg BW was shown. Since

there was a treatment arm with the approved dosage of 2 mg/kg BW, this arm was the primarily relevant treatment arm, however. Patients and investigators were blinded regarding the dosage of pembrolizumab (2 mg/kg BW or 10 mg/kg BW).

Patients with advanced (unresectable or metastatic) melanoma who were refractory to treatment with ipilimumab were included in the study. The patients had to have received at least 2 doses of ipilimumab for the treatment of their advanced melanoma, and the disease must have progressed within 24 weeks after the last dose. Patients whose tumour had a BRAF V600 mutation had to have received pretreatment with vemurafenib, dabrafenib or an approved BRAF and/or mitogen-activated extracellular signal-regulated kinase (MEK) inhibitor. The patients were allowed to have received additional systemic treatments for their advanced disease.

540 patients were randomly assigned in a ratio of 1:1:1 to the 3 treatment arms – stratified by Eastern Cooperative Oncology Group Performance Status (ECOG PS), lactate dehydrogenase (LDH) level and BRAF mutation status – 180 to the relevant pembrolizumab arm (dose 2 mg/kg BW), and 179 to the chemotherapy arm.

The primary outcomes of the study were overall survival and progression-free survival (PFS). Further patient-relevant outcomes were disease-related symptoms, health status, health-related quality of life and AEs. Table 8 shows the planned duration of follow-up of the patients for the individual outcomes.

Two interim analyses were planned in the study. The first interim analysis was to be performed after an observation period of 3 months of 120 patients (about 10 months after the start of the study). The aim of the first interim analysis was to discontinue one of both pembrolizumab arms in case it was notably less effective. No information was available on the time point of the first interim analysis. The second interim analysis was planned after at least 270 cases of disease progression. The aim of the second interim analysis was to show the superiority of pembrolizumab in comparison with the control arm. The data cut-off for the second interim analysis was conducted on 12 May 2014. The final analysis was planned after the death of 370 patients.

Under consideration of certain criteria, patients in the chemotherapy were allowed to switch to one of both pembrolizumab arms after 12 weeks on progression of the disease. After a wash-out phase of 28 days, suitable patients were randomized and blinded to the allocation to one of both pembrolizumab arms. At the time point of the second interim analysis, 86 of 179 patients (48.0%) had switched from the chemotherapy arm to treatment with pembrolizumab.

Implementation of the appropriate comparator therapy

The G-BA saw individual treatment specified by the physician under consideration of the approval status and the respective prior therapy as appropriate comparator therapy for pretreated patients. In the KEYNOTE 002 study, the investigators could only chose from

several options of chemotherapy as comparator therapy. Other drug classes were not available. Due to the pretreatment of the patients at least with ipilimumab, patients with BRAF V600 mut tumour additionally with a BRAF/MEK inhibitor, it can be assumed that chemotherapy actually constituted the individual treatment in the sense of the ACT for the patients at the time point of the study (see also Section 2.7.2 of the full dossier assessment).

The type of chemotherapy was specified for all 540 included patients by the respective investigator before randomization for the case of allocation to the chemotherapy arm. Options of chemotherapy were dacarbazine, temozolomide, paclitaxel, carboplatin and the combination of paclitaxel and carboplatin. Following a recommendation of the US regulatory authority Food and Drug Administration (FDA), carboplatin as monotherapy was disallowed as an option in the framework of a change to the protocol on 22 April 2013.

Relevant subpopulation of the study

From the options of chemotherapy in the KEYNOTE 002 study, only dacarbazine is approved in Germany for the treatment of advanced melanoma. The relevant subpopulation of the study therefore includes patients for whom treatment with dacarbazine was specified before randomization in case of allocation to the chemotherapy arm. These were only 45 of 179 patients (25.1%) in the chemotherapy arm. The proportion of patients in the relevant pembrolizumab arm for whom dacarbazine was planned is unknown.

The company only presented results of the total study population in the dossier. Data on the characteristic “type of chemotherapy allocated by the investigator before randomization” were available in the framework of the subgroup analyses. However, these only differentiated between chemotherapeutic agents with the active metabolites monomethyl triazenoimidazole carboxamide (MTIC) (dacarbazine, temozolomide) and paclitaxel-based chemotherapies.

Hence there were no evaluable data for the derivation of an added benefit of pembrolizumab for pretreated patients for whom chemotherapy is the individually optimized treatment.

Study KEYNOTE 006

The KEYNOTE 006 study was a multicentre, randomized, active-controlled, open-label phase 3 study for the approval of pembrolizumab. The study had 3 treatment arms: pembrolizumab administered at a dosage of 10 mg/kg BW every 3 weeks or every 2 weeks, and ipilimumab at a dosage of 3 mg/kg BW every 3 weeks for 4 treatment cycles as comparator arm. The treatment arm with pembrolizumab 10 mg/kg BW every 3 weeks and the treatment arm with ipilimumab were relevant for the present benefit assessment.

The dosage of pembrolizumab (10 mg/kg BW every 3 weeks or every 2 weeks) was not in compliance with the approval. A dosage of 2 mg/kg BW every 3 weeks is approved [3]. According to the documents for the approval [4], the EMA assumes that there is no difference in efficacy or safety between 2 mg/kg BW and 10 mg/kg BW every 3 weeks. An analysis of the data of the studies KEYNOTE 001 and KEYNOTE 002 conducted by the Institute

produced no relevant differences between the 2 dosages regarding efficacy and harm outcomes (see Table 37 in Appendix A of the full dossier assessment). It is therefore assumed that the results of a treatment regimen with 10 mg/kg BW every 3 weeks are transferable to a treatment regimen with 2 mg/kg BW every 3 weeks. The KEYNOTE 006 study was therefore used for the present benefit assessment although the dosage did not comply with the approval. However, this caused uncertainty regarding the interpretability of the study results for answering the research question of the benefit assessment. More details on this can be found in Section 2.7.3.4.1 of the full dossier assessment.

Patients with advanced (unresectable or metastatic) melanoma were enrolled in the study. The patients had received previous systemic treatment for their advanced melanoma or were treatment-naive. Patients who had a tumour with BRAF V600 mutation were allowed therapy with a BRAF inhibitor as pretreatment. Patients who had not had treatment with a BRAF inhibitor could be included at the investigator's discretion if additional criteria (LDH level not elevated, no clinically significant tumour-related symptoms, no rapidly progressive disease). This only applied to a small proportion of patients, however. Excluded were patients who had received previous treatment with ipilimumab or another drug against the cytotoxic T-lymphocyte-associated antigen-4 (anti-CTLA-4), a drug against the programmed cell death 1 protein (anti-PD-1) or against the ligand of PD-1 or PD-2 (anti-PD-L1 or anti-PD-L2).

The patients were assigned to the 3 study arms stratified according to treatment line, ECOG PS and PD-L1 expression. 277 patients were allocated to the pembrolizumab arm (10 mg/kg BW every 3 weeks) relevant for the present benefit assessment; 278 patients were allocated to the ipilimumab arm.

The primary outcomes of the study were overall survival and PFS. Further patient-relevant outcomes were disease-related symptoms, health status, health-related quality of life and AEs. Overall survival was recorded every 3 months after cessation of the study medication. Health-related quality of life was recorded up to 30 days after the last dose of the study medication or until the start of a new treatment. AEs were also recorded up to 30 days after the last dose of the study medication or until the start of a new treatment. SAEs were recorded up to 90 days after the last dose of the study medication.

Two interim analyses were planned in the study. The first interim analysis was to be performed after an observation period of 6 months of all patients and after about 260 cases of progression. The aim of the first interim analysis was to show a clinical advantage in PFS. The data cut-off for the first interim analysis was conducted on 3 September 2014. The second interim analysis was to be performed after a minimum observation period of 9 months and after the death of about 290 patients. If the number of 290 deaths was not achieved, the second interim analysis was to be performed after a minimum observation period of 12 months. The aim of the second interim analysis was to show the effect of the treatment on overall survival. The data cut-off of the second interim analysis was conducted on 3 March 2015 after a minimum observation period of 12 months had been achieved and 289 patients

had died. Following the recommendation of an external Data Monitoring Committee, the study was ended prematurely at the time point of the second interim analysis because the data on overall survival were showing superiority of pembrolizumab in comparison with ipilimumab. This criterion for discontinuation had been defined a priori. The patients in the ipilimumab arm could then switch to treatment with pembrolizumab. Although the study had been ended, the patients were to be observed regarding overall survival and AEs until the planned final analysis. The final analysis is to be performed as planned after at least 435 patients have died or all patients have been observed for at least 21 months.

