Medicinrådet

Bilag til Medicinrådets anbefaling vedrørende nivolumab som adjuverende behandling til patienter med kræft i spiserør eller mavemund efter neoadjuvant kemoradioterapi og radikal resektion uden komplet patologisk remission

Vers. 1.0

Bilagsoversigt

1. Ansøgers notat til Rådet vedr. nivolumab
2. Forhandlingsnotat fra Amgros vedr. nivolumab
3. Ansøgers endelige ansøgning vedr. nivolumab

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Virum, d. 20. maj 2022

Til Medicinrådet

Bristol Myers Squibbs tilbagemelding på høring over udkast til "Medicinrådets anbefaling vedrørende nivolumab som adjuverende behandling til patienter med kræft i spiserør eller mavemund efter neoadjuvant kemoradioterapi og radikal resektion uden komplet patologisk remission"

Bristol Myers Squibb (BMS) imødeser Medicinrådets anbefaling vedr. behandling med Nivolumab som adjuverende behandling til patienter med kræft i spiserør og mavemund efter kemoradioterapiog kirurgi planlagt til behandling af Medicinrådet d.15. juni 2022. Således godt 9 måneder efter Medicinrådet modtog ansøgningen fra BMS (21 ugers validering og 20 ugers evaluering). BMS takker hermed for muligheden for at give en tilbagemelding på udkastet til Medicinrådets vurdering, som vi overordnet set er enige i. BMS dog vil benytte høringssvaret til at gøre opmærksom på fire faktorer:

1. **Præsentation af resultater: Ansøgers resultater bør præsenteres sammen med Medicinrådets resultater**

BMS appellerer kraftigt til, at ansøgers hovedanalyse præsenteres i samme tabel eller umiddelbart efter Medicinrådets hovedanalyse. Dette vil bidrage væsentligt til gennemsigtigheden af de implikationer, Medicinrådets ændrende antagelser medfører.

2. **Fast dosering versus vægtbaseret dosering**

BMS er tilfredse med Medicinrådets sensitivitetsanalyse for vægtbaseret dosering, som er yderst relevant.

Vi foreslår, at denne bruges i hovedanalysen, idet dansk klinisk praksis er anvendelse af vægtbaseret dosering frem for fast dosering. I Medicinrådets nylige evaluering af pembrolizumab + kemoterapi som 1. linjebehandling til samme cancerform, esophaguscancer (baseret på Keynote 590), anvendte Medicinrådet også en vægtbaseret dosering i hovedanalysen.

BMS har en forventning til, at immunterapi generelt vurderes under ens forudsætninger i Medicinrådets hovedanalyser for at sikre en ensartet metodisk tilgang i evalueringerne.

3. **Ekstrapolering af sygdomsfri overlevelse og helbredelse**

Vi finder det principielt ikke rimeligt, Medicinrådet først anvender baggrundsbefolkningens dødelighed fra år 5 frem for år 3. Man må antage, at patienterne anses for at være kurerede eller sygdomsfri, når deres kontrolforløb på hospitalet afsluttes. Dette må være en forudsætning for, at patienten ikke længere skal følges på hospitalet.

Patienter med adenokarcinomer kontrolleres som bekendt blot i 2 år på hospitalet og afsluttes herefter til egen læge. Patienter med planocellulære karcinomer følges i 5 år på hospitalet. Som det også angives i Medicinrådets udkast til vurdering af nivolumab har hovedparten af patienterne adenokarcinom hvorfor vi finder det mere rimeligt med en skæringsdato, der ligger tættere på 2 år frem for 5 år i.e. 3 år.

Ydermere finder vi det metodisk modstridende, at Medicinrådet ikke accepterer helbredelse - heller ikke efter 5 år, men en ekstrapolering af sygdomsfri overlevelse med Gompertz, samtidig med dødeligheden er lig baggrundsbefolkningens efter 5 år. I nærværende ansøgning er det ikke afgørende for resultatet, men principielt er det modstridende, at man ikke accepterer en helbredelse og dermed risiko for progression lig nul, når man accepterer, dødelighed for sygdom er lig nul.

4. **Efterfølgende behandling**

Antallet af patienter, der modtager efterfølgende behandling, er nedjusteret fra 80% [redacted] til 36%, hvoraf sidste antages at være et gennemsnit af 30% og 42% for hhv. nivolumab-gruppen og placebo-gruppen i studiet Checkmate 577. Vi henleder opmærksomheden på, at disse tal er baseret på det totale antal patienter i hver gruppe; således også de, der endnu *ikke* har haft et DFS-event. Hvis man ser på gruppen af patienter, der har haft et DFS [redacted] De 80% er således et estimat for situationen i den kliniske hverdag.

Siden indsendelsen af denne ansøgning, er pembrolizumab + kemoterapi pr. 26. januar 2022 blevet anbefalet af Medicinrådet som ny standard behandling i 1.linie af relevant patientgruppe. Det er derfor vigtigt at tage højde for, at der i dag vil være øgede lægemiddelomkostninger til immunterapi til patienter, der ikke modtager adjuverende immunterapi og progredierer i forhold til lægemiddelomkostninger indregnet i ansøgningen

Med venlig hilsen,

Anders Thelborg
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23.05.2022
DBS/CAF

Forhandlingsnotat

Dato for behandling i Medicinrådet	15.06.2022
Leverandør	Bristol Meyer Squibb (BMS)
Lægemiddel	Opdivo (nivolumab)
Ansøgt indikation	Nivolumab som adjuverende behandling til patienter med kræft i spiserør eller mavemund efter neoadjuvant kemoradioterapi og radikal resektion uden komplet remission

Forhandlingsresultat

Amgros har opnået 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]

Leverandøren tilbød en yderligere rabat i forbindelse med igangsættelse af prisregulering af alle immunterapierne i februar 2022. Prisen vil være gældende indtil 31.12 2023. Amgros har mulighed for at aktivere prisreguleringen igen, hvis der kommer øget konkurrence og dermed mulighed for at få bedre priser på alle immunterapier.

Konkurrencesituationen

Der er på nuværende tidspunkt ingen konkurrence på Opdivo (nivolumab) til denne indikation.

[redacted]

Status fra andre lande

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

Konklusion

[redacted]

[1] https://nyemetoder.no/metoder/nivolumab-opdivo-indikasjon-xiv
[2] https://www.nice.org.uk/guidance/ta746/chapter/1-Recommendations

Application for the assessment of Opdivo® as monotherapy for adjuvant treatment of adult patients with esophageal or gastro-esophageal junction cancer who have residual pathologic disease following prior neoadjuvant chemoradiotherapy and complete resection

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 (Danish Medicines Council) 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	240 mg every 2 weeks over 30 minutes or 480 mg every 4 weeks over 30 minutes for the first 16 weeks followed by 480 mg every 4 weeks over 30 minutes until disease progression or unacceptable toxicity for a total treatment duration of up to 1 year
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)	**Adjuvant treatment of esophageal or gastro-esophageal junction cancer** OPDIVO as monotherapy is indicated for the adjuvant treatment of adult patients with esophageal or gastro-esophageal junction cancer who have residual pathologic disease following prior neoadjuvant chemoradiotherapy and complete resection

Other approved therapeutic indications	**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 (second line) **Malignant pleural mesothelioma** OPDIVO in combination with ipilimumab is indicated for the first-line treatment of adult patients with unresectable malignant pleural mesothelioma. **Melanoma** OPDIVO as monotherapy or in combination with ipilimumab is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults Relative to nivolumab monotherapy, an increase in progression-free survival 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 **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 **Esophageal squamous cell carcinoma**

Overview of the pharmaceutical	
	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. **Mismatch repair deficient (dMMR) or microsatellite instability-high (MSI-H) colorectal Cancer** OPDIVO in combination with ipilimumab is indicated for the treatment of adult patients with dMMR/MSI-H metastatic CRC after prior fluoropyrimidine-based combination chemotherapy
Will dispensing be restricted to hospitals?	Yes
Combination therapy and/or co-medication	No
Packaging – types, sizes/number of units, and concentrations	Nivolumab (10 mg/mL): Single-use vials 40 mg/4 mL 100 mg/10 mL 240 mg/24 mL
Orphan drug designation	No

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2. Abbreviations

Abbreviation	Definition
AC	Adenocarcinoma
AE	Adverse event
AIC	Akaike information criterion
AJCC	American Joint Committee on Cancer
ALK	Anaplastic lymphoma kinase
ATC	Anatomical therapeutic chemical
BIC	Bayesian information criterion
BICR	Blinded independent central review
BSA	Body surface area
CAP	Capacitabine
CEAC	Cost-effectiveness acceptability curve
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CIS	Cisplatine
CM	CheckMate
CRC	Colorectal cancer
CRT	Chemoradiotherapy
CT	Computed tomography
DBL	Database lock
DEGC	Dansk Esophago-Gastrisk Cancer Gruppe
DoT	Duration of treatment
DFS	Disease-free survival
DKK	Danish Kroner
DMC	Danish Medicines Council
DMFS	Distant metastasis-free survival

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Abbreviation	Definition
DRG	Diagnose Relateret Gruppering
DSA	Deterministic sensitivity analysis
EAC	esophageal adenocarcinoma
EC	Esophageal cancer
ECOG	Eastern Cooperative Oncology Group
ECS	Esophageal cancer subscale
EGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
EQ-5D	EuroQoL 5-dimensions questionnaire
ESCC	Esophageal squamous cell carcinoma
FACT-E	Functional Assessment of Cancer Therapy – Esophageal
FACT-G7	Functional Assessment of Cancer Therapy-General 7-item version
FLOT	5FU, Folinic acid, Oxaliplatin, and Docetaxel
FOLFOX	Folinic acid, fluorouracil, and oxaliplatin
FU	Fluorouracil
GC	Gastric cancer
GEJC	Gastroesophageal junction cancer
GERD	Gastroesophageal reflux disease
GI	Gastrointestinal
HE	Health Economic
HER2	Human epidermal growth factor receptor 2
HR	Hazard ratio
HRQoL	Health-related quality of life
HSUV	Health-state utility value
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio

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Abbreviation	Definition
IKNL	Netherlands comprehensive cancer organisation
ITT	Intention-to-treat
IV	Intravenous
KM	Kaplan-Meier
KN	KeyNote
KOL	Key opinion leader
LSM	Least squares mean
LY	Life year
Mg	Milligram
Ml	Millimetre
MID	Minimally important difference.
NA	Not applicable
NCT	National clinical trial
NE	Not estimable
NICE	National Institute of Clinical Excellence
NR	Not reported
NREV	Nationella Registret för Esofagus- och Ventrikelcancer
OS	Overall survival
OX	Oxaliplatin
PD-L1	Programmed death-ligand 1
PF	Progression free
PFS	Progression free survival
PK	Pharmacokinetics
PP	Per pack
PPP	Pharmacy purchase price
PRO	Patient-reported outcomes

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Abbreviation	Definition
PS	Performance status
PSA	Probabilistic sensitivity analysis
QALY	Quality adjusted life years
QoL	Quality of life
RCT	Randomised control trial
SCC	Squamous cell carcinoma
SE	Standard error
SmPC	Summary of Product Characteristics
SOC	Standard of care
STA	Single technology assessment
TNM	Tumour, node, metastasis
TRAE	Treatment related adverse events
TTD	Time-to-treatment discontinuation
TTR	Time-to-recurrence
UI	Utility index
UK	United Kingdom
US	United states
VAS	Visual analogue scale
VAT	Value added tax
W&W	Watch and wait
XELOX	Oxaliplatin and capecitabine
ypTNM	Post-neoadjuvant tumour, node, metastasis.

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3. Tables and Figures

3.1 List of Tables

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4. Summary

Nivolumab is an immune checkpoint inhibitor expected **to be used in patients with esophageal or gastro-esophageal junction cancer who have residual pathologic disease following prior neoadjuvant chemo-radio therapy (CRT) and complete resection**, and has been approved in July 2021 for use in this indication by the European Commission (BMS 2021b). Adjuvant use of nivolumab has been shown to be effective, with long-term treatment benefit observed in adjuvant melanoma (CheckMate 238).

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). GEJC is generally segmented into three subtypes based on the location of the tumour epicentre: Siewert type I, type II and type III, see Figure 1 (Siewert 1998, Berlth 2019). 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 Dansk Esophago-Gastrisk Cancer Gruppe (DEGC) 2019 annual report, 320 cases of EC and 626 cases of GEJC cancer (across stages) were registered in Denmark in 2019 (DEGC 2020a). Of the patients with stage I-III disease, only 10.6% of patients with EC and 32.7% of patients with GEJC received treatment with curative intent (DEGC 2020a). Although patients with resectable stage II or stage III EC or GEJC may receive treatments with curative intent, many do not obtain a pathologic complete response (pCR), despite intensive treatment strategies (Walsh 1996, Bosset 1997, van Meerten 2006, Reynolds 2007, van Hagen 2012, Blum Murphy 2017). Patients who do not have a pathologic complete response following neoadjuvant CRT and resection have a high risk of recurrence (42% vs. 17% in patients with pCR) and thereby poor prognosis (Oppedijk 2014).

The 5-year survival rate for patients with locally advanced EC or GEJC at diagnosis when treated with a standard of care (SOC) ranges between 45% (among patients with locally advanced, resectable GC/GEJC in the FLOT4 trial) and 47% (according to long-term follow-up of patients with locally advanced, resectable EC/GEJC included in the CROSS trial) (Shapiro 2015, Al-Batran 2019), highlighting an **unmet need to improve both the risk of disease recurrence and related long term survival** in these patients. However, the current standard of care following neoadjuvant CRT and resection is to watch and wait.

In Danish guidelines peri-operative or pre-operative therapy is SOC for patients with curable adenocarcinoma in EC and GEJC disease and with good performance status (PS) (DEGC 2020b). Both options are equally recommended:

- peri-operative fluorouracil + leucovorin + oxaliplatin + docetaxel (FLOT) combination chemotherapy
- pre-operative chemoradiotherapy (CRT) with chemoradiotherapy for oesophageal cancer followed by surgery study (CROSS) (DEGC 2020b).

For patients with resectable ESCC or squamous cell carcinoma of the GEJ and good general condition, Danish guidelines recommend pre-operative CRT treatment as standard of care (SOC) (DEGC 2020b).

The yearly number of Danish patients with esophageal or gastro-esophageal junction cancer who have residual pathologic disease following prior neoadjuvant CRT and complete resection eligible for nivolumab is estimated to be 28 patients in 2022, increasing to 83 patients by 2026 based on input from the clinical expert present at the dialogue meeting with the DMC (Danish clinical expert 2021).

The pivotal trial, **CheckMate 577**, is a global, phase 3 randomised, multicentre, double-blind, placebo-controlled study to evaluate adjuvant nivolumab in adults with resected EC or GEJC who have residual pathologic disease

following prior neoadjuvant CRT. As currently there is no adjuvant treatment for patients who have received neoadjuvant CRT and resection, placebo was considered to be an appropriate comparator in the trial (Kelly 2021). DFS, the primary endpoint, is considered a meaningful measurement of clinical benefit in the adjuvant setting as it directly measures disease recurrence, is not impacted by subsequent therapies, and has been shown to have a strong correlation with OS (Ascierto 2020, BMS 2020a, Weber 2020, Leung 2021). Furthermore, clinical experts stated that mortality in patients who are disease-free and alive at 2–3 years is equivalent to the normal population.

Analysis of the primary endpoint showed adjuvant nivolumab demonstrated:

- a statistically significant improvement in **disease free survival** (DFS) versus placebo, with a 31% reduction in the risk of disease progression or death (HR, 0.69; 96.4% CI: 0.56 to 0.86; p<0.001). There was a sustained separation of the DFS curves, indicating a durable benefit, and a doubling of median DFS with a clinically meaningful 11.4-month improvement versus placebo (median DFS: 22.4 months [95% CI: 16.6 to 34.0] with nivolumab and 11.0 months [95% CI: 8.3 to 14.3]) with placebo) (Kelly 2021).
- Additionally, adjuvant nivolumab demonstrated a 26% reduction in the risk of distant metastasis or death with nivolumab versus placebo (HR, 0.74 [95% CI: 0.60 to 0.92]) (Kelly 2021).
- [redacted]

In terms of **health-related quality of life (HRQoL)**, patients treated with adjuvant nivolumab maintained their HRQoL and it was comparable to placebo (Kelly 2021). The use of nivolumab demonstrated trends of improvement, or maintenance from baseline in HRQoL, similar to those observed with placebo (Kelly 2021). Nivolumab had limited additional impact on patients being bothered by side effects versus placebo (Kelly 2021).

