Medicinrådet

Bilag til Medicinrådets anbefaling vedrørende nivolumab i kombination med kemoterapi til 1. linje-behandling af fremskredent HER2-negativ adenokarcinom i mavesæk, mavemund eller spiserør og PD-L1 CPS ≥ 5

Vers. 1.0

Bilagsoversigt

1. Ansøgers notat til Rådet vedr. nivolumab i kombination med kemoterapi
2. Forhandlingsnotat fra Amgros vedr. nivolumab i kombination med kemoterapi
3. Ansøgers endelige ansøgning vedr. nivolumab i kombination med kemoterapi

Bristol Myers Squibb
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Virum, 23. september 2022.

Til Medicinrådet

Bristol Myers Squibbs tilbagemelding på udkast til vurderingsrapport for nivolumab i kombination med kemoterapi til behandling af HER2-negative adenokarcinomer i mavesæk, mavemund eller spiserør med en PD-L1 CPS ≥ 5

Bristol Myers Squibb (BMS) imødeser Medicinrådets anbefaling vedr. nivolumab i kombination med kemoterapi til behandling af 1. liniebehandling af fremskredent HER2-negativ adenokarcinom i mavesæk, mavemund eller spiserør og PD-L1 CPS ≥ 5, planlagt til d. 26. oktober 2022, ca. 10 måneder efter MR modtog ansøgningen d. 17. december 2021.

BMS takker hermed for muligheden for at give en tilbagemelding på udkastet.

Indledningsvis glæder BMS sig over, Medicinrådet i det store hele er enig i antagelserne, et effektivt samarbejde med sekretariatet, samt at sagsbehandlingstiden siden Dag 0 er reduceret i forhold til tidligere sager.

BMS er dog uforstående over for Medicinrådets praksisændring; at man *ikke* kan dele hætteglas mellem patienterne. Denne ændring medfører et væsentligt medicinspild ikke kun for nærværende behandling, men også for behandlinger til øvrige sygdomme.

Dette har ikke været gængs praksis i tidligere BMS-ansøgninger og er heller ikke tilfældet i andre anbefalinger udstedt af Medicinrådet, som f.eks. ansøgningen om brug af et lægemiddel med samme virkningsmekanisme til en lignende patientgruppe (pembrolizumab i kombination med kemoterapi til patienter med kræft i spiserøret eller den gastro-esofageale overgang (KEYNOTE 590), anbefalet 26.januar 2022).

Fra et økonomisk og miljømæssigt perspektiv virker det forkert at smide effektiv medicin ud og det synes ikke at repræsentere egentlig praksis på de behandlende afdelinger i Danmark (jf. Medicinrådets egne tidligere anbefalinger af behandlinger til lignende og andre indikationer).

Slutteligt vil BMS gerne opfordre til, at medicin bliver vurderet på lige vilkår.

Hvis nye lægemidler eller indikationer skal evalueres med medicinspild, så bør man sikre en ens praksis gældende for alle relevante lægemidler således, at behandlingsomkostninger med komparator i alle tilfælde også inkluderer medicinspild.

Med venlig hilsen,

Anders Thelborg
Adm. direktør
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26. september 2022
DBS/CAF

Forhandlingsnotat

Dato for behandling i Medicinrådet	26.10.2022
Leverandør	BMS
Lægemiddel	Opdivo (nivolumab)
Ansøgt indikation	OPDIVO i kombination med fluoropyrimidin- og platinbaseret kombinationskemoterapi er indiceret til førstelinjebehandling af voksne patienter med HER2-negativ fremskredent eller metastatisk adenokarcinom i ventrikel, gastroøsofageal junction eller esofagus, hvis tumorer udtrykker PD-L1 med en kombineret positiv score (CPS) ≥ 5.

Forhandlingsresultat

Amgros har følgende pris på Opdivo (nivolumab).

Tabel 1: Forhandlingsresultat Opdivo (nivolumab)

Lægemiddel	Styrke/dosis/	Pakningsstørrelse	AIP (DKK)	Forhandlet SAIP (DKK)	Rabatprocent ift. AIP
Opdivo (nivolumab)	240 mg/24 ml	1 stk.	22.003,74	[redacted]	[redacted]
Opdivo (nivolumab)	100 mg/10 ml	1 stk.	9.168,23	[redacted]	[redacted]
Opdivo (nivolumab)	40 mg/4 ml	1 stk.	3.690,68	[redacted]	[redacted]

Prisen vil være gældende indtil 31.12.2023.

[redacted]

Konkurrencesituationen

Der er på nuværende tidspunkt ingen konkurrence på Opdivo (nivolumab) til denne indikation. Keytruda (pembrolizumab) i kombination med kemoterapi er godkendt til behandling af lokalt fremskredent inoperabelt eller metastatisk karcinom i spiserøret eller HER2-negativ adenokarcinom i den gastro-esofageale overgang. Der er et overlap på 16% mellem patientpopulationerne.

[redacted]

Tabel 2: Sammenligning af lægemiddelpriser på 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 68 kg jf. Medicinrådets vurderingsrapport på Opdivo (nivolumab)

Status fra andre lande

Norge: Under vurdering[1].
Sverige: Anbefalet[2].
England: Under vurdering[3].

Konklusion

[redacted]

[1] Nivolumab (Opdivo) - Indikasjon XV (nyemetoder.no)
[2] NT-rådets generella rekommendation för PD-(L)1-hämmare - Janusinfo.se
[3] Project information | Nivolumab with platinum- and fluoropyrimidine-based chemotherapy for untreated HER2-negative advanced gastric, gastro-oesophageal junction or oesophageal adenocarcinoma [ID1465] | Guidance | NICE

Application for the assessment of Opdivo®, in combination with fluoropyrimidine- and platinum-based combination chemotherapy, for the first-line treatment of adult patients with HER-2 negative advanced or metastatic gastric, gastro-esophageal junction or esophageal adenocarcinoma whose tumours express PD-L1 with a CPS ≥ 5

Disclaimer

Bristol-Myers Squibb (BMS) Pharma EEIG considers that the information provided is not available in the public domain and contains confidential information and personal data relevant to the EU regulatory reviewers, that we have been asked by the EMA to remove. We are providing this information to DMC only for the purpose of DMC exercising its public health duties in relation to the assessment of the Medicinal Product Opdivo (nivolumab). In the event that a 3rd party requests access to this information, BMS Pharma EEIG must be informed and the requested information can only be disclosed after written agreement by BMS Pharma EEIG.

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1. Basic information

Contact information	
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Overview of the pharmaceutical	
Proprietary name	Opdivo®
Generic name	Nivolumab
Marketing authorization holder in Denmark	Bristol-Myers Squibb
ATC code	L01XC17
Pharmacotherapeutic group	Antineoplastic agents, monoclonal antibodies
Active substance(s)	Nivolumab
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	360 mg nivolumab administered intravenously over 30 minutes in combination with fluoropyrimidine- and platinum-based chemotherapy administered every 3 weeks or 240 mg nivolumab administered intravenously over 30 minutes in combination with fluoropyrimidine and platinum-based chemotherapy administered every 2 weeks
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)	OPDIVO in combination with fluoropyrimidine- and platinum-based combination chemotherapy for the first-line treatment of adult patients with HER-2 negative advanced or metastatic gastric, gastro-esophageal juntion or esophageal adenocarcinoma whose tumours express PD-L1 with a combined positive score (CPS) ≥ 5
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.

Overview of the pharmaceutical	
	Relative to nivolumab monotherapy, an increase in progression-free survival and overall survival 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** 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** OPDIVO in combination with ipilimumab is indicated for the first-line treatment of adult patients with unresectable malignant pleural mesothelioma. **Renal cell carcinoma** 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** OPDIVO as monotherapy is indicated for the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma after autologous stem cell transplant and treatment with brentuximab vedotin. **Squamous cell cancer of the head and neck** 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. **Mismatch repair deficient or microsatellite instability high colorectal cancer** OPDIVO in combination with ipilimumab is indicated for the treatment of adult patients with mismatch repair deficient or microsatellite instability-high metastatic colorectal cancer after prior fluoropyrimidine-based combination chemotherapy. **Esophageal squamous cell carcinoma** 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 oesophageal or gastro-oesophageal junction cancer**

Overview of the pharmaceutical	
	OPDIVO as monotherapy is indicated for the adjuvant treatment of adult patients with oesophageal or gastro-oesophageal junction cancer who have residual pathologic disease following prior neoadjuvant chemoradiotherapy.
Will dispensing be restricted to hospitals?	Yes
Combination therapy and/or co-medication	Yes
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

2. Abbreviations

Abbreviation	Description of abbreviation
ADA	Anti-drug antibody
AE	Adverse event
AFT	Accelerated failure time
AIC	Akaike's information criterion
AIDS	Acquired immunodeficiency syndrome
AUP	Average unit price
BIC	Bayesian Information Criterion
BICR	Blinded independent central review
BID	Twice daily
BSA	Body surface area
CEAC	Cost-effectiveness acceptability curve
CI	Confidence interval
CPS	Combined positive score
CR	Complete response
DBL	Database lock
DEGC	Dansk Esophago-Gastrisk Cancer Gruppe
DKK	Danish krone
DMC	Danish Medicines Council
DOR	Duration of response
DRR	Durable response rate
DSA	Deterministic sensitivity analyses
DSU	Decision support unit
EAC	Esophageal adenocarcinoma

Abbreviation	Description of abbreviation
EC	Esophageal cancer
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
EQ-5D	EuroQoL-5 Dimension questionnaire
ESCC	Esophageal squamous cell carcinoma
ESMO	European Society for Medical Oncology
FACT-Ga	Functional Assessment of Cancer Therapy – Gastric
FOLFOX	Folinic acid, fluorouracil and oxaliplatin
FU	Follow-up
GC	Gastric cancer
GEJ	Gastro-esophageal junction
GEJC	Gastro-esophageal junction cancer
HER-2	Human epidermal growth factor receptor 2
HIV	Human immunodeficiency virus
HR	Hazard ratio
HSUV	Health state utility value
HTA	Health technology assessment
HUI	Health Utility Index
ICER	Incremental cost-effectiveness ratio
IHC	Immunohistochemistry
IMAE	Immune-mediated adverse event
IPI	Ipilimumab
IQR	Interquartile range
IRT	Item response theory
ITT	Intention-to-treat
IV	Intravenous
KM	Kaplan-Meier
KOL	Key opinion leader
MRI	Magnetic resonance imaging
MSI	Microsatellite instability
MSS	Microsatellite stable
N/A	Not available
NCCN	National Comprehensive Cancer Network
NICE	National Institute for Health and Care Excellence
NIVO	Nivolumab
OR	Odds Ratio
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease

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Abbreviation	Description of abbreviation
PD-L1	Programmed death-ligand 1
PF	Progression free
PFS	Progression-free survival
PH	Proportional hazard
PICO	Population, Interventions, Comparators, Outcomes, and Study design
PR	Partial response
PRO	Patient-reported outcome
PS	Performance status
PSA	Probabilistic sensitivity analysis
QALY	Quality-adjusted life year
QD	Once daily
RCT	Randomised controlled trial
RECIST	Response Evaluation Criteria in Solid Tumours
ROW	Rest of the world
SAE	Serious adverse event
SD	Stable disease
SE	Standard error
SLR	Systematic Literature Review
TMB	Tumour mutational burden
TPS	Tumour proportion score
TRAE	Treatment-related adverse event
TSST	Time to second subsequent line therapy
TTD	Time to treatment discontinuation
TTR	Time to treatment response
TTSD	Time to symptom deterioration
UI	Utility Index
UK	United Kingdom
US	United States
USA	United States of America
VAS	Visual analogue scale
VAT	Value added tax
WHO	World Health Organisation
WTP	Willingness to pay
XELOX	Capecitabine plus oxaliplatin

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3. Tables and Figures

3.1 List of Tables

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4. Summary

On October 21 2021, the European Commission approved nivolumab in combination with fluoropyrimidine- and platinum-based combination chemotherapy, for the **first-line treatment of adult patients with HER-2 negative advanced or metastatic gastric, gastro-esophageal junction or esophageal adenocarcinoma whose tumours express PD-L1 with a combined positive score (CPS) ≥ 5** (European Commission 2021).

Nivolumab is a human immunoglobulin-G subclass 4 (IgG4) monoclonal antibody that binds to the programmed cell death protein-1 (PD-1) receptor and blocks its interaction with the two ligands that are specific to PD-1 (PD-L1 and PD-L2).

Gastroesophageal cancer is a heterogeneous disease that is typically segmented into three distinct entities: esophageal cancer (EC), gastroesophageal junction cancer (GEJC), and gastric cancer (GC). There are two major histological subtypes of EC: esophageal squamous cell carcinoma (ESCC), the most common histological EC type, and esophageal adenocarcinoma (EAC) which makes up a small proportion of EC (Arnold 2020).

Based on the Dansk Esophago-Gastrisk Cancer Gruppe (DEGC) 2019 annual report, 224 cases of GC, 278 cases of EC (of which 2 cases are of EAC), and 617 cases of GEJC across disease stages were registered in Denmark in 2019 (N=1119) (DECV 2019, DEGC 2020a, DEGC 2021). Of these patients, 198 are estimated to received palliative treatment (DECV 2019, DEGC 2020a, DEGC 2021).

Mortality remains high in patients with GC, GEJC and EAC, mainly due to diagnosis at a late stage and the overall poor prognosis (DEGC 2020b).

Overall, the 1-year and 5-year relative survival rates for GC in Denmark were 58% and 28% in males and 61% and 34% in females, respectively (based on 2015–2019 data) (NORDCAN 2019b, NORDCAN 2019a). Survival rates in GC, GEJC, and EC patients treated with palliative chemotherapy are low, with a 1-year survival rate of 34.3% after starting the first systemic therapy (DEGC 2020a), **highlighting an unmet need for treatments that can improve survival** in these patients. In the Danish guidelines, the **current standard of care** is a two-compound combination therapy of a fluoropyrimidine and a platinum, or a triplet of a fluoropyrimidine, a platinum and a taxane, depending on the treatment goals, side effects profile and patient request (DEGC 2020a).

In Denmark, the XELOX comparator in the CheckMate 649 trial is the most appropriate comparator aligned to Danish clinical practice. As stated previously by the DMC, if treatment regimens can be considered equivalent, it is sufficient to only use one as a comparator (Medicinrådet 2021b).

The pivotal trial, CheckMate 649, is a global, phase 3 randomised, multicentre, open-label, active-controlled study to evaluate nivolumab plus chemotherapy in the first-line treatment of patients with previously untreated, unresectable, non-HER-2-positive GC, EC, or GEJC, and histologically confirmed predominant adenocarcinoma, regardless of PD-L1 expression (Janjigian 2021b). The dual primary endpoints in CheckMate 649 for the nivolumab plus chemotherapy versus chemotherapy alone arms were OS and PFS (as assessed by blinded independent central review [BICR]) in patients with PD-L1 positive tumours defined by CPS ≥5. Key secondary endpoints were OS in PD-L1 CPS ≥1, CPS ≥ 10 or all randomised patients, PFS (BICR assessed) in PD-L1 CPS ≥1, CPS ≥ 10 or all randomised patients and ORR (Moehler 2020b, Janjigian 2021b). Baseline characteristics for patients enrolled in CheckMate 649 were comparable to Danish population (Janjigian 2021b). Table 1 summarises the OS and PFS study outcomes.

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Table 1: CheckMate 649 outcomes for patients with PD-L1 CPS ≥5 at minimum follow-up times of 12.1 and 24.0 months

	Minimum 12.1 month follow-up		Minimum 24.0 month follow-up	
	Nivolumab plus chemotherapy	Chemotherapy alone	Nivolumab plus chemotherapy	Chemotherapy alone
Median overall survival, months (95% CI)	14.4 (13.1–16.2)	11.1 (10.0–12.1)	14.1 (13.1–16.2)	11.1 (10.0–12.1)
Hazard ratio	0.71 (98.4% CI, 0.59–0.86)		0.70 (95% CI, 0.61–0.81)	
Median progression-free survival, months (95% CI)	7.7 (7.0–9.2)	6.0 (5.6–6.9)	8.1 (7.0–9.2)	6.1 (5.6–6.9)
Hazard ratio	0.68 (98% CI, 0.56–0.81)		0.70 (95% CI, 0.60–0.81)	

Abbreviations: CI: confidence interval; CPS: combined positive score; PD-L1: programmed cell death 1
Reference: (Janjigian 2021a, Janjigian 2021b)

- For the **OS primary endpoint,** there was a 29% reduction in the risk of death compared with chemotherapy alone, in patients with PD-L1 CPS ≥5 (HR 0.71 [98.4% CI, 0.59–0.86]; P<0.0001) at a minimum follow-up of 12.1 months. The median OS in the nivolumab plus chemotherapy arm vs. the chemotherapy alone arm was 14.4 months (95% CI, 13.1–16.2) vs. 11.1 months (95% CI, 10.0–12.1), respectively (Janjigian 2021b).
- **At a minimum follow-up of 24.0 months, nivolumab plus chemotherapy maintained clinically meaningful improvements in OS** compared to chemotherapy alone in patients with PD-L1 CPS ≥5 (HR: 0.70 [95% CI, 0.61–0.81]; Figure 5) (Janjigian 2021a). Median OS was 14.1 months (95% CI, 13.1–16.2) in the nivolumab plus chemotherapy arm and 11.1 months (95% CI, 10.0–12.1) in the chemotherapy alone arm (Janjigian 2021a).
- For the **PFS primary endpoint,** there was a 32% reduction in the risk of progression per BICR compared with chemotherapy (HR: 0.68 [98% CI, 0.56–0.81]; P<0.0001) (Janjigian 2021b), in patients with PD-L1 CPS ≥5, at a minimum follow-up of 12.1 months. Median PFS was 7.7 (95% CI, 7.0–9.2) vs 6.0 (95% CI, 5.6–6.9) months in the nivolumab plus chemotherapy vs. chemotherapy alone arms, respectively (Janjigian 2021b).
- **At minimum follow-up of 24.0 months, PFS benefit was maintained for nivolumab plus chemotherapy** compared with chemotherapy alone (HR: 0.70 [95% CI, 0.60–0.81]; Figure 8) (Janjigian 2021a). Median PFS was 8.1 (95% CI, 7.0–9.2) vs. 6.1 (95% CI, 5.6–6.9) months in the nivolumab plus chemotherapy vs. chemotherapy alone arm, respectively (Janjigian 2021a).

Patients with PD-L1 CPS ≥5 who were treated with nivolumab plus chemotherapy had higher **ORR** rate compared with chemotherapy alone at a minimum follow-up of 12.1 months (59.8% [95% CI, 54.7–64.8] vs. 45.3% [95% CI, 40.3–50.4], respectively) (Janjigian 2021b). At longer follow-up of 24.0 months, ORR rates remained similar in both groups; however, **complete response rates increased from 11.6% to 13% in the nivolumab plus chemotherapy group compared with 6.9% to 7% in the chemotherapy alone arm** (Janjigian 2021a)**.**

[redacted]

The **safety profile** for nivolumab plus chemotherapy in CheckMate 649 was consistent with the known safety profiles for both nivolumab and chemotherapy administered either as monotherapy or in combination (Janjigian 2021b).

As the standard of care in Denmark corresponds to the comparator in CheckMate 649, no indirect treatment comparison was performed.

The yearly number of Danish patients with **HER-2 negative advanced or metastatic gastric, gastro-esophageal junction or esophageal adenocarcinoma, whose tumours express PD-L1 with a CPS ≥ 5,** who are eligible for nivolumab plus chemotherapy is estimated to be approximately 86 patients. Assuming a market share of 50% for nivolumab plus chemotherapy in year one and in later years 100% would result in [redacted]

The cost-effectiveness analysis show that **nivolumab plus chemotherapy** [redacted]

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5. The patient population, the intervention and choice of comparator

5.1 The medical condition and patient population

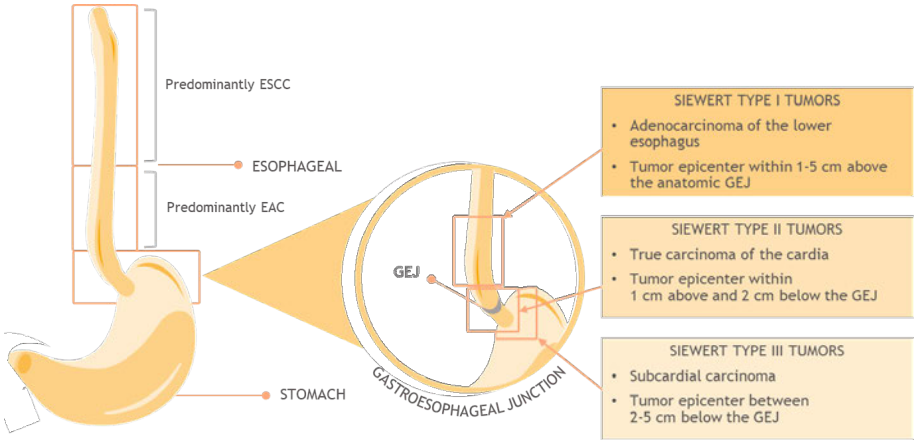
5.1.1 Disease description

Gastroesophageal cancer is a heterogeneous disease and is characterised by tumours in the esophagus, the gastroesophageal junction (GEJ) or stomach regions of the digestive system. Thus, it is typically segmented into three distinct entities (Figure 1):

- Esophageal cancer (EC)
  - squamous cell carcinoma (ESCC)
  - adenocarcinoma (EAC)
- Gastroesophageal junction (cardia) cancer (GEJC)
- Gastric (non-cardia) cancer (GC)

Around 90% of GC and GEJC are adenocarcinomas (Cancer Genome Atlas Research 2017). The most common type of EC is ESCC, only a small proportion is EAC. GC, GEJC, and EAC are biologically and genetically similar, and generally treated in a similar manner (Smyth 2016, Helsedirektoratet 2018, JGCA 2018, Wang 2019, DEGC 2020a, Helsedirektoratet 2020, NCCN 2020). This document will refer to EC data (encompassing both the EAC and ESCC subtypes) when no specific EAC data is available.

Figure 1: Three types of gastroesophageal cancer



Abbreviations: EAC: esophageal adenocarcinoma; ESCC: esophageal squamous cell carcinoma; GEJ: gastroesophageal junction.
Reference: (Zhang 2012, Cancer Research UK 2018, Ajani 2019)

GC, including GEJC, is a heterogeneous disease with several established risk factors, including environmental, genetic, and behavioral factors. The etiology of this disease is complex and multifactorial. H. pylori is a major risk factor for GC in Western countries, but not for GEJC (Cavaleiro-Pinto 2011, Karimi 2014). Additional risk factors for both GC and GEJC include older age, male sex, tobacco smoking, race, family history, low physical activity, low fiber intake, and radiation exposure (Karimi 2014).

As part of the molecular subtyping of GC, GEJC and EAC, several biomarkers with prognostic and predictive value have been identified (Elimova 2015, Jin 2015, Kang 2020). These include: HER-2, MSI-H/dMMR, PD-L1, TMB, and cMET and VEGFR2:

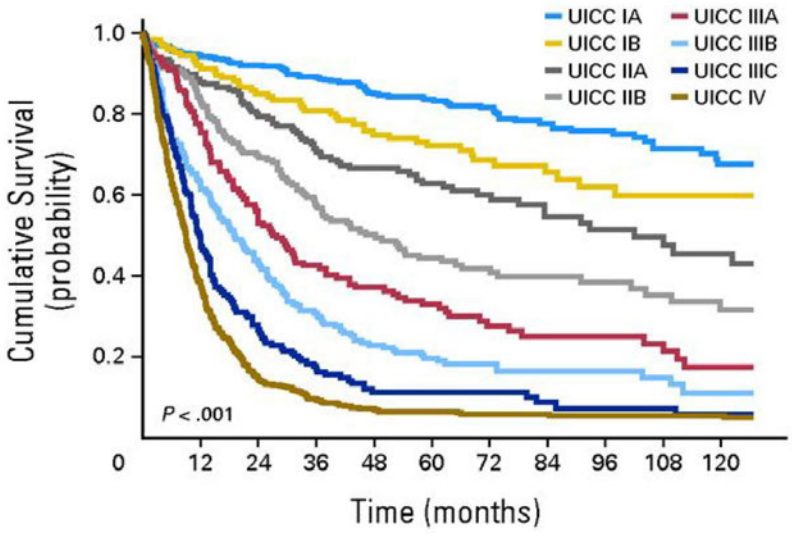
- HER2-positivity is detected in 15–20% of patients with GC (Jorgensen 2012, Curea 2017) and in around 23% of EAC cases (range, 0–52%) (Mohamed 2014).
- MSI-H pooled prevalence has been estimated at 11% (9–12%) and dMMR pooled prevalence was estimated at 8% for gastric cancers (2–17%) (Lorenzi 2020)
- PD-L1 expression occurs in 25–65% of gastric tumours, and status may change as a result of treatment or as the disease progresses (Chung 2016, Janjigian 2017, Kang 2017).
    - There are two key methods for scoring PD-L1: tumour proportion score (TPS) and combined positive score (CPS) (Sundar 2020). TPS involves the measurement of PD-L1 expression only within the tumour cell, whereas CPS was developed to consider the expression of PD-L1 on tumour cells and immune cells combined (Sundar 2020). CPS has shown better enrichment for efficacy of checkpoint inhibitors than tumour cell PD-L1 expression in advanced gastric, gastro-esophageal junction, or esophageal adenocarcinoma (Kulangara 2018, Shitara 2018, Lei 2019).

5.1.2 Epidemiology

Gastric cancer (including GEJC) is the fifth most common cancer worldwide, with an estimated 1.09 million new cases and age-standardised incidence of 11.1 per 100,000, representing 5.6% of all new cancer cases in 2020 (GLOBOCAN 2020). In 2018, an estimated 181,000 carcinoma cases occurred in the GEJ and 853,000 in the stomach (Arnold 2020). Danish epidemiology data is included in section 5.1.5 of this submission.

The 5-year survival rate is lower for patients with advanced or metastatic disease compared to patients with locally advanced disease, whereas survival rate for patients with stage 4 disease is only 7% (Figure 2) (Reim 2013).

Figure 2: Survival curves in patients with GC by stage as per the Union for International Cancer Control seventh edition



Abbreviations: UICC: Union for International Cancer Control.
Source: (Reim 2013)

5.1.3 Disease presentation and diagnosis

Gastric cancer is asymptomatic in early stages or associated with nonspecific symptoms such as dyspepsia, bloating, mild nausea, loss of appetite and/or heartburn (Gunderson 2013, Cancer Research UK 2016, Kulangara 2018). Common symptoms in advanced stage disease include difficulty swallowing (dysphagia), anorexia, weight loss that may result from decreased appetite and/or a feeling of fullness after eating only small amounts, localised persistent abdominal pain, ascites, jaundice, persistent heartburn or indigestion, nausea, and vomiting (ACS 2017, Kulangara 2018). Patients may also experience blood loss from the stomach, which can lead to anaemia, fatigue, and breathlessness, and the presence of blood in the faeces (Cancer Research UK 2016, ACS 2017, Kulangara 2018).

Early EC (EAC and ESCC) typically causes no signs or symptoms (Mayo Clinic 2018). The most common presentation of EC is solid food dysphagia and unintentional weight loss over several months (Kleinberg 2014, Mayo Clinic 2018). Additional typical symptoms include chest pain (including pressure and burning), worsening indigestion or heartburn, and coughing or hoarseness (Mayo Clinic 2018).

Most GC patients (>80%) worldwide are diagnosed with unresectable advanced GC due to early nonspecific symptoms and the lack of early detection programs (Correa 2013, Kamiya 2018). Similarly, EC (both EAC and ESCC) is often diagnosed at advanced stages. In the US, an estimated 18.3% of EAC cases are diagnosed at stage 3, and 37% at stage 4 (Then 2020).

5.1.4 Unmet need

Mortality remains high in patients with GC, GEJC and EAC, mainly due to diagnosis at a late stage and the overall poor prognosis (DEGC 2020a). Overall, the 1-year and 5-year relative survival rates for GC in Denmark were 58% and 28% in males and 61% and 34% in females, respectively (based on 2015–2019 data) (NORDCAN 2019b, NORDCAN 2019a). For patients with intended curable treatment, the 5-year survival rate is approximately 45%. However, survival rates in patients with GC, GEJC, and EC treated with palliative chemotherapy are lower, with 1-year survival rate of 34.3% after starting the first systemic therapy (DEGC 2020a).

Prevalence and incidence in Denmark

EC and GC is the 8th most common form of cancer in Denmark. The median age at the time of diagnosis for EC, GEJC, and GC is 71, 70, and 70 years, respectively (DEGC 2020a). The most common histological type of cancer of the esophagus is ESCC, which is predominately located high and/or in the middle of the esophagus. Only a small proportion (approximately 3%) of carcinomas in the esophagus are adenocarcinomas (DECV 2019, DEGC 2020a). The incidence of adenocarcinoma in GEJC has increased in recent years and is now higher than both squamous cell carcinomas of the esophagus and adenocarcinomas of the distal part of the stomach (DEGC 2020a). Across EC, GEJC and GC, diagnosis was more common in men, with 66%, 81%, and 60% in men, respectively (DEGC 2020a).

In Denmark, there was an estimated 661 new cases of GC and GEJC, and 575 cases of EC per year (based on NORDCAN 2015–2019 incidence data) (NORDCAN 2019a, NORDCAN 2019b). Based on the Dansk Esophago Gastrisk Cancer Gruppe (DEGC) database, there were 221, 320, 626 new cases of GC, EC, GEJC, respectively, in 2019 (Table 2); note, this included all new cases diagnosed across stages (DEGC 2020a). Of these patients, 60.2%, 83.4%, and 62.0% of GC, EC, GEJC patients, respectively, received palliative treatment (DEGC 2020a). Furthermore, of the GC, EC, and GEJC patients who received palliative care, 68.4%, 46.8%, and 58.8%, respectively, had stage IV disease (DEGC 2020a).

Table 2: Incidence and prevalence of GC, GEJC and EC in Denmark between 2015 and 2019 (all stages across histologies)

	2015	2016	2017	2018	2019
GC and GEJC					

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	2015	2016	2017	2018	2019
New cases of GC in Denmark (DEGC 2020a)	247	273	220	236	221
New cases of GEJC in Denmark (DEGC 2020a)	535	575	594	635	626
Age-standardised incidence rate Nordic (per 100,000 person-years) in Denmark (GC and GEJC) (NORDCAN 2020a)	Male: 13.8 Female: 6.5	Male: 13.6 Female: 6.5	Male: 14.2 Female: 6.7	Male: 15.3 Female: 5.6	Male: 15.4 Female: 6.0
Prevalence in Denmark (GC and GEJC) (NORDCAN 2020c)	Male: 1,224 Female: 666 Total: 1,890	Male: 1,297 Female: 733 Total: 2,030	Male: 1,378 Female: 781 Total: 2,159	Male: 1,449 Female: 810 Total: 2,259	Male: 1,495 Female: 841 Total: 2,336
EC					
New cases in Denmark (DEGC 2020a)	264	301	264	288	320
Age-standardised incidence rate Nordic (per 100,000 person-years) in Denmark (NORDCAN 2020a)	Male: 13.5 Female: 3.5	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: 808 Female: 291 Total: 1,099	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
Total new cases of GC, GEJC and EC	1,046	1,149	1,078	1,159	**1,167**

Abbreviation: EAC: esophageal adenocarcinoma; EC: esophageal cancer; ESCC; esophageal squamous cell carcinoma; GC: gastric cancer; GEJC: gastroesophageal junction cancer.
Reference: (DECV 2016, DEGC 2020a, NORDCAN 2020a, NORDCAN 2020c, NORDCAN 2020b)

5.1.5 Patient populations relevant for this application

[redacted]

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Table 3: The number of patients eligible for nivolumab plus chemotherapy if approved for reimbursement in Denmark

	Year 1	Year 2	Year 3	Year 4	Year 5
Nr of patients in Denmark who are expected to use nivolumab plus chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]					

5.2 Current treatment options and choice of comparator(s)

5.2.1 Current treatment options

The treatment of patients with GC, GEJC, and EAC in Denmark are based on the DEGC Onkologisk behandling af non-kurabel cancer i esophagus, GEJ og ventrikel (2020) guidelines (DEGC 2020a) and follow the same treatment recommendations, with options including palliative chemotherapy and external radiation brachytherapy, the latter being for symptom relief (DEGC 2020a).

Guidelines recommend the following, with recommendations marked A the strongest and recommendations marked D the weakest (as per the Oxford Centre for Evidence-Based Medicine Levels of Evidence and Grades of Recommendations) (DEGC 2020a):

- Patients with non-curable adenocarcinoma of the esophagus, GEJ or stomach should be offered palliative chemotherapy (A) which should be a combination therapy (A)
- Patients should be offered two-compound combination therapy with fluoropyrimidine and platinum or triplet fluoropyrimidine, platinum and taxane depending on treatment goals, side effect profile and patient request (A)
- Patients with tumour overexpression and/or amplification of HER2 should be offered trastuzumab treatment and combination chemotherapy (A)
- Palliative external radiation therapy (C) and brachytherapy (A) can be used to provide symptomatic relief e.g. from bleeding, pain, or obstruction

5.2.2 Choice of comparator(s)

In Denmark, as well as in Norway [redacted] the XELOX comparator in the CheckMate 649 trial is the most appropriate comparator aligned to Danish clinical practice (DEGC 2020a). As stated previously by the DMC, if treatment regimens can be considered equivalent, it is sufficient to only use one as a comparator (Medicinrådet 2021b).

5.2.3 Description of the comparator(s)

An overview of chemotherapy regimens containing a fluoropyrimidine either in combination with oxaliplatin plus leucovorin (FOLFOX), or with only oxaliplatin (XELOX) in the CheckMate 649 trial is presented in Table 4. The XELOX regimen can be considered equivalent to the standard of care chemotherapy regimen used in Denmark.

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Table 4: Description of chemotherapy regimens used in CheckMate 649

Product description	
Name of preparation/pharmaceutical	Chemotherapy regimens containing a fluoropyrimidine in combination with either oxaliplatin (as XELOX) or with oxaliplatin and leucovorin (as FOLFOX)
Active ingredient	Oxaliplatin Capecitabine Leucovorin Fluorouracil
Pharmaceutical form	Concentrate for solution for infusion (all except capecitabine which is administered orally)
Strength	Oxaliplatin 130 mg/m^2 (XELOX) or 85 mg/m^2 (FOLFOX) Capecitabine 1000 mg/m^2 Leucovorin 400 mg/m^2 Fluorouracil 400 mg/m^2 or 1200 mg/m^2
Recommended daily dose	XELOX Oxaliplatin 130 mg/m^2 IV on Day 1 of each treatment cycle + capecitabine 1000 mg/m^2 orally twice daily (BID) on Days 1 to 14 of each treatment cycle, Q3W FOLFOX Oxaliplatin 85 mg/m^2 + leucovorin 400 mg/m^2 + fluorouracil 400 mg/m^2 IV on Day 1 of each treatment cycle, and fluorouracil 1200 mg/m^2 IV continuous infusion over 24 hours daily (QD) or per local standard on Days 1 and 2 of each treatment cycle, Q2W
Should the intervention be used with other drugs?	No
Treatment length/criteria for termination of treatment	Treatment was given until disease progression (PD) (unless treatment beyond progression was permitted), unacceptable toxicity, or subject withdrawal of consent, whichever occurred first.
Required monitoring, under administration or during treatment period	Please see SmPC for each product*
Requirements of diagnostics or other tests	No
Medically approved indication /-s	Please see SmPC for each product*

Abbreviations: BID: orally twice daily; FOLFOX: 5-fluorouracil plus leucovorin plus oxaliplatin; PD: disease progression; Q2W: every two weeks; QD: daily; SmPC: summary of product characteristics; XELOX: capecitabine plus oxaliplatin.
Reference: (Janjigian 2021b)
Note: *SmPC available at EMA

5.3 The intervention

Details of the intervention are listed below in Table 5.

