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Pembrolizumab (MSI-H or dMMR gastric cancer) –

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

Extract

[1] Translation of Sections I 1 to I 5 of the dossier assessment *Pembrolizumab (Magenkarzinom mit MSI-H oder dMMR) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 26 October 2022). Please note: This document was translated by an external translator and is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

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
BSA	body surface area
BSC	best supportive care
CTCAE	Common Terminology Criteria for Adverse Events
dMMR	mismatch repair deficient
ECOG-PS	Eastern Cooperative Oncology Group – Performance Status
EORTC	European Organisation for Research and Treatment of Cancer
EQ-5D	European Quality of Life – 5 Dimensions
FAS	full analysis set
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
GEJ	gastro-oesophageal junction
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MSI-H	microsatellite instability high
PD-L1	programmed cell death ligand 1
PT	Preferred Term
QLQ-C30	Quality of Life Questionnaire – Core 30
QLQ-STO22	EORTC QLQ – Gastric Cancer 22
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SOC	System Organ Class
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. 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 25 July 2022.

Research question

The aim of the present report is to assess the added benefit of pembrolizumab in comparison with the appropriate comparator therapy (ACT) in adult patients with unresectable or metastatic microsatellite instability high (MSI-H) or mismatch repair deficient (dMMR) gastric cancer who have disease progression on or following at least 1 prior therapy.

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

Table 2: Research questions of the benefit assessment of pembrolizumab

Research question	Therapeutic indication	ACT[a, b]
1	Adults with unresectable or metastatic MSI-H or dMMR gastric cancer who have disease progression on or following 1 prior therapy[c]	Treatment of physician's choice[d]
2	Adults with unresectable or metastatic MSI-H or dMMR gastric cancer who have disease progression on or following at least 2 prior therapies[c]	Trifluridine/tipiracil

a. Presented is the respective ACT specified by the G-BA.
b. According to the G-BA, the ACT was specified in light of on the fact that 95% of stomach cancers are adenocarcinomas. Therefore, no separate ACT was defined for other histologies.
c. Presumably, curative treatment with definitive chemoradiotherapy is not an option for patients with unresectable cancer.
d. For the present treatment situation, guidelines recommend systemic therapy. Based on their approval status, options for this purpose are the drug ramucirumab or the drug combination ramucirumab plus paclitaxel. The drugs irinotecan, docetaxel, and paclitaxel (monotherapy) have not been approved for the present therapeutic indication. There is a discrepancy between the drugs approved in the therapeutic indication and those recommended by guidelines. As part of a clinical trial, the following treatment options are deemed suitable comparators for treatment according to physician's choice: irinotecan, docetaxel, paclitaxel, and ramucirumab in combination with paclitaxel. Added benefit can be assessed versus one of the cited treatment options within the framework of a single-comparator study.

ACT: appropriate comparator therapy; dMMR: mismatch repair deficiency; G-BA: Federal Joint Committee; MSI-H: microsatellite instability high

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

- patients with disease progression on or following 1 prior therapy
- patients with disease progression on or following at least 2 prior therapies

The company used the specified ACT.

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

Research question 1: Patients with disease progression on or following 1 prior therapy

Study pool and study design

A subpopulation of the KEYNOTE 061 study was used for the benefit assessment. The KEYNOTE 061 study is an open-label randomized controlled trial (RCT) comparing pembrolizumab versus paclitaxel. The study enrolled adult patients with metastatic or locally advanced, unresectable gastric or gastro-oesophageal junction (GEJ) adenocarcinoma with progression on or following first-line therapy with a platinum-fluoropyrimidine doublet.

A total of 592 patients were randomly allocated in a 1:1 ratio to treatment with pembrolizumab (N = 296) or paclitaxel (N = 296).

Pembrolizumab treatment was largely in compliance with the specifications of the Summary of Product Characteristics (SPC). According to the guidelines, while not approved for this therapeutic indication, paclitaxel is being used for the same. The KEYNOTE 061 study administered paclitaxel intravenously on Days 1, 8, and 15 of a 28-day cycle at a dose of 80 mg/m² body surface area (BSA), followed by a pause on Day 22.

In the KEYNOTE 061 study, treatment was continued until confirmed disease progression, unacceptable toxicity, treatment discontinuation upon the investigator's discretion, or withdrawal of consent. For pembrolizumab, an additional discontinuation criterion was reaching a maximum of 35 treatment cycles.

The study documents provide no information on restrictions regarding subsequent therapies, except that comparator arm participants were not allowed to switch to the intervention arm treatment.

Coprimary outcomes of the KEYNOTE 061 study were overall survival and progression-free survival, each surveyed in patients with tumours expressing programmed cell death ligand 1 (PD-L1). Patient-relevant secondary outcomes were overall survival in all patients irrespective of the tumour's PD-L1 status as well as morbidity, health-related quality of life, and adverse events (AEs) outcomes.

Relevant subpopulation

For assessing the added benefit of pembrolizumab, the company included patients with MSI-H gastric carcinoma. The subpopulation submitted by the company therefore comprised 11 patients in the intervention arm and 10 patients in the comparator arm. This subpopulation was used to inform the benefit assessment.

Data cut-offs

Generally, the results used were from the last data cut-off at study end, 10 June 2021. For patient-reported outcomes, however, results were available only from a data cut-off implemented on 26 October 2017.

Risk of bias

The risk of bias across outcomes was rated as low for the KEYNOTE 061 study. The risk of bias for the outcome of overall survival was deemed low. However, the certainty of results was downgraded for this outcome. This downgrading was due to a lack of information on subsequent therapies as well as the unavailability of the trifluridine/tipiracil drug combination, which is primarily recommended no sooner than third-line therapy. The risk of bias was rated as high for the results of each of the outcomes of the side effects category. No usable analyses are available for the outcome of health status, as measured with the European Quality of Life – 5 Dimensions (EQ-5D) visual analogue scale (VAS), or for the outcome of symptoms and health-related quality of life, as measured with 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). Overall, at most hints, e.g. of an added benefit, can be derived for all outcomes on the basis of the available data.

Results

Time-to-event analyses are used for all outcomes.

Mortality

Overall survival

For the outcome of overall survival, a statistically significant difference was found in favour of pembrolizumab in comparison with paclitaxel. This results in a hint of an added benefit of pembrolizumab in comparison with paclitaxel.

Morbidity

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

No usable analyses were available for the symptoms outcomes, measured with the EORTC QLQ-C30 and the EORTC QLQ-STO22. Consequently, there is no hint of added benefit of pembrolizumab in comparison with paclitaxel; an added benefit is therefore not proven.

Health status (EQ-5D VAS)

No usable analyses are available for the outcome of health status, measured with the EQ-5D VAS. Consequently, there is no hint of added benefit of pembrolizumab in comparison with paclitaxel; an added benefit is therefore not proven.

Health-related quality of life

EORTC QLQ-C30

No usable analyses are available for health-related quality of life, measured with the EORTC QLQ-C30. Consequently, there is no hint of added benefit of pembrolizumab in comparison with paclitaxel; an added benefit is therefore not proven.

Side effects

Serious adverse events (SAEs), severe AEs, discontinuation due to AEs, immune-mediated SAEs, immune-mediated severe AEs

No statistically significant differences between treatment groups were found for any of the outcomes of SAEs, severe AEs, discontinuation due to AEs, immune-mediated SAEs, or immune-mediated severe AEs. Hence there was no hint of greater or lesser harm from pembrolizumab in comparison with paclitaxel for any of them; greater or lesser harm is therefore not proven.

Further specific AEs

No usable analyses (time-to-event analyses) by Preferred Terms (PTs) or System Organ Classes (SOCs) are available for selecting further specific AEs.

