Medicinrådet

Bilag til Medicinrådets anbefaling vedr. nivolumab i kombination med platin- og fluoropyrimidinbaseret kemoterapi til 1. linje-behandling af planocellulært karcinom i spiserøret med PD-L1 TPS ≥ 1 %

Vers. 1.0

Bilagsoversigt

1. Ansøgers notat til Rådet vedr. nivolumab + kemoterapi til planocellulært karcinom i spiserøret
2. Forhandlingsnotat fra Amgros vedr. nivolumab + kemoterapi til planocellulært karcinom i spiserøret
3. Ansøgers endelige ansøgning vedr. nivolumab + kemoterapi til planocellulært karcinom i spiserøret

Bristol Myers Squibb
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Virum,15. december 2022

Til Medicinrådet

Bristol Myers Squibbs tilbagemelding på udkast til vurderingsrapport for nivolumab i kombination med kemoterapi til førsteliniebehandling af ikke-resekterbar, recidiverende eller metastatisk planocellulært karcinom i spiserøret med en PD-L1 TPS ≥ 1

Bristol Myers Squibb (BMS) imødeser Medicinrådets anbefaling af nivolumab i kombination med kemoterapi til planocellulær spiserørskræft planlagt til Rådsmødet d. 25. januar 2023 og glæder sig over, Medicinrådet er enig i valg af økonomisk model og hovedparten af antagelserne heri.

Det undrer dog, at Medicinrådet har valgt at opjustere den gennemsnitlige vægt fra 59 kg (CheckMate 648) og 62,6 kg (KEYNOTE 590) til 76,5 kg, som er angivet som gennemsnitsvægten for den almindelige kvinde eller mand i alderen +65 år.

Patienter med spiserørskræft er karakteriseret ved ofte at have synkebesvær og et betydeligt vægttab forud for diagnosticering. Antagelsen om at en patient med fremskreden spiserørskræft vejer det samme som en almindelig person virker derfor ikke plausibelt. En opjustering af kropsvægten med ca. 25% vil medføre en tilsvarende overvurdering af lægemiddelomkostninger, når man benytter vægtbaseret dosering.

I vurderingen af pembrolizumab + kemoterapi (26. januar 2022) til selvsamme patientpopulation blev vægten ikke opjusteret.

I nærværende sag spiller det en mindre rolle, fordi der er tale om en cost-minimization analyse. Men ud fra en generel betragtning synes denne praksis ikke korrekt.

Afslutningsvist er BMS dog glad for at have haft et effektivt samarbejde med sekretariatet, samt at sagsbehandlingstiden fra Dag 0 nu er inden for målsætningen.

Med venlig hilsen,

Anders Thelborg
Adm. direktør
Bristol Myers Squibb, Denmark

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21. december 2022
DBS/CAF

Forhandlingsnotat

Dato for behandling i Medicinrådet	25. januar 2023
Leverandør	BMS
Lægemiddel	Opdivo (nivolumab)
Ansøgt indikation	Opdivo (nivolumab) i kombination med kemoterapi til 1. linjebehandling af planocellulært karcinom i spiserøret med PD-L1 > 1%

Forhandlingsresultat

Amgros har følgende pris på Opdivo (nivolumab):

Tabel 1: Forhandlingsresultat Opdivo (nivolumab)

Lægemiddel	Styrke	Pakningsstørrelse	AIP (DKK)	Forhandlet SAIP (DKK)	Rabatprocent ift. AIP
Opdivo (nivolumab)	240 mg/24 ml	1 stk.	21.453,65	[redacted]	[redacted]
Opdivo (nivolumab)	100 mg/10 ml	1 stk.	8.939,02	[redacted]	[redacted]
Opdivo (nivolumab)	40 mg/4 ml	1 stk.	3.598,42	[redacted]	[redacted]

Prisen vil være gældende indtil 31.12.2023.

[redacted]

Konkurrencesituationen

På nuværende tidspunkt er Keytruda (pembrolizumab) i kombination med kemoterapi godkendt til behandling af lokalt fremskredent inoperabelt eller metastatisk karcinom i spiserøret eller HER2-negativ adenokarcinom i den gastro-esofageale overgang.

[redacted]

Tabel 2: Sammenligning af lægemiddeludgiftpå Opdivo (nivolumab) og Keytruda (pembrolizumab)

Lægemiddel	Dosis	Pakningsstørrelse	Pakningspris SAIP (DKK)	Antal behandlinger/år	Årlig lægemiddeludgift SAIP pr. år (DKK)
Opdivo (nivolumab)	4,5 mg/kg hver 3. uge*	100 mg/10ml	[redacted]	17	[redacted]
Keytruda (pembrolizumab)	2 mg/kg hver 3 uge*	25 mg/ml (4 ml)	[redacted]	17	[redacted]

*Gennemsnitsvægt på 76,5 kg jf. Medicinrådets vurderingsrapport på Opdivo (nivolumab) til behandling af planocellulært spiserørskræft i 1. linje.

Status fra andre lande

Norge: Under vurdering[1].
Sverige: Opdivo (nivolumab) er en del af en samlet rekommandation for PL-L1 hæmmere[2].
England: Anbefalet[3].

Konklusion

[redacted]

[1] https://nyemetoder.no/metoder/nivolumab-opdivo-indikasjon-xvii
[2] NT-rådets process för PD-(L)1-hämmare - Janusinfo.se
[3] https://www.nice.org.uk/guidance/ta707/chapter/1-Recommendations

Application for the assessment of nivolumab in combination with fluoropyrimidine- and platinum-based combination chemotherapy 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%

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1 Basic information

Contact information	
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Overview of the pharmaceutical	
Proprietary name	OPDIVO® plus fluoropyrimidine- and cisplatin-containing chemotherapy
Generic name	Nivolumab plus chemotherapy
Marketing authorization holder in Denmark	Bristol Myers Squibb™
ATC code	L01FF01
Pharmacotherapeutic group	Antineoplastic agents, monoclonal antibodies
Active substance(s)	OPDIVO® plus fluoropyrimidine- and cisplatin-containing chemotherapy
Pharmaceutical form(s)	Concentrate for solution for infusion
Mechanism of action	Nivolumab is a human immunoglobulin G4 (IgG4) monoclonal antibody (HuMAb), which binds to the programmed death-1 (PD-1) receptor
Dosage regimen	**Nivolumab** 240 mg nivolumab (IV) every 2 weeks or 480 mg nivolumab every 4 weeks **Chemotherapy** 4-week cycle consisting of: • Fluorouracil (IV) 800 mg per m^2 days 1-5 • Cisplatin (IV) 80 mg per m^2 on day 1
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)	Nivolumab in combination with fluoropyrimidine- and platinum-based combination chemotherapy is indicated for the first-line treatment of adult patients with unresectable advanced, recurrent or metastatic esophageal squamous cell carcinoma with tumour cell PD-L1 expression ≥ 1%

Other approved therapeutic indications	**Melanoma** OPDIVO as monotherapy or in combination with ipilimumab is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults Relative to nivolumab monotherapy, an increase in progression-free survival (PFS) and overall survival (OS) for the combination of nivolumab with ipilimumab is established only in patients with low tumour PD-L1 expression **Adjuvant treatment of melanoma** OPDIVO as monotherapy is indicated for the adjuvant treatment of adults with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection **Non-small cell lung cancer (NSCLC)** OPDIVO in combination with ipilimumab and 2 cycles of platinum-based chemotherapy is indicated for the first-line treatment of metastatic non-small cell lung cancer in adults whose tumours have no sensitising EGFR mutation or ALK translocation OPDIVO as monotherapy is indicated for the treatment of locally advanced or metastatic non-small cell lung cancer after prior chemotherapy in adults **Malignant pleural mesothelioma (MPM)** OPDIVO in combination with ipilimumab is indicated for the first-line treatment of adult patients with unresectable malignant pleural mesothelioma **Renal cell carcinoma (RCC)** OPDIVO as monotherapy is indicated for the treatment of advanced renal cell carcinoma after prior therapy in adults OPDIVO in combination with ipilimumab is indicated for the first-line treatment of adult patients with intermediate/poor-risk advanced renal cell carcinoma OPDIVO in combination with cabozantinib is indicated for the first-line treatment of adult patients with advanced renal cell carcinoma **Classical Hodgkin lymphoma (cHL)** OPDIVO as monotherapy is indicated for the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma after autologous stem cell transplant (ASCT) and treatment with brentuximab vedotin **Squamous cell cancer of the head and neck (SCCHN)** OPDIVO as monotherapy is indicated for the treatment of recurrent or metastatic squamous cell cancer of the head and neck in adults progressing on or after platinum-based therapy **Urothelial carcinoma** OPDIVO as monotherapy is indicated for the treatment of locally advanced unresectable or metastatic urothelial carcinoma in adults after failure of prior platinum-containing therapy **Adjuvant treatment of urothelial carcinoma** OPDIVO as monotherapy is indicated for the adjuvant treatment of adults with muscle invasive urothelial carcinoma (MIUC) with tumour cell PD-L1 expression ≥ 1%, who are at high risk of recurrence after undergoing radical resection of MIUC **Mismatch repair deficient (dMMR) or microsatellite instability-high (MSI-H) colorectal cancer (CRC)** OPDIVO in combination with ipilimumab is indicated for the treatment of adult

Overview of the pharmaceutical	
	patients with mismatch repair deficient or microsatellite instability-high metastatic colorectal cancer after prior fluoropyrimidine-based combination chemotherapy. **Esophageal squamous cell carcinoma (ESCC)** OPDIVO as monotherapy is indicated for the treatment of adult patients with unresectable advanced, recurrent or metastatic esophageal squamous cell carcinoma after prior fluoropyrimidine- and platinum-based combination chemotherapy OPDIVO in combination with fluoropyrimidine- and platinum-based combination chemotherapy 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%. OPDIVO as monotherapy is indicated for the treatment of adult patients with unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma after prior fluoropyrimidine- and platinum-based combination chemotherapy. **Adjuvant treatment of esophageal or gastro-esophageal junction cancer (EC or GEJC)** OPDIVO as monotherapy is indicated for the adjuvant treatment of adult patients with esophageal or gastro-esophageal junction cancer who have residual pathologic disease following prior neoadjuvant chemoradiotherapy **Gastric, gastro-esophageal junction (GEJ) or esophageal adenocarcinoma** OPDIVO in combination with fluoropyrimidine- and platinum-based combination chemotherapy is indicated for the first-line treatment of adult patients with HER2-negative advanced or metastatic gastric, gastro-esophageal junction or esophageal adenocarcinoma whose tumours express PD-L1 with a combined positive score ≥ 5
Will dispensing be restricted to hospitals?	Yes
Combination therapy and/or co-medication	Yes, nivolumab plus fluoropyrimidine- and cisplatin-containing chemotherapy
Packaging – types, sizes/number of units, and concentrations	Nivolumab (10 mg/mL): Single-use vials 40 mg/4 mL 100 mg/10 mL 240 mg/24 mL
Orphan drug designation	No

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2 Abbreviations

Abbreviation	Description of abbreviation
ADC	Adenocarcinoma
AE	adverse event
AJCC	American Joint Committee on Cancer
ALK	anaplastic lymphoma kinase
APC	antigen-presenting cell
ASR	age-standardized incidence rate
AUC	area under curve
AUP	Pharmacy selling price
BICR	Blinded Independent Central Review
BMS	Bristol-Myers Squibb
BSC	best supportive care
CAPOX	capecitabine and oxaliplatin
CBC	complete blood count
CF	5-fluorouracil and cisplatin
CI	confidence interval
CPS	combined positive score
CR	Complete response
CRC	Colorectal cancer
CRF	Case record form
CRT	Chemoradiotherapy
CSR	Clinical study report
CT	Chemotherapy
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
DBL	Data base lock
DCF	docetaxel plus cisplatin plus 5-fluorouracil
DEGC	Dansk Esophago Gastrisk Cancer Gruppe
DFS	disease-free survival
DKK	Danish kronor
DMC	Danish Medicines Council
dMMR	deficient mismatch repair
DOR	duration of response
EAC	esophageal adenocarcinoma

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EC	esophageal cancer
ECF	epirubicin plus cisplatin plus 5-fluorouracil
ECOG	Eastern Cooperative Oncology Group
ECS	esophageal cancer subscale
EGFR	epidermal growth factor receptor
EMA	European Medicines Agency
EOX	epirubicin plus oxaliplatin plus capecitabine
EQ-5D	EuroQol five-dimension questionnaire
EORTC QLQ-C30	European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire
ESCC	esophageal squamous cell carcinoma
ESMO	European Society of Medical Oncology
EU	European Union
EU5	United Kingdom, Germany, France, Italy and Spain
FACT-E	Functional Assessment of Cancer Therapy- Esophageal
FDA	US Food and Drug Administration
FLOT	Docetaxel plus oxaliplaton plus leucovorin plus 5-fluorouracil plus leucovorin plus capecitabine
FOLFIRI	5-fluorouracil plus leucovorin plus irinotecan
FOLFOX	5- fluorouracil plus leucovorin plus oxaliplatin
5-FU	5-fluorouracil
GAC	gastric adenocarcinoma
GC	Gastric cancer
GEJ	gastroesophageal junction
GEJC	gastroesophageal junction cancer
GERD	gastroesophageal reflux disease
GI	Gastrointestinal
HER2	human epidermal growth factor receptor 2
HR	hazard ratio
HRQoL	health-related quality of life
IFN-γ	type II interferon gamma
IHC	Immunohistochemistry
IMAE	immune-mediate adverse event
INV	Investigator
IRT	Interactive Response Technology

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ITT	Intent to treat
IV	Intravenous
KM	Kaplan-Meier
1L	first-line
2L	second-line
LSM	Least square mean
MHC	major histocompatibility complex
M:I	mortality to incidence rate
MID	
MMR	mismatch repair
MSI-H	microsatellite instability-high
NCCN	National Comprehensive Cancer Network
NR	Not reported
NSCLC	non small cell lung cancer
n/a	Not available
OGJ	esophagogastric junction
ORR	objective response rate
OS	overall survival
PAR	population attributable risk
PCR	polymerase chain reaction
PD	progression of disease / progressive disease
PD-1	programmed cell death 1 receptor
PD-L1	programmed death ligand 1
PD-L2	programmed death ligand 2
PFS	progression-free survival
PFS2	Time to second progression
PS	performance status
q2w	every two weeks
q3w	every three weeks
q4w	every four weeks
RCC	Renal cell carcinoma
RFS	recurrence-free survival
ROW	Rest of world
RT	Radiotherapy

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SAE	Severe adverse event
SD	standard deviation
SE	standard error
SLR	Systematic literature review
SOC	standard of care
TCE	toxicity composite endpoint
TNM	tumour, node, metastasis
TP	paclitaxel plus cisplatin
TPS	tumour cell PD-L1 expression
TRAE	Treatment-related adverse event
TSST	time to second subsequent therapy
TTD	Time to discontinuation
UI	uncertainty interval
US	United States of America
VAS	visual analog scale
VAT	Value added tax

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3 Tables and Figures

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4 Summary

BMS is seeking reimbursement for nivolumab in combination with fluoropyrimidine and platinum-containing chemotherapy, hereafter called nivolumab plus chemotherapy, for the first line (1L) treatment of patients with advanced, recurrent or metastatic esophageal squamous cell carcinoma (ESCC) with tumour cell PD-L1 expression (TPS) ≥ 1%. The reimbursement dossier is based on results from the pivotal phase III CheckMate 648 study.

Population

Esophageal cancer (EC) is an aggressive cancer, with poor patient outcomes and limited treatment modalities, especially for advanced disease patients (Cheng 2018). There are two major histological subtypes of EC, which differ in terms of epidemiology and etiology: esophageal adenocarcinoma (EAC) and esophageal squamous cell carcinoma (ESCC) (Arnold 2015).Patients are commonly diagnosed at an advanced disease stage.

ESCC is the most prevalent form of EC, accounting for around 87% of cases worldwide (GLOBOCAN 2020). Patients with ESCC have a 5-year overall survival (OS) estimated at ~15% (Then 2020). Metastatic ESCC is incurable; the goal of treatment is to improve patient quality of life and to prolong survival (Batra 2019, NCCN 2021).

In Denmark, there were 278 patients with newly diagnosed EC (ESCC and EAC) in 2020. It is estimated that 90 ESCC patients received first line systemic treatment in Denmark in 2019. Danish treatment guidelines in EC recommend that for patients with non-curable ESCC who are in a good performance status should be offered palliative chemotherapy: dual substance (fluoropyrimidine and platinum) or triple substance (fluoropyrimidine, platinum and taxane). Additionally, palliative external beam radiotherapy and brachytherapy can be used for local nuisances such as bleeding, pain or obstruction (DEGC 2020c). As of early 2022, pembrolizumab plus chemotherapy has become an additional treatment option for ESCC, recommended by the Danish Medicines Council for patients with locally advanced inoperable or metastatic carcinoma of the esophagus or HER2-negative adenocarcinoma of the gastro-esophageal junction, Siewert type I, in adults with the biomarker PD-L1 CPS ≥ 10 (Medicinrådet 2022).

Intervention

CheckMate 648 is a global, randomized, open-label Phase 3 study evaluating nivolumab combined with 5-FU plus cisplatin (nivolumab plus chemotherapy) versus 5-FU plus cisplatin (chemotherapy) in subjects with 1L advanced or metastatic ESCC. The primary endpoints were OS and PFS by BICR in patients whose tumours express PD-L1 (TPS ≥1%). The secondary endpoints were ORR by BICR in patients whose tumours express PD-L1 (TPS ≥1%) (Chau 2021).

Immunotherapies targeting the programmed death-ligand 1 (PD-L1) pathway, including nivolumab, have been emerging as a promising way to treat cancers in the upper gastro-intestinal (GI) tract. Nivolumab-based therapies have been approved in human epidermal growth receptor 2 (HER2) negative gastric cancer (GC), gastroesophageal junction cancer (GEJC), EAC, and adjuvant treatment of esophageal or gastro-esophageal junction cancer and 2L ESCC (EMA 2018, BMS 2020a, BMS 2021f).

Outcomes: CheckMate 648

Nivolumab plus chemotherapy provided a **statistically significant and clinically meaningful improvement in OS** over chemotherapy alone both for patients whose tumours express PD-L1 (TPS ≥1%) and for all-comers (BMS 2021e). In particular, nivolumab plus chemotherapy delivered a **6.4-month OS improvement** in patients whose tumours express PD-L1 (TPS ≥1%)[15.05 (95% CI, 11.9-18.6) versus 9.07 (95% CI, 7.7-10.0) months for chemotherapy alone, and a hazard ratio of 0.59 (95% CI, 0.46–0.76), p<0.0001] (BMS 2022, European Medicin Agency 2022b).

The co-primary endpoint PFS per blinded independent central review (BICR), was demonstrated favourable in patients whose tumours express PD-L1 (TPS ≥1%), where the median PFS per BICR was 6.93 months for nivolumab plus chemotherapy (95% CI, 5.68–8.35) versus 4.44 months for chemotherapy alone (95% CI, 2.89–5.82) [HR: 0.66 (95% CI,

0.50–0.87)] (BMS 2022, European Medicin Agency 2022b). Nivolumab plus chemotherapy has a safety profile similar to the chemotherapy arm (BMS 2021e). The rate of grade 3-4 TRAEs leading to discontinuation was low in the nivolumab plus chemotherapy arm [redacted] and comparable to the chemotherapy arm [redacted] (BMS 2022).

Combining nivolumab with chemotherapy has been investigated prior to the CheckMate 648 study. Based on the encouraging clinical activity with acceptable safety profile the combination of 5-FU and cisplatin plus nivolumab was evaluated in CheckMate 648, demonstrating superior clinical efficacy compared to chemotherapy (BMS 2021e).

Comparative efficacy

No head-to-head evidence is available comparing nivolumab plus chemotherapy with the relevant comparator, pembrolizumab plus chemotherapy, in the first line treatment of adult patients with unresectable advanced, recurrent or metastatic ESCC whose tumours express PD-L1 (TPS ≥1%) with regards to efficacy and safety. As such, an indirect treatment comparison (ITC) was conducted, comparing the relevant studies CheckMate 648 (nivolumab plus chemotherapy) and KEYNOTE 590 (pembrolizumab plus chemotherapy).

While there were some differences in study design and patient populations the studies, baseline characteristics support that the study arms in CheckMate 648 and KEYNOTE 590 are comparable in terms of age, gender distribution, and performance status.

Results from the ITC for the primary endpoints are presented in Table 1. Data is presented at a 20-month minimum follow-up for nivolumab plus chemotherapy for both OS and PFS, and at a 34.8-month and 22.6-month median follow-up for OS and PFS, respectively, for pembrolizumab plus chemotherapy. For neither OS nor PFS was a statistically significant difference identified, hence, in terms of efficacy, nivolumab plus chemotherapy can be considered equivalent to pembrolizumab plus chemotherapy.

Adverse events data was collected and reported differently in the CheckMate 648 and KEYNOTE 590 studies, therefore, an ITC was not possible and a descriptive comparison was considered. At the 20-month minimum follow-up for nivolumab plus chemotherapy and 22.6-month median follow-up for pembrolizumab plus chemotherapy, the results of the descriptive analysis of CheckMate 648 and KEYNOTE 590 suggest a similar safety profiles of nivolumab and pembrolizumab in combination with chemotherapy. The safety profiles of nivolumab plus chemotherapy and pembrolizumab plus chemotherapy are also consistent with the known profiles of the individual components at similar doses (European Medicin Agency 2022a, European Medicin Agency 2022b).

