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Pembrolizumab (melanoma) –

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

Extract

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

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
AJCC	American Joint Committee on Cancer
BRAF	BRAF: rapidly accelerated fibrosarcoma – isoform B
CT	CT: computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	CTLA-4: cytotoxic T-lymphocyte-associated antigen 4
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
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MEK	mitogen-activated extracellular signal-regulated kinase
MRI	magnetic resonance imaging
PD-L1	Programmed Death-Ligand 1
PT	Preferred Term
RFS	recurrence-free survival
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SOC	System Organ Class
SPC	Summary of Product Characteristics
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 29 March 2019.

Research question

The aim of the present report was to assess the added benefit of pembrolizumab as monotherapy in comparison with "watchful waiting" as appropriate comparator therapy (ACT) in the adjuvant treatment of adults with stage III melanoma and lymph node involvement after complete resection.

Table 2: Research question of the benefit assessment of pembrolizumab

Subindication	**ACT**[a]
Adjuvant treatment of adults with stage III[b] melanoma and lymph node involvement after complete resection	Watchful waiting[c]
a: Presentation of the respective ACT specified by the G-BA. b: By AJCC classification. c: The G-BA did not further specify the ACT "watchful waiting". For information on the definition of the ACT in the present assessment, see Section 2.3.2 ACT: appropriate comparator therapy; AJCC: American Joint Committee on Cancer; G-BA: Federal Joint Committee	

The company followed the G-BA's specification on the ACT.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier.

Results

Study pool and study characteristics

One relevant study (KEYNOTE-054) was available for the benefit assessment. The KEYNOTE-054 study is an ongoing, randomized, double-blind, placebo-controlled multicentre study. Adult patients with completely resected, histologically confirmed stage III cutaneous melanoma (according to version 7 of the classification by the American Joint Committee on Cancer [AJCC]) and lymph node involvement were included in the study. Patients with in transit or satellite metastases, patients with disease stage IIIA according to AJCC 7 classification with lymph node metastasis ≤ 1 mm as well as patients with general condition corresponding to an Eastern Cooperative Oncology Group Performance Status (ECOG PS) > 1

were excluded from the study. There were no data for these patients, although they were comprised by the approval.

The study included a total of 1019 patients, randomized in a 1:1 ratio either to treatment with pembrolizumab (N = 514) or placebo (N = 505).

The KEYNOTE-054 study is divided into 2 parts. Part 1 comprises the initially adjuvant treatment and the subsequent observation period until the patient possibly proceeds to part 2 of the study. Part 2 of the study comprises possible treatment with pembrolizumab after occurrence of recurrence and the subsequent observation period. For all outcomes, the company only presented analyses on part 1 of the study.

Treatment of patients in part 1 of the study was performed in accordance with the Summary of Product Characteristics (SPC), except for the treatment duration. The SPC specifies a maximum treatment duration of 1 year, while treatment in the KEYNOTE-054 study was 1 year or 18 doses; therefore, treatment could also exceed 1-year duration. However, based on the available data on the treatment duration it is assumed that this fact has no relevant impact on the present benefit assessment.

During and after treatment, the patients were closely examined for recurrences (see Section on the ACT below). After occurrence of recurrence, both patients and the respective treating physician were unblinded. These patients could participate in part 2 of the study under certain conditions and could receive pembrolizumab as subsequent therapy within this framework.

The primary outcome of the study was “recurrence-free survival” (RFS). Patient-relevant secondary outcomes were overall survival, symptoms, health status, health-related quality of life, and side effects.

Data cut-offs

The KEYNOTE-054 study is currently ongoing. Due to the longer observation period, the second data cut-off (2 May 2018) was used for the outcome “recurrence” in the present benefit assessment. For all other outcomes, only analyses on the first data cut-off (2 October 2017) were available.

At the second data cut-off, the majority of the study population had only been observed for the occurrence of recurrence over a period from 1.5 to 2.75 years. The high-risk period for the occurrence of recurrence was thus not completely covered in the present therapeutic indication (3 years following primary diagnosis). Data for the period following treatment were limited.

Implementation of the ACT “watchful waiting”

The examinations performed in the KEYNOTE-054 study do not fully comply with the recommendations of the S3 guideline. In the KEYNOTE-054 study, patients were examined closely and specifically for the detection of recurrences, the examination regiment applied in

the KEYNOTE-054 study was thus considered to be a sufficient approximation to the ACT "watchful waiting".

Risk of bias

The risk of bias at study level and for the results on the outcomes "recurrence" and "discontinuation due to AEs" was rated as low. The risk of bias was rated as high for all other results of the outcomes used in the benefit assessment for which usable data were available. However, due to other aspects, the certainty of results was only moderate for the results on the outcomes "recurrence" and "discontinuation due to AEs". Therefore, at most hints, e.g. of an added benefit, could be derived for all outcomes.

Mortality

Overall survival

The KEYNOTE-054 study is currently ongoing. According to the study protocol, no interim analysis was planned for the outcome "overall survival". A final analysis is planned to take place after a total of 380 deaths. At the time point of the first data cut-off (2 October 2017), 25 patients in the pembrolizumab arm and 35 patients in the placebo arm had died.

Morbidity

Recurrence

A statistically significant difference in favour of pembrolizumab in comparison with placebo was shown between the treatment groups for the outcome "recurrence" (second data cut-off: 2 May 2018). This resulted in a hint of an added benefit of pembrolizumab in comparison with the ACT "watchful waiting" for the outcome "recurrence".

The result on "RFS", which was presented as supplementary information, also showed a statistically significant difference in favour of pembrolizumab in comparison with placebo between the treatment groups (second data cut-off: 2 May 2018).

Symptoms

There are no usable analyses for symptoms, measured with the symptom scales of the cancer-specific instrument European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30). This resulted in no hint of an added benefit of pembrolizumab in comparison with the ACT "watchful waiting"; an added benefit is therefore not proven.

Health status (European Quality of Life-5 Dimensions [EQ-5D] visual analogue scale [VAS])

The dossier contained no evaluable data for the outcome "health status" measured with the EQ-5D VAS. This resulted in no hint of an added benefit of pembrolizumab in comparison with the ACT "watchful waiting"; an added benefit is therefore not proven.

Health-related quality of life

EORTC QLQ-C30 (functional scales and global health status" scale)

There are no usable analyses for "health-related quality of life", recorded with the functional scales and with the scale for recording the global health status of the cancer-specific instrument EORTC QLQ-C30. This resulted in no hint of an added benefit of pembrolizumab in comparison with the ACT "watchful waiting"; an added benefit is therefore not proven.

Side effects

Serious adverse events (SAEs), severe adverse events (severe AEs) (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3) and discontinuation due to AEs

A statistically significant difference to the disadvantage of pembrolizumab in comparison with placebo was shown between the treatment groups for SAEs, severe AEs (CTCAE grade ≥ 3) and discontinuation due to adverse events (AEs). This resulted in one hint of greater harm each from pembrolizumab in comparison with the ACT "watchful waiting".

Specific AEs

- Immune-related AEs

  A statistically significant difference to the disadvantage of pembrolizumab in comparison with placebo was shown between the study arms for immune-related AEs. However, there is an effect modification by the characteristic "Programmed Death-Ligand 1 (PD-L1) expression status". This resulted in no hint of greater or lesser harm for patients with a negative PD-L1 expression status; greater or lesser harm for these patients is therefore not proven. For patients with a positive PD-L1 expression status, there is a hint of greater harm from pembrolizumab in comparison with the ACT "watchful waiting".

- Serious immune-related AEs and severe immune-related AEs (CTCAE grade ≥ 3)

  A statistically significant difference to the disadvantage of pembrolizumab in comparison with placebo was shown between the treatment groups for "serious immune-related AEs" and "severe immune-related AEs (CTCAE grade ≥ 3)". This resulted in one hint of greater harm each from pembrolizumab in comparison with the ACT "watchful waiting".

- SAEs/severe AEs (CTCAE grade ≥ 3): general disorders and administration site conditions (System Organ Class [SOC], SAE), gastrointestinal disorders (SOC, severe AE [CTCAE grade ≥ 3]) and respiratory, thoracic and mediastinal disorders (SOC, severe AE [CTCAE grade ≥ 3])

  There is a statistically significant difference to the disadvantage of pembrolizumab in comparison with placebo between the treatment groups for the outcomes "general disorders and administration site conditions (SOC, SAE)", "gastrointestinal disorders (SOC, severe AE [CTCAE grade ≥ 3])" and "respiratory, thoracic and mediastinal disorders (SOC, severe AE [CTCAE grade ≥ 3])". This resulted in one hint of greater harm each from pembrolizumab in comparison with the ACT "watchful waiting".

- AEs: “infections and infestations (SOC)”, “skin and subcutaneous tissue disorders (SOC)”, “dry mouth (preferred term [PT])”, “dyspepsia (PT)”, “decreased appetite (PT)”, “musculoskeletal pain (PT)” and “dyspnoea (PT)”

  There is a statistically significant difference to the disadvantage of pembrolizumab in comparison with placebo between the treatment groups for the outcomes “infections and infestations (SOC)”, “skin and subcutaneous tissue disorders (SOC)”, “dry mouth (PT)”, “dyspepsia (PT)”, “decreased appetite (PT)”, “musculoskeletal pain (PT)” and “dyspnoea (PT)”. This resulted in one hint of greater harm each from pembrolizumab in comparison with the ACT “watchful waiting”.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

On the basis of the results presented, the extent and probability of the added benefit of the drug pembrolizumab compared with the ACT is assessed as follows:

The overall assessment showed one positive and several negative effects of pembrolizumab in comparison with “watchful waiting”.