Research question 2: Patients with disease progression on or following at least 2 prior therapies

Results

The company submitted a comparison of individual arms from different studies between pembrolizumab (KEYNOTE 158 study) and trifluridine/tipiracil (TAGS RCT). The KEYNOTE 158 study is an ongoing, single-arm, cross-entity study on pembrolizumab in adult patients with advanced (metastatic and/or unresectable) solid tumours. For comparing individual arms, the company used a subpopulation of 23 patients with MSI-H gastric carcinoma and at least 2 prior therapies. The TAGS study is a double-blind RCT comparing trifluridine/tipiracil + best supportive care (BSC) versus placebo + BSC. It enrolled adult patients with unresectable, metastatic gastric adenocarcinoma, including GEJ adenocarcinoma. Patients had to have received at least 2 prior treatment regimens for advanced disease. In its comparison of individual arms to assess added benefit, the company used all patients of the trifluridine/tipiracil arm (gastric adenocarcinoma and GEJ adenocarcinoma). No information is available on the study population's MSI-H or dMMR status.

This benefit assessment's research question is to assess the added benefit of pembrolizumab versus the ACT in adult patients with unresectable or metastatic gastric carcinoma with MSI-H or dMMR. Patients whose tumours exhibit neither MSI-H nor dMMR, in contrast, are excluded from the research question. Hence, the TAGS study's trifluridine/tipiracil arm generally fails to reflect this benefit assessment's research question and is unsuitable for deriving added benefit.

Apart from that, the comparisons between individual arms as presented by the company constitute comparisons without a common comparator. Due to the lack of randomization, these comparisons are subject to inherent uncertainty and are not an adequate method for conducting an indirect comparison. Furthermore, any of the effects found in this comparison of individual arms from different studies may potentially result solely from systematic bias due to confounders.

Results on added benefit

Since no suitable data are available for the present research question, there is no hint of an added benefit of pembrolizumab in comparison with the ACT; an added benefit is therefore not proven.

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

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

Research question 1: Patients with disease progression on or following 1 prior therapy

All things considered, there is only 1 favourable effect for the outcome of overall survival. This effect results in a hint of major added benefit. Neither favourable nor unfavourable effects were found in the outcome category of side effects. No usable data are available for the outcome categories of morbidity and health-related quality of life.

The low number of patients in the relevant subpopulation is associated with low precision for the side effects outcomes. This makes it impossible to quantify the added benefit in connection with weighing the benefits versus harm.

In summary, for adult patients with unresectable or metastatic MSI-H or dMMR gastric carcinoma who have disease progression on or following 1 prior therapy, this results in a hint of non-quantifiable added benefit of pembrolizumab in comparison with the ACT.

Data are available only for patients for whom paclitaxel is a suitable treatment option in accordance with treatment of physician's choice. No data are available for patients for whom another treatment option is deemed a suitable treatment of physician's choice.

[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].

Research question 2: Patients with disease progression on or following at least 2 prior therapies

The company has presented no suitable data to assess the added benefit of pembrolizumab in comparison with the ACT in adult patients with unresectable or metastatic MSI-H or dMMR gastric carcinoma who have disease progression on or following at least 2 prior therapies; hence, there is no proof of added benefit.

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

Table 3: Pembrolizumab – probability and extent of added benefit

Research question	**Therapeutic indication**	**ACT[a, b]**	**Probability and extent of added benefit**
1	Adults with unresectable or metastatic MSI-H or dMMR gastric cancer who have disease progression on or following 1 prior therapy[c]	Treatment of physician's choice[d]	Hint of non-quantifiable added benefit[e, f]
2	Adults with unresectable or metastatic MSI-H or dMMR gastric cancer who have disease progression on or following at least 2 prior therapies[c]	Trifluridine/tipiracil	Added benefit not proven

a. Presented is the respective ACT specified by the G-BA.
b. According to the G-BA, the ACT was specified in light of on the fact that 95% of stomach cancers are adenocarcinomas. Therefore, no separate ACT was defined for other histologies.
c. Presumably, curative treatment with definitive chemoradiotherapy is not an option for patients with unresectable cancer.
d. For the present treatment situation, guidelines recommend systemic therapy. Based on their approval status, options for this purpose are the drug ramucirumab or the drug combination ramucirumab plus paclitaxel. The drugs irinotecan, docetaxel, and paclitaxel (monotherapy) have not been approved for the present therapeutic indication. There is a discrepancy between the drugs approved in the therapeutic indication and those recommended by guidelines. As part of a clinical trial, the following treatment options are deemed suitable comparators for treatment according to physician's choice: irinotecan, docetaxel, paclitaxel, and ramucirumab in combination with paclitaxel. The added benefit can be assessed versus one of the cited treatment options within the framework of a single-comparator study.
e. Only patients with an ECOG-PS of 0 or 1 were included in the KEYNOTE 061 study. It remains unclear whether the observed effects are transferable to patients with an ECOG-PS ≥ 2.
f. Data are available only for patients for whom paclitaxel constitutes a suitable treatment option according to physician's choice. No data are available for patients for whom another option is deemed a suitable treatment according to physician's choice.

ACT: appropriate comparator therapy; dMMR: mismatch repair deficiency; ECOG-PS: Eastern Cooperative Oncology Group – Performance Status; G-BA: Federal Joint Committee; MSI-H: microsatellite instability high

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

I 2 Research question

The aim of the present report is to assess the added benefit of pembrolizumab in comparison with the ACT in adult patients with unresectable or metastatic MSI-H or dMMR gastric cancer who have disease progression on or following at least 1 prior therapy.

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

Table 4: Research questions of the benefit assessment of pembrolizumab

Research question	Therapeutic indication	ACT[a, b]
1	Adults with unresectable or metastatic MSI-H or dMMR gastric cancer who have disease progression on or following 1 prior therapy[c]	Treatment of physician's choice[d]
2	Adults with unresectable or metastatic MSI-H or dMMR gastric cancer who have disease progression on or following at least 2 prior therapies[c]	Trifluridine/tipiracil

a. Presented is the respective ACT specified by the G-BA.
b. According to the G-BA, the ACT was specified in light of on the fact that 95% of stomach cancers are adenocarcinomas. Therefore, no separate ACT was defined for other histologies.
c. Presumably, curative treatment with definitive chemoradiotherapy is not an option for patients with unresectable cancer.
d. For the present treatment situation, guidelines recommend systemic therapy. Based on their approval status, options for this purpose are the drug ramucirumab or the drug combination ramucirumab plus paclitaxel. The drugs irinotecan, docetaxel, and paclitaxel (monotherapy) have not been approved for the present therapeutic indication. There is a discrepancy between the drugs approved in the therapeutic indication and those recommended in guidelines. As part of a clinical trial, the following treatment options are deemed suitable comparators for treatment according to physician's choice: irinotecan, docetaxel, paclitaxel, and ramucirumab in combination with paclitaxel. The added benefit can be assessed versus one of the cited treatment options within the framework of a single-comparator study.

ACT: appropriate comparator therapy; dMMR: mismatch repair deficiency; G-BA: Federal Joint Committee; MSI-H: microsatellite instability high

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

- patients with disease progression on or following 1 prior therapy
- patients with disease progression on or following at least 2 prior therapies

The company followed the specification of 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.

I 3 Research question 1: Patients with disease progression on or following 1 prior therapy

I 3.1 Information retrieval and study pool

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

Sources of the company in the dossier:

- study list on pembrolizumab (status: 1 June 2022)
- bibliographical literature search on pembrolizumab (last search on 9 May 2022)
- search in trial registries / trial results databases for studies on pembrolizumab (last search on 18 May 2022)
- search on the G-BA website for pembrolizumab (last search on 18 May 2022)

To check the completeness of the study pool:

- search in trial registries for studies on pembrolizumab (last search on 18 August 2022); for search strategies, see I Appendix A of the full dossier assessment

The check did not identify any additional relevant studies.

