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Pembrolizumab (MSI-H or dMMR colorectal cancer) –

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

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Pembrolizumab (Kolorektalkarzinom mit MSI-H oder dMMR) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 29 June 2021). 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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[2] Table numbers start with "2" as numbering follows that of the full dossier assessment.

List of abbreviations

Abbreviation	Meaning
5FU	5-fluorouracil
ACT	appropriate comparator therapy
AE	adverse event
all-RAS	all-rat sarcoma viral oncogene homologue
BRAF	rapidly accelerated fibrosarcoma – isoform B
CTCAE	Common Terminology Criteria for Adverse Events
dMMR	mismatch repair deficient
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EGFR	epidermal growth factor receptor
FOLFIRI	folinic acid + 5-fluorouracil + irinotecan
FOLFOX	folinic acid + 5-fluorouracil + oxaliplatin
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IHC	immunohistochemistry
IPCW	inverse probability of censoring weights
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
KRAS	Kirsten rat sarcoma viral oncogene homologue;
mFOLFOX6	folinic acid + 5-fluorouracil + oxaliplatin, modified regimen
MSI-H	high-frequency microsatellite instability
NRAS	neuroblastoma rat sarcoma viral oncogene homologue
PCR	polymerase chain reaction
PFS	progression-free survival
PROs	patient-reported outcomes
RAS	rat sarcoma viral oncogene homologue
RCT	randomized controlled trial
RECIST	Response Evaluation Criteria-In-Solid-Tumours
RPFST	rank preserving structural failure time
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SOC	System Organ Class
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 is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 31 March 2021.

Research question

The aim of the present report is the assessment of the added benefit of pembrolizumab in comparison with the appropriate comparator therapy (ACT) in adult patients with metastatic colorectal cancer whose tumours have high-frequency microsatellite instability (MSI-H) or are mismatch repair deficient (dMMR) in the first-line setting.

The research questions shown in Table 2 resulted from the ACT specified by the G-BA.

Table 2: Research questions of the benefit assessment of pembrolizumab

Research question	Therapeutic indication[a]	ACT[b]
1	Adult patients with metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer for whom intensive treatment is suitable; first-line treatment	Individual treatment depending on the all-RAS mutation status, the location of the primary tumour and the risk of toxicity induced by bevacizumab, choosing from the following options ▪ combination therapy of 5-fluorouracil + folinic acid + oxaliplatin (FOLFOX) ▪ combination therapy of 5-fluorouracil + folinic acid + irinotecan (FOLFIRI) ▪ combination therapy of 5-fluorouracil + folinic acid + oxaliplatin (FOLFOX) and an anti-EGFR treatment (cetuximab or panitumumab) - (only for patients with RAS wild type) ▪ combination therapy of 5-fluorouracil + folinic acid + irinotecan (FOLFIRI) and an anti-EGFR treatment (cetuximab or panitumumab) - (only for patients with RAS wild type) ▪ combination therapy of 5-fluorouracil + folinic acid + oxaliplatin (FOLFOX) and bevacizumab ▪ combination therapy of 5-fluorouracil + folinic acid + irinotecan (FOLFIRI) and bevacizumab
2	Adult patients with metastatic MSI-H or dMMR colorectal cancer for whom intensive treatment is unsuitable; first-line treatment	▪ 5-fluorouracil + folinic acid ± bevacizumab or ▪ capecitabine ± bevacizumab or ▪ combination therapy of 5-fluorouracil + folinic acid + oxaliplatin (reduced intensity) ± bevacizumab or ▪ combination therapy of 5-fluorouracil + folinic acid + irinotecan (reduced intensity) ± bevacizumab

a. For the present therapeutic indication, it is assumed that treatment with curative intent or primary resection is not an option for the patients with metastatic colorectal cancer.
b. Presentation of the respective ACT specified by the G-BA.

5-FU: 5-fluorouracil; dMMR: mismatch repair deficiency: EGFR: epidermal growth factor receptor; EGFR: epidermal growth factor receptor; FOLFIRI: folinic acid + 5-fluorouracil + irinotecan; FOLFOX 5-fluorouracil + folinic acid + oxaliplatin; G-BA: Federal Joint Committee; MSI-H: high-frequency microsatellite instability; RAS: rat sarcoma viral oncogene homologue

In the present assessment, the following terms are used for the patient populations of the 2 research questions:

- Research question 1: Patients for whom intensive therapy is suitable
- Research question 2: Patients for whom intensive therapy is unsuitable

Deviating from the G-BA, the company did not differentiate between the population of patients for whom intensive treatment is suitable or unsuitable. The company specified the ACT determined by the G-BA for research question 1 for all patients in the therapeutic indication.

Concurring with the G-BA's specification, the present assessment was conducted for the two research questions 1 and 2, each in comparison with the ACT specified by the G-BA.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) were used for the derivation of the added benefit.

Research question 1: Patients for whom intensive therapy is appropriate

Study pool and study design

The study pool for the benefit assessment of pembrolizumab in comparison with the ACT consisted of the study KEYNOTE 177.

The KEYNOTE 177 study is an ongoing, open-label, randomized, active-controlled multicentre study on the comparison of pembrolizumab with individual treatment choosing from a chemotherapy (folinic acid + 5-fluorouracil (5FU) + oxaliplatin (FOLFOX), administered as modified regimen mFOLFOX6, or folinic acid + 5FU + irinotecan [FOLFIRI] ± bevacizumab or cetuximab.

The study included adult patients with metastatic MSI-H or dMMR colorectal cancer. The patients were not allowed to have received prior systemic therapy in the metastatic stage; any prior adjuvant chemotherapy for the treatment of an earlier stage of the colorectal cancer had to be completed 6 months before the start of the study. The patients had to have a good general condition (Eastern Cooperative Oncology Group Performance Status [ECOG PS] ≤ 1) and adequate organ function.

The KEYNOTE 177 study included a total of 307 patients, randomized in a 1:1 ratio either to treatment with pembrolizumab (N = 153) or to chemotherapy, consisting of mFOLFOX6 or FOLFIRI ± bevacizumab or cetuximab (N = 154). Prior to randomization, the investigator determined which of the cited therapy options each patient should receive if assigned to the control arm.

Treatment with pembrolizumab in the intervention arm and treatment in the control arm was largely in compliance with the requirements of the Summary of Product Characteristics (SPC). Deviating from the requirements of the SPC, treatment with pembrolizumab was limited to a maximum treatment duration of 35 cycles (approx. 2 years). However, according to the SPC, treatment with pembrolizumab should only be performed until progression of the cancer or the occurrence of unacceptable toxicity. However, in the KEYNOTE 177 study, 57 (37.3%) patients in the intervention arm discontinued their therapy with pembrolizumab after a maximum treatment duration of 35 cycles without having achieved the reasons for discontinuation described in the SPC. Therefore, there was no further treatment in accordance with the SPC. As there is no information on when these 57 patients showed progression of the cancer, it is unclear whether and how long the further treatment should have lasted according to the SPC.

Co-primary outcomes of the study were "overall survival" and "progression-free survival (PFS)". Patient-relevant secondary outcomes were outcomes on morbidity, health-related quality of life and adverse events (AEs).

Implementation of the ACT

Prior to randomization, the investigator determined which of the cited therapies each patient should receive if assigned to the control arm of the multi-comparator study KEYNOTE 177. The options comprised FOLFOX or FOLFIRI ± bevacizumab or cetuximab. Treatment was chosen on the basis of eligibility criteria not described in more detail by the company. Due to the exclusion of patients with an ECOG PS > 1, the requirement of the presence of adequate organ function at baseline and the performance of appropriate laboratory tests and organ examinations before the start of a new cycle, it can be assumed that intensive therapy was basically suitable for the patients included in KEYNOTE 177. Moreover, based on the information provided in the patient characteristics on the all-rat sarcoma viral oncogene homologue (all-RAS) mutation status and the location of the primary tumour, it is assumed that these criteria were taken into account when choosing the possible combination partner bevacizumab or cetuximab. Overall, the ACT was considered adequately implemented.

Risk of bias

The risk of bias across outcomes was rated as low for the KEYNOTE 177 study.

There was a high risk of bias for the results of the outcome "overall survival". Overall, there are no usable data for the outcome categories of morbidity and health-related quality of life. For this reason, the risk of bias for the outcomes of these outcome categories was not assessed. The risk of bias for the results of the outcomes of the outcome category of side effects was rated as high in each case.

Results

Mortality

Overall survival

No statistically significant difference between the treatment groups was shown for the outcome "overall survival". This resulted in no hint of an added benefit of pembrolizumab in comparison with individual treatment; an added benefit is therefore not proven.

Morbidity

Symptoms (European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 [EORTC QLQ-C30] and European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 29 [EORTC QLQ-CR29])

There were no usable data for the outcomes on symptoms recorded with the EORTC QLQ-C30 and the EORTC QLQ-CR29. This resulted in no hint of an added benefit of pembrolizumab in comparison with individual treatment in each case; an added benefit is therefore not proven.

Health status (EQ-5D visual analogue scale [VAS])

There were no usable data for the outcome "health status" recorded with the EQ-5D VAS. This resulted in no hint of an added benefit of pembrolizumab in comparison with individual treatment; an added benefit is therefore not proven.

Health-related quality of life

EORTC QLQ-C30 and EORTC QLQ-CR29

There were no usable data for the outcomes on health-related quality of life recorded with the EORTC QLQ-CR29. This resulted in no hint of an added benefit of pembrolizumab in comparison with individual treatment in each case; an added benefit is therefore not proven.

Side effects

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

A statistically significant difference in favour of pembrolizumab in comparison with chemotherapy ± bevacizumab or cetuximab was shown for each of the outcomes "SAEs" and "severe AEs" (CTCAE grade ≥ 3)". This resulted in a hint of lesser harm from pembrolizumab in comparison with individual treatment for each of these outcomes.

Discontinuation due to AEs and immune-related severe AEs (CTCAE grade ≥ 3)

No statistically significant difference between the treatment groups was shown for the outcomes "discontinuation due to AEs", and "immune-related severe AEs (CTCAE grade ≥ 3)". In each case, this resulted in no hint of greater or lesser harm from pembrolizumab in comparison with individual therapy; greater or lesser harm is therefore not proven.

Immune-related SAEs

A statistically significant difference to the disadvantage of pembrolizumab in comparison with chemotherapy ± bevacizumab or cetuximab was shown for the outcome "immune-related SAEs". This resulted in a hint of greater harm from pembrolizumab in comparison with individual treatment.

Further specific AEs

mucosal inflammation (AEs), reduced appetite (AEs), peripheral neuropathy (AEs), peripheral sensory neuropathy (AEs), epistaxis (AEs), alopecia (AEs), palmar-plantar erythrodysaesthesia syndrome (AEs), gastrointestinal disorders (severe AEs), fatigue (severe AEs), infections and infestations (severe AEs), hypokalaemia (severe AEs)

There was a statistically significant difference in favour of pembrolizumab in comparison with chemotherapy ± bevacizumab or cetuximab for each of the specific AEs "mucosal inflammation (AEs)", "reduced appetite (AEs)", "peripheral neuropathy (AEs)", "peripheral sensory neuropathy (AEs)", "epistaxis (AEs)", "alopecia (AEs)", "palmar-plantar erythrodysaesthesia syndrome (AEs)", "gastrointestinal disorders (severe AEs)", "fatigue (severe AEs)",

"infections and infestations (severe AEs)" and "hypokalaemia (severe AEs). This resulted in a hint of lesser harm from pembrolizumab in comparison with individual treatment for each of these outcomes.