Implementation of the appropriate comparator therapy

The G-BA saw individual treatment specified by the physician under consideration of the approval status and the respective prior therapy as appropriate comparator therapy for pretreated patients (research question 1). There was no choice regarding the comparator therapy in the KEYNOTE 006 study. However, due to the type of pretreatment of the patients it can be assumed for the pretreated patients (all of whom had not yet received ipilimumab) that, at the time point of the study, ipilimumab actually represented a comprehensible implementation of the ACT in the sense of individual treatment specified by the physician. Further explanations can be found in Section 2.7.3.4.1 of the full dossier assessment.

Relevant subpopulation

The subpopulation of the KEYNOTE 006 study relevant for research question 1 consisted of the pretreated patients. 91 of 277 patients (32.9%) in the relevant pembrolizumab arm (10 mg/kg BW every 3 weeks), and 97 of 278 patients (34.9%) in the ipilimumab arm had already been pretreated with systemic treatment for their advanced melanoma. One patient in the pembrolizumab arm had already received 2 previous systemic treatments.

Table 9 shows the characteristics of the total population of the patients in the included KEYNOTE 006 study. No data on these characteristics were available for the relevant subpopulation of pretreated patients. Table 10 shows the mutation status and the type of pretreatment of the patients in the relevant subpopulation of the KEYNOTE 006 study.

Table 9: Characteristics of the study population– RCT, direct comparison: pembrolizumab vs. ipilimumab

Study **Characteristics** **Category**	**Pembrolizumab** **N = 277**	**Ipilimumab** **N = 278**
KEYNOTE 006		
Age [years], mean (SD)	61 (14)	60 (14)
Sex [F/M], %	37/63	42/58
Skin colour, n (%)		
White	271 (97.8)	272 (97.8)
Non-white	5 (1.8)	6 (2.2)
Missing	1 (0.4)	0 (0.0)
Time since diagnosis, mean (SD)	ND	ND
Tumour stage, n (%)		
III	1 (0.4)	2 (0.7)
IIIA	0 (0.0)	1 (0.4)
IIIB	2 (0.7)	1 (0.4)
IIIC	6 (2.2)	9 (3.2)
IV	268 (96.8)	265 (95.3)
Metastases, n (%)		
M0	8 (2.9)[a]	13 (4.7)[a]
M1	4 (1.4)	5 (1.8)
M1A	34 (12.3)	30 (10.8)
M1B	41 (14.8)	52 (18.7)
M1C	190 (68.6)[a]	178 (64.0)[a]
BRAF V600 mutation status, n (%)		
Mutant	97 (35.0)	107 (38.5)
Wild type	178 (64.3)	170 (61.2)
Not determined	2 (0.7)	1 (0.4)
Baseline LDH serum level, n (%)		
Normal	175 (63.2)	178 (64.0)
Elevated (≥ 110% ULN)	98 (35.4)	91 (32.7)
Missing	4 (1.4)	9 (3.2)
Brain metastases, n (%)		
Yes	27 (9.7)	28 (10.1)
No	247 (89.2)	249 (89.6)
Missing	3 (1.1)	1 (0.4)
PD-L1 expression, n (%)		
Positive (APS ≥ 2)	221 (79.8)	225 (80.9)
Negative (APS 0 or 1)	54 (19.5)	47 (16.9)
Missing	2 (0.7)	6 (2.2)

(continued)

Table 9: Characteristics of the study population– RCT, direct comparison: pembrolizumab vs. ipilimumab (continued)

Study **Characteristics** **Category**	**Pembrolizumab** **N = 277**	**Ipilimumab** **N = 278**
ECOG performance status, n (%)		
0	189 (68.2)	188 (67.6)
1	88 (31.8)	90 (32.4)
Pretreatment with systemic therapies[b]		
Yes	92 (33.2)[c]	97 (34.9)
No	185 (66.8)	181 (65.1)
Study discontinuations[d], n (%)	101 (36.5)	146 (52.5)
Treatment discontinuations[e], n (%)	177 (63.9)	109 (39.2)

a: Data from the CSR from 14 August 2015. In each case one patient was classified differently in comparison with the CSR from 18 May 2015.
b: Systemic therapies for the treatment of advanced melanoma.
c: Institute's calculation. One patient received pembrolizumab as third-line therapy.
d: The majority of the patients were classified as patients who discontinued the study because they died (76.2% in the pembrolizumab arm and 66.4% in the ipilimumab arm).
e: Due to the fixed treatment regimen of ipilimumab (4 doses maximum), the rates of treatment discontinuations are not comparable between the treatment arms.

APS: Allred proportion score; BRAF: serine/threonine-protein kinase B-Raf (rapidly accelerated fibrosarcoma – isoform B); CSR: clinical study report; ECOG: Eastern Cooperative Oncology Group; F: female; LDH: lactate dehydrogenase; M: male; N: number of randomized patients; n: number of patients in the category; PD-L1: programmed cell death ligand 1; RCT: randomized controlled trial; SD: standard deviation; ULN: upper limit of normal; vs.: versus

Table 10: Mutation status and type of pretreatment of the pretreated patients – RCT, direct comparison: pembrolizumab vs. ipilimumab

Study Characteristics Category	Pembrolizumab N = 92[a]	Ipilimumab N = 97[a]
KEYNOTE 006		
BRAF V600 mutation[b], n (%)	49[a] (53.3[c])	60 (61.9[c])
Type of pretreatment, n[d] (%)[e]		
BRAF/MEK inhibitor	44 (89.8)	52 (86.7)
Chemotherapy	4 (8.2)	4 (6.7)
Immunotherapy	1 (2.0)	3 (5.0)
BRAF V600 wild type[f], n (%)	43 (46.7[c])	36 (37.1[c])
Type of pretreatment, n[d] (%)[g]		
BRAF/MEK inhibitor	1 (2.3)	3 (8.3)
Chemotherapy	37 (86.0)	25 (69.4)
Immunotherapy	6 (14.0)	9 (25.0)

a: Resulting from the information on patients in third- and second-line treatment.
b: Pretreated patients whose tumour has BRAF V600 mutation.
c: Institute's calculation.
d: The patient numbers do not sum up to the total number of patients. Discrepancies cannot be clarified from the CSR.
e: Institute's calculation; percentages refer to the number of pretreated patients with BRAF V600 mutation.
f: Pretreated patients whose tumour has no BRAF V600 mutation.
g: Institute's calculation; percentages refer to the number of pretreated patients without BRAF V600 mutation.
BRAF: serine/threonine-protein kinase B-Raf (rapidly accelerated fibrosarcoma – isoform B); CSR: clinical study report; MEK: mitogen-activated extracellular signal-regulated kinase; N: number of randomized (or included) patients; n: number of patients in the category; RCT: randomized controlled trial; vs.: versus

The characteristics of the patients in the KEYNOTE 006 study were balanced between the study arms. The mean age was 61 and 60 years. More men (about 60%) than women (about 40%) were included; most patients were white (97.8%). Most patients had tumour stage IV (about 97% and 95%); the extent of metastases was mainly M1C (69% and 64%). More than one third of the patients had a tumour with BRAF V600 mutation. The prognostic factors were mainly favourable for the patients. Almost 2 thirds of the patients had normal LDH levels; only about 10% of the patients had brain metastases. About 80% of the patients had increased expression of programmed cell death ligand 1 (PD-L1).

