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

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
ACT	appropriate comparator therapy
AE	adverse event
CPS	combined positive score
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30;
EORTC QLQ-OG25	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Oesophago-Gastric 25
EORTC QLQ-STO22	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Gastric Cancer 22
FP	5-fluorouracil + cisplatin
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)
PD-L1	programmed cell death ligand 1
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics
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 trastuzumab and a fluoropyrimidine- and platinum-based 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 trastuzumab and a fluoropyrimidine- and platinum-based chemotherapy compared to the appropriate comparator therapy (ACT) for first-line treatment of adults with locally advanced unresectable or metastatic human epidermal growth factor receptor 2 (HER2)-positive gastric or gastro-oesophageal junction adenocarcinoma whose tumours express programmed cell death ligand 1 (PD-L1) (combined positive score [CPS] ≥ 1).

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

Table 2: Research questions of the benefit assessment of pembrolizumab in combination with trastuzumab and a fluoropyrimidine- and platinum-based chemotherapy

Therapeutic indication	**ACT**[a]
Adults with locally advanced unresectable or metastatic HER2-positive gastric or gastro-oesophageal junction adenocarcinoma whose tumours express PD-L1 (CPS ≥ 1); first-line treatment[b]	▪ Trastuzumab in combination with capecitabine and cisplatin or ▪ trastuzumab in combination with 5-fluorouracil and cisplatin
a. Presented is the respective ACT specified by the G-BA. b. It is assumed that radiotherapy with curative intent is not indicated for the patients in the present therapeutic indication. ACT: appropriate comparator therapy; CPS: combined positive score; G-BA: Federal Joint Committee; HER2: human epidermal growth factor receptor 2; PD-L1: programmed cell death ligand 1	

The G-BA adjusted the ACT in October 2023, as shown in Table 2. The company followed the ACT initially defined by the G-BA in November 2022 and named a treatment of physician's choice as the ACT, selecting the following combination therapies: trastuzumab in combination with capecitabine and cisplatin, trastuzumab in combination with 5-fluorouracil and cisplatin, trastuzumab in combination with capecitabine and oxaliplatin, trastuzumab in combination with 5-fluorouracil and oxaliplatin.

The present benefit assessment was conducted versus the ACT. 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 the added benefit. This concurs with the company's inclusion criteria.

Study pool and study design

A subpopulation of the KEYNOTE-811 study was used for the benefit assessment.

The KEYNOTE-811 study is an ongoing, double-blind RCT comparing pembrolizumab in combination with trastuzumab and a fluoropyrimidine- and platinum-based chemotherapy versus placebo in combination with trastuzumab and a fluoropyrimidine- and platinum-based chemotherapy. The fluoropyrimidine- and platinum-based chemotherapy regimens used in the study were 5-fluorouracil + cisplatin (FP), capecitabine + oxaliplatin (CAPOX) and a combination of S-1 (fixed combination of tegafur, gimeracil and oteracil) and oxaliplatin. However, only treatment with FP is included in the G-BA's ACT.

The study included adults with HER2-positive locally advanced unresectable or metastatic gastric or gastro-oesophageal junction (GEJ) adenocarcinoma who had not yet received any therapy for the treatment of advanced disease. Patients had to have Eastern Cooperative Oncology Group Performance Status (ECOG PS) ≤ 1. Both patients with positive and negative PD-L1 status were included.

Within the scope of the study, 2 cohorts were planned, one being a global cohort and the other a Japan-specific cohort. The Japan-specific cohort is not relevant for the present benefit assessment due to the treatment regimen (S-1 + oxaliplatin) deviating from the ACT.

The global cohort of the study comprises 698 patients who were randomly assigned in a 1:1 ratio to treatment with pembrolizumab (N = 350) or placebo (N = 348), each in combination with trastuzumab and either FP or CAPOX.

In the KEYNOTE-811 study, treatment was continued until confirmed disease progression, unacceptable toxicity, treatment discontinuation upon the investigator's discretion, withdrawal of consent, or treatment for a maximum of 35 cycles. A maximum treatment duration of 35 cycles is not in line with the Summary of Product Characteristics (SPC), according to which treatment with pembrolizumab should be continued until the cancer progresses or until unacceptable toxicity occurs.

Primary outcomes of the KEYNOTE 811 study were overall survival and progression-free survival. Outcomes on symptoms, health status, health-related quality of life and adverse events (AEs) were recorded as secondary patient-relevant outcomes.

Relevant subpopulation

The approval of pembrolizumab in the present therapeutic indication is limited to patients whose tumours express PD-L1 (CPS ≥ 1). The subpopulation presented by the company in Module 4 A includes all 298 patients in the intervention arm and 296 patients in the comparator arm with a CPS ≥ 1. This subpopulation includes both patients treated with CAPOX and FP. The G-BA has defined treatment with trastuzumab in combination with cisplatin and either 5-fluorouracil or capecitabine as an ACT. Therefore, only the subpopulation of patients with a CPS ≥ 1 who received the chemotherapy regimen FP is relevant for the benefit assessment compared to the G-BA's ACT. These were 47 patients in the intervention arm and 43 patients in the comparator arm. Information on these patients is available as part of subgroup analyses, as the chosen chemotherapy regimen (FP vs. CAPOX) is a prespecified subgroup feature.

Risk of bias

The risk of bias across outcomes was rated as low for the KEYNOTE-811 study. Except for the outcome “overall survival”, the risk of bias at outcome level was rated as high. For symptoms outcomes, measured with the EORTC QLQ-C30 and the EORTC QLQ-STO22, the outcome “health status”, measured with the visual analogue scale (VAS) of the EQ-5D, as well as the outcomes “health-related quality of life”, measured with the EORTC QLQ-C30, the outcome of discontinuation due to AEs, cardiac disorders, immune-related SAEs and severe AEs as well as possibly further specific AEs there is no assessment of the risk of bias, since either no or no suitable analyses are available. The available information allows deriving no more than an indication, e.g. of an added benefit, for the outcome of overall survival. For all other outcomes, for which results relevant for benefit assessment are available, at most hints, e.g. of an added benefit, can be determined.

Results

Mortality

Overall survival

For the outcome of overall survival, no statistically significant difference between treatment groups was found. This results in no indication of an added benefit of pembrolizumab + trastuzumab + 5-fluorouracil + cisplatin in comparison with trastuzumab + 5-fluorouracil + cisplatin; an added benefit is therefore not proven.

Morbidity

Symptoms (EORTC QLQ-C30 and EORTC QLQ-STO22)

With regard to symptoms outcomes, measured using the EORTC QLQ-C30 and the EORTC QLQ-STO22, the available analyses on first deterioration cannot be interpreted due to a lack of information on response rates for the relevant subpopulation and are therefore not used for

the benefit assessment, but only presented as a supplement. This results in no hint of an added benefit of pembrolizumab + trastuzumab + 5-fluorouracil + cisplatin in comparison with trastuzumab + 5-fluorouracil + cisplatin; an added benefit is therefore not proven in each case.

Even assuming that the response rates were sufficiently high and the results could therefore be interpreted, there was only a single, no more than minor effect between the treatment groups for the symptom of diarrhoea.

Health status (EQ-5D VAS)

With regard to the outcome of health status, measured using the EQ-5D VAS, the available analyses on first deterioration cannot be interpreted due to a lack of information on response rates for the relevant subpopulation and are therefore not used for the benefit assessment, but only presented as a supplement. This results in no hint of an added benefit of pembrolizumab + trastuzumab + 5-fluorouracil + cisplatin in comparison with trastuzumab + 5-fluorouracil + cisplatin; an added benefit is therefore not proven.

