IQWiG Reports – Commission No. A22-55

Nivolumab (oesophageal carcinoma, combination with ipilimumab) –

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

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Nivolumab (Ösophaguskarzinom, Kombination mit Ipilimumab) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 28 July 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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[2] Table numbers start with "2" as numbering follows that of the full dossier assessment.

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
BSA	body surface area
CTCAE	Common Terminology Criteria for Adverse Events
ECOG-PS	Eastern Cooperative Oncology Group – Performance Status
ECS	Esophageal Cancer Subscale
EMA	European Medicines Agency
EQ-5D	European Quality of Life Questionnaire – 5 Dimensions
FACT-E	Functional Assessment of Cancer Therapy – Esophageal
FACT-G	Functional Assessment of Cancer Therapy – General
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
imAEs	immune-mediated adverse events
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MMRM	mixed model for repeated measures
PD-L1	programmed death ligand-1
PFS	progression-free survival
PT	Preferred Term
RCT	randomized controlled trial
RECIST	Response Evaluation Criteria in Solid Tumours
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SOC	System Organ Class
SPC	Summary of Product Characteristics
VAS	visual analogue scale

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug nivolumab. 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 2 May 2022.

Research question

The aim of the present report is to assess the added benefit of nivolumab in combination with ipilimumab in comparison with the appropriate comparator therapy (ACT) as first-line treatment of adult patients with unresectable advanced, recurrent, or metastatic oesophageal squamous cell carcinoma with tumour cell programmed death ligand-1 (PD-L1) expression ≥ 1%.

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

Table 2: Research question of the benefit assessment of nivolumab

Therapeutic indication	**ACT[a]**
Adult patients with unresectable[b] advanced, recurrent or metastatic oesophageal squamous cell carcinoma with tumour cell PD-L1 expression ≥ 1%; first-line treatment; combination therapy with ipilimumab	Cisplatin[c] in combination with 5-fluorouracil
a. Presented is the respective ACT specified by the G-BA. b. In accordance with the CheckMate 648 study's inclusion criteria, the G-BA assumes that, in this therapeutic indication, patients with unresectable cancer are not indicated for curative treatment with definitive chemoradiotherapy. c. The G-BA presumes the patients to be candidates for cisplatin-containing chemotherapy. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; PD-L1: programmed cell death ligand 1	

The company follows the G-BA's 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. Randomized controlled trials (RCTs) are used for deriving added benefit. This concurs with the company's inclusion criteria.

Study pool and study design

For the benefit assessment of nivolumab in combination with ipilimumab, the CheckMate 648 study was included.

The CheckMate 648 study is an ongoing, open-label, 3-arm RCT which compares nivolumab either in combination with ipilimumab (hereinafter referred to as nivolumab + ipilimumab) or in combination with 5-fluorouracil and cisplatin (hereinafter referred to as nivolumab + chemotherapy) versus 5-fluorouracil and cisplatin combination chemotherapy (hereinafter referred to as chemotherapy). For the present benefit assessment, the only relevant comparison is the nivolumab + ipilimumab arm (intervention arm) versus the chemotherapy arm (comparator arm).

The CheckMate 648 study enrolled adult patients who, according to the criteria of the American Joint Committee on Cancer (AJCC 7th edition), had histologically confirmed oesophageal squamous cell carcinoma or adenosquamous carcinoma (with predominant squamous differentiation) which was classified as unresectable advanced, recurrent, or metastatic. Furthermore, patients had to be non-amenable to curative therapy, such as definitive chemoradiotherapy and/or surgery, and they were to be in good general health in accordance with Eastern Cooperative Oncology Group – Performance Status (ECOG-PS) ≤ 1.

A total of 970 patients were enrolled in the CheckMate 648 study and randomized at a 1:1:1 ratio to treatment with either nivolumab + ipilimumab (N = 325), nivolumab + chemotherapy (N = 321), or chemotherapy (N = 324).

Nivolumab treatment in the intervention arm (nivolumab + ipilimumab) was administered in 2-week cycles, in line with the specifications of the Summary of Product Characteristics (SPC).

In the comparator arm, chemotherapy was likewise administered in 4-week cycles. Cisplatin was dosed in accordance with the SPC. The 5-fluorouracil dosage deviated from the approval statement. In the CheckMate 648 study, a 5-fluorouracil dose of 800 mg/m^2 body surface area (BSA) was administered on Days 1 to 5 of a 4-week cycle. This corresponds to a total dose of 4000 mg/m² BSA per cycle. For combination chemotherapy with cisplatin, the 5-fluorouracil SPC specifies a dosage of 1000 mg/m^{2}BSA on Days 1 through 5 of a 3-week to 4-week cycle. This corresponds to a total dose of 5000 mg/m² BSA per cycle. Overall, this deviating 5-fluorouracil dosage did not have any further consequences for the present benefit assessment. Otherwise, the administered chemotherapy was largely in line with the SPC, including with regard to dose adjustments, delays, and reductions.

The study population was treated until either disease progression, the occurrence of unacceptable toxicity, or discontinuation of study treatment. Furthermore, in line with approval, nivolumab treatment in the intervention arm was limited to a maximum of 24 months. Additionally, continuation of nivolumab therapy (in the form of monotherapy or in combination with ipilimumab) was allowed after disease progression determined by the investigators in accordance with the Response Evaluation Criteria in Solid Tumours (RECIST) 1.1. As a precondition, this required for the patient to tolerate treatment and the investigator to expect a clinical benefit from treatment continuation. After the identification of another progression event, treatment was discontinued.

The primary outcomes of the CheckMate 648 study were overall survival and progression-free survival (PFS). Secondary outcomes were from the categories: morbidity, health-related quality of life, and side effects.

The present benefit assessment uses the results from the 2nd data cut-off of 23 August 2021.

Relevant subpopulation

According to approval, nivolumab in combination with ipilimumab is indicated for the first-line treatment of adult patients with unresectable advanced, recurrent, or metastatic oesophageal squamous cell carcinoma with tumour cell PD-L1 expression ≥ 1%. In line with nivolumab approval, the company's Module 4 T takes into account only the CheckMate 648 subpopulation of patients with tumour cell PD-L1 expression ≥ 1%. This subpopulation comprises 158 patients in the intervention arm relevant for the present benefit assessment (nivolumab + ipilimumab) as well as 157 patients in the comparator arm (chemotherapy).

Risk of bias and certainty of conclusions

The risk of bias across outcomes is rated as low for the CheckMate 648 study. The outcome-specific risk of bias is rated as high for the results of all patient-relevant outcomes except overall survival. No usable data are available for the outcomes of health status and health-related quality of life; therefore, the risk of bias was not assessed.

On the basis of the available information, at most indications, e.g. of an added benefit, can be derived for the outcome of overall survival, and at most hints can be derived for all other outcomes due to high risk of bias.

Results

Mortality

Overall survival

For the outcome of overall survival, a statistically significant difference was found in favour of nivolumab + ipilimumab in comparison with chemotherapy. Notably, the Kaplan-Meier curves on this outcome cross. In the first few months, the Kaplan-Meier curve falls more steeply in the nivolumab + ipilimumab arm than in the chemotherapy arm. At about 6 months after study start, the Kaplan-Meier curves cross, and only in the further course does an advantage of nivolumab + ipilimumab become apparent. This suggests that some patient groups draw less benefit or no benefit at all from the intervention. The characteristics of this patient group cannot be determined on the basis of the data submitted by the company. The crossing of the Kaplan-Meier curves might be based in part on an effect modification, but no statistically significant interaction was found for any of the subgroup characteristics examined in the CheckMate 648 study. On the basis of exploratory post hoc analyses, the European regulatory authority included a corresponding warning in the SPC, according to which physicians should take into account the delayed onset of nivolumab effect in combination with ipilimumab before initiating treatment in patients with poorer prognostic factors and/or aggressive disease.

Overall, this results in an indication of added benefit of nivolumab + ipilimumab in comparison with chemotherapy.

Morbidity

Health status

No usable data are available for the outcome of health status, surveyed with the European Quality of Life Questionnaire – 5 Dimensions (EQ-5D) visual analogue scale (VAS). This results in no hint of an added benefit of nivolumab + ipilimumab in comparison with chemotherapy; an added benefit is therefore not proven.

Health-related quality of life

Functional Assessment of Cancer Therapy – Esophageal (FACT-E)

No usable data are available for the outcome of health-related quality of life, recorded with the FACT-E total score. This results in no hint of an added benefit of nivolumab + ipilimumab in comparison with chemotherapy; an added benefit is therefore not proven.

Side effects

Serious adverse events (SAEs)

For the outcome of SAEs, a statistically significant difference was found between treatment groups to the disadvantage of nivolumab + ipilimumab in comparison with chemotherapy. This results in a hint of greater harm from nivolumab + ipilimumab in comparison with chemotherapy.

Severe adverse events (AEs) and discontinuation due to AEs

There was no statistically significant difference between treatment groups for either of the outcomes of severe AEs or discontinuation due to AEs. This resulted in no hint of greater or lesser harm from nivolumab + ipilimumab in comparison with chemotherapy; greater or lesser harm is therefore not proven.

Specific AEs

Immune-mediated SAEs, immune-mediated severe AEs

For each of the outcomes of immune-mediated SAEs and immune-mediated severe AEs, a statistically significant difference between treatment groups was found to the disadvantage of nivolumab + ipilimumab versus chemotherapy. This results in a hint of greater harm from nivolumab + ipilimumab in comparison with chemotherapy for each of them.