One third of the patients included were pretreated (33.2% in the pembrolizumab arm and 34.9% in the ipilimumab arm). These represented the relevant subpopulation for research question 1. BRAF V600 mutation was present in 53.3% of these patients in the pembrolizumab arm, and in 61.9% in the ipilimumab arm. Most of these patients had received previous treatment with a BRAF/MEK inhibitor (89.8% of the patients in the pembrolizumab arm and 86.7% of the patients in the ipilimumab arm). The remaining patients had received chemotherapy or immunotherapy.

The majority of the pretreated patients without BRAF V600 mutation (46.7% in the pembrolizumab arm and 37.1% in the ipilimumab arm), had previously received chemotherapy in both relevant treatment arms (86.0% of the patients in the pembrolizumab arm and 69.4% of the patients in the ipilimumab arm). 14.0% of the patients in the pembrolizumab arm had received immunotherapy, and 25.0% in the ipilimumab arm). Although the patients had no BRAF V600 mutation, one patient (2.3%) in the pembrolizumab arm and 3 patients (8.3%) in the ipilimumab arm had received previous treatment with a BRAF/MEK inhibitor.

Table 11 shows the mean and median treatment duration of the patients in the KEYNOTE 006 study.

Table 11: Information on the course of the study – RCT, direct comparison: pembrolizumab vs. ipilimumab

Study **Duration of the study phase** **Outcome category**	**Pembrolizumab** **N = 277**	**Ipilimumab** **N = 256**
Study KEYNOTE 006		
Treatment duration [days]		
Median [min; max]	168 [1, 519]	63 [1, 92]
Mean (SD)	218.7 (165.6)	50.1 (21.4)
Observation period morbidity, health-related quality of life, adverse events		
Median [min; max]	ND	ND
Mean (SD)	ND	ND

max: maximum; min: minimum; N: number of randomized patients who received at least one dose of the study medication; n: number of patients in the category; ND: no data; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

The treatment duration of the total population of the KEYNOTE 006 study differed between the 2 relevant treatment arms. The median treatment duration of the patients in the pembrolizumab arm (168 days) was substantially longer than in the ipilimumab arm (63 days). This was caused by the fixed treatment regimen of ipilimumab. According to the approval, ipilimumab is administered only 4 times every 3 weeks [5]. Hence only a maximum treatment period of 10 weeks (one dose every 3 weeks, with a maximum of 4 doses in total) is possible. No information on the observation period was available.

Table 12 shows the risk of bias at study level.

Table 12: Risk of bias at study level – RCT, direct comparison: pembrolizumab vs. ipilimumab

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			
KEYNOTE 006	Yes	Yes	No	No	Yes	Yes	Low
RCT: randomized controlled trial; vs.: versus							

The risk of bias at study level was rated as low for the KEYNOTE 006 study. This concurs with the company's assessment.

Limitations resulting from the open-label study design are described in Section 2.3.2 with the outcome-specific risk of bias.

2.3.2 Results on added benefit (research question 1)

2.3.2.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment (for reasons, see Section 2.7.3.4.3 of the full dossier assessment):

- Mortality
  - overall survival
- Morbidity
  - symptoms (EORTC QLQ-C30)
  - health status (EQ-5D VAS)
- Health-related quality of life
  - health-related quality of life (EORTC QLQ-C30)
- Adverse events
  - SAEs
  - severe AEs (CTCAE grade ≥ 3)
  - discontinuation due to AEs

The choice of patient-relevant outcomes deviated from that of the company, which used further outcomes in the dossier (Module 4 B) (see Section 2.7.3.4.3 of the full dossier assessment).

Table 13 shows the outcomes for which data were available in the included studies.

Table 13: Matrix of outcomes – RCT, direct comparison, pretreated patients: pembrolizumab vs. ipilimumab

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)
KEYNOTE 006	Yes	Yes	Yes	Yes	Yes	Yes	Yes

a: Recorded with the EORTC QLQ-C30 symptom scales.
b: Recorded with the EORTC QLQ-C30 functional scales.

AE: adverse event; 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; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus

The available documents contained data for all relevant outcomes for the KEYNOTE 006 study. Further information can be found in Section 2.7.3.4.3 of the full dossier assessment.

2.3.2.2 Risk of bias

Table 14 shows the risk of bias for the relevant outcomes.

Table 14: Risk of bias at study and outcome level – RCT, direct comparison, pretreated patients: pembrolizumab vs. ipilimumab

Study	Study level	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)
KEYNOTE 006	L	L	H[c]	H[d]	H[c]	H[e]	H[e]	H[e]

a: Recorded with the EORTC QLQ-C30 symptom scales.
b: Recorded with the EORTC QLQ-C30 functional scales.
c: Due to potentially informative censoring, lack of blinding in subjective recording of outcomes and a relevant high proportion of patients who were not included in the analysis or because this proportion differed between the treatment groups to a relevant degree.
d: Due to lack of blinding in subjective recording of outcomes and a relevant high proportion of patients who were not included in the analysis or because this proportion differed between the treatment groups to a relevant degree.
e: Due to potentially informative censoring.
AE: adverse event; 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; H: high; L: low; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus

There was a low risk of bias for the outcome “overall survival”. This concurs with the company’s assessment. The outcomes on symptoms, on health status and on health-related quality of life have a high bias because of the lack of blinding and of a relevant high proportion of patients who were not included in the assessment. In addition, there was potentially informative censoring regarding the outcomes on symptoms and health-related quality of life. This assessment of the risk of bias also concurs with that of the company. There was also a high risk of bias, which was caused by potentially informative censoring, for the outcomes on AEs (SAEs; discontinuation due to AEs, severe AEs of CTCAE grade ≥ 3). In contrast, the company rated the risk of bias for these outcomes as low. Further information can be found in Section 2.7.3.4.2 of the full dossier assessment.

2.3.2.3 Results

Table 15 to Table 19 summarize the results on the comparison of pembrolizumab with individual treatment (ipilimumab) in pretreated patients with advanced (unresectable or

metastatic) melanoma. The results for the relevant subpopulation were taken from the subgroup analyses of the characteristic "G-BA-relevant characteristic regarding pretreatment and BRAF V600 status". The analyses on the outcomes on overall survival and on AEs were based on the data cut-off of the second interim analysis after a minimum observation period of 12 months; the dossier contained no information for the outcomes on morbidity and health-related quality of life. Where necessary, the data from the company's dossier were supplemented by the Institute's calculations.

Table 15: Results on overall survival – RCT, direct comparison, pretreated patients: pembrolizumab vs. ipilimumab

Study **Outcome category** **Outcome**	**Pembrolizumab**		**Ipilimumab**		**Pembrolizumab vs. ipilimumab**
	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[a]**
KEYNOTE 006					
Mortality					
Overall survival	91	NC [12.7; NC] ND	97	14.0 [10.9; NC] ND	0.69 [0.44; 1.09]; 0.112

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).

CI: confidence interval; ECOG PS: Eastern Cooperative Oncology Group Performance Status; HR: hazard ratio; N: number of analysed patients: NC: not calculable; ND: no data; PD-L1: programmed cell death ligand 1; RCT: randomized controlled trial; vs.: versus

Table 16: Results on morbidity (symptoms), time to deterioration – RCT, direct comparison, pretreated patients: pembrolizumab vs. ipilimumab

Study Outcome category	Pembrolizumab		Ipilimumab		Pembrolizumab vs. ipilimumab
Outcome	**N**	**Median time in days [95% CI] Patients with event n (%)**	**N**	**Median time in days [95% CI] Patients with event n (%)**	**HR [95% CI][a]; p-value[a]**
KEYNOTE 006					
Morbidity (symptoms)					
EORTC QLQ-C30 symptom scales – time to worsening of symptoms[b, c]					
Dyspnoea	85	87.0 [85.0; NC] ND	81	NA [68.0; NC] ND	0.90 [0.55; 1.46]; 0.660
Fatigue	85	43.0 [29.0; 85.0] ND	81	44.0 [42.0; 85.0] ND	1.05 [0.72; 1.55]; 0.787
Insomnia	85	88.0 [81.0; NC] ND	81	85.0 [44.0; 87.0] ND	0.82 [0.52; 1.30]; 0.396
Pain	85	85.0 [47.0; 88.0] ND	81	85.0 [44.0; NC] ND	1.00 [0.64; 1.55]; 0.984
Appetite loss	85	88.0 [85.0; NC] ND	81	87.0 [85.0; NC] ND	1.02 [0.62; 1.68]; 0.946
Diarrhoea	85	NC [85.0; NC] ND	81	85.0 [68.0; NC] ND	0.69 [0.42; 1.13]; 0.141
Nausea and vomiting	85	NC [85.0; NC] ND	81	85.0 [44.0; NC] ND	0.74 [0.45; 1.19]; 0.211
Constipation	85	88.0 [84.0; NC] ND	81	86.0 [84.0; NC] ND	1.06 [0.66; 1.69]; 0.816

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.