A hint of major added benefit was shown for the outcome “recurrence”. This was offset by several negative effects: With regard to serious/severe side effects, there were several hints of greater harm with extents up to “major”. For non-serious/non-severe side effects, there are also several hints of greater harm, partly in subgroups; the extents are up to “considerable”. There are no usable analyses on “health-related quality of life”, “symptoms” and “health status”. The negative effects did not completely outweigh the advantage in recurrence, but resulted in a downgrading of the extent of the added benefit.

In summary, there is a hint of considerable added benefit of pembrolizumab versus the ACT “watchful waiting” for patients with completely resected stage III melanoma with lymph node involvement.

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

[3] 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, added benefit not proven, or less benefit). For further details see [1,2].

Table 3: Pembrolizumab – extent and probability of added benefit

Subindication	**ACT[a]**	**Probability and extent of added benefit**
Adjuvant treatment of adults with stage III[b] melanoma and lymph node involvement after complete resection[c]	Watchful waiting	Hint of considerable added benefit

a: Presentation of the respective ACT specified by the G-BA.
b: By AJCC classification.
c: In accordance with the approval, the therapeutic indication to be assessed comprised patients with stage III disease and lymph node involvement after complete resection. However, the KEYNOTE-054 study only included patients with stage IIIa lymph node metastasis > 1 mm. Patients with in transit or satellite metastases were excluded from the study. Hence, the study population does not completely cover the therapeutic indication. It is unclear whether the observed effects can be transferred to patients with in transit or satellite metastases. Moreover, it is unclear whether the observed effects can be transferred to patients with lymph node metastasis ≤ 1 mm and stage IIIA disease according to AJCC 7 classification; according to the current AJCC 8 classification, patients who had been allocated to stage IIIA pursuant to AJCC 7 classification can also have other disease stages (IIIA or IIIB or IIIC).
ACT: appropriate comparator therapy; AJCC: American Joint Committee on Cancer; G-BA: Federal Joint Committee

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

2.2 Research question

The aim of the present report was to assess the added benefit of pembrolizumab as monotherapy in comparison with watchful waiting as ACT in the adjuvant treatment of adults with stage III melanoma and lymph node involvement after complete resection.

Table 4: Research question of the benefit assessment of pembrolizumab

Subindication	**ACT[a]**
Adjuvant treatment of adults with stage III[b] melanoma and lymph node involvement after complete resection	Watchful waiting[c]

a: Presentation of the respective ACT specified by the G-BA.
b: By AJCC classification.
c: The G-BA did not further specify the ACT “watchful waiting”. For information on the definition of the ACT in the present assessment, see Section 2.3.2.
ACT: appropriate comparator therapy; AJCC: American Joint Committee on Cancer; G-BA: Federal Joint Committee

The company followed the G-BA’s specification on the ACT.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier.

2.3 Information retrieval and study pool

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

Sources of the company in the dossier:

- study list on pembrolizumab (status: 11 January 2019)
- bibliographical literature search on pembrolizumab (last search on 11 January 2019)
- search in trial registries for studies on pembrolizumab (last search on 10 January 2019)

To check the completeness of the study pool:

- search in trial registries for studies on pembrolizumab (last search on 3 April 2019)

The check identified no additional relevant study.

2.3.1 Studies included

The study listed in the following Table 5 was included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: pembrolizumab vs. watchful waiting

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-054	Yes	Yes	No
a: Study sponsored by the company. RCT: randomized controlled trial; vs.: versus			

Section 2.6 contains a reference list for the study included.

2.3.2 Study characteristics

Table 6 and Table 7 describe the study used for the benefit assessment.

Table 6: Characteristics of the study included – RCT, direct comparison: pembrolizumab vs. placebo

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
KEYNOTE-054	RCT, double-blind, parallel	Adults with completely resected[d], histologically confirmed stage III[b] cutaneous melanoma and lymph node involvement[c]. Only patients with ECOG PS 0 or 1 were included:	Pembrolizumab (N = 514) placebo (N = 505)	Screening: up to 8 weeks Treatment[e]: 1 year or 18 doses, or until recurrence, unacceptable toxicity, occurrence of a new malignant disease, treatment discontinuation following the physician's or patients decision Observation[e, f]: outcome-specific, at most until death, discontinuation of participation in the study or end of study	134 centres in: Australia, Austria, Belgium, Canada, Denmark, Finland, France, Germany, Israel, Italy, Japan, Netherlands, New Zealand, Norway, Poland, Portugal, Russia, Serbia, Spain, Sweden, Switzerland, United Kingdom, USA 07/2015[g]–ongoing Data cut-offs[h]: ▪ 2 October 2017 ▪ 2 May 2018	primary: RFS Secondary: overall survival, symptoms, health status, health-related quality of life, AEs

a: Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes only include information on relevant available outcomes for this benefit assessment.
b: By AJCC classification version 7 [3]. Patients with stage IIIA disease and lymph node metastasis ≤ 1 mm were excluded from the study.
c: Patients with in transit or satellite metastases were excluded from the study.
d: The time point of resection had to be at most 13 weeks prior to the first treatment with the study medication.
e: Information only refers to part 1 of the study. According to the study protocol, the patients in the pembrolizumab or placebo arm could, under certain circumstances, receive pembrolizumab (again) after occurrence of recurrence (part 2 of the study).
g: Outcome-specific information is provided in Table 9.
g: Discrepant information in Module 5; it is unclear whether the first visit of the first patient took place on 22 June 2015 or on 22 July 2015.
h: Originally, an interim analysis had not been planned in the study protocol. Protocol version 6.0 introduced the performance of an interim analysis for the outcome "RFS" after ~ 330 RFS events (first data cut-off: 2 October 2017). Within the framework of the approval procedure, the EMA subsequently requested the second data cut-off of 2 May 2018 for the outcome "RFS".

AE: adverse event; AJCC: American Joint Committee on Cancer; ECOG PS: Eastern Cooperative Oncology Group Performance Status; EMA: European Medicines Agency; N: number of randomized patients; RCT: randomized controlled trial; RFS: "recurrence-free survival"; vs.: versus

Table 7: Characteristics of the interventions – RCT, direct comparison: pembrolizumab vs. placebo

Study	Intervention	Comparison
KEYNOTE-054	Pembrolizumab 200 mg every 3 weeks, IV infusion	Placebo, every 3 weeks, IV infusion
	Treatment interruptions up to treatment discontinuations due to AEs were permitted	
	Permitted pretreatment: ▪ completed radiotherapy after lymph node dissection ≤ 13 weeks after surgery and before start of study medication ▪ melanoma surgery ▪ previous interferon therapy for the treatment of primary melanomas with larger tumour thickness without lymph node involvement **Non-permitted pretreatment:** ▪ antibodies against CTLA4, PD-1, PD-L1 or PD-L2 ▪ systemic steroid therapy or other immunosuppressive therapies ≤ 7 days before start of the study medication **Permitted concomitant treatment:** ▪ supportive treatment **Concomitant treatment prohibited:** ▪ other anticancer therapies ▪ immunosuppressants (except for the treatment of immune-related AEs) ▪ systemic corticosteroids, except for the treatment of endocrinopathies that occur in the course of the study and require hormone replacement therapy ▪ live vaccines ≤ 30 days before the first study medication and during the study	

AE: adverse event; CTLA-4: cytotoxic T-lymphocyte-associated antigen 4; IV: intravenously; 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

The KEYNOTE-054 study is an ongoing, randomized, double-blind, placebo-controlled multicentre study. Adult patients with completely resected, histologically confirmed stage III cutaneous melanoma (according to version 7 of the classification by the AJCC) [3] and lymph node involvement were included in the study. Patients with in transit or satellite metastases, patients with disease stage IIIA and lymph node metastasis ≤ 1 mm as well as patients with general condition corresponding to an ECOG PS > 1 were excluded from the study. There were no data for these patients, although they were comprised by the approval [4,5].

It is unclear whether the observed effects can be transferred to patients with in transit or satellite metastases as well as to patients with lymph node metastasis ≤ 1 mm and stage IIIA disease according to AJCC 7 classification; according to the current AJCC 8 classification, patients who had been allocated to stage IIIA pursuant to AJCC 7 classification can also have other disease stages (IIIA or IIIB or IIIC) [6].

Further criteria for study inclusion were a maximum period of 13 weeks between the last resection and the start of the study medication as well as the availability of tumour material for the testing of the Programmed Cell Death-Ligand 1 (PD-L1) expression. Radiotherapy after lymph node dissection was permitted as pre-treatment. However, this treatment had to be completed before the start of the study medication.

The study included a total of 1019 patients, randomized in a 1:1 ratio either to treatment with pembrolizumab (N = 514) or placebo (N = 505). Randomization was stratified by disease stage (IIIA, IIIB, IIIC [1-3 positive lymph nodes], IIIC [≥ 4 positive lymph nodes] according to AJCC version 7) and geographical region (North America, Europe, Australia, other).

