IQWiG Reports – Commission No. A21-144

Pembrolizumab (cancer of the oesophagus or the gastroesophageal junction)

–

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

Extract

[1] Translation of Sections 2.1 to 2.7 of the dossier assessment *Pembrolizumab (*Karzinom des Ösophagus oder gastroösophagealen Übergangs*) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.1; Status: 1 April 2022). 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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IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

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

List of abbreviations

Abbreviation	Meaning
5-FU	5-fluorouracil
ACT	appropriate comparator therapy
AE	adverse event
BSA	body surface area
CNS	central nervous system
CPS	combined positive score
CTCAE	Common Terminology Criteria for Adverse Events
ECOG PS	
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C 30
EORTC QLQ-OES18	Quality of Life Questionnaire-Oesophageal Cancer 18 items
EQ-5D VAS	European Quality of Life-5 Dimensions visual analogue scale
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HER2	human epidermal growth factor receptor 2
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
PD-L1	programmed cell death ligand 1
PT	Preferred Term
RCT	randomized controlled trial
RCT	Randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SOC	System Organ Class
SPC	Summary of Product Characteristics

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 16 November 2021.

Research question

Aim of the present report is the assessment of the added benefit of pembrolizumab in combination with platinum-based and fluoropyrimidine-based chemotherapy in comparison with the appropriate comparator therapy (ACT) in the first-line treatment of locally advanced, unresectable (not curatively treatable according to the G-BA) or metastatic cancer of the oesophagus or human epidermal growth factor receptor 2 (HER2)-negative adenocarcinoma of the gastroesophageal junction in adults whose tumours express programmed cell death ligand 1 (PD-L1) (combined positive score [CPS] ≥ 10).

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	ACT[a]
A	Adult patients with locally advanced or metastatic, squamous cell carcinoma of the oesophagus that cannot be treated curatively[b] and whose tumours express PD-L1 (CPS ≥ 10); first-line treatment	Cisplatin in combination with 5-fluorouracil (5-FU)[c]
B1	Adult patients with locally advanced or metastatic HER2-negative adenocarcinoma of the oesophagus or of the gastroesophageal junction that cannot be treated curatively[b] and whose tumours express PD-L1 (CPS ≥ 10); first-line treatment	Treatment of physician's choice[d]
B2	Adult patients with locally advanced or metastatic HER2-positive adenocarcinoma of the oesophagus that cannot be treated curatively[b] and whose tumours express programmed cell death ligand 1 (PD-L1) (CPS ≥ 10); first-line treatment	HER2-targeted therapy according to physician's choice[e]

a. Presented is the respective ACT specified by the G-BA.
b. According to the G-BA , it is assumed for the present therapeutic indication that curative treatment with definitive radiochemotherapy is not an option for patients with unresectable cancer.
c. According to the G-BA it is assumed that cisplatin-containing chemotherapy is suitable for the patients.
d. Guidelines mention several platinum- and fluoropyrimidine-based combination chemotherapies: S-1 (tegafur/gimeracil/oteracil) + cisplatin or capecitabine + cisplatin [XP], 5-FU + cisplatin, 5-FU + oxaliplatin + folinic acid [FLO and FOLFOX], capecitabine + oxaliplatin, infusional 5-FU + folinic acid + cisplatin [PLF], epirubicin + cisplatin + capecitabine [ECX], epirubicin + oxaliplatin + capecitabine [EOX], epirubicin + cisplatin + infusional 5-FU [ECF], docetaxel + cisplatin + infusional 5-FU [DCF], 5-FU + oxaliplatin + epirubicin, infusional 5-FU + folinic acid + oxaliplatin + docetaxel [FLOT regimen]. However, only the drugs 5-FU, docetaxel as well as cisplatin are approved in the present therapeutic indication. There is a discrepancy between the drugs approved for the therapeutic indication and those recommended in the guidelines. In the context of treatment of physician's choice, the G-BA considered the treatment options cited here to be suitable comparators. The choice of the used comparator has to be justified in the dossier.
e. Guidelines recommend the combination therapy of the anti-HER2 antibody trastuzumab with cisplatin and fluoropyrimidines (5-FU or capecitabine), but this is not (explicitly) approved for the present therapeutic indication. Only the drugs 5-FU as well as cisplatin are approved in the present therapeutic indication. There is a discrepancy between the drugs approved for the therapeutic indication and those recommended in the guidelines. Within the framework of the HER2-targeted therapy according to physician's choice, the company considered trastuzumab in combination with cisplatin and capecitabine or 5-FU to be a suitable comparator. The choice of the used comparator has to be justified in the dossier.

5-FU: 5-fluorouracil; ACT: appropriate comparator therapy; CPS: combined positive score; G-BA: Federal Joint Committee; HER2: human epidermal growth factor receptor 2; PD-L1: programmed cell death ligand 1

In the present benefit assessment, the following terms are used for the patient populations of the 3 research questions:

- Research question A: patients with squamous cell carcinoma of the oesophagus and CPS ≥ 10

- Research question B1: patients with HER2-negative adenocarcinoma of the oesophagus or of the gastroesophageal junction and CPS ≥ 10
- Research question B2: patients with HER2-positive adenocarcinoma of the oesophagus and CPS ≥ 10

The company stated that it followed the ACT for research questions A and B1. In doing so, the company stated that it chose the option cisplatin in combination with 5-fluorouracil (5-FU) and the combination cisplatin in combination with capecitabine for research question B1. For research question B2, the company made no explicit statement on the ACT and referred to the fact that no data were available for the relevant patient population for the ACT specified by the G-BA. Overall, however, the company made its statement on the added benefit for the entire target population without making separate statements for the respective subpopulations of research questions A, B1 and B2. Concurring with the G-BA's specification, the present assessment was conducted separately for the three research questions A, B1 and B2, 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 A: patients with squamous cell carcinoma of the oesophagus and CPS ≥ 10

Study pool and study design

Data of a relevant subpopulation of the KEYNOTE 590 study were used for research question A of the benefit assessment. KEYNOTE 590 is an ongoing, double-blind, randomized, active controlled, multicentre study on the comparison of pembrolizumab in combination with cisplatin and 5-FU (pembrolizumab + cisplatin + 5-FU) versus placebo in combination with cisplatin and 5-FU (placebo + cisplatin + 5-FU).

The study included adult patients with squamous cell carcinoma or adenocarcinoma of the oesophagus or adenocarcinoma of the gastroesophageal junction (Siewert type I only), each in the locally advanced or metastatic stage. Patients with HER2-positive adenocarcinoma of the gastroesophageal junction were excluded from the study. Either a newly obtained or an archived tissue sample of the included patients had to be available for the PD-L1 analysis by means of immunohistochemistry (no information on the test used in the company's dossier).

Patients were not allowed to have received prior treatment at this stage of the disease. Prior treatment with curative intent was considered treatment at this stage of the disease if the disease had progressed during or within 6 months of that treatment.

The patients had to have a good general condition (Eastern Cooperative Oncology Group Performance Status [ECOG PS] ≤ 1). Patients with ECOG PS ≥ 2 or active central nervous

system (CNS) metastases were excluded from the participation in the study; hence, no data are available for them.

Patients were stratified by histology (adenocarcinoma vs. squamous cell carcinoma), region (Asia versus rest of the world) and ECOG PS (0 vs. 1) and randomly assigned either to the intervention arm (pembrolizumab + cisplatin + 5-FU; N = 373) or to the comparator arm (placebo + cisplatin + 5-FU; N = 376).

In the KEYNOTE 590 study, treatment with pembrolizumab largely corresponded to the recommendations of the Summary of Product Characteristics (SPC). However, there are uncertainties regarding treatment, which are described in the following section.

Primary outcomes of the KEYNOTE 590 study were overall survival and progression-free survival (PFS). Outcomes on symptoms, health status, health-related quality of life and AEs were recorded as further patient-relevant outcomes.

Uncertainties regarding the treatment

The treatment duration with pembrolizumab or placebo and with 5-FU was limited to a maximum of 35 cycles (approx. 2 years) in both study arms of KEYNOTE 590. However, according to the approval, treatment with pembrolizumab should be continued until progression of the cancer or the occurrence of unacceptable toxicity. Due to the small number of affected patients, it is not assumed that the restriction to a maximum of 35 treatment cycles represents a relevant limitation of the treatment.

Likewise, treatment with cisplatin was restricted to 6 cycles in both study arms of the KEYNOTE 590 study. The SPC and current national guidelines provide no information on the duration of treatment with cisplatin. Therefore, there is uncertainty regarding the question of whether further cycles of treatment with cisplatin would have been an option for the patients.

The 5-FU dose used in the KEYNOTE 590 study deviates from the approved dose for the oesophageal carcinoma. In the KEYNOTE 590 study, a total dose of 4000 mg/m² body surface area (BSA)/cycle was planned in both study arms, for example in the form of a dose of 800 mg/m² BSA/day on days 1 to 5 or 1000 mg/m² BSA/day on days 1 to 4 of a 3-week cycle. The SPC of 5-FU for the treatment of oesophageal carcinoma, in contrast, stipulates a dose of 1000 mg/m² BSA/day on days 1 to 5 of a 3- to 4-week cycle. Hence, this corresponds to a total dose of 5000 mg/m² BSA/cycle. It is unclear to what extent this deviation affects the results of patient-relevant outcomes.

These uncertainties regarding the treatment result in a reduced certainty of conclusions of the KEYNOTE 590 study.

Relevant subpopulation

The subpopulation of patients with squamous cell carcinoma of the oesophagus and CPS ≥ 10 is relevant to answer the present research question. The company presented analyses of a

corresponding subpopulation of KEYNOTE 590. It comprises 143 patients each in the intervention and the comparator arm.

Risk of bias

The risk of bias across outcomes was rated as low for the KEYNOTE 590 study. Except for the outcome "overall survival", the risk of bias at outcome level was rated as low. Overall, there were no usable data for the outcomes on symptoms and health-related quality of life as well as for the outcome ""discontinuation due to AEs". For this reason, the risk of bias for these outcomes was not assessed. Moreover, due to the uncertainties regarding the treatment, at most hints, for example of an added benefit, can be derived on the basis of the KEYNOTE 590 study for all outcomes for which usable data are available.

Results

Mortality

Overall survival

There is a statistically significant difference in favour of pembrolizumab + cisplatin + 5-FU in comparison with placebo + cisplatin + 5-FU for the outcome "overall survival". This resulted in a hint of an added benefit of pembrolizumab + cisplatin + 5-FU in comparison with cisplatin + 5-FU.

Morbidity

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

For the outcome "health status (EQ-5D VAS)", the mean change until week 18 versus baseline is considered. There was no statistically significant difference between the treatment arms. This resulted in no hint of an added benefit of pembrolizumab + cisplatin + 5-FU in comparison with cisplatin + 5-FU; an added benefit is therefore not proven.

Symptoms

There were no usable data on symptoms. This resulted in no hint of an added benefit of pembrolizumab + cisplatin + 5-FU in comparison with cisplatin + 5-FU for the outcome "symptoms"; an added benefit is therefore not proven.

Health-related quality of life

There were no usable data on health-related quality of life. This resulted in no hint of an added benefit of pembrolizumab + cisplatin + 5-FU in comparison with cisplatin + 5-FU for the outcome "health-related quality of life"; an added benefit is therefore not proven.

Side effects

Serious adverse events (AEs), severe adverse events (AEs) and immune-related severe AEs

No statistically significant difference between the treatment arms was shown for the outcomes "SAEs", "severe AEs" and "immune-related severe AEs". This resulted in no hint of greater or

lesser harm from pembrolizumab + cisplatin + 5-FU in comparison with cisplatin + 5-FU; greater or lesser harm is therefore not proven for these outcomes.

Discontinuation due to AEs

There were no usable data for the outcome "discontinuation due to AEs". This resulted in no hint of greater or lesser harm from pembrolizumab + cisplatin + 5-FU in comparison with cisplatin + 5-FU for this outcome; greater or lesser harm is therefore not proven for this outcome.

Immune-related SAEs

There is a statistically significant difference to the disadvantage of pembrolizumab + cisplatin + 5-FU in comparison with placebo + cisplatin + 5-FU for the outcome “immune-related SAEs”. This resulted in a hint of greater harm from pembrolizumab + cisplatin + 5-FU in comparison with cisplatin + 5-FU.

Further specific AEs

There is a statistically significant difference in favour of pembrolizumab + cisplatin + 5-FU versus placebo + cisplatin + 5-FU for each of the specific AEs “musculoskeletal and connective tissue disorders (System Organ Class [SOC], AEs)”, "general disorders and administration site conditions (SOC, SAEs)”, “platelet count decreased (Preferred Term [PT, severe AEs)” and “decreased weight (PT, severe AEs)”. In each case, this resulted in a hint of lesser harm from pembrolizumab + cisplatin + 5-FU in comparison with cisplatin + 5-FU.

Research question B1: Patients with HER2-negative adenocarcinoma of the oesophagus or of the gastroesophageal junction and CPS ≥ 10

Study pool and study design

Data of the respective relevant subpopulations of the KEYNOTE 590 study and the KEYNOTE 062 study were used for research question B1 of the present benefit assessment. The study KEYNOTE 590 is described under research question A. KEYNOTE 062 is a partially blinded, randomized, controlled, multicentre study on the comparison of pembrolizumab as monotherapy versus pembrolizumab in combination with platinum- and fluoropyrimidine-based chemotherapy, implemented as a combination with cisplatin and either 5-FU or capecitabine (pembrolizumab + cisplatin + 5-FU/capecitabine; hereinafter referred to as intervention arm), and versus placebo + cisplatin in combination with either 5-FU or capecitabine (placebo + cisplatin + 5-FU/capecitabine; hereinafter referred to as comparator arm). The study arm with pembrolizumab as monotherapy was unblinded, but is irrelevant for the present benefit assessment. The two study arms relevant for the benefit assessment were double-blind.

The study included adult patients with locally advanced or metastatic adenocarcinoma of the gastroesophageal junction or the stomach. Patients were not allowed to have received prior treatment at this stage of the disease, but could have received prior treatment with curative

intent, if this treatment had been completed at least 6 months before randomization. The tumours of all patients included had to be PD-L1-positive (defined as CPS ≥ 1 in the study protocol; identified by immunohistochemistry using a tissue sample; test used: Dako PD-L1 IHC 22C3 pharmDx test) and HER2/neu-negative (determined according to local standards).

Patients had to have a good general condition (ECOG PS ≤ 1 within 3 days before the first dose of the study treatment). Patients with ECOG PS ≥ 2 or active CNS metastases were excluded from the participation in the study; hence, no data are available for them.

Patients were randomly assigned to one of the 3 study arms (pembrolizumab as monotherapy: N = 256; intervention arm [pembrolizumab + cisplatin + 5-FU/capecitabine]: N = 257; comparator arm [placebo + cisplatin + 5-FU/capecitabine]: N = 250) stratified by geographical region (Europe/North America versus Asia versus rest of the world), disease stage (locally advanced unresectable versus metastatic) and therapeutic strategy (5-FU versus capecitabine).

Capecitabine could be administered according to local guidelines, although the use of 5-FU was preferred according to the study protocol. The decision on the type of the fluoropyrimidine used (5-FU or capecitabine) was made by the physician and was to be taken before randomization.

In the studies KEYNOTE 590 and KEYNOTE 062, treatment with pembrolizumab largely corresponded to the recommendations of the SPC. However, there are uncertainties regarding treatment, which are described in the following section.

Primary outcomes of the KEYNOTE 062 study were overall survival and PFS. Outcomes on symptoms, health status, health-related quality of life and AEs were recorded as further patient-relevant outcomes.

Uncertainties regarding the treatment

The duration of the study treatment was limited to a maximum of 35 cycles (approx. 2 years) in both study arms of the studies KEYNOTE 590 and the KEYNOTE 062. However, according to the approval, treatment with pembrolizumab should be continued until progression of the cancer or the occurrence of unacceptable toxicity. Information on how many patients of the relevant subpopulation of the studies received the planned maximum number of treatment cycles and were not treated further thereafter although such treatment would have basically been possible according to the approval, is not available.

Likewise, treatment with cisplatin was restricted to 6 cycles in both study arms of the KEYNOTE 590 study. The SPC and current national guidelines provide no information on the duration of treatment with cisplatin. Therefore, there is uncertainty regarding the question of whether further cycles of treatment with cisplatin would have been an option for the patients.

In both studies, the 5-FU dose deviates from the specifications of the SPC. Capecitabine is exclusively approved for the stomach cancer. At first, the dose used in the KEYNOTE 062 study corresponds to the specification of this SPC. However, in the case of continuous

administration, the dose should be reduced to 625 mg/m² BSA twice daily, which was not implemented in the KEYNOTE 062 study. Moreover, the extent to which this SPC can be applied to the patients with cancer of the gastroesophageal junction included in the study is unclear. Where guidelines provide data on dose recommendations, these are inconsistent.

These uncertainties regarding the treatment result in a reduced certainty of conclusions of the studies KEYNOTE 590 and KEYNOTE 062.

Relevant subpopulation

The subpopulations of patients with adenocarcinoma of the oesophagus or the gastroesophageal junction and CPS ≥ 10 are relevant to answer the present research question. The company presented analyses on corresponding subpopulations of KEYNOTE 590 and KEYNOTE 062, but did not use them to derive the added benefit.

Research question B1 exclusively refers to patients with HER2-negative tumours. The HER2 status of the tumours of patients with adenocarcinoma of the gastroesophageal junction was determined before inclusion in the studies KEYNOTE 590 and KEYNOTE 062. Patients with HER2-positive adenocarcinoma of the gastroesophageal junction were excluded from both studies. However, the HER2 status of the tumours of patients with adenocarcinoma of the oesophagus was not determined within the framework of the KEYNOTE 590 study. Hence, the HER2 status of these patients in the subpopulation of KEYNOTE 590 presented by the company is unknown. Based on identified publications, a proportion of approx. 30% of patients with HER2-positive tumours appears possible for the advanced or metastatic adenocarcinoma of the oesophagus. However, even assuming a very high proportion of up to 40% of HER2-positive patients with adenocarcinoma of the oesophagus in the subpopulation presented by the company, the total proportion of HER2-negative patients in this population would still be over 80%. For this reason, it seems adequate in the present situation to use the results of the subpopulation to derive the added benefit. Thus, the subpopulations of the studies KEYNOTE 590 and KEYNOTE 062 presented by the company are relevant for the benefit assessment. However, the certainty of conclusions of KEYNOTE 590 regarding the subpopulation relevant for research question B1 is reduced, because there is uncertainty regarding the proportion of patients with HER2-negative tumours.

Comparability of the studies KEYNOTE 590 and KEYNOTE 062 for the quantitative interpretation of the results

As far as the relevant subpopulations are concerned, the studies KEYNOTE 590 and KEYNOTE 062 are largely comparable with regard to the study design, the inclusion and exclusion criteria and the characteristics of the patients included. Differences exist in the selection of the fluoropyrimidine (5-FU or capecitabine) used as part of the therapy according to physician's choice, and in the exact location of the adenocarcinoma (oesophagus or gastroesophageal junction). Overall, the two studies KEYNOTE 590 and KEYNOTE 062 are sufficiently comparable and are summarized in a meta-analysis.

Risk of bias

The risk of bias across outcomes was rated as low for both studies. At outcome level, the risk of bias in both studies was rated as high for all outcomes except "overall survival". For the KEYNOTE 590 study, there are no usable data for the outcomes of the categories "morbidity (health status and symptoms)" and for the outcome "health-related quality of life". For the outcomes of the category "health status" and for the outcome "discontinuation due to AEs", no usable data are available for the KEYNOTE 062 study either. Hence, the risk of bias of the results is not assessed for these outcomes. Moreover, due to the uncertainties regarding the proportion of patients with HER2-negative tumours in the KEYNOTE 590 study and due to the uncertainties regarding the treatment in both studies, at most indications, e.g. of an added benefit, can be derived for all outcomes for which usable data are available.

Results

Mortality

Overall survival

There was no statistically significant difference between the treatment arms for the outcome "overall survival". This resulted in no hint of an added benefit of pembrolizumab + cisplatin + 5-FU/capecitabine in comparison with cisplatin + 5-FU/capecitabine. An added benefit for this outcome is therefore not proven.

Morbidity

Symptoms

For the outcomes on symptoms, usable data are only available for the KEYNOTE 062 study. Outcomes on symptoms were recorded using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C 30 (EORTC QLQ-C30 symptom scales).

There is a statistically significant difference in favour of pembrolizumab + cisplatin + 5-FU/capecitabine for the outcome "dyspnoea". For an outcome of the category of non-serious/non-severe symptoms/late complications, the present effect is no more than marginal. This resulted in no hint of an added benefit of pembrolizumab + cisplatin + 5-FU/capecitabine in comparison with cisplatin + 5-FU/capecitabine; an added benefit is therefore not proven.

No statistically significant differences between the treatment arms were shown for the outcomes "fatigue", "nausea and vomiting", "pain", "insomnia", "appetite loss" and "diarrhoea". This resulted in no hint of an added benefit of pembrolizumab + cisplatin + 5-FU/capecitabine in comparison with cisplatin + 5-FU/capecitabine; an added benefit is therefore not proven for these outcomes.

Health status

There were no usable data on health status. This resulted in no hint of an added benefit of pembrolizumab + cisplatin + 5-FU/capecitabine in comparison with cisplatin + 5-FU/capecitabine for the outcome "health status"; an added benefit is therefore not proven.

Health-related quality of life

For the health-related quality of life outcomes, usable data are only available for the KEYNOTE 062 study. The outcomes of health-related quality of life were recorded using the EORTC QLQ-C30 symptom scales.

For all outcomes of health-related quality of life (global health status, physical functioning, role functioning, emotional functioning, cognitive functioning and social functioning), there is no statistically significant difference between the treatment arms. This resulted in no hint of an added benefit of pembrolizumab + cisplatin + 5-FU/capecitabine in comparison with cisplatin + 5-FU/capecitabine; an added benefit is therefore not proven for this outcome.