Gastrointestinal disorders (AEs), mucosal inflammation (AEs), alopecia (AEs), hiccups (AEs), renal and urinary disorders (AEs), vomiting (SAEs), anaemia (severe AEs), neutrophil count decreased (severe AEs), nervous system disorders (severe AEs)

For each of the outcomes of gastrointestinal disorders (AEs), mucosal inflammation (AEs), alopecia (AEs), hiccups (AEs), renal and urinary disorders (AEs), vomiting (SAEs), anaemia (severe AEs), neutrophil count decreased (severe AEs), and nervous system disorders (severe

AEs), there is a statistically significant difference between treatment groups in favour of nivolumab + ipilimumab in comparison with chemotherapy. For each of them, this results in a hint of lesser harm from nivolumab + ipilimumab in comparison with chemotherapy.

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 nivolumab in comparison with the ACT is assessed as follows:

Overall, both favourable and unfavourable effects of nivolumab + ipilimumab were found in comparison with chemotherapy.

On the side of the favourable effects, there was an indication of major added benefit for the outcome of overall survival. However, due to the Kaplan-Meier curves crossing at about 6 months, this effect in favour of nivolumab + ipilimumab becomes apparent only in the further course of treatment. On the basis of the data presented by the company, it is impossible to determine the extent to which patient characteristics or other factors explain the crossing of the Kaplan-Meier curves. Hence, it cannot be definitively determined which patients draw major benefit from the intervention. On the basis of exploratory post hoc analyses, the European regulatory authority included a corresponding warning in the SPC, according to which physicians should take into account the delayed onset of nivolumab effect in combination with ipilimumab before initiating treatment in patients with poorer prognostic factors and/or aggressive disease.

For numerous specific outcome of the side effects category, there are also hints of lesser harm for both serious/severe side effects and for nonserious/nonsevere side effects of different extents. Regarding unfavourable effects, in contrast, hints of greater harm, some of them of major extent, were found for the outcomes of SAEs and immune-mediated serious or severe AEs, but this did not call into question the favourable effect concerning overall survival.

For the outcome categories of morbidity and health-related quality of life, no usable data suitable for being taken into account in the overall conclusion on added benefit are available.

Given the available evidence, the extent is deemed non-quantifiable.

[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].

In summary, for adult patients with unresectable advanced, recurrent, or metastatic oesophageal squamous cell carcinoma with tumour cell PD-L1 expression ≥1%, there is an indication of non-quantifiable added benefit of nivolumab + ipilimumab in comparison with the ACT of chemotherapy.

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

Table 3: Nivolumab – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adult patients with unresectable[b] advanced, recurrent or metastatic oesophageal squamous cell carcinoma with tumour cell PD-L1 expression ≥ 1%; first-line treatment	Cisplatin[c] in combination with 5-fluorouracil	Indication of non-quantifiable added benefit[d]

a. Presented is the respective ACT specified by the G-BA.
b. In accordance with the CheckMate 648 study's inclusion criteria, the G-BA assumes that in this therapeutic indication, patients with unresectable cancer are not indicated for curative treatment with definitive chemoradiotherapy.
c. The G-BA presumes the patients to be candidates for cisplatin-containing chemotherapy.
d. The CheckMate 648 study included only patients with an ECOG-PS of 0 or 1. It remains unclear whether the observed effects are transferable to patients with an ECOG PS ≥ 2. According to the SPC, physicians should consider the delayed onset of nivolumab effect in combination with ipilimumab before initiating treatment in patients with poorer prognostic features and/or aggressive disease.

ACT: appropriate comparator therapy; ECOG-PS: Eastern Cooperative Oncology Group – Performance Status; G-BA: Federal Joint Committee; PD-L1: programmed death ligand 1

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

2.2 Research question

The aim of the present report is to assess the added benefit of nivolumab in combination with ipilimumab in comparison with the ACT as first-line treatment of adult patients with unresectable advanced, recurrent, or metastatic oesophageal squamous cell carcinoma with tumour cell PD-L1 expression ≥ 1%.

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

Table 4: Research question of the benefit assessment of nivolumab

Therapeutic indication	**ACT[a]**
Adult patients with unresectable[b] advanced, recurrent or metastatic oesophageal squamous cell carcinoma with tumour cell PD-L1 expression ≥ 1%; first-line treatment; combination therapy with ipilimumab	Cisplatin[c] in combination with 5-fluorouracil
a. Presented is the respective ACT specified by the G-BA. b. In accordance with the CheckMate 648 study's inclusion criteria, the G-BA assumes that in this therapeutic indication, patients with unresectable cancer are not indicated for curative treatment with definitive chemoradiotherapy. c. The G-BA presumes the patients to be candidates for cisplatin-containing chemotherapy. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; PD-L1: programmed cell death ligand 1	

The company follows the G-BA's 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. RCTs are used for deriving added benefit. This concurs with the company's inclusion criteria.

2.3 Information retrieval and study pool

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

Sources of the company in the dossier:

- study list on nivolumab + ipilimumab (status: 15 March 2022)
- bibliographical literature search on nivolumab + ipilimumab (last search on 15 March 2022)
- search in trial registries/trial results databases for studies on nivolumab + ipilimumab (last search on 15 March 2022)
- search on the G-BA website for nivolumab + ipilimumab (last search on 15 March 2022)

To check the completeness of the study pool:

- search in trial registries for studies on nivolumab (last search on 13 May 2022); for search strategies, see Appendix A of the full dossier assessment

The check did not identify any additional relevant study.

2.3.1 Studies included

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

Table 5: Study pool – RCT, direct comparison: nivolumab + ipilimumab versus chemotherapy[a]

Study	Study category			Available sources		
	Study for the approval of the drug to be assessed (yes/no)	Sponsored study[b] (yes/no)	Third-party study (yes/no)	Clinical study report (CSR) (yes/no [citation])	Registry entries[c] (yes/no [citation])	Publication and other sources[d] (yes/no [citation])
CA209-648 (CheckMate 648[e])	Yes	Yes	No	Yes[f] [3]	Yes [4-6]	Yes [7,8]

a. Cisplatin in combination with 5-fluorouracil.
b. Study for which the company was sponsor.
c. Citation of the study registry entries and, if available, of the reports on study design and/or results listed in the study registries.
d. Other sources: documents from the search on the G-BA website and other publicly available sources.
e. In the following tables, the study is referred to by this acronym.
f. The study report contains results only for the 1st data cut-off (18 January 2021). The present benefit assessment used the 2nd data cut-off (23 August 2021). See Section 2.3.2.

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

For the benefit assessment of nivolumab in combination with ipilimumab, the CheckMate 648 study was included. This concurs with the company's study pool. The subpopulation relevant for the present assessment, patients with tumour cell PD-L1 expression ≥ 1%, is described in Section 2.3.2.

2.3.2 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: nivolumab + ipilimumab versus chemotherapy[a] (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[b]
CheckMate 648	RCT, open-label, parallel-group	Adult patients (≥ 18 years) ▪ With unresectable advanced, recurrent, or metastatic oesophageal squamous cell carcinoma[c] ▪ Without prior systemic cancer therapy for advanced or metastatic disease[d] ▪ ECOG-PS 0 or 1	▪ Nivolumab + ipilimumab (N = 325) ▪ Nivolumab + chemotherapy[a,e] (N = 321) ▪ Chemotherapy[a] (N = 324) Relevant subpopulation thereof (tumour cell PD-L1 expression ≥ 1%): ▪ nivolumab + ipilimumab (n = 158) ▪ chemotherapy[a] (n = 157)	▪ Screening: ≤ 28 days ▪ Treatment: Until disease progression[f], unacceptable toxicity, revocation of consent, study end, or study treatment with nivolumab + ipilimumab for a maximum of 24 months (whichever occurs first) ▪ Observation[g]: outcome-specific, at the longest until death, withdrawal of consent, or end of the study	187 study centres in Argentina, Australia, Austria, Brazil, Canada, Chile, China, Columbia, Czech Republic, Denmark, France, Hong Kong, Italy, Japan, Mexico, Peru, Poland, Romania, Russia, Singapore, South Korea, Spain, Taiwan, Turkey, United Kingdom, and United States 06/2017 – ongoing[h] Data cut-off: ▪ 18 January 2021[i] ▪ 23 August 2021[j]	Primary: OS and PFS in patients with tumour cell PD-L1 expression ≥ 1% Secondary: mortality, morbidity, health-related quality of life, AEs

Table 6: Characteristics of the study included – RCT, direct comparison: nivolumab + ipilimumab versus chemotherapy[a] (multipage table)

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

a. Cisplatin in combination with 5-fluorouracil.
b. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes include only information on relevant available outcomes for this benefit assessment.
c. Histologically confirmed squamous cell carcinoma or adenosquamous cell carcinoma (with predominant squamous differentiation) according to AJCC 7th edition [9].
d. Prior adjuvant, neoadjuvant, or definitive chemotherapy/radiotherapy/chemoradiotherapy for oesophageal squamous cell carcinoma is permissible, provided it was (a) performed in the context of curative therapy and (b) completed before study enrolment. After completion of a neoadjuvant or adjuvant chemotherapy or after completion of multimodal therapy (chemotherapy and chemoradiotherapy) in locally advanced disease, a recurrence-free interval of 24 weeks is required.
e. The arm is irrelevant for the assessment and is not presented in the tables below.
f. After progression as defined by RECIST 1.1 criteria, continuing treatment in the intervention arm (nivolumab + ipilimumab) with nivolumab monotherapy or with nivolumab in combination with ipilimumab was allowed, provided said treatment was tolerated by the patient and deemed to be of clinical benefit by the investigator.
g. Outcome-specific information is provided in Table 8.
h. Planned end: 16 August 2024.
i. 1st data cut-off from 18 January 2021 (data lock on 1 March 2021): predefined final analysis of PFS and interim analysis of OS (because the interim analysis reached the required significance threshold for determining superiority in OS, this analysis represents the final analysis of OS).
j. Second data cut-off from 23 August 2021 (data lock on 4 October 2021): additional data cut-off upon EMA request to support the approval procedure.