The KEYNOTE-054 study is divided into 2 parts. Part 1 comprises the initially adjuvant treatment and the subsequent observation period until the patient possibly proceeds to part 2 of the study. Part 2 of the study comprises possible treatment with pembrolizumab after occurrence of recurrence and the subsequent observation period. For all outcomes, the company only presented analyses on part 1 of the study.

Treatment of patients in part 1 of the study was performed in accordance with the regimen described in Table 7. The SPC specifies a maximum duration of 1 year for adjuvant melanoma treatment [4,5]. However, treatment in the KEYNOTE-054 study comprised 1 year or 18 doses. The study report shows that 66 patients (13%) in the pembrolizumab arm and 72 patients (14%) in the placebo arm were treated for 1 year or longer. At the time point of the first data cut-off (2 October 2017), maximum treatment duration was 15.7 months in the pembrolizumab arm and 13.9 months in the placebo arm. Overall, it can be assumed that relatively few patients were treated for longer than 1 year, so that this does not have any relevant impact on the present benefit assessment.

During and after treatment, the patients were closely examined for recurrences (see Section on the ACT below). After occurrence of recurrence, both patients and the respective treating physician were unblinded. These patients could participate in part 2 of the study under certain conditions and could receive pembrolizumab as subsequent therapy within this framework. Patients from the pembrolizumab arm could only receive pembrolizumab as follow-up therapy if they had previously received adjuvant therapy for 1 year and the recurrence occurred within a period of > 6 months after the end of adjuvant treatment. These restrictions did not apply to patients in the placebo arm.

At the time point of the first data cut-off (2 October 2017), 1 patient (0.2%) in the pembrolizumab arm and 109 patients (21.6%) in the placebo arm had proceeded to part 2 of the study. No corresponding data were available at the time point of the second data cut-off (2 May 2018). At that time, a total of 107 patients (20.8%) in the pembrolizumab arm and 220 patients (43.6%) in the placebo arm had received follow-up therapy. The majority of follow-up therapies in the placebo arm consisted of anti-PD1/anti-PD-L1 antibody (152 or 30.1%, 147 or 29.1% of which pembrolizumab). In the pembrolizumab arm, the majority of the follow-up therapies

were equally distributed to treatment with an anti-CTLA4 antibody (30 or 5.8%), a rapidly accelerated fibrosarcoma – isoform B (BRAF) inhibitor (25 or 4.9%), an anti-PD-1/anti-PD-L1 antibody (20 or 3.9%) and a mitogen-activated extracellular signal-regulated kinase (MEK) inhibitor (11 or 2.1%). Appendix A of the full dossier assessment shows a detailed list of the systemic follow-up therapies. Data on subsequent local therapies such as resection and radiotherapy are not available.

The primary outcome of the study was "RFS". Patient-relevant secondary outcomes were overall survival, symptoms, health status, health-related quality of life, and side effects.

Data cut-offs

The company presented 2 data cut-offs in the dossier:

- First data cut-off: 2 October 2017
- Second data cut-off: 2 May 2018 (for the outcomes "RFS" and "time to first subsequent therapy)"

The KEYNOTE-054 study is currently ongoing. Originally, an interim analysis had not been planned in the study protocol. Protocol version 6.0 (of 2 October 2017) introduced the performance of an interim analysis for the outcome "RFS" after ~ 330 RFS events (first data cut-off: 2 October 2017). Within the framework of the approval procedure, the EMA subsequently requested the second data cut-off of 2 May 2018 for the outcome "RFS".

At the second data cut-off, the majority of the study population had only been observed for the occurrence of recurrence over a period from 1.5 to 2.75 years. The high-risk period for the occurrence of recurrence was thus not completely covered in the present therapeutic indication (3 years following primary diagnosis) (see Section 2.7.4.3.3 of the full dossier assessment).

ACT

Operationalisation of the ACT "watchful waiting"

For the present benefit assessment, the ACT "watchful waiting" was operationalized as a follow-up strategy which particularly comprises diagnosis of the recurrences in accordance with S3-guideline "diagnosis, therapy and follow-up of melanoma" [7].

The S3-guideline specifies a risk-adapted follow-up, i.e. under consideration of factors like time since primary diagnosis and disease stage according to AJCC classification. The S3-guideline recommends patients in the therapeutic indication of the present assessment to undergo the diagnostic tests presented in Table 8 in addition to a regular targeted self-examination for the early detection of recurrences.

Table 8: Follow-up scheme of the routine diagnosis recommended by the S3-guideline[a]

	Time since primary diagnosis		
Examination	Year 1–3	Year 4 + 5	Year 6–10
Physical examination	every 3 months	every 3 months	every 6 months
Imaging examinations[b]	every 6 months	-[c]	-[c]
Lymph node sonography	every 3 months	every 6 months	-[c]
Tumour marker S100B	every 3 months	every 6 months	-[c]

a: See reference [7].
b: Cross-sectional imaging (CT or MRI).
c: A general recommendation for routine performance was not indicated.
CT: computed tomography; MRI: magnetic resonance imaging

Implementation of the ACT "watchful waiting" in the KEYNOTE-054 study

The comparator arm of the KEYNOTE-054 study was a sufficient approximation to the ACT "watchful waiting". This is explained below:

The following examinations for the assessment of the health status or the detection of recurrences were performed in the KEYNOTE-054 study:

- Physical examination
- CT and/or MRI of thoracic, abdominal and pelvic area; possibly CT/MRI of the neck area (in case of primary melanoma in the head and neck area); further CTs and/or MRIs according to clinical indication
- Histological/cytological examination in case of suspected recurrence

Physical examination was performed every 6 weeks during the treatment phase, then every 12 weeks until occurrence of a recurrence. A CT/MRI of the thoracic, abdominal and pelvic area was performed every 12 weeks in the first two years, every 6 months in the years 3 to 5, and thereafter annually until occurrence of a recurrence. Subcutaneous metastasis and lymph node metastasis were to be documented using ultrasound technology. A histological/cytological confirmation should be performed for each recurrence, except for brain metastases. After occurrence of a recurrence, only patients who had proceeded to part 2 of the study underwent further systematic examination for disease progression/second recurrence. In the other patients, information on follow-up therapies and subsequent health status should be requested.

The examinations performed in the KEYNOTE-054 study do not fully comply with the recommendations of the S3 guideline. However, in the KEYNOTE-054 study, patients were closely and specifically examined for recurrences; the examination regiment applied in the KEYNOTE-054 study was thus considered to be a sufficient approximation to the ACT "watchful waiting" described above.

Planned duration of follow-up observation

Table 9 shows the planned follow-up observation period of the patients for the individual outcomes.

Table 9: Planned duration of follow-up – RCT, direct comparison: pembrolizumab vs. placebo

Study **Outcome category** **Outcome**	**Planned follow-up observation**
KEYNOTE-054	
Mortality	
Overall survival	every 12 weeks from the end of the adjuvant therapy or the occurrence of a recurrence until death, withdrawal of consent, loss to follow-up or end of study
Morbidity	
RFS	every 12 weeks in the first two years, then every 6 months for 3 years, then annually until occurrence of a recurrence, death, withdrawal of consent, loss to follow-up or end of study
Symptoms (EORTC QLQ-C30)	every 12 weeks for 2 years, then every 6 months for a further 2-year period
Health status (EQ-5D VAS)	every 12 weeks for 2 years, then every 6 months for a further 2-year period
Health-related quality of life (EORTC QLQ-C30)	every 12 weeks for 2 years, then every 6 months for a further 2-year period
Side effects	
AEs	up to 30 days after treatment discontinuation or end of treatment
SAEs	until 90 days after treatment discontinuation or end of treatment, or until 30 days after treatment discontinuation if a new anticancer treatment is initiated

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; RFS: recurrence-free survival; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

In the KEYNOTE-054 study, monitoring of symptoms, health status and health-related quality of life was not to be performed over the entire study duration, but up to 4 years after randomization. However, the company only presented analyses on part 1 of the study; available recordings from part 2 of the study and thus recordings on a prolonged monitoring period remained unconsidered in the company's analysis (see Section 2.7.4.3.2 of the full dossier assessment).

The monitoring periods for side effects were systematically shortened, because they were only recorded for the time of treatment with the study medication (plus 30 days for AEs or 90 days for SAEs). To be able to draw a reliable conclusion on the total study period or the time until death of the patients, it would be necessary, however, to record these outcomes over the total period of time, as was the case for "survival".

Patient characteristics

Table 10 shows the characteristics of the patients in the study included.