OPDIVO® (nivolumab) is expected to be used in combination with fluoropyrimidine and a platinum-based combination chemotherapy as first-line treatment of adult patients with HER-2 negative advanced or metastatic gastric, gastro-esophageal juntion or esophageal adenocarcinoma whose tumours express PD-L1 with a CPS ≥ 5. The current standard

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of care in these patients is combination chemotherapy; OPDIVO® (nivolumab) plus chemotherapy will be used in place of chemotherapy alone in this patient population.

Table 5: Product description for nivolumab

Product description	
Dosing	360 mg nivolumab administered intravenously over 30 minutes in combination with fluoropyrimidine and platinum-based chemotherapy administered every 3 weeks or 240 mg nivolumab administered intravenously over 30 minutes in combination with fluoropyrimidine, leucovorin and platinum-based chemotherapy administered every 2 weeks
Method of administration	Intravenous
Treatment duration	Until disease progression, unacceptable toxicity, or up to 24 months
Should the pharmaceutical be administered with other medicines?	No
Monitoring	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
Need for diagnostic or other tests	PD-L1 CPS test

Abbreviations: CPS: combined positive score.
Source: (Janjigian 2021b)

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6. Literature search and identification of efficacy and safety studies

6.1 Identification and selection of relevant studies

Current treatment options in Denmark for patients with HER-2 negative advanced or metastatic gastric, gastro-esophageal junction or esophageal adenocarcinoma whose tumours express PD-L1 with a CPS ≥ 5 include combination palliative chemotherapy, e.g., two-compound combination therapy with fluoropyrimidine and platinum or triplet fluoropyrimidine, platinum and taxane treatment (DEGC 2020a). The active comparator in CheckMate 649 (i.e., XELOX/FOLFOX) corresponds to the current standard of care in Denmark—as the XELOX comparator in the CheckMate 649 trial is the most appropriate comparator aligned to Danish clinical practice. As stated previously by the DMC, it is sufficient to only use one treatment as a comparator (Medicinrådet 2021b). Therefore, it was not necessary to conduct a literature review to identify further comparators.

[redacted]

Table 6: Relevant studies included in the assessment

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)
First-line nivolumab plus chemotherapy versus chemotherapy alone for advanced gastric, gastro-esophageal junction, and esophageal adenocarcinoma (CheckMate 649): a randomised, open-label, phase 3 trial - Janjigian et al. Lancet 2021	CheckMate 649	NCT02872116	October 12, 2016 October 6, 2022

Source: (Janjigian 2021b)

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

6.1.1 ATTRACTION-4

6.1.1.1 Study overview

ATTRACTION-4 is a phase 2/3 study in previously untreated unresectable advanced or recurrent GC/GEJC, with patients randomised to receive nivolumab plus chemotherapy (S-1 plus oxaliplatin or capecitabine plus oxaliplatin) or placebo plus chemotherapy. Part 1 was conducted at 13 centres in Japan and South Korea, Part 2 is ongoing at 138 sites in Japan, South Korea, and Taiwan (Boku 2019). However, ATTRACTION-4 and CheckMate 649 are different trials using different designs, patient populations, treatment interventions, dosing, and schedules, and therefore, inter-trial comparisons should not be made due to these differences:

- CheckMate 649 was a global study in 29 countries, whereas ATTRACTION-4 was limited to patients from Japan, South Korea, and Taiwan (Boku 2020, Janjigian 2021b). Longer OS has been observed in Asian vs. Western patients in several trials (ToGA, AVAGAST, RAINBOW) (Ohtsu 2011, Sawaki 2012, Wilke 2014). This is possibly due to the natural course of the disease, the stage at diagnosis, or disease management (Smyth 2021)
- ATTRACTION-4 assessed PFS and OS as the primary endpoints in all randomized patients (i.e., regardless of PD-L1 expression level); CheckMate 649 enrolled patients regardless of PD-L1 expression and assessed PFS

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and OS in patients with PD-L1 CPS ≥5 followed by PFS and OS in the all randomized population as part of the analysis hierarchy (Boku 2020, Janjigian 2021b)

- CheckMate 649 enrolled patients with GC and EAC; ATTRACTION-4 only enrolled patients with GC and did not include EAC (Boku 2020, Shitara 2020, Janjigian 2021b)
- Although both CheckMate 649 and ATTRACTION-4 used nivolumab in combination with chemotherapy, different chemotherapy backbones were used: SOX/XELOX in ATTRACTION-4, XELOX/FOLFOX in Checkmate 649, reflecting SOC differences in Japan/Korea and Taiwan and the rest of the world (Boku 2020, Janjigian 2021b)

Table 7 compares the main study characteristics between CheckMate 649 and ATTRACTION-4.

Table 7: Main characteristics of CheckMate 649 and ATTRACTION-4

Trial name:	CheckMate 649	ATTRACTION-4
Objective	To evaluate the efficacy of nivolumab plus chemotherapy (XELOX [capecitabine + oxaliplatin] or FOLFOX [leucovorin + 5-FU + oxaliplatin]) versus chemotherapy (XELOX or FOLFOX) in patients with previously untreated advanced or metastatic gastric/GEJ cancer or EAC	To evaluate the efficacy and safety nivolumab with chemotherapy in unresectable advanced or recurrent gastric cancer (including esophagogastric junction cancer) not previously treated with the first-line therapy. Part 1 evaluates the tolerability, safety, and efficacy of nivolumab in combination with SOX therapy (Tegafur / gimeracil / oteracil potassium + Oxaliplatin) or XELOX therapy (Capecitabine + Oxaliplatin). In part 2, the investigator or the sub-investigator will choose a SOX or XELOX therapy, taking into account the condition of each subject. Part 2 is planned to evaluate the efficacy and safety of ONO-4538 + chemotherapy in comparison with placebo + chemotherapy
Study type and design	Phase 3, open-label, 3-arm randomised multicentre study The study was conducted at 175 study sites in 29 countries	Phase 2/3, quadruple-masking, multicentre, randomized study The study was conducted in 130 centers limited to Japan, South Korea, and Taiwan
Sample size (n)	1,581 randomised to nivolumab plus chemotherapy or chemotherapy alone	724 randomized to nivolumab plus chemotherapy or placebo + chemotherapy

Trial name:	CheckMate 649	ATTRACTION-4
Main inclusion and exclusion criteria	Inclusion Criteria: • Men or women, at least 18 years old with inoperable, locally advanced, or metastatic GC, EC, orGEJC, and histologically confirmed predominant adenocarcinoma • No prior systemic treatment, including HER2 inhibitors, as primary therapy for advanced or metastatic disease • Prior neoadjuvant or adjuvant treatment (chemotherapy and/or radiotherapy) must have been completed at least 6 months prior to randomisation • Presence of at least one measurable lesion or evaluable disease by CT or MRI per RECIST 1.1 criteria • ECOG PS score of 0 or 1 • An evaluable tumour cell PD-L1 expression classification (≥1% or <1%, or indeterminate) by the central lab Exclusion Criteria: • Known HER2-positive status • Untreated CNS metastases; ascites which cannot be controlled with appropriate interventions A grade 1 peripheral neuropathy • Active known or suspected autoimmune disease • Any serious or uncontrolled medical disorder or active infection	Inclusion Criteria: • Patients with unresectable advanced or recurrent gastric cancer (including esophagogastric junction cancer) that has not been treated with the • Not treated with first-line therapy with systemic antitumor agents for advanced or recurrent gastric cancer (including esophagogastric junction cancer) • Have measurable lesions as defined in RECIST Guideline Version 1.1 • ECOG PS score 0 or 1 Exclusion Criteria: • Have multiple cancers • Have a current or past history of severe hypersensitivity to any other antibody products • Patients with any metastasis in the brain or meninx that is symptomatic or requires treatment • Patients with active, known or suspected autoimmune disease
Intervention	• Nivolumab 360 mg plus XELOX (oxaliplatin 130 mg/m^2 IV on Day 1 of each treatment cycle + capecitabine 1000 mg/m^2 orally BID on Days 1 to 14 of each treatment cycle) every 3 weeks or • Nivolumab 240 mg plus FOLFOX (oxaliplatin 85 mg/m^2 + leucovorin 400 mg/m^2 + fluorouracil 400 mg/m^2 IV on Day 1 of each treatment cycle, and fluorouracil 1200 mg/m^2 IV continuous infusion over 24 hours daily [QD] or per local standard on Days 1 and 2 of each treatment cycle) every 2 weeks	• Nivolumab 360 mg solution intravenously for 30 min in every 3 weeks; oxaliplatin 130 mg/m2 (BSA) solution intravenously for 2 hours once-daily, followed by 20 days off, plus Tegafur-gimeracil-oteracil potassium combination drug 40 - 60 mg bid orally in 14 days, followed by 7 days off • Nivolumab solution intravenously for 30 min in every 3 weeks; oxaliplatin 130 mg/m2 (body surface area) solution intravenously for 2 hours once-daily, followed by 20 days off, plus Capecitabine 1200 - 2100 mg bid orally in 14 days, followed by 7 days off

Trial name:	CheckMate 649	ATTRACTION-4
Comparator(s)	XELOX every 3 weeks or FOLFOX every 2 weeks (as described above)	Placebo + chemotherapy group, either SOX therapy or XELOX • Placebo solution intravenously for 30 min in every 3 weeks; oxaliplatin 130 mg/m2 (body surface area) solution intravenously for 2 hours once-daily, followed by 20 days off, plus Tegafur-gimeracil-oteracil potassium combination drug 40 - 60 mg bid or Capecitabine 1000 mg/ m2 (body surface area) bid orally in 14 days, followed by 7 days off

Abbreviation: BICR: blinded independent central review; BID: twice daily; CPS: combined positive score; CSN: central nervous system; EC: esophageal; ECOG: Eastern Cooperative Oncology Group; GC: gastric cancer; FACT-Ga: Functional Assessment of Cancer Therapy – Gastric; FOLFOX: leucovorin calcium plus fluorouracil plus oxaliplatin; GEJC: gastroesophageal junction cancer; MSI: Microsatellite instability; ORR: objective response rate; OS: overall survival; PD-L1: programmed cell death 1; PFS: progression-free survival; PS: performance status; Q#W: every # weeks; QD: daily; RECIST: Response Evaluation Criteria in Solid Tumours; XELOX: capecitabine plus oxaliplatin.

In previous evaluations of nivolumab for 2L esophageal squamous cell carcinoma (Medicinrådet 2021a), the DMC had similarly stated non-transferability of the ATTRACTION-3 trial to the Danish clinical population. ATTRACTION-4 was not included in the regulatory submission to the European Medicines Agency, and therefore, has not been included in this submission.

7. Efficacy and safety

7.1 Efficacy and safety - study overview

7.1.1 CheckMate 649

7.1.1.1 Study overview

Nivolumab plus chemotherapy in the first-line treatment of patients with previously untreated advanced or metastatic GC/GEJC and EAC has been studied in one key phase 3 trial, CheckMate 649 (Janjigian 2021b). Patients were recruited worldwide at 172 sites. An overview of the study is presented in Figure 4 and Table 8 below. The focus of this application is the nivolumab plus chemotherapy vs. chemotherapy alone arms.

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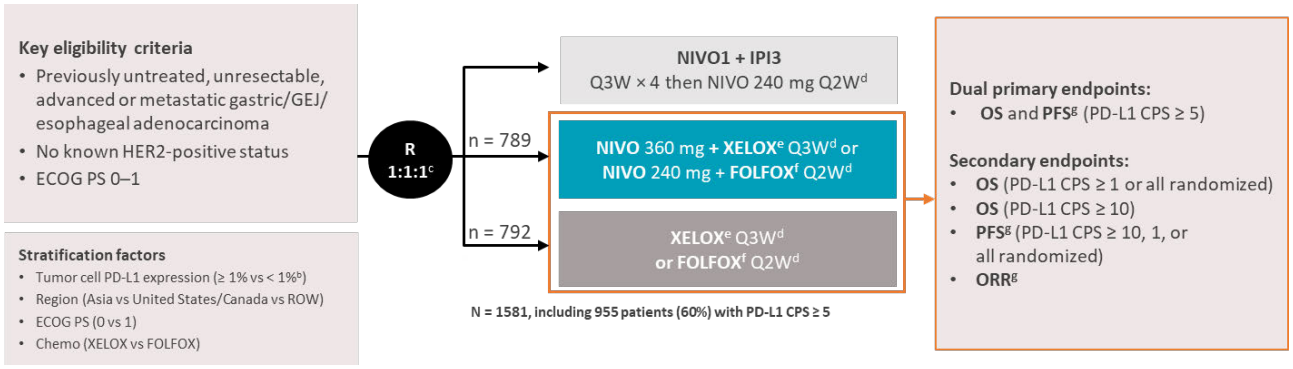
Figure 4: CheckMate 649 study design



[a]ClinicalTrials.gov number, NCT02872116; [b]< 1% includes indeterminate tumour cell PD-L1 expression; determined by PD-L1 IHC 28-8 pharmDx assay (Dako); [c]After NIVO + chemo arm was added and before new patient enrollment in the NIVO1+IPI3 group was closed; [d]Until documented disease progression (unless consented to treatment beyond progression for NIVO + chemo), discontinuation due to toxicity, withdrawal of consent, or study end. NIVO is given for a maximum of 2 years; [e]Oxaliplatin 130 mg/m2 IV (day 1) and capecitabine 1000 mg/m2 orally twice daily (days 1–14); [f]Oxaliplatin 85 mg/m2, leucovorin 400 mg/m2, and FU 400 mg/m2 IV (day 1) and FU 1200 mg/m2 IV daily (days 1–2); [g]BICR assessed

Abbreviations: CPS: combined positive score; ECOG: Eastern Cooperative Oncology Group; FOLFOX: leucovorin calcium plus fluorouracil plus oxaliplatin; GEJ: gastroesophageal junction; IPI: ipilimumab; ORR: objective response rate; OS: overall survival; PD-L1: programmed cell death 1; PFS: progression-free survival; PS: performance status; Q2W: every two weeks; Q3W: every three weeks; ROW: rest of the world; XELOX: capecitabine plus oxaliplatin.

Source: (Janjigian 2021b)

Table 8: Overview of CheckMate 649

CheckMate 649 (NCT02872116)	
Study design	Phase 3, multi-centre, randomised, open-label, active-controlled study. Patients were randomised to receive nivolumab plus chemotherapy or ipilimumab, or chemotherapy alone. Randomization was stratified by tumour cell PD-L1 (≥1% vs. <1%), region (Asia vs. US/Canada vs. rest of world), ECOG performance status (0 vs. 1), and chemotherapy (XELOX vs. FOLFOX) Treatment for all arms was continued until documented disease progression, unacceptable toxicity, or withdrawal of consent. Treatment with nivolumab monotherapy following nivolumab plus ipilimumab, was given for up to 24 months in the absence of disease progression or unacceptable toxicity.
Study size	This application focuses on results of the nivolumab plus XELOX/FOLFOX vs. XELOX/FOLFOX treatment arms: 1,581 patients randomised to receive nivolumab plus XELOX/FOLFOX (n=789) and XELOX/FOLFOX (n=792) of which 955 (60%) were PD-L1 positive with a CPS ≥ 5
Patient population	Patients with previously untreated advanced or metastatic gastric/GEJ cancer or EAC, and histologically confirmed predominant adenocarcinoma
Intervention for N 1581 patients	Nivolumab 360 mg plus XELOX every 3 weeks or nivolumab 240 mg plus FOLFOX every 2 weeks
Comparator	XELOX every 3 weeks or FOLFOX every 2 weeks
Follow-up	Minimum follow-up: 24.0 months
Is the study used in the HE-model?	Yes
Reason for including/Excluding from HE-model	Pivotal trial including key comparator
Reported primary endpoint	OS in PD-L1 positive (CPS ≥ 5) Nivolumab plus chemotherapy vs. chemotherapy alone mOS: 12.1 months: 14.4 (95% CI, 13.1–16.2) vs. 11.1 (95% CI, 10.0–12.1) months; HR: 0.71 (95% CI, 0.59–0.86; p<0.0001) 24.0 months: 14.4 (95% CI, 13.1–16.2) vs. 11.1 (95% CI, 10.0–12.1) months; HR: 0.70 (95% CI, 0.61–0.81) PFS assessed by blinded independent central review (BICR) in PD-L1 positive (CPS ≥ 5) Nivolumab plus chemotherapy vs. chemotherapy alone mPFS: 12.1 months: 7.7 (95% CI, 7.0–9.2) vs. 6.0 (95% CI, 5.6–6.9) months; HR: 0.68 (95% CI, 0.56–0.81; p<0.0001) 24.0 months: 8.1 (95% CI, 7.0–9.2) vs. 6.1 (95% CI, 5.6–6.9) months; HR: 0.70 (95% CI, 0.60–0.81)
Other reported endpoints	ORR in PD-L1 positive (CPS ≥ 5) OS, PFS, ORR in all randomised patients EQ-5D-3L VAS and UI (CPS ≥ 5) EQ-5D-3L VAS and UI (all randomised patients) FACT-Ga total score TTSD

Abbreviations: BICR: blinded independent central review; CPS: combined positive score; EAC: esophageal adenocarcinoma; ECOG: Eastern Cooperative Oncology Group; EQ-5D-3L: EuroQoL 5 Dimensions 3 Level Version questionnaire; FACT-Ga: Functional Assessment of Cancer Therapy – Gastric; FOLFOX: leucovorin + 5FU + oxaliplatin; GEJ: gastroesophageal junction; ORR: objective response rate; OS: overall survival; PD-L1:

programmed death-ligand 1; PFS: progression-free survival; TTSD: time to symptom deterioration; UI: utility index; VAS: visual analogue scale; XELOX: capecitabine + oxaliplatin.
Source: (Janjigian 2021a, Janjigian 2021b)

7.1.1.2 Study design

CheckMate 649 was a randomised, multi-centre, active-controlled, open-label, phase 3 study of the clinical efficacy of nivolumab plus ipilimumab or nivolumab plus chemotherapy (XELOX [capecitabine + oxaliplatin] or FOLFOX [leucovorin + 5-FU + oxaliplatin]) versus chemotherapy alone (XELOX or FOLFOX) in patients with previously untreated advanced or metastatic GC/GEJC or EAC (Janjigian 2021b) (Figure 4). [redacted]

Eligible patients were men or women, ≥18 years old, with previously untreated, unresectable, non-HER-2-positive GC, EC, or GEJC, and histologically confirmed predominant adenocarcinoma, regardless of PD-L1 expression (Janjigian 2021b).

Additional inclusion criteria were as follows:

- No prior systemic treatment, including HER2 inhibitors, as primary therapy for advanced or metastatic disease
- Prior adjuvant treatment (chemotherapy and/or radiotherapy) must have been completed at least 6 months prior to randomization
- Presence of at least one measurable lesion or evaluable disease by CT or MRI per Response Evaluation Criteria in Solid Tumours (RECIST) 1.1 criteria
- Eastern Cooperative Oncology Group (ECOG) performance status (PS) score of 0 or 1
- An evaluable tumour cell PD-L1 expression classification (≥1% or <1%, or indeterminate) by the central lab

Key exclusion criteria were as follows:

- Known HER2-positive status
- Presence of tumour cells in the brain or spinal cord that have not been treated
- Active known or suspected autoimmune disease
- Any serious or uncontrolled medical disorder or active infection
- Known history of positive test for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS)
- Any positive test result for hepatitis B or C indicating acute or chronic infection

Patients were randomised to receive nivolumab plus chemotherapy or ipilimumab or chemotherapy alone (Janjigian 2021b):

- Nivolumab 360 mg plus XELOX every 3 weeks or nivolumab 240 mg plus FOLFOX every 2 weeks
- XELOX every 3 weeks or FOLFOX every 2 weeks
- Nivolumab 1 mg/kg plus ipilimumab 3 mg/kg intravenously every 3 weeks for 4 doses, followed by nivolumab 240 mg monotherapy given every 2 weeks

Treatment in all arms was continued until documented disease progression, unacceptable toxicity, or withdrawal of consent (Janjigian 2021b). Treatment with nivolumab was given for up to 24 months in the absence of disease progression or unacceptable toxicity (Janjigian 2021b).

Randomization was stratified by tumour cell PD-L1 (≥1% vs. <1%), region (Asia vs. US/Canada vs. rest of world), ECOG performance status (0 vs. 1), and chemotherapy (XELOX vs. FOLFOX) (Janjigian 2021b).

7.1.1.3 Study endpoints

The dual primary endpoints in CheckMate 649 for the nivolumab plus chemotherapy versus chemotherapy alone arms were OS and PFS (as assessed by blinded independent central review [BICR]) in patients with PD-L1 positive tumours defined by CPS ≥5 (Table 9) (Janjigian 2021b).

The key secondary endpoints were OS in PD-L1 CPS ≥1, CPS ≥ 10 or all randomised patients, PFS (BICR assessed) in PD-L1 CPS ≥1, CPS ≥ 10 or all randomised patients and ORR (Moehler 2020a, Janjigian 2021b).

For the nivolumab plus chemotherapy arm, health-related quality of life (HRQoL) was a key prespecified exploratory endpoint and was assessed using EQ-5D-3L visual analog scale (EQ-5D-3L VAS), Functional Assessment of Cancer Therapy-General (FACT-Ga), and selected components including the single item GP5 ("I am bothered by side effects of treatment") , GC subscale (GaCS), and the 7-item version of the FACT-General (FACT-G7) (BMS 2020, Janjigian 2021b).

Table 9: CheckMate 649 endpoints for nivolumab plus XELOX/FOLFOX vs. XELOX/FOLFOX

Endpoints	Outcome measures
Primary	OS in PD-L1 positive (CPS ≥5) patients based on the PD-L1 immunohistochemistry (IHC) 28-8 pharmDX
	PFS (per BICR) in PD-L1 positive (CPS ≥5) patients
Secondary	OS in PD-L1 positive (CPS ≥1) patients and in all randomised patients (hierarchically tested)
	OS in PD-L1 positive (CPS ≥10) patients
	PFS (per BICR) in PD-L1 positive (CPS ≥1, ≥10) patients or all randomised patients
	ORR (per BICR) in PD-L1 positive (CPS ≥1, ≥5, ≥10) patients or all randomised patients
	Safety and tolerability
Exploratory	DRR by BICR and by investigator
	DOR by BICR and by investigator
	TTSD using GaCS of FACT-Ga
	PFS and ORR by investigator in subjects with different PD-L1 CPS cutoffs
	PFS2 or TSST
	PFS and ORR by BICR and by investigator and OS in subjects with different PD-L1 CPS cutoffs
	Incidence of death, AEs, SAEs, IMAEs and select AEs
	OS, PFS, and ORR in subjects with different MSI status
	Nivolumab ADA and characterization of Nab
	EQ-5D-3L descriptive system and VAS
	FACT-Ga including GaCS and FACT-G7

aSecondary endpoints were included in testing hierarchy. ADA: anti-drug antibodies; AE: adverse event; BICR, blinded independent central review; CPS, combined positive score; DOR: duration of response; DRR: durable response rate; EQ-5D-3L: EuroQoL 5-dimension 3-level questionnaire; FACT-Ga: Functional Assessment of Cancer Therapy-Gastric; FACT-G7: 7-item version of the FACT-General; FOLFOX, leucovorin + 5-FU + oxaliplatin; GaCS: gastric cancer subscale; IHC: immunhistochemistry; IMAE: immune-mediated adverse event; NAb: neutralizing antibodies; ORR, objective response rate; OS, overall survival; PD-L1, programmed cell death ligand 1; PFS, progression-free survival; PFS2: PFS after next line of treatment; SAE: serious adverse event; TSST: time to second subsequent line therapy; TTSD, time to symptom deterioration; XELOX, capecitabine + oxaliplatin
Source: (BMS 2018, Janjigian 2021b)

7.1.1.4 Statistical testing hierarchy

For the dual primary endpoints of PFS and OS in the comparison of nivolumab plus chemotherapy in randomised patients with PD-L1 CPS ≥5, a 2-sided significance level of 2% and 3% was allocated to PFS and OS, respectively (Janjigian 2021b). If the OS comparison in patients with PD-L1 CPS ≥5 between nivolumab plus chemotherapy and chemotherapy alone was significant, then OS in patients with PD-L1 CPS ≥1 and OS in all randomised were sequentially tested at a 2-sided 1.5% significance level (Janjigian 2021b). The trial was designed to conduct the final PFS and interim OS analyses at 12-month minimum follow-up and final OS analysis at 24-month minimum follow-up (Janjigian 2021b). Results from both database locks (DBLs) have been presented (Janjigian 2021a, Janjigian 2021b).

7.1.1.5 Patient baseline characteristics

This application focuses on results of the nivolumab plus chemotherapy vs. chemotherapy alone treatment arms in patients with HER-2 negative disease and whose tumours express PD-L1 with a CPS ≥ 5. [redacted] 789 in the nivolumab plus chemotherapy arm and 792 in the chemotherapy alone arm, including 955 patients (60%) with PD-L1 CPS ≥ 5 (BMS 2020, Janjigian 2021b). [redacted]

7.1.1.5.1 Patients with PD-L1 CPS ≥5: baseline demographics

[redacted] 473 (60.6%) patients had CPS ≥5 and in the chemotherapy alone arm, 482 (61.8%) had CPS ≥5 (BMS 2020, Janjigian 2021b). Baseline demographics for patients with PD-L1 CPS ≥5 are presented in Table 10.

Baseline demographics and disease characteristics in patients with PD-L1 CPS ≥5 were consistent with that in all randomised patients and balanced between the two treatment arms. Stratification factors were also balanced (Janjigian 2021b). The median age of patients with PD-L1 CPS ≥5 was 62.0 years. Most patients were white (68.6%) and male (71.2%) (Janjigian 2021b). Most patients were diagnosed with GC (69.8%); 17.8% had GEJ cancer and 12.4% had EAC (Janjigian 2021b). [redacted]

Table 10: Baseline demographics and characteristics in patients with PD-L1 CPS ≥5

Characteristic	Nivolumab plus chemotherapy (N=473)	Chemotherapy (N=482)
Median age (range), years	63 (54 – 69)	62 (54 – 68)
Age categorization, n (%)		
<65	266 (56)	286 (59)
≥65	207 (44)	196 (41)
Sex, M/F, n (%)	331 (70)/142 (30)	349 (72)/133 (28)
Race, n (%)		
White	328 (69)	327 (67)
Black or African American	2 (<1)	7 (<1)

Characteristic		Nivolumab plus chemotherapy (N=473)	Chemotherapy (N=482)
	American Indian Or Alaska Native	10 (2)	10 (2)
	Asian	119 (25)	117 (24)
	Other	14 (3)	21 (4)
Region, n (%)			
	Asia (including China)	117 (25)	111 (23)
	US and Canada	67 (14)	70 (15)
	Rest of world	289 (61)	301 (62)
Primary tumour location at initial diagnosis, n (%)			
	GEJ cancer	84 (18)	86 (18)
	Gastric cancer	333 (70)	334 (69)
	EAC	56 (12)	62 (13)
Disease status classification, n (%)			
	Locally recurrent	3 (1<)	1 (<1)
	Metastatic	454 (96)	461 (96)
	Locally advanced	16 (3)	20 (4)
Signet ring cell‡		72 (15)	69 (14)
Site of metastases (%)			
	Liver	191 (40)	271 (45)
	Peritoneum	101 (21)	96 (20)
	Central Nervous System	1 (<1)	0
Microsatellite instability, n (%)			
	MSI-H	18 (4)	16 (3)
	MSS	423 (89)	423 (88)
	Invalid/not reported	32 (7)	43 (9)
Tumour cell PD-L1 expression			
	1%†	363 (77)	362 (75)
	≥1%	110 (23)	120 (25)
HER-2 status, n (%)			
	Positive	3 (0.6)	4 (0.8)
	Negative	272 (57.5)	271 (56.2)
	Unknown	2 (0.4)	3 (0.6)
	Not reported	196 (41.4)	204 (42.3)

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Characteristic	Nivolumab plus chemotherapy (N=473)	Chemotherapy (N=482)
ECOG PS*, n (%)		
0	194 (41)	203 (42)
1	279 (59)	278 (58)
Not reported	0	1 (<1)
Chemotherapy regimen§		
FOLFOX	237/468 (51)	242/465 (52)
XELOX	231/468 (49)	223/465 (48)

*Based on case report form. All randomised patients had ECOG performance status of 0 or 1 based on interactive response technology. †Includes indeterminate tumour cell PD-L1 expression. ‡Per World Health Organization histologic classification. §Patients who received at least one dose of the assigned treatment
Abbreviations: EAC, esophageal adenocarcinoma; ECOG PS, Eastern Cooperative Oncology Group performance status; GEJ, gastroesophageal junction cancer; MSI-H, microsatellite instability-high; MSS, microsatellite stable.
Source: (BMS 2020, Janjigian 2021b)

Baseline characteristics and disease characteristics in all randomised patients were balanced between the nivolumab plus chemotherapy and the chemotherapy alone arms, detailed in Appendix K (Janjigian 2021b).

7.1.1.5.2 Treatment discontinuation

[redacted]

Table 11: CheckMate 649 patient disposition

Characteristic	Nivolumab plus chemotherapy (N=789*)	Chemotherapy (N=792*)
Discontinued treatment, %	89.3	94.9
Reasons for discontinuation, %		
Disease progression	[redacted]	[redacted]
Study drug toxicity	[redacted]	[redacted]
Death	[redacted]	[redacted]
AE unrelated to study drug	[redacted]	[redacted]
Subject request to discontinue	[redacted]	[redacted]
Withdrawn consent	[redacted]	[redacted]
Lost to follow-up	[redacted]	[redacted]
Maximum clinical benefit	[redacted]	[redacted]
Poor/non-compliance	[redacted]	[redacted]
No longer meets study criteria	[redacted]	[redacted]
Completed treatment as per protocol	[redacted]	[redacted]
Other	[redacted]	[redacted]

*values consider all randomised patients.
Abbreviations: AE: adverse event.
Source: (BMS 2020, Janjigian 2021b)

7.2 Efficacy and safety – results per study

A summary of the key efficacy and safety findings for CheckMate 649 is provided below. Detailed information about included outcomes and results can be found in Appendix D.

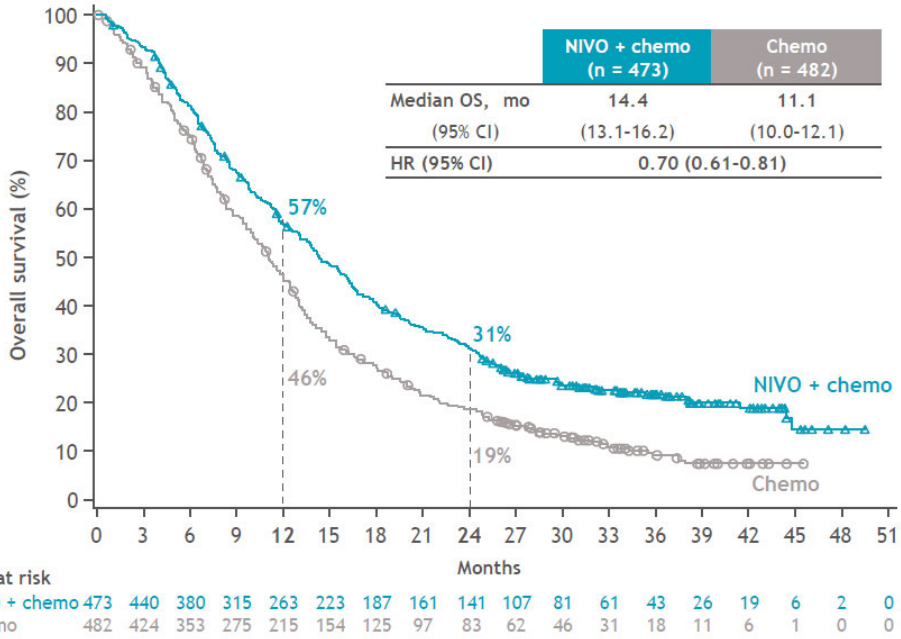
7.2.1 Efficacy

7.2.1.1 OS in patients with PD-L1 CPS ≥5 (primary endpoint)

7.2.1.1.1 All patients with PD-L1 CPS ≥5 (minimum follow-up 24.0 months)

At a minimum follow-up of 24.0 months, nivolumab plus chemotherapy continued to demonstrate clinically meaningful improvements in OS compared to chemotherapy alone in patients with PD-L1 CPS ≥5 (HR: 0.70 [95% CI, 0.61–0.81]; Figure 5) (Janjigian 2021a). Median OS was 14.4 (95% CI, 13.1–16.2) months in the nivolumab plus chemotherapy arm and 11.1 (95% CI, 10.0–12.1) months in the chemotherapy alone arm. The 2-year OS rates were 31% [redacted] and 19% [redacted], respectively (Figure 5) (BMS 2021, Janjigian 2021a).

Figure 5: Kaplan-Meier of OS in all patients with PD-L1 CPS ≥5 (minimum follow-up 24.0 months)



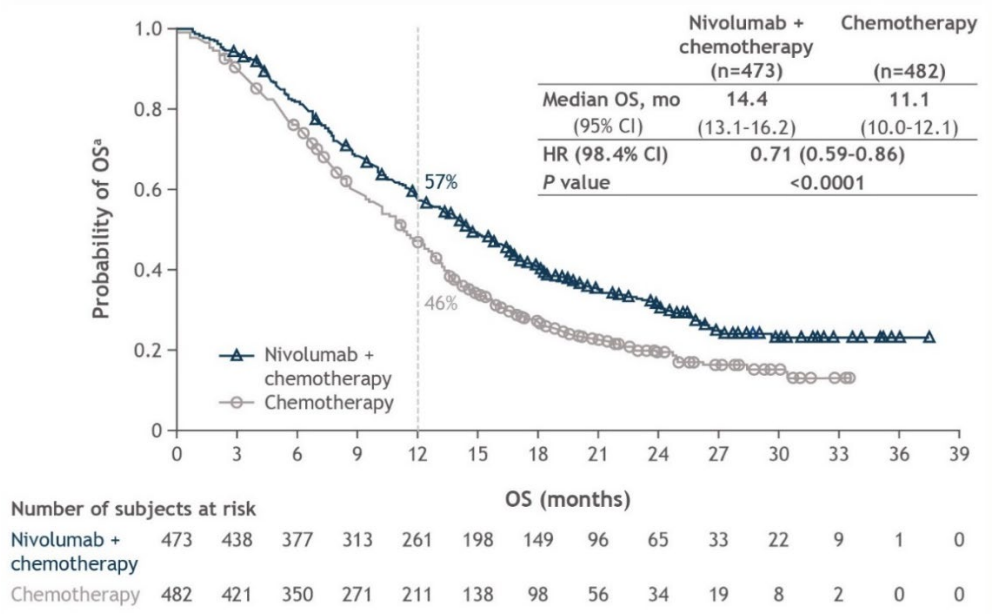
Abbreviations: CI: confidence interval; HR: hazard ratio; mo: month; OS: overall survival.
Source: (Janjigian 2021a).