AE: adverse event; AJCC: American Joint Committee on Cancer; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; EMA: European Medicines Agency; n: relevant subpopulation; N: number of randomized patients; OS: overall survival; PD-L1: programmed cell death ligand 1; PFS: progression-free survival; RCT: randomized controlled trial; RECIST: Response Evaluation Criteria In Solid Tumours

Table 7: Characteristics of the intervention – RCT, direct comparison: nivolumab + ipilimumab versus chemotherapy[a] (multipage table)

Study	Intervention	Comparison
CheckMate 648	▪ Nivolumab: 3 mg/kg BW, i.v., on Day 1 of a 2-week cycle + ▪ Ipilimumab: 1 mg/kg BW i. v. every 6 weeks (i.e. on Day 1 of each third 2-week nivolumab cycle; each at least 30 minutes after nivolumab infusion)	Chemotherapy: ▪ 5-fluorouracil: 800 mg/m² BSA per day i.v., continuous infusion from Day 1 to Day 5 of a 4-week cycle + ▪ Cisplatin: 80 mg/m² BSA, i.v., on Day 1 of a 4-week cycle
	Dose adjustments ▪ In case of AEs, dose delays and interruptions were allowed. ▪ Nivolumab + ipilimumab ▫ Dose reduction or dose escalation was disallowed. ▫ In case of premature discontinuation of nivolumab, ipilimumab was discontinued as well. In case of premature discontinuation of ipilimumab, it was possible to continue nivolumab therapy. ▪ Chemotherapy ▫ In case of AEs, dose reductions for 5-fluorouracil and cisplatin were allowed according to a defined regimen (maximum of 2 adjustments per treatment component allowed; treatment discontinuation in case of continued toxicity). ▫ Discontinuation of one or both chemotherapy component(s) upon investigator's discretion allowed. In case of discontinuation of one chemotherapy component, it was possible to continue administering the other component upon the investigator's discretion.	
	Non-permitted pretreatment ▪ Anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibodies, or other antibodies or drugs specifically targeting T-cell co-stimulation or checkpoint pathways ▪ Systemic cancer treatment as primary therapy of advanced or metastatic disease except for adjuvant, neoadjuvant, or definitive chemotherapy/radiotherapy/chemoradiotherapy administered as part of curative treatment of oesophageal carcinoma and completed before study start. **Permitted concomitant treatment** ▪ Bisphosphonates and RANK-L inhibitors for the prevention or reduction of skeletal-related events in bone metastases (if initiated before the 1st dose of the study medication) ▪ Palliative radiotherapy (according to protocol specifications) ▪ Supportive treatment for chemotherapy **Non-permitted concomitant treatment[b]** ▪ Immunosuppressants ▪ Immunosuppressant dose of systemic corticosteroids from 14 days before the start of the study medication[c] ▪ Any antineoplastic therapy	

a. Cisplatin in combination with 5-fluorouracil.
b. Except treatment of adverse side effects.
c. Topical, ocular, intraarticular, intranasal, and inhaled corticosteroids (with minimal systemic absorption) were allowed. As steroid replacement therapy, prednisone > 10 mg/day was allowed. Short-term treatment (< 3 weeks) with corticosteroids for the prophylaxis or treatment of nonautoimmune disease was allowed.

AE: adverse event; BSA: body surface area; BW: body weight; CD137: Cluster of Differentiation 137; CTLA-4: cytotoxic T-lymphocyte-associated protein-4; i.v.: intravenous; PD-1: programmed cell death protein-1; PD-L1 / L2: programmed cell death ligand 1/2; RANK-L: receptor activator of NF-κB ligand; RCT: randomized controlled trial

The CheckMate 648 study is an ongoing, open-label, 3-arm RCT which compares nivolumab either in combination with ipilimumab (hereinafter referred to as nivolumab + ipilimumab) or in combination with 5-fluorouracil and cisplatin (hereinafter referred to as nivolumab + chemotherapy) versus 5-fluorouracil and cisplatin combination chemotherapy (hereinafter referred to as chemotherapy). For the present benefit assessment, the only relevant comparison is the nivolumab + ipilimumab arm (intervention arm) versus the chemotherapy arm (comparator arm).

The CheckMate 648 study enrolled adult patients who, according to the criteria of the American Joint Committee on Cancer (AJCC 7th edition [9]), had a histologically confirmed oesophageal squamous cell carcinoma or an adenosquamous carcinoma (with predominant squamous differentiation) which was rated as unresectable advanced, recurrent, or metastatic. Furthermore, patients had to be non-amenable to curative therapy, such as definitive chemoradiotherapy and/or surgery, and they were to be in good general health in accordance with ECOG-PS ≤ 1. The study excluded patients with adenocarcinoma, those with symptomatic or treatment-requiring metastasis in the brain or in the meninges as well as patients at high risk of haemorrhage or fistula due to apparent tumour invasion of organs adjacent to the oesophageal lesions.

A prerequisite for randomization was the presence of an analysable tumour PD-L1 expression classification (≥ 1% or < 1% or no clear test results available). This classification was established by a central laboratory using the Dako PD-L1 IHC 28-8 pharmDx assay [7]. Study inclusion was independent from PD-L1 expression status.

A total of 970 patients were enrolled in the CheckMate 648 study and randomized at a 1:1:1 ratio to treatment with either nivolumab + ipilimumab (N = 325), nivolumab + chemotherapy (N = 321), or chemotherapy (N = 324). Stratification was conducted using the characteristics of tumour cell PD-L1 expression (≥ 1% versus < 1% [including ambiguous test result]), region (East Asia [Japan, Korea, Taiwan] versus rest of Asia [China, Hong Kong, Singapore] versus rest of the world), Eastern Cooperative Oncology Group – Performance Status (ECOG-PS) (0 versus 1), and number of organs with metastases (≤ 1 versus ≥ 2).

In the intervention arm (nivolumab + ipilimumab), nivolumab was administered in 2-week cycles and largely in line with SPC specifications [10]. According to the SPC [10,11], ipilimumab was administered in combination at 6-week intervals, i.e. in every 3rd nivolumab cycle. In line with approval, nivolumab dose modifications (dose reduction or dose escalation) were disallowed, while dose delays due to toxicity were allowed.

In the comparator arm, chemotherapy was likewise administered in 4-week cycles. Cisplatin dosage was administered in line with the SPC [12]. The 5-fluorouracil dosage deviated from the approval statement. In the CheckMate 648 study, a 5-fluorouracil dose of 800 mg/m² BSA was administered on Days 1 to 5 of a 4-week cycle. This corresponds to a total dose of 4000 mg/m² BSA per cycle. For combination chemotherapy with cisplatin, the 5-fluorouracil

SPC specifies a dosage of 1000 mg/m² BSA on Days 1 through 5 of a 3-week to 4-week cycle [13]. This corresponds to a total dose of 5000 mg/m² BSA per cycle. The S3 guideline does not provide any recommendation regarding the 5-fluorouracil dosage [14]. In combination with cisplatin, the National Comprehensive Cancer Network (NCCN) guideline recommends a 5-fluorouracil dose of 750 to 1000 mg/m² BSA/day on Days 1 to 4 of a 4-week cycle [15]. This corresponds to a maximum total dose of 4000 mg/m² BSA per cycle, but the recommended number of treatment days per cycle departs from the procedure used in the CheckMate 648 study. Overall, this deviating 5-fluorouracil dosage did not have any further consequences for the present benefit assessment. Other than that, chemotherapy largely corresponded to the specifications of the SPC [12,13], including in terms of dose adjustments, dose delays, and dose reductions.

The study population was treated until either disease progression, the occurrence of unacceptable toxicity, or discontinuation of study treatment. Furthermore, in line with approval, nivolumab treatment in the intervention arm was limited to a maximum of 24 months. Additionally, continuation of nivolumab therapy (in the form of monotherapy or in combination with ipilimumab) was allowed after disease progression was determined by the investigators in accordance with RECIST 1.1. As a precondition, this required that the patient tolerate treatment and the investigator expect a clinical benefit from treatment continuation. After the identification of another progression event, treatment was discontinued.

The primary outcomes of the CheckMate 648 study were overall survival and PFS. Secondary outcomes were outcomes from the categories: morbidity, health-related quality of life, and side effects.

Relevant subpopulation of the CheckMate 648 study

According to approval, nivolumab in combination with ipilimumab is indicated for the first-line treatment of adult patients with unresectable advanced, recurrent, or metastatic oesophageal squamous cell carcinoma with tumour cell PD-L1 expression ≥ 1%.

The CheckMate 648 study included patients irrespective of their PD-L1 expression status. To be enrolled in the study, however, patients had to have an analysable tumour cell PD-L1 expression classification (≥ 1% or < 1% or equivocal test result).

In line with nivolumab approval, the company's Module 4 T takes into account only the CheckMate 648 subpopulation of patients with tumour cell PD-L1 expression ≥ 1%. This subpopulation comprises 158 patients in the intervention arm relevant for the present benefit assessment (nivolumab + ipilimumab) as well as 157 patients in the comparator arm (chemotherapy).

Overall, the subpopulation formed by the company adequately reflects the relevant population in the present therapeutic indication. The subpopulation formed by the company is therefore used for the present benefit assessment.

Data cut-offs

The CheckMate 648 study is still ongoing. At the time the benefit was assessed, 2 data cut-offs were available:

- 1st data cut-off (18 January 2021, database lock 1 March 2021): predefined final analysis of the outcome of PFS and interim analysis of the outcome of overall survival
- 2nd data cut-off (23 August 2021, database lock 4 October 2021): according to the information provided by the company in Module 4 T, this data cut-off was requested by the European Medicines Agency (EMA) to support the approval procedure

In Module 4 T, the company presents analyses of the 2nd data cut-off for all outcomes relevant for the present benefit assessment and describes it as the most current data cut-off which, to date, offers the longest possible observation period for overall survival. Based on the approval documents, the EMA request for updated efficacy data is plausible [16]. However, the study report presented by the company is dated 8 June 2021 and therefore excludes the 2nd data cut-off. The company has not submitted a study report for the 2nd data cut-off.