Table 10: Characteristics of the study population – RCT, direct comparison: pembrolizumab vs. placebo

Study Characteristics Category	Pembrolizumab	Placebo[a]
KEYNOTE-054	N = 514	N = 505
Age [years], mean (SD)	54 (14)	54 (14)
< 50, n (%)	193 (38)	186 (37)
50-64, n (%)	196 (38)	193 (38)
65-74, n (%)	97 (19)	98 (19)
≥ 75, n (%)	28 (5)	28 (6)
Sex [F/M], %	37/63	40/60
Geographical region, n (%)		
North America	38 (7)	37 (7)
Europe	341 (66)	336 (67)
Australia/New Zealand	111 (22)	112 (22)
Other	24 (5)	20 (4)
Disease stage according to AJCC 7 classification[b], n (%)		
IIIA	80 (16)	80 (16)
IIIB	237 (46)	230 (46)
IIIC (1-3 positive lymph nodes)	95 (18)	93 (18)
IIIC (≥ 4 positive lymph nodes)	102 (20)	102 (20)
PD-L1 expression status[c], n (%)		
Positive	428 (83)	425 (84)
Negative	59 (11)	57 (11)
Unknown	27 (5)	23 (5)
BRAF mutation status, n (%)		
Positive	245 (48)	262 (52)
Negative	233 (45)	214 (42)
Unknown	36 (7)	29 (6)
ECOG PS, n (%)		
0	485 (94)	475 (94)
1	29 (6)	30 (6)
Disease duration: time from first diagnosis to randomization	ND[d]	ND[d]
Treatment discontinuation, n (%)	209 (41)[e]	204 (40)[f]
Study discontinuation, n (%)	ND	ND

(continued)

Table 10: Characteristics of the study population – RCT, direct comparison: pembrolizumab vs. placebo (continued)

a: Sufficient approximation to the ACT "watchful waiting" (see Section 2.3.2).
b: Information on the staging according to AJCC 8 classification was not available.
c: Samples in which IHC membrane staining of the tumour cells and tumour-associated immune cells was ≥ 1% were regarded as PD-L1 positive.
d: According to the study protocol, the time point of the last resection had to be at most 13 weeks prior to the first study medication.
e: The most common reasons for treatment discontinuation in the pembrolizumab arm were occurrence of recurrences in 110 (21.4%) or occurrence of AEs in 70 (13.6%) of the patients.
f: The most frequent reasons for treatment discontinuation in the placebo arm were occurrence of recurrences in 180 (35.6%) or occurrence of AEs in 11 (2.2%) of the patients.

ACT: appropriate comparator therapy; AE: adverse event; AJCC: American Joint Committee on Cancer; BRAF: rapidly accelerated fibrosarcoma – isoform B (serine/threonine-protein kinase B-Raf); ECOG PS: Eastern Cooperative Oncology Group Performance Status; F: female; IHC: immunohistochemical; M: male; n: number of patients in the category; N: number of randomized patients; ND: no data; PD-L1: programmed cell death ligand 1; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

The demographic and clinical characteristics of the patients in both treatment arms were largely comparable. The mean age of the patients was 54 years, and the majority was male. According to AJCC classification version 7 [3], which had been valid at the time of randomization, the number of patients in the individual stages of disease was comparable in both treatment arms. Thus, 16% of the patients had stage IIIA disease at the time point before resection, 46% had stage IIIB disease, 18% had stage IIIC disease (1-3 positive lymph nodes) and 20% had disease stage IIIC (≥ 4 positive lymph nodes). Data on the distribution according to the current AJCC 8 classification were not available [6]. At the time point of randomization, the majority of the patients (94%) had an ECOG PS of 0.

The number of patients with treatment discontinuation were comparable in both treatment arms. 21.4% of the patients in the pembrolizumab arm discontinued treatment due to a recurrence, and 13.6% due to AEs, whilst 35.6% of the patients in the placebo arm discontinued treatment due to a recurrence and 2.2% due to AEs.

Data on the comparability of the disease duration as well as of the number of patients who discontinued the study between the two treatment arms were not available.

Treatment duration and observation period

Table 11 shows the mean/median treatment duration of the patients and the mean/median observation period for individual outcomes.

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

Study **Duration of the study phase** **Outcome category**	**Pembrolizumab**	**Placebo**[a]
KEYNOTE-054	N = 509	N = 502
Treatment duration [days] (first data cut-off: 2 October 2017)		
Median [min; max]	357 [1; 478]	357 [1; 424]
Mean (SD)	282 (120)	275 (123)
Observation period [days]		
Recurrence[b]: (second data cut-off on 2 May 2018)	ND	ND
Symptoms, health status, health-related quality of life (first data cut-off 2 October 2017)	ND	ND
Side effects (first data cut-off: 2 October 2017)		
AEs		
Median [min; max]	375 [21; 780]	387 [21; 448]
Mean (SD)	290 (128)	304 (124)
SAEs		
Median [min; max]	393 [21; 900]	418 [21; 508]
Mean (SD)	335 (132)	347 (131)

a: Sufficient approximation to the ACT "watchful waiting" (see Section 2.3.2).
b: At the time point of the first data cut-off of 2 October 2017, the median observation period from the time point of randomization until death or data cut-off was [min; max]: 16.0 [4.4; 25.3] months in the pembrolizumab arm and 16.0 [2.5; 24.7] months in the placebo arm. The mean (SD) was: 16.3 (3.3) months in the pembrolizumab arm and 16.2 (3.4) months in the placebo arm.
ACT: appropriate comparator therapy; AE: adverse event; max: maximum; min: minimum; N: study population as treated (allocation according to actually received study medication); ND: no data; RCT: randomized controlled trial; SAE: serious adverse event; SD: standard deviation; vs.: versus

In both treatment arms, the median treatment time of the patients was 357 days. Minor differences in the median observation period were shown for "side effects". Data on the observation period for the outcomes "recurrence" (second data cut-off: 2 May 2018), "symptoms", "health status" and "health-related quality of life" were not available. At the time point of the first data cut-off of 2 October 2017, the median observation period from the time point of randomization until death or data cut-off was 16.0 months in both treatment arms.

Risk of bias across outcomes (study level)

Table 12 shows the risk of bias across outcomes (risk of bias at study level).

Table 12: Risk of bias across outcomes (study level) – RCT, direct comparison: pembrolizumab vs. placebo

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patients	Treating staff			
KEYNOTE-054	Yes	Yes	Yes	Yes	Yes	Yes	Low
RCT: randomized controlled trial; vs.: versus							

The risk of bias across outcomes was rated as low for the KEYNOTE-054 study. This concurs with the company's assessment.

2.4 Results on added benefit

2.4.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment (for reasons, see Section 2.7.4.3.2 of the full dossier assessment):

- Mortality
  - overall survival
- Morbidity
  - recurrence
  - symptoms, recorded with the EORTC QLQ-C30 symptom scales
  - health status measured with the EQ-5D visual analogue scale
- health-related quality of life
  - health-related quality of life, measured with EORTC QLQ-C30 (functional scales and global health status scale)
- Side effects
  - SAEs
  - severe AEs (CTCAE-grade ≥ 3)
  - discontinuation due to AEs
  - immune-related AEs
  - serious immune-related AEs
  - severe immune-related AEs (CTCAE grade ≥ 3)

- Further specific AEs

The choice of patient-relevant outcomes deviated from that of the company, which additionally used “time to first subsequent therapy” as outcome in the dossier (Module 4 A). In the present benefit assessment, analyses on the proportion of patients with events were used for the outcome “recurrence” (see Section 2.7.4.3.2 of the full dossier assessment), whilst the company considered an event time analysis (“RFS”). Besides immune-related AEs, serious immune-related AEs and severe immune-related AEs (CTCAE grade ≥ 3), the company used no further specific AEs.

In its dossier, the company presented analyses on the first data cut-off for all outcomes that were relevant for the present benefit assessment. The dossier shows results for the outcome “recurrence” at both the first and the second data cut-off (see Section 2.3.2). In the present benefit assessment, the second data cut-off was used for the outcome “recurrence”, because the observation period was longer and because at this time point the number of observed events corresponded approximately to the number of events originally planned for the final evaluation of recurrences. For the outcomes on side effects, the available evaluations on the first data cut-off were used. For the remaining outcomes, there were no usable data (see Section 2.7.4.3.2 of the full dossier assessment).

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

Table 13: Matrix of outcomes – RCT, direct comparison: pembrolizumab vs. placebo

Study	Outcomes											
	Overall survival	**Recurrence[a]**	**Symptoms (EORTC QLQ-C30)**	**Health status (EQ-5D VAS)**	**Health-related quality of life (EORTC QLQ-C30)**	**SAEs**	**Severe AEs (CTCAE grade ≥ 3)**	**discontinuation due to AEs**	**Immune-related adverse events**	**Serious immune-related AEs**	**Severe immune-related AEs (CTCAE grade ≥ 3)**	**Further specific AEs[b]**
KEYNOTE-054	No[c]	Yes	No[d]	No[d]	No[d]	Yes	Yes	Yes	Yes	Yes	Yes	Yes

a: Proportion of patients with local/regional recurrence, distant metastases or death due to any cause (see Section 2.7.4.3.2 of the full dossier assessment)

b: The following events are considered (MedDRA coding): "infections and infestations (SOC, AE)", "skin and subcutaneous tissue disorders (SOC, AE)", "dry mouth (PT, AE)", "dyspepsia (PT, AE)", "decreased appetite (PT, AE)", "musculoskeletal pain (PT, AE)" and "dyspnoea (PT, AE)", general disorders and administration site conditions (SOC, SAE), gastrointestinal disorders (SOC, severe AE [CTCAE grade ≥ 3]) and "respiratory, thoracic and mediastinal disorders (SOC, severe AE [CTCAE grade ≥ 3])".

c: There was no analysis planned at the time point of the first and second data cut-off (see Section 2.7.4.3.2 of the full dossier assessment)

d: No usable analyses were available; for reasons, see Section 2.7.4.3.2 of the full dossier assessment.