7.2.1.1.2 All patients with PD-L1 CPS ≥5 (minimum follow-up 12.1 months)

At a minimum follow-up of 12.1 months, nivolumab plus chemotherapy demonstrated a statistically significant and clinically relevant 29% reduction in the risk of death compared with chemotherapy alone in patients with PD-L1 CPS ≥5 (HR 0.71 [98.4% CI, 0.59–0.86]; P<0.0001) (Figure 6) (Janjigian 2021b). Median OS was 3.3 months longer in the nivolumab plus chemotherapy arm compared with the chemotherapy alone arm: 14.4 months (95% CI, 13.1–16.2) vs. 11.1 months (95% CI, 10.0–12.1) (Janjigian 2021b). [redacted]

Separation of the Kaplan-Meier curves favoring nivolumab plus chemotherapy over chemotherapy alone occurred early (at <1 month), with increased separation over time (Janjigian 2021b). [redacted]

Figure 6: Kaplan-Meier of OS in all patients with PD-L1 CPS ≥5 (minimum follow-up 12.1 months)



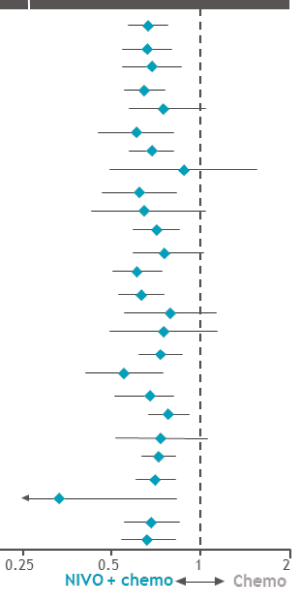
Abbreviations: CI: confidence interval; HR: hazard ratio; mo: month; OS: overall survival.
Source: (Moehler 2020a, Janjigian 2021b).

7.2.1.1.3 Predefined subgroups in patients with PD-L1 CPS ≥5 (minimum follow-up 12.1 months)

At a minimum follow-up of 12.1 months, OS HRs for almost all subgroups favored nivolumab plus chemotherapy over chemotherapy alone, including the subgroups of region, tumour location, histology (presence of signet ring cell, Lauren classification), metastases (liver, peritoneal), MSI status, tumour cell PD-L1 expression, and HER2 status (Figure 7) (Janjigian 2021b).

Figure 7: Forest plot of OS in predefined subgroups, patients with PD-L1 CPS ≥5 (minimum follow-up 12.1 months)

Category (PD-L1 CPS ≥ 5)	Subgroup	Median OS (95% CI), months		Unstratified HR for death (95% CI)
		NIVO + chemo	Chemo	
Overall (N = 955)		14.4 (13.1, 16.2)	11.1 (10.0, 12.1)	0.70 (0.60, 0.81)
Age, years	< 65 (n = 552)	14.8 (12.4, 16.5)	11.0 (9.9, 12.5)	0.69 (0.56, 0.84)
	≥ 65 (n = 403)	14.3 (12.2, 16.8)	11.2 (9.3, 12.7)	0.72 (0.57, 0.91)
Sex	Male (n = 680)	14.4 (13.1, 16.8)	10.8 (9.7, 12.0)	0.67 (0.56, 0.80)
	Female (n = 275)	14.4 (11.2, 16.4)	12.1 (9.8, 13.1)	0.78 (0.59, 1.03)
Race	Asian (n = 236)	16.1 (13.8, 23.1)	11.5 (8.5, 13.9)	0.63 (0.46, 0.85)
	White (n = 655)	14.0 (13.2, 16.2)	11.1 (10.0, 12.4)	0.71 (0.59, 0.86)
	Other (n = 64)	9.8 (5.4, 23.9)	10.6 (7.6, 13.7)	0.93 (0.51, 1.71)
Region	Asia (n = 228)	15.6 (12.9, 21.1)	11.8 (9.0, 13.9)	0.64 (0.47, 0.87)
	US/Canada (n = 137)	16.8 (11.8, 26.0)	12.6 (11.2, 15.2)	0.67 (0.43, 1.03)
	ROW (n = 590)	13.6 (11.4, 15.7)	10.4 (9.1, 11.6)	0.74 (0.61, 0.89)
ECOG PS	0 (n = 397)	17.6 (15.0, 20.5)	13.8 (12.5, 16.2)	0.79 (0.61, 1.02)
	1 (n = 557)	12.6 (11.1, 14.3)	8.8 (7.8, 10.1)	0.63 (0.52, 0.76)
Primary tumor location	GC (n = 667)	15.0 (13.1, 16.6)	10.5 (9.0, 12.0)	0.66 (0.55, 0.79)
	GEJC (n = 170)	14.2 (11.8, 20.5)	13.1 (10.8, 16.2)	0.84 (0.57, 1.22)
	EAC (n = 118)	11.2 (8.4, 16.8)	11.3 (8.5, 12.9)	0.78 (0.51, 1.21)
Tumor cell PD-L1 expression	< 1% (n = 724)	14.2 (12.6, 16.1)	11.6 (10.6, 12.7)	0.75 (0.63, 0.90)
	≥ 1% (n = 230)	16.2 (11.8, 23.7)	8.8 (6.3, 11.2)	0.56 (0.40, 0.77)
Liver metastases	Yes (n = 408)	13.1 (11.2, 16.1)	9.8 (8.2, 11.4)	0.63 (0.50, 0.80)
	No (n = 518)	15.5 (13.6, 16.8)	12.0 (10.6, 13.0)	0.76 (0.62, 0.94)
Signet ring cell carcinoma	Yes (n = 141)	12.1 (8.6, 15.5)	9.0 (6.9, 12.5)	0.71 (0.49, 1.03)
	No (n = 814)	15.1 (13.5, 16.8)	11.3 (10.1, 12.5)	0.69 (0.59, 0.82)
MSI status	MSS (n = 846)	14.4 (13.0, 16.2)	11.1 (10.1 12.5)	0.73 (0.62, 0.85)
	MSI-H (n = 34)	NA (5.4, NA)	8.8 (3.7, 16.5)	0.33 (0.12, 0.87)
Chemotherapy regimen	FOLFOX (n = 479)	14.3 (12.1, 16.8)	11.3 (10.1, 12.6)	0.71 (0.57, 0.88)
	XELOX (n = 454)	15.0 (12.9, 16.5)	11.0 (9.2, 15.6)	0.69 (0.55, 0.85)



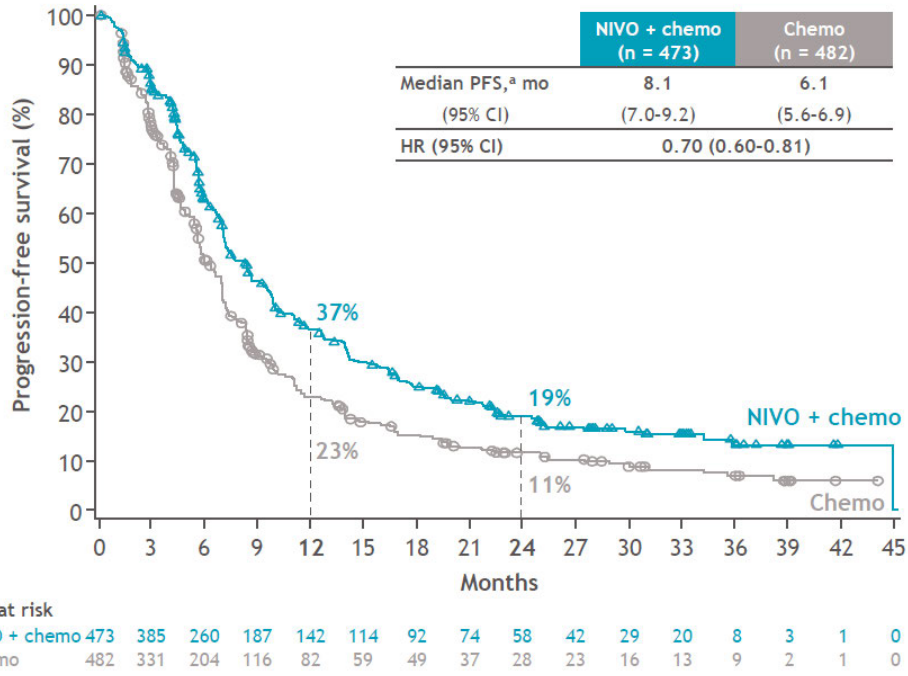
HR is not computed for subset (except age, race, region, and sex) category with less than 10 subjects per treatment group.
Abbreviations: EAC: esophageal adenocarcinoma; ECOG: Eastern Cooperative Oncology Group; FOLFOX: leucovorin (folinic acid) plus fluorouracil plus oxaliplatin; GEJ: gastroesophageal junction cancer; MSI-H: microsatellite instability-high; MSS: microsatellite stable; XELOX: capecitabine plus oxaliplatin.
Source: (BMS 2020, Moehler 2020a, Janjigian 2021b).

7.2.1.2 PFS in patients with PD-L1 CPS ≥5 (primary endpoint)

7.2.1.2.1 All patients with PD-L1 CPS ≥5 (minimum follow-up 24.0 months)

In patients with PD-L1 CPS ≥5, at minimum follow-up of 24 months, nivolumab plus chemotherapy continued to demonstrate a statistically significant and clinically relevant 30% reduction in the risk of progression per BICR (primary definition) compared to chemotherapy alone (HR: 0.70 [95% CI, 0.60–0.81]), (Figure 9) (Janjigian 2021b). Median PFS was significantly improved by 2 months in the nivolumab plus chemotherapy arm compared to chemotherapy alone (8.1 [95% CI, 7.0–9.2] vs. 6.1 [95% CI, 5.6–6.9] months) (Janjigian 2021b). PFS rates were higher with nivolumab plus chemotherapy compared to chemotherapy alone: 37% [redacted] vs. 23% [redacted] at 12 months and 19% [redacted] vs. 11% [redacted] respectively (BMS 2020, BMS 2021, Janjigian 2021b).

Figure 8: Kaplan-Meier of PFS, all patients with PD-L1 CPS ≥5 (minimum follow-up 24.0 months)

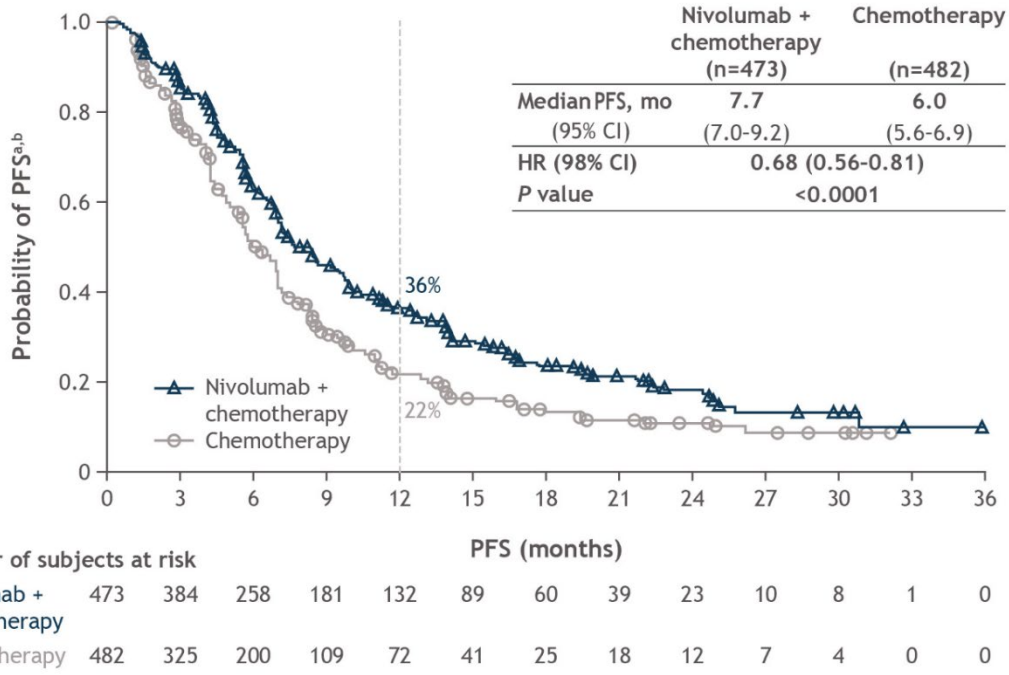


[a]Per BICR assessment
Abbreviation: CI: confidence interval; HR: hazard ratio; mo: month; PFS: progression-free-survival.
Source: (Janjigian 2021a)

7.2.1.2.2 All patients with PD-L1 CPS ≥5 (minimum follow-up 12.1 months)

In patients with PD-L1 CPS ≥5, nivolumab plus chemotherapy demonstrated a statistically significant and clinically relevant 32% reduction in the risk of progression per BICR (primary definition) compared with chemotherapy alone (HR: 0.68 [98% CI, 0.56–0.81]; P<0.0001), at minimum follow-up of 12.1 months (Figure 9) (Janjigian 2021b). Median PFS was significantly improved by 1.7 months in the nivolumab plus chemotherapy arm compared with chemotherapy alone (7.7 [95% CI, 7.0–9.2] vs. 6.0 [95% CI, 5.6–6.9] months) (Janjigian 2021b). PFS rates were higher for nivolumab plus chemotherapy compared with chemotherapy alone: [redacted], and 36% [redacted] vs. 22% [redacted] at 12 months, respectively (BMS 2020, Janjigian 2021b).

Figure 9: Kaplan-Meier of PFS, all randomised patients with PD-L1 CPS ≥5 (minimum follow-up 12.1 months)



[a]Per BICR assessment
Abbreviation: CI: confidence interval; HR: hazard ratio; mo: month; PFS: progression-free-survival.
Source: (Moehler 2020a, Janjigian 2021b)

7.2.1.2.3 Predefined subgroups in patients with PD-L1 CPS ≥5 (minimum follow-up 12.1 months)

[redacted]

7.2.1.3 Secondary endpoints

7.2.1.3.1 Objective response rate in patients with PD-L1 CPS ≥5 (minimum follow-up 24.0 months)

The objective response rate (ORR) remained higher with nivolumab plus chemotherapy vs. chemotherapy alone with longer follow-up (minimum follow-up 24.0 months; Table 12) (Janjigian 2021a). Additionally responses deepened relative to the 12.1 month follow-up, with 5 additional complete responses in the nivolumab plus chemotherapy PD-L1 CPS ≥5 group vs. 0 for chemotherapy alone (Janjigian 2021a, Janjigian 2021b).

Table 12: Response per BICR in all patients with PD-L1 CPS ≥5 (minimum follow-up 24.0 months)

Response per BICR	Nivolumab plus chemotherapy (N=378)[a]	Chemotherapy (N=390)[a]
ORR, % (95% CI)	60 (50–65)	45 (40–50)
CR	13	7
PR	47	38
SD	28	34
PD	7	11
Unable to determine	5	10

[a]Randomised patients who had target lesion measurements at baseline per BICR assessment
Abbreviations: CI: confidence interval; CR: complete response; DRR: durable response rate; ORR: objective response rate; PD: progressive disease; PR: partial response; SD: stable disease.
Source: (Janjigian 2021a)

7.2.1.3.2 Objective response rate in patients with PD-L1 CPS ≥5 (minimum follow-up 12.1 months)

In patients with measurable disease and PD-L1 CPS ≥5, at minimum follow-up of 12.1 months, an improvement in BICR-assessed ORR was observed in those treated with nivolumab plus chemotherapy compared with chemotherapy alone [redacted] (BMS 2020, Janjigian 2021b) (Table 13). The ORR was 60% for patients treated with nivolumab plus chemotherapy (12% CR, 48% PR) compared with 45% for patients treated with chemotherapy alone (7% CR, 38% PR) (Janjigian 2021b).

Over time there was an increase in complete response (CR) and partial response (PR) rates for patients receiving nivolumab plus chemotherapy. [redacted] (Table 13).

Table 13: Best overall response, ORR, and DRR, per BICR in all patients with PD-L1 CPS ≥5 (minimum follow-up 12.1 months)

	Nivolumab plus chemotherapy (N=378)	Chemotherapy (N=391)
Best overall response, n (%)		
CR	44 (11.6)	27 (6.9)
PR	182 (48.1)	150 (38.4)
SD	104 (27.5)	132 (33.8)
PD	26 (6.9)	42 (10.7)
Unable to determine	22 (5.8)	40 (10.2)
ORR (CR+PR), n (% [95% CI])[a]	226 (59.8 [redacted]	177 (45.3 [redacted]
Difference of ORR[b,c]	16.1%	
[redacted]		
[redacted]		
[redacted]		
[redacted]		
[redacted]		

[redacted]

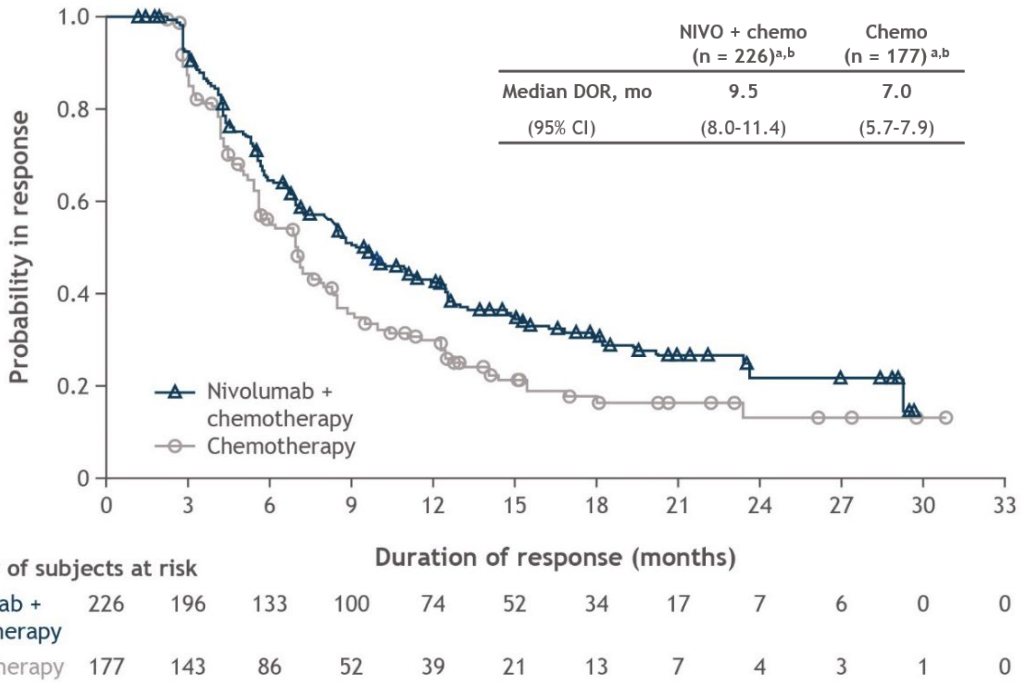
Abbreviations: CI: confidence interval; CR: complete response; DRR: durable response rate; ORR: objective response rate; PD: progressive disease; PR: partial response; SD: stable disease.
Source: (BMS 2020, Janjigian 2021b)

7.2.1.3.3 Time to treatment response and duration of response in patients with PD-L1 CPS ≥5 (minimum follow-up 12.1 months)

In patients with PD-L1 CPS ≥5 who had measurable disease that responded to treatment, the median time to treatment response (TTR) was 1.5 (95% CI, 1.4–2.8) months in the nivolumab plus chemotherapy arm and 1.5 (95% CI, 1.4–2.7) months in the chemotherapy alone arm (Janjigian 2021a). Median duration of response (DOR) (95% CI) was longer in the nivolumab plus chemotherapy arm by 2.5 months compared with the chemotherapy alone arm (9.5 months [8.0–11.4] vs. 7.0 months [5.7–7.9]) (Moehler 2020b, Janjigian 2021b) (Figure 10).

[redacted]

Figure 10: Kaplan-Meier plot of DOR per BICR, all responders with PD-L1 CPS ≥5 (minimum follow-up 12.1 months)



[a]Randomised patients who had target lesion measurements at baseline per BICR assessment; [b]Number of responders.
Abbreviations: CI: confidence interval; DOR: duration of response; mo: month.
Source: (BMS 2020, Moehler 2020a, Janjigian 2021b)

Efficacy outcomes for all randomised patient population are summarised in Appendix K.

[redacted]

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Patient-reported outcomes for all randomised patient population are summarised in Appendix K.

7.2.2 Safety

7.2.2.1 Safety summary (minimum follow-up 24.0 months)

At longer follow-up (minimum 24.0 months), no new safety signals were identified with nivolumab plus chemotherapy. A summary of treatment-related adverse events (TRAEs) in all randomised patients is presented below in Section 23 (Janjigian 2021a). The most common Grade 3–4 TRAEs for nivolumab plus chemotherapy included neutropenia, decreased neutrophil count, and anaemia, whereas neutropenia, decreased neutrophil count, and diarrhoea were the most common Grade 3-4 TRAEs in the chemotherapy alone arm (Janjigian 2021a). The incidence of TRAEs in patients with PD-L1 CPS ≥5 was also consistent with the all randomized patient group (Janjigian 2021a).

Table 14: Summary of TRAEs, all randomised patients (minimum follow-up 24.0 months)

All treated[a], n (%)	Nivolumab plus chemotherapy (N=782)[b]		Chemotherapy (N=767)[b]	
	Any grade	Grade 3–4	Any Grade	Grade 3–4
Any TRAEs[c]	739 (95)	471 (60)	682 (89)	344 (45)
Serious TRAEs[c]	175 (22)	133 (17)	94 (12)	77 (10)
TRAEs leading to discontinuation[c,d]	300 (38)	141 (18)	188 (25)	70 (9)
Treatment-related deaths[e]	16 (2)[f]		4 (<1)[g]	

[a]Patients who received ≥ 1 dose of study drug; [b]Concurrently randomised to NIVO + chemo vs chemo; [c]Assessed in all treated patients during treatment and for up to 30 days after the last dose of study treatment; [d]TRAEs leading to discontinuation of any drug in the regimen; [e]Treatment-related deaths were reported regardless of timeframe; [f]Included 4 events of pneumonitis, 2 events of febrile neutropenia or neutropenic fever, and 1 event each of acute cerebral infarction, disseminated intravascular coagulation, Gastro-intestinal bleeding, Gastro-intestinal toxicity, infection, intestinal mucositis, mesenteric thrombosis, pneumonia, septic shock, and stroke; [g]Included 1 event each of asthenia and severe hyporexia, diarrhoea, pneumonitis, and pulmonary thromboembolism; [i]Included 2 events of cardiac failure and 1 event each of acute hepatic failure, autoimmune hepatitis, general physical health deterioration, herpes simplex reactivation, hypophysitis, immune-mediated enterocolitis, multiple organ dysfunction syndrome, pneumonitis, and upper GI hemorrhage; [j]Included 1 event each of diarrhoea, pancytopenia, and pulmonary embolism.
Abbreviations: TRAE: treatment-related adverse event.
Source: (Janjigian 2021a)

A summary of TRAEs with potential immunologic etiology in all randomised patients is presented below in Table 15 (Janjigian 2021a). The majority of events were Grade 1 or 2, with Grade 3–4 events occurring in ≤ 5% of patients in the nivolumab plus chemotherapy arm across organ categories (Janjigian 2021a). Please note that the definition of select AEs is based on nivolumab experience, thus the list of MedDRA select AEs is based on nivolumab, and the select AEs in the chemotherapy only arm are presented for comparison.

Table 15: Summary of TRAEs with potential immunologic etiology, all randomised patients (minimum follow-up 24.0 months)

All treated[a,b], n (%)	Nivolumab plus chemotherapy (N=782)[c]		Chemotherapy (N=767)[c]	
	Any grade	Grade 3–4[d]	Any Grade	Grade 3–4
Endocrine	109 (14)	6 (<1)	3 (<1)	0
Gastrointestinal	266 (34)	43 (5)	208 (27)	25 (3)
Hepatic	207 (26)	31 (4)	138 (18)	17 (2)
Pulmonary	41 (5)	14 (2)	4 (<1)	1 (<1)
Renal	29 (4)	7 (<1)	9 (1)	2 (<1)
Skin	218 (28)	27 (3)	108 (14)	8 (1)

[a]Patients who received ≥ 1 dose of study drug; [b]AEs were assessed in all treated patients during treatment and for up to 30 days after the last dose of study treatment; [c]Concurrently randomised to NIVO + chemo vs chemo; [d]The most common grade 3–4 events (≥ 2%) were diarrhoea (n = 35), aspartate aminotransferase increased (n = 13), palmar-plantar erythrodysesthesia (n = 12).

7.2.2.2 Abbreviations: TRAE: treatment-related adverse event. Source: (Janjigian 2021a)Adverse events in all randomized patients (minimum follow-up 12.1 months)

Overall, the safety profile of nivolumab plus chemotherapy in patients with previously untreated advanced or metastatic GC, GEJC, or EAC was consistent with the known safety profiles for the nivolumab and chemotherapy components (Janjigian 2021b). No new safety signals or toxicities were identified, relative to each agent neither as monotherapy nor in combination (Janjigian 2021b). The safety profile for nivolumab plus chemotherapy in patients with CPS ≥5 and CPS ≥1 was consistent with that in all treated patients (Janjigian 2021b).

The safety population included all treated patients. The following section includes safety results for all subjects (N=1,549) that were both randomised and treated in the nivolumab plus chemotherapy and chemotherapy alone arms in CheckMate 649 (Janjigian 2021b).

The overall frequencies for all-cause adverse events (AEs) and treatment-related adverse events (TRAEs) were similar across the two arms (Janjigian 2021b). The addition of nivolumab to chemotherapy resulted in a ≤4% increase in the most common grade 3 or 4 TRAEs (Table 16). [redacted]

The most common TRAE across both arms were nausea, diarrhoea, peripheral neuropathy, anaemia, fatigue, vomiting, neutropenia, decreased appetite, thrombocytopenia, and aspartate aminotransferase increased (BMS 2020, Janjigian 2021b). [redacted] Grade 3–4 TRAEs of potential immunologic etiology occurred in ≤5% of patients in the nivolumab plus chemotherapy arm (Moehler 2020a).

Table 16: Summary of safety, all randomised patients (minimum follow-up 12.1 months)

	Nivolumab plus chemotherapy (N=782)		Chemotherapy (N=767)	
	Any grade	Grade 3–4	Any Grade	Grade 3–4
All-cause AEs	[redacted]	[redacted]	[redacted]	[redacted]
All-cause SAEs	[redacted]	[redacted]	[redacted]	[redacted]
All-cause AEs leading to discontinuation	[redacted]	[redacted]	[redacted]	[redacted]
Treatment-related AEs	738 (94.4)	462 (59.1)	679 (88.5)	341 (44.5)
Treatment-related SAEs	172 (22.0)	131 (16.8)	93 (12.1)	77 (10.0)
Treatment-related AEs leading to discontinuation	284 (36.3)	132 (16.9)	181 (23.6)	67 (8.7)
Treatment-related AEs in ≥5% of patients in any treatment group				
Nausea	323 (41.3)	20 (2.6)	292 (38.1)	19 (2.5)
Diarrhoea	253 (32.4)	35 (4.5)	206 (26.9)	24 (3.1)
Neuropathy peripheral[a]	221 (28.3)	31 (4.0)	190 (24.8)	22 (2.9)
Anaemia	203 (26.0)	47 (6.0)	171 (22.3)	21 (2.7)
Fatigue	202 (25.8)	30 (3.8)	173 (22.6)	17 (2.2)
Vomiting	195 (24.9)	17 (2.2)	166 (21.6)	24 (3.1)
Neutropenia	191 (24.4)	118 (15.1)	181 (23.6)	93 (12.1)
Neutrophil count decreased	158 (20.2)	83 (10.6)	118 (15.4)	67 (8.7)
Thrombocytopenia	157 (20.1)	19 (2.4)	145 (18.9)	13 (1.7)
Decreased appetite	157 (20.1)	14 (1.8)	139 (18.1)	13 (1.7)
Platelet count decreased	156 (19.9)	20 (2.6)	115 (15.0)	19 (2.5)
Peripheral sensory neuropathy[a]	137 (17.5)	16 (2.0)	119 (15.5)	14 (1.8)
Aspartate aminotransferase increased	122 (15.6)	12 (1.5)	69 (9.0)	5 (0.7)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Nivolumab plus chemotherapy (N=782)		Chemotherapy (N=767)	
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All-cause select AEs				
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Treatment-related select AEs				
Endocrine	107 (13.7)	5 (0.6)	3 (0.4)	0
Gastrointestinal	262 (33.5)	43 (5.5)	207 (27.0)	25 (3.3)
Hepatic	203 (26.0)	29 (3.7)	134 (17.5)	16 (2.1)
Pulmonary	40 (5.1)	14 (1.8)	4 (0.5)	1 (0.1)
Renal	26 (3.3)	6 (0.8)	8 (1.0)	1 (0.1)

	Nivolumab plus chemotherapy (N=782)		Chemotherapy (N=767)	
Skin	214 (27.4)	26 (3.3)	105 (13.7)	6 (0.8)

Abbreviations: AE: adverse event; SAE: serious adverse event.
Note: [a] The coded preferred term "neuropathy peripheral" versus " peripheral sensory neuropathy" depend on how the site reports the AE verbatim term in the eCRF. There is no clinical difference between these terms, it is a matter of how the site/investigator reports the event/AE verbatim term in the eCRF.
Source: (BMS 2020, Moehler 2020a)

7.2.2.3 Deaths (minimum follow-up 12.1 months)

Sixteen deaths in the nivolumab plus chemotherapy group and four deaths in the chemotherapy alone arm were considered treatment related (Janjigian 2021b). Preferred terms for cause of death were per investigator assessment (Janjigian 2021b). Twelve treatment-related deaths in the nivolumab plus chemotherapy arm were due to (Janjigian 2021b):

- Three cases of pneumonitis
- Two cases of febrile neutropenia or neutropenic fever
- One case each of gastrointestinal bleeding, gastrointestinal toxicity, infection, intestinal mucositis, pneumonia, septic shock, and stroke.

An additional four deaths due to other reasons were specified as related to treatment by the investigator (Janjigian 2021b). These included one case each of acute cerebral infarction, mesenteric thrombosis, disseminated intravascular coagulation, and pneumonitis (Janjigian 2021b). Of the 16 deaths in the nivolumab plus chemotherapy group, four were deemed to be related to nivolumab, five to nivolumab plus chemotherapy, and seven to chemotherapy alone (Janjigian 2021b).

Treatment-related deaths in the chemotherapy alone group were due to diarrhoea, asthenia and severe loss of appetite, pulmonary thromboembolism, and pneumonitis (Janjigian 2021b).

7.3 Comparative analyses of efficacy and safety

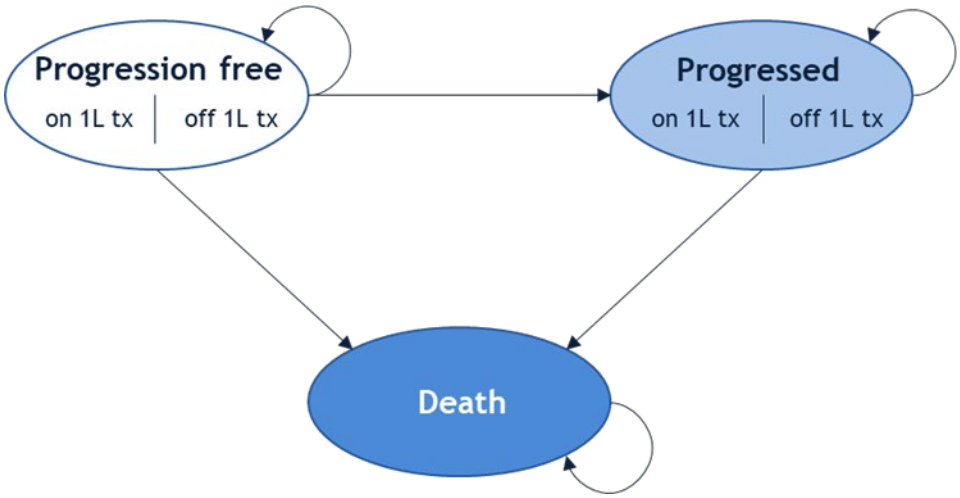
As the comparator arm in the pivotal CheckMate 649 study (XELOX/FOLFOX) can be considered equivalent to other chemotherapy regimens used as standard of care in this patient population in Denmark, no indirect treatment comparison was conducted. The CheckMate 649 trial results provide head-to-head data for nivolumab plus chemotherapy vs. chemotherapy alone (the recommended treatment in Denmark as per guidelines) (DEGC 2020a).

8. Health economic analysis

8.1 Model structure

A partitioned survival analysis was used to model the transition of patients between three health states i.e., Progression-free (PF), Progressed disease (PD) and Death (Figure 15). These health states are reflective of the natural disease process in GC, GEJC and EAC and correspond to the primary and secondary endpoints in the CheckMate 649 trial. The model structure accounts for time on treatment within the PF and PD health states.

Figure 15: Model structure



Abbreviations: 1L; first line, tx; treatment

The distribution of patients across health states over time (schematic overview presented in Figure 16) is estimated based on the OS and PFS over time as observed in the trial. This information is extrapolated to cover the model's complete time horizon (see section 8.3.2 and section 8.3.3). Time on treatment can be estimated by either using PFS or time to treatment discontinuation (TTD); the latter was used for the base case. An alternative modeling approach based upon the mean number of doses from CheckMate 649 was also included in the model.

$$PF(t) = S_{PFS}(t)$$

$$PD(t) = S_{OS}(t) - S_{PFS}(t)$$

$$Death(t) = 1 - S_{OS}(t)$$

$$On\ tx(t) = S_{PFS}(t) \mid S_{TTD}(t)$$

With $S_x(t)$ being the survival probability of x at time = t.

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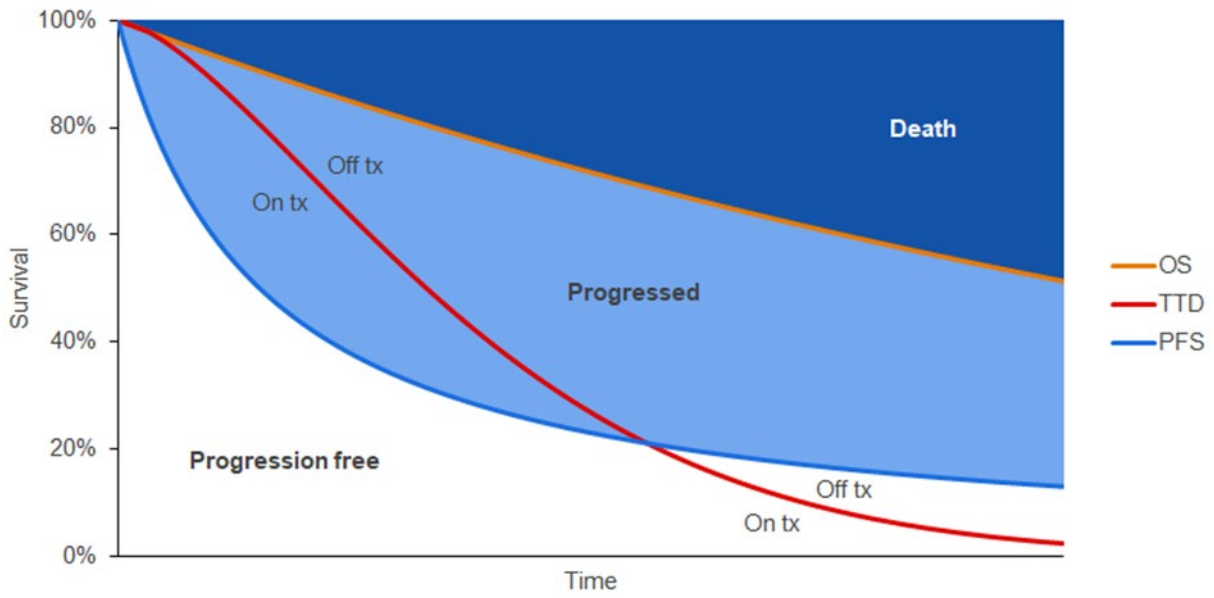
Figure 16: Example of health state occupancy over time in a partitioned survival model



Abbreviations: OS; overall survival, PFS; progression free survival, TTD; time to treatment discontinuation, Tx; treatment.
Note: this figure is not reflective of survival for 1L GC, GEJC or EAC patients, but is provided for illustrative purposes to clarify the relationships between the PFS, TTD, and OS curves and occupancy in the model's three health states.