The **safety profile** of nivolumab in the adjuvant EC/GEJC setting was in line with previous reports in gastroesophageal and other solid tumours (Kang 2017, Kudo 2017, Weber 2017, Janjigian 2018, Kato 2019, Kelly 2021):

- Adjuvant nivolumab was well tolerated in CheckMate 577. Rates of all-cause adverse events were similar across treatment arms, including grade 3 or 4 adverse events and serious adverse events (Table 12) (Kelly 2021). [redacted]

To evaluate the cost-effectiveness of adjuvant treatment with nivolumab compared to watch and wait (W&W) among patients with this indication, a partitioned survival model was developed. The results from the cost-effectiveness analysis show that adjuvant treatment with nivolumab improves health outcomes compared with watch and wait with an expected gain of [redacted] per patient. Over a 30-year time horizon and 3.5% discount rate, the cost per patient is expected to increase by DKK 473 180 (when drug acquisition costs are based upon list prices). [redacted]

Sensitivity analyses shows that the ICER per QALY is relatively stable towards changes in most input values and model assumptions. It confirms that drug acquisition costs and the cost of subsequent treatment are the main drivers of cost-effectiveness. In terms of budget impact, recommendation of adjuvant nivolumab treatment is expected to [redacted]

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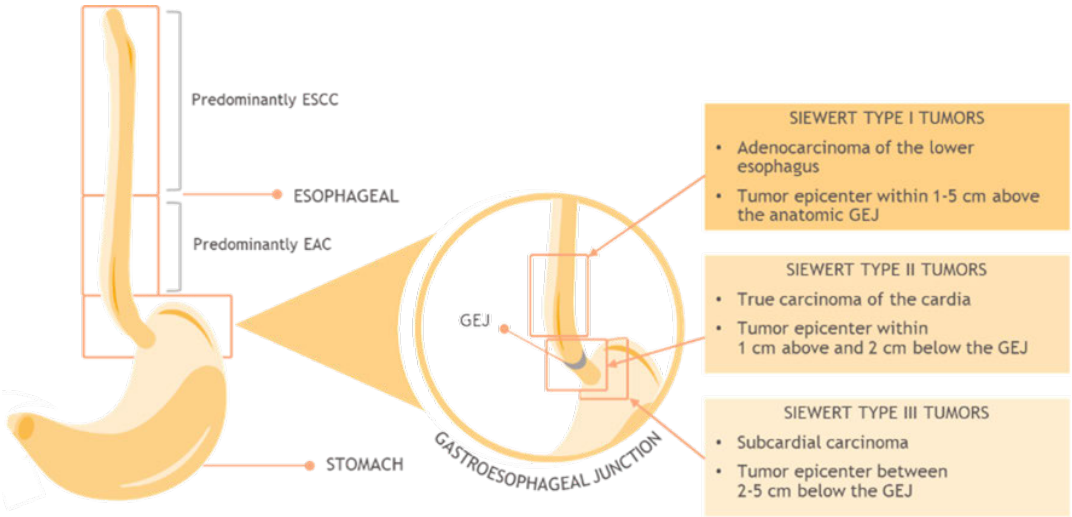
5. The patient population, the intervention and choice of comparator

5.1 The medical condition and patient population

5.1.1 Disease description

Gastroesophageal cancer is a heterogeneous disease that is typically segmented into three distinct entities: esophageal cancer (EC), gastroesophageal junction cancer (GEJC), and gastric cancer (GC) (Figure 1). GEJC is generally segmented into three subtypes based on the location of the tumour epicentre: Siewert type I, type II and type III, see Figure 1 (Siewert 1998, Berlth 2019). 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). ESCC most commonly forms in the middle- or upper-third of the esophagus, whereas EAC usually forms in the lower-third of the esophagus (Zhang 2012). GEJC are typically adenocarcinomas (Zhang 2019).

Figure 1: Three types of gastroesophageal cancer



EAC, esophageal adenocarcinoma; ESCC, esophageal squamous cell carcinoma; GEJ, gastroesophageal junction.

Image adapted from: (Cancer Research UK 2018). Source: (Zhang 2012, Ajani 2019)

The main risk factor for EC is tobacco usage; in additional specifically, alcohol consumption is a major risk factor for ESCC, while gastroesophageal reflux disease (GERD), Barrett's esophagus, and obesity are major risk factors for EAC (Kleinberg 2014). Risk factors for GEJC includes GERD and obesity.

5.1.2 Epidemiology

In 2020, there were an estimated 604,100 new EC cases globally, accounting for 3.1% of the total number of new cancer cases (GLOBOCAN 2020). The incidence of EC varies widely by region: 79.7% of cases occur in Asia, compared with 8.8% in Europe and 3.4% in North America (NIH 2019, Orphanet 2019, GLOBOCAN 2020). Data on GEJC as a separate disease entity are not available from the GLOBOCAN database; GEJC is grouped with GC for which there was an estimated 1,089,103 cases (5.6%) in 2020 (GLOBOCAN 2020). In 2018, an estimated 181,000 cases occurred in the GEJ (Arnold 2020).

EC is one of the most aggressive forms of cancer (Zhang 2013), and is the sixth leading cause of cancer-related deaths globally in 2020, with an estimated 544,076 deaths and mortality to incidence rate of 90% (GLOBOCAN 2020).

5.1.3 Disease presentation and diagnosis

During the early stages of disease, EC is often asymptomatic (American Cancer Society 2020a, American Cancer Society 2020b). Once symptoms appear, EC usually presents with solid-food dysphagia and weight loss (Kleinberg 2014). These symptoms may last several months (Kleinberg 2014), and in combination with a history of smoking and alcohol intake are indicative of ESCC (Pennathur 2013). Chest pain, in the absence of myocardial ischemia, and anemia secondary to chronic GI bleeding from the mucosal lesion, are also possible and are more typical of EAC. These clinical signs and symptoms warrant further testing, specifically endoscopic evaluation and diagnostic imaging (Kleinberg 2014). The clinical manifestation of most patients suffering from GEJC is dysphagia, which only becomes symptomatic at an advanced stage (Liu 2020).

5.1.4 Unmet need

Although patients with resectable stage II or stage III EC or GEJC may receive treatments with curative intent, many do not obtain a pathologic complete response (pCR) despite intensive treatment strategies. For example, in the CROSS trial, among 161 neoadjuvant treated and resected patients, only 29% had pCR (van Hagen 2012) and approximately 75% of patients have residual pathologic disease following chemoradiation therapy (Walsh 1996, Bosset 1997, van Meerten 2006, Reynolds 2007, Blum Murphy 2017).

Patients who do not have a pCR following neoadjuvant CRT and resection have a high risk of recurrence and thereby poor prognosis in comparison to patients who have pCR after surgery. In an analysis of the CROSS study and a preceding phase 2 trial investigating the same preoperative regimen, 17% of patients with a pCR developed recurrent disease compared with 42% of patients who did not achieve a pCR over a minimum follow-up period of 24 months (Oppedijk 2014).

In the US, 5-year survival in patients with localised and regional EC (2010–2016) was 47% and 25%, respectively (American Cancer Society 2021b). For patients with stomach cancer (gastric cancer or GEJC), 5-year survival in patients with localised and regional disease was 70% and 32% (American Cancer Society 2021a). Likewise, in the UK, 5-year survival was 30% and 15% in patients with stage II and stage III EC (2013–2017), respectively (Cancer Research UK 2019). Five-year survival for patients with stomach cancer was 35% and 25% for those with stage II and stage III disease, respectively (Cancer Research UK 2020).

The 5-year survival rate for patients with locally advanced EC or GEJC at diagnosis when treated with a standard of care (SOC) ranges between 45% (among patients with locally advanced, resectable GC/GEJC in the FLOT4 trial) and 47% (according to long-term follow-up of patients with locally advanced, resectable EC/GEJC included in the CROSS trial) (Shapiro 2015, Al-Batran 2019). These data indicate that about 1 in 2 patients with EC or GEJC presenting with locally advanced disease will not be alive after 5 years and there is a medical unmet need to improve long term survival in these patients.

Currently there is no active treatment but only observation/watch and wait for patients with residual disease following prior CRT and complete resection. Given the high risk of recurrence, improving outcomes for these patients remains an urgent goal, driving the need for effective and tolerable therapies following surgery.

5.1.5 Prevalence and incidence in Denmark

Based on Dansk Esophago-Gastrisk Cancer Gruppe (DEGC) 2019 annual report, 1167 new patients with EC (n=320), GEJC (n=626) or gastric (n=221) cancers were registered in Denmark in 2019; note, this included all cases of EC, GEJC, and gastric cancer across stages (Table 1) (DEGC 2020a). Of the 320 newly diagnosed EC cases, 66% were men, the average age at diagnosis was 71 years, and the majority received palliative therapy (>80%) (DEGC 2020a). Only 34 EC (10.6%) patients with stage I- III disease received therapy with curative intent (DEGC 2020a).

Of the 626 newly diagnosed GEJC patients >80% were male with an average age of 70 yrs. Approximately one-third of GEJC patients (32.7%; n=205) received treatment with curative intent (including resection), having stage I- III disease at the time of diagnosis (DEGC 2020a).

Table 1: Incidence and prevalence of gastric, GEJC and esophageal cancer in Denmark the past 5 years (all stages)

	2015	2016	2017	2018	2019
Gastric cancer and GEJC					
New cases of GEJC in Denmark (DEGC 2020a)	535	575	594	635	626
Age-standardised incidence rate (per 100,000 person-years) in Denmark (gastric and GEJC) (NORDCAN 2020a)	Male: 13.8 Female: 6.5	Male: 13.6 Female: 6.5	Male: 14.2 Female: 6.6	Male: 15.1 Female: 5.5	-
Prevalence in Denmark (gastric and GEJC) (NORDCAN 2020c)	Male: 1,221 Female: 662 Total: 1,883	Male: 1,294 Female: 728 Total: 2,022	Male: 1,375 Female: 775 Total: 2,150	Male: 1,439 Female: 802 Total: 2,241	-
Esophageal cancer					
New cases in Denmark (DEGC 2020a)	264	301	264	288	320
Age-standardised incidence rate (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: 15.0 Female: 4.3	-
Prevalence in Denmark (NORDCAN 2020b)	Male: 808 Female: 290 Total: 1,098	Male: 854 Female: 317 Total: 1,171	Male: 896 Female: 364 Total: 1,260	Male: 1,039 Female: 376 Total: 1,415	-

Abbreviation: GEJC: gastroesophageal junction cancer.

Source: (DEGC 2020a, NORDCAN 2020a, NORDCAN 2020c, NORDCAN 2020b)

5.1.6 Patient populations relevant for this application

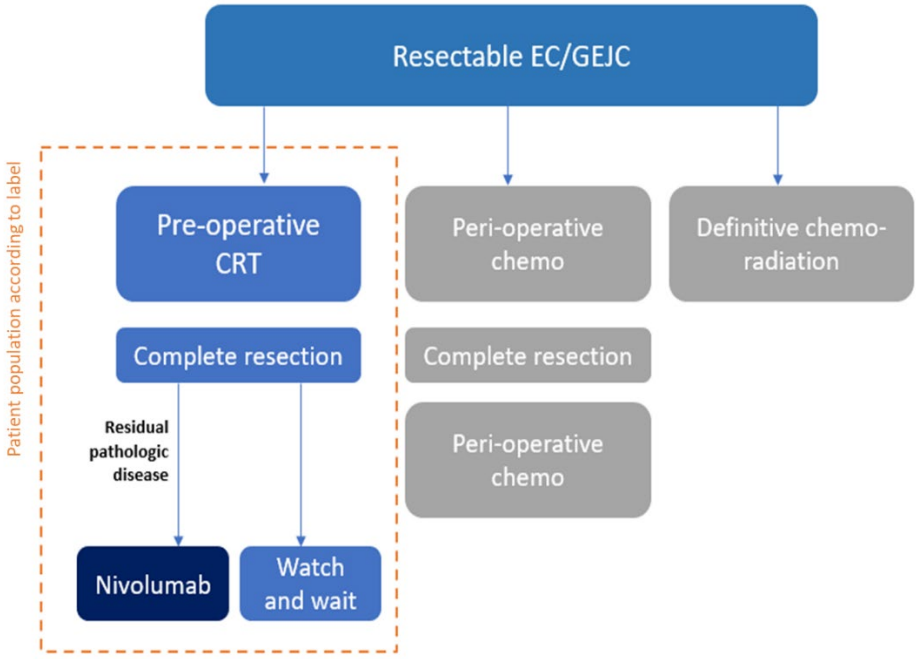
The estimated number of patients with esophageal and gastroesophageal junction cancer who have residual pathologic disease following prior neoadjuvant chemoradiotherapy and complete resection eligible for

treatment with nivolumab are based on the Dansk Esophago-Gastrisk Cancer Gruppe annual report, and NORDCAN as explained above in section 5.1.5. [redacted]

[redacted]

Figure 2 describes the approved label patient population for nivolumab. [redacted]

Figure 2: Approved patient population according to label



Abbreviations: CRT: chemoradiotherapy; EC: esophageal cancer; GEJC: gastroesophageal junction cancer.

[redacted]

Table 2: Estimated number of patients treated with nivolumab year 2022-2026

Year	2022	2023	2024	2025	2026
Number of patients in Denmark who are expected to use the pharmaceutical in the coming years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

5.2 Current treatment options and choice of comparator(s)

5.2.1 Current treatment options

The Danish (DEGC) "Onkologisk behandling af patienter med kurable karcinomer i esophagus, GEJ og ventrikel" 2020 guidelines by Dansk Esophago-Gastrisk Cancer Gruppe include recommendations for patients with curable EC or GEJC (DEGC 2020b).

Classification of cancer between the esophagus and stomach i.e. GEJ is shown below [redacted] Based on treatment guidelines, patients with Type III GEJC are treated similarly to gastric cancer in Denmark.

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Locally advanced EC/GEJC is generally treated with a multimodality regimen (DEGC 2020b). Standard of care (SOC) regimens differ according to histology and between curable and palliative treatment. SOC treatments for curative intent in patients with EC/GEJC broadly include either preoperative CRT or perioperative combination chemotherapy (DEGC 2020b).

According to the Danish guidelines for curable **adenocarcinoma** in EC and GEJC, peri-operative or pre-operative therapy is SOC for patients with resectable disease and with good performance status (PS). Both options are equally recommended (Level A) listed in the national guidelines (DEGC 2020b):

- Patients with resectable adenocarcinoma of the esophagus, GEJ and gastric (cT1N1-3M0 or cT2-4N0-3 M0) can be recommended peri-operative combination chemotherapy
    - In the AIO study, more patients treated with the peri-operative combination chemotherapy FLOT-regimen vs. control arm were resected with signs of increased down-staging with higher fraction of small tumours ≤ypT1 (25% vs 15%) and more patients being lymph node negative (Al-Batran 2019). The FLOT regimen demonstrated an OS benefit (35 months vs. 50 months median overall survival [mOS]) with an increase in the 5 year OS rate from 36 to 45% (Al-Batran 2019) (DEGC 2020b)
- Patients in good PS with resectable adenocarcinoma (cT1N1-3M0 or cT2-4N0-3 M0) in the esophagus or GEJ - Siewert type I-II - can be recommended pre-operative CRT
    - Based on meta-analysis and studies described in more detail in the Danish guidelines for curative intended treatment, pre-operative CRT followed by resection is recommend equally to peri-operative FLOT regimen as SOC to patients with resectable adenocarcinoma in EC and GEJ, Siewert I/II (DEGC 2020b). The chemotherapy includes carboplatin and paclitaxel concurrent with radiation (e.g. 41.4 Gy/23 factions) (DEGC 2020b)

For patients with curable **ESCC or squamous cell carcinoma** of the GEJ, Danish guidelines recommend pre-operative treatment as SOC for patients with resectable disease and good general condition (DEGC 2020b). Specifically, pre-operative CRT is recommended for those with resectable disease (cT1N1-3M0 or cT2-4N0-3 M0), based on the CROSS study (van Hagen 2012). The 5 year follow-up data from the CROSS study demonstrated an increased in mOS from 24 months to >48 months with a HR 0.68. The clinical benefit was even better for patients with squamous cell carcinoma, with an increase in mOS from 21 months to >81 months (Shapiro 2015).

There are currently no treatment options recommended for patients with EC and GEJC following pre-operative CRT and complete resection; the current standard of care is watch and wait (DEGC 2020b). According to the clinical expert present at the DMC dialogue meeting, the majority of patients (predominantly EAC) are not followed up after treatment is finished, except for phone call with a nurse for 2 years(Danish clinical expert 2021). A few patients (predominantly EC) are followed up to 5 years.

5.2.2 Choice of comparator

The relevant comparator for OPDIVO® (nivolumab) in adult patients with esophageal or gastro-esophageal junction cancer who have residual pathologic disease following prior neoadjuvant chemoradiotherapy and complete resection is watch and wait. There are currently no treatment options recommended for patients with EC and GEJC following pre-operative CRT and complete resection; the current standard of care in Denmark is watch and wait (DEGC 2020b).

5.2.3 Description of the comparator(s)

N/A

5.3 The intervention

Details of the intervention are listed below in Table 3.

OPDIVO® (nivolumab) is expected to be used in patients with esophageal or gastro-esophageal junction cancer who have residual pathologic disease following prior neoadjuvant chemoradiotherapy and complete resection. There is currently no adjuvant treatment recommended for patient population and the standard of care is watch and wait (DEGC 2020b); OPDIVO® (nivolumab) will be used in place of watch and wait in this patient population.