I 3.1.1 Studies included

The study presented in the following table was included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: pembrolizumab versus paclitaxel

Study	Study category			Available sources		
	Study for the approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	Clinical study report (CSR) (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication (yes/no [citation])
MK-3475-061 (KEYNOTE 061[c])	No	Yes	No	Yes [3,4]	Yes [5,6]	Yes [7]

a. Study for which the company was sponsor.
b. Citation of the trial registry entries and, if available, of the reports on 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; G-BA: Federal Joint Committee; RCT: randomized controlled trial

Concurring with the company, the study pool for research question 1 of the present benefit assessment comprises the KEYNOTE 061 RCT, which compared pembrolizumab with paclitaxel. Consequently, the study lends itself only to drawing conclusions on the added benefit

of pembrolizumab in patients for whom paclitaxel represents a suitable treatment according to physician's choice.

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

I 3.1.2 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 versus paclitaxel (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
KEYNOTE 061	RCT, open-label, parallel-group	Adults (≥ 18 years) with metastatic or locally advanced unresectable gastric or gastro-oesophageal junction adenocarcinoma with ▪ progression on or following first-line therapy with a platinum-fluoropyrimidine doublet ▪ PD-L1 expression of the tumour[b] ▪ ECOG-PS 0 or 1	Pembrolizumab (N = 296) Paclitaxel (N = 296) Relevant subpopulation thereof[c]: ▪ Pembrolizumab (n = 11) ▪ Paclitaxel (n = 10)	▪ Screening: up to 28 days ▪ Treatment: until disease progression, unacceptable toxicity, treatment discontinuation upon the physician's discretion, withdrawal of consent, or completion of pembrolizumab treatment with a maximum of 35 cycles (about 2 years)[d] ▪ Observation[e]: outcome-specific, at most until death or end of study	140 study centres in Argentina, Australia, Belgium, Canada, Chile, Columbia, Denmark, England, Estonia, Finland, Germany, Guatemala, Hong Kong, Ireland, Israel, Italy, Japan, Malaysia, Mexico, New Zealand, Norway, Poland, Russia, Singapore, Spain, South Africa, South Korea, Taiwan, Turkey, United States 05/2015 – 06/2021 Data cut-offs[f]: ▪ 26/10/2017 (final analysis for overall survival[g]) ▪ 10/06/2021 (analysis at study end[g, h])	Primary[i]: progression-free survival, overall survival Secondary: overall survival[j], morbidity, health-related quality of life, AEs

Table 6: Characteristics of the study included – RCT, direct comparison: pembrolizumab versus paclitaxel (multipage table)

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

a. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes only include information on relevant available outcomes for this benefit assessment.
b. From 20 March 2016, the recommendation was not to include any patients with negative PD-L1 status (implemented with Amendment 7 of the protocol dated 18 August 2016). The first patient was included on 11 May 2015. The last patient was enrolled on 27 July 2016. A total of 99 patients (33%) versus 96 patients (32%) with negative PD-L1 status were included.
c. Patients with gastric cancer and MSI-H.
d. Discontinuation of pembrolizumab treatment was an option if patients met all of the following criteria: (a) achieved confirmed complete response, (b) received at least 24 weeks of pembrolizumab treatment, and (c) received at least 2 pembrolizumab treatments after the date the 1st complete response was determined. In case of radiologically confirmed disease progression in the further course, patients 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 pembrolizumab treatment ("second course phrase") for a maximum of 1 year. At study end (10 June 2021 data cut-off), a total of 20 patients (7%) from the total population and 6 patients (55%) from the relevant subpopulation had completed study treatment with pembrolizumab. Information on the number of patients who, until study end, received treatment in the second course phase is not available for the total population nor for the relevant subpopulation.
e. Outcome-specific information is described in Table 8.
f. Alongside the data cut-offs for the final analysis of overall survival and at study end, other data cut-offs were implemented for interim analyses. The last data cut-off (10 June 2021) was used for deriving added benefit. For patient-reported outcomes, however, results are available only from a 26 October 2017 data cut-off (see Section I 3.1.2.3).
g. The final analysis was planned to occur after at least 290 events for overall survival in patients with PD-L1-expressing tumours or about 15 months after the last patient was randomized, whichever was later.
h. Planned to occur after the last visit or study discontinuation or after the last patient was lost to follow-up. In 14 patients (7%) versus 6 patients (3%) with PD-L1-expressing tumours, the reason for study discontinuation was "study discontinuation by sponsor"; in the relevant subpopulation, this applied to 5 patients (45%) versus 1 patient (10%). It is unclear what prompted the timing of the last visit and hence study end (see Section I 3.1.2.3).
i. In patients with PD-L1-expressing tumours.
j. In all patients, irrespective of PD-L1 status.

AE: adverse event; ECOG-PS: Eastern Cooperative Oncology Group – Performance Status; MSI-H: microsatellite instability high; n: relevant subpopulation; N: number of randomized patients; PD-L1: programmed cell death ligand 1; RCT: randomized controlled trial

Table 7: Characteristics of the intervention – RCT, direct comparison: pembrolizumab versus paclitaxel

Study	Intervention	Comparison
KEYNOTE 061	Pembrolizumab 200 mg i.v. every 3 weeks	Paclitaxel 80 mg/m² BSA i.v. on Days 1, 8 and 15 of each 28-day cycle
	▪ No dose adjustments allowed ▪ Dose interruptions or permanent discontinuation of the study medication according to the SPC [8]	▪ Dose reductions down to permanent discontinuation due to AEs were allowed
	Pretreatment ▪ First-line therapy with platinum-fluoropyrimidine doublet **Nonpermitted pretreatment** ▪ Immunotherapy with an anti-PD 1, anti-PD-L1, or anti-PD-L2 drug ▪ Systemic steroid therapy or another form of immunosuppressive therapy within 7 days before the 1st dose of the study treatment ▪ Administration of an anticancer monoclonal antibody within 4 weeks prior to study start ▪ Chemotherapy, targeted therapy with small molecules, or radiotherapy within 2 weeks prior to study start **Permitted concomitant treatment** ▪ Appropriate supportive treatment if deemed necessary by the investigator ▪ Radiotherapy of symptomatic solitary lesions or of the brain in consultation with the sponsor **Nonpermitted concomitant treatment** (during the screening and treatment phase) ▪ Antineoplastic systemic chemotherapy or biologic therapy ▪ Radiotherapy (see allowed concomitant treatment for exceptions) ▪ Pembrolizumab arm: systemic glucocorticoids for purposes other than the treatment of symptoms of immunological origin	

AE: adverse event; BSA: body surface area; 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 3.1.2.1 Study design

The KEYNOTE 061 study is an open-label RCT comparing pembrolizumab versus paclitaxel. The study enrolled adult patients with metastatic or locally advanced, unresectable gastric or GEJ adenocarcinoma with progression on or following first-line therapy with a platinum-fluoropyrimidine doublet. At study start, patient inclusion was allowed irrespective of the tumour's PD-L1 expression. Protocol amendment 7 specified that, starting on 20 March 2016, only patients with PD-L1-expressing tumours were to be enrolled; a total of 99 patients (33%) versus 96 patients (32%) exhibited no PD-L1 expression of the tumour. Enrolment was limited to patients with Eastern Cooperative Oncology Group Performance Status (ECOG-PS) ≤ 1.

A total of 592 patients were randomly allocated in a 1:1 ratio to treatment with pembrolizumab (N = 296) or paclitaxel (N = 296). Randomization was stratified by region (Europe, Israel, North America, Australia versus Asia [including Japan, Korea, Hong Kong, Taiwan, Malaysia, Philippines, Singapore] versus the rest of the world [including South America]), time to disease progression on first-line therapy (< 6 months versus ≥ 6 months), and tumour PD-L1expression (positive versus negative).