Health state occupancy for PF, PD, and death is based on the PFS per independent review committee and OS curves from the CheckMate 649 trial. The area under the PFS curve (see the blue curve in the example in Figure 16) represents the mean time patients are progression free. The area between the PFS and OS curves reflects the mean time in PD, and the area above the orange OS curve represents death. The more efficacious the treatment, the smaller the death area. In every model cycle, patients accrue quality adjusted life years (QALYs) and costs that are associated with the PF and PD health states.

The Partitioned survival model (PSM) is frequently used for modelling oncology treatments. The partitioning into PF and PD states is a well-established method within oncology, which means that the modeled treatments appropriately reflect the relevant clinical pathways. Therefore the PSA is a good choice for this assessment as it also facilitates comparability and reproducibility across different treatments in the oncology space. Another benefit of partitioned survival analysis is that it enables survival extrapolations to be based upon time-to-event data with few structural limitations.

8.1.1 Main outcomes

The main outcomes of the model were the costs associated with each treatment, as well as the health outcomes expressed in terms of life years (LYs) and quality-adjusted life years (QALYs). The main single-value metric of cost-effectiveness was the incremental cost-effectiveness ratio (ICER). Cost-effectiveness acceptability curves (CEACs) were also generated to assess how the probability of cost-effectiveness varies with increasing willingness-to-pay (WTP) thresholds.

8.1.2 Time to treatment discontinuation

Although most oncology treatments are prescribed until biological progression (according to response evaluation criteria in solid tumours [RECIST] 1.1 criteria) (Nishino 2010), treatment with nivolumab is recommended until 'clinical' progression i.e., as long as clinical benefit is observed, which is plausible even after biological progression. Furthermore, oncologic treatments could be discontinued before biological progression, due to e.g., adverse events. In both cases,

the PFS curve neither correctly reflects patients' time on treatment nor the corresponding treatment costs. Hence, the partitioned survival analysis model includes a time-to-treatment discontinuation (TTD) curve to estimate patients' time on treatment. The model accounts for the probability of patients in PF and PD to be on and off a given treatment. The CheckMate 649 trial included a stopping rule for nivolumab after 24 months.

The analyses of the TTD curves for the separate treatments within a regimen, revealed that oxaliplatin was discontinued by almost all patients in both arms after 12 months, which is much earlier compared to the other treatments included in the regimens. Therefore, the estimated doses for oxaliplatin based on the combined TTD curve will overestimate the actual number of doses used in the trial. Since almost all patients in both trial arms have discontinued oxaliplatin by 12 months, the mean number of doses of oxaliplatin received per patient in each arm of CheckMate 649 is used to calculate oxaliplatin costs.

At 12 months, for subjects with PD-L1 CPS ≥ 5:

- In the nivolumab plus XELOX groups, 4 out of 231 patients (1.7%) were still being treated with oxaliplatin
- In the XELOX alone group, 10 out of 223 patients (4.8%) were still being treated with oxaliplatin
- In the nivolumab plus FOLFOX groups, 2 out of 237 patients (0.8%) were still being treated with oxaliplatin
- In the FOLFOX alone group, 6 out of 242 patients (2.5%) were still being treated with oxaliplatin

The methods used to extrapolate the TTD curve is presented in section 19.5.

8.1.3 Cycle length

A cycle length of 1 week was used for the cost-effectiveness model. Since the nivolumab plus XELOX treatment regimen is administered once every three weeks and the nivolumab plus FOLFOX regimen is administered once every two weeks, a cycle length of 1 week was chosen as it is the common denominator. Furthermore, this cycle length is sufficiently short to capture differences in survival and can also easily accommodate a variety of treatment dosage and monitoring regimens.

8.1.3.1 Half-cycle correction

In health economic modeling Half-cycle correction is applied to account for the fact that state transitions can occur at any time during the cycle. Applying the Half-cycle correction, therefore, has an effect on the distribution of patients in the different health states across the time horizon and will as a consequence impact the resulting total costs and QALYs.

8.1.4 Perspective

This analysis uses a limited societal perspective including patient costs. The economic model also has the possibility of applying a more limited payer perspective. Results from the latter are reported as a scenario analysis.

8.1.5 Time horizon

The model adopts a time horizon of 15 years. This time horizon was chosen in accordance with DMC guidelines (Medicinrådet 2021c), since it accounts for all expected and significant costs and clinical benefits related to the intervention and its comparators, during the patients' entire lifetime. Given the expected overall survival, however, increasing the time horizon beyond 15 years should have a marginal impact on both costs and health outcomes. Nonetheless, this was explored through scenario analysis by increasing the time horizon to 25 years.

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8.1.6 Discounting

A discount rate of 3.5% is applied for both costs and health outcomes within the base case analysis (Finansministeriet 2021, Medicinrådet 2021c). Since the model time horizon is limited to 15 years, the same discount rate is applied throughout the entire time horizon in the analysis. A discount rate of 0% was explored through scenario analysis.

8.2 Relationship between the data for relative efficacy, parameters used in the model and relevance for Danish clinical practice

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

Table 17 describes the input data used in the economic model.

Table 17: Input data used in the model

[redacted]

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[redacted]	[redacted]	[redacted]
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8.2.2 Relationship between the clinical documentation, data used in the model and Danish clinical practice

8.2.2.1 Patient population

Danish clinical practice:

The aim of the cost-effectiveness analysis is to capture the likely outcomes in Danish clinical practice as accurately as possible. [redacted]

Clinical documentation submitted (in relation to clinical practice):

In CheckMate 649, the median age of patients with PD-L1 CPS ≥5 was 62.0 years (Janjigian 2021b); [redacted] The majority of patients were white (68.6%) and there were more males (71.2%) than females. Most patients were diagnosed with GC (69.8%); 17.8% had GEJ cancer and 12.4% had EAC (Janjigian 2021b). [redacted]

Model submitted (according to clinical documentation and clinical practice):

Following feedback from the clinical experts, patient baseline characteristics from CheckMate 649 (HER-2 negative with PD-L1 tumour expression CPS ≥ 5) were used in the economic model, except for the patient age at which treatment is

started, for which the mean value of the clinical expert-provided values was used (Norwegian KOL interview 2021). The data used for the economic analysis is presented in Table 18.

Table 18: Patient characteristics

Patient population	Clinical documentation	Clinical practice	Used in Model
Proportion of females (%)	[redacted]	[redacted]	[redacted]
Mean age at treatment start (years)	[redacted]	[redacted]	[redacted]
Mean bodyweight (kg)	[redacted]	[redacted]	[redacted]
Mean BSA (m^2)	[redacted]	[redacted]	[redacted]

Abbreviations: BSA: body surface area
Note: * No value for clinical practice could be identified specifically for a population with PD-L1 tumour expression CPS ≥ 5. Instead, this input relies upon values from CM649 (CPS > 5), with clinical experts conforming the validity of using these values as a proxy for patient characteristics (CPS ≥ 5) in clinical practice.
Reference: (Norwegian KOL interview 2021)

8.2.2.2 Intervention

The intervention in this analysis is nivolumab plus chemotherapy, in line with the CheckMate 649 trial. The Chemotherapy component can be either XELOX or FOLFOX. Both were included in the CheckMate 649 trial and were concluded to have the same clinical efficacy. 49.3% of the patients with tumour CPS ≥ 5 in CheckMate 649 received nivolumab plus XELOX and 50.7% received nivolumab plus FOLFOX. However, for the base case analysis, only XELOX was used since It is considered to be best aligned to Danish clinical practice, and since XELOX and FOLFOX can be considered to be equivalent (see section 5.2.2).

The dosage assumptions in this analysis follow the dosing schedule from the trial. Depending on the chemotherapy component prescribed, patients receive one of the following two dosage regimens:

1. Patients assigned to nivolumab plus XELOX receive 360 mg nivolumab (IV) and a cocktail consisting of 130 mg/m^2 oxaliplatin (IV) on day 1 of a 3-weeks treatment cycle, and 1000 mg/m^2 capecitabine (oral) administered twice daily on days 1 to 14 of the cycle.
2. Patients assigned to nivolumab plus FOLFOX receive 240 mg nivolumab (IV) plus a cocktail of 85 mg/m^2 oxaliplatin (IV), 400 mg/m^2 leucovorin (IV) and 400 mg/m^2 fluorouracil(IV), administered on day 1 of a 2-weeks treatment cycle and 1200 mg/m^2 fluorouracil (IV) as a continuous infusion for 24 hours daily on days 1 and 2 of each the cycle.

In this analyis no distinciton is made between nivolumab plus chemotherapy patients receiving XELOX and FOLFOX, as no substantial difference in efficacy was found for the CheckMate 649 patient subgroups receiving either regimen backbones. Note that use of XELOX vs FOLFOX was a stratification factor in the CheckMate 649 trial. Furthermore, clinical experts consider XELOX and FOLFOX as having equivalent efficacy in first-line gastroesophageal adenocarcinoma patients (Norwegian KOL interview 2021). The impact of changing this distribution is explored through scenario analyses.

For the survival analyses, the combined data of the nivolumab plus XELOX and nivolumab plus FOLFOX is used, without distinguishing between the individual treatments (see section 8.3). Within the model, the drug acquisition cost is calculated for each treatment separately, and the total acquisition costs is weighted by the proportion of patients on the respective treatment (see section 8.5.2). Note that for the base case, 100% of patients were assumed to be treated with nivolumab plus XELOX. Likewise, the resource use for each chemotherapy regimen is estimated by multiplying the quantity of each regimen specific resource use with the proportion of patients on the regimen (see section 8.5.1). For adverse events, utilities and subsequent treatment, data were only available per treatment arm, i.e. no distinction between XELOX and FOLFOX were made (see sections 8.5.3, 8.4, and 8.5.4, respectively).

Table 19: Intervention baseline characteristics

Intervention	Clinical documentation	Used in the model (Danish clinical practice)
Posology		
Nivolumab plus XELOX	CheckMate 649 trial	Nivolumab plus oxaliplatin 130 mg/m^2 IV on day 1 of each treatment cycle of 3 weeks, and capecitabine 1000 mg/m^2 orally twice daily on days 1 to 14 of each treatment cycle of 3 weeks
Nivolumab plus FOLFOX		Nivolumab 240 mg administered IV over 30 minutes + oxaliplatin 85 mg/m^2, leucovorin 400 mg/m^2, and fluorouracil 400 mg/m^2 administered on day 1 of each treatment cycle of 2 weeks and fluorouracil 1200 mg/m^2 IV continuous infusion over 24 hours daily on days 1 and 2 of each treatment cycle of 2 weeks
Length of treatment		
Nivolumab plus XELOX	CheckMate 649 trial	7.11 months
Ipilimumab plus FOLFOX		

Abbreviations: FOLFOX: 5-fluorouracil plus leucovorin plus oxaliplatin; IV: intravenous; XELOX: capecitabine plus oxaliplatin.

8.2.2.3 Comparators

In line with the CheckMate 649 trial, the comparator in this analysis was chemotherapy alone, which could be either XELOX or FOLFOX. In the CheckMate 649 trial 59.8% and 40.2% of the patients with CPS ≥ 5 received XELOX and FOLFOX respectively. However, in the base case analysis, XELOX was used as the comparator for 100% of the patients since it best aligns to Danish clinical practice, and since XELOX and FOLFOX can be considered equivalent (see section 5.2.2). Clinical experts verified that this aligned with contemporary clinical practice.

Similar to the intervention arm, the dosage assumptions for the comparator in this analysis follow the dosing schedule from the CheckMate 649 trial. Depending on the chemotherapy regimen prescribed, patients receive one of the following 2 regimens:

1. Patients assigned to XELOX receive a cocktail consisting of 130 mg/m^2 oxaliplatin (IV) on day 1 of a 3-weeks treatment cycle, and 1000 mg/m^2 capecitabine (oral) administered twice daily on days 1 to 14 of the cycle.
2. Patients assigned to FOLFOX receive a cocktail of 85 mg/m^2 oxaliplatin, 400 mg/m^2 leucovorin (IV) and 400 mg/m^2 fluorouracil (IV), administered on day 1 of a 2-weeks treatment cycle and 1200 mg/m^2 fluorouracil (IV) as a continuous infusion for 24 hours daily on days 1 and 2 of each the cycle.

Just as for the intervention (section 8.2.2.2), this analysis assumes no difference in the clinical outcomes between these two chemotherapy regimens. This is based upon both clinical expert opinion and the absence of significant differences in outcome in the CheckMate 649 trial. Combined data from patients on XELOX and FOLFOX is used in the survival analyses, adverse event data, utility analyses and subsequent treatment data (see sections 8.5.3, 8.4, and 8.5.4, respectively). However, drug acquisition costs and resource use (sections 8.5.2 and 8.5.1, respectively) are calculated based upon the share of patients given each treatment. In the base case, 100% of patients were assumed to receive XELOX treatment.

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Table 20: Comparator baseline characteristics

Intervention	Clinical documentation	Used in the model (Danish clinical practice)
Posology		
XELOX	CheckMate 649 trial	Oxaliplatin 130 mg/m^2 administered IV on day 1 of each treatment cycle of 3 weeks, and capecitabine 1000 mg/m^2 administered orally twice daily on days 1 to 14 of each treatment cycle of 3 weeks
FOLFOX		Oxaliplatin 85 mg/m^2, leucovorin 400 mg/m^2, and fluorouracil 400 mg/m^2 administered on day 1 of each treatment cycle of 2 weeks and fluorouracil 1200 mg/m^2 IV continuous infusion over 24 hours daily on days 1 and 2 of each treatment cycle of 2 weeks
Length of treatment		
XELOX	CheckMate 649 trial	4.6 months
FOLFOX		

Abbreviations: FOLFOX: 5-fluorouracil plus leucovorin plus oxaliplatin; IV: intravenous; XELOX: capecitabine plus oxaliplatin.

8.2.2.4 Relative efficacy outcomes

Danish clinical practice:

The current standard of care in patients with previously untreated advanced or metastatic GC/GEJC and EAC is fluoropyrimidine and platinum-based combination chemotherapy (Norwegian KOL interview 2021). Therefore the chemotherapy alone comparator in CheckMate 649 is both relevant and transferable to Danish clinical practice.

Clinical documentation submitted (in relation to clinical practice):

The clinical documentation for this submission is almost entirely based upon CheckMate 649. Since the comparator in CheckMate 649 is also the current standard of care in Denmark, no indirect comparisons were required for this submission.

The relative efficacy outcomes in CheckMate 649 are described in Section 7.2. Table 21 presents the median OS, PFS and TTD observed in patients with tumour PD-L1 expression with CPS ≥ 5 in CheckMate 649.

Table 21: Survival outcomes in CheckMate 649 for HER-2 negative patients with tumour PD-L1 expression CPS ≥ 5

Clinical efficacy outcome	Clinical documentation
Median OS nivolumab plus chemotherapy (months)	[redacted]
Median OS chemotherapy alone (months)	[redacted]
Median PFS nivolumab plus chemotherapy (months)	[redacted]
Median PFS chemotherapy alone (months)	[redacted]
Median TTD nivolumab plus chemotherapy (months)	[redacted]

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Clinical efficacy outcome	Clinical documentation
Median TTD chemotherapy alone (months)	[redacted]

Abbreviations: CI: confidence interval; OS: overall survival; PFS: progression-free survival; TTD: time to treatment discontinuation.

Model submitted (according to clinical documentation and clinical practice):

The efficacy outcomes for OS, PFS, and TTD for both nivolumab plus chemotherapy and chemotherapy alone are presented in Sections 8.3.2, 8.3.3 and 8.3.4, respectively.

8.2.2.5 Adverse reaction outcomes

Danish clinical practice:

The current clinical practice for treating adverse events related to this disease and its management is described in section 8.5.3.

Clinical documentation submitted (in relation to clinical practice):

Overall, the safety profile of nivolumab plus chemotherapy in patients with previously untreated advanced or metastatic GC, GEJC, or EAC was consistent with the known safety profiles of the nivolumab and chemotherapy components (Janjigian 2021b). No new safety signals or toxicities were identified, relative to each agent either as monotherapy or in combination (Janjigian 2021b). The safety profile of nivolumab plus chemotherapy in patients with CPS ≥5 was consistent with that in all treated patients (BMS 2020, Moehler 2020a).

The overall frequencies of all-cause adverse events (AEs) and treatment-related adverse events (TRAEs) were similar across the two arms (Janjigian 2021b). The addition of nivolumab to chemotherapy resulted in a ≤4% increase in the most common grade 3 or 4 TRAEs (Table 16). [redacted]

The most common TRAE across both arms were nausea, diarrhoea, peripheral neuropathy, anaemia, fatigue, vomiting, neutropenia, decreased appetite, thrombocytopenia and increased levels of aspartate aminotransferase (BMS 2020, Janjigian 2021b). [redacted] Grade 3–4 TRAEs of potential immunologic aetiology occurred in ≤5% of patients in the nivolumab plus chemotherapy arm (Moehler 2020a).

Model submitted (according to clinical documentation and clinical practice):

The cost-effectiveness model includes grade 3 & 4 adverse events (AEs) that occurred in at least 5% of the ITT population across the trial arms of the CheckMate 649 trial. The utility loss per AE was considered for the duration of the AE. The costs for the AEs were calculated per event. Adverse events specific utility losses and costs are presented in sections 8.4.2 and 8.5.3, respectively.

The incidence of AEs for patients treated with nivolumab plus chemotherapy and chemotherapy alone was sourced from the CheckMate 649 clinical trial. While the model includes grade 3 & 4 AEs that occurred in at least 5% of the ITT population, only patients with PD-L1 expression CPS ≥ 5 were included when calculating the probability of adverse events. Table 22 summarises the AE data included in the base case analysis.

Table 22: Adverse events included in the economic model, incidence per treatment arm

Grade 3-4 adverse events	Nivolumab plus chemotherapy	Chemotherapy

Nausea	1.30%	2.40%
Diarrhoea	3.40%	3.00%
Vomiting	1.90%	3.00%
Neuropathy peripheral	4.90%	2.20%
Neutrophil count decreased	11.10%	8.80%
Platelet count decreased	2.60%	3.20%
Lipase increased	4.70%	2.10%
Anaemia	6.20%	2.80%
Neutropenia	15.40%	12.00%
Fatigue	3.20%	2.40%

8.3 Extrapolation of relative efficacy

8.3.1 Time to event data – summarised

Time to event data was obtained from the latest available data from CheckMate 649 (database lock [DBL] in July 2021). To appropriately reflect the indication for this application, only data from patients with tumour PD-L1 expression CPS ≥ 5 was included in this analyses. Survival models were constructed in line with best modelling practices (Latimer 2011) and curve selections were based upon either statistical fit alone or statistical fit in combination with external validation using relevant available external data sets.

The OS, PFS and TTD Kaplan Meier (KM) curves and the numbers at risk for patients with CPS ≥ 5 in CheckMate 649 (based on the July 2021 database lock), are presented in [redacted] to [redacted] In the TTD curve for the nivolumab plus XELOX/FOLFOX arm ([redacted]), a significant drop can be seen at 24 months. This is because the maximum treatment duration for nivolumab in CheckMate 649 was set to 24 months. Note that the TTD curve represents discontinuation from all components of the treatment regimen and that the model assumes that all treatment discontinuation takes place simultaneously at 24 months.

[redacted]

[redacted]

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[redacted]

[redacted]

The extrapolation methods for OS, PFS and TTD are presented in sections 8.3.2, 8.3.3 and 8.3.4, respectively. More details about the extrapolation methods are also presented in Appendix G.

8.3.2 Overall survival

8.3.2.1 Extrapolation approach for overall survival

The estimation of the long-term OS of the target population for this submission was based on extrapolations of the time-to-event data from CheckMate 649. In line with best modelling practices (Latimer 2011), statistical tests comparing nivolumab plus chemotherapy against chemotherapy alone were performed to test whether the assumption of proportional hazards was met. The result of this analysis is presented in Appendix G.

Even if it was not possible to reject the proportional hazards function with the statistical tests, the two trial arms included agents of different therapeutic classes, the experimental arm including nivolumab, an immuno-oncology agent which has a different mechanism of action to the chemotherapy agents, promoting anti-tumour activity from the immune system. [redacted]

Seven standard parametric models and six cubic spline models were fitted to the OS data from CheckMate 649 (PD-L1 expression CPS ≥ 5), both as dependent and independent extrapolations. The statistical fit for these models were then compared to the Kaplan-Meier (KM curves) from CheckMate 649. For the base case, independent models were used for the OS extrapolations. The predicted survival and statistical fit for all the models is presented in Table 23. Standard parametric models are presented in Figure 20 and Figure 21 and Cubic spline models are presented in Figure 22 and Figure 23 To evaluate the model's sensitivity to variations in the extrapolation settings, a scenario analysis using the

best-fitting dependent model was conducted. More information about the extrapolation process and the justification for the methodological choices is presented in Appendix G, along with the statistical assessment of the dependent models.

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Table 23: Extrapolated survival and statistical fit for independent models, overall survival

Survival model	Nivolumab plus chemotherapy					Chemotherapy				
	Median survival (months)	1-year survival (%)	5-year survival (%)	AIC	BIC	Median survival (months)	1-year survival (%)	5-year survival (%)	AIC	BIC
[redacted]										

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8.3.2.2 Model fit and comparison to external data

For the chemotherapy alone arm, the 5-year modeled OS was compared to published long-term follow up data, in first-line gastroesophageal adenocarcinoma patients. Five publications that report overall survival of up to 5 years, in the target population, were identified (Table 24). Chau et al. reported combined OS results for patients enrolled in four first-line chemotherapy trials in the UK and Australia, whereas all the other studies were observational (Chau 2009, Davidson 2018, Dijksterhuis 2020, Merchant 2021, Shankaran 2021).

Davidson et al., 2018 was based on patients at a single UK hospital (Royal Marsden, London), whereas Dijksterhuis et al. (Dijksterhuis 2020) and Merchant et al. (Merchant 2021) were population-based registry studies covering all patients in the Netherlands and the Ontario, Canada, respectively.

The highest 5-year survival rate was 5% and was reported by Merchant et al. (Merchant 2021). Noteworthy, 8% of the patients in this study were treated with trastuzumab and were also presumably HER-2 positive. Since trastuzumab is known to provide better outcomes than chemotherapy, this survival rate is presumably higher than that for patients on chemotherapy alone in CheckMate 649. All the other studies included only chemotherapy treated patients and reported a maximum 5-year survival of 3.5%. One of the limitations of all these studies is that none of them exclusively explored a HER-2 negative population with PD-L1 expression CPS ≥ 5. It should however be noted that the differences in OS between the ITT and CPS ≥ 5 populations in the chemotherapy alone arm of CheckMate 649 were small.

Table 24: Published long-term Overall survival data for first-line chemotherapy for GC, GEJC, or EAC

Study	n	Country	1-year OS	2-year OS	4-year OS	5-year OS
Chau et al., 2009	2,110	UK and Australia	36.8%	13.2%	4%	3.5%
Davidson et al., 2018	296	UK	51%	17.5%	4%	3%
Dijksterhaus et al., 2019	980	Netherlands	27%	8%	2%	Not reported
Shankaran et al., 2020	2,326	USA	38.8%	14.8%	4.5%	3%
Merchant et al., 2021*	2,207	Canada	30.5%	11.5%	5.5%	5%*

*Note that 8% of patients in Merchant et al study received trastuzumab and will therefore have enjoyed better outcomes than chemotherapy treated patients.

Abbreviations: EAC: adenocarcinoma of the esophagus; GC: gastric cancer;; GEJC: gastroesophageal junction cancer; n: number of patients; OS: overall survival

8.3.2.3 Selection of survival curves

As the OS data is quite mature with curves that are flattening out, standard parametric models may struggle to capture the shape of the KM, while the spline models better capture the curves, this can be seen in the smothered hazard plots in Appendix L – Smoothed hazard plots for CheckMate 649.

For nivolumab plus chemotherapy, the odds spline (1 knot) model was selected as the base case distribution for OS extrapolations on account of it yielding the best fitting curve (see Table 23). This model not only provided a good overall fit, but visual inspection showed that it avoided consistently either under- or overestimating the survival compared to

the Kaplan-Meier (KM) data from CheckMate 649; see below in [redacted] Compared to the second-best fitting model (odds spline [2 knots], included as scenario analysis), this yielded a slightly lower long-term survival.

For chemotherapy, the 1-knot odds spline model was again chosen for the base case. This model yielded one of the best fitting curves (see Table 23) as well as a plausible 5-year survival when compared to observed real-world data (see above, Table 24). Again, visual comparison with KM data from CheckMate 649 corroborated the choice of this as the most suitable model. By contrast, the independent model with the second best fit (Normal spline [1 knot], included as scenario analysis) predicted a substantially lower 5-year survival for patients treated with chemotherapy.

To assess the sensitivity of the cost-effectiveness results to the choice of extrapolation model, a scenario using the best-fitting dependent model was selected in the scenario analysis. The 2-knot hazard spline model showed the best statistical fit among the dependent models (see Appendix G). [redacted] For this reason, dependent modelling using the spline hazards (2 knots) model was used for OS extrapolations in the scenario analysis using dependent modelling.

The parameter values for the selected base case models are presented in Table 25. The resulting OS curve for both nivolumab plus chemotherapy and chemotherapy are shown in Figure 25. More details about the justification for the curve selection is presented in Appendix G.

Table 25: Selected model and parameterizations – Overall Survival (PD-L1 CPS ≥ 5 population)

Survival curve	Selected distribution	Input parameters
Nivolumab plus chemotherapy	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]

Abbreviations: CPS: combines positive score; PD-L1, programmed death-ligand 1.

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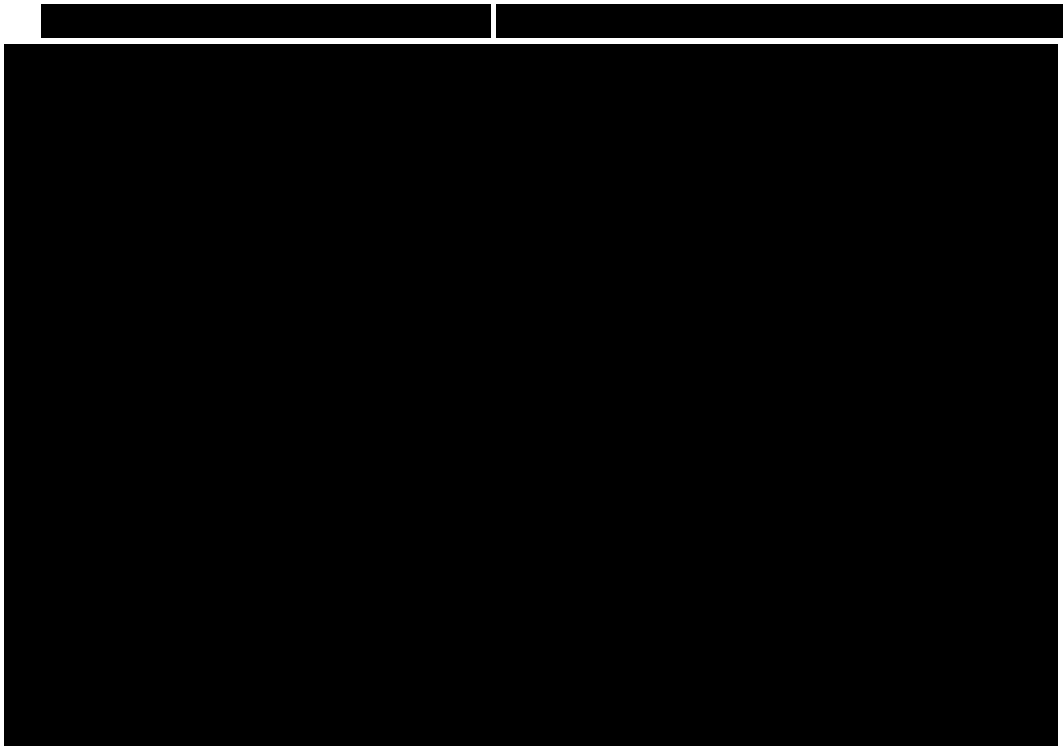
[redacted]

[redacted]

8.3.2.3.1 Scenario analyses

A number of scenario analyses on OS and PFS extrapolation where performed (see Scenario 11-14 in Table 48). The graphical illustrations of those are presented below.

[redacted]



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8.3.2.4 Background mortality

The model includes life tables to estimate background mortality (i.e., mortality due to any cause) to reflect the Danish population's general mortality, and to make sure that mortality hazards for patients cannot be lower than the mortality hazard observed in the general population at any point in time. As a result, an average patient cannot live longer than the average member of the general population. The adjustment is implemented by selecting the highest hazard from the hazard of the extrapolated OS and the hazard of the general population OS. This means that from whichever point the background mortality hazard exceeds the extrapolated hazard from the trial, the patient's mortality hazard will be following the background mortality instead. The background mortality was estimated assuming the same sex distribution as in CheckMate 649 at trial baseline.

Age- and sex-adjusted life tables for Denmark were obtained from Statistics Denmark (Statistics Denmark 2021). The mortality hazard was calculated based on the proportion of male and female patients assumed for this analysis (28.8% female, see section 8.2.2.1). The average mortality rates for years 2016 to 2020 were assumed for this analysis, these rates are included in Appendix M. In the absence of survival data beyond 100 years of age, a simplifying assumption was made that the sex-adjusted mortality hazard would increase by 2 percentage points per year between years 101 and 110. At age 110, the mortality hazard was set to 100%.

8.3.3 Progression-free survival

8.3.3.1 Extrapolation approach and model fit

The long-term PFS was based on extrapolations of the time-to-event data from CheckMate 649. In line with best modelling practices (Latimer 2011), statistical tests comparing nivolumab plus chemotherapy against chemotherapy alone were performed to test whether the assumption of proportional hazards was met. Based on the results of these tests, it was concluded that the proportional hazard assumption was violated, and that the independent models were best suited to estimate long-term progression-free survival. The result of this analysis is presented in Appendix G.

Seven standard parametric models and six cubic spline models were fit to the PFS data from CheckMate 649 (PD-L1 expression CPS ≥ 5) as independent extrapolations. The predicted survival and statistical fit for all the models is presented in Table 26. Standard parametric models are presented in Figure 29 and Figure 30 and cubic spline models are presented in Figure 31 and Figure 32.More information about the extrapolation process and the justification for the methodological choices is presented in Appendix G.

Table 26: PFS independent models for PD-L1 CPS ≥ 5 population

Model	Nivolumab plus chemotherapy		Chemotherapy	
	AIC	BIC	AIC	BIC
Exp.	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]
Gen. gam.	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Log-logis.	[redacted]	[redacted]	[redacted]	[redacted]
Log-norm.	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]

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1-k hazard	[redacted]	[redacted]	[redacted]	[redacted]
2-k hazard	[redacted]	[redacted]	[redacted]	[redacted]
1-k normal	[redacted]	[redacted]	[redacted]	[redacted]
2-k normal	[redacted]	[redacted]	[redacted]	[redacted]
1-k odds	[redacted]	[redacted]	[redacted]	[redacted]
2-k odds	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AIC: Akaike's information criterion; BIC: Bayesian information criterion; Exp: Exponential; Gen. gam: generalised gamma; Log-logis: log-logistic; log-norm: log-normal; 1-k: 1-knot; 2-k: 2-knot.

[redacted]

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[redacted]

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8.3.3.2 Selection of survival curves

In the base case analysis, the 2 knots normal spline model was selected to extrapolate PFS for both the nivolumab plus chemotherapy arm and chemotherapy alone, as it provided the best fit, both based on the AIC/BIC criterion as well as visual inspection. To assess the uncertainty associated with proportional hazards assumption made, a scenario analysis was performed where PFS was extrapolated using the best-fitting dependent model i.e., the 2 knots hazard spline model.

The posterior distribution parameter values for the selected PFS base case models are presented in Table 27. The resulting PFS curves for both nivolumab plus chemotherapy and chemotherapy alone are shown in [redacted] More details about the justification for the curve selection is presented in Appendix G.

Table 27: Selected model and parametrizations (PFS)

Survival curve	Selected distribution	Input parameters
Nivolumab plus chemotherapy	[redacted]	[redacted]

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Chemotherapy	[redacted]	[redacted]

Abbreviations: PFS: progression-free survival.

[redacted]

[redacted]

8.3.4 Duration of treatment

8.3.4.1 Extrapolation approach

Time to treatment discontinuation (TTD) was extrapolated based upon time-to-event data from CheckMate 649, specifically for patients with tumour PD-L1 expression levels CPS ≥ 5. Both treatment with nivolumab plus chemotherapy and chemotherapy alone consisted of several drugs (see sections 8.2.2.2 and 8.1.2). In this analysis, patients were only considered to be discontinued after they discontinued all treatments from the regimen. The CheckMate 649 trial included a stopping rule for nivolumab after 24 months. The TTD for both treatment arms in CheckMate 649 is presented in [redacted]

[redacted]

[redacted]

One problem with the TTD approach is that it cannot capture the discontinuation of individual drugs within a treatment; patients either receive the treatment as a whole or discontinue each of its components. Therefore, an alternative modeling approach based upon the observed mean number of doses for each drug within CheckMate 649 was included as a modeling option. Since the CheckMate 649 trial data is very mature, it is plausible to calculate the drug acquisition and administration costs for nivolumab plus chemotherapy and chemotherapy alone via the mean number of doses. The trial has a follow-up of more than 42 months and less than 3% of the patients are still on treatment. The mean number of doses per drug and treatment within CheckMate 649 for patients with PD-L1 expression levels ≥ 5 is presented in Table 28. This was based upon the database lock in July 2021 (BMS 2021).

Table 28: Mean number of doses per drug and treatment within CheckMate 649 (CPS ≥ 5)

Nivolumab plus XELOX (mean doses)		Nivolumab plus FOLFOX (mean doses)		XELOX (mean doses)		FOLFOX (mean doses)	
Nivolumab	[redacted]	Nivolumab	[redacted]	Oxaliplatin	[redacted]	Oxaliplatin	[redacted]
Oxaliplatin	[redacted]	Oxaliplatin	[redacted]	Capecitabine	[redacted]	Leucovorin	[redacted]
Capecitabine	[redacted]	Leucovorin	[redacted]			Fluorouracil (400mg)	[redacted]
		Fluorouracil (400mg)	[redacted]			Fluorouracil (1200 mg)	[redacted]
		Fluorouracil (1200 mg)	[redacted]				

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8.3.4.2 Selection of survival curves

Based upon results from statistical test, the assumption of proportional hazards was rejected, and independent modelling was used for TTD extrapolation. Seven standard parametric models and six cubic spline models were fitted to the OS data of CheckMate 649 (PD-L1 expression CPS ≥ 5). More details about this is presented in Appendix G. However, neither of the extrapolation models were able to account for the drop in TTD survival expected due to the 24-month treatment cap of nivolumab (see Figure 34). For this reason, KM data from CheckMate 649 was used for the model's TTD until after the treatment cap. This limit was set to 25 months, since it was assumed that treatment discontinuation due to the treatment cap would be registered within a month. Beyond 25 month, extrapolated data based upon the most suitable extrapolation models were used. Independent models were used since the proportional hazards assumption was rejected (see Appendix G for more details).