Table 3: Product description of nivolumab

Product description	
Dosing	240 mg every 2 weeks over 30 minutes or 480 mg every 4 weeks over 30 minutes for the first 16 weeks followed by 480 mg every 4 weeks over 30 minutes
Method of administration	Intravenous
Treatment duration	Until disease progression or unacceptable toxicity for a total treatment duration of up to 1 year
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	No testing required

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6. Literature search and identification of efficacy and safety studies

6.1 Identification and selection of relevant studies

There are currently no treatment options recommended for patients with EC and GEJC following pre-operative CRT and complete resection; the current standard of care in Denmark is watch and wait (DEGC 2020b). The CheckMate 577 trial includes the relevant comparator for Denmark, placebo i.e. watch and wait. Therefore, the outcomes of the systematic literature review of efficacy and safety (detailed in Appendix A: Literature search for efficacy and safety of intervention and comparator(s) have not been used in the clinical and economic sections of the dossier as it will not provide additional relevant documentation. As a systematic literature review (SLR) had previously been conducted in relation to CheckMate 577—to support health technology assessments for different country settings—the processes and outcomes of the SLR have been included for reference (Appendix A).

6.2 List of relevant studies

Table 4: Relevant studies included in the assessment

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)
LBA9_PR Adjuvant nivolumab in resected esophageal or gastroesophageal junction cancer (EC/GEJC) following neoadjuvant chemoradiation therapy (CRT): First results of the CheckMate 577 study - Kelly et al. Ann Oncol 2020 Adjuvant Nivolumab in Resected Esophageal or Gastroesophageal Junction Cancer - Kelly et al. N Engl J Med 2021	CheckMate 577	NCT02743494	May 23, 2016 October 11, 2025

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

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7. Efficacy and safety

7.1 Efficacy and safety - study overview

7.1.1 CheckMate 577

7.1.1.1 Study overview

CheckMate 577 (NCT02743494) is a global, phase 3 randomised, multicentre, double-blind, placebo-controlled study to evaluate adjuvant nivolumab in adults with resected EC or GEJC who have residual pathologic disease following prior neoadjuvant CRT (Figure 5) (Clinicaltrials.gov 2020, Kelly 2021). An overview is presented in Table 5 below. For detailed study characteristics refer to appendix B.

Table 5: Overview of CheckMate 577

CheckMate 577 (NCT02743494)	
Study design	Global phase 3 randomised, multicentre, double-blind, placebo-controlled study. • Patients were randomised (2:1) to either nivolumab or placebo monotherapy • Patients were stratified according to: ◦ tumour PD-L1 expression (≥1% versus <1% or indeterminate or non-evaluable), ◦ pathologic evidence in lymph nodes (ypN0 versus ≥ypN1), ◦ and histology (squamous cell type versus adenocarcinoma) • Treatment continued until disease recurrence, unacceptable toxicity, or patient withdrawal of consent with a maximum of 1-year total duration of study medication
Study size	794 randomised patients
Patient population	Patients with stage II or stage III (per AJCC 7th edition) EC or GEJC (either adenocarcinoma or squamous cell carcinoma), completion of neoadjuvant CRT followed by surgery, and diagnosis of residual pathologic disease (≥ypT1 or ≥ypN1) after being surgically rendered free of disease with negative margins (R0) following complete resection
Intervention	Nivolumab 240 mg administered as IV infusion over 30 minutes every 2 weeks for 16 weeks (8 doses) followed by 480 mg administered as IV infusion over 30 minutes every 4 weeks beginning at week 17 (2 weeks after the 8th dose) for a maximum of 1 year.
Comparator	Placebo
Follow-up	Preliminary analysis: median follow-up 24.4 months (data cut-off, July 3, 2020) Follow-up, ad hoc analysis: median follow-up 32.2 months (data cut-off, February 18, 2021)
Is the study used in the HE-model?	Yes
Reason for including/Excluding from HE-model	Pivotal trial

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CheckMate 577 (NCT02743494)	
Reported primary endpoint	DFS[a]
Other reported endpoints	OS[b]
	DMFS
	EQ-5D[a]
	FACT-E, ECS, FACT-G7
	Safety and tolerability[1]

[a]Endpoint used in the health economic model, [b]OS data were not mature at pre-specified interim primary endpoint analysis

Abbreviations: AJCC: American Joint Committee on Cancer; CRT: chemoradiotherapy; DFS: disease-free survival; DMFS: distant metastasis-free survival; EC: esophageal cancer; ECS: esophageal cancer subscale; EQ-5D: EuroQoL 5-dimensions questionnaire; FACT-E: Functional Assessment of Cancer Therapy – Esophageal; FACT-G7: Functional Assessment of Cancer Therapy-General 7-item version; GEJC: gastroesophageal junction cancer; IV: intravenous; OS: overall survival; PD-L1: programmed death-ligand 1; ypTNM, post-neoadjuvant tumor, node, metastasis.

Source: (Kelly 2021)

7.1.1.2 CheckMate 577 study design

CheckMate 577 (NCT02743494) is a global, phase 3 randomised, multicentre, double-blind, placebo-controlled study to evaluate adjuvant nivolumab in adults with resected EC or GEJC who have residual pathologic disease following prior neoadjuvant CRT (Figure 5) (Clinicaltrials.gov 2020, Kelly 2021).

As the only current SOC for patients who have received neoadjuvant CRT and resection is surveillance, placebo was considered to be an appropriate comparator in the trial (Kelly 2021).

The study was conducted at 170 study locations across 29 countries, including one site in Denmark, (Kelly 2021).

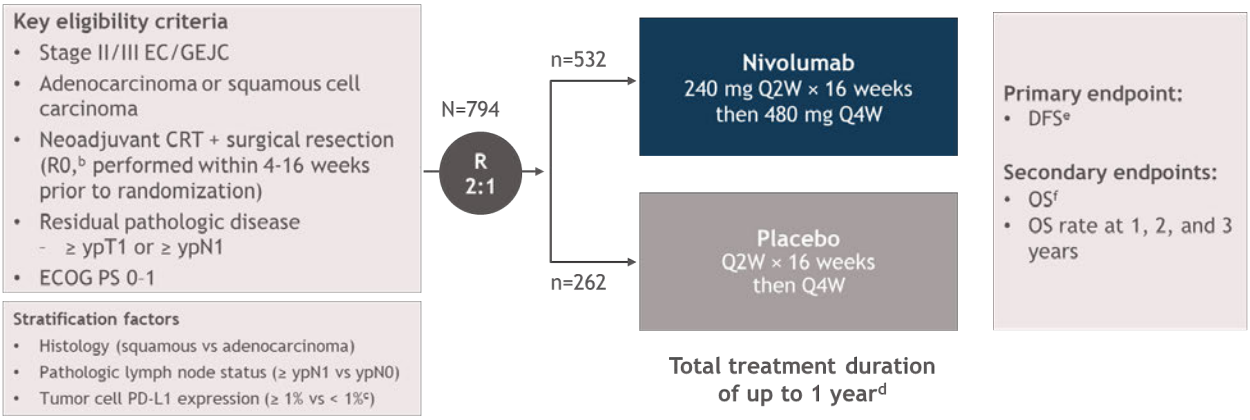
Key inclusion criteria were (Kelly 2021):

- Diagnosis of stage II or stage III (per AJCC 7th edition) EC or GEJC (either adenocarcinoma or squamous cell carcinoma)
- Completion of neoadjuvant CRT followed by surgery, and diagnosis of residual pathologic disease (≥ypT1 or ≥ypN1) after being surgically rendered free of disease with negative margins (R0) following complete resection
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1

Key exclusion criteria were (Kelly 2021):

- Cervical esophageal carcinoma
- Stage IV resectable disease
- Not having received concurrent CRT prior to resection

Figure 5: CheckMate 577



[a]Patients must have been surgically rendered free of disease with negative margins on resected specimens defined as no vital tumor present within 1 mm of the proximal, distal, or circumferential resection margins; [b]< 1% includes indeterminate/nonevaluable tumor cell PD-L1 expression; [c]Until disease recurrence, unacceptable toxicity, or withdrawal of consent; [d]Assessed by investigator, the study required at least 440 DFS events to achieve 91% power to detect an average HR of 0.72 at a two-sided α of 0.05, accounting for a pre-specified interim analysis; eThe study will continue as planned to allow for future analysis of OS.

Abbreviations: CRT: chemoradiotherapy; DFS: disease-free survival; ECOG: Eastern Cooperative group; EC: esophageal cancer; GEJC: gastroesophageal junction cancer; OS: overall survival; PD-L1: programmed death ligand 1; PS: performance status; Q2W: every 2 weeks; Q4W: every 4 weeks; ypTNM: post-neoadjuvant tumor, node, metastasis.

Source: (Kelly 2021)

Between July 2016 and August 2019 patients were randomised (2:1) to either nivolumab or placebo monotherapy. Randomisation was conducted using an interactive voice/web response system and stratified according to: tumour PD-L1 expression (≥1% versus <1% or indeterminate or non-evaluable), pathologic evidence in lymph nodes (ypN0 versus ≥ypN1), and histology (squamous cell type versus adenocarcinoma) (Kelly 2021).

Patients randomised to nivolumab received 240 mg administered as IV infusion over 30 minutes every 2 weeks for 16 weeks (8 doses) followed by 480 mg administered as IV infusion over 30 minutes every 4 weeks beginning at week 17 (2 weeks after the 8th dose) (Kelly 2021). Patients received placebo administered as IV infusion over 30 minutes following the same schedule as nivolumab (Kelly 2021).

Treatment continued for a maximum of 1-year total duration of study medication, or until disease recurrence, unacceptable toxicity, or patient withdrawal of consent (Kelly 2021).

7.1.1.3 Study endpoints

The primary endpoint was disease-free survival (DFS), which was defined as the time between the date of randomisation and the first date of recurrence or death, whichever occurred first, prior to subsequent anticancer therapy (Table 6) (BMS 2020a). Recurrence was defined as the appearance of one or more new lesions (local, regional, or distant in location from the primary resected site; confirmed by imaging or cytology/pathology) as assessed by investigators (BMS 2020a).

Secondary endpoints were overall survival (OS) and OS rates (at 1, 2, and 3 years) (Table 6) (Kelly 2021). [redacted]

Exploratory endpoints included safety and tolerability, distant metastasis-free survival (DMFS), and patient-reported outcomes (PROs) (evaluated with the Functional Assessment of Cancer Therapy-Esophageal [FACT-E] scale and the three-level version of the European Quality of Life–5 Dimensions questionnaire [EQ-5D-3L]) (Table 6) (BMS 2020a, Kelly 2021).

Table 6: CheckMate 577 endpoints

CheckMate 577 endpoints	
Primary	DFS
Secondary	OS
Exploratory	Safety and tolerability
	DMFS
	Evaluation of PD-L1 as a predictive biomarker
	Immunogenicity
	PK/exposure response
	EQ-5D-3L
	FACT-E, ECS, and FACT-G7
	PFS2

Abbreviations: DFS: disease-free survival; DMFS: distant metastasis-free survival; ECS: Esophageal Cancer Subscale; EQ-5D-3L: EuroQol 5 dimensional 3-level questionnaire; FACT-E: Functional Assessment of Cancer Therapy-Esophageal; FACT-G7: Functional Assessment of Cancer Therapy-General 7-item version; PD-L1: programmed death ligand 1; PFS2: progression-free survival after the next line of subsequent therapy: PK: pharmacokinetics.

Sources: (BMS 2020a, Kelly 2021).

7.1.1.4 Patient baseline characteristics

The analyses presented here describe data from all 794 randomised patients: the nivolumab arm included 532 patients and the placebo arm comprised 262 patients. Baseline characteristics were similar across both arms (Table 7).

Around 60% of patients had EC and 40% had GEJC. More patients (71%) had adenocarcinoma than squamous cell carcinoma (29%). Baseline tumor cell PD-L1 expression of 1% or greater was found in 17% of patients (89 of 532) in the nivolumab arm and in 15% of patients (40 of 262) in the placebo arm, which is representable of real-world data. More than two-thirds of patients were from Western regions (Europe, United States, and Canada) (Table 7) (Kelly 2021). The median age was 62.0 years in the nivolumab arm and 61.0 years in the placebo arm.

[redacted]

Table 7: Baseline characteristics of the intent-to-treat population (N=794)

Baseline characteristics		Nivolumab (n=532)	Placebo (n=262)
Median age (range), years		62.0 (26–82)	61.0 (26–86)
Male, n (%)		449 (84)	222 (85)
Race, n (%)[a]			
	White	432 (81)	216 (82)
	Asian	83 (16)	34 (13)
	Black	7 (1)	2 (<1)
	Other	10 (2)	9 (3)
Region, n (%)			
	Europe	202 (38)	101 (39)
	United States and Canada	167 (31)	88 (34)
	Asia	77 (14)	29 (11)
	Rest of world[b]	86 (16)	44 (17)
ECOG PS, n (%)			
	0	308 (58)	156 (60)
	1	224 (42)	106 (40)
Disease stage at initial diagnosis, n (%)[c]			
	II	179 (34)	99 (38)
	III	351 (66)	163 (62)
Tumor location at initial diagnosis, n (%)			
	EC	320 (60)	155 (59)
	GEJC	212 (40)	107 (41)
Histology, n (%)[d]			
	Adenocarcinoma	376 (71)	187 (71)
	Squamous cell carcinoma	155 (29)	75 (29)
Tumor cell PD-L1 expression, n (%)[e]			

Baseline characteristics	Nivolumab (n=532)	Placebo (n=262)
< 1%	374 (70)	196 (75)
≥ 1%	89 (17)	40 (15)
Indeterminate/non-evaluable	69 (13)	26 (10)
Pathologic lymph node status at trial entry, n (%)[f]		
≥ypN1, %	305 (57)	152 (58)
ypN0	227 (43)	109 (42)
Pathologic tumour status at trial entry, n (%)[g]		
ypT0	31 (6)	16 (6)
ypT1/ypT2	202 (38)	106 (40)
ypT3/ypT4	296 (56)	140 (53)

[a]Race information was not reported for one patient from the placebo arm; [b]Rest of world comprises Argentina, Australia, Brazil, Israel, Mexico, and Turkey; [c]Disease stage at initial diagnosis was not reported for two patients from the nivolumab arm; [d]One patient from the nivolumab arm had Other histology (protocol deviation); [e]Tumor cell PD-L1 expression determined from tumour tissue specimen after completion of chemoradiotherapy by the PD-L1 IHC 28-8 pharmDX assay (Dako), except for 40 patients who had tumour tissue quantifiable only prior to chemoradiotherapy; [f]Pathologic lymph node status was not known for one patient from the placebo arm; [g]Pathologic tumour status was not known for three patients from the nivolumab arm

Abbreviations: ECOG: Eastern Cooperative group; EC: esophageal cancer; GEJC: gastroesophageal junction cancer; PD-L1: programmed death ligand 1; PS: performance status; ypTNM: post-neoadjuvant tumour, node, metastasis

Source: (Kelly 2021)

7.1.1.5 Treatment discontinuation

The percentage of patients discontinuing treatment were similar in both the nivolumab and placebo arms (94% and 93%, respectively). The most frequent reason for discontinuation in the nivolumab arm was treatment completion (43%), while the most frequent reason for discontinuation in the placebo arm was disease progression (43%) (Table 8) (Kelly 2021). [redacted] The median duration of treatment was 10.1 months for nivolumab and 9.0 months for placebo (Kelly 2021).

Table 8: Treatment discontinuation in CheckMate 577

Characteristic	Nivolumab (n=532)	Placebo (n=260)
Discontinued treatment, n (%)	501 (94)	241 (93)
Reasons for discontinuation, n (%)[a]		
Treatment completion	229 (43)	99 (38)
Disease progression	149 (28)	113 (43)
AEs related to treatment	57 (11)	8 (3)
AEs not related to treatment	15 (3)	9 (3)
Patient request	42 (8)	9 (3)
Other[b]	9 (2)	3 (1)

The safety population included 792 patients: two patients did not receive at least one dose of trial treatment.

[a]The numbers do not always add up to the total because some patients had more than 1 reason for discontinuation from treatment;
[b]Included poor/non-compliance (n=1), lost to follow-up (n=1), death (n=1), and additional reasons (n=9)

Abbreviations: AE, adverse event
Source: (Kelly 2021)

7.1.1.6 Subsequent therapy

Subsequent therapy, including systemic anticancer therapy, radiotherapy, and surgery, was administered to 30% (157 of 532) of patients in the nivolumab arm and 42% (111 of 262) in the placebo arm (Table 9). Of the 214 patients who received subsequent systemic therapy, 125 (23%) were in the nivolumab arm and 89 (34%) were in the placebo arm (Kelly et al., 2021). Few of these patients received subsequent immunotherapy (4 of 532 patients [<1%] and 19 of 262 patients [7%], respectively) (Kelly et al., 2021).

Table 9: Subsequent therapies

Therapy	Nivolumab (n=532)	Placebo (n=262)
Patients with any subsequent therapies, n (%)	157 (30)	111 (42)
Radiotherapy	43 (8)	41 (16)
Surgery	28 (5)	20 (8)
Systemic therapy	125 (23)	89 (34)
Immunotherapy	4 (<1)	19 (7)
Targeted therapy	13 (2)	11 (4)
Other systemic cancer therapy/chemotherapy	123 (23)	85 (32)

Source: (Kelly 2021)

7.2 Efficacy and safety – results per study

A summary of the key efficacy and safety findings for CheckMate 577 is provided below. Detailed information about included outcomes and results can be found in Appendix D.

