Pembrolizumab (gastric or gastro-oesophageal junction adenocarcinoma, HER2-negative)

Benefit assessment according to §35a SGB V[1]

EXTRACT

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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.

Patient and family involvement

No feedback was received in the framework of the present dossier assessment.

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Part I: Benefit assessment

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

I List of abbreviations

Abbreviation	Meaning
5-FU	5-fluorouracil
ACT	appropriate comparator therapy
AE	adverse event
BSA	body surface area
CPS	combined positive score
CTCAE	Common Terminology Criteria for Adverse Events
ECOG PS	Eastern Cooperative Oncology Group Performance Statu
EORTC	European Organisation for Research and Treatment of Cancer
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
GEJ	gastro-oesophageal junction
HER2	human epidermal growth factor receptor 2
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
NCCN	National Comprehensive Cancer Network
PD-L1	programmed cell death ligand 1
PT	Preferred Term
QLQ-C30	Quality of Life Questionnaire-Core 30
QLQ-STO22	Quality of Life Questionnaire-Gastric Cancer 22 items
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
VAS	visual analogue scale

I 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 (in combination with fluoropyrimidine and platinum-containing chemotherapy). 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 3 January 2024.

Research question

The aim of this report is to assess the added benefit of pembrolizumab in combination with fluoropyrimidine and platinum-containing chemotherapy (hereinafter referred to as pembrolizumab + chemotherapy) compared with the appropriate comparator therapy (ACT) for first-line treatment of locally advanced unresectable or metastatic human epidermal growth factor receptor 2 (HER2)-negative gastric or gastro-oesophageal junction (GEJ) adenocarcinoma in adult patients whose tumours express programmed cell death ligand 1 (PD-L1) (combined positive score [CPS] ≥ 1).

First-line treatment with pembrolizumab in the presence of locally advanced unresectable or metastatic HER2-negative GEJ adenocarcinoma in adult patients whose tumours express PD-L1 (CPS ≥ 10) was already part of an earlier benefit assessment. This has no consequences for the present benefit assessment, however.

The research question presented in Table 2 results from the ACT specified by the G-BA.

Table 2: Research question of the benefit assessment of pembrolizumab

Therapeutic indication	**ACT**[a, b, c, d]
Adults with locally advanced unresectable or metastatic HER2-negative gastric or gastro-oesophageal junction adenocarcinoma whose tumours express PD-L1 (CPS ≥ 1)[e]; in combination with fluoropyrimidine and platinum-containing chemotherapy for first-line treatment	▪ Cisplatin + capecitabine or ▪ oxaliplatin + capecitabine or ▪ cisplatin + S-1 (tegafur/gimeracil/oteracil) or ▪ cisplatin + 5-fluorouracil (only for patients with oesophageal adenocarcinoma[f]) or ▪ cisplatin + 5-fluorouracil + folinic acid (only for patients with oesophageal adenocarcinoma[f]) or ▪ epirubicin + cisplatin + capecitabine or ▪ epirubicin + cisplatin + 5-fluorouracil or ▪ epirubicin + oxaliplatin + capecitabine or ▪ docetaxel + cisplatin + 5-fluorouracil or ▪ nivolumab in combination with fluoropyrimidine and platinum-containing combination chemotherapy (only for tumours with PD-L1 expression [CPS ≥ 5]) or ▪ 5-fluorouracil + oxaliplatin + epirubicin (only for patients with oesophageal adenocarcinoma[f])

a. Presented is the ACT specified by the G-BA.
b. It is assumed for the present therapeutic indication that curative treatment with definitive radiochemotherapy is not an option for patients with unresectable cancer.
c. The ACT comprises several alternative treatment options. According to the G-BA, individual treatment options only represent a comparator therapy for those members of the patient population who have the patient and disease characteristics shown in brackets. The alternative treatment options are only to be regarded as equally appropriate in the area in which the patient populations have the same characteristics.
d. To demonstrate added benefit for the total population, any treatment option can be used that is not restricted by patient and disease characteristics given in brackets. If the ACT comprises several alternative treatment options without restrictions, the added benefit for the total population can be demonstrated versus one of these alternative treatment options; this can usually be performed in the context of a single-comparator study. In contrast, the sole comparison with a treatment option which represents a comparator therapy only for part of the patient population is generally insufficient to demonstrate added benefit for the total population.
e. First-line treatment with pembrolizumab in the presence of locally advanced unresectable or metastatic HER2-negative GEJ adenocarcinoma in adult patients whose tumours express PD-L1 (CPS ≥ 10) was already part of an earlier benefit assessment. This has no consequences for the present benefit assessment, however.
f. In the present assessment, this includes patients with GEJ adenocarcinoma.

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

On 9 January 2024, after the company had submitted the dossier (29 December 2023), the G-BA modified the ACT as shown in Table 2. In Module 3 A, the company referred to the previously specified ACT (treatment of physician's choice) from 21 February 2023, which did not contain any restrictions regarding the use of different drug combinations depending on location (e.g. oesophagus), and also included the following drug combinations in addition to the above-mentioned drug combinations:

- 5-fluorouracil (5-FU) + oxaliplatin
- 5-FU + oxaliplatin + folinic acid
- docetaxel + oxaliplatin + 5-FU + folinic acid
- docetaxel + oxaliplatin + 5-FU

The company claimed to have followed the ACT specified by the G-BA. Correspondingly, the information provided by the company in the dossier relates to the original ACT. The present assessment is implemented in comparison with the current ACT specified by the G-BA (see Table 2).

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) are used to derive added benefit. This concurs with the company's inclusion criteria.

Study pool and study design

The studies KEYNOTE 062, KEYNOTE 590 and KEYNOTE 859 were included in the present benefit assessment.

KEYNOTE 062 study

The KEYNOTE 062 study is a completed, partially blinded, multicentre RCT comparing pembrolizumab as monotherapy versus pembrolizumab in combination with cisplatin + capecitabine or cisplatin + 5-FU and versus placebo in combination with cisplatin + capecitabine or cisplatin + 5-FU (the fluoropyrimidine and platinum-containing combination therapy is referred to below as "chemotherapy"). The study arm with pembrolizumab as monotherapy was unblinded, but is irrelevant for the present benefit assessment. The 2 study arms relevant for the benefit assessment were double-blind.

Adult patients with locally advanced unresectable or metastatic gastric or GEJ adenocarcinoma with negative HER2 status (determined according to local standards) were enrolled in the study. The tumours of all included patients had to be PD-L1-positive (CPS ≥ 1). Patients had to have a good general condition corresponding to an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1.

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 geographic region (Europe/Israel/North America/Australia versus Asia versus rest of the world, disease status (locally advanced unresectable versus metastatic), and chemotherapy (5-FU versus capecitabine).

Primary outcomes of the KEYNOTE 062 study were overall survival and progression-free survival. Other patient-relevant outcomes recorded in the study were health status and outcomes on symptoms, health-related quality of life and side effects.

For the present benefit assessment, the data of the prespecified third data cut-off (26 March 2019) from Module 5 of the dossier are used primarily.

KEYNOTE 590 study

The KEYNOTE 590 study is a completed, double-blind, multicentre RCT comparing pembrolizumab in combination with cisplatin + 5-FU versus placebo in combination with cisplatin + 5-FU (the fluoropyrimidine and platinum-containing combination therapy is referred to below as “chemotherapy”).

Adult patients with locally advanced unresectable or metastatic squamous cell carcinoma or adenocarcinoma of the oesophagus or adenocarcinoma of the GEJ (only Siewert type I) with negative HER2 status (determined according to local standards) were enrolled in the study. The PD-L1 expression of the tumours of all included patients had to be known. Patients had to have a good general condition corresponding to an ECOG PS of 0 or 1.

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

Primary outcomes of the KEYNOTE 590 study were overall survival and progression-free survival. Other patient-relevant outcomes recorded in the study were health status and outcomes on symptoms, health-related quality of life and side effects.

For the present benefit assessment, the data of the prespecified first data cut-off (2 July 2020) are to be used primarily. Corresponding data are not available for the relevant subpopulation.

KEYNOTE 859 study

The KEYNOTE 859 study is a double-blind, multicentre RCT comparing pembrolizumab in combination with cisplatin + 5-FU or oxaliplatin + capecitabine versus placebo in combination

with cisplatin + 5-FU or oxaliplatin + capecitabine (the fluoropyrimidine and platinum-containing combination therapy is referred to below as “chemotherapy”).

Adult patients with locally advanced unresectable or metastatic gastric or GEJ adenocarcinoma with negative HER2 status were enrolled in the study. The PD-L1 expression of the tumours of all included patients had to be known. Patients had to have a good general condition corresponding to an ECOG PS of 0 or 1.

Patients were randomly assigned to either the intervention arm (pembrolizumab + chemotherapy; N = 790) or the comparator arm (placebo + chemotherapy; N = 789), stratified by region (Europe/Israel/North America/Australia versus Asia versus rest of the world), chemotherapy (cisplatin + 5-FU versus oxaliplatin + capecitabine) and PD-L1 expression status (CPS < 1 versus CPS ≥ 1).

Primary outcome of the KEYNOTE 859 study was overall survival. Other patient-relevant outcomes recorded in the study were health status and outcomes on symptoms, health-related quality of life and side effects.

For the present benefit assessment, the data of the prespecified first data cut-off (3 October 2022) are used primarily.

Treatment in the studies KEYNOTE 062, KEYNOTE 590 and KEYNOTE 859

The studies KEYNOTE 062, KEYNOTE 590 and KEYNOTE 859 investigated the administration of pembrolizumab versus placebo, each in addition to a chemotherapy component.

In the studies KEYNOTE 062, KEYNOTE 590 and KEYNOTE 859, treatment with pembrolizumab and the drug combinations of the chemotherapy was largely carried out in compliance with the recommendations in the Summaries of Product Characteristics (SPCs), but there are uncertainties regarding the treatment, which are described in the following section.

Uncertainties regarding the treatment

It should be noted that both oxaliplatin and capecitabine are approved for the treatment of gastric cancer, but not for the treatment of GEJ adenocarcinoma (or oesophageal carcinoma). This has no consequences for the present assessment.

Number of treatment cycles

In the study arms of the 3 studies, treatment with pembrolizumab or placebo and chemotherapy was limited to a maximum of 35 cycles (approx. 2 years). Treatment with cisplatin and oxaliplatin could be discontinued after 6 cycles (KEYNOTE 062 and KEYNOTE 859) or was limited to 6 cycles (KEYNOTE 590). According to the approval, however, pembrolizumab treatment is to be continued until cancer progression or the occurrence of unacceptable

toxicity. According to the approval, there is no fixed upper limit on the number of treatment cycles for treatment with cisplatin, oxaliplatin, 5-FU and capecitabine.

For the studies KEYNOTE 062, KEYNOTE 590 und KEYNOTE 859, there is no information on how many patients of the relevant subpopulation of the study, or of the subpopulation used as approximation, received the planned maximum number of treatment cycles and received no further subsequent treatment although such treatment would have been possible in principle according to the approval.

Dosage of 5-FU

According to the specification of the G-BA, chemotherapy with cisplatin + 5-FU is an ACT exclusively for patients with oesophageal adenocarcinoma. For this patient population, the dosage of 5-FU in the 3 studies deviated from the specifications of the approval.

A total dose of 4000 mg/m² body surface area (BSA)/cycle was planned in all 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 (only study KEYNOTE 590). 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 should be noted that according to the approval, a cycle length of 3 to 4 weeks is 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. In combination with cisplatin, the National Comprehensive Cancer Network (NCCN) guideline recommends a 5-FU dose of 800 mg/m² BSA/day on Days 1 to 5 of a 3-week cycle, however.

Overall, the 5-FU dosage used in the studies KEYNOTE 062, KEYNOTE 590 and KEYNOTE 859 deviates from the approved dosage for oesophageal carcinoma. It is unclear to what extent this deviation affects the results of patient-relevant outcomes.

Relevant subpopulations of the studies

For the 3 studies, the company only considered the subpopulation of patients with GEJ or gastric adenocarcinoma with PD-L1 status CPS ≥ 1. However, the subpopulations of the KEYNOTE 062 and KEYNOTE 859 studies include a potentially relevant proportion of patients with gastric cancer and administration of 5-FU, for whom the ACT was thus not implemented. In addition, for all 3 studies in Module 4 A, the company only presented the results for non-predefined data cut-offs. The results presented by the company in Module 4 A were therefore not used for the present benefit assessment.

Subpopulations relevant for the benefit assessment or used as approximation

KEYNOTE 062 study

The subpopulation of the KEYNOTE 062 study relevant for the benefit assessment consists of adult patients with locally advanced unresectable or metastatic HER2-negative gastric or GEJ adenocarcinoma whose tumours express PD-L1 (CPS ≥ 1) and who were treated in accordance with the ACT. Primarily the latest data cut-off planned a priori or requested by the regulatory authorities must be taken into account.

The company considered a subpopulation (intervention arm: N = 255; comparator arm: N = 250) that is almost identical to the total population (disregarding the pembrolizumab monotherapy arm). Two patients are missing in the intervention arm for whom a violation of exclusion criteria was apparently subsequently identified. However, this subpopulation includes a potentially relevant proportion of patients who were not treated in compliance with the ACT. The data are therefore not used for the present benefit assessment.

The extent to which interpretable conclusions can be drawn for the relevant subpopulation on the basis of the information available for the KEYNOTE 062 study was examined. The study documents contain results from subgroup analyses for the characteristic of chemotherapy (cisplatin + 5-FU versus cisplatin + capecitabine). The ACT was implemented in the study for the subgroup of patients who received the drug combination of cisplatin + capecitabine, as this option represents an ACT for both GEJ and gastric adenocarcinoma. This patient population (intervention arm: N = 159; comparator arm: N = 155) was therefore used as an approximation for the relevant subpopulation. The subgroup of patients who received cisplatin + 5-FU was not used for the present benefit assessment. This drug combination represents an ACT exclusively for patients with GEJ adenocarcinoma. Information on the proportion of these patients in the subgroup cannot be inferred from the available documents. It should be noted that, due to the restriction to a subgroup, data from patients (with GEJ adenocarcinoma and treatment with cisplatin + 5-FU) are not considered for the subpopulation used as approximation, although these are relevant for the present benefit assessment. For this reason, the certainty of results from the KEYNOTE 062 study is reduced. In deviation from the company's procedure, the data on the prespecified data cut-off from 26 March 2019 were used for the benefit assessment.

KEYNOTE 590 study

The subpopulation of the KEYNOTE 590 study relevant for the benefit assessment includes patients with locally advanced unresectable or metastatic HER2-negative GEJ adenocarcinoma whose tumours express PD-L1 (CPS ≥ 1; intervention arm: N = 37; comparator arm: N = 43). However, the company only presented data on a non-prespecified data cut-off for this subpopulation. The data presented by the company were therefore not used for the present benefit assessment. The proportion of this subpopulation in all patients belonging to either

this subpopulation or one of the 2 subpopulations of KEYNOTE 062 or KEYNOTE 859 used as approximation is < 5%; the lack of corresponding results for the assessment of added benefit is therefore negligible.