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; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale; vs.: versus

2.4.2 Risk of bias

Table 14 describes the risk of bias for the results of the relevant outcomes.

Table 14: Risk of bias across outcomes and outcome-specific risk of bias – RCT, indirect comparison: pembrolizumab vs. placebo

Study	Study level	Outcomes											
		Overall survival	Recurrence[a]	Symptoms (EORTC QLQ-C30)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30)	SAEs	Severe AEs (CTCAE grade ≥ 3)	discontinuation due to AEs	Immune-related adverse events	Serious immune-related AEs	Severe immune-related AEs (CTCAE grade ≥ 3)	Further specific AEs[b]
KEYNOTE-054	L	-[c]	L	–[d]	–[d]	–[d]	H[e]	H[e]	L	H[e]	H[e]	H[e]	H[e]

a: Proportion of patients with local/regional recurrence, distant metastases or death due to any cause (see Section 2.7.4.3.2 of the full dossier assessment)
b: The following events are considered (MedDRA coding): "infections and infestations (SOC, AE)", "skin and subcutaneous tissue disorders (SOC, AE)", "dry mouth (PT, AE)", "dyspepsia (PT, AE)", "decreased appetite (PT, AE)", "musculoskeletal pain (PT, AE)" and "dyspnoea (PT, AE)", general disorders and administration site conditions (SOC, SAE), gastrointestinal disorders (SOC, severe AE [CTCAE grade ≥ 3]) and "respiratory, thoracic and mediastinal disorders (SOC, severe AE [CTCAE grade ≥ 3])".
c: There was no analysis planned at the time point of the first and second data cut-off (see Section 2.7.4.3.2 of the full dossier assessment)
d: No usable analyses were available; for reasons, see Section 2.7.4.3.2 of the full dossier assessment.
e: Incomplete observations with potentially biasing influence.

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; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale; vs.: versus

For "overall survival", there was no analysis planned at the time point of the first and second data cut-off (see Section 2.7.4.3.2 of the full dossier assessment). There are no usable analyses for "health status" measured with the EQ-5D VAS as well as on "symptoms" and "health related quality of life", measured with the symptom scales or the functional scales and the "global health status" scale of the EORTC QLQ-C30 instrument (see Section 2.7.4.3.2 of the full dossier assessment). The risk of bias for the results on these outcomes is therefore not assessed.

Concurring with the company, the risk of bias for the results on the outcome "recurrence" is rated as low; however, the company considered the event time analysis for this purpose. However, due to other aspects, the certainty of results was only moderate for this outcome; therefore, at most a hint can be determined (see Section 2.7.4.3.3 of the full dossier assessment).

Deviating from the company, the risk of bias was rated as high for the analyses of all outcomes on side effects due to incomplete observations with potentially biasing influence, except for the

outcome “discontinuation due to AEs” (see Section 2.7.4.2 of the full dossier assessment). The company considered no further specific AEs apart from immune-related AEs and did therefore not assess their risk of bias.

The certainty of conclusions for the outcome “discontinuation due to AEs” was restricted despite a low risk of bias (see Section 2.7.4.2 of the full dossier assessment).

2.4.3 Results

Table 15, Table 16 and Table 17 summarize the results on the comparison of pembrolizumab with placebo in patients with completely resected stage III melanoma and lymph node involvement. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company’s dossier. The Kaplan-Meier curves for the used event time analyses can be found in Appendix B (all appendices can be found in the full dossier assessment). Common AEs, SAEs, severe AEs (CTCAE grade ≥ 3) and discontinuation due to AEs are listed in Appendix C of the full dossier assessment. Appendix D shows a list of the common immune-related AEs and all severe immune-related AEs (CTCAE grade ≥ 3).

Table 15: Results (morbidity, dichotomous) – RCT, direct comparison: pembrolizumab vs. placebo

Study Outcome category Outcome	Pembrolizumab N	Pembrolizumab Patients with event n (%)	Placebo[a] N	Placebo[a] Patients with event n (%)	Pembrolizumab vs. placebo[a] RR [95% CI] p-value
KEYNOTE-054					
Morbidity (second data cut-off: 2 May 2018)					
Recurrence[b,c]	514	158 (30.7)	505	246 (48.7)	0.63 [0.54; 0.74][d] < 0.001[e]
Local/regional recurrence	514	59 (11.5)	505	83 (16.4)	–[f]
Distant metastases	514	88 (17.1)	505	138 (27.3)	–[f]
Local/regional recurrence and distant metastases[g]	514	9 (1.8)	505	24 (4.8)	–[f]
Death	514	2 (0.4)	505	1 (0.2)	–[f]
	L	**Median time to event in months [95% CI] Patients with event n (%)**	**L**	**Median time to event in months [95% CI] Patients with event n (%)**	**HR [95% CI] p-value**
Supplementary information:					
RFS	514	NA 158 (30.7)	505	21.7 [17.1; NC] 246 (48.7)	0.56 [0.44; 0.72][h] < 0.001[h, i]

a: Sufficient approximation to the ACT "watchful waiting" (see Section 2.3.2).
b: Proportion of patients with local/regional recurrence, distant metastases or death due to any cause, whichever occurred first (see Section 2.7.4.3.2 of the full dossier assessment); the individual components are presented in the lines below.
c: At the time point of the first data cut-off on 2 October 2017, 135 patients (26.3%) in the pembrolizumab arm and 216 patients (42.8%) in the placebo arm had recurrences:
RR [95% CI]; p-value: 0.61 [0.51; 0.73]; < 0.001.
d: Institute's calculation.
e: Institute's calculation, unconditional exact test (CSZ method according to [8]).
f: No calculation of effect estimations. The presented events do not completely represent the outcome. Only events that were used for the formation of the composite outcome are presented.
g: Patients had local/regional recurrence and distant metastases at the same time (diagnosis within 30 days).
h: Effect estimation HR and 95% confidence interval from Cox proportional hazards model with treatment as covariate, stratified by disease stage (IIIA [metastases > 1 mm], IIIB, IIIC [1-3 positive lymph nodes], IIIC [≥ 4 positive lymph nodes]) at the time point of randomization.
i: Wald p-value.

ACT: appropriate comparator therapy; CI: confidence interval; CSZ: convexity, symmetry, z score; HR: hazard ratio; n: number of patients with event; N: number of analysed patients; NA: not achieved; NC: not calculable; RCT: randomized controlled trial; RFS: recurrence-free survival; RR: relative risk; vs.: versus

Table 16: Results (mortality, morbidity, health-related quality of life, side effects, time to event) – RCT, direct comparison: pembrolizumab vs. placebo

Study Outcome category Outcome	Pembrolizumab N	Pembrolizumab Median time to event in months [95% CI] Patients with event n (%)	Placebo[a] N	Placebo[a] Median time to event in months [95% CI] Patients with event n (%)	Pembrolizumab vs. placebo[a] HR [95% CI] p-value
KEYNOTE-054					
Mortality					
Overall survival	There was no analysis planned at the time point of the first and second data cut-off[b]				
Morbidity					
Symptoms (EORTC QLQ-C30 symptom scales)				No usable analyses[c]	
Health status (EQ-5D VAS)				No usable analyses[c]	
Health-related quality of life					
EORTC QLQ-C30 functional scales and global health status scale				No usable analyses[c]	
Side effects (first data cut-off: 2 October 2017)					
AEs (additional information)	509	0.7 [0.7; 0.8] 475 (93.3)	502	0.8 [0.7; 0.9] 453 (90.2)	–
SAEs	509	NA 128 (25.1)	502	NA 82 (16.3)	1.56 [1.18; 2.06][d] 0.002[d, e]
Severe AEs (CTCAE grade ≥ 3)	509	NA [14.0; NC] 158 (31.0)	502	NA 96 (19.1)	1.66 [1.29; 2.14][d] < 0.001[d, e]
Discontinuation due to AEs	509	NA 70 (13.8)	502	NA 18 (3.6)	3.78 [2.25; 6.34][d] < 0.001[d, e]
Immune-related AEs	509	NA [13.9; NC] 173 (34.0)	502	NA 38 (7.6)	5.15 [3.63; 7.32][d] < 0.001[d, e]
Serious immune-related AEs	509	NA 42 (8.3)	502	NA 3 (0.6)	14.00 [4.34; 45.15][d] < 0.001[d, e]
Severe immune-related AEs (CTCAE grade ≥ 3)	509	NA 36 (7.1)	502	NA 3 (0.6)	11.74 [3.62; 38.12][d] < 0.001[d, e]

(continued)

Table 16: Results (mortality, morbidity, health-related quality of life, side effects, time to event) – RCT, direct comparison: pembrolizumab vs. placebo

a: Sufficient approximation to the ACT "watchful waiting" (see Section 2.3.2).
b: The KEYNOTE-054 study is currently ongoing. According to the study protocol, no interim analysis was planned for the outcome "overall survival". A final analysis is planned to take place after a total of 380 deaths. At the time point of the first data cut-off (2 October 2017), 25 patients in the pembrolizumab arm and 35 patients in the placebo arm had died.
c: No usable analyses were available; for reasons, see Section 2.7.4.3.2 of the full dossier assessment.
d: From Cox proportional hazards model with treatment as covariate.
e: Wald p-value.