7.2.1 Efficacy

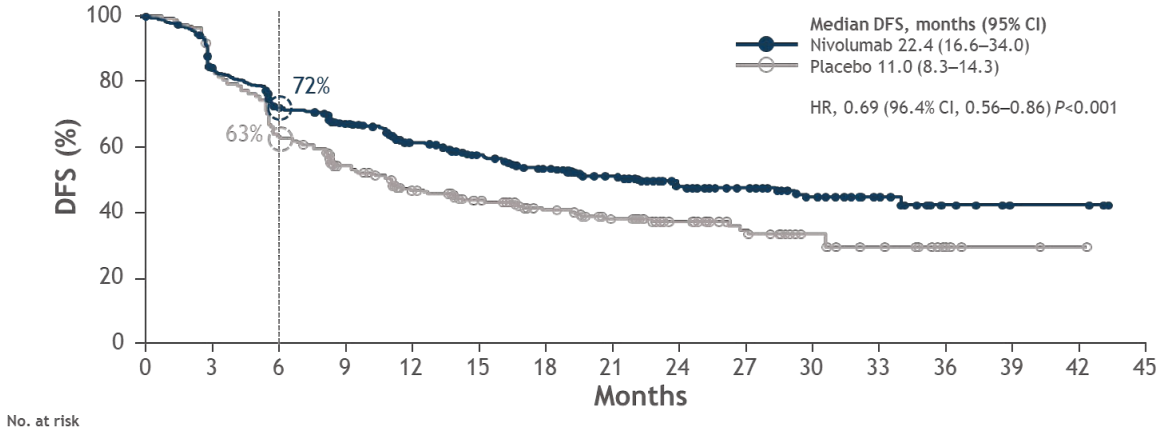
7.2.1.1 Disease-free survival (primary endpoint)

7.2.1.1.1 Disease-free survival in all randomised patients

7.2.1.1.1.1 Median follow-up 24.4 months

At the preliminary follow-up with a median follow-up of 24.4 months, adjuvant nivolumab demonstrated a statistically significant improvement in DFS versus placebo, with a 31% reduction in the risk of disease progression or death (HR, 0.69; 96.4% CI: 0.56 to 0.86; p<0.001) (Figure 6). There was a sustained separation of the DFS curves, indicating a durable benefit, and a doubling of median DFS with a clinically meaningful 11.4-month improvement versus placebo (median DFS: 22.4 months [95% CI: 16.6 to 34.0] with nivolumab and 11.0 months [95% CI: 8.3 to 14.3]) with placebo) (Figure 6). At 6 months, the DFS rates were 72% (95% CI: 68 to 76) in the nivolumab arm and 63% (95% CI: 57 to 69) in the placebo arm (Kelly 2021).

Figure 6: Disease-free survival in all randomised patients (N=794; median follow-up 24.4 months)



Per investigator assessment.

CI: confidence interval; DFS: disease-free survival; HR: hazard ratio

Source: (Kelly 2021)

7.2.1.1.1.2 Median follow-up 32.2 months

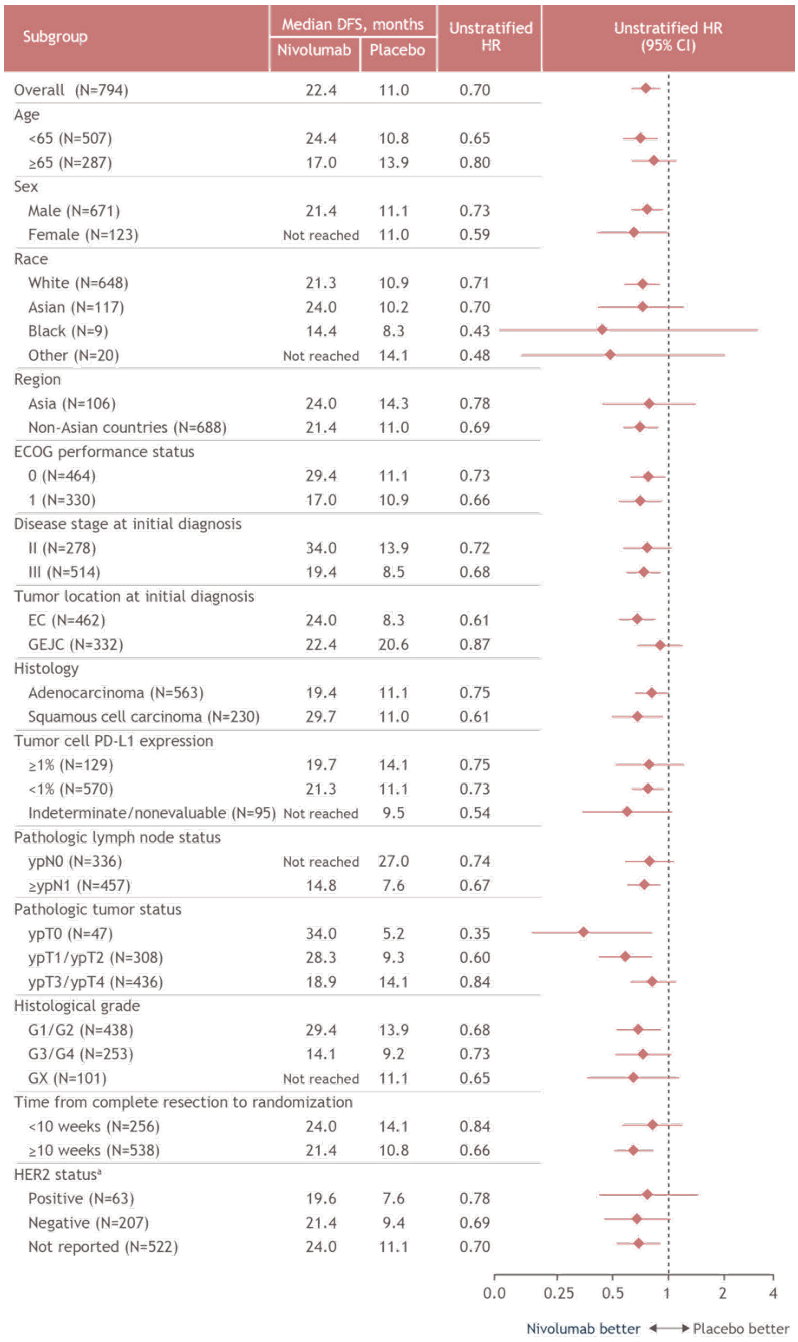
[redacted]

7.2.1.1.2 Disease-free survival in pre-specified subgroups

7.2.1.1.2.1 Median follow-up 24.4 months

At the preliminary follow-up with a median follow-up of 24.4 months, analysis of DFS by pre-specified baseline demographic and disease characteristics consistently favoured nivolumab over placebo across pre-specified subgroups based on demographics and baseline disease characteristics, including CheckMate 577 stratification factors (histology, pathologic lymph node status, and tumour cell PD-L1 expression) (Figure 8) (Kelly 2021).

Figure 8: Disease-free survival (subgroup analysis) in all randomised patients (N=794; median follow-up 24.4 months)

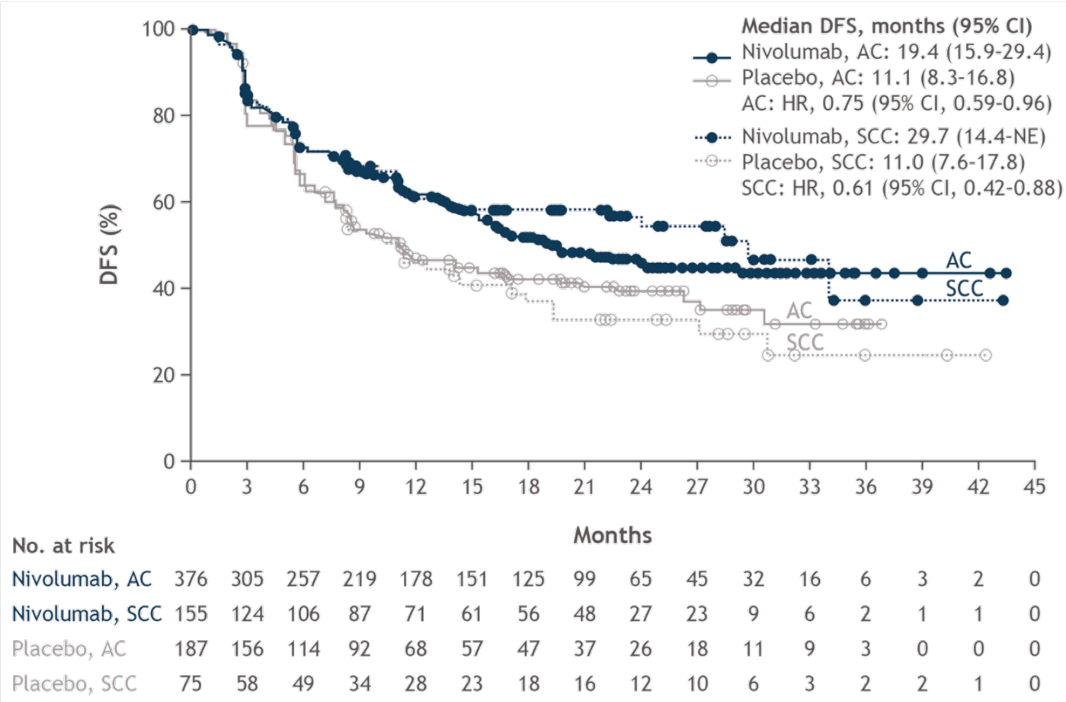


Abbreviations: CI: confidence interval; EC: esophageal cancer; ECOG: Eastern Cooperative Group; GEJC: gastroesophageal junction cancer; PD-L1: programmed death ligand 1; PS: performance status; ypTNM: post-neoadjuvant tumor, node, metastasis.

Source: (Kelly 2021)

The separation of the DFS curves was sustained in a pre-specified exploratory subgroup analysis by histology, with numerically longer DFS observed for both squamous and adenocarcinoma histologies with nivolumab versus placebo (Figure 9) (Kelly 2021).

Figure 9: Pre-specified exploratory subgroup analysis: disease-free survival (stratified by histology) in all randomised patients (N=794; median follow-up 24.4 months)



Abbreviations: AC: adenocarcinoma; CI: confidence interval; NE: not estimable; SCC: squamous cell carcinoma
Source: (Kelly 2021)

7.2.1.1.2.2 Median follow-up 32.2 months

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

7.2.1.3 Distant metastasis-free survival (DMFS) (median follow-up 24.4 months)

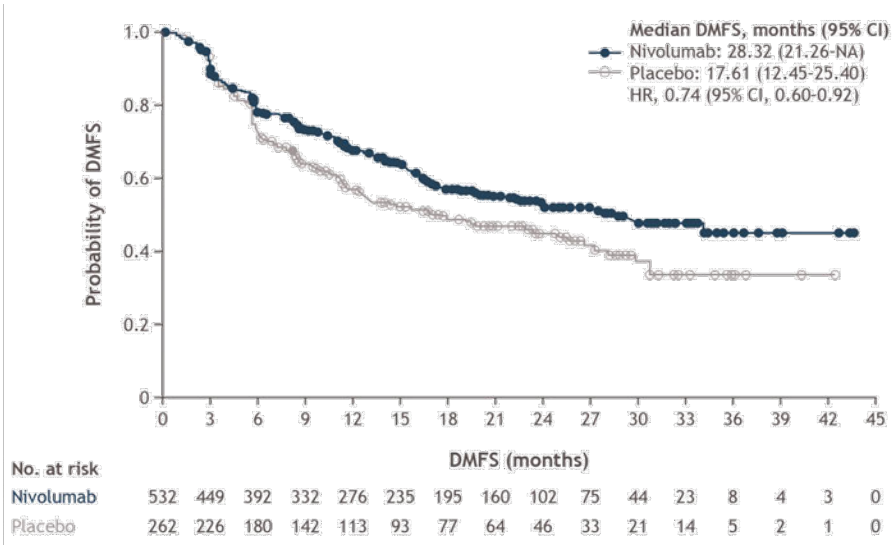
[redacted]

There was a 26% reduction in the risk of distant metastasis or death with nivolumab versus placebo (HR, 0.74 [95% CI: 0.60 to 0.92]). Median DMFS was 28.3 months (95% CI: 21.3 to not estimable)

with nivolumab and 17.6 months (95% CI: 12.5 to 25.4) with placebo. At 6 months, DMFS rates were 78% (95% CI, 74 to 81.5) in the nivolumab arm and 71% (95% CI, 65 to 76) in the placebo arm (Figure 11) (Kelly 2021).

[redacted]

Figure 11: Distant metastasis-free survival in all randomised patients (N=794; median follow-up 24.4 months)



Per investigator assessment.
Abbreviations: CI: confidence interval; NE: not estimable
Source: (Kelly 2021)

7.2.1.4 Patient-reported outcomes (median follow-up 24.4 months)

The patient-reported outcomes population in CheckMate 577 included randomly assigned patients who had an assessment at screening/baseline and at least one follow-up assessment. EuroQoL five-dimension three-level questionnaire (EQ-5D-3L) visual analogue scale (VAS) and utility index (UI) and Functional Assessment of Cancer Therapy – Esophageal (FACT-E) were administered at baseline and then every four weeks during the 12-month treatment period.

Completion rates in patients expected to have an assessment (i.e., alive and had not dropped out of study) were high: 95% or more at baseline and approximately 90% during the 12-month treatment period (Kelly 2021, van Cutsem 2021). The data was captured during the July 2020 data base lock, with the median follow-up of 24.4 months.

Overall, nivolumab demonstrated trends of improvement, or maintenance from baseline in HRQoL, similar to those observed with placebo (Kelly 2021). Nivolumab had limited additional impact on patients being bothered by side effects versus placebo (Kelly 2021). Impact on HRQoL is an important consideration when introducing an active treatment; findings from CheckMate 577 support the use of adjuvant nivolumab.

7.2.1.4.1 EuroQoL five-dimension three-level questionnaire (EQ-5D-3L) (median follow-up 24.4 months)

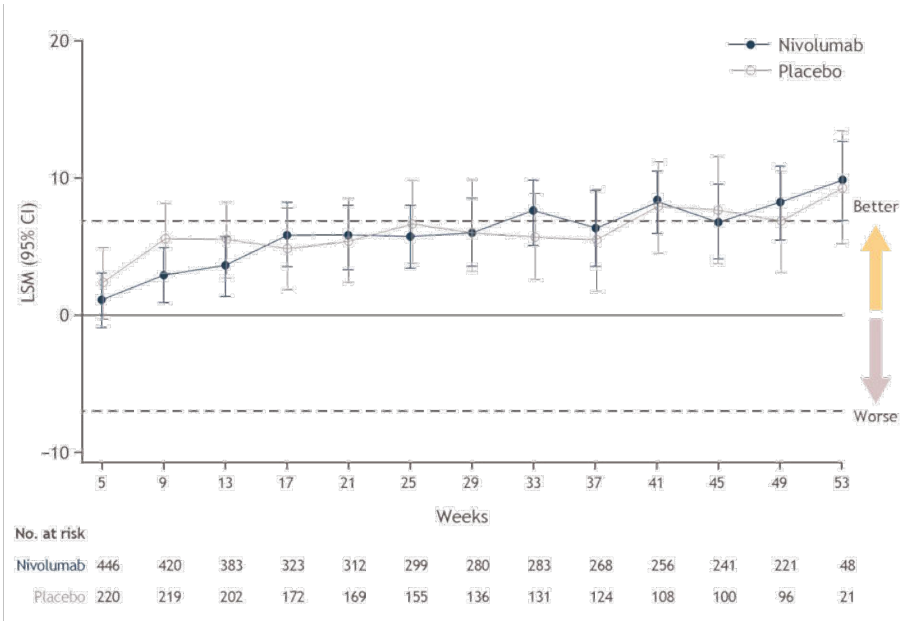
Least squares means of EQ-5D-3L VAS and UI scores showed similar trends for improvement from baseline at most time points through to week 53 for both nivolumab and placebo (Figure 12; Figure 13). A clinically

meaningful improvement in EQ-5D-3L VAS from baseline was observed at several time points in both the nivolumab and placebo arms, with no clinically meaningful differences between treatment arms (Kelly 2021).

There was no difference between treatment arms in mean change from baseline (on treatment) across both measures (treatment arm difference [least squares means]: VAS, -0.2 [95% CI: -2.8 to 2.5]; p=0.893; UI -0.008 [95% CI: -0.030 to 0.015]; p=0.501). All subgroups performed similarly to the overall population (van Cutsem 2021).