KEYNOTE 859 study

The subpopulation relevant for the benefit assessment consists of adult patients with locally advanced unresectable or metastatic HER2-negative gastric or GEJ adenocarcinoma whose tumours express PD-L1 (CPS ≥ 1) and who were treated in accordance with the ACT. Primarily the latest data cut-off planned a priori or requested by the regulatory authorities must be taken into account.

As approximation, the subpopulation presented by the company were used for the benefit assessment. In this subpopulation, a proportion of up to 13% of patients with gastric cancer may have received cisplatin + 5-FU, which deviates from the ACT. It is not assumed that this proportion has a relevant influence on the results. For this subpopulation, the results for the prespecified data cut-off (3 October 2022) were used, which were available in the study documents.

Risk of bias

The risk of bias across outcomes is rated as low for both studies (KEYNOTE 062 and KEYNOTE 859). Despite the low risk of bias, the certainty of results is reduced in the studies KEYNOTE 062 and KEYNOTE 859, as there are uncertainties regarding the treatment and/or the subpopulation used as approximation. Since no results from the KEYNOTE 590 study were used for the present assessment, the risk of bias is not assessed.

The risk of bias of the results on the outcome of overall survival from the 2 studies KEYNOTE 062 and KEYNOTE 859 is rated as low in each case. Nevertheless, as described above, the certainty of results is limited. For the outcomes in the categories of morbidity, health-related quality of life and side effects, no suitable data are available for conducting a quantitative or qualitative summary; the risk of bias of the results for these outcomes is therefore not assessed.

In summary, the risk of bias due to the above-mentioned uncertainties results in a moderate qualitative certainty of results for both studies. Thus, no more than indications, for example of an added benefit, can be derived for patient-relevant outcomes for which a quantitative or qualitative summary is possible.

No suitable data for a quantitative or qualitative summary for patient-relevant outcomes except for the outcome of overall survival

Data on the outcome of overall survival at a prespecified data cut-off were available for both studies (KEYNOTE 062, KEYNOTE 859). In this assessment, the results of this outcome are analysed in a meta-analysis.

For the categories of morbidity, health-related quality of life and side effects, the database was incomplete across the studies:

For the subpopulation of the KEYNOTE 062 study derived from the subgroup analysis, which was used as an approximation, no data for the prespecified data cut-off were available for the outcomes in the categories of morbidity, health-related quality of life and side effects. For the categories of morbidity, health-related quality of life and side effects, data were only available for a non-prespecified data cut-off used by the company in Module 4 A. However, these were only selectively available for outcomes that showed a statistically significant interaction for the characteristic of chemotherapy (cisplatin + 5-FU versus cisplatin + capecitabine).

For the subpopulation of the KEYNOTE 859 study used as an approximation, results on a prespecified data cut-off were available for the outcomes in the categories of morbidity and health-related quality. However, these data were incomplete, as results were not presented for all scales of the EORTC instruments used. The suitability of the operationalizations and analyses was therefore not examined. No results for a prespecified data cut-off were available for outcomes in the side effects category overall. For the non-prespecified data cut-off used by the company in Module 4 A, results were available for the subpopulation of the KEYNOTE 859 study used as an approximation for all used outcomes in the categories of morbidity, health-related quality of life and side effects.

No quantitative or qualitative summary was made for outcomes in the categories of morbidity, health-related quality of life and side effects due to the incomplete database. The results of the KEYNOTE 859 study alone, for example for outcomes in the categories of morbidity and health-related quality of life, were also not assessed because the proportion of patients from KEYNOTE 859 was only 80% in the subpopulations of both studies used as an approximation. If only the results of the KEYNOTE 859 study were assessed, an important proportion of patients would thus be disregarded. Irrespective of this, it should be noted that a quantitative or qualitative summary of results requires the presence of comparable operationalizations of the outcomes.

Overall, only data on the outcome of overall survival are therefore available for the present benefit assessment.

Results

Mortality

Overall survival

For the outcome of overall survival, the results of the time-to-event analyses for the data cut-offs prespecified in the studies KEYNOTE 062 and KEYNOTE 859 are presented. There is moderate certainty of results in each case.

For the outcome of overall survival, the conducted meta-analysis found a statistically significant difference in favour of pembrolizumab + chemotherapy in comparison with placebo + chemotherapy. There is an indication of an added benefit of pembrolizumab + chemotherapy in comparison with chemotherapy.

Morbidity

Health status (EQ-5D visual analogue scale [VAS]) and symptoms (European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 [EORTC QLQ-C30], EORTC Quality of Life Questionnaire-Gastric Cancer 22 items [QLQ-STO22])

For the outcomes in the morbidity category, no suitable data are available to perform a quantitative or qualitative summary. There is no hint of an added benefit of pembrolizumab + chemotherapy in comparison with chemotherapy for any of them; an added benefit is therefore not proven.

Health-related quality of life

EORTC QLQ-C30

For the outcome of health-related quality of life, recorded with the EORTC QLQ-C30, no suitable data are available to perform a quantitative or qualitative summary. There is no hint of an added benefit of pembrolizumab + chemotherapy in comparison with chemotherapy; an added benefit is therefore not proven.

Side effects

Serious adverse events (SAEs), severe adverse events (AEs) (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3), discontinuation due to AEs, immune-mediated severe SAEs, immune-mediated severe AEs (CTCAE grade ≥ 3) and hand-foot syndrome (Preferred Term [PT], AEs)

For the outcomes in the side effects category, no suitable data are available to perform a quantitative or qualitative summary. There is no hint of greater or lesser harm from pembrolizumab + chemotherapy in comparison with chemotherapy for any of them; greater or lesser harm is therefore not proven.

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

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

Overall, there was an indication of a major added benefit for overall survival. The results on the outcomes in the categories of morbidity, health-related quality of life and side effects are unsuitable for the present benefit assessment. However, even any disadvantages in these outcomes are not assumed to completely call into question the positive effect in the outcome of overall survival. However, it is not possible to quantify the overall extent of added benefit.

In summary, there is an indication of a non-quantifiable added benefit of pembrolizumab in combination with chemotherapy compared with chemotherapy for adult patients with locally advanced unresectable or metastatic HER2-negative gastric or GEJ adenocarcinoma whose tumours express PD-L1 (CPS ≥ 1) in first-line treatment.

Table 3 summarizes the probability and extent of added benefit of pembrolizumab.

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) “proof”, (2) “indication”, (3) “hint”, or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or less benefit). For further details see [1,2].

Table 3: Pembrolizumab – probability and extent of added benefit (multipage table)

Therapeutic indication	**ACT**[a, b, c, d]	**Probability and extent of added benefit**
Adults with locally advanced unresectable or metastatic HER2-negative gastric or gastro-oesophageal junction adenocarcinoma whose tumours express PD-L1 (CPS ≥ 1)[e]; in combination with fluoropyrimidine and platinum-containing chemotherapy for first-line treatment	▪ Cisplatin + capecitabine or ▪ oxaliplatin + capecitabine or ▪ cisplatin + S-1 (tegafur/gimeracil/oteracil) or ▪ cisplatin + 5-fluorouracil (only for patients with oesophageal adenocarcinoma[f]) or ▪ cisplatin + 5-fluorouracil + folinic acid (only for patients with oesophageal adenocarcinoma[f]) or ▪ epirubicin + cisplatin + capecitabine or ▪ epirubicin + cisplatin + 5-fluorouracil or ▪ epirubicin + oxaliplatin + capecitabine or ▪ docetaxel + cisplatin + 5-fluorouracil or ▪ nivolumab in combination with fluoropyrimidine and platinum-containing combination chemotherapy (only for tumours with PD-L1 expression [CPS ≥ 5]) or ▪ 5-fluorouracil + oxaliplatin + epirubicin (only for patients with oesophageal adenocarcinoma[f])	Indication of non-quantifiable added benefit[g]

Table 3: Pembrolizumab – probability and extent of added benefit (multipage table)

Therapeutic indication	**ACT**[a, b, c, d]	**Probability and extent of added benefit**
a. Presented is the ACT specified by the G-BA. b. It is assumed for the present therapeutic indication that curative treatment with definitive radiochemotherapy is not an option for patients with unresectable cancer. c. The ACT comprises several alternative treatment options. According to the G-BA, individual treatment options only represent a comparator therapy for those members of the patient population who have the patient and disease characteristics shown in brackets. The alternative treatment options are only to be regarded as equally appropriate in the area in which the patient populations have the same characteristics. d. To demonstrate added benefit for the total population, any treatment option can be used that is not restricted by patient and disease characteristics given in brackets. If the ACT comprises several alternative treatment options without restrictions, the added benefit for the total population can be demonstrated versus one of these alternative treatment options; this can usually be performed in the context of a single-comparator study. In contrast, the sole comparison with a treatment option which represents a comparator therapy only for part of the patient population is generally insufficient to demonstrate added benefit for the total population. e. First-line treatment of adult patients with locally advanced unresectable or metastatic HER2-negative GEJ adenocarcinoma whose tumours express PD-L1 (CPS ≥ 10) with pembrolizumab was already part of an earlier benefit assessment. This has no consequences for the present benefit assessment, however. f. In the present assessment, this includes patients with GEJ adenocarcinoma. g. The studies KEYNOTE 062, KEYNOTE 590 and KEYNOTE 859 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. ACT: appropriate comparator therapy; CPS: combined positive score; ECOG PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee; GEJ: gastro-oesophageal junction; HER2: human epidermal growth factor receptor 2; PD-L1: programmed cell death ligand 1		

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

I 2 Research question

The aim of this report is to assess the added benefit of pembrolizumab in combination with fluoropyrimidine and platinum-containing chemotherapy (hereinafter referred to as pembrolizumab + chemotherapy) compared with the ACT for first-line treatment of locally advanced unresectable or metastatic HER2-negative gastric or GEJ adenocarcinoma in adult patients whose tumours express PD-L1 (CPS ≥ 1).

First-line treatment with pembrolizumab in the presence of locally advanced unresectable or metastatic HER2-negative GEJ adenocarcinoma in adult patients whose tumours express PD-L1 (CPS ≥ 10) was already part of an earlier benefit assessment [3,4]. This has no consequences for the present benefit assessment, however.

The research question presented in Table 4 results from the ACT specified by the G-BA.

Table 4: Research question of the benefit assessment of pembrolizumab

Therapeutic indication	**ACT**[a, b, c, d]
Adults with locally advanced unresectable or metastatic HER2-negative gastric or gastro-oesophageal junction adenocarcinoma whose tumours express PD-L1 (CPS ≥ 1)[e]; in combination with fluoropyrimidine and platinum-containing chemotherapy for first-line treatment	▪ Cisplatin + capecitabine or ▪ oxaliplatin + capecitabine or ▪ cisplatin + S-1 (tegafur/gimeracil/oteracil) or ▪ cisplatin + 5-fluorouracil (only for patients with oesophageal adenocarcinoma[f]) or ▪ cisplatin + 5-fluorouracil + folinic acid (only for patients with oesophageal adenocarcinoma[f]) or ▪ epirubicin + cisplatin + capecitabine or ▪ epirubicin + cisplatin + 5-fluorouracil or ▪ epirubicin + oxaliplatin + capecitabine or ▪ docetaxel + cisplatin + 5-fluorouracil or ▪ nivolumab in combination with fluoropyrimidine and platinum-containing combination chemotherapy (only for tumours with PD-L1 expression [CPS ≥ 5]) or ▪ 5-fluorouracil + oxaliplatin + epirubicin (only for patients with oesophageal adenocarcinoma[f])

a. Presented is the ACT specified by the G-BA.
b. It is assumed for the present therapeutic indication that curative treatment with definitive radiochemotherapy is not an option for patients with unresectable cancer.
c. The ACT comprises several alternative treatment options. According to the G-BA, individual treatment options only represent a comparator therapy for those members of the patient population who have the patient and disease characteristics shown in brackets. The alternative treatment options are only to be regarded as equally appropriate in the area in which the patient populations have the same characteristics.
d. To demonstrate added benefit for the total population, any treatment option can be used that is not restricted by patient and disease characteristics given in brackets. If the ACT comprises several alternative treatment options without restrictions, the added benefit for the total population can be demonstrated versus one of these alternative treatment options; this can usually be performed in the context of a single-comparator study. In contrast, the sole comparison with a treatment option which represents a comparator therapy only for part of the patient population is generally insufficient to demonstrate added benefit for the total population.
e. First-line treatment with pembrolizumab in the presence of locally advanced unresectable or metastatic HER2-negative GEJ adenocarcinoma in adult patients whose tumours express PD-L1 (CPS ≥ 10) was already part of an earlier benefit assessment [3,4]. This has no consequences for the present benefit assessment, however.
f. In the present assessment, this includes patients with GEJ adenocarcinoma.

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

On 9 January 2024, after the company had submitted the dossier (29 December 2023), the G-BA modified the ACT as shown in Table 4. In Module 3 A, the company referred to the previously specified ACT (treatment of physician's choice) from 21 February 2023, which did not contain any restrictions regarding the use of different drug combinations depending on location (e.g. oesophagus), and also included the following drug combinations in addition to the above-mentioned drug combinations:

- 5-FU + oxaliplatin
- 5-FU + oxaliplatin + folinic acid
- docetaxel + oxaliplatin + 5-FU + folinic acid
- docetaxel + oxaliplatin + 5-FU

The company claimed to have followed the ACT specified by the G-BA. Correspondingly, the information provided by the company in the dossier relates to the original ACT. The present assessment is implemented in comparison with the current ACT specified by the G-BA (see Table 4).

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs are used to derive added benefit. This concurs with the company's inclusion criteria.

I 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: 17 November 2023)
- bibliographical literature search on pembrolizumab (last search on 12 November 2023)
- search in trial registries/trial results databases for studies on pembrolizumab (last search on 12 November 2023)
- search on the G-BA website for pembrolizumab (last search on 12 November 2023)

To check the completeness of the study pool:

- search in trial registries for studies on pembrolizumab (last search on 15 January 2024); for search strategies, see I Appendix A of the full dossier assessment

The check did not identify any additional relevant study.

I 3.1 Studies included

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

Table 5: Study pool – RCT, direct comparison: pembrolizumab + chemotherapy[a] vs. placebo + chemotherapy[a]

Study	Study category			Available sources		
	Study for the approval of the drug to be assessed (yes/no)	Sponsored study[b] (yes/no)	Third-party study (yes/no)	CSR (yes/no [citation])	Registry entries[c] (yes/no [citation])	Publication (yes/no [citation])
MK-3475-062 (KEYNOTE 062[d])	No	Yes	No	Yes [5]	Yes [6,7]	Yes [8,9]
MK-3475-590 (KEYNOTE 590[d])	Yes[e]	Yes	No	Yes [10]	Yes [11,12]	Yes [13,14]
MK-3475-895 (KEYNOTE 859[d])	Yes	Yes	No	Yes [15]	Yes [16,17]	Yes [18,19]

a. The following chemotherapies were used in the studies: cisplatin + 5-FU or cisplatin + capecitabine in KEYNOTE 062, cisplatin + 5-FU in KEYNOTE 590, and cisplatin + 5-FU or oxaliplatin + capecitabine in KEYNOTE 859.
b. Study for which the company was sponsor.
c. Citation of the trial registry entries and, if available, of the reports on study design and/or results listed in the trial registries.
d. In the following tables, the study is referred to by this acronym.
e. No approval study for the therapeutic indication relevant in the present assessment.