ACT: appropriate comparator therapy; AE: adverse event; CI: 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; n: number of patients with event; N: number of analysed patients; NA: not achieved; NC: not calculable; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

Table 17: Results (side effects, dichotomous) – RCT, direct comparison: pembrolizumab vs. placebo

Study Outcome category Outcome	Pembrolizumab N	Pembrolizumab Patients with event n (%)	Placebo[a] N	Placebo[a] Patients with event n (%)	Pembrolizumab vs. placebo[a] RR [95% CI][b] p-value[c]
KEYNOTE-054					
Side effects (first data cut-off: 2 October 2017)					
Specific AEs					
Infections and infestations (SOC, AE)	509	225 (44.2)	502	167 (33.3)	1.33 [1.13; 1.56] < 0.001
Skin and subcutaneous tissue disorders (SOC, AE)	509	272 (53.4)	502	198 (39.4)	1.35 [1.18; 1.55] < 0.001
Dry mouth (PT, AE)	509	30 (5.9)	502	10 (2.0)	2.96 [1.46; 5.99] 0.001
Dyspepsia (PT, AE)	509	19 (3.7)	502	6 (1.2)	3.12 [1.26; 7.76] 0.010
Decreased appetite (PT, AE)	509	36 (7.1)	502	13 (2.6)	2.73 [1.47; 5.09] < 0.001
Musculoskeletal pain (PT, AE)	509	23 (4.5)	502	8 (1.6)	2.84 [1.28; 6.28] 0.007
dyspnoea (PT, AE)	509	46 (9.0)	502	25 (5.0)	1.81 [1.13; 2.91] 0.012
General disorders and administration site conditions (SOC, SAE)	509	11 (2.2)	502	0 (0)	22.68 [1.34; 383.91] < 0.001
Gastrointestinal disorders (SOC, severe AE [CTCAE grade ≥ 3])	509	26 (5.1)	502	10 (2.0)	2.56 [1.25; 5.26] 0.008
Respiratory, thoracic and mediastinal disorders (SOC, severe AE [CTCAE-Grad ≥ 3])	509	10 (2.0)	502	2 (0.4)	4.93 [1.09; 22.39] 0.022

a: Sufficient approximation to the ACT "watchful waiting" (see Section 2.3.2).
b: Institute's calculation.
c: Institute's calculation, unconditional exact test (CSZ method according to [8])

ACT: appropriate comparator therapy; AE: adverse event; CI: confidence interval; CSZ: convexity, symmetry, z score; CTCAE: Common Terminology Criteria for Adverse Events; n: number of patients with (at least one) event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SOC: System Organ Class; vs.: versus

Based on the available data, at most hints, e.g. of an added benefit, can be determined for all outcomes (see Sections 2.4.2, 2.7.4.2 and 2.7.4.3.3 of the full dossier assessment).

Mortality

Overall survival

The KEYNOTE-054 study is currently ongoing. According to the study protocol, no interim analysis was planned for the outcome "overall survival". A final analysis is planned to take place after a total of 380 deaths. At the time point of the first data cut-off (2 October 2017), 25 patients in the pembrolizumab arm and 35 patients in the placebo arm had died.

Morbidity

Recurrence

A statistically significant difference in favour of pembrolizumab in comparison with placebo was shown between the treatment groups for the outcome "recurrence" (second data cut-off: 2 May 2018). This resulted in a hint of an added benefit of pembrolizumab in comparison with the ACT "watchful waiting" for the outcome "recurrence".

This concurs with the company's assessment insofar as the company derived an indication of major added benefit. However, the company used the event time analysis for this purpose and considered the analyses for the first and second data cut-offs together.

The result on "RFS", which was presented as supplementary information, also showed a statistically significant difference in favour of pembrolizumab in comparison with placebo between the treatment groups (second data cut-off: 2 May 2018).

Symptoms

There are no usable analyses for symptoms, measured with the symptom scales of the cancer-specific instrument EORTC QLQ-C30 (see Section 2.7.4.3.2 of the full dossier assessment). This resulted in no hint of an added benefit of pembrolizumab in comparison with the ACT watchful waiting; an added benefit is therefore not proven.

This concurs with the company's assessment which also derived no added benefit or lesser benefit; however, it used the analyses on the time to first confirmed deterioration for this purpose.

Health status (EQ-5D VAS)

The dossier contained no evaluable analyses for the outcome "health status" measured with the EQ-5D VAS (see Section 2.7.4.3.2 of the full dossier assessment). This resulted in no hint of an added benefit of pembrolizumab in comparison with the ACT watchful waiting; an added benefit is therefore not proven.

This concurs with the company's assessment which also derived no added benefit or lesser benefit; however, it used the analyses on the time to first confirmed deterioration by ≥ 7 or ≥ 10 points for this purpose.

Health-related quality of life

EORTC QLQ-C30 (functional scales and global health status scale)

There are no usable analyses for "health-related quality of life", recorded with the functional scales and with the scale for recording the global health status of the cancer-specific instrument EORTC QLQ-C30 (see Section 2.7.4.3.2 of the full dossier assessment). This resulted in no hint of an added benefit of pembrolizumab in comparison with the ACT "watchful waiting"; an added benefit is therefore not proven.

This concurs with the company's assessment which also derived no added benefit or lesser benefit; however, it used the analyses on the time to first confirmed deterioration for this purpose.

Side effects

SAEs, severe AEs (CTCAE grade ≥ 3) and discontinuation due to AEs

A statistically significant difference to the disadvantage of pembrolizumab in comparison with placebo was shown between the treatment groups for SAEs, severe AEs (CTCAE grade ≥ 3) and discontinuation due to AEs. This resulted in a hint of greater harm from pembrolizumab in comparison with the ACT "watchful waiting".

This concurs with the company's assessment insofar as the company derived an indication of lesser benefit.

Specific AEs

Immune-related AEs

A statistically significant difference to the disadvantage of pembrolizumab in comparison with placebo was shown between the study arms for immune-related AEs. However, there is an effect modification by the characteristic "PD-L1 expression status". This resulted in no hint of greater or lesser harm for patients with a negative PD-L1 expression status; greater or lesser harm for these patients is therefore not proven. For patients with a positive PD-L1 expression status, there is a hint of greater harm from pembrolizumab in comparison with the ACT "watchful waiting" (see Section 2.4.4).

This concurs with the company's assessment insofar as the company derived an indication of lesser benefit; however, he did not consider the subgroup analyses.

Serious immune-related AEs and severe immune-related AEs (CTCAE grade ≥ 3)

A statistically significant difference to the disadvantage of pembrolizumab in comparison with placebo was shown between the treatment groups for "serious immune-related AEs" and "severe immune-related AEs (CTCAE grade ≥ 3)". This resulted in a one hint of greater harm each from pembrolizumab in comparison with the ACT "watchful waiting".

This concurs with the company's assessment insofar as the company derived an indication of lesser benefit.

SAEs/severe AEs (CTCAE grade ≥ 3): general disorders and administration site conditions (SOC, SAE), gastrointestinal disorders (SOC, severe AE [CTCAE grade ≥ 3]) and respiratory, thoracic and mediastinal disorders (SOC, severe AE [CTCAE grade ≥ 3])

There is a statistically significant difference to the disadvantage of pembrolizumab in comparison with placebo between the treatment groups for the outcomes "general disorders and administration site conditions (SOC, SAE)", "gastrointestinal disorders (SOC, severe AE [CTCAE grade ≥ 3])" and "respiratory, thoracic and mediastinal disorders (SOC, severe AE [CTCAE grade ≥ 3])". This resulted in a hint of greater harm from pembrolizumab in comparison with the ACT "watchful waiting".

AEs: "infections and infestations (SOC)", "skin and subcutaneous tissue disorders (SOC)", "dry mouth (PT)", "dyspepsia (PT)", "decreased appetite (PT)", "musculoskeletal pain (PT)" and "dyspnoea (PT)"

There is a statistically significant difference to the disadvantage of pembrolizumab in comparison with placebo between the treatment groups for the outcomes "infections and infestations (SOC)", "skin and subcutaneous tissue disorders (SOC)", "dry mouth (PT)", "dyspepsia (PT)", "decreased appetite (PT)", "musculoskeletal pain (PT)" and "dyspnoea (PT)". This resulted in a hint of greater harm from pembrolizumab in comparison with the ACT "watchful waiting".

This deviates from the assessment of the company, which used no further specific AEs besides "immune-related AEs", "serious immune-related AEs" and "severe immune-related AEs" (CTCAE grade ≥ 3).