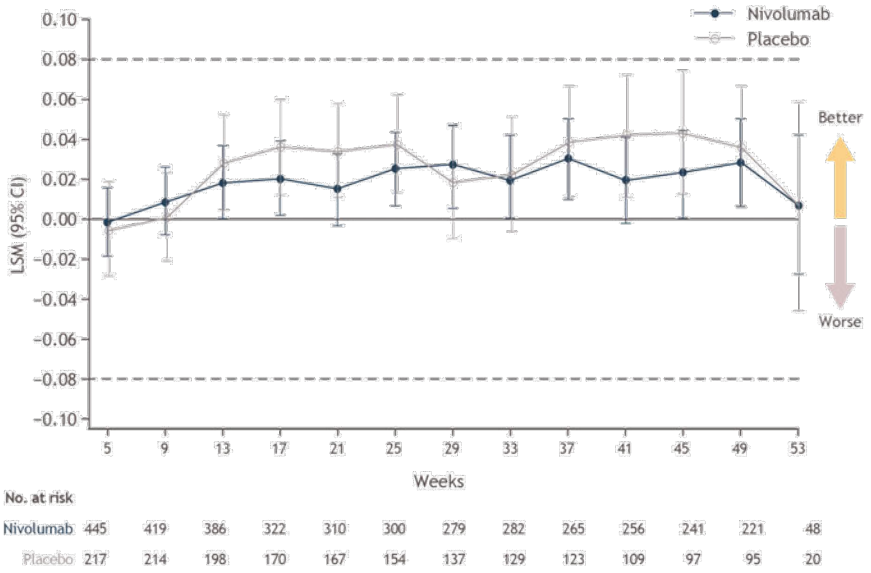
There were no statistically significant differences in time to first deterioration in VAS or UI and again all subgroups performed similarly to the overall population (van Cutsem 2021).

Figure 12: EQ-5D-3L VAS in the patient-reported outcomes population (median follow-up 24.4 months)



Change from baseline of 7 for the visual analogue scale was considered clinically meaningful (as indicated by dashed line) (Pickard 2007)
Abbreviations: CI: confidence interval; EQ-5D-3L: EuroQoL five-dimension three-level questionnaire; LSM: least squares mean.
Source: (Kelly 2021)

Figure 13: EQ-5D-3L UI in the patient-reported outcomes population (median follow-up 24.4 months)

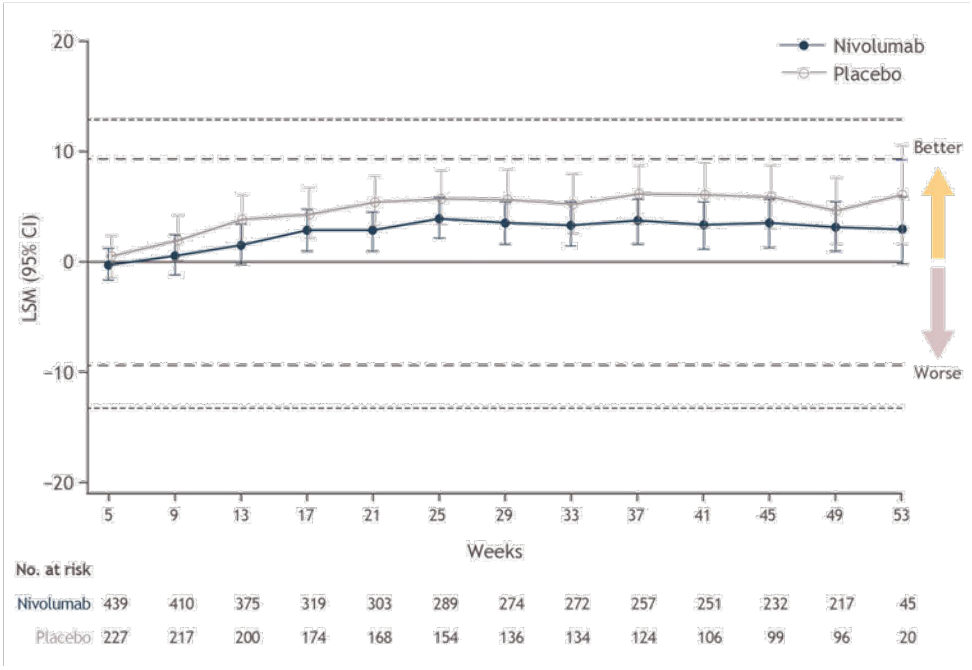


Change from baseline of 0.08 for the utility index was considered clinically meaningful (as indicated by dashed line) (Pickard 2007)
Abbreviations: CI: confidence interval; EQ-5D-3L: EuroQoL five-dimension three-level questionnaire; LSM: least squares mean.
Source: (Kelly 2021)

7.2.1.4.2 Functional Assessment of Cancer Therapy – Esophageal (FACT-E) (median follow-up 24.4 months)

Least squares means of FACT-E total scores showed similar trends for improvement from baseline at most time points through to week 53 for both nivolumab and placebo (Figure 14) (Kelly 2021).

Figure 14: FACT-E in the patient-reported outcomes population (median follow-up 24.4 months)



Dashed lines indicate a clinically meaningful change of 9.5 points, and dotted lines indicate a sensitivity score change of 13.1 points (Darling 2006, Ringash 2007). Error bars indicate 95% CI.

Abbreviations: CI: confidence interval; FACT-E: functional assessment of cancer therapy – esophageal; LSM: least squares mean.
Source: (Kelly 2021)

No clinically meaningful differences were observed between treatment arms in FACT-E scales (mean change from baseline on treatment; least squares means). The majority of scales within FACT-E showed no statistically significant differences compared with placebo, except for the esophageal cancer subscale, which did favour placebo. However, despite being statistically significant, this was not a clinically meaningful difference as assessed by the minimally important difference (Table 10). All subgroups performed similarly to the overall population (van Cutsem 2021).

There were no statistically significant differences in time to first deterioration in FACT-E scales and again all subgroups performed similarly to the overall population (van Cutsem 2021).

Table 10: FACT-E treatment arm difference in the patient-reported outcomes population (median follow-up 24.4 months)

FACT-E	LSM change from baseline (95% CI)		Treatment arm difference LSM (95% CI) P value
	Nivolumab	Placebo	
FACT-E total score (MID=9.5)	2.7 (1.1-4.4)	4.8 (2.7-6.9)	-2.1 (-4.4-0.3) 0.086
Physical well-being (MID=2)	0.3 (-0.1-0.7)	0.6 (0.1-1.1)	-0.3 (-0.8-0.2) 0.220
Social well-being (MID=2)	-0.3 (-0.7-0.1)	-0.3 (-0.8-0.1)	0.1 (-0.4-0.6) 0.801
Emotional well-being (MID=2)	0.3 (0.0-0.07)	0.6 (0.2-1.0)	-0.3 (-0.7-0.2) 0.218
Functional well-being (MID=2)	0.7 (0.3-1.2)	1.0 (0.5-1.6)	-0.3 (-0.9-0.3) 0.347
Esophageal cancer subscale (MID=4)	2.1 (1.4-2.8)	3.3 (2.4-4.2)	-1.2 (-2.2 to -0.2) 0.020

Mixed model for repeated measures included data from time points up to week 53 where both treatment arms had 10 or more patients

Abbreviations: CI: confidence interval; FACT-E: functional assessment of cancer therapy – esophageal; LSM: least squares mean; MID: minimally important difference.

Source: (van Cutsem 2021)

7.2.2 Safety

7.2.2.1 Safety population

The safety population in CheckMate 577 was all randomly assigned patients who received at least one dose of nivolumab or placebo, corresponding to 532 patients in the nivolumab arm and 260 patients in the placebo arm (Kelly 2021).

The safety profile of nivolumab in the adjuvant EC/GEJC setting was in line with previous reports in gastroesophageal and other solid tumours (Kang 2017, Kudo 2017, Weber 2017, Janjigian 2018, Kato 2019, Kelly 2021).

7.2.2.2 Treatment exposure (median follow-up 24.4 months)

At the preliminary follow-up with a median follow-up of 24.4 months, the median duration of treatment was 10.1 months (range, <0.1–14.2) in the nivolumab arm and 9.0 months (range, <0.1–15.0) in the placebo arm. A total of 86% of patients treated with nivolumab received 90% or more of the planned doses (relative dose intensity). More than half of all patients did not experience a dose delay and, of those that did, the majority had only one dose delayed. The rate of dose delays was similar between treatment arms (Table 11) (Kelly 2021).

[redacted]

Table 11: Treatment exposure summary for all treated patients (safety population: N=792) (median follow-up 24.4 months)

Characteristic	Nivolumab[a] (n=532)	Placebo[a] (n=260)
Median duration of treatment (range), months	10.1 (<0.1–14.2)	9.0 (<0.1–15.0)
[redacted]	[redacted]	[redacted]
Relative dose intensity, n (%)[b]		
≥90%	459 (86)	N/A
70% - <90%	67 (13)	N/A
50% - <70%	4 (<1)	N/A
<50%	2 (<1)	N/A
Number of doses delayed per patient — n (%)		
0	306 (58)	147 (57)
1	148 (28)	68 (26)
2	51 (10)	30 (12)
3	17 (3)	9 (3)
≥4	10 (2)	6 (2)

[a]All randomised patients who received at least one dose of trial treatment. [b]The relative dose intensity for a patient is calculated as the ratio of the actual cumulative total doses (mg) a patient received over the planned doses (mg) a patient should receive.
Abbreviations: N/A, not applicable
Source: (BMS 2020a, Kelly 2021)

7.2.2.3 Adverse events

7.2.2.3.1 Median follow-up 24.4 months

At the preliminary follow-up with a median follow-up of 24.4 months, adjuvant nivolumab was well tolerated in CheckMate 577. Rates of all-cause adverse events were similar across treatment arms, including grade 3 or 4 adverse events and serious adverse events (Table 12) (Kelly 2021). [redacted]

Treatment-related adverse events were more common with nivolumab than placebo (any grade treatment-related adverse events: 71% with nivolumab and 46% with placebo) although most were grade 1 or 2; 13% of patients treated with nivolumab, and 6% of patients treated with placebo reported treatment-related adverse events that were grade 3 or 4. Rates of serious treatment-related adverse events, and treatment-related adverse events leading to discontinuation were less than 10% in both treatment arms (Table 12) (Kelly 2021).

Table 12: Safety summary for all treated patients (safety population: N=792) (median follow-up 24.4 months)

Patients, n (%)	Nivolumab[a] (n=532)		Placebo[a] (n=260)	
	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4
Any AEs[b]	**510 (96)**	**183 (34)**	**243 (93)**	**84 (32)**
Serious AEs	158 (30)	107 (20)	78 (30)	53 (20)
AEs leading to discontinuation	68 (13)	38 (7)	20 (8)	16 (6)
Any TRAEs[b,c]	**376 (71)**	**71 (13)**	**119 (46)**	**15 (6)**
Serious TRAEs[c]	40 (8)	29 (5)	7 (3)	3 (1)
TRAEs leading to discontinuation[c]	48 (9)	26 (5)	8 (3)	7 (3)
TRAEs in ≥5% of treated patients in either arm[b]				
Fatigue	90 (17)	6 (1)	29 (11)	1 (< 1)
Diarrhea	88 (17)	2 (<1)	39 (15)	2 (<1)
Pruritus	53 (10)	2 (<1)	9 (3)	0
Rash	52 (10)	4 (<1)	10 (4)	1 (<1)
Hypothyroidism	50 (9)	0	4 (2)	0
Nausea	47 (9)	0	13 (5)	0
Hyperthyroidism	35 (7)	0	1 (<1)	0
Arthralgia	30 (6)	1 (<1)	4 (2)	0
Aspartate aminotransferase increased	29 (5)	2 (<1)	10 (4)	0
Asthenia	28 (5)	0	4 (2)	0
Decreased appetite	26 (5)	0	5 (2)	0

[a]Patients who received ≥1 dose of study treatment (safety population); [b]Events reported between first dose and 30 days after last dose of study drug; [c]One grade 5 TRAE was recorded in either arm (cardiac arrest in the nivolumab arm that was reported as not treatment related after database lock)
Abbreviations: AE: adverse event; TRAE: treatment-related adverse event
Source: (Kelly 2021)

7.2.2.3.2 Median follow-up 32.2 months

[redacted]

7.2.2.4 Select treatment-related adverse events with potential immunologic etiology

7.2.2.4.1 Median follow-up 24.4 months

At the preliminary follow-up with a median follow-up of 24.4 months, the majority of select treatment-related adverse events with potential immunologic etiology were grade 1 or 2; grade 3 or 4 adverse events occurred in ≤1% of patients in the nivolumab arm and there were no grade 5 adverse events (Table 14). The most common grade 3 or 4 select treatment-related adverse events with potential immunologic etiology in the nivolumab arm were pneumonitis (n=4) and rash (n=4) (<1% each); in the placebo arm, these events occurred in one patient each (<1%) (Kelly 2021).

Table 14: Select treatment-related adverse events with potential immunologic etiology for all treated patients (safety population: N=792) (median follow-up 24.4 months)

Select TRAEs[b,c n] (%)	Nivolumab[a] (n=532)		Placebo[a] (n=262)	
	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4
Endocrine	93 (17)	5 (<1)	6 (2)	0
Gastrointestinal	91 (17)	4 (<1)	40 (15)	3 (1)
Hepatic	49 (9)	6 (1)	18 (7)	4 (2)
Pulmonary	23 (4)	6 (1)	4 (2)	1 (<1)
Renal	7 (1)	1 (<1)	2 (<1)	0
Skin	130 (24)	7 (1)	28 (11)	1 (<1)

[a]Patients who received ≥1 dose of study treatment; [b]Select TRAEs are those with potential immunologic etiology that require frequent monitoring/intervention; [c]Events reported between first dose and 30 days after last dose of study drug

Abbreviation: TRAE: treatment-related adverse event.

Source: (Kelly 2021)

7.2.2.4.2 Median follow-up 32.2 months

[redacted]

[redacted]

7.3 Comparative analyses of efficacy and safety

There are no currently no treatment options recommended for patients with EC and GEJC following pre-operative CRT and complete resection; the current standard of care in Denmark is watch and wait (DEGC 2020b). The CheckMate 577 trial includes the relevant comparator for Denmark, placebo i.e. watch and wait. Therefore, no indirect comparative analyses were conducted.

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8. Health economic analysis

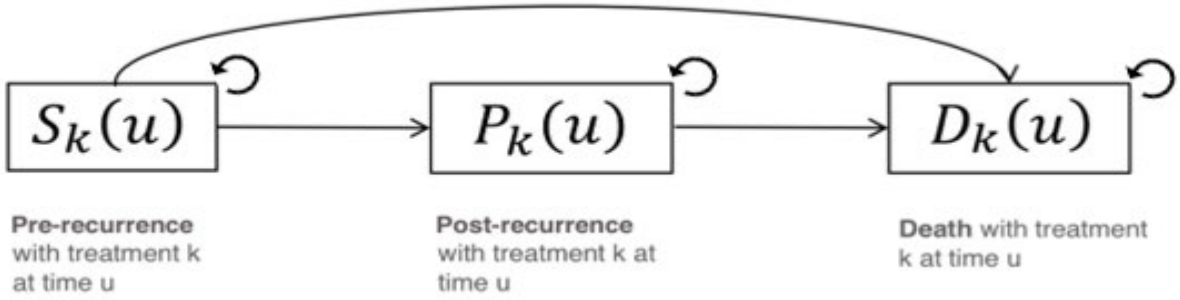
8.1 Model

The primary objective of this health economic analysis was to evaluate the cost-effectiveness of nivolumab in monotherapy compared to W&W for the adjuvant treatment of adult patients with EC or GEJC who had residual pathologic disease following prior pre-operative chemoradiotherapy and complete resection, as evaluated in the CheckMate 577 trial.

8.1.1 Model structure

A three-health state Markov model with a lifetime time horizon and one-month cycle length will be employed to investigate the cost-effectiveness of nivolumab compared to W&W. The three health states in the model include: pre-recurrence, post-recurrence and death as shown in Figure 15

Figure 15: Model schematic



All patients are assumed to begin in the pre-recurrence health state where they can either remain, transition to death, or transition to the post-recurrence health state. Patients in the post-recurrence health state can remain or transition to death. Thus, the model requires informing three key transition probabilities: transition from pre-recurrence to death, transition from pre-recurrence to post-recurrence, and transition from post-recurrence to death.

The model was developed in Microsoft Excel® and programmed using standard Excel functions wherever possible.

In the model, W&W is named surveillance and the terms W&W and surveillance are both used in this dossier to denote the comparator arm.

8.1.1.1 Statistical analyses – transition from pre-recurrence to post-recurrence

The primary statistical analyses required for the model were specific to the parametric curve fitting and extrapolation of DFS which informed the transition from pre-recurrence to post-recurrence. For DFS, both independent standard and flexible (spline and fractional polynomial) models were considered. The process for fitting parametric survival curves to patient-level data was based on guidance from the National Institute for Health and Care Excellence (NICE) (Latimer 2011).

The risk of disease recurrence is known to be greatest during the first three years following resection. As time goes by, disease recurrence among patients becomes increasingly unlikely. To reflect this, the model allows for the risk of recurrence to decrease to 0% to reflect patients no longer experiencing recurrence and achieving cure. In the base case, this time point is assumed to be 3 years, the time at which a patient without any

recurrence is considered "cured" within clinical practice, and no follow-up is routinely performed. The Danish clinical expert in the Medicines Council's dialog meeting confirmed that the risk of recurrence in patients who are disease free after 2-3 year is very small (Danish clinical expert 2021) . The extrapolation of DFS is utilized to estimate the transition up to this time point. Beyond this, the model assumes patients do not progresses to the post-recurrence health state and remain in the pre-recurrence health state until death due to any cause. More details are presented in section 8.3.1.3.