Blood and lymphatic system disorders (severe AEs)

A statistically significant difference in favour of pembrolizumab in comparison with chemotherapy ± bevacizumab or cetuximab was shown for the outcome "blood and lymphatic system disorders (severe AEs)". There was an effect modification by the characteristic "sex" for this outcome. This resulted in a hint of lesser harm from pembrolizumab in comparison with individual treatment for both men and women.

Arthralgia (AEs)

A statistically significant difference to the disadvantage of pembrolizumab in comparison with chemotherapy ± bevacizumab or cetuximab was shown for the outcome "arthralgia (AEs)". This resulted in a hint of greater harm from pembrolizumab in comparison with individual treatment.

Research question 2: Patients for whom intensive therapy is unsuitable

Results

The company presented no data for the assessment of the added benefit of pembrolizumab in comparison with the ACT in the first-line setting in adult patients with metastatic MSI-H or dMMR colorectal cancer, for whom intensive treatment is unsuitable. This resulted in no hint of an added benefit of pembrolizumab in comparison with the ACT; an added benefit is therefore not proven.

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:

Research question 1: Patients for whom intensive therapy is appropriate

In the overall consideration of the data, there are mainly positive effects of pembrolizumab in comparison with individual treatment. These effects were shown exclusively in the outcome category of side effects in serious/severe and in non-serious/non-severe side effects.

[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].

This resulted in a hint of lesser harm with the extent "considerable" or "major" for the superordinate outcomes "SAEs" and "severe AEs (CTCAE grade ≥ 3)". Among the severe AEs, there were several specific AEs in favour of pembrolizumab with the extent "minor" to "major". Hints of lesser harm with the extent "considerable" in the category "non-serious/non-severe side effects" were shown for several outcomes.

In contrast, there are hints of greater harm from pembrolizumab compared to individual treatment in immune-related SAEs and non-serious/non-severe side effects for the outcome "arthralgia" with the extent "considerable" or "major".

There are no usable data for the outcome categories of morbidity and health-related quality of life.

In the present situation, the added benefit is thus based exclusively on differences in the category of side effects. A balancing of the effects under consideration of the outcome categories of morbidity and health-related quality of life is not possible, however, because data were not usable. It is therefore not possible to assess whether and to what extent the advantages in side effects are also reflected in the morbidity and health-related quality of life of the patients. Due to the size of the observed effects in the side effects, however, it cannot be assumed that these can be completely questioned by the missing data in the outcome categories of morbidity and health-related quality of life.

In summary, there is a hint of considerable added benefit of pembrolizumab in comparison with individual treatment in the first-line setting for adult patients with metastatic MSI-H or dMMR colorectal cancer, for whom intensive treatment is suitable.

Research question 2: Patients for whom intensive therapy is unsuitable

Added benefit not proven as the company presented no data for the assessment of the added benefit of pembrolizumab in comparison with the ACT in the first-line setting in adult patients with metastatic MSI-H or dMMR colorectal cancer, for whom intensive treatment is unsuitable.

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

Table 3: Pembrolizumab – probability and extent of added benefit

Research question	**Therapeutic indication**[a]	**ACT**[b]	**Probability and extent of added benefit**
1	Adult patients with metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer for whom intensive treatment is suitable; first-line treatment	Individual treatment depending on the all-RAS mutation status, the location of the primary tumour and the risk of toxicity induced by bevacizumab, choosing from the following options ▪ combination therapy of 5-fluorouracil + folinic acid + oxaliplatin (FOLFOX) ▪ combination therapy of 5-fluorouracil + folinic acid + irinotecan (FOLFIRI) ▪ combination therapy of 5-fluorouracil + folinic acid + oxaliplatin (FOLFOX) and an anti-EGFR treatment (cetuximab or panitumumab) - (only for patients with RAS wild type) ▪ combination therapy of 5-fluorouracil + folinic acid + irinotecan (FOLFIRI) and an anti-EGFR treatment (cetuximab or panitumumab) - (only for patients with RAS wild type) ▪ combination therapy of 5-fluorouracil + folinic acid + oxaliplatin (FOLFOX) and bevacizumab ▪ combination therapy of 5-fluorouracil + folinic acid + irinotecan (FOLFIRI) and bevacizumab	Hint of considerable added benefit[c]
2	Adult patients with metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer for whom intensive treatment is unsuitable; first-line treatment	▪ 5-fluorouracil + folinic acid ± bevacizumab or ▪ capecitabine ± bevacizumab or ▪ combination therapy of 5-fluorouracil + folinic acid + oxaliplatin (reduced intensity) ± bevacizumab or ▪ combination therapy of 5-fluorouracil + folinic acid + irinotecan (reduced intensity) ± bevacizumab	Added benefit not proven

a. For the present therapeutic indication, it is assumed that treatment with curative intent or primary resection is not an option for the patients with metastatic colorectal cancer.
b. Presentation of the respective ACT specified by the G-BA.
c. The KEYNOTE 177 study included only patients with an ECOG PS of 0 or 1. It remains unclear whether the observed effects can be transferred to patients with an ECOG PS of ≥ 2.

5-FU: 5-fluorouracil; dMMR: mismatch repair deficiency; ECOG PS: Eastern Cooperative Oncology Group Performance Status; EGFR: epidermal growth factor receptor; FOLFIRI: folinic acid + 5-fluorouracil + irinotecan; FOLFOX 5-fluorouracil + folinic acid + oxaliplatin; G-BA: Federal Joint Committee; MSI-H: high-frequency microsatellite instability; RAS: rat sarcoma viral oncogene homologue

The approach for the derivation of 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 is the assessment of the added benefit of pembrolizumab in comparison with the ACT in adult patients with metastatic colorectal cancer whose tumours have MSI-H or are dMMR in the first-line setting

The research questions shown in Table 4 resulted from the ACT specified by the G-BA.

Table 4: Research questions of the benefit assessment of pembrolizumab

Research question	Therapeutic indication[a]	ACT[b]
1	Adult patients with metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer for whom intensive treatment is suitable; first-line treatment	Individual treatment depending on the all-RAS mutation status, the location of the primary tumour and the risk of toxicity induced by bevacizumab, choosing from the following options ▪ combination therapy of 5-fluorouracil + folinic acid + oxaliplatin (FOLFOX) ▪ combination therapy of 5-fluorouracil + folinic acid + irinotecan (FOLFIRI) ▪ combination therapy of 5-fluorouracil + folinic acid + oxaliplatin (FOLFOX) and an anti-EGFR treatment (cetuximab or panitumumab) - (only for patients with RAS wild type) ▪ combination therapy of 5-fluorouracil + folinic acid + irinotecan (FOLFIRI) and an anti-EGFR treatment (cetuximab or panitumumab) - (only for patients with RAS wild type) ▪ combination therapy of 5-fluorouracil + folinic acid + oxaliplatin (FOLFOX) and bevacizumab ▪ combination therapy of 5-fluorouracil + folinic acid + irinotecan (FOLFIRI) and bevacizumab
2	Adult patients with metastatic MSI-H or dMMR colorectal cancer for whom intensive treatment is unsuitable; first-line treatment	▪ 5-fluorouracil + folinic acid ± bevacizumab or ▪ capecitabine ± bevacizumab or ▪ combination therapy of 5-fluorouracil + folinic acid + oxaliplatin (reduced intensity) ± bevacizumab or ▪ combination therapy of 5-fluorouracil + folinic acid + irinotecan (reduced intensity) ± bevacizumab

a. For the present therapeutic indication, it is assumed that treatment with curative intent or primary resection is not an option for the patients with metastatic colorectal cancer.
b. Presentation of the respective ACT specified by the G-BA.

5-FU: 5-fluorouracil; dMMR: mismatch repair deficiency: EGFR: epidermal growth factor receptor; FOLFIRI: folinic acid + 5-fluorouracil + irinotecan; FOLFOX 5-fluorouracil + folinic acid + oxaliplatin; G-BA: Federal Joint Committee; MSI-H: high-frequency microsatellite instability; RAS: rat sarcoma viral oncogene homologue

In the present assessment, the following terms are used for the patient populations of the 2 research questions:

- Research question 1: Patients for whom intensive therapy is appropriate
- Research question 2: Patients for whom intensive therapy is unsuitable

Deviating from the G-BA, the company did not differentiate between the population of patients for whom intensive treatment is suitable or unsuitable. The company specified the ACT determined by the G-BA for research question 1 for all patients in the therapeutic indication. It justified this with the fact that pembrolizumab is approved for the entire therapeutic indication, that patients in the first line should receive the most intensive therapy possible according to the guidelines and that monotherapy with 5-FU is not effective in patients with metastatic MSI-H or dMMR colorectal cancer.

The company's reasoning is not substantive. The differentiation of the populations of patients for whom intensive treatment is suitable or unsuitable corresponds to the recommendations of the current guidelines [3,4]. Patients for whom intensive treatment is unsuitable should receive the most effective suitable therapy according to their general condition. Moreover, the ACT specified by the G-BA includes various options; monotherapy with 5-FU was therefore not necessary.

Concurring with the G-BA's specification, the present assessment was conducted for the two research questions 1 and 2, each in comparison with the ACT specified by the G-BA.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs were used for the derivation of the added benefit. This concurs with the company's inclusion criteria.

2.3 Research question 1: Patients for whom intensive therapy is suitable

2.3.1 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: 15 January 2021)
- bibliographical literature search on pembrolizumab (last search on 20 January 2021)
- search in trial registries/trial results databases for studies on pembrolizumab (last search on 20 January 2021)
- search on the G-BA website for pembrolizumab (last search on 20 January 2021)

The completeness of the study pool was checked by:

- search in trial registries for studies on pembrolizumab (last search on 9 April 2021); for search strategies, see Appendix C of the full dossier assessment

The check did not identify any additional relevant study.

2.3.1.1 Studies included

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

Table 5: Study pool – RCT, direct comparison: pembrolizumab vs. chemotherapy[a] ± bevacizumab or cetuximab (patients for whom intensive therapy is suitable)

Study	Study category			Available sources		
	Study for the approval of the drug to be assessed (yes/no)	Sponsored study[b] (yes/no)	Third-party study (yes/no)	CSR yes/no [citation])	Registry entries[c] (yes/no [citation])	Publication and other sources[d] (yes/no [citation])
KEYNOTE 177	Yes	Yes	No	No[e]	Yes [5,6]	Yes [7,8]

a. mFOLFOX6 or FOLFIRI.
b. Study for which the company was sponsor.
c. Citation of the study registry entries and, if available, of the reports on study design and/or results listed in the study registries.
d. Other sources: documents from the search on the G-BA website and other publicly available sources.
e. Due to the working conditions during the coronavirus pandemic, the present assessment was conducted without access to the CSR in Module 5 of the dossier.