5-FU: 5-fluorouracil; CSR: clinical study report; RCT: randomized controlled trial

The studies KEYNOTE 062, KEYNOTE 590 and KEYNOTE 859 were included in the present benefit assessment. The study pool is consistent with that selected by the company. The subpopulations of the 3 studies relevant for the assessment and the subpopulations used as approximation, if applicable, are described in Section I 3.2.3 (see Table 8).

I 3.2 Study characteristics

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

Table 6: Characteristics of the included studies – RCT, direct comparison: pembrolizumab + chemotherapy[a] vs. placebo + chemotherapy[a] (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[b]
KEYNOTE 062	RCT, partially blinded[c], parallel	Adult patients[d] with locally advanced unresectable or metastatic gastric or GEJ adenocarcinoma whose tumours express PD-L1 (CPS ≥ 1) in the first-line treatment with negative HER2 status	Pembrolizumab (N = 256)[e] Pembrolizumab + chemotherapy (cisplatin + 5-FU/capecitabine)[f] (N = 257) Placebo + chemotherapy (cisplatin + 5-FU/capecitabine)[f] (N = 250) Relevant subpopulation[g]: pembrolizumab + chemotherapy (cisplatin + 5-FU (only for GEJ adenocarcinoma)/ capecitabine) (n: unknown)[f] placebo + chemotherapy (cisplatin + 5-FU (only for GEJ adenocarcinoma)/ capecitabine) (n: unknown)[f]	Screening: ≤ 21 days Treatment: until disease progression, unacceptable toxicity, physician's decision, withdrawal of consent, complete response, or a maximum of 35 cycles[h] Observation[i]: outcome-specific, at the longest until death, withdrawal of consent, or study end	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 10/2015–6/2022 Data cut-offs: 26 March 2018[j] 26 September 2018[j] 26 March 2019[k] 19 April 2021[l] 6 June 2022 (study end)	Primary: overall survival, progression-free survival Secondary: morbidity, health-related quality of life, AEs

Table 6: Characteristics of the included studies – RCT, direct comparison: pembrolizumab + chemotherapy[a] vs. placebo + chemotherapy[a] (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[b]
KEYNOTE 590	RCT, double-blind, parallel	Adult patients[d] with locally advanced unresectable or metastatic adenocarcinoma or squamous cell carcinoma of the oesophagus, or with advanced or metastatic HER2-negative GEJ adenocarcinoma (Siewert type I) in the first-line treatment	Pembrolizumab + chemotherapy (cisplatin + 5-FU) (N = 373) Placebo + chemotherapy (cisplatin + 5-FU) (N = 376) Relevant subpopulation[m] pembrolizumab + chemotherapy (cisplatin + 5-FU) (n = 37) placebo + chemotherapy (cisplatin + 5-FU) (n = 43)	Screening: ≤ 28 days Treatment: until disease progression, unacceptable toxicity, physician's decision or withdrawal of consent, complete response, or a maximum of 35 cycles Observation[i]: outcome-specific, at the longest until death, withdrawal of consent, or study end	168 centres in: Argentina, Australia, Brazil, Canada, Chile, China, Columbia, 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 7/2017–7/2023 Data cut-offs: 2 July 2020[n] 9 July 2021[l, o] 10 July 2023 (study end)	Primary: overall survival, progression-free survival Secondary: morbidity, health-related quality of life, AEs

Table 6: Characteristics of the included studies – RCT, direct comparison: pembrolizumab + chemotherapy[a] vs. placebo + chemotherapy[a] (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[b]
KEYNOTE 859	RCT, double-blind, parallel	Adult patients[d] with locally advanced unresectable or metastatic gastric or GEJ adenocarcinoma in the first-line treatment with negative HER2 status	Pembrolizumab + chemotherapy (cisplatin + 5-FU or oxaliplatin + capecitabine)[f] (N = 790) Placebo + chemotherapy (cisplatin + 5-FU or oxaliplatin + capecitabine)[f] (N = 789) Relevant subpopulation[g]: pembrolizumab + chemotherapy (cisplatin + 5-FU (only for GEJ adenocarcinoma) or oxaliplatin + capecitabine)[f] (n: unknown) placebo + chemotherapy (cisplatin + 5-FU (only for GEJ adenocarcinoma) or oxaliplatin + capecitabine)[f] (n: unknown)	Screening: ≤ 28 days Treatment: until disease progression, unacceptable toxicity, physician's decision or withdrawal of consent, complete response, or a maximum of 35 cycles[h] Observation[i]: outcome-specific, at the longest until death, withdrawal of consent, or study end	215 centres in: Argentina, Australia, Brazil, Canada, Chile, China, Columbia, Costa Rica, Czech Republic, Denmark, France, Germany, Guatemala, Hong Kong, Hungary, Ireland, Israel, Italy, Japan, Mexico, New Zealand, Peru, Poland, Russia, South Africa, South Korea, Spain, Switzerland, Taiwan, Turkey, Ukraine, United Kingdom, United States 11/2018–ongoing Data cut-offs: 3 October 2022[p] 22 August 2023[l]	Primary: overall survival Secondary: morbidity, health-related quality of life, AEs

Table 6: Characteristics of the included studies – RCT, direct comparison: pembrolizumab + chemotherapy[a] vs. placebo + chemotherapy[a] (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[b]
a. The following chemotherapies were used in the studies: cisplatin + 5-FU or cisplatin + capecitabine in KEYNOTE 062, cisplatin + 5-FU in KEYNOTE 590, and cisplatin + 5-FU or oxaliplatin + capecitabine in KEYNOTE 859. b. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes include only information on relevant available outcomes for this benefit assessment. c. The study arm with a pembrolizumab monotherapy was unblinded. d. With ECOG PS 0 or 1. e. The arm is not relevant for the benefit assessment and is not shown in the following tables. f. The investigator's decision on the type of chemotherapy used was to be made prior to randomization in the study. g. Patients whose tumours express PD-L1 (CPS ≥ 1). For the KEYNOTE 062 study, the information provided by the company in Module 4 A can be interpreted as meaning that, contrary to the inclusion criteria, 2 patients with PD-L1-negative tumours (CPS < 1) were included in the study; according to the CSR, 1 patient was included. h. Patients with stable disease or a complete or partial response after 35 cycles (24 months) of treatment were allowed to resume treatment for up to 17 cycles if disease progression was confirmed (Second Course Phase). i. Outcome-specific information is provided in Table 9. j. Interim analysis. k. Final analysis, planned after an observation period of at least 22 months after randomization of the last patient and 415 OS events in the study arms with pembrolizumab + chemotherapy (cisplatin + 5-FU/capecitabine) and placebo + chemotherapy (cisplatin + 5-FU/capecitabine). l. Non-prespecified data cut-off (long-term follow-up). m. Patients with GEJ adenocarcinoma whose tumours express PD-L1 (CPS ≥ 1). n. Final analysis, 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. o. This non-prespecified analysis was carried out post-hoc for a presentation at a scientific congress. No CSR is available. Results on OS and side effects were analysed. p. Final analysis, originally planned as interim analysis after 403 OS events in the population with CPS ≥ 10 and 12 months after randomization of the last patient. 5-FU: 5-fluorouracil; AE: adverse event; CPS: combined positive score; CSR: clinical study report; ECOG PS: Eastern Cooperative Oncology Group Performance Status; GEJ: gastro-oesophageal junction; HER2: human epidermal growth factor receptor 2; n: number of patients in the 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 + chemotherapy[a] vs. placebo + chemotherapy[a] (multipage table)

Study	Intervention	Comparison
KEYNOTE 062	Pembrolizumab 200 mg IV (as 30-minute infusion) on the first day of a 3-week cycle (max 35 cycles)[b] + cisplatin 80 mg/m² BSA IV on the first day of each 3-week cycle (max 35 cycles)[c] + 5-FU 800 mg/m² BSA/day IV, continuous administration on Days 1–5 of a 3-week cycle (a total of 4000 mg/m² BSA per cycle; max 35 cycles)[d] or capecitabine 1000 mg/m² BSA twice daily, orally, on Days 1–14 of a 3-week cycle (max 35 cycles)[d]	Placebo on the first day of a 3-week cycle (max 35 cycles) + cisplatin 80 mg/m² BSA IV on the first day of each 3-week cycle (max 35 cycles)[c] + 5-FU 800 mg/m² BSA/day IV, continuous administration on Days 1–5 of a 3-week cycle (a total of 4000 mg/m² BSA per cycle; max 35 cycles)[d] or capecitabine 1000 mg/m² BSA twice daily, orally, on Days 1–14 of a 3-week cycle (max 35 cycles)[d]
	Dose adjustments: ▪ Pembrolizumab/placebo: no dose reduction allowed; treatment interruption or discontinuation in case of toxicity ▪ Chemotherapy (cisplatin/5-FU/capecitabine): stepwise 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[e]	
	Disallowed pretreatment ▪ treatment of the locally advanced unresectable or metastatic carcinoma[f] ▪ systemic treatment of an active autoimmune disease with disease-modifying agents, corticosteroids or immunosuppressants in the last 2 years ▪ chronic systemic steroid therapy (≥ 10 mg prednisone equivalent/day) or any other form of immunosuppressive therapy within 7 days prior the first dose of study treatment ▪ ongoing systemic treatment of an active infection ▪ anti-PD-1, anti-PD-L1, or anti-PD-L2 drugs ▪ radiotherapy within 14 days of randomization **Concomitant treatment** <u>Disallowed</u> ▪ other antineoplastic systemic chemotherapy or biological therapy ▪ other immunotherapy ▪ radiotherapy[g] ▪ systemic glucocorticoids[h] ▪ in case of therapy with 5-FU/capecitabine: brivudine, sorivudine analogues, and other inhibitors of the enzyme DPD ▪ in case of therapy with cisplatin: phenytoin <u>Allowed</u> ▪ 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 7: Characteristics of the intervention – RCT, direct comparison: pembrolizumab + chemotherapy[a] vs. placebo + chemotherapy[a] (multipage table)

Study	Intervention	Comparison
KEYNOTE 590	Pembrolizumab 200 mg IV (as 30-minute infusion) on the first day of a 3-week cycle (max 35 cycles) + cisplatin 80 mg/m² BSA IV on the first day of each 3-week cycle (max 6 cycles) + 5-FU 800 mg/m² BSA/day IV, continuous administration on Days 1–5 of a 3-week cycle (max 35 cycles) or according to local standards (a total of 4000 mg/m² BSA per cycle)	Placebo on the first day of a 3-week cycle (max 35 cycles) + cisplatin 80 mg/m² BSA IV on the first day of each 3-week cycle (max 6 cycles) + 5-FU 800 mg/m² BSA/day, continuous administration from Day 1 to 5 of a 3-week cycle (max 35 cycles) or according to local standards (a total of 4000 mg/m² BSA per cycle)
	Dose adjustments: ▪ Pembrolizumab/placebo: no dose reduction allowed; treatment interruption or discontinuation in case of toxicity ▪ Chemotherapy (cisplatin/5-FU): stepwise 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	
	Disallowed pretreatment ▪ treatment of the locally advanced unresectable or metastatic carcinoma[i] ▪ systemic treatment of an active autoimmune disease with disease-modifying agents, corticosteroids or immunosuppressants in the last 2 years ▪ chronic systemic steroid therapy (≥ 10 mg prednisone equivalent/day) or any other form of immunosuppressive therapy within 7 days prior the first dose of study treatment ▪ ongoing systemic treatment of an active infection ▪ anti-PD-1, anti-PD-L1, or anti-PD-L2 agents, or agent directed to another co-inhibitory T-cell receptor ▪ radiotherapy within 14 days of randomization **Concomitant treatment** <u>Disallowed</u> ▪ other antineoplastic systemic chemotherapy or biological therapy ▪ other chemotherapies or immunotherapies ▪ radiotherapy[g] ▪ systemic glucocorticoids[h] ▪ in case of therapy with 5-FU/capecitabine: brivudine, sorivudine analogues, and other inhibitors of the enzyme DPD ▪ in case of therapy with cisplatin: phenytoin <u>Allowed</u> ▪ supportive treatment for 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 + chemotherapy[a] vs. placebo + chemotherapy[a] (multipage table)

Study	Intervention	Comparison
KEYNOTE 859	Pembrolizumab 200 mg IV (as 30-minute infusion) on the first day of a 3-week cycle (max 35 cycles)[b]	Placebo on the first day of a 3-week cycle (max 35 cycles)
	+	+
	cisplatin 80 mg/m² BSA IV on the first day of each 3-week cycle (max 35 cycles)[c]	cisplatin 80 mg/m² BSA IV on the first day of each 3-week cycle (max 35 cycles)[c]
	+	+
	5-FU 800 mg/m² BSA/day IV, continuous administration on Days 1–5 of a 3-week cycle (max 35 cycles) or according to local standards (a total of 4000 mg/m² BSA per cycle)	5-FU 800 mg/m² BSA/day IV, continuous administration from day 1 to 5 of a 3-week cycle (max 35 cycles) or according to local standards (a total of 4000 mg/m² BSA per cycle)
	or	or
	+	+
	oxaliplatin 130 mg/m² BSA IV on the first day of each 3-week cycle (max 35 cycles)[c]	oxaliplatin 130 mg/m² BSA IV on the first day of each 3-week cycle (max 35 cycles)[c]
	+	+
	capecitabine 1000 mg/m² BSA twice daily, orally, on Days 1–14 of a 3-week cycle (max 35 cycles)	capecitabine 1000 mg/m² BSA twice daily, orally, on Days 1–14 of a 3-week cycle (max 35 cycles)
	Dose adjustments: ▪ Pembrolizumab/placebo: no dose reduction allowed; treatment interruption or discontinuation in case of toxicity ▪ Chemotherapy (cisplatin/5-FU/oxaliplatin + capecitabine): stepwise dose reduction in case of toxicity; reduced dose could not be increased again; at most 3 adjustments allowed for oxaliplatin and at most 2 adjustments allowed for 5-5U, cisplatin and capecitabine, treatment discontinuation in case of further toxicity[j]	

Table 7: Characteristics of the intervention – RCT, direct comparison: pembrolizumab + chemotherapy[a] vs. placebo + chemotherapy[a] (multipage table)