Even assuming that the response rates were sufficiently high and the results could therefore be interpreted, there would be no advantages or disadvantages for the intervention in the outcomes “health status”.

Health-related quality of life

EORTC QLQ-C30

With regard to health-related quality of life, measured using the EORTC QLQ-C30, the available analyses on first deterioration cannot be interpreted due to a lack of information on response rates for the relevant subpopulation and are therefore not used for the benefit assessment, but only presented as a supplement. This results in no hint of an added benefit of pembrolizumab + trastuzumab + 5-fluorouracil + cisplatin in comparison with trastuzumab + 5-fluorouracil + cisplatin; an added benefit is therefore not proven.

Even assuming that the response rates were sufficiently high and the results could therefore be interpreted, there would be no advantages or disadvantages for the intervention in the outcomes on health-related quality of life.

Side effects

SAEs, severe AEs

There were no statistically significant differences between treatment groups for the outcomes of SAEs and severe AEs. This results in no hint of greater or lesser harm from pembrolizumab + trastuzumab + 5-fluorouracil + cisplatin in comparison with trastuzumab + 5-fluorouracil + cisplatin; an added benefit is therefore not proven in each case.

Discontinuation due to AEs, cardiac disorders (severe AEs), immune-related SAEs, immune-related severe AEs

No suitable or no analyses are available for the outcomes of discontinuation due to AEs, cardiac disorders (severe AEs), immune-related AEs and immune-related severe AEs. This results in no hint of greater or lesser harm from pembrolizumab + trastuzumab + 5-fluorouracil + cisplatin in comparison with trastuzumab + 5-fluorouracil + cisplatin; an added benefit is therefore not proven in each case.

Immune-related AEs occur specifically in connection with treatment with PD-1 inhibitors such as pembrolizumab. Since no analyses on outcomes of immune-related AEs are available for the relevant subpopulation, no potentially negative effects of the intervention on the outcome of immune-related AEs were identified.

Other specific AEs

It was not possible to select any further specific AEs because suitable analyses (time-to-event analyses) by preferred terms (PT) and system organ class (SOC) were not fully available for the relevant subpopulation.

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

On the basis of the results presented, the probability and extent of the added benefit of the drug pembrolizumab in combination with trastuzumab and a fluoropyrimidine- and platinum-based chemotherapy in comparison with the ACT is assessed as follows:

Overall, neither positive nor negative effects were shown based on the available data. The impact of the missing data in the relevant subpopulation cannot be conclusively determined. The additional results presented on patient-reported outcomes in the categories of morbidity and health-related quality of life show no more than minor effects between the treatment groups. In view of the lack of analyses on immune-related AEs, a potential disadvantage for the intervention is to be expected.

In summary, for patients with locally advanced, non-resectable or metastatic HER2-positive gastric or GEJ adenocarcinoma whose tumours express PD-L1 (CPS ≥ 1, there is no hint of an

[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].

added benefit from pembrolizumab + trastuzumab + 5-fluorouracil + cisplatin over trastuzumab + 5-fluorouracil + cisplatin, thus an added benefit is not proven.

Table 3 shows a summary of probability and extent of the added benefit of pembrolizumab + trastuzumab + 5-fluorouracil + cisplatin.

Table 3: Pembrolizumab + trastuzumab + 5-fluorouracil + cisplatin – probability and extent of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
Adults with locally advanced unresectable or metastatic HER2-positive gastric or gastro-oesophageal junction adenocarcinoma whose tumours express PD-L1 (CPS ≥ 1); first-line treatment[b]	▪ Trastuzumab in combination with capecitabine and cisplatin or ▪ trastuzumab in combination with 5-fluorouracil and cisplatin	Added benefit not proven
a. Presented is the respective ACT specified by the G-BA. b. It is assumed that radiotherapy with curative intent is not indicated for the patients in the present therapeutic indication. ACT: appropriate comparator therapy; CPS: combined positive score; G-BA: Federal Joint Committee; HER2: human epidermal growth factor receptor 2; PD-L1: programmed cell death ligand 1		

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 trastuzumab and a fluoropyrimidine- and platinum-based chemotherapy compared to the ACT for first-line treatment of adults with locally advanced unresectable or metastatic human epidermal growth factor receptor 2 (HER2)-positive gastric or gastro-oesophageal junction adenocarcinoma whose tumours express programmed cell death ligand 1 (PD-L1) (combined positive score [CPS] ≥ 1).

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

Table 4: Research questions of the benefit assessment of pembrolizumab in combination with trastuzumab and a fluoropyrimidine- and platinum-based chemotherapy

Therapeutic indication	**ACT[a]**
Adults with locally advanced unresectable or metastatic HER2-positive gastric or gastro-oesophageal junction adenocarcinoma whose tumours express PD-L1 (CPS ≥ 1); first-line treatment[b]	▪ Trastuzumab in combination with capecitabine and cisplatin or ▪ trastuzumab in combination with 5-fluorouracil and cisplatin
a. Presented is the respective ACT specified by the G-BA. b. It is assumed that radiotherapy with curative intent is not indicated for the patients in the present therapeutic indication. ACT: appropriate comparator therapy; CPS: combined positive score; G-BA: Federal Joint Committee; HER2: human epidermal growth factor receptor 2; PD-L1: programmed cell death ligand 1	

The G-BA adjusted the ACT in October 2023, as shown in Table 4. The company followed the ACT initially defined by the G-BA in November 2022 and named a treatment of physician's choice as the ACT, selecting the following combination therapies: trastuzumab in combination with capecitabine and cisplatin, trastuzumab in combination with 5-fluorouracil and cisplatin, trastuzumab in combination with capecitabine and oxaliplatin, trastuzumab in combination with 5-fluorouracil and oxaliplatin.

The present benefit assessment is conducted in comparison with the ACT currently specified by the G-BA.

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 the 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: 20 November 2023)
- bibliographical literature search on pembrolizumab (last search on 11 November 2023)
- search in trial registries/trial results databases for studies on pembrolizumab (last search on 11 November 2023)
- search on the G-BA website for pembrolizumab (last search on 11 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 study presented in the following table was included in the benefit assessment.

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

Study	Study category			Available sources		
	Study for the approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	CSR (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication (yes/no [citation])
MK-3475-811 (KEYNOTE-811[c])	Yes	Yes	No	Yes [3,4]	Yes [5,6]	Yes [7-9]

a. Study sponsored by the company.
b. References of trial registry entries and any available reports on the study design and/or results listed in the trial registries.
c. In the tables below, the study will be referred to using this acronym.
CSR: clinical study report; RCT: randomized controlled trial

In agreement with the company, the study pool of the present benefit assessment comprises the RCT KEYNOTE-811, in which pembrolizumab + trastuzumab + fluoropyrimidine- and platinum-based chemotherapy was compared with placebo + trastuzumab + fluoropyrimidine- and platinum-based chemotherapy. The fluoropyrimidine- and platinum-

based chemotherapy regimens used in the study were 5-fluorouracil + cisplatin (FP), capecitabine + oxaliplatin (CAPOX) and a combination of S-1 (fixed combination of tegafur, gimeracil and oteracil) and oxaliplatin. However, only treatment with FP is included in the G-BA's ACT.

The section below describes the study as well as the study's subpopulation relevant for the assessment.