Pembrolizumab treatment was largely in compliance with the specifications of the SPC [8]. 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 [8]. By the 10 June 2021 data cut-off at the end of the KEYNOTE 061 study, study treatment with pembrolizumab had been completed by 20 patients (7%) from the total population and 6 patients (55%) from the relevant subpopulation (see Section I 3.1.2.2 for the definition). Neither for the total population nor for the relevant subpopulation are data available 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.

Paclitaxel is not approved in the therapeutic indication [9]. The KEYNOTE 061 study administered paclitaxel intravenously on Days 1, 8, and 15 of a 28-day cycle at a dose of 80 mg/m² BSA, followed by a pause on Day 22. While the S3 guideline on the diagnosis and treatment of gastric and GEJ adenocarcinoma discusses a weekly dosage of 80 mg/m^2 BSA [10], the publications cited in the guideline [11,12] applied the dosing regimen implemented in the KEYNOTE 061 study, including a pause on Day 22.

In the KEYNOTE 061 study, treatment was continued until confirmed disease progression, unacceptable toxicity, treatment discontinuation upon the investigator's discretion, or withdrawal of consent. For pembrolizumab, an additional discontinuation criterion was reaching of a maximum of 35 treatment cycles (see above).

The study documents provide no information on restrictions regarding subsequent therapies, except that comparator arm participants were not allowed to switch to the intervention arm treatment. No information on subsequent therapies is available for the relevant subpopulation (see Section I 3.1.2.7).

Coprimary outcomes of the KEYNOTE 061 study were overall survival and progression-free survival, each in patients with tumours expressing PD-L1. Patient-relevant secondary outcomes were overall survival in all patients irrespective of the tumour's PD-L1 status as well as morbidity, health-related quality of life, and AE outcomes.

I 3.1.2.2 Relevant subpopulation

The tumour's microsatellite stability was tested in all KEYNOTE 061 study participants. A total of 15 of 296 patients (< 1%) in the intervention arm and 12 of 296 patients (< 1%) in the comparator arm had MSI-H tumours (gastric or GEJ tumours). For assessing the added benefit of pembrolizumab in the present research question, Module 4 C of the company's dossier included patients with MSI-H gastric cancer. The subpopulation submitted by the company comprised 11 patients in the intervention arm and 10 patients in the comparator arm. According to the guidelines, tumours whose centre is located > 2 cm from the GEJ are classified as gastric cancer even if they involve the GEJ [10,13]. Presumably, the KEYNOTE 061 study allocated

GEJ tumours in accordance with guidelines. Therefore, the company's restriction to MSI-H gastric tumours is adequate and is taken into account in the benefit assessment.

I 3.1.2.3 Data cut-offs

The KEYNOTE 061 study enrolled the first patient in May 2015. Between January 2016 and October 2019, analyses were conducted for a total of 8 data cut-offs (interim analyses and final analysis for overall survival). Another analysis was performed at study end.

The final analysis of overall survival was planned to occur after at least 290 patients with PD-L1-expressing tumours had died or about 15 months after the last patient was randomized, whichever was later. The final analysis of overall survival was conducted using the 26 October 2017 data cut-off. The study report is based on said data cut-off [3].

In Module 4 C, the company presents results on the 10 June 2021 data cut-off. For this data cut-off at study end, results are available in a shortened study report [4]. The study end was planned to occur after the last visit or study discontinuation or after the last patient was lost to follow-up. At the time the study was terminated by the company, few patients were still being observed. In 14 patients (7%) versus 6 patients (3%) with PD-L1-expressing tumours, the reason for study discontinuation was "study discontinuation by sponsor"; within the relevant subpopulation, this applied to 5 patients (45%) versus 1 patient (10%). It is unclear why the study was terminated at exactly this time point. However, the results presented in the dossier's Module 4 C for the relevant subpopulation, which was analysed post hoc, are unlikely to suffer from reporting bias. Therefore, the present benefit assessment is generally based on the results of the last data cut-off, 10 June 2021. For the patient-reported outcomes, however, results are available only from the 26 October 2017 data cut-off (see Section I 3.1.2.3 on the usability of these results).

I 3.1.2.4 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 follow-up observation – RCT, direct comparison: pembrolizumab versus paclitaxel

Study Outcome category Outcome	Planned follow-up observation
KEYNOTE 061	
Mortality	
Overall survival	▪ Until death, revocation of consent, or end of study (whichever is first)
Morbidity	
Symptoms (EORTC QLQ-C30 and EORTC QLQ-STO22) and health status (EQ-5D VAS)	▪ 30 days after the last dose of the study treatment[a]
Health-related quality of life (EORTC QLQ-C30)	▪ 30 days after the last dose of the study treatment[a]
Side effects	
AEs	▪ 30 days after the last dose of the study treatment or start of a new antineoplastic treatment (whichever occurred first)[b]
SAEs	▪ 90 days (or 30 days if the patient starts a new antineoplastic therapy) after the last dose of the study drug (whichever occurred first)[b]

a. Prior to this, the survey was performed in accordance with the study protocol after Week 24 for up to 1 year or until treatment end (whichever occurred first); it is unclear whether the information "up to 1 year" refers to the time after study start or the time after Week 24.
b. In the second-course phase, observation was resumed in the intervention arm. No information is available on the number of patients who received pembrolizumab treatment in the second-course phase up to the present data cut-off of 10 June 2021.

AE: adverse event; 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; EQ-5D: European Quality of Life – 5 Dimensions; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale

In the KEYNOTE 061 study, only overall survival was recorded until study end. The observation durations for the morbidity and health-related quality of life outcomes are systematically shortened because after Week 24, they were surveyed only for up to 1 year or until treatment end (whichever was first) plus 30 days. The observation durations for the side effects outcomes were recorded only for the period of treatment with the study medication (plus 30 or 90 days). 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 3.1.2.5 Characteristics of the relevant subpopulation

Table 9 shows the patient characteristics of the included study.

Table 9: Characteristics of the relevant subpopulation as well as study/treatment discontinuation – RCT, direct comparison: pembrolizumab versus paclitaxel (multipage table)

Study Characteristic Category	Pembrolizumab N = 11	Paclitaxel N = 10
KEYNOTE 061		
Sex [f/m], %	73/27	20/80
Age [years], mean (SD)	68 (6)	61 (10)
Region, n (%)		
Asia	4 (36)	3 (30)
Europe/Israel/North America/Australia	6 (55)	6 (60)
Rest of the world	1 (9)	1 (10)
ECOG-PS, n (%)		
0	4 (36)	3 (30)
1	7 (64)	7 (70)
Disease status, n (%)		
Locally advanced	0 (0)	1 (10)
Metastatic	11 (100)	9 (90)
Tumour's PD-L1 expression status, n (%)		
Positive	9 (82)	9 (90)
Negative	2 (18)	1 (10)
HER2 status, n (%)		
Positive	1 (9)	0 (0)
Negative	10 (91)	10 (100)
Prior surgical intervention for gastric cancer, n (%)		
No	7 (64)	3 (30)
Yes (partial gastrectomy)	1 (9)	2 (20)
Yes (subtotal gastrectomy)	2 (18)	1 (10)
Yes (total gastrectomy)	1 (9)	4 (40)
Histology type, n (%)		
Adenocarcinoma	10 (91)	9 (90)
Mixed tumour, determinable type	0 (0)	1 (10)
Other	1 (9)	0 (0)
Histology subtype, n (%)		
Diffuse	4 (36)	1 (10)
Intestinal metaplasia	0 (0)	4 (40)
Unknown	7 (64)	5 (50)
Number of metastasised organs, n (%)		
0–2	6 (55)	7 (70)
≥ 3	5 (45)	3 (30)
Peritoneal metastases, n (%)	3 (27)	2 (20)
Treatment discontinuation, n (%)[a]	5 (45)	10 (100)

Table 9: Characteristics of the relevant subpopulation as well as study/treatment discontinuation – RCT, direct comparison: pembrolizumab versus paclitaxel (multipage table)

Study Characteristic Category	Pembrolizumab N = 11	Paclitaxel N = 10
Study discontinuation, n (%)[b]	11 (100)[c]	10 (100)

a. Common reasons for treatment discontinuation in the intervention arm versus control arm were the following (percentages based on randomized patients): disease progression (36% versus 50%), clinical progression (9% versus 10%), and complete response (0% versus 20%).
b. Common reasons for study discontinuation in the intervention arm versus control arm were the following (percentages based on randomized patients): death (45% versus 90%) and study terminated by sponsor (45% versus 10%).
c. According to the dossier's Module 4 C, 1 patient is still "ongoing" in the study. This information is not plausible because the study was terminated by the company.