Study	Intervention	Comparison
	Disallowed pretreatment ▪ treatment of the locally advanced unresectable or metastatic carcinoma[f] ▪ systemic treatment of an active autoimmune disease with disease-modifying agents, corticosteroids or immunosuppressants in the last 2 years ▪ chronic systemic steroid therapy (≥ 10 mg prednisone equivalent/day) or any other form of immunosuppressive therapy within 7 days prior the first dose of study treatment ▪ ongoing systemic treatment of an active infection ▪ anti-PD-1, anti-PD-L1, or anti-PD-L2 agents or agent directed to another co-inhibitory T-cell receptor ▪ antineoplastic systemic therapy within 4 weeks of randomization ▪ radiotherapy within 14 days before the first dose of study treatment[k] **Concomitant treatment** <u>Disallowed</u> ▪ other antineoplastic systemic chemotherapy or biological therapy ▪ other chemotherapy or immunotherapy ▪ radiotherapy[g] ▪ systemic glucocorticoids[l] ▪ in case of therapy with 5-FU/capecitabine: brivudine, sorivudine analogues, and other inhibitors of the enzyme DPD ▪ in case of therapy with cisplatin: phenytoin <u>Allowed</u> ▪ supportive treatment for chemotherapy ▪ systemic (≤ 10 mg prednisone equivalent/day), inhaled or topical corticosteroids[m] for the treatment of side effects	

Table 7: Characteristics of the intervention – RCT, direct comparison: pembrolizumab + chemotherapy[a] vs. placebo + chemotherapy[a] (multipage table)

Study	Intervention	Comparison
a. The following chemotherapies were used in the studies: cisplatin + 5-FU or cisplatin + capecitabine in KEYNOTE 062, cisplatin + 5-FU in KEYNOTE 590, and cisplatin + 5-FU or oxaliplatin + capecitabine in KEYNOTE 859. b. 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 radiographic disease progression (Second Course Phase). c. Treatment could be limited to 6 cycles according to local standards. d. Although use of 5-FU was preferred according to the study protocol, capecitabine could be administered according to local guidelines. The decision regarding the type of fluoropyrimidine used (5-FU or capecitabine) was made by the physician and was to be taken before randomization. e. If chemotherapy was discontinued in the intervention arm, treatment with pembrolizumab could be continued; if chemotherapy was discontinued in the comparator arm, the study treatment had to be terminated completely. f. Prior neoadjuvant/adjuvant treatment was allowed if it had been completed > 6 months before randomization. g. Radiotherapy for symptomatic treatment of solitary lesions or to the brain were allowed following consultation with the sponsor. h. Except for modulating symptoms from an AE that is suspected to have an immunologic aetiology or for cisplatin supportive care. i. Prior treatment with curative intent, including neoadjuvant/adjuvant treatment, given as chemotherapy or chemoradiotherapy, using standard of care agents or definitive chemoradiation, counted as prior treatment of advanced or metastatic disease if disease progression occurred during treatment or within 6 months of cessation of treatment. j. If chemotherapy was discontinued, treatment with pembrolizumab/placebo could be continued. k. In palliative radiotherapy (≤ 2 weeks) to the CNS, a 1-week wash-out phase was allowed. l. Except for modulating symptoms from an AE that is suspected to have an immunologic aetiology and for anti-emetic prophylaxis following NCCN or institutional guidelines. m. Higher doses were only permitted after authorization by the sponsor. 5-FU: 5-fluorouracil; AE: adverse event; BSA: body surface area; CNS: central nervous system; DPD: dihydropyrimidine dehydrogenase; IV: intravenous; max: maximum; NCCN: National Comprehensive Cancer Network; PD-1: programmed cell death 1; PD-L1: programmed cell death ligand 1; PD-L2: programmed cell death ligand 2; RCT: randomized controlled trial		

I 3.2.1 Study design

KEYNOTE 062 study

The KEYNOTE 062 study is a completed, partially blinded, multicentre RCT comparing pembrolizumab as monotherapy versus pembrolizumab in combination with cisplatin + capecitabine or cisplatin + 5-FU and versus placebo in combination with cisplatin + capecitabine or cisplatin + 5-FU (the fluoropyrimidine and platinum-containing combination therapy is referred to below as “chemotherapy”). The study arm with pembrolizumab as monotherapy was unblinded, but is irrelevant for the present benefit assessment. The 2 study arms relevant for the benefit assessment were double-blind.

Adult patients with locally advanced unresectable or metastatic gastric or GEJ adenocarcinoma with negative HER2 status (determined according to local standards) were enrolled in the study. Patients were not allowed to have received prior treatment at this stage of the disease, but could have received prior (neo)adjuvant treatment 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). Patients had to have a good general condition corresponding to an ECOG PS of 0 or 1. Patients with active central nervous system metastases were excluded from study participation.

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 geographic region (Europe/Israel/North America/Australia versus Asia versus rest of the world, disease status (locally advanced unresectable versus metastatic), and chemotherapy (5-FU versus capecitabine).

Section I 3.2.2 below describes the treatments used in the KEYNOTE 062 study together for the 3 included studies.

Primary outcomes of the KEYNOTE 062 study were overall survival and progression-free survival. Other patient-relevant outcomes recorded in the study were health status and outcomes on symptoms, health-related quality of life and side effects.

Data cut-offs

Five data cut-offs were implemented for the KEYNOTE 062 study:

- First data cut-off dated 26 March 2018: prespecified interim analysis, planned after 317 events in the primary outcome of overall survival in patients of the 2 treatment arms relevant for the benefit assessment and at least 10 months after randomization of the last patient
- Second data cut-off dated 26 September 2018: prespecified interim analysis, planned after 369 events in the primary outcome of overall survival in patients of the 2 treatment arms relevant for the benefit assessment and at least 16 months after randomization of the last patient
- Third data cut-off dated 26 March 2019: prespecified final analysis after 415 events in the primary outcome of overall survival in patients of the 2 treatment arms relevant for the benefit assessment and at least 22 months after randomization of the last patient

- Fourth data cut-off dated 19 April 2021: non-prespecified long-term follow-up
- Fifth data cut-off dated 6 June 2022: data cut-off at the end of the study

For its assessment in Module 4 A, the company used the results of the non-prespecified fourth data cut-off dated 19 April 2021. The company justified this by stating that a gain in information can be assumed due to the longer observation period compared with the final third data cut-off on 26 March 2019. According to the module templates in the dossier, the results of the data cut-offs that were either predefined or requested by the regulatory authorities should be presented. For the present benefit assessment, the data of the prespecified third data cut-off from Module 5 of the dossier are used primarily.

KEYNOTE 590 study

The KEYNOTE 590 study is a completed, double-blind, multicentre RCT comparing pembrolizumab in combination with cisplatin + 5-FU versus placebo in combination with cisplatin + 5-FU (the fluoropyrimidine and platinum-containing combination therapy is referred to below as “chemotherapy”).

Adult patients with locally advanced unresectable or metastatic squamous cell carcinoma or adenocarcinoma of the oesophagus or adenocarcinoma of the GEJ (only Siewert type I) with negative HER2 status (determined according to local standards) were enrolled in the study. Patients were not allowed to have received any previous treatment in this disease stage. Previous treatment with curative intent counts as first-line therapy if disease progression occurred during therapy or 6 months after therapy.

The PD-L1 expression of the tumours of all included patients had to be known. Positive PD-L1 expression is defined in the study protocol as CPS ≥ 1, determined from a tissue sample by immunohistochemistry (no details of the test used). Patients had to have a good general condition corresponding to an ECOG PS of 0 or 1. Patients with active central nervous system metastases were excluded from study participation.

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

Section I 3.2.2 below describes the treatments used in the KEYNOTE 590 study together for the 3 included studies.

Primary outcomes of the KEYNOTE 590 study were overall survival and progression-free survival. Other patient-relevant outcomes recorded in the study were health status and outcomes on symptoms, health-related quality of life and side effects.

Data cut-offs

Three data cut-offs were implemented for the KEYNOTE 590 study:

- First data cut-off dated 2 July 2020: final data cut-off (initially prespecified as interim analysis), planned after 460 events in the primary outcome of progression-free survival and 391 events in the primary outcome of overall survival in the population of patients with squamous cell carcinoma of the oesophagus and at least 13 months after randomization of the last patient
- Second data cut-off dated 9 July 2021: non-prespecified long-term follow-up
- Third data cut-off dated 10 July 2023: data cut-off at the end of the study

For its assessment in Module 4 A, the company used the results of the non-prespecified second data cut-off dated 9 July 2021. The company justified this by stating that a gain in information can be assumed due to the longer observation period compared with the final first data cut-off dated 2 July 2020. According to the module templates in the dossier, the results of the data cut-offs that were either predefined or requested by the regulatory authorities should be presented. For the present benefit assessment, the data of the prespecified first data cut-off are to be used primarily. Corresponding data are not available for the relevant subpopulation (see Section I 3.2.3).

KEYNOTE 859 study

The KEYNOTE 859 study is a double-blind, multicentre RCT comparing pembrolizumab in combination with cisplatin + 5-FU or oxaliplatin + capecitabine versus placebo in combination with cisplatin + 5-FU or oxaliplatin + capecitabine (the fluoropyrimidine and platinum-containing combination therapy is referred to below as “chemotherapy”).

The study included adult patients with locally advanced unresectable or metastatic gastric or GEJ adenocarcinoma with negative HER2 status, defined as immunohistochemistry (0 or 1+) or fluorescence in situ hybridization (HER2:CEP17 ratio < 2 with an average HER2 copy number < 4 signals/cell), determined according to local standards (test used: Dako Hercep and Dako HER2 IQFISH pharmDx). Patients were not allowed to have received prior treatment at this stage of the disease, but could have received (neo)adjuvant treatment if this treatment had been completed at least 6 months before randomization.

The PD-L1 expression of the tumours of all included patients had to be known. Positive PD-L1 expression is defined in the study protocol as CPS ≥ 1, determined from a tissue sample by immunohistochemistry (test used: Agilent PD-L1 IHC 22C3 pharmDx). Patients had to have a good general condition corresponding to an ECOG PS of 0 or 1. Patients with active central nervous system metastases were excluded from study participation.

Patients were randomly assigned to either the intervention arm (pembrolizumab + chemotherapy; N = 790) or the comparator arm (placebo + chemotherapy; N = 789), stratified by region (Europe/Israel/North America/Australia versus Asia versus rest of the world), chemotherapy (cisplatin + 5-FU versus oxaliplatin + capecitabine) and PD-L1 expression status (CPS < 1 versus CPS ≥ 1).

Section I 3.2.2 below describes the treatments used in the KEYNOTE 859 study together for the 3 included studies.

Primary outcome of the KEYNOTE 859 study was overall survival. Other patient-relevant outcomes recorded in the study were health status and outcomes on symptoms, health-related quality of life and side effects.

Data cut-offs

Two data cut-offs were implemented for the KEYNOTE 859 study:

- First data cut-off dated 3 October 2022: final data cut-off (initially prespecified as interim analysis), planned after 403 events in the primary outcome of overall survival in the population of patients with CPS ≥ 10 and about 12 months after randomization of the last patient
- Second data cut-off dated 22 August 2023: non-prespecified long-term follow-up

For its assessment in Module 4 A, the company used the results of the non-prespecified second data cut-off dated 22 August 2023. The company justified this by stating that a gain in information can be assumed due to the longer observation period compared with the final first data cut-off dated 3 October 2022. According to the module templates in the dossier, the results of the data cut-offs that were either predefined or requested by the regulatory authorities should be presented. For the present benefit assessment, the data of the prespecified first data cut-off are used primarily.

I 3.2.2 Treatment in the studies KEYNOTE 062, KEYNOTE 590 and KEYNOTE 859

The studies KEYNOTE 062, KEYNOTE 590 and KEYNOTE 859 investigated the administration of pembrolizumab versus placebo, each in addition to a chemotherapy component.

In the KEYNOTE 062 study, chemotherapy consisted of cisplatin and either 5-FU or capecitabine, with preferable use of 5-FU. The decision regarding the type of fluoropyrimidine used (5-FU or capecitabine) was made by the physician and was to be taken before randomization. In the KEYNOTE 590 study, the chemotherapy component consisted exclusively of cisplatin + 5-FU. The patients in the KEYNOTE 859 study received cisplatin + 5-FU or oxaliplatin + capecitabine. There were no specifications regarding preferential administration of the fluoropyrimidine used (5-FU or capecitabine) in this study.

In all study arms of the 3 studies (KEYNOTE 062, KEYNOTE 590 and KEYNOTE 859), treatment was performed in 3-week cycles until a reason for discontinuation arose (disease progression, unacceptable toxicity, physician's decision, withdrawal of consent, or complete response) for a maximum of 35 cycles; the treatment components cisplatin and oxaliplatin could be limited (KEYNOTE 062 and KEYNOTE 859) or were limited (KEYNOTE 590) to 6 cycles. Detailed information on the administration of the individual components can be found in Table 7.

Patients in the studies KEYNOTE 062 study and the KEYNOTE 859 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 radiographic disease progression (Second Course Phase). This option was also available in both studies for patients who had discontinued treatment with pembrolizumab after at least 8 cycles when stable disease was achieved.

After discontinuation of either pembrolizumab or one or all drug components of the chemotherapy in the studies KEYNOTE 062, KEYNOTE 590 and KEYNOTE 859, treatment could be continued with the remaining drug component(s). In all 3 studies, there were no restrictions regarding subsequent therapies after the end of the study medication (an overview of the first subsequent oncological therapies can be found in Table 12 and Table 13). It was not planned that patients in the comparator arm switch to the intervention arm treatment.

In the studies KEYNOTE 062, KEYNOTE 590 and KEYNOTE 859, treatment with pembrolizumab and the drug combinations of the chemotherapy was largely carried out in compliance with the recommendations in the SPCs [20-24], but there are uncertainties regarding the treatment, which are described in the following section.

Uncertainties regarding the treatment

It should be noted that both oxaliplatin and capecitabine are approved for the treatment of gastric cancer, but not for the treatment of GEJ adenocarcinoma (or oesophageal carcinoma) [23,24]. This has no consequences for the present assessment.

Number of treatment cycles

In the study arms of the 3 studies, treatment with pembrolizumab or placebo and chemotherapy was limited to a maximum of 35 cycles (approx. 2 years). Treatment with cisplatin and oxaliplatin could be discontinued after 6 cycles (KEYNOTE 062 and KEYNOTE 859) or was limited to 6 cycles (KEYNOTE 590). According to the approval, however, pembrolizumab treatment is to be continued until cancer progression or the occurrence of unacceptable toxicity [20]. For treatment with cisplatin, oxaliplatin, 5-FU and capecitabine, there is no fixed upper limit on the number of treatment cycles according to approval [21-24].

For the studies KEYNOTE 062, KEYNOTE 590 und KEYNOTE 859, there is no information on how many patients of the relevant subpopulation of the study, or of the subpopulation used as approximation, received the planned maximum number of treatment cycles and received no further subsequent treatment although such treatment would have been possible in principle according to the approval.

For the KEYNOTE 590 study, it can be seen that, in relation to the total study population, only 32 (8.6%) patients in the intervention arm received the maximum specified number of 35 treatment cycles with pembrolizumab. 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 contrast, the number of patients who received 6 treatment cycles of cisplatin in the total population of the KEYNOTE 590 study was 206 (55.7%) in the intervention arm and 205 (55.4%) in the comparator arm. 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 [25]. 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

According to the specification of the G-BA, chemotherapy with cisplatin + 5-FU is an ACT exclusively for patients with oesophageal adenocarcinoma. For this patient population, the dosage of 5-FU in the 3 studies deviated from the specifications of the approval.