I 3.2 Study characteristics

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

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

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
KEYNOTE-811	RCT, double-blind, parallel	Adults[b] with histologically or cytologically confirmed, locally advanced unresectable or metastatic HER2-positive[c] gastric or gastro-oesophageal junction adenocarcinoma, who have not yet received therapy for the advanced disease ▪ ECOG PS ≤ 1	<u>Global cohort</u> pembrolizumab + trastuzumab + FP or CAPOX (N = 350) placebo + trastuzumab + FP or CAPOX (N = 348) thereof with PD-L1 CPS ≥ 1: pembrolizumab + trastuzumab + FP or CAPOX (n = 298) placebo + trastuzumab + FP or CAPOX (n = 296) relevant subpopulation thereof[d] pembrolizumab + trastuzumab + FP (n = 47) placebo + trastuzumab + FP (n = 43) <u>Japan cohort</u>[e] pembrolizumab + trastuzumab + SOX (N = 20) placebo + trastuzumab + SOX (N = 20)	Screening: ≤ 28 days treatment: until disease progression, unacceptable toxicity, investigator's decision, withdrawal of consent, complete response or until completion of treatment for a maximum of 35 cycles (approx. 2 years) with pembrolizumab/placebo[f] observation[g]: outcome-specific, at the longest until death, withdrawal of consent, or end of the study	160 study centres in Australia, Brazil, Chile, China, Germany, France, Great Britain, Guatemala, Ireland, Israel, Italy, Japan, Poland, Russia, Spain, South Korea, Turkey, Ukraine, United States[h] 10/2018–ongoing Data cut-offs: ▪ 14 Jul 2020[i] ▪ 25 May 2022[j] ▪ 29 Mar 2023[k]	Primary: overall survival, PFS Secondary: morbidity, health-related quality of life, AEs

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

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

a. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes include only information on relevant available outcomes for this benefit assessment.
b. As part of the screening, the PD-L1 status was determined using a tumour sample. Both patients with positive and negative PD-L1 status were included.
c. Tumours with IHC 3+ or with IHC 2+ in combination with ISH+ (or FISH) were deemed HER2-positive.
d. Patients whose tumours express PD-L1 (CPS ≥ 1) and who are undergoing FP treatment.
e. This cohort is not relevant for the assessment and is no longer shown in the following tables.
f. Discontinuation of the pembrolizumab/placebo treatment could be considered if the patients achieved a confirmed complete response, were treated with pembrolizumab/placebo for at least 8 cycles, and received at least 2 treatments with pembrolizumab/placebo after the date on which the 1st complete response was observed. Patients from the pembrolizumab arm, who met the above criteria or exhibited stable disease, partial response, or complete response, and had discontinued the study medication after 35 cycles of pembrolizumab for reasons other than disease progression or intolerance, were eligible for another course of treatment for a maximum of 1 year (17 cycles) with pembrolizumab in case of disease progression in the further course that was radiologically confirmed by the investigator ("second course phase"). At the time of the third data cut-off, 8 (approx. 3%) of all patients with PD-L1 CPS ≥ 1 in the intervention arm were in the second course phase. Patients could also, at the discretion of the investigator and after consultation with the sponsor, receive up to 1 year of further treatment with trastuzumab and one of the drugs 5-fluorouracil or capecitabine or S-1 after the completion of 35 cycles.
g. Outcome-specific information is provided in Table 8.
h. The data originate from Module 4 A, according to the CSR 192 study centres in 20 countries; discrepant data are not explained by the company.
i. Interim analysis to take place after at least 8.5 months of observation time following randomization of 260 patients.
j. Interim analysis to take place after at least 542 events in the outcome of PFS (approx. 9 months after randomization of the last patient).
k. Interim analysis to take place after at least 606 events in the outcome of PFS (approx. 18 months after randomization of the last patient).

AE: adverse event; CAPOX: capecitabine + oxaliplatin; CPS: combined positive score; FP: 5-fluorouracil + cisplatin; FISH: fluorescence in situ hybridization; HER2: human epidermal growth factor receptor 2; IHC: immunohistochemistry; ISH: in situ hybridization; n: subpopulation; N: number of randomized patients; PD-L1: programmed cell death ligand 1; PFS: progression-free survival; RCT: randomized controlled trial; SOX: S-1 + oxaliplatin

Table 7: Characteristics of the interventions – RCT, direct comparison: pembrolizumab + trastuzumab + 5-fluorouracil + cisplatin vs. placebo + trastuzumab + 5-fluorouracil + cisplatin (multipage table)

Study	Intervention	Comparison
KEYNOTE-811	Pembrolizumab 200 mg IV (as 30-minute infusion) on day 1 of each 3-week cycle + trastuzumab 8 mg/kg single initial dose and 6 mg/kg maintenance dose IV on day 1 of each 3-week cycle + **FP**: ▪ cisplatin 80 mg/m² BSA, IV, on day 1 of each 3-week cycle[a] + ▪ 5-FU 800 mg/m² BSA/day, continuous IV administration from day 1 to day 5 of a 3-week cycle or according to local standards (a total of 4000 mg/m² BSA per cycle) or **CAPOX**: ▪ oxaliplatin 130 mg/m² BSA, IV, on day 1 of each 3-week cycle + ▪ capecitabine orally 1000 mg/m² BSA twice daily on days 1 to 14 of each 3-week cycle	Placebo IV (as 30-minute infusion) on day 1 of each 3-week cycle + trastuzumab 8 mg/kg single initial dose and 6 mg/kg maintenance dose IV on day 1 of each 3-week cycle + **FP**: ▪ cisplatin 80 mg/m² BSA, IV, on day 1 of each 3-week cycle[a] + ▪ 5-FU 800 mg/m² BSA/day, continuous IV administration from day 1 to day 5 of a 3-week cycle or according to local standards (a total of 4000 mg/m² BSA per cycle) or **CAPOX**: ▪ oxaliplatin 130 mg/m² BSA, IV, on day 1 of each 3-week cycle + ▪ capecitabine 1000 mg/m² BSA twice daily on days 1 to 14 of each 3-week cycle
	Dose adjustment: ▪ pembrolizumab and trastuzumab: no dose reduction allowed; therapy interruption or discontinuation possible in case of toxicity, medical/surgical events or logistical reasons not related to the study therapy ▪ chemotherapy: gradual dose reduction in case of toxicity; reduced dose could not be increased again; at most 2 (cisplatin, capecitabine, and 5-FU) or 3 (oxaliplatin) adjustments per therapy component allowed, treatment discontinuation in case of further toxicity	

Table 7: Characteristics of the interventions – RCT, direct comparison: pembrolizumab + trastuzumab + 5-fluorouracil + cisplatin vs. placebo + trastuzumab + 5-fluorouracil + cisplatin (multipage table)

Study	Intervention	Comparison
	Prior treatment not allowed ▪ previous treatment of locally advanced inoperable or metastatic gastric or gastro-oesophageal junction adenocarcinoma ▪ Prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 drug or with a drug directed against another co-inhibitory T-cell receptor ▪ radiotherapy ≤ 14 days before randomization ▪ live vaccines ≤ 30 days before the first dose of study medication **Concomitant treatment** allowed ▪ supportive treatment for chemotherapy not allowed ▪ antineoplastic immunotherapy, chemotherapies or biologic treatments not predefined in the protocol ▪ clinical test medications other than pembrolizumab ▪ radiotherapy except after consultation with the sponsor for symptomatic treatment of solitary lesions or the brain ▪ live vaccinesb ▪ systemic glucocorticoids except for the regulation of symptoms of an AE with suspected immunological aetiology, prevention of vomiting, premedication for contrast agent allergies, treatment of COPD exacerbations or chronic substitution ≤ 10 mg/day prednisone equivalent ▪ brivudine, sorivudine analogues and other inhibitors of the enzyme dihydropyrimidine dehydrogenase should not be administered together with 5-FU or capecitabine therapy ▪ phenytion should not be started with cisplatin therapy	

a. Treatment is limited to 6 cycles; longer treatment was possible at the investigator's discretion.
b. All approved COVID-19 vaccines are allowed.