8.1.1.2 Statistical analyses – transition from post-recurrence to death

Modelling of post-recurrence survival relied upon the simplifying assumption that the survival for both treatment arms would be the same once the patient has transitioned to the post-recurrence state, i.e. assuming zero treatment effect after recurrence. This assumption was necessary in the absence of sufficiently long follow-up data from CheckMate 577. The validity of this modelling approach was verified by clinical experts. They agreed that this approach was sensible in the absence of long-term data and confirmed that the treatment received following a recurrence would be highly similar for both treatment arms (Norwegian KOL interview 2021a, Norwegian KOL interview 2021b, Swedish KOL interview 2021a, Swedish KOL interview 2021b).

In the base case, the transition from post-recurrence to death is based on data from a registry dataset from the Netherlands (IKNL) that was obtained and matched to the CheckMate 577 population. Matching was performed in terms of tumour staging, prior therapy, resection status, and residual pathological disease. Alternative data sources were also available, although the choice of data had limited impact upon the model's results given the assumption that post-recurrence survival would be the same for each treatment arm.

The methods used to extrapolate post-recurrence survival is presented in greater details in section 8.3.3.

8.1.1.3 Statistical analyses – transition from pre-recurrence to death

Due to the limited number of events in CheckMate 577, the transition from pre-recurrence to death was informed by general population mortality estimated from Danish life tables and is independent of treatment. This assumes that the increased mortality risk associated with the underlying tumour is captured by the higher mortality risk in the post-recurrence state.

8.1.2 Key assumptions

8.1.2.1 Cycle length

The cycle length in the model is one month. This cycle length was chosen as a balance between model precision around the timing of trial events and computational burden. The model incorporated a half-cycle correction, which accounts for the potential difference in patients within each health state at the beginning or end of each cycle (Naimark 2013).

8.1.2.2 Perspective

The base case model applies a limited societal perspective.

8.1.2.3 Discounting

A discount rate of 3.5% is applied for both costs and health outcomes within the base case analysis (Finansministeriet 2021, Medicinrådet 2021). A scenario analysis is included where no discounting is applied.

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8.1.2.4 Time horizon

In the base case, the time horizon was set to 30-years to reflect a lifetime horizon. This is based on the median age of patients enrolled in CheckMate 577. Analyses assuming shorter time horizons were included as scenarios to test the sensitivity of the model results to the time horizon selected.

8.1.3 Validation

The cost-effectiveness model underwent two types of validation:

- Technical verification, in which a senior programmer reviewed all model worksheets, formulae, and accompanying statistical analyses for technical integrity with each revision to the model
- Face validation, in which the assumptions used in the analytic approach were reviewed through an advisory board with both clinical and health economic experts

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

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Table 16 summarises the input data used in the model. The clinical effect parameters, the subsequent treatment, the occurrence of adverse events and the QoL estimates are based on the CheckMate 577 trial data, whereas the estimated resource consumption is based on Swedish KOL input combined with Danish unit costs. The Swedish KOL input was used as per DMC advice as no suitable Danish clinical expert could be identified for this purpose. Survival extrapolation and state occupancy is described in more detail in section 8.3. Utility values for health states and adverse events are discussed in section 8.4. The clinical effect data are derived from the CheckMate 577 trial and extrapolated using the functions described in Table 16 below.

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Table 16: Input data used in the base case health economic model

Name of inputs	Value used in model	How is the value used in the model/Comments	Source
Clinical effect data			
DFS nivolumab	Extrapolation based upon CM577 DFS data	Gompertz piecewise 6-months	CheckMate 577
DFS W&W		Gompertz piecewise 6-months	
Post-recurrence survival nivolumab	IKNL data, matched to the relevant population	Exponential	IKNL (IKNL 2020)
Post-recurrence survival W&W		Exponential	
Background mortality nivolumab	Mortality from CM 577 for 3 years, then general Danish population mortality	After 3 years, background mortality is identical for both treatment arms	CheckMate 577, Statistics Denmark (Statistik 2021)
Background mortality W&W			
DoT nivolumab	DoT KM curve from CM 577, treatment cap at 12 months	N/A	CheckMate 577
DoT W&W		N/A	
Adverse events			
Fatigue	After nivolumab: 1.1% After W&W: 0.4%	Any treatment-emergent grade 3 or above events occurring in at least 5% of patients in either treatment arm	CheckMate 577
Diarrhoea	After nivolumab: 0.4% After W&W: 0.8%		
Pruritus	After nivolumab: 0.4% After W&W: 0.0%		
Rash	After nivolumab: 0.8% After W&W: 0.4%		
Arthralgia	After nivolumab: 0.2% After W&W: 0.0%		
Aspartate aminotransferase increased	After nivolumab: 0.4% After W&W: 0.0%		
Adverse event disutilities			
Fatigue (SE)*	-0.073460 (0.01849)	N/A	Nafees 2008
Diarrhoea (SE)*	-0.046800 (0.01553)		Nafees 2008

Name of inputs	Value used in model	How is the value used in the model/Comments	Source
Pruritus (SE)*	-0.032480 (0.01171)		Assumed same as rash
Rash (SE)*	-0.032480 (0.01171)		Nafees 2008
Arthralgia (SE)*	-0.069000 (n/a)		NICE TA378
Aspartate aminotransferase increased	0.000000		Assumption
Health state utility values			
Pre-recurrence	[redacted]	[redacted]	[redacted]
Post-recurrence	[redacted]	[redacted]	[redacted]
Death	0		Per definition

Note: *Confidence intervals unavailable; standard error presented in lieu of confidence intervals where available.

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

8.2.2.1 Patient population

8.2.2.1.1 Danish clinical practice

In Denmark, the average age at diagnosis of stomach cancer (including GEJC) is 71 years, and the majority of patients are men (66%) (DEGC 2020a).The average age at diagnosis for GEJC patients is 70 years and over 80% of the diagnosed patients are male (DEGC 2020a).

8.2.2.1.2 Clinical documentation submitted (in relation to clinical practice):

In CheckMate 577, approximate 60% of the patients had EC and 40% had GEJC. More patients (71%) had adenocarcinoma than squamous cell carcinoma (29%). More than two-thirds of the patients were from Western regions (Europe, United States, and Canada). The median age (range) was 62.0 (26–86) years and the majority of the patients were white (82%). More males were enrolled in the study, with 85% male across the two treatment arms.

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

The input values used in the model were obtained from interviews with Swedish clinical experts (Swedish KOL interview 2021b); it was assumed that patients in Danish clinical practice would be similar to the Swedish setting. The experts were presented with the patient characteristics from CheckMate 577, but were asked to estimate the typical characteristics for a patient in their own clinical setting.

In the model base case, the average age of the simulated cohort is 64.5 years, based upon feedback from the Swedish clinical experts. This is similar to the patients enrolled in CheckMate 557, where the average age was 62. According to the clinical experts, this is expected, as younger patients tend to be overrepresented in clinical trials. However, the experts also stated that patients diagnosed with earlier stage disease, suitable for complete resection with preoperative CRT tend to be relatively young compared to the overall patient population (including all disease stages). A scenario analysis is therefore included where patient age is set to 62 years, the same age as in CheckMate 577.

The proportion of males expected to be eligible in Swedish clinical practice was estimated to 82%, closely aligned with the CheckMate 577 trial (85%). The average weight was estimated to 80 kg, in line with the average patient weight in the Swedish National registry for EC and GEJC (NREV 2020). The body surface area (BSA) was estimated using the Du Bois formula (Du Bois 1916) based upon this weight and an average height of 179 cm for men and 166 cm for women. The patient characteristics used in the model is shown in Table 17.

Table 17: Patient population

Patient population	Clinical documentation	Used in the model	Danish clinical practice
Median age, years	62.0[a]	64.5[b]	64.5[c]
Proportion male, %	84.5 [a]	82 [b]	82 [c]
Mean weight, kg	72.3 [a]	80 [b]	80 [c]
Body surface area, m2	NR [a]	1.90 [b]	1.90 [c]

[a]Kelly 2021. [b]Swedish clinical experts (Swedish KOL interview, 2021, Swedish KOL interview, 2021). [c]Assumption: Based on Swedish clinical experts, assuming Swedish and Danish patient populations are aligned

8.2.2.2 Intervention

8.2.2.2.1 Danish clinical practice:

In clinical practice, nivolumab should be administered 240 mg every 2 weeks over 30 minutes or 480 mg every 4 weeks over 30 minutes for the first 16 weeks followed by 480 mg every 4 weeks over 30 minutes until disease progression or unacceptable toxicity for a total treatment duration of up to 1 year, see Table 18.

8.2.2.2.2 Clinical documentation submitted (in relation to clinical practice):

In the CheckMate 577 trial, nivolumab was administered 240 mg every 2 weeks over 30 minutes or 480 mg every 4 weeks over 30 minutes for the first 16 weeks followed by 480 mg every 4 weeks over 30 minutes until disease progression or unacceptable toxicity, or patient withdrawal of consent for a total treatment duration of up to 1 year (Kelly 2021), see Table 18.

[redacted]

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

The posology included in the model reflected the CheckMate 577 trial regimen. An optimal vial dosing was used to calculate the nivolumab dose cost (using a flat 240 mg dose per 2 weeks, i.e., 2 vials of 10 ml and one vial of 4 ml), see Table 18.

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Table 18: Intervention, nivolumab

Intervention	Clinical documentation (including source)	Used in the model (number/value including source)	Expected Danish clinical practice (including source if known)
Posology	240 mg every 2 weeks over 30 minutes or 480 mg every 4 weeks over 30 minutes for the first 16 weeks followed by 480 mg every 4 weeks over 30 minutes	240 mg every 2 weeks over 30 minutes or 480 mg every 4 weeks over 30 minutes for the first 16 weeks followed by 480 mg every 4 weeks over 30 minutes	240 mg every 2 weeks over 30 minutes for the first 16 weeks followed by 480 mg every 4 weeks over 30 minutes
Stopping criteria	Until disease progression or unacceptable toxicity for a total treatment duration of up to 1 year	Until disease progression or unacceptable toxicity, or patient withdrawal of consent for a total treatment duration of up to 1 year	Until disease progression or unacceptable toxicity for a total treatment duration of up to 1 year

8.2.2.3 Comparators

8.2.2.3.1 Danish clinical practice:

There are currently no treatment options recommended for patients with EC or GEJC following pre-operative CRT and complete resection in Denmark; the current standard of care is W&W (DEGC 2020b).

8.2.2.3.2 Clinical documentation submitted (in relation to clinical practice):

In the CheckMate 577 trial, nivolumab was compared to placebo.

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

The comparator in the model is W&W as per standard of care in Denmark (DEGC 2020b).

8.2.2.4 Relative efficacy outcomes

8.2.2.4.1 Danish clinical practice:

As the current standard of care in Denmark for EC and GEJC is W&W, the clinical documentation from CheckMate 577 is highly relevant for Danish clinical practice.

8.2.2.4.2 Clinical documentation submitted (in relation to clinical practice):

As the current standard of care in Denmark for EC and GEJC is W&W, the clinical documentation from CheckMate 577 is highly relevant for Danish clinical practice. Therefore, no indirect comparisons have been used for this health-economic analysis.

The primary efficacy outcome, DFS, has been used to inform the health economic model:

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- In CheckMate 577, adjuvant nivolumab demonstrated a statistically significant improvement in DFS versus placebo, with a 31% reduction in the risk of disease progression or death (HR, 0.69; 96.4% CI: 0.56 to 0.86; p<0.001)

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

The model is based on data from the CheckMate 577 trial, which includes the relevant comparator for Danish clinical practice i.e., placebo/W&W/surveillance.

Table 19: Summary of text regarding relative efficacy

Clinical efficacy outcome	Clinical documentation	Used in the model (value)
Median DFS nivolumab	22	21.00
Median DFS W&W	11	11.00
Median post-recurrence survival nivolumab	5.2	N/A †
Median post-recurrence survival W&W	5.2	N/A †
Median DoT nivolumab	12	12
Median DoT W&W ‡	N/A	N/A

Abbreviations: DFS: disease-free survival; DoT: duration of therapy; W&W: Watch & Wait

† Median survival post-recurrence was modelled based upon external data, due to the limited follow-up time and number of patients experiencing recurrence in CheckMate 577. For more details, see section 8.3.3

‡ Nivolumab treatment was limited to 12 months according to CheckMate 577 design. In the economic model, a treatment cap at 12 months was included (see section 8.3.2).

8.2.2.5 Adverse reaction outcomes

8.2.2.5.1 Clinical documentation submitted (in relation to clinical practice):

The safety profile of nivolumab in the adjuvant EC/GEJC setting was in line with previous reports in gastroesophageal and other solid tumours (Kang 2017, Kudo 2017, Weber 2017, Janjigian 2018, Kato 2019, Kelly 2021). Adjuvant nivolumab was well tolerated in CheckMate 577. Rates of all-cause adverse events were similar across treatment arms, including grade 3 or 4 adverse events and serious adverse events. Treatment-related adverse events were more common with nivolumab than placebo (any grade treatment-related adverse events: 71% with nivolumab and 46% with placebo) although most were grade 1 or 2; 13% of patients treated with nivolumab, and 6% of patients treated with placebo reported treatment-related adverse events that were grade 3 or 4. Rates of serious treatment-related adverse events, and treatment-related adverse events leading to discontinuation were less than 10% in both treatment arms (Kelly 2021).

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

The incidence of AEs for patients treated with nivolumab and W&W was sourced from the CheckMate 577 clinical trial. In the base case scenario, the inclusion criteria for AEs in the model were treatment-related Grade 3+ AEs experienced at any grade by at least 5% of the subjects in any arm (considering nivolumab and placebo). If an AE met the criteria in only one arm, arm-specific incidence rates were used. Table 20 summarizes the AE data included in the base case analysis.

Table 20: Treatment-related Grade 3+ AEs included in model, for any AE experienced by at least 5% of the subjects in any arm

Adverse reaction outcome	Nivolumab	W&W
Fatigue	1.1%	0.4%
Diarrhoea	0.4%	0.8%
Pruritus	0.4%	0.0%
Rash	0.8%	0.4%
Arthralgia	0.2%	0.0%
Aspartate aminotransferase increased	0.4%	0.0%

8.3 Extrapolation of relative efficacy

8.3.1 Disease-free survival

8.3.1.1 DFS vs. Time to recurrence

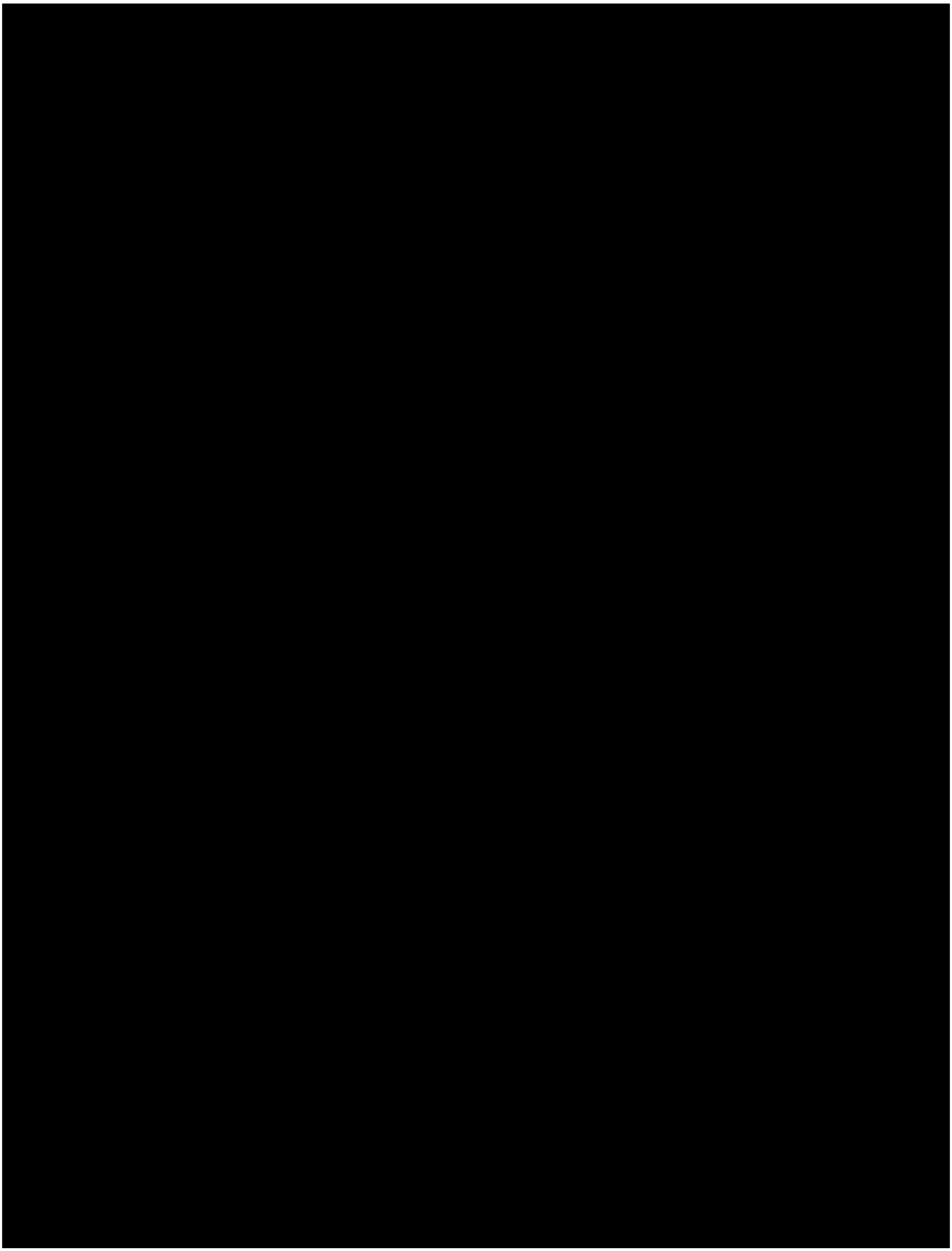
The base case model assumes that the transition from pre-recurrence to death is based on Danish age-, and sex-specific life tables. The primary endpoint DFS is defined as time to recurrence OR death due to any cause, based on CheckMate 577 data. To ensure mortality was not double counted, a comparison of DFS and time to recurrence (TTR) was undertaken (Figure 16).