A total dose of 4000 mg/m² BSA/cycle was planned in all 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 (only study KEYNOTE 590). 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 should be noted that according to the approval, a cycle length of 3 to 4 weeks is possible, whereas a fixed cycle length of 3 weeks had been planned in the study [22].

The current national S3 guideline does not provide any recommendation regarding the 5-FU dosage [25,26]. In combination with cisplatin, the NCCN guideline recommends a 5-FU dose of 800 mg/m² BSA/day on Days 1 to 5 of a 3-week cycle, however [27].

Overall, the 5-FU dosage used in the studies KEYNOTE 062, KEYNOTE 590 and KEYNOTE 859 deviates from the approved dosage for oesophageal carcinoma. It is unclear to what extent this deviation affects the results of patient-relevant outcomes.

Summary of uncertainties

The uncertainties regarding treatment described above result in a reduced certainty of results in the studies KEYNOTE 062, KEYNOTE 590 and KEYNOTE 859.

I 3.2.3 Overview of the subpopulations of the studies

The 3 studies KEYNOTE 062, KEYNOTE 590 and KEYNOTE 859 were included in the present benefit assessment.

The total populations of the 3 studies and the subpopulations for the studies presented by the company in Module 4 A are not suitable for the present benefit assessment. This is explained below, stating the subpopulation relevant for the assessment and the subpopulation used as approximation.

Table 8 provides an overview of the different populations in the studies KEYNOTE 062, KEYNOTE 590 and KEYNOTE 859.

Table 8: Overview of the different populations in the studies KEYNOTE 062, KEYNOTE 590 and KEYNOTE 859 (multipage table)

Study	Subpopulation presented by the company in Module 4 A	Relevant subpopulation[a]	Subpopulation used as approximation
Adults with locally advanced unresectable or metastatic HER2-negative adenocarcinoma whose tumours express PD-L1 (CPS ≥ 1); pembrolizumab in first-line treatment			
KN062	▪ Location: stomach or GEJ ▪ Chemotherapy: cisplatin + 5-FU or cisplatin + capecitabine ▪ Proportion of patients with gastric cancer and administration of 5-FU[b]: up to 38% ▪ N (N_I vs. N_C): 505 (255 vs. 250) ▪ Company presented results for the following data cut-off: 4/2021 (not prespecified)	▪ Location: stomach or GEJ ▪ Chemotherapy: cisplatin + 5-FU **(only for GEJ)** or cisplatin + capecitabine ▪ Proportion of patients with gastric cancer and administration of 5-FU[b]: **0%** ▪ N unknown ▪ Relevant data cut-off: **latest prespecified data cut-off**[c]	▪ Location: stomach or GEJ ▪ Chemotherapy: –[d] cisplatin + capecitabine ▪ Proportion of patients with gastric cancer and administration of 5-FU[b]: **0%** ▪ N (N_I vs. N_C): 314 (159 vs. 155) ▪ Result on overall survival for the following data cut-off was used: 3/2019 (prespecified)
KN590	▪ Location: GEJ ▪ Chemotherapy: cisplatin + 5-FU ▪ N (N_I vs. N_C): 80 (37 vs. 43) ▪ Company presented results for the following data cut-off: 7/2021 (not prespecified)	▪ Location: GEJ ▪ Chemotherapy: cisplatin + 5-FU ▪ N (N_I vs. N_C): 80 (37 vs. 43) ▪ Relevant data cut-off: **latest prespecified data cut-off**[c]	▪ –[e]
KN859	▪ Location: stomach or GEJ ▪ Chemotherapy: cisplatin + 5-FU or oxaliplatin + capecitabine ▪ Proportion of patients with gastric cancer and administration of 5-FU[b]: up to 13% ▪ N (N_I vs. N_C): 1235 (618 vs. 617) ▪ Company presented results for the following data cut-off: 8/2023 (not prespecified)	▪ Location: stomach or GEJ ▪ Chemotherapy: cisplatin + 5-FU **(only for GEJ)** or oxaliplatin + capecitabine ▪ Proportion of patients with gastric cancer and administration of 5-FU[b]: **0%** ▪ N unknown ▪ Relevant data cut-off: **latest prespecified data cut-off**	▪ Location: stomach or GEJ ▪ Chemotherapy: cisplatin + 5-FU or oxaliplatin + capecitabine ▪ Proportion of patients with gastric cancer and administration of 5-FU[b]: up to 13% ▪ N (N_I vs. N_C): 1235 (618 vs. 617) ▪ Result on overall survival for the following data cut-off was used: 10/2022 (prespecified)

Table 8: Overview of the different populations in the studies KEYNOTE 062, KEYNOTE 590 and KEYNOTE 859 (multipage table)

Study	Subpopulation presented by the company in Module 4 A	Relevant subpopulation[a]	Subpopulation used as approximation
Adults with locally advanced unresectable or metastatic HER2-negative adenocarcinoma whose tumours express PD-L1 (CPS ≥ 1); pembrolizumab in first-line treatment			

a. The relevant subpopulation includes only patients with PD-L1-expressing tumours of the stomach or GEJ (CPS ≥ 1). Patients with gastric cancer who were treated with cisplatin + 5-FU are not included in the relevant subpopulation. The differences between the subpopulation presented by the company in Module 4 A and the relevant subpopulation are printed in **bold**.
b. The treatment of locally advanced unresectable or metastatic HER2-negative gastric adenocarcinoma with PD-L1-expressing tumours (CPS ≥ 1) using cisplatin + 5-FU does not correspond to the ACT.
c. It is questionable whether the data cut-off at study end was prespecified in the studies KN062 and KN590.
d. The assessment used the subpopulation of patients treated with chemotherapy consisting of cisplatin + capecitabine as an approximation. This subpopulation only includes patients who were treated in accordance with the ACT.
e. No results at the relevant data cut-off are available for the relevant subpopulation. The proportion of this subpopulation in all patients belonging to either this subpopulation or one of the 2 subpopulations of KN062 or KN859 used as approximation is < 5%; the lack of corresponding results for the assessment of added benefit is therefore negligible.

5-FU: 5-fluorouracil; CPS: combined positive score; GEJ: gastro-oesophageal junction; HER2: human epidermal growth factor receptor 2; KN062: KEYNOTE 062; KN590: KEYNOTE 590; KN859: KEYNOTE 859; N: number of patients; N_I: number of patients in the intervention group; N_C: number of patients in the comparator group; PD-L1: programmed cell death ligand 1

For the 3 studies, the company only considered the subpopulation of patients with GEJ or gastric adenocarcinoma with PD-L1 status CPS ≥ 1 (see Table 8). However, the subpopulations of the KEYNOTE 062 and KEYNOTE 859 studies include a potentially relevant proportion of patients with gastric cancer and administration of 5-FU, for whom the ACT was thus not implemented. In addition, for all 3 studies in Module 4 A, the company only presented the results for non-predefined data cut-offs (see Section I 3.2.1). The results presented by the company in Module 4 A were therefore not used for the present benefit assessment.

Subpopulations relevant for the benefit assessment or used as approximation

The following text describes the relevant subpopulation for each individual study and explains whether it was possible to use a subpopulation as an approximation for the present benefit assessment.

KEYNOTE 062 study

The subpopulation of the KEYNOTE 062 study relevant for the benefit assessment consists of adult patients with locally advanced unresectable or metastatic HER2-negative gastric or GEJ adenocarcinoma whose tumours express PD-L1 (CPS ≥ 1) and who were treated in accordance with the ACT. Primarily the latest data cut-off planned a priori or requested by the regulatory authorities must be taken into account.

The company considered a subpopulation (intervention arm: N = 255; comparator arm: N = 250) that is almost identical to the total population (disregarding the pembrolizumab monotherapy arm). Two patients are missing in the intervention arm for whom a violation of exclusion criteria was apparently subsequently identified (the company described this for only one patient). However, this subpopulation includes a potentially relevant proportion of patients who were not treated in compliance with the ACT. Assuming that, in the subpopulation presented by the company (N = 505), all patients treated with cisplatin + 5-FU (N = 191) had gastric cancer (N = 349), this results in a proportion of 38% (191/505 patients) whose treatment did not correspond to the ACT. The data are therefore not used for the present benefit assessment.

The extent to which interpretable conclusions can be drawn for the relevant subpopulation on the basis of the information available for the KEYNOTE 062 study was examined. The study documents contain results from subgroup analyses for the characteristic of chemotherapy (cisplatin + 5-FU versus cisplatin + capecitabine). The ACT was implemented in the study for the subgroup of patients who received the drug combination of cisplatin + capecitabine, as this option represents an ACT for both GEJ and gastric adenocarcinoma. This patient population (intervention arm: N = 159; comparator arm: N = 155) was therefore used as an approximation for the relevant subpopulation. The subgroup of patients who received cisplatin + 5-FU was not used for the present benefit assessment. This drug combination

represents an ACT exclusively for patients with GEJ adenocarcinoma. Information on the proportion of these patients in the subgroup cannot be inferred from the available documents. It should be noted that, due to the restriction to a subgroup, data from patients (with GEJ adenocarcinoma and treatment with cisplatin + 5-FU) are not considered for the subpopulation used as approximation, although these are relevant for the present benefit assessment. For this reason, the certainty of results from the KEYNOTE 062 study is reduced. In deviation from the company's procedure, the data on the prespecified data cut-off from 26 March 2019 were used for the benefit assessment.

KEYNOTE 590 study

The subpopulation relevant for the benefit assessment consists of patients with locally advanced unresectable or metastatic HER2-negative GEJ adenocarcinoma whose tumours express PD-L1 (CPS ≥ 1) at the latest predefined data cut-off (or at a data cut-off requested by the regulatory authorities).

The subpopulation presented by the company corresponds to the relevant subpopulation (intervention arm: N = 37; comparator arm: N = 43). The company only presented data on a non-prespecified data cut-off for this subpopulation, however. The data presented by the company were therefore not used for the present benefit assessment. The proportion of this subpopulation in all patients belonging to either this subpopulation or one of the 2 subpopulations of KEYNOTE 062 or KEYNOTE 859 used as approximation is < 5%; the lack of corresponding results for the assessment of added benefit is therefore negligible.

KEYNOTE 859 study

The subpopulation relevant for the benefit assessment consists of adult patients with locally advanced unresectable or metastatic HER2-negative gastric or GEJ adenocarcinoma whose tumours express PD-L1 (CPS ≥ 1) and who were treated in accordance with the ACT. Primarily the latest data cut-off planned a priori or requested by the regulatory authorities must be taken into account.

The subpopulation presented by the company comprises patients whose tumours express PD-L1 (CPS ≥ 1; intervention arm: N = 618; comparator arm: N = 617). Assuming that the subpopulation presented by the company includes all patients from the total population who had gastric cancer and were treated with a combination of cisplatin + 5-FU, this results in a proportion of up to 13% of patients whose treatment did not correspond to the ACT. Here, the company presented data on a non-prespecified data cut-off.

The benefit assessment used the subpopulation presented by the company as an approximation, as the inclusion of up to 13% of patients with inappropriate implementation of the ACT is not assumed to have a relevant influence on the results. In departure from the

company's approach, the results for the prespecified data cut-off (3 October 2022), which were available in the study documents, were used for this subpopulation.

Summary of the subpopulations used as approximation

The results of the studies KEYNOTE 062 and KEYNOTE 859 at a prespecified data cut-off are presented in the present benefit assessment. For the KEYNOTE 062 study, the subgroup of patients treated with cisplatin + capecitabine is considered for this. For the KEYNOTE 859 study, the subpopulation presented by the company in Module 4 A is used. The KEYNOTE 590 study is not presented further.

I 3.2.4 Planned duration of follow-up observation

Table 9 shows the planned duration of patient follow-up observation for the individual outcomes.

Table 9: Planned duration of follow-up observation – RCT, direct comparison: pembrolizumab + chemotherapy[a] vs. placebo + chemotherapy[a], subpopulation with HER2-negative gastric or GEJ adenocarcinoma with PD-L1-expressing tumours (CPS ≥ 1)

Study **Outcome category** **Outcome**	**Planned follow-up observation**
KEYNOTE 062	
Mortality	
Overall survival	Until death, withdrawal of consent or end of study
Morbidity	
Symptoms, health status (EORTC QLQ-C30, EORTC QLQ-STO22, EQ-5D VAS)	Up to 1 year or up to 30 days after treatment discontinuation or end of treatment
Health-related quality of life (EORTC QLQ-C30)	Up to 1 year or up to 30 days after treatment discontinuation or end of treatment
Side effects	
AEs, severe AEs	Up to 30 days after treatment discontinuation or end of treatment
SAEs	Up to 90 days after treatment discontinuation or end of treatment or up to 30 days after treatment discontinuation or end of treatment when starting a new antineoplastic therapy
KEYNOTE 859	
Mortality	
Overall survival	Until death, withdrawal of consent or end of study
Morbidity	
Symptoms, health status (EORTC QLQ-C30, EORTC QLQ-STO22, EQ-5D VAS)	Up to 30 days after treatment discontinuation or end of treatment
Health-related quality of life (EORTC QLQ-C30)	Up to 30 days after treatment discontinuation or end of treatment
Side effects	
AEs, severe AEs	Up to 30 days after treatment discontinuation or end of treatment
SAEs	Up to 90 days after treatment discontinuation or end of treatment or up to 30 days after treatment discontinuation or end of treatment when starting a new antineoplastic therapy

a. The following chemotherapies were used in the studies: cisplatin + 5-FU or cisplatin + capecitabine in KEYNOTE 062, and cisplatin + 5-FU or oxaliplatin + capecitabine in KEYNOTE 859.

5-FU: 5-fluorouracil; AE: adverse event; CPS: combined positive score; EORTC: European Organisation for Research and Treatment of Cancer; HER2: human epidermal growth factor receptor 2; PD-L1: programmed cell death ligand 1; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-STO22: Quality of Life Questionnaire-Gastric Cancer 22 items; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale

The observation periods for outcomes in the categories of morbidity, health-related quality of life, and side effects are systematically shortened in both studies because these outcomes were surveyed only for the period of treatment with the study drug (plus 30 days or 90 days). Drawing a reliable conclusion on the total study period or the time to patient death, however, would require surveying these outcomes for the total period, as was done for survival.