5-FU: 5-fluorouracil; FOLFIRI: folinic acid + 5-fluorouracil + irinotecan; mFOLFOX6: folinic acid + 5-fluorouracil + oxaliplatin (modified regimen); RCT: randomized controlled trial

The study KEYNOTE 177 was used for the benefit assessment. The study pool concurs with that of the company.

The KEYNOTE 177 study mainly included patients for whom intensive treatment was suitable. Therefore, the results of the total population of the study are used for research question 1 in the present benefit assessment.

Deviating from this, the company did not further differentiate between the populations of patients for whom intensive therapy was suitable or not suitable, and used the results of the total population of the KEYNOTE 177 study to assess the added benefit for all patients in the therapeutic indication.

2.3.1.2 Study characteristics

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

Table 6; Characteristics of the included study – RCT, direct comparison: pembrolizumab vs. chemotherapy a ± bevacizumab or cetuximab (patients for whom intensive therapy is suitable)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[b]
KEYNOTE 177	RCT, open-label, parallel	Adult patients (≥ 18 years) with metastatic colorectal cancer with MSI-H or dMMR in the first-line setting[c], with ECOG PS 0 or 1	Pembrolizumab (N = 153) chemotherapy[a] ± bevacizumab or cetuximab (N = 154)	Screening: up to 42 days before start of treatment treatment: until disease progression, unacceptable toxicity, occurrence of intercurrent diseases that make further treatment impossible, treatment discontinuation following the decision of the physician or the patient (pembrolizumab: at most 24 months[d]) observation[e]: outcome-specific, at most until death, discontinuation of participation in the study or end of study	120 study centres in 23 countries: Australia, Belgium, Brazil, Canada, Denmark, Finland, France, Germany, Ireland, Israel, Italy, Japan, Netherlands, Norway, Singapore, South Africa, South Korea, Spain, Sweden, Switzerland, Taiwan, United Kingdom, USA 11/2015–ongoing data cut-offs: first data cut-off[f]: 19 October 2018 second data cut-off: 19 February 2020	Primary: overall survival, PFS (BICR) Secondary: morbidity, health-related quality of life, AEs

a. mFOLFOX6 or FOLFIRI.
b. 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.
c. Patients had to be untreated at the metastatic stage. Prior adjuvant chemotherapy completed at least 6 months prior to randomization was allowed.
d. Patients who achieved complete response after at least 8 cycles of treatment with pembrolizumab were allowed to interrupt treatment after a further 2 cycles. Treatment could be continued for further a 17 cycles in the event of subsequent confirmed disease progression. Patients who had tumour response after 24 months of treatment and did not receive any other follow-up therapy could also be treated with pembrolizumab for a further 17 cycles in the event of subsequent confirmed disease progression. At the time of the second data cut-off, 7 patients in the intervention arm were in the second phase of treatment.
e. Outcome-specific information is provided in Table 8.
f. Prespecified interim analysis; this analysis was only reviewed by an external data monitoring committee with the recommendation to continue the study as planned. The sponsor remained blinded for this data cut-off; relevant data are not available.

AE: adverse event; 5-FU: 5-fluorouracil; BICR: blinded independent central review committee; dMMR: mismatch repair deficiency; ECOG PS: Eastern Cooperative Oncology Group Performance Status; FOLFIRI: folinic acid + 5-fluorouracil + irinotecan; mFOLFOX6: folinic acid + 5-fluorouracil + oxaliplatin (modified regimen); MSI-H: high-frequency microsatellite instability; N: number of randomized patients; RCT: randomized controlled trial

Table 7: Characteristics of the intervention – RCT, direct comparison: pembrolizumab vs. chemotherapy a ± bevacizumab or cetuximab (patients for whom intensive therapy is suitable) (multipage table)

Study	Intervention	Comparison[b]
KEYNOTE 177	Pembrolizumab 200 mg IV as infusion administered over 30 minutes every 3 weeks	mFOLFOX6: oxaliplatin 85 mg/m² BSA IV over 2 hours once every 2 weeks folinic acid 400 mg/m² BSA IV over 2 hours once every 2 weeks[c] 5-FU 400 mg/m² BSA IV bolus injection once every 2 weeks, followed by 5-FU 1200 mg/m² BSA/day on days 1 and 2 (2400 mg/m² BSA for 46–48 hours) IV injection every 2 weeks or FOLFIRI: irinotecan 180 mg/m² BSA IV over 30-90 minutes once every 2 weeks folinic acid 400 mg/m² BSA IV over 30-90 minutes once every 2 weeks[c] 5-FU 400 mg/m² BSA IV bolus injection once every 2 weeks, followed by 5-FU 1200 mg/m² BSA/day on days 1 and 2 (2400 mg/m² BSA for 46–48 hours) IV injection every 2 weeks ± bevacizumab 5 mg/kg BW over 30-90 minutes once every 2 weeks or cetuximab 400 mg/m² BSA IV once over 2 hours, thereafter weekly 250 mg/m² BSA IV over 1 hour
	Dose adjustment: ▪ pembrolizumab: dose interruption/treatment discontinuation allowed in case of immune-related or infusion-related AEs[d] ▪ mFOLFOX6 or FOLFIRI ± bevacizumab or cetuximab: allowed in case of AEs[e]	
	Permitted pretreatment ▪ adjuvant chemotherapy for the treatment of early-stage colorectal cancer, if this chemotherapy was completed at least 6 months before randomization **non-permitted pretreatment** ▪ systemic therapy for metastatic colorectal cancer (stage VI) ▪ other test therapies ≤ 4 weeks before randomization ▪ systemic therapy for autoimmune disorders within 2 years before randomization ▪ radiotherapy ≤ 4 weeks before randomization with existing side effects ▪ immune checkpoint inhibitors (e.g. anti-PD-1, anti-PD-L1, anti-PD-L2 or anti-CTLA-4 substance) **Permitted concomitant treatment** ▪ any therapy that, at the investigator's discretion, is necessary for the patient's well-being (including local palliative treatment in consultation with the sponsor) **non-permitted concomitant treatment** ▪ antineoplastic systemic chemotherapies or immunotherapies not predefined in the protocol ▪ clinical test medications other than pembrolizumab ▪ live vaccines within 30 days before the first dose of the study medication and during the study treatment ▪ glucocorticoids for purposes other than the regulation of symptoms of an event of clinical interest with suspected immunological aetiology	

Table 7: Characteristics of the intervention – RCT, direct comparison: pembrolizumab vs. chemotherapy a ± bevacizumab or cetuximab (patients for whom intensive therapy is suitable) (multipage table)

Study	Intervention	Comparison[b]
a. mFOLFOX6 or FOLFIRI. b. Specified before randomization at the discretion of the investigator. c. Or (receptor activator of nuclear factor kappa-B ligand [L]) folinic acid 200 mg/m² BSA IV over 2 hours once every 2 weeks in combination with oxaliplatin, or over 30–90 minutes in combination with irinotecan. d. Procedure for the occurrence of immune-related AEs according to predefined recommendations of the company. e. Procedure in accordance with local standard. 5-FU: 5-fluorouracil; AE: adverse event; CTLA-4: cytotoxic T-lymphocyte-associated antigen 4; FOLFIRI: folinic acid + 5-fluorouracil + irinotecan; IV: intravenous; BSA: body surface area; BW: body weight; mFOLFOX6: folinic acid + 5-fluorouracil + oxaliplatin (modified regimen); PD-1: programmed cell death protein1; PD-L1: programmed cell death ligand 1; PD-L2: programmed cell death ligand 2; RCT: randomized controlled trial		

The KEYNOTE 177 study is an ongoing, open-label, randomized, active-controlled multicentre study on the comparison of pembrolizumab with individual treatment choosing from a chemotherapy (FOLFOX), administered as modified regimen mFOLFOX6, or FOLFIRI ± bevacizumab or cetuximab.

The study included adult patients with metastatic MSI-H or dMMR colorectal cancer. The patients were not allowed to have received prior systemic therapy in the metastatic stage; any prior adjuvant chemotherapy for the treatment of an earlier stage of the colorectal cancer had to be completed 6 months before the start of the study. The patients had to have a good general condition ECOG PS ≤ 1) and adequate organ function. Patients with ECOG PS > 1 and active brain metastases were excluded from participation in the study; hence, no data are available for them.

The presence of MSI-H or dMMR was determined locally by polymerase chain reaction (PCR) or immunohistochemistry (IHC).

The KEYNOTE 177 study included a total of 307 patients, randomized in a 1:1 ratio either to treatment with pembrolizumab (N = 153) or to chemotherapy, consisting of mFOLFOX6 or FOLFIRI ± bevacizumab or cetuximab (N = 154). Prior to randomization, the investigator determined which of the cited therapy options each patient should receive if assigned to the control arm.

Treatment with pembrolizumab in the intervention arm and treatment in the control arm was largely in compliance with the requirements of the SPC [9-15]. Deviating from the requirements of the SPC, treatment with pembrolizumab was limited to a maximum treatment duration of 35 cycles (approx. 2 years). However, according to the SPC, treatment with pembrolizumab should be continued until progression of the cancer or until the occurrence of unacceptable toxicity [9]. However, in the KEYNOTE 177 study, 57 (37.3%) patients in the intervention arm

discontinued their therapy with pembrolizumab after a maximum treatment duration of 35 cycles without having achieved the reasons for discontinuation described in the SPC. Therefore, there was no further treatment in accordance with the SPC. As there is no information on when these 57 patients showed progression of the cancer, it is unclear whether and how long the further treatment should have lasted according to the SPC.

Moreover, the study population was treated until progression (determined using Response Evaluation Criteria-In-Solid-Tumours [RECIST] criteria version 1.1), occurrence of unacceptable side effects or intercurrent diseases that made further treatment impossible or decision by the investigator or the patient. If disease progression was confirmed, a switch from the control to the intervention arm was possible after a washout period of 30 days.

Co-primary outcomes of the study were "overall survival" and "PFS". Patient-relevant secondary outcomes were outcomes on morbidity, health-related quality of life and AEs.

Implementation of the ACT

The G-BA specified individual treatment depending on the all-rat sarcoma viral oncogene homologue (RAS) mutation status, the location of the primary tumour, and the risk of bevacizumab-induced toxicity as ACT for patients for whom intensive therapy was appropriate, choosing from FOLFOX or FOLFIRI ± bevacizumab or anti-epidermal growth factor receptor (EGFR) therapy (cetuximab or panitumumab).

Prior to randomization, the investigator determined which of the cited therapies each patient should receive if assigned to the control arm of the multi-comparator study KEYNOTE 177. The options comprised FOLFOX or FOLFIRI ± bevacizumab or cetuximab. Treatment was chosen on the basis of eligibility criteria not described in more detail by the company. Due to the exclusion of patients with an ECOG PS > 1, the requirement of the presence of adequate organ function at baseline and the performance of appropriate laboratory tests and organ examinations before the start of a new cycle, it can be assumed that intensive therapy was basically suitable for the patients included in KEYNOTE 177.