Table 1: Nivolumab plus chemotherapy versus pembrolizumab plus chemotherapy: indirect treatment comparison results for the overall survival endpoint

Outcome	CheckMate 648 (nivolumab plus chemotherapy, n=321)	KEYNOTE 590 (pembrolizumab plus chemotherapy, n=373)	HR Bucher's ITC
OS HR (95% CI), follow-up	0.59 (0.46, 0.75), Minimum 20 month	0.59 (0.45, 0.76) Median 34.8 months	1.00 (0.696, 1.437)
PFS HR (95% CI), follow-up	0.66 (0.59, 0.87) Minimum 20 month	0.53 (0.40, 0.69) Median 22.6 months	1.245 (0.891, 1.740)

Abbreviations: HR, hazard ratio; ITC, independent treatment comparison; OS, overall survival; PFS, progression free survival.

Health economic evaluation

For the health economic assessment of nivolumab plus chemotherapy (CheckMate 648) in advanced, recurrent or metastatic ESCC in Denmark the current standard of care, pembrolizumab plus chemotherapy (KEYNOTE 590), is the most appropriate comparator. To estimate the indirect relative effectiveness between the two treatment strategies,

the Bucher Indirect Treatment Comparison methodology (Bucher ITC) was utilized. The results of the Bucher ITC showed no statistically significant difference between the clinical efficacy of nivolumab plus chemotherapy and pembrolizumab plus chemotherapy. Further a descriptive comparison of safety was carried out that indicated no signs of differences in safety profiles between the two treatment combinations. Therefore, a cost-minimization analysis (cost-min) was performed.

In the base case, the results of the cost-min were presented using the two approved dosing regiments for nivolumab, bi-weekly or 4-weekly dosing. In both cases, there was fixed dosing applied and the treatment duration for both treatments was [redacted] as per CheckMate 648. The base case results [redacted] for bi-weekly dosing and [redacted] for 4-weekly dosing for nivolumab plus chemotherapy compared to pembrolizumab plus chemotherapy.

For the budget impact analysis, the eligible patient population for each of the 5-years was 45 patients and it was assumed that there would be a market share of 80% by year 5 for nivolumab plus chemotherapy. The costs included in the analysis were drug acquisition costs, administration costs, monitoring costs, and indirect costs. Under these assumptions and a treatment frequency of every 4 weeks for nivolumab plus chemotherapy, the total budget impact in year 5 was [redacted]

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5 The patient population, the intervention and choice of comparator

The medical condition and patient population

5.1 Disease description

Esophageal cancer (EC) is one of the most aggressive forms of cancer; for 90% of diagnosed patients, the disease is fatal, and EC represents the seventh leading cause of cancer deaths globally (Sung 2021). EC is often diagnosed at an advanced stage (Smyth 2018). At the early stages of the disease, EC is often asymptomatic (Mayo Clinic 2021). Patients commonly seek treatment upon developing dysphagia due to the obstructing tumour, among other symptoms, when their disease is already advanced (Pennathur 2013).

There are two major subtypes of EC that differ greatly in terms of physiology, epidemiology, and etiology: esophageal adenocarcinoma (EAC) and esophageal squamous cell carcinoma (ESCC)(Arnold 2015). ESCC develops in squamous cells lining the upper and middle third of the esophagus. EAC, on the other hand, develops in glandular cells in the lower third of the esophagus (Arnold 2015). This document will refer to EC data (encompassing both the EAC and ESCC subtypes) when no specific ESCC data is available.

ESCC is the most prevalent form of EC, accounting for 87% of cases worldwide and is the predominant histological form in Asia and most of Europe, including Denmark (Arnold 2017, Wong 2018, DEGC 2020b, GLOBOCAN 2020). Despite differences in the incidence of ESCC between Asia and the West (Europe and North America), studies have shown little variations in gene expression profiles or gene methylations between tumours of Asian and Caucasian cancer patients, reflecting the common characteristics of ESCC tumours between patients in these ethnic groups (Chen 2017).

Major risk factors for ESCC include smoking and alcohol consumption (Abnet 2018). A decline in the prevalence of smoking in Western countries is expected to drive a decrease in the rates of ESCC (Abnet 2018).

5.2 Epidemiology

In 2020, there were an estimated 604,100 new EC cases globally, accounting for 3.1% of cancer cases worldwide (GLOBOCAN 2020). EC accounted for 544,076 deaths worldwide (GLOBOCAN 2020). EC has one of the highest mortality to incidence ratios in the world, at 90.1% (GLOBOCAN 2020).

ESCC is more common in men than in women (Wang 2018). In the Nordics, more men than women are diagnosed with EC (Arnold 2015). In Denmark, the age-standardized incidence rate for ESCC is 2.4 and 1.5 for men and women, respectively (Arnold 2015).

5.3 Disease presentation and diagnosis

5.3.1.1 Disease Presentation

Early EC typically causes no signs or symptoms (Mayo Clinic 2021). Solid food dysphagia is the primary symptom leading patients with ESCC to seek medical attention (Pennathur 2013). In addition to dysphagia, patients commonly present with weight loss, pain, and/or fatigue (Short 2017). Symptoms of EC are summarized in Figure 1.

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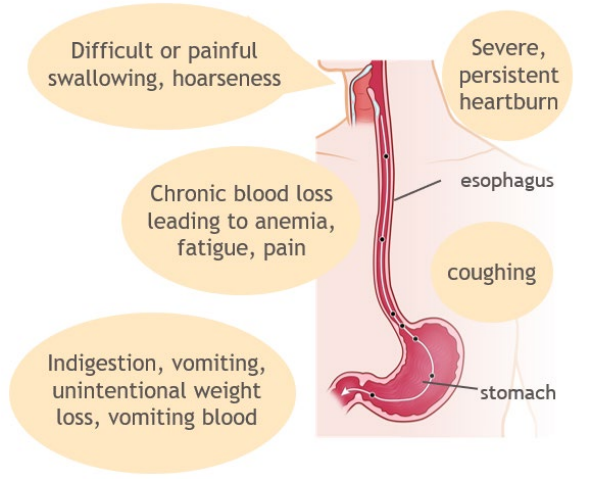
Figure 1: EC symptoms



Source: (Mayo Clinic, 2021)

5.3.1.2 Diagnosis

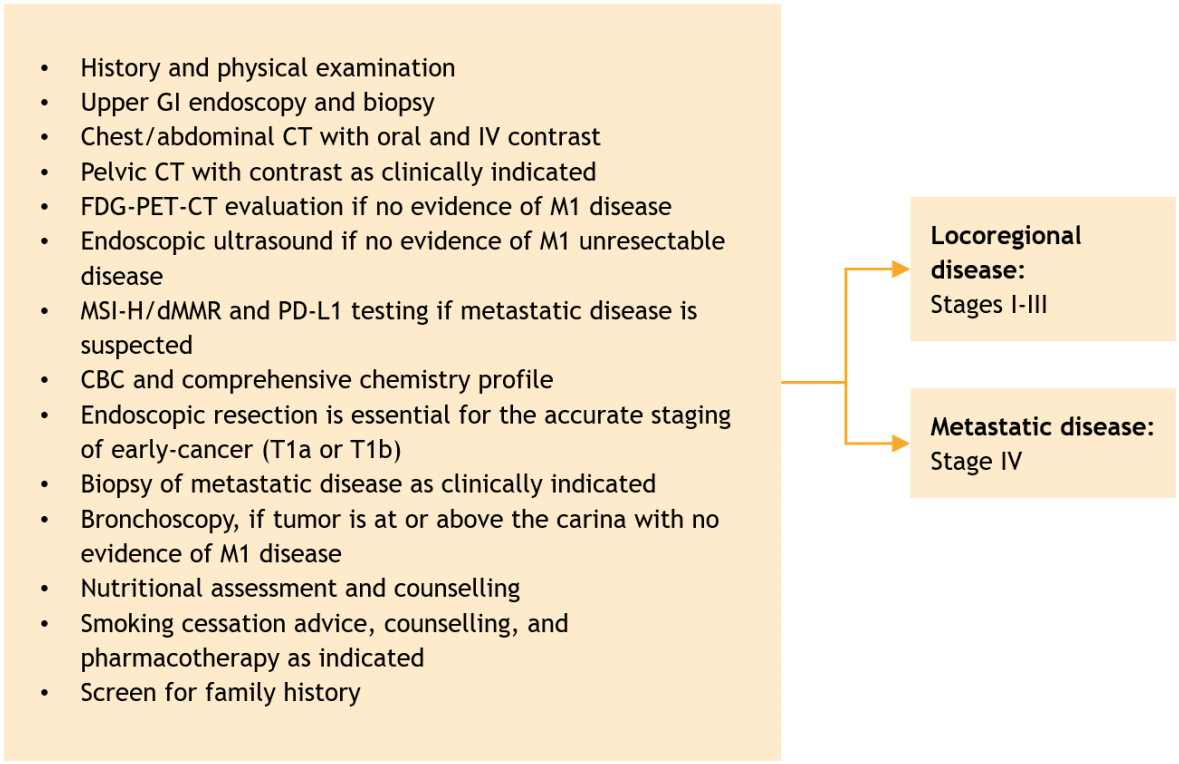
Endoscopic evaluation and diagnostic imaging are used to confirm the diagnosis of EC (Kleinberg 2014). In Denmark, endoscopy including biopsy is the first diagnostic choice for cancer of the upper gastrointestinal tract. However, if patients are considered ineligible for surgery, computer tomography (CT) scan of the thorax and abdomen is recommended (DEGC 2020b). Differentiation between ESCC and EAC is based on histological variations that are identified via immunohistochemical (IHC) staining of biopsy samples taken from the esophagus (Lordick 2016).

Given often asymptomatic (or non-specific symptoms) in early stages, EC is often diagnosed at advanced stages. Globally, 45–71% of EC cases are diagnosed with regional or distant metastatic disease (Zhang 2013, Cheng 2018, Patel 2018). Early-stage disease often recurs: in the EU5, approximately 72% of patients first diagnosed with resectable tumours will develop metastatic disease (Olabisi J 2017).

5.3.1.3 Staging

The work-up and staging of ESCC is summarized in Figure 2. Staging of ESCC is used to define prognosis and guide optimal treatment strategies for patients. ESCC is staged according to the widely accepted American Joint Committee on Cancer (AJCC) staging system. It uses TNM values to indicate the severity of the tumour (T), nodal involvement (N), and metastases (M) (Aca 2020). Each value is subdivided into different grades ranging from T1–T4, N1–N3, and M0–M1, with increasing clinical severity for each value. The TNM definitions can also be grouped into five stages (stage 0–stage IV). Metastatic disease is defined by the spread of cancer to distant lymph nodes or organs. This corresponds to grades T4, N2, or M1 onwards, or stage IVA onwards. For more detail, please see Section23, Appendix K.

Figure 2: Work up and staging of ESCC

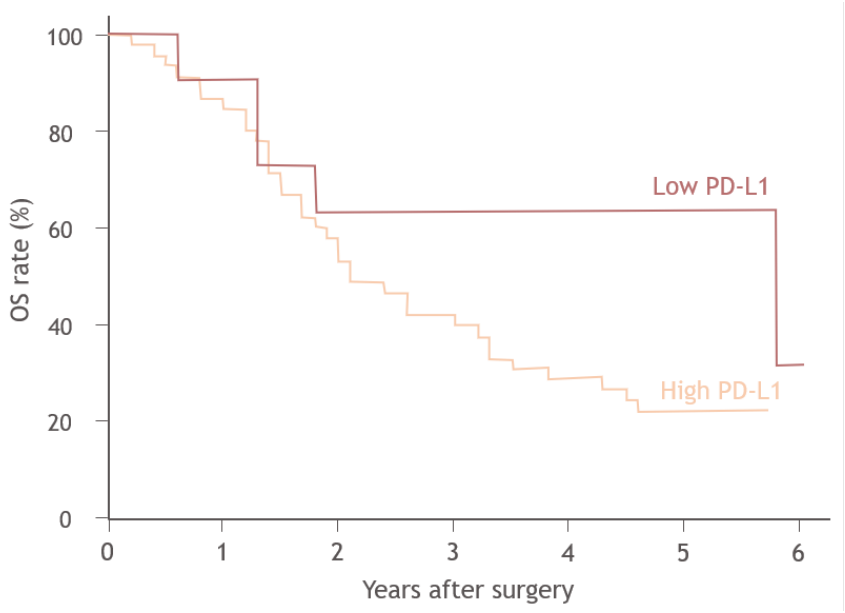


Abbreviations: CBC, complete blood count; CT, computed tomography; dMMR, deficient mismatch repair; ESCC, esophageal squamous cell carcinoma; FDG-PET/CT, fluorodeoxyglucose positron emission tomography/computerized tomography; GI, gastrointestinal; IV, intravenous; MSI-H, microsatellite instability-high; PD-L1, programmed cell death ligand 1
Source: adapted from NCCN (2020)

5.3.1.4 Biomarkers in ESCC

Few biomarkers with prognostic value have been identified in ESCC. Programmed death-ligand 1 (PD-L1) has been studied as a potential prognostic marker in ESCC, but further studies are required to demonstrate its predictive value (Ohigashi 2005). One study of 99 Chinese patients with post-surgical EC (who did not receive pre-operative chemotherapy treatment) revealed that patients with membrane and cytoplasm PD-L1 expression had significantly poorer OS than those negative for PD-L1 expression [hazard ratio (HR)=2.157; 95% CI, 1.1017–4.577; p=0.0452] and that PD-L1 expression was significantly correlated to tumour invasion depth (p=0.0261 for PD-L1 membrane and cytoplasm expression; p=0.0331 for PD-L1 nuclear expression) (Chen 2014).

Figure 3: OS rate by PD-L1 cytoplasm and membrane expression



Abbreviations: PD-L1, programmed death ligand 1; OS, overall survival
Source: adapted from (Chen 2014)

5.3.1.5 Etiology

ESCC is associated with multiple risk factors, including, but not limited to, age, diet, genetic predisposition, and exposure to environmental carcinogens. Alcohol consumption is an important risk factor, increasing risk by 6 to 9-fold in the EU and North America (Abnet 2018). Smoking is another major risk factor in ESCC, especially in developed countries, where it accounts for a large proportion of population-attributable risk (an approximate 3 to 9-fold relative risk in current smokers) (Abnet 2018). A study conducted in a high-income country showed that smokers who also consume alcohol have a higher risk of developing ESCC than the smokers who do not consume alcohol (Pandeya 2013).

Behavioral risk factors, such as smoking, are decreasing in European and North American countries. In Europe (across 27 countries), the estimated prevalence of smoking among men decreased between 2005 and 2015 with a median decline of about 1.5% a year (or almost 23% overall) (WHO 2019). As a consequence, ESCC cases are expected to decline in Western countries (Arnold 2017). Regional variations in this trend can cause differences in ESCC incidence across geographies.

Several genetic conditions are associated with an increased risk of ESCC, including tylosis EC and Fanconi anemia (Blaydon 2012, Abnet 2018). Patients with deficiencies in alcohol metabolizing genes (ALDH2 and ADH1B) who consume alcohol also have a higher risk of developing ESCC (Abnet 2018).

5.4 Burden of disease

5.4.1.1 Prognosis and survival

Prognosis and survival is poor for patients with 1L advanced or metastatic ESCC. Moreover, the recurrence rate is high for patients treated at earlier stages of the disease, suggesting that many of these patients will ultimately develop metastatic ESCC.

Overall, the 1-year and 5-year relative survival rates for EC in Denmark were 48.3% and 29.3% in males and 49.7% and 18.8% in females, respectively (based on 2015–2019 data) (NORDCAN 2019b, NORDCAN 2019a)

Early tumour recurrence is the leading cause of death for ESCC patients having undergone EC resection (Zhang 2021). Although esophagectomy remains the standard of care to treat resectable EC, 27.1%–52.6% of patients who undergo the surgery can experience postoperative recurrence (Kawamoto 2018). A high number (47.3%–78.0%) of these are locoregional recurrences (Kawamoto 2018). This suggests that even if EC is diagnosed early, patients will commonly recur and require additional treatment at a later stage.

5.4.1.2 Prevalence and incidence in Denmark

EC is the 8th most common form of cancer in Denmark. The median age at the time of diagnosis for EC is 70, and diagnosis is more common in men than women (DEGC 2020b). The most common histological type of cancer of the esophagus is ESCC. Only a small proportion (approximately 3%) of carcinomas in the esophagus are adenocarcinomas (DEGC 2020b).

Based on the Dansk Esophago Gastrisk Cancer Gruppe (DEGC) database, there were 278 new cases of EC in 2020 (Table 2); note, this included all new cases diagnosed across stages. Of these patients, 90.2% received palliative treatment. Furthermore, of the EC patients who received palliative care, 43.6% had stage IV disease (DEGC Årsrapport 2020 2020).

Table 2: the development in incidence and prevalence of EC in Denmark the past 5 years

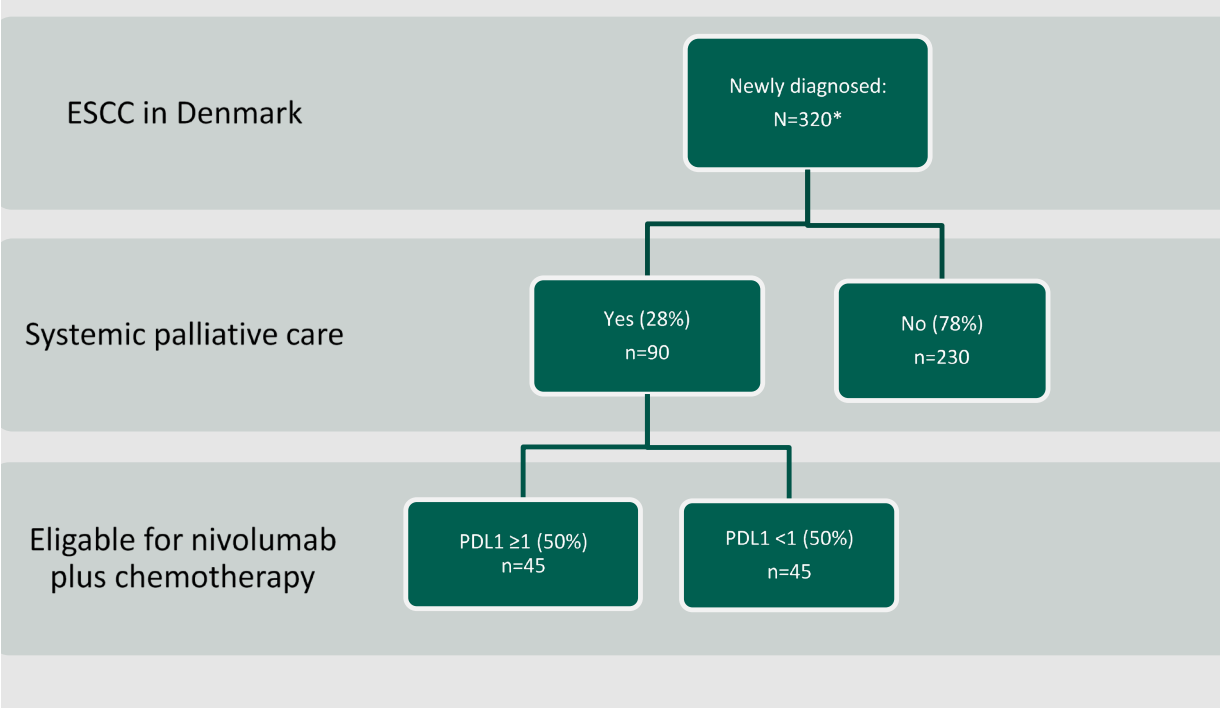
	2016	2017	2018	2019	2020
New cases in Denmark (DEGC 2020a)	301	264	288	320	278
Age-standardised incidence rate Nordic (per 100,000 person-years) in Denmark (NORDCAN 2020a)	Male: 12.4 Female: 4.7	Male: 13.3 Female: 4.1	Male: 14.8 Female: 4.2	Male: 13.2 Female: 4.3	-
Prevalence in Denmark (NORDCAN 2020b)	Male: 854 Female: 318 Total: 1,172	Male: 895 Female: 365 Total: 1,260	Male: 1,032 Female: 377 Total: 1,409	Male: 1,019 Female: 364 Total: 1,383	-

Abbreviations: EC, esophageal cancer
Reference: (DEGC 2020b, NORDCAN 2020a, NORDCAN 2020b)

5.4.1.3 Patient populations relevant for this application

The maximum number of patients that will receive nivolumab is expected to be 45 patients annually, see Figure 4 and Table 3 below.

Figure 4: Overview of number of eligible patients in Denmark



Abbreviations: ESCC, esophageal squamous cell carcinoma
Reference: (Medicinrådet 2022)
Note: *2019 estimates.