5-FU: 5-fluorouracil; AE: adverse event; BSA: body surface area; COPD: chronic obstructive pulmonary disease; CPS: combined positive score; FP: 5-fluorouracil + cisplatin; IV: intravenous; PD-1: programmed cell death 1; PD-L1: programmed cell death ligand 1; PD-L2: programmed cell death ligand 2; RCT: randomized controlled trial

The KEYNOTE-811 study is an ongoing, double-blind RCT comparing pembrolizumab in combination with trastuzumab and a fluoropyrimidine- and platinum-based chemotherapy versus placebo in combination with trastuzumab and a fluoropyrimidine- and platinum-based chemotherapy. The study included adults with HER2-positive locally advanced unresectable or metastatic gastric or gastro-oesophageal junction (GEJ) adenocarcinoma who had not yet received any therapy for the treatment of advanced disease. Patients had to have Eastern Cooperative Oncology Group Performance Status (ECOG PS) ≤ 1.

Determination of PD-L1 expression of the tumour tissue was required for study inclusion. Both patients with positive and negative PD-L1 status were included. The test used for PD-L1 testing was the Agilent PD-L1 IHC 22C3 pharmDx kit.

Within the scope of the study, 2 cohorts were planned, one being a global cohort and the other a Japan-specific cohort. Randomization into the individual cohorts was carried out separately and a joint analysis was not planned. In the global cohort, FP and CAPOX were administered as fluoropyrimidine- and platinum-based combination chemotherapy regimens, whereas in the Japan-specific cohort, a combination of S-1 (a fixed combination of tegafur, gimeracil and oteracil) and oxaliplatin was used. The Japan-specific cohort is not relevant for the present benefit assessment due to the treatment regimen deviating from the ACT and is not commented on further below.

The global cohort of the study comprises 698 patients who were randomly assigned in a 1:1 ratio to treatment with pembrolizumab (N = 350) or placebo (N = 348), each in combination with trastuzumab and either FP or CAPOX. Randomization was stratified by region (Western Europe/Israel/North America/Australia vs. Asia vs. the rest of the world), PD-L1 status (negative [CPS < 1] vs. positive [CPS ≥ 1]) and chemotherapy (FP vs. CAPOX). Which chemotherapy (FP or CAPOX) the patients were to receive was decided by the investigator prior to randomization. Only a subpopulation of the global cohort is relevant for the present benefit assessment; this is explained in the section on the relevant subpopulation (see Section I 3.2.1).

Pembrolizumab treatment was largely in compliance with the specifications of the SPC [10]. In deviation from the SPC, pembrolizumab treatment was limited to a maximum treatment duration of 35 cycles (approx. 2 years). According to the SPC, pembrolizumab treatment is to be continued until cancer progression or the occurrence of unacceptable toxicity [10]. Information on the treatment status with the study medication at the 3rd data cut-off relevant for the assessment (see Section I 3.2.2) is not available for the relevant subpopulation (PD-L1 CPS ≥ 1 and FP therapy, see Section I 3.2.1). Data are only available for the 2nd data cut-off for patients treated with FP regardless of PD-L1 status. At this time, 1 out of 53 patients (approx. 2%) in the pembrolizumab arm had completed treatment and 7 patients (approx. 13%) were still undergoing treatment. There are no data available for these patients or for the relevant subpopulation on the number of patients for whom continued treatment would have been medically indicated as per pembrolizumab approval after the end of the 35 cycles at the 3rd data cut-off. In view of the expected small number of patients affected, the lack of data for the relevant subpopulation in the present benefit assessment is of no consequence.

In both study arms of the global cohort, patients received a combination therapy of trastuzumab + FP or trastuzumab + CAPOX in addition to pembrolizumab or placebo (see Table 7). Only patients who have received trastuzumab in combination with FP and who also

have a positive PD-L1 status are relevant for the present benefit assessment (see Section I 3.2.1). According to the SPC, trastuzumab in combination with cisplatin and 5-fluorouracil or capecitabine is approved for the treatment of adults with HER2-positive metastatic gastric or GEJ adenocarcinoma [11]. For patients with locally advanced gastric or GEJ adenocarcinoma, trastuzumab in combination with cisplatin and 5-fluorouracil or capecitabine is not explicitly approved. However, locally advanced disease is present in only 4 (4%) of patients treated with FP regardless of PD-L1 status (see Table 7). This proportion is considered negligible. Treatment with trastuzumab in the study was largely in compliance with the specifications of the SPC [11]. In contrast to this, the study only provided for treatment over 35 cycles, analogous to pembrolizumab/placebo administration, whereas the SPC provides for treatment until progression. However, patients were able to continue trastuzumab + 5-fluorouracil or trastuzumab + capecitabine for 1 additional year following the completion of the 35 cycles, after consultation with the investigator and the sponsor. The SPCs for cisplatin and 5-fluorouracil does not contain any information on the recommended dosage in relation to the combination therapy used [12,13]. The dosages used in the study are recommended according to current National Comprehensive Cancer Network (NCCN) guidelines, however [14,15]. In the study, the administration of cisplatin was limited to 6 cycles, which corresponds to the procedure in the approval study for trastuzumab + cisplatin + 5-fluorouracil or capecitabine in the present therapeutic indication [11]. Longer treatment was possible at the investigator's discretion. Neither the SPC for cisplatin nor the guidelines provide information on a maximum treatment duration with cisplatin [12,14-16]. According to the S3 guideline for gastric and gastro-oesophageal junction adenocarcinomas, the duration of palliative drug tumour therapy should be decided depending on the tumour response, therapy-associated toxicity and patient expectations [16]. In the corresponding section, the procedure in the approval study for trastuzumab is cited as an example where, deviating from the usual procedure, the treatment did not continue until progression or unacceptable toxicity, with the restriction of chemotherapy to 6 cycles.

In the KEYNOTE-811 study, treatment was continued until confirmed disease progression, unacceptable toxicity, treatment discontinuation upon the investigator's discretion, withdrawal of consent, or for a maximum of 35 cycles (see above).

After discontinuation of either pembrolizumab or placebo, trastuzumab, cisplatin or oxaliplatin and/or 5-fluorouracil or capecitabine, treatment could be continued with the remaining drug component(s). The study materials do not contain any information on restrictions regarding subsequent therapies. In the event of progression, patients in the pembrolizumab arm could be treated with pembrolizumab again for up to 1 year (17 cycles) under certain conditions ("second course phase"; see Table 6). At the time of the third data cut-off, 8 (approx. 3%) of all patients with PD-L1 CPS ≥ 1 in the intervention arm were in the second course phase. Treatment switching from the intervention to the comparator therapy

or vice versa was not permitted. No information on subsequent therapies is available for the relevant subpopulation (see below).

Primary outcomes of the KEYNOTE 811 study were overall survival and progression-free survival. Outcomes on symptoms, health status, health-related quality of life and adverse events (AEs) were recorded as secondary patient-relevant outcomes.