ECOG-PS: Eastern Cooperative Oncology Group – Performance Status; f: female; HER2: human epidermal growth factor receptor 2; m: male; n: number of patients in the category; N: number of randomized patients; PD-L1: programmed cell death ligand 1; RCT: randomized controlled trial; SD: standard deviation

The characteristics of the KEYNOTE 061 study's subpopulation relevant for the assessment are largely comparable between the 2 treatment arms. The mean patient age was about 68 years in the intervention arm and 61 years in the comparator arm. The proportion of women was much higher in the intervention arm, at 73%, than in the comparator arm, at 20%. Slightly more than half of all patients were from Europe, Israel, North America, or Australia, while about 30% were from Asia. Almost all patients had a PD-L1-expressing tumour (82% versus 90%).

The percentage of patients with treatment discontinuation was 45% in the intervention arm and 100% in the comparator arm. All patients discontinued the study, at the latest when the sponsor terminated the study. The most common reason for study discontinuation was patient death (45% versus 90%).

I 3.1.2.6 Information on the course of the study

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

Table 10: Information on the course of the study – RCT, direct comparison: pembrolizumab versus paclitaxel

Study **Duration of the study phase** **Outcome category**	**Pembrolizumab** **N = 11**	**Paclitaxel** **N = 10**
KEYNOTE 061		
Treatment duration [months]		
Median [min; max]	15.2 (ND)	3.1 (ND)
Mean (SD)	ND	ND
Observation duration[a] [months]		
Overall survival		
Median [min; max]	41.8 (ND)	14.0 (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		
AEs		
Median [min; max]	16.2 (ND)	4.1 (ND)
Mean (SD)	ND	ND
SAEs		
Median [min; max]	18.0 (ND)	5.7 (ND)
Mean (SD)	ND	ND

a. No information available for the calculation.

AE: adverse event; 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; EQ-5D: European Quality of Life – 5 Dimensions; max: maximum; min: minimum; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; SAE: serious adverse event; SD: standard deviation; VAS: visual analogue scale

The median treatment duration in the intervention arm was 15.2 months, nearly 5 times as long as in the comparator arm (3.1 months). The median observation duration for overall survival is 41.8 months in the intervention arm and 14.0 months in the comparator arm. No information is available on the observation duration for the morbidity and health-related quality of life outcomes. For these outcomes, the observation duration was coupled to treatment end (see Table 8). Therefore, it is safe to assume that, for these outcomes, the observation duration is shortened with respect to overall survival. The median observation durations were much longer in the intervention arm than in the comparator arm for AEs (16.2 versus 4.1 months) and SAEs (18.0 versus 5.7 months).

I 3.1.2.7 Subsequent therapies

The company did not submit any information on subsequent therapies in the subpopulation relevant for the assessment. The study documents on the 2017 and 2021 data cut-offs likewise provide no information on subsequent therapies for the total population nor for the assessment-relevant subpopulation. Only the main publication of the KEYNOTE 061 study provides information on the 2017 data cut-off for the study's total population. This information shows that 46% of patients in the intervention arm versus 58% of patients in the comparator arm received at least 1 subsequent therapy [7].

Information on subsequent therapies received by the relevant subpopulation at the 2021 data cut-off is relevant for the interpretation of the submitted results, particularly if the treatment duration is much shorter than the study duration, as is the case in the KEYNOTE 061 study. The drug combination of trifluridine/tipiracil, which was not available as a subsequent therapy for the majority of the study period, plays a key role starting in third-line therapy: according to the current 2022 guideline, trifluridine/tipiracil is to be used in advanced gastric cancer where oral therapy is possible [14]. If intravenous therapy is preferred, irinotecan or a taxane can be administered alternatively, unless they were already used in a prior therapy line [14]. As the sole treatment option as of the third line of treatment, trifluridine/tipiracil was also specified as the ACT in the present therapeutic indication (see Table 4, research question 2 of this report). In Europe and the USA, this treatment combination was approved for the therapeutic indication of gastric cancer in 2019; consequently, this treatment option was unavailable at least for the first few years of the study (the KEYNOTE 061 study recruited patients between May 2015 and July 2016).

The lack of information on subsequent therapies as well as the unavailability of the trifluridine/tipiracil drug combination, which is primarily recommended for third line and later courses of treatment, make it unclear overall whether the study adequately reflects current practice in the German healthcare system. This applies to all outcomes which were observed beyond treatment end, and in the present scenario, particularly to overall survival. Therefore, the certainty of results was reduced for the outcome of overall survival (see Section I 3.2.2).

I 3.1.2.8 Risk of bias across outcomes (study level)

Table 11 shows the risk of bias across outcomes (risk of bias at study level).

Table 11: Risk of bias across outcomes (study level) – RCT, direct comparison: pembrolizumab versus paclitaxel

Study	Adequate random sequence generation	Allocation concealment	Blinding		Nonselective reporting	No additional aspects	Risk of bias at study level
			Patients	Treatment providers			
KEYNOTE 061	Yes	Yes	No	No	Yes	Yes	Low
RCT: randomized controlled trial							

The risk of bias across outcomes was rated as low for the KEYNOTE 061 study.

Limitations resulting from the open-label study design are described in Section I 3.2.2 under outcome-specific risk of bias.

I 3.1.3 Transferability of the study results to the German health care context

The company reports that the KEYNOTE 061 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 study results to the German health care context.

I 3.2 Results on added benefit

I 3.2.1 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
  - SAEs
  - severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3)
  - discontinuation due to AEs
  - immune-mediated SAEs and severe AEs
  - further specific AEs, if any

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

Table 12 shows the outcomes for which data were available in the included study.

Table 12: Matrix of outcomes – RCT, direct comparison: pembrolizumab versus paclitaxel

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	Immune-mediated SAEs[b]	Immune-mediated severe AEs[a,b]	Further specific AEs
KEYNOTE 061	Yes	No[c]	No[c]	No[c]	Yes	Yes	Yes	Yes	Yes	No[d]

a. 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 20") was used.
c. No usable data; see body of text for reasons.
d. No usable analyses (time-to-event analyses) of AEs by PT and SOC 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; EQ-5D: European Quality of Life – 5 Dimensions; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

Unusable analyses on patient-reported outcomes

The company's dossier presents analyses of first deterioration by at least 15 points in the form of time-to-event analyses of the EORTC QLQ-C30, EORTC QLQ-STO22, and EQ-5D VAS at the 26 October 2017 data cut-off. Additionally, the company provides descriptive information on the course of the study separately for the 2 treatment arms.