The base case settings for TTD in each treatment arm are shown in Table 29 and in Figure 35 In the base case analysis, the 1 knot hazard spline model was selected to extrapolate TTD for the nivolumab plus chemotherapy arm and the 1 knot odds spline model was selected for chemotherapy alone. More details about how the extrapolations were derived are presented in Appendix G. A scenario using mean number of doses per treatment component was included as scenario analysis.

Table 29: Selected model and parametrizations (TTD)

Survival curve	Selected distribution †	Input parameters
Nivolumab plus chemotherapy	[redacted]	[redacted]
	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]
	[redacted]	[redacted]

Abbreviations: CM649: CheckMate 649; KM: Kaplan-Meier; CPS: combined positive score; TTD: time to treatment discontinuation

† A piecewise approach was used, where KM data from CheckMate 649 was used for the first time period. Beyond this, extrapolations of the TTD curve was made based upon the best-fitting model.

[redacted]

8.4 Documentation of health-related quality of life (HRQoL)

8.4.1 Overview of health state utility values (HSUV)

HRQoL was one of the secondary endpoints in CheckMate 649 and was measured using two different instruments i.e., the FACT-Ga and the EQ-5D-3L. For the purpose of this analysis, result from the EQ-5D-3L were used to align with the preferred framework for Danish health technology assessment (HTA) evaluations (Medicinrådet 2021c).

As a criterion for inclusion in the EQ-5D-3L analysis, patients had to complete at least one measurement. If a patient had more than one observation per visit, all observations were recorded and included in the analysis. Patients with measurements performed at screening (i.e. before the baseline measurement, with a visit number below 0) were analyzed as if they had their first measurement on day 0 as it was not expected that this would bias the results.

The EQ-5D-3L assessment scheme from CheckMate 649 was as follows:

- On treatment phase
  - Assessed every 6 weeks (± 3 days) from cycle 1 day 1, regardless of treatment schedule.
- Follow-up phase
  - Follow-up visit 1: 30 days (± 7 days) after last dose.
  - Follow-up visit 2: 84 days (± 7 days) after follow-up visit 1.
  - Every 3 months (± 14 days) after follow-up visit 2, via a phone contact or in-person visit.

The analysis was performed on the population with CPS ≥ 5 of the October 2020 database lock (DBL) of the CheckMate 649 trial. Subgroup analyses with nivolumab plus XELOX, nivolumab plus FOLFOX, XELOX alone and FOLFOX alone were performed. The final health state utility values (HSUVs) for the nivolumab plus chemotherapy was a weighted average between utility scores for nivolumab plus XELOX (49.3%) and nivolumab plus FOLFOX (50.7%), with weights based upon the proportion of patients with CPS ≥ 5 who received each treatment in CheckMate 649. Similarly, the HSUVs for chemotherapy were a weighted average of patients treated with XELOX (59.2%) and FOLFOX (40.2%).

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The overall population size with CPS ≥ 5 was 955, of which 473 were in the nivolumab plus chemotherapy arm and 482 were in the chemotherapy alone arm. For the July 2021 data cut, EQ-5D-3L data were available for 920 individual patients, of which 462 received nivolumab plus chemotherapy and 458 received chemotherapy alone. Since patients were assessed multiple times, the final analysis was based upon a total of 5965 PF observations and 1191 PD observations.

Health state-based utility analyses were based on the following outcomes:

- Time from randomization to the date of the first observation of PD or death due to any cause.
- Subjects who died without a reported prior PD (and died without start of subsequent therapy) were considered to have progressed on the date of death.
- Subjects who did not have PD and who did not die, were censored at the date of the last evaluable tumour assessment on or prior to initiation of subsequent anti-cancer therapy (including all systemic therapies, surgery for curative or palliative reason, radiotherapy with curative or palliative reason).
- Subjects who did not have any on-study tumour assessments and did not die (or died after initiation of subsequent anticancer therapy) were censored at the randomization date.
- Subjects who started any subsequent anti-cancer therapy without a prior reported PD were censored at the last tumour assessment prior to or on the initiation of the subsequent anti-cancer therapy.
- Some subjects did not have measurable lesion at baseline when assessed by blinded independent central review (BICR). These subjects' images were reviewed by BICR and assessed for appearance of new lesion.
- PFS was defined as the time from randomization to the date of progression (new lesion) or death due to any cause. Subjects who did not have a new lesion or did not die were censored at their last imaging procedure date.

Two different types of analyses were performed: descriptive analysis and linear mixed models' analyses (LMMs). The latter was used to account for repeated measures within the same person over time. However, only the results of the descriptive analysis were included in the cost-effectiveness model as this method is more conventionally used for health-state based utility valuation, and because its simpler methodology is more transparent and less sensitive to methodological choices.

For this analysis, the EQ-5D-5L value set (Jensen 2021b) was applied to the EQ-5D-3L (July 2021 data cut) responses by the means of a validated mapping method (van Hout 2021). The mapping was done according to the preferred method which was an ordinal logistic regression that disregarded age and gender and accounted for unobserved heterogeneity using a latent factor. The HSUVs used in the model are presented in section 8.4.2. Utilities were described using mean, median, standard deviation, standard error, variance, interquartile range, minimum and maximum values by health state (progression-free (PF) and progressed disease (PD)), by treatment status (on treatment and off treatment), and by treatment

When using treatment specific utility values, in which a distinction is made between patients on different treatments, it is assumed that the impact of AEs on the QoL is already considered and hence no AE utility decrements should be added to avoid double counting. However, when general health state utility values are used in the model, it is recommended to include utility decrements due to AEs. Those AE decrements were calculated by multiplying AE disutility values by AE duration estimates and subtracted once in the first model cycle. Disutility values associated with the AEs were informed by literature. Since these were obtained from different sources and derived from different populations and settings, no attempt was made to convert these disutility values to a Danish utility set.

It should be noted that no literature review was undertaken to identify progression-based utility values for this analysis. Since HSUV valuation through EQ-5D was performed within CheckMate 649, this was considered the best source of

HSUVs for this indication. Literature reviews were performed to identify disutility values associated with adverse events only.

8.4.2 Health state utility values used in the health economic model

The progression-based HSUVs used for the cost-effectiveness model are the EQ-5D-5L values mapped from the EQ-5D-3L July 2021 DBL using the van Hout method and Danish utility weights (described in 8.4.1), and are presented in Table 30. Since there was a statistically significant difference in health-related quality of life (HRQoL) between treatments even when controlling for disease progression, treatment-specific utility values were used for the base case analysis. Another strength of using treatment-specific HSUVs is that they do not rely on disutility values for adverse events derived from separate settings, a source of uncertainty when using the general health state utility values. A scenario using general HSUVs plus AE disutility values is included as scenario analysis. Disutilities decrements are taken into account once in the first model cycle.

Table 30: Summary of the health state utility values used in the model

Health state	HSUV	SE	95% CI†
Progression-free (overall)	[redacted]	[redacted]	[redacted]
Progression-free (nivo + chemo)	[redacted]	[redacted]	[redacted]
Progression-free (chemo)	[redacted]	[redacted]	[redacted]
Progressed disease (overall)	[redacted]	[redacted]	[redacted]
Progressed disease (nivo + chemo)	[redacted]	[redacted]	[redacted]
Progressed disease (chemo)	[redacted]	[redacted]	[redacted]

Abbreviations: Chemo: chemotherapy; CI: Confidence interval; HSUV: health state utility value; Nivo: nivolumab; SE: standard error

† Confidence intervals are calculated based upon a normal distribution

The utility loss associated with adverse events are presented in Table 31. Having not found indication-specific disutility values in the SLR, disutility values for relevant AEs were taken from publications for other indications. These publications were previously used to inform cost-effectiveness analyses for other oncology indications. Note that these utility values are not used in the CEM when treatment arm specific utility values are used.

Table 31: Adverse event parameters and resulting QALY decrements

Adverse event	Disutility	SE	Duration (days)	QALY loss	Source
Nausea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Neuropathy peripheral	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Neutrophil count decreased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Adverse event	Disutility	SE	Duration (days)	QALY loss	Source
Platelet count decreased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lipase increased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: QALY: quality-adjusted life year; SE: standard error

In CheckMate 649, HSUVs were recorded separately not only by treatment arm but also by which type of chemotherapy that patients received: XELOX or FOLFOX. HSUVs were generally higher for patients treated with nivolumab plus XELOX. However, since this analysis assumes no difference between clinical effect of the two chemotherapy regimens, the conservative option of pooling the HSUVs for nivolumab plus XELOX and nivolumab plus FOLFOX into one single set of HSUVs. No imputation method was used for missing data, which was assumed to be missing at random. An advantage of this approach was that this increased the patient numbers used in each analysis, hence providing more stable and reliable HSUV estimates. Complete HSUVs by treatment and progression status are presented in Appendix I.

8.4.2.1 Age-adjusted utilities

In line with DMC guidelines, an age-adjustment of the utility values was performed to ensure that the relative level of utility values would decline in a rate consistent with the expected decline in health-related quality of life (HRQoL) observed within the general Danish population. The adjustment index recommended by the DMC was used for this analysis (Medicinrådet 2021c).

8.5 Resource use and costs

Cost input values for the analysis were obtained through interviews with clinical experts (Norwegian KOL interview 2021). Due to a lack of opportunity of interviewing Danish clinical experts, estimates from Norwegian clinical experts were used for this analysis, assuming that these would serve as a reasonable proxy for resource usage in Danish clinical practice (see section 8.2.2.1). The experts were allowed to see the estimated resource usage for gastric cancer treatment in Sweden (where similar clinical expert interviews had been held) but could freely estimate the frequencies they deemed appropriate for a Norwegian clinical setting. They were also asked to list any other health care resources that they thought may be applicable.

Different sources were used to obtain the unit cost for all resource types. All costs were updated to 2021 prices.

Sections 8.5.1 to 8.5.5 summarises the cost data identified for the economic analysis for the following cost types: drug monitoring costs (PF and PD health states), drug acquisition and administration costs, cost of treatment-related adverse events (AEs), subsequent treatment costs, diagnostic test costs, and indirect/patient costs.

8.5.1 Disease management costs

The frequency of each HRU was sourced through interviews with Swedish clinicians and is presented in Table 33. The Norwegian clinical expert who provided input on the treatment algorithm suggested there would not be any difference in HRU between the pre-progression and post-progression health states. As such, health-state specific monitoring is not

included in the base case analysis, but a scenario has been present where health-state specific monitoring has been included.

Table 32: Health-state specific monitoring frequency, per week

Resource name	Progression-free	Progressed disease	Cost DKK	Reference
Outpatient visit	0.125 (every 2 months)	0.25 (every month)	1456	Freqeuncy per Swedish KOL. Kommunernes og Regionernes Løndatakontor 2021, Specialeansvarlige overlæger. bruttolön APR 2021 (103296DKK). available from: https://krl.dk/#/sirka Calculated: salary/hours per month and multiplied by two
Complete blood count	0.125 (every 2 months)	0.25 (every month)	460	Freqeuncy per Swedish KOL. Rigshospitalets Labportal (2021). Test code for CBC tests included (codes): NPU02902 (cost for test assumed as proxy for codes: NPU01960, NPU01961, NPU02593), NPU01473 (cost for test assumed as proxy for codes: B-Hb (Hemoglobin), Erc(B)-MCV, Erc(B)-MCH, Erc(B)-MCHC), and RGH00982. https://labportal.rh.dk/Labportal.asp
Renal function test	0	0.25 (every month)	261	Freqeuncy per Swedish KOL. Rigshospitalets Labportal (2021). Test code for renal tests included (codes): NPU01459, NPU01472, NPU03429, NPU03230, NPU01536, NPU23745, NPU02192, NPU04998, NPU19673 https://labportal.rh.dk/Labportal.asp
Hepatic function test	0	0.25 (every month)	213	Freqeuncy per Swedish KOL. Rigshospitalets Labportal (2021). Test code for hepatic tests included (codes): NPU19651, NPU19654, NPU27783, NPU19673, NPU01370, NPU03278. https://labportal.rh.dk/Labportal.asp
CT scan	0.125 (every 2 months)	0.105 (every 2-3 months)	2007	Freqeuncy per Swedish KOL. Sundhedsdatastyrelsen (2021). Interactive DRG: 30PR06 CT scan, complicated (UXCD10) CT scan of the upper abdomen, (DK929) Disease of the digestive system UNS. Available at: http://interaktivdrg.sundhedsdata.dk/

Abbreviations: CT: computed tomography; DKK; Danish krone, KOL, key opinion leader

8.5.2 Drug monitoring costs

The monitoring costs are outlined in Table 32. The monitoring costs reflect treatment specific resource use, such as labs and scans, which are required to ensure patients are tolerating the treatment well. These resources are typically outlined within the product labels and require local clinical input. Therefore, these costs are treatment specific.

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Table 33. Treatment specific resource use and costs, per week

	Outpatient visit	CT Scan	Hepatic function test	Renal function test	Complete blood count
Nivolumab plus XELOX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab plus FOLFOX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
XELOX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FOLFOX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Costs (DKK)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Source	[redacted]				

Abbreviations: CT: computed tomography; DKK; Danish krone, FOLFOX: 5-fluorouracil plus leucovorin plus oxaliplatin; XELOX: capecitabine plus oxaliplatin.

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8.5.3 Drug acquisition and administration costs

The drug acquisition costs for the treatment and comparators are presented in Table 33. Unit costs (AUP excl. VAT) were sourced from the Medicinpriser.dk (September 2021). 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 oncology assessment submissions.

The same dosing and acquisition costs were used for subsequent treatment as for the intervention and comparator. On top of this, some additional drugs were available within subsequent treatment.

Table 34: Drug acquisition costs (in DKK) 1L gastric, gastro-esophageal junction, or esophageal adenocarcinoma

	Dose per tablet	Units per package	Cost per package	Cost per mg	Reference/source for costs
Nivolumab	40 mg	1	3,690.69	92.27	Medicinpriser.dk (2021) https://www.medicinpriser.dk/Default.aspx?id=15&vnr=539385
	100 mg	1	9,168.23	91.68	Medicinpriser.dk (2021) https://www.medicinpriser.dk/Default.aspx?id=15&vnr=579240
	240 mg	1	22,003.74	91.68	Medicinpriser.dk (2021) https://www.medicinpriser.dk/Default.aspx?id=15&vnr=479954
Oxaliplatin	50 mg	1	145.00	2.90	Medicinpriser.dk (2021) https://www.medicinpriser.dk/Default.aspx?id=15&vnr=099957
	100 mg	1	240.00	2.40	Medicinpriser.dk (2021) https://www.medicinpriser.dk/Default.aspx?id=15&vnr=483681
	200 mg	1	480.00	2.40	Medicinpriser.dk (2021) https://www.medicinpriser.dk/Default.aspx?id=15&vnr=559404
Capecitabine	150 mg	60	193.50	0.02	Medicinpriser.dk (2021) https://www.medicinpriser.dk/Default.aspx?id=15&vnr=161150
	500 mg	120	250.00	0.00	Medicinpriser.dk (2021) https://www.medicinpriser.dk/Default.aspx?id=15&vnr=581539
Leucovorin	100 mg	1	111.00	1.11	Medicinpriser.dk (2021) https://www.medicinpriser.dk/Default.aspx?id=15&vnr=489899
	350 mg		220.00	0.63	Medicinpriser.dk (2021) https://www.medicinpriser.dk/Default.aspx?id=15&vnr=563008

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	Dose per tablet	Units per package	Cost per package	Cost per mg	Reference/source for costs
	1000 mg	1	340.00	0.34	Medicinpriser.dk (2021) https://www.medicinpriser.dk/Default.aspx?id=15&vnr=183562
Fluorouracil	500 mg	1	70.00	0.14	Medicinpriser.dk (2021) https://www.medicinpriser.dk/Default.aspx?id=15&vnr=068671
	2500 mg	1	200.00	0.08	Medicinpriser.dk (2021) https://www.medicinpriser.dk/Default.aspx?id=15&vnr=382001
	5000 mg	1	400.00	0.08	Medicinpriser.dk (2021) https://www.medicinpriser.dk/Default.aspx?id=15&vnr=382001
Cisplatin	50 mg	1	100.00	2.00	Medicinpriser.dk (2021) https://www.medicinpriser.dk/Default.aspx?id=15&vnr=565141
	100 mg	1	200.00	2.00	Medicinpriser.dk (2021) https://www.medicinpriser.dk/Default.aspx?id=15&vnr=548680
Irinotecan	40 mg	1	n/a	n/a	Medicinpriser.dk (2021) https://www.medicinpriser.dk/Default.aspx?id=15&vnr=598049
	100 mg	1	125	1.25	Medicinpriser.dk (2021) https://www.medicinpriser.dk/Default.aspx?id=15&vnr=548680
	300 mg	1	3050	10.17	Medicinpriser.dk (2021) https://www.medicinpriser.dk/Default.aspx?id=15&vnr=178347
	500 mg	1	350	0.70	Medicinpriser.dk (2021)https://www.medicinpriser.dk/Default.aspx?id=15&vnr=380487
Doxorubicin	10 mg	1	150	15.00	Medicinpriser.dk (2021) https://www.medicinpriser.dk/Default.aspx?id=15&vnr=178347
	20 mg	1	n/a	n/a	Medicinpriser.dk (2021) https://www.medicinpriser.dk/Default.aspx?id=15&vnr=445169
	50 mg	1	120	2.40	Medicinpriser.dk (2021) https://www.medicinpriser.dk/Default.aspx?id=15&vnr=537758
	100 mg	1	360	1.80	Medicinpriser.dk (2021)https://www.medicinpriser.dk/Default.aspx?id=15&vnr=127770

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	Dose per tablet	Units per package	Cost per package	Cost per mg	Reference/source for costs
Epirubicin	10 mg	1	n/a	n/a	Medicinpriser.dk (2021) https://www.medicinpriser.dk/Default.aspx?id=15&vnr=169283
	20 mg	1	110	2.20	Medicinpriser.dk (2021)https://www.medicinpriser.dk/Default.aspx?id=15&vnr=127770
	50 mg	1	980	9.80	Medicinpriser.dk (2021)https://www.medicinpriser.dk/Default.aspx?id=15&vnr=102879
	200 mg	1	442.76	2.21	Medicinpriser.dk (2021) https://www.medicinpriser.dk/Default.aspx?id=15&vnr=066645
Ramucirumab	100 mg	1	4202.65	42.03	Medicinpriser.dk (2021)https://www.medicinpriser.dk/Default.aspx?id=15&vnr=102879
	500 mg	1	20458.87	40.92	Medicinpriser.dk (2021) https://www.medicinpriser.dk/Default.aspx?id=15&vnr=066667
Paclitaxel	30 mg	1	n/a	n/a	Medicinpriser.dk (2021) https://www.medicinpriser.dk/Default.aspx?id=15&vnr=575246
	100 mg	1	110.5	1.10	Medicinpriser.dk (2021) https://www.medicinpriser.dk/Default.aspx?id=15&vnr=180634
	150 mg	1	1500	10.00	Medicinpriser.dk (2021) https://www.medicinpriser.dk/Default.aspx?id=15&vnr=539629
	300 mg	1	201.5	0.67	Medicinpriser.dk (2021) https://www.medicinpriser.dk/Default.aspx?id=15&vnr=076384

Abbreviations: DKK; Danish krone, FOLFOX: 5-fluorouracil plus leucovorin plus oxaliplatin; XELOX: capecitabine plus oxaliplatin.

The dosage and treatment regimens are presented in Table 34. The dose intensities for each treatment are based on data from the CheckMate 649 trial.

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Table 35: Treatment regimens 1L gastric, gastro-esophageal junction, or esophageal adenocarcinoma

Combination	Treatment	Administration route	Administration frequency	Dose	Dose intensity	Vial sharing
Nivolumab plus XELOX	Nivolumab	IV	Q3W (max 24 months)	360 mg	92%	100%
	Oxaliplatin	IV	Q3W	130 mg/m^2	85%	100%
	Capecitabine	Oral	Q3W 2D 14 consecutive days	1,000 mg/m^2	78%	100%
Nivolumab plus FOLFOX	Nivolumab	IV	Q2W (max 24 months)	240 mg	90%	100%
	Oxaliplatin	IV	Q2W	85 mg/m^2	87%	100%
	Leucovorin	IV	Q2W	400 mg/m^2	79%	100%
	Fluorouracil	IV	Q2W	400 mg/m^2	91%	100%
	Fluorouracil	IV	Q2W 2D 14 consecutive days	1,200 mg/m^2	91%	100%
XELOX	Oxaliplatin	IV	Q3W	130 mg/m2	88%	100%
	Capecitabine	Oral	Q3W 2D 14 consecutive days	1,000 mg/m2	85%	100%
FOLFOX	Oxaliplatin	IV	Q2W	85 mg/m2	87%	100%
	Leucovorin	IV	Q2W	400 mg/m2	83%	100%
	Fluorouracil	IV	Q2W	400 mg/m2	92%	100%
	Fluorouracil	IV	Q2W 2D 14 consecutive days	1,200 mg/m2	92%	100%

Abbreviations: DKK; Danish krone, FOLFOX: 5-fluorouracil plus leucovorin plus oxaliplatin; IV: intravenous; Q2W: every two weeks; Q3W: every 3 weeks; XELOX: capecitabine plus oxaliplatin.

Table 35 outlines the administration costs for the IV treatments included in the model. The administration costs were sourced from Sundhedsdatastyrelsen (Sundhedsdatastyrelsen 2021b).

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Table 36: Administration cost per included IV treatments

Name of resource	Cost (DKK)	Comment	Reference DK (2021)
Administration cost for nivolumab	**2277.00**	Same cost considered for both treatment settings	Sundhedsdatastyrelsen (2021). Medicingivning ved intravenøs injektion, (DK929) Disease of the digestive system UNS. Available at: http://interaktivdrg.sundhedsdata.dk/
Complex parenteral chemotherapy delivery - Day case and outpatient setting	**2277.00**	Same cost considered for both treatment settings	Sundhedsdatastyrelsen (2021). Medicingivning ved intravenøs injektion, (DK929) Disease of the digestive system UNS. Available at: http://interaktivdrg.sundhedsdata.dk/

Abbreviations: DKK: Danish krone; IV: intravenous.

In all treatment regimens XELOX and FOLFOX, with or without nivolumab all drugs are administrated on day 1 of the treatment cycle and therefore one administration cost is applied per treatment cycle.

8.5.4 Costs of adverse events

Any adverse events associated with gastric cancer treatment occurring for ≥3% of patients in CheckMate 649 were included in the cost-effectiveness model. Out of these, only resource usage for events of grade 3 – 4 were included in the model, as any costs arising from lower grade events were assumed to be minor. Norwegian clinical experts were contacted to validate how each adverse event of grade 3 – 4 would be treated within a Norwegian clinical context.

Table 36 outlines the unit costs associated with the treatment of adverse events included in the base case model (included adverse events are outlined in Table 22 above). The unit costs were sourced using the Danish DRG tariffs (Sundhedsdatastyrelsen 2021a).

Table 37: Costs of Adverse Events

AE	Unit cost per event (DKK)	Share of patients with AE requiring the resource	Comment / Reference for unit costs
Nausea	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	

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AE	Unit cost per event (DKK)	Share of patients with AE requiring the resource	Comment / Reference for unit costs
			[redacted]
Vomiting	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	
Neuropathy peripheral	[redacted]	[redacted]	[redacted]
Neutrophil count decreased	[redacted]	[redacted]	[redacted]
Platelet count decrease	[redacted]	[redacted]	[redacted]
Lipase increase	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]

Abbreviations: AE: adverse event; DKK: Danish krone.

8.5.5 Costs of subsequent treatment

Upon disease progression, or termination of the 1L treatment, patients might receive subsequent lines of therapy. Norwegian clinical experts were consulted about which subsequent treatments would be applicable in Norwegian clinical practice. The proportion of patients progressing to second line treatment are presented in Table 37. These proportions were obtained from CheckMate 649, but their validity for a Norwegian clinical setting were verified by the Norwegian clinical experts. We have assumed Danish clinical practice to be the same as Norwegian as we did not have the opportunity to discuss with Danish clinical experts (see section 8.2.2.1). Table 38 shows the distribution of second

line treatments according to Norwegian clinical experts, as well as the distribution observed in CheckMate 649. For the latter, only 2L treatments received by at least 3% of the ITT population were included. The dosing for the different 2L treatments is presented in Table 39. Duration of subsequent treatment in Table 39 is based on data from the CheckMate 649 clinical trial.

Table 38: Proportion of patients receiving subsequent treatment

1L Treatment	Proportion receiving 2L treatment	Reference/source
Nivolumab plus chemotherapy	37.2%	CheckMate 649
Chemotherapy	40.2%	CheckMate 649

Abbreviations: 2L: second line.

Table 39: Distribution of subsequent treatments per 1L treatment

1L treatment	Nivolumab	Ramucirumab	Fluorouracil	Irinotecan	Oxaliplatin	Paclitaxel	Reference
Nivolumab plus chemotherapy	0%	0%	0%	50%	0%	50%	Clinical expert feedback
Chemotherapy	0%	0%	0%	50%	0%	50%	Clinical expert feedback
Nivolumab plus chemotherapy	0%	21.1%	15.8%	21.1%	6.3%	35.7%	CheckMate 649
Chemotherapy	0%	16.3%	20.3%	22.6%	8.2%	32.6%	CheckMate 649

Abbreviations: 1L: first line.

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Table 40: Subsequent treatment dosing and administration

2L treatment	Cost per package	Total package dose (mg)	Dose per admin (mg)*	Number of admins per cycle (N)	Admin route	Monitoring costs per cycle	Mean time on subsequent treatment (months)	Treatment costs per admin	Reference
Nivolumab	4312.32	40	360	0.33	IV	10	[redacted]	38 810.88	SmPC
Ramucirumab	5583.84	100	542	0.50	IV	10	[redacted]	30 361.93	SmPC
Fluorouracil	263.68	5000	704	1.00	IV	10	[redacted]	37.14	SmPC
Irinotecan	7233.68	40	616	0.33	IV	10	[redacted]	8916.95	SmPC
Oxaliplatin	1798.72	50	150	0.50	IV	10	[redacted]	5384.82	SmPC
Paclitaxel	3426.88	100	210	0.33	IV	10	[redacted]	7196.44	SmPC

Abbreviations: 2L: second line; IV: intravenous; SmPC: summary of product characteristics.

For the base case, subsequent treatments are based upon the estimations from the Norwegian clinical experts, since this was deemed to be most reflective of the resource usage that could be expected within Danish clinical practice. Two alternative scenarios were also included as scenario analyses: one where the subsequent treatments were based upon CheckMate 649, and one where no costs were included for subsequent treatment in either treatment arm.

8.5.6 Indirect costs

Indirect costs were included in the base case in line with HTA guidelines (Medicinrådet 2021c). They include disease management costs that fall on patients and caregivers. The number of visits per model cycle was based upon estimations by Norwegian clinical experts, in turn based upon the number of administrations for XELOX/FOLFOX) and the frequency of drug monitoring (Norwegian KOL interview 2021). The experts further estimated that a caregiver could accompany the patient on up to 50% of all visits. It was assumed that this would be similar in Danish clinical practice.

As a simplification it was also assumed that a duration of 2 hours per week are spend patient time, both nivolumab plus chemotherapy and chemotherapy alone. This simplification is based on nivolumab having a 30-minute infusion time, where the other 1.5 hours are estimated for additional time for the visit and for transportation.

The input values used for indirect costs in the cost-effectiveness analysis are presented in Table 40. Results when these costs are excluded (i.e., a payer only perspective is applied) are included as scenario analysis.

Table 41: Indirect costs included in the model

Input	Cost (DKK)	Base case
Transportation costs	100.00	As per Værdisætning af enhedsomkostninger (2020): stated assumed 100 kr
Caregiver time costs (per hour)	182.64	As per Værdisætning af enhedsomkostninger (2020): 179 as per document, inflated to AUG 2021, https://www.dst.dk/en/Statistik/emner/oekonomi/prisindeks/forbrugerprisindeks

Patient time costs (per hour)	182.64	As per Værdisætning af enhedsomkostninger (2020): 179 as per document, inflated to AUG 2021, https://www.dst.dk/en/Statistik/emner/oekonomi/prisindeks/forbrugerprisindeks

Abbreviations: DKK: Danish krone

8.5.7 Terminal care costs

End of life/terminal care costs were applied as a one-off cost for all patients entering the death state across the time horizon of the model. Resource usage was estimated by Danish clinical experts and the cost for end of life/terminal care is presented in Table 41. Note that patients might require more than one resource, as such, the share of patients does not equal 100%. In a scenario analysis, 30 days hospice care was considered as the only terminal treatment for all patients.

Table 42: Terminal care costs included in the model

Resource	Share of patients requiring resource (%)†	Frequency (days)	Unit cost (DKK)	Reference for unit costs
Terminal care in hospital	58	6	1734	Sundhedsdatastyrelsen (2021). Interactive DRG: 04MA98 (BXBA)Specialiseret palliativ indsats; (DC349M) Kræft i bronkier eller lunge med metastaser. Available at: http://interaktivdrg.sundhedsdata.dk/
Hospice Care (30 days)‡	25	1	60 340	Sundhedsdatastyrelsen (2021). Interactive DRG: 06MA11 (BXBA) Specialiseret palliativ indsats (DK229) Sygdom i øsofagus UNS, Kontaktdage 30, Takst 5.130. Available at: http://interaktivdrg.sundhedsdata.dk/
Advanced medical home care	75	60	414	Kommunernes og Regionernes Løndatakontor 2021, Husassistenter, KL. bruttolön May 2021 (29373 DKK). available from: https://krl.dk/ Calculated: salary/hours per month and multiplied by two according to Medicine council 2020.
Total average cost per terminal care event	N/A	N/A	39 749	Estimation based upon inputs above

Abbreviations: DKK: Danish krone; N/A: not applicable

† It was assumed that the same patient could receive both hospital care and hospice/advanced medical home care. This is since many patients are hospitalized at some point during their final months.

‡ Frequency and unit cost are for a 30 day period

8.6 Results

8.6.1 Base case overview

The settings applied in the economic model for the base case analysis are presented in Table 42.

Table 43: Summary of settings used for the base case analysis

Input	Base case
Intervention	[redacted]
Comparator	[redacted]
Type of model	[redacted]
Time horizon	[redacted]
Treatment line	[redacted]
Patient characteristics	[redacted]
Measurement and valuation of health effects	[redacted]
Included costs	[redacted]
Dosage of pharmaceutical (nivolumab plus XELOX)	[redacted]
Dosage of pharmaceutical (nivolumab plus FOLFOX) †	[redacted]
Dosage of comparator (XELOX)	[redacted]
Dosage of comparator (FOLFOX) †	[redacted]

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Input	Base case
Survival extrapolation (OS)	[redacted]
Survival extrapolation (PFS)	[redacted]
Duration of treatment	[redacted]
Subsequent treatment	[redacted]
Discount rate	[redacted]

Abbreviations: OS: overall survival; PFS: progression-free survival; TTD: time to treatment discontinuation. FOLFOX: 5-fluorouracil plus leucovorin plus oxaliplatin; XELOX: capecitabine plus oxaliplatin
† Not applied in base case where it is assumed that 100% of chemotherapy consists of XELOX

8.6.2 Base case results

Base case results were generated in the economic model using deterministic analysis. The base case analysis shows that treatment with nivolumab plus chemotherapy is associated with substantial increases in both overall and progression-free survival compared to treatment with chemotherapy alone. The expected survival over time by treatment arm for the base case is presented in Table 43.

Table 44: Survival outcomes by treatment and time, base case analysis

Undiscounted survival	Nivolumab plus chemotherapy	Chemotherapy	Difference
Survival after 1 year	[redacted]	[redacted]	[redacted]
Survival after 5 years	[redacted]	[redacted]	[redacted]
Survival after 10 years	[redacted]	[redacted]	[redacted]
Survival after 15 years	[redacted]	[redacted]	[redacted]
Median survival (months)	[redacted]	[redacted]	[redacted]
Median survival (years)	[redacted]	[redacted]	[redacted]
Mean survival (total life years)	[redacted]	[redacted]	[redacted]
Total undiscounted years	[redacted]	[redacted]	[redacted]
Progression free (years)	[redacted]	[redacted]	[redacted]
Progressed (years)	[redacted]	[redacted]	[redacted]

[redacted]

Table 45: Total costs for nivolumab plus chemotherapy compared to chemotherapy, base case results (DKK)

Costs	Nivolumab plus chemotherapy	Chemotherapy	Difference
Total	[redacted]	[redacted]	[redacted]
Treatment acquisition	[redacted]	[redacted]	[redacted]
Treatment administration	[redacted]	[redacted]	[redacted]
Treatment-specific monitoring	[redacted]	[redacted]	[redacted]
Subsequent treatment	[redacted]	[redacted]	[redacted]
Indirect costs	[redacted]	[redacted]	[redacted]
Terminal care	[redacted]	[redacted]	[redacted]
Adverse events	[redacted]	[redacted]	[redacted]

Abbreviations: DKK: Danish krone

[redacted]

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Table 46: Total quality-adjusted life years for nivolumab plus chemotherapy compared to chemotherapy, base case results

Costs	Nivolumab plus chemotherapy	Chemotherapy	Difference
Total QALYs	[redacted]	[redacted]	[redacted]
Progression free	[redacted]	[redacted]	[redacted]
Progressed disease	[redacted]	[redacted]	[redacted]
Adverse events	[redacted]	[redacted]	[redacted]

Abbreviations: QALY: quality-adjusted life year

[redacted]

Table 47: Summary of cost-effectiveness results, base case analysis

Outcome	Nivolumab plus XELOX or FOLFOX	XELOX or FOLFOX	Difference
Total costs (DKK)	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]
ICER (DKK)	[redacted]		

Abbreviations: DKK: Danish krone; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; FOLFOX: 5-fluorouracil plus leucovorin plus oxaliplatin; XELOX: capecitabine plus oxaliplatin

8.7 Sensitivity analyses

Besides the base case analysis, univariate deterministic sensitivity analyses (DSA) and multivariate probabilistic sensitivity analyses (PSA) were conducted. These sensitivity analyses aimed to assess the robustness of the model's results in regard to its input values. To further assess the impact on structural assumptions, scenario analyses were performed. As well, discounts on the AIP price of nivolumab and its effects on the ICER have also been presented.

For the sensitivity analyses each model parameter was varied following a prespecified distribution for that parameter. The mean of this distribution was typically equal to the point estimate used in the base case analysis. The standard error (SE) of the distribution was set according to any distributional information provided in the original source. Where no such information was available, the SE was assumed to be 10% of the mean estimate unless stated otherwise.

8.7.1 Deterministic sensitivity analyses

In the one-way sensitivity analyses several parameters were excluded from the analyses. These include drug prices as the uncertainty around the price is negligible, and the efficacy inputs as the uncertainty for this is multivariate. Figure 36 shows the results of the one-way sensitivity analyses for the base case analysis. The figure presents the 15 parameters with the most influence on the ICER. The individual parameters with the greatest impact on the ICER were the age-adjusted utilities, as well as the utility values for health states, due to the model's structure.