Side effects

SAEs, severe AEs, immune-related SAEs and immune-related severe AEs

No statistically significant difference between the treatment arms was shown for the outcomes "SAEs", "severe AEs", "immune-related SAEs" and "immune-related severe AEs". This resulted in no hint of greater or lesser harm from pembrolizumab + cisplatin + 5-FU/capecitabine in comparison with cisplatin + 5-FU/capecitabine; greater or lesser harm is therefore not proven for these outcomes.

Discontinuation due to AEs

There were no usable data for the outcome "discontinuation due to AEs". This resulted in no hint of greater or lesser harm from pembrolizumab + cisplatin + 5-FU/capecitabine in comparison with cisplatin + 5-FU/capecitabine for this outcome; greater or lesser harm is therefore not proven for this outcome.

Further specific AEs

There is a statistically significant difference to the disadvantage of pembrolizumab + cisplatin + 5-FU/capecitabine for the specific AE "endocrine disorders (SOC, AEs)". This resulted in an indication of greater harm from pembrolizumab + cisplatin + 5-FU in comparison with cisplatin + 5-FU.

Research question B2: Patients with HER2-positive adenocarcinoma of the oesophagus and CPS ≥ 10

In its dossier, the company presented no suitable data to assess the added benefit of pembrolizumab in combination with platinum- and fluoropyrimidine-based chemotherapy compared with the ACT for adult patients with locally advanced or metastatic, not curatively treatable, HER2-positive adenocarcinoma of the oesophagus with PD-L1-expressing tumours (CPS ≥ 10) in the first line.

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 A

For research question A, the overall consideration shows both positive and negative effects of pembrolizumab + cisplatin + 5-FU compared to cisplatin in combination with 5-FU as ACT.

On the side of the positive effects, there was a hint of major added benefit for the outcome "overall survival". Moreover, a hint of lesser harm with the extents "minor" to "major" is shown for several specific AEs in the outcome categories "serious/severe AEs" and "non-serious/non-severe AEs". On the side of negative effects, in contrast, there is a hint of greater harm with the extent "considerable" for the outcome "immune-related AEs", which in particular does not call into question the positive effect in overall survival, however.

In summary, there is a hint of major added benefit of pembrolizumab + cisplatin + 5-FU over the ACT for patients with locally advanced or metastatic, not curatively treatable squamous cell carcinoma of the oesophagus with PD-L1 expressing tumours (CPS ≥ 10).

Research question B1

For research question B1, the overall consideration only shows a negative effect of pembrolizumab + cisplatin + 5-FU/capecitabine versus treatment of physician's choice as ACT in the outcome category "side effects". This negative effect concerns the specific AE "endocrine disorders" (indication of greater harm with the extent "considerable"). In the overall consideration of the available results, this negative effect is not sufficient to derive a lesser benefit from pembrolizumab + cisplatin + 5-FU/capecitabine.

In summary, there is no hint of an added benefit of pembrolizumab + cisplatin + 5-FU/capecitabine over the ACT for patients with locally advanced or metastatic, not curatively treatable HER2-negative adenocarcinoma of the oesophagus or the gastroesophageal junction with PD-L1-expressing tumours (CPS ≥ 10) in first-line therapy, an added benefit is therefore not proven.

[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].

Data are available only for patients for whom cisplatin + 5-FU or cisplatin + capecitabine is a suitable treatment option concurring with treatment of physician's choice. No data are available for patients for whom another treatment option is suitable according to physician's choice.

Research question B2

In its dossier, the company presented no data on research question B2 to assess the added benefit of pembrolizumab in combination with platinum- and fluoropyrimidine-based chemotherapy compared with the ACT for adult patients with locally advanced or metastatic, not curatively treatable HER2-positive adenocarcinoma of the oesophagus with PD-L1-expressing tumours (CPS ≥ 10) in the first line. This resulted in no hint of an added benefit of pembrolizumab in combination with platinum- and fluoropyrimidine-based chemotherapy in comparison with the ACT; an added benefit is therefore not proven.

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

Table 3: Pembrolizumab in combination with platinum- and fluoropyrimidine-based chemotherapy – probability and extent of added benefit (multipage table)

Research question	**Therapeutic indication**	**ACT[a]**	**Probability and extent of added benefit**
A	Adult patients with locally advanced or metastatic, squamous cell carcinoma of the oesophagus that cannot be treated curatively[b] and whose tumours express PD-L1 (CPS ≥ 10); first-line treatment	Cisplatin in combination with 5-FU[c]	Hint of major added benefit[d]
B1	Adult patients with locally advanced or metastatic HER2-negative adenocarcinoma of the oesophagus or of the gastroesophageal junction that cannot be treated curatively[b] and whose tumours express PD-L1 (CPS ≥ 10); first-line treatment	Treatment of physician's choice[e]	Added benefit not proven[d,f]
B2	Adult patients with locally advanced or metastatic HER2-positive adenocarcinoma of the oesophagus that cannot be treated curatively[b] and whose tumours express PD-L1 (CPS ≥ 10); first-line treatment	HER2-targeted therapy according to physician's choice[g]	Added benefit not proven[d]

Table 3: Pembrolizumab in combination with platinum- and fluoropyrimidine-based chemotherapy – probability and extent of added benefit (multipage table)

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
a. Presented is the respective ACT specified by the G-BA. b. According to the G-BA, it is assumed for the present therapeutic indication that curative treatment with definitive radiochemotherapy is not an option for patients with unresectable cancer. c. According to the G-BA it is assumed that cisplatin-containing chemotherapy is suitable for the patients. c. The studies KEYNOTE 590 and KEYNOTE 062 included only patients with an ECOG PS of 0 or 1. It remains unclear whether the observed effects are transferable to patients with an ECOG PS ≥ 2. e. Guidelines mention several platinum- and fluoropyrimidine-based combination chemotherapies: S-1 (tegafur/gimeracil/oteracil) + cisplatin or capecitabine + cisplatin [XP], 5-FU + cisplatin, 5-FU + oxaliplatin + folinic acid [FLO and FOLFOX], capecitabine + oxaliplatin, infusional 5-FU + folinic acid + cisplatin [PLF], epirubicin + cisplatin + capecitabine [ECX], epirubicin + oxaliplatin + capecitabine [EOX], epirubicin + cisplatin + infusional 5-FU [ECF], docetaxel + cisplatin + infusional 5-FU [DCF], 5-FU + oxaliplatin + epirubicin, infusional 5-FU + folinic acid + oxaliplatin + docetaxel [FLOT regimen]. However, only the drugs 5-FU, docetaxel as well as cisplatin are approved in the present therapeutic indication. There is a discrepancy between the drugs approved for the therapeutic indication and those recommended in the guidelines. In the context of treatment of physician's choice, the treatment options cited here are considered to be suitable comparators. The added benefit can be assessed versus one of the cited treatment options within the framework of a single-comparator study. The choice of the used comparator has to be justified in the dossier. f. Data are only available for patients for whom cisplatin + 5-FU or cisplatin + capecitabine is a suitable treatment option according to physician's choice. No data are available for patients for whom another treatment option is suitable according to physician's choice. g. Guidelines recommend the combination therapy of the anti-HER2 antibody trastuzumab with cisplatin and fluoropyrimidines (5-FU or capecitabine), but this is not (explicitly) approved for the present therapeutic indication. Only the drugs 5-FU as well as cisplatin are approved in the present therapeutic indication. There is a discrepancy between the drugs approved for the therapeutic indication and those recommended in the guidelines. Within the framework of the HER2-targeted therapy according to physician's choice, trastuzumab in combination with cisplatin and capecitabine or 5-FU is considered to be a suitable comparator. The added benefit can be assessed versus one of the cited treatment options within the framework of a single-comparator study. The choice of the used comparator has to be justified in the dossier. 5-FU: 5-fluorouracil; ACT: appropriate comparator therapy; CPS: combined positive score; G-BA: Federal Joint Committee			

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

Aim of the present report is the assessment of the added benefit of pembrolizumab in combination with platinum- and fluoropyrimidine-based chemotherapy in comparison with the ACT in the first-line treatment of locally advanced, unresectable (not curatively treatable according to the G-BA) or metastatic carcinoma of the oesophagus or HER2-negative adenocarcinoma of the gastroesophageal junction in adults whose tumours express PD-L1 (CPS ≥ 10).

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	ACT[a]
A	Adult patients with locally advanced or metastatic, squamous cell carcinoma of the oesophagus that cannot be treated curatively[b] and whose tumours express PD-L1 (CPS ≥ 10); first-line treatment	Cisplatin in combination with 5-fluorouracil (5-FU)[c]
B1	Adult patients with locally advanced or metastatic HER2-negative adenocarcinoma of the oesophagus or of the gastroesophageal junction that cannot be treated curatively[b] and whose tumours express PD-L1 (CPS ≥ 10); first-line treatment	Treatment of physician's choice[d]
B2	Adult patients with locally advanced or metastatic HER2-positive adenocarcinoma of the oesophagus that cannot be treated curatively[b] and whose tumours express PD-L1 (CPS ≥ 10); first-line treatment	HER2-targeted therapy according to physician's choice[e]

a. Presented is the respective ACT specified by the G-BA.
b. According to the G-BA, it is assumed for the present therapeutic indication that curative treatment with definitive radiochemotherapy is not an option for patients with unresectable cancer.
c. According to the G-BA it is assumed that cisplatin-containing chemotherapy is suitable for the patients.
d. Guidelines mention several platinum- and fluoropyrimidine-based combination chemotherapies: S-1 (tegafur/gimeracil/oteracil) + cisplatin or capecitabine + cisplatin [XP], 5-FU + cisplatin, 5-FU + oxaliplatin + folinic acid [FLO and FOLFOX], capecitabine + oxaliplatin, infusional 5-FU + folinic acid + cisplatin [PLF], epirubicin + cisplatin + capecitabine [ECX], epirubicin + oxaliplatin + capecitabine [EOX], epirubicin + cisplatin + infusional 5-FU [ECF], docetaxel + cisplatin + infusional 5-FU [DCF], 5-FU + oxaliplatin + epirubicin, infusional 5-FU + folinic acid + oxaliplatin + docetaxel [FLOT regimen]. However, only the drugs 5-FU, docetaxel as well as cisplatin are approved in the present therapeutic indication. There is a discrepancy between the drugs approved for the therapeutic indication and those recommended in the guidelines. In the context of treatment of physician's choice, the G-BA considered the treatment options cited here to be suitable comparators. The choice of the used comparator has to be justified in the dossier.
e. Guidelines recommend the combination therapy of the anti-HER2 antibody trastuzumab with cisplatin and fluoropyrimidines (5-FU or capecitabine), but this is not (explicitly) approved for the present therapeutic indication. Only the drugs 5-FU as well as cisplatin are approved in the present therapeutic indication. There is a discrepancy between the drugs approved for the therapeutic indication and those recommended in the guidelines. Within the framework of the HER2-targeted therapy according to physician's choice, the company considered trastuzumab in combination with cisplatin and capecitabine or 5-FU to be a suitable comparator. The choice of the used comparator has to be justified in the dossier.

5-FU: 5-fluorouracil; ACT: appropriate comparator therapy; CPS: combined positive score; G-BA: Federal Joint Committee; HER2: human epidermal growth factor receptor 2; PD-L1: programmed cell death ligand 1

In the present benefit assessment, the following terms are used for the patient populations of the 3 research questions:

- Research question A: patients with squamous cell carcinoma of the oesophagus and CPS ≥ 10
- Research question B1: patients with HER2-negative adenocarcinoma of the oesophagus or of the gastroesophageal junction and CPS ≥ 10
- Research question B2: patients with HER2-positive adenocarcinoma of the oesophagus and CPS ≥ 10

The company stated that it followed the ACT for research questions A and B1. In doing so, the company stated that it chose the option cisplatin in combination with 5-FU and the combination cisplatin in combination with capecitabine for research question B1. For research question B2, the company made no explicit statement on the ACT and referred to the fact that no data were available for the relevant patient population for the ACT specified by the G-BA. Overall, however, the company made its statement on the added benefit for the entire target population without making separate statements for the respective subpopulations of research questions A, B1 and B2. Concurring with the G-BA's specification, the present assessment was conducted separately for the three research questions A, B1 and B2, 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 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: 29 September 2021)
- bibliographical literature search on pembrolizumab (last search on 22 September 2021)
- search in trial registries/trial results databases for studies on pembrolizumab (last search on 22 September 2021)
- search on the G-BA website for pembrolizumab (last search on 1 October 2021)

To check the completeness of the study pool:

- search in trial registries for studies on pembrolizumab (last search on 26 November 2021); for search strategies, see Appendix A of the full dossier assessment

The company identified the 2 studies KEYNOTE 590 and KEYNOTE 062 and included them in its study pool. The check did not identify any additional relevant study.

The company used the results of the KEYNOTE 590 study to derive the added benefit, but did not differentiate between the subpopulations relevant for research questions A and B1. The company states that a conclusion on the extent and probability of the added benefit cannot be drawn for the subpopulation of research question B2 on the basis of the available data. Nevertheless, based on the population with PD-L1-expressing tumours (CPS ≥ 10) of the KEYNOTE 590 study, the company derived an added benefit across research questions for the entire target population of the present therapeutic indication.

Although the company identifies the KEYNOTE 062 study as a relevant study, it states that this study is only included for reasons of completeness. However, from the point of view of the company, KEYNOTE 062 is no suitable evidence for the derivation of the added benefit.

The approach of the company is not appropriate. This is explained in the sections on the respective research questions.

For the present benefit assessment, data of a relevant subpopulation of the KEYNOTE 590 study were used for research question A, and data of the respective relevant subpopulations of KEYNOTE 590 and KEYNOTE 062 were used for research question B1. The company presented no relevant studies for research question B2. Detailed information on each relevant subpopulation can be found in Section 2.4.1.2 (research question A) and Section 2.5.1.2 (research question B1) of the present benefit assessment.

2.4 Research question A: patients with squamous cell carcinoma of the oesophagus and CPS ≥ 10

2.4.1 Study included

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

Table 5: Study pool – RCT, direct comparison: pembrolizumab + cisplatin + 5-FU vs. cisplatin + 5-FU

Study	Study category			Available sources		
	Study for the approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	Clinical study report (CSR)[b] (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication (yes/no [citation])
MK-3475-590 (KEYNOTE 590[c])	Yes	Yes	No	Yes [3]	Yes [4,5]	Yes [6,7]

a. Study for which the company was sponsor.
b. Citation of the study registry entries and, if available, of the reports on study design and/or results listed in the study registries.
c. In the following tables, the study is referred to with this abbreviated form.

5-FU: 5-fluorouracil; RCT: randomized controlled trial

The KEYNOTE 590 study was included in the present benefit assessment for research question A. The subpopulation of the study relevant for the present assessment is described in Section 2.4.1.2.

As described in Section 2.2, the company used the results of the population with PD-L1-expressing tumours (CPS ≥ 10) of the KEYNOTE 590 study to derive the added benefit, without drawing separate conclusions on the added benefit for the respective subpopulations of research

questions A, B1 and B2. The approach of the company is not appropriate. This is explained in Section 2.4.1.2.

In the KEYNOTE 590 study, the combination of pembrolizumab with platinum- and fluoropyrimidine-based chemotherapy was only implemented as combination with cisplatin and 5-FU. Therefore, no data are available for the combination of pembrolizumab with other approved drugs within the framework of platinum- and fluoropyrimidine-based chemotherapy.

Exclusion of the KEYNOTE 062 study for research question 1

In addition to KEYNOTE 590, the study pool of the company in Module 4 A also comprises the KEYNOTE 062 study for all research questions, which the company, however, does not consider a suitable evidence for the derivation of the added benefit.

KEYNOTE 062 only includes patients with adenocarcinoma of the stomach or of the gastroesophageal junction, but no patients with squamous cell carcinoma of the oesophagus and thus no patients relevant for research question A.

The patient population examined in the KEYNOTE 062 study does not correspond to the subpopulation relevant for research question A (patients with squamous cell carcinoma of the oesophagus and CPS ≥ 10). Therefore, the lack of inclusion of the KEYNOTE 062 study by the company for research question A is appropriate.

2.4.1.1 Study characteristics

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

Table 6: Characteristics of the study included – RCT, direct comparison: pembrolizumab + cisplatin + 5-FU vs. placebo + cisplatin + 5-FU (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
KEYNOTE 590	RCT, double-blind, parallel	Adult patients[b] with locally advanced unresectable or metastatic adenocarcinoma or squamous cell carcinoma of the oesophagus or advanced or metastatic adenocarcinoma of the gastroesophageal junction (Siewert type I) in the first line	Pembrolizumab + cisplatin + 5-FU (N = 373) placebo + cisplatin + 5-FU (N = 376) relevant subpopulation thereof[c]: pembrolizumab + cisplatin + 5-FU (n = 143) placebo + cisplatin + 5-FU (N = 143)	Screening: ≤ 28 days treatment: until disease progression, unacceptable toxicity, decision of the physician, withdrawal of consent, complete response or a maximum of 35 cycles observation[d]: outcome-specific, at most until death, withdrawal of consent or end of the study	168 centres in: Argentina, Australia, Brazil, Canada, Columbia, Chile, China, Costa Rica, Denmark, France, Germany, Guatemala, Hong Kong, Japan, Malaysia, Peru, Romania, Russia, South Africa, South Korea, Spain, Taiwan, Thailand, Turkey, United Kingdom, United States 07/2017–ongoing data cut-offs: 2 July 2020 (final analysis[e]) 9 July 2021[f] (post hoc)	Primary: overall survival, progression-free survival secondary: morbidity, health-related quality of life, AEs

a. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes only include information on relevant available outcomes for this benefit assessment.
b. With ECOG PS 0 or 1 and PD-L1 status determined by immunohistochemistry using a tissue sample (no information on the used assay in the company's dossier) .
c. patients with squamous cell carcinoma of the oesophagus and CPS ≥ 10
d. Outcome-specific information is provided in Table 8.
e. The data cut-off was originally planned as the first interim analysis after at least 13 months of observation of the last patient after randomization, 460 PFS events and 391 OS events in the population of patients with squamous cell carcinoma of the oesophagus, but represents the final analysis of the study.
f. Was performed for a presentation in the context of a scientific congress; a corresponding CSR is not available. Results on mortality and side effects were analysed.

5-FU: 5-fluorouracil; AE: adverse event; CPS: combined positive score; ECOG PS: Eastern Cooperative Oncology Group Performance Status; n: relevant subpopulation; N: number of randomized patients; OS: overall survival; PD-L1: programmed cell death ligand 1; PFS: progression-free survival; RCT: randomized controlled trial

Table 7: Characteristics of the intervention – RCT, direct comparison: pembrolizumab + cisplatin + 5-FU vs. placebo + cisplatin + 5-FU, subpopulation with squamous cell carcinoma of the oesophagus and CPS ≥ 10 (multipage table)

Study	Intervention	Comparison
KEYNOTE 590	Pembrolizumab 200 mg IV (as 30-minute infusion) on day 1 of a 3-week cycle[a] + cisplatin 80 mg/m² BSA, IV, on day 1 of each 3-week cycle[b] + 5-FU 800 mg/m² BSA/day, continuous administration from day 1 to 5 of a 3-week cycle or according to local standards (a total of 4000 mg/m² BSA per cycle)[a]	Placebo[a] + cisplatin 80 mg/m² BSA, IV, on day 1 of each 3-week cycle[b] + 5-FU 800 mg/m² BSA/day, continuous administration from day 1 to 5 of a 3-week cycle or according to local standards (a total of 4000 mg/m² BSA per cycle)[a]
	Dose adjustments ▪ pembrolizumab or placebo: no dose reduction allowed; treatment interruption or discontinuation in case of toxicity ▪ chemotherapy (cisplatin and 5-FU): gradual dose reduction in case of toxicity; reduced dose could not be increased again; at most 2 adjustments per therapy component allowed, treatment discontinuation in case of further toxicity	
	Pretreatment not allowed ▪ previous treatment of the advanced or metastatic carcinoma[c] ▪ systemic treatment of an active autoimmune disorder with disease-modifying agents, corticosteroids or immunosuppressants in the last 2 years ▪ chronic systemic steroid therapy (≥ 10 mg prednisone equivalent per day) or another form of immunosuppressive therapy within 7 days before the first dose of the study treatment ▪ ongoing systemic treatment of an active infection ▪ prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent or with an agent directed against another co-inhibitory T-cell receptor ▪ radiotherapy within 14 days before randomization **concomitant treatment** not allowed ▪ antineoplastic systemic chemotherapy or biologic therapy ▪ chemotherapies or immunotherapies not predefined in the protocol ▪ radiotherapy (note: radiotherapy for the symptomatic treatment of solitary lesions or on the brain were allowed after consultation with the sponsor) ▪ systemic glucocorticoids for purposes other than the regulation of symptoms of an AE with suspected immunological aetiology or to support the treatment with cisplatin/5-FU ▪ brivudine, sorivudine analogues and other inhibitors of the enzyme dihydropyrimidine dehydrogenase should not be administered together with 5-FU therapy allowed: ▪ supportive treatment for the chemotherapy ▪ oral or IV corticosteroids or other anti-inflammatory drugs for the treatment of side effects	

Table 7: Characteristics of the intervention – RCT, direct comparison: pembrolizumab + cisplatin + 5-FU vs. placebo + cisplatin + 5-FU, subpopulation with squamous cell carcinoma of the oesophagus and CPS ≥ 10 (multipage table)

Study	Intervention	Comparison
a. Treatment up to a maximum of 35 cycles – corresponds to approx. 2 years. b. Treatment is limited to 6 cycles. c. Prior treatment with curative intent, including neoadjuvant/adjuvant treatment administered as chemotherapy or radiochemotherapy using standard drugs or definitive radiochemotherapy, was considered prior treatment of the advanced or metastatic disease in this context if the disease had progressed during the treatment or within 6 months. 5-FU: 5-fluorouracil; BSA: body surface area; CPS: combined positive score; IV: intravenous; PD-1: programmed cell death 1; PD-L1/PD-L2: programmed cell death ligand 1/2; RCT: randomized controlled trial		

KEYNOTE 590 is an ongoing, double-blind, randomized, active controlled, multicentre study on the comparison of pembrolizumab in combination with cisplatin and 5-FU (pembrolizumab + cisplatin + 5-FU) versus placebo in combination with cisplatin and 5-FU (placebo + cisplatin + 5-FU).