2.4.4 Subgroups and other effect modifiers

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

- sex (male, female)
- age (< 65 years/≥ 65 years)
- geographical region (Europe; North America, Australia and New Zealand; other)
- Disease stage (IIIA, IIIB, IIIC [1-3 positive lymph nodes]; IIIC [≥ 4 positive lymph nodes] according to the AJCC 7 classification)
- Disease stage (IIIA, IIIB, IIIC, IIID according to the AJCC 8 classification)
- BRAF mutation status (positive, negative)
- PD-L1 expression status (positive, negative)

The mentioned characteristics with the corresponding subgroups had all been defined a priori in the study protocol: sex, age, BRAF and PD-L1 expression status should be investigated as possible prognostic factors for the outcomes "RFS" and "overall survival". The characteristics "geographical region" and "disease stage according to the AJCC 7 classification" are the two stratification factors of the KEYNOTE-054 study. In the study, the geographical region was stratified as follows: Europe, North America, Australia, other. However, the company considered the following subgroups: Europe, North America, Australia and New Zealand, other. The subgroup analysis presented by the company was used for the present benefit assessment. In the present benefit assessment, subgroup analyses according to the AJCC 7 classification [3] current at the time of study planning and to the current AJCC 8 classification were considered to be relevant for the characteristic "disease stage" [6]. According to the new AJCC 8 classification, patients were partly assigned to other stages (IIIA-C) than they would have been according to the AJCC 7 classification; moreover, stage IIID has been added.

For the outcome "recurrence", only subgroup analyses for the event time analysis considered by the company ("RFS") are available in the dossier. Therefore, the Institute calculated subgroup analyses regarding the proportion of patients with recurrence. Related information was available only for the first data cut-off (2 October 2017) and only for the characteristics "sex", "geographical region", "disease stage according to AJCC 7 classification", "BRAF mutation status" and "PD-L1 expression status".

The dossier contains subgroup analyses for the characteristics "sex", "geographical region", "disease stage according to AJCC 7 classification", "BRAF mutation status" and "PD-L1 expression status" for the following outcomes: "SAEs", "severe AEs" (CTCAE grade ≥ 3), "discontinuation due to AEs", "immune-related AEs", "serious immune-related AEs" and "severe immune-related AEs" (CTCAE grade ≥ 3). For the other specific AEs used in the benefit assessment, subgroup analyses are not available for any of the characteristics mentioned.

For the subgroup characteristic "age", subgroup analyses on the subgroups of patients < 65 years and ≥ 65 years defined a priori are not available for any of the outcomes. Instead, the company considered the following subgroups post hoc: < 50 years and ≥ 50 years. The company did not provide a reason for this.

For the subgroup characteristic "disease stage according to AJCC 8 classification", subgroup analyses are not available for any of the outcomes.

Interaction tests were performed when at least 10 patients per subgroup were included in the analysis. For binary data, there must be 10 events in at least 1 subgroup.

Only the results with an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05) are presented. In addition, subgroup results were only presented if there was a statistically significant and relevant effect in at least one subgroup.

Table 18: Subgroups – RCT, direct comparison: pembrolizumab vs. placebo

Study Outcome Characteristic Subgroup	Pembrolizumab N	Pembrolizumab Median time to event in months [95% CI] Patients with event n (%)	Placebo[a] N	Placebo[a] Median time to event in months [95% CI] Patients with event n (%)	Pembrolizumab vs. placebo[a] HR [95 % CI][b]	Pembrolizumab vs. placebo[a] p-value[b,c]
KEYNOTE-054						
Side effects						
Immune-related adverse events						
PD-L1 expression status[d]						
Positive	423	NA [13.90; NC] 151 (35.7)	423	NA 28 (6.6)	6.30 [4.21; 9.43]	< 0.001
Negative	59	NA 15 (25.4)	57	NA 9 (15.8)	1.54 [0.68; 3.53]	0.303
Total					Interaction:	0.003[e]

a: Sufficient approximation to the ACT "watchful waiting" (see Section 2.3.2).
b: From Cox proportional hazards model with treatment as covariate.
c: Wald p-value.
d: Samples in which IHC membrane staining of the tumour cells and tumour-associated immune cells was ≥ 1% were regarded as PD-L1 positive.
e: p-value from Q test for heterogeneity.
AE: adverse event; ACT: appropriate comparator therapy; CI: confidence interval; HR: hazard ratio; IHC: immunohistochemical; n: number of patients with event; N: all randomized patients who had received at least 1 dose of the study medication and for whom there was at least one recording of patient-relevant outcomes; NA: not achieved; NC: not calculable; PD-L1: programmed cell death ligand 1; RCT: randomized controlled trial; vs.: versus

The available subgroup analyses result in an effect modification for immune-related AEs by the characteristic "PD-L1 expression status".

A statistically significant difference to the disadvantage of pembrolizumab in comparison with placebo between the treatment groups was shown for the outcome "immune-related AEs" for patients with positive PD-L1 expression status. This resulted in a hint of greater harm from pembrolizumab in comparison with the ACT "watchful waiting" for this subgroup.

For patients with a negative PD-L1 expression status, in contrast, there was no statistically significant difference between the treatment groups. Hence, for this subgroup, there was no hint of greater or lesser harm from pembrolizumab in comparison with the ACT "watchful waiting"; greater or lesser harm is therefore not proven.

This deviates from the assessment of the company insofar as the company did not consider subgroup analyses.

2.5 Probability and extent of added benefit

Probability and extent of the added benefit at outcome level are presented below. The various outcome categories and the effect sizes were taken into account. The methods used for this purpose are explained in the *General Methods* of IQWiG [1].

The procedure for deriving an overall conclusion on the added benefit based on the aggregation of the conclusions deduced at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

2.5.1 Assessment of the added benefit at outcome level

The extent of the respective added benefit at outcome level was estimated from the results presented in Section 2.4 (see Table 19).

Determination of the outcome category for outcomes on morbidity and side effects

It could not be inferred from the dossier for all outcomes considered in the present benefit assessment whether they were serious/severe or non-serious/non-severe. The classification of these outcomes is justified below.

Recurrence

The outcome "recurrence" is considered to be severe/serious. On the one hand, recurrence of the cancer can be life-threatening, or rather a recurrence shows that the attempt to cure a potentially life-threatening disease with the curative therapy approach was not successful. On the other hand, death is considered a recurrence event.

Discontinuation due to AEs

The majority of the AEs resulting in treatment discontinuation were non-serious. Information on the severity according to CTCAE classification was not available. The outcome "discontinuation due to AEs" was therefore allocated to the outcome category "non-serious/non-severe side effects".

Specific AEs

The outcomes "immune-related AEs", "infections and infestations (SOC, AE)", "skin and subcutaneous tissue disorders (SOC, AEs)", "dry mouth (PT, AE)", "dyspepsia (PT, AE)", "decreased appetite (PT, AE)", "musculoskeletal pain (PT, AE)" and "dyspnoea (PT, AE)" were allocated to the category "non-serious/non-severe side effects", because the majority of the AEs was non-serious/non-severe (CTCAE grade < 3).

Table 19: Extent of added benefit at outcome level: pembrolizumab vs. watchful waiting

Outcome category **Outcome**	**Pembrolizumab vs. watchful waiting** **Median time to event (months) or proportion of events (%)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality		
Overall survival	There was no analysis planned at the time point of the first and second data cut-off[c]	Lesser benefit/added benefit not proven
Morbidity		
Recurrence	30.7 % vs. 48.7 % RR: 0.63 [0.54; 0.74]; p < 0.001 probability: "hint"	Outcome category: Serious/severe symptoms/late complications $CI_u < 0.75$ and risk ≥ 5 % Added benefit, extent: "major"
Symptoms (EORTC QLQ-C30 symptom scales)	No usable analyses[d]	Lesser benefit/added benefit not proven
Health status (EQ-5D VAS)	No usable analyses[d]	Lesser benefit/added benefit not proven
Health-related quality of life		
EORTC QLQ-C30 functional scales and global health status" scale	No usable analyses[d]	Lesser benefit/added benefit not proven
Side effects		
SAEs	NA vs. NA HR: 1.56 [1.18; 2.06] HR: 0.64 [0.49; 0.85][e] p = 0.002 probability: "hint"	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ greater harm, extent: "considerable"
Severe AEs (CTCAE grade ≥ 3)	NA vs. NA HR: 1.66 [1.29; 2.14] HR: 0.60 [0.47; 0.78][e] p < 0.001 probability: "hint"	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ greater harm, extent: "considerable"
Discontinuation due to AEs	NA vs. NA HR: 3.78 [2.25; 6.34] HR: 0.26 [0.16; 0.44][e] p < 0.001 probability: "hint"	Outcome category: Non-serious/non-severe side effects $CI_u < 0.80$ greater harm, extent: "considerable"

(continued)

Table 19: Extent of added benefit at outcome level: pembrolizumab vs. watchful waiting (continued)