Table 3: The number of patients eligible for nivolumab in Denmark

Year	Year 1	Year 2	Year 3	Year 4	Year 5
Nr of patients in Denmark who are expected to use nivolumab	45	45	45	45	45

Current treatment options and choice of comparator

5.5 Current treatment options

The treatment of patients with EC in Denmark are based on the DEGC "*Onkologisk behandling af non-kurabel cancer i esophagus, GEJ og ventrikel (2020) guidelines*" and follow the same treatment recommendations, with options including palliative chemotherapy, which can be dual substance (fluoropyrimidine and platinum) or triple substance (fluoropyrimidine, platinum and taxane), and external radiation brachytherapy, the latter being for symptom relief (DEGC 2020b). As of January 2022, pembrolizumab in combination with chemotherapy is recommended as first-line treatment for patients with locally advanced inoperable or metastatic carcinoma of the esophagus or HER2-negative gastroesophageal junction adenocarcinoma, Siewert Type I, in adults whose tumours express PD-L1 with a CPS ≥ 10 (Medicinrådet 2022).

Danish treatment guidelines for EC recommend that for patients with non-curable ESCC (DEGC 2020b):

- patients in good general condition with non-resectable or metastatic disease should be offered palliative chemotherapy

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- palliative external beam radiotherapy and brachytherapy can be used for local nuisances such as bleeding, pain, or obstruction.

5.6 Choice of comparator

The relevant comparator for nivolumab plus chemotherapy in Denmark is pembrolizumab plus chemotherapy. As pembrolizumab in combination with chemotherapy has been recommended by the DMC for treatment of metastatic carcinoma of the oesophagus with the biomarker PD-L1 CPS ≥ 10, the treatment recommendation is aligned with the ESCC PD-L1 expressing population in the the CheckMate 648 study.

5.7 Description of the comparator

An overview of pembrolizumab plus chemotherapy is presented in Table 4.

Table 4: Product description of pembrolizumab plus chemotherapy

Product description	
Name of preparation/pharmaceutical	Keytruda plus platinum- or fluoropyrimidine- based chemotherapy
Active ingredient	Pembrolizumab plus chemotherapy
Pharmaceutical form	Concentrate for solution for infusion
Strength	Pembrolizumab: Single-use vials 45 mg/4 mL
Recommended daily dose	Pembrolizumab 2 mg/kg every 3 weeks Chemotherapy Capecitabin (IV) 2000 mg/m^2 days 1-14 every 3 weeks Oxaliplatin (IV) 130 mg/m^2 every 3 weeks
Should the intervention be used with other drugs?	Combination therapy, pembrolizumab plus chemotherapy
Treatment length/criteria for termination of treatment	Until disease progression or unacceptable toxicity
Required monitoring, under administration or during treatment period	Patients should be monitored continuously as an adverse reaction may occur
Requirements of diagnostics or other tests	PD-L1 testing, HER2
Medically approved indications	Please see respective SmPC's

Abbreviations: HER2, human epidermal growth factor receptor 2; IV, Intravenous; PD-L1, Programmed death Ligand-1

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The intervention

An overview of nivolumab plus chemotherapy is presented in Table 5.

Table 5: Product description of nivolumab plus chemotherapy

Product description	
Name of preparation/pharmaceutical	Nivolumab plus fluoropyrimidine- and cisplatin-containing chemotherapy
Active ingredient	Nivolumab plus chemotherapy
Pharmaceutical form	Concentrate for solution for infusion
Strength	Nivolumab (10 mg/mL): Single-use vials 40 mg/4 mL 100 mg/10 mL 240 mg/24 mL
Recommended daily dose	Nivolumab 240 mg nivolumab (IV) every 2 weeks or 480 mg nivolumab every 4 weeks Chemotherapy 4 week cycle consisting of: • Fluorouracil (IV) 800 mg per m2 days 1-5 • cisplatin (IV) 80 mg per m2 on day 1
Should the intervention be used with other drugs?	No
Treatment length/criteria for termination of treatment	Until disease progression, unacceptable toxicity, or up to 24 months
Required monitoring, under administration or during treatment period	Patients should be monitored continuously (at least up to 5 months after the last dose), as an adverse reaction with nivolumab may occur at any time during or after discontinuation of therapy
Requirements of diagnostics or other tests	PD-L1 testing
Medically approved indications	Please see Section 1 for a list of medically approved indications

Abbreviations: IV, Intravenous; PD-L1, Programmed death Ligand-1

5.8 Mechanism of action

Nivolumab is a fully human, immunoglobulin type 4, PD-1 receptor-blocking monoclonal antibody that prevents inactivation or reactivates the ability of T-cells to attack the tumour (Brahmer 2010, Menzies 2013). Nivolumab binds to PD-1 receptors on T-cells with high affinity and selectively disrupts inhibitory signaling triggered by PD-L1 and programmed cell death ligand 2 (PD-L2), thereby restoring normal T-cell antitumour function (Figure 5) (Brahmer 2010).

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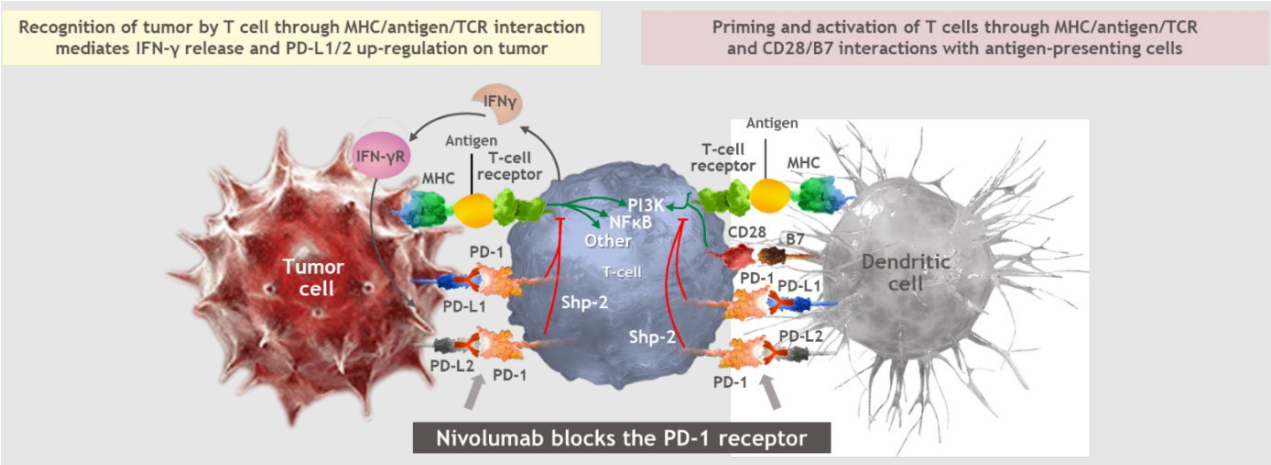
Figure 5: Nivolumab mechanism of action



Abbreviations: IFN-γ, interferon-gamma; IFN-γR, interferon-gamma-γ receptor; MHC, major histocompatibility complex; NFκB, nuclear factor kappa B; PD-1, programmed death receptor-1; PD-L1, programmed death ligand 1; PD-L2, programmed death ligand 2; PI3K, phosphoinositide 3-kinase; Shp-2, SH2-domain-containing protein tyrosine phosphatase; TCR, T-cell receptor
Source: (BMS 2021a) adapted from (Pardoll 2012, Brahmer 2013)

5.9 Pack size and price

The strength, pack size, and pharmacy selling price per pack for nivolumab in Denmark is included in Table 6 below.

Table 6: The strength, pack size, and pharmacy purchase price per pack

Treatment	Strength	Pack size	Price per pack (PP excl. VAT, DKK)
Nivolumab	10 mg/ml	4 ml	3690.69
	10 mg/ml	10 ml	9168.23
	10 mg/ml	24 ml	22 003.74

Abbreviations: DKK, Danish krone; PP, pharmacy purchase price; VAT, value added tax
Reference: (www.medicinpriser.dk 2022)

6 Literature search and identification of efficacy and safety studies

Identification and selection of relevant studies

A systematic literature review (SLR) was conducted to identify randomised control trials (RCT) evidence assessing treatments for first-line unresectable advanced, recurrent, or metastatic EC with a focus on studies evaluating patients with ESCC. The original SLR was conducted on 14 Janurary 2021, with an updated search conducted 4 October 2021. The SLR has been presented in detail in Section 13 Appendix A.

List of relevant studies

As described in Section 5.2, the relevant comparator for nivolumab plus chemotherapy in the Danish clinical setting is pembrolizumab plus chemotherapy. There are no available relevant studies that compare nivolumab plus chemotherapy with pembrolizumab plus chemotherapy in the 1L ESCC patient population. As such, 2 studies—1 for nivolumab plus chemotherapy (CheckMate 648) and 1 for pembrolizumab plus chemotherapy (KEYNOTE 590)—were identified and considered in a indirect treatment comparison (ITC) (Table 7).

For detailed information about included studies, refer to Section 14 Appendix B.

Table 7: Relevant studies included in the assessment

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Used in comparison of
Nivolumab Combination Therapy in Advanced Esophageal Squamous-Cell Carcinoma Doki et al. NEJM 2022	CheckMate 648 (Doki 2022)	NCT03143153	Start: JUN 2017 Expected competition: AUG 2024	Nivolumab plus chemotherapy
Pembrolizumab plus chemotherapy versus chemotherapy alone for first-line treatment of advanced oesophageal cancer (KEYNOTE-590): a randomised, placebo-controlled, phase 3 study Sun et al. Lancet 2021	KEYNOTE-590 (Sun 2021a)	NCT03189719	Start: JUL 2017 Expected competition: JUN 2023	Pembrolizumab plus chemotherapy

Abbreviation: National clinical trial number

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7 Efficacy and safety

The relevant comparator for nivolumab plus chemotherapy in Denmark is pembrolizumab plus chemotherapy. There is no head-to-head evidence comparing nivolumab in combination with fluoropyrimidine- and platinum-based chemotherapy with pembrolizumab in combination with fluoropyrimidine- and platinum-based chemotherapy as first line treatment of adult patients with unresectable advanced, recurrent or metastatic ESCC whose tumours express PD-L1 (TPS ≥1%) with regards to efficacy and safety. Hence, an indirect treatment comparison (ITC) analysis is needed; see Section 7.2.1.

Below the pivotal study CheckMate 648 is presented.

Efficacy and safety of nivolumab plus chemotherapy compared to chemotherapy for inoperable, advanced, recurrent, or metastatic esophageal squamous cell carcinoma whose tumours express PD-L1 (TPS ≥1%)

7.1 Relevant studies: CheckMate 648

7.1.1.1 Study design

CheckMate 648 is a randomized, global, open-label, Phase 3 study of nivolumab plus chemotherapy or nivolumab plus ipilimumab versus chemotherapy alone in previously untreated unresectable, advanced, recurrent, or metastatic ESCC (BMS 2021e). This study determines if nivolumab plus chemotherapy improves OS and/or PFS over SoC chemotherapy in patients with ESCC whose tumours express PD-L1 (TPS ≥1%) (European Medicin Agency 2022b). Additional objectives include further characterization of the efficacy, adverse event profile, pharmacokinetics, patient-reported outcomes, and potential predictive biomarkers of nivolumab plus chemotherapy in patients with ESCC (BMS 2021e, European Medicin Agency 2022b). The study was conducted at 187 study locations across 26 countries between June 2017 and is currently ongoing (BMS 2021e, European Medicin Agency 2022b).

In this submission, two data base locks (DBLs) are reported: for MAR 2021 with a minimum follow-up of 12 months, and for OCT 2021 with a minimum follow-up of 20 months (BMS 2021e, European Medicin Agency 2022b); for the minimum follow-up of 12 months data, please see Section 25, Appendix M.

Between June 2017 and November 2019, 970 patients were randomized 1:1:1 in 3 arms to receive nivolumab plus chemotherapy (n=321); nivolumab plus ipilimumab (n=325); or chemotherapy alone (n=324) as represented in Figure 6 (Chau 2021). In the nivolumab plus chemotherapy arm, nivolumab (240 mg) was administered via IV infusion over 30 minutes every 2 weeks (i.e., on Day 1 and Day 15) and 5-FU (800 mg/m²) was administered via an IV continuous infusion for 5 days, followed by cisplatin (80 mg/m²) as an IV infusion over 30 to 120 minutes every 4 weeks (BMS 2021e, European Medicin Agency 2022b). In the nivolumab plus ipilimumab arm, nivolumab (3 mg/kg) was administered via IV over 30 minutes every 2 weeks, and ipilimumab (1 mg/kg) was administered via IV over 30 minutes every 6 weeks (BMS 2021e, European Medicin Agency 2022b). Lastly, in the chemotherapy alone arm, 5-FU (800 mg/m²) was administered via an IV continuous infusion for 5 days, followed by cisplatin (80 mg/m²) as an IV infusion over 30 to 120 minutes every 4 weeks (Chau 2021).

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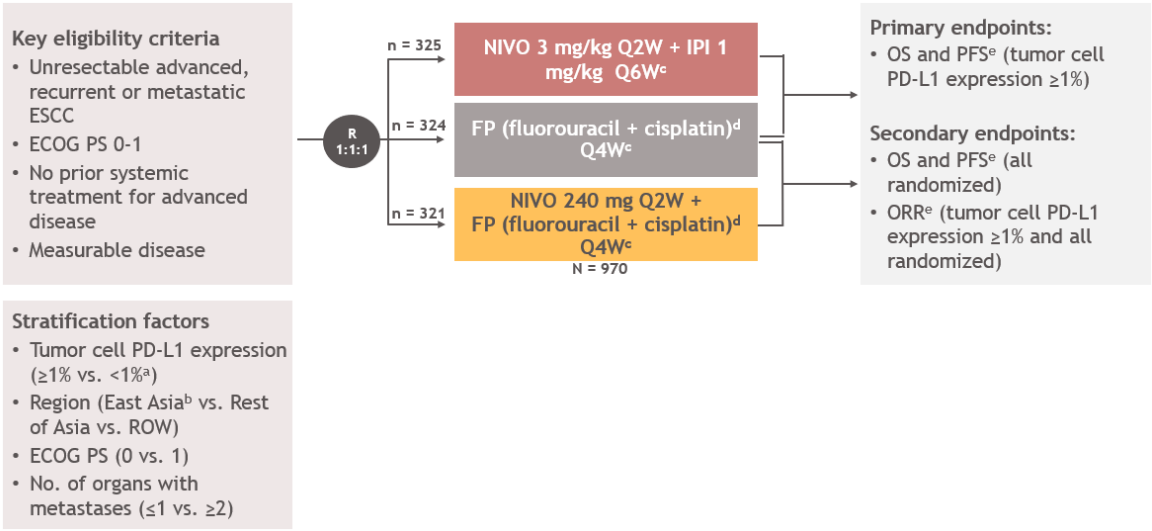
Figure 6: CheckMate 648 study design



[a]<1% includes indeterminate tumour cell PD-L1 expression; determined by PD-L1 IHC 28-8 pharmDx assay (Dako); [b]East Asia includes patients from Japan, Korea, and Taiwan; [c]Until documented disease progression (unless consented to treatment beyond progression for nivolumab plus ipilimumab or nivolumab plus chemotherapy), discontinuation due to toxicity, or withdrawal of consent. Nivolumab is given alone or in combination with ipilimumab for a maximum of 2 years; [d]Fluorouracil 800 mg/m² (days 1-5) and cisplatin 80 mg/m2 IV (day 1); [e]Per Blinded Independent Central Review (BICR)
Abbreviations: ESCC, esophageal squamous cell carcinoma; ECOG, Eastern Cooperative Oncology Group; IHC, immunohistochemistry; IPI, ipilimumab; NIVO, nivolumab; ORR, overall response rate; OS, overall survival; PD-L1, programmed death ligand 1; PFS, progression-free survival; PS, performance status; Q2W, every 2 weeks; Q4W, every 4 weeks; Q6W, every 6 weeks; ROW, rest of the world
Source: (Chau 2021)

Study randomization was stratified according to tumour cell PD-L1 expression (TPS ≥1% vs. <1% or indeterminate), region (East Asia including Japan, Korea, and Taiwan vs. rest of Asia vs. the rest of the world (ROW)), ECOG performance status (PS) of 0 or 1, and the number of organs with metastases (≤1 vs. ≥2) (Chau 2021). Treatment continued until disease recurrence, unacceptable toxicity, or patient withdrawal of consent with a maximum of 24 months (Chau 2021).

PD-L1 is expressed in many tumour types and its expression has been noted to correlate with decreased immune system function and a worse clinical prognosis. In ESCC, PD-L1 expression has been suggested as a prognostic biomarker (Ohigashi 2005). [redacted]

The primary endpoints were OS and PFS per BICR in patients whose tumours express PD-L1 (TPS ≥1%) for both nivolumab plus chemotherapy versus chemotherapy alone (Chau 2021). OS was defined as the time between the date of randomization and the date of death. PFS was defined as the time from randomization to the date of the first documented progression of disease (PD) per Blinded Independent Central Review (BICR) or death due to any cause (Chau 2021). Secondary endpoints were OS and PFS per BICR in all randomized patients (all-comers) and ORR in patients whose tumours express PD-L1 (TPS ≥1%) and all-comers (Chau 2021).

Exploratory endpoints included PFS in patients whose tumours express PD-L1 (TPS ≥1%) and all-comers per investigator (INV), ORR in patients whose tumours express PD-L1 (TPS ≥1%) and all-comers per INV, duration of response (DOR) per BICR and INV, safety, and tolerability for nivolumab plus chemotherapy versus chemotherapy alone.

For detailed study characteristics refer to section 14, Appendix B.

7.1.1.2 Overview of key patient characteristics

The analyses presented here describe data from the pivotal CheckMate 648 clinical trial. Baseline characteristics of all 970 randomized patients are shown in Section 24 Appendix L. The nivolumab plus chemotherapy arm included 321

patients and the chemotherapy arm included 324 patients. Baseline characteristics were similar across both study arms regardless of PD-L1 expression.

For baseline characteristics of patients included in each study refer to Section 15 Appendix C.

7.2 Efficacy and safety – results for CheckMate 648

The results presented in this section are from the pivotal phase III trial, CheckMate 648. Two data-base locks (DBLs) were available: 1) an updated analysis available as of October 2021 with a 20-month minimum follow-up (BMS 2022, European Medicin Agency 2022b), and 2) the primary analysis was performed on the DBL from March 2021, with a 12-month minimum follow-up (BMS 2021e); please see Section 25, Appendix M for efficacy and safety data for the 12-month minimum follow-up .

7.2.1.1 Results: Nivolumab plus chemotherapy (20-month minimum follow-up)

7.2.1.1.1 Summary of key results

[redacted] The key outcomes from the CheckMate 648 trial are summarised in Table 8 below.

Table 8: Summary of key efficacy results for nivolumab plus chemotherapy versus chemotherapy alone in all-randomized patients whose tumours express PD-L1 (TPS ≥1%) (20-month minimum follow-up)

	All randomized patients whose tumours express PD-L1 (TPS ≥1%)	
Efficacy parameter	**Nivolumab + chemotherapy (n=158)**	**Chemotherapy alone (n=157)**
OS	**Primary endpoint**	
Median OS, months[b]	15.05 (95% CI, 11.93–18.63)	9.07 (95% CI, 7.69–10.02)
HR (95% CI)[a]	0.59 (0.46–0.76)	
OS rate at 12 months, %[b]	[redacted]	[redacted]
OS rate at 18 months, %[b]	[redacted]	[redacted]
PFS per BICR	**Primary endpoint**	
Median PFS per BICR, months	6.93 (95% CI, 5.68–8.35)	4.44 (95% CI, 2.89–5.82)
HR (95% CI)[a]	0.66 (0.50–0.87)	
PFS rate at 12 months, %	25.39 (95% CI, 18.27–33.11)	10.30 (95% CI, 4.64–18.59)
PFS rate at 18 months, %	[redacted]	[redacted]
ORR per BICR	**Secondary Endpoint**	
ORR per BICR, %	53.2% (95% CI, 45.1–61.1)	19.7% (95% CI, 13.8–26.8)
CR, %	16.5%	5.1%
DOR per BICR	**Exploratory Endpoint**	
Median DOR, months	8.38 (95% CI, 6.90–12.35)	5.68 (95% CI, 4.40–8.67)
PFS per INV	**Exploratory Endpoint**	
PFS per INV, months	[redacted]	[redacted]
HR[a]	[redacted]	
PFS2/TSST per INV	**Exploratory Endpoint**	
Median PFS2/TSST per INV, months[b]	[redacted]	[redacted]
HR[a]	[redacted]	

[a]Stratified Cox proportional hazards model. HR is nivolumab plus chemotherapy over chemotherapy alone
[b]Based on Kaplan-Meier estimates
Abbreviations: BICR, blinded independent central review; CI, confidence interval; CR, complete response; DOR, duration of response; HR, hazard ratio; INV, investigator; ORR, objective response rate; OS, overall survival; PD-L1, programmed death ligand 1; PFS, progress-free survival; PFS2, time to second disease progression; TPS, tumour PD-L1 scorel; TSST, time to second subsequent therapy
Source: (BMS 2022, European Medicin Agency 2022b)

7.2.1.1.2 Overall survival

At 20-month minimum follow-up, improvement in OS was demonstrated in patients whose tumours express PD-L1 (TPS ≥1%) in the nivolumab plus chemotherapy arm versus the chemotherapy alone arm (BMS 2021e, European Medicin Agency 2022b). In the PD-L1 (TPS ≥1%) population, median OS favours nivolumab plus chemotherapy over chemotherapy alone (15.0 [95% CI, 11.93–18.63] versus 9.1 [95% CI, 7.69–10.02] months, respectively), with an HR of 0.59 (95% CI, 0.46–0.76) (BMS 2022, European Medicin Agency 2022b). [redacted] These results show a clear, statistically

significant OS benefit in the nivolumab plus chemotherapy arm in the subpopulation of patients whose tumours express PD-L1 (TPS ≥1%).