The study included adult patients with squamous cell carcinoma or adenocarcinoma of the oesophagus or adenocarcinoma of the gastroesophageal junction (Siewert type I only), each in the locally advanced or metastatic stage. Patients with HER2-positive adenocarcinoma of the gastroesophageal junction were excluded from the study. Either a newly obtained or an archived tissue sample of the included patients had to be available for the PD-L1 analysis by means of immunohistochemistry (no information on the assay used in the company's dossier).

Patients were not allowed to have received prior treatment at this stage of the disease. Prior treatment with curative intent was considered treatment at this stage of the disease if the disease had progressed during or within 6 months of that treatment.

The patients had to have a good general condition (ECOG PS ≤ 1). Patients with ECOG PS ≥ 2 or active CNS metastases were excluded from the participation in the study; hence, no data are available for them.

Patients were stratified by histology (adenocarcinoma vs. squamous cell carcinoma), region (Asia versus rest of the world) and ECOG PS (0 vs. 1) and randomly assigned either to the intervention arm (pembrolizumab + cisplatin + 5-FU; N = 373) or to the comparator arm (placebo + cisplatin + 5-FU; N = 376).

In both study arms, treatment was performed for a maximum of 35 cycles in 3-week cycles until a reason for discontinuation occurred (disease progression, unacceptable toxicity, physician’s decision, withdrawal of consent or complete response), with the cisplatin treatment component limited to a maximum of 6 cycles. After discontinuation of either pembrolizumab, cisplatin and/or 5-FU, treatment could be continued with the remaining drug component(s). There were no restrictions regarding subsequent therapies after the end of the study medication (an

overview of the subsequent oncological therapies can be found in 11). A switch of the patients in the comparator arm to the treatment of the intervention arm was not planned.

In the KEYNOTE 590 study, treatment with pembrolizumab largely corresponded to the recommendations of the SPC. However, there are uncertainties regarding the treatment, which are described in the following section [8-10].

Primary outcomes of the KEYNOTE 590 study were overall survival and progression-free survival (PFS). Outcomes on symptoms, health status, health-related quality of life and AEs were recorded as further patient-relevant outcomes.

Uncertainties regarding the treatment

Number of treatment cycles

In both study arms, the study treatment with pembrolizumab or placebo and with 5-FU was limited to a maximum of 35 cycles (approx. 2 years), and treatment with cisplatin was limited to 6 cycles. However, according to the approval, treatment with pembrolizumab should be continued until progression of the cancer or the occurrence of unacceptable toxicity [8]. According to the approval, there is no fixed upper limit on the number of treatment cycles for treatment with 5-FU and cisplatin [9,10].

In the total population of the KEYNOTE 590 study, only 14 (3.8%) patients in the intervention arm received the maximum specified number of 35 treatment cycles with pembrolizumab. 8 (2.2%) patients in the intervention arm and 2 (0.5%) patients in the comparator arm received a maximum of 35 treatment cycles with 5-FU. Due to the small number of affected patients, it is not assumed that the restriction to a maximum of 35 treatment cycles represents a relevant limitation of the treatment.

In the total population of KEYNOTE 590, 206 (55.7%) patients in the intervention arm and 205 (55.4%) patients in the comparator arm received 6 treatment cycles with cisplatin. Thereafter, these patients received no further treatment with cisplatin, although this would have been possible in principle according to the approval. The current national S3 guideline includes no recommendation regarding the duration of treatment with cisplatin [11]. Therefore, there is uncertainty regarding the question of whether further cycles of treatment with cisplatin would have been an option for the patients.

Dosage of 5-FU

The 5-FU dosage in the study deviates from the specifications of the approval [10]. In the KEYNOTE 590 study, a total dose of 4000 mg/m² BSA/cycle was planned in both study arms, for example in the form of a dose of 800 mg/m² BSA/day on days 1 to 5 or 1000 mg/m² BSA/day on days 1 to 4 of a 3-week cycle. The SPC of 5-FU for the treatment of oesophageal carcinoma, in contrast, stipulates a dose of 1000 mg/m² BSA/day on days 1 to 5 of a 3-4-week cycle. Hence, this corresponds to a total dose of 5000 mg/m² BSA/cycle. It should be noted that according to

the approval, a cycle length of 3-4 weeks was possible, whereas a fixed cycle length of 3 weeks had been planned in the study.

The current national S3 guideline includes no recommendation regarding the dosage of 5-FU [11]. In contrast, in combination with cisplatin, the NCCN guideline recommends a 5-FU dose of 750 to 1000 mg/m² BSA/day on days 1 to 4 of a 4-week cycle [12]. The cycle length recommended there thus deviates from the cycle length in the KEYNOTE 590 study.

Overall, the 5-FU dose used in the KEYNOTE 590 study deviates from the approved dose for the oesophageal carcinoma. It is unclear to what extent this deviation affects the results of patient-relevant outcomes.

Summary of the uncertainties regarding the treatment

The uncertainties described above regarding the treatment result in a reduced certainty of conclusions of the KEYNOTE 590 study.

2.4.1.2 Relevant subpopulation

The company explained that it was going to assess the added benefit of pembrolizumab across all questions on the basis of the subpopulation of the label-enabling KEYNOTE 590 study, which includes patients with CPS ≥ 10 irrespective of the tumour histology (squamous cell carcinoma or adenocarcinoma). Hence, this population comprised the subpopulations of the study relevant for research questions A and B1. The company justified this approach with the fact that the informative value based on this population was to be regarded as the strongest and that the characteristic “histology“ did not represent a relevant effect modifier for the patient-relevant outcomes in the present therapeutic indication.

The argumentation of the company for pooling the patient populations of research questions A and B1 is not substantive. A missing relevant effect modification for the characteristic “histology” is no sufficient reason to pool the populations. Furthermore, the differentiation of the populations according to the histology of the carcinoma, in particular between squamous cell and adenocarcinoma, corresponds to the recommendations of the current S3 guideline [11]. According to this guideline, a distinction between squamous cell carcinoma and adenocarcinoma of the oesophagus is clinically relevant due to the different biological behaviour of these two histologic types. Consequently, the therapy recommendations also differ depending on the histological type of the carcinoma. Accordingly, the G-BA specified a different ACT for patients with squamous cell carcinoma than for patients with adenocarcinoma, whereby the option of treatment with cisplatin in combination with 5-FU is possible overlapping for both populations.

Hence, the subpopulation of patients with squamous cell carcinoma of the oesophagus and CPS ≥ 10 is relevant to answer the present research question. The company presented analyses on a corresponding subpopulation of KEYNOTE 590, but did not use it to derive the added benefit.

The subpopulation of patients with squamous cell carcinoma of the oesophagus and CPS ≥ 10 presented by the company is relevant for the benefit assessment and comprises 143 patients each in the intervention and the comparator arm.

2.4.1.3 Data cut-offs

For the study, data are available on 2 data cut-offs:

- First data cut-off of 2 July 2020: preplanned interim analysis, conducted as final analysis
- Second data cut-off of 9 July 2021: post-hoc analysis, which according to the company was carried out for a presentation at a scientific congress; a study report is not available

In Module 4 A, the company presented the results of both data cut-offs. The results of the final analysis of 2 July 2020 were used in the present benefit assessment.

2.4.1.4 Treatment duration and 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 + cisplatin + 5-FU vs. placebo + cisplatin + 5-FU, subpopulation with squamous cell carcinoma of the oesophagus and CPS ≥ 10

Study outcome category outcome	Planned follow-up observation
KEYNOTE 590	
Mortality	
Overall survival	Until death, withdrawal of consent or end of study
Morbidity	
Symptoms, health status (EORTC QLQ-C30, EORTC QLQ-OES18, EQ-5D VAS)	Up to 30 days after treatment discontinuation or end of treatment[a]
Health-related quality of life (EORTC QLQ-C30)	Up to 30 days after treatment discontinuation or end of treatment[a]
Side effects	
AEs, severe AEs	Up to 30 days after treatment discontinuation or end of treatment
SAEs	Until 90 days after treatment discontinuation or end of treatment, or until 30 days after treatment discontinuation or end of treatment when starting a new antineoplastic therapy

a. Patient-reported outcomes were recorded during treatment for a maximum of 1 year as well as at the end of treatment and 30 days after the end of treatment.

5-FU: 5-fluorouracil; AE: adverse event; CPS: combined positive score; EORTC: European Organisation for Research and Treatment of Cancer; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-OES18: Quality of Life Questionnaire-Oesophageal Cancer 18 items; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale

The observation periods for the outcomes on morbidity, health-related quality of life and side effects were systematically shortened because, as stated in Table 8, they were only recorded for the time period of treatment with the study medication plus 30 days or plus a maximum of 90 days (for SAEs) (see also Section 2.4.1.6).

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.

2.4.1.5 Characteristics of the relevant subpopulation

Table 9 shows the characteristics of the subpopulation with squamous cell carcinoma of the oesophagus and CPS ≥ 10 in the included study KEYNOTE 590.

Table 9: Characteristics of the study population – RCT, direct comparison: pembrolizumab + cisplatin + 5-FU vs. placebo + cisplatin + 5-FU, subpopulation with squamous cell carcinoma of the oesophagus and CPS ≥ 10

Study characteristic category	**Pembrolizumab + cisplatin + 5-FU N = 143**	**Placebo + cisplatin + 5-FU N = 143**
Study KEYNOTE 590		
Age [years], mean (SD)	63 (9)	62 (9)
Sex [F/M], %	20/80	19/81
Family origin		
Asian	98 (69)	99 (69)
White	32 (22)	30 (21)
American and Alaskan natives	5 (4)	6 (4)
Black or African American	2 (1)	0 (0)
Several	2 (1)	4 (3)
Unknown	4 (3)	4 (3)
Disease status		
Metastatic	134 (94)	128 (90)
Unresectable - locally advanced	9 (6)	15 (11)
ECOG PS, n (%)		
0	61 (43)	54 (38)
1	82 (57)	89 (62)
Treatment discontinuation, n (%)[a]	121 (85)	134 (96)
Study discontinuation, n (%)[b]	94 (66)	121 (85)

a. Common reasons for treatment discontinuation in the intervention versus the control arm were: disease progression (62% vs. 74%), AEs (11% vs. 15%), decision of the patient (9% vs. 6 %). Data are based on the population with at least one intake of the study medication (143 vs. 140 patients).
b. The most common reason for study discontinuation in the intervention vs. the control arm was death (65% vs. 85%).

5-FU: 5-fluorouracil; CPS: combined positive score; ECOG PS: Eastern Cooperative Oncology Group Performance Status; F: female; M: male; n: number of patients in the category; N: number of patients in the category; N: number of patients in the relevant subpopulation; RCT: randomized controlled trial; SD: standard deviation

The patient characteristics were balanced between the study arms. The mean age of the patients in the relevant subpopulation was 63 years; most of them were male and of Asian family origin; only about one fifth each were female or of white family origin. Almost all patients had metastatic disease. 43% of the patients in the intervention arm and 38% of the patients in the comparator arm had an ECOG PS of 0.

In both treatment arms, the most common reasons for treatment discontinuation were disease progression (intervention arm: 62%; control arm: 74%), followed by AEs (intervention arm: 11%; control arm: 15%), with frequencies differing between the arms.

2.4.1.6 Treatment duration and observation period as well as subsequent therapies

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

Table 10: Information on the course of the study – RCT, direct comparison: pembrolizumab + cisplatin + 5-FU vs. placebo + cisplatin + 5-FU, subpopulation with squamous cell carcinoma of the oesophagus and CPS ≥ 10

Study **duration of the study phase** **outcome category**	**Pembrolizumab + cisplatin + 5-FU** **N = 143**	**Placebo + cisplatin + 5-FU** **N = 143**
KEYNOTE 590		
Treatment duration [months]	ND[a]	ND[a]
Observation period [months]		
Overall survival	ND[a]	ND[a]
Morbidity	ND	ND
Health-related quality of life	ND	ND
Side effects	ND[a]	ND[a]

a. Module 4 A of the dossier states the median treatment duration for the KEYNOTE 590 study to be 5.8 months in the intervention arm and 4.9 months in the comparator arm. A median observation period of 13.3 months and 9.4 months was reported for the outcome "overall survival", 6.8 months and 5.7 months for AEs and 8.7 months and 7.0 months for SAEs in the intervention arm and the comparator arm, respectively. The data provide no information as to which population this information refers. They are assumed to refer to the total population with CPS≥ 10 regardless of histology and primary diagnosis.

5-FU: 5-fluorouracil; AE: adverse event; CPS: combined positive score; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; SAE: serious adverse event SD: standard deviation

Information on the treatment and observation periods explicitly referring to the relevant subpopulation of research question A are not available for the KEYNOTE 590 study.

Module 4 A provides information on the treatment duration and observation periods. However, it is not clear to which population these refer. It can be assumed, however, that they refer to the population of patients with CPS ≥ 10 considered by the company, irrespective of histology and primary diagnosis. A median treatment duration of 5.8 months in the intervention arm and 4.9 months in the comparator arm was reported for this population. A median observation period of 13.3 months and 9.4 months was reported for the outcome "overall survival", 6.8 months and 5.7 months for AEs and 8.7 months and 7.0 months for SAEs in the intervention arm and the comparator arm, respectively.

Table 11 shows which subsequent therapies patients received after discontinuation of the study medication.

Table 11: Information on the first subsequent oncological therapy – RCT, direct comparison: pembrolizumab + cisplatin + 5-FU vs. placebo + cisplatin + 5-FU, subpopulation with squamous cell carcinoma and CPS ≥ 10

Study therapy class drug	Patients with subsequent therapy n (%)	
	pembrolizumab + cisplatin + 5-FU N = 143	placebo + cisplatin + 5-FU N = 143
KEYNOTE 590		
First subsequent oncological therapy[a]		
Systemic therapy	54 (37.8)	52 (36.4)
Systemic therapy and radiotherapy	5 (3.5)	4 (2.8)
Systemic therapy with/without radiotherapy	59 (41.3)	56 (39.2)
Antineoplastic treatments	59 (41.3)	56 (39.2)
Paclitaxel	26 (18.2)	29 (20.3)
Docetaxel	14 (9.8)	10 (7.0)
Fluorouracil	12 (8.4)	8 (5.6)
Cisplatin	10 (7.0)	7 (4.9)
Carboplatin	5 (3.5)	3 (2.1)
Nab-paclitaxel	3 (2.1)	2 (1.4)
Nedaplatin	3 (2.1)	1 (0.7)
Oxaliplatin	3 (2.1)	1 (0.7)
Afatinib	1 (0.7)	2 (1.4)
Irinotecan hydrochloride	1 (0.7)	2 (1.4)
Methotrexate	2 (1.4)	0 (0)
Pembrolizumab	0 (0)	2 (1.4)
Anlotinib	1 (0.7)	0 (0)
Apatinib	0 (0)	1 (0.7)
Bleomycin	1 (0.7)	0 (0)
Capecitabine	0 (0)	1 (0.7)
Gimeracil (+) oteracil (+) tegafur	1 (0.7)	0 (0)
Ifosfamide	1 (0.7)	0 (0)
Ipilimumab	0 (0)	1 (0.7)
Nimotuzumab	0 (0)	1 (0.7)
Nivolumab	0 (0)	1 (0.7)
Recombinant human endostatin	1 (0.7)	0 (0)
Immunostimulants	0 (0)	1 (0.7)
Recombinant human interleukin-2	0 (0)	1 (0.7)
Radiotherapy	14 (9.8)	19 (13.3)
Died without follow-up therapy	45 (31.5)	60 (42.0)
No follow-up therapy	25 (17.5)	8 (5.6)

a. A patient with several simultaneously administered systemic therapies is assigned to this therapy class only once.

5-FU: 5-fluorouracil; CPS: combined positive score; n: number of patients with subsequent therapy; N: number of analysed patients; RCT: randomized controlled trial

After discontinuation of the study treatment, patients could receive subsequent oncological therapies without restrictions. The proportion of patients with certain subsequent therapies such as systemic therapy or radiotherapy was comparable between the study arms.

2.4.1.7 Risk of bias across outcomes (study level)

Table 12: Risk of bias across outcomes (study level) – RCT, direct comparison: pembrolizumab + cisplatin + 5-FU vs. placebo + cisplatin + 5-FU, subpopulation with squamous cell carcinoma of the oesophagus and CPS ≥ 10

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	Absence of other aspects	Risk of bias at study level
			Patients	Treating staff			
KEYNOTE 590	Yes	Yes	Yes	Yes	Yes	Yes	Low
5-FU: 5-fluorouracil; CPS: combined positive score; RCT: randomized controlled trial							

The risk of bias across outcomes was rated as low for the KEYNOTE 590 study.

2.4.1.8 Transferability of the study results to the German health care context

The company states that the results of the KEYNOTE 590 study (CPS ≥ 10) can be transferred to the German healthcare context due to the characteristics of the examined patient population, the study design and the use of pembrolizumab in combination with platinum- and fluoropyrimidine-based chemotherapy in accordance with the approval, and states further that there is also no indication of a deviating efficacy or safety of pembrolizumab in the subgroups by region.

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

2.4.2 Results on added benefit

2.4.2.1 Outcomes included

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

- Mortality
  - overall survival
- Morbidity
  - health status, recorded using the EQ-5D VAS

  - symptoms recorded with the EORTC QLQ-C30 and Quality of Life Questionnaire-Oesophageal Cancer 18 items (EORTC QLQ-OES18)
- Health-related quality of life
  - recorded with the EORTC QLQ-C30
- Side effects
  - SAEs
  - severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3)
  - discontinuation due to AEs
  - immune-related AEs (SAEs and severe AEs)
  - further specific AEs (SOC, PT), if any

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

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

Table 13: Matrix of outcomes – RCT, direct comparison: pembrolizumab + cisplatin + 5-FU vs. placebo + cisplatin + 5-FU, subpopulation with squamous cell carcinoma of the oesophagus and CPS ≥ 10

Study	Outcomes											
	Overall survival	Health status (EQ-5D VAS)	Symptoms (EORTC QLQ-C30, QLQ-OES18)	Health-related quality of life (EORTC QLQ-C30)	SAEs	Severe AEs[a]	Discontinuation due to AEs	Immune-related SAEs and severe AEs[a]	Musculoskeletal and connective tissue disorders (SOC, AE)	General disorders and administration site conditions (SOC, SAE)	Platelet count decreased (PT, severe AEs[a])	Weight decreased (PT, severe AEs[a])
KEYNOTE 590	Yes	Yes	No[b]	No[b]	Yes	Yes	No[b]	Yes	Yes	Yes	Yes	Yes

a. Severe AEs are operationalized as CTCAE grade 3–5.
b. No usable data available; see following running text for reasons.

5-FU: 5-fluorouracil; AE: adverse event; CPS: combined positive score; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; PT: Preferred Term; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-OES18: Quality of Life Questionnaire-Oesophageal Cancer 18 items; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

Notes on outcomes and analyses

Health status

In its dossier, the company presented responder analyses for the time to first deterioration by ≥ 7 or ≥ 10 points (scale range 0 to 100) for the outcome "health status" (EQ-5D VAS). These were not used for the dossier assessment. As explained in the *General Methods* of the Institute [1,13], 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 adjusted analyses on the mean change until week 18 versus baseline predefined for the relevant subpopulation of research question A in the study report of the KEYNOTE 590 study are used for the present assessment. The responder analyses presented by the company are presented as supplementary information in Appendix B of the full dossier assessment.

Symptoms and health-related quality of life

The information on the operationalization of the EORTC QLQ-C30 and the EORTC QLQ-OES18 in the KEYNOTE 590 study provided in Module 4 A of the dossier is contradictory. The company stated that it would provide analyses for the time to first deterioration of ≥ 10 points. However, the company occasionally refers to the operationalization of the analyses presented as time to first confirmed deterioration, without describing how a confirmed deterioration is defined. Results on the time to first confirmed deterioration for individual scales of the EORTC QLQ-C30 and the EORTC QLQ-OES18 can be found in the study report of the KEYNOTE 590 study. These results presented in the study report differ from the results presented in Module 4 A for the corresponding scales. Overall, it is unclear whether these discrepancies between the results presented in Module 4 A and those in the study report can be explained by different operationalization. In Module 4 A, the company does not explain the deviations from the study report with regard to approach and results.

For these reasons, the results of the KEYNOTE 590 study for EORTC QLQ-C30 and EORTC QLQ-OES18 presented in Module 4 A are considered unusable and are not used for the assessment.

Discontinuation due to AEs

For the outcome “discontinuation due to AEs”, it cannot be inferred from the information provided by the company in Module 4 A whether the analyses refer to the time to discontinuation of all drug components or to discontinuation of at least one drug component. According to the study protocol, patients could continue treatment with the remaining drugs after discontinuation of individual drugs. An analysis on the discontinuation of all drug components alone cannot be meaningfully interpreted in the present data situation (3 drug components in the intervention arm and 2 drug components in the comparator arm). Regardless of this, analyses on the discontinuation of at least 1 drug component are to be preferred, as any AE leading to discontinuation of any treatment component is relevant. Consequently, results for the analysis of the time to discontinuation of at least one drug component are required for the benefit assessment.

For these reasons, the results of the KEYNOTE 590 study for the outcome "discontinuation due to AEs” presented in Module 4 A are considered unusable and are not used for the assessment.