The criteria for the choice of the possible combination partner bevacizumab or cetuximab (all-RAS mutation status, localisation of the primary tumour), which can also be objectified via the guidelines [3,4], are not explicitly named in the study documents. However, the patient characteristics provide information on the all-RAS mutation status and on the location of the primary tumour. It is therefore assumed that these were taken into account when choosing the combination partner bevacizumab or cetuximab. Overall, the ACT was considered adequately implemented.

Data cut-offs

To date, 2 data cut-offs have been performed in the KEYNOTE 177 study:

- First data cut-off (19 October 2018): pre-planned interim analysis after approx. 162 PFS events and after an observation period of at least 6 months of all patients after randomization. This data cut-off was only reviewed by an external data monitoring committee; data are not available.
- Second data cut-off (19 February 2020): pre-planned interim analysis after approx. 209 PFS events or after an observation period of at least 24 months of all patients after randomization.

The final data cut-off is still pending and is planned to take place after 190 deaths or 12 months after the second interim analysis; whichever occurs first.

The results on the second data cut-off presented by the company are analysed in the present benefit assessment.

Follow-up observation

Table 8 shows the planned duration of follow-up observation of the patients for the individual outcomes.

Table 8: Planned duration of the follow-up observation – RCT, direct comparison: pembrolizumab vs. chemotherapy a ± bevacizumab or cetuximab (patients for whom intensive therapy is suitable)

Study **outcome category** **outcome**	**Planned follow-up observation**
KEYNOTE 177	
Mortality	
Overall survival	Until death, withdrawal of consent or end of study
Morbidity	
Symptoms (EORTC QLQ-C30 and EORTC QLQ-MY20), health status (EQ-5D VAS)	At most up to week 45 or until end of treatment, whichever is first, and 30 days after the last dose of the study medication.
Health-related quality of life EORTC-QLQ-C30 and EORTC-QLQ-CR29	At most up to week 45 or until end of treatment, whichever is first, and 30 days after the last dose of the study medication
Side effects	
AEs and severe AEs[b]	Up to 30 days after the last dose of the study medication
SAEs	Up to 90 days after the last dose of the study medication or 30 days in case of initiation of a subsequent therapy

a. mFOLFOX6 or FOLFIRI.
b. Severe AEs are operationalized as CTCAE grade ≥ 3.

5-FU: 5-fluorouracil; AE: adverse event; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EORTC-QLQ-CR29: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire for Colorectal Cancer; FOLFIRI: folinic acid + 5-fluorouracil + irinotecan; mFOLFOX6: folinic acid + 5-fluorouracil + oxaliplatin (modified regimen); RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale

The monitoring periods for the outcomes on side effects were systematically shortened, because they were only recorded for the time of treatment with the study medication (plus 30 days or up to 90 days for SAEs). The observation periods for patient-reported outcomes (PROs) on symptoms, health status and health-related quality of life were also systematically shortened, as they were maximally recorded until week 45 or end of treatment, whichever occurred first, as well as 30 days after end of treatment. 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.

Characteristics of the study population

Table 9 shows the characteristics of the patients in the study included.

Table 9: Characteristics of the study population – RCT, direct comparison: pembrolizumab vs. chemotherapy a ± bevacizumab or cetuximab (patients for whom intensive therapy is suitable) (multipage table)

Study characteristic category	**Pembrolizumab N[b] = 153**	**Chemotherapy[a] ± bevacizumab/cetuximab N[b] = 154**
KEYNOTE 177		
Age [years], mean (SD)	62 (15)	61 (15)
Sex [F/M], %	54/46	47/53
Family origin, n (%)		
Asian	24 (16)	26 (17)
Black or African American	9 (6)	5 (3)
Caucasian	113 (74)	116 (75)
Missing	7 (5)	7 (5)
Region, n (%)		
Asia	22 (14)	26 (17)
Western Europe/North America	109 (71)	113 (73)
Rest of the world	22 (14)	15 (10)
ECOG PS, n (%)		
0	75 (49)	84 (55)
1	78 (51)	70 (45)
Location of primary tumour[c], n (%)		
Right side	102 (67)	107 (69)
Left side	46 (30)	42 (27)
Other	4 (3)	5 (3)
Missing	1 (1)	0 (0)
Metastases, n (%)		
Hepatic or pulmonary	86 (56)	73 (47)
Other metastases	67 (44)	81 (53)
Diagnosed stage, n (%)		
Recurrent	80 (52)	74 (48)
Newly diagnosed stage	73 (48)	80 (52)
Prior systemic therapy, n (%)		
Adjuvant only	33 (22)	37 (24)
Neoadjuvant only	2 (1)	3 (2)
Neoadjuvant and adjuvant	3 (2)	5 (3)
None	115 (75)	109 (71)

Table 9: Characteristics of the study population – RCT, direct comparison: pembrolizumab vs. chemotherapy a ± bevacizumab or cetuximab (patients for whom intensive therapy is suitable) (multipage table)

Study characteristic category	**Pembrolizumab N[b] = 153**	**Chemotherapy[a] ± bevacizumab/cetuximab N[b] = 154**
mutation status, n (%)		
BRAF/KRAS/NRAS, all wild type	34 (22)	35 (23)
KRAS/NRAS mutated and BRAF V600E non-mutated	33 (22)	38 (25)
BRAF V600E mutated and KRAS/NRAS non-mutated	34 (22)	40 (26)
BRAF V600E and KRAS/NRAS mutated	0 (0)	3 (2)
Other[d]	52 (34)	38 (25)
MSI-high status[e], n (%)		
Positive	153 (100)	153 (99)
Negative	0 (0)	1 (1)
Treatment discontinuation, n (%)	94 (61)	137 (96[f])
Study discontinuation, n (%)	58 (38)	75 (49)

a. mFOLFOX6 or FOLFIRI.
b. Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
c. If the tumour was located on the left and on the right side, the patient was assigned to the category "others".
d. Others: BRAF V600E, KRAS and NRAS mutated, if at least one mutation status had not been determined or is missing or the BRAF mutation was not of type V600E.
e. MSI status locally recorded with PCR or IHC.
f. The percentage refers to 143 patients who started treatment in the control arm.

5-FU: 5-fluorouracil; BRAF: rapidly accelerated fibrosarcoma – isoform B; F: female; IHC: immunohistochemistry; KRAS: Kirsten rat sarcoma viral oncogene homologue; ECOG PS: Eastern Cooperative Oncology Group Performance Status; FOLFIRI: folinic acid + 5-fluorouracil + irinotecan; M: male; mFOLFOX6: folinic acid + 5-fluorouracil + oxaliplatin (modified regimen); MSI: microsatellite instability; n: number of patients in the category, N: number of randomized patients; NRAS: neuroblastoma rat sarcoma viral oncogene homologue; PCR: polymerase chain reaction; RCT: randomized controlled trial; SD: standard deviation

The patient characteristics are largely balanced between the study arms pembrolizumab or chemotherapy ± bevacizumab or cetuximab. The mean age of the was 62 and 61 years, and the proportion of female and male patients was comparable in both study arms. 49% and 55% of the patients had an ECOG PS of 0. In almost 70% of the patients, the primary tumour was located on the right side, in approx. 30% of the patients on the left side.

While 22% and 23% of patients had wild-type rapidly accelerated fibrosarcoma – isoform B (BRAF)/Kirsten rat sarcoma viral oncogene homologue (KRAS)/neuroblastoma rat sarcoma viral oncogene homologue (NRAS) tumour mutation status, 22% in the intervention arm and 25% in the control arm had KRAS/NRAS mutations but no BRAF V600E mutation. Mutations in both KRAS/NRAS and a BRAF V600E mutation were present in 0% or 2% of the patients.

Information on the course of the study

Table 10 shows the mean and median treatment duration of the patients and the mean and median observation period for individual outcomes.

Table 10; Information on the course of the study – RCT, direct comparison: pembrolizumab vs. chemotherapy a ± bevacizumab or cetuximab (patients for whom intensive therapy is suitable)

Study **duration of the study phase** **outcome category**	**Pembrolizumab** **N = 153**	**Chemotherapy[a] ± bevacizumab/cetuximab** **N = 154**
KEYNOTE 177		
Treatment duration[b] [months]		
Median [min; max]	11.1 [0; 30.6]	5.7 [0.1; 39.6]
Mean (SD)	13.3 (10.3)	8.3 (8.0)
Observation period [months]		
Overall survival[c]		
Median [Q1; Q3]	27.9 [ND]	25.9 [ND]
Mean (SD)	ND	ND
Morbidity	ND	ND
Health-related quality of life	ND	ND
Side effects (AE/severe AEs[d])		
Median [Q1; Q3]	12.1 [ND]	6.6 [ND]
Mean (SD)	ND	ND
Side effects (SAEs)		
Median [Q1; Q3]	14.1 [ND]	7.3 [ND]
Mean (SD)	ND	ND

a. mFOLFOX6 or FOLFIRI.
b. Data are based on 153 or 143 patients of the intervention or the control arm.
c. The company did not provide any information on the determination of observation periods.
d. Severe AEs are operationalized as CTCAE grade ≥ 3.

5-FU: 5-fluorouracil; FOLFIRI: folinic acid + 5-fluorouracil + irinotecan; max: maximum; mFOLFOX6: folinic acid + 5-fluorouracil + oxaliplatin (modified regimen); min: minimum; N: number of randomized patients; ND: no data; Q1: first quartile; Q3: third quartile; RCT: randomized controlled trial; SD: standard deviation

With 11.1 months, the median treatment duration was almost twice as long in the pembrolizumab arm in comparison with the control arm (5.7 months). The median observation period for the outcome "overall survival" was comparable between the two study arms. Information on the observation period for the outcome category "morbidity" and "health-related quality of life" is not available. The median observation period for AEs and severe AEs was 5.5 months longer in the pembrolizumab arm than in the control arm; and 6.8 months longer for SAEs.

Information on subsequent therapies

Table 11 shows, which subsequent therapies patients received after discontinuing the study medication.