[redacted]

7.2.1.1.3 Progression-free survival

At 20-month minimum follow-up, PFS per BICR was demonstrated favourable in patients whose tumours express PD-L1 (TPS ≥1%) in the nivolumab plus chemotherapy arm versus the chemotherapy alone arm (BMS 2022, European Medicin Agency 2022b). In the PD-L1 (TPS ≥1%) population, median PFS per BICR favours nivolumab plus chemotherapy over chemotherapy alone (6.93 [95% CI, 5.68–8.35] versus 4.44 [95% CI, 2.89–5.82] months, respectively), with an HR of 0.66 (95% CI, 0.50–0.87) (BMS 2022, European Medicin Agency 2022b). This is a significant improvement of [redacted] versus chemotherapy alone (HR of 0.65 (98.5% CI, 0.46-0.92), p=0.0023) (BMS 2021e, European Medicin Agency 2022b).

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[redacted]

7.2.1.1.4 Patient-reported outcomes

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

[redacted]

[redacted]

7.2.1.1.4.2 EQ-5D

[redacted]

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7.2.1.2 Safety: nivolumab plus chemotherapy (20-month minimum follow-up)

[redacted]

7.2.1.2.1 Duration and discontinuation of treatment

[redacted]

Table 9: Median duration of treatment at different time intervals (20-month minimum follow-up)

Treatment duration		All treated	
		Nivolumab + chemotherapy (n=310)	Chemotherapy alone (n=304)
Median duration of treatment , months (range)		[redacted]	[redacted]
Duration of therapy, months (%)	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]

[redacted]

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Table 10: Number of patients discontinuing treatment grouped by reason for discontinuation (20-month minimum follow-up)

Discontinuation of treatment	All treated	
	Nivolumab + chemotherapy (n=310)	Chemotherapy alone (n=304)
Discontinued treatment, n (%)	[redacted]	[redacted]
Reasons for treatment discontinuation, n (%)		
Disease progression	[redacted]	[redacted]
AE related to treatment	[redacted]	[redacted]
AE not related to treatment	[redacted]	[redacted]
Patient request	[redacted]	[redacted]
Other[a]	[redacted]	[redacted]

[redacted]

7.2.1.2.2 Adverse events and deaths

[redacted]

Table 11: Proportion of patients experiencing all-cause and treatment-related adverse events, grouped by severity (20-month minimum follow-up)

Patients, n (%)	Nivolumab + Chemotherapy (n=310)		Chemotherapy alone (n=304)	
	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4
All-Causality				
Any AEs	[redacted]	[redacted]	[redacted]	[redacted]
Serious AEs	[redacted]	[redacted]	[redacted]	[redacted]
AEs leading to discontinuation	[redacted]	[redacted]	[redacted]	[redacted]
TRAEs				
Any AEs	[redacted]	[redacted]	[redacted]	[redacted]
Serious AEs	[redacted]	[redacted]	[redacted]	[redacted]
AEs leading to discontinuation	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

[redacted]

Table 12: Death summary for nivolumab plus chemotherapy and chemotherapy alone arm (20-month minimum follow-up)

Patients, n (%)	Nivolumab + Chemotherapy (n=310)	Chemotherapy alone (n=304)
[redacted]	[redacted]	[redacted]
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]

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Table 13: Summary of adverse events with potential immunologic etiology for all treated patients (20-month minimum follow-up)

Patients, n (%)	Nivolumab + Chemotherapy (n=310)		Chemotherapy alone (n=304)	
	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				

[redacted]

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Table 14: Treatment-related adverse events with potential immunologic etiology leading to discontinuation for all-randomized treated patients (20-month minimum follow-up)

Patients, n (%)	Nivolumab + Chemotherapy (n=310)		Chemotherapy alone (n=304)	
	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4
[redacted]				

Table 15: Other events of special interest for all-treated patient (20-month minimum follow-up)

Patients, n (%)	Nivolumab + Chemotherapy (n=310)		Chemotherapy alone (n=304)	
	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4
[redacted]				

7.2.1.3 Treatment discontinuation

7.2.1.3.1 Reasons for discontinuation in the all-comer population

[redacted]

Table 16: Patient disposition for all treated patients (safety population: n=936)

Characteristic	Nivolumab plus chemotherapy (n=310)	Chemotherapy alone (n=304)
[redacted]		

7.2.1.3.2 Reasons for discontinuation in patients whose tumours express PD-L1 (TPS ≥1%)

[redacted]

Table 17: Patient disposition for all treated patients whose tumours express PD-L1 (TPS ≥1%) (safety population: n=458)

Characteristic	Nivolumab plus chemotherapy (n=155)	Chemotherapy alone (n=145)
[redacted]		

Comparative analyses of efficacy and safety of nivolumab compared with pembrolizumab patients

7.3 Indirect treatment comparison analyses of efficacy and safety

There is no head-to-head evidence comparing nivolumab in combination with fluoropyrimidine- and platinum-based chemotherapy with pembrolizumab in combination with fluoropyrimidine- and platinum-based chemotherapy as first line treatment of adult patients with unresectable advanced, recurrent or metastatic ESCC with tumour cell PD-L1 expression ≥ 1% with regards to efficacy and safety; hence, an indirect treatment comparison (ITC) analysis is needed.

7.3.1.1 Testing of proportional hazard assumption

[redacted]

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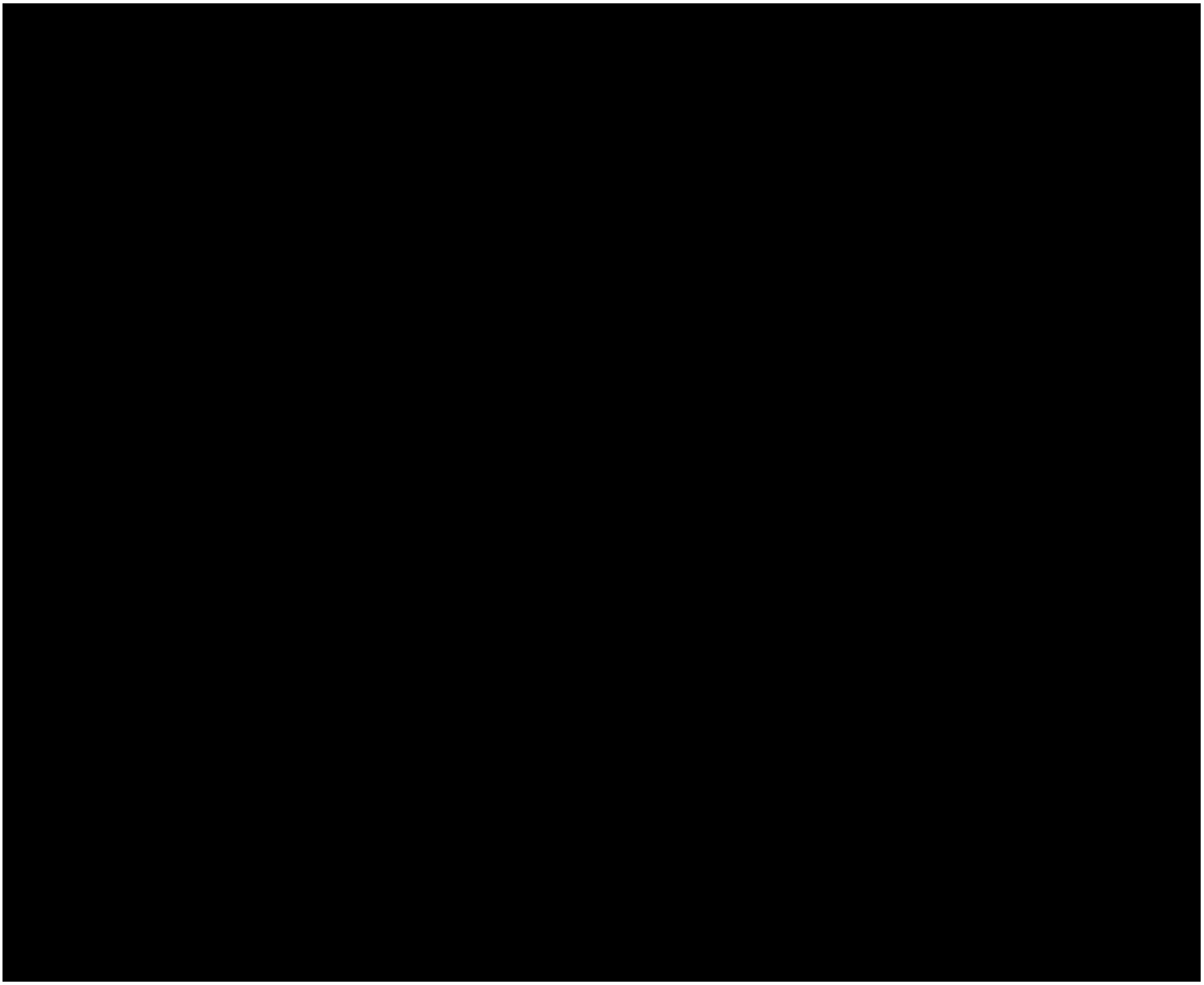

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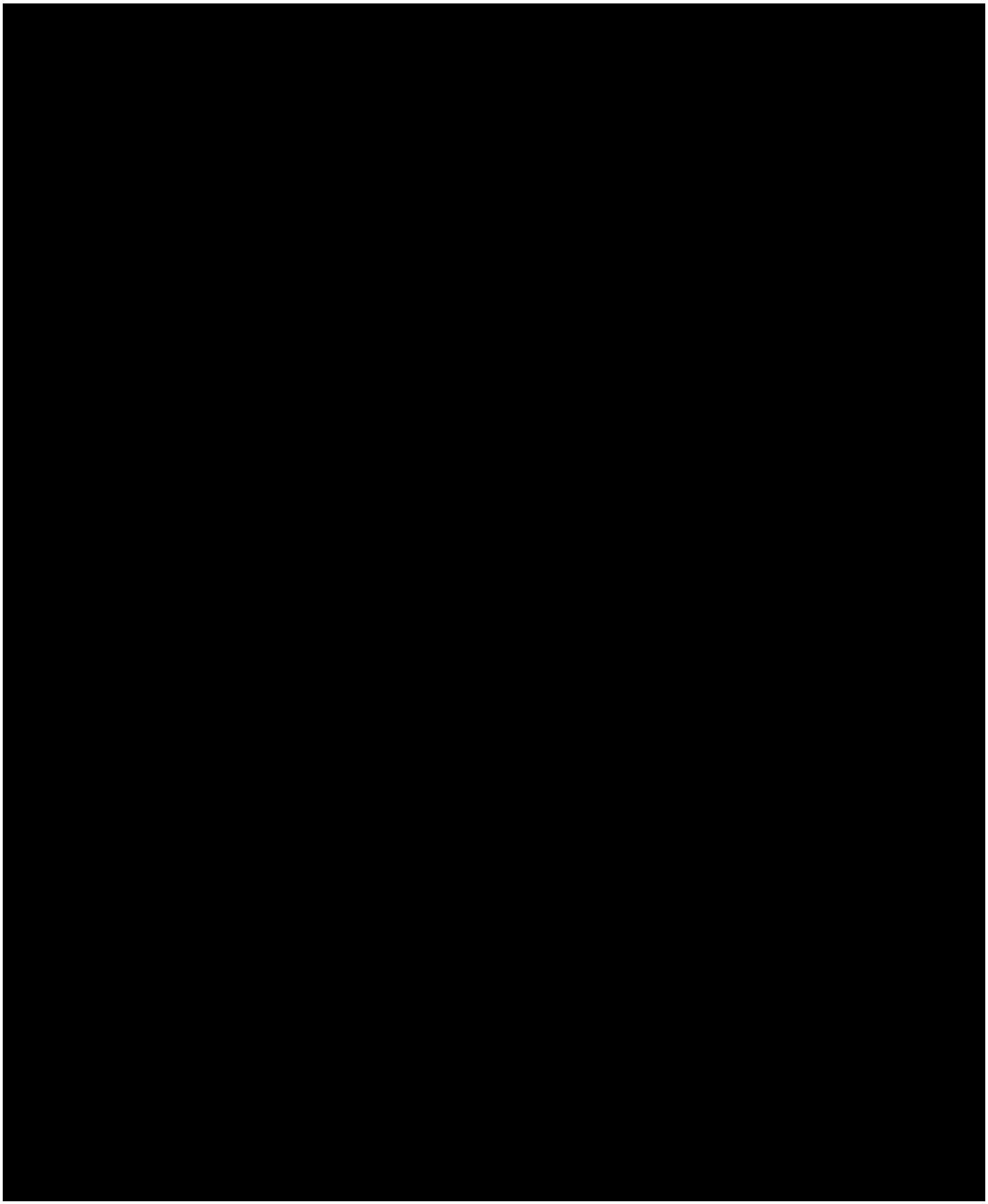

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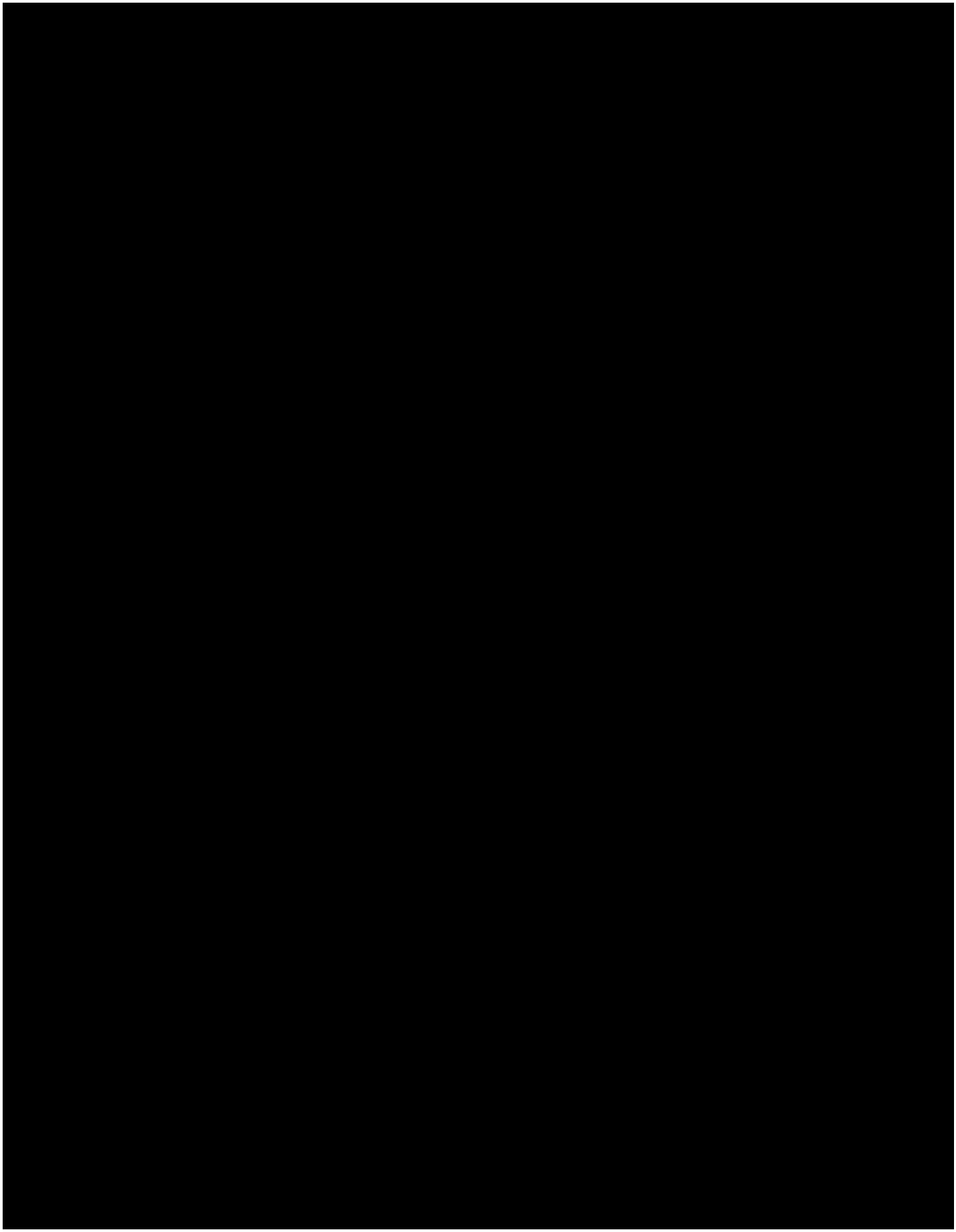

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7.3.1.2 Method of synthesis

An SLR of existing evidence was conducted, followed by a Bucher's ITC, to support the understanding of the comparative efficacy and safety of nivolumab plus chemotherapy and pembrolizumab plus chemotherapy in this patient population. [redacted] To make a relevant comparison with the current standard of care in Denmark, pembrolizumab plus chemotherapy (KEYNOTE 590), there was only one relevant trial: CheckMate 648. Please see Section 14 Appendix B for more information on both the CheckMate 648 and KEYNOTE 590 trials.

- CheckMate 648:
    - Global, randomized, open-label Phase 3 study evaluating nivolumab combined with 5-FU plus cisplatin (nivolumab plus chemotherapy) versus 5-FU plus cisplatin (chemotherapy) in subjects with 1L advanced or metastatic ESCC
    - The primary endpoints were OS and PFS by BICR in patients whose tumours express PD-L1 (TPS ≥1%)
    - The secondary endpoint were ORR by BICR in patients whose tumours express PD-L1 (TPS ≥1%) (Chau 2021)
- KEYNOTE-590:
    - Randomized, double-blinded Phase 3 study evaluating pembrolizumab in combination with fluoropyrimidine- and platinum-based chemotherapy in subjects with 1L advanced inoperable or metastatic ESCC or HER2-negative adenocarcinoma in GEJ Siewert type 1
    - The primary endpoints were:
        - OS for ESCC with PD-L1 CPS≥10, ESCC, PD-L1 CPS≥10 and ITT
        - PFS for ESCC, PD-L1 CPS ≥10 and ITT-population
    - The secondary endpoints were:
        - Objective response rate per RECIST 1.1 by investigator
        - Duration of response
        - Health related quality of life (EORTC QLQ-C30/QLQ-OES18) (Sun 2021a)

The two studies identified in the clinical SLR have common comparator control arms to perform an anchored ITC:

- CheckMate 648 (control arm: fluoropyrimidine- and platinum-based chemotherapy) (Chau 2021)
- KEYNOTE 590 (control arm: fluoropyrimidine- and platinum-based chemotherapy) (Sun 2021a)

[redacted]

7.3.1.3 Study design

Table 18 summarise the key aspects of the CheckMate 648 and KEYNOTE 590 trial designs. Both studies are phase 3 RCTs. CheckMate 648 is a phase 3, global, randomized, open-label trial that evaluated the efficacy and safety of nivolumab plus chemotherapy or nivolumab plus ipilimumab versus chemotherapy alone. KEYNOTE 590 is a phase 3, randomized, double-blind, placebo-controlled trial that evaluated pembrolizumab plus chemotherapy versus placebo plus chemotherapy. Patients in the nivolumab plus chemotherapy arm of CheckMate 648 received nivolumab 240 mg IV Q2W plus chemotherapy Q4W, while patients in KEYNOTE 590 received pembrolizumab 200 mg IV Q3W plus chemotherapy Q3W. No crossover was allowed in either study.