I 3.2.1 Relevant subpopulation

The approval of pembrolizumab in the present therapeutic indication is limited to patients whose tumours express PD-L1 (CPS ≥ 1) [10,17]. The subpopulation presented by the company in Module 4 A includes all 298 patients in the intervention arm and 296 patients in the comparator arm with a CPS ≥ 1. The company uses this subpopulation to derive the added benefit. This includes both patients treated with both CAPOX and FP. The G-BA has defined treatment with trastuzumab in combination with cisplatin and either 5-fluorouracil or capecitabine as an ACT. Therefore, only the subpopulation of patients with a CPS ≥ 1 who received the chemotherapy regimen FP is relevant for the benefit assessment compared to the G-BA's ACT. These were 47 patients in the intervention arm and 43 patients in the comparator arm. Data on these patients are available from subgroup analyses, as the chosen chemotherapy treatment regimen (FP vs. CAPOX) is a prespecified subgroup feature. However, the company does not present this population separately in Module 4 A, so that information on patient characteristics, treatment and study discontinuations, treatment and observation durations, subsequent therapies, response rates for patient-reported outcomes, frequent AEs, specific AEs and subgroup analyses as well as the presentation of Kaplan-Meier curves for the event time analyses are missing. The absence of the above information is taken into account at the relevant points in the benefit assessment.

I 3.2.2 Data cut-offs

Currently, there are 3 data cut-offs for the KEYNOTE 811 study:

- 1st data cut-off: interim analysis to take place after at least 8.5 months of observation time following randomization of 260 patients
- 2nd data cut-off: interim analysis to take place after at least 542 events in the outcome of PFS (approx. 9 months after randomization of the last patient)
- 3rd data cut-off: interim analysis to take place after at least 606 events in the outcome of PFS (approx. 18 months after randomization of the last patient)

The final analysis of the study is to be event-driven after approximately 551 events in the outcome of overall survival and at least 28 months after the randomization of the last patient. In the event that events occur more slowly than expected, the planned interim analyses as well as the planned final analysis could be performed according to the study protocol with up

to 3 additional months of follow-up observation or when the specified number of events was observed, whichever occurred first.

The current third data cut-off is relevant for the present benefit assessment. The company also uses this data cut-off to derive the added benefit.

I 3.2.3 Planned duration of follow-up observation

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

Table 8: Planned duration of the follow-up observation – RCT, direct comparison: pembrolizumab + trastuzumab + 5-fluorouracil + cisplatin vs. placebo + trastuzumab + 5-fluorouracil + cisplatin

Study **Outcome category** **Outcome**	**Planned follow-up observation**
KEYNOTE-811	
Mortality	
Overall survival	Until death, withdrawal of consent, or end of study (whichever occurred first)
Morbidity	
Symptoms, health status (EORTC QLQ-C30, EORTC QLQ- STO22, EQ-5D VAS)	30 days after treatment discontinuation or end of treatment[a]
Health-related quality of life	
EORTC QLQ-C30	30 days after treatment discontinuation or end of treatment[a]
Side effects[b]	
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, whichever occurred first

a. Patient-reported outcomes were recorded during treatment for a maximum of 1 year or until the end of treatment, whichever occurred first, and 30 days after the end of treatment. In deviation from the information provided by the company in Module 4 A, the questionnaires were only recorded every 2nd cycle after week 12 (every 6 weeks).
b. In the second course phase, the observation of AEs in the intervention arm was resumed; it is unclear whether these surveys were included in the AE analyses presented. At the time of the third data cut-off, 8 (approx. 3%) of all patients with PD-L1 CPS ≥ 1 in the intervention arm were in the second course phase. Data on the proportion in the relevant subpopulation are not available.

AE: adverse event; CPS: combined positive score; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30; EORTC QLQ-STO22: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Gastric Cancer 22; PD-L1: programmed cell death ligand 1; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale

In the KEYNOTE-811 study, only overall survival was recorded until study end. The observation periods for the morbidity and health-related quality of life outcomes are systematically shortened because they were only recorded for up to 1 year or up to 30 days after the end of treatment (whichever occurred first). The observation periods for the side effects outcomes were recorded only for the duration of treatment with the study medication (plus 30 or 90 days). However, drawing a reliable conclusion on the total study period or the time until patient death would require for the outcomes of the morbidity, health-related quality of life, and side effects categories to be recorded over the total period of time, as was the case for survival.

I 3.2.4 Characteristics of the relevant subpopulation

The characteristics of the assessment-relevant subpopulation of the KEYNOTE 811 study (PD-L1 CPS ≥ 1 and FP treatment, see Section I 3.2.1) are not available. The characteristics of all patients in the study who were treated with the FP regime are shown approximately in Section I, Appendix B, Table 17 of the full dossier assessment. This also includes 6 patients (approx. 12%) per treatment arm with negative PD-L1 status (CPS< 1). The selected chemotherapy (FP or CAPOX) was a stratification factor of the study. The mean patient age was about 57 years in the intervention arm and 60 years in the comparator arm. The proportion of men was much higher in the intervention arm, at 79%, than in the comparator arm, at 67%. Around 60 % of all patients came from Western Europe, Israel, North America or Australia. Almost all patients had metastatic disease (94% versus 98%). The primary localization of the carcinoma (GEJ vs. stomach) was 58% vs. 42% in the intervention arm and 45% vs. 55% in the comparator arm.

Information on patients who discontinued treatment or the study are not available for the relevant data cut-off, neither for the population presented as a supplement nor for the relevant subpopulation.

I 3.2.5 Information on the course of the study

Table 9 shows the treatment duration of the patients and the observation period for individual outcomes.

Table 9: Information on study progression – RCT, direct comparison: pembrolizumab + trastuzumab + 5-fluorouracil + cisplatin vs. placebo + trastuzumab + 5-fluorouracil + cisplatin

Study **Duration of the study phase** **Outcome category**	**Pembrolizumab + trastuzumab + FP** **N[a] = 47**	**Placebo + trastuzumab + FP** **N[a] = 43**
KEYNOTE-811		
Treatment duration [months]		
Median [min; max]	ND[b]	ND[b]
Mean (SD)	ND	ND
Observation period [months]		
Overall survival		
Median [min; max]	ND	ND
Mean (SD)	ND	ND
Morbidity (EORTC QLQ-C30, EORTC QLQ-STO22, EQ-5D VAS)		
Median [min; max]	ND	ND
Mean (SD)	ND	ND
Health-related quality of life (EORTC QLQ-C30)		
Median [min; max]	ND	ND
Mean (SD)	ND	ND
Side effects		
Median [min; max]	ND	ND
Mean (SD)	ND	ND

a. Number of randomized patients with positive PD-L1 status (CPS ≥ 1), who have received FP therapy.
b. In the CSR (for the 2nd data cut-off), the median [min; max] of treatment duration in months for patients regardless of PD-L1 status, who have received therapy with FP, is reported to be 8.0 [0.9; 25.3] in the intervention arm and 6.4 [0.2; 35.1] in the comparator arm.

CPS: combined positive score; CSR: clinical study report; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EORTC QLQ-STO22: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Gastric Cancer Module; FP: 5-fluorouracil + cisplatin; max: maximum; min: minimum; N: number of patients; ND: no data; PD-L1: programmed cell death ligand 1; RCT: randomized controlled trial; SD: standard deviation; VAS: visual analogue scale

For the KEYNOTE 811 study, there is no information available for the relevant subpopulation regarding the treatment duration and observation period.

In the CSR, there are details on the treatment duration for the 2nd data cut-off relating to patients treated with FP, regardless of their PD-L1 status. For these patients, the median treatment duration in the intervention arm was 8.0 months and in the comparator arm it was 6.4 months.

I 3.2.6 Subsequent therapies

The company did not submit any information on subsequent therapies in the subpopulation relevant for the assessment.