CI: confidence interval; 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; NC: not calculable; ND: no data; PD-L1: programmed cell death ligand 1; RCT: randomized controlled trial; vs.: versus

Table 17: Results on morbidity (health status), mean change at week 12 – RCT, direct comparison, pretreated patients: 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]	80	66.1 (23.2)	−2.6 (26.2)	71	64.8 (24.4)	−3.6 (24.5)	1.65 [−6.01; 9.31]; 0.673

a: MD, CI and p-value result from a constrained longitudinal data analysis 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.
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 18: Results on health-related quality of life, time to deterioration – RCT, direct comparison, pretreated patients: pembrolizumab vs. ipilimumab

Study Outcome category	Pembrolizumab		Ipilimumab		Pembrolizumab vs. ipilimumab
Outcome	**N**	**Median time in days [95% CI] Patients with event n (%)**	**N**	**Median time in days [95% CI] Patients with event n (%)**	**HR [95% CI][a]; p-value[a]**
KEYNOTE 006					
Health-related quality of life					
EORTC QLQ-C30 functional scales – time to worsening of health-related quality of life[b, c]					
Global health status/quality of life	85	86.0 [84.0; NC] ND	81	85.0 [44.0; 90.0]	0.87 [0.55; 1.37]; 0.553
Emotional functioning	85	88.0 [86.0; NC] ND	81	86.0 [82.0; NC] ND	0.80 [0.49; 1.31]; 0.375
Cognitive functioning	85	88.0 [84.0; NC] ND	81	84.0 [43.0; 86.0] ND	0.73 [0.47; 1.13]; 0.158
Physical functioning	85	88.0 [50.0; NC] ND	81	85.0 [43.0; 103.0] ND	0.92 [0.59; 1.14]; 0.719
Role functioning	85	86.0 [84.0; NC] ND	81	85.0 [44.0; 103.0] ND	0.85 [0.55; 1.33]; 0.475
Social functioning	85	86.0 [84.0; 88.0] ND	81	87.0 [50.0; NC] ND	1.15 [0.72; 1.84]; 0.570

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.

CI: confidence interval; 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; NC: not calculable; ND: no data; PD-L1: programmed cell death ligand 1; RCT: randomized controlled trial; vs.: versus

Table 19: Results on AEs – RCT, direct comparison, pretreated patients: pembrolizumab vs. ipilimumab

Study Outcome category	Pembrolizumab		Ipilimumab		Pembrolizumab vs. ipilimumab
Outcome	**N**	**Median time in months [95% CI] Patients with event n (%)**	**N**	**Median time in months [95% CI] Patients with event n (%)**	**HR [95% CI][a]; p-value**
KEYNOTE 006					
Adverse events					
AEs	91	0.4 [0.2; 0.6] ND	88	0.3 [0.1; 0.5] ND	–
SAEs	91	16.7 [10.9; NC] ND	88	NC ND	0.54 [0.30; 0.98]; 0.043
Severe AEs (CTCAE grade ≥ 3)	91	16.7 [13.6; NC] ND	88	NC ND	0.46 [0.24; 0.87]; 0.017
Discontinuation due to AEs	91	NC ND	88	NC ND	0.28 [0.09; 0.88]; 0.029

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; N: number of analysed patients; NC: not calculable; ND: no data; PD-L1: programmed cell death ligand 1; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus

The pembrolizumab dosage (10 mg/kg BW) used in the KEYNOTE 006 study was not compliant with the approval, which led to an uncertainty in the interpretability of the study results.

The company assessed the added benefit irrespective of the patients' pretreatment. In Module 4 B, the company presented the results for the relevant subpopulation of the present research question in form of subgroup analyses, but derived no added benefit for this subpopulation from them. Hence it is not described in how far the assessment of the outcomes in the present benefit assessment deviates from that of the company.

Mortality

Overall survival

There was no statistically significant difference between the treatment arms for the outcome "overall survival". This resulted in no hint of an added benefit of pembrolizumab in comparison with individual treatment (ipilimumab); an added benefit is therefore not proven.

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.

No statistically significant difference between the treatment arms was shown for any of the symptoms considered. This resulted in no hint of an added benefit of pembrolizumab in comparison with individual treatment 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). This resulted in no hint of an added benefit of pembrolizumab in comparison with individual treatment with ipilimumab; an added benefit is therefore not proven.

Health-related quality of life

Aspects of health-related quality of life were recorded with the functional scales and with the scale for the recording of the global health status/quality of life 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 arms was shown in health-related quality of life for any of the domains considered. This resulted in no hint of an added benefit of pembrolizumab in comparison with individual treatment with ipilimumab; an added benefit is therefore not proven.

Adverse events

The higher dosage of pembrolizumab in the KEYNOTE 006 study in comparison with the approval resulted in an increased uncertainty. However, it is assumed for the outcomes on AEs that the effect of the increased dosage on the treatment effect was to the disadvantage of pembrolizumab. The further aspects resulting in a high risk of bias in these outcomes did not raise general doubts about this direction of the bias. Hence in this case, the certainty of results for the outcomes on AEs in effects in favour of pembrolizumab was not downgraded.

Serious adverse events

A statistically significant difference in favour of pembrolizumab was shown for the outcome “SAEs”. This resulted in an indication of lesser harm from pembrolizumab in comparison with individual treatment with ipilimumab.

Severe adverse events (CTCAE grade ≥ 3)

There was a statistically significant difference in favour of pembrolizumab for the outcome "severe AEs (CTCAE grade ≥ 3)". This resulted in an indication of lesser harm from pembrolizumab in comparison with individual treatment with ipilimumab.

Discontinuation due to adverse events

A statistically significant difference in favour of pembrolizumab was shown for the outcome "discontinuation due to AEs". This resulted in an indication of lesser harm from pembrolizumab in comparison with individual treatment with ipilimumab.

2.3.2.4 Subgroups and other effect modifiers

The dossier contained no subgroup analyses for the relevant subpopulation.

2.3.3 Extent and probability of added benefit (research question 1)

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.

2.3.3.1 Assessment of added benefit at outcome level

The data presented in Section 2.3.2 resulted in hints of lesser harm from pembrolizumab for the outcomes on AEs – SAEs, severe AEs (CTCAE grade ≥ 3) and discontinuation due to AEs. The extent of the respective added benefit at outcome level was estimated from these results (see Table 20).

Determination of the outcome category for the outcome "discontinuation due to adverse events"

The assessment of the outcome category of "discontinuations due to AEs" depends on the severity of the AEs that led to discontinuation. However, there was no information on the proportion of SAEs from the discontinuations for the relevant subpopulation. With respect to the total study population, the proportion of SAEs from the discontinuations due to AEs was 75% for the pembrolizumab arm, and 76% for the ipilimumab arm. Since the proportion of SAEs from the discontinuations due to AEs was very high in the total population of the study, it can be assumed that this proportion was also above 50% in the relevant subpopulation. The results of the outcome "discontinuation due to AEs" were therefore allocated to the outcome category "serious/severe symptoms/late complications" in the present case.