I 3.2.5 Patient characteristics

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

Table 10: Characteristics of the study populations and study/treatment discontinuation – RCT, direct comparison: pembrolizumab + chemotherapy[a] vs. placebo + chemotherapy[a], subpopulation with HER2-negative gastric or GEJ adenocarcinoma with PD-L1-expressing tumours (CPS ≥ 1) (multipage table)

Study	KEYNOTE 062[b, c]		KEYNOTE 859[b]	
Characteristic Category	Pembrolizumab + chemotherapy[a]	Placebo + chemotherapy[a]	Pembrolizumab + chemotherapy[a]	Placebo + chemotherapy[a]
	N = 159	N = 155	N = 618	N = 617
Age [years], mean (SD)	ND	ND	60 (12)	61 (12)
Sex [F/M], %	ND	ND	32/68	27/73
Geographical region, n (%)				
Western Europe/Israel/North America/Australia	ND	ND	166 (27)	166 (27)
Asia	ND	ND	201 (33)	200 (32)
Rest of the world (incl. South America)	ND	ND	251 (41)	251 (41)
Chemotherapy, n (%)				
Capecitabine + cisplatin	ND	ND	–	–
Capecitabine + oxaliplatin	–	–	528 (85)	528 (86)
5-FU + cisplatin	ND	ND	90 (15)	89 (14)
PD-L1 status (CPS threshold: 10), n (%)				
CPS ≥ 10	ND	ND	280 (45)	273 (44)
CPS < 10	ND	ND	336 (54)	344 (56)
Missing/not evaluable	ND	ND	2 (< 1)	0 (0)
ECOG PS, n (%)				
0	ND	ND	223 (36)	228 (37)
1	ND	ND	395 (64)	389 (63)
Missing	ND	ND	–	–

Table 10: Characteristics of the study populations and study/treatment discontinuation – RCT, direct comparison: pembrolizumab + chemotherapy[a] vs. placebo + chemotherapy[a], subpopulation with HER2-negative gastric or GEJ adenocarcinoma with PD-L1-expressing tumours (CPS ≥ 1) (multipage table)

Study Characteristic Category	KEYNOTE 062[b, c]		KEYNOTE 859[b]	
	Pembrolizumab + chemotherapy[a]	Placebo + chemotherapy[a]	Pembrolizumab + chemotherapy[a]	Placebo + chemotherapy[a]
	N = 159	N = 155	N = 618	N = 617
Primary location, n (%)				
Stomach	ND	ND	494 (80)	453 (73)
Gastro-oesophageal junction	ND	ND	123 (20)	164 (27)
Missing	ND	ND	1 (< 1)	0 (0)
Disease status, n (%)				
Locally advanced	ND	ND	26 (4)	24 (4)
Metastatic	ND	ND	591 (96)	593 (96)
Missing	ND	ND	1 (< 1)	0 (0)
Prior gastrectomy/ oesophagectomy, n (%)				
Yes	ND	ND	109 (18)	105 (17)
No	ND	ND	506 (82)	508 (82)
Missing	ND	ND	3 (< 1)	4 (< 1)
Treatment discontinuation, n (%) (data cut-off: KEYNOTE 859 3 Oct 2022)	ND	ND	529 (86[d])[e]	586 (95[d])[e]
Study discontinuation, n (%) (data cut-off: KEYNOTE 859 3 Oct 2022)	ND	ND	469 (76)[f]	534 (87)[f]

a. The following chemotherapies were used in the studies: cisplatin + 5-FU or cisplatin + capecitabine in KEYNOTE 062, and cisplatin + 5-FU or oxaliplatin + capecitabine in KEYNOTE 859.
b. Patients in the subpopulation used as an approximation, see Table 8.
c. No data are available for the subpopulation used as an approximation in the present benefit assessment.
d. Institute's calculation.
e. Common reasons for treatment discontinuation in the intervention arm vs. comparator arm were the following (percentages based on randomized patients in the presented subpopulation): disease progression (63% vs. 73%), AEs (14% vs. 12%), withdrawal of consent (5% vs. 6%). In addition, 52 (8%) vs. 13 (2%) completed treatment, and 3 (< 1%) vs. 1 (< 1%) never started treatment.
f. The most common reason for study discontinuation in the intervention arm vs. comparator arm was the following (percentages based on randomized patients in the presented subpopulation): death (74% vs. 84%).

5-FU: 5-fluorouracil; AE: adverse event; CPS: combined positive score; ECOG PS: Eastern Cooperative Oncology Group Performance Status; F: female; HER2: human epidermal growth factor receptor 2; M: male; n: number of patients in category; N: number of randomized patients in the presented subpopulation; PD-L1: programmed cell death ligand 1; RCT: randomized controlled trial; SD: standard deviation

No information on study characteristics is available for the subpopulation of the KEYNOTE 062 study used as an approximation.

The patient characteristics of the KEYNOTE-859 study's subpopulation used as an approximation are largely balanced between the 2 treatment arms. More patients with gastric cancer were included in the intervention arm (80%) than in the comparator arm (73%). The mean age of the patients was 60 years, and the majority was male (70%). More than 3 quarters of patients (86%) received chemotherapy with oxaliplatin + capecitabine. Almost all patients had metastatic disease (96%). The most common reasons for treatment discontinuation in both treatment arms were disease progression, followed by AEs.

A statement on the comparability of the study characteristics between the KEYNOTE 062 and KEYNOTE 859 subpopulations used as an approximation is not possible. This does not call into question the feasibility of a quantitative or qualitative summary. For the benefit assessment, a fixed-effect model is used to calculate meta-analyses.

I 3.2.6 Information on the course of the study

Table 11 shows patients' median treatment duration and the median observation period for individual outcomes.

Table 11: Information on the course of the study – RCT, direct comparison: pembrolizumab + chemotherapy[a] vs. placebo + chemotherapy[a]; subpopulation with HER-negative gastric or GEJ adenocarcinoma with PD-L1 expressing tumours (CPS ≥ 1) (multipage table)

Study **Duration of the study phase** **Outcome category/outcome**	**Pembrolizumab + chemotherapy[a]**	**Placebo + chemotherapy[a]**
KEYNOTE 062[b, c], data cut-off: 26 Mar 2019	N = 159	N = 155
Treatment duration [months]	ND[d]	ND[d]
Observation period [months]		
Overall survival[e]	ND[f]	ND[f]
Morbidity	ND	ND
Health-related quality of life	ND	ND
AEs	ND	ND
SAEs	ND	ND
KEYNOTE 859[b], data cut-off: 3 Oct 2022	N = 618	N = 617
Treatment duration [months]		
Median [min; max]	ND[g]	ND[g]
Mean (SD)	ND[g]	ND[g]
Observation period [months]		
Overall survival[e]		
Median [min; max]	13.0 [0.2; 45.9]	11.5 [0.1; 45.5]
Mean (SD)	15.7 (11.0)	13.3 (9.5)
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]	ND	ND
Mean (SD)	ND	ND
SAEs		
Median [min; max]	ND	ND
Mean (SD)	ND	ND

Table 11: Information on the course of the study – RCT, direct comparison: pembrolizumab + chemotherapy[a] vs. placebo + chemotherapy[a]; subpopulation with HER-negative gastric or GEJ adenocarcinoma with PD-L1 expressing tumours (CPS ≥ 1) (multipage table)

Study	**Pembrolizumab + chemotherapy[a]**	**Placebo + chemotherapy[a]**
Duration of the study phase		
Outcome category/outcome		

a. The following chemotherapies were used in the studies: cisplatin + 5-FU or cisplatin + capecitabine in KEYNOTE 062, and cisplatin + 5-FU or oxaliplatin + capecitabine in KEYNOTE 859.
b. Patients in the subpopulation used as an approximation, see Table 8.
c. No data are available for the subpopulation used as an approximation in the present benefit assessment.
d. For the total population (excluding the pembrolizumab monotherapy arm), in which all patients in the study are analysed according to the treatment they actually received ("as treated"; 250 vs. 244 patients), the median treatment duration [min; max] provided is 5.9 [0; 28.1] months in the intervention arm and 4.7 [0; 28.5] months in the comparator arm. The mean treatment duration (SD) provided is 8.0 (7.14) months in the intervention arm and 6.0 (5.5) months in the comparator arm.
e. The individual observation period is defined as the time to death or, in the case of all patients who are still alive, until the data cut-off.
f. For the total population (excluding the pembrolizumab monotherapy arm; 257 vs. 250 patients), the median observation period [min; max] provided is 12.5 [0.3; 41.0] months in the intervention arm and 11.1 [0.2; 41.2] months in the comparator arm. The mean observation period (SD) provided is 14.4 (9.9) months in the intervention arm and 13.3 (9.0) months in the comparator arm.
g. For the total population, in which all patients in the study are analysed according to the treatment they actually received ("as treated"; 785 vs. 787 patients), the median treatment duration [min; max] provided is 6.7 [0; 33.7] months in the intervention arm and 5.6 [0; 29.7] months in the comparator arm. The mean treatment duration (SD) provided is 9.1 (7.5) months in the intervention arm and 7.2 (6.0) months in the comparator arm.

5-FU: 5-fluorouracil; AE: adverse event; CPS: combined positive score; HER2: human epidermal growth factor receptor 2; max: maximum; min: minimum; N: number of analysed patients; ND: no data; PD-L1:programmed cell death ligand 1; RCT: randomized controlled trial; SAE: serious adverse event; SD: standard deviation

No information on the course of the study referring explicitly to the subpopulation used as an approximation is available for the KEYNOTE 062 study. In the total population, the median observation period was 5.9 months in the intervention arm and 4.7 months in the comparator arm. The median observation period in the total population was 12.5 months in the intervention arm and 11.1 months in the comparator arm.

No information on treatment duration referring explicitly to the subpopulation used as an approximation is available for the KEYNOTE 859 study. In the total population, the median observation period was 6.7 months in the intervention arm and 5.6 months in the comparator arm. The median observation period for overall survival in the subpopulation used as an approximation was 13 months in the intervention arm and 11.5 months in the comparator arm.

I 3.2.7 Information on subsequent therapies

Table 12 and Table 13 show the subsequent therapies patients received after discontinuation of the study medication.

Table 12: Information on the first subsequent oncological therapy – RCT, direct comparison: pembrolizumab + chemotherapy[a] vs. placebo + chemotherapy[a], subpopulation with HER2-negative gastric or GEJ adenocarcinoma with PD-L1-expressing tumours (CPS ≥ 1) (KEYNOTE 062 study)

Study **Therapy class** **Drug**	**Patients with subsequent therapy n[b] (%)**	
	Pembrolizumab + chemotherapy[a] **N = 159**	**Placebo + chemotherapy[a]** **N = 155**
KEYNOTE 062[c], data cut-off 19 April 2021		
Total	ND	ND
Radiotherapy	ND	ND
Systemic therapy and radiotherapy	ND	ND
Systemic therapy	ND	ND
Died without subsequent therapy	ND	ND
No subsequent therapy	ND	ND

a. The chemotherapy used in the KEYNOTE 062 study was cisplatin + 5-FU or cisplatin + capecitabine.
b. No data are available for the subpopulation used as an approximation in the present benefit assessment.
c. Patients in the subpopulation used as an approximation, see Table 8.

5-FU: 5-fluorouracil; CPS: combined positive score; HER2: human epidermal growth factor receptor 2; n: number of patients with subsequent therapy; N: number of analysed patients; PD-L1: programmed cell death ligand 1; RCT: randomized controlled trial

Table 13: Information on the first subsequent oncological therapy (≥ 1% of patients in ≥ 1 treatment arm) – RCT, direct comparison: pembrolizumab + chemotherapy[a] vs. placebo + chemotherapy[a], subpopulation with HER2-negative gastric or GEJ adenocarcinoma with PD-L1-expressing tumours (CPS ≥ 1) (KEYNOTE 859 study) (multipage table)

Study	**Patients with subsequent therapy n (%)**	
Therapy class **Drug**	**Pembrolizumab + chemotherapy[a]** **N = 618**	**Placebo + chemotherapy[a]** **N = 617**
KEYNOTE 859, data cut-off 22 Aug 2023[b]		
Total	298 (48.2)[c]	314 (50.9)[c]
Radiotherapy	24 (3.9)	33 (5.3)
Systemic therapy and radiotherapy[d]	0 (0.0)	1 (0.2)
Systemic therapy	274 (44.3)	280 (45.4)
Chemotherapy	251 (40.6)	264 (42.8)
Paclitaxel	118 (19.1)	132 (21.4)
Fluorouracil	48 (7.8)	49 (7.9)
Irinotecan	43 (7.0)	48 (7.8)
Docetaxel	28 (4.5)	28 (4.5)
Nab-paclitaxel	25 (4.0)	22 (3.6)
Capecitabine	18 (2.9)	20 (3.2)
Oxaliplatin	11 (1.8)	24 (3.9)
Gimeracil; oteracil potassium; tegafur	18 (2.9)	10 (1.6)
Cisplatin	17 (2.8)	9 (1.5)
Carboplatin	9 (1.5)	6 (1.0)
Irinotecan hydrochloride	6 (1.0)	2 (0.3)
Other treatments	54 (8.7)	52 (8.4)
Calcium folinate	19 (3.1)	19 (3.1)
Folinic acid	5 (0.8)	9 (1.5)
Other drugs	5 (0.8)	6 (1.0)
PD-1/PD-L1 immune checkpoint inhibitors	11 (1.8)	16 (2.6)
Pembrolizumab	5 (0.8)	6 (1.0)
VEGF/VEGFR inhibitor	74 (12.0)	84 (13.6)
Ramucirumab	65 (10.5)	75 (12.2)
Rivoceranib mesylate	1 (0.2)	6 (1.0)
Died without subsequent therapy	244 (39.5)	274 (44.4)
No subsequent therapy	76 (12.3)	29 (4.7)

a. The chemotherapy used in the KEYNOTE 859 study was cisplatin + 5-FU or oxaliplatin + capecitabine.
b. Non-prespecified second data cut-off (long-term follow-up).
c. Institute's calculation.
d. Patients who received both systemic therapy and radiotherapy are only counted once in this category.

Table 13: Information on the first subsequent oncological therapy (≥ 1% of patients in ≥ 1 treatment arm) – RCT, direct comparison: pembrolizumab + chemotherapy[a] vs. placebo + chemotherapy[a], subpopulation with HER2-negative gastric or GEJ adenocarcinoma with PD-L1-expressing tumours (CPS ≥ 1) (KEYNOTE 859 study) (multipage table)

Study	**Patients with subsequent therapy n (%)**	
Therapy class **Drug**	**Pembrolizumab + chemotherapy[a]** **N = 618**	**Placebo + chemotherapy[a]** **N = 617**
5-FU: 5-fluorouracil; CPS: combined positive score; HER2: human epidermal growth factor receptor 2; n: number of patients with subsequent therapy; N: number of analysed patients; PD-1: programmed cell death 1; PD-L1: programmed cell death ligand 1; RCT: randomized controlled trial; VEGF: vascular endothelial growth factor; VEGFR: vascular endothelial growth factor receptor		

In both studies, subsequent oncological therapies could be administered without restriction after discontinuation of the study treatment.

No information on subsequent therapies is available for the subpopulation of the KEYNOTE 062 study used as an approximation.

For the KEYNOTE 859 subpopulation used as an approximation, information on subsequent therapies is available only for the data cut-off of the non-prespecified long-term follow-up dated 22 August 2023. This is sufficiently informative for the consideration of the subsequent therapies used in the study. The proportion of patients with systemic therapy and/or radiotherapy was comparable between both study arms. Further chemotherapy was most commonly used, in particular paclitaxel or irinotecan. This corresponds to the recommendations of the current national S3 guideline [26]. Radiotherapy, in contrast, was only used in a few patients. In both study arms, a comparable number of patients died without subsequent therapy, and more patients in the intervention arm did not receive any subsequent therapy.

A statement on the comparability of the subsequent therapies between the KEYNOTE 062 and KEYNOTE 859 subpopulations used as an approximation is not possible. This does not call into question the feasibility of a quantitative or qualitative summary.