The main differences in inclusion/exclusion criteria between the studies were:

- The primary difference between the two studies is that patients in CheckMate 648 had unresectable advanced, recurrent or metastatic ESCC, whereas patients in KEYNOTE 590 had unresectable or metastatic ESCC/EAC or Siewert type I GEJ adenocarcinoma; ESCC, EAC and Siewert type I GEJ adenocarcinoma patients were included in the KEYNOTE 590 study, thus the primary part of the trial population was ESCC patients (approximately 73% vs. approximately 27% adenocarcinoma)
- In CheckMate 648, patients were randomized in a 1:1:1 manner as the study also included a nivolumab plus ipilimumab arm; However, the focus of the application and the ITC is nivolumab plus chemotherapy versus pembrolizumab plus chemotherapy, of which the latter is the current standard of care in this patient group

Table 18: Summary of study design in CheckMate 648 and KEYNOTE 590

	CheckMate 648	KEYNOTE 590
Phase	3	3
Design	Randomized Control Trial	Randomized Control Trial
Intervention	Nivolumab 240 mg IV Q2W + Chemotherapy Q4W Nivolumab 3mg/kg Q2W+ ipilimumab 1 mg/kg Q6W	Pembrolizumab 200 mg IV Q3W + chemotherapy Q3W
Comparator	Chemotherapy (5-FU plus cisplatin) Q4W	Placebo plus chemotherapy (5-FU plus cisplatin) Q3W

Location	Multicentre, global	Multicentre, global
Method of randomisation	1:1:1	1:1
Crossover	Not allowed	Not allowed
Treatment line	First line	First Line
Diagnosis	Unresectable advanced, recurrent, or metastatic ESCC	Unresectable or metastatic ESCC/EAC or Siewert type I GEJ adenocarcinoma
ECOG PS	0-1	0-1

Abbreviations: 5-FU, Fluorouracil; EAC, esophageal adenocarcinoma; ECOG PS, Eastern Cooperative Oncology Group Performance Score; ESCC, esophageal squamous cell carcinoma; GEJ, gastroesophageal junction; Q#W, every # weeks

Table 19 outline the baseline characteristics of the nivolumab arm and the pembrolizumab for the patients on which the ITC will be based (for further details, see Section 15 Appendix C). [redacted]

Table 19: Baseline characteristics from the nivolumab plus chemotherapy arm and pembrolizumab plus chemotherapy arm in CheckMate 648 and KEYNOTE 590

	CheckMate 648 (n=939) (nivolumab plus chemotherapy, n=321)	KEYNOTE 590 (n=743) (pembrolizumab plus chemotherapy, n=373)
Characteristics, n (%)		
Median age, years (range)	64 (40-90)	64 (28-94)
Male	253 (79)	306 (82)
Asia region	225 (70)	201 (54)
ECOG PS 1	171 (53)	223 (60)
Metastatic disease	184 (57)	344 (92)

Recurrent, locoregional	21 (7)	NA
Recurrent, distant	77 (22)	NA
Unresectable/locally advanced	44 (14)	29 (8)
Squamous cell carcinoma	311 (97)	274 (73.5)
Adenocarcinoma	NA	99 (27)
- **Esophageal**	NA	58 (16)
- **GEJ (Siewert I)**	NA	41 (11)
PD-L1 status		
CPS>10	NA	186 (49.9)
TPS>1%	158 (49)	NA

Abbreviations: CPS, combined positive score; ECOG, Eastern Cooperative Oncology Group; NA, Not available; PS, Performance Score; GEJ, gastroesophageal junction; PD-L1, programmed death-ligand 1; TPS, tumor proportion score.

7.3.1.3.1 Primary and secondary endpoints

Table 20 summarise the primary and secondary endpoints of the CheckMate 648 and KEYNOTE 590 studies. The specific data input for each variable in the ITC are described in detail in the results section (7.2.1.4).

Table 20: Primary and secondary endpoints of CheckMate 648 and KEYNOTE 590

	CheckMate 648	KEYNOTE 590
Primary	OS and PFS as per BICR[a] in: • Patients with tumor cell PD-L1 ≥1%	OS and PFS as per investigator/BICR in: • All patients • Patients with ESCC • CPS>10 or more • ESCC and CPS>10
Secondary	OS and PFS in all randomized patients Objective response rate (tumor cell PD-L1 > 1% and all randomized)	Objective response rate per RECIST 1.1 by investigator Duration of response Health related quality of life (EORTC QLQ-C30/QLQ-OES18)

Abbreviations: BICR, blinded independent central review; CPS, combined positive score; EORTC QLQ-C30, European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire; ESCC, esophageal squamous cell carcinoma; OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression free survival; RECIST, Response Evaluation Criteria in Solid Tumors
[a] According to the hierarchical testing procedure, the end points were assessed first in patients with tumor-cell PD-L1 expression of 1% or greater and then in the overall population

7.3.1.4 Results from indirect comparison

The primary endpoints from the two studies are not completely identical as CheckMate 648 used BICR to evaluate OS and PFS, whereas OS and PFS in KEYNOTE 590 were by per investigator assessment. The PD-L1 status is determined as per tumor cell expression (TPS) in CheckMate 648 and as a combined positive score of tumor and immune cell expression (CPS) in KEYNOTE 590. KEYNOTE 590 included both EAC and ESCC patients.

Only the endpoints concerning the ESCC and the relevant biomarker cut-offs were used in the analysis to match the patient population in CheckMate 648.

For nivolumab plus chemotherapy OS and PFS, the data cut with minimum 20 months follow up was chosen because it was the most recent data cut (European Medicin Agency 2022b).

For pembrolizumab plus chemotherapy OS, the data cut with median 34.8 months was chosen (Metges 2022), where as for PFS ESCC per BICR, the data cut with median 22.6 months was chosen (Sun 2021b) since PFS ESCC per BICR was not updated in the data cut with median 34.8 months follow up.

7.3.1.4.1 Overall Survival

The overall survival HR for nivolumab plus chemotherapy was 0.59 (95% CI, 0.46–0.75) (European Medicin Agency 2022b) (TPS≥1 and 20 months FU per BICR), which is almost identical to the HR for pembrolizumab plus chemotherapy (CPS≥10 and 34 months FU per Investigator assessed) of 0.59 (95% CI, 0.45–0.76) (Metges 2022). Using Bucher's method, the HR is 1.00 (95% CI, 0.696–1.437) concluding there is no statistical difference between the two treatment regiments (Table 21).

7.3.1.4.2 Progression Free Survival

PFS in CheckMate 648 is per BICR in patients whose tumours express PD-L1 (TPS ≥1%), whereas PFS in KEYNOTE 590 is investigator assessed in ESCC with CPS≥10.

The PFS HR for nivolumab plus chemotherapy is 0.66 (95% CI, 0.59–0.87) and HR for pembrolizumab plus chemotherapy is 0.53 (95% CI, 0.40–0.69). Using Bucher's method the HR is 1.245 (95% CI, 0.891–1.740) concluding there is no statistical difference between the two treatment regiments concerning PFS (Table 21).

Table 21: Nivolumab plus chemotherapy versus pembrolizumab plus chemotherapy: indirect treatment comparison results for the overall survival endpoint

Outcome	CheckMate 648 (nivolumab plus chemotherapy, n=321)	KEYNOTE 590 (pembrolizumab plus chemotherapy, n=373)	HR Bucher's ITC
OS HR (95% CI), follow-up	0.59 (0.46, 0.75), Minimum 20 month	0.59 (0.45, 0.76) Median 34.8 months	1.00 (0.696, 1.437)
PFS HR (95% CI), follow-up	0.66 (0.59, 0.87) Minimum 20 month	0.53 (0.40, 0.69) Median 22.6 months	1.25 (0.891, 1.740)

Abbreviations: CI, Confidence interval; HR, hazard ratio; ITC, independent treatment comparison; OS, overall survival; PFS, progression free survival.

7.3.1.5 Summary of indirect treatment comparison efficacy results

An ITC was performed to compare the efficacy and safety of nivolumab plus chemotherapy and pembrolizumab plus chemotherapy due to the lack of a head-to-head trial. For neither OS or PFS was a statistically significant difference identified, hence, in terms of efficacy, nivolumab plus chemotherapy can be considered equivalent to pembrolizumab plus chemotherapy.

7.3.1.6 Descriptive comparison: safety analysis

As there is no head-to-head evidence comparing nivolumab plus chemotherapy with pembrolizumab plus chemotherapy, the comparative safety of nivolumab plus chemotherapy and pembrolizumab plus chemotherapy in patients with ESCC cannot be directly inferred from a trial.

As mentioned above, the AEs are collected and reported differently in CheckMate 648 and KEYNOTE 590, and hence, it is not possible to conduct an indirect comparison.

7.3.1.6.1 Treatment-related adverse events

The descriptive comparative results of AEs in CheckMate 648 and KEYNOTE 590 are presented in Table 22. The AEs reported from KEYNOTE 590 represents both adenocarcinomas as well as squamous cell carcinomas. As the AEs are reported with different percentage cut-offs of occurrence (most common in ≥5% versus ≥10%) and grade (≥3 versus 3 or 4) in KEYNOTE 590 and CheckMate 648, respectively, the descriptive analysis will include type of AE and frequency based on the reporting method in each study.

Both the CheckMate 648 and KEYNOTE 590 reported AEs for the primary analyses at 20-month minimum follow-up and 22.6-month median follow-up, respectively.

Overall, results of the descriptive analysis of CheckMate 648 and KEYNOTE 590 suggest a similar safety profiles of nivolumab and pembrolizumab in combination with chemotherapy. The safety profiles of nivolumab plus chemotherapy and pembrolizumab plus chemotherapy are also consistent with the known profiles of the individual components at similar doses (European Medicin Agency 2022a, European Medicin Agency 2022b).

As presented in Table 22, for nivolumab plus chemotherapy the most common TRAE of any grade occurring in more than 10% of patients were: decreased appetite, stomatitis, anaemia, decreased neutrophil count, fatigue, diarrhoea, constipation and vomiting. Similarly, for pembrolizumab plus chemotherapy the most common treatment related adverse event of any grade reported in more than 5% of patients were: nausea, decreased appetite, anaemia, fatigue, decreased neutrophil count, nausea, vomiting, neutropenia and stomatitis.

For TRAE of grade 3 or 4, the most common with nivolumab plus chemotherapy was anaemia and decreased neutrophil count. For pembrolizumab plus chemotherapy, the most common TRAE of grade 3 or higher were decreased neutrophil count, neutropenia and anaemia. Treatment related deaths were also similar between nivolumab plus chemotherapy and pembrolizumab plus chemotherapy. The AEs reported in the two studies and the shared mechanism of action between nivolumab or pembrolizumab in combination with chemotherapy support that the safety profiles are expectedly similar.

In CheckMate 648 most of the TRAE of potential immunologic cause were grade 1 or 2. No more than 6% of the events across the treatment groups were of grade 3 or 4. In KEYNOTE 590, 95 patients (26%) experienced adverse events of special interest (i.e., immune-mediated adverse events and infusion reactions). Grade 3 or higher immune-mediated adverse events occurred in 26 patients (7%).

Table 22: Adverse events reported in CheckMate 648 and KEYNOTE 590[d]

Patients	CheckMate 648 20-month minimum follow-up				KEYNOTE 590 22.6-month median follow-up			
	Nivolumab plus Chemotherapy (n=310)		Chemotherapy (n=304)		Pembrolizumab plus chemotherapy (n=370)		Chemotherapy (n=370)	
	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4	Any grade	Grade 3+[a]	Any grade	Grade 3+[a]
All-causality, n (%)								
Any AEs	308 (99.4)	226 (72.9)	301 (99)	170 (55.9)	370 (100)	318 (86)	368 (99)	308 (83)
Serious AEs	186 (60.0)	145 (46.8)	130 (42.8)	100 (32.9)	NR	NR	NR	NR
AEs leading to discontinuation	130 (41.9)	56 (18.1)	81 (26.6)	33 (10.9)	90 (24)	NR	74 (20)	NR

TRAEs, n (%)								
Any AEs	297 (95.8)	151 (48.7)	275 (90.5)	110 (36.2)	364 (98)	226 (72)	360 (97)	250 (68)
Serious AEs	74 (23.9)	58 (18.7)	49 (16.1)	40 (13.2)	NR	NR	NR	NR
TRAEs leading to discontinuation	106 (34.2)	30 (9.7)	63 (20.7)	18 (5.9)	NR	NR	NR	NR
Most common TRAEs, %[b]								
Nausea	59	4	52	3	63	7	59	6
Decreased appetite	43	4	43	3	39	4	32	4
Stomatitis	32	6	23	2	26	6	25	4
Anemia	30	10	22	6	39	12	44	15
Decreased neutrophil count	21	8	17	8	36	23	29	17
Fatigue	20	2	16	4	36	6	29	5
Diarrhea	19	1	15	2	26	3	23	2
Constipation	19	1	22	<1	14	0	17	0
Vomiting	18	2	16	3	30	6	27	5
Malaise	16	<1	15	0	12	1	11	1
Decreased white-cell count	14	4	9	2	24	9	19	5
Hiccups	14	0	17	0	11	0	9	0
Increase blood creatinine level	13	<1	11	<1	18	1	19	<1
Decreased platelet count	12	1	11	2	16	2	15	5
Mucosal inflammation	11	3	9	1	16	3	18	4
Alopecia	10	0	11	0	14	0	11	0
Hypothyroidism	6	0	0	0	10	0	6	0
Neutropenia	n/a	n/a	n/a	n/a	26	14	24	16
Asthenia	n/a	n/a	n/a	n/a	12	3	9	1
Decreased weight	n/a	n/a	n/a	n/a	12	1	13	2
Hyponatraemia	n/a	n/a	n/a	n/a	9	5	11	5
Leukopenia	n/a	n/a	n/a	n/a	6	2	8	33
Thrombcytopenia	n/a	n/a	n/a	n/a	7	1	9	3
Tinnitus	n/a	n/a	n/a	n/a	9	1	7	0

Hyperthyroidism	n/a	n/a	n/a	n/a	5	0	1	0
Increased aspartate aminotransferase	n/a	n/a	n/a	n/a	5	1	5	1
Decreased lymphocyte count	n/a	n/a	n/a	n/a	6	2	5	1
Dehydration	n/a	n/a	n/a	n/a	5	2	4	2
Hypokalaemia	n/a	n/a	n/a	n/a	9	5	11	5
Hypo-magnesaemia	n/a	n/a	n/a	n/a	6	1	4	1
Dysgeusia	n/a	n/a	n/a	n/a	9	0	9	0
Peripheral neuropathy	n/a	n/a	n/a	n/a	9	<1	9	0
Peripheral sensory neuropathy	n/a	n/a	n/a	n/a	9	<1	8	<1
Pneumonitis	n/a	n/a	n/a	n/a	5	2	0	0
Pruritus	n/a	n/a	n/a	n/a	6	<1	2	0
Rash	n/a	n/a	n/a	n/a	8	0	5	<1
AEs of special interest, immune mediated, %[c]								
Pneumonitis	3.7	2.2	0	0	6	1	1	<1
Diarrhea/Colitis	3.4	1.2	0	0	2	1	2	1
Hepatitis	4.0	2.8	0	0	1	1	0	0
Nephritis/Renal dysfunction	1.2	0.6	0	0	<1	0	1	<1
Rash	13.7	2.5	0.7	0.3	n/a	n/a	n/a	n/a
Hypersensitivity	0.3	0	0	0	n/a	n/a	n/a	n/a
Adrenal Insufficiency	5.6	2.2	0	0	1	1	1	0
Hypophysitis	6.5	3.1	0	0	1	<1	0	0
Hypothyroidism/ Thyroiditis	15.5	0.3	0	0	11	0	6	0
Hyperthyroidism	5.9	0.6	0.3	0	6	<1	1	0
Diabetes Mellitus/ Type 1 diabetes	1.6	0.6	0	0	<1	<1	0	0
Infusion reaction	n/a	n/a	n/a	n/a	2	<1	1	0

Severe skin reaction	n/a	n/a	n/a	n/a	1	1	1	1
Pancreatitis	n/a	n/a	n/a	n/a	1	0	<1	<1
Myositis	n/a	n/a	n/a	n/a	<1	<1	0	0
Thyroiditis	n/a	n/a	n/a	n/a	<1	<1	0	0

Abbreviations: AE, adverse events; TRAE, treatment related adverse events.
[a] Treatment-related grade 5 events included febrile neutropenia, diarrhoea, multiple organ dysfunction, hepatic failure, pneumonia, acute kidney injury, interstitial lung disease, pneumonitis, and pulmonary embolism, which each occurred in one patient in the pembrolizumab plus chemotherapy group, and febrile neutropenia, death, multiple organ dysfunction syndrome, sepsis, and interstitial lung disease, which each occurred in one patient in the placebo plus chemotherapy group.
[b] In CheckMate 648 AEs that occured in ≥ 10% of patients were reported, while in KEYNOTE 590, AEs that occurred in ≥5% were reported.
[c] For CheckMate 648, patients who received ≥1 dose of study treatment were included, where select TRAEs are those with potential immunologic etiology that require frequent monitoring/intervention, and consider events reported between first dose and 30 days after last dose of study drug. For KEYNOTE 590, immune-mediated adverse events and infusion reactions were based on a list of terms specified by the sponsor, regardless of attribution to any study treatment by investigators.
[d] Differences in collecting and registering of safety data between CheckMate 648 and KEYNOTE 590 can effect comparibility of reported safety data outcomes .
Source: (Sun 2021b, Doki 2022)

8 Health economic analysis

Model

To assess the clinical effectiveness of nivolumab plus chemotherapy (CheckMate 648) in advanced ESCC in Denmark, pembrolizumab plus chemotherapy (KEYNOTE 590) was determined to be the appropriate comparator.

The results of the Bucher ITC (see Section 7.2.1) showed no statistically significant difference between the clinical efficacy of nivolumab plus chemotherapy and pembrolizumab plus chemotherapy, and therefore, a cost-minimization analysis (cost-min) was performed.

8.1 Presentation of input data used in the model and how they were obtained

Table 23: Input data used in the model

Resource/Input	Value	Reference/source for costs
Posology		
Nivolumab Q4W	Dosing interval every 4-weeks, with fixed dosing of 480mg	SmPC (European Medicin Agency 2022b)
Nivolumab Q2W	Dosing interval every 2-weeks, with fixed dosing of 240mg or weight based dosing of 3 mg/kg	
Pembrolizumab Q3W	Dosing interval every 3-weeks, with fixed dosing of 200mg or weight based dosing of 2 mg/kg	SmPC (European Medicin Agency 2022a)
Treatment duration		
Nivolumab plus chemotherapy	[redacted]	[redacted]
Pembrolizumab plus chemotherapy	7.31 months	Area under curve method from time to treatment discontinuation kaplan-meieir used on data from KEYNOTE 590 (Sun 2021a)
Durg acquisition costs		
Nivolumab	40 mg – 3,690.69 DKK 100mg – 9,168.23 DKK 240 mg - 22,003.74 DKK	(Medicinpriser.dk 2022)
Pembrolizumab	100 mg – 23,204.61 DKK	(Medicinpriser.dk 2022)
Administration costs	2,358 DKK	(Sundhedsdatastyrelsen (2022) 2022)
Indirect costs		
Transportation costs	140.00 DKK	(enhedsomkostninger 2022)
Patient time costs (per hour)	181.00 DKK	(enhedsomkostninger 2022)

Abbreviations: DKK, Danish krona; EMA, European Medincines Agency; SmPC, Summary of product characteristics; Q2W, every 2 weeks; Q4W, every 4 weeks

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8.2 Relationship between the clinical documentation, data used in the model and Danish clinical practice

The relevant patient population, intervention and comparators for the cost-min and how they compare and any differences between Danish practice, the clinical documentation and the model are discussed in the sections below

8.2.1.1 Patient population

The Danish patient population

The relevant patient population is expected to be adult patients with locally advanced resectable or metastatic ESCC.

Patient population in the clinical documentation submitted

In CheckMate 648 the patient poulation had unresectable advanced, recurrent or metastatic ESCC.

Patients in KEYNOTE 590 had unresectable or metastatic ESCC/EAC or Siewert type I GEJ adenocarcinoma; Since ESCC, EAC, and Siewert type I GEJ adenocarcinoma patients were included in the KEYNOTE 590 study, the primary part of the trial population was ESCC patients (approximately 73% versus approximately 27% adenocarcinoma) for the ITC (Sun 2021a).

Section 7.2 discusses the Bucher's ITC and the relevant populations in more detail.

Patient population in the health economic analysis submitted

The patient population used in the cost-min are ESCC patients, as per the populations in CheckMate 648 and KEYNOTE 590.

Table 24: Patient population

Patient population	Clinical documentation	Used in the model	Danish clinical practice
Patient population	CheckMate 648 population had unresectable advanced, recurrent or metastatic ESCC (European Medicin Agency 2022b). The KEYNOTE 590 population had unresectable or metastatic ESCC/EAC or Siewert type I GEJ adenocarcinoma; Both ESCC, EAC and Siewert type I GEJ adenocarcinoma patients were included in the KEYNOTE 590 study, thus the primary part of the trial population was ESCC patients (approximately 73% versus approximately 27% adenocarcinoma) for the ITC	Patients with unresectable advanced, recurrence or metastatic ESCC as per CheckMate 648 and KEYNOTE 590 (Sun 2021a)	Adult patients with locally advanced resectable or metastatic ESCC

Abbreviations: EAC, esophageal adenocarcinoma; ESCC, esophageal squamous cell carcinoma; GEJ, gastroesophageal junction; ITC, indirect treatment comparison; DKK, Danish krona; EMA, European Medicines Agency; SmPC, Summary of product characteristics; Q2W, every 2 weeks; Q4W, every 4 weeks

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8.2.1.2 Intervention

Intervention as expected in Danish clinical practice (as defined in section 2.2)

Nivolumab currently has two approved dosing regimens when administered in combination with chemotherapy i.e., 240 mg every other week (or weight based dosing of 3mg/kg every other week) and 480 mg every fourth week, whereas the approved dosage for pembrolizumab is 200 mg every third week. For the base case analysis fixed dosing was assumed for both treatment strategies, weight-based dosing was explored by way of scenario analysis.

Intervention in the clinical documentation submitted

Nivolumab (240 mg) was administered via IV infusion over 30 minutes every 2 weeks (i.e., on Day 1 and Day 15) and 5-FU (800 mg/m²) was administered via an IV continuous infusion for 5 days, followed by cisplatin (80 mg/m²) as an IV infusion over 30 to 120 minutes every 4 weeks (European Medicin Agency 2022b).

Intervention as in the health economic analysis submitted

The cost-min followed the approved dosing regimens, with base case results presented for Nivolumab being administered as 240mg every 2 weeks or 480mg every 4 weeks (European Medicin Agency 2022b). In the base case, fixed dosing is assumed.