2.4.2.2 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 + cisplatin + 5-FU vs. placebo + cisplatin + 5-FU, subpopulation with squamous cell carcinoma of the oesophagus and CPS ≥ 10

Study		Outcomes											
	Study level	Overall survival	Health status (EQ-5D VAS)[a]	Symptoms (EORTC QLQ-C30, EORTC QLQ-OES18)	Health-related quality of life (EORTC QLQ-C30)	SAEs	Severe AEs[b]	Discontinuation due to AEs	Immune-related SAEs and severe AEs[b]	Musculoskeletal and connective tissue disorders (SOC, AE)	General disorders and administration site conditions (SOC, SAE)	Platelet count decreased (PT, severe AEs[b])	Weight decreased (PT, severe AEs[b])
KEYNOTE 590	L	L	H[c]	–[d]	–[d]	H[e]	H[e]	–[d]	H[e]	H[e]	H[e]	H[e]	H[e]

a. Analysis only refers to the time from randomization to week 18 after randomization.
b. Severe AEs are operationalized as CTCAE grade 3–5.
c. Decreasing response to questionnaire over the course of the study.
d. No usable data available; see Section 2.4.2.1 for reasons.
e. Incomplete observations for potentially informative reasons.

5-FU: 5-fluorouracil; AE: adverse event; CPS: combined positive score; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; H: high; L: low; PT: Preferred Term; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-OES18: Quality of Life Questionnaire-Oesophageal Cancer 18 items; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

The outcome-specific risk of bias is rated as high for all patient-relevant outcomes except for all-cause mortality.

For the outcome "health status", the risk of bias of the results is rated as high due to the decreasing response rate of the corresponding questionnaire over the course of the study.

No usable data are available for the outcomes of the categories "symptoms" and "health-related quality of life" (for reasons, see Section 2.4.2.1), so that the risk of bias was not assessed.

The risk of bias of the results was rated as high for the outcomes "SAEs" and "severe AEs" as well as for "specific AEs". The planned follow-up observation period after end of treatment was 30 days for these outcomes in both studies. The observation period of the outcomes thus significantly depends on the treatment discontinuations. Due to a possible correlation between the reason for treatment discontinuation and these outcomes, there are incomplete observations for potentially informative reasons.

Summary assessment of the certainty of conclusions

In addition to the described outcome-specific risk of bias, due to the uncertainties regarding the treatment, at most hints, for example of an added benefit, can be derived on the basis of the KEYNOTE 590 study for all outcomes for which usable data are available (see Section 2.4.1.1).

2.4.2.3 Results

Table 15 and Table 16 summarize the results on the comparison of pembrolizumab + cisplatin + 5-FU with placebo + cisplatin + 5-FU in patients with locally advanced or metastatic squamous cell carcinoma of the oesophagus that cannot be treated curatively and whose tumours express PD-L1 (CPS ≥ 10) in the first-line treatment. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier.

Results on common AEs, common SAEs and common severe AEs (CTCAE grade ≥ 3), as well as on all AEs that led to treatment discontinuation are presented in Appendix C of the full dossier assessment. Kaplan-Meier curves on the event time analyses are presented in Appendix D.

Table 15: Results (mortality, side effects) – RCT, direct comparison: pembrolizumab + cisplatin + 5-FU vs. placebo + cisplatin + 5-FU, subpopulation with squamous cell carcinoma of the oesophagus and CPS ≥ 10 (multipage table)

Study **outcome category** **outcome**	**Pembrolizumab + cisplatin + 5-FU**		**Placebo + cisplatin + 5-FU**		**Pembrolizumab + cisplatin + 5-FU vs. placebo + cisplatin + 5-FU**
	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]; p-value[a]**
KEYNOTE 590					
Mortality					
Overall survival	143	13.9 [11.1; 17.7] 94 (65.7)	143	8.8 [7.8; 10.5] 121 (84.6)	0.57 [0.43; 0.75]; < 0.001
Morbidity					
			No usable data		
Health-related quality of life					
			No usable data		
Side effects					
AEs (supplementary information)	143	0.4 [0.3; 0.4] 143 (100.0)	140	0.4 [0.4; 0.6] 140 (100.0)	–
SAEs	143	35.6 [16.4; 62.1] 78 (54.5)	140	25.7 [16.7; 48.0] 79 (56.4)	0.87 [0.64; 1.20]; 0.405[b]
Severe AEs[c]	143	4.4 [3.1; 6.3] 126 (88.1)	140	5.0 [3.3; 8.9] 119 (85.0)	1.01 [0.78; 1.30]; 0.952[b]
Discontinuation due to AEs			No usable data		
Immune-related SAEs (PT collection)[d]	143	NA 12 (8.4)	140	NA 2 (1.4)	5.36 [1.20; 24.00]; 0.028[b]
Immune-related severe AEs (PT collection)[d]	143	NA 12 (8.4)	140	NA 3 (2.1)	3.30 [0.93; 11.77]; 0.065[b]
Musculoskeletal and connective tissue disorders (SOC, AEs)	143	NA [55.6; NC] 27 (18.9)	140	53.1 [34.1; NC] 44 (31.4)	0.41 [0.25; 0.67]; < 0.001[b]
General disorders and administration site conditions (SOC, SAEs)	143	NA 2 (1.4)	140	NA 15 (10.7)	0.11 [0.02; 0.47]; 0.003[b]
Platelet count decreased (PT, severe AEs)	143	NA 3 (2.1)	140	NA 11 (7.9)	0.25 [0.07; 0.90]; 0.033[b]
Weight decreased (PT, severe AEs)	143	NA 1 (0.7)	140	NA 9 (6.4)	0.07 [0.01; 0.58]; 0.013[b]

Table 15: Results (mortality, side effects) – RCT, direct comparison: pembrolizumab + cisplatin + 5-FU vs. placebo + cisplatin + 5-FU, subpopulation with squamous cell carcinoma of the oesophagus and CPS ≥ 10 (multipage table)

Study **outcome category** **outcome**	**Pembrolizumab + cisplatin + 5-FU**		**Placebo + cisplatin + 5-FU**		**Pembrolizumab + cisplatin + 5-FU vs. placebo + cisplatin + 5-FU**
	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]; p-value[a]**

a. Unless stated otherwise: HR and CI from Cox proportional hazards model, stratified by region (Asia versus rest of the world) and ECOG PS (0 vs. 1) with associated p-value from 2-sided Wald test.
b. HR and CI from Cox proportional hazards model, unstratified with associated p-value from 2-sided Wald test.
c. Operationalized as CTCAE grade ≥ 3.
d. Predefined list of PTs subject to continuous updating (version 18).

5-FU: 5-fluorouracil; AE: adverse event; CI: confidence interval; CPS: combined positive score; CTCAE: Common Terminology Criteria for Adverse Events; ECOG PS: Eastern Cooperative Oncology Group Performance Status; EORTC: European Organisation for Research and Treatment of Cancer; HR: hazard ratio; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; NC: not calculable; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class

Table 16: Results (morbidity, continuous) – RCT, direct comparison: pembrolizumab + cisplatin + 5-FU vs. placebo + cisplatin + 5-FU, subpopulation with squamous cell carcinoma of the oesophagus and CPS ≥ 10

Study outcome category outcome	Pembrolizumab + cisplatin + 5-FU			Placebo + cisplatin + 5-FU			Pembrolizumab + cisplatin + 5-FU vs. placebo + cisplatin + 5-FU
	N[a]	values at baseline mean (SD)	change until week 18 mean [95% CI][b]	N[a]	values at baseline mean (SD)	change until week 18 mean [95% CI][b]	MD [95% CI]; p-value[b]
KEYNOTE 590							
Morbidity							
Health status (EQ-5D VAS)[c]	ND	74.8 (17.0)	-4.46 [-7.94; -0.97]	ND	75.1 (15.5)	-4.35 [−8.06; -0.65]	-0.10 [-4.96; 4.76]; 0.967

a. Number of patients considered in the analysis for the calculation of the effect estimation; the values at baseline may be based on other patient numbers.
b. cLDA model [14] adjusted for region (Asia versus rest of the world) and ECOG PS (0 vs. 1) as well as the interaction between treatment and study visit.
c. Higher (increasing) values indicate better health status, positive effects (intervention minus control) indicate an advantage for the intervention (scale range 0 to 100).

5-FU: 5-fluorouracil; CI: confidence interval; cLDA: constrained longitudinal data analysis; CPS: combined positive score; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; MD: mean difference; N: number of analysed patients; RCT: randomized controlled trial; SD: standard deviation; VAS: visual analogue scale

On the basis of the available information, at most hints, e.g. of an added benefit, can be determined due to the high risk of bias of the results or due to the limited certainty of results with regard to all outcomes (see Section 2.4.2.2).

Mortality

Overall survival

There is a statistically significant difference in favour of pembrolizumab + cisplatin + 5-FU in comparison with placebo + cisplatin + 5-FU for the outcome “overall survival”. This resulted in a hint of an added benefit of pembrolizumab + cisplatin + 5-FU in comparison with cisplatin + 5-FU.

Morbidity

Health status (EQ-5D VAS)

For the outcome “health status (EQ-5D VAS)”, the mean change until week 18 versus baseline is considered. There was no statistically significant difference between the treatment arms. This resulted in no hint of an added benefit of pembrolizumab + cisplatin + 5-FU in comparison with cisplatin + 5-FU; an added benefit is therefore not proven.

Symptoms

There were no usable data on symptoms (see Section 2.4.2.1). This resulted in no hint of an added benefit of pembrolizumab + cisplatin + 5-FU in comparison with cisplatin + 5-FU for the outcome “symptoms”; an added benefit is therefore not proven.

Health-related quality of life

There were no usable data on health-related quality of life (see Section 2.4.2.1). This resulted in no hint of an added benefit of pembrolizumab + cisplatin + 5-FU in comparison with cisplatin + 5-FU for the outcome “health-related quality of life”; an added benefit is therefore not proven.

Side effects

According to the study protocol, progression events of the underlying oncological disease were not recorded as AEs. The MedDRA terms “progression of neoplasms”, “progression of malignant neoplasms” and “disease progression” were excluded from the AE recording.

SAEs, severe AEs and immune-related severe AEs

No statistically significant difference between the treatment arms was shown for the outcomes "SAEs", "severe AEs” and "immune-related severe AEs”. This resulted in no hint of greater or lesser harm from pembrolizumab + cisplatin + 5-FU in comparison with cisplatin + 5-FU; greater or lesser harm is therefore not proven for these outcomes.

Discontinuation due to AEs

There were no usable data for the outcome "discontinuation due to AEs". This resulted in no hint of greater or lesser harm from pembrolizumab + cisplatin + 5-FU in comparison with cisplatin + 5-FU for this outcome; greater or lesser harm is therefore not proven for this outcome.

Immune-related SAEs

There is a statistically significant difference to the disadvantage of pembrolizumab + cisplatin + 5-FU in comparison with placebo + cisplatin + 5-FU for the outcome “immune-related SAEs”. This resulted in a hint of greater harm from pembrolizumab + cisplatin + 5-FU in comparison with cisplatin + 5-FU.

Further specific AEs

“musculoskeletal and connective tissue disorders (SOC, AEs)”, “general disorders and administration site conditions (SOC, SAEs)”, “platelet count decreased (PT, severe AEs)” and “decreased weight (PT, severe AEs)”

There is a statistically significant difference in favour of pembrolizumab + cisplatin + 5-FU versus placebo + cisplatin + 5-FU for each of the specific AEs “musculoskeletal and connective tissue disorders (SOC, AEs)”, "general disorders and administration site conditions (SOC, SAEs)”, “platelet count decreased (PT, severe AEs)” and “decreased weight (PT, severe AEs)”.

In each case, this resulted in a hint of lesser harm from pembrolizumab + cisplatin + 5-FU in comparison with cisplatin + 5-FU.

It should be noted that it is unclear whether the AE "weight decreased" is a side effect of the treatment or a consequence of the underlying disease due to its connection with the symptoms of the underlying disease of oesophageal carcinoma.

2.4.2.4 Subgroups and other effect modifiers

The following potential effect modifiers were considered for the present benefit assessment:

- Sex (male versus female)
- age (< 65 years versus ≥ 65 years)
- Disease stage (locally advanced vs. metastatic)

A priori, subgroup analyses for the three characteristics mentioned were planned only for the outcome "overall survival". The subgroup analyses of the company were conducted post hoc for the patient-relevant outcomes of the categories "morbidity", "health-related quality of life" and "side effects". Subgroup analyses for the outcomes "immune-related SAEs" and "immune-related severe AEs" 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 at least 10 events in at least one subgroup.

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

Using the methods described above, the available subgroup results did not show any effect modifications.

2.4.3 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.

2.4.3.1 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 2.4.2 (see Table 17).

Determination of the outcome category for the outcomes on side effects

It cannot be directly inferred from the dossier whether the following outcomes were serious/severe or non-serious/non-severe. The classification of these outcomes is justified.

Specific AEs

For the specific AE "musculoskeletal and connective tissue disorders (SOC, AEs)" it can be inferred from the information in Module 4 A that all events that occurred were non-serious or non-severe (CTCAE grade < 3). The specific AE was therefore assigned to the outcome category "non-serious/non-severe side effects".

Table 17: Extent of added benefit at outcome level: pembrolizumab + cisplatin + 5-FU vs. cisplatin + 5-FU (patients with squamous cell carcinoma of the oesophagus and CPS ≥ 10) (multipage table)

Outcome category **outcome** **effect modifier** **subgroup**	**Pembrolizumab + cisplatin + 5-FU vs. cisplatin + 5-FU** **median time to event (months) or MD** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Mortality		
Overall survival	13.9 vs. 8.8 months HR: 0.57 [0.43; 0.75]; p < 0.001 probability: "hint"	Outcome category: mortality $CI_u < 0.85$ added benefit, extent: "major"
Morbidity		
EQ-5D VAS	Mean (until week 18): -4.46 vs. -4.35 MD: -0.10 [-4.96; 4.76]; p = 0.967	Lesser/added benefit not proven
Health-related quality of life		
Health-related quality of life	No usable data[c]	Lesser/added benefit not proven
Side effects		
SAEs	35.6 vs. 25.7 months HR: 0.87 [0.64; 1.20]; p = 0.405	Greater/lesser harm not proven
Severe AEs	4.4 vs. 5.0 months HR: 1.01 [0.78; 1.30]; p = 0.952	Greater/lesser harm not proven
Discontinuation due to AEs	No usable data[c]	Greater/lesser harm not proven
Immune-related SAEs	NA vs. NA HR: 5.36 [1.20; 24.00] HR: 0.19 [0.04; 0.83][d]; p = 0.028 probability: "hint"	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ greater harm, extent: "considerable"
Immune-related severe AEs	NA vs. NA HR: 3.30 [0.93; 11.77]; p = 0.065	Greater/lesser harm not proven
Musculoskeletal and connective tissue disorders (AEs)	NA vs. 53.1 months HR: 0.41 [0.25; 0.67]; p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ lesser harm, extent: "considerable"
General disorders and administration site conditions (SAEs)	NA vs. NA HR: 0.11 [0.02; 0.47]; p = 0.003 probability: "hint"	Outcome category: serious/severe side effects $CI_u < 0.75$, risk ≥ 5% lesser harm, extent: "major"
Platelet count decreased (severe AEs)	NA vs. NA HR: 0.25 [0.07; 0.90]; p = 0.033 probability: "hint"	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ lesser harm; extent: minor

Table 17: Extent of added benefit at outcome level: pembrolizumab + cisplatin + 5-FU vs. cisplatin + 5-FU (patients with squamous cell carcinoma of the oesophagus and CPS ≥ 10) (multipage table)

Outcome category **outcome** **effect modifier** **subgroup**	**Pembrolizumab + cisplatin + 5-FU vs. cisplatin + 5-FU** **median time to event (months) or MD** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Weight decreased (severe AEs)	NA vs. NA HR: 0.07 [0.01; 0.58]; p = 0.013 probability: "hint"	Outcome category: serious/severe side effects CI_u < 0.75, risk ≥ 5% lesser harm, extent: "major"

a. Probability provided if there is a statistically significant and relevant effect.
b. 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).
c. See Section 2.4.2.1 for reasons.
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: European Organization for Research and Treatment of Cancer; HR: hazard ratio; MD: mean difference; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-OE18: Quality of Life Questionnaire-Oesophageal Cancer 18 items; SAE: serious adverse event; VAS: visual analogue scale

2.4.3.2 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 + cisplatin + 5-FU vs. cisplatin + 5-FU (patients with squamous cell carcinoma of the oesophagus and CPS ≥ 10)

Positive effects	**Negative effects**
Mortality ▪ overall survival: hint of an added benefit – extent: “major”	–
Serious/severe side effects ▪ general disorders and administration site conditions (SAEs): hint of lesser harm – extent: "major" ▪ platelet count decreased (severe AEs): hint of lesser harm – extent: “minor” ▪ weight decreased (severe AEs): hint of lesser harm – extent: “major”	Serious/severe side effects ▪ immune-related SAEs: hint of greater harm – extent: “considerable”
Non-serious/non-severe side effects ▪ musculoskeletal and connective tissue disorders (AEs); hint of lesser harm, extent: "considerable"	–
There were no usable data for the outcomes on symptoms and health-related quality of life as well as for the outcome ““discontinuation due to AEs”.	
5-FU: 5-fluorouracil; AEs: adverse events; CPS: combined positive score; SAEs: serious adverse events	

The overall consideration showed both positive and negative effects of pembrolizumab + cisplatin + 5-FU vs. cisplatin + 5-FU.

On the side of the positive effects, there was a hint of major added benefit for the outcome “overall survival”. Moreover, a hint of lesser harm with the extents “minor” to “major” is shown for several specific AEs in the outcome categories “serious/severe side effects” and “non-serious/non-severe side effects”. On the side of negative effects, in contrast, there is a hint of greater harm with the extent “considerable” for the outcome "immune-related AEs”, which in particular does not call into question the positive effect in overall survival, however.

In summary, there is a hint of major added benefit of pembrolizumab + cisplatin + 5-FU over the ACT cisplatin + 5-FU for patients with locally advanced or metastatic, not curatively treatable squamous cell carcinoma of the oesophagus with PD-L1 expressing tumours (CPS ≥ 10).

The assessment described above deviates from that of the company insofar as the company drew no separate conclusion on the added benefit of patients with squamous cell carcinoma of the oesophagus and CPS ≥ 10. Overall, the company derived an indication of a major added benefit for the target population in the therapeutic indication. This approach is not followed in the present benefit assessment due to the reasons stated in Section 2.2.

2.5 Research question B1: patients with HER2-negative adenocarcinoma of the oesophagus or of the gastroesophageal junction and CPS ≥ 10

2.5.1 Studies included

The studies listed in the following Table 19 were included in the benefit assessment.

Table 19: Study pool – RCT, direct comparison: pembrolizumab + cisplatin + 5-FU/capecitabine vs. cisplatin + 5-FU/capecitabine

Study	Study category			Available sources		
	Study for the approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	CSR (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication (yes/no [citation])
MK-3475-590 (KEYNOTE 590[c])	Yes	Yes	No	Yes [3]	Yes [4,5]	Yes [6,7]
MK-3475-062 (KEYNOTE 062[c])	No[d]	Yes	No	Yes [15]	Yes [16,17]	Yes [18,19]

a. Study for which the company was sponsor.
b. Citation of the study registry entries and, if available, of the reports on study design and/or results listed in the study registries.
c. In the following tables, the study is referred to with this abbreviated form.
d. No approval study for the therapeutic indications relevant in the present assessment.

5-FU: 5-fluorouracil; G-BA: Federal Joint Committee; RCT: randomized controlled trial

The studies KEYNOTE 590 and KEYNOTE 062 were included in the present benefit assessment for research question B1. The respective subpopulations of the 2 studies who are relevant for the present assessment are described in Section 2.5.1.2.

In the studies KEYNOTE 590 and KEYNOTE 062, pembrolizumab in combination with platinum- and fluoropyrimidine-based chemotherapy was compared with cisplatin + 5-FU (and in the KEYNOTE 062 study also with cisplatin + capecitabine). These studies are therefore only suitable for making statements on the added benefit of pembrolizumab in combination with platinum- and fluoropyrimidine-based chemotherapy for the patient group for whom cisplatin + 5-FU (or cisplatin + capecitabine) represents a suitable treatment according to physician's choice.

In the studies KEYNOTE 590 and KEYNOTE 062, the combination of pembrolizumab with platinum- and fluoropyrimidine-based chemotherapy was only implemented as combination with cisplatin and 5-FU as well as with cisplatin and capecitabine. Therefore, no data are available for the combination of pembrolizumab with other approved drugs within the framework of platinum- and fluoropyrimidine-based chemotherapy.

The study pool of the company includes the 2 studies KEYNOTE 590 and KEYNOTE 062 for all research questions, whereby the company considers the KEYNOTE 062 study an unsuitable evidence for the derivation of an added benefit.

The company only used KEYNOTE 590 for the derivation of the added benefit for research question B1. However, as described in Section 2.3, the company used the results of the population with PD-L1-expressing tumours (CPS ≥ 10) of the KEYNOTE 590 study to derive the added benefit without drawing separate conclusions on the added benefit for the respective subpopulations of research questions A, B1 and B2. However, the company did not use the results of the KEYNOTE 062 study.

The approach of the company is not appropriate. For the KEYNOTE 590 study. this is explained in Section 2.4.1.2, and for KEYNOTE 062 in the following section.

Relevance of the study 062 for the present assessment

The company identified the KEYNOTE 062 study, which included patients with advanced gastric adenocarcinoma and adenocarcinoma of the gastroesophageal junction who are PD-L1 positive (defined in the study as CPS ≥ 1) and HER2 negative. The company included this study as a relevant study in its study pool. However, it states that this study was only named for reasons of completeness. From the company's point of view, KEYNOTE 062 does not present a suitable evidence for the derivation of the added benefit.

The company justifies this by stating that the KEYNOTE 062 study was not designed to separately consider patients with adenocarcinoma of the gastroesophageal junction and CPS ≥ 10 who are relevant for the present therapeutic indication. The analyses of all outcomes were not stratified. From the company's point of view, this leads to a possible bias at study level for the relevant subpopulation. For the above-mentioned reasons, the company did not use the KEYNOTE 062 study to derive the added benefit.