Table 11: Information on subsequent therapies[a] – RCT, direct comparison: pembrolizumab vs. chemotherapy b ± bevacizumab or cetuximab (patients for whom intensive therapy is suitable)

Study drug class or drug	Patients with subsequent therapy n (%)	
	pembrolizumab N = 153	chemotherapy[b] ± bevacizumab/cetuximab N = 154
KEYNOTE 177		
Total	44 (28.8)	100 (64.9)[c]
Pembrolizumab (switch of treatment from control to intervention)	0 (0)	56 (36.4)
Other subsequent therapy	44 (28.8)	44 (28.6)
Anti-PD-1/anti-PD-L1 therapy	9 (5.9)[d]	35 (22.7)
Anticholinergics [e]	2 (1.3)	0 (0)
CD40 inhibitor	0 (0)	1 (0.6)
CTLA-4 inhibitor	0 (0)	4 (2.6)
Chemotherapy	35 (22.9)	18 (11.7)
EGFR inhibitor	8 (5.2)	4 (2.6)
Oestrogen derivatives[e]	1 (0.7)	0 (0)
Folic acid derivatives	24 (15.7)	12 (7.8)
ICOS inhibitor	1 (0.7)	1 (0.6)
Nucleoside analogue/thymidine phosphorylase inhibitor	1 (0.7)	2 (1.3)
TIM3 inhibitor	1 (0.7)	1 (0.6)
VEGF inhibitor	22 (14.4)	11 (7.1)

a. Table taken from EPAR [7] as there are discrepancies between the information in Table 4-27 in Module 4 B of the dossier and Section 4.3.1.2.1 of the dossier.
b. mFOLFOX6 or FOLFIRI.
c. Institute's calculation.
d. Including patients who had received a second treatment phase with pembrolizumab. At the time of the second data cut-off, these were 7 patients.
e. Medication was not directly related to colorectal cancer therapy.

5-FU: 5-fluorouracil; CD: cluster of differentiation; CTLA-4: cytotoxic T-lymphocyte-associated antigen 4; EGFR: epidermal growth factor receptor; EPAR: European Public Assessment Report; FOLFIRI: folinic acid + 5-fluorouracil + irinotecan; ICOS: inducible costimulator molecule; mFOLFOX6: folinic acid + 5-fluorouracil + oxaliplatin (modified regimen); n: number of patients with subsequent therapy; N: number of analysed patients; PD-1: programmed cell death protein1; PD-L1: programmed cell death ligand 1; RCT: randomized controlled trial; TIM: t-cell immunoglobulin mucin; VEGF: vascular endothelial growth factor

Subsequent therapy was allowed for patients in both study arms after disease progression. Overall, 28.8% of the patients in the intervention arm and 64.9% of the patients in the control arm had received subsequent systemic therapy at the present data cut-off. Chemotherapy was

the most common subsequent therapy in the intervention arm. The most common subsequent therapy in the control arm was anti-programmed cell death protein1 (PD-1)/anti-programmed cell death ligand 1 (PD-L1) therapy. In this context, 56 (36.4%) patients received pembrolizumab as part of a treatment switch from control to intervention and 35 (22.7%) received anti-PD-1/PD-L1 therapy other than pembrolizumab.

A switch from control to intervention took place in deviation from the approval, as pembrolizumab is only approved for the first-line treatment of metastatic colorectal cancer [9]. According to the German S3 guideline, possible treatment with immune checkpoint inhibitors in further lines of therapy (for MSI-H or dMMR tumours) is to be evaluated, but currently, this is not an approved treatment option [3]. Switching from the control to the experimental intervention or another anti-PD-1/anti-PD-L1 therapy can have a potentially biasing effect on the results of the benefit assessment. This aspect was therefore taken into account in the assessment of the outcome-specific risk of bias for outcomes where the results were possibly affected (see Section 2.3.2.2).

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. chemotherapy a ± bevacizumab or cetuximab (patients for whom intensive therapy is suitable)

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 177	Yes	Yes	No	No	Yes	No[b]	Low

a. mFOLFOX6 or FOLFIRI.
b. According to the protocol, patients in the control arm could switch to treatment with pembrolizumab or another anti-PD-1/anti-PD-L1 therapy in case of confirmed progression; 36% or 23% performed such a switch.

FOLFIRI: folinic acid + 5-fluorouracil + irinotecan; mFOLFOX6: folinic acid + 5-fluorouracil + oxaliplatin (modified regimen); RCT: randomized controlled trial

The risk of bias across outcomes was rated as low for the KEYNOTE 177 study. This concurs with the company's assessment.

In the assessment of the bias aspects across outcomes, the option to switch from the control arm to treatment with pembrolizumab or another anti-PD-1/PD-L1 therapy after progression was considered to be another biasing aspect; this deviates from the company's assessment.

However, this did not result in a high risk of bias across outcomes, but was considered in the assessment of the respective outcome-specific risk of bias.

Limitations resulting from the open-label study design are described under the outcome-specific risk of bias in Section 2.3.2.2.

Transferability of the study results to the German health care context

The company stated that the study results could be transferred to the German healthcare context due to the patient characteristics of the study population, the study design and the approval-compliant use of pembrolizumab. Moreover, the company described that subgroups by geographic region show no indication of a deviating efficacy or safety of pembrolizumab.

The company did not provide any further information on the transferability of the study results to the German health care context.

2.3.2 Results on added benefit

2.3.2.1 Outcomes included

The following patient-relevant outcomes were to be considered in the assessment:

- Mortality
  - overall survival
- Morbidity
  - symptoms measured with the EORTC QLQ-C30 and EORTC-QLQ-CR29 symptom scales
  - health status recorded with the EQ-5D VAS
- Health-related quality of life
  - health-related quality of life measured with the functional scales of the EORTC QLQ-C30 and scales of the EORTC QLQ-CR29
- Side effects
  - SAEs
  - severe AEs (CTCAE grade ≥ 3)
  - discontinuation due to AEs
  - immune-related SAEs and severe AEs
  - further specific AEs, if any

The choice of patient-relevant outcomes deviates from that of the company, which used further outcomes in the dossier (Module 4B).

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

Table 13: Matrix of outcomes – RCT, direct comparison: pembrolizumab vs. chemotherapy a ± bevacizumab or cetuximab (patients for whom intensive therapy is suitable)

Study	Outcomes								
	Overall survival	Symptoms (EORTC QLQ-C30 and EORTC QLQ-CR29)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30 and EORTC QLQ-CR29)	SAEs	Severe AEs[b]	Discontinuation due to AEs	Immune-related SAEs and severe AEs[b]	Further specific AEs[c]
KEYNOTE 177	Yes	No[d]	No[d]	No[d]	Yes	Yes	Yes	Yes	Yes

a. mFOLFOX6 or FOLFIRI.
b. Severe AEs are operationalized as CTCAE grade ≥ 3.
c. The following events were considered (MedDRA coding): "mucosal inflammation (PT, AEs)", "reduced appetite (PT, AEs)", "arthralgia (PT, AEs)", "peripheral neuropathy (PT, AEs)", "peripheral sensory neuropathy (PT, AEs)", "epistaxis (PT, AEs)", "alopecia" (PT, AE)", "palmar-plantar erythrodysaesthesia syndrome (PT, AEs)", "blood and lymphatic system disorders (SOC, severe AEs)", "gastrointestinal disorders (SOC, severe AEs)", "fatigue (PT, severe AEs)", "infections and infestations (SOC, severe AEs)", "hypokalaemia (PT, severe AEs)".
d. No usable data available; see following running text for reasons.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer-Breast Cancer Module; EORTC-QLQ-CR29: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 29; FOLFIRI: folinic acid + 5-fluorouracil + irinotecan; mFOLFOX6: folinic acid + 5-fluorouracil + oxaliplatin (modified regimen); 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

Note on the outcome "overall survival"

To investigate the possible influence of the switch of treatment, the company presented the rank preserving structural failure time (RPFST), inverse probability of censoring weights (IPCW) and two-stage models as sensitivity analyses for the outcome "overall survival". The presented sensitivity analyses are not relevant for the benefit assessment, as these analyses are based on unverifiable assumptions and are also not sufficiently documented by the company [16].

Analyses of the company on the PROs "symptoms (EORTC QLQ-C30 and EORTC QLQ-CR29)", "health status (EQ-5D VAS)" and "health-related quality of life EORTC QLQ-C30 and EORTC QLQ-CR29)" were not usable.

In its dossier, the company presented responder analyses for the time to first deterioration for the PROs on symptoms and health-related quality of life, recorded with the EORTC QLQ-C30 and the EORTC QLQ-CR29, and on the health status, recorded with the EQ-5D VAS. Moreover, the company presented responder analyses on the time to confirmed deterioration as supplementary information. The presented analyses were assessed as unusable. This is justified below:

In the KEYNOTE 177 study, the treatment regimens differed between the study arms. Pembrolizumab was administered in a 3-week cycle, chemotherapy in a 2-week cycle (see Table 7). The PROs were recorded at baseline, week 2 in the control arm and week 3 in the intervention arm and at weeks 6, 9, 12, 18, 27, 36 and up to at most week 45 or end of treatment, whichever occurred first, and 30 days after end of treatment. This resulted in different documentation times of the PROs within the treatment cycles in the two study arms. In the intervention arm, recordings were made at each start of a new cycle, whereas recordings in the control arm took place on weeks 9, 27 and 45 in the middle of the cycle. This resulted in an unequal reflection of the treatment stress in the course of the cycle in the study arms. In contrast to the intervention arm, recordings in the control arm also considered times with potentially higher treatment stress (recordings in the middle of the cycle), resulting in a possible bias of the results. The company presented no corresponding sensitivity analyses for the assessment of a possible impact of the different recording times within the treatment cycle. Due to the unequally represented courses of treatment in the study arms and a resulting potential impact on the results, the results of the PROs (measured using the EORTC QLQ-C30, EORTC QLQ-CR29 and EQ-5D VAS) provide no usable data and are thus not used for the assessment. In order to be able to check the influence of the unequally mapped burden between the arms on the results, further analyses would have been required, for example analyses that disregard the surveys of these time points.

Irrespective of this, the response thresholds used by the company were not continuously suitable.

As explained in the *General Methods* of the Institute [1,17], for a response criterion to reflect with sufficient certainty a patient-noticeable change, it should correspond to a predefined value of at least 15% of the scale range of an instrument (in post-hoc analyses exactly 15% of the scale range). The response criteria chosen by the company for the EQ-5D VAS (time to deterioration by ≥ 7 or ≥ 10 points: scale range 0-100) did not fulfil this requirement. The following applies to the suitability of the response threshold of ≥ 10 points used by the company for the EORTC QLQ-C30 and EORTC QLQ-CR29 (respective scale range 0-100): For the EORTC QLQ-C30 and its additional modules, the analysis with a previously accepted response threshold of 10 points is considered a sufficient approximation to an analysis with a 15% threshold (15 points) in certain constellations and is used for the benefit assessment (for

explanation see [18]). Regardless of this, analyses with the previously accepted response threshold of 10 points for the EORTC QLQ-C30 as well as all additional modules of the EORTC will primarily be used for a transitional period until the adjusted module templates for the dossier come into force (see FAQs of the G-BA [19]).