I 3.2.7 Risk of bias across outcomes (study level)

Table 10 shows the risk of bias across outcomes (risk of bias at study level).

Table 10: Risk of bias across outcomes (study level) – RCT, direct comparison: pembrolizumab + trastuzumab + 5-fluorouracil + cisplatin vs. placebo + trastuzumab + 5-fluorouracil + cisplatin

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-811	Yes	Yes	Yes	Yes	Yes	Yes	Low
RCT: randomized controlled trial							

The risk of bias across outcomes for the KEYNOTE-811 study is rated as low.

I 3.3 Transferability of the study results to the German health care context

The company reports that the KEYNOTE-811 study results are transferable to the German health care context due to the characteristics of the investigated patient population, the study design, the adequate implementation of the ACT, and the approval-compliant use of pembrolizumab.

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
  - Symptoms surveyed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30 (EORTC QLQ-C30) and the EORTC QLQ – Gastric Cancer 22 (EORTC QLQ-STO22)
  - Health status, surveyed using the EQ-5D VAS
- Health-related quality of life
  - Recorded with the EORTC QLQ-C30
- Side effects
  - Serious adverse events (SAEs)
  - Severe AEs (Common-Terminology-Criteria-for-Adverse-Events[CTCAE] grade ≥ 3)
  - Discontinuation due to AEs
  - Cardiac disorders (SOC, severe AEs)
  - Immune-related SAEs and severe 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 11 shows the outcomes for which data were available in the included study.

Table 11: Matrix of outcomes – RCT, direct comparison: pembrolizumab + trastuzumab + 5 fluorouracil + cisplatin vs. placebo + trastuzumab + 5-fluorouracil + cisplatin

Study	Outcomes										
	Overall survival	Symptoms (EORTC QLQ-C30, EORTC QLQ-STO22)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30)	SAEs	Severe AEs[a]	Discontinuation due to AEs	Cardiac disorders (SOC, severe AEs[a])	Immune-related SAEs[b]	Immune-related severe AEs[a,b]	Other specific AEs
KEYNOTE-811	Yes	No[c]	No[c]	No[c]	Yes	Yes	No[c]	No[d]	No[d]	No[d]	No[e]

a. Severe AEs are operationalized as CTCAE grade ≥ 3.
b. In each case, the operationalization of the company-specific MedDRA PT collection from the outcome of adverse events of special interest ("AEOSI, Version 23") was used.
c. No suitable data available; see body of text for reasons.
d. No data for relevant subpopulation.
e. Suitable analyses (time-to-event analyses) of AEs by PT and SOC for the relevant subpopulation not fully available; selecting specific AEs is therefore impossible.

AE: adverse event; AEOSI: adverse event of special interest; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer – Core 30; EORTC QLQ-STO22: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Gastric Cancer 22; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

Notes on outcomes and analyses

Validity of the EORTC QLQ-STO22 for the considered patient population

The EORTC QLQ-STO22 is a gastric cancer-specific add-on module to the EORTC QLQ-C30. There is no specific EORTC questionnaire for patients with GEJ carcinoma. Data on the proportion of patients with gastric or GEJ adenocarcinoma are not available for the relevant subpopulation (PD-L1-positive [CPS ≥ 1] and FP treatment, see Section I 3.2.1). In the approximately considered patient population with FP-treatment regardless of the PD-L1 status, about half of the patients had a gastric adenocarcinoma and the other half had a GEJ adenocarcinoma of the (see Table 17 of the full dossier assessment). According to the current guidelines, GEJ carcinomas are classified as either oesophageal cancer (types I and II) or gastric cancer (type III) according to the Siewert classification [18,19]. Such a classification does not exist for the patients with a GEJ adenocarcinoma in the study. For patients with gastric, oesophageal or GEJ cancer, the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Oesophago-Gastric 25 (QLQ-OG25) was developed. A comparison of the items of the QLQ-OG25 with the QLQ-STO22 shows that the 2 instruments

are largely identical. Considering the extensive agreement between QLQ-STO22 and QLQ-OG25, QLQ-STO22 appears to be sufficiently valid for the considered patient population in the current situation, even though it was primarily developed only for gastric cancer.

Unusable analyses on patient-reported outcomes

For the patient-reported outcomes, the company presented in its dossier analyses for the first deterioration by at least 10 points for the EORTC QLQ-C30 and the EORTC QLQ-STO22 and by at least 15 points for the EQ-5D VAS in the form of time-to-event analyses. Additionally, the company provides descriptive information on the course of the study separately for the 2 treatment arms.

For these analyses, the company presented information on the return rates of the questionnaires in the dossier only for the patient population it considered. This includes all patients with PD-L1 CPS ≥ 1 regardless of the therapy received. However, as the subpopulation relevant to the assessment (CPS ≥ 1 and FP treatment, see Section I 3.2.1) only accounts for around 15% of this population, the available information on the responses for the relevant subpopulation is not informative. It is therefore not possible to estimate the proportion of missing values for the subpopulation relevant to the assessment. Therefore, the available analyses on the outcomes of symptoms, health status and health-related quality of life are not used for the benefit assessment and are only presented as supplementary information (see I Appendix C of the full dossier assessment).

Discontinuation due to AEs

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

For these reasons, the present analyses for the outcome “discontinuation due to AEs” are considered unusable and are not used for the assessment.

Missing data for specific AEs

There are no analyses available for the relevant subpopulation regarding cardiac disorders or immune-mediated AEs. Furthermore, suitable analyses (time-to-event analyses) for AEs according to preferred terms (PT) and SOC for the relevant subpopulation are not fully available, and therefore it was not possible to select any further specific AE.

I 4.2 Risk of bias

Table 12 describes the risk of bias for the results of the relevant outcomes.

Table 12: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: pembrolizumab + trastuzumab + 5-fluorouracil + cisplatin vs. placebo + trastuzumab + 5-fluorouracil + cisplatin

Study	Study level	Outcomes										
		Overall survival	Symptoms (EORTC QLQ-C30, EORTC QLQ-STO22)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30)	SAEs	Severe AEs[a]	Discontinuation due to AEs	Cardiac disorders (SOC, severe AEs[a])	Immune-related SAEs[b]	Immune-related severe AEs[a,b]	Other specific AEs
KEYNOTE-811	L	L	–[c]	–[c]	–[c]	H[d]	H[d]	–[e]	–[f]	–[f]	–[f]	–[g]

a. Severe AEs are operationalized as CTCAE grade ≥ 3.
b. In each case, the operationalization of the company-specific MedDRA PT collection from the outcome of adverse events of special interest ("AEOSI, Version 23") was used.
c. No suitable data available; see Section I 4.1 for reasons.
d. Incomplete observations to be assumed for potentially informative reasons; (for reasons, see body of text).
e. No usable data; see Section I 4.1 for reasons.
f. No data available for the relevant subpopulation
g. Suitable analyses (time-to-event analyses) of AEs by PT and SOC for the relevant subpopulation not fully available; selecting specific AEs is therefore impossible.

AE: adverse event; AEOSI: adverse event of special interest; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer – Core 30; EORTC QLQ-STO22: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Gastric Cancer 22; H: high; L: low; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

The risk of bias of the result on the outcome of overall survival was rated as low.