The submitted analyses of first deterioration are unusable because they excluded too many patients from the analysis. The company reports that the full analysis set (FAS) population was used for analysing the patient-reported outcomes. The FAS population is defined as all randomized patients who had received at least 1 dose of the study medication and for whom at least 1 survey of patient-reported outcomes was available. According to the results tables in the company's dossier, this comprises 10 or 9 of the 11 patients in the intervention arm and 8 of the 10 patients in the control arm, depending on the outcome. However, assessing deterioration from baseline requires both a baseline value and at least 1 other subsequent survey; therefore, the single survey required for allocation to the FAS population is insufficient. In the company's time-to-event analyses, this resulted in censoring at Day 1 in both study arms. Censoring on Day 1 means that the corresponding patient is excluded from the analysis. Hence, the number of patients actually included in the analysis is lower than the number indicated by the company in the results tables. The Kaplan-Meier curves show that censoring on Day 1 occurred in all patient-reported outcomes. For several outcomes, this resulted in only 14 out of the total 21 patients from the relevant subpopulation being included in the analysis. Due to this reduction in the already low number of patients in the relevant subpopulation, the results for the patient-reported outcomes were deemed unusable in the present scenario. Irrespective of this problem, no statistically significant differences between treatment groups were found for any of the scales.

I 3.2.2 Risk of bias

Table 13 describes the risk of bias for the results of the relevant outcomes.

Table 13: Risk of bias across outcomes and outcome-specific risk of bias – RCT, indirect comparison: pembrolizumab versus paclitaxel

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	Immune-mediated SAEs[b]	Immune-mediated severe AEs[a,b]	Further specific AEs
KEYNOTE 061	L	L[c]	–[d]	–[d]	–[d]	H[e]	H[e]	H[f]	H[e]	H[e]	–[g]

a. 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 20") was used.
c. Despite the low risk of bias, the certainty of results is reduced for the outcome of overall survival (see Section I 3.1.2.7).
d. No usable data available; see Section I 3.2.1 for the reasoning.
e. Incomplete observations for potentially informative reasons.
f. Lack of blinding in subjective decision for discontinuation.
g. No usable analyses (time-to-event analyses) of AEs by PT and SOC available; selection of 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; EQ-5D: European Quality of Life – 5 Dimensions; 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. However, the certainty of results was downgraded for this outcome. This is due to the lack of information on subsequent therapies as well as the non-availability of the drug combination of trifluridine/tipiracil, which is primarily recommended for third-line or later courses of therapy (see Section I 3.1.2.7).

The risk of bias was rated as high for the results of each of the outcomes of the side effects category. All outcomes in the category except discontinuation due to AEs suffer from incomplete observations for potentially informative reasons due to (a) the follow-up observation being linked to treatment duration and (b) a possible association between outcome and reason for treatment discontinuation. The risk of bias for the outcome of discontinuation due to AEs is high due to the lack of blinding in subjective recording of outcomes.

For the outcome of health status, measured with the EQ-5D VAS, as well as the outcomes of symptoms and health-related quality of life, measured with the EORTC QLQ-C30 and

EORTC QLQ-STO22, the risk of bias is not assessed because no usable analyses were available (see Section I 3.2.1).

I 3.2.3 Results

Table 14 summarizes the results on the comparison of pembrolizumab with paclitaxel for research question 1 of the present benefit assessment.

The Kaplan-Meier curves on the time-to-event analyses are presented in I Appendix B of the full dossier assessment, whereas the results on common AEs, SAEs, and severe AEs as well as discontinuation due to AEs are found in I Appendix C of the full dossier assessment.

Table 14: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: pembrolizumab versus paclitaxel (multipage table)

Study Outcome category Outcome	Pembrolizumab N	Pembrolizumab Median time to event in months [95% CI] Patients with event n (%)	Paclitaxel N	Paclitaxel Median time to event in months [95% CI] Patients with event n (%)	Pembrolizumab versus paclitaxel HR [95% CI]; p-value[a]
KEYNOTE 061 (data cut-off: 10 June 2021)					
Mortality					
Overall survival	11	NR [6.1; NC] 5 (45.5)	10	8.9 [1.6; 16.7] 9 (90.0)	0.25 [0.08; 0.80]; 0.020
Morbidity					
Symptoms					
EORTC QLQ-C30 EORTC QLQ-STO22	No usable data[b]				
Health status					
EQ-5D VAS	No usable data[b]				
Health-related quality of life					
EORTC QLQ-C30	No usable data[b]				
Side effects					
AEs (supplementary information)	11	0.9 [0.1; 10.7] 11 (100)	10	2.2 [0.1; 6.0] 9 (90.0)	–
SAEs	11	NR [3.3; NC] 5 (45.5)	10	NR [9.4; NC] 2 (20.0)	2.59 [0.50; 13.41]; 0.256
Severe AEs[c]	11	NR [2.1; NC] 5 (45.5)	10	NR [1.0; NC] 3 (30.0)	1.60 [0.38; 6.68]; 0.523
Discontinuation due to AEs	11	NR 0 (0)	10	NR [12.3; NC] 1 (10.0)	–; 0.289
Immune-mediated AEs[d] (presented as supplementary information)	ND	ND	ND	ND	ND
Immune-mediated SAEs[d]	11	NR [14.7; NC] 1 (9.1)	10	NR 0 (0)	–; 0.371
Immune-mediated severe AEs[c, d]	11	NR [14.7; NC] 1 (9.1)	10	NR 0 (0)	–; 0.414
Further specific AEs	No usable data[e]				

Table 14: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: pembrolizumab versus paclitaxel (multipage table)

Study Outcome category Outcome	Pembrolizumab		Paclitaxel		Pembrolizumab versus paclitaxel
	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI]; p-value[a]

a. HR, CI, and p-value: Cox proportional hazards model (unstratified, unadjusted); score test in case of 0 events in 1 treatment arm.
b. Analyses are available only for the 26 October 2017 data cut-off; see Section I 3.2.1 for reasoning regarding unusability.
c. Operationalized as CTCAE grade ≥ 3.
d. In each case, the operationalization of the company-specific MedDRA PT collection from the outcome of adverse events of special interest ("AEOSI, Version 20") was used.
e. No usable analyses (time-to-event analyses) of AEs by PT and SOC 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 – Core 30; EORTC QLQ-STO22: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Gastric Cancer 22; EQ-5D: European Quality of Life – 5 Dimensions; H: high; HR: hazard ratio; L: low; 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; NR: not reached; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

Based on the available information, at most hints, e.g. of an added benefit, can be determined for all outcomes (see Section I 3.2.2 for reasoning).

Mortality

Overall survival

For the outcome of overall survival, a statistically significant difference was found in favour of pembrolizumab in comparison with paclitaxel. This results in a hint of an added benefit of pembrolizumab in comparison with paclitaxel.

Morbidity

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

No usable data were available for the outcomes on symptoms, measured with the EORTC QLQ-C30 and the EORTC QLQ-STO22 (see Section I 3.2.1). Consequently, there is no hint of added benefit of pembrolizumab in comparison with paclitaxel; an added benefit is therefore not proven.

Health status (EQ-5D VAS)

There were no usable analyses for the outcome of health status, recorded using the EQ-5D VAS (see Section I 3.2.1). Consequently, there is no hint of added benefit of pembrolizumab in comparison with paclitaxel; an added benefit is therefore not proven.

Health-related quality of life

EORTC QLQ-C30

There were no usable analyses for health-related quality of life, measured with the EORTC QLQ-C30 (see Section I 3.2.1). Consequently, there is no hint of added benefit of pembrolizumab in comparison with paclitaxel; an added benefit is therefore not proven.

Side effects

SAEs, severe AEs, discontinuation due to AEs, immune-mediated SAEs, immune-mediated severe AEs

For each of the outcomes of SAEs, severe AEs, discontinuation due to AEs, immune-mediated SAEs, and immune-mediated severe AEs, no statistically significant differences between treatment groups were found. Hence there was no hint of greater or lesser harm from pembrolizumab in comparison with paclitaxel for any of them; greater or lesser harm is therefore not proven.

Further specific AEs

No usable analyses (time-to-event analyses) by Preferred Terms (PTs) or System Organ Classes (SOCs) are available for selecting further specific AEs.