As expected, DFS is marginally less than TTR. This difference is accounted for by the background mortality included in the model as these patients would transition from pre-recurrence to death rather than from pre-recurrence to post-recurrence. Therefore, it is assumed that DFS is the appropriate data source to estimate the transition from pre-recurrence to post-recurrence. The impact of basing the pre-recurrence to death transition probability on TTR instead of DFS is explored in the scenario analysis.

[redacted]

8.3.1.2 Proportional hazards assumption testing

The process for fitting parametric survival curves to patient-level data was based on guidance from the National Institute for Health and Care Excellence (NICE) (Latimer 2011). This process first involved the assessment of the proportional hazards assumption through visual inspection of the hazards over time and log-cumulative hazard plots which are outlined in Figure 17 and Figure 18. These show that over time, the change in hazards for both treatment arms is not constant. Moreover, the hazard curves converge and cross each other, indicating violation of the proportional hazards assumption. This was confirmed through visual inspection of the Schoenfeld residual plots for the two treatment arms in CheckMate 577, which showed that residuals are not parallel to the horizontal axis over time (Figure 19). It was evident from these plots that the proportional hazards assumption did not hold. Therefore, independent parametric models were fit to the nivolumab and W&W arm separately.



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8.3.1.3 Time-to-recurrence cap

According to clinical experts across the Nordics, in patients following neoadjuvant CRT and resection, disease recurrence is most likely to occur within 2-3 years, this was validated by Danish clinical experts at the Medicines Council dialog meeting. (Danish clinical expert 2021). After this, the risk of disease recurrence is very small. In clinical practice, a patient is generally considered cured if no disease recurrence has occurred during the follow-up following resection. Beyond this time point, disease recurrence is considered unlikely, and no follow-up is performed. In Danish clinical practice, follow-up is usually performed via phone call from a nurse for 2 years for EAC patients [redacted]) while ESCC patients are followed for 5 years [redacted]), although on average for three years (Danish clinical expert 2021, Norwegian KOL interview 2021a, Norwegian KOL interview 2021b, Swedish KOL interview 2021a, Swedish KOL interview 2021b).

This assumption aligns well with the change in the mortality hazard over time observed in CheckMate 577. This is shown above in Figure 17, and suggests that already after 3 years the mortality hazard for patients treated with nivolumab or surveillance converges with background mortality.

To reflect the negligible risk of tumour recurrence beyond 3 years, the model assumes that no transition from pre-recurrence to post-recurrence will occur beyond 3 years from treatment start. This assumption applies to both treatment arms. Beyond 3 years, mortality among patients in the pre-recurrence state is completely mediated through the direct transition from pre-recurrence to death. The time until the risk of disease recurrence is reduced to zero is varied in scenario analyses between 5 and 10 years. A scenario without any such cap is also included.

8.3.1.4 Parametric extrapolation

To determine the most appropriate parametric function to extrapolate DFS, alternative methods of parametric analyses were explored. These included:

- **Standard parametric models** (7 parametric models in total): standard parametric models included exponential, weibull, gompertz, log-logistic, log normal, gamma, and generalized gamma
- **Spline parametric models** (15 parametric models in total): Spline models are "structurally flexible" extensions of the standard parametric distributions. They are similar to piecewise models as they are flexible mathematical functions defined by piecewise polynomials joined at points on the x-axis (time) known as knots. Spline models were fit on three different scales: hazards, odds, and normal. Within each scale, spline models with up to 5-knots were evaluated.
- **Fractional polynomial models** (10 parametric models in total): Fractional polynomial models, as outlined by Ouwens et al 2010 and Jansen et al 2015, provide an alternative to splines where the hazard functions of the interventions in a trial are modelled using known parametric survival functions or fractional polynomials (Ouwens 2010, Jansen 2015)). Second order fractional polynomials allowing p1=0 or 1 and p2=-1, -0.5, 0, 0.5, or 1 were fit (Jansen 2015).). In essence, these second order fractional polynomial models are extensions of the Weibull and Gompertz models and allow arc- and bathtub shaped hazard functions, which emulate parametric distributions such as log-logistic and log normal.
- **Piecewise models** (14 parametric models in total): the use of Kaplan-Meier data up to 3-months and 6-months followed by standard parametric models

Table 21 provides a summary of the goodness-of-fit statistics of each of the models evaluated. Additional details on each of the functional forms tested is outlined in Appendix G. The visual fit of the models tested for nivolumab and surveillance are presented in Appendix G. These include both the observed period within CheckMate 577 and the long-term extrapolation for the full model time horizon of 30-years. The best statistical fit was achieved with piecewise 6-month extrapolations for both nivolumab and surveillance, out of which extrapolations based upon the Gompertz distribution yielded the lowest AIC values.

Table 21: Goodness of fit statistics of parametric models fit to CheckMate 577 DFS

Approach	Nivolumab			W&W		
	Distribution	AIC	BIC	Distribution	AIC	BIC
Standard parametric	[redacted]					

Approach	Nivolumab			W&W		
	Distribution	AIC	BIC	Distribution	AIC	BIC
Spline hazards	[redacted]					
Spline odds	[redacted]					
Spline normal	[redacted]					
Fractional polynomial	[redacted]					
Piecewise 3-months	[redacted]					
Piecewise 6-months	[redacted]					

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Abbreviations: AIC: Akaike information criterion; BIC: Bayesian Information Criteria

8.3.1.5 Choice of parametric curves

Based on all parametric forms evaluated, a subset of parametric models for nivolumab and surveillance were shortlisted as the ones with the most plausible fit. These were presented to health economists and clinicians in an international advisory board. This subset of models represented the best fitting models in terms of AIC criteria within each approach evaluated in Table 21; and provided a range of long-term DFS estimates. That is, if survival models generated nearly identical long-term DFS estimates the model with the simplest parametric form was chosen. For example, in the spline normal models tested (Appendix G, Figure 34) the long-term extrapolations for surveillance were nearly identical across the 1-knot to 5-knot models. Therefore, only the 1-knot and 2-knot models were presented to health economists and clinicians as the 1-knot model provided the best statistical fit in terms of AIC criteria and the 2-knot model provided an alternative fit which was similar to the 3-knot, 4-knot, and 5-knot models.

[redacted] As per CM577 protocol subjects was evaluated for disease recurrence every 12 weeks from the date of first treatment, this causes an artificial drop in the DFS curve particularly at 3 and 6 months and affects the hazard. The piecewise approaches generally provided a better fit with Kaplan-Meier (KM) data from CheckMate 577, particularly when study data was used until 6 months. For both treatment arms, the Gompertz Piecewise 6-months curve yielded the best fit (see Table 21), and aligned very well with the survival predicted by the Spline odds models. For this reason, Piecewise 6-month Gompertz were chosen for the base case instead. Figure 20 shows the DFS extrapolated using the Gompertz piecewise model (6 months) for both treatment arms, compared to the Kaplan-Meier data from CheckMate 577. The impact of instead using the Spline odds functions were included in scenario analyses.

The survival extrapolations used in the base case showed very good fit with the survival data from CheckMate 577. Figure 20 shows the survival extrapolations for the DFS curve for each treatment arm compared to the KM data from CheckMate 577.

The models tested for nivolumab were validated against a publication which estimated the recurrence-free survival associated with neoadjuvant chemoradiation as this provided the most similar population to CheckMate 577 in the published literature (Alnaji 2016) .

Table 22 and Table 23 present the extrapolations used in the base case and scenario analyses and compares these to the available data sources. These tables account for background mortality which is further described in Section 9.3.4. Furthermore, these tables also incorporate the base case assumption that the risk of recurrence decreases to 0% after 3-years, further described in Section 8.3.1.3.

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Table 22: Long-term extrapolation of parametric models fit to surveillance, fit to data

Distribution	6m	1yr	3yr
Modelled survival: Gompertz Piecewise 6-months	[redacted]	[redacted]	[redacted]
Modelled survival: Spline odds 1-knot	[redacted]	[redacted]	[redacted]
CheckMate 577 (July 2020 DBL)	[redacted]		
CheckMate 577 (February 2021 DBL)	[redacted]	[redacted]	
(Alnaji 2016)	[redacted]	[redacted]	[redacted]

Abbreviations: DBL: data base lock

Table 23: Long-term extrapolation of parametric models fit to nivolumab, fit to data

Distribution	6m	1yr	3yr
Modelled survival: Gompertz Piecewise 6-months	[redacted]	[redacted]	[redacted]
Modelled survival: Spline odds 2-knots	[redacted]	[redacted]	[redacted]
CheckMate 577 (July 2020 DBL)	[redacted]		
CheckMate 577 (February 2021 DBL)	[redacted]	[redacted]	
(Alnaji 2016)	[redacted]	[redacted]	[redacted]

Abbreviations: DBL: data base lock

8.3.1.6 External validation of disease-free survival

To ensure that DFS extrapolations for W&W were credible, survival extrapolations from the model were compared to data matched to the CM577 population from the Swedish NREV registry (NREV 2020). Survival data from NREV is presented in Figure 21. Although the survival data from NREV were based upon few subjects only, it aligns well with the survival predictions from the model and clinical experts (see section 8.3.1.5 and Table 22). It also shows evidence of the expected plateauing of survival beyond the first three years, as discussed in section 9.3.1.3.

8.3.1.7 Summary of disease-free survival extrapolation:

For the base case analysis, DFS extrapolations were based upon Piecewise 6-month Gompertz for both the nivolumab and surveillance arm. This was justified since 1) these curves showed the best statistical fit (see Table 21) to study data from CheckMate 577, and 2) the predicted survival aligned well with the 5-year DFS estimated by the advisory board (section 8.3.1.5). Survival extrapolations based upon Spline odds models (2 knots for nivolumab and 1 knot for surveillance) were included as scenario analysis. A scenario using generalized F distribution for both treatment arms was also included.

Transitions from disease-free to post-recurrence was capped at 3 years in the base case, to reflect the clinical assumption that a tumour recurrence beyond this point is unlikely (see section 8.3.1.3). Alternative caps of the time beyond which tumour recurrence is no longer possible were included as scenario analyses.

8.3.2 Time to treatment discontinuation

In the base case, the duration of treatment was based upon to time-treatment discontinuation (TTD) in the CheckMate 577 trial. This was deemed to reflect treatment costs in clinical practice more accurately than if duration of treatment would have been based upon disease-free survival. In the model, the proportion of patients in DFS is adjusted for the proportion of patients on treatment as outlined in Figure 22. The alternative approach of basing the duration of treatment upon the modelled DFS was explored as a scenario.

A treatment cap at maximum 12 months treatment with nivolumab was applied, [redacted] The relevance of this treatment cap was also verified with Nordic clinical experts, who strongly suggested that nivolumab treatment (if approved on the Danish market) would adhere to the maximum recommended treatment duration of 12 months (Norwegian KOL interview 2021a, Norwegian KOL interview 2021b, Swedish KOL interview 2021a, Swedish KOL interview 2021b).

The drug acquisition and administration costs for nivolumab are assumed to apply during the entire treatment duration. These costs per model cycle are outlined in Section 8.5.2.

8.3.3 Post-recurrence survival

The post-recurrence survival could not be estimated from CheckMate 577 due to the limited follow-up time in the study. Instead, clinical feedback and alternative data sources were used to generate survival extrapolations for patients in the post-recurrence state. Feedback from clinical experts suggests that it is reasonable to assume that the mortality rate for patients in the post-recurrence state is predominantly dependent on the sheer existence of metastasized disease and that impact of any relevant events prior to recurrence (e.g., treatment) or the time spent in the post-recurrence state would be small in comparison. For this reason, the post-recurrence survival was assumed to be identical for both treatment arms. The validity of this assumption within a Danish clinical context was validated with clinical experts (Norwegian KOL interview 2021a, Norwegian KOL interview 2021b, Swedish KOL interview 2021a, Swedish KOL interview 2021b).

Alternative data sources were available for estimating post-recurrence survival. First, a registry dataset from the Netherlands was identified: Netherlands Comprehensive Cancer Organization (IKNL). During a BMS held advisory board, the clinical experts had chosen the Integraal Kankercentrum Nederland (Netherlands Comprehensive Cancer Organization; IKNL) as the most appropriate source to inform post-recurrence survival for the intention-to-treat (ITT) population and all subgroups (BMS 2021e). This nationwide cohort study included patients diagnosed with non-metastatic ESCC, EAC, GEJC and GC in the Netherlands. All patients in the Netherlands diagnosed with non-metastatic ESCC, EAC, and GEJC in 2015 and 2016 were included, with the exception of patients diagnosed or treated in two specific hospitals (BMS 2020b). The IKNL data were obtained and matched to the CheckMate 577 population by adding extra inclusion criteria to the ESCC, EAC, and GEJC patients to align the analysis population with the CheckMate 557 trial population[redacted]

Secondly, a meta-analysis was performed for the chemotherapy arms from two primary studies: CheckMate 649 and KEYNOTE 590 (Kato 2020, Clinicaltrials.gov 2021). CheckMate 649 is a BMS sponsored study evaluating the efficacy and safety of folinic acid, fluorouracil, and oxaliplatin (FOLFOX) and capecitabine plus oxaliplatin (XELOX) in esophageal junction cancer as a comparator to nivolumab plus ipilimumab. KEYNOTE 590 is evaluating the efficacy and safety of cisplatin and 5-fluororacil in advanced/metastatic EC as a comparator to pembrolizumab. The active control chemotherapy arms of these two studies were pooled to estimate the transition from post-recurrence to death. The chemotherapy arms of CheckMate 649 and KEYNOTE 590 were selected as these treatments reflect standard of care in a 1st line metastatic EC setting in many countries. The use of these treatments in a metastatic setting was validated with clinical experts in an advisory board. [redacted] The median OS observed in the KEYNOTE 590 (9.8 months [95% CI 8.8-10.8 months], ITT population) and CheckMate 649 (11.9 months [95% CI 10.8-13.8 months], EAC/GEJC population) were consistent with historical data.

A summary of the alternative data sources for post-recurrence survival estimation is presented in Table 24. Both were included as extrapolation options in the economic model, and results were explored for both settings. Since post-recurrence survival does not differ between treatment arms by assumption, the choice of data source for post-recurrence survival is not a major driver of results in the model.

Nonetheless, the IKNL data set was chosen as the base case, since the population used for this data set aligned better with the target population of this analysis. [redacted] The impact of instead using the 1st line metastatic EC data for survival extrapolations is explored through scenario analyses.

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Table 24: Summary of post-recurrence survival data sources

Characteristics	CheckMate 577	IKNL	First-line metastatic EC	
			CheckMate 649	KEYNOTE 590
Sample size	532	359	236	274
Study design	RCT	Registry	RCT	RCT
Tumour type/location	EC, GEJC	ESCC, EAC, GEJC	EAC, GEJC	ESCC
Distant recurrence (% of all recurrence)	70.3%	80.6% (ESCC), 90.8% (EAC), 93.7% (GEJC)	NR	NR
Pre-operative treatment	CRT	Platinum-based CRT	NR	NR
Setting	Global	Netherlands	Global	Global
Disease stage	Resected (R0) resection with residual disease and ECOG PS 0-1	Recurrent/unresectable advanced, non-pCR, TNM stage II/III	Advanced unresectable or metastatic	Advanced unresectable or metastatic
Time between prior and neo/adjuvant therapy	NA	NR	6 months	NR
OS observation period	NA	From time of recurrence	From trial enrolment	From trial enrolment

Abbreviations: EAC: Esophageal adenocarcinoma; EC: esophageal cancer; ECOG PS: European Co-operative Oncology Group Performance Score; ESCC: esophageal squamous cell carcinoma; CRT: chemoradiotherapy; GEJC: gastroesophageal junction cancer; NA: not applicable; NR: not reported; OS: overall survival; pCR: pathological complete response; RCT: randomized controlled trial

Whilst the IKNL data source could be used for informing the probability of transition from post-recurrence to death, the IKNL data source was not considered for the pre-recurrence to death transition. As the information was available from the CheckMate 577 trial, there was no need to use external sources. Further, pre-recurrence mortality from IKNL that matched CheckMate 577 enrolment was not available. [redacted] For these reasons, the IKNL data was only used for informing the transition probability from 'post-recurrence' to 'death' in the model.