The risk of bias for the SAEs and severe AEs was rated as high. The survey was tied to the (premature or planned) end of treatment. Information is missing for the relevant subpopulation about the reasons that led to treatment discontinuation (and thus also to discontinuation of observation), including information on the frequency per treatment arm. Furthermore, it would be desirable to have information about when these discontinuations occurred. However, 2nd data cut-off data on the frequencies of discontinuation reasons for patients regardless of their PD-L1 status who received treatment with FP indicate very high discontinuation rates due to potentially informative reasons in both arms (see Table 17 of the full dossier assessment). A similar problem can be assumed for the relevant subpopulation, leading to a high risk of bias.

For symptoms outcomes, measured with the EORTC QLQ-C30 and the EORTC QLQ-STO22, the outcome "health status", measured with the EQ-5D VAS, as well as the outcomes "health-related quality of life", measured with the EORTC QLQ-C30, the outcome of discontinuation due to AEs, cardiac disorders, immune-related SAEs and severe AEs as well as possibly further specific AEs there is no assessment of the risk of bias, since either no or no suitable analyses are available (see Section I 4.1).

I 4.3 Results

Table 13 summarises the results comparing pembrolizumab + trastuzumab + 5-fluorouracil + cisplatin with placebo + trastuzumab + 5-fluorouracil + cisplatin in patients with locally advanced, unresectable or metastatic HER2-positive gastric or GEJ adenocarcinoma whose tumours express PD-L1 (CPS ≥ 1). Where necessary, IQWiG calculations are provided to supplement the data from the company's dossier.

Results on frequent AEs, frequent SAEs, frequent severe AEs, all AEs that led to treatment discontinuation, as well as on frequent immune-related AEs, SAEs and severe AEs are not (fully) available for the relevant subpopulation and are therefore not presented. Kaplan-Meier curves for the time-to-event analyses are also not available for the relevant subpopulation.

Table 13: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: pembrolizumab + trastuzumab + 5-fluorouracil + cisplatin vs. placebo + trastuzumab + 5-fluorouracil + cisplatin (multipage table)

Study Outcome category Outcome	Pembrolizumab + trastuzumab + FP		Placebo + trastuzumab + FP		Pembrolizumab + trastuzumab + FP vs. placebo + trastuzumab + FP
	N	Median time to event in months [95% CI][a] Patients with event n (%)	N	Median time to event in months [95% CI][a] Patients with event n (%)	HR [95 %-CI]; p-value[b]
KEYNOTE-811					
Mortality					
Overall survival	47	16.4 [10.2; 20.1] 40 (85.1)	43	11.2 [8.2; 15.3] 38 (88.4)	0.77 [0.50; 1.21]; 0.260
Morbidity					
Symptoms					
EORTC QLQ-C30			No suitable data available[c]		
EORTC QLQ-STO22			No suitable data available[c]		
Health status					
EQ-5D VAS			No suitable data available[c]		
Health-related quality of life					
EORTC QLQ-C30			No suitable data available[c]		
Side effects					
AEs (supplementary information)	47	0.1 [0.1; 0.3][d] 46 (97.9)	42	0.2 [0.1; 0.3][d] 42 (100.0)	–
SAEs	47	13.3 [5.3; NC][d] 23 (48.9)	42	12.6 [4.5; NC][d] 21 (50.0)	0.88 [0.48; 1.60]; 0.673
Severe AEs[e]	47	2.3 [1.1; 3.7][d] 39 (83.0)	42	2.4 [1.4; 6.7][d] 28 (66.7)	1.37 [0.84; 2.22]; 0.209
Discontinuation due to AEs			No suitable data available[c]		
Cardiac disorders (SOC, severe AEs[e])	ND	ND	ND	ND	ND
Immune-related AEs[f] (supplementary information)	ND	ND	ND	ND	–
Immune-related SAEs[f]	ND	ND	ND	ND	ND
Immune-related severe AEs[e,f]	ND	ND	ND	ND	ND
Other specific AEs			No suitable data available[g]		

Table 13: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: pembrolizumab + trastuzumab + 5-fluorouracil + cisplatin vs. placebo + trastuzumab + 5-fluorouracil + cisplatin (multipage table)

Study Outcome category Outcome	Pembrolizumab + trastuzumab + FP		Placebo + trastuzumab + FP		Pembrolizumab + trastuzumab + FP vs. placebo + trastuzumab + FP
	N	Median time to event in months [95% CI][a] Patients with event n (%)	N	Median time to event in months [95% CI][a] Patients with event n (%)	HR [95 %-CI]; p-value[b]

a. Kaplan-Meier estimate.
b. HR, CI and p-value: Cox proportional hazards model with Wald CI and two-sided Wald test, unstratified.
c. For explanation see Section I 4.1; results on morbidity and health-related quality of life are also presented in Section I Appendix B of the full dossier assessment.
d. Institute's calculation from weeks to months.
e. Operationalized as CTCAE grade ≥ 3.
f. In each case, the operationalization of the company-specific MedDRA PT collection from the outcome of adverse events of special interest ("AEOSI, Version 23") was used.
g. Suitable analyses (time-to-event analyses) of AEs by PT and SOC for the relevant subpopulation not fully available; selecting specific AEs is therefore impossible.

AE: adverse event; AEOSI: adverse event of special interest; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EORTC QLQ-STO22: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Gastric Cancer 22; FP: 5-fluorouracil + cisplatin; HR: hazard ratio; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least 1) event; N: number of analysed patients; NC: not calculable; ND: no data; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

The available information allows deriving no more than an indication, e.g. of an added benefit, for the outcome of overall survival. For all other outcomes, for which results relevant for benefit assessment are available, at most hints, e.g. of an added benefit, can be determined (see Section I 4.2).

Mortality

Overall survival

For the outcome of overall survival, no statistically significant difference between treatment groups was found. This results in no indication of an added benefit of pembrolizumab + trastuzumab + 5-fluorouracil + cisplatin in comparison with trastuzumab + 5-fluorouracil + cisplatin; an added benefit is therefore not proven.

Morbidity

Symptoms (EORTC QLQ-C30 and EORTC QLQ-STO22)

With regard to symptoms outcomes, measured using the EORTC QLQ-C30 and the EORTC QLQ-STO22, the available analyses on first deterioration cannot be interpreted due to a lack of information on response rates for the relevant subpopulation and are therefore not used for the benefit assessment (see Section I 4.1). This results in no hint of an added benefit of pembrolizumab + trastuzumab + 5-fluorouracil + cisplatin in comparison with trastuzumab + 5-fluorouracil + cisplatin; an added benefit is therefore not proven in each case.

The results regarding the symptoms outcomes are additionally presented in Section I Appendix C of the full dossier assessment. Even assuming that the response rates were sufficiently high and the results could therefore be interpreted, there was only a single, no more than minor effect between the treatment groups for the symptom of diarrhoea.

Health status (EQ-5D VAS)

With regard to the outcome of health status, measured using the EQ-5D VAS, the available analyses on first deterioration cannot be interpreted due to a lack of information on response rates for the relevant subpopulation and are therefore not used for the benefit assessment (see Section I 4.1). This results in no hint of an added benefit of pembrolizumab + trastuzumab + 5-fluorouracil + cisplatin in comparison with trastuzumab + 5-fluorouracil + cisplatin; an added benefit is therefore not proven.

The results regarding the outcome of health status are additionally presented in Section I Appendix C of the full dossier assessment. Even assuming that the response rates were sufficiently high and the results could therefore be interpreted, there would be no advantages or disadvantages for the intervention in the outcome “health status”.

Health-related quality of life

EORTC QLQ-C30

With regard to health-related quality of life, measured using the EORTC QLQ-C30, the available analyses on first deterioration cannot be interpreted due to a lack of information on response rates for the relevant subpopulation and are therefore not used for the benefit assessment (see Section I 4.1). This results in no hint of an added benefit of pembrolizumab + trastuzumab + 5-fluorouracil + cisplatin in comparison with trastuzumab + 5-fluorouracil + cisplatin; an added benefit is therefore not proven.