Table 20: 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	Median: NA vs. 14.0 months HR: 0.69 [0.44; 1.09] p = 0.112	Lesser benefit/added benefit not proven
Morbidity		
EORTC QLQ-C30 symptom scales – time to deterioration by at least 10 points		
Dyspnoea	Median: 87.0 vs. NC days HR: 0.90 [0.55; 1.46] p = 0.660	Lesser benefit/added benefit not proven
Fatigue	Median: 43.0 vs. 44.0 days HR: 1.05 [0.72; 1.55] p = 0.787	Lesser benefit/added benefit not proven
Insomnia	Median: 88.0 vs. 85.0 days HR: 0.82 [0.52; 1.30] p = 0.396	Lesser benefit/added benefit not proven
Pain	Median: 85.0 vs. 85.0 days HR: 1.00 [0.64; 1.55] p = 0.984	Lesser benefit/added benefit not proven
Appetite loss	Median: 88.0 vs. 87.0 days HR: 1.02 [0.62; 1.68] p = 0.946	Lesser benefit/added benefit not proven
Diarrhoea	Median: NA vs. 85.0 days HR: 0.69 [0.42; 1.13] p = 0.141	Lesser benefit/added benefit not proven
Nausea and vomiting	Median: NA vs. 85.0 days HR: 0.74 [0.45; 1.19] p = 0.211	Lesser benefit/added benefit not proven
Constipation	Median: 88.0 vs. 86.0 days HR: 1.06 [0.66; 1.69] p = 0.816	Lesser benefit/added benefit not proven
Health status		
EQ-5D VAS	Mean change: −2.6 vs. −3.6 MD: 1.65 [−6.01; 9.31] p = 0.673	Lesser benefit/added benefit not proven

(continued)

Table 20: Extent of added benefit at outcome level: pembrolizumab vs. ipilimumab (pretreated patients) (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]
Health-related quality of life		
EORTC QLQ-C30 functional scales – time to deterioration by at least 10 points		
Global health status/quality of life	Median: 86.0 vs. 85.0 days HR: 0.87 [0.55; 1.37] p = 0.553	Lesser benefit/added benefit not proven
Emotional functioning	Median: 88.0 vs. 86.0 days HR: 0.80 [0.49; 1.31] p = 0.375	Lesser benefit/added benefit not proven
Cognitive functioning	Median: 88.0 vs. 84.0 days HR: 0.73 [0.47; 1.13] p = 0.158	Lesser benefit/added benefit not proven
Physical functioning	Median: 88.0 vs. 85.0 days HR: 0.92 [0.59; 1.14] p = 0.719	Lesser benefit/added benefit not proven
Role functioning	Median: 86.0 vs. 85.0 days HR: 0.85 [0.55; 1.33] p = 0.475	Lesser benefit/added benefit not proven
Social functioning	Median: 86.0 vs. 87.0 days HR: 1.15 [0.75; 1.84] p = 0.570	Lesser benefit/added benefit not proven
Adverse events		
Serious adverse events	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”

(continued)

Table 20: 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; EQ-5D: European Quality of Life-5 Dimensions; HR: hazard ratio; MD: mean difference; NC: not calculable; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

2.3.3.2 Overall conclusion on added benefit

Table 21 summarizes the results that were considered in the overall conclusion on the extent of added benefit.

Table 21: Positive and negative effects from the assessment of pembrolizumab in comparison with ipilimumab (pretreated patients)

Positive effects	**Negative effects**
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)	
AE: adverse event; CTCAE: Common Terminology Criteria of Adverse Events; SAE: serious adverse event	

Overall, 3 positive effects of the same probability with different extent remain in the category "serious/severe AEs".

There was an indication of lesser harm from pembrolizumab with the extent "minor" for the outcome "SAEs". For the outcomes "severe AEs (CTCAE grade ≥ 3)" and "discontinuation due to AEs", there was an indication of lesser harm from pembrolizumab with the extent "considerable". The results on the other outcome categories also have to be considered for balancing the benefit and harm. These did not raise doubts about the advantage of pembrolizumab resulting from the adverse events.

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.

The added benefit is not proven for patients who are pretreated, but for whom ipilimumab is not an option as the ACT.

This deviates from the company's approach, which, based on the KEYNOTE 002 study, derived an indication of major added benefit of pembrolizumab in comparison with individual chemotherapy for a different subpopulation of pretreated patients, i.e. patients with advanced (unresectable or metastatic) melanoma with previous BRAF/MEK inhibitor therapy and/or chemotherapy and progression of their cancer under or after ipilimumab.

2.3.4 List of included studies (research question 1)

KEYNOTE 002

Merck Sharp & Dohme. Randomized, phase II study of MK-3475 versus chemotherapy in patients with advanced melanoma [online]. In: EU-Clinical Trials Register. [Accessed: 15 September 2015]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2012-003030-17.

Merck Sharp & Dohme. Randomized, phase II study of MK-3475 versus chemotherapy in patients with advanced melanoma: study P002; clinical study report [unpublished]. 2015.

Merck Sharp & Dohme. Study of pembrolizumab (MK-3475) versus chemotherapy in participants with advanced melanoma (P08719/KEYNOTE-002): full text view [online]. In: ClinicalTrials.gov. 3 August 2015 [accessed: 15 September 2015]. URL: https://ClinicalTrials.gov/show/NCT01704287.

KEYNOTE 006

Merck Sharp & Dohme. A multicenter, randomized, controlled, three-arm, phase III study to evaluate the safety and efficacy of two dosing schedules of MK-3475 compared to ipilimumab in patients with advanced melanoma: study P006; clinical study report [unpublished]. 2015.

Merck Sharp & Dohme. A multi-center, randomized, controlled, three-arm, phase III study to evaluate the safety and efficacy of two dosing schedules of MK-3475 compared to ipilimumab in patients with advanced melanoma [online]. In: EU-Clinical Trials Register. [Accessed: 15 September 2015]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2012-004907-10.

Merck Sharp & Dohme. Study to evaluate the safety and efficacy of two different dosing schedules of pembrolizumab (MK-3475) compared to ipilimumab in participants with advanced melanoma (MK-3475-006/KEYNOTE-006): full text view [online]. In: ClinicalTrials.gov. 3 June 2015 [accessed: 15 September 2015]. URL: https://ClinicalTrials.gov/show/NCT01866319.

Robert C, Schachter J, Long GV, Arance A, Grob JJ, Mortier L et al. Pembrolizumab versus ipilimumab in advanced melanoma. N Engl J Med 2015; 372(26): 2521-2532.

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

2.4.1 Information retrieval and study pool (research question 2)

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

Sources of the company in the dossier:

- study lists on pembrolizumab (status: 1 June 2015)
- bibliographical literature search on pembrolizumab (last search on 18 May 2015)
- search in trial registries for studies on pembrolizumab (last search on 19 May 2015)

To check the completeness of the study pool:

- search in trial registries for studies on pembrolizumab (last search on 31 August 2015)

The search comprised both studies in which pembrolizumab was used in the approval-compliant dose of 2 mg/kg BW and studies with dosages of 10 mg/kg BW pembrolizumab.

No additional relevant study was identified from the check.

2.4.1.1 Studies included

The study listed in the following table was included in the benefit assessment.

Table 22: Study pool – RCT, direct comparison, treatment-naive patients with BRAF V600 wt tumour: pembrolizumab vs. ipilimumab

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
KEYNOTE 006	Yes	Yes	No
a: Study for which the company was sponsor, or in which the company was otherwise financially involved. BRAF: serine/threonine-protein kinase B-Raf (rapidly accelerated fibrosarcoma – isoform B); RCT: randomized controlled trial; vs.: versus			

The KEYNOTE 006 study was included although pembrolizumab was used in a dosage of 10 mg/kg BW, which was not compliant with the approval. It is assumed in the present situation that the results of a treatment regimen with 10 mg/kg BW every 3 weeks are transferable to a treatment regimen with 2 mg/kg BW every 3 weeks. More details on this can be found in Section 2.7.3.4.1 of the full dossier assessment.

Section 2.4.4 contains a reference list for the studies included.

2.4.1.2 Study characteristics

Characteristics of the study and of the interventions

The characteristics of the KEYNOTE 006 study are described in Section 2.3.1.2 on research question 1 (Table 6, Table 7, Table 8).