The approach of the company is not appropriate. As KEYNOTE 062 is a randomized study, the results are usable despite the unstratified analysis. Hence, the KEYNOTE 062 study was not included in the present benefit assessment.

The KEYNOTE 062 study only includes relevant data for research questions B1. These are the data of the subpopulation of patients with adenocarcinoma of the gastroesophageal junction whose tumours express PD-L1 with a CPS ≥ 10. The company presented the results for this subpopulation in Module 4 A. These results were used for the present benefit assessment.

2.5.1.1 Study characteristics

Table 20 and Table 21 describe the studies used for the benefit assessment.

Table 20: Characteristics of the studies included – RCT, direct comparison: pembrolizumab + cisplatin + 5-FU/capecitabine vs. placebo + cisplatin + 5-FU/capecitabine (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
KEYNOTE 590	RCT, double-blind, parallel	Adult patients[b] with locally advanced unresectable or metastatic adenocarcinoma or squamous cell carcinoma of the oesophagus or advanced or metastatic adenocarcinoma of the gastroesophageal junction (Siewert type I) in the first line	Pembrolizumab + cisplatin + 5-FU (N = 373) Placebo + cisplatin + 5-FU (N = 376) relevant subpopulation thereof[c]: pembrolizumab + cisplatin + 5-FU (n = 43) placebo + cisplatin + 5-FU (N = 54)	Screening: ≤ 28 days treatment: until disease progression, unacceptable toxicity, decision of the physician, withdrawal of consent, complete response or a maximum of 35 cycles observation[d]: outcome-specific, at most until death, withdrawal of consent or end of the study	168 centres in: Argentina, Australia, Brazil, Canada, Columbia, Chile, China, Costa Rica, Denmark, France, Germany, Guatemala, Hong Kong, Japan, Malaysia, Peru, Romania, Russia, South Africa, South Korea, Spain, Taiwan, Thailand, Turkey, United Kingdom, United States 07/2017–ongoing data cut-offs: 2 July 2020 (final analysis[e]) 9 July 2021[f] (post hoc)	Primary: overall survival, progression-free survival secondary: morbidity, health-related quality of life, AEs

Table 20: Characteristics of the studies included – RCT, direct comparison: pembrolizumab + cisplatin + 5-FU/capecitabine vs. placebo + cisplatin + 5-FU/capecitabine (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
KEYNOTE 062	RCT, partially blinded[g], parallel	Adult patients with locally advanced unresectable or metastatic adenocarcinoma of the stomach or of the gastroesophageal junction in the first line with positive PD-L1 status (defined in the study as CPS ≥ 1) and negative HER2 status	Pembrolizumab (N = 256)[h] pembrolizumab + cisplatin + 5-FU/capecitabine (N = 257) placebo + cisplatin + 5-FU/capecitabine (N = 250) relevant subpopulation thereof[i]: pembrolizumab + cisplatin + 5-FU/capecitabine (N = 30)[j] placebo + cisplatin + 5-FU/capecitabine (N = 20)[j]	Screening: ≤ 21 days treatment: until disease progression, unacceptable toxicity, decision of the physician, withdrawal of consent, complete response or a maximum of 35 cycles observation[d]: outcome-specific, at most until death, withdrawal of consent or end of the study	201 centres in: Argentina, Australia, Austria, Belgium, Brazil, Czech Republic, Chile, Columbia, Germany, Guatemala, Hong Kong, Hungary, Italy, Japan, Latvia, Lithuania, Mexico, Netherlands, New Zealand, Poland, Puerto Rico, Russia, South Africa, South Korea, Spain, Switzerland, Taiwan, United Kingdom, United States 10/2015–03/2019 data cut-offs: 26 March 2019 (final analysis)[k]	Primary: overall survival, progression-free survival secondary: morbidity, health-related quality of life, AEs

Table 20: Characteristics of the studies included – RCT, direct comparison: pembrolizumab + cisplatin + 5-FU/capecitabine vs. placebo + cisplatin + 5-FU/capecitabine (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]

a. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes only include information on relevant available outcomes for this benefit assessment.
b. With ECOG PS 0 or 1 and PD-L1 status determined by immunohistochemistry using a tissue sample (test used: Dako PD-L1 IHC 22C3 pharmDx).
c. Patients with HER2-negative adenocarcinoma of the oesophagus or the gastroesophageal junction with CPS ≥ 10; patients with adenocarcinoma of the oesophagus were not tested for their HER2 status. Patients with adenocarcinoma of the gastroesophageal junction and positive HER2 status were excluded from the study. For the proportion of patients with positive HER2 status in the population relevant to research question B1, see Section 2.5.1.2.
d. Outcome-specific information is provided in Table 22.
e. The data cut-off was originally planned as the first interim analysis after at least 13 months of observation of the last patient after randomization, 460 PFS events and 391 OS events in the population of patients with squamous cell carcinoma of the oesophagus, but represents the final analysis of the study.
f. Was performed for a presentation in the context of a scientific congress; a corresponding CSR is not available. Results on mortality and side effects are presented.
g. The study arm with a pembrolizumab monotherapy was unblinded.
h. The arm is not relevant for the benefit assessment and is no longer shown in the following tables.
i. Patients with adenocarcinoma of the gastroesophageal junction with CPS ≥ 10.
j. Treatment with 5-FU was given to 14 (47%) patients in the intervention arm and 9 (45%) patients in the comparator arm; treatment with capecitabine was given to 16 (53%) patients in the intervention arm and 11 (55%) patients in the comparator arm (percentages: Institute's calculation).
k. The data cut-off was planned after an observation period of at least 22 months after randomization of the last patient and 415 OS events in study arms 2 and 3.

5-FU: 5-fluorouracil; AE: adverse event; CPS: combined positive score; ECOG PS: Eastern Cooperative Oncology Group Performance Status; FU: fluorouracil; HER2: human epidermal growth factor receptor 2; n: relevant subpopulation; N: number of randomized patients; OS: overall survival; PD-L1: programmed cell death ligand 1; PFS: progression-free survival; RCT: randomized controlled trial

Table 21: Characteristics of the intervention – RCT, direct comparison: pembrolizumab + cisplatin + 5-FU/capecitabine vs. placebo + cisplatin + 5-FU/capecitabine (multipage table)

Study	Intervention	Comparison
KEYNOTE 590	See Table 7	
KEYNOTE 062	Pembrolizumab 200 mg IV (as 30-minute infusion) on day 1 of a 3-week cycle[a] + cisplatin 80 mg/m² BSA, IV, on day 1 of each 3-week cycle[b] + 5-FU 800 mg/m² BSA/day, continuous administration from day 1 to 5 of a 3-week cycle (a total of 4000 mg/m² BSA per cycle)[c] or capecitabine: 1000 mg/m² BSA twice daily, orally, on days 1–14 of a 3-week cycle[c]	Placebo[a] + cisplatin 80 mg/m² BSA, IV, on day 1 of each 3-week cycle[b] + 5-FU 800 mg/m² BSA/day, continuous administration from day 1 to 5 of a 3-week cycle (a total of 4000 mg/m² BSA per cycle)[c] or capecitabine: 1000 mg/m² BSA twice daily, orally, on days 1–14 of a 3-week cycle[c]
	Dose adjustments ▪ pembrolizumab or placebo: no dose reduction allowed; treatment interruption or discontinuation in case of toxicity ▪ chemotherapy (cisplatin/5-FU/capecitabine): gradual dose reduction in case of toxicity; reduced dose could not be increased again; at most 2 adjustments per therapy component allowed, treatment discontinuation in case of further toxicity	
	Pretreatment not allowed ▪ prior treatment of the locally advanced, unresectable or metastatic carcinoma[d] ▪ systemic treatment of an active autoimmune disorder with disease-modifying agents, corticosteroids or immunosuppressants in the last 2 years ▪ chronic systemic steroid therapy (≥ 10 mg prednisone equivalent per day) or another form of immunosuppressive therapy within 7 days before the first dose of the study treatment ▪ ongoing systemic treatment of an active infection ▪ prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent ▪ radiotherapy within 14 days before randomization	
	Concomitant treatment not allowed ▪ antineoplastic systemic chemotherapies or biologic treatments not predefined in the protocol ▪ immunotherapies not predefined in the protocol ▪ radiotherapy (note: radiotherapy for the symptomatic treatment of solitary lesions or on the brain were allowed after consultation with the sponsor) ▪ systemic glucocorticoids for purposes other than the regulation of symptoms of an AE with suspected immunological aetiology or to support the treatment with cisplatin ▪ brivudine, sorivudine analogues and other inhibitors of the enzyme dihydropyrimidine dehydrogenase should not be administered together with 5-FU/capecitabine therapy ▪ phenytoin should not be administered together with cisplatin allowed: ▪ supportive treatment according to local standards for the chemotherapy ▪ oral or IV corticosteroids or other anti-inflammatory drugs for the treatment of side effects	

Table 21: Characteristics of the intervention – RCT, direct comparison: pembrolizumab + cisplatin + 5-FU/capecitabine vs. placebo + cisplatin + 5-FU/capecitabine (multipage table)

Study	Intervention	Comparison
a. Treatment until unacceptable toxicity or treatment discontinuation following the decision by the physician or the patient (up to a maximum of 35 cycles - corresponding to about 2 years) b. Treatment could be limited to 6 cycles according to local standards. c. Capecitabine could be administered according to local guidelines, although the use of 5-FU was preferred according to the study protocol. The decision on the type of the fluoropyrimidine used (5-FU or capecitabine) was made by the physician and should be taken before randomization. d. Prior neoadjuvant/adjuvant treatment was allowed if it had been completed > 6 months before randomization. 5-FU: 5-fluorouracil; BSA: body surface area; CPS: combined positive score; IV: intravenous; PD-1: programmed cell death 1; PD-L1/PD-L2: programmed cell death ligand 1/2; RCT: randomized controlled trial		

For the general description of the KEYNOTE 590 study, see Section 2.4.1.1.

KEYNOTE 062 is a partially blinded, randomized, controlled, multicentre study on the comparison of pembrolizumab as monotherapy versus pembrolizumab in combination with cisplatin and either 5-FU or capecitabine (pembrolizumab + cisplatin + 5-FU/capecitabine; hereinafter referred to as intervention arm), and versus placebo + cisplatin in combination with either 5-FU or capecitabine (placebo + cisplatin + 5-FU/capecitabine; hereinafter referred to as comparator arm). The study arm with pembrolizumab as monotherapy was unblinded, but is irrelevant for the present benefit assessment. The two study arms relevant for the benefit assessment were double-blind.

The study included adult patients with locally advanced or metastatic adenocarcinoma of the gastroesophageal junction or the stomach. Patients were not allowed to have received prior treatment at this stage of the disease, but could have received prior treatment with curative intent, if this treatment had been completed at least 6 months before randomization. The tumours of all patients included had to be PD-L1-positive (defined as CPS ≥ 1 in the study protocol; identified by immunohistochemistry using a tissue sample; test used: Dako PD-L1 IHC 22C3 pharmDx test) and HER2/neu-negative (determined according to local standards).

Patients had to have a good general condition (ECOG PS ≤ 1 within 3 days before the first dose of the study treatment). Patients with ECOG PS ≥ 2 or active CNS metastases were excluded from the participation in the study; hence, no data are available for them.

Patients were randomly assigned to one of the 3 study arms (pembrolizumab as monotherapy: N = 256; intervention arm [pembrolizumab + cisplatin + 5-FU/capecitabine]: N = 257; comparator arm [placebo + cisplatin + 5-FU/capecitabine]: N = 250) stratified by geographical region (Europe/North America versus Asia versus rest of the world), disease stage (locally advanced unresectable versus metastatic) and therapeutic strategy (5-FU versus capecitabine).

In all study arms, treatment was performed for a maximum of 35 cycles in 3-week cycles until a reason for discontinuation occurred (disease progression, unacceptable toxicity, physician's

decision, withdrawal of consent or complete response), where the cisplatin treatment component could be limited to a maximum of 6 cycles. Patients who had stable disease or a complete or partial response after 35 cycles could be treated with pembrolizumab for up to 17 additional cycles in case of a radiographically identified progress (second course phase). This option was also available for patients who had discontinued treatment with pembrolizumab after at least 8 cycles when stable disease was achieved.

Capecitabine could be administered according to local guidelines, although the use of 5-FU was preferred according to the study protocol. The decision on the type of the fluoropyrimidine used (5-FU or capecitabine) was made by the physician and was to be taken before randomization.

After discontinuation of either pembrolizumab, cisplatin and/or 5-FU or capecitabine, treatment could be continued with the remaining drug component(s). There were no restrictions regarding subsequent therapies after the end of the study medication (an overview of the subsequent oncological therapies can be found in Table 25 and Table 26). A switch of the patients in the comparator arm to the treatment of the intervention arm was not planned.

In the studies KEYNOTE 590 and KEYNOTE 062, treatment with pembrolizumab largely corresponded to the recommendations of the SPC. However, there are uncertainties regarding the treatment, which are described in the following section [8-10,20].

Primary outcomes of the KEYNOTE 062 study were overall survival and PFS. Outcomes on symptoms, health status, health-related quality of life and AEs were recorded as further patient-relevant outcomes.

Uncertainties regarding the treatment

In the KEYNOTE 062 study, the investigators determined before randomization whether the patients received 5-FU or capecitabine as the fluoropyrimidine component of the treatment. It must be noted that capecitabine is approved for the treatment of the gastric cancer, but not for the treatment of the cancer of the gastroesophageal junction [20]. However, the combination of cisplatin + capecitabine within the framework of a therapy of physician's choice is considered a suitable comparator in the present benefit assessment (see Table 4).

Number of cycles

Study treatment was restricted to a maximum of 35 therapy cycles (approx. 2 years) in the KEYNOTE 062 study. However, according to the approval, treatment with pembrolizumab should be continued until progression of the cancer or the occurrence of unacceptable toxicity [8]. According to the approval, there is no fixed upper limit on the number of treatment cycles for treatment with cisplatin and 5-FU. Information on how many patients of the relevant subpopulation of the study received the planned maximum number of treatment cycles and were not treated further thereafter although such treatment would have basically been possible according to the approval, is not available.

The restrictions regarding the number of cycles in the KEYNOTE 590 study are described in Section 2.4.1.1.

Dosage of 5-FU and capecitabine

Both patients with adenocarcinoma of the oesophagus and patients with adenocarcinoma of the gastroesophageal junction are considered in the present research question B1.

While the relevant subpopulation of the KEYNOTE 590 study included both patients with oesophageal cancer and those with cancer of the gastroesophageal junction, KEYNOTE 062 included only patients with cancer of the gastroesophageal junction. For the patients with oesophageal cancer in the KEYNOTE 590 study, the uncertainties described in Section 2.4.1.1 apply with regard to the dosage of 5-FU.

Neither 5-FU nor capecitabine are explicitly approved for the treatment of cancer of the gastroesophageal junction. However, in current guidelines, cancer of the gastroesophageal junction is classified either as oesophageal or gastric cancer, depending on its location according to Siewert type. In doing so, Siewert types I and II are classified as oesophageal cancer, while Siewert type III is classified as gastric cancer [11,12,21].

5-FU is approved for the treatment of both oesophageal carcinoma and gastric carcinoma. For the treatment of oesophageal cancer, the SPC for 5-FU specifies a dose of 1000 mg/m² BSA/day on days 1 to 5 of a 3-4 week cycle, which corresponds to a total dose of 5000 mg/m² BSA/cycle. Deviating from this, the SPC for 5-FU recommends daily single doses of 500 to 600 mg/m² BSA as intravenous bolus injection for the treatment of the gastric cancer [10]. In the KEYNOTE 590 study, a total dose of 4000 mg/m² BSA/cycle was planned in both study arms, for example in the form of a dose of 800 mg/m² BSA/day on days 1 to 5 or 1000 mg/m² BSA/day on days 1 to 4 of a 3-week cycle. In the KEYNOTE 062 study, a dose of 800 mg/m² BSA/day on days 1 to 5 of a 3-week cycle was planned in both study arms, which also corresponds to a total dose of 4000 mg/m² BSA/cycle. The treatment regimen used in the studies thus deviates from the specifications of the SPC.

Capecitabine is exclusively approved for the treatment of the gastric cancer. The SPC recommends a dose of 800 to 1000 mg/m² BSA twice daily on days 1 to 14 of a 3-week cycle [10]. The dosing regimen used in the KEYNOTE 062 study corresponds to this specification. In the case of continuous administration, the dose should be reduced to 625 mg/m² BSA twice daily, which was not planned in the KEYNOTE 062 study. As the KEYNOTE 062 study included patients with all 3 Siewert types, but the company's dossier provided no information on the proportions of the individual Siewert types, the proportion of patients who could be classified as gastric cancer according to Siewert type is unclear.

Where guidelines provide data on dose recommendations, these are inconsistent [11,12,21].

Summary of the uncertainties regarding the treatment

The uncertainties described above regarding the treatment result in a reduced certainty of conclusions of the studies KEYNOTE 590 and KEYNOTE 062.

2.5.1.2 Relevant subpopulation

The subpopulations of patients with adenocarcinoma of the oesophagus or the gastroesophageal junction and CPS ≥ 10 are relevant to answer the present research question. The company presented analyses on corresponding subpopulations of KEYNOTE 590 and KEYNOTE 062, but did not use them to derive the added benefit.

Research question 1 exclusively refers to patients with HER2-negative tumours. The HER2 status of the tumours of patients with adenocarcinoma of the gastroesophageal junction was determined before inclusion in the studies KEYNOTE 590 and KEYNOTE 062. Patients with HER2-positive adenocarcinoma of the gastroesophageal junction were excluded from both studies. However, the HER2 status of the tumours of patients with adenocarcinoma of the oesophagus was not determined within the framework of the KEYNOTE 590 study. Hence, the HER2 status of these patients in the subpopulation of KEYNOTE 590 presented by the company is unknown.

The company states that, deviating from the G-BA's specification, it presents the results for subpopulations B1 and B2 from the KEYNOTE 590 study in summarized form. The company justified this with the fact that the patients with adenocarcinoma of the oesophagus in the KEYNOTE 590 study had not been tested for their HER2 status, as such testing was dependent on the approval status of HER2-targeted therapies and was therefore not planned on a cross-country basis in the study. A separate presentation according to the subpopulations B1 (Her2-negative) and B2 (HeR2-positive) specified by the G-BA was thus impossible. The company therefore summarized the results for all patients with adenocarcinoma of the oesophagus irrespective of their HER2 status and presented them together with the results for patients with HER2-negative adenocarcinoma of the gastroesophageal junction. From the company's point of view, this is methodologically in line with subpopulation B1 defined by the G-BA, as the proportion of patients with HER2-positive adenocarcinoma of the oesophagus in the KEYNOTE 590 study can be assumed to be less than 20%. The company based this statement on a non-systematic search for publications that investigate the proportion of HER2-positive tumours in patients with adenocarcinomas of the oesophagus. [22-26]. According to this, a range of 13-17% is to be assumed for the proportion of patients with HER2-positive tumours in all patients with advanced or metastatic adenocarcinoma of the oesophagus.

The company's reasoning is not adequate. The epidemiological data submitted by the company on the proportion of HER2-positive adenocarcinomas of the oesophagus are incomplete. The stated range of 13-17% cannot be justified on the basis of the publications cited by the company, as the majority of them do not distinguish between adenocarcinomas of the oesophagus and adenocarcinomas of the gastroesophageal junction; one of the cited publications explicitly

refers to adenocarcinomas of the gastroesophageal junction and not of the oesophagus [22]. Based on further publications not identified by the company's search, a higher proportion of patients with HER2-positive tumours appears possible for the advanced or metastatic adenocarcinoma of the oesophagus, for example of approx. 30% [12,27-29].

However, the relevant subpopulation of the KEYNOTE 590 study - as explained above - includes also patients with adenocarcinoma of the gastroesophageal junction whose HER2 status is negative besides patients with adenocarcinoma of the oesophagus with unknown HER2 status but (see Table 23). Even assuming a very high proportion of up to 40% of HER2-positive patients with adenocarcinoma of the oesophagus in the subpopulation presented by the company, the total proportion of HER2-negative patients in this population would still be over 80%. For this reason, it seems adequate in the present situation to use the results of the subpopulation to derive the added benefit [1].

Thus, the subpopulations of the studies KEYNOTE 590 and KEYNOTE 062 presented by the company are relevant for the benefit assessment. However, the certainty of conclusions of KEYNOTE 590 regarding the subpopulation relevant for research question B1 is reduced, because there is uncertainty regarding the proportion of patients with HER2-negative tumours

2.5.1.3 Data cut-offs

For the general description of the KEYNOTE 590 study, see Section 2.4.1.3.

Results of the data cut-off of 26 March 2019 are available for the KEYNOTE 062 study. This data cut-off is the final analysis of the study. These data serve as the basis for the benefit assessment.

2.5.1.4 Treatment duration and follow-up observation

Table 22 shows the planned duration of follow-up observation of the patients for the individual outcomes.

Table 22: Planned duration of the follow-up observation – RCT, direct comparison: pembrolizumab + cisplatin + 5-FU/capecitabine vs. placebo + cisplatin + 5-FU/capecitabine

Study **outcome category** **outcome**	**Planned follow-up observation**
KEYNOTE 590	See Table 8
KEYNOTE 062	
Mortality	
Overall survival	Until death, withdrawal of consent or end of study
Morbidity	
Symptoms/health status (EORTC QLQ-C30/EQ-5D VAS)	Up to 30 days after treatment discontinuation or end of treatment[a]
Health-related quality of life (EORTC QLQ-C30)	Up to 30 days after treatment discontinuation or end of treatment[a]
Side effects	
AEs, severe AEs	Up to 30 days after treatment discontinuation or end of treatment
SAEs	Until 90 days after treatment discontinuation or end of treatment, or until 30 days after treatment discontinuation or end of treatment when starting a new antineoplastic therapy

a. Patient-reported outcomes were recorded during treatment for a maximum of 1 year as well as at the end of treatment and 30 days after the end of treatment.