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Figure 36: One-way sensitivity analysis for nivolumab plus chemotherapy vs. chemotherapy, parameters with most impact on the ICER

Abbreviations: DKK: Danish krone; ICER: incremental cost effectiveness ratio; PFS: progression free survival; PD: progressed disease; FOLFOX: 5-fluorouracil plus leucovorin plus oxaliplatin; XELOX: capecitabine plus oxaliplatin

8.7.2 Probabilistic sensitivity analyses

[redacted]

[redacted]

[redacted]

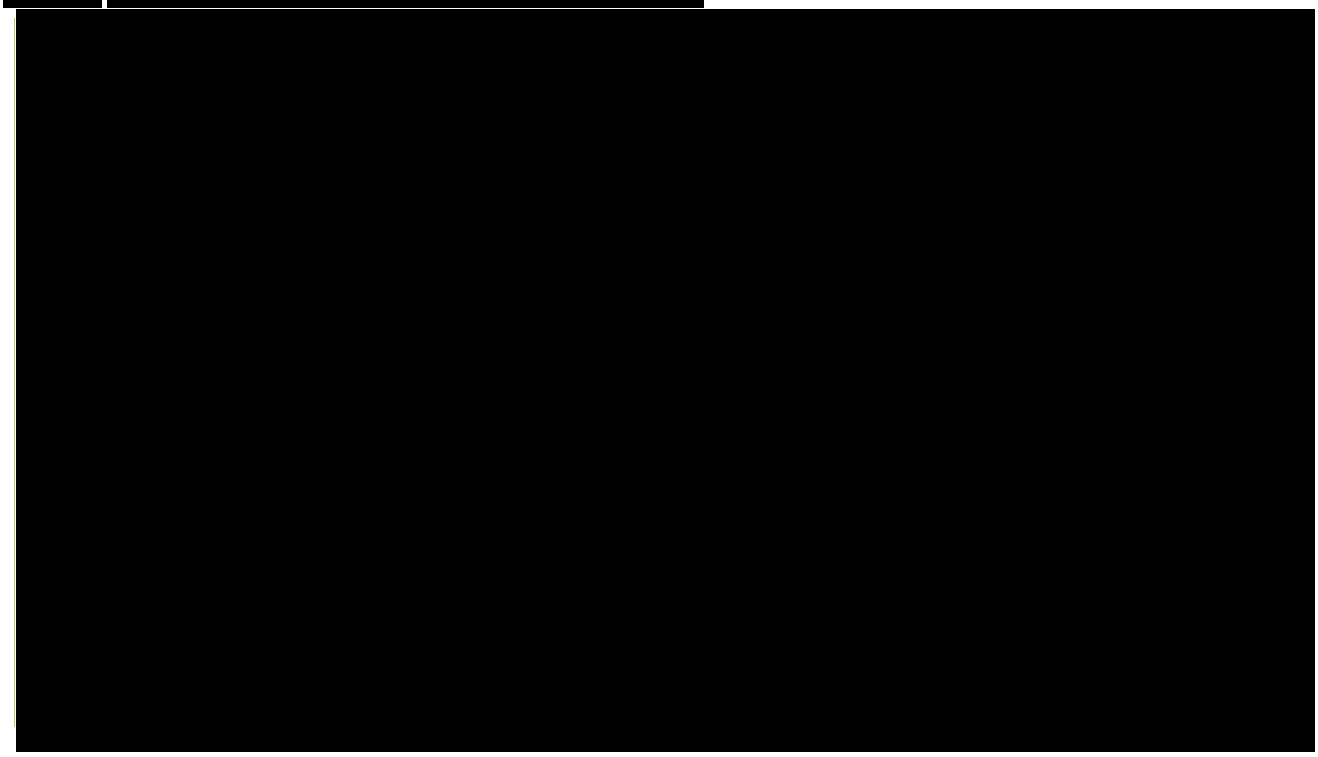
[redacted]

Table 48: PSA results

	Total costs		Total QALYs		ICER
	Mean (DKK)	95% CrI (DKK)	Mean	95% CrI	Mean (DKK)
Nivolumab plus XELOX/FOLFOX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
XELOX/FOLFOX	[redacted]	[redacted]	[redacted]	[redacted]	

Abbreviations: CrI: Credibility interval; DKK: Danish Krone; ICER: incremental cost-effectiveness ratio; PSA: probalistic sensitivity analysis; QALY: quality-adjusted life year; FOLFOX: 5-fluorouracil plus leucovorin plus oxaliplatin; XELOX: capecitabine plus oxaliplatin

[redacted]



[redacted]

8.7.3 Scenario analyses

Scenario analyses were undertaken to investigate the effect of certain model inputs on costs and outcomes. Table presents the scenario analyses performed. Table 49 presents the results of the different scenarios.

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Table 49: List of scenario analyses

Scenario	Scenario description	Base case
Scenario 1		
Scenario 2		
Scenario 3		
Scenario 4		
Scenario 5		
Scenario 6		
Scenario 7		
Scenario 8		
Scenario 9		
Scenario 10		
Scenario 11		
Scenario 12		
Scenario 13		
Scenario 14		
Scenario 15		
Scenario 16		

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Table 50: Results of scenario analyses

Scenario	Cost nivolumab plus chemotherapy (DKK)	Cost chemotherapy (DKK)	Incremental costs (DKK)	QALYs nivolumab plus chemotherapy	QALYs chemotherapy	Incremental QALYs	ICER (DKK)
Base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 1: No discounting (0% for both costs and QALYs)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 2: Payer perspective (no patient costs)	[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]	[redacted]	[redacted]

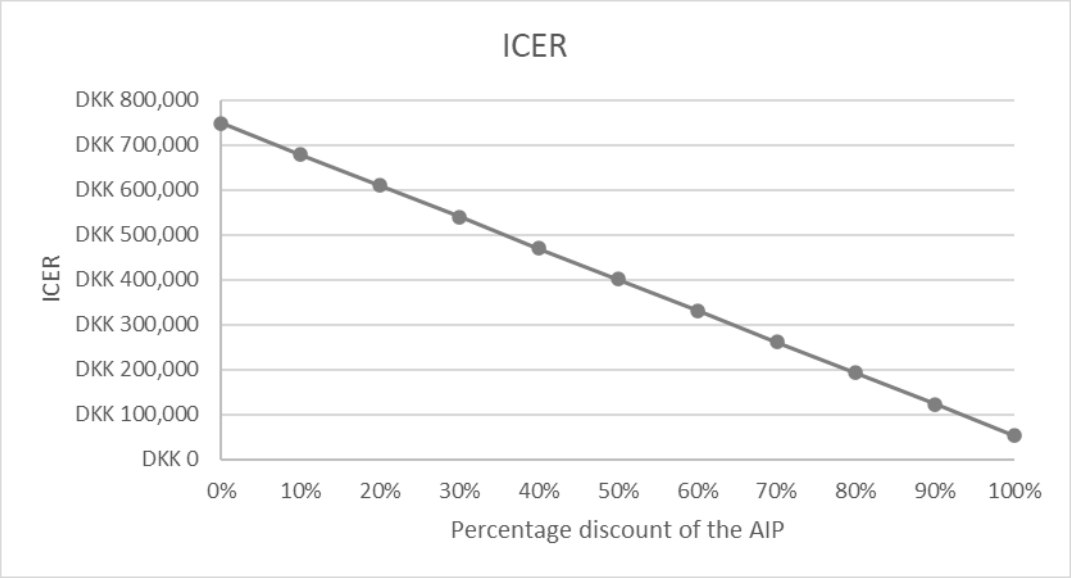
Scenario	Cost nivolumab plus chemotherapy (DKK)	Cost chemotherapy (DKK)	Incremental costs (DKK)	QALYs nivolumab plus chemotherapy	QALYs chemotherapy	Incremental QALYs	ICER (DKK)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[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]

Abbreviations: DKK: Danish Krone; ICER: incremental cost-effectiveness ratio; OS: overall survival; PFS: progression-free survival; QALY: quality-adjusted life year; TTD: time to treatment discontinuation FOLFOX: 5-fluorouracil plus leucovorin plus oxaliplatin; XELOX: capecitabine plus oxaliplatin.

8.7.4 Price-of-drug effects

A percentage discount has been applied to the acquisition cost of nivolumab in the nivolumab + XELOX treatment arm (base case intervention). Please see Figure 40 and Table 7 below.

Figure 40: ICER price at different nivolumab costs, from AIP with discounts



Abbreviations: AIP, pharmaceutical purchase price; ICER, incremental cost-effectiveness ratio

Table 51: ICER price at different nivolumab costs, from AIP with discounts

Discount rate	Nivolumab cost	ICER
0%	DKK 33,099	DKK 747,963
10%	DKK 29,789	DKK 678,499
20%	DKK 26,479	DKK 553,463
30%	DKK 23,169	DKK 403,421
40%	DKK 19,860	DKK 263,381
50%	DKK 16,550	DKK 158,351
60%	DKK 13,240	DKK 95,333
70%	DKK 9,930	DKK 65,925
80%	DKK 6,620	DKK 55,842
90%	DKK 3,310	DKK 53,573
100%	DKK 0	DKK 53,321

Abbreviations: DKK, Danish krone; ICER, incremental cost-effectiveness ratio

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9. Budget impact analysis

9.1 Number of patients

A budget impact analysis was performed to assess the expected additional expenditure for the relevant payer if nivolumab plus chemotherapy is induced. The economic model described in section 8 was used for estimating total costs. The increased expected survival from treatment with nivolumab plus chemotherapy is captured within this analysis. However, unlike the cost-effectiveness analysis, the discount rate for costs were set to 0%.

In line with guidelines from the DMC, a time horizon of 5 years was used for this analysis (Medicinrådet 2021c). [redacted]

The total number of patients receiving each treatment if nivolumab plus chemotherapy is recommended as standard treatment is presented in Table 51. If nivolumab plus chemotherapy is not recommended, all patients are assumed to be treated with chemotherapy alone. The number of patients per year and treatment in this scenario is presented in Table 52.

Table 52: Number of patients expected to be treated over the next five-year period - if nivolumab plus chemotherapy is introduced

	Year 1	Year 2	Year 3	Year 4	Year 5
Nivolumab plus chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total number of patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 53: Number of patients expected to be treated over the next five-year period - if nivolumab plus chemotherapy is NOT introduced

	Year 1	Year 2	Year 3	Year 4	Year 5
Nivolumab plus chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total number of patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

9.2 Expenditure per patient

The total cost per patient treated with nivolumab plus chemotherapy for years 1-5 is presented in Table 53. The equivalent costs for treating patients with chemotherapy alone is presented in Table 54.

Table 54: Detailed costs per patient and year for patients treated with nivolumab plus chemotherapy (DKK)

	Year 1	Year 2	Year 3	Year 4	Year 5
Treatment acquisition	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment administration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment-specific monitoring	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent treatment acquisition	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent treatment administration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent monitoring	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse events (costs)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviation: DKK: Danish krone

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Table 55: Detailed costs per patient and year for patients treated with chemotherapy (DKK)

	Year 1	Year 2	Year 3	Year 4	Year 5
Treatment acquisition	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment administration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment-specific monitoring	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent treatment acquisition	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent treatment administration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent monitoring	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse events (costs)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviation: DKK: Danish krone

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The annual costs per treatment can also be more broadly categorized depending on which actor within the Danish medical system they befall. Table 55 and Table 56 present the annual cost per treatment, according to this categorization.

Table 56: Costs per patient and year for patients treated with nivolumab plus chemotherapy (DKK), per Danish health care system

	Year 1	Year 2	Year 3	Year 4	Year 5
Drug costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Administrative costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hospital costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other regional costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse reaction costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviation: DKK: Danish krone

Note: Results are presented for a discount rate of 0%

Table 57: Costs per patient and year for patients treated with chemotherapy (DKK), per Danish health care system

	Year 1	Year 2	Year 3	Year 4	Year 5
Drug costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Administrative costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hospital costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Disease management costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse reaction costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviation: DKK: Danish krone

Note: Results are presented for a discount rate of 0%

9.3 Budget impact

Table 57 presents the total cost if nivolumab plus chemotherapy would be recommended as standard treatment. The equivalent costs for a scenario where nivolumab would not be recommended is presented in Table 58.

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Table 58: Total cost if nivolumab plus chemotherapy would be recommended as standard treatment (DKK)

	Year 1	Year 2	Year 3	Year 4	Year 5
Nivolumab plus chemotherapy					
Number of patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Costs of new patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Costs of patients from previous years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total cost for nivolumab plus chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy					
Number of patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Costs of new patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Costs of patients from previous years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total cost for chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total cost					
Total cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviation: DKK: Danish krone

Note: Results are presented for a discount rate of 0%

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Table 59: Total cost if nivolumab plus chemotherapy would NOT be recommended as standard treatment (DKK)

	Year 1	Year 2	Year 3	Year 4	Year 5
Nivolumab plus chemotherapy					
Number of patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Costs of new patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Costs of patients from previous years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total cost for nivolumab plus chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy					
Number of patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Costs of new patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Costs of patients from previous years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total cost for chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total cost					
Total cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviation: DKK: Danish krone

Note: Results are presented for a discount rate of 0%

The overall budget impact from a recommendation of nivolumab plus chemotherapy is defined as the difference in costs between scenarios with and without the recommendation. The budget impact of the recommendation is presented in Table 59. Further, the budget impact per Danish health care actor is presented in Table 60.

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Table 60: Expected annual budget impact if nivolumab plus chemotherapy is recommended as standard treatment (DKK)

	Year 1	Year 2	Year 3	Year 4	Year 5
Cost if treatment is accepted	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost if treatment is not accepted	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total budget impact	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviation: DKK: Danish krone

Note: Results are presented for a discount rate of 0%

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Table 61: Expected annual budget impact if nivolumab plus chemotherapy is recommended as standard treatment, per Danish health care actor (DKK)

	Year 1	Year 2	Year 3	Year 4	Year 5
Drug costs					
Cost if treatment is accepted	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost if treatment is not accepted	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total budget impact, drug costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Administrative costs					
Cost if treatment is accepted	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost if treatment is not accepted	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total budget impact	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hospital costs					
Cost if treatment is accepted	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost if treatment is not accepted	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total budget impact	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse reaction costs					
Cost if treatment is accepted	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost if treatment is not accepted	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total budget impact (DKK)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviation: DKK: Danish krone

Note: Results are presented for a discount rate of 0%

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10. Discussion on the submitted documentation

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13. Appendix A – Literature search for efficacy and safety of intervention and comparator(s)

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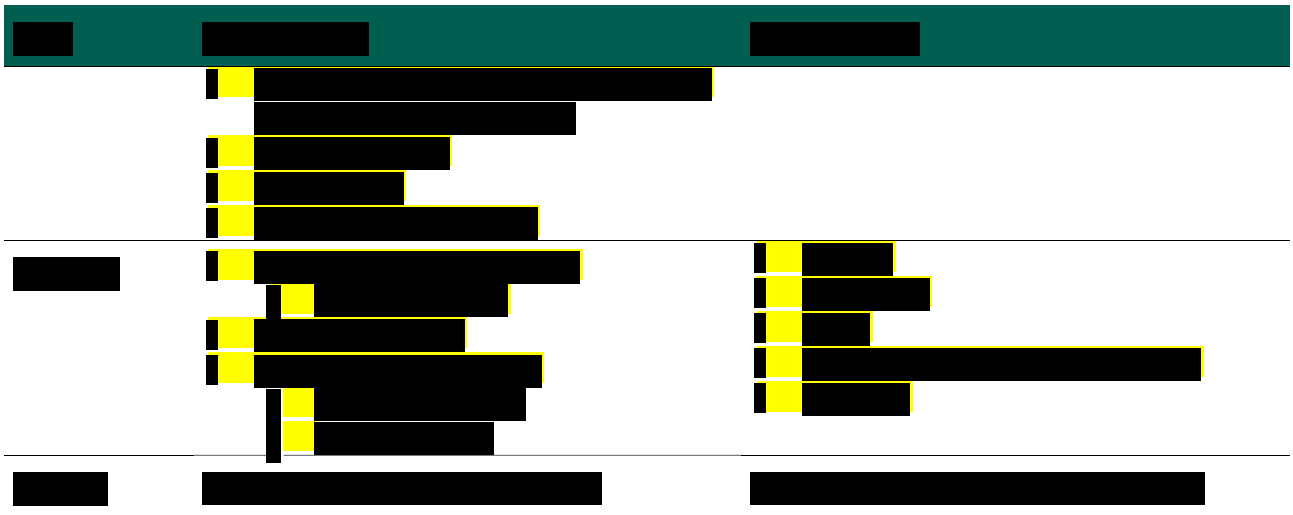

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14. Appendix B – Main characteristics of included studies

Table 64: Main characteristics of included studies

Trial name: CheckMate 649	NCT number: NCT02872116
Objective	To evaluate the efficacy of nivolumab plus chemotherapy (XELOX [capecitabine + oxaliplatin] or FOLFOX [leucovorin + 5-FU + oxaliplatin]) versus chemotherapy (XELOX or FOLFOX) in patients with previously untreated advanced or metastatic gastric/GEJ cancer or EAC
Publications – title, author, journal, year	Moehler M, Shitara K, Garrido M, et al. Moehler M, Shitara K, Garrido M, et al. Nivolumab (nivo) plus chemotherapy (chemo) versus chemo as first-line (1L) treatment for advanced gastric cancer/gastroesophageal junction cancer (GC/GEJC)/esophageal adenocarcinoma (EAC): First results of the CheckMate 649 study. Ann Oncol. 2020;31 (suppl_4):S1142-S1215 (abs LBA1146_PR) Janjigian, Y. Y., Shitara, K., Moehler, M., Garrido, M., Salman, P., et al. (2021). First-line nivolumab plus chemotherapy versus chemotherapy alone for advanced gastric, gastro-oesophageal junction, and oesophageal adenocarcinoma (CheckMate 649): a randomised, open-label, phase 3 trial. Lancet 398(10294): 27-40. Janjigian, Y. Y., Ajani, J. A., Moehler, M., Garrido, M., Gallardo, C., et al. (2021). Nivolumab plus chemotherapy or ipilimumab vs chemotherapy as first-line treatment for advanced gastric cancer/gastroesophageal junction cancer/esophageal adenocarcinoma: CheckMate 649 study. 2021 ESMO congress.
Study type and design	CheckMate 649 was a Phase 3, open-label, 3-arm randomised multicentre study. The study was conducted at 175 study sites in 29 countries. Patients were randomised to receive nivolumab plus chemotherapy (XELOX or FOLFOX) or ipilimumab or chemotherapy (XELOX or FOLFOX). Randomisation was stratified by tumour cell PD-L1 (≥1% vs. <1%), region (Asia vs. US/Canada vs. rest of world), ECOG performance status (0 vs. 1), and chemotherapy (XELOX vs. FOLFOX) Treatment for all arms was continued until documented disease progression, unacceptable toxicity, or withdrawal of consent. Treatment with nivolumab monotherapy was given for up to 24 months in the absence of disease progression or unacceptable toxicity.
Sample size (n)	1,581 randomised to nivolumab plus chemotherapy or chemotherapy alone

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Trial name: CheckMate 649	NCT number: NCT02872116
Main inclusion and exclusion criteria	Inclusion Criteria: • Men or women, at least 18 years old with inoperable, locally advanced, or metastatic GC, EC, orGEJC, and histologically confirmed predominant adenocarcinoma • No prior systemic treatment, including HER2 inhibitors, as primary therapy for advanced or metastatic disease • Prior neoadjuvant or adjuvant treatment (chemotherapy and/or radiotherapy) must have been completed at least 6 months prior to randomisation • Presence of at least one measurable lesion or evaluable disease by CT or MRI per RECIST 1.1 criteria • ECOG PS score of 0 or 1 • An evaluable tumour cell PD-L1 expression classification (≥1% or <1%, or indeterminate) by the central lab Exclusion Criteria: • Known HER2-positive status • Untreated CNS metastases; ascites which cannot be controlled with appropriate interventions A grade 1 peripheral neuropathy • 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
Intervention	• Nivolumab 360 mg plus XELOX (oxaliplatin 130 mg/m^2 IV on Day 1 of each treatment cycle + capecitabine 1000 mg/m^2 orally BID on Days 1 to 14 of each treatment cycle) every 3 weeks or • Nivolumab 240 mg plus FOLFOX (oxaliplatin 85 mg/m^2 + leucovorin 400 mg/m^2 + fluorouracil 400 mg/m^2 IV on Day 1 of each treatment cycle, and fluorouracil 1200 mg/m^2 IV continuous infusion over 24 hours daily [QD] or per local standard on Days 1 and 2 of each treatment cycle) every 2 weeks
Comparator(s)	XELOX every 3 weeks or FOLFOX every 2 weeks (as described above)
Follow-up time	Minimum follow-up: 12.1 months The median follow-up at the time of the database lock was 13.1 months (range: 0.1–37.5 months) for the nivolumab plus chemotherapy arm and 11.1 months (range: 0–36.6 months) for the chemotherapy alone arm
Is the study used in the health economic model?	Yes

Trial name: CheckMate 649	NCT number: NCT02872116
Primary, secondary and exploratory endpoints	**Endpoints included in this application:** The dual primary endpoints for the nivolumab plus chemotherapy versus chemotherapy arms were OS and PFS (as assessed by BICR) in patients with PD-L1 positive tumours defined by CPS ≥5. Key secondary endpoints were OS in PD-L1 CPS ≥1, CPS ≥ 10 or all randomised patients, PFS (BICR assessed) in PD-L1 CPS ≥1, CPS ≥ 10 or all randomised patients and ORR, and safety. Exploratory endpoints included health-related quality of life (HRQoL) as measured by EQ-5D and FACT-Ga. **Other endpoints:** Other exploratory endpoints such as PFS2 and clinical outcomes by MSI status are not included in this application.
Method of analysis	For the dual primary endpoints of PFS and OS in the comparison of nivolumab plus chemotherapy with chemotherapy in randomised patients with PD-L1 CPS ≥5, a 2-sided significance level of 2% was allocated to PFS and 3% was allocated to OS. If the OS comparison in patients with PD-L1 CPS ≥5 between nivolumab plus chemotherapy and chemotherapy was significant, then OS in patients with PD-L1 CPS ≥1 and OS in all randomised were sequentially tested at a 2-sided 1.5% significance level. The trial was designed to conduct the final PFS and interim OS analyses at 12-month minimum follow-up and final OS analysis at 24-month minimum follow-up.
Subgroup analyses	Prespecified subgroups included region, ECOG PS, chemotherapy regimen, age, gender, tumour location, histology, disease stage/status, prior therapy, Lauren classification, time from initial disease diagnosis to randomisation, peritoneal metastases, peritoneal metastases, liver metastases, MSI status, tumour cell PD-L1 expression, and HER2 status.
Other relevant information	n/a

Abbreviation: BICR: blinded independent central review; BID: twice daily; CPS: combined positive score; CSN: central nervous system; EC: esophageal; ECOG: Eastern Cooperative Oncology Group; GC: gastric cancer; FACT-Ga: Functional Assessment of Cancer Therapy – Gastric; FOLFOX: leucovorin calcium plus fluorouracil plus oxaliplatin; GEJC: gastroesophageal junction cancer; MSI: Microsatellite instability; ORR: objective response rate; OS: overall survival; PD-L1: programmed cell death 1; PFS: progression-free survival; PS: performance status; Q#W: every # weeks; QD: daily; RECIST: Response Evaluation Criteria in Solid Tumours; XELOX: capecitabine plus oxaliplatin.

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

Table 65 presents the baseline demographics for patients with PD-L1 CPS ≥5. For the all-comer population, see Section 23.1 Appendix K.

Table 65: Baseline demographics and characteristics in patients with PD-L1 CPS ≥5

Characteristic	Nivolumab plus chemotherapy (N=473)	Chemotherapy (N=482)
Median age (range), years	63 (54 – 69)	62 (54 – 68)
Age categorization, n (%)		
<65	266 (56)	286 (59)
≥65	207 (44)	196 (41)
Sex, M/F, n (%)	331 (70)/142 (30)	349 (72)/133 (28)
Race, n (%)		
White	328 (69)	327 (67)
Black or African American	2 (<1)	7 (<1)
American Indian Or Alaska Native	10 (2)	10 (2)
Asian	119 (25)	117 (24)
Other	14 (3)	21 (4)
Region, n (%)		
Asia (including China)	117 (25)	111 (23)
US and Canada	67 (14)	70 (15)
Rest of world	289 (61)	301 (62)
Primary tumour location at initial diagnosis, n (%)		
GEJ cancer	84 (18)	86 (18)
Gastric cancer	333 (70)	334 (69)
EAC	56 (12)	62 (13)
Disease status classification, n (%)		
Locally recurrent	3 (1<)	1 (<1)
Metastatic	454 (96)	461 (96)
Locally advanced	16 (3)	20 (4)
Signet ring cell‡	72 (15)	69 (14)
Site of metastases (%)		

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Characteristic		Nivolumab plus chemotherapy (N=473)	Chemotherapy (N=482)
	Liver	191 (40)	271 (45)
	Peritoneum	101 (21)	96 (20)
	Central Nervous System	1 (<1)	0
Microsatellite instability, n (%)			
	MSI-H	18 (4)	16 (3)
	MSS	423 (89)	423 (88)
	Invalid/not reported	32 (7)	43 (9)
Tumour cell PD-L1 expression			
	1%[†]	363 (77)	362 (75)
	≥1%	110 (23)	120 (25)
HER-2 status, n (%)			
	Positive	3 (0.6)	4 (0.8)
	Negative	272 (57.5)	271 (56.2)
	Unknown	2 (0.4)	3 (0.6)
	Not reported	196 (41.4)	204 (42.3)
ECOG PS*, n (%)			
	0	194 (41)	203 (42)
	1	279 (59)	278 (58)
	Not reported	0	1 (<1)
Chemotherapy regimen[§]			
	FOLFOX	237/468 (51)	242/465 (52)
	XELOX	231/468 (49)	223/465 (48)

*Based on case report form. All randomised patients had ECOG performance status of 0 or 1 based on interactive response technology. [†]Includes indeterminate tumour cell PD-L1 expression. [‡]Per World Health Organization histologic classification. [§]Patients who received at least one dose of the assigned treatment

Abbreviations: EAC, esophageal adenocarcinoma; ECOG PS, Eastern Cooperative Oncology Group performance status; GEJ, gastroesophageal junction cancer; MSI-H, microsatellite instability-high; MSS, microsatellite stable.

Source: (BMS 2020, Janjigian 2021b)

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16. Appendix D – Efficacy and safety results per study

16.1 Definition, validity and clinical relevance of included outcome measures

Efficacy

The outcomes measures in focus of the current application are the gold standard measures for oncology trials, OS, PFS, DoR and ORR. The parameters used to assess the efficacy of nivolumab plus chemotherapy vs. chemotherapy were consistent with other studies exploring the use of anti-cancer agents in subjects with previously untreated advanced or metastatic GC, GEJC, or EAC.

Safety

Along with standard safety assessments collected throughout the study, attention was paid to the identification and assessment of select adverse events (AEs), immune-mediated adverse events (IMAEs), and other events of special interest (OESIs) that are potentially associated with the use of nivolumab.

PROs

The EQ-5D was used to assess overall health status average symptom burden and was used to assess GC, GEJC, or EAC symptoms. The utility data generated from the EQ-5D is recommended for and commonly used in cost-effectiveness analyses. The FACT-Ga questionnaire and selected components were used to assess gastric cancer-related quality of life.

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16.2 Results per study

Table 66: Overview of efficacy and safety results for CheckMate 649

				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**CI**	***P* value**	**Difference**	**CI**	***P* value**		
Median OS in patients with PD-L1 CPS ≥5 (minimum 24 month follow-up)	Nivo + chemo	473	14.4 (95% CI: 13.1–16.2)	4.5	96.6% CI: 1.8-7.7		HR:0.71	98.4% CI: 0.59-0.86	<0.0001	The proportion of patients who survived at a given timepoint was derived from the Kaplan-Meier method with corresponding two-sided 95% CIs calculated based on the Greenwood formula for variance derivation based on log-log transformation. An estimate of the difference in ORR, and corresponding 95% CI was calculated using the Clopper-Pearson method. For subgroup analyses of OS, PFS, and objective response, unstratified HRs and corresponding 95% CIs for nivolumab plus chemotherapy relative to chemotherapy were calculated using a Cox proportional-hazards regression model with treatment as the covariate. For	(Janjigian 2021a)
	Chemo	482	11.1 (95% CI: 10.0–12.1)								
Median PFS in patients with PD-L1 CPS ≥5 (minimum 24 month follow-up)	Nivo + chemo	473	7.7 (95% CI: 7.0-9.2)	2.8-	96.6% CI: 1.4-4.8	-	HR: 0.68	98% CI: 0.56–0.81	<0.0001		(Janjigian 2021a)
	Chemo	482	6.05 (95% CI: 5.6-6.9)								
ORR in patients with PD-L1 CPS ≥5 (minimum 24 month follow-up)	Nivo + chemo	378[a]	226 (95% CI: 55-65)						-		(Janjigian 2021a)
	Chemo	390[a]	177 (95% CI: 40 – 50)								
Median DOR in patients with PD-L1 CPS ≥5 (minimum 12.1	Nivo + chemo	226	9.5 (95% CI: 8.0–11.4)	-	-	-	-	-	-		(Janjigian 2021a)
	Chemo	177	7.0 (5.7–7.9)								

				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**CI**	***P* value**	**Difference**	**CI**	***P* value**		
month follow-up)										OS and PFS, the stratified log-rank test was used to compare the treatment groups and the stratified Cox proportional hazards regression model was used to estimate the HR. The proportional hazards assumption was tested using a Cox model with treatment and treatment by time interaction at prespecified significance level of 0·1. For time-to-event endpoints, the median was estimated using the Kaplan-Meier method, and the corresponding two-sided 95% confidence intervals (CIs) were calculated using the log-log transformation method.	

Abbreviation: BICR: blinded independent central review; CI: confidence interval; CSR: clinical study report; DOR: duration of response; HR: Hazard ratio; ORR: objective response rate; OS: overall survival; PD-L1: programmed death-ligand 1; PFS: progression-free survival

[a]Randomised patients who had target lesion measurements at baseline per BICR assessment

17. Appendix E – Safety data for intervention and comparator(s)

The safety data for the intervention and the comparators are described in Table 66..

Table 67: Summary of safety, all randomised patients (minimum follow-up 12.1 months)

	Nivolumab plus chemotherapy (N=782)		Chemotherapy (N=767)	
	Any grade	Grade 3–4	Any Grade	Grade 3–4
All-cause AEs	[redacted]	[redacted]	[redacted]	[redacted]
All-cause SAEs	[redacted]	[redacted]	[redacted]	[redacted]
All-cause AEs leading to discontinuation	[redacted]	[redacted]	[redacted]	[redacted]
Treatment-related AEs	738 (94.4)	462 (59.1)	679 (88.5)	341 (44.5)
Treatment-related SAEs	172 (22.0)	131 (16.8)	93 (12.1)	77 (10.0)
Treatment-related AEs leading to discontinuation	284 (36.3)	132 (16.9)	181 (23.6)	67 (8.7)
Treatment-related AEs in ≥5% of patients in any treatment group				
Nausea	323 (41.3)	20 (2.6)	292 (38.1)	19 (2.5)
Diarrhoea	253 (32.4)	35 (4.5)	206 (26.9)	24 (3.1)
Neuropathy peripheral[a]	221 (28.3)	31 (4.0)	190 (24.8)	22 (2.9)
Anaemia	203 (26.0)	47 (6.0)	171 (22.3)	21 (2.7)
Fatigue	202 (25.8)	30 (3.8)	173 (22.6)	17 (2.2)
Vomiting	195 (24.9)	17 (2.2)	166 (21.6)	24 (3.1)
Neutropenia	191 (24.4)	118 (15.1)	181 (23.6)	93 (12.1)
Neutrophil count decreased	158 (20.2)	83 (10.6)	118 (15.4)	67 (8.7)
Thrombocytopenia	157 (20.1)	19 (2.4)	145 (18.9)	13 (1.7)
Decreased appetite	157 (20.1)	14 (1.8)	139 (18.1)	13 (1.7)
Platelet count decreased	156 (19.9)	20 (2.6)	115 (15.0)	19 (2.5)
Peripheral sensory neuropathy[a]	137 (17.5)	16 (2.0)	119 (15.5)	14 (1.8)
Aspartate aminotransferase increased	122 (15.6)	12 (1.5)	69 (9.0)	5 (0.7)
[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]

	Nivolumab plus chemotherapy (N=782)		Chemotherapy (N=767)	
[redacted]				
All-cause select AEs				
[redacted]				
Treatment-related select AEs				
Endocrine	107 (13.7)	5 (0.6)	3 (0.4)	0
Gastrointestinal	262 (33.5)	43 (5.5)	207 (27.0)	25 (3.3)
Hepatic	203 (26.0)	29 (3.7)	134 (17.5)	16 (2.1)
Pulmonary	40 (5.1)	14 (1.8)	4 (0.5)	1 (0.1)
Renal	26 (3.3)	6 (0.8)	8 (1.0)	1 (0.1)
Skin	214 (27.4)	26 (3.3)	105 (13.7)	6 (0.8)

Abbreviations: AE: adverse event; SAE: serious adverse event.

Source: (BMS 2020, Moehler 2020a)

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18. Appendix F – Comparative analysis of efficacy and safety

N/A

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19. Appendix G – Extrapolation

19.1 Overview of time-to-event analysis

The Kaplan Meier (KM) curves for both arms of the CPS ≥ 5 subgroup of the CheckMate 649 trial and the number of patients at risk for OS, PFS, and TTD, based on the July 2021 database lock, are shown in Figure 42 to Figure 44, respectively. In the TTD curve from the nivolumab plus XELOX/FOLFOX arm (Figure 44), a drop is seen at 24 months. Note that this TTD curve represents discontinuation from all components of the treatment regimen received. This drop is due to the maximum treatment duration of nivolumab in the CheckMate 649 trial, which is set to 24 months. After 24 months, all patients who discontinued chemotherapy before the 24 months, will discontinue treatment at once because all patients will discontinue nivolumab at this point.

The median survival for both arms for the CheckMate 649 trial, together with the HR (95% confidence interval [CI]) for OS, PFS, and TTD are shown in Table 67. The cost-effectiveness model utilises the most up to date efficacy data from CheckMate 649, from the July 2021 database lock. The CheckMate 649 public disclosure has been based on the July 2020 database lock (Moehler 2020a).