[redacted]

[redacted]

Table 25: Intervention

Intervention	Clinical documentation	Used in the model	Expected Danish clinical practice
Posology	In CheckMate 648, Nivolumab (240 mg) was administered via IV infusion over 30 minutes every 2 weeks (i.e., on Day 1 and Day 15) and 5-FU (800 mg/m²) was administered via an IV continuous infusion for 5 days, followed by cisplatin (80 mg/m²) as an IV infusion over 30 to 120 minutes every 4 weeks (European Medicin Agency 2022b)	The base case results are presented using each of the approved dosing regimens for Nivolumab. These are either 240mg every 2 weeks or 480mg every 4 weeks (European Medicin Agency 2022b)	Nivolumab is currently approved in clinical practice for 240mg every 2 weeks 480mg every 4 weeks or 3mg/kg every 2 weeks (European Medicin Agency 2022b)
Length of treatment (time on treatment) (mean/median)	In CheckMate 648, treatment was continued until disease progression, unacceptable toxicity, or up to 24 months (Chau 2021) [redacted]	[redacted]	Until disease progression, unacceptable toxicity, or up to 24 months (European Medicin Agency 2022b)

Abbreviations: 5-FU, Fluorouracil; AUC, Area under curve ; IV, Intravenous; TTD, Time to Treatment Discontinuation

8.2.1.3 Comparator

The current Danish clinical practice (as described in section 5.2)

The relevant comparators for nivolumab plus chemotherapy in Denmark is pembrolizumab plus chemotherapy. As pembrolizumab in combination with chemotherapy has been recommended by the DMC for treatment carcinoma of the esophagus in patients with the biomarker PD-L1 CPS ≥ 10, the treatment recommendation is aligned with the carcinoma of the esophagus PD-L1 expressing population as part of the CheckMate 648 study.

The recommended dose for Pembrolizumab is to be administered as 2mg/kg every three weeks (Medicinrådet 2022), whilst the dosing for the chemothereapy drugs of Capecitabin and Oxaliplatin the administration is;

- Capecitabin (IV) 2000 mg/m^2 days 1-14 every 3 weeks (Medicinrådet 2022)
- Oxaliplatin (IV) 130 mg/m^2 every 3 weeks (Medicinrådet 2022)

Treatment is given until disease progression,unacceptable toxicity or up to 2 years (European Medicin Agency 2022a).

Comparator in the clinical documentation submitted

In KEYNOTE 590, patients received 200 mg of pembrolizumab, introvenously every three weeks and chemotherapy every three weeks (5-fluorouracil 800 mg/m² on days 1–5 plus cisplatin 80 mg/m² on day 1 [for a maximum of 6 cycles]).

In KEYNOTE 590, pembrolizumab treatment continued until disease progression, unacceptable toxic effects, withdrawal of consent, or the end of the trial. Patients could receive treatment of Pembrolizumab for approximately 2 years (35 treatment cycles).

In the cost-min, pembrolizumab was calculated at 200 mg every three weeks, as per KEYNOTE 590. In the base case, fixed dosing was assumed.

For the duration of treatment used in the cost-min, the mean treatment duration was calculated from KEYNOTE 590, using the trapezoidal integration method, defined as the area under curve (AUC) for the time to treatment discontinuation Kaplan-Meier (TTD-KM) curves. The TTD using the AUC from KEYNOTE 590 was 7.31 months (Medicinrådet 2022).

Table 26: Comparator

Comparator	Clinical documentation	Used in the model	Expected Danish clinical practice
Posology	In the KEYNOTE 590 trial, pembrolizumab dosing is 200mg every three weeks. Whilst, Chemothereapy is administered every three weeks (Sun 2021a).	Dosing in the model is as per the KEYNOTE 590 trial, with pembrolizumab dosing of 200 mg IV every three weeks. Chemotherapy is excluded from the cost-min as it would have a net zero costs with the intervention arm.	Pembrolizumab is administered as 2mg/kg every three weeks. For the chemotherapy drugs, Capecitabin is administered intravenously at 2000 mg/m^2, days 1-14 every 3 weeks and Oxaliplatin is administered intravenously at 130 mg/m^2 every 3 weeks (Medicinrådet 2022) (European Medicin Agency 2022a).
Length of treatment (time on treatment) (mean/median)	In KEYNOTE 590, pembrolizumab was administered for a maximum of approximately 2 years (35 cycles) and was continued until disease progression, unacceptable toxicity, withdrawal of consent, or the end of the trial. The TTD using the AUC from KEYNOTE 590 was was 7.31 months (European Medicin Agency 2022a).	The TTD using AUC from KEYNOTE 590 was 7.31 months and this was used as the treatment duration in a scenario in the cost-min (European Medicin Agency 2022a); the base case assumes the same TTD as nivolumab 8.0 months.	Until disease progression, unacceptable toxicity or upto 2 years of treatment (European Medicin Agency 2022a).

Abbreviations: AUC, Area under curve ; IV, Intravenous; TTD, Time to Treatment Discontinuation

8.2.1.4 Relative efficacy outcomes

As a cost-min is being conducted, the relative efficacy outcomes are not relevant. See section 7.2 for the comparative analysis of efficacy and safety of nivolumab compared with pembrolizumab.

8.2.1.5 Adverse reaction outcomes

The results of the descriptive analysis from the Bucher ITC for CheckMate 648 and KEYNOTE 590 suggest a similar safety profiles of nivolumab and pembrolizumab in combination with chemotherapy. The safety profiles of nivolumab plus chemotherapy and pembrolizumab plus chemotherapy are also consistent with the known profiles of the individual components at similar doses (European Medicin Agency 2022a, European Medicin Agency 2022b). Therefore, given the similar profiles it is assumed that adverse events and the associated costs would be the same between the two treatments and there are excluded from the cost-min.

Extrapolation of relative efficacy

As a cost-min is being conducted, this section is not relevant.

Documentation of health-related quality of life (HRQoL)

As a cost-min is being conducted, this section is not relevant.

Resource use and costs

8.2.1.6 Unit costs and resource use

Both nivolumab and pembrolizumab are PD-L1 inhibitors with a PD-L1 restriction as per label and are using the same backbone chemotherapy (5-FU + cisplatin) in their respective trials (European Medicin Agency 2022a), however the backbone chemotherapy is used every 3rd week in the combination with pembrolizumab and every 4th week in the combination with nivolumab. Most of the unit cost and resource use inputs between the two treatment strategies are assumed to be the same, with the exception of the costs associated with the acquisition and administration of nivolumab and pembrolizumab respectively. For simplification reasons, therefore, only drug acquisition cost, drug administration and patient related costs for nivolumab and pembrolizumab have been included in this cost-min.

8.2.1.7 Drug acquisition and administration costs

Drug acquisition costs for the two treatment strategies are presented in Table 27. Unit costs (AIP) were sourced from the Medicinpriser.dk (April 2022). The cost per dose for each treatment was calculated by assuming vial sharing. This was based on knowledge of the Danish clinical setting through Danish clinical expert feedback from past nivolumab health technology assessment submissions. The same administration cost was used for both treatment strategies (see Table 28). For the scenario where nivolumab is administered every second week, administration cost was also added when the backbone chemotherapy was administered alone (every fourth week). [redacted]

Table 27: Drug aqustion costs and administraton costs for nivolumab and pembrolizumab respectively

Treatment	Dose per tablet	Units per package	Cost per package	Cost per mg	Reference/source for costs
Nivolumab	40 mg	1	3690.69	92.27	(Medicinpriser.dk 2022)
	100 mg	1	9168.23	91.68	(Medicinpriser.dk 2022)
	240 mg	1	22 003.74	91.68	(Medicinpriser.dk 2022)
Pembrolizumab	100 mg	1	23 204.61	232.05	(Medicinpriser.dk 2022)
Fluorouracil	500 mg	1	70.00		(Medicinpriser.dk 2022)
	2500 mg	1	200.00		(Medicinpriser.dk 2022)
	5000 mg	1	400.00		(Medicinpriser.dk 2022)
Cisplatin	50 mg	1	100.00		(Medicinpriser.dk 2022)
	100 mg	1	200.00		(Medicinpriser.dk 2022)

Abbreviations: DKK, Danish krone; IV, intravenous; mg, milligrams

Table 28: Administration cost

Name of resource	Cost (DKK)	Comment	Reference DK (2021)
Administration	2358	Same cost considered for both treatment settings	(Sundhedsdatastyrelsen (2022) 2022)

Abbreviations: DKK, Danish krone

8.2.1.8 Indirect costs

Indirect costs were included in the base case in line with health technology assessment guidelines (Medicinrådet 2021). They include disease management costs that fall on patients and caregivers. [redacted]

In the scenario where nivolumab was administered every second week, indirect costs were also applied when the backbone chemo was administered alone (every fourth week).

The input values used for indirect costs in the cost-minimization analysis are presented in Table 29.

Table 29: Indirect costs included in the model

Input	Cost (DKK)	Frequency (assumed)	Base case
Transportation costs	140.00	[redacted]	(enhedsomkostninger 2022)
Patient time costs (per hour)	181.00	[redacted]	(enhedsomkostninger 2022)

Abbreviations: DKK, Danish krone

Results

The base case settings for the cost-minare presented in Table 30.

Table 30: Base case overview

Input	Setting
Intervention	Nivolumab
Comparator	Pembrolizumab
Type of model	Cost minimization model
Time horizon	N/A
Treatment line	[redacted]
Measurement and valuation of health effects	N/A
Included costs	Drug acquisition costs Drug administration costs Indirect treatment costs
Dosage of pharmaceutical	Assumed fixed dosing Nivolumab – Q4W, Q2W Pembrolizumab – Q3W
Average time on treatment	Assumed the same treatment duration of Nivolumab for both the intervention and comparator [redacted]

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Parametric function for PFS	N/A
Parametric function for OS	N/A

8.3 Base case results

[redacted]

Table 31: cost-min base case results, Q2W

Per patient (DKK)	Intervention	Comparator	Difference
Total costs	[redacted]	[redacted]	[redacted]
Drug acquisition costs	[redacted]	[redacted]	[redacted]
Chemo therapy cost	[redacted]	[redacted]	[redacted]
Administrative costs	[redacted]	[redacted]	[redacted]
Indirect costs	[redacted]	[redacted]	[redacted]
Incremental results		[redacted]	
Incremental cost vs Pembrolizumab		[redacted]	

Abbreviations: DKK, Danish krone; Q2W, every 2 weeks

Table 32: cost-min base case results, Q4W

Per patient (DKK)	Intervention	Comparator	Difference
Total costs	[redacted]	[redacted]	[redacted]
Drug acquisition costs	[redacted]	[redacted]	[redacted]
Chemo therapy cost	[redacted]	[redacted]	[redacted]
Administrative costs	[redacted]	[redacted]	[redacted]
Indirect costs	[redacted]	[redacted]	[redacted]
Incremental results		[redacted]	
Incremental cost vs Pembrolizumab		[redacted]	

Abbreviations: DKK, Danish krone; Q4W, every 4 weeks

Sensitivity analyses

8.4 Deterministic sensitivity analyses

A one-way sensitivity was conducted to explore the effect on the model results of assuming different TTDs, weight-based dosing (average weight used are from CheckMate 648 and KEYNOTE 590, see Table 33, with a weight based dose for Q4W of 6 mg/kg from CM577), and a difference in the patient average weight for the two different strategies. These scenarios are summarised in Table 34.

Table 33: Patient weight

Treatment strategy	Average weight (kg)	Source
Nivolumab	58.99	CheckMate 648
Pembrolizumab	62.56	DMC evaluation report KEYNOTE 590

Abbreviation: kg, Kilogram

Table 34: One-way sensitivity analysis

Scenarios		Base case
Dosing	**TTD**	
Fixed dose	Pembrolizumab TTD from KN590 Nivolumab TTD from CM648	Fixed dose TTD CM648
Fixed dose	TTD as per KN590	Fixed dose TTD CM648
Weight base dosing as per CM648	TTD as per CM648	Fixed dose TTD CM648
Weight based dosing as per KN590	TTD as per CM648	Fixed dose TTD CM648
Weight based dosing as per trial	TTD as per CM648	Fixed dose TTD CM648

Abbreviation: TTD, Time to Treatment Discontinuation

[redacted]

Table 35: Model results given different scenarios

Scenarios	Results difference versus pembrolizumab in DKK	
	CheckMate 648 Q4W dosing	CheckMate 648 Q2W dosing
Fixed dose/TTD as per KN590	[redacted]	[redacted]
Weight base dosing as per CM648	[redacted]	[redacted]
Weight based dosing as per KN590	[redacted]	[redacted]
Weight based dosing as per trial	[redacted]	[redacted]

Abbreviations: DKK: Danish krone; Q2W, every 2 weeks; Q4W, every 4 weeks; TTD, Time to Treatment Discontinuation

8.5 Probabilistic sensitivity analyses

As a cost-min was conducted, a probabilistic sensitivity analysis was not relevant.

9 Budget impact analysis

A budget impact analysis was performed for the expected additional cost of introducing nivolumab plus chemotherapy into the Danish clinical setting. In line with the guidelines, a 5-year time horizon was used for the analysis. The costs included within the analysis were drug acquisition, administration, monitoring, and indirect costs.

Number of patients

The total number of patients used in the budget impact analysis were a total of 45 eligible patients year, as calculated in section 5.1.4.3. If granted pre-approved reimbursement, it was assumed that 80% of the eligible patients would be treated with nivolumab plus chemotherapy by year 5, with a linear increase each year. If not granted pre-approved reimbursement, it was estimated that 0% would be treated with nivolumab plus chemotherapy.

Table 36: Number of patients expected to be treated over the next five-year period - if the pharmaceutical is introduced

	Year 1	Year 2	Year 3	Year 4	Year 5
For the pharmaceutical under consideration, costs per patient: Nivolumab plus chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
For competitive pharmaceutical 1: Pembrolizumab plus chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total number of patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 37: Number of patients expected to be treated over the next five-year period - if the pharmaceutical is NOT introduced

	Year 1	Year 2	Year 3	Year 4	Year 5
For the pharmaceutical under consideration, costs per patient: Nivolumab plus chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
For competitive pharmaceutical 1: Pembrolizumab plus chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total number of patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Expenditure per patient

The cost per patient per year for nivolumab plus chemotherapy and pembrolizumab plus chemotherapy are presented in Table 38 and Table 39. The costs per patient in a scenario where nivolumab plus chemotherapy is and is not recommended are presented.

Table 38: Costs per patient per year - if the pharmaceutical is recommended

DKK	Year 1	Year 2	Year 3	Year 4	Year 5
For the pharmaceutical under consideration, costs per patient: Nivolumab plus chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
For competitive pharmaceutical 1: Pembrolizumab plus chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: DKK, Danish krone

Table 39: Costs per patient per year - if the pharmaceutical is NOT recommended

DKK	Year 1	Year 2	Year 3	Year 4	Year 5
For the pharmaceutical under consideration, costs per patient: Nivolumab plus chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
For competitive pharmaceutical 1: Pembrolizumab plus chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: DKK, Danish krone

Budget impact

Based on the number of patients expected to be treated per year and the market penetration shown in Table 36 and Table 37, the results of the budget impact analysis show a Year 5 budget impact of [redacted] when comparing a scenario without approval of nivolumab to a scenario with approval. [redacted]

Table 40: Expected budget impact of recommending the pharmaceutical for the current indication

DKK	Year 1	Year 2	Year 3	Year 4	Year 5
The pharmaceutical under consideration is recommended	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Of which: Drug acquisition costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Of which: Administration costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Of which: Monitoring costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Of which: Indirect costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Minus: **The pharmaceutical under consideration is NOT recommended**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Of which: Drug acquisition costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Of which: Administration costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Of which: Monitoring costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Of which: Indirect costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Budget impact of the recommendation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviation: DKK, Danish krone

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10 Discussion on the submitted documentation

[redacted]

11 List of experts

[redacted]

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13 Appendix A – Literature search for efficacy and safety of intervention and comparator

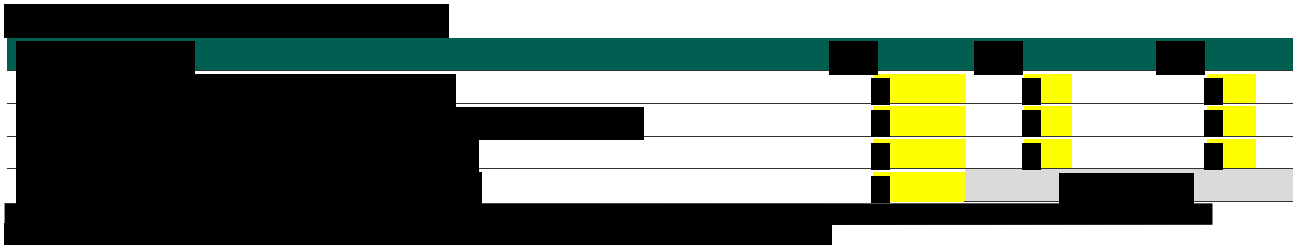
A systematic literature review (SLR) was conducted to identify randomised control trials (RCT) evidence assessing treatments for first-line unresectable advanced, recurrent, or metastatic EC with a focus on studies evaluating patients with ESCC.

[redacted]

Search strategy

[redacted]

[redacted]



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Systematic selection of studies

[redacted]

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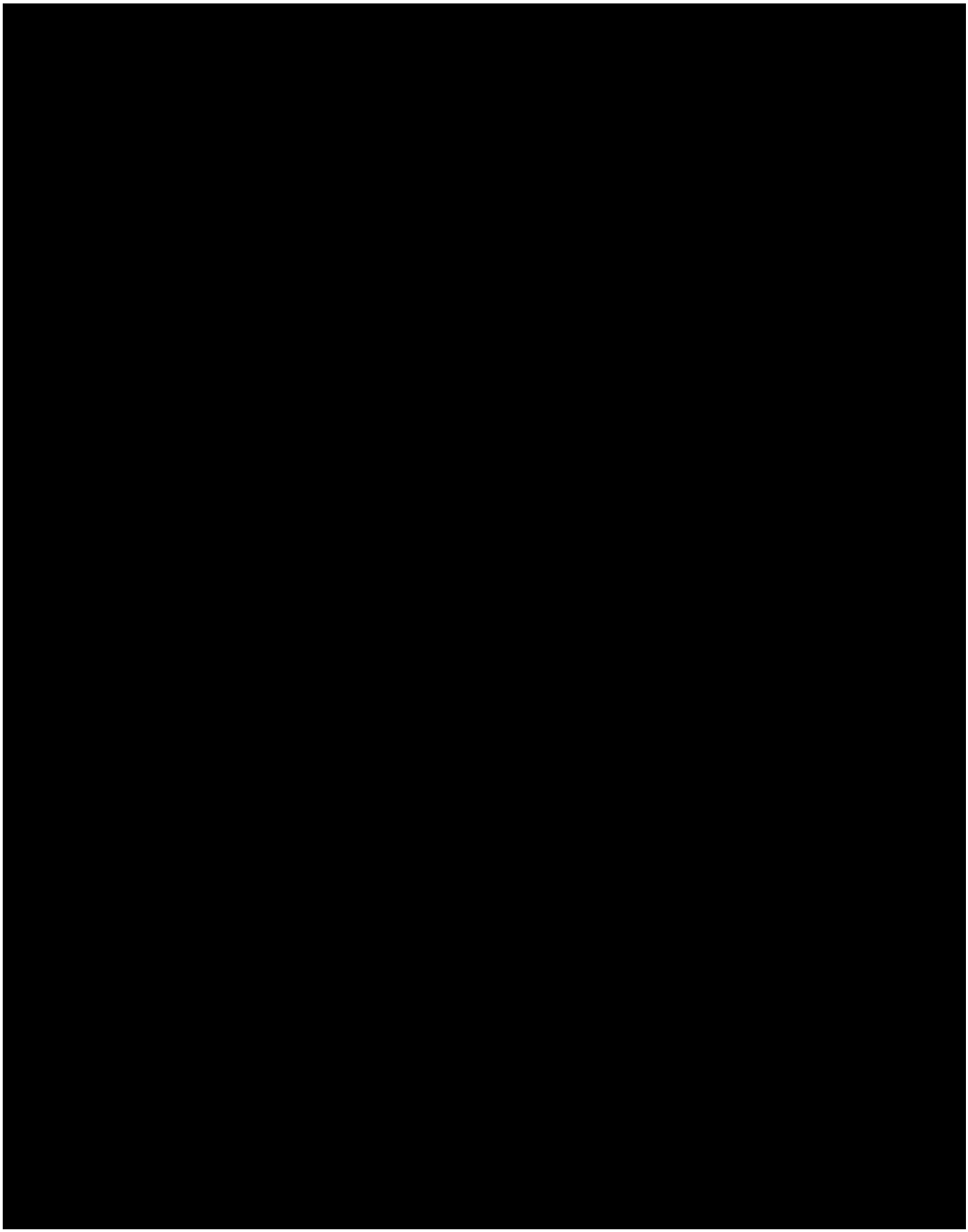

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[redacted]. As described in Section 5.2 and Section 6, the relevant comparator for nivolumab plus chemotherapy in the Danish clinical setting is pembrolizumab plus chemotherapy. [redacted]. There were no available relevant studies that compared nivolumab plus chemotherapy with pembrolizumab plus chemotherapy in the 1L ESCC patient population. As such, 2 studies—1 for nivolumab plus chemotherapy and 1 for pembrolizumab plus chemotherapy—were identified and considered in a indirect treatment comparison (ITC).