Characteristics of the relevant subpopulation

The characteristics of the total population of the patients in the included study KEYNOTE 006 are described in Table 9 in Section 2.3.1.2 on research question 1. No data were available on these characteristics for the relevant subpopulation of treatment-naive patients with BRAF V600 wt tumour.

Of the total of 555 patients included in the relevant treatment arms of the KEYNOTE 006 study, 366 patients (65.9%) had not received any systemic treatment of their advanced melanoma. These were 185 of 277 patients (66.8%) in the relevant pembrolizumab arm; 181 of 278 patients (65.1%) in the ipilimumab arm were treatment-naive (see Table 9). Of these treatment-naive patients, 135 of 185 patients (73.0%) in the pembrolizumab arm had a tumour without BRAF V600 mutation (BRAF V600 wt); and 134 of 181 patients (74.0%) in the ipilimumab arm had a BRAF V600 wt tumour (see Table 23). These patients represented the relevant subpopulation of the present research question 2.

Table 23: Mutation status of the treatment-naive patients – RCT, direct comparison: pembrolizumab vs. ipilimumab

Study Characteristics Category	Pembrolizumab N = 185	Ipilimumab N = 181
KEYNOTE 006		
BRAF V600 mutation status, n (%)		
Mutant	48 (25.9[a])	47 (26.0[a])
Wild type	135 (73.0[a])	134 (74.0[a])
a: Institute's calculation. BRAF: serine/threonine-protein kinase B-Raf (rapidly accelerated fibrosarcoma – isoform B); N: number of randomized patients; RCT: randomized controlled trial; vs.: versus		

Treatment duration

Table 11 in Section 2.3.1.2 on research question 1 shows the mean and median treatment duration of the patients in the KEYNOTE 006 study. The treatment duration of the total population of the KEYNOTE 006 study differed between the 2 relevant treatment arms. The median treatment duration of the patients in the pembrolizumab arm (168 days) was substantially longer than in the ipilimumab arm (63 days). This was caused by the fixed treatment regimen of ipilimumab. According to the approval, ipilimumab is administered only 4 times every 3 weeks [5]. Hence only a maximum treatment period of 10 weeks (one dose

every 3 weeks, with a maximum of 4 doses in total) is possible. No information on the observation period was available.

Risk of bias

The risk of bias at study level is shown in Section 2.3.1.2 on research question 1 (Table 12). It was rated as low for the KEYNOTE 006 study included. This concurs with the company's assessment.

Limitations resulting from the open-label study design are described in Section 2.3.2.2 on research question 1 with the outcome-specific risk of bias.

2.4.2 Results on added benefit (research question 2)

2.4.2.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment (for reasons, see Section 2.7.3.4.3 of the full dossier assessment):

- Mortality
  - overall survival
- Morbidity
  - symptoms (EORTC QLQ-C30)
  - health status (EQ-5D VAS)
- Health-related quality of life
  - health-related quality of life (EORTC QLQ-C30)
- Adverse events
  - SAEs
  - severe AEs (CTCAE grade ≥ 3)
  - discontinuation due to AEs

The choice of patient-relevant outcomes deviated from that of the company, which used further outcomes in the dossier (Module 4 B) (see Section 2.7.3.4.3 of the full dossier assessment).

Table 24 shows the outcomes for which data were available in the included studies.

Table 24: Matrix of outcomes – RCT, direct comparison, treatment-naive patients with BRAF V600 wt tumour: pembrolizumab vs. ipilimumab

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)
KEYNOTE 006	Yes	Yes	Yes	Yes	Yes	Yes	Yes

a: Recorded with the EORTC QLQ-C30 symptom scales.
b: Recorded with the EORTC QLQ-C30 functional scales.
AE: adverse event; BRAF: serine/threonine-protein kinase B-Raf (rapidly accelerated fibrosarcoma – isoform B); BRAF V600 wt: BRAF V600 wildtype; 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; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

The available documents contained data for all relevant outcomes for the KEYNOTE 006 study. Further information can be found in Section 2.7.3.4.3 of the full dossier assessment.

2.4.2.2 Risk of bias

The risk of bias at outcome level is described in Section 2.3.2.2 on research question 1. 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.

2.4.2.3 Results

Table 25 to Table 29 summarize the results on the comparison of pembrolizumab with ipilimumab in treatment-naive patients with advanced (unresectable or metastatic) melanoma without BRAF V600 mutation. As in research question 1, the results for the relevant subpopulation were taken from the subgroup analyses. The analyses on the outcomes on overall survival and on AEs were based on the data cut-off of the second interim analysis after a minimum observation period of 12 months; the dossier contained no information for the outcomes on morbidity and health-related quality of life. Where necessary, the data from the company's dossier were supplemented by the Institute's calculations.

Table 25: Results on overall survival – RCT, direct comparison, treatment-naive patients with BRAF V600 wt tumour: pembrolizumab vs. ipilimumab

Study **Outcome category**	**Pembrolizumab**		**Ipilimumab**		**Pembrolizumab vs. ipilimumab**
Outcome	**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[a]**
KEYNOTE 006					
Mortality					
Overall survival	135	NC ND	134	15.4 [9.8; NC] ND	0.65 [0.44; 0.96]; 0.032

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);
BRAF V600 wt: BRAF V600 wild type; CI: confidence interval; ECOG PS: Eastern Cooperative Oncology Group Performance Status; HR: hazard ratio; N: number of analysed patients; NC: not calculable; ND: no data; PD-L1: programmed cell death ligand 1; RCT: randomized controlled trial; vs.: versus

Table 26: Results on morbidity (symptoms), time to deterioration – RCT, direct comparison, treatment-naive patients with BRAF V600 wt tumour: pembrolizumab vs. ipilimumab

Study Outcome category	Pembrolizumab		Ipilimumab		Pembrolizumab vs. ipilimumab
Outcome	**N**	**Median time in days [95% CI] Patients with event n (%)**	**N**	**Median time in days [95% CI] Patients with event n (%)**	**HR [95% CI][a]; p-value[a]**
KEYNOTE 006					
Morbidity (symptoms)					
EORTC QLQ-C30 symptom scales – time to worsening of symptoms[b, c]					
Dyspnoea	129	86.0 [84.0; NC] ND	112	84.0 [45.0; 86.0] ND	0.76 [0.53; 1.09]; 0.133
Fatigue	129	43.0 [42.0; 84.0] ND	112	24.0 [22.0; 42.0] ND	0.66 [0.49; 0.91]; 0.010
Insomnia	129	87.0 [85.0; NC] ND	112	85.0 [43.0; NC] ND	0.77 [0.54; 1.11]; 0.164
Pain	129	83.0 [42.0; 86.0] ND	112	83.0 [43.0; 85.0] ND	0.95 [0.68; ND[d]]; 0.746
Appetite loss	129	86.0 [84.0; 95.0] ND	112	85.0 [69.0; 107.0] ND	0.82 [0.57; 1.19]; 0.292
Diarrhoea	129	86.0 [85.0; NC] ND	112	84.0 [83.0; 87.0] ND	0.71 [0.49; 1.03]; 0.072
Nausea and vomiting	129	87.0 [85.0; 95.0] ND	112	69.0 [42.0; 93.0] ND	0.67 [0.46; 0.97]; 0.034
Constipation	129	87.0 [85.0; 107.0] ND	112	86.0 [84.0; NC] ND	0.84 [0.57; 1.23]; 0.367

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.
d: The upper limit of the CI is cited as 0.32 in Module 4 B. Since this value is below the lower threshold, it is assumed that this was a transcription error, which cannot be verified, however.