Table 68: Median survival and HR for PFS, TTD, and OS of CheckMate 649 for patients with PD-L1 expression CPS ≥ 5

	Database Lock	Median survival Nivolumab plus XELOX/FOLFOX	Median survival XELOX/FOLFOX	HR (95% CI)	Median survival Nivolumab plus XELOX/ FOLFOX generated from model	Median survival XELOX/ FOLFOX generated from model
OS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]		
PFS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]		
TTD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]		

Abbreviations: OS: overall survival; PFS: progression-free survival; HR: hazard ratio; CI: confidence interval; TTD: time to treatment discontinuation; FOLFOX: 5-fluorouracil plus leucovorin plus oxaliplatin; XELOX: capecitabine plus oxaliplatin

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19.2 Fitting parametric distributions

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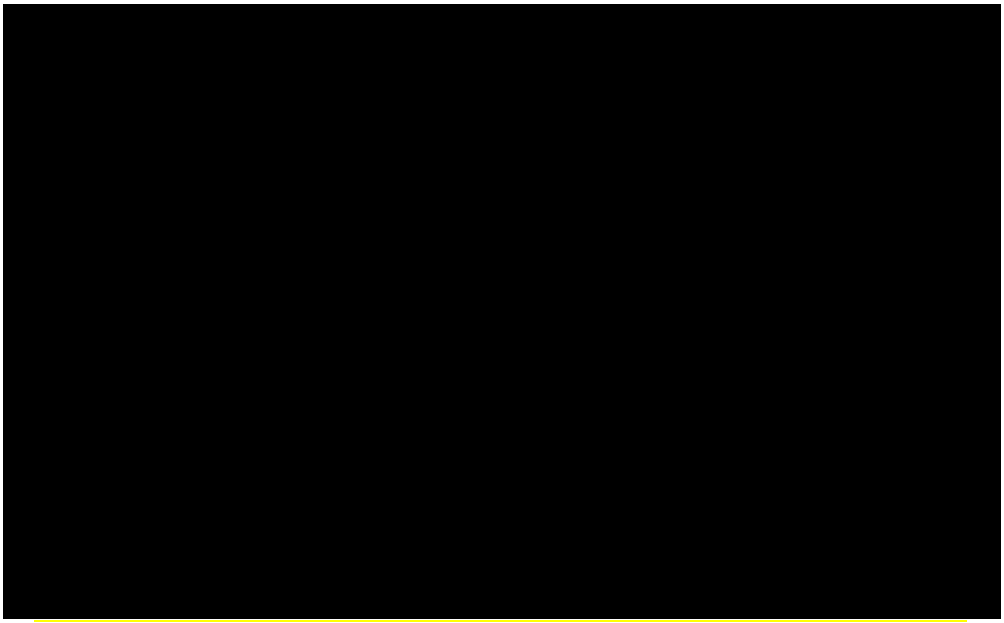

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19.4 Progression-free survival

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20. Appendix H – Literature search for HRQoL data

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21. Appendix I – Mapping of HRQoL data

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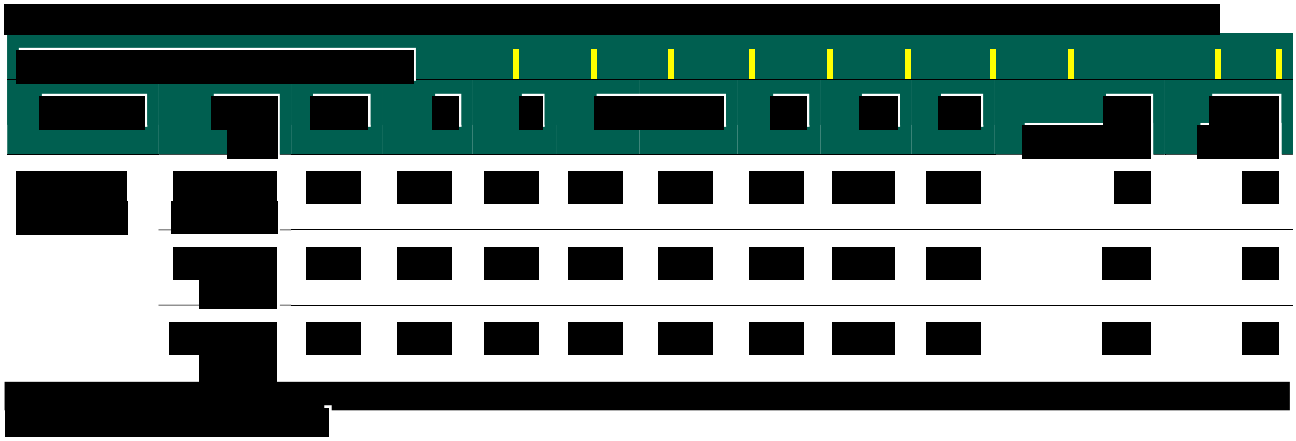

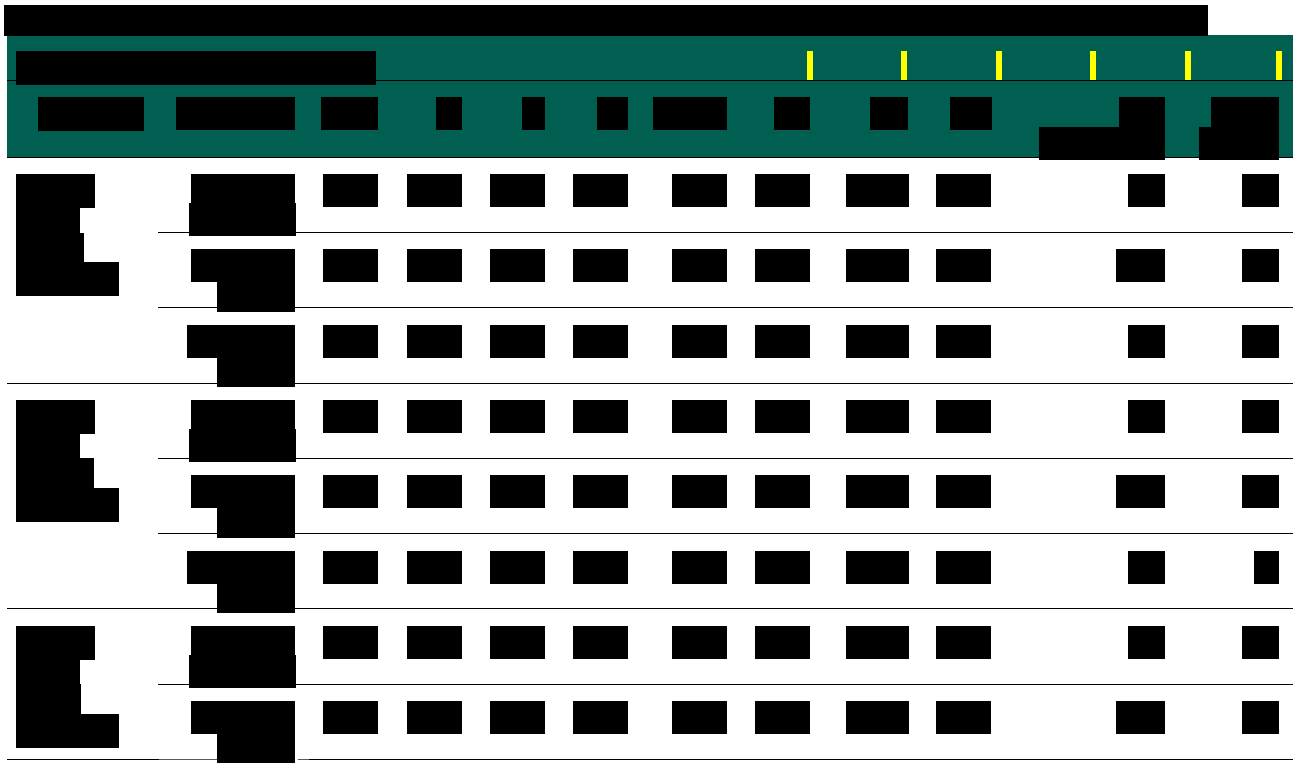

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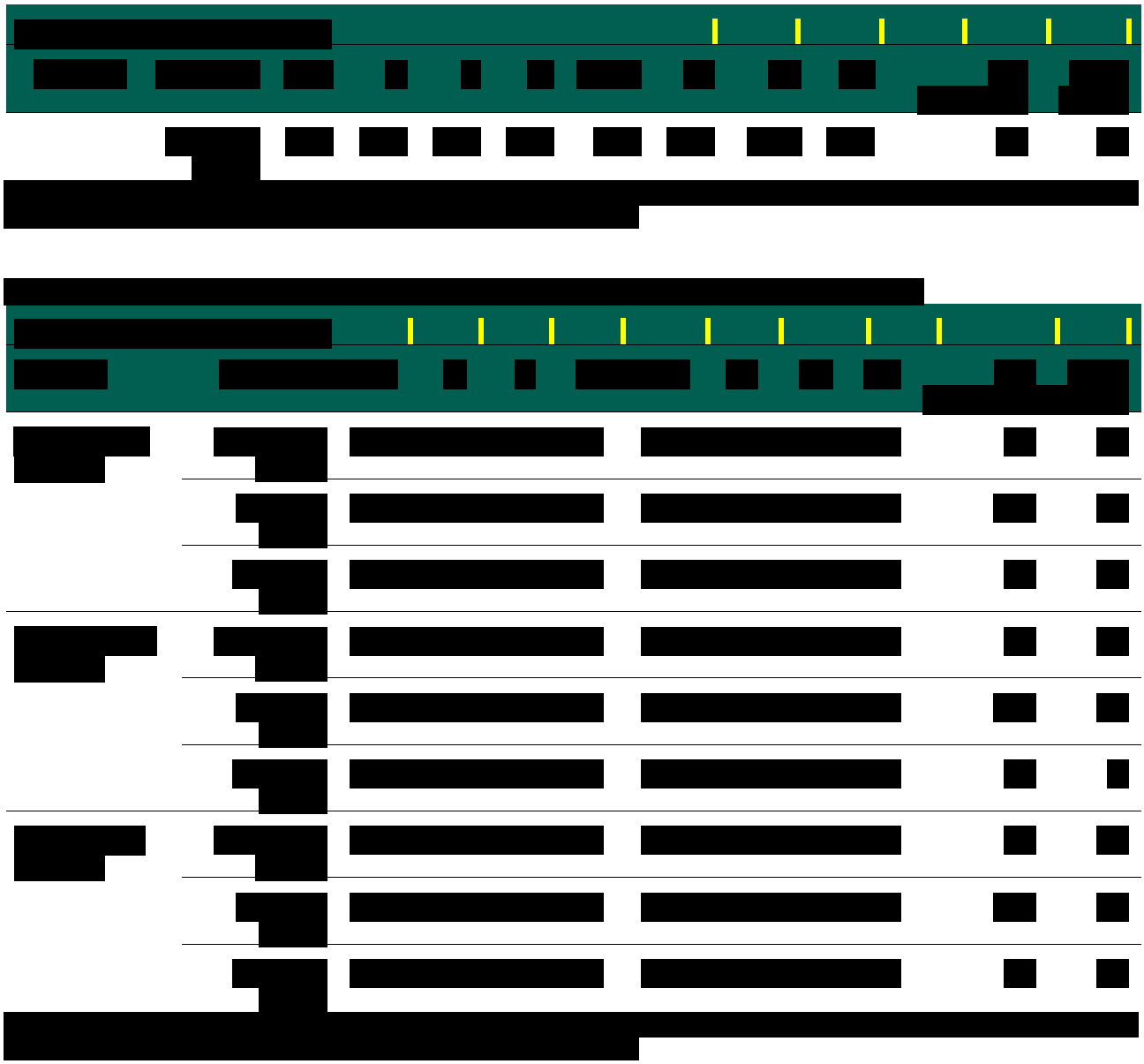

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22. Appendix J – Probabilistic sensitivity analyses

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23. Appendices K – CheckMate 649 all randomised patients

23.1 All randomised patients: baseline demographics

Baseline characteristics and disease characteristics in all randomised patients were balanced between the nivolumab plus chemotherapy and the chemotherapy alone arms (Table 77Table) (Janjigian 2021b). Stratification factors were also balanced (BMS 2020).

The median age of all randomised patients was 61 years. Most patients were white (69%), male (70%), and had an ECOG PS of 1 (58%) (Janjigian 2021b). Most patients were diagnosed with GC (70.2%); 16.4% had GEJC and 13.3% had EAC (Janjigian 2021b).

Table 78: Baseline demographics and characteristics in all randomised patients

Characteristic	Nivolumab plus chemotherapy (N=789)	Chemotherapy (N=792)
Median age (range), years	62 (18-88)	61 (21-90)
Age categorization, n (%)		
<65	473 (59.9)	488 (61.6)
Sex, M/F, n (%)	540 (68.4)/ 249 (31.6)	560 (70.7)/ 232 (29.3)
Race, n (%)		
Region, n (%)		
Asia (including China)	178 (22.6)	178 (22.5)
US and Canada	131 (16.6)	132 (16.7)
Rest of world	480 (60.8)	482 (60.9)
Initial diagnosis, n (%)		
GEJ cancer[a]	132 (16.7)	128 (16.2)
Gastric cancer	554 (70.2)	556 (70.2)
EACb	103 (13.1)	108 (13.6)

Characteristic	Nivolumab plus chemotherapy (N=789)	Chemotherapy (N=792)
[redacted]		
Disease status classification, n (%)		
Locally recurrent	5 (0.6)	2 (0.3)
Metastatic	757 (95.9)	756 (95.5)
Locally advanced	27 (3.4)	34 (4.3)
WHO histologic classification (cell type), n (%)		
[redacted]		
Liver metastases		
[redacted]		
Microsatellite instability, n (%)		
MSI-H	23 (2.9)	21 (2.7)
MSS	695 (88.1)	682 (86.1)
[redacted]		
PD-L1 CPS expression status, n (%)	N=781	N=780
≥1	641 (82.1)	655 (84.0)
<1	140 (17.9)	125 (16.0)
[redacted]		

[a]GEJ cancer represents patients with diagnosis GEJ and Siewert-Stein Type II or III or unknown. [b]EAC represents patients with diagnosis EAC or GEJ cancer with Siewert-Stein Type I

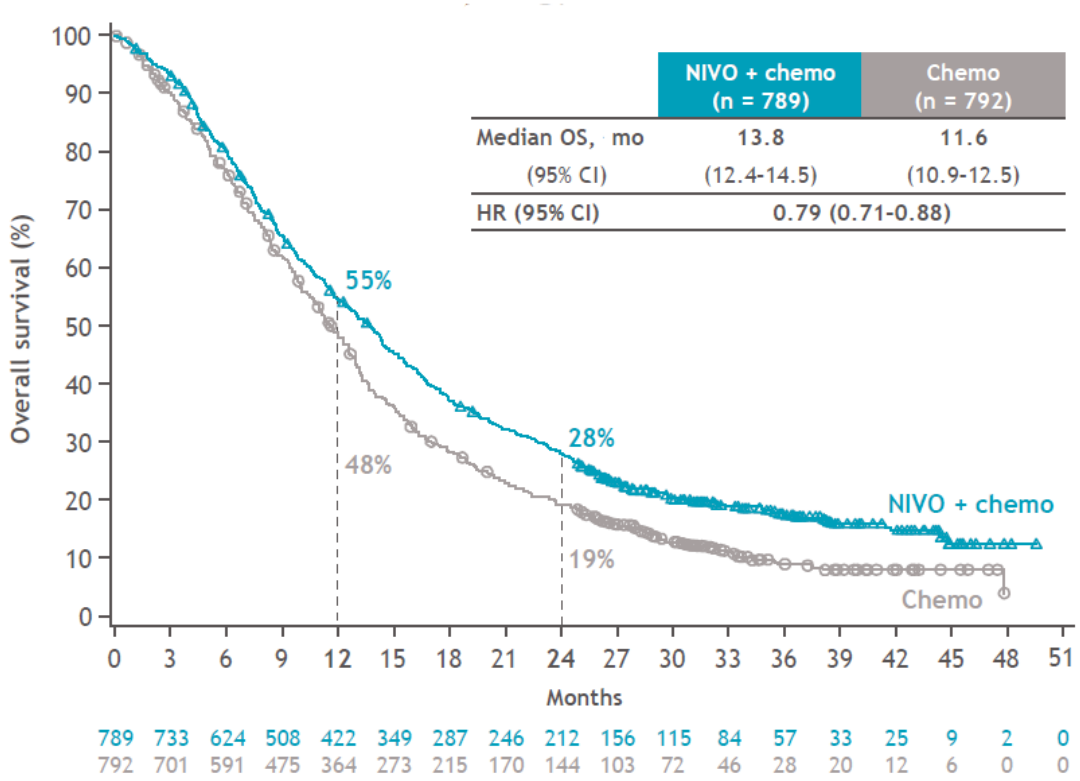
Abbreviations: CPS: combined positive score; EAC: esophageal adenocarcinoma; ECOG PS: Eastern Cooperative Oncology Group performance status; GEJ: gastroesophageal junction cancer; MSI-H: microsatellite instability-high; MSS: microsatellite stable

Source: (BMS 2020, Janjigian 2021b)

23.2 OS in all randomised patients (minimum follow-up 24.0 months)

At a minimum follow-up of 24.0 months, nivolumab plus chemotherapy maintained clinically meaningful improvements in OS compared to chemotherapy in all randomised patients (HR: 0.79 [95% CI, 0.71–0.88]; Figure 56) (Janjigian 2021a). Median OS was 13.8 (95% CI, 12.4–14.5) months in the nivolumab plus chemotherapy arm and 11.6 (95% CI, 10.9–12.5) months in the chemotherapy alone arm; 2-year OS rates were 28% [redacted] and 19% [redacted] respectively (Figure 56) (BMS 2021, Janjigian 2021a).

Figure 56: Kaplan-Meier of OS, all randomised patients (minimum follow-up 24.0 months)



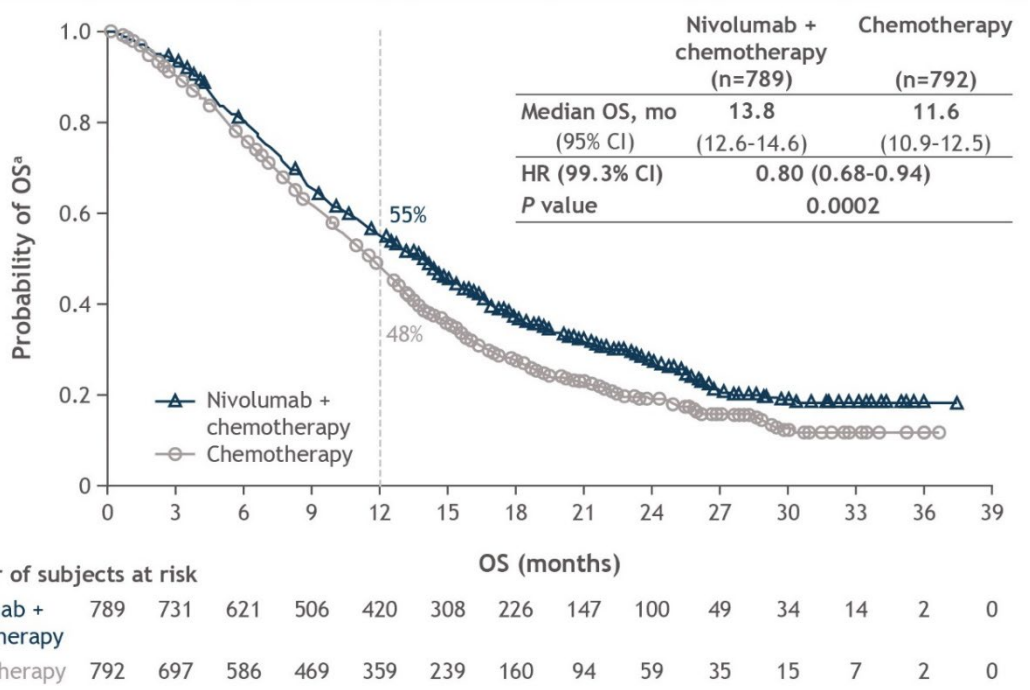
Abbreviations: CI: confidence interval; HR: hazard ratio; mo: month; OS: overall survival.
Source: (Janjigian 2021a).

23.3 OS in all randomised patients (minimum follow-up 12.1 months)

In all randomised patients, nivolumab plus chemotherapy demonstrated a statistically significant and clinically meaningful 20% reduction in the risk of death compared to chemotherapy (HR 0.80 [99.3% CI, 0.68–0.94]; P=0.0002, Figure 57) (Janjigian 2021b). Median OS was 2.2 months longer in the nivolumab plus chemotherapy arm compared to the chemotherapy alone arm (13.8 months [95% CI, 12.6–14.6] vs. 11.6 months [95% CI, 10.9–12.5]) (Janjigian 2021b). [redacted]

Separation of the Kaplan-Meier curves favouring nivolumab plus chemotherapy over chemotherapy occurred at approximately 2 months, with increased separation over time (Janjigian 2021b). [redacted]

Figure 57: Kaplan-Meier of OS, all randomised patients (minimum follow-up 12.1 months)



[a]Minimum follow-up 12.1 months

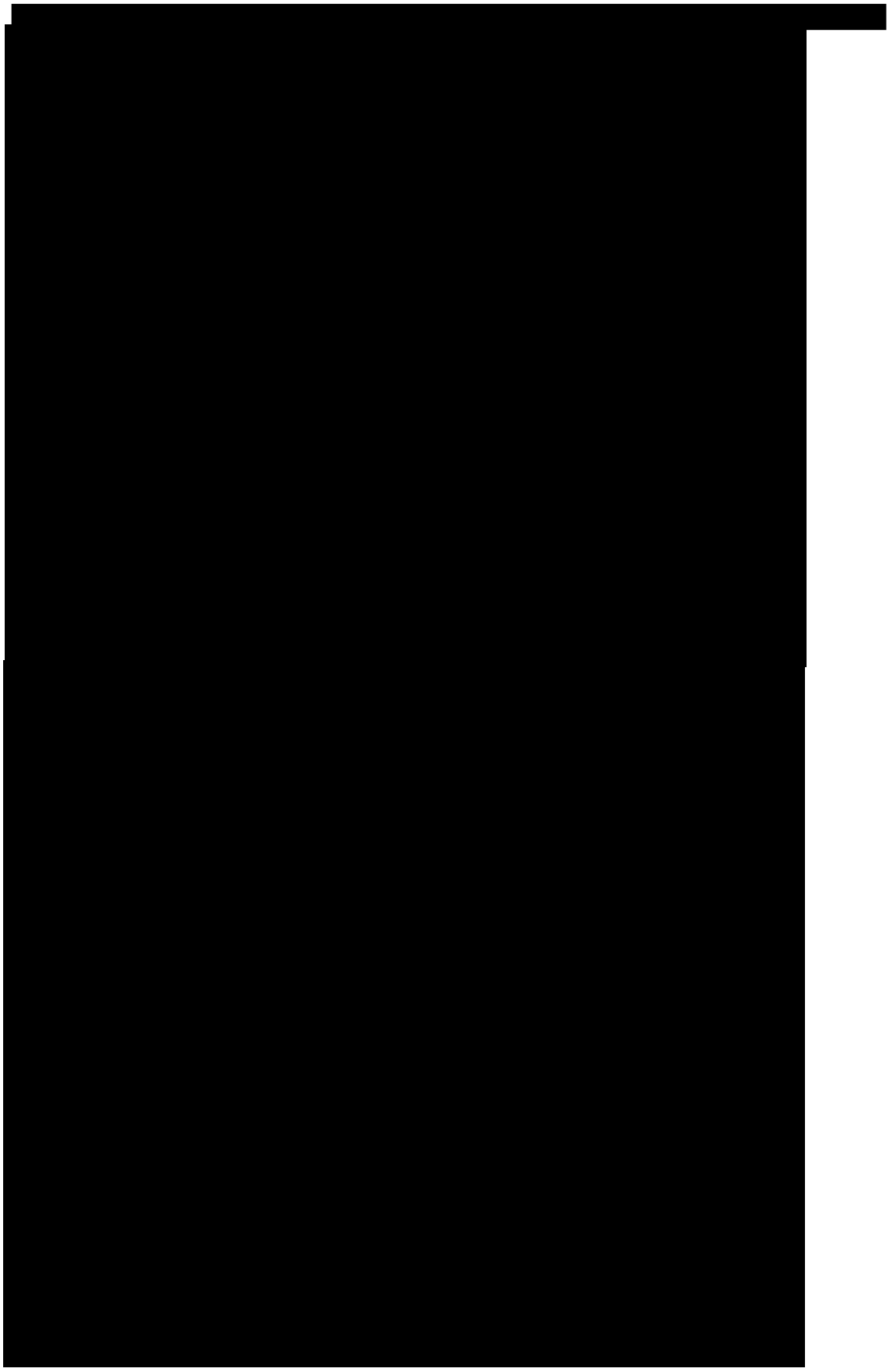
Abbreviations: CI: confidence interval; HR: hazard ratio; mo: month; OS: overall survival

Source: (Moehler 2020a)

23.4 OS in predefined subgroups for all randomised patients (minimum follow-up 12.1 months)

In a subgroup analysis for all randomised patients, OS HRs (95% CIs) for most subgroups favoured (HR <1) nivolumab plus chemotherapy over chemotherapy alone, including the subgroups of region, tumour location, histology (presence of signet ring cell, Lauren classification), metastases (liver, peritoneal), MSI status, tumour cell PD-L1 expression, and HER2 status (

[redacted] (Janjigian 2021b).



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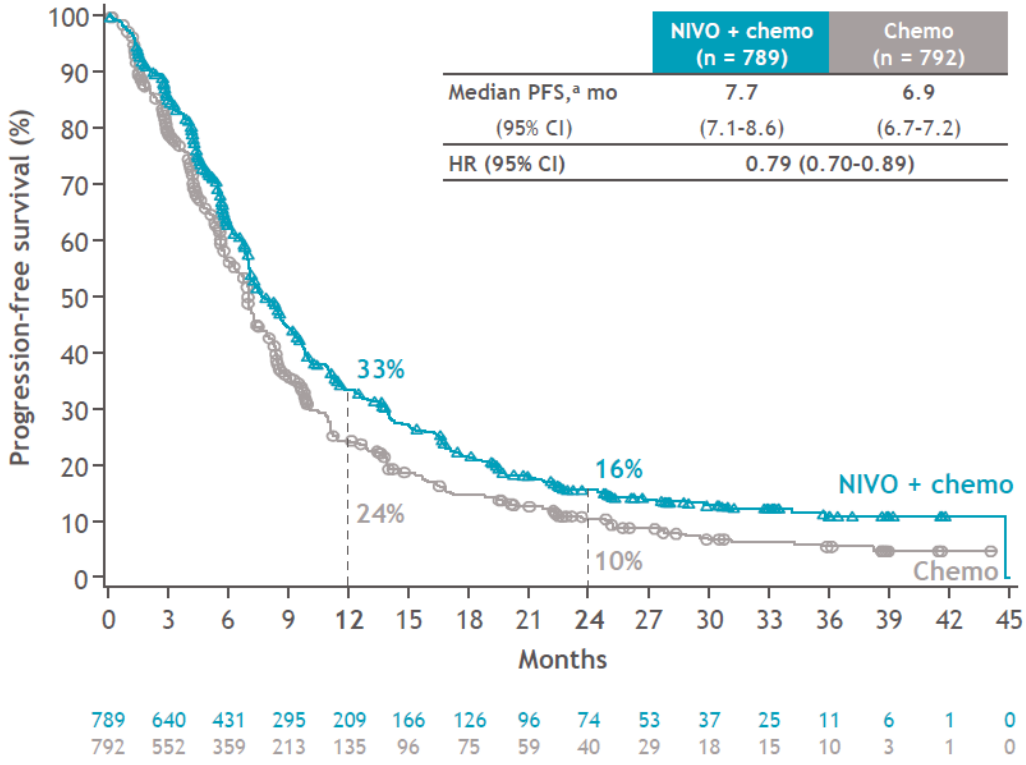
23.5 PFS in all randomised patients (minimum follow-up 24.0 months)

At minimum follow-up of 24.0 months, PFS benefit was maintained with nivolumab plus chemotherapy compared to chemotherapy alone (HR: 0.70 [95% CI, 0.60–0.81]; Figure 59) (Janjigian 2021a). Median PFS was 7.7 (95% CI, 7.1–8.6) months in the nivolumab plus chemotherapy group compared to 6.9 (95% CI, 6.7–7.2) months in the chemotherapy alone group; 2-year PFS rates were 16% [redacted] and 10% [redacted] respectively (Figure 59) (BMS 2021, Janjigian 2021a).

Figure 59: Kaplan-Meier of PFS, all randomised patients with PD-L1 CPS ≥5 (minimum follow-up 24.0 months)

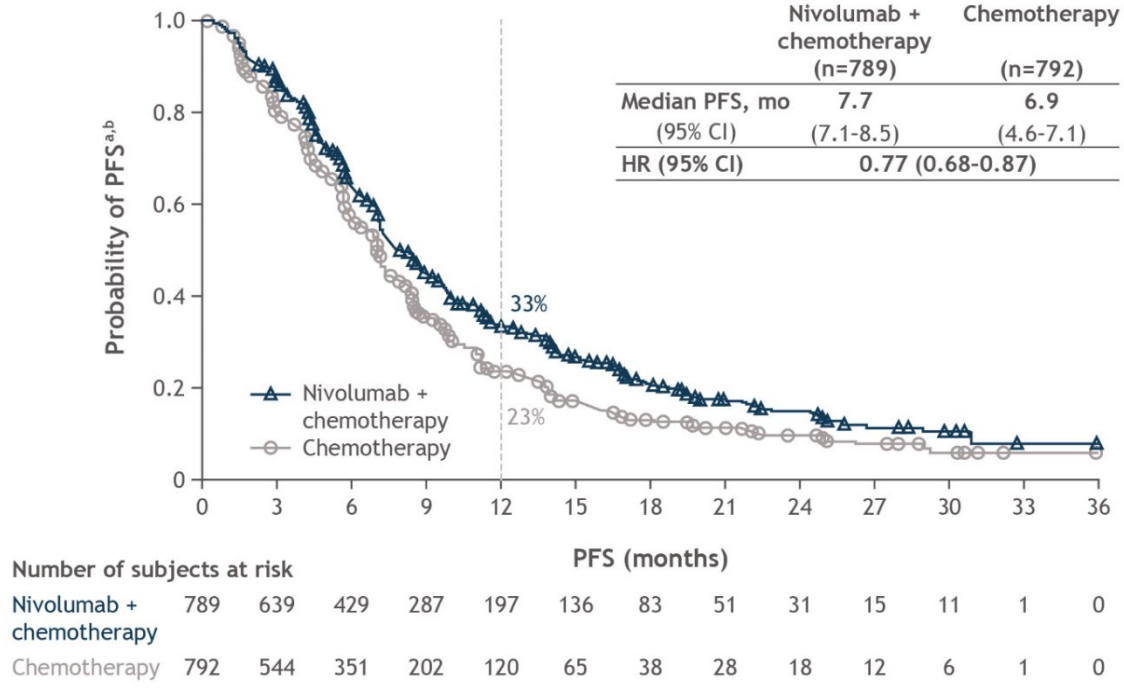


[a]Per BICR assessment
Abbreviation: CI: confidence interval; HR: hazard ratio; mo: month; PFS: progression-free-survival.
Source: (Janjigian 2021a)

23.6 PFS in all randomised patients (minimum follow-up 12.1 months)

In all randomised patients, an improvement of PFS per BICR was observed with nivolumab plus chemotherapy compared to chemotherapy alone; this result was not tested for statistical significance (HR 0.77 [95% CI, 0.68–0.87]) (Figure 60) (Janjigian 2021b). Median PFS was 7.7 months (95% CI, 7.1–8.5) in the nivolumab plus chemotherapy arm compared to 6.9 months (95% CI, 6.60–7.13) in the chemotherapy alone arm (Janjigian 2021b). PFS rates were higher with nivolumab plus chemotherapy compared to chemotherapy alone: 62.6% (95% CI, 59.0–66.0) vs 55.7% (95% CI, 51.9–59.3) at 6 months, and 33.4% (95% CI, 29.9–37.0) vs 23.2% (95% CI, 19.9–26.7) at 12 months, respectively (BMS 2020, Janjigian 2021b). Separation of the Kaplan-Meier curves favouring nivolumab plus chemotherapy over chemotherapy alone at approximately 2 months, with increased separation over time (Janjigian 2021b).

Figure 60. Kaplan-Meier of PFS per BICR, all randomised patients (minimum follow-up 12.1 months)



aPer BICR assessment; bMinimum follow-up 12.1 months

Abbrevations: CI: confidence interval; HR: hazard ratio; mo: month; PFS: progression-free-survival.

Source: (Moehler 2020a)

23.7 Objective response rates in all randomised patients (minimum follow-up 24.0 months)

ORR remained higher with nivolumab plus chemotherapy vs. chemotherapy alone with longer follow-up in all randomised patients (minimum follow-up 24.0 months; Table 78) (Janjigian 2021a). Additionally responses deepened relative to the 12.1 month follow-up, with 6 additional complete responses in the nivolumab plus chemotherapy group vs. 0 for chemotherapy alone (Janjigian 2021a, Janjigian 2021b).

Table 79: Response per BICR in all patients with PD-L1 CPS ≥5 (minimum follow-up 24.0 months)

Response per BICR	Nivolumab plus chemotherapy (N=603)[a]	Chemotherapy (N=607)[a]
ORR, % (95% CI)	58 (54–62)	46 (42–50)
CR	11	6
PR	47	40
SD	29	33
PD	7	10

[a]Randomised patients who had target lesion measurements at baseline per BICR assessment

Abbreviations: CI: confidence interval; CR: complete response; DRR: durable response rate; ORR: objective response rate; PD: progressive disease; PR: partial response; SD: stable disease.

Source: (Janjigian 2021a)

23.8 Objective response rates in all randomised patients (minimum follow-up 12.1 months)

In all randomised patients with measurable disease, an improvement of 12% in BICR-assessed ORR was observed in the nivolumab plus chemotherapy arm compared to chemotherapy alone (58.0% [95% CI, 54.0–62.0] vs. 46.1% [95% CI, 42.0–50.1]; OR 1.61 [95% CI, 1.28–2.02]) (Janjigian 2021b).

A higher proportion of patients in the nivolumab plus chemotherapy arm had a best overall response of CR or PR, and fewer patients had progressive disease, compared to the chemotherapy alone arm. [redacted]

Table 80. Best overall response per BICR in all randomised patients with measurable disease (minimum follow-up 12.1 months)

	Nivolumab plus chemotherapy (N=603)	Chemotherapy (N=608)
Best overall response, n (%)		
CR	59 (9.8)	39 (6.4)
PR	291 (48.3)	241 (39.6)
SD	171 (28.4)	200 (32.9)
PD	41 (6.8)	61 (10.0)
Unable to determine	41 (6.8)	67 (11.0)
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	
[redacted]	[redacted]	
[redacted]	[redacted]	

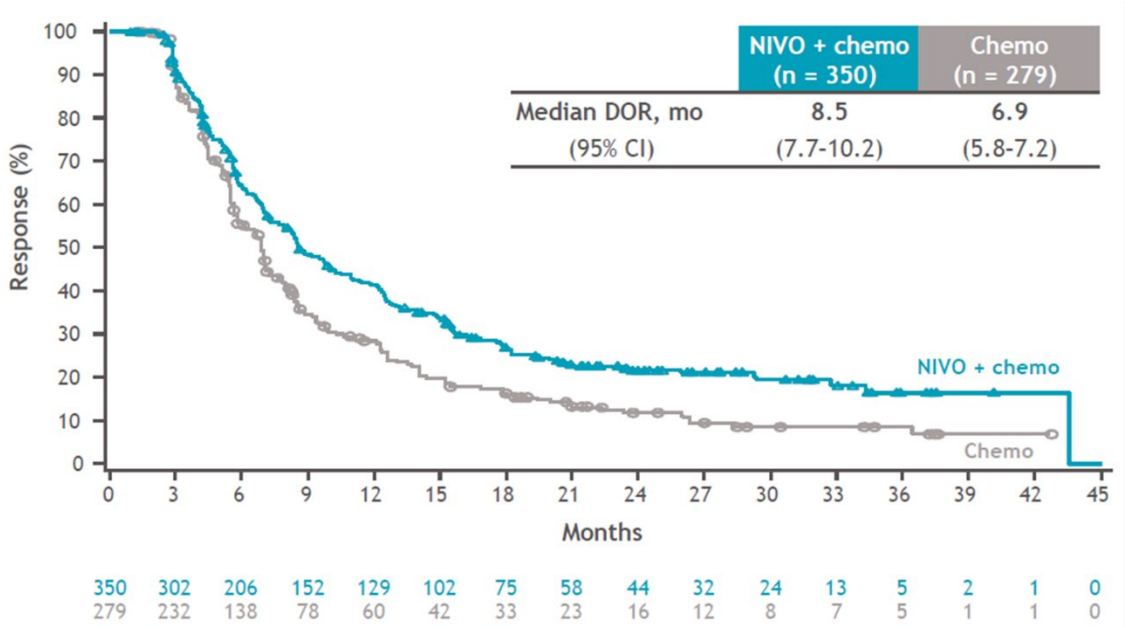
[a]Confirmed CR or PR per RECIST 1.1. Confidence interval based on Clopper-Pearson method [redacted]

Abbreviations: CI: confidence interval; CR: complete response; DRR: durable response rate; ORR: objective response rate; PD: progressive disease; PR: partial response; SD: stable disease.
Source: (BMS 2020, Janjigian 2021b).