8.3.3.1 Parametric extrapolation for post-recurrence survival

Exponential distributions were fitted to the IKNL and pooled data to estimate the transition over the model time horizon. Distributions based upon a constant hazard rate are easily incorporated into a Markov-state model. Since these types of models measure time in discrete units, the transition probabilities during each cycle are affected by the cycle length. For any distributions based upon a non-constant hazard rate this may result in transition probabilities that are subject to somewhat arbitrary cut-offs. By contrast, the exponential distribution relies upon a constant hazard rate, hence eliminating the need for structural assumptions around which hazard rates should be applied during each model cycle. With the current model structure, it is not possible to choose any other models, other than the default exponential model. Given the Markov model properties that require

use of non-time-dependent transition probabilities when modelling transitions from the post-recurrence state, the exponential survival model was deemed most appropriate as it fulfils this requirement. Furthermore, comparing the exponential model and the best fitting Gen-F model (based on the AIC criterion) showed similar prediction of post-recurrence long-term survival (see Table 25).

Table 25: Comparison of statistical fit among alternative models for post-recurrence survival extrapolation, first line data base

Distribution	AIC
Generalized F	[redacted]
Log-logistic	[redacted]
Gamma	[redacted]
Weibull	[redacted]
Log normal	[redacted]
Gompertz	[redacted]
Exponential	[redacted]

Abbreviations: AIC: Akaike information criterion

Figure 23 and Figure 24 outline the short- and long-term standard parametric models fit to post-recurrence survival. It is evident from the long-term extrapolation, that all models tested predict similar long-term post-recurrence survival. Furthermore, as the transition from post-recurrence to death is assumed to be independent of treatment, model results were not particularly sensitive towards the choice of extrapolation curve.

[redacted]

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8.3.4 Background mortality

Three different modelling approaches were available for estimating the probability of transitioning directly from DFS to death.

As a first option, the unadjusted general population mortality could be applied based on the general Danish population. However, it is plausible that the survival for the relevant patient population could be lower than that of the general population, even without disease recurrence.

A second option could be to adjust the general Danish population mortality by the observed mortality hazard observed among disease-free patients in CheckMate 577. This approach would mean a consistently higher mortality hazard among the treated patients than for their peers who never experienced esophageal or gastro-esophageal junction cancer in the first place. However, it may lead to overly pessimistic survival estimations, since CheckMate 577 data was only available for the first years following treatment, and there is reason to believe that the increased mortality risk of these patients compared to the general population would decrease over time (see Figure 17 above). To estimate the hazard ratio used for this adjustment, the mortality risk in CheckMate 577 was compared against general population life tables for Denmark. The general population life tables were adjusted for age (starting age 64.5) and were weighted by the percentage male (82%) and female (18%) as outlined in Table 17. Following this, patient-level data from CheckMate 577 was generated based on Danish lifetables for patients aged 64.5 years using the Guyot method. The patient level data from CheckMate

577 and lifetables were stacked and run through a Cox model to estimate a HR with a corresponding 95% confidence interval. The resulting HR [redacted]) was applied to the general population mortality data by year to reflect the increased mortality seen in CheckMate 577.

[redacted]

The third option was to adjust the general population hazard by the observed mortality hazard observed among disease-free patients in CheckMate 577, but only for the first three years, i.e., the time for which CheckMate 577 data was available. Beyond this, mortality hazards would be based upon the general population mortality.

Following discussions with Nordic clinical experts, the third approach (elevated mortality for 3 years followed by general population mortality) was deemed the most appropriate for the base case analysis, since it was hard to estimate how the relative mortality among DFS patients would develop beyond the trial's follow-up (Norwegian KOL interview 2021a, Norwegian KOL interview 2021b, Swedish KOL interview 2021a, Swedish KOL interview 2021b). The other two alternative approaches were explored in scenario analyses.

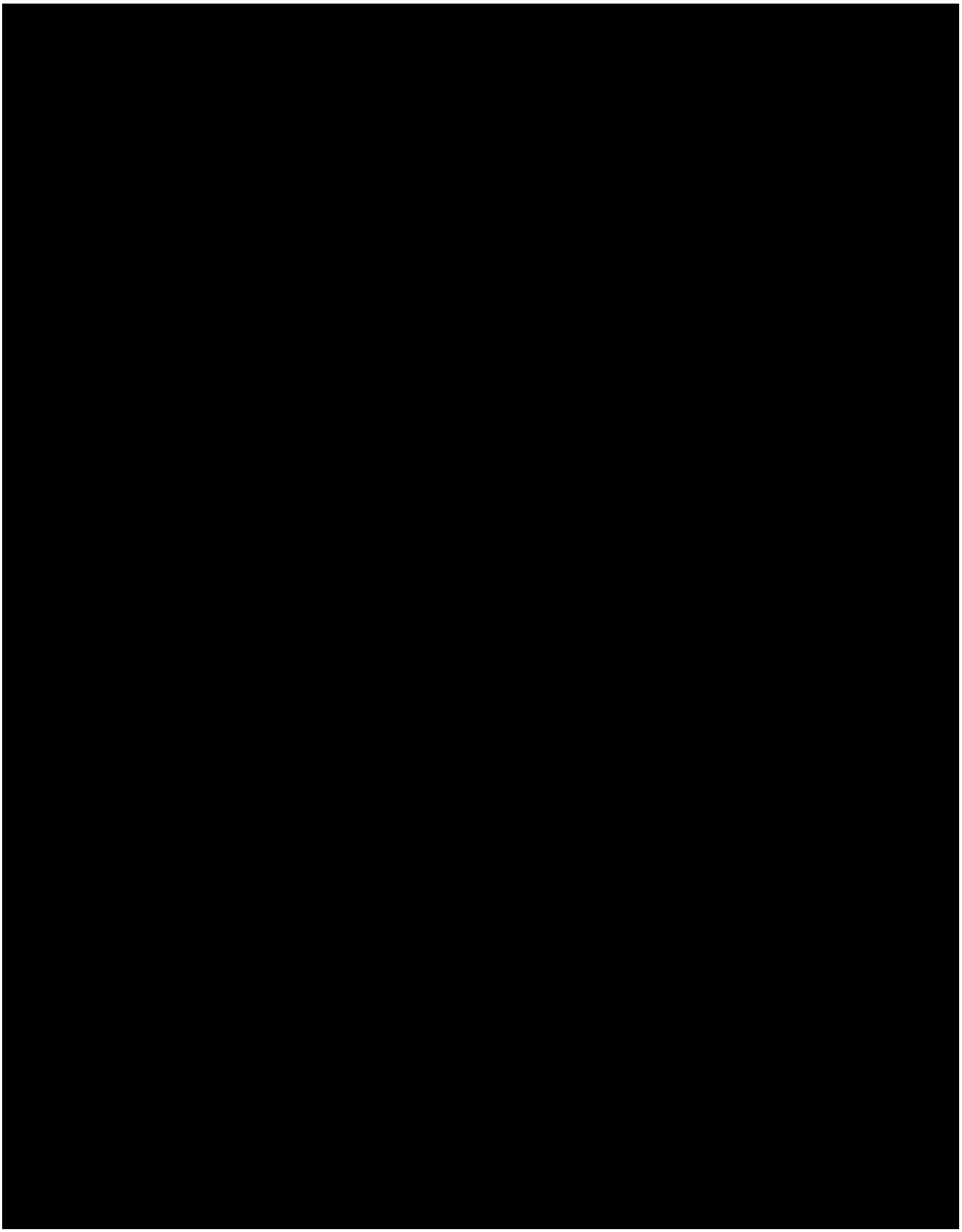
This HR was applied for the first 3 years as it is from this point that the rate of death is low in CheckMate 577 and a plateau is observed. Following clinical validation in the dialogue meeting, it is assumed in the base case that post 3-years patients that have not experienced recurrence have a very low risk of recurrence and hence a mortality equivalent to the general population.

A scenario of where the mortality is continuously uplifted to the CheckMate 577 level is presented in Section 8.7.3. CheckMate 577 was only available for the first few years, however as discussed, there is reason to believe that the increased mortality risk of these patients compared to the general population would decrease over time and, hence, this might be an overly pessimistic scenario.

Age- and sex-adjusted life tables for Denmark were obtained from Statistics Denmark (Statistik 2021). The mortality hazard was calculated based on the proportion of male and female patients assumed for this analysis (see section 8.2.2.1.3). The average mortality rates for years 2016 to 2020 were assumed for this analysis, these rates are included in the economic model. 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 years between years 101 and 110. At age 110, the mortality risk was set to 100%.

8.3.4.1 Proportional hazards testing

Proportional hazards are also presented for the pre-recurrence survival versus the general mortality of Denmark ([redacted]), as well as the Schoenfeld residual plots ([redacted]).



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

8.4.1 Overview of health state utility values (HSUV)

8.4.1.1 Health state utility values collected in CheckMate 577 study

The CheckMate 577 study collected patient reported outcomes using the EQ-5D-3L (EuroQol Group 1990). Analyses were conducted based on a pre-specified patient reported outcomes statistical analysis plan using the trial data based on all randomized subjects providing EQ-5D-3L data. The primary purpose of the analysis was to identify mean EQ-5D values for the economic model in terms of utility values assigned to the pre-recurrence and post-recurrence health states. The utility analysis used the EQ-5D-3L index score, utilizing all scheduled data collected (including baseline, follow-up, and survival follow-up).

To estimate mean values of EQ-5D-3L for each health state required, a mixed model approach was used to account for repeated EQ-5D-3L measurements per subject within a health state.

The variable(s) defining health states and their interaction, if any, were included in the model as fixed effects. Random intercept was used to account for repeated measurements within each subject. Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) based on maximum likelihood approach were used to examine the significance of treatment, where lower AIC and BIC values indicate better fit. The -2*log-Likelihood statistics were also presented from which chi-square statistics can be derived to evaluate statistical significance of added variables between nested models. The number of patients, the number of EQ-5D-3L assessments, least squares means (LSM), standard errors, and 95% confidence intervals (CIs) for the value of EQ-5D-3L index were presented.

There were 784 subjects in the 577 study with at least one observed utility index (UI) value available. [redacted] When comparing dates of patient reported outcome (PRO) assessments to dates of recurrence provided by the investigator, PRO assessments prior to the date of recurrence were considered to be prior to recurrence; PRO assessments on the same date or afterwards were considered to be post-recurrence.

No imputation was used to handle missing data for the EQ-5D-3L. [redacted] The estimation of mean utility per health state was conducted using a repeated-measures mixed model, accounting for multiple utility values per subject.

8.4.1.2 EQ-5D-5L health state utility values

The five-level version of the EQ-5D (EQ-5D-5L) is the recommended version to be used for estimation of QALYs in the latest Danish guidelines for the economic evaluation of new treatments (Medicinrådet 2021). In the absence of EQ-5D-5L data in CheckMate 577 a parametric predictive model was used for mapping the EQ-5D-3L values into EQ-5D-5L (van Hout 2021a). For each EQ-5D-3L assessment, the health state (e.g., 11111 or 33333) was converted into index values by using the value sets mapped from the EQ-5D-5L Danish value set (Jensen 2021a). The index value obtained for each individual assessment was then used in the modelling to estimate the mean utility values within each health state.

Two alternative approaches to utility values were also considered and derived for the model. Firstly, an approach using treatment-specific utility values was explored. However, when controlling for progression status, there were no statistically significant differences in HRQoL between the treatment arms. For this reason, only the overall values were used in this analysis (i.e. progression-based utilities without any treatment-specific

differences). Secondly, time-to-death (TTD) utility values were also explored. However, progression-based utility values were used for this analysis since they align with the health-state based model structure (see section 8.1.1).

More information about the HRQoL utility values and mapping used for this analysis is presented in Appendix I.

8.4.2 Health state utility values used in the health economic model

The model utilizes the progression-based health state utilities (i.e., pre-recurrence and post-recurrence) collected in the CheckMate 577 trial, mapped to the Danish value set (see section 8.4.1.2). The progression-based utility values used in the cost-effectiveness model are presented in Table 26.

Furthermore, patients who experienced an adverse event (AE) were also assumed to experience decrements to their health-related quality of life (HRQoL). Adverse event-related disutility values were obtained from published literature. Where an explicit duration of the event was not explicit within the literature, the utility decrement was applied throughout the entire model cycle. These AE-related utility decrements are presented in Table 26.

For AE, the reported utilities by the utilities reported by Nafees et al 2008 (Nafees 2008) was used. Nafees et al 2008 (Nafees 2008) have been used in over 30 different economic evaluations by bodies such as the National Institute for Health & Clinical Excellence (NICE), and the Scottish Medicines Consortium (SMC). Hence they were chosen for the base case.

While a later Nafees et al 2017 (Nafees 2017) study has also been published collecting EQ-5D, comparing the utilities in the two different studies shows that the values from the later study were lower than those reported in Nafees et al 2008 (Nafees 2008). It should be noted that Nafees et al 2008 (Nafees 2008) used the standard gamble valuation method, whereas the Nafees et al 2017 (Nafees 2017) study used Time Trade Off (TTO). Evidence suggests that these two methods do not produce the same estimates and differences may be greater for more severe states, whereby TTO produces lower utilities. In addition utilities in the later publication are based on a first-line setting rather than the second-line treatment setting which had been the focus of the Nafees et al 2008 (Nafees 2008) study.

Using the disutilities from the later study for fatigue, diarrhoea, pruritus, and rash have limited impact on the ICER, the model can easily be updated by changing the values on the utilities tab in the cost effectiveness model.

Table 26: Summary of the HSUV used in the model

	Results [95% CI]	Instrument	Tariff (value set) used	Sources
Health state				
Pre-recurrence	[redacted]	[redacted]	[redacted]	[redacted]
Post-recurrence	[redacted]	[redacted]	[redacted]	[redacted]
Adverse events	**Standard Error***			**Sources**
Fatigue	-0.07346 (0.01849)			Nafees et al 2008 (Nafees 2008)
Diarrhoea	-0.04680 (0.01553)			Nafees et al 2008 (Nafees 2008)
Pruritus	-0.03248 (0.01171)			Assumed same as rash
Rash	-0.03248 (0.01171)			Nafees et al 2008 (Nafees 2008)
Arthralgia	-0.06900 (n/a)			Value used in UK NICE appraisal for Ramucirumab in gastric cancer (NICE 2016)
Aspartate aminotransferase increased	0.00000			Assumption

Note: *Confidence intervals unavailable; standard error presented in lieu of confidence intervals where available.

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 2021).

8.5 Resource use and costs

Clinical experts were consulted to ensure that resource usage would reflect Danish clinical practice as accurately as possible. However, no suitable Danish clinical expert could be identified for this purpose since they were all part of the DMC's expert committee, something that made it impossible to seek their input according to DMC's guidelines. For this reason, DMC advised that input obtained from Swedish and Norwegian clinical experts could be used instead. Swedish expert input was chosen to reflect the Danish setting due to the higher granularity

their answers provided compared to the Norwegian experts (Swedish KOL interviews conducted in May 2021, data on file). These experts specified disease management costs associated with patients in the pre-recurrence and post-recurrence health states as described in Table 27 and Table 28.

Unit costs were collected from resources as recommended by the DMC guidelines (Medicinrådet 2020): the Danish Medicinpriser.dk (Medicinpriser.dk 2021), Kommunernes og Regionernes Løndatakontor (Kommunernes og Regionernes Løndatakontor 2021), the interactive DRG grouper by Sundhedsdatastyrelsen (Sundhedsdatastyrelsen 2021), and the Rigshospitalets Labportal (Rigshospitalets Labportal 2021).

8.5.1 Disease management costs

8.5.1.1 Disease management costs in the pre-recurrence health state

The disease management costs associated with patients in the pre-recurrence health state are presented in Table 27. The model specifies the resource use in the first 5 years in the pre-recurrence health state as some disease management resource use, and hence costs, will not remain the same year on year. Physician visits (i.e., oncologist and thoracic surgeon) solely consider the surgeon costs; costs for tests and examinations (i.e., blood cell cunt, renal and hepatic tests, nutritional tests, and CT-scan) are separately sourced with estimated frequencies. This was verified with the Swedish clinical experts.

Table 27 Disease management resource use and costs in for patients in the pre-recurrence health state

Resource name	Frequency per cycle	Unit costs (DKK)	Reference
Oncologist visit	0	1456.62	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 according to Medicine council 2020.
Thoracic surgeon	0.33	1456.62	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 according to Medicine council 2020.
CT Scan (chest and other)	0	2007	Sundhedsdatastyrelsen (2021). Interactive DRG: 30PR06 CT-scanning, kompliceret (UXCD10) CT-skanning af øvre abdomen (DK229) Sygdom i øsofagus UNS. Available at: http://interaktivdrg.sundhedsdata.dk/
Blood cell count	0.33	460	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	0.33	261	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	0.33	213	Rigshospitalets Labportal (2021). Test code for hepatic tests included (codes): NPU19651, NPU19654, NPU27783, NPU19673, NPU01370, NPU03278. https://labportal.rh.dk/Labportal.asp
Oncology nurse visit	0	583.87	Kommunernes og Regionernes Løndatakontor 2021, Sygeplejersker. bruttolön APR 2021 (41405DKK). available from: https://krl.dk/#/sirka Calculated: salary/hours per month and multiplied by two according to Medicine