2.3.2.2 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, direct comparison: pembrolizumab vs. chemotherapy a ± bevacizumab or cetuximab (patients for whom intensive therapy is suitable)

Study		Outcomes								
	Study level	Overall survival	Symptoms (EORTC QLQ-C30 and EORTC QLQ-CR29)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30 and EORTC QLQ-CR29)	SAEs	Severe AEs[b]	Discontinuation due to AEs	Immune-related SAEs and severe AEs[b]	Further specific AEs[c]
KEYNOTE 177	L	H[d]	-[e]	-[e]	-[e]	H[f]	H[f]	H[f, g]	H[f]	H[f, g]

a. mFOLFOX6 or FOLFIRI.
b. Severe AEs are operationalized as CTCAE grade ≥ 3.
c. The following events were considered (MedDRA coding): "mucosal inflammation (PT, AEs)", "reduced appetite (PT, AEs)", "arthralgia (PT, AEs)", "peripheral neuropathy (PT, AEs)", "peripheral sensory neuropathy (PT, AEs)", "epistaxis (PT, AEs)", "alopecia" (PT, AE)", "palmar-plantar erythrodysaesthesia syndrome (PT, AEs)", "blood and lymphatic system disorders (SOC, severe AEs)", "gastrointestinal disorders (SOC, severe AEs)", "fatigue (PT, severe AEs)", "infections and infestations (SOC, severe AEs)", "hypokalaemia (PT, severe AEs)".
d. High proportion of patients who switched from the control arm to treatment with pembrolizumab or another anti-PD-1/anti-PD-L1 therapy (36% and 23%).
e. No usable data available; for reasons, see Section 2.3.2.1 of the present dossier assessment.
f. Large difference between the treatment arms (> 5 percentage points) regarding the proportion of patients who were not considered in the analysis. Moreover, incomplete observations for potentially informative reasons (except discontinuation due to AEs).
g. Lack of blinding in subjective recording of outcomes (except for specific AEs with CTCAE grade ≥ 3) or subjective request for treatment discontinuation (discontinuation due to AEs).

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer-Breast Cancer Module; EORTC-QLQ-CR29: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 29; FOLFIRI: folinic acid + 5-fluorouracil + irinotecan; H: high; L: low; mFOLFOX6: folinic acid + 5-fluorouracil + oxaliplatin (modified regimen); 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

The risk of bias was rated as high for the result of the outcome "overall survival". The progression-related switch of 36% and 23% of patients in the control arm, respectively, to subsequent therapy with pembrolizumab or another anti-PD-1/PD-L1 therapy is not in compliance with the approval. Pembrolizumab is only approved for the first-line treatment of metastatic MSI-H or dMMR colorectal cancer, whereas other anti-PD-1/anti-PD-L1 therapies are not approved for this therapeutic indication [20-23].

This deviates from the assessment of the company, which assumed a low risk of bias for this outcome.

There are no usable data for the outcomes on symptoms and health-related quality of life (recorded with the EORTC QLQ-C30 and EORTC QLQ-CR29) as well as for the outcome "health status" (recorded with the EQ-5D VAS) (for reasons, see Section 2.3.2.1). Therefore, the risk of bias was not assessed. This deviates from the assessment of the company, which used the outcomes "symptoms" and "health status" as well as "health-related quality of life" recorded with the EORTC QLQ-C30, the EORTC QLQ-CR29 and the EQ-5D VAS for the assessment and assumed a high risk of bias for each of these.

The risk of bias of the results of the outcomes in the side effects category is assessed as high in each case due to the great difference between the treatment groups (> 5 percentage points) with regard to the proportion of patients not included in the analysis.

Moreover, there is a high risk of bias of the results (with the exception of "discontinuation due to AEs") due to incomplete observations for potentially informative reasons. Planned follow-up observation after the end of treatment was 30 and 90 days for these outcomes, respectively, and resulted in significant differences in the median observation period between treatment groups ([severe] AEs: 12.1 vs. 6.6 months; SAEs: 14.1 vs. 7.3 months). The observation period was thus determined by the reasons for treatment discontinuation (largely by disease progression), which clearly differed between the treatment arms. Treatment discontinuation was 61.4% in the intervention arm and 95.8% in the control arm, of which 53.2% and 62.8%, respectively, were due to disease progression and 23.4% and 12.4%, respectively, were due to AEs. Due to a possible correlation between the reason for treatment discontinuation and these outcomes, there are incomplete observations for potentially informative reasons.

With the exception of the specific AEs with CTCAE grade ≥ 3, the high risk of bias of the results for the other outcomes of the category "side effects ("discontinuation due to AEs" and "further specific AEs") is also due to the lack of blinding in subjective recording of outcomes or subjective request for treatment discontinuation.

This assessment deviates from that of the company, which assumed a low risk of bias for the results on these outcomes.

2.3.2.3 Results

Table 15 summarizes the results for the comparison of pembrolizumab with chemotherapy ± bevacizumab or cetuximab in first-line treatment of patients with metastatic MSI-H or dMMR colorectal cancer for whom intensive treatment is suitable. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier.

Kaplan-Meier curves on the event time analyses are presented in Appendix A. The results on the common AEs, SAEs and severe AEs, as well as on all AEs that led to treatment discontinuation are presented in Appendix B of the full dossier assessment.

Table 15: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: pembrolizumab vs. chemotherapy a ± bevacizumab or cetuximab (patients for whom intensive therapy is suitable (multipage table)

Study outcome category outcome	Pembrolizumab		Chemotherapy[a] ± bevacizumab/cetuximab		Pembrolizumab vs. chemotherapy[a] ± bevacizumab/cetuximab
	N	median time to event in months [95% CI] patients with event n (%)	N	median time to event in months [95% CI] patients with event n (%)	HR [95% CI][b]; p-value[c]
KEYNOTE 177					
Mortality					
Overall survival	153	NA 56 (36.6)	154	34.8 [26.3; NC] 69 (44.8)	0.77 [0.54; 1.09]; 0.140
Morbidity					
Symptoms (EORTC QLQ-C30)			No usable data available[d]		
Symptoms (EORTC QLQ-CR29)			No usable data available[d]		
Health status (EQ-5D VAS)			No usable data available[d]		
Health-related quality of life					
EORTC QLQ-C30			No usable data available[d]		
EORTC QLQ-CR29			No usable data available[d]		
Side effects					
AEs (supplementary information)[e]	153	0.3 [0.1; 0.5][f] 149 (97.4)	143	0.1 [0.1; 0.1][f] 142 (99.3)	-
SAEs[e]	153	24.6 [14.0; NC][f] 62 (40.5)	143	8.0 [3.7; 20.6][f] 75 (52.4)	0.61 [0.43; 0.85]; 0.004
Severe AEs[e, g]	153	10.8 [6.3; 14.1][f] 86 (56.2)	143	2.1 [1.5; 2.6][f] 111 (77.6)	0.41 [0.31; 0.55]; < 0.001
Discontinuation due to AEs[e]	153	NA 21 (13.7)	143	NA [27.5; NC][f] 17 (11.9)	0.88 [0.46; 1.70]; 0.710
Immune-related SAEs[e, h]	153	NA 16 (10.5)	143	NA 1 (0.7)	12.04 [1.59; 91.28]; 0.016
Immune-related severe AEs[e, g, h]	153	NA 14 (9.2)	143	NA 3 (2.1)	3.10 [0.88; 10.95]; 0.079
Mucosal inflammation (PT, AEs)	153	NA 7 (4.6)	143	NA 27 (18.9)	0.19 [0.08; 0.44]; < 0.001
Decreased appetite (PT, AEs)	153	NA 36 (23.5)	143	14.9 [6.9; NC][f] 58 (40.6)	0.49 [0.32; 0.74]; < 0.001
Arthralgia (PT, AEs)	153	NA 28 (18.3)	143	NA 7 (4.9)	3.12 [1.35; 7.19]; 0.008
Peripheral neuropathy (PT, AEs)	153	NA 1 (0.7)	143	NA 27 (18.9)	0,03 [0.00; 0.22]; < 0.001

Table 15: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: pembrolizumab vs. chemotherapy a ± bevacizumab or cetuximab (patients for whom intensive therapy is suitable (multipage table)

Study outcome category outcome	Pembrolizumab		Chemotherapy[a] ± bevacizumab/cetuximab		Pembrolizumab vs. chemotherapy[a] ± bevacizumab/cetuximab
	N	median time to event in months [95% CI] patients with event n (%)	N	median time to event in months [95% CI] patients with event n (%)	HR [95% CI][b]; p-value[c]
Peripheral sensory neuropathy (PT, AEs)	153	NA 3 (2.0)	143	NA 31 (21.7)	0,07 [0.02; 0.22]; < 0.001
Epistaxis (PT, AEs)	153	NA 2 (1.3)	143	NA 23 (16.1)	0,07 [0.02; 0.28]; < 0.001
Alopecia (PT, AEs)	153	NA 11 (7.2)	143	NA 29 (20.3)	0,29 [0.14; 0.59]; < 0.001
Palmar-plantar erythrodysaesthesia syndrome (PT, AEs)	153	NA 1 (0.7)	143	NA [17.0; NC][f] 25 (17.5)	0,03 [0.00; 0.19]; < 0.001
Blood and lymphatic system disorders (SOC, severe AEs[g])	153	NA 12 (7.8)	143	NA 39 (27.3)	0,24 [0.12; 0.46]; < 0.001
Gastrointestinal disorders (SOC, severe AEs[g])	153	NA 31 (20.3)	143	NA [9.5; NC][f] 52 (36.4)	0,40 [0.25; 0.63]; < 0.001
Fatigue (PT, severe AEs[g])	153	NA 6 (3.9)	143	NA 13 (9.1)	0.32 [0.12; 0.86]; 0.024
Infections and infestations (SOC, severe AEs[g])	153	NA 14 (9.2)	143	NA 23 (16.1)	0.51 [0.26; 0.99]; 0.046
Hypokalaemia (PT, severe AEs[g])	153	NA 2 (1.3)	143	NA 9 (6.3)	0.18 [0.04; 0.85]; 0.030

a. mFOLFOX6 or FOLFIRI.
b. HR and CI: Cox proportional hazards model.
c. p-value: Wald test.
d. No usable data available; for reasons, see Section 2.3.2.1 of the present dossier assessment.
e. Overall rate without AEs ascribed to the progression of the underlying disease, defined as MedDRA terms "neoplasm progression", „malignant neoplasm progression" and „disease progression".
f: Institute's calculation (conversion from weeks to months).
g. Operationalized as CTCAE grade ≥ 3.
h. Predefined PT list of the company (version 17.1).

A5-FU: 5-fluorouracil; AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer-Breast Cancer Module; EORTC-QLQ-CR29: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 29; FOLFIRI: folinic acid + 5-fluorouracil + irinotecan; HR: hazard ratio; mFOLFOX6: folinic acid + 5-fluorouracil + oxaliplatin (modified regimen); MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with event; N: number of analysed patients; NA: not achieved; NC: not calculable; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

On the basis of the available information, no more than hints, e.g. of an added benefit, can be determined for all outcomes.

Mortality

Overall survival

No statistically significant difference between the treatment groups was shown for the outcome "overall survival". This resulted in no hint of an added benefit of pembrolizumab in comparison with individual treatment; an added benefit is therefore not proven.

This concurs with the company's assessment.

Morbidity

Symptoms (EORTC QLQ-C30 and EORTC QLQ-CR29)

In each case, there were no usable data for the outcomes on symptoms recorded with the EORTC QLQ-C30 and the EORTC QLQ-CR29 (see Section 2.3.2.1). This resulted in no hint of an added benefit of pembrolizumab in comparison with individual treatment in each case; an added benefit is therefore not proven.