5-FU: 5-fluorouracil; AE: adverse event; CPS: combined positive score; EORTC: European Organisation for Research and Treatment of Cancer; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale

In both studies, the observation periods for the outcomes on morbidity, health-related quality of life and side effects were systematically shortened because, as stated in Table 22, they were only recorded for the time period of treatment with the study medication plus 30 days or plus a maximum of 90 days (for SAEs) (see also Section 2.5.1.6).

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.

2.5.1.5 Characteristics of the relevant subpopulation

Table 23 shows the characteristics of the patients in the studies included.

Table 23: Characteristics of the study populations – RCT, direct comparison: pembrolizumab + cisplatin + 5-FU/capecitabine vs. placebo + cisplatin + 5-FU/capecitabine, subpopulation with adenocarcinoma of the oesophagus or the gastroesophageal junction (multipage table)

Study characteristic category	KEYNOTE 590		KEYNOTE 062	
	Pembrolizumab + cisplatin + 5-FU	Placebo + cisplatin + 5-FU	Pembrolizumab + cisplatin + 5-FU/capecitabine	Placebo + cisplatin + 5-FU/capecitabine
	N = 43	N = 54	N = 30	N = 20
Age [years], mean (SD)	61 (13)	59 (9)	62 (11)	55 (14)
Sex [F/M], %	12/88	17/83	23/77	25/75
Family origin, n (%)				
White	28 (65)	39 (72)	26 (87)	18 (90)
Asian	8 (19)	8 (15)	4 (13)	1 (5)
American and Alaskan natives	2 (5)	1 (2)	0 (0)	1 (5)
Black or African American	0 (0)	1 (2)	0 (0)	0 (0)
Several	0 (0)	2 (4)	0 (0)	0 (0)
Unknown	5 (12)	3 (6)	0 (0)	0 (0)
Primary diagnosis, n (%)				
Adenocarcinoma of the oesophagus[a]	21 (49)	29 (54)	0 (0)	0 (0)
Adenocarcinoma of the gastroesophageal junction[b]	22 (51)	25 (46)	30 (100)	20 (100)
Disease status				
Metastatic	41 (95)	52 (96)	28 (93)	19 (95)
Locally advanced[c]	2 (5)	2 (4)	2 (7)	1 (5)
ECOG PS, n (%)				
0	23 (54)	26 (48)	17 (57)	6 (30)
1	20 (47)	27 (50)	13 (43)	14 (70)
2	0 (0)	1 (2)	0 (0)	0 (0)
Treatment discontinuation, n (%)[d]	35 (83)	53 (100)	28 (93)	19 (95)
Study discontinuation, n (%)[e]	30 (70)	44 (82)	24 (80)	16 (80)

Table 23: Characteristics of the study populations – RCT, direct comparison: pembrolizumab + cisplatin + 5-FU/capecitabine vs. placebo + cisplatin + 5-FU/capecitabine, subpopulation with adenocarcinoma of the oesophagus or the gastroesophageal junction (multipage table)

Study characteristic category	KEYNOTE 590		KEYNOTE 062	
	Pembrolizumab + cisplatin + 5-FU	Placebo + cisplatin + 5-FU	Pembrolizumab + cisplatin + 5-FU/capecitabine	Placebo + cisplatin + 5-FU/capecitabine
	N = 43	N = 54	N = 30	N = 20

a. Patients with adenocarcinoma of the oesophagus were not tested for their HER2 status.
b. Patients with adenocarcinoma of the gastroesophageal junction and positive HER2 status were excluded from both studies. KEYNOTE 590 only included patients with Siewert type I, whereas patients with all three Siewert types could be included in KEYNOTE 062.
c. For the KEYNOTE 590 study designated as "unresectable - locally advanced".
d. Common reasons for treatment discontinuation in the intervention arm vs. control arm of the KEYNOTE 590 study comprised: disease progression (69% vs. 87%), AEs (12% vs. 6%). Information for the relevant subpopulation of the KEYNOTE 062 study is not available. Data are based on the population with at least one intake of the study medication (KEYNOTE 590 study: 42 vs. 53 patients; KEYNOTE 062 study: 30 vs. 20 patients)
e. The reason for all study discontinuations in the intervention arm and the control arm of the KEYNOTE 590 study was the death of the patients. Information for the relevant subpopulation of the KEYNOTE 062 study is not available.

5-FU: 5-fluorouracil; CPS: combined positive score; ECOG PS: Eastern Cooperative Oncology Group Performance Status; F: female; M: male; n: number of patients in the category; N: number of patients in the category; N: number of patients in the relevant subpopulation; RCT: randomized controlled trial; SD: standard deviation

The patient characteristics are largely balanced between both the two study arms of the individual studies and between the two studies. In both studies, the mean age was about 60 years with the patients in the comparator arm of the KEYNOTE 062 study being slightly younger with a mean age of 55 years. The majority were male and of white family origin. As already described in Section 2.5.1.2, the relevant subpopulation of the KEYNOTE 590 study comprised approximately equal numbers of patients with adenocarcinoma of the oesophagus and with adenocarcinoma of the gastroesophageal junction, while the relevant subpopulation of the KEYNOTE study exclusively included patients with adenocarcinoma of the gastroesophageal junction. More than 90% of the patients in the study arms of both studies had metastatic disease.

In both treatment arms of the KEYNOTE 590 study, the most common reasons for treatment discontinuation were disease progression (intervention arm: 69%; control arm: 87%), followed by AEs (intervention arm: 12%; control arm: 6%), with frequencies differing between the arms. For the relevant subpopulation of the KEYNOTE 062 study, no information is available on the reasons for treatment discontinuations.

2.5.1.6 Treatment duration and observation period as well as subsequent therapies

Table 24 shows the median treatment duration of the patients and the median observation period for individual outcomes.

Table 24: Information on the course of the study – RCT, direct comparison: subpopulation with adenocarcinoma of the oesophagus or the gastroesophageal junction and CPS ≥ 10

Study **duration of the study phase** **outcome category**	**Pembrolizumab + cisplatin + 5-FU/capecitabine[a]** **N = 43**	**Placebo + cisplatin + 5-FU/capecitabine[a]** **N = 54**
KEYNOTE 590		
Treatment duration [months]	ND[b]	ND[b]
Observation period [months]		
Overall survival	ND[b]	ND[b]
Morbidity	ND	ND
Health-related quality of life	ND	ND
Side effects	ND[b]	ND[b]
KEYNOTE 062		
Treatment duration [months]		
Median [min; max]	6.7 [ND]	5.5 [ND]
Mean (SD)	ND	ND
Observation period[c] [months]		
Overall survival		
Median [min; max]	11.8 [ND]	10.4 [ND]
Mean (SD)	ND	ND
Morbidity		
Median [min; max]	ND	ND
Mean (SD)	ND	ND
Health-related quality of life		
Median [min; max]	ND	ND
Mean (SD)	ND	ND
AEs		
Median [min; max]	7.7 [ND]	6.5 [ND]
Mean (SD)	ND	ND
SAEs		
Median [min; max]	9.3 [ND]	8.5 [ND]
Mean (SD)	ND	ND

a. In KEYNOTE 590, 5-FU was used. In KEYNOTE 062, 5-FU or capecitabine was used.
b. Module 4 A of the dossier states the median treatment duration for the KEYNOTE 590 study to be 5.8 months in the intervention arm and 4.9 months in the comparator arm. A median observation period of 13.3 months and 9.4 months was reported for the outcome "overall survival", 6.8 months and 5.7 months for AEs and 8.7 months and 7.0 months for SAEs in the intervention arm and the comparator arm, respectively. The data provide no information as to which population this information refers. It can be assumed, however, that they refer to the population of patients with CPS ≥ 10 considered by the company.
c. The company did not provide any information on the determination of observation periods.

5-FU: 5-fluorouracil; AE: adverse event: CPS: combined positive score; max: maximum; min: minimum; N: number of analysed patients; ND: no data; SD: standard deviation; SAE: serious adverse event

Information on the treatment and observation periods explicitly referring to the relevant subpopulation of research question B1 are not available for the KEYNOTE 590 study. It is not clear from the data provided by the manufacturer in Module 4 A of the dossier to which population they refer. It can be assumed, however, that they refer to the population of patients with CPS ≥ 10 considered by the company, irrespective of histology and primary diagnosis.

In the KEYNOTE 062 study, the median treatment duration of the relevant subpopulation was slightly longer in the intervention arm (6.7 months) than in the comparator arm (5.5 months). The median observation period for the outcomes of mortality and side effects is also slightly longer in the intervention arm than in the comparator arm. Information on the observation periods for the outcomes of morbidity and health-related quality of life is not available.

Table 25 and Table 26 show which subsequent therapies patients received after discontinuation of the study medication.

Table 25: Information on the first subsequent oncological therapy – RCT, direct comparison: pembrolizumab + cisplatin + 5-FU/capecitabine vs. placebo + cisplatin + 5-FU/capecitabine, subpopulation with adenocarcinoma of the oesophagus or the gastroesophageal junction and CPS ≥ 10, KEYNOTE 590 study

Study **therapy class** **drug**	**Patients with subsequent therapy n (%)**	
	pembrolizumab + cisplatin + 5-FU **N = 43**	**placebo + cisplatin + 5-FU** **N = 54**
KEYNOTE 590		
First subsequent oncological therapy[a]		
Systemic therapy and radiotherapy	0 (0)	0 (0)
Systemic therapy	16 (37.2)	25 (46.3)
Antineoplastic treatments	16 (37.2)	25 (46.3)
Paclitaxel	9 (20.9)	14 (25.9)
Ramucirumab	6 (14.0)	11 (20.4)
Oxaliplatin	4 (9.3)	4 (7.4)
Fluorouracil	3 (7.0)	5 (9.3)
Irinotecan hydrochloride	1 (2.3)	3 (5.6)
Cisplatin	2 (4.7)	1 (1.9)
Nab-paclitaxel	1 (2.3)	2 (3.7)
Capecitabine	1 (2.3)	1 (1.9)
Gimeracil (+) oteracil (+) tegafur	1 (2.3)	0 (0)
Carboplatin	0 (0)	1 (1.9)
Pembrolizumab	0 (0)	1 (1.9)
Radiotherapy	4 (9.3)	5 (9.3)
Died without follow-up therapy	15 (34.9)	22 (40.7)
No follow-up therapy	8 (18.6)	2 (3.7)

a. A patient with several simultaneously administered systemic therapies is assigned to this therapy class only once.

5-FU: 5-fluorouracil; CPS: combined positive score; n: number of patients with subsequent therapy; N: number of analysed patients; RCT: randomized controlled trial

Table 26: Information on the first subsequent oncological therapy – RCT, direct comparison: pembrolizumab + cisplatin + 5-FU/capecitabine vs. placebo + cisplatin + 5-FU/capecitabine, subpopulation with adenocarcinoma of the oesophagus or the gastroesophageal gastroesophageal junction and CPS ≥ 10, KEYNOTE 062 study

Study **therapy class** **drug**	**Patients with subsequent therapy n (%)**	
	pembrolizumab + cisplatin + 5-FU **N = 30**	**placebo + cisplatin + 5-FU** **N = 20**
KEYNOTE 062		
First subsequent oncological therapy[a]		
Systemic therapy and radiotherapy	0 (0)	0 (0)
Systemic therapy	14 (46.7)	13 (65.0)
Antineoplastic and immunomodulatory therapies	14 (46.7)	13 (65.0)
Paclitaxel	5 (16.7)	6 (30.0)
Ramucirumab	5 (16.7)	4 (20.0)
Docetaxel	3 (10.0)	1 (5.0)
Irinotecan hydrochloride	2 (6.7)	1 (5.0)
Pembrolizumab	0 (0)	2 (10.0)
Nab-paclitaxel	1 (3.3)	1 (5.0)
Fluorouracil	2 (6.7)	0 (0)
Oxaliplatin	2 (6.7)	0 (0)
Dendritic cells	0 (0)	1 (5.0)
Nivolumab	0 (0)	1 (5.0)
Regorafenib	0 (0)	1 (5.0)
Anti-DKK1 monoclonal antibody (unspecified)	1 (3.3)	0 (0)
Capecitabine	1 (3.3)	0 (0)
Radiotherapy	3 (10.0)	0 (0)
Died without follow-up therapy	10 (33.3)	6 (30.0)
No follow-up therapy	3 (10.0)	1 (5.0)

a. A patient with several simultaneously administered systemic therapies is assigned to this therapy class only once.

5-FU: 5-fluorouracil; CPS: combined positive score; DKK1: Dickkopf-related protein 1; n: number of patients with subsequent therapy; N: number of analysed patients; RCT: randomized controlled trial

In both studies, subsequent oncological therapies could be administered without restriction after discontinuation of the study treatment. Hereby, systemic therapies were used most frequently, especially paclitaxel or ramucirumab. This corresponds to the recommendations of the current national S3 guideline [21]. Radiotherapy, in contrast, was only used in a few patients. In both studies, a comparable number of patients died in the intervention arm and in the comparator arm without subsequent therapy, and more patients in the intervention arm did not receive any subsequent therapy.

2.5.1.7 Risk of bias across outcomes (study level)

Table 27 shows the risk of bias across outcomes (risk of bias at study level).

Table 27: Risk of bias across outcomes (study level) – RCT, direct comparison: pembrolizumab + cisplatin + 5-FU/capecitabine vs. placebo + cisplatin + 5-FU/capecitabine, subpopulation with adenocarcinoma of the oesophagus or the gastroesophageal junction and CPS

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	Absence of other aspects	Risk of bias at study level
			Patients	Treating staff			
KEYNOTE 590	Yes	Yes	Yes	Yes	Yes	Yes	Low
KEYNOTE 062	Yes	Yes	Yes[a]	Yes[a]	Yes	Yes	Low

a. KEYNOTE 062 was a partially blinded study. Randomization took place in three study arms, one of which (pembrolizumab as monotherapy) was unblinded. However, this study arm was not relevant for the present benefit assessment. The both study arms relevant for the benefit assessment (pembrolizumab + cisplatin + 5-FU/capecitabine vs. placebo + cisplatin + 5-FU/capecitabine) were blinded.

5-FU: 5-fluorouracil; CPS: combined positive score; RCT: randomized controlled trial

The risk of bias across outcomes was rated as low for both studies.

However, the certainty of conclusions of KEYNOTE 590 regarding the subpopulation relevant for research question B1 is reduced despite the low risk of bias, because there is uncertainty regarding the proportion of patients with HER2-negative tumours (see Section 2.5.1.2). Moreover, the certainty of conclusions of both studies is reduced because of uncertainties regarding treatment (see Section 2.5.1.1).

2.5.1.8 Transferability of the study results to the German health care context

With regard to the KEYNOTE 590 study (subpopulation with CPS ≥ 10), the company stated that the related results can be transferred to the German healthcare context due to the characteristics of the examined patient population, the study design and the use of pembrolizumab in combination with platinum- and fluoropyrimidine-based chemotherapy in accordance with the approval, and stated further that there is also no indication of a deviating efficacy or safety of pembrolizumab in the subgroups by region.

With regard to the KEYNOTE 062 study, the company stated that its results could be transferred to the German health care context due to the characteristics of the examined patient population, the study design and the use of pembrolizumab in combination with platinum- and fluoropyrimidine-based chemotherapy in accordance with the approval.

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

2.5.1.9 Comparability of the studies KEYNOTE 590 and KEYNOTE 062 for the quantitative interpretation of the results

As far as the relevant subpopulations are concerned, the studies KEYNOTE 590 and KEYNOTE 062 are largely comparable with regard to the study design, the inclusion and exclusion criteria and the characteristics of the patients included. Differences exist in the selection of the fluoropyrimidine (5-FU or capecitabine) used as part of the therapy according to physician's choice, and in the exact location of the adenocarcinoma (oesophagus or gastroesophageal junction) (see Section 2.5.1.2). Overall, the two studies KEYNOTE 590 and KEYNOTE 062 are sufficiently comparable and are summarized in a meta-analysis.

2.5.2 Results on added benefit

2.5.2.1 Outcomes included

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

- Mortality
  - overall survival
- Morbidity
  - health status, recorded using the EQ-5D VAS
  - symptoms, recorded with the EORTC QLQ-C30 and the EORTC QLQ-OES18
- Health-related quality of life
  - recorded with the EORTC QLQ-C30
- Side effects
  - SAEs
  - severe AEs (CTCAE grade ≥ 3)
  - discontinuation due to AEs
  - immune-related AEs (SAEs and severe AEs)
  - further specific AEs (SOC, PT), if any

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

Table 28 shows for which outcomes data were available in the studies included.

Table 28: Matrix of outcomes – RCT, direct comparison: pembrolizumab + cisplatin + 5-FU/capecitabine vs. placebo + cisplatin + 5-FU/capecitabine

Study	Outcomes									
	Overall survival	Health status (EQ-5D VAS)	Symptoms (EORTC QLQ-C30)	Symptoms (EORTC QLQ-OES18)	Health-related quality of life (EORTC QLQ-C30)	SAEs	Severe AEs[a]	Discontinuation due to AEs	Immune-related SAEs and severe AEs[a]	Endocrine disorders (SOC, AEs)
KEYNOTE 590	Yes	No[b]	No[b]	No[b]	No[b]	Yes	Yes	No[b]	Yes	Yes
KEYNOTE 062	Yes	No[b]	Yes[c]	No[c]	Yes	Yes	Yes	No[b]	Yes	Yes

a. Severe AEs are operationalized as CTCAE grade 3–5.
b. No usable data available; see following running text for reasons.
c. In the KEYNOTE 062 study, the symptoms were only recorded with the EORTC QLQ-C30 and not with the EORTC QLQ-OES18.

5-FU: 5-fluorouracil; AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-OES18: Quality of Life Questionnaire-Oesophageal Cancer 18 items; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

Notes on outcomes and analyses

Health status

In its dossier on both studies, the company presented responder analyses for the time to first deterioration by ≥ 7 or ≥ 10 points (scale range 0 to 100) for the outcome "health status" (EQ-5D VAS). These were not used for the dossier assessment. As explained in the *General Methods* of the Institute [1,13], 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). A calculation of the mean difference by the Institute would only have been possible for periods of time that would have been too short in relation to the entire observation period of the study to make a valid statement on the added benefit, due to the strongly decreasing responses to the questionnaires in the relevant subpopulation early on in the course of both studies.

For these reasons, the data available on the results of the health status are considered unusable and are not used for the assessment.

Symptoms and health-related quality of life

EORTC QLQ-C30 and EORTC QLQ-OES18

The results of the KEYNOTE 590 study for EORTC QLQ-C30 and EORTC QLQ-OES18 presented in Module 4 A are considered unusable and are not used for the assessment. For reasons, see Section 2.4.2.1. Therefore, only data from the KEYNOTE 062 study and thus only for the EORTC QLQ-C30 are available for the benefit assessment.

For the KEYNOTE 062 study, the company's dossier presents responder analyses for the EORTC QLQ-C30 for the time to first deterioration by ≥ 10 points (respective scale range 0 to 100). As explained in the *General Methods* of the Institute [1,13], 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). 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 [30]). 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 [31]).

EORTC QLQ- STO22

In Module 4 A, the company additionally presented results of the KEYNOTE 062 study for the EORTC QLQ-STO22 questionnaire. This questionnaire is an additional module to the EORTC QLQ-C30 specifically developed for patients with gastric cancer. However, the subpopulation of the KEYNOTE 062 study relevant for research question B1 exclusively included patients with cancer of the gastroesophageal junction. The QLQ-STO22 lacks items related to swallowing, coughing and speaking, which are necessary to fully represent the symptoms of patients with carcinoma of the gastroesophageal junction. The QLQ-STO22 therefore does not adequately represent the symptoms of these patients and is not used for assessment.

Side effects

Discontinuation due to AEs

For the outcome "discontinuation due to AEs", it cannot be inferred from the information provided by the company in Module 4 A whether the analyses refer to the time to discontinuation of all drug components or to discontinuation of at least one drug component. According to the study protocol, patients could continue treatment with the remaining drugs after discontinuation of individual drugs. An analysis on the discontinuation of all drug components alone cannot be meaningfully interpreted in the present data situation (3 drug components in the intervention arm and 2 drug components in the comparator arm). Regardless of this, analyses on the discontinuation of at least 1 drug component are to be preferred, as any AE leading to discontinuation of any treatment component is relevant. Consequently, results

for the analysis of the time to discontinuation of at least one drug component are required for the benefit assessment.

For these reasons, the results of the studies KEYNOTE 590 and KEYNOTE 062 for the outcome "discontinuation due to AEs" presented in Module 4 A are considered unusable and are not used for the assessment.

Immune-related SAEs and severe AEs

In the studies KEYNOTE 590 and KEYNOTE 062, the outcomes "immune-related SAEs" and "immune-related severe AEs" were operationalized each using a predefined PT list. The operationalization of the outcomes was based on different versions of this PT list, which means that certain PTs are not included in both PT lists. However, all immune-related SAEs and immune-related severe AEs actually occurring in the relevant subpopulations of both studies are PTs covered by both versions of the list. For this reason, the results for these outcomes can be compared and summarised in a meta-analysis.

2.5.2.2 Risk of bias

Table 29 describes the risk of bias for the results of the relevant outcomes.

Table 29: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: pembrolizumab + cisplatin + 5-FU/capecitabine vs. placebo + cisplatin + 5-FU/capecitabine, subpopulation with adenocarcinoma of the oesophagus or the gastroesophageal junction and CPS ≥ 10

Study		Outcomes									
	Study level	Overall survival	Health status (EQ-5D VAS)	Symptoms (EORTC QLQ-C30)	Symptoms (EORTC QLQ-OES18)	Health-related quality of life (EORTC QLQ-C30)	SAEs	Severe AEs[a]	Discontinuation due to AEs	Immune-related SAEs and severe AEs[a]	Endocrine disorders (SOC, AEs)
KEYNOTE 590	L	L	–[b]	–[b]	–[b]	–[b]	H[c]	H[c]	–[b]	H[c]	H[c]
KEYNOTE 062	L	L	–[b]	H[c]	–[d]	H[c]	H[c]	H[c]	–[b]	H[c]	H[c]

a. Severe AEs are operationalized as CTCAE grade 3–5.
b. No usable data available; see Section 2.5.2.1 for reasons.
c. Incomplete observations for potentially informative reasons.
d. Outcome not recorded.