23.9 Duration of response in all randomised patients (minimum follow-up 24.0 months)

At minimum follow-up of 24.0 months, responses were more durable with nivolumab plus chemotherapy vs. chemotherapy alone (Figure 61) (Janjigian 2021a). Median DOR was 8.5 (95% CI, 7.7–10.2) months in the nivolumab plus chemotherapy arm compared to 6.9 (95% CI, 5.8–7.2) months in the chemotherapy alone arm (Janjigian 2021a).

Figure 61: Kaplan-Meier plot of DOR per BICR, all responders (minimum follow-up 24.0 months)



Abbreviations: CI: confidence interval; DOR: duration of response; mo: month; n=number of responders.
Source: (Janjigian 2021a)

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23.11 Patient-reported outcomes in all randomised patients

Baseline scores of all PRO assessments in CheckMate 649 were consistent between treatment arms, indicating baseline health status and quality of life were similar between patients in the two treatment arms for all randomised patients.

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24. Appendix L – Smoothed hazard plots for CheckMate 649

24.1 Overall survival

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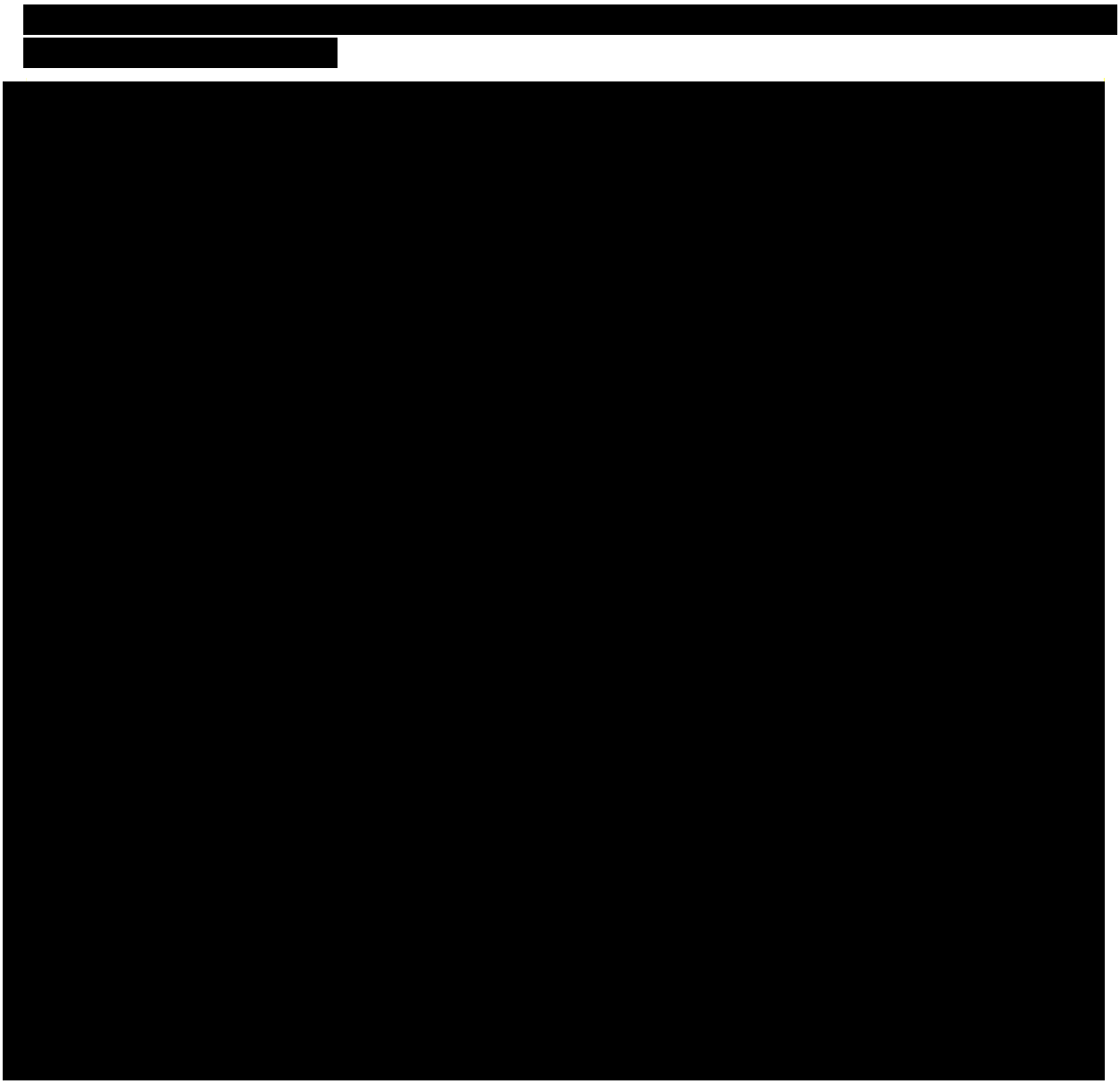

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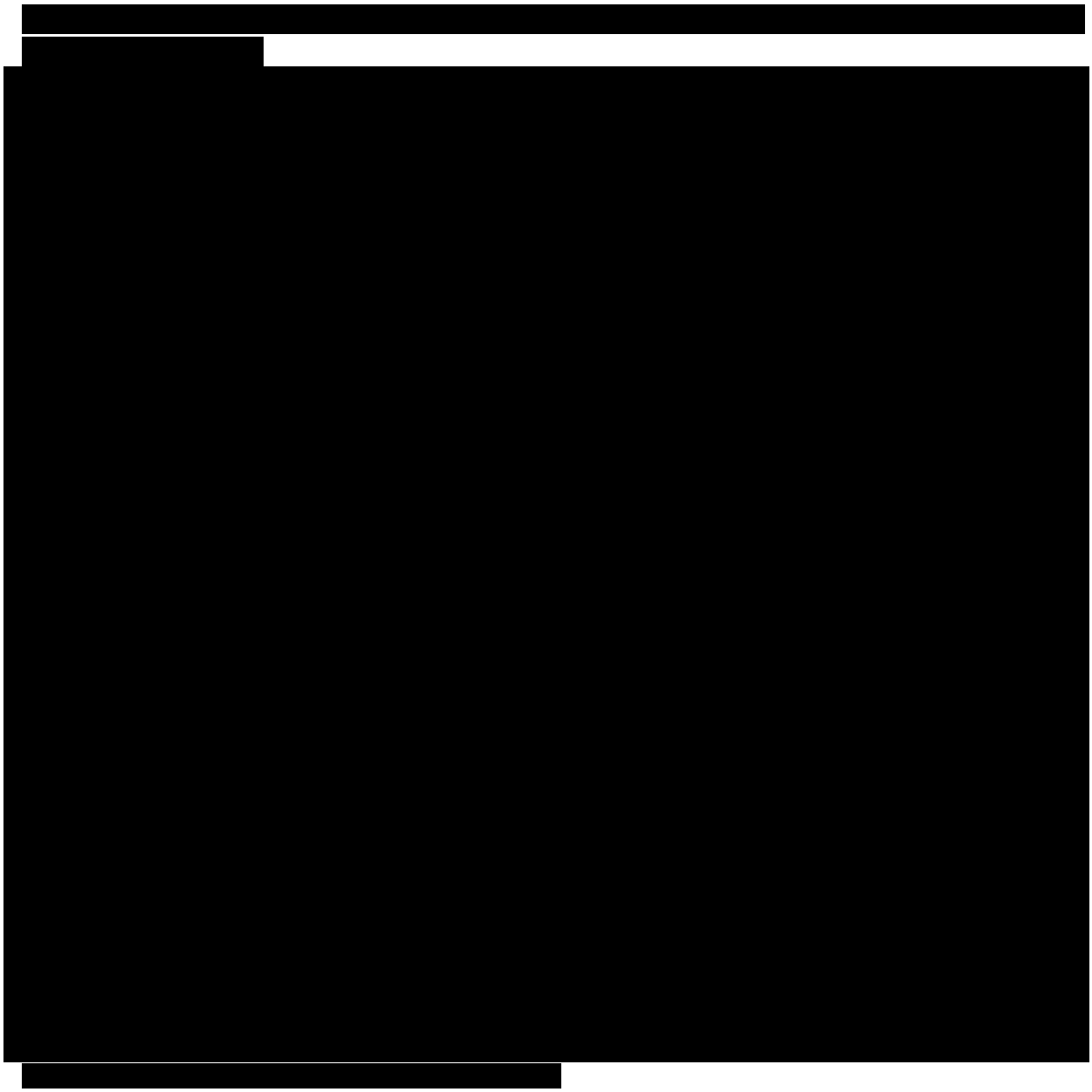

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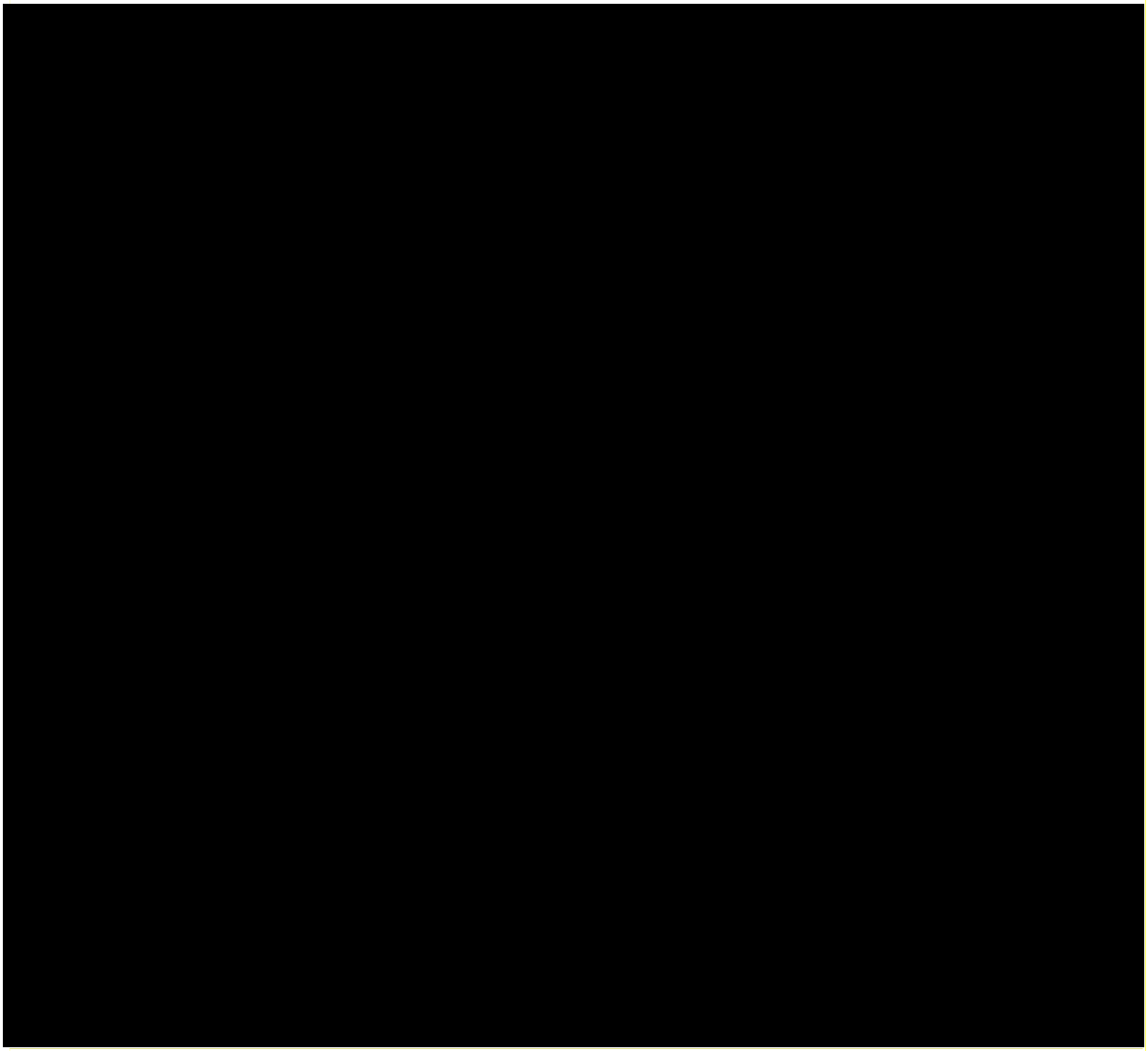

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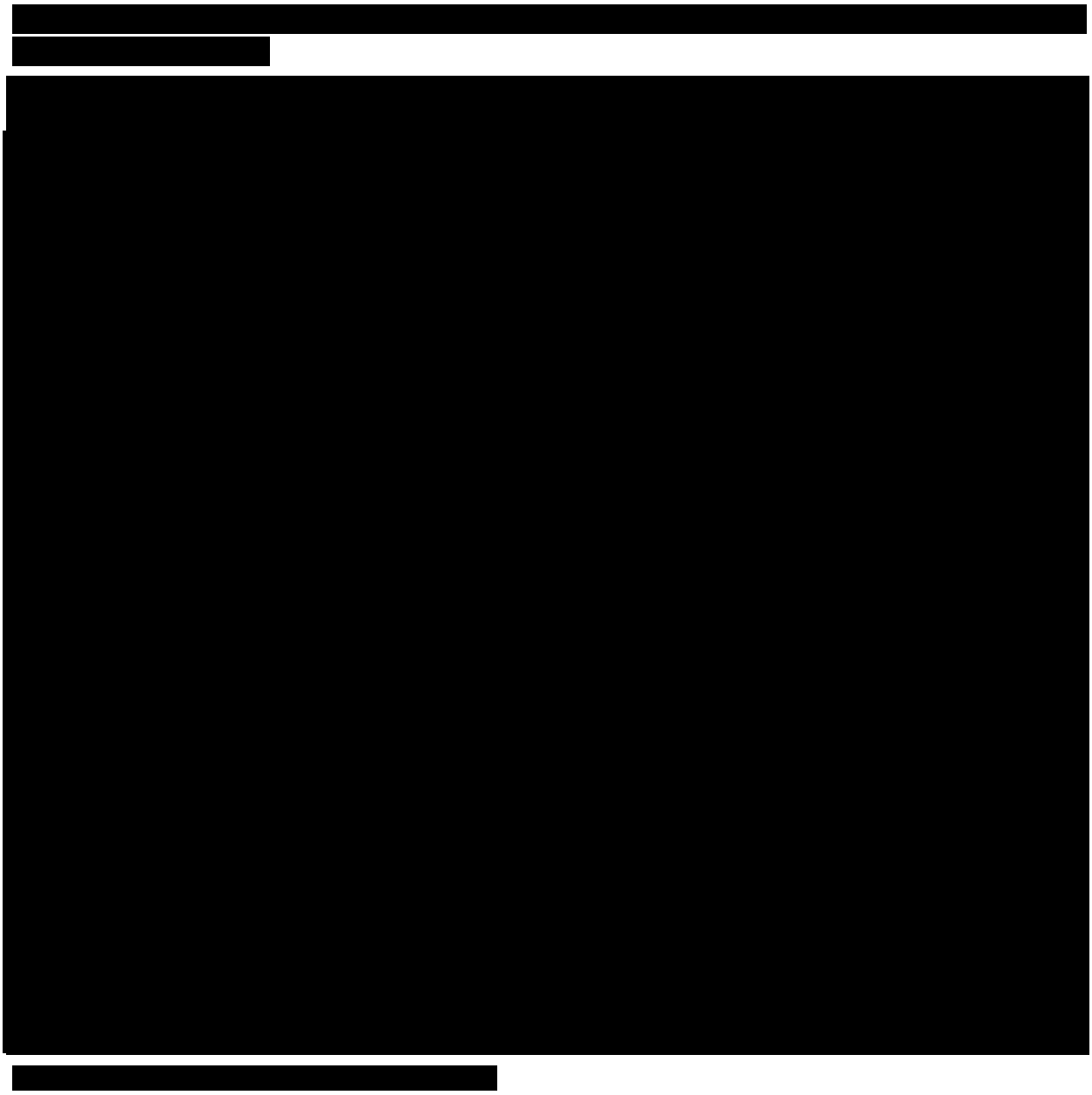

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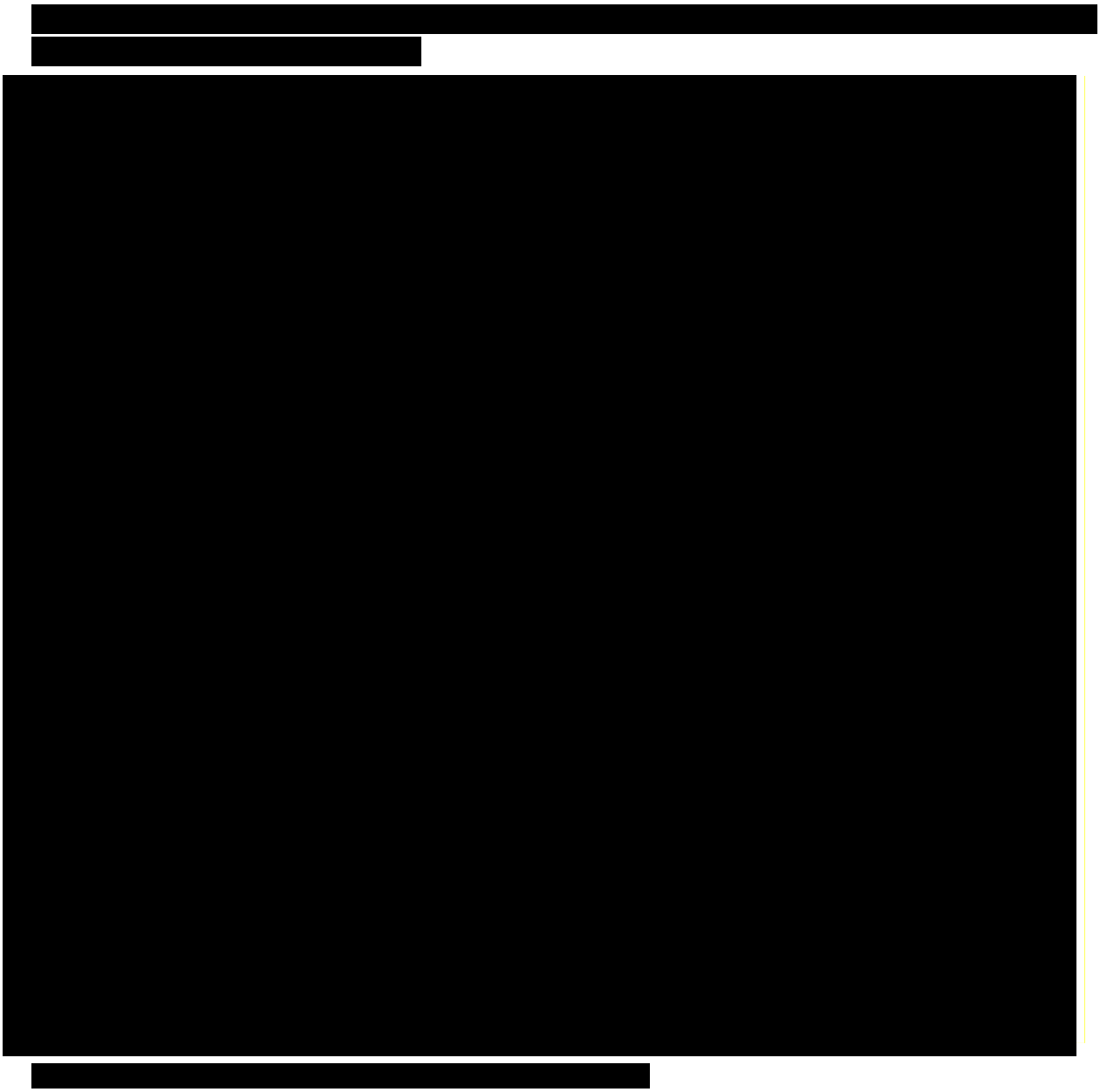

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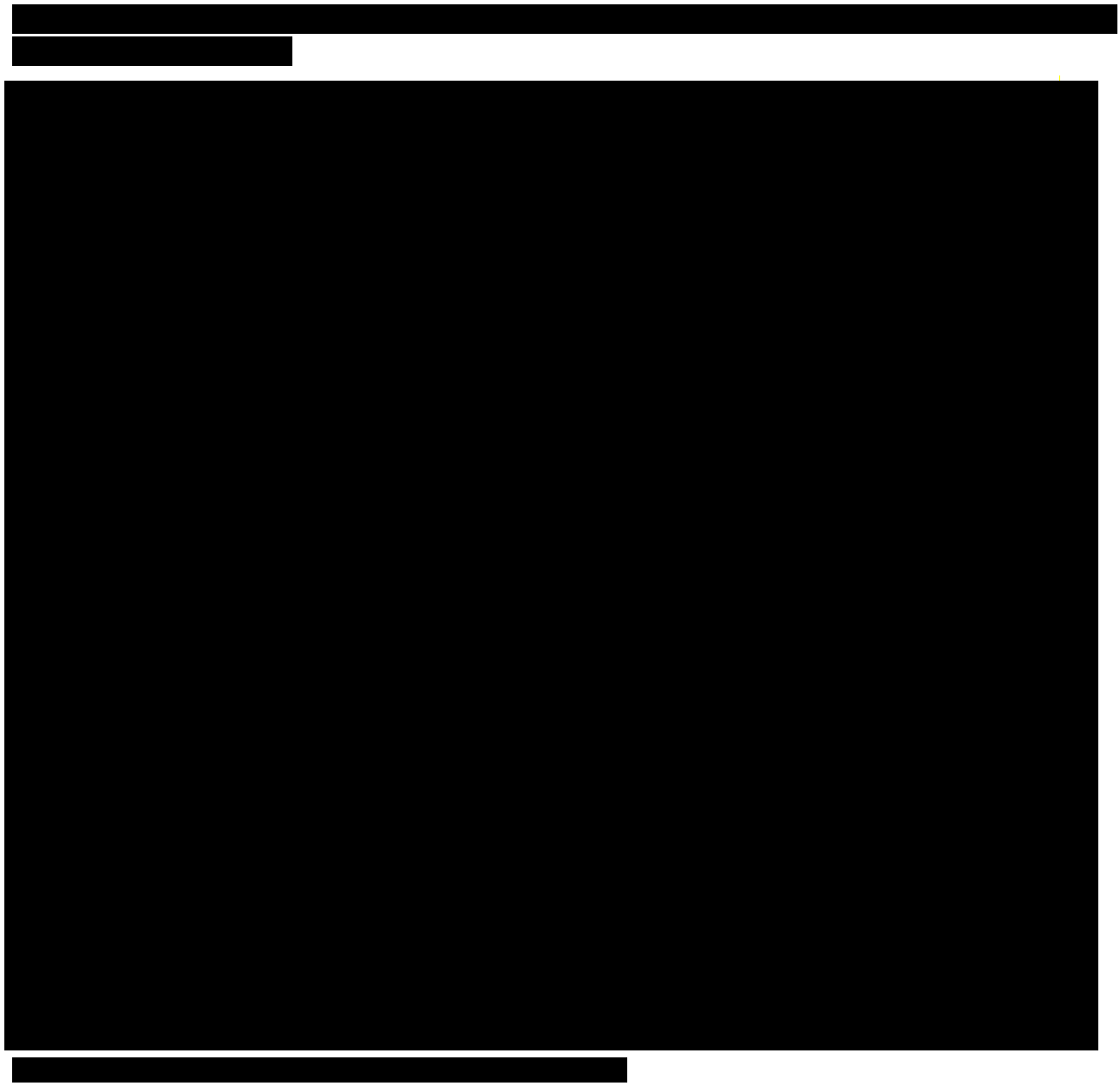

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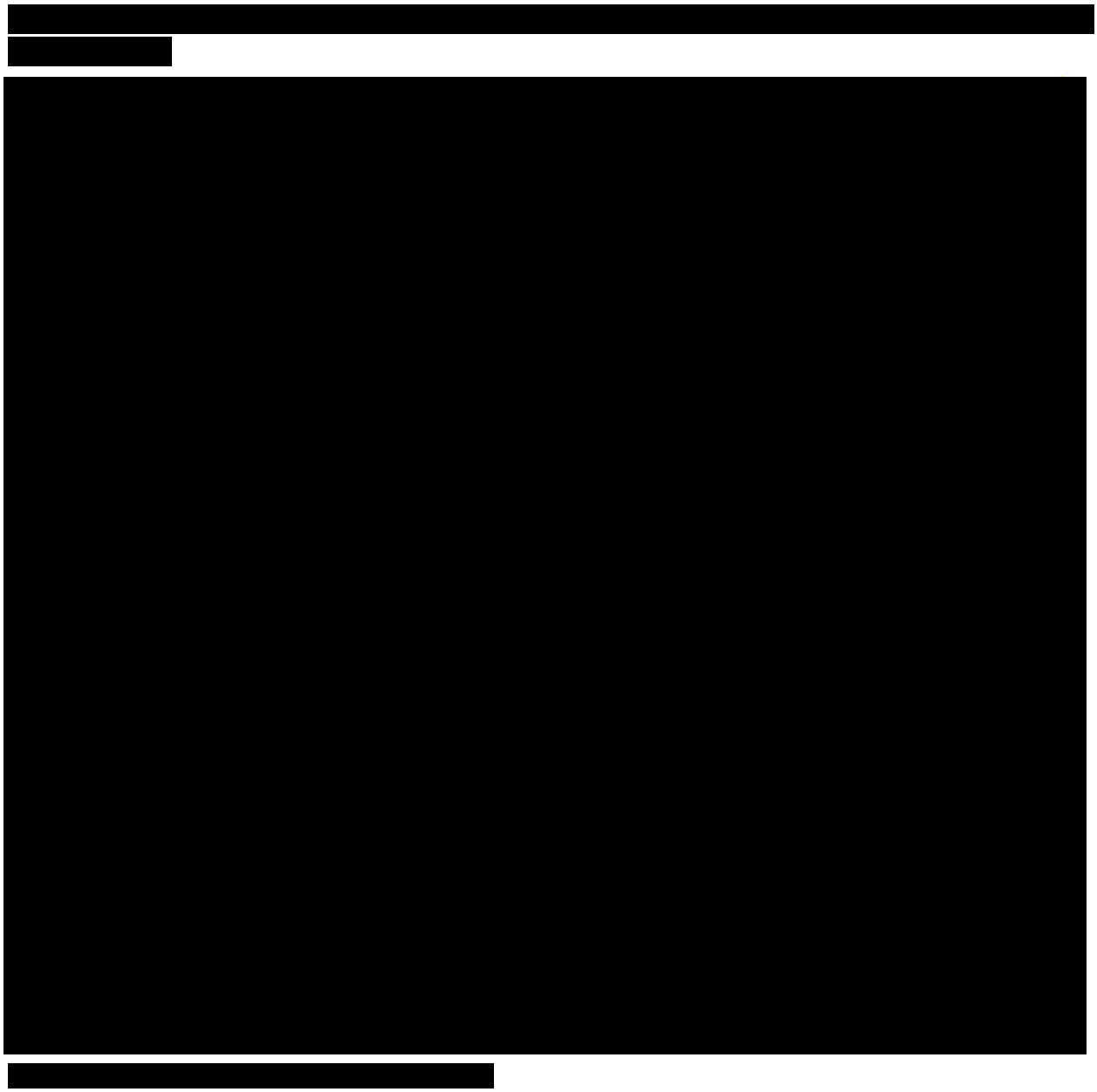

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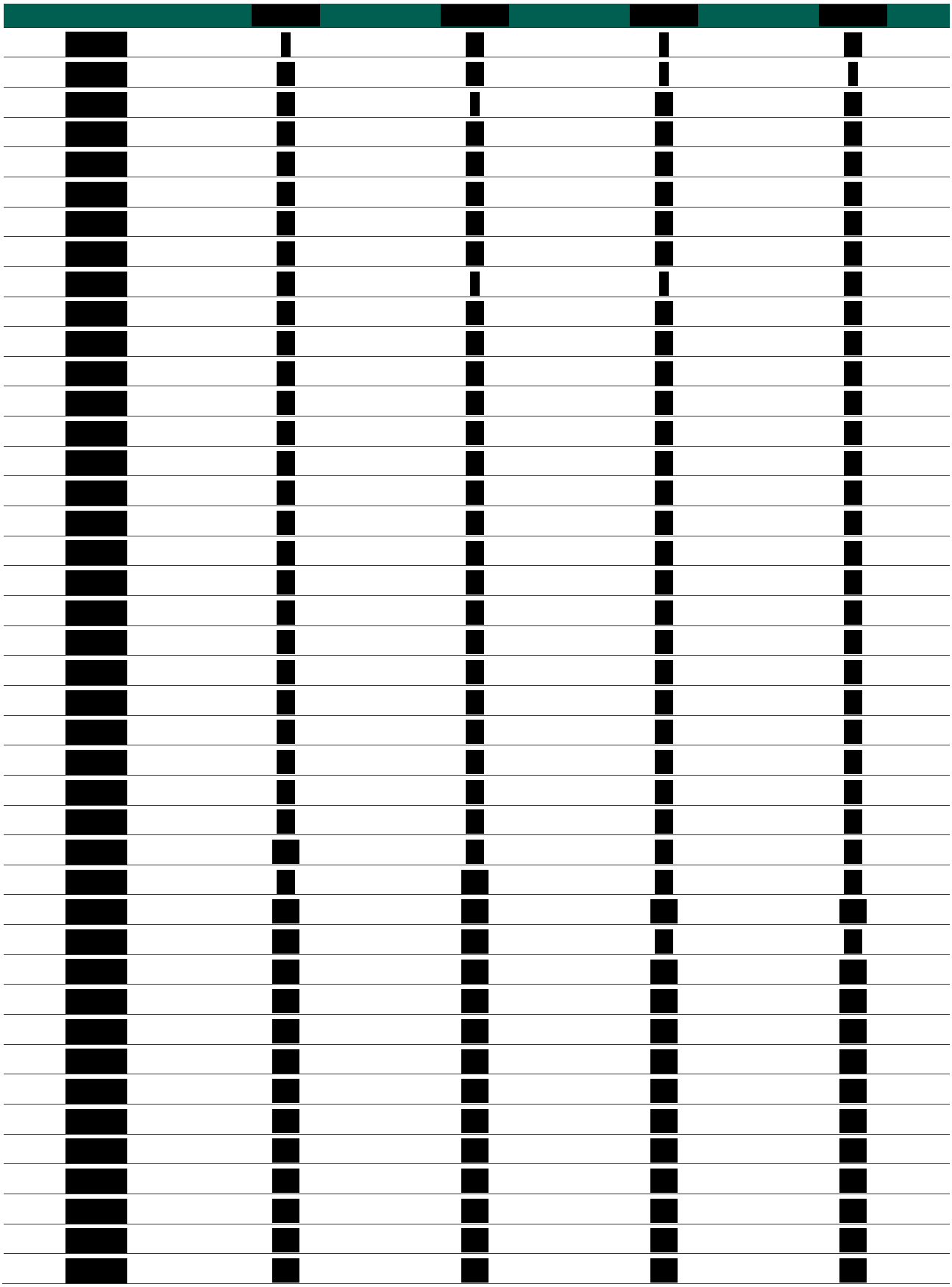

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26. Appendix N – Systematic literature reviews

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27. Appendix O – Health related quality of life, supplemental data

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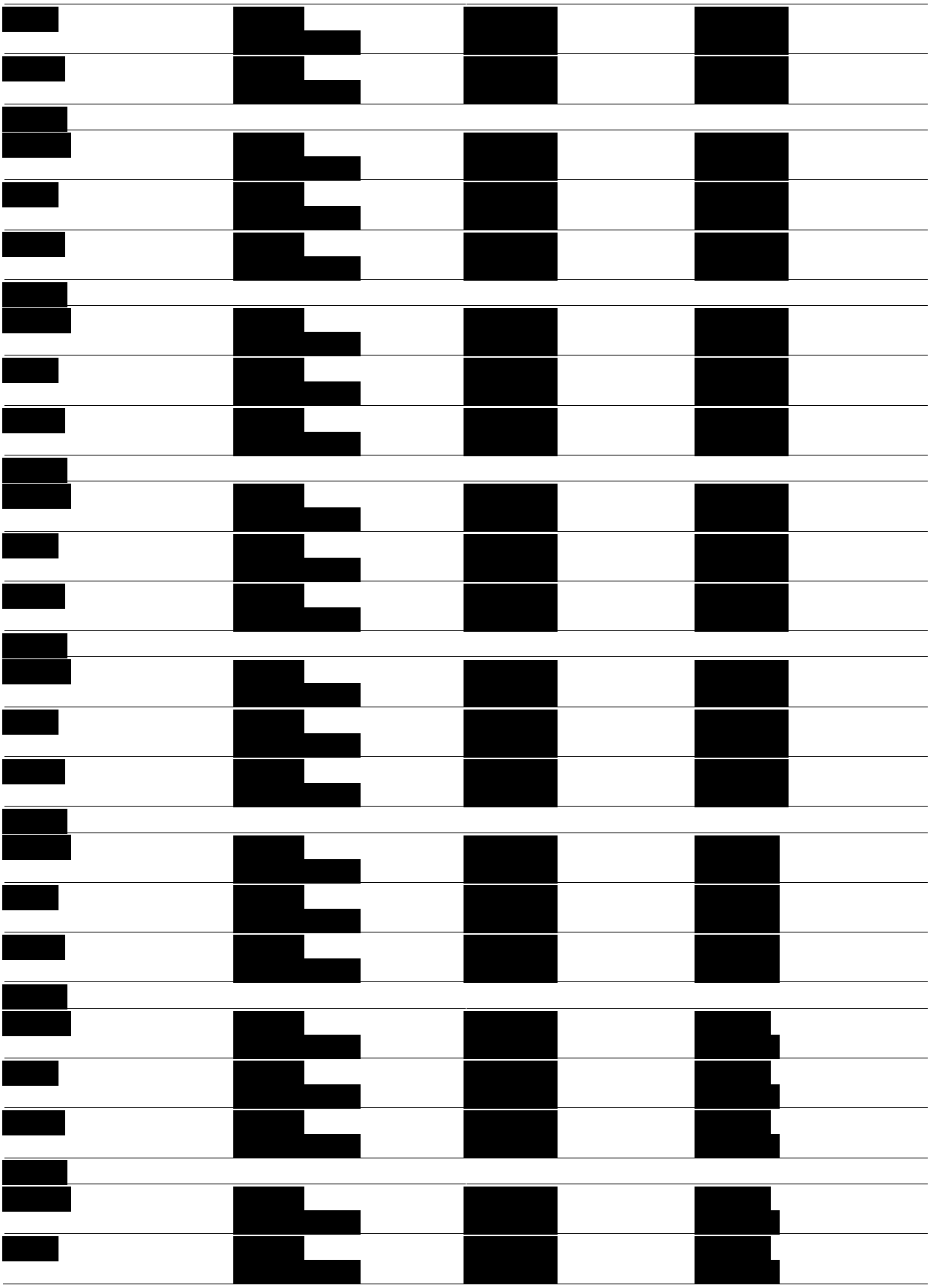

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