Table 51: Overview of study design for studies included in the technology assessment/analysis

Study/ID	Aim	Study design	Patient population	Intervention and comparator sample size (n)	Primary outcome and follow-up period	Secondary outcome and follow-up period
CheckMate 648 (Doki 2022) (Doki 2022)	To compare how long subjects with EC live overall or live without disease progression after receiving nivolumab and ipilimumab or nivolumab combined with fluorouracil plus cisplatin versus fluorouracil plus cisplatin	Phase III, open-label	Advanced ESCC, with PD-L1 expressing	N=970 Intervention: nivolumab plus ipilimumab or nivolumab plus fluorouracil and cisplatin Comparator: n/a	OS in participants with tumor cell PD-L1 up to 20 months PFS assessed by BICR in participants with tumor cell PD-L1 up to 9 months	OS in all randomized participants up to 16 months PFS by BICR in all randomized participants up to 16 months ORR as assessed by BICR up to 40 months
KEYNOTE-590 (Sun 2021a)	To evaluate efficacy and safety of pembrolizumab plus standard of care chemotherapy with cisplatin and 5-FU versus placebo plus SOC chemotherapy with cisplatin and 5-FU as first-line treatment in participants with locally advanced or metastatic EC	Phase III, double-blind	locally advanced or metastatic EC	ITT, N=749 For ESCC, n=548 Intervention: pembrolizumab plus fluorouracil and cisplatin Comparator: placebo	OS in: ESCC with PD-L1 CPS ≥ 10; participants with ESCC; participants with PD-L1 CPS ≥ 10; all participants PFS per RECIST 1.1 investigator assessed in: ESCC; with PD-L1 CPS ≥ 10; in all patients	ORR per RECIST 1.1 investigator assessed DOR per RECIST 1.1 investigator assessed Safety EORTC QLQ-C30 GHS/QoL EORTC QLQ-OES18

Abbreviations: 5-FU, Fluorouracil; BICR, blinded independent central review; CPS, Combined positive score; EORTC QLQ-C30, European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire; ITT, Intention to treat; OS: Overall survival; PD-L1, Programmed death ligand-1; PFS, Progression free survival; RECIST, Response Evaluation Criteria in Solid Tumours; SOC, Standard of care

Quality assessment

[redacted]

Unpublished data

[redacted]

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14 Appendix B – Main characteristics of included studies

Table 52: Main study characteristics for CheckMate 648

Trial name: CheckMate 648	NCT number: NCT03143153
Objective	This study determines if nivolumab plus chemotherapy improves OS and/or PFS over SoC chemotherapy in patients with ESCC whose tumours express PD-L1 (TPS ≥1%) (European Medicin Agency 2022b). Additional objectives include further characterization of the efficacy, adverse event profile, pharmacokinetics, patient-reported outcomes, and potential predictive biomarkers of nivolumab plus chemotherapy in patients with ESCC
Publications – title, author, journal, year	Doki et al. (2022) Nivolumab Combination Therapy in Advanced Esophageal Squamous-Cell Carcinoma. NEJM, 386(5):449-462.
Study type and design	Randomized, global, open-label, phase 3 study Patient population: previously untreated unresectable, advanced, recurrent, or metastatic ESCC
Sample size (n)	N=970
Main inclusion and exclusion criteria	Inclusion Criteria: • Must have histologically confirmed squamous cell carcinoma or adenosquamous cell carcinoma of esophagus • Male or Female at least 18 years of age • Must have esophageal cancer that cannot be operated on, or treated with definitive chemoradiation with curative intent, that is advanced, reoccurring or has spread out • Must have full activity or, if limited, must be able to walk and carry out light activities such as light house work or office work • Must agree to provide tumor tissue sample, either from a previous surgery or biopsy within 6 months or fresh, prior to the start of treatment in this study Exclusion Criteria • Presence of tumor cells in the brain or spinal cord which are symptomatic or require treatment • Active known or suspected autoimmune disease • Any serious or uncontrolled medical disorder or active infection • Known history of positive test for human immunodeficiency virus or known acquired immunodeficiency syndrome • Any positive test result for hepatitis B or C indicating acute or chronic infection and/or detectable virus Other protocol defined inclusion/exclusion criteria could apply
Intervention	Nivolumab plus chemotherapy (fluorouracil plus cisplatin)
Comparator	Chemotherapy (fluorouracil plus cisplatin)
Follow-up time	MAR 2021: minimum follow-up of 12 months OCT 2021: minimum follow-up of 20 months

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Trial name: CheckMate 648	NCT number: NCT03143153
Is the study used in the health economic model?	Yes, market authorization trial for nivolumab plus chemotherapy or nivolumab plus ipilimumab for the first-line treatment of adults with ESCC
Primary, secondary and exploratory endpoints	**Primary endpoint:** • OS and PFS per BICR **Secondary endpoint:** • PFS in patients whose tumours express PD-L1 (TPS ≥1%) and all-comers per investigator (INV) • ORR in patients whose tumours express PD-L1 (TPS ≥1%) and all-comers per INV • Duration of response (DOR) per BICR and INV • Safety and tolerability
Method of analysis	OS and PFS as assessed by BICR in all subjects with tumor cell PD-L1 expression ≥ 1% were planned to be compared between nivolumab plus chemotherapy and chemotherapy alone using a two-sided log-rank test, stratified by: ECOG performance status (0 vs. 1); and number of organs with metastases (≤ 1 vs. ≥ 2). The HR of PFS and OS with its associated two-sided 100(1- α)% confidence intervals (CIs) were estimated via a stratified Cox model with treatment arm as the only covariate in the model. Median OS and PFS for each treatment arm were estimated and plotted using the Kaplan-Meier product-limit method. Median OS and PFS along with 95% CIs were constructed based on a log-log transformed CI for the survival function. Family-wise Type I error was protected in the strong sense across all primary and secondary endpoints. The p-values from sensitivity analyses for efficacy endpoints were for descriptive purposes only and not adjusted for multiplicity.
Subgroup analyses	Main subgroup analysis in concern for this submission is PD-L1 expressing patients
Other relevant information	n/a

Abbreviations: BICR, blinded independent central review; CI, Confidence interval; EORTC QLQ-C30, European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire; HR, Hazard ratio; INV, Investigator; OS: Overall survival; PD-L1, Programmed death ligand-1; PFS, Progression free survival; SOC, Standard of care; TPS, Tumor Proportion Score

Table 53: Main study characteristics for KEYNOTE 590

Trial name: KEYNOTE 590	NCT number: NCT03189719
Objective	The purpose of this trial is to evaluate efficacy and safety of pembrolizumab plus standard of care (SOC) chemotherapy with cisplatin and 5-fluorouracil (5-FU) versus placebo plus SOC chemotherapy with cisplatin and 5-FU as first-line treatment in participants with locally advanced or metastatic esophageal carcinoma
Publications – title, author, journal, year	Sun et al. (2021) Pembrolizumab plus chemotherapy versus chemotherapy alone for first-line treatment of advanced oesophageal cancer (KEYNOTE-590): a randomised, placebo-controlled, phase 3 study. Lancet
Study type and design	Randomized, double-blind, placebo-controlled, phase 3 study Patient population: locally advanced unresectable or metastatic adenocarcinoma or squamous cell carcinoma of the esophagus or advanced/metastatic Siewert type 1 adenocarcinoma of the esophagogastric junction

Trial name: KEYNOTE 590	NCT number: NCT03189719
Sample size (n)	ITT, N=749 For ESCC, n=548
Main inclusion and exclusion criteria	Inclusion Criteria: • Histologically- or cytologically-confirmed diagnosis of locally advanced unresectable or metastatic adenocarcinoma or squamous cell carcinoma of the esophagus or advanced/metastatic Siewert type 1 adenocarcinoma of the esophagogastric junction • Measurable disease per RECIST 1.1 as determined by the local site investigator/radiology assessment • Eastern Cooperative Group (ECOG) performance status of 0 to 1 • Newly obtained or archival tissue sample for PD-L1 by immunohistochemistry analysis • Female participants of childbearing potential must have a negative urine or serum pregnancy test within 72 hours prior to randomization and be willing to use an adequate method of contraception for the course of the study through 120 days after the last dose of study treatment and up to 180 days after last dose of cisplatin • Male participants of childbearing potential must agree to use an adequate method of contraception starting with the first dose of study treatment through 120 days after the last dose of study treatment and up to 180 days after last dose of cisplatin, and refrain from donating sperm during this period • Adequate organ function Exclusion Criteria • Locally advanced esophageal carcinoma that is resectable or potentially curable with radiation therapy (as determined by local investigator) • Previous therapy for advanced/metastatic adenocarcinoma or squamous cell cancer of the esophagus or advanced/metastatic Siewert type 1 adenocarcinoma of the esophagogastric junction • Had major surgery, open biopsy, or significant traumatic injury within 28 days prior to randomization, or anticipation of the need for major surgery during the course of study treatment • Known additional malignancy that is progressing or requires active treatment; Exceptions include early-stage cancers (carcinoma in situ or Stage 1) treated with curative intent, basal cell carcinoma of the skin, squamous cell carcinoma of the skin, in situ cervical cancer, in situ breast cancer that has undergone potentially curative therapy, and in situ or intramucosal pharyngeal cancer • Active central nervous system metastases and/or carcinomatous meningitis. • Active autoimmune disease that has required systemic treatment in past 2 years • Diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior to the first dose of study treatment, or has a history of organ transplant, including allogeneic stem cell transplant • History of (non-infectious) pneumonitis that required steroids or has current pneumonitis, or has an active infection requiring systemic therapy

Trial name: KEYNOTE 590	NCT number: NCT03189719
	• Pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the study, starting with the screening visit through 120 days after the last dose of study medication and up to 180 days after last dose of cisplatin • Received prior therapy with an anti-programmed cell death protein-1 (anti-PD-1), anti-PD-L1, or anti-PD-L2 agent or with an agent directed to another co-inhibitory T-cell receptor or has previously participated in a pembrolizumab clinical trial • Severe hypersensitivity (≥ Grade 3) to any study treatment (pembrolizumab, cisplatin, or 5-FU) and/or any of its excipients • Known history of active tuberculosis or human immunodeficiency virus (HIV) infection • Known history of or is positive for hepatitis B or hepatitis C • Received a live vaccine within 30 days prior to the first dose of study treatment • Radiotherapy within 14 days of randomization. Participants who received radiotherapy >14 days prior to randomization must have completely recovered from any radiotherapy-related AEs/toxicities
Intervention	Pembrolizumab plus chemotherapy (fluorouracil plus cisplatin)
Comparator	Placebo plus chemotherapy (fluorouracil plus cisplatin)
Follow-up time	Up to 34 months
Is the study used in the health economic model?	Yes, used in comparison to nivolumab plus chemotherapy

Primary, secondary and exploratory endpoints	**Primary endpoint:**
	• OS in:
	  ○ ESCC with PD-L1 CPS ≥ 10
	  ○ randomized participants with ESCC
	  ○ participants with PD-L1 CPS ≥ 10
	  ○ all participants
	• PFS per RECIST 1.1 investigator assessed in:
	  ○ ESCC
	  ○ with PD-L1 CPS ≥ 10
	  ○ in all patients
	Secondary endpoint:
	• ORR per RECIST 1.1 investigator assessed
	• DOR per RECIST 1.1 investigator assessed
	• Safety
	• EORTC QLQ-C30 GHS/QoL
	• EORTC QLQ-OES18

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Trial name: KEYNOTE 590	NCT number: NCT03189719
Method of analysis	Primary efficacy analyses were done in the intention-to treat population of all randomised patients. Safety was assessed in all randomised patients who received at least one dose of study treatment (the as-treated population). The Kaplan-Meier method was used to estimate OS, PFS, and DOR. Between-group differences in OS and PFS were assessed using a stratified log-rank test. Differences in objective response rate were assessed with the stratified Miettinen and Nurminen method. Between-group treatment effect (with a nominal 95% CI) across pre-specified subgroups was estimated for the primary endpoints in patients with ESCC and PD-L1 CPS of 10 or more, ESCC, PD-L1 CPS of 10 or more, and in all randomised patients. A stratified Cox proportional hazards model with Efron's method of tie handling was used to estimate HRs and associated 95% CIs. A prespecifed sensitivity analysis of PFS per RECIST version 1.1 by masked independent central review was done to assess the robustness of the PFS by investigator assessment endpoint. Exploratory analyses examined between-group treatment differences in patients by PD-L1 status, and in patients from Asian and non-Asian regions. A post-hoc analysis examined between-group treatment differences by histology and PD-L1 status.
Subgroup analyses	Main subgroup analysis in concern for this submission is ESCC and PD-L1 CPS ≥ 10 patients
Other relevant information	n/a

Abbreviations: 5-FU, Fluorouracil; BICR, blinded independent central review; CPS, Combined positive score; DOR, Duration of response; EORTC QLQ-C30, European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire; ESCC, Esophageal squamous cell carcinoma; ITT, Intention to treat; ORR, Objective response rate; OS: Overall survival; PD-L1, Programmed death ligand-1; PFS, Progression free survival; RECIST, Response Evaluation Criteria in Solid Tumours; SOC, Standard of care; TPS, Treatment proportion score

15 Appendix C – Baseline characteristics of patients in studies used for the comparative analysis of efficacy and safety

Characteristics	CheckMate 648		KEYNOTE 590	
	Nivolumab plus chemotherapy (n=321)	Chemotherapy (n=324)	Pembrolizumab plus chemotherapy (n=373)	Chemotherapy (n=376)
Median age (range), years	64.0 (40-90)	64.0 (26-81)	64 (28-94)	62 (27-89)
Mean age (SD), years	63.1 (9.2)	63.3 (8.7)	-	-
Male, n (%)	253 (78.8)	275 (84.9)	306 (82)	319 (85)
Race, n (%)				
Asian	227 (70.7)	227 (70.1)	201 (54)	199 (53)
Non-Asian	94 (29.3)	97 (29.9)	172 (46)	177 (47)
Region, n (%)				
Asia[a]	225 (70.1)	226 (69.8)	196 (53)	197 (52)
Non-Asia	96 (29.9)	98 (30.2)	177 (47)	179 (48)
ECOG PS, n (%)				
0	150 (46.7)	154 (47.5)	149 (40)	150 (40)
1	171 (53.3)	170 (52.5)	223 (60)	225 (60)
2	-	-	1 (<1)	1 (<1)
Not Reported	0 (0)	1 (0.3)	-	-
Disease stage at initial diagnosis, n (%)				
I-III	114 (35.5)	117 (36.1)	-	-
IV	206 (64.2)	206 (63.6)	-	-
Not Reported	1 (0.3)	1 (0.3)	-	-
Tumour location at initial diagnosis, n (%)				
Upper Thoracic	60 (18.7)	51 (15.7)	-	-
Middle Thoracic	121 (37.7)	134 (41.4)	-	-
Lower Thoracic	112 (34.9)	119 (36.7)	-	-
Gastroesophageal Junction	28 (8.7)	18 (5.6)	-	-
Not Reported	0 (0)	2 (0.6)	-	-
Disease status at current diagnosis, n (%)				
Metastatic	-	-	344 (92)	339 (90)
Recurrent – Loco-Regional	21 (6.5)	25 (7.7)	-	-
Recurrent – Distant	72 (22.4)	60 (18.5)	-	-

De Novo Metastatic[b]	184 (57.3)	187 (57.7)	-	-
Unresectable Advanced	44 (13.7)	52 (16.0)	29 (8)	37 (10)
Histology, n (%)				
Squamous cell carcinoma	311 (96.9)	318 (98.1)	274 (73)	274 (73)
Adenosquamous carcinoma	9 (2.8)	6 (1.9)	99 (27)	102 (27)
Other	1 (0.3)[b]	0 (0)	-	-
Tumour cell PD-L1 expression, n (%)				
≥ 1%	158 (49.2)	156 (48.5)	-	-
< 1% or indeterminate	163 (50.8)	168 (51.5)	-	-
CPS ≥ 10	-	-	186 (50)	197 (52)
CPS < 10	-	-	175 (47)	172 (46)
CPS status undetermined	-	-	12 (3)	7 (2)
Smoking status, n (%)				
Current of former smoker	254 (79)	256 (79)	-	-
Never smoked or unknown	67 (21)	68 (21)	-	-

[a]Asia consists of China, Hong Kong, Japan, Korea, Singapore, and Taiwan
[b]Implies metastatic disease at initial diagnosis
Abbreviations: CPS, Combined positive score; ECOG PS, Eastern Cooperative group performance score; PD-L1, programmed death ligand 1; SD, standard deviation
Source: (BMS CSR, 2021)(European Medicin Agency 2022b)

Comparability of patients across studies

Comparability of patients across studies described in Section 7.2 above.

Comparability of the study populations with Danish patients eligible for treatment

Differences between the study populations and the Danish patient population and how this affects transferability of results to Danish clinical practice are described in Section 8 above.

16 Appendix D – Efficacy and safety results per study

Definition, validity and clinical relevance of included outcome measures

[redacted]

Results per study

Table 54: Results for CheckMate 648

Results for CheckMate 648 (NCT03143153)												
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Median OS PD-L1 (TPS ≥1%) 20-month minimum	Nivolumab plus chemotherapy	158	15.0 (95% CI 11.93-18.63)	[redacted]	[redacted]		HR: 0.59	0.46–0.76		OS and PFS as assessed by BICR in all subjects with tumor cell PD-L1 expression ≥ 1% were planned to be compared between nivolumab plus chemotherapy and chemotherapy alone using a two-sided log-rank test, stratified by: ECOG performance status (0 vs. 1); and number of organs with metastases (≤ 1 vs. ≥ 2). The HR of PFS and OS with its associated two-sided 100(1-α)% confidence intervals (CIs) were estimated via a stratified Cox model with treatment arm as the only covariate in the model. Median OS and PFS for each	(BMS 2022, European Medicin Agency 2022b)
	Chemotherapy alone	157	9.1 (95% CI 7.69-10.02)								
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]			[redacted]
	[redacted]	[redacted]	[redacted]								
Median PFS PD-L1 (TPS ≥1%) 20-month minimum	Nivolumab plus chemotherapy	158	6.93 (95% CI 5.68–8.35)	[redacted]	[redacted]		HR: 0.66	0.50–0.87			(BMS 2022) (European Medicin Agency 2022b)
	Chemotherapy alone	157	4.44 (95% CI 2.89–5.82)								
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]			[redacted]
	[redacted]	[redacted]	[redacted]								

Results for CheckMate 648 (NCT03143153)								
ORR PD-L1 (TPS ≥1%) 20-month minimum	Nivolumab plus chemotherapy	158	53.2% (95% CI, 45.1–61.1)	[redacted]	[redacted]	2.07	1.91-3.82	treatment arm were estimated and plotted using the Kaplan-Meier product-limit method. Median OS and PFS along with 95% CIs were constructed based on a log-log transformed CI for the survival function. Family-wise Type I error was protected in the strong sense across all primary and secondary endpoints. The p-values from sensitivity analyses for efficacy endpoints were for descriptive purposes only and not adjusted for multiplicity.	(BMS 2022) (European Medicin Agency 2022b)
	Chemotherapy alone	157	19.7% (95% CI, 13.8–26.8)						
ORR PD-L1 (TPS ≥1%) 12-month minimum	Nivolumab plus chemotherapy	158	53.2% (95% CI, 45.1–61.1)	[redacted]	[redacted]	2.07	1.91-3.82		[redacted]
	Chemotherapy alone	157	19.7% (95% CI, 13.8–26.8)						
Median DOR PD-L1 (TPS ≥1%) 20-month minimum	Nivolumab plus chemotherapy	158	8.38 (95% CI 6.90–12.35)						(BMS 2022) (European Medicin Agency 2022b)
	Chemotherapy alone	157	5.68 (95% CI 4.40–8.67)						
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]
	[redacted]	[redacted]	[redacted]						
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]
	[redacted]	[redacted]	[redacted]						
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]
	[redacted]	[redacted]	[redacted]						

Results for CheckMate 648 (NCT03143153)											
[redacted]											

Abbreviations: 5-FU, Fluorouracil; AE, Adverse event; BICR, blinded independent central review; CI, Confidence interval; CPS, Combined positive score; DOR, Duration of response; HR, Hazard ratio; ORR, Objective response rate; OS: Overall survival; PD-L1, Programmed death ligand-1; PFS, Progression free survival; RECIST, Response Evaluation Criteria in Solid Tumours; SAE, Serious adverse event; SOC, Standard of care; TPS, Treatment proportion score; TRAE, Treatment related adverse event

Table 55: Results for KEYNOTE 590

Results for KEYNOTE 590 (NCT03189719)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Median OS ESCC PD-L1 (CPS ≥10) median 22.6-months	Pembrolizumab plus chemotherapy	143	13.9 (95% CI 11.1-17.7)	[redacted]	[redacted]		HR: 0.57	0.43-0.75	0.0001	Safety was assessed in all randomised patients who received at least one dose of study treatment (the as-treated population). The Kaplan-Meier method was used to estimate OS, PFS, and DOR. Between-group differences in OS and PFS	(Sun 2021b)
	Chemotherapy alone	143	8.8 (95% CI 7.8-10.5)								
Median PFS ESCC PD-L1 (CPS ≥10)	Pembrolizumab plus chemotherapy	143	6.3 (95% CI 6.2-6.9)	[redacted]	[redacted]		HR:0.65	0.54-0.78	0.0001		(Sun 2021b)

Results for KEYNOTE 590 (NCT03189719)									
median 22.6-months	Chemotherapy alone	143	5.8 (95% CI 5.0-6.0)					were assessed using a stratified log-rank test. Differences in ORR were assessed with the stratified Miettinen and Nurminen method. Between-group treatment effect (with a nominal 95% CI) across pre-specified subgroups was estimated for the primary endpoints in patients with ESCC and PD-L1 CPS. A stratified Cox proportional hazards model with Efron's method of tie handling was used to estimate HRs and associated 95% CIs. A pre-specified sensitivity analysis of PFS per RECIST version 1.1 by masked independent central review was done to assess the robustness of the PFS by investigator assessment endpoint.	
Any AE median 22.6-months	Pembrolizumab plus chemotherapy	370	370 (100%)	-	-	-	-		(Sun 2021b)
	Chemotherapy alone	370	368 (99%)						
Grade ≥3 AEs median 22.6-months	Pembrolizumab plus chemotherapy	370	318 (86%)	-	-	-	-		(Sun 2021b)
	Chemotherapy alone	370	308 (83%)						
AE leading to dis-contiuation median 22.6-months	Pembrolizumab plus chemotherapy	370	90 (24%)	-	-	-	-		(Sun 2021b)
	Chemotherapy alone	370	74 (20%)						
TRAE median 22.6-months	Pembrolizumab plus chemotherapy	370	364 (98%)	-	-	-	-		(Sun 2021b)
	Chemotherapy alone	370	360 (97%)						

Abbreviations: 5-FU, Fluorouracil; AE, Adverse event; CI, Confidence interval; CPS, Combined positive score; DOR, Duration of response; ESCC, Esophageal squamous cell carcinoma; HR, Hazard ratio; ORR, Objective response rate; OS: Overall survival; PD-L1, Programmed death ligand-1; PFS, Progression free survival; RECIST, Response Evaluation Criteria in Solid Tumours; SAE, Serious adverse event; SOC, Standard of care; TPS, Treatment proportion score; TRAE, Treatment related adverse event

17 Appendix E – Safety data for intervention and comparator

The safety data for the intervention and the comparator is described in Table 56 below. For the safety data, please also see the descriptions in Section 7.2 and Section 16, Appendix D.