5-FU: 5-fluorouracil; AE: adverse event; CPS: combined positive score; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; H: high; L: low; PT: Preferred Term; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-OES18: Quality of Life Questionnaire-Oesophageal Cancer 18 items; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

In both studies (KEYNOTE 590 and KEYNOTE 062), the outcome-specific risk of bias was rated as high for all patient-relevant outcomes except for all-cause mortality.

For the KEYNOTE 590 study, there are no usable data for the outcomes of the categories "morbidity (health status and symptoms)" and for the outcome "health-related quality of life". For the outcomes "health status" and "discontinuation due to AEs", no usable data are available for the KEYNOTE 062 study either. Hence, the risk of bias of the results is not assessed for these outcomes.

In the KEYNOTE 062 study, there are usable data on the basis of the EORTC QLQ-C30 for the two outcome categories "morbidity" and "health-related quality of life". The risk of bias of the results is rated as high due to incomplete observations for potentially informative reasons. Data on "symptoms" using the EORTC QLQ-OES18 were not recorded in the KEYNOTE 062 study.

The risk of bias of the results was rated as high for the outcomes "SAEs" and "severe AEs" as well as for "specific AEs". The planned follow-up observation period after end of treatment was 30 days for these outcomes in both studies. The observation period of the outcomes thus significantly depends on the treatment discontinuations. Due to a possible correlation between the reason for treatment discontinuation and these outcomes, there are incomplete observations for potentially informative reasons.

Summary assessment of the certainty of conclusions

In addition to the described outcome-specific risk of bias, at most indications, e.g. of an added benefit, could be derived for all outcomes for which usable data are available. This is due to the uncertainties regarding the proportion of patients with HER2-negative tumours in the KEYNOTE 590 study (see Section 2.5.1.2) and the uncertainties regarding treatment in both studies (see Section 2.5.1.1).

2.5.2.3 Results

Table 30 summarizes the results on the comparison of pembrolizumab + cisplatin + 5-FU/capecitabine with placebo + cisplatin + 5-FU/capecitabine in patients with locally advanced or metastatic HER2-negative adenocarcinoma of the oesophagus or the gastroesophageal junction that cannot be treated curatively and whose tumours express PD-L1 (CPS ≥ 10) in the first-line treatment. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier.

Results on common AEs, common SAEs and common severe AEs (CTCAE grade ≥ 3), as well as on all AEs that led to treatment discontinuation are presented in Appendix C of the full dossier assessment. Kaplan-Meier curves on the event time analyses as well as Forest plots on the meta-analyses calculated by the Institute are presented in Appendix D.

Table 30: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: pembrolizumab + cisplatin + 5-FU/capecitabine vs. placebo + cisplatin + 5-FU/capecitabine, subpopulation with adenocarcinoma of the oesophagus or the gastroesophageal junction and CPS ≥ 10 (multipage table)

Outcome category **outcome** **study**	**Pembrolizumab + cisplatin + 5-FU/capecitabine**		**Placebo + cisplatin + 5-FU/capecitabine**		**Pembrolizumab + cisplatin + 5-FU/capecitabine vs. placebo + cisplatin + 5-FU/capecitabine**
	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]; p-value**
Mortality					
Overall survival					
KEYNOTE 590	43	12.1 [9.6; 18.7] 30 (69.8)	54	10.7 [8.2; 15.3] 44 (81.5)	0.83 [0.52; 1.34]; 0.447[a]
KEYNOTE 062	30	11.8 [9.1; 17.2] 24 (80.0)	20	10.4 [6.5; 18.5] 16 (80.0)	0.95 [0.50; 1.78]; 0.866[b]
Total[c]					0.87 [0.60; 1.27]; 0.476
Morbidity					
Health status (EQ-5D VAS)					
KEYNOTE 590	No usable data				
KEYNOTE 062	No usable data				
Symptoms (EORTC QLQ-C30)[d]					
Fatigue					
KEYNOTE 590	No usable data				
KEYNOTE 062	28	1.4 [1.0; 2.3] 24 (85.7)	20	0.8 [0.7; 3.0] 15 (75.0)	0.84 [0.44; 1.61]; 0.597[b]
Nausea and vomiting					
KEYNOTE 590	No usable data				
KEYNOTE 062	28	1.9 [0.8; 5.3] 19 (67.9)	20	1.4 [0.7; 1.6] 17 (85.0)	0.56 [0.29; 1.08]; 0.085[b]
Pain					
KEYNOTE 590	No usable data				
KEYNOTE 062	28	6.5 [2.4; 8.8] 16 (57.1)	20	3.3 [1.5; NC] 12 (60.0)	0.80 [0.38; 1.69]; 0.551[b]
Dyspnoea					
KEYNOTE 590	No usable data				
KEYNOTE 062	28	8.6 [4.4; NC] 12 (42.9)	20	2.6 [0.8; 6.0] 13 (65.0)	0.43 [0.19; 0.94]; 0.035[b]

Table 30: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: pembrolizumab + cisplatin + 5-FU/capecitabine vs. placebo + cisplatin + 5-FU/capecitabine, subpopulation with adenocarcinoma of the oesophagus or the gastroesophageal junction and CPS ≥ 10 (multipage table)

Outcome category **outcome** **study**	**Pembrolizumab + cisplatin + 5-FU/capecitabine**		**Placebo + cisplatin + 5-FU/capecitabine**		**Pembrolizumab + cisplatin + 5-FU/capecitabine vs. placebo + cisplatin + 5-FU/capecitabine**
	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]; p-value**
Insomnia					
KEYNOTE 590	No usable data				
KEYNOTE 062	28	NA [2.7; NC] 11 (39.3)	20	6.0 [0.7; NC] 10 (50.0)	0.64 [0.27; 1.52]; 0.315[b]
Appetite loss					
KEYNOTE 590	No usable data				
KEYNOTE 062	28	5.8 [1.4; 10.2] 18 (64.3)	20	3.4 [1.5; 6.0] 13 (65.0)	0.65 [0.31; 1.37]; 0.257[b]
Constipation					
KEYNOTE 590	No usable data				
KEYNOTE 062	28	3.0 [1.4; NC] 15 (53.6)	20	3.2 [1.4; 6.1] 14 (70.0)	0.76 [0.36; 1.57]; 0.454[b]
Diarrhoea					
KEYNOTE 590	No usable data				
KEYNOTE 062	28	4.4 [1.4; NC] 15 (53.6)	20	NA [0.7; NC] 9 (45.0)	1.04 [0.45; 2.38]; 0.924[b]
Health-related quality of life					
EORTC QLQ-C30[e]					
Global health status					
KEYNOTE 590	No usable data				
KEYNOTE 062	28	8.3 [2.4; 10.2] 16 (57.1)	20	2.4 [1.4; 7.4] 13 (65.0)	0.59 [0.28; 1.26]; 0.176[b]
Physical functioning					
KEYNOTE 590	No usable data				
KEYNOTE 062	28	4.2 [1.4; 5.9] 21 (75.0)	20	1.4 [0.8; 2.2] 15 (75.0)	0.60 [0.31; 1.17]; 0.136[b]
Role functioning					
KEYNOTE 590	No usable data				
KEYNOTE 062	28	2.1 [1.4; 5.1] 23 (82.1)	20	2.2 [0.7; NC] 13 (65.0)	1.10 [0.56; 2.17]; 0.785[b]

Table 30: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: pembrolizumab + cisplatin + 5-FU/capecitabine vs. placebo + cisplatin + 5-FU/capecitabine, subpopulation with adenocarcinoma of the oesophagus or the gastroesophageal junction and CPS ≥ 10 (multipage table)

Outcome category **outcome** **study**	**Pembrolizumab + cisplatin + 5-FU/capecitabine**		**Placebo + cisplatin + 5-FU/capecitabine**		**Pembrolizumab + cisplatin + 5-FU/capecitabine vs. placebo + cisplatin + 5-FU/capecitabine**
	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]; p-value**
Emotional functioning					
KEYNOTE 590				No usable data	
KEYNOTE 062	28	5.9 [1.4; NC] 15 (53.6)	20	6.1 [1.4; NC] 8 (40.0)	1.21 [0.51; 2.85]; 0.670[b]
Cognitive functioning					
KEYNOTE 590				No usable data	
KEYNOTE 062	28	3.4 [1.4; 9.7] 17 (60.7)	20	1.5 [0.7; NC] 12 (60.0)	0.75 [0.35; 1.57]; 0.442[b]
Social functioning					
KEYNOTE 590				No usable data	
KEYNOTE 062	28	4.4 [1.6; NC] 16 (57.1)	20	1.9 [1.0; 4.7] 15 (75.0)	0.62 [0.31; 1.27]; 0.191[b]
Side effects					
AEs (supplementary information)					
KEYNOTE 590	42	0.4 [0.3; 0.4] 42 (100.0)	53	0.3 [0.3; 0.7] 52 (98.1)	–
KEYNOTE 062	30	0.3 [0.3; 0.6] 30 (100.0)	20	0.6 [0.1; 1.0] 19 (95.0)	–
SAEs					
KEYNOTE 590	42	15.6 [8.0; 27.9] 28 (66.7)	53	31.1 [17.1; 60.3] 30 (56.6)	1.34 [0.80; 2.26]; 0.266[b]
KEYNOTE 062	30	11.6 [2.1; NC] 19 (63.3)	20	36.7 [5.6; NC] 9 (45.0)	1.64 [0.74; 3.64]; 0.220[b]
Total[c]					1.42 [0.92; 2.20]; 0.112
Severe AEs[f]					
KEYNOTE 590	42	4.7 [2.4; 7.4] 37 (88.1)	53	6.3 [3.9; 11.6] 44 (83.0)	1.14 [0.73; 1.77]; 0.567[b]
KEYNOTE 062	30	5.4 [3.0; 9.0] 26 (86.7)	20	5.6 [1.1; 29.4] 15 (75.0)	1.31 [0.69; 2.49]; 0.407[b]
Total[c]					1.19 [0.83; 1.72]; 0.344

Table 30: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: pembrolizumab + cisplatin + 5-FU/capecitabine vs. placebo + cisplatin + 5-FU/capecitabine, subpopulation with adenocarcinoma of the oesophagus or the gastroesophageal junction and CPS ≥ 10 (multipage table)

Outcome category **outcome** **study**	**Pembrolizumab + cisplatin + 5-FU/capecitabine**		**Placebo + cisplatin + 5-FU/capecitabine**		**Pembrolizumab + cisplatin + 5-FU/capecitabine vs. placebo + cisplatin + 5-FU/capecitabine**
	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]; p-value**
Discontinuation due to AEs					
KEYNOTE 590	No usable data				
KEYNOTE 062	No usable data				
Immune-related SAEs (PT collection)[g]					
KEYNOTE 590	42	NA 3 (7.1)	53	NA 1 (1.9)	3.88 [0.40; 37.33]; 0.240[b]
KEYNOTE 062	30	NA 2 (6.7)	20	NA 1 (5.0)	1.19 [0.11; 13.20]; 0.886[b]
Total[c]					2.22 [0.43; 11.51]; 0.343
Immune-related severe AEs (PT collection)[g]					
KEYNOTE 590	42	NA 3 (7.1)	53	NA 1 (1.9)	3.59 [0.37; 34.57]; 0.268[b]
KEYNOTE 062	30	NA 2 (6.7)	20	NA 1 (5.0)	1.03 [0.09; 11.48]; 0.981[b]
Total[c]					2.00 [0.38; 10.50]; 0.411
Endocrine disorders (AE, SOC)[h]					
KEYNOTE 590	42	NA 8 (19.0)	53	NA 2 (3.8)	RR: 5.05 [1.13; 22.52]; 0.034[i, j]
KEYNOTE 062	30	NA 5 (16.7)	20	NA 0 (0)	RR: 7.45 [0.43; 127.74]; 0.062[i,k]
Total[l]					RR: 5.65 [1.48; 21.58]; 0.011

Table 30: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: pembrolizumab + cisplatin + 5-FU/capecitabine vs. placebo + cisplatin + 5-FU/capecitabine, subpopulation with adenocarcinoma of the oesophagus or the gastroesophageal junction and CPS ≥ 10 (multipage table)

Outcome category outcome study	Pembrolizumab + cisplatin + 5-FU/capecitabine		Placebo + cisplatin + 5-FU/capecitabine		Pembrolizumab + cisplatin + 5-FU/capecitabine vs. placebo + cisplatin + 5-FU/capecitabine
	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]; p-value
a. HR and CI from Cox proportional hazards model, stratified by region (Asia versus rest of the world) and ECOG PS (0 vs. 1) with associated p-value from 2-sided Wald test. b. HR and CI from Cox proportional hazards model, unstratified with associated p-value from 2-sided Wald test. c. Institute's calculation; meta-analysis with fixed effect (method with inverse variance). d. Time to first deterioration; a score increase by ≥ 10 points from baseline is defined as a clinically relevant deterioration (scale range 0 to 100). e. Time to first deterioration; a score decrease by ≥ 10 points from baseline is defined as a clinically relevant deterioration (scale range 0 to 100). f. Operationalized as CTCAE grade ≥ 3. d. Predefined list of PTs subject to continuous updating (Version 18). h. The main underlying events are hyperthyroidism (KEYNOTE 590) and hypothyroidism (KEYNOTE 062). There is no information on how many of these events were CTCAE grade 1 and thus not symptomatic. i. Institute's calculation of effect, CI (asymptotic) and p-value (unconditional exact test; CSZ method according to [32]. j. The company reports an HR of 4.96 [1.05; 23.35] and a p-value of 0.043 for the KEYNOTE 590 study; for the meta-analytical summary, the RR is used as a makeshift. This is appropriate to the extent that both estimates are close to each other. k. For the KEYNOTE 062 study, the company reports a p-value of 0.091 based on the score test statistics. l. Institute's calculation, meta-analysis with fixed effect (Mantel/Haenszel method). 5-FU: 5-fluorouracil; AE: adverse event; CI: confidence interval; CPS: combined positive score; CTCAE: Common Terminology Criteria for Adverse Events; ECOG PS: Eastern Cooperative Oncology Group Performance Status; EORTC: European Organisation for Research and Treatment of Cancer; HR: hazard ratio; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; NC: not calculable; PT: Preferred Term; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-OE18: Quality of Life Questionnaire-Oesophageal Cancer 18 items; QLQ-STO22: Quality of Life Questionnaire-Gastric Cancer 22 items; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class				

On the basis of the available information, at most indications, e.g. of an added benefit, can be determined due to the high risk of bias of the results or due to the limited certainty of results with regard to all outcomes of both studies (see Section 2.5.2.2).

Mortality

Overall survival

There was no statistically significant difference between the treatment arms for the outcome "overall survival". This resulted in no hint of an added benefit of pembrolizumab + cisplatin +

5-FU/capecitabine in comparison with cisplatin + 5-FU/capecitabine. An added benefit for this outcome is therefore not proven.

Morbidity

Health status

There were no usable data on health status. This resulted in no hint of an added benefit of pembrolizumab + cisplatin + 5-FU/capecitabine in comparison with cisplatin + 5-FU/capecitabine for the outcome "health status"; an added benefit is therefore not proven.

Symptoms

For the outcomes on symptoms, usable data are only available for the KEYNOTE 062 study. Outcomes on symptoms were recorded using the EORTC QLQ-C30 symptom scales.

Dyspnoea

There is a statistically significant difference in favour of pembrolizumab + cisplatin + 5-FU/capecitabine for the outcome "dyspnoea". For an outcome of the category of non-serious/non-severe symptoms/late complications, the present effect is no more than marginal. This resulted in no hint of an added benefit of pembrolizumab + cisplatin + 5-FU/capecitabine in comparison with cisplatin + 5-FU/capecitabine; an added benefit is therefore not proven.

Fatigue, nausea and vomiting, pain, insomnia, appetite loss, constipation and diarrhoea

No statistically significant differences between the treatment arms were shown for the outcomes "fatigue", "nausea and vomiting", "pain", "insomnia", "appetite loss" and "diarrhoea". This resulted in no hint of an added benefit of pembrolizumab + cisplatin + 5-FU/capecitabine in comparison with cisplatin + 5-FU/capecitabine; an added benefit is therefore not proven for these outcomes.

Health-related quality of life

For the health-related quality of life outcomes, usable data are only available for the KEYNOTE 062 study. The outcomes of health-related quality of life were recorded using the EORTC QLQ-C30 symptom scales.

For all outcomes of health-related quality of life (global health status, physical functioning, role functioning, emotional functioning, cognitive functioning and social functioning), there is no statistically significant difference between the treatment arms. This resulted in no hint of an added benefit of pembrolizumab + cisplatin + 5-FU/capecitabine in comparison with cisplatin + 5-FU/capecitabine; an added benefit is therefore not proven for this outcome.

Side effects

According to the study protocol, progression events of the underlying oncological disease were not recorded as AEs. The MedDRA terms "progression of neoplasms", "progression of malignant neoplasms" and "disease progression" were excluded.

SAEs, severe AEs, immune-related SAEs and immune-related severe AEs

No statistically significant difference between the treatment arms was shown for the outcomes "SAEs", "severe AEs", "immune-related SAEs" and "immune-related severe AEs". This resulted in no hint of greater or lesser harm from pembrolizumab + cisplatin + 5-FU/capecitabine in comparison with cisplatin + 5-FU/capecitabine; greater or lesser harm is therefore not proven for these outcomes.

Discontinuation due to AEs

There were no usable data for the outcome "discontinuation due to AEs". This resulted in no hint of greater or lesser harm from pembrolizumab + cisplatin + 5-FU/capecitabine in comparison with cisplatin + 5-FU/capecitabine; greater or lesser harm is therefore not proven for this outcome.

Further specific AEs

Endocrine disorders (SOC, AEs)

There is a statistically significant difference to the disadvantage of pembrolizumab + cisplatin + 5-FU/capecitabine for the specific AE "endocrine disorders (SOC, AEs)". This resulted in an indication of greater harm from pembrolizumab + cisplatin + 5-FU in comparison with cisplatin + 5-FU.

2.5.2.4 Subgroups and other effect modifiers

The following potential effect modifiers were considered for the present benefit assessment:

- Sex (male versus female)
- Age (< 65 years vs. ≥ 65 years)
- Disease stage (locally advanced vs. metastatic)

A priori, subgroup analyses for the three characteristics mentioned were planned only for the outcome "overall survival" in both studies. The subgroup analyses were conducted post hoc for the patient-relevant outcomes of the categories "morbidity", "health-related quality of life" and "side effects". 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 at least 10 events in at least one subgroup.

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

For analyses on the outcome "overall survival" and the outcomes of the outcome category "AEs", the company conducted interaction tests separately for each study. The company performed no joint consideration of the subgroup results of both studies. Hence, the present benefit assessment checked whether a significant effect modification at the level of 0.2 was present in both studies. If this was the case, an interaction test was conducted at the meta-level of both studies using Q test. Hereinafter, the results are only presented for subgroup analyses with an effect modification with a statistically significant interaction between treatment and subgroup characteristic in the studies included (p-value < 0.05). In addition, subgroup results are only presented if there is a statistically significant and relevant effect in at least one subgroup.

Using the methods described above, the available subgroup results did not show any effect modifications.

2.5.3 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.

2.5.3.1 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 2.5.2 (see Table 31).

Determination of the outcome category for the outcomes on side effects

It cannot be directly inferred from the dossier whether the following outcomes were serious/severe or non-serious/non-severe. The classification of these outcomes is justified.

Dyspnoea (EORTC QLQ-C30)

Module 4 A did not provide any information on the classification of the severity category for the outcome "dyspnoea", recorded with the EORTC QLQ-C30 symptom scales. Therefore, this outcome was assigned to the outcome category of non-serious/non-severe symptoms.