I 3.2.8 Risk of bias across outcomes (study level)

Table 14 shows the risk of bias across outcomes (risk of bias at study level).

Table 14: Risk of bias across outcomes (study level) – RCT, direct comparison: pembrolizumab + chemotherapy[a] vs. placebo + chemotherapy[a], subpopulation with HER2-negative gastric or GEJ adenocarcinoma with PD-L1-expressing tumours (CPS ≥ 1)

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patients	Treating staff			
KEYNOTE 062	Yes	Yes	Yes[b]	Yes[b]	Yes	Yes	Low
KEYNOTE 859	Yes	Yes	Yes	Yes	Yes	Yes	Low

a. The following chemotherapies were used in the studies: cisplatin + 5-FU or cisplatin + capecitabine in KEYNOTE 062, and cisplatin + 5-FU or oxaliplatin + capecitabine in KEYNOTE 859.
b. KEYNOTE 062 is a partially blinded study. Patients were randomized in 3 study arms. Patients and treating staff in the arm not relevant for the benefit assessment (pembrolizumab as monotherapy) were not blinded. In the 2 arms relevant for the benefit assessment, patients and treating staff were blinded.

5-FU: 5-fluorouracil; CPS: combined positive score; HER2: human epidermal growth factor receptor 2; PD-L1: programmed cell death ligand 1; RCT: randomized controlled trial

The risk of bias across outcomes was rated as low for both studies. Despite the low risk of bias, the certainty of results is reduced in the studies KEYNOTE 062 and KEYNOTE 859, as there are uncertainties regarding the treatment and the subpopulation used an approximation (Section I 3.2.2 and Section I 3.2.3). Since no results from the KEYNOTE 590 study were used for the present assessment, the risk of bias is not assessed.

I 3.2.9 Transferability of the study results to the German health care context

With regard to the studies KEYNOTE 062, KEYNOTE 590 and KEYNOTE 859, the company stated that their results could be transferred to the German health care context due to the characteristics of the investigated patient population, the study design and the approval-compliant use of pembrolizumab in combination with fluoropyrimidine and platinum-based chemotherapy.

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

I 4 Results on added benefit

I 4.1 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 using the EORTC QLQ-C30 and EORTC QLQ-STO22
- Health-related quality of life
  - recorded using the EORTC QLQ-C30
- Side effects
  - SAEs
  - severe AEs (CTCAE grade ≥ 3)
  - discontinuation due to AEs
  - immune-mediated SAEs
  - immune-mediated severe AEs (CTCAE grade ≥ 3)
  - hand-foot syndrome (PT, AEs)
  - other specific AEs, if any

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

Table 15 shows the outcomes for which data were available in the studies included.

Table 15: Matrix of outcomes – RCT, direct comparison: pembrolizumab + chemotherapy[a] vs. placebo + chemotherapy[a], subpopulation with HER2-negative gastric or GEJ adenocarcinoma with PD-L1-expressing tumours (CPS ≥ 1)

Study	Outcomes										
	Overall survival	Health status (EQ-5D VAS)	Symptoms (EORTC QLQ-C30, EORTC QLQ-STO22[b])	Health-related quality of life (EORTC QLQ-C30)	SAEs	Severe AEs[c]	Discontinuation due to AEs[d]	Immune-mediated SAEs	Immune-mediated severe AEs[c]	Hand-foot syndrome (PT, AEs)	Other specific AEs
KEYNOTE 062	Yes	–	–	–	–	–	–	–	–	–	–
KEYNOTE 859	Yes	Yes	Yes	Yes	No[f]	No[f]	No[f]	No[f]	No[f]	No[f]	No[g]

a. The following chemotherapies were used in the studies: cisplatin + 5-FU or cisplatin + capecitabine in KEYNOTE 062, and cisplatin + 5-FU or oxaliplatin + capecitabine in KEYNOTE 859.
b. The EORTC QLQ-STO22 questionnaire only reflects the symptoms of patients with gastric cancer.
c. Severe AEs are operationalized as CTCAE grade ≥ 3.
d. 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. 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). Analyses on the discontinuation of at least one drug component are to be preferred, as any AE leading to discontinuation of any treatment component is relevant.
e. No data were available to perform a quantitative or qualitative summary; see the following section for reasons.
f. No data on the prespecified data cut-off for the subpopulation with PD-L1-expressing tumours (CPS ≥ 1).
g. No suitable analyses on AEs available, a choice of specific AEs is therefore impossible.

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; HER2: human epidermal growth factor receptor 2; PD-L1: programmed cell death ligand 1; PT: Preferred Term; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-STO22: Quality of Life Questionnaire-Gastric Cancer 22 items; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale

Notes on outcomes

No suitable data for a quantitative or qualitative summary for patient-relevant outcomes except for the outcome of overall survival

Data on the outcome of overall survival at a prespecified data cut-off were available for both studies (KEYNOTE 062, KEYNOTE 859). In this assessment, the results of this outcome are analysed in a meta-analysis.

For the categories of morbidity, health-related quality of life and side effects, the database was incomplete across the studies:

For the subpopulation of the KEYNOTE 062 study derived from the subgroup analysis, which was used as an approximation (see Section I 3.2.2), no data for the prespecified data cut-off were available for the outcomes in the categories of morbidity, health-related quality of life and side effects. For the categories of morbidity, health-related quality of life and side effects, data were only available for a non-prespecified data cut-off used by the company in Module 4 A. However, these were only selectively available for outcomes that showed a statistically significant interaction for the characteristic of chemotherapy (cisplatin + 5-FU versus cisplatin + capecitabine).

For the subpopulation of the KEYNOTE 859 study used as an approximation, results on a prespecified data cut-off were available for outcomes in the categories of morbidity and health-related quality. However, these data were incomplete, as results were not presented for all scales of the EORTC instruments used. The suitability of the operationalizations and analyses was therefore not examined. No results for a prespecified data cut-off were available for outcomes in the side effects category overall. For the non-prespecified data cut-off used by the company in Module 4 A, results were available for the subpopulation of the KEYNOTE 859 study used as an approximation for all used outcomes in the categories of morbidity, health-related quality of life and side effects.

No quantitative or qualitative summary was made for outcomes in the categories of morbidity, health-related quality of life and side effects due to the incomplete database. The results of the KEYNOTE 859 study alone, for example for outcomes in the categories of morbidity and health-related quality of life, were also not assessed because the proportion of patients from KEYNOTE 859 was only 80% in the subpopulations of both studies used as an approximation. If only the results of the KEYNOTE 859 study were assessed, an important proportion of patients would thus be disregarded. Irrespective of this, it should be noted that a quantitative or qualitative summary of results requires the presence of comparable operationalizations of the outcomes.

Overall, only data on the outcome of overall survival are therefore available for the present benefit assessment.

I 4.2 Risk of bias

Table 16 describes the risk of bias for the results of the relevant outcomes.

Table 16: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: pembrolizumab + chemotherapy[a] vs. placebo + chemotherapy[a], subpopulation with HER2-negative gastric or GEJ adenocarcinoma with PD-L1-expressing tumours (CPS ≥ 1)

Study	Study level	Outcomes										
		Overall survival	Health status (EQ-5D VAS)	Symptoms (EORTC QLQ-C30, EORTC QLQ-STO22[b])	Health-related quality of life (EORTC QLQ-C30)	SAEs	Severe AEs[c]	Discontinuation due to AEs	Immune-mediated SAEs	Immune-mediated severe AEs[c]	Hand-foot syndrome (PT, AEs)	Other specific AEs
KEYNOTE 062	L	L[d]					–[e]					
KEYNOTE 859	L	L[d]	–[e]	–[e]	–[e]	–[e]	–[e]	–[e]	–[e]	–[e]	–[e]	–[f]

a. The following chemotherapies were used in the studies: cisplatin + 5-FU or cisplatin + capecitabine in KEYNOTE 062, and cisplatin + 5-FU or oxaliplatin + capecitabine in KEYNOTE 859.
b. The EORTC QLQ-STO22 questionnaire only reflects the symptoms of patients with gastric cancer.
c. Severe AEs are operationalized as CTCAE grade ≥ 3.
d. Despite the low risk of bias, the certainty of conclusions for the outcome of overall survival is reduced (see Section I 3.2.2 and Section I 3.2.3)
e. No data were available to perform a quantitative or qualitative summary; see Section I 4.1 for reasons.
f. No suitable analyses on AEs available, a choice of specific AEs is therefore impossible.

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; HER2: human epidermal growth factor receptor 2; L: low; PD-L1: programmed cell death ligand 1; PT: Preferred Term; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-STO22: Quality of Life Questionnaire-Gastric Cancer 22 items; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale

The risk of bias of the results on the outcome of overall survival from the 2 studies KEYNOTE 062 and KEYNOTE 859 is rated as low in each case. Nevertheless, the certainty of results of the 2 studies is limited due to deviations between the subpopulation used as an approximation and the relevant subpopulation (KEYNOTE 062 study) and due to uncertainties regarding the treatment (studies KEYNOTE 062 and KEYNOTE 859) (see Section I 3.2.2 and Section I 3.2.3).

For the outcomes in the categories of morbidity, health-related quality of life and side effects, no suitable data are available for conducting a quantitative or qualitative summary (see Section I 4.1); the risk of bias of the results for these outcomes is therefore not assessed.

Summary assessment of the certainty of conclusions

The risk of bias and the uncertainties regarding the deviations between the subpopulation used as an approximation and the relevant subpopulation (KEYNOTE 062) as well as the

uncertainties regarding the treatment (KEYNOTE 062 and KEYNOTE 859) result in a moderate qualitative certainty of results for the 2 studies KEYNOTE 062 and KEYNOTE 859. Thus, no more than indications, for example of an added benefit, can be derived for patient-relevant outcomes for which a quantitative or qualitative summary is possible.

I 4.3 Results

Table 17 summarizes the results of the comparison of pembrolizumab with chemotherapy in patients with locally advanced unresectable or metastatic HER2-negative gastric or GEJ adenocarcinoma whose tumours express PD-L1-(CPS ≥ 1) in first-line treatment. Where necessary, IQWiG calculations are provided to supplement the data from the company's dossier.

Kaplan-Meier curves on the time-to-event analyses as well as forest plots on the meta-analyses calculated by the Institute are presented in Appendix B of the full dossier assessment.

Table 17: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: pembrolizumab + chemotherapy[a] vs. placebo + chemotherapy[a], subpopulation with HER2-negative gastric or GEJ adenocarcinoma whose tumours express PD-L1 (CPS ≥ 1) (multipage table)

Outcome category Outcome Study	Pembrolizumab + chemotherapy[a]		Placebo + chemotherapy[a]		Pembrolizumab + chemotherapy[a] vs. placebo + chemotherapy[a]
	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 062[b]	159[c]	ND 125 (78.6)	155[c]	ND 132 (85.2)	0.77 [0.6; 0.98]; 0.037[d]
KEYNOTE 859[e]	618[c]	13.0 [11.6; 14.2] 464 (75.1)	617[c]	11.4 [10.5; 12.0] 526 (85.3)	0.74 [0.65; 0.84]; < 0.001[f]
Total					0.75 [0.67; 0.84]; < 0.001[g]
Morbidity					
KEYNOTE 062 KEYNOTE 859	No suitable data for a quantitative or qualitative summary[h]				
Total	–				

Table 17: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: pembrolizumab + chemotherapy[a] vs. placebo + chemotherapy[a], subpopulation with HER2-negative gastric or GEJ adenocarcinoma whose tumours express PD-L1 (CPS ≥ 1) (multipage table)

Outcome category Outcome Study	Pembrolizumab + chemotherapy[a]		Placebo + chemotherapy[a]		Pembrolizumab + chemotherapy[a] vs. placebo + chemotherapy[a]
	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
Health-related quality of life					
KEYNOTE 062 KEYNOTE 859	No suitable data for a quantitative or qualitative summary[h]				
Total	–				
Side effects					
KEYNOTE 062 KEYNOTE 859	No suitable data for a quantitative or qualitative summary[h]				
Total	–				

a. The following chemotherapies were used in the studies: cisplatin + 5-FU or cisplatin + capecitabine in KEYNOTE 062, and cisplatin + 5-FU or oxaliplatin + capecitabine in KEYNOTE 859.
b. Prespecified third data cut-off: 26 March 2019.
c. Patients in the subpopulation used as an approximation, see Table 8.
d. Effect and CI: Cox proportional hazards model, unstratified; p-value: Institute's calculation based on 95% CI.
e. Prespecified first data cut-off: 3 October 2022.
f. Effect and CI: Cox proportional hazards model; stratified by region (Europe/Israel/North America/Australia vs. Asia vs. rest of the world) and chemotherapy (FP vs. CAPOX); if strata were too small, they were merged as prespecified in the SAP; p-value: Institute's calculation based on 95% CI
g. Institute's calculation; meta-analysis with fixed effect; method with inverse variance.
h. See Section I 4.1 for the reasoning.

5-FU: 5-fluorouracil; CAPOX: capecitabine and oxaliplatin; CPS: combined positive score; FP: cisplatin and 5-fluorouracil; HER2: human epidermal growth factor receptor 2; HR: hazard ratio; N: number of analysed patients; n: number of patients with (at least one) event; ND: no data; PD-L1: programmed cell death ligand 1; RCT: randomized controlled trial; SAP: statistical analysis plan

Based on the available information, at most indications, e.g. of an added benefit, can be determined for all outcomes (see Section I 4.2).

Mortality

Overall survival

For the outcome of overall survival, the results of the time-to-event analyses for the data cut-offs prespecified in the studies KEYNOTE 062 and KEYNOTE 859 are presented. There is moderate certainty of results in each case.

For the outcome of overall survival, the conducted meta-analysis found a statistically significant difference in favour of pembrolizumab + chemotherapy in comparison with placebo + chemotherapy. There is an indication of an added benefit of pembrolizumab + chemotherapy in comparison with chemotherapy.

Morbidity

Health status (EQ-5D VAS) and symptoms (EORTC QLQ-C30, EORTC QLQ-STO22)

For the outcomes in the morbidity category, no suitable data are available to perform a quantitative or qualitative summary. There is no hint of an added benefit of pembrolizumab + chemotherapy in comparison with chemotherapy for any of them; an added benefit is therefore not proven.

Health-related quality of life

EORTC QLQ-C30

For the outcome of health-related quality of life, recorded with the EORTC QLQ-C30, no suitable data are available to perform a quantitative or qualitative summary. There is no hint of an added benefit of pembrolizumab + chemotherapy in comparison with chemotherapy; an added benefit is therefore not proven.

Side effects

SAEs, severe AEs (CTCAE grade ≥ 3), discontinuation due to AEs, immune-mediated severe SAEs, immune-mediated severe AEs (CTCAE grade ≥ 3) and hand-foot syndrome (PT, AEs)

For the outcomes in the side effects category, no suitable data are available to perform a quantitative or qualitative summary. There is no hint of greater or lesser harm from pembrolizumab + chemotherapy in comparison with chemotherapy for any of them; greater or lesser harm is therefore not proven.