The present benefit assessment uses the results from the 2nd data cut-off of 23 August 2021.

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: nivolumab + ipilimumab versus chemotherapy[a]

Study **Outcome category** **Outcome**	**Planned follow-up observation**
CheckMate 648	
Mortality	
Overall survival	Until death, withdrawal of consent, or end of study (whichever is first)
Morbidity	
Health status (EQ-5D VAS)	Until 114 (± 14) days after the last dose of the study drug[b] (i.e. until the 2nd follow-up visit)
Health-related quality of life (FACT-E)	Until 114 ± 14 days after the last dose of the study drug[c] (i.e. until the 2nd follow-up visit)
Side effects (all outcomes in the category of side effects)	Until 114 (± 14) days after the last dose of the study drug[d] (i.e. until the 2nd follow-up visit)

a. Cisplatin in combination with 5-fluorouracil.

b. Inconsistent information on the duration of follow-up observation was provided within the study documents as well as between study documents and Module 4 T. The operationalization presented by the company in Module 4 T is based on the surveys up to the 2nd follow-up visit. However, the study documents fail to unambiguously show whether the outcome was surveyed only until the 2nd follow-up visit or also throughout the subsequent follow-up observation phase for overall survival. For instance, the study documents include analyses of EQ-5D VAS at individual follow-up points for overall survival (e.g. surveys of 2 versus 2 patients at the 1st follow-up for overall survival; data are available only for the 1st data cut-off from 18 January 2021).

c. The FACT-E questionnaire comprises the FACT-General questionnaire (FACT-G) and the ECS. The study documents clearly show that after the 2nd follow-up visit, health-related quality of life was surveyed using the FACT-G7 (shortened version of the FACT-G) and the ECS rather than the entire FACT-E questionnaire. Neither alone nor in combination with the ECS scale is the FACT-G7 suitable for depicting health-related quality of life (see Section 2.4.1). It is unclear why completed FACT-E questionnaires were found for individual follow-up observations of overall survival in both the intervention arm and in the comparator arm (e.g. surveys of 2 versus 3 patients at the 1st follow-up for overall survival; data are available only for the 1st data cut-off of 18 January 2021).

d. For the outcomes of the side effects category, the company's Module 4 T additionally presents analyses of the 2nd data cut-off; rather than taking into account the entire planned observation period, these analyses reportedly included only the events which occurred up to 100 days after the last treatment with the study medication.

ECS: Esophageal Cancer Subscale; EQ-5D: European Quality of Life Questionnaire – 5 Dimensions; FACT-E: Functional Assessment of Cancer Therapy–Esophageal; FACT-G: Functional Assessment of Cancer Therapy–General; FACT-G7: Functional Assessment of Cancer Therapy–General 7-Item Version; RCT: randomized controlled trial; VAS: visual analogue scale

The observation periods for the outcomes of health-related quality of life and side effects were systematically shortened because they were recorded only for the time period of treatment with the study medication (plus 114 [± 14] days).

For the outcomes of the side effects category, the company's Module 4 T additionally presents analyses of the 2nd data cut-off; rather than taking into account the entire planned observation period, these analyses reportedly included only the events which occurred up to 100 days after

the last treatment with the study medication. Data on the entire study duration or until death are missing. However, drawing a reliable conclusion on the total study period or the time to patient death would require recording these outcomes for the total period, as was done for survival.

For the morbidity outcome of health status (surveyed with the EQ-5D VAS), inconsistent information provided within the study documents and between the study documents and Module 4 T leaves it unclear whether the outcome was surveyed until the 2nd follow-up visit (until 114 [± 14] days after the last dose of the study medication) or until death (follow-up for overall survival). However, since the documents provide data from very few patients for the follow-up time points for overall survival, it is safe to assume that these surveys were intended to be conducted only until the 2nd follow-up visit, and no further systematic surveys were carried out. Some of the responder analyses presented in the company's Module 4 T for the outcome of health status are also based exclusively on the period until the 2nd follow-up visit. For the outcome of health status, data are therefore likewise available only for a shortened observation period.

Characteristics of the relevant subpopulation

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

Table 9: Characterization of the study population as well as study/treatment discontinuation – RCT, direct comparison: nivolumab + ipilimumab [a] versus chemotherapy[a], (relevant subpopulation) (multipage table)

Study **Characteristic** **Category**	**Nivolumab + ipilimumab** **N[b] = 158**	**Chemotherapy[a]** **N[b] = 157**
CheckMate 648		
Age [years], mean (SD)	61 (9)	63 (9)
Sex [f/m], %	17/83	17/83
Family origin n (%)		
Caucasian	34 (21.5)	38 (24.2)
Asian[c]	117 (74.1)[d]	113 (72.0)[d]
Other	7 (4.4)[d]	6 (3.8)[d]
ECOG PS, n (%)		
0	71 (44.9)	70 (44.6)
1	87 (55.1)	85 (54.1)
Not reported	0 (0)	2 (1.3)
Histology at first diagnosis, n (%)		
Squamous cell carcinoma	157 (99.4)	155 (98.7)
Adenosquamous carcinoma[e]	1 (0.6)	2 (1.3)
Disease status, n (%)		
Recurrent – locoregional	8 (5.1)	14 (8.9)
Recurrent – distant metastasis	25 (15.8)	27 (17.2)
De-novo metastatic	107 (67.7)	89 (56.7)
Unresectable advanced	18 (11.4)	27 (17.2)
Disease duration: time from first diagnosis to randomization, n (%)		
< 1 year	128 (81.0)	126 (80.3)
1 to < 3 years	25 (15.8)	22 (14.0)
3 to < 5 years	4 (2.5)	4 (2.5)
≥ 5 years	0 (0)	5 (3.2)
Not reported	1 (0.6)	0 (0)
Prior surgery[f], n (%)		
Yes	38 (24.1)	38 (24.2)
No	120 (75.9)	119 (75.8)
Prior radiotherapy n (%)		
Yes	26 (16.5)	28 (17.8)
No	132 (83.5)	129 (82.2)
Tumour cell PD-L1 expression, n (%)		
< 10%	55 (34.8)	60 (38.2)
≥ 10%	103 (65.2)	97 (61.8)
Treatment discontinuation (2nd data cut-off), n (%)[g]	156 (98.7)	145 (92.4[d])
Study discontinuation (2nd data cut-off), n (%)	ND[h]	ND[h]

Table 9: Characterization of the study population as well as study/treatment discontinuation – RCT, direct comparison: nivolumab + ipilimumab [a] versus chemotherapy[a], (relevant subpopulation) (multipage table)

Study Characteristic Category	Nivolumab + ipilimumab N[b] = 158	Chemotherapy[a] N[b] = 157

a. Cisplatin in combination with 5-fluorouracil.
b. Number of randomized patients. Values which are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
c. Includes Asian Indian, Chinese, Japanese, and Asian (other).
d. Institute's calculation.
e. With predominant squamous differentiation.
f. Except biopsy.
g. Common reasons for treatment discontinuation in the intervention versus control arms: disease progression (81 versus 97); toxicity of the study medication (35 versus 14); AEs unrelated to the study medication (11 versus 5); patient's discretion (8 versus 11 patients).
h. According to information provided in the study report on the 1st data cut-off, 110 patients in the nivolumab + ipilimumab arm versus 126 patients in the control arm prematurely discontinued the study. Common reasons for study discontinuation were death (103 versus 112) as well as withdrawal of consent (6 versus 14).

ECOG-PS: Eastern Cooperative Oncology Group Performance Status; f: female; m: male; n: number of patients in the category; N: number of randomized patients; ND: no data; PD-L1: programmed cell death ligand 1; RCT: randomized controlled trial; SD: standard deviation

The characteristics of the patients in the included relevant subpopulation were balanced between the 2 treatment arms. The mean patient age was about 62 years; most patients were male (83%) and of Asian ancestry (74.1% versus 72%). Slightly more than half of the patients had an ECOG-PS of 1. Almost the entire relevant subpopulation had oesophageal squamous cell carcinoma, while only a few patients had adenosquamous carcinoma with predominant squamous differentiation. Disease status was predominantly metastatic (de novo metastatic: 67.7% versus 56.7%; recurrent – distant metastases: 15.8% versus 17.2%). Furthermore, 63.5% of the relevant subpopulation had a tumour cell PD-L1 expression ≥ 10%.

Information on the course of the study

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

Table 10: Information on the course of the study – RCT, direct comparison: nivolumab + ipilimumab versus chemotherapy[a] (relevant subpopulation)

Study **Duration of the study phase** **Outcome category**	**Nivolumab + ipilimumab** **N = 158**	**Chemotherapy[a]** **N = 145**
CheckMate 648, (2nd data cut-off)		
Treatment duration [months]		
Median [min; max]	3.01 [0.0; 24.0]	2.96 [0.0; 17.2]
Mean (SD)	6.03 (ND)	3.64 (ND)
Duration of follow-up observation [months]		
Overall survival[b]		
Median [min; max]	12.96 [0.3; 45.9]	8.57 [0.0; 43.1]
Mean (SD)	15.96 (ND)	11.18 (ND)
Morbidity (health status – EQ-5D VAS)	ND	ND
Health-related quality of life – (FACT-E)	ND	ND
Side effects	ND	ND

a. Cisplatin in combination with 5-fluorouracil.
b. Time from randomization until last contact or patient death.

EQ-5D: European Quality of Life Questionnaire – 5 Dimensions; FACT-E: Functional Assessment of Cancer Therapy – Esophageal; max: maximum; min: minimum; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation; VAS: visual analogue scale

In the CheckMate 648 study, the relevant subpopulation's median treatment duration was equal in the intervention arm and in the comparator arm (about 3 months). Differences in observation period are found for overall survival, where the median observation period reported by the company is 13 versus 8.6 months. No information on the relevant subpopulation's observation period was available for the outcomes of the morbidity, health-related quality of life, and side effects categories.