BRAF: serine/threonine-protein kinase B-Raf (rapidly accelerated fibrosarcoma – isoform B);
BRAF V600 wt: BRAF V600 wild type; CI: confidence interval; 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; NC: not calculable; ND: no data;
PD-L1: programmed cell death ligand 1; RCT: randomized controlled trial; vs.: versus

Table 27: Results on morbidity (health status), mean change at week 12 – RCT, direct comparison, treatment-naive patients with BRAF V600 wt tumour: pembrolizumab vs. ipilimumab

Study Outcome category Outcome	Pembrolizumab			Ipilimumab			Pembrolizumab vs. ipilimumab
	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]	124	71.1 (21.3)	−7.3 (25.4)	109	72.8 (22.0)	−9.5 (28.0)	1.18 [−5.34; 7.70]; 0.722

a: MD, CI and p-value result from a constrained longitudinal data analysis 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);
BRAF V600 wt: BRAF V600 wild type; 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 28: Results on health-related quality of life, time to deterioration – RCT, direct comparison, treatment-naive patients with BRAF V600 wt tumour: pembrolizumab vs. ipilimumab

Study Outcome category Outcome	Pembrolizumab N	Pembrolizumab Median time in days [95% CI] Patients with event n (%)	Ipilimumab N	Ipilimumab Median time in days [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 worsening of health-related quality of life[b, c]					
Global health status/quality of life	129	84.0 [43.0; 86.0] ND	112	83.0 [43.0; 84.0] ND	0.94 [0.67; 1.32]; 0.718
Emotional functioning	129	87.0 [85.0; NC] ND	112	85.0 [60.0; NC] ND	0.76 [0.51; 1.12]; 0.166
Cognitive functioning	129	85.0 [64.0; 86.0] ND	112	84.0 [49.0; 85.0] ND	0.98 [0.69; 1.38]; 0.902
Physical functioning	129	86.0 [84.0; 95.0] ND	112	83.0 [43.0; 85.0] ND	0.79 [0.56; 1.12]; 0.179
Role functioning	129	84.0 [42.0; 86.0] ND	112	46.0 [40.0; 84.0] ND	0.83 [0.60; 1.15]; 0.258
Social functioning	129	85.0 [64.0; NC] ND	112	44.0 [42.0; 83.0] ND	0.68 [0.48; 0.95]; 0.023

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);
BRAF V600 wt: BRAF V600 wild type; CI: confidence interval; 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; NC: not calculable; ND: no data;
PD-L1: programmed cell death ligand 1; RCT: randomized controlled trial; vs.: versus

Table 29: Results on AEs – RCT, direct comparison, treatment-naive patients with BRAF V600 wt tumour: pembrolizumab vs. ipilimumab

Study Outcome category	Pembrolizumab		Ipilimumab		Pembrolizumab vs. ipilimumab
Outcome	**N**	**Median time in months [95% CI] Patients with event n (%)**	**N**	**Median time in months [95% CI] Patients with event n (%)**	**HR [95% CI][a]; p-value[a]**
KEYNOTE 006					
Adverse events					
AEs	135	0.3 [0.2; 0.5] ND	122	0.4 [0.3; 0.6] ND	–
SAEs	135	NC ND	122	NC ND	0.70 [0.44; 1.13]; 0.145
Severe AEs (CTCAE grade ≥ 3)	135	NC ND	122	NC ND	0.72 [0.43; 1.23]; 0.228
Discontinuation due to AEs	135	NC ND	122	NC ND	0.63 [0.29; 1.37]; 0.240

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); BRAF V600 wt: BRAF V600 wild type; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; ECOG PS: Eastern Cooperative Oncology Group Performance Status; HR: hazard ratio; N: number of analysed patients; NC: not calculable; ND: no data; PD-L1: programmed cell death ligand 1; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus

The pembrolizumab dosage (10 mg/kg BW) used in the KEYNOTE 006 study was not compliant with the approval, which led to an uncertainty in the interpretability of the study results.

The company assessed the added benefit irrespective of the patients' pretreatment. In Module 4 B, the company presented the results for the relevant subpopulation of the present research question in form of subgroup analyses, but derived no added benefit for this subpopulation from them. Hence it is not described in how far the assessment of the outcomes in the present benefit assessment deviates from that of the company.

Mortality

Overall survival

A statistically significant difference in favour of pembrolizumab was shown for the outcome "overall survival". The risk of bias was rated as low. However, the increased dosage of pembrolizumab in the KEYNOTE 006 study resulted in a reduced certainty of conclusions regarding the outcome "overall survival". It cannot be assessed whether the effect of the increased dosage was in favour or to the disadvantage of pembrolizumab. This resulted in a hint of an added benefit of pembrolizumab in comparison with ipilimumab.

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 the outcomes "fatigue" and "nausea and vomiting". The extent of the effect in these non-serious/non-severe outcomes was no more than marginal.

No statistically significant difference between the treatment arms was shown for any of the remaining outcomes "dyspnoea", "insomnia", "pain", "appetite loss", "diarrhoea" 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.

A statistically significant difference in favour of pembrolizumab was shown for the outcome "social functioning". The risk of bias for this outcome was rated as high. This resulted in a hint of an added benefit of pembrolizumab in comparison with ipilimumab.

No statistically significant difference between the treatment arms was shown for any of the remaining outcomes "global health status/quality of life", "emotional functioning", "cognitive functioning", "physical functioning" and "role 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

Serious adverse events, severe adverse events (CTCAE grade ≥ 3), discontinuation due to adverse events

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

2.4.2.4 Subgroups and other effect modifiers

The dossier contained no subgroup analyses for the relevant subpopulation.

2.4.3 Extent and probability of added benefit (research question 2)

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.

2.4.3.1 Assessment of added benefit at outcome level

The data presented in Section 2.4.2 resulted in a hint of an added benefit for each of the outcomes “all-cause mortality” (mortality) and “social functioning” (health related quality of life). The extent of the respective added benefit at outcome level was estimated from these results (see Table 30).

Determination of the outcome category for the EORTC QLQ-C30 symptom scales

The assessment to which outcome category the statistically significant results of the EORTC QLQ-C30 symptom scales are allocated depends on the severity of the symptom under consideration (in this case fatigue as well as nausea and vomiting). The AEs “fatigue” as well as “nausea and vomiting” recorded in the KEYNOTE 006 study were used by CTCAE grades to be able to assess the severity of these events. No information on AEs by CTCAE grades was available for the relevant subpopulation, however. For the total study population, the AEs “fatigue” as well as “nausea and vomiting” were mostly not severe (CTCAE grade 1 and 2). The proportion of non-severe fatigue (Preferred Term [PT]) (CTCAE grade 1 and 2) was 97% for the pembrolizumab arm and 89% for the ipilimumab arm; the proportion of non-severe nausea (PT) was 99% for the pembrolizumab arm and 93% for the ipilimumab arm; the proportion of non-severe vomiting (PT) was 96% for the pembrolizumab arm and 94% for the ipilimumab arm. Hence the proportion of non-severe AEs was 89% or higher. The results of the symptoms “fatigue” as well as “nausea and vomiting” were allocated to the outcome category “non-serious/non-severe symptoms/late complications”.

Table 30: 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		
EORTC QLQ-C30 symptom scales – time to deterioration by at least 10 points		
Dyspnoea	Median: 86.0 vs. 84.0 days HR: 0.76 [0.53; 1.09] p = 0.133	Lesser benefit/added benefit not proven
Fatigue	Median: 43.0 vs. 24.0 days HR: 0.66 [0.49; 0.91] p = 0.010	Outcome category: non-serious/non-severe symptoms/late complications $0.90 \leq CI_u < 1.00$ Lesser benefit/added benefit not proven[c]
Insomnia	Median: 87.0 vs. 85.0 days HR: 0.77 [0.54; 1.11] p = 0.164	Lesser benefit/added benefit not proven
Pain	Median: 83.0 vs. 83.0 days HR: 0.95 [0.68; ND[d]] p = 0.746	Lesser benefit/added benefit not proven
Appetite loss	Median: 86.0 vs. 85.0 days HR: 0.82 [0.57; 1.19] p = 0.292	Lesser benefit/added benefit not proven
Diarrhoea	Median: 86.0 vs. 84.0 days HR: 0.71 [0.49; 1.03] p = 0.072	Lesser benefit/added benefit not proven
Nausea and vomiting	Median: 87.0 vs. 69.0 days HR: 0.67 [0.46; 0.97] p = 0.034	Outcome category: non-serious/non-severe symptoms/late complications $0.90 \leq CI_u < 1.00$ Lesser benefit/added benefit not proven[c]
Constipation	Median: 87.0 vs. 86.0 days HR: 0.84 [0.57; 1.23] p = 0.367	Lesser benefit/added benefit not proven