I 4.4 Subgroups and other effect modifiers

The following subgroup characteristics were taken into account for the present benefit assessment:

- age (< 65 years versus ≥ 65 years)
- sex (male versus female)

- disease status (locally advanced versus metastatic)

Interaction tests are performed if at least 10 patients per subgroup are included in the analysis. Moreover, for binary data, there have to be at least 10 events in at least one subgroup.

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

For the respective prespecified data cut-off, no suitable data for the implementation of cross-study interaction tests or for the generation of cross-study subgroup results on the basis of meta-analyses for the relevant subgroup characteristics are available for the subpopulations of the studies KEYNOTE 062 and KEYNOTE 859 used as an approximation. For the outcomes of immune-mediated SAEs and immune-mediated severe AEs, subgroup analyses are completely missing. Therefore, no subgroup analyses are used for the benefit assessment overall.

I 5 Probability and extent of added benefit

The probability and extent of 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 IQWiG *General Methods* [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.

I 5.1 Assessment of added benefit at outcome level

The extent of the respective added benefit at outcome level is estimated from the results presented in Chapter I 4 (see Table 18).

Table 18: Extent of added benefit at outcome level: pembrolizumab + chemotherapy[a] vs. placebo + chemotherapy[a], subpopulation with HER2-negative gastric or GEJ adenocarcinoma with PD-L1-expressing tumours (CPS ≥ 1) (multipage table)

Outcome category **Outcome**	**Pembrolizumab + chemotherapy[a] vs. placebo + chemotherapy[a]** **Median time to event (months)** **Effect estimation [95% CI];** **p-value** **Probability[b]**	**Derivation of extent[c]**
Outcomes with observation over the entire study duration		
Mortality		
Overall survival	ND or 13.0 vs. ND or 11.4 months[d] HR: 0.75 [0.67; 0.84]; p < 0.001 Probability: “indication”	Outcome category: mortality CI_u < 0.85 Added benefit; extent: “major”
Outcomes with shortened observation period		
Morbidity		
Health status (EQ-5D VAS)	No suitable data for a quantitative or qualitative summary[e]	Lesser/added benefit not proven
Symptoms (EORTC QLQ-C30)	No suitable data for a quantitative or qualitative summary[e]	Lesser/added benefit not proven
Symptoms (EORTC QLQ-STO22)	No suitable data for a quantitative or qualitative summary[e]	Lesser/added benefit not proven

Table 18: Extent of added benefit at outcome level: pembrolizumab + chemotherapy[a] vs. placebo + chemotherapy[a], subpopulation with HER2-negative gastric or GEJ adenocarcinoma with PD-L1-expressing tumours (CPS ≥ 1) (multipage table)

Outcome category **Outcome**	**Pembrolizumab + chemotherapy[a] vs. placebo + chemotherapy[a]** **Median time to event (months)** **Effect estimation [95% CI];** **p-value** **Probability[b]**	**Derivation of extent[c]**
Health-related quality of life		
EORTC QLQ-C30	No suitable data for a quantitative or qualitative summary[e]	Lesser/added benefit not proven
Side effects		
SAEs	No suitable data for a quantitative or qualitative summary[e]	Greater/lesser harm not proven
Severe AEs	No suitable data for a quantitative or qualitative summary[e]	Greater/lesser harm not proven
Discontinuation due to AEs	No suitable data for a quantitative or qualitative summary[e]	Greater/lesser harm not proven
Immune-mediated SAEs	No suitable data for a quantitative or qualitative summary[e]	Greater/lesser harm not proven
Immune-mediated severe AEs	No suitable data for a quantitative or qualitative summary[e]	Greater/lesser harm not proven
Hand-foot syndrome (AEs)	No suitable data for a quantitative or qualitative summary[e]	Greater/lesser harm not proven

a. The following chemotherapies were used in the studies: cisplatin + 5-FU or cisplatin + capecitabine in KEYNOTE 062, and cisplatin + 5-FU or oxaliplatin + capecitabine in KEYNOTE 859.
b. Probability provided if statistically significant differences are present.
c. Depending on the outcome category, estimations of effect size use different limits based on the upper limit of the confidence interval (CI_u).
d. Median time to event per treatment arm in the 2 included studies; no data on the median time to event were available for the KEYNOTE 062 study.
e. See Section I 4.1 for the reasoning.

5-FU: 5-fluorouracil; AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; CPS: combined positive score; EORTC: European Organisation for Research and Treatment of Cancer; HER2: human epidermal growth factor receptor 2; HR. hazard ratio; PD-L1: programmed cell death ligand 1; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-STO22: Quality of Life Questionnaire-Gastric Cancer 22 items; SAE: serious adverse event; VAS: visual analogue scale

I 5.2 Overall conclusion on added benefit

Table 19 summarizes the results taken into account in the overall conclusion on the extent of added benefit.

Table 19: Positive and negative effects from the assessment of pembrolizumab + chemotherapy[a] in comparison with chemotherapy[a], subpopulation with HER2-negative gastric or GEJ adenocarcinoma with PD-L1-expressing tumours (CPS ≥ 1)

Positive effects	**Negative effects**
Outcomes with observation over the entire study duration	
Mortality ▪ Overall survival: indication of added benefit – extent: "major"	–
Suitable data for a quantitative or qualitative summary of all outcomes in the categories of morbidity, health-related quality of life and side effects are missing.	
a. The following chemotherapies were used in the studies: cisplatin + 5-FU or cisplatin + capecitabine in KEYNOTE 062, and cisplatin + 5-FU or oxaliplatin + capecitabine in KEYNOTE 859. 5-FU: 5-fluorouracil; CPS: combined positive score; HER2: human epidermal growth factor receptor 2; PD-L1: programmed cell death ligand 1	

Overall, there was an indication of a major added benefit for overall survival. The results on the outcomes in the categories of morbidity, health-related quality of life and side effects are unsuitable for the present benefit assessment. In view of the lack of analyses on immune-mediated AEs, a potential disadvantage for the intervention is to be expected. However, even any disadvantages in these outcomes are not assumed to completely call into question the positive effect in the outcome of overall survival. However, it is not possible to quantify the overall extent of added benefit.

In summary, there is an indication of a non-quantifiable added benefit of pembrolizumab in combination with chemotherapy compared with chemotherapy for adult patients with locally advanced unresectable or metastatic HER2-negative gastric or GEJ adenocarcinoma whose tumours express PD-L1 (CPS ≥ 1) in first-line treatment.

Table 20 summarizes the result of the assessment of the added benefit of pembrolizumab in comparison with the ACT.

Table 20: Pembrolizumab – probability and extent of added benefit (multipage table)

Therapeutic indication	**ACT**[a, b, c, d]	**Probability and extent of added benefit**
Adults with locally advanced unresectable or metastatic HER2-negative gastric or gastro-oesophageal junction adenocarcinoma whose tumours express PD-L1 (CPS ≥ 1)[e]; in combination with fluoropyrimidine and platinum-containing chemotherapy for first-line treatment	▪ Cisplatin + capecitabine or ▪ oxaliplatin + capecitabine or ▪ cisplatin + S-1 (tegafur/gimeracil/oteracil) or ▪ cisplatin + 5-fluorouracil (only for patients with oesophageal adenocarcinoma[f]) or ▪ cisplatin + 5-fluorouracil + folinic acid (only for patients with oesophageal adenocarcinoma[f]) or ▪ epirubicin + cisplatin + capecitabine or ▪ epirubicin + cisplatin + 5-fluorouracil or ▪ epirubicin + oxaliplatin + capecitabine or ▪ docetaxel + cisplatin + 5-fluorouracil or ▪ nivolumab in combination with fluoropyrimidine and platinum-containing combination chemotherapy (only for tumours with PD-L1 expression [CPS ≥ 5]) or ▪ 5-fluorouracil + oxaliplatin + epirubicin (only for patients with oesophageal adenocarcinoma[f])	Indication of non-quantifiable added benefit[g]

Table 20: Pembrolizumab – probability and extent of added benefit (multipage table)

Therapeutic indication	ACT[a, b, c, d]	Probability and extent of added benefit
a. Presented is the ACT specified by the G-BA. b. It is assumed for the present therapeutic indication that curative treatment with definitive radiochemotherapy is not an option for patients with unresectable cancer. c. The ACT comprises several alternative treatment options. According to the G-BA, individual treatment options only represent a comparator therapy for those members of the patient population who have the patient and disease characteristics shown in brackets. The alternative treatment options are only to be regarded as equally appropriate in the area in which the patient populations have the same characteristics. d. To demonstrate added benefit for the total population, any treatment option can be used that is not restricted by patient and disease characteristics given in brackets. If the ACT comprises several alternative treatment options without restrictions, the added benefit for the total population can be demonstrated versus one of these alternative treatment options; this can usually be performed in the context of a single-comparator study. In contrast, the sole comparison with a treatment option which represents a comparator therapy only for part of the patient population is generally insufficient to demonstrate added benefit for the total population. e. First-line treatment with pembrolizumab of adult patients with locally advanced unresectable or metastatic HER2-negative GEJ adenocarcinoma whose tumours express PD-L1 (CPS ≥ 10) was already part of an earlier benefit assessment [3,4]. This has no consequences for the present benefit assessment, however. f. In the present assessment, this includes patients with GEJ adenocarcinoma. g. The studies KEYNOTE 062, KEYNOTE 590 and KEYNOTE 859 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. ACT: appropriate comparator therapy; CPS: combined positive score; ECOG PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee; GEJ: gastro-oesophageal junction; HER2: human epidermal growth factor receptor 2; PD-L1: programmed cell death ligand 1		

The assessment described above deviates from that of the company, which derived proof of considerable added benefit.

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

I 6 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. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Allgemeine Methoden; Version 7.0 [online]. 2023 [Accessed: 06.10.2023]. URL: https://www.iqwig.de/methoden/allgemeine-methoden_version-7-0.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://doi.org/10.1002/bimj.201300274.

3. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Pembrolizumab (Karzinom des Ösophagus oder gastroösophagealen Übergangs) – Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung [online]. 2022 [Accessed: 11.07.2023]. URL: https://www.iqwig.de/download/a21-144_pembrolizumab_nutzenbewertung-35a-sgb-v_v1-1.pdf.

4. Gemeinsamer Bundesausschuss. Nutzenbewertungsverfahren zum Wirkstoff Pembrolizumab (Neues Anwendungsgebiet: Karzinom des Ösophagus oder gastroösophagealen Übergangs, PD-L1-Expression ≥ 10 (CPS), Erstlinie, Kombination mit Platin- und Fluoropyrimidin-basierter Chemotherapie) [online]. 2022 [Accessed: 13.03.2024]. URL: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/756/.

5. 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; study KEYNOTE 062; Clinical Study Report [unpublished]. 2019.

6. 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: 22.01.2024]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2015-000972-88.

7. 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]. 2023 [Accessed: 22.01.2024]. URL: https://clinicaltrials.gov/study/NCT02494583.

8. 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://doi.org/10.1001/jamaoncol.2020.3370.

9. 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; 4(6).

10. 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.

11. 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: 22.01.2024]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2017-000958-19.

12. Merck Sharp & Dohme. First-line Esophageal Carcinoma Study With Chemo vs. Chemo Plus Pembrolizumab; (MK-3475-590/KEYNOTE-590) [online]. 2023 [Accessed: 07.03.2024]. URL: https://clinicaltrials.gov/study/NCT03189719.

13. 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://doi.org/10.2217/fon-2018-0609.

14. 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://doi.org/10.1016/S0140-6736(21)01234-4.

15. Merck Sharp & Dohme. A Phase 3, randomized, double-blind clinical study of pembrolizumab (MK-3475) plus chemotherapy versus placebo plus chemotherapy as first-line treatment in participants with HER2 negative, previously untreated, unresectable or metastatic gastric or gastroesophageal junction adenocarcinoma; study KEYNOTE 859; Clinical Study Report [unpublished]. 2023.

16. Merck Sharp & Dohme. A Phase 3, randomized, double-blind clinical study of pembrolizumab (MK-3475) plus chemotherapy versus placebo plus chemotherapy as first-line treatment in participants with HER2 negative, previously untreated, unresectable or metastatic gastric or gastroesophageal junction adenocarcinoma (KEYNOTE-859) [online]. [Accessed: 22.01.2024]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2018-001757-27.

17. Merck Sharp & Dohme. Pembrolizumab (MK-3475) Plus Chemotherapy Versus Placebo Plus Chemotherapy in Participants Gastric or Gastroesophageal Junction (GEJ) Adenocarcinoma; (MK-3475-859/KEYNOTE-859) [online]. 2024 [Accessed: 22.01.2024]. URL: https://clinicaltrials.gov/study/NCT03675737.

18. Tabernero J, Bang YJ, Van CE et al. KEYNOTE-859; A Phase III study of pembrolizumab plus chemotherapy in gastric/gastroesophageal junction adenocarcinoma. Future Oncol 2021; 22(17).

19. Rha SY, Oh DY, Yañez P et al. Pembrolizumab plus chemotherapy versus placebo plus chemotherapy for HER2-negative advanced gastric cancer (KEYNOTE-859); a multicentre, randomised, double-blind, phase 3 trial. Lancet Oncol 2023; 24(11): 1181-1195. https://doi.org/10.1016/s1470-2045(23)00515-6.

20. Merck Sharp & Dohme. Fachinformation KEYTRUDA (Pembrolizumab) 25 mg/ml Konzentrat zur Herstellung einer Infusionslösung; Stand: Dezember. 2023.

21. Accord Healthcare. Fachinformation Cisplatin Accord 1 mg/ml Konzentrat zur Herstellung einer Infusionslösung; Stand: April. 2023.

22. Bendalis. Fachinformation Benda-5 FU 50 mg/ml Injektionslösung; Stand: November. 2021.

23. T. A. D. Pharma. Fachinformation Ecansya 150 mg/-300 mg/-500 mg Filmtabletten; Stand: April. 2021.

24. medac Gesellschaft für klinische Spezialpräparate. Fachinformation medoxa 5 mg/ml Konzentrat zur Herstellung einer Infusionslösung; Stand: Januar [online]. 2023.

25. Leitlinienprogramm Onkologie. S3-Leitlinie Diagnostik und Therapie der Plattenepithelkarzinome und Adenokarzinome des Ösophagus; Langversion 4.0 [online]. 2023 [Accessed: 19.01.2024]. URL: https://register.awmf.org/assets/guidelines/021-023OLl_S3_Diagnostik-Therapie-Plattenepithelkarzinome-Adenokarzinome-Oesophagus_2023-12.pdf.

26. Leitlinienprogramm Onkologie. S3-Leitlinie Magenkarzinom; Langversion 2.0; 2019 AWMF Registernummer: 032/009OL [online]. 2019 [Accessed: 09.11.2023]. URL: https://www.leitlinienprogramm-onkologie.de/leitlinien/magenkarzinom/.

27. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology; Esophagael and Esophagogastric Junction Cancers; Version 4.2023 [online]. 2024 [Accessed: 06.02.2024]. URL: https://www.nccn.org/professionals/physician_gls/pdf/esophageal.pdf.

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