Table 56: Safety data for nivolumab and chemotherapy versus pembrolizumab and chemotherapy

Patients, n (%)	CheckMate 648 20-month minimum follow-up				KEYNOTE 590 22.6-month median follow-up			
	Nivolumab plus Chemotherapy (n=310)		Chemotherapy (n=304)		Pembrolizumab plus chemotherapy (n=370)		Chemotherapy (n=370)	
	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4
All-Causality								
Any AEs	308 (99.4)	226 (72.9)	301 (99)	170 (55.9)	370 (100)	318 (86)	368 (99)	308 (83)
Serious AEs	186 (60.0)	145 (46.8)	130 (42.8)	100 (32.9)	NR	NR	NR	NR
AEs leading to discontinuation	130 (41.9)	56 (18.1)	81 (26.6)	33 (10.9)	90 (24)	NR	74 (20)	NR
TRAEs								
Any AEs	297 (95.8)	151 (48.7)	275 (90.5)	110 (36.2)	364 (98)	226 (72)	360 (97)	250 (68)
Serious AEs	74 (23.9)	58 (18.7)	49 (16.1)	40 (13.2)	NR	NR	NR	NR
TRAEs leading to discontinuation	106 (34.2)	30 (9.7)	63 (20.7)	18 (5.9)	NR	NR	NR	NR
Most common TRAEs, %[b]								
Nausea	59	4	52	3	63	7	59	6
Decreased appetite	43	4	43	3	39	4	32	4
Stomatitis	32	6	23	2	26	6	25	4
Anemia	30	10	22	6	39	12	44	15
Decreased neutrophil count	21	8	17	8	36	23	29	17
Fatigue	20	2	16	4	36	6	29	5
Diarrhea	19	1	15	2	26	3	23	2
Constipation	19	1	22	<1	14	0	17	0
Vomiting	18	2	16	3	30	6	27	5
Malaise	16	<1	15	0	12	1	11	1
Decreased white-cell count	14	4	9	2	24	9	19	5
Hiccups	14	0	17	0	11	0	9	0
Increase blood creatinine level	13	<1	11	<1	18	1	19	<1
Decreased platelet count	12	1	11	2	16	2	15	5

Mucosal inflammation	11	3	9	1	16	3	18	4
Alopecia	10	0	11	0	14	0	11	0
Hypothyroidism	6	0	0	0	10	0	6	0
Neutropenia	n/a	n/a	n/a	n/a	26	14	24	16
Asthenia	n/a	n/a	n/a	n/a	12	3	9	1
Decreased weight	n/a	n/a	n/a	n/a	12	1	13	2
Hyponatraemia	n/a	n/a	n/a	n/a	9	5	11	5
Leukopenia	n/a	n/a	n/a	n/a	6	2	8	33
Thrombcytopenia	n/a	n/a	n/a	n/a	7	1	9	3
Tinnitus	n/a	n/a	n/a	n/a	9	1	7	0
Hyperthyroidism	n/a	n/a	n/a	n/a	5	0	1	0
Increased aspartate aminotransferase	n/a	n/a	n/a	n/a	5	1	5	1
Decreased lymphocyte count	n/a	n/a	n/a	n/a	6	2	5	1
Dehydration	n/a	n/a	n/a	n/a	5	2	4	2
Hypokalaemia	n/a	n/a	n/a	n/a	9	5	11	5
Hypo-magnesaemia	n/a	n/a	n/a	n/a	6	1	4	1
Dysgeusia	n/a	n/a	n/a	n/a	9	0	9	0
Peripheral neuropathy	n/a	n/a	n/a	n/a	9	<1	9	0
Peripheral sensory neuropathy	n/a	n/a	n/a	n/a	9	<1	8	<1
Pneumonitis	n/a	n/a	n/a	n/a	5	2	0	0
Pruritus	n/a	n/a	n/a	n/a	6	<1	2	0
Rash	n/a	n/a	n/a	n/a	8	0	5	<1
AEs of special interest, immune mediated, %[c]								
Pneumonitis	3.7	2.2	0	0	6	1	1	<1
Diarrhea/Colitis	3.4	1.2	0	0	2	1	2	1
Hepatitis	4.0	2.8	0	0	1	1	0	0
Nephritis/Renal dysfunction	1.2	0.6	0	0	<1	0	1	<1
Rash	13.7	2.5	0.7	0.3	n/a	n/a	n/a	n/a
Hypersensitivity	0.3	0	0	0	n/a	n/a	n/a	n/a
Adrenal Insufficiency	5.6	2.2	0	0	1	1	1	0

Hypophysitis	6.5	3.1	0	0	1	<1	0	0
Hypothyroidism/ Thyroiditis	15.5	0.3	0	0	11	0	6	0
Hyperthyroidism	5.9	0.6	0.3	0	6	<1	1	0
Diabetes Mellitus/ Type 1 diabetes	1.6	0.6	0	0	<1	<1	0	0
Infusion reaction	n/a	n/a	n/a	n/a	2	<1	1	0
Severe skin reaction	n/a	n/a	n/a	n/a	1	1	1	1
Pancreatitis	n/a	n/a	n/a	n/a	1	0	<1	<1
Myositis	n/a	n/a	n/a	n/a	<1	<1	0	0
Thyroiditis	n/a	n/a	n/a	n/a	<1	<1	0	0

Abbreviations: AE, adverse events; TRAE, treatment related adverse events.

[a] Treatment-related grade 5 events included febrile neutropenia, diarrhoea, multiple organ dysfunction, hepatic failure, pneumonia, acute kidney injury, interstitial lung disease, pneumonitis, and pulmonary embolism, which each occurred in one patient in the pembrolizumab plus chemotherapy group, and febrile neutropenia, death, multiple organ dysfunction syndrome, sepsis, and interstitial lung disease, which each occurred in one patient in the placebo plus chemotherapy group.

[b] In CheckMate 648 AEs that occured in ≥ 10% of patients were reported, while in KEYNOTE 590, AEs that occurred in ≥5% were reported.

[c] For CheckMate 648, patients who received ≥1 dose of study treatment were included, where select TRAEs are those with potential immunologic etiology that require frequent monitoring/intervention, and consider events reported between first dose and 30 days after last dose of study drug. For KEYNOTE 590, Immune-mediated adverse events and infusion reactions were based on a list of terms specified by the sponsor, regardless of attribution to any study treatment by investigators.

[d] Differences in collecting and registering of safety data between CheckMate 648 and KEYNOTE 590 can effect comparibility of reported safety data outcomes .

Source: (Sun 2021b, Doki 2022)

18 Appendix F – Comparative analysis of efficacy and safety

Table 57: Comparative analysis of nivolumab plus chemotherapy to pembrolizumab plus chemotherapy

Table A4 Meta-analysis of studies comparing nivolumab plus chemotherapy to pembrolizumab plus chemotherapy for patients with advanced, metastatic, or recurrent ESCC

Outcome	Studies included in the analysis	Relative difference in effect			Method used for quantitative synthesis	Result used in the health economic analysis?
		Difference	CI	*P* value		
Overall survival	CheckMate 648 and KEYNOTE 590 (Sun 2021b, European Medicin Agency 2022b, European Medicin Agency 2022a, Metges 2022)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Progression free survival	CheckMate 648 and KEYNOTE 590 (Sun 2021b, European Medicin Agency 2022b, European Medicin Agency 2022a, Metges 2022)	[redacted]	[redacted]	[redacted]		[redacted]

Abbreviations: CI, Confidence interval; ESCC, Esophageal squamous cell carcinoma; SLR, Systematic literature review; TRAE, treatment related adverse events

19 Appendix G – Extrapolation

As a cost-min was performed, extrapolation methods were not required and this appendix is not relevant for the analysis.

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20 Appendix H – Literature search for HRQoL data

HRQoL data was not considered in the economic model, since a cost-min was preformed, and therefore, no SLR was required.

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21 Appendix I – Mapping of HRQoL data

As a cost-min was performed, HRQoL data is not relevant for the analysis.

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22 Appendix J – Probabilistic sensitivity analyses

As a cost-min was performed, a probabilistic sensitivity analys was not required for the analysis and only a one-way sensitivity analysis was performed.

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23 Appendix K – Disease staging

AJCC histological description: squamous cell esophageal cancer

Table 58: AJCC histological description for ESCC

AJCC Stage	Stage description of ESCC
0	The cancer is only in the epithelium (the top layer of cells lining the inside of the esophagus). It has not started growing into the deeper layers. This stage is also known as high-grade dysplasia. It has not spread to any lymph nodes or distant organs. The cancer grade does not apply. The cancer can be located anywhere in the esophagus.
IA	The cancer is growing into the lamina propria or muscularis mucosa (the tissue under the epithelium). It has not spread to any lymph nodes or distant organs. The cancer is grade 1 or an unknown grade and located anywhere in the esophagus.
IB	The cancer is growing into the lamina propria, muscularis mucosa (the tissue under the epithelium), submucosa or the thick muscle layer (muscularis propria). It has not spread to nearby lymph nodes or to distant organs. The cancer can be any grade or an unknown grade and located anywhere in the esophagus.
IIA	The cancer is growing into the thick muscle layer (muscularis propria). It has not spread to nearby lymph nodes or to distant organs. The cancer can be grade 2 or 3 or an unknown grade and located anywhere in the esophagus.
	OR
	The cancer is growing into the outer layer of the esophagus (the adventitia). It has not spread to nearby lymph nodes or to distant organs. The cancer can be any of the following: Any grade and located in the lower esophagus OR Grade 1 and located in the upper or middle esophagus.
IIB	The cancer is growing into the outer layer of the esophagus (the adventitia). It has not spread to nearby lymph nodes or to distant organs. The cancer can be any of the following: Grade 2 or 3 and located in the upper or middle of the esophagus OR An unknown grade and located anywhere in the esophagus OR Any grade and have an unknown location in the esophagus.
	OR
	The cancer is growing into the lamina propria, muscularis mucosa (the tissue under the epithelium) or into the submucosa. It has spread to 1 or 2 nearby lymph nodes. The cancer can be any grade and located anywhere in the esophagus.
IIIA	The cancer is growing into the lamina propria, muscularis mucosa (the tissue under the epithelium), submucosa or the thick muscle layer (muscularis propria). It has spread to no more than 6 nearby lymph nodes. It has not spread to distant organs. The cancer can be any grade and located anywhere in the esophagus.
IIIB	The cancer is growing into: The thick muscle layer (muscularis propria) and spread to no more than 6 nearby lymph nodes OR The outer layer of the esophagus (the adventitia) and spread to no more than 6 nearby lymph nodes OR The pleura (the thin layer of tissue covering the lungs), the pericardium (the thin sac surrounding the heart), or the diaphragm (the muscle below the lungs that separates the chest from the abdomen) and spread to no more than 2 nearby lymph nodes. It has not spread to distant organs. The cancer can be any grade and located anywhere in the esophagus.
IVA	The cancer is growing into: The pleura (the thin layer of tissue covering the lungs), the pericardium (the thin sac surrounding the heart), or the diaphragm (the muscle below the lungs that separates the chest from the abdomen) and spread to no more than 6 nearby lymph nodes OR The trachea (windpipe), the aorta (the large blood vessel coming from the heart), the spine, or other crucial structures and no more than 6 nearby lymph nodes OR

	Any layers of the esophagus and spread to 7 or more nearby lymph nodes. It has not spread to distant organs. The cancer can be any grade and located anywhere in the esophagus.
IVB	The cancer has spread to distant lymph nodes and/or other organs such as the liver and lungs. The cancer can be any grade and located anywhere in the esophagus.

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24 Appendix L – CheckMate 648 study results for the all-comer population

20-month minimum follow-up (all-comers)

24.1 Overall survival

Table 59: Analyses of OS for nivolumab plus chemotherapy versus chemotherapy alone for all-comers

Subgroup	Median OS, months		Unstratified HR (95% CI)
	Nivolumab + chemotherapy (n=321)	Chemotherapy alone (n=324)	
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]

12-month minimum follow-up (all-comers)

24.2 Overall survival (all-comers)

[redacted] The OS curves showed sustained separation favouring nivolumab plus chemotherapy beyond six months consistent with the pattern observed with nivolumab plus chemotherapy in solid tumours (Figure 19) (Kato 2019).

[redacted] In several studies investigating the outcomes of patients with advanced ESCC after 1L chemotherapy, median OS did not exceed 1 year (Ross 2002, Cao 2009, Wang 2013, Davidson 2017, Kato 2019). Moreover, ESCC is an aggressive disease that requires immediate treatment (Cheng 2018). [redacted]

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[redacted]

24.3 Progression-free survival (all-comers)

[redacted]

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Table 61: Exploratory PFS analyses for all-comers

	Nivolumab plus chemotherapy (n=321)		Chemotherapy alone (n=324)		PFS HR (95% CI) nivolumab plus chemotherapy vs chemotherapy alone	p-value
	Event No. (%)	mPFS, months (95% CI)	Event No. (%)	mPFS, months (95% CI)		
PFS per BICR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PFS per BICR accounting for assessment on/after subsequent therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PFS per INV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PFS2/TSST per INV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; INV, investigator; N.A., not available; No, number; PFS, progression-free survival; PFS2; time to second objective disease progression; TSST, time to subsequent therapy
Source: [redacted]

[redacted]

Table 62: Censor of patients per BICR

Per BICR	Nivolumab plus chemotherapy (n=321)	Chemotherapy alone (n=324)
Patients censored due to subsequent therapy (primary PFS definition), n (%)	[redacted]	[redacted]
Patients with PFS event after subsequent therapy, n (%)	[redacted]	[redacted]
Duration between subsequent therapy date and following PFS event date, median (min, max)	[redacted]	[redacted]

Abbreviations: BICR, blinded independent central review; max, maximum; min, minimum; PFS, progression-free survival
Source: [redacted]

[redacted]

Table 63: Censor of patients per INV

Per INV	Nivolumab plus chemotherapy (n=321)	Chemotherapy alone (n=324)
Patients censored due to subsequent therapy (primary PFS definition), n (%)	[redacted]	[redacted]
Patients with PFS event after subsequent therapy, n (%)	[redacted]	[redacted]
Duration between subsequent therapy date and following PFS event date, median (min, max)	[redacted]	[redacted]

Abbreviations: INV, investigator max, maximum; min, minimum; PFS, progression-free survival
Source: [redacted]

24.4 Objective response rate (all-comers)

[redacted]

[redacted]

Table 64. Response rates for all-comers

	Nivolumab plus chemotherapy (n=321)	Chemotherapy alone (n=324)
Objective response rate, n (%)	[redacted]	[redacted]
Best overall response, n (%)		
Complete response	[redacted]	[redacted]
Partial response	[redacted]	[redacted]
Stable disease	[redacted]	[redacted]
Progressive disease	[redacted]	[redacted]
Unable to determine	[redacted]	[redacted]

Abbreviations: CI, confidence interval
Source: [redacted]

24.5 Duration of response (all-comers)

[redacted]

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[redacted]

24.6 Subsequent therapy (all-comers)

[redacted]

24.7 Patient-reported outcomes (all-comers)

[redacted]

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24.8 EQ-5D (all-comers)

[redacted]

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[redacted]

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

[redacted]

[redacted]

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[redacted]

[redacted]

Table 65: FACT-E treatment arm least squares mean difference in the patient-reported outcomes, all-comers

FACT-E	LSM change from baseline (+/- SE)		Treatment arm difference LSM (95% CI) P value
	Nivolumab plus chemotherapy	Chemotherapy alone	
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			

[redacted]

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25 Appendix M – CheckMate 648 study results in the patient population whose tumours express PD-L1 (TPS ≥1%), minimum 12-month follow-up

25.1 Overall survival [(tumours express PD-L1 (TPS ≥1%)])

[redacted]

25.2 Progression-free survival [(tumours express PD-L1 (TPS ≥1%)]

[redacted]

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[redacted]

[redacted]

25.3 Objective response rate (PD-L1 expressing tumours)

[redacted]

[redacted]

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Table 66: Response rates for patients whose tumours express PD-L1 (TPS ≥1%) (12-month minimum follow-up)

	Nivolumab plus chemotherapy (n=158)	Chemotherapy alone (n=157)
Objective response rate, n (%)	[redacted]	[redacted]
Best overall response, n (%)		
Complete response	[redacted]	[redacted]
Partial response	[redacted]	[redacted]
Stable disease	[redacted]	[redacted]
Progressive disease	[redacted]	[redacted]
Unable to determine	[redacted]	[redacted]

Abbreviations: CI, Confidence interval; PD-L1: Programmed death ligand-1; TPS, Treatment proportion score
Source: [redacted]

[redacted]

25.4 Duration of response (PD-L1 expressing tumours)

[redacted]

[redacted]

25.5 Safety: nivolumab plus chemotherapy (12-month minimum follow-up)

[redacted]

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25.5.1 Treatment exposure

[redacted]

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Table 67: Exposure summary for all-comers (safety population: n=626)(12-month minimum follow-up)

Characteristic	Interventional arm			Comparator arm	
	Nivolumab[a] (n=310)	Cisplatin[a] (n=310)	5-FU[a] (n=310)	Cisplatin (n=304)	5-FU (n=302)
[redacted]					

[redacted]

25.5.2 Adverse events

The safety of treatment with nivolumab plus chemotherapy was consistent with that of other trials in gastroesophageal and other solid tumours (Kanda 2016, Moehler 2020). It was also consistent between pre-specified subgroups (PD-L1 status, geographical regions) and the overall study population.

[redacted]

Table 68: Safety summary for all treated patients (safety population: n=614) (12-month minimum follow-up)

Patients, n (%)	Nivolumab plus Chemotherapy[a] (n=310)		Chemotherapy alone[a] (n=304)	
	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4
[redacted]				

[redacted]

25.5.3 Selected treatment-related adverse events with potential immunologic etiology

[redacted]

Table 69: Treatment-related select adverse events with potential immunologic etiology for all-randomized treated patients (safety population: n=314) (12-month minimum follow-up)

Select TRAEs[b,c], %	Nivolumab[a] plus chemotherapy (n=310)		Chemotherapy alone[a] (n=304)	
	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4
Pneumonitis	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhea/Colitis	[redacted]	[redacted]	[redacted]	[redacted]
Hepatitis	[redacted]	[redacted]	[redacted]	[redacted]
Nephritis/Renal dysfunction	[redacted]	[redacted]	[redacted]	[redacted]
Rash	[redacted]	[redacted]	[redacted]	[redacted]
Adrenal Insufficiency	[redacted]	[redacted]	[redacted]	[redacted]
Hypophysitis	[redacted]	[redacted]	[redacted]	[redacted]

Hypothyroidism/Thyroiditis	[redacted]	[redacted]	[redacted]	[redacted]
Hyperthyroidism	[redacted]	[redacted]	[redacted]	[redacted]
Diabetes Mellitus	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

[redacted]

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