Outcome category **Outcome**	**Pembrolizumab vs. watchful waiting** **Median time to event (months) or proportion of events (%)** **Effect estimation [95% CI]** **p-value** **Probability[a]**	**Derivation of extent[b]**
Immune-related AEs PD-L1 expression status Positive	NA vs. NA HR: 6.30 [4.21; 9.43] HR: 0.16 [0.11; 0.24][e] p < 0.001 probability: "hint"	Outcome category: Non-serious/non-severe side effects $CI_u < 0.80$ greater harm, extent: "considerable"
Negative	NA vs. NA HR: 1.54 [0.68; 3.53]; p = 0.303	Greater/lesser harm not proven
Serious immune-related AEs	NA vs. NA HR: 14.00 [4.34; 45.15] HR: 0.07 [0.02; 0.23][e] p < 0.001 probability: "hint"	Outcome category: serious/severe side effects: $CI_u < 0.75$ and risk ≥ 5 % greater harm, extent: "major"
Severe immune-related AEs (CTCAE grade ≥ 3)	NA vs. NA HR: 11.74 [3.62; 38.12] HR: 0.09 [0.03; 0.28][e] p < 0.001 probability: "hint"	Outcome category: serious/severe side effects: $CI_u < 0.75$ and risk ≥ 5 % greater harm, extent: "major"
Infections and infestations (SOC, AE)	44.2 % vs. 33.3 % RR: 1.33 [1.13; 1.56] RR: 0.75 [0.64; 0.88][e] p < 0.001 probability: "hint"	Outcome category: Non-serious/non-severe side effects $0.80 \leq CI_u < 0.90$ greater harm, extent: "minor"
Skin and subcutaneous tissue disorders (SOC, AE)	53.4 % vs. 39.4 % RR: 1.35 [1.18; 1.55] RR: 0.74 [0.65; 0.85][e] p < 0.001 probability: "hint"	Outcome category: Non-serious/non-severe side effects $0.80 \leq CI_u < 0.90$ greater harm, extent: "minor"
Dry mouth (PT, AE)	5.9 % vs. 2.0 % RR: 2.96 [1.46; 5.99] RR: 0.34 [0.17; 0.68][e] p = 0.001 probability: "hint"	Outcome category: Non-serious/non-severe side effects $CI_u < 0.80$ greater harm, extent: "considerable"

(continued)

Table 19: Extent of added benefit at outcome level: pembrolizumab vs. watchful waiting (continued)

Outcome category **Outcome**	**Pembrolizumab vs. watchful waiting** **Median time to event (months) or proportion of events (%)** **Effect estimation [95% CI]** **p-value** **Probability[a]**	**Derivation of extent[b]**
Dyspepsia (PT, AE)	3.7 % vs. 1.2 % RR: 3.12 [1.26; 7.76] RR: 0.32 [0.13; 0.79][e] p = 0.010 probability: “hint”	Outcome category: Non-serious/non-severe side effects $CI_u < 0.80$ greater harm, extent: “considerable”
Decreased appetite (PT, AE)	7.1 % vs. 2.6 % RR: 2.73 [1.47; 5.09] RR: 0.37 [0.20; 0.68][e] p < 0.001 probability: “hint”	Outcome category: Non-serious/non-severe side effects $CI_u < 0.80$ greater harm, extent: “considerable”
Musculoskeletal pain (PT, AE)	4.5 % vs. 1.6 % RR: 2.84 [1.28; 6.28] RR: 0.35 [0.16; 0.78][e] p = 0.007 probability: “hint”	Outcome category: Non-serious/non-severe side effects $CI_u < 0.80$ greater harm, extent: “considerable”
Dyspnoea (PT, AE)	9.0 % vs. 5.0 % RR: 1.81 [1.13; 2.91] RR: 0.55 [0.34; 0.88][e] p = 0.012 probability: “hint”	Outcome category: Non-serious/non-severe side effects $0.80 \leq CI_u < 0.90$ greater harm, extent: “minor”
General disorders and administration site conditions (SOC, SAE)	2.2 % vs. 0 % RR: 22.68 [1.34; 383.91] RR: 0.04 [0.003; 0.746][e] p < 0.001 probability: “hint”	Outcome category: serious/severe side effects: $CI_u < 0.75$ and risk < 5 % greater harm, extent: “considerable”
Gastrointestinal disorders (SOC, severe AE [CTCAE grade ≥ 3])	5.1 % vs. 2.0 % RR: 2.56 [1.25; 5.26] RR: 0.39 [0.19; 0.80][e] p = 0.008 probability: “hint”	Outcome category: serious/severe side effects: $0.75 \leq CI_u < 0.90$ greater harm, extent: “considerable”
Respiratory, thoracic and mediastinal disorders (SOC, severe AE [CTCAE-Grad ≥ 3])	2.0 % vs. 0.4 % RR: 4.93 [1.09; 22.39] RR: 0.20 [0.04; 0.92][e] p = 0.022 probability: “hint”	Outcome category: serious/severe side effects: $0.90 \leq CI_u < 1.00$ greater harm, extent: “minor”

(continued)

Table 19: Extent of added benefit at outcome level: pembrolizumab vs. watchful waiting (continued)

a: Probability provided if there is a statistically significant and relevant effect.
b: Estimations of effect size are made depending on the outcome category with different limits based on the CI_u.
c: There was no analysis planned at the time point of the first and second data cut-off (see Section 2.7.4.3.2 of the full dossier assessment).
d: No usable analyses were available; for reasons, see Section 2.7.4.3.2 of the full dossier assessment.
e: Institute's calculation, reversed direction of effect to enable use of limits to derive the extent of the added benefit.

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; NA: not achieved; PD-L1: programmed cell death ligand 1; PT: Preferred Term; RR: relative risk; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale; vs.: versus

2.5.2 Overall conclusion on added benefit

Table 20 summarizes the results considered in the overall conclusion on the extent of added benefit.

Table 20: Positive and negative effects from the assessment of pembrolizumab in comparison with watchful waiting

Positive effects	**Negative effects**
Serious/severe symptoms/late complications ▪ Recurrence: Hint of added benefit - extent: "major"	Serious/severe side effects ▪ SAEs and severe AEs (CTCAE grade ≥ 3): in each case: hint of greater harm – extent: "considerable" ▪ Specific AEs: ▫ Serious immune-related AEs and severe immune-related AEs (CTCAE grade ≥ 3): in each case hint of greater harm – extent: "major" ▫ General disorders and administration site conditions (SOC, SAE) and gastrointestinal disorders (SOC, severe AE [CTCAE grade ≥ 3]): in each case: hint of greater harm – extent: "considerable" ▫ Respiratory, thoracic and mediastinal disorders (SOC, severe AE [CTCAE-Grad ≥ 3]): hint of greater harm – extent: "minor"
–	Non-serious/non-severe side effects: ▪ Discontinuation due to AEs: hint of greater harm – extent: "considerable" ▪ Specific AEs: ▫ Immune-related AEs: - PD-L1 expression status positive: hint of greater harm – extent: "considerable" ▫ Dry mouth (PT, AE), dyspepsia (PT, AE), decreased appetite (PT, AE) and musculoskeletal pain (PT, AE): in each case: hint of greater harm – extent: "considerable" ▫ Infections and infestations (SOC, AE), skin and subcutaneous tissue disorders (SOC, AE) and dyspnoea (PT, AE): in each case hint of greater harm – extent: "minor"
There are no usable analyses on "health-related quality of life", "symptoms" and "health status" (see Section 2.7.4.3.2 of the full dossier assessment).	
AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; PD-L1: programmed cell death ligand 1; PT: Preferred Term; SAE: serious adverse event; SOC: System Organ Class;	

The overall assessment showed one positive and several negative effects of pembrolizumab in comparison with "watchful waiting".

A hint of major added benefit was shown for the outcome "recurrence". This was offset by several negative effects: With regard to serious/severe side effects, there were several hints of greater harm with extents up to "major". For non-serious/non-severe side effects, there are also several hints of greater harm, partly in subgroups; the extents are up to "considerable". There are no usable analyses on "health-related quality of life", "symptoms" and "health status". The negative effects did not completely outweigh the advantage in recurrence, but resulted in a downgrading of the extent of the added benefit.

In summary, there is a hint of considerable added benefit of pembrolizumab versus the ACT "watchful waiting" for patients with completely resected stage III melanoma with lymph node involvement.

Table 21 summarizes the result of the assessment of the added benefit of pembrolizumab in comparison with the ACT.

Table 21: Pembrolizumab – extent and probability of added benefit

Subindication	**ACT[a]**	**Probability and extent of added benefit**
Adjuvant treatment of adults with stage III[b] melanoma and lymph node involvement after complete resection[c]	Watchful waiting	Hint of considerable added benefit

a: Presentation of the respective ACT specified by the G-BA.
b: By AJCC classification.
c: In accordance with the approval, the therapeutic indication to be assessed comprised patients with stage III disease and lymph node involvement after complete resection [4,5]. However, the KEYNOTE-054 study only included patients with stage IIIA lymph node metastasis > 1 mm. Patients with in transit or satellite metastases were excluded from the study. Hence, the study population does not completely cover the therapeutic indication. It is unclear whether the observed effects can be transferred to patients with in transit or satellite metastases. Moreover, it is unclear whether the observed effects can be transferred to patients with lymph node metastasis ≤ 1 mm and stage IIIA disease according to AJCC 7 classification; according to the current AJCC 8 classification, patients who had been allocated to stage IIIA pursuant to AJCC 7 classification can also have other disease stages (IIIA or IIIB or IIIC).

ACT: appropriate comparator therapy; AJCC: American Joint Committee on Cancer; G-BA: Federal Joint Committee

The assessment described above deviates from that of the company, which derived an indication of major added benefit instead.

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

2.6 List of included studies

KEYNOTE-054

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Merck Sharp & Dohme. Adjuvant immunotherapy with anti-PD-1 monoclonal antibody Pembrolizumab (MK-3475) versus placebo after complete resection of high-risk stage III melanoma: a randomized, double-blind phase 3 trial of the EORTC Melanoma Group: study MK-3475-054/KEYNOTE-054; Zusatzanalysen [unpublished]. 2018.

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Please see full dossier assessment for full reference list.

The reference list contains citations provided by the company in which bibliographical information may be missing.

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