Specific AEs

For the specific AE "endocrine disorders (SOC, AEs)" it can be inferred from the information in Module 4 A that all events that occurred were non-serious or non-severe (CTCAE grade < 3). The specific AE was therefore assigned to the outcome category "non-serious/non-severe side effects"

Table 31: Extent of added benefit at outcome level: pembrolizumab + cisplatin + 5-FU/capecitabine vs. cisplatin + 5-FU/capecitabine (patients with adenocarcinoma of the oesophagus or the gastroesophageal junction and CPS ≥ 10) (multipage table)

Outcome category **outcome** **effect modifier** **subgroup**	**Pembrolizumab + cisplatin + 5-FU/capecitabine vs. cisplatin + 5-FU/capecitabine** **median time to event (months) or proportion of events (%)** **effect estimation [95% CI]; p-value** **probability**[a]	**Derivation of extent**[b]
Mortality		
Overall survival	11.8−12.1 vs. 10.4−10.7 months[c] HR: 0.87 [0.60; 1.27]; p = 0.476	Lesser/added benefit not proven
Morbidity		
Health status (EQ-5D VAS)	No usable data[d]	Lesser/added benefit not proven
Symptoms (EORTC QLQ-C30 - time to first deterioration by ≥ 10 points)		
Fatigue	1.4 vs. 0.8 months HR: 0.84 [0.44; 1.61]; p = 0.597	Lesser/added benefit not proven
Nausea and vomiting	1.9 vs. 1.4 months HR: 0.56 [0.29; 1.08]; p = 0.085	Lesser/added benefit not proven
Pain	6.5 vs. 3.3 months HR: 0.80 [0.38; 1.69]; p = 0.551	Lesser/added benefit not proven
Dyspnoea	8.6 vs. 2.6 months HR: 0.43 [0.19; 0.94]; p = 0.035 probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications $0.90 \leq CI_u < 1.00$ lesser benefit/added benefit not proven[e]
Insomnia	NA vs. 6.0 months HR: 0.64 [0.27; 1.52]; p = 0.315	Lesser/added benefit not proven
Appetite loss	5.8 vs. 3.4 months HR: 0.65 [0.31; 1.37]; p = 0.257	Lesser/added benefit not proven
Constipation	3.0 vs. 3.2 months HR: 0.76 [0.36; 1.57]; p = 0.454	Lesser/added benefit not proven
Diarrhoea	4.4 months vs. NA HR: 1.04 [0.45; 2.38]; p = 0.924	Lesser/added benefit not proven

Table 31: Extent of added benefit at outcome level: pembrolizumab + cisplatin + 5-FU/capecitabine vs. cisplatin + 5-FU/capecitabine (patients with adenocarcinoma of the oesophagus or the gastroesophageal junction and CPS ≥ 10) (multipage table)

Outcome category **outcome** **effect modifier** **subgroup**	**Pembrolizumab + cisplatin + 5-FU/capecitabine vs. cisplatin + 5-FU/capecitabine** **median time to event (months) or proportion of events (%)** **effect estimation [95% CI]; p-value** **probability**[a]	**Derivation of extent**[b]
Health-related quality of life		
Quality of life (EORTC QLQ-C30 - time to first deterioration by ≥ 10 points)		
Global health status	8.3 vs. 2.4 months HR: 0.59 [0.28; 1.26]; p = 0.176	Lesser/added benefit not proven
Physical functioning	4.2 vs. 1.4 months HR: 0.60 [0.31; 1.17]; p = 0.136	Lesser/added benefit not proven
Role functioning	2.1 vs. 2.2 months HR: 1.10 [0.56; 2.17]; p = 0.785	Lesser/added benefit not proven
Emotional functioning	5.9 vs. 6.1 months HR: 1.21 [0.51; 2.85]; p = 0.670	Lesser/added benefit not proven
Cognitive functioning	3.4 vs. 1.5 months HR: 0.75 [0.35; 1.57]; p = 0.442	Lesser/added benefit not proven
Social functioning	4.4 vs. 1.9 months HR: 0.62 [0.31; 1.27]; p = 0.191	Lesser/added benefit not proven
Side effects		
SAEs	11.6−15.6 vs. 31.1−36.7 months[c] HR: 1.42 [0.92; 2.20]; p = 0.112	Greater/lesser harm not proven
Severe AEs	4.7−5.4 vs. 5.6−6.3 months[c] HR: 1.19 [0.83; 1.72]; p = 0.344	Greater/lesser harm not proven
Discontinuation due to AEs	No usable data[d]	Greater/lesser harm not proven
Immune-related SAEs	NA vs. NA HR: 2.22 [0.43; 11.51]; p = 0.343	Greater/lesser harm not proven
Immune-related severe AEs	NA vs. NA HR: 2.00 [0.38; 10.50]; p = 0.411	Greater/lesser harm not proven

Table 31: Extent of added benefit at outcome level: pembrolizumab + cisplatin + 5-FU/capecitabine vs. cisplatin + 5-FU/capecitabine (patients with adenocarcinoma of the oesophagus or the gastroesophageal junction and CPS ≥ 10) (multipage table)

Outcome category **outcome** **effect modifier** **subgroup**	**Pembrolizumab + cisplatin + 5-FU/capecitabine vs. cisplatin + 5-FU/capecitabine** **median time to event (months) or proportion of events (%)** **effect estimation [95% CI]; p-value** **probability[a]**	**Derivation of extent[b]**
Endocrine disorders (AEs)	16.7–19.0 % vs. 0–3.8 %[c] RR: 5.65 [1.48; 21.58] RR: 0.18 [0.05; 0.68][f]; p = 0.011 Probability: "indication"	Outcome category: non-serious/non-severe side effects CI_u < 0.80 Greater harm, extent: “considerable”

a. Probability provided if there is a statistically significant and relevant effect.
b. 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).
c. Minimum and maximum proportions of events or months to event in each treatment arm in the studies included.
d. For reasons, see Section 2.5.2.1.
e. The extent of the effect in this non-serious/non-severe outcome was no more than marginal.
f. 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: European Organization for Research and Treatment of Cancer; HR: hazard ratio; MD: mean difference; NA: not achieved; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-OE18: Quality of Life Questionnaire-Oesophageal Cancer 18 items; RR: relative risk; SAE: serious adverse event

2.5.3.2 Overall conclusion on added benefit

Table 32 summarizes the results considered in the overall conclusion on the extent of added benefit.

Table 32: Positive and negative effects from the assessment of pembrolizumab + cisplatin + 5-FU/capecitabine vs cisplatin + 5-FU/capecitabine

Positive effects	**Negative effects**
▪ –	Non-serious/non-severe side effects ▪ endocrine disorders (AEs): indication of greater harm – extent: "considerable"
No usable data are available for the outcomes “health status” and “discontinuation due to AEs”. 5-FU: 5-fluorouracil; AEs: adverse events	

The overall consideration only shows a negative effect of pembrolizumab + cisplatin + 5-FU/capecitabine versus treatment of physician’s choice as ACT in the outcome category “side

effects". This negative effect concerns the specific AE "endocrine disorders" (indication of greater harm with the extent "considerable"). In the overall consideration of the available results, this negative effect is not sufficient to derive a lesser benefit from pembrolizumab + cisplatin + 5-FU/capecitabine.

In summary, there is no hint of an added benefit of pembrolizumab + cisplatin + 5-FU/capecitabine over the ACT cisplatin + 5-FU/capecitabine for patients with locally advanced or metastatic, not curatively treatable HER2-negative adenocarcinoma of the oesophagus or the gastroesophageal junction with PD-L1-expressing tumours (CPS ≥ 10) in first-line therapy, an added benefit is therefore not proven.

The assessment described above deviates from that of the company, which, on the basis of a joint population from the subpopulations of the KEYNOTE 590 study that are relevant for research questions A and B1, derived an indication of a major added benefit for research questions A and B1.

Data are available only for patients for whom cisplatin + 5-FU or cisplatin + capecitabine is a suitable treatment option concurring with treatment of physician's choice. No data are available for patients for whom another treatment option is suitable according to physician's choice.

2.6 Research question B2: Patients with HER2-positive adenocarcinoma of the oesophagus and CPS ≥ 10

2.6.1 Information retrieval and study pool

For information on the compilation and completeness of the study pool, see Section 2.3.

No relevant study was identified from the check. This concurs with the company's assessment.

2.6.2 Results on added benefit

In its dossier, the company presented no data to assess the added benefit of pembrolizumab in combination with platinum- and fluoropyrimidine-based chemotherapy compared with the ACT for adult patients with locally advanced or metastatic, not curatively treatable, HER2-positive adenocarcinoma of the oesophagus with PD-L1-expressing tumours (CPS ≥ 10) in the first line. This resulted in no hint of an added benefit of pembrolizumab in combination with platinum- and fluoropyrimidine-based chemotherapy in comparison with the ACT; an added benefit is therefore not proven.

2.6.3 Probability and extent of added benefit

As the company did not provide suitable data for the assessment of the added benefit of pembrolizumab in combination with platinum- and fluoropyrimidine-based chemotherapy versus the ACT for adult patients with locally advanced or metastatic, non-curatively treatable HER2-positive adenocarcinoma of the oesophagus with PD-L1-expressing tumours (CPS ≥ 10) in the first line, an added benefit is not proven.

This deviates from the assessment of the company insofar as the company also arrived at the conclusion that statements on the added benefit cannot be drawn for these patient populations. Nevertheless, as an overall conclusion, the company derived an added benefit for the patient population of the entire therapeutic indication (and thus also for the patient population of question B2).

2.7 Probability and extent of added benefit – summary

The result of the assessment of the added benefit of pembrolizumab in combination with platinum- and fluoropyrimidine-based chemotherapy in comparison with the ACT is summarized in Table 33.

Table 33: Pembrolizumab in combination with platinum- and fluoropyrimidine-based chemotherapy – probability and extent of added benefit (multipage table)

Research question	**Therapeutic indication**	**ACT[a]**	**Probability and extent of added benefit**
A	Adult patients with locally advanced or metastatic, squamous cell carcinoma of the oesophagus that cannot be treated curatively[b] and whose tumours express PD-L1 (CPS ≥ 10); first-line treatment	Cisplatin in combination with 5-FU[c]	Hint of major added benefit[d]
B1	Adult patients with locally advanced or metastatic HER2-negative adenocarcinoma of the oesophagus or of the gastroesophageal junction that cannot be treated curatively[b] and whose tumours express PD-L1 (CPS ≥ 10); first-line treatment	Treatment of physician's choice[e]	Added benefit not proven[d,f]
B2	Adult patients with locally advanced or metastatic HER2-positive adenocarcinoma of the oesophagus that cannot be treated curatively[b] and whose tumours express PD-L1 (CPS ≥ 10); first-line treatment	HER2-targeted therapy according to physician's choice[g]	Added benefit not proven[d]

Table 33: Pembrolizumab in combination with platinum- and fluoropyrimidine-based chemotherapy – probability and extent of added benefit (multipage table)

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
a. Presented is the respective ACT specified by the G-BA. b. According to the G-BA, it is assumed for the present therapeutic indication that curative treatment with definitive radiochemotherapy is not an option for patients with unresectable cancer. c. According to the G-BA, it is assumed that cisplatin-containing chemotherapy is suitable for the patients. c. The studies KEYNOTE 590 and KEYNOTE 062 included only patients with an ECOG PS of 0 or 1. It remains unclear whether the observed effects are transferable to patients with an ECOG PS ≥ 2. e. Guidelines mention several platinum- and fluoropyrimidine-based combination chemotherapies: S-1 (tegafur/gimeracil/oteracil) + cisplatin or capecitabine + cisplatin [XP], 5-FU + cisplatin, 5-FU + oxaliplatin + folinic acid [FLO and FOLFOX], capecitabine + oxaliplatin, infusional 5-FU + folinic acid + cisplatin [PLF], epirubicin + cisplatin + capecitabine [ECX], epirubicin + oxaliplatin + capecitabine [EOX], epirubicin + cisplatin + infusional 5-FU [ECF], docetaxel + cisplatin + infusional 5-FU [DCF], 5-FU + oxaliplatin + epirubicin, infusional 5-FU + folinic acid + oxaliplatin + docetaxel [FLOT regimen]. However, only the drugs 5-FU, docetaxel as well as cisplatin are approved in the present therapeutic indication. There is a discrepancy between the drugs approved for the therapeutic indication and those recommended in the guidelines. In the context of treatment of physician's choice, the treatment options cited here are considered to be suitable comparators. The added benefit can be assessed versus one of the cited treatment options within the framework of a single-comparator study. The choice of the used comparator has to be justified in the dossier. f. Data are only available for patients for whom cisplatin + 5-FU or cisplatin + capecitabine is a suitable treatment option according to physician's choice. No data are available for patients for whom another treatment option is suitable according to physician's choice. g. Guidelines recommend the combination therapy of the anti-HER2 antibody trastuzumab with cisplatin and fluoropyrimidines (5-FU or capecitabine), but this is not (explicitly) approved for the present therapeutic indication. Only the drugs 5-FU as well as cisplatin are approved in the present therapeutic indication. There is a discrepancy between the drugs approved for the therapeutic indication and those recommended in the guidelines. Within the framework of the HER2-targeted therapy according to physician's choice, trastuzumab in combination with cisplatin and capecitabine or 5-FU is considered to be a suitable comparator. The added benefit can be assessed versus one of the cited treatment options within the framework of a single-comparator study. The choice of the used comparator has to be justified in the dossier. 5-FU: 5-fluorouracil; ACT: appropriate comparator therapy; CPS: combined positive score; G-BA: Federal Joint Committee			

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.

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

1. Institute for Quality and Efficiency in Health Care. General Methods; Version 6.0 [online]. 2020 [Accessed: 22.03.2021]. URL: https://www.iqwig.de/methoden/general-methods_version-6-0.pdf.

2. Skipka G, Wieseler B, Kaiser T et al. Methodological approach to determine minor, considerable, and major treatment effects in the early benefit assessment of new drugs. Biom J 2016; 58(1): 43-58. https://dx.doi.org/10.1002/bimj.201300274.

3. Merck Sharp & Dohme. A Randomized, Double-Blind, Placebo-Controlled Phase III Clinical Trial of Pembrolizumab (MK-3475) in Combination with Cisplatin and 5-Fluorouracil versus Placebo in Combination with Cisplatin and 5-Fluorouracil as First-Line Treatment in Subjects with Advanced/Metastatic Esophageal Carcinoma; study KEYNOTE-590; Clinical Study Report [unpublished]. 2021.

4. Merck Sharp & Dohme. First-line Esophageal Carcinoma Study With Chemo vs. Chemo Plus Pembrolizumab (MK-3475-590/KEYNOTE-590) [online]. 2021 [Accessed: 11.01.2022]. URL: https://clinicaltrials.gov/ct2/show/NCT03189719.

5. Merck Sharp & Dohme. A Randomized, Double-Blind, Placebo-Controlled Phase III Clinical Trial of Pembrolizumab (MK-3475) in Combination with Cisplatin and 5-Fluorouracil versus Placebo in Combination with Cisplatin and 5-Fluorouracil as First-Line Treatment in Subjects with Advanced/Metastatic Esophageal Carcinoma (KEYNOTE-590) [online]. [Accessed: 11.01.2022]. URL: https://www.clinicaltrialsregister.eu/ctr-search/trial/2017-000958-19/DE.

6. Sun JM, Shen L, Shah MA et al. Pembrolizumab plus chemotherapy versus chemotherapy alone for first-line treatment of advanced oesophageal cancer (KEYNOTE-590): a randomised, placebo-controlled, phase 3 study. Lancet 2021; 398(10302): 759-771. https://dx.doi.org/10.1016/S0140-6736(21)01234-4.

7. Kato K, Shah MA, Enzinger P et al. KEYNOTE-590: Phase III study of first-line chemotherapy with or without pembrolizumab for advanced esophageal cancer. Future Oncol 2019; 15(10): 1057-1066. https://dx.doi.org/10.2217/fon-2018-0609.

8. MSD. KEYTRUDA 25 mg/ml Konzentrat zur Herstellung einer Infusionslösung [online]. 2021 [Accessed: 17.11.2021]. URL: https://www.fachinfo.de.

9. TEVA. Cisplatin Teva 1 mg / ml Konzentrat zur Herstellung einer Infusionslösung [online]. 2017 [Accessed: 17.11.2021]. URL: https://www.fachinfo.de.

10. Hikma Farmacêutica SA. Fachinformation RIBOFLUOR® (5-Fluorouracil) 50 mg/ml Injektionslösung. Stand: Februar. 2017.

11. Leitlinienprogramm Onkologie. S3-Leitlinie Diagnostik und Therapie der Plattenepithelkarzinome und Adenokarzinome des Ösophagus; Langversion 3.0 [online]. 2021 [Accessed: 29.11.2021]. URL: https://www.awmf.org/uploads/tx_szleitlinien/021-023OLl_S3_Plattenepithel_Adenokarzinom_Oesophagus_2021-11.pdf.

12. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology; Esophageal and Esophagogastric Junction Cancers, Version 4.2021 [online]. 2021 [Accessed: 07.02.2022]. URL: https://www.nccn.org/.

13. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Dokumentation und Würdigung der Anhörung zum Entwurf der Allgemeinen Methoden 6.0 [online]. 2020 [Accessed: 27.01.2021]. URL: https://www.iqwig.de/methoden/allgemeine-methoden_dwa-entwurf-fuer-version-6-0_v1-0.pdf.

14. Liang KY, Zeger SL. Longitudinal Data Analysis of Continuous and Discrete Responses for Pre-Post Designs. Sankhya Ser B 2000; 62(1): 134-148.

15. Merck. A Randomized, Active-Controlled, Partially Blinded, Biomarker Select, Phase III Clinical Trial of Pembrolizumab as Monotherapy and in Combination with Cisplatin+5-Fluorouracil versus Placebo+Cisplatin+5- Fluorouracil as First-Line Treatment in Subjects with Advanced Gastric or Gastroesophageal Junction (GEJ) Adenocarcinoma; study KEYNOTE-062; Clinical Study Report [unpublished]. 2019.

16. Merck Sharp & Dohme. Study of Pembrolizumab (MK-3475) as First-Line Monotherapy and Combination Therapy for Treatment of Advanced Gastric or Gastroesophageal Junction Adenocarcinoma (MK-3475-062/KEYNOTE-062) [online]. 2021 [Accessed: 11.01.2022]. URL: https://clinicaltrials.gov/ct2/show/NCT02494583.

17. Merck Sharp & Dohme. A Randomized, Active-Controlled, Partially Blinded, Biomarker Select, Phase III Clinical Trial of Pembrolizumab as Monotherapy and in Combination with Cisplatin+5-Fluorouracil versus Placebo+Cisplatin+5-Fluorouracil as First-Line Treatment in Subjects with Advanced Gastric or Gastroesophageal Junction (GEJ) Adenocarcinoma [online]. [Accessed: 11.01.2022]. URL: https://www.clinicaltrialsregister.eu/ctr-search/trial/2015-000972-88/DE.

18. Shitara K, Van Cutsem E, Bang YJ et al. Efficacy and Safety of Pembrolizumab or Pembrolizumab Plus Chemotherapy vs Chemotherapy Alone for Patients With First-line, Advanced Gastric Cancer: The KEYNOTE-062 Phase 3 Randomized Clinical Trial. JAMA Oncol 2020; 6(10): 1571-1580. https://dx.doi.org/10.1001/jamaoncol.2020.3370.

19. Van Cutsem E, Valderrama A, Bang YJ et al. Quality of life with first-line pembrolizumab for PD-L1-positive advanced gastric/gastroesophageal junction adenocarcinoma: results from the randomised phase III KEYNOTE-062 study. ESMO Open 2021; 6(4): 100189. https://dx.doi.org/10.1016/j.esmoop.2021.100189.

20. medac. Capecitabin medac 150/500 mg Filmtabletten [online]. 2021 [Accessed: 17.11.2021]. URL: https://www.fachinfo.de.

21. Leitlinienprogramm Onkologie. S3-Leitlinie Magenkarzinom Diagnostik und Therapie der Adenokarzinome des Magens und ösophagogastralen Übergangs; Langversion 2.0 [online]. 2019 [Accessed: 29.11.2021]. URL: https://www.awmf.org/uploads/tx_szleitlinien/032-009l_S3_Magenkarzinom_Diagnostik_Therapie_Adenokarzinome_oesophagogastraler_Uebergang_2019-12.pdf.

22. Langer R, Von Rahden BH, Nahrig J et al. Prognostic significance of expression patterns of c-erbB-2, p53, p16INK4A, p27KIP1, cyclin D1 and epidermal growth factor receptor in oesophageal adenocarcinoma: a tissue microarray study. J Clin Pathol 2006; 59(6): 631-634. https://dx.doi.org/10.1136/jcp.2005.034298.

23. Plum PS, Gebauer F, Krämer M et al. HER2/neu (ERBB2) expression and gene amplification correlates with better survival in esophageal adenocarcinoma. BMC Cancer 2019; 19(1): 38. https://dx.doi.org/10.1186/s12885-018-5242-4.

24. Reichelt U, Duesedau P, Tsourlakis M et al. Frequent homogeneous HER-2 amplification in primary and metastatic adenocarcinoma of the esophagus. Mod Pathol 2007; 20(1): 120-129. https://dx.doi.org/10.1038/modpathol.3800712.

25. Salem ME, Puccini A, Xiu J et al. Comparative Molecular Analyses of Esophageal Squamous Cell Carcinoma, Esophageal Adenocarcinoma, and Gastric Adenocarcinoma. Oncologist 2018; 23(11): 1319-1327. https://dx.doi.org/10.1634/theoncologist.2018-0143.

26. Yoon HH, Shi Q, Sukov WR et al. Adverse prognostic impact of intratumor heterogeneous HER2 gene amplification in patients with esophageal adenocarcinoma. J Clin Oncol 2012; 30(32): 3932-3938. https://dx.doi.org/10.1200/jco.2012.43.1890.

27. Dijksterhuis WPM, Verhoeven RHA, Meijer SL et al. Increased assessment of HER2 in metastatic gastroesophageal cancer patients: a nationwide population-based cohort study. Gastric Cancer 2020; 23(4): 579-590. https://dx.doi.org/10.1007/s10120-020-01039-7.

28. Langer R, Rauser S, Feith M et al. Assessment of ErbB2 (Her2) in oesophageal adenocarcinomas: summary of a revised immunohistochemical evaluation system, bright field double in situ hybridisation and fluorescence in situ hybridisation. Mod Pathol 2011; 24(7): 908-916. https://dx.doi.org/10.1038/modpathol.2011.52.

29. Koopman T, Smits MM, Louwen M et al. HER2 positivity in gastric and esophageal adenocarcinoma: clinicopathological analysis and comparison. J Cancer Res Clin Oncol 2015; 141(8): 1343-1351. https://dx.doi.org/10.1007/s00432-014-1900-3.

30. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Atezolizumab (hepatozelluläres Karzinom) – Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung [online]. 2021 [Accessed: 07.02.2022]. URL: https://www.iqwig.de/download/a20-97_atezolizumab_nutzenbewertung-35a-sgb-v_v1-0.pdf.

31. Gemeinsamer Bundesausschuss. Antworten auf häufig gestellte Fragen zum Verfahren der Nutzenbewertung; Wie soll, vor dem Hintergrund der Veröffentlichung des Methodenpapiers 6.0 des IQWiG am 5. November 2020, derzeit in der Dossiererstellung mit der Bestimmung von klinischen Relevanzschwellen bei komplexen Skalen umgegangen werden? [online]. [Accessed: 05.08.2021]. URL: https://www.g-ba.de/themen/arzneimittel/arzneimittel-richtlinie-anlagen/nutzenbewertung-35a/faqs.

32. Martín Andrés A, Silva Mato A. Choosing the optimal unconditioned test for comparing two independent proportions. Computat Stat Data Anal 1994; 17(5): 555-574. https://dx.doi.org/10.1016/0167-9473(94)90148-1.

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