Due to inconsistent information in the study documents (see Table 8), it is unclear whether the outcome of health status was to be observed until the 2nd follow-up visit or until death. Since very few surveys were collected for this outcome during the follow-up period, it is safe to assume that surveys were to be conducted only until the 2nd follow-up visit. In addition, the responder analysis found in Module 4 T comprises surveys only until the 2nd follow-up visit.

For outcomes in the morbidity, health-related quality of life, and side effects categories, the observation period is linked to treatment end. For these outcomes, the observation period was therefore a maximum of 128 days (114 [± 14] days) after treatment. The side effects analysis presented in Module 4 T comprises only surveys taken up to 100 days after treatment end. Based on the information provided on treatment duration plus 128 days, the estimated median observation duration was about 7.3 months in the intervention arm and in the comparator arm. Hence, the observation durations for these outcomes were shortened in comparison with overall survival (about 13 months versus 8.6 months). For side effects, it must be noted that the side

effects analysis provided in Module 4 T comprises only surveys performed up to 100 days after treatment end.

This evidence scenario has consequences regarding the interpretability of the outcomes which were observed for a shorter period (see Section 2.4.1).

Information on subsequent therapies

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

Table 11: Information on subsequent therapies – RCT, direct comparison: nivolumab + ipilimumab versus chemotherapy[b] (relevant subpopulation) (multipage table)

Study Drug class Drug	Patients with subsequent therapy n (%)	
	Nivolumab + ipilimumab N = 158	Chemotherapy[b] N = 157
CheckMate 648		
Subsequent radiotherapy	35 (22.2)	52 (33.1)
curative	4 (2.5)	3 (1.9)
palliative	31 (19.6)	49 (31.2)
Subsequent surgical procedure	4 (2.5)	2 (1.3)
curative	1 (0.6)	0 (0)
palliative	3 (1.9)	2 (1.3)
Subsequent systemic therapy	83 (52.5)	89 (56.7)
Anti PD-L1 immunotherapies	6 (3.8)	24 (15.3)
Nivolumab	6 (3.8)	17 (10.8)
Camrelizumab	0 (0)	2 (1.3)
Pembrolizumab	0 (0)	2 (1.3)
Sintilimab	0 (0)	1 (0.6)
Sugemalimab	0 (0)	1 (0.6)
Tislelizumab	0 (0)	1 (0.6)
Other systemic therapies	82 (51.9)	83 (52.9)
Fluorouracil	55 (34.8)	34 (21.7)
Cisplatin	52 (32.9)	22 (14.0)
Paclitaxel	29 (18.4)	38 (24.2)
Docetaxel	15 (9.5)	20 (12.7)
Oxaliplatin	11 (7.0)	5 (3.2)
Carboplatin	8 (5.1)	6 (3.8)
Gimeracil / oteracil potassium / tegafur	6 (3.8)	4 (2.5)
Nedaplatin	6 (3.8)	9 (5.7)
Capecitabine	5 (3.2)	0 (0)
Irinotecan	5 (3.2)	5 (3.2)
Gimeracil	4 (2.5)	2 (1.3)
Oteracil potassium	4 (2.5)	2 (1.3)
Tegafur	4 (2.5)	3 (1.9)
Vinorelbine tartrate	2 (1.3)	0 (0)
Antineoplastic substances	1 (0.6)	0 (0)
Apatinib mesylate	1 (0.6)	0 (0)
Astragalus mongholicus root / oxymatrine / Panax ginseng dry extract	1 (0.6)	0 (0)
Bevacizumab	1 (0.6)	1 (0.6)
Calcium levofolinate	1 (0.6)	0 (0)
Cetuximab	1 (0.6)	0 (0)

Table 11: Information on subsequent therapies – RCT, direct comparison: nivolumab + ipilimumab versus chemotherapy[b] (relevant subpopulation) (multipage table)

Study **Drug class** **Drug**	**Patients with subsequent therapy n (%)**	
	Nivolumab + ipilimumab **N = 158**	**Chemotherapy[b]** **N = 157**
Fluorouracil / folinic acid	1 (0.6)	0 (0)
Gemcitabine	1 (0.6)	1 (0.6)
Gemcitabine hydrochloride	1 (0.6)	1 (0.6)
Gimeracil/oteracil	1 (0.6)	0 (0)
Lobaplatin	1 (0.6)	1 (0.6)
Methotrexate	1 (0.6)	1 (0.6)
Methotrexate sodium	1 (0.6)	0 (0)
Paclitaxel, albumin-bound	1 (0.6)	1 (0.6)
Paclitaxel, liposomal	1 (0.6)	0 (0)
Tegafur/uracil	1 (0.6)	1 (0.6)
Human albumin / paclitaxel	0 (0)	2 (1.3)
Astragalus mongholicus root / *Eleutherococcus senticosus* root with rhizome / *Mylabris* spp. / Panax ginseng root	0 (0)	1 (0.6)
Brucea javanica oil / glycerol / lecithin	0 (0)	2 (1.3)
Catequentinib	0 (0)	1 (0.6)
Etoposide	0 (0)	1 (0.6)
Experimental antineoplastic therapies	0 (0)	3 (1.9)
Irinotecan hydrochloride	0 (0)	1 (0.6)
Lentinan	0 (0)	1 (0.6)
Marsdenia tenacissima stem	0 (0)	1 (0.6)
Mitomycin	0 (0)	1 (0.6)
Vinorelbine	0 (0)	2 (1.3)

a. It was possible for patients to have received more than 1 type of subsequent therapy.
b. Cisplatin in combination with 5-fluorouracil.

n: number of patients with subsequent therapy; N: number of analysed patients; PD-L1: programmed cell death ligand 1; RCT: randomized controlled trial

The study documents do not list any limitations regarding the type of subsequent therapies. No planned switch of comparator arm patients into the intervention arm has been described for the CheckMate 648 study.

After discontinuation of the study medication, most of the patients in the relevant subpopulation received systemic subsequent therapy (52.5% versus 56.7%). In both study arms, this therapy typically comprised chemotherapy, e.g. with the fluorouracil (34.8% versus 21.7%), cisplatin (32.9% versus 14.0%), or the taxanes of paclitaxel (18.4% versus 24.2%) and docetaxel (9.5% versus 12.7%). Furthermore, 3.8% of patients in the intervention arm and 10.8% of those in the comparator arm received nivolumab subsequent therapy. According to the guideline issued by

the German Society for Haematology and Medical Oncology (DGHO), these subsequent therapies represent relevant options in second-line treatment of oesophageal squamous cell carcinoma [17].

Risk of bias across outcomes (study level)

Table 12 shows the risk of bias across outcomes (risk of bias at study level).

Table 12: Risk of bias across outcomes (study level) – RCT, direct comparison: nivolumab + ipilimumab versus chemotherapy[a]

Study	Adequate random sequence generation	Allocation concealment	Blinding		Nonselective reporting	No additional aspects	Risk of bias at study level
			Patients	Treating staff			
CheckMate 648	Yes	Yes	No	No	Yes	Yes	Low

a. Cisplatin in combination with 5-fluorouracil.
RCT: randomized controlled trial

The risk of bias across outcomes is rated as low for the CheckMate 648 study.

Limitations resulting from the open-label study design are described in Section 2.4 with outcome-specific risk of bias.

Transferability of the study results to the German health care context

In the company's view, the results of the CheckMate 648 study's relevant subpopulation are transferable to the to the German health care context due to age at disease onset and sex ratios being comparable. The company argues that the mean age at disease onset in Germany is 68 years, and men are 3 times more likely to develop oesophageal carcinoma. Additionally, the company cites patient ancestry (73% Asian; 23% White), arguing that, due to the tumour's biological characteristics, Asian and White patients can be expected to exhibit a comparable response.

Furthermore, the company's reasoning is based on disease-specific patient characteristics, such as the high percentage of patients in the relevant subpopulation who exhibit current or prior alcohol and/or tobacco consumption as well as lymph node involvement. Finally, the company notes that the treatment used in the comparator arm (chemotherapy arm) represents the most common therapy in the German health care context.

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

2.4 Results on added benefit

2.4.1 Outcomes included

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

- Mortality
  - overall survival
- Morbidity
  - health status, surveyed using the EQ-5D VAS
- Health-related quality of life
  - measured using the FACT-E total score
- Side effects
  - SAEs
  - severe AEs, operationalized as Common Terminology Criteria for Adverse Events (CTCAE) grade ≥ 3
  - discontinuation due to AEs
  - immune-mediated SAEs
  - immune-mediated severe AEs
  - further 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 T).

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

Table 13: Matrix of outcomes – RCT, direct comparison: nivolumab + ipilimumab versus chemotherapy[a]

Study	Outcomes								
	Overall survival	Health status (EQ-5D VAS)	Health-related quality of life (FACT-E)	SAEs[b]	Severe AEs[b,c]	Discontinuation due to AEs[b]	Immune-mediated SAEs[d]	Immune-mediated severe AEs[c,d]	Further specific AEs[e]
CheckMate 648	Yes	No[f]	No[f]	Yes	Yes	Yes	Yes	Yes	Yes

a. Cisplatin in combination with 5-fluorouracil.
b. Excludes progression events of the underlying disease (according to the company's list, several PTs of the SOC "benign, malignant, and unspecified [including cysts and polyps]").
c. Severe AEs are operationalized as CTCAE grade ≥ 3.
d. In each case, the operationalization of a specific MedDRA PT collection ("select AEs") was used.
e. The following events were taken into account (PTs and SOCs, MEdDRA coded): gastrointestinal disorders (SOC, AEs), mucosal inflammation (PT, AEs), alopecia (PT, AEs), hiccups (PT, AEs), renal and urinary disorders (SOC, AEs), vomiting (PT, SAEs), anaemia (PT, severe AEs), neutrophil count decreased (PT, severe AEs), nervous system disorders (SOC, severe AEs).
f. No usable data available; see body of text below for reasons.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EQ-5D: European Quality of Life Questionnaire – 5 Dimensions; FACT-E: Functional Assessment of Cancer Therapy-Esophageal; 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 the outcomes of health status (surveyed with EQ-5D VAS) and health-related quality of life (surveyed with FACT-E)

Relevant operationalization for the outcome of health-related quality of life

- In the CheckMate 648 study, health-related quality of life was surveyed with the FACT-E questionnaire. The FACT-E questionnaire comprises the FACT-General questionnaire (FACT-G) and the Esophageal Cancer Subscale (ECS). In the CheckMate 648 study, the FACT-E questionnaire was surveyed until the 2nd follow-up visit (corresponds to 114 [± 14] days after the last dose of the study medication). Afterwards, only the FACT-G7 (a shortened version of the FACT-G) and the ECS were recorded, rather than the complete FACT-E questionnaire. However, the FACT-G7 and ECS instruments are unsuitable for reflecting the complex construct of health-related quality of life. Only the data on the FACT-E total score can therefore be taken into account for the outcome of health-related quality of life.