(continued)

Table 30: Extent of added benefit at outcome level: pembrolizumab vs. ipilimumab (treatment-naive patients with BRAF V600 wt 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]
Health status		
EQ-5D VAS	Mean change: −7.3 vs. −9.5 MD: 1.18 [−5.34; 7.70] p = 0.722	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: 84.0 vs. 83.0 days HR: 0.94 [0.67; 1.32] p = 0.718	Lesser benefit/added benefit not proven
Emotional functioning	Median: 87.0 vs. 85.0 days HR: 0.76 [0.51; 1.12] p = 0.166	Lesser benefit/added benefit not proven
Cognitive functioning	Median: 85.0 vs. 84.0 days HR: 0.98 [0.69; 1.38] p = 0.902	Lesser benefit/added benefit not proven
Physical functioning	Median: 86.0 vs. 83.0 days HR: 0.79 [0.56; 1.12] p = 0.719	Lesser benefit/added benefit not proven
Role functioning	Median: 84.0 vs. 46.0 days HR: 0.83 [0.60; 1.15] p = 0.258	Lesser benefit/added benefit not proven
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”
Adverse events		
SAEs	Median: NC vs. NC HR: 0.70 [0.44; 1.13] p = 0.145	Greater/lesser harm not proven
Severe AEs (CTCAE grade ≥ 3)	Median: NC vs. NC HR: 0.72 [0.43; 1.23] p = 0.228	Greater/lesser harm not proven
Discontinuation due to AEs	Median: NC vs. NC HR: 0.63 [0.29; 1.37] p = 0.240	Greater/lesser harm not proven

(continued)

Table 30: Extent of added benefit at outcome level: pembrolizumab vs. ipilimumab (treatment-naive patients with BRAF V600 wt tumour) (continued)

a: Probability provided if statistically significant differences are present that are 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.
d: The upper limit of the CI is cited as 0.32 in Module 4 B. Since this value is below the lower threshold, it is assumed that this was a transcription error, which cannot be verified, however.

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; 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 31 summarizes the results that were considered in the overall conclusion on the extent of added benefit.

Table 31: 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” (quality of life: social functioning)	

Overall, 2 positive effects of the same probability and the same extent remain.

There was a hint of a minor added benefit in the category “mortality” for the outcome “overall survival”. There was also a hint of a minor added benefit in the category “health-related quality of life” for the outcome “social functioning”.

In summary, there is a hint of a minor 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.

This deviates from the company’s approach, which, based on the total population of the KEYNOTE 006 study, derived an indication of major added benefit for patients with advanced (unresectable or metastatic) melanoma who are treatment-naive and whose tumour has no BRAF V600 mutation or who have been pretreated with a BRAF/MEK inhibitor or chemotherapy.

2.4.4 List of included studies (research question 2)

KEYNOTE 006

Merck Sharp & Dohme. A multicenter, randomized, controlled, three-arm, phase III study to evaluate the safety and efficacy of two dosing schedules of MK-3475 compared to ipilimumab in patients with advanced melanoma: study P006; clinical study report [unpublished]. 2015.

Merck Sharp & Dohme. A multi-center, randomized, controlled, three-arm, phase III study to evaluate the safety and efficacy of two dosing schedules of MK-3475 compared to ipilimumab in patients with advanced melanoma [online]. In: EU-Clinical Trials Register. [Accessed: 15 September 2015]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2012-004907-10.

Merck Sharp & Dohme. Study to evaluate the safety and efficacy of two different dosing schedules of pembrolizumab (MK-3475) compared to ipilimumab in participants with advanced melanoma (MK-3475-006/KEYNOTE-006): full text view [online]. In: ClinicalTrials.gov. 3 June 2015 [accessed: 15 September 2015]. URL: https://ClinicalTrials.gov/show/NCT01866319.

Robert C, Schachter J, Long GV, Arance A, Grob JJ, Mortier L et al. Pembrolizumab versus ipilimumab in advanced melanoma. N Engl J Med 2015; 372(26): 2521-2532.

2.5 Research question 3: treatment-naive patients with BRAF V600 mut tumour

2.5.1 Information retrieval and study pool (research question 3)

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 pembrolizumab (status: 1 June 2015)
- bibliographical literature search on pembrolizumab (last search on 18 May 2015)
- search in trial registries for studies on pembrolizumab (last search on 19 May 2015)

To check the completeness of the study pool:

- search in trial registries for studies on pembrolizumab (last search on 31 August 2015)

The company identified neither direct comparative studies nor studies for an indirect comparison for research question 3. No relevant direct comparative studies were identified from the check of completeness either.

2.5.2 Results on added benefit (research question 3)

There were no data for the assessment of the added benefit of pembrolizumab for treatment-naive patients with BRAF V600 mut tumour. The added benefit of pembrolizumab versus the ACT vemurafenib is therefore not proven for these patients.

2.5.3 Extent and probability of added benefit (research question 3)

Since no data were available, there was no proof of added benefit of pembrolizumab in comparison with the ACT vemurafenib specified by the G-BA for treatment-naive patients with a BRAF V600 mut tumour. Hence there are also no patient groups for whom a therapeutically important added benefit can be derived.

The company also derived no added benefit for this research question.

2.5.4 List of included studies (research question 3)

Not applicable as no studies were included in the benefit assessment.

2.6 Extent and probability of added benefit – summary

The result of the assessment of the added benefit of pembrolizumab in comparison with the ACT is summarized in Table 32.

Table 32: Pembrolizumab – extent and probability of added benefit

Research question	Therapeutic indication	ACT[a]	Subpopulation	Extent and probability of added benefit
1	Pretreated patients	Individual treatment specified by the treating physician under consideration of the approval status and the respective prior therapy	Pretreated patients for whom ipilimumab is the adequate treatment	Indication of considerable added benefit
			Pretreated patients for whom ipilimumab is not the adequate treatment	Added benefit not proven
2	Treatment-naive patients with BRAF V600 wt tumour	Dacarbazine or **ipilimumab**	-	Hint of minor added benefit
3	Treatment-naive patients with BRAF V600 mut tumour	Vemurafenib	-	Added benefit not proven

a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the choice of the company is printed in bold.

ACT: appropriate comparator therapy; BRAF: serine/threonine-protein kinase B-Raf (rapidly accelerated fibrosarcoma – isoform B); BRAF V600 mut: BRAF V600 mutant; BRAF V600 wt: BRAF V600 wild type; G-BA: Federal Joint Committee

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

References for English extract

Please see full dossier assessment for full reference list.

1. Institute for Quality and Efficiency in Health Care. General Methods: version 4.2 [online]. 22 April 2015 [accessed: 20 October 2015]. URL: https://www.iqwig.de/download/IQWiG_General_Methods_Version_%204-2.pdf.

2. Skipka G, Wieseler B, Kaiser T, Thomas S, Bender R, Windeler J et al. Methodological approach to determine minor, considerable, and major treatment effects in the early benefit assessment of new drugs. Biom J 2015; 58(1): 43-58

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4. European Medicines Agency. Keytruda: European public assessment report [online]. 21 May 2015 [accessed: 20 August 2015]. URL: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/003820/WC500190992.pdf.

5. Bristol-Myers Squibb. Yervoy 5 mg/ml Konzentrat zur Herstellung einer Infusionslösung: Fachinformation [online]. June 2015 [accessed: 16 September 2015]. URL: http://www.fachinfo.de.

The full report (German version) is published under https://www.iqwig.de/de/projekte-ergebnisse/projekte/arzneimittelbewertung/a15-33-pembrolizumab-nutzenbewertung-gemaess-35a-sgb-v-dossierbewertung.6907.html.