This deviates from the assessment of the company, which used the respective responder analyses for the time to first deterioration for the assessment and overall derived an indication of added benefit for the outcome category "morbidity".

Health status (EQ-5D VAS)

There were no usable data for the outcome "health status" recorded with the EQ-5D VAS (see Section 2.3.2.1). This resulted in no hint of an added benefit of pembrolizumab in comparison with individual treatment; an added benefit is therefore not proven.

This deviates from the assessment of the company, which used the respective responder analyses for the time to first deterioration for the assessment and overall derived an indication of added benefit for the outcome category "morbidity".

Health-related quality of life

EORTC QLQ-C30 and EORTC QLQ-CR29

In each case, there were no usable data for the outcomes on health-related quality of life recorded with the EORTC QLQ-C30 and the EORTC QLQ-CR29 (see Section 2.3.2.1). This resulted in no hint of an added benefit of pembrolizumab in comparison with individual treatment in each case; an added benefit is therefore not proven.

This deviates from the assessment of the company, which used the respective responder analyses for the time to first deterioration for the assessment and overall derived an indication of added benefit for the outcome category "health-related quality of life".

Side effects

The company derived an indication of added benefit for the outcome category "side effects" based on the results on the superordinate outcomes "AEs", "SAEs" and "severe AEs (CTCAE grade ≥ 3)". It drew no conclusion on individual outcomes. The company only presented the outcomes "immune-related SAEs" and "immune-related severe AEs" as supplementary information without considering the results for the derivation of the added benefit. The company drew no separate conclusion on the added benefit for individual specific AEs. For these reasons, a description of the extent to which the statement on the added benefit made here differs from the assessment of the company is omitted for the following outcomes on side effects.

SAEs and severe AEs (CTCAE grade ≥ 3)

A statistically significant difference in favour of pembrolizumab in comparison with chemotherapy ± bevacizumab or cetuximab was shown for each of the outcomes "SAEs" and "severe AEs" (CTCAE grade ≥ 3)". This resulted in a hint of lesser harm from pembrolizumab in comparison with individual treatment for each of these outcomes.

Discontinuation due to AEs and immune-related severe AEs (CTCAE grade ≥ 3)

No statistically significant difference between the treatment groups was shown for the outcomes "discontinuation due to AEs", and "immune-related severe AEs (CTCAE grade ≥ 3)". In each case, this resulted in no hint of greater or lesser harm from pembrolizumab in comparison with individual therapy; greater or lesser harm is therefore not proven.

Immune-related SAEs

A statistically significant difference to the disadvantage of pembrolizumab in comparison with chemotherapy ± bevacizumab or cetuximab was shown for the outcome "immune-related SAEs". This resulted in a hint of greater harm from pembrolizumab in comparison with individual treatment.

Further specific AEs

mucosal inflammation (AEs), reduced appetite (AEs), peripheral neuropathy (AEs), peripheral sensory neuropathy (AEs), epistaxis (AEs), alopecia (AEs), palmar-plantar erythrodysaesthesia syndrome (AEs), gastrointestinal disorders (severe AEs), fatigue (severe AEs), infections and infestations (severe AEs), hypokalaemia (severe AEs)

There was a statistically significant difference in favour of pembrolizumab in comparison with chemotherapy ± bevacizumab or cetuximab for each of the specific AEs "mucosal inflammation (AEs)", "reduced appetite (AEs)", "peripheral neuropathy (AEs)", "peripheral sensory neuropathy (AEs)", "epistaxis (AEs)", "alopecia (AEs)", "palmar-plantar erythrodysaesthesia syndrome (AEs)", "gastrointestinal disorders (severe AEs)", "fatigue (severe AEs)", "infections and infestations (severe AEs)" and "hypokalaemia (severe AEs). This resulted in a hint of lesser harm from pembrolizumab in comparison with individual treatment for each of these outcomes.

Blood and lymphatic system disorders (severe AEs)

A statistically significant difference in favour of pembrolizumab in comparison with chemotherapy ± bevacizumab or cetuximab was shown for the outcome "blood and lymphatic system disorders (severe AEs)". An effect modification by the characteristic "sex" was shown for this outcome (see Section 2.3.2.4). This resulted in a hint of lesser harm from pembrolizumab in comparison with individual treatment for both men and women.

Arthralgia (AEs)

A statistically significant difference to the disadvantage of pembrolizumab in comparison with chemotherapy ± bevacizumab or cetuximab was shown for the outcome "arthralgia (AEs)". This resulted in a hint of greater harm from pembrolizumab in comparison with individual treatment.

2.3.2.4 Subgroups and other effect modifiers

The following potential effect modifiers were considered in the present assessment:

- age (≤ 70 years vs. > 70 years)
- sex (men vs. women)
- metastases (hepatic or pulmonary vs. other metastases)

The mentioned characteristics were defined a priori. However, the company only presented subgroup analyses for all 3 characteristics for the outcome "overall survival". For the other patient-relevant outcomes of the categories "morbidity", "health-related quality of life" and "AEs", analyses of the subgroup characteristics used for the benefit assessment are only available for age and sex. For the outcomes "immune-related SAEs" and "immune-related severe AEs", subgroup analyses are completely missing.

Interaction tests were performed when at least 10 patients per subgroup were included in the analysis. Moreover, for binary data, there had to be 10 events in at least one 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 are only presented if there is a statistically significant and relevant effect in at least one subgroup.

Table 16 shows the results of the subgroup analyses. Kaplan-Meier curves on the event time analyses on the subgroups are presented in Appendix A of the full dossier assessment.

Table 16: Subgroups (side effects) – RCT, direct comparison: pembrolizumab vs. chemotherapya ± bevacizumab or cetuximab (patients for whom intensive therapy is suitable)

Study outcome characteristic subgroup	Pembrolizumab		Chemotherapy[a] ± bevacizumab/cetuximab		Pembrolizumab vs. chemotherapy[a] ± bevacizumab/cetuximab	
	N	median time to event in months [95 % CI] patients with event n (%)	N	median time to event in months [95 % CI] patients with event n (%)	HR [95 % CI][b]	p-value[c]
KEYNOTE 177						
Side effects						
Blood and lymphatic system disorders (SOC, severe AEs[d])						
Sex						
Women	82	NA 10 (12.2)	68	NA 18 (26.5)	0.39 [0.18; 0.85]	0.018
Men	71	NA 2 (2.8)	75	NA 21 (28.0)	0.08 [0.02; 0.36]	< 0.001
Total					Interaction	0.036[e]

a. mFOLFOX6 or FOLFIRI.
b. HR and CI: Cox proportional hazards model.
c. p-value: Wald test.
d. Operationalized as CTCAE grade ≥ 3.
e. Interaction test: Cox proportional hazards model with corresponding interaction term.

5-FU: 5-fluorouracil; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; FOLFIRI: folinic acid + 5-fluorouracil + irinotecan; HR: hazard ratio; mFOLFOX6: folinic acid + 5-fluorouracil + oxaliplatin (modified regimen); n: number of patients with event; N: number of analysed patients; NA: not achieved; RCT: randomized controlled trial; SOC: System Organ Class

Side effects

Further specific AEs

Blood and lymphatic system disorders (severe AEs)

There was an effect modification by the characteristic "sex" for the outcome "blood and lymphatic system disorders (System Organ Class [SOC], AEs)". A statistically significant difference in favour of pembrolizumab in comparison with chemotherapy ± bevacizumab or cetuximab was shown for this outcome for both men and women. This resulted in a hint of lesser harm from pembrolizumab in comparison with individual treatment for women and men respectively.

This deviates from the approach of the company in that it presents subgroup analyses but does not take them into account when deriving the added benefit.

2.3.3 Probability and extent of added benefit

Probability and extent of the added benefit at outcome level are derived below, 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 the 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 the added benefit at outcome level

The extent of the respective added benefit at outcome level is estimated from the results presented in Section 2.3.2 (see Table 17).

Table 17: Extent of added benefit at outcome level – pembrolizumab vs. chemotherapya ± bevacizumab or cetuximab (patients for whom intensive therapy is suitable) (multipage table)

Outcome category **outcome** **effect modifier** **subgroup**	**Pembrolizumab vs. chemotherapy[a] ± bevacizumab/cetuximab** **median time to event (months)** **effect estimation [95% CI]** **p-value** **probability[b]**	**Derivation of extent[c]**
Mortality		
Overall survival	NA vs. 34.8 HR: 0.77 [0.54; 1.09]; p = 0.140	Lesser benefit/added benefit not proven
Morbidity		
Symptoms (EORTC QLQ-C30)	No usable data available	Lesser benefit/added benefit not proven
Symptoms (EORTC QLQ-CR29)	No usable data available	Lesser benefit/added benefit not proven
Health status (EQ-5D VAS)	No usable data available	Lesser benefit/added benefit not proven
Health-related quality of life		
EORTC QLQ-C30	No usable data available	Lesser benefit/added benefit not proven
EORTC QLQ-CR29	No usable data available	Lesser benefit/added benefit not proven
Side effects		
SAEs	24.6 vs. 8.0 HR: 0.61 [0.43; 0.85] p = 0.004 probability: "hint"	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ lesser harm, extent: "considerable"
Severe AEs	10.8 vs. 2.1 HR: 0.41 [0.31; 0.55]; p < 0.001 probability: "hint"	Outcome category: serious/severe side effects $CI_u < 0.75$, risk ≥ 5% lesser harm, extent: "major"
Discontinuation due to AEs	NA vs. NA HR: 0.88 [0.46; 1.70] p = 0.710	Greater/lesser harm not proven
Immune-related SAEs	NA vs. NA HR: 12.04 [1.59; 91.28]; HR: 0.08 [0.01; 0.63][d]; p < 0.016 probability: "hint"	Outcome category: serious/severe side effects $CI_u < 0.75$, risk ≥ 5% greater harm, extent: "major"
Immune-related severe AEs	NA vs. NA HR: 3.10 [0.88; 10.95] p = 0.079	Greater/lesser harm not proven
Mucosal inflammation (AEs)	NA vs. NA HR: 0.19 [0.08; 0.44] p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ lesser harm, extent: "considerable"

Table 17: Extent of added benefit at outcome level – pembrolizumab vs. chemotherapya ± bevacizumab or cetuximab (patients for whom intensive therapy is suitable) (multipage table)