Unusable analyses for the outcomes of health status and health-related quality of life

- For the outcomes of health status (surveyed using the EQ-5D VAS) and health-related quality of life (recorded with the FACT-E), the company's Module 4 T presents, among other things, responder analyses of time to definitive deterioration. The company defines definitive deterioration as a clinically relevant deterioration without subsequent improvement to a value which no longer represents a clinically relevant deterioration. As a response criterion, the company used, among others, 15 points for the EQ-5D VAS and 27 points for the FACT-E, which corresponds to 15% of the scale range of the respective instrument and hence meets the criteria specified by the IQWiG General Methods [1].

  The responder analyses on "definitive deterioration" do not supply any usable data for either outcome. This is explained below:

  The observation period is shortened for both outcomes. For the outcome of health status as measured with the EQ-5D VAS, inconsistent information on the planned duration of follow-up observation between Module 4T and the study documents leaves it unclear whether this outcome was to be observed only until the 2nd follow-up visit or until death (see Section 2.3.2). For both outcomes, the responder analyses presented by the company in Module 4T are based only on analyses until the 2nd follow-up visit (114 ± 14 days after the last dose of the study medication). The outcome of health-related quality of life, surveyed with the FACT-E questionnaire, was surveyed only until the 2nd follow-up visit.

  No information is available for either outcome on the actual observation duration applicable to the study's relevant subpopulation. When estimating the median observation duration for both study arms by adding the maximum follow-up observation period of 128 days (114 [± 14] days) to the median treatment duration, the resulting observation duration for these outcomes is shortened compared to the observation duration for overall survival. For instance, the relevant subpopulation's median observation duration for overall survival was about 13 months (intervention arm) or about 8.6 months (comparator arm, see Table 10). The estimated median observation durations for the outcomes on morbidity and health-related quality of life, in contrast, are about 7.3 months in both study arms and therefore cover only a part of the total possible observation period. In this situation, it is therefore inappropriate to speak of "definitive deterioration". Rather, this is at most a deterioration confirmed over the shortened observation period.

  Regarding the median observation period calculated for both study arms, about 7.3 months, it must be noted that according to the return rates submitted by the company, the questionnaire return rate is lower in the comparator arm than in the intervention arm. Hence, the median observation duration is presumably longer in the intervention arm than in the comparator arm. Sustained deterioration across all surveys is potentially more difficult to achieve in the longer-observed intervention arm (nivolumab + ipilimumab).

  Overall, the responder analyses on the outcomes of health status and health-related quality of life cannot be interpreted without further information. In this situation, analyses of first deterioration are needed, but were not presented in Module 4 T.

All told, the responder analyses available on definitive deterioration cannot be used in the present benefit assessment.

Unusable analyses of mean change for the outcomes of health status and health-related quality of life

- For the outcomes of health status and health-related quality of life, the company's Module 4 T provides as supplementary information analyses of mean change during treatment, calculated on the basis of a mixed model for repeated measures (MMRM). This operationalization takes into account only the observation time points at which patients were treated with the study medication. Data which were collected during follow-up observation are disregarded in the present analysis. Furthermore, since the MMRM analysis includes only those observations which were made on 10 or more patients receiving treatment, only the surveys up to Week 37 were taken into account in the available MMRM analyses. The interpretation requires for the entire observation period to be included in the analyses. Values collected after treatment end must be included in the analyses for the benefit assessment, and in case of premature treatment end, they must be transparently matched to the corresponding times from randomization (i.e. the visits at the corresponding times). Due to the described deficiencies, the available MMRM analyses are likewise unsuitable for the benefit assessment and were therefore disregarded in the benefit assessment.

Notes on side effect outcomes

- Immune-mediated AEs: In Appendix 4 G of Module 4 T, the company presents analyses on the predefined specific immune-mediated AEs (imAEs), specific AEs (select AEs) as well as AEs of special interest (AESI). In addition, analyses of serious events and severe events (operationalized as CTCAE grade ≥ 3) are available for each of these outcomes. The company stated in the dossier that, with the exception of endocrine imAEs, the AEs of particular interest (which the company called imAEs) were those requiring immunomodulatory therapy. This operationalization is unsuitable for fully representing immune-mediated AEs. The outcome of AEs of particular interest, which the company referred to as "select AEs", however, constitutes a selection of System Organ Class (SOCs) and Preferred Terms (PTs) which are typical immune-mediated AEs and which can require immunosuppressant treatment (e.g. with corticosteroids), but not necessarily so. In addition, the dossier contains the list of PTs which were included as events in the analysis of the "select AEs". This operationalization is deemed a sufficient approximation of immune-mediated AEs. Both SAEs and severe AEs (CTCAE grade ≥ 3) were considered in the process. A list of the categories of immune-mediated AEs, immune-mediated SAEs, and severe immune-mediated AEs (CTCAE grade ≥ 3) which occurred in the CheckMate 648 study is provided as supplementary information in Appendix D of the full dossier assessment.

2.4.2 Risk of bias

Table 14 describes the risk of bias for the results of the relevant outcomes.

Table 14: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: nivolumab + ipilimumab versus chemotherapy[a]

Study	Study level	Outcomes								
		Overall survival	Health status (EQ-5D VAS)	Health-related quality of life (FACT-E)	SAEs	Severe AEs[b]	Discontinuation due to AEs	Immune-mediated SAEs[c]	Immune-mediated severe AEs[b, c]	Further specific AEs[d]
CheckMate 648	L	L	-[e]	-[e]	H[f]	H[f]	H[g]	H[f]	H[f]	H[f, h]

a. Cisplatin in combination with 5-fluorouracil.
b. Severe AEs are operationalized as CTCAE grade ≥ 3.
c. In each case, the operationalization of a specific MedDRA PT collection "select AEs" was used.
d. The following events were taken into account (PTs and SOCs; MEdDRA coded): gastrointestinal disorders (SOC, AEs), mucosal inflammation (PT, AEs), alopecia (PT, AEs), hiccups (PT, AEs), renal and urinary disorders (SOC, AEs), vomiting (PT, SAEs), anaemia (PT, severe AEs), neutrophil count decreased (PT, severe AEs), nervous system disorders (SOC, severe AEs).
e. No usable data available; see Section 2.4.1 for the reasoning.
f. Incomplete observations for potentially informative reasons.
g. Lack of blinding in the presence of subjective decision on treatment discontinuation.
h. Lack of blinding in the presence of subjective outcome surveying (in the case of serious/severe AEs).

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EQ-5D: European Quality of Life Questionnaire – 5 Dimensions; FACT-E: Functional Assessment of Cancer Therapy–Esophageal; 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 outcome-specific risk of bias is rated as high for the results of all patient-relevant outcomes except overall survival.

No usable data are available for the outcomes of health status or health-related quality of life (for reasons, see Section 2.4.1); therefore, the risk of bias was not assessed.

The risk of bias of results is deemed high for the outcomes of SAEs, severe AEs, immune-mediated SAEs, immune-mediated severe AEs as well as other specific AEs (gastrointestinal disorders [SOC, AEs], mucosal inflammation [PT, AEs], alopecia [PT, AEs], hiccups [PT, AEs], renal and urinary disorders [SOC, AEs], vomiting [PT, SAEs], anaemia [PT, severe AEs], neutrophil count decreased [PT, severe AEs], nervous system disorders [SOC, severe AEs]). These outcomes suffer from incomplete observation for potentially informative reasons (largely due to the observation end 114 [± 14] days after treatment discontinuation, which in turn was

predominantly due to disease progression; see Section 2.3.2). For nonserious/nonsevere AEs, the risk of bias of results is additionally increased due to lack of blinding in subjective outcome recording. The risk of bias for the outcome of discontinuation due to AEs was rated as high because of lack of blinding with subjective decision on treatment discontinuation.

2.4.3 Results

Table 15 summarizes the results of the comparison of nivolumab + ipilimumab versus chemotherapy in the first-line treatment of adult patients with unresectable advanced, recurrent, or metastatic oesophageal squamous cell carcinoma with tumour cell PD-L1 expression ≥ 1%. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier.

Kaplan-Meier curves on the presented event time analyses can be found in Appendix B of the full dossier assessment. Module 4 T, Appendix 4 G contains no Kaplan-Meier curves for the specific AEs (gastrointestinal disorders [SOC, AEs], mucosal inflammation [PT, AEs], alopecia [PT, AEs], hiccups [PT, AEs], renal and urinary disorders [SOC, AEs], vomiting [PT, SAEs], anaemia [PT, severe AEs], neutrophil count decreased [PT, severe AEs], nervous system disorders [SOC, severe AEs]). Results on common AEs, SAEs, severe AEs, and discontinuations due to AEs are presented in Appendix C of the full dossier assessment. A list of the immune-mediated AEs, immune-mediated SAEs, and severe immune-mediated AEs (CTCAE grade ≥ 3) categories in which events occurred is presented as supplementary information in Appendix D of the full dossier assessment.