I 3.2.4 Subgroups and other effect modifiers

For the relevant subpopulation of the KEYNOTE 061 study, the company reports not investigating any subgroup analyses regarding potential effect modifiers due to the small sample size. The company's approach is appropriate.

I 3.3 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 *General Methods* of IQWiG [1].

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

I 3.3.1 Assessment of added benefit at outcome level

The extent of the respective added benefit at outcome level was estimated from the results presented in Section I 3.2 (see Table 15).

Table 15: Extent of added benefit at outcome level: pembrolizumab versus paclitaxel (multipage table)

Outcome category **Outcome**	**Pembrolizumab versus paclitaxel** **Median time to event in months** **HR [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Total observation period		
Mortality		
Overall survival	NR vs. 8.9 0.25 [0.08; 0.80] p = 0.020 Probability: hint	Outcome category: mortality $CI_u < 0.85$ Added benefit, extent: major
Shortened follow-up period		
Morbidity		
Symptoms (EORTC QLQ-C30 and QLQ-STO22)	No usable data[c]	Lesser/added benefit not proven
Health status (EQ-5D VAS)	No usable data[c]	Lesser/added benefit not proven
Health-related quality of life		
EORTC QLQ-C30	No usable data[c]	Lesser/added benefit not proven
Side effects		
SAEs	NR vs. NR 2.59 [0.50; 13.41] p = 0.256	Greater/lesser harm not proven
Severe AEs	NR vs. NR 1.60 [0.38; 6.68] p = 0.523	Greater/lesser harm not proven
Discontinuation due to AEs	NR vs. NR – p = 0.289	Greater/lesser harm not proven
Immune-mediated SAEs	NR vs. NR – p = 0.371	Greater/lesser harm not proven
Immune-mediated severe AEs	NR vs. NR – p = 0.414	Greater/lesser harm not proven
Further specific AEs	No usable 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, estimations of effect size are made with different limits based on the upper limit of the confidence interval (CI_u).
c. See Section I 3.2.1 for a rationale.
d. No usable analyses (time-to-event analyses) of AEs by PT and SOC available; selecting specific AEs is therefore impossible.

Table 15: Extent of added benefit at outcome level: pembrolizumab versus paclitaxel (multipage table)

Outcome category **Outcome**	**Pembrolizumab versus paclitaxel** **Median time to event in months** **HR [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
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; EQ-5D: European Quality of Life – 5 Dimensions; HR: hazard ratio; NR: not reached; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale		

I 3.3.2 Overall conclusion on added benefit

Table 16 summarizes the results included in the overall conclusion on the extent of added benefit.

Table 16: Favourable and unfavourable effects from the assessment of pembrolizumab in comparison with paclitaxel

Favourable effects	**Unfavourable effects**
Total observation period	
Mortality ▪ Overall survival Hint of an added benefit – extent: major	–
Shortened observation period	
–	–
No usable data are available on the outcome categories of morbidity and health-related quality of life or for the selection of other specific AEs.	

All things considered, there is only 1 favourable effect for the outcome of overall survival. This effect results in a hint of major added benefit. Neither favourable nor unfavourable effects were found in the outcome category of side effects. No usable data are available for the outcome categories of morbidity and health-related quality of life.

The low number of patients in the relevant subpopulation is associated with low precision for the side effects outcomes. In the weighing of benefits versus harm, this makes it impossible to quantify the added benefit.

In summary, for adult patients with unresectable or metastatic MSI-H or dMMR gastric carcinoma who have disease progression on or following 1 prior therapy, this results in a hint of non-quantifiable added benefit of pembrolizumab in comparison with the ACT.

Data are available only for patients for whom paclitaxel is a suitable treatment option in accordance with treatment of physician's choice. No data are available for patients for whom another treatment option is suitable according to physician's choice.

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

I 4 Research question 2: Patients with disease progression on or following at least 2 prior therapies

I 4.1 Information retrieval and study pool

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

Sources of the company in the dossier:

- study list on pembrolizumab (status: 1 June 2022)
- bibliographical literature search on pembrolizumab (last search on 9 May 2022)
- search in trial registries/trial results databases for studies on pembrolizumab (last search on 18 May 2022)
- search on the G-BA website for pembrolizumab (last search on 18 May 2022)
- bibliographical literature search on the ACT (last search on 2 May 2022)
- search in trial registries/trial results databases for studies on the ACT (last search on 9 May 2022)
- search on the G-BA website for the ACT (last search on 17 May 2022)

To check the completeness of the study pool:

- search in trial registries for studies on pembrolizumab (last search on 18 August 2022); for search strategies, see I Appendix A of the full dossier assessment

The check of completeness of the study pool identified no RCTs for a direct or adjusted indirect comparison via a common comparator versus the ACT specified by the G-BA.

Since it identified no RCTs for a direct comparison, the company conducted an information retrieval for further investigations and presented a comparison of individual arms from different studies.

The company reports that it disregarded MSI-H/dMMR status in its study selection if it identified no suitable study when taking into account the MSI-H/dMMR status. Disregarding the MSI-H/dMMR status in the study selection is inappropriate because this benefit assessment's research question specifies for the added benefit of pembrolizumab versus the ACT to be assessed in patients with dMMR or MSI-H gastric cancer. Patients whose tumours exhibit neither MSI-H nor dMMR, in contrast, are excluded from the research question.

Furthermore, the company reports that, where several studies of different evidence levels were found to be relevant, it took into account only the studies of the highest evidence level. When comparing individual arms from different studies, this approach is inadequate. For instance, in the comparison of individual arms, single-arm studies are potentially of equal relevance as

individual arms from RCTs. It is unclear whether the company's approach resulted in the exclusion of potentially relevant studies.

On the intervention side, the company identified the single-arm study KEYNOTE 158 [15-19] and the single-arm study KEYNOTE 059 [20-23]. For comparing individual arms, however, the company used only the results of the KEYNOTE 158 study. The company reports disregarding the results of the KEYNOTE 059 study due to the small sample size of the subpopulation with MSI-H gastric carcinoma.

On the comparator side, the company failed to find any studies taking into account MSI-H/dMMR status and therefore looked for studies irrespective of MSI-H/dMMR status on that side. As a result, the company identified the TAGS RCT [24-28], from which it used the trifluridine/tipiracil arm its comparison of individual arms.

A check of the study pool's completeness on the ACT side was foregone because for patients in this research question, the data submitted by the company are unsuitable for drawing any conclusions on the added benefit of pembrolizumab in comparison with the ACT. This is explained below.

Data presented by the company

Study on pembrolizumab: KEYNOTE 158

The KEYNOTE 158 study is an ongoing, single-arm, cross-entity study on pembrolizumab in adult patients with advanced (metastatic and/or unresectable) solid tumours. At enrolment, patients had to exhibit disease progression on a prior therapy or intolerance to at least 1 prior therapy. The number of prior therapies is not limited. Pembrolizumab is dosed in accordance with the SPC [8].

Patients were placed into different cohorts for various tumour entities (Cohort A to Cohort J, none of which was for patients with gastric carcinoma). Furthermore, patients with MSI-H or dMMR tumours were placed, regardless of entity, in Cohort K (MSI-H only) and Cohort L (MSI-H or dMMR; conducted in China), each of which included patients with gastric cancer.

For the comparison of individual arms in the present research question, the company used a subpopulation of Cohort K on the intervention side. This cohort comprises 23 patients with gastric cancer and MSI-H as well as at least 2 prior therapies. The company did not provide any information on patients from Cohort L who are potentially relevant for the present research question. According to the European Public Assessment Report, by 16 March 2022, Cohort L had included 8 patients with gastric cancer and MSI-H/dMMR [29].