The results regarding the health-related quality of life outcomes are additionally presented in Section I Appendix C of the full dossier assessment. Even assuming that the response rates were sufficiently high and the results could therefore be interpreted, there would be no

advantages or disadvantages for the intervention in the outcomes on health-related quality of life.

Side effects

According to the study protocol, progression events of the underlying oncological disease were not to be recorded as AEs. The Medical Dictionary for Regulatory Activities (MedDRA) terms “neoplasm progression”, “malignant neoplasm progression” and “disease progression” were excluded from the AE recording.

SAEs, severe AEs

There were no statistically significant differences between treatment groups for the outcomes of SAEs and severe AEs. This results in no hint of greater or lesser harm from pembrolizumab + trastuzumab + 5-fluorouracil + cisplatin in comparison with trastuzumab + 5-fluorouracil + cisplatin; an added benefit is therefore not proven in each case.

Discontinuation due to AEs, cardiac disorders (severe AEs), immune-related SAEs, immune-related severe AEs

No suitable or no analyses are available for the outcomes of discontinuation due to AEs, cardiac disorders (severe AEs), immune-related AEs and immune-related severe AEs (see Section I 4.1). This results in no hint of greater or lesser harm from pembrolizumab + trastuzumab + 5-fluorouracil + cisplatin in comparison with trastuzumab + 5-fluorouracil + cisplatin; an added benefit is therefore not proven in each case.

Immune-related AEs occur specifically in connection with treatment with PD-1 inhibitors such as pembrolizumab. Since no analyses on outcomes of immune-related AEs are available for the relevant subpopulation, no potentially negative effects of the intervention on the outcome immune-related AEs were identified.

Other specific AEs

It was not possible to select any further specific AEs because suitable analyses (time-to-event analyses) by PT and SOC were not fully available for the relevant subpopulation.

I 4.4 Subgroups and other effect modifiers

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

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

Subgroup analyses of the 2 characteristics mentioned were planned a priori. For the outcomes “immune-related SAEs” and “immune-related severe AEs”, subgroup analyses are completely missing.

The subgroup analyses conducted by the company in Module 4 A refer to all patients with positive PD-L1 status (CPS ≥ 1). There are no subgroup results for the relevant subpopulation.

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 14).

Table 14: Extent of added benefit at outcome level: pembrolizumab + trastuzumab + 5-fluorouracil + cisplatin vs. trastuzumab + 5-fluorouracil + cisplatin (multipage table)

Outcome category **Outcome**	**Pembrolizumab + trastuzumab + 5-fluorouracil + cisplatin vs. placebo + trastuzumab + 5-fluorouracil + cisplatin** **Median time to event in months** **HR [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Outcomes with observation over the entire study duration		
Mortality		
Overall survival	16.4 vs. 11.2 0.77 [0.50; 1.21] p = 0.260	Lesser/added benefit not proven
Outcomes with shortened observation period		
Morbidity		
Symptoms (EORTC QLQ-C30 and QLQ-STO22)	No suitable data[c]	Lesser/added benefit not proven
Health status (EQ-5D VAS)	No suitable data[c]	Lesser/added benefit not proven
Health-related quality of life		
EORTC QLQ-C30	No suitable data[c]	Lesser/added benefit not proven

Table 14: Extent of added benefit at outcome level: pembrolizumab + trastuzumab + 5-fluorouracil + cisplatin vs. trastuzumab + 5-fluorouracil + cisplatin (multipage table)

Outcome category **Outcome**	**Pembrolizumab + trastuzumab + 5-fluorouracil + cisplatin vs. placebo + trastuzumab + 5-fluorouracil + cisplatin** **Median time to event in months** **HR [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Side effects		
SAEs	13.3 vs. 12.6 0.88 [0.48; 1.60] p = 0.673	Greater/lesser harm not proven
Severe AEs	2.3 vs. 2.4 1.37 [0.84; 2.22] p = 0.209	Greater/lesser harm not proven
Discontinuation due to AEs	No suitable data[c]	Greater/lesser harm not proven
Cardiac disorders (severe AEs)	No suitable data[c]	Greater/lesser harm not proven
Immune-related SAEs	No data[c]	Greater/lesser harm not proven
Immune-related severe AEs	No data[c]	Greater/lesser harm not proven
Other specific AEs	No data[d]	Greater/lesser harm not proven

a. Probability provided if there is a statistically significant and relevant effect.
b. Depending on the outcome category, the effect size is estimated using different limits based on the upper limit of the confidence interval (CI_u).
c. For an explanation, see section (Section I 4.1).
d. Suitable analyses (time-to-event analyses) of AEs by PT and SOC for the relevant subpopulation not fully available; selecting specific AEs is therefore impossible.

AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30; EORTC QLQ-STO22: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Gastric Cancer 22; HR: hazard ratio; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

I 5.2 Overall conclusion on added benefit

Table 15 summarizes the results taken into account in the overall conclusion on the extent of added benefit.

Table 15: Positive and negative effects from the assessment of pembrolizumab + trastuzumab + 5-fluorouracil + cisplatin+ vs. trastuzumab + 5-fluorouracil + chemotherapy

Positive effects	**Negative effects**
Outcomes with observation over the entire study duration	
–	–
Outcomes with shortened observation period	
–	–
No suitable data are available on the outcome categories of morbidity and health-related quality of life, on cardiac disorders and immune-related AEs or for the selection of other specific AEs.	
AE: adverse event	

Overall, neither positive nor negative effects were shown based on the available data. The impact of the missing data in the relevant subpopulation cannot be conclusively determined. The additional results presented on patient-reported outcomes in the categories of morbidity and health-related quality of life show no more than minor effects between the treatment groups. In view of the lack of analyses on immune-related AEs, a potential disadvantage for the intervention is to be expected.

In summary, for patients with locally advanced, non-resectable or metastatic HER2-positive gastric or GEJ adenocarcinoma whose tumours express PD-L1 (CPS ≥ 1, there is no hint of an added benefit from pembrolizumab + trastuzumab + 5-fluorouracil + cisplatin over trastuzumab + 5-fluorouracil + cisplatin, thus an added benefit is not proven.

The result of the assessment of the added benefit of pembrolizumab + trastuzumab + 5-fluorouracil + cisplatin in comparison with the ACT is summarized in Table 16.

Table 16: Pembrolizumab + trastuzumab + 5-fluorouracil + cisplatin – probability and extent of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
Adults with locally advanced unresectable or metastatic HER2-positive gastric or gastro-oesophageal junction adenocarcinoma whose tumours express PD-L1 (CPS ≥ 1); first-line treatment[b]	▪ Trastuzumab in combination with capecitabine and cisplatin or ▪ trastuzumab in combination with 5-fluorouracil and cisplatin	Added benefit not proven
a. Presented is the respective ACT specified by the G-BA. b. It is assumed that radiotherapy with curative intent is not indicated for the patients in the present therapeutic indication. ACT: appropriate comparator therapy; CPS: combined positive score; G-BA: Federal Joint Committee; HER2: human epidermal growth factor receptor 2; PD-L1: programmed cell death ligand 1		

The assessment described above deviates from that of the company, which, in deviation from the present benefit assessment, uses all patients with PD-L1 CPS ≥ 1 to derive the added benefit and, based on this, derives an indication 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.

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The full report (German version) is published under https://www.iqwig.de/en/projects/a24-01.html.