Table 15: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: nivolumab + ipilimumab versus chemotherapy[a] (relevant subpopulation) (multipage table)

Study Outcome category Outcome	Nivolumab + ipilimumab		Chemotherapy[a]		Nivolumab + ipilimumab vs. chemotherapy[a]
	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI]; p-value[b]
CheckMate 648					
Mortality					
Overall survival	158	13.70 [11.2; 17.4] 119 (75.3)	157	9.07 [7.7; 10.0] 130 (82.8)	0.63 [0.49; 0.82]; < 0.001
Morbidity					
EQ-5D VAS	No usable data[c]				
Health-related quality of life					
FACT-E	No usable data[c]				
Side effects					
AEs (supplementary information)[d]	158	0.39 [0.3; 0.5] 157 (99.4)	145	0.10 [0.07; 0.1] 144 (99.3)	-
SAEs[d]	158	2.92 [2.0; 3.9] 115 (72.8)	145	6.41 [4.4; 8.2] 77 (53.1)	1.42 [1.06; 1.90]; 0.020
Severe AEs[d, e]	158	3.25 [2.3; 3.9] 122 (77.2)	145	2.99 [2.0; 3.8] 108 (74.5)	0.85 [0.65; 1.11]; 0.277
Discontinuation due to AEs[d,f]	158	21.19 [12.5; NC] 48 (30.4)	145	14.23 [10.1; NC] 31 (21.4)	1.17 [0.74; 1.87]; 0.500
Immune-mediated AEs[g] (supplementary information)	158	1.41 [1.0; 1.6] 122 (77.2)	145	5.55 [3.7; 6.4] 79 (54.5)	-
Immune-mediated SAEs[g]	158	NR [23.1; NC] 37 (23.4)	145	NR 7 (4.8)	4.82 [2.13; 10.92]; < 0.001
Immune-mediated severe AEs[e,g]	158	NR [14.6; NC] 40 (25.3)	145	NR 11 (7.6)	3.41 [1.74; 6.69]; < 0.001
Gastrointestinal disorders (AEs)	158	2.23 [1.6; 3.5] 123 (77.8)	145	0.20 [0.1; 0.2] 132 (91.0)	0.37 [0.28; 0.48]; < 0.001
Mucosal inflammation (AEs)	158	NR 1 (0.6)	145	NR 19 (13.1)	-[h]; < 0.001
Alopecia (AEs)	158	NR 8 (5.1)	145	NR 21 (14.5)	0.23 [0.09; 0.58]; < 0.001
Hiccups (AEs)	158	NR 8 (5.1)	145	NR 30 (20.7)	0.23 [0.10; 0.49]; < 0.001
Renal and urinary disorders (AEs)	158	NR 12 (7.6)	145	NR 30 (20.7)	0.32 [0.16; 0.62]; < 0.001
Vomiting (SAEs)	158	NR 3 (1.9)	145	NR 9 (6.2)	0.25 [0.07; 0.96]; 0.030

Table 15: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: nivolumab + ipilimumab versus chemotherapy[a] (relevant subpopulation) (multipage table)

Study Outcome category Outcome	Nivolumab + ipilimumab		Chemotherapy[a]		Nivolumab + ipilimumab vs. chemotherapy[a]
	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI]; p-value[b]
Anaemia (severe AEs[e])	158	NR 16 (10.1)	145	NR 26 (17.9)	0.49 [0.25; 0.93]; 0.027
Neutrophil count decreased (severe AEs[e])	158	NR 4 (2.5)	145	NR 13 (9.0)	0.24 [0.08; 0.746]; 0.008
Nervous system disorders (severe AEs[e])	158	NR 3 (1.9)	145	NR 8 (5.5)	0.28 [0.08; 1.08]; 0.0496[i]

a. Cisplatin in combination with 5-fluorouracil.
b. HR and CI: Cox proportional hazards model; p-value: log rank test; each stratified by ECOG-PS (0, 1) and number of organs with metastases (≤ 1, ≥ 2) according to IRT.
c. See Section 2.4.1 for a rationale.
d. Excluding progression events of the underlying disease (several PTs of the SOC "benign, malignant and unspecified [including cysts and polyps]" according to the company's list).
e. Operationalized as CTCAE grade ≥ 3.
f. Discontinuation of 1 or more components.
g. In each case, the operationalization of a specific MedDRA PT collection ("select AEs") was used.
h. No presentation of effect estimation and CI, as these are not informative.
i. Discrepancy between p-value and CI due to different calculation methods.

AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; ECOG-PS: Eastern Cooperative Oncology Group-Performance Status; EQ-5D: European Quality of Life Questionnaire – 5 Dimensions; FACT-E: Functional Assessment of Cancer Therapy – Esophageal; HR: hazard ratio; IRT: interactive response technology; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least 1) event; N: number of analysed patients; NC: not calculable; NR: not reached; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

On the basis of the available information, at most indications, e.g. of an added benefit, can be derived for the outcome of overall survival, and at most hints can be derived for all other outcomes due to high risk of bias.

Mortality

Overall survival

For the outcome of overall survival, a statistically significant difference was found in favour of nivolumab + ipilimumab in comparison with chemotherapy. Notably, the Kaplan-Meier curves on this outcome cross (see Figure 2 of the full dossier assessment). In the first few months, the Kaplan-Meier curve falls more steeply in the nivolumab + ipilimumab arm than in the chemotherapy arm. At about 6 months after study start, the Kaplan-Meier curves cross, and only in the further course does an advantage of nivolumab + ipilimumab become apparent. This

suggests that some patient groups reap less benefit or no benefit at all from the intervention. The characteristics of this patient group cannot be determined on the basis of the data submitted by the company. The crossing of the Kaplan-Meier curves might be based in part on an effect modification, but no statistically significant interaction was found for any of the subgroup characteristics examined in the CheckMate 648 study. On the basis of exploratory post hoc analyses, the European regulatory authority included a corresponding warning in the SPC, according to which physicians should consider the delayed onset of nivolumab effect in combination with ipilimumab before initiating treatment in patients with poorer prognostic features and/or aggressive disease [8,10].

Overall, this results in an indication of added benefit of nivolumab + ipilimumab in comparison with chemotherapy.

Morbidity

Health status

There were no usable data for the outcome health status, recorded with the EQ-5D VAS (for reasoning, see Section 2.4.1). This results in no hint of an added benefit of nivolumab + ipilimumab in comparison with chemotherapy; an added benefit is therefore not proven.

Health-related quality of life

FACT-E

No usable data were available for the outcome of health-related quality of life, recorded with the FACT-E total score (for reasoning, see Section 2.4.1). This results in no hint of an added benefit of nivolumab + ipilimumab in comparison with chemotherapy; an added benefit is therefore not proven.

Side effects

SAEs

For the outcome of SAEs, a statistically significant difference was found between treatment groups to the disadvantage of nivolumab + ipilimumab in comparison with chemotherapy. This results in a hint of greater harm from nivolumab + ipilimumab in comparison with chemotherapy.

Severe AEs and discontinuation due to AEs

There was no statistically significant difference between treatment groups for either of the outcomes of severe AEs or discontinuation due to AEs. This results in no hint of greater or lesser harm from nivolumab + ipilimumab in comparison with chemotherapy; greater or lesser harm is therefore not proven.

Specific AEs

Immune-mediated SAEs, immune-mediated severe AEs

For each of the outcomes of immune-mediated SAEs and immune-mediated severe AEs, a statistically significant difference between treatment groups was found to the disadvantage of nivolumab + ipilimumab versus chemotherapy. This results in a hint of greater harm from nivolumab + ipilimumab in comparison with chemotherapy for each of them.

Gastrointestinal disorders (AEs), mucosal inflammation (AEs), alopecia (AEs), hiccups (AEs), renal and urinary disorders (AEs), vomiting (SAEs), anaemia (severe AEs), neutrophil count decreased (severe AEs), nervous system disorders (severe AEs)

For each of the outcomes of gastrointestinal disorders (AEs), mucosal inflammation (AEs), alopecia (AEs), hiccups (AEs), renal and urinary disorders (AEs), vomiting (SAEs), anaemia (severe AEs), neutrophil count decreased (severe AEs), and nervous system disorders (severe AEs), there is a statistically significant difference between treatment groups in favour of nivolumab + ipilimumab in comparison with chemotherapy. For each of them, this results in a hint of lesser harm from nivolumab + ipilimumab in comparison with chemotherapy.

2.4.4 Subgroups and other effect modifiers

The following potential effect modifiers were taken into account for the present benefit assessment:

- age (< 65 years versus ≥ 65 years and < 75 years versus ≥ 75 years)
- sex (male versus female)
- disease status for current diagnosis (recurrent – locoregional versus recurrent – distant metastasis versus de novo metastatic versus unresectable advanced)

The subgroup characteristics selected in the present benefit assessment had been defined a priori, but only for the outcomes of overall survival and PFS and for some of the side effects outcomes.

Interaction tests are performed if at least 10 patients per subgroup are included in the analysis. Moreover, for binary data, there had to be at least 10 events in at least 1 subgroup.

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

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

2.5 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 constitutes a proposal by IQWiG. The G-BA decides on the added benefit.

2.5.1 Assessment of the added benefit at outcome level

The extent of the respective added benefit at outcome level was estimated from the results presented in Section 2.4 (see Table 16).