Regarding the KEYNOTE 158 study, the company used the 15 October 2021 data cut-off (interim analysis XIII) for all outcomes except patient-reported outcomes. For the patient-reported outcomes, data are available only from the 5 October 2020 data cut-off (interim analysis XI). The results from both data cut-offs also constitute the basis for the marketing

authorization [29]. According to the company, another data cut-off was implemented for a final analysis on 12 January 2022, but no corresponding study report is available at this time.

The study's primary outcome was the objective response rate. Additionally, outcomes were surveyed on mortality, morbidity, health-related quality of life, and side effects.

Alongside results from the comparison of individual arms from different studies, the company presented noncomparative results of the KEYNOTE 158 study.

Study on trifluridine/tipiracil: TAGS

The TAGS study is a completed, double-blind RCT comparing trifluridine/tipiracil + BSC versus placebo + BSC. Benefit assessment A19-85 on trifluridine/tipiracil in previously treated patients with metastatic gastric cancer describes this study in detail [28]. The study enrolled adult patients with unresectable, metastatic gastric adenocarcinoma, including GEJ adenocarcinoma. Patients had to have received at least 2 prior treatment regimens for advanced disease. A total of 507 patients were randomly allocated in a 2:1 ratio to treatment with either trifluridine/tipiracil + BSC (N = 337) or placebo + BSC (N = 170). No information is available on the study population's MSI-H or dMMR status.

The TAGS study administered the trifluridine/tipiracil drug combination in compliance with the SPC [30].

For comparing individual arms, the company used primarily the results of the total population in the trifluridine/tipiracil arm (gastric adenocarcinoma including GEJ adenocarcinoma, N = 337; data cut-off for the outcome of overall survival: 30 April 2018; data cut-off for morbidity and side effects outcomes: 31 March 2018) because, according to the company, complete data on all relevant outcome categories are available only for said total population. For the outcome of overall survival, the company has presented as supplementary information results from the subpopulation excluding patients with GEJ adenocarcinoma (N = 239) (31 March 2018 data cut-off from the Mansoor et al. publication [24]).

The study's primary outcome was overall survival. Patient-relevant outcomes from the categories of morbidity, health-related quality of life and side effects were also surveyed.

Comparisons between individual arms from the KEYNOTE 158 and TAGS studies unsuitable for assessing the added benefit of pembrolizumab

The company submitted a comparison between individual arms from a time-to-event analysis of pembrolizumab (KEYNOTE 158 study) versus trifluridine/tipiracil (TAGS RCT). For the trifluridine/tipiracil arm of the TAGS RCT, the company used the total population for the outcomes of overall survival, SAES, and severe AEs. Additionally, the company presents an analysis on the outcome of overall survival with the TAGS RCT's subpopulation with gastric adenocarcinoma.

Comparator side fails to reflect the population of the research question

This benefit assessment's research question is to assess the added benefit of pembrolizumab versus the ACT in adult patients with unresectable or metastatic gastric carcinoma with MSI-H or dMMR. Conversely, patients whose tumours exhibit neither MSI-H nor dMMR are excluded from the research question. The TAGS study provides no information on the approval-justifying and potentially prognostic criterion of MSI-H or dMMR tumour status. Given that only about 3.8% to 4.8% of metastatic gastric cancer cases involve MSI-H/dMMR tumours (see Sections II. 1.3.1 and II. 1.3.2 of the full benefit assessment), it is safe to assume that a similarly low percentage of TAGS participants' tumours exhibited this characteristic. Hence, the comparator side does not reflect the population of this benefit assessment's research question 2.

Irrespective of this problem, it is not appropriate for the company to derive added benefit based on patients with gastric and GEJ tumours in this therapeutic indication (gastric cancer only), particularly since the company limited its analysis to patients with gastric cancer in this assessment's research question 1 (see Section I 3.1.2.2).

Further limitations

The company reports disregarding the results of the KEYNOTE 059 study in the comparison of individual arms due to the low sample size of the subpopulation analysed. The KEYNOTE 059 study is a single-arm study on pembrolizumab in adult patients with recurrent or metastatic gastric cancer which is incurable by local therapies. According to the company, the subpopulation relevant for the present research question comprises 5 patients. The company's approach of disregarding this subpopulation of the KEYNOTE 059 study in the comparison of individual arms is not appropriate. Five additional patients from the KEYNOTE 059 study would indeed be of relevance given the fact that on the intervention side, the company uses only 23 patients from the KEYNOTE 158 study. When combining both studies, this means that results from a total of 18% (5/28) of patients are missing.

Irrespective of the 2 points of criticism discussed above, the comparisons of individual arms as presented by the company represent comparisons without a common comparator. Due to the lack of randomization, these comparisons are subject to inherent uncertainty and fail to represent an adequate method for an indirect comparison [1]. Furthermore, any of the effects found in this comparison of individual arms from different studies may potentially result solely from systematic bias due to confounders.

I 4.2 Results on added benefit

The company has presented no suitable data to assess the added benefit of pembrolizumab in comparison with the ACT in adult patients with unresectable or metastatic MSI-H or dMMR gastric cancer who have disease progression on or following at least 2 prior therapies. This results in no hint of an added benefit of pembrolizumab in comparison with the ACT; an added benefit is therefore not proven.

I 4.3 Probability and extent of added benefit

The company has presented no suitable data to assess the added benefit of pembrolizumab in comparison with the ACT in adult patients with unresectable or metastatic MSI-H or dMMR gastric carcinoma who have disease progression on or following at least 2 prior therapies; hence, there is no proof of added benefit.

This assessment deviates from that by the company, which derived a hint of a non-quantifiable added benefit on the basis of a comparison of individual arms from different studies.

I 5 Probability and extent of added benefit – summary

Table 17 summarizes the results of the assessment of the added benefit of pembrolizumab in comparison with the ACT.

Table 17: Pembrolizumab – probability and extent of added benefit

Research question	Therapeutic indication	ACT[a, b]	Probability and extent of added benefit
1	Adults with unresectable or metastatic MSI-H or dMMR gastric cancer who have disease progression on or following 1 prior therapy[c]	Treatment of physician's choice[d]	Hint of non-quantifiable added benefit[e, f]
2	Adults with unresectable or metastatic MSI-H or dMMR gastric cancer who have disease progression on or following at least 2 prior therapies[c]	Trifluridine/tipiracil	Added benefit not proven

a. Presented is the respective ACT specified by the G-BA.
b. According to the G-BA, the ACT was specified in light of on the fact that 95% of stomach cancers are adenocarcinomas. Therefore, no separate ACT was defined for other histologies.
c. Presumably, curative treatment with definitive chemoradiotherapy is not an option for patients with unresectable cancer.
d. For the present treatment situation, guidelines recommend systemic therapy. Based on their approval status, options for this purpose are the drug ramucirumab or the drug combination ramucirumab plus paclitaxel. The drugs irinotecan, docetaxel, and paclitaxel (monotherapy) have not been approved for the present therapeutic indication. There is a discrepancy between the drugs approved in the therapeutic indication and those recommended in guidelines. As part of a clinical trial, the following treatment options are deemed suitable comparators for treatment according to physician's choice: irinotecan, docetaxel, paclitaxel, and ramucirumab in combination with paclitaxel. The added benefit can be assessed versus one of the cited treatment options within the framework of a single-comparator study.
e. Only patients with an ECOG-PS of 0 or 1 were included in the KEYNOTE 061 study. It remains unclear whether the observed effects are transferable to patients with an ECOG-PS ≥ 2.
f. Data are available only for patients for whom paclitaxel constitutes a suitable treatment option according to physician's choice. No data are available for patients for whom another treatment option is suitable according to physician's choice.

ACT: appropriate comparator therapy; dMMR: mismatch repair deficiency; ECOG-PS: Eastern Cooperative Oncology Group – Performance Status; G-BA: Federal Joint Committee; MSI-H: microsatellite instability high

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

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Please see full dossier assessment for full reference list.

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

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