Outcome category **outcome** **effect modifier** **subgroup**	**Pembrolizumab vs. chemotherapy[a] ± bevacizumab/cetuximab** **median time to event (months)** **effect estimation [95% CI]** **p-value** **probability[b]**	**Derivation of extent[c]**
Decreased appetite (AEs)	NA vs. 14.9 HR: 0.49 [0.32; 0.74] p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ lesser harm, extent: "considerable"
Arthralgia (AEs)	NA vs. NA HR: 3.12 [1.35; 7.19] HR: 0.32 [0.14; 0.74][d] p = 0.008 probability: "hint"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ greater harm, extent: "considerable"
Peripheral neuropathy (AEs)	NA vs. NA HR: 0.03 [0.00; 0.22] p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ lesser harm, extent: "considerable"
Peripheral sensory neuropathy (AEs)	NA vs. NA HR: 0.07 [0.02; 0.22] p < 0.001 Probability: "hint"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ lesser harm, extent: "considerable"
Epistaxis (AEs)	NA vs. NA HR: 0.07 [0.02; 0.28] p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ lesser harm, extent: "considerable"
Alopecia (AEs)	NA vs. NA HR: 0.29 [0.14; 0.59] p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ lesser harm, extent: "considerable"
Palmar-plantar erythrodysaesthesia syndrome (AEs)	NA vs. NA HR: 0.03 [0.00; 0.19] p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ lesser harm, extent: "considerable"
Blood and lymphatic system disorders (severe AEs)		
sex		
Women	NA vs. NA HR: 0.39 [0.18; 0.85] p = 0.018 probability: "hint"	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ lesser harm, extent: "considerable"
Men	NA vs. NA HR: 0.08 [0.02; 0.36] p < 0.001 probability: "hint"	Outcome category: serious/severe side effects $CI_u < 0.75$, risk ≥ 5% lesser harm, extent: "major"

Table 17: Extent of added benefit at outcome level – pembrolizumab vs. chemotherapya ± bevacizumab or cetuximab (patients for whom intensive therapy is suitable) (multipage table)

Outcome category **outcome** **effect modifier** **subgroup**	**Pembrolizumab vs. chemotherapy[a] ± bevacizumab/cetuximab** **median time to event (months)** **effect estimation [95% CI]** **p-value** **probability[b]**	**Derivation of extent[c]**
Gastrointestinal disorders (severe AEs)	NA vs. NA HR: 0.40 [0.25; 0.63] p < 0.001 probability: "hint"	Outcome category: serious/severe side effects $CI_u < 0.75$, risk ≥ 5% lesser harm, extent: "major"
Fatigue (severe AEs)	NA vs. NA HR: 0.32 [0.12; 0.86] p = 0.024 probability: "hint"	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ lesser harm, extent: "considerable"
Infections and infestations (severe AEs)	NA vs. NA HR: 0.51 [0.26; 0.99] p = 0.046 probability: "hint"	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ lesser harm, extent: "minor"
Hypokalaemia (severe AEs)	NA vs. NA HR: 0.18 [0.04; 0.85] p = 0.030 probability: "hint"	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ lesser harm, extent: "considerable"

a. mFOLFOX6 or FOLFIRI.
b. Probability provided if a statistically significant and relevant effect is present.
c. Depending on the outcome category, estimations of effect size are made with different limits based on the upper limit of the confidence interval (CI_u).
d. Institute's calculation; reversed direction of effect to enable use of limits to derive the extent of the added benefit.

5-FU: 5-fluorouracil; AE: adverse event; CI: confidence interval; CI_u: upper limit of the confidence interval; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EORTC-QLQ-CR29: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire for Colorectal Cancer; FOLFIRI: folinic acid + 5-fluorouracil + irinotecan; HR: hazard ratio; mFOLFOX6: folinic acid + 5-fluorouracil + oxaliplatin (modified regimen); NA: not achieved; SAE: serious adverse event; VAS: visual analogue scale

2.3.3.2 Overall conclusion on added benefit

Table 18 summarizes the results considered in the overall conclusion on the extent of added benefit.

Table 18: Positive and negative effects from the assessment of pembrolizumab vs. individual treatment (patients for whom intensive therapy was suitable)

Positive effects	**Negative effects**
Serious/severe side effects ▪ SAEs: hint of lesser harm – extent: "considerable" ▪ severe AEs: hint of lesser harm – extent: "major" including ▫ blood and lymphatic system disorders - sex (women) hint of lesser harm – extent "considerable" - sex (male): hint of lesser harm – extent: "major" ▫ gastrointestinal disorders: hint of lesser harm – extent: "major" ▫ fatigue: hint of lesser harm – extent: "considerable" ▫ infections and infestations: hint of lesser harm – extent: "minor" ▫ hypokalaemia: hint of lesser harm – extent: "considerable"	Serious/severe side effects ▪ immune-related SAEs: hint of greater harm – extent: "major"
Non-serious/non-severe side effects ▪ mucosal inflammation (AEs) ▪ decreased appetite (AEs) ▪ peripheral neuropathy (AEs) ▪ peripheral sensory neuropathy (AEs) ▪ epistaxis (AEs) ▪ alopecia (AEs) ▪ palmar-plantar erythrodysaesthesia syndrome (AEs) in each case hint of lesser harm – extent: "considerable"	Non-serious/non-severe side effects ▪ arthralgia (AEs): Hint of greater harm - extent: "considerable"
There are no usable data for the outcome categories of morbidity and health-related quality of life. AEs: adverse events; SAE: serious adverse event	

In the overall consideration of the data, there are mainly positive effects of pembrolizumab in comparison with individual treatment. These effects were shown exclusively in the outcome category of side effects in serious/severe and in non-serious/non-severe side effects.

This resulted in a hint of lesser harm with the extent "considerable" or "major" for the superordinate outcomes "SAEs" and "severe AEs (CTCAE grade ≥ 3)". Among the severe AEs, there were several specific AEs in favour of pembrolizumab with the extent "minor" to "major". Hints of lesser harm with the extent "considerable" in the category "non-serious/non-severe side effects" were shown for several outcomes.

In contrast, there are hints of greater harm from pembrolizumab compared to individual treatment in immune-related SAEs and non-serious/non-severe side effects for the outcome "arthralgia" with the extent "considerable" or "major".

There are no usable data for the outcome categories of morbidity and health-related quality of life.

In the present situation, the added benefit is thus based exclusively on differences in the category of side effects. A balancing of the effects under consideration of the outcome categories of morbidity and health-related quality of life is not possible, however, because data were not usable. It is therefore not possible to assess whether and to what extent the advantages in side effects are also reflected in the morbidity and health-related quality of life of the patients. Due to the size of the observed effects in the side effects, however, it cannot be assumed that these can be completely questioned by the missing data in the outcome categories of morbidity and health-related quality of life.

In summary, there is a hint of considerable added benefit of pembrolizumab in comparison with individual treatment in the first-line setting for adult patients with metastatic MSI-H or dMMR colorectal cancer, for whom intensive treatment is suitable.

The assessment described above deviates from that of the company. The company did not differentiate between the populations of patients for whom intensive therapy was suitable or unsuitable and derived an indication of a significant added benefit for all patients in the therapeutic indication on the basis of the results of the total population of the KEYNOTE 177 study.

2.4 Research question 2: Patients for whom intensive therapy is unsuitable

2.4.1 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: 1 January 2021)
- bibliographical literature search on pembrolizumab (last search on 20 January 2021)
- search in trial registries/trial results databases for studies on pembrolizumab (last search on 20 January 2021)
- search on the G-BA website for pembrolizumab (last search on 20 January 2021)

The completeness of the study pool was checked by:

- search in trial registries for studies on pembrolizumab (last search on 9 April 2021); for search strategies, see Appendix C of the full dossier assessment

The check of the completeness of the study pool produced no suitable RCTs on the direct comparison of pembrolizumab versus the ACT.

This approach deviates from that of the company. The company did not differentiate between the populations of patients for whom intensive therapy was suitable or not suitable, and used

the results of the total population of the KEYNOTE 177 study to assess the added benefit for all patients in the therapeutic indication.

The present benefit assessment used the results of the KEYNOTE 177 study only for research question 1, as this study mainly included patients for whom intensive therapy was suitable (see Section 2.3).

2.4.2 Results on added benefit

The company presented no data for the assessment of the added benefit of pembrolizumab in comparison with the ACT in the first-line setting in adult patients with metastatic MSI-H or dMMR colorectal cancer, for whom intensive treatment is unsuitable. This resulted in no hint of an added benefit of pembrolizumab in comparison with the ACT; an added benefit is therefore not proven.

2.4.3 Probability and extent of added benefit

Added benefit not proven as the company presented no data for the assessment of the added benefit of pembrolizumab in comparison with the ACT in the first-line setting in adult patients with metastatic MSI-H or dMMR colorectal cancer, for whom intensive treatment is unsuitable.

The assessment described above deviates from that of the company. The company did not differentiate between the populations of patients for whom intensive therapy was suitable or unsuitable and derived an indication of a significant added benefit for all patients in the therapeutic indication on the basis of the results of the total population of the KEYNOTE 177 study.

2.5 Probability and extent of added benefit – summary

The result of the assessment of the added benefit of pembrolizumab in comparison with the ACT is summarized in Table 19.

Table 19: Pembrolizumab – probability and extent of added benefit

Research question	Therapeutic indication[a]	ACT[b]	Probability and extent of added benefit
1	Adult patients with metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer for whom intensive treatment is suitable; first-line treatment	Individual treatment depending on the all-RAS mutation status, the location of the primary tumour and the risk of toxicity induced by bevacizumab, choosing from the following options ▪ combination therapy of 5-fluorouracil + folinic acid + oxaliplatin (FOLFOX) ▪ combination therapy of 5-fluorouracil + folinic acid + irinotecan (FOLFIRI) ▪ combination therapy of 5-fluorouracil + folinic acid + oxaliplatin (FOLFOX) and an anti-EGFR treatment (cetuximab or panitumumab) - (only for patients with RAS wild type) ▪ combination therapy of 5-fluorouracil + folinic acid + irinotecan (FOLFIRI) and an anti-EGFR treatment (cetuximab or panitumumab) - (only for patients with RAS wild type) ▪ combination therapy of 5-fluorouracil + folinic acid + oxaliplatin (FOLFOX) and bevacizumab ▪ combination therapy of 5-fluorouracil + folinic acid + irinotecan (FOLFIRI) and bevacizumab	Hint of considerable added benefit[c]
2	Adult patients with metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer for whom intensive treatment is unsuitable; first-line treatment	▪ 5-fluorouracil + folinic acid ± bevacizumab or ▪ capecitabine ± bevacizumab or ▪ combination therapy of 5-fluorouracil + folinic acid + oxaliplatin (reduced intensity) ± bevacizumab or ▪ combination therapy of 5-fluorouracil + folinic acid + irinotecan (reduced intensity) ± bevacizumab	Added benefit not proven

a. For the present therapeutic indication, it is assumed that treatment with curative intent or primary resection is not an option for the patients with metastatic colorectal cancer.
b. Presentation of the respective ACT specified by the G-BA.
c. The KEYNOTE 177 study included only patients with an ECOG PS of 0 or 1. It remains unclear whether the observed effects can be transferred to patients with an ECOG PS of ≥ 2.

5-FU: 5-fluorouracil; dMMR: mismatch repair deficiency; ECOG PS: Eastern Cooperative Oncology Group Performance Status; EGFR: epidermal growth factor receptor; FOLFIRI: folinic acid + 5-fluorouracil + irinotecan; FOLFOX 5-fluorouracil + folinic acid + oxaliplatin; G-BA: Federal Joint Committee; MSI-H: high-frequency microsatellite instability; RAS: rat sarcoma viral oncogene homologue

The approach for the derivation of an overall conclusion on the 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.

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