Table 16: Extent of added benefit at outcome level: nivolumab + ipilimumab versus chemotherapy[a] (relevant subpopulation) (multipage table)

Observation period **Outcome category** **Outcome**	**Nivolumab + ipilimumab vs. chemotherapy[a]** **Median time to event (months)** **Effect estimation [95% CI];** **p-value** **Probability[b]**	**Derivation of extent[c]**
Total observation period		
Mortality		
Overall survival	13.70 vs. 9.07 months HR: 0.63 [0.49; 0.82]; p < 0.001 Probability: indication	Outcome category: mortality $CI_u < 0.85$ Added benefit; extent: major[d]
Shortened observation period		
Morbidity		
Health status (EQ-5D VAS)	No usable data[e]	Lesser/added benefit not proven
Health-related quality of life		
FACT-E	No usable data[e]	Lesser/added benefit not proven
Side effects		
SAEs	2.92 vs. 6.41 months HR: 1.42 [1.06; 1.90]; HR[f]: 0.70 [0.52; 0.94]; p = 0.020 Probability: hint	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ Greater harm; extent: minor
Severe AEs	3.25 vs. 2.99 months HR: 0.85 [0.65; 1.11]; p = 0.277	Greater/lesser harm not proven
Discontinuation due to AEs	21.19 vs. 14.23 months 1.17 [0.74; 1.87]; p = 0.500	Greater/lesser harm not proven
Immune-mediated SAEs	NR vs. NR HR: 4.82 [2.13; 10.92]; HR[f]: 0.21 [0.09; 0.47]; p < 0.001 Probability: hint	Outcome category: serious/severe side effects $CI_u < 0.75$, risk ≥ 5% Greater harm; extent: major
Immune-mediated severe AEs	NR vs. NR HR: 3.41 [1.74; 6.69]; HR[f]: 0.29 [0.15; 0.57]; p < 0.001 Probability: hint	Outcome category: serious/severe side effects $CI_u < 0.75$, risk ≥ 5% Greater harm; extent: major
Gastrointestinal disorders (AEs)	2.23 vs. 0.20 months HR: 0.37 [0.28; 0.48]; p < 0.001 Probability: hint	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ Lesser harm; extent: considerable

Table 16: Extent of added benefit at outcome level: nivolumab + ipilimumab versus chemotherapy[a] (relevant subpopulation) (multipage table)

Observation period **Outcome category** **Outcome**	**Nivolumab + ipilimumab vs. chemotherapy[a]** **Median time to event (months)** **Effect estimation [95% CI];** **p-value** **Probability[b]**	**Derivation of extent[c]**
Mucosal inflammation (AEs)	NR vs. NR HR: -[g] $p < 0.001$ Probability: hint	Outcome category: non-serious/non-severe side effects Lesser harm; extent: non-quantifiable[h]
Alopecia (AEs)	NR vs. NR HR: 0.23 [0.09; 0.58]; $p < 0.001$ Probability: hint	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ Lesser harm; extent: considerable
Hiccups (AEs)	NR vs. NR HR: 0.23 [0.10; 0.49]; $p < 0.001$ Probability: hint	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ Lesser harm; extent: considerable
Renal and urinary disorders (AEs)	NR vs. NR HR: 0.32 [0.16; 0.62]; $p < 0.001$ Probability: hint	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ Lesser harm; extent: considerable
Vomiting (SAEs)	NR vs. NR HR: 0.25 [0.07; 0.96]; $p = 0.030$ Probability: hint	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ Lesser harm; extent: minor
Anaemia (severe AEs)	NR vs. NR HR: 0.49 [0.25; 0.93]; $p = 0.027$ Probability: hint	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ Lesser harm; extent: minor
Neutrophil count decreased (severe AEs)	NR vs. NR HR: 0.24 [0.08; 0.746]; $p = 0.008$ Probability: hint	Outcome category: serious/severe side effects $CI_u < 0.75$, risk ≥ 5% Lesser harm, extent: major
Nervous system disorders (severe AEs)	NR vs. NR HR: 0.28 [0.08; 1.08]; $p = 0.0496$ Probability: hint	Outcome category: serious/severe side effects Lesser harm[h]; extent: minor[i]

Table 16: Extent of added benefit at outcome level: nivolumab + ipilimumab versus chemotherapy[a] (relevant subpopulation) (multipage table)

Observation period **Outcome category** **Outcome**	**Nivolumab + ipilimumab vs. chemotherapy[a]** **Median time to event (months)** **Effect estimation [95% CI];** **p-value** **Probability[b]**	**Derivation of extent[c]**
a. Cisplatin in combination with 5-fluorouracil. b. Probability provided if a statistically significant and relevant effect is present. c. Depending on the outcome category, estimations of effect size use different limits based on the upper limit of the confidence interval (CI_u). d. Kaplan-Meier curves cross after about 6 months (see Figure 2 of the full dossier assessment); the major added benefit is found only in the later course of treatment. e. See Section 2.4.1 for reasons. f. Institute's calculation; reversed direction of effect to enable use of limits to derive the extent of the added benefit. g. No presentation of effect estimation and CI, as these are not informative. h. The result of the statistical test is decisive for the derivation of the added benefit. i. Discrepancy between CI and p-value; the extent is rated as minor. AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; EQ-5D: European Quality of Life Questionnaire – 5 Dimensions; FACT-E: Functional Assessment of Cancer Therapy-Esophageal; HR: hazard ratio; NR: not reached; SAE: serious adverse event; VAS: visual analogue scale		

2.5.2 Overall conclusion on added benefit

Table 17 summarizes the results which were factored into the overall conclusion on the extent of added benefit.

Table 17: Favourable and unfavourable effects from the assessment of nivolumab + ipilimumab in comparison with chemotherapy[a] (relevant subpopulation)

Favourable effects	Unfavourable effects
Total observation period	
Mortality ▪ Overall survival: indication of added benefit – extent: major[b]	–
Shortened observation period	
Serious/severe side effects ▪ Vomiting (SAEs), anaemia, nervous system disorders (severe AEs each): each hint of lesser harm; extent: minor ▪ Neutrophil count decreased (severe AEs): hint of lesser harm; extent: major	Serious/severe side effects ▪ SAEs: hint of greater harm; extent: minor ▪ Immune-mediated SAEs: hint of greater harm; extent: major ▪ Immune-mediated severe AEs: hint of greater harm; extent: major
Non-serious/non-severe side effects ▪ Gastrointestinal disorders, alopecia, hiccups, renal and urinary disorders (AEs each): each hint of lesser harm; extent: considerable ▪ Mucosal inflammation (AEs): hint of lesser harm; extent: nonquantifiable	–
No usable data are available on outcomes of the morbidity category (health status [EQ-5D VAS]) and health-related quality of life (FACT-E).	
a. Cisplatin in combination with 5-fluorouracil. b. Kaplan-Meier curves cross after about 6 months (see Figure 2 of the full dossier assessment); the major added benefit is found only in the later course of treatment. According to the SPC, physicians should consider the delayed onset of nivolumab effect in combination with ipilimumab before initiating treatment in patients with poorer prognostic features and/or aggressive disease [10]. AE: adverse event; EQ-5D: European Quality of Life Questionnaire – 5 Dimensions; FACT-E: Functional Assessment of Cancer Therapy – Esophageal; SAE: serious adverse event; VAS: visual analogue scale	

Overall, both favourable and unfavourable effects of nivolumab + ipilimumab were found in comparison with chemotherapy.

In terms of favourable effects, there was an indication of major added benefit for the outcome of overall survival. However, due to the Kaplan-Meier curves crossing at about 6 months, this effect in favour of nivolumab + ipilimumab becomes apparent only in the further course of treatment. On the basis of the data presented by the company, it is impossible to determine the extent to which patient characteristics or other factors explain the crossing of the Kaplan-Meier curves. Hence, it cannot be conclusively determined which patients reap major benefit from the intervention. On the basis of exploratory post hoc analyses, the European regulatory authority included a corresponding warning in the SPC, according to which physicians should consider the delayed onset of nivolumab effect in combination with ipilimumab before initiating treatment in patients with poorer prognostic features and/or aggressive disease [8,10].

For numerous specific outcome of the side effects category, there are also hints of lesser harm for both serious/severe side effects and for nonserious/nonsevere side effects of different

extents. Regarding unfavourable effects, in contrast, hints of greater harm, some of them of major extent, were found for the outcomes of SAEs and immune-mediated serious or severe AEs, but this did not call into question the favourable effect concerning overall survival.

For the outcome categories of morbidity and health-related quality of life, no usable data suitable for being taken into account in the overall conclusion on added benefit are available.

Given the available evidence, the extent is deemed non-quantifiable.

In summary, for adult patients with unresectable advanced, recurrent, or metastatic oesophageal squamous cell carcinoma with tumour cell PD-L1 expression ≥ 1%, there is an indication of non-quantifiable added benefit of nivolumab + ipilimumab in comparison with the ACT of chemotherapy.

Table 18 summarizes the result of the assessment of added benefit of nivolumab in combination with ipilimumab in comparison with the ACT.

Table 18: Nivolumab – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adult patients with unresectable[b] advanced, recurrent or metastatic oesophageal squamous cell carcinoma with tumour cell PD-L1 expression ≥ 1%; first-line treatment	Cisplatin[c] in combination with 5-fluorouracil	Indication of non-quantifiable added benefit[d]

a. Presented is the respective ACT specified by the G-BA.
b. In accordance with the CheckMate 648 study's inclusion criteria, the G-BA assumes that, for this therapeutic indication, patients with unresectable cancer are not indicated for curative treatment with definitive chemoradiotherapy.
c. The G-BA presumes the patients to be candidates for cisplatin-containing chemotherapy.
d. The CheckMate 648 study included only patients with an ECOG-PS of 0 or 1. It remains unclear whether the observed effects are transferable to patients with an ECOG PS ≥ 2. According to the SPC, physicians should consider the delayed onset of nivolumab effect in combination with ipilimumab before initiating treatment in patients with poorer prognostic features and/or aggressive disease [10].

ACT: appropriate comparator therapy; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee; PD-L1: programmed death ligand 1

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

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

References for English extract

Please see full dossier assessment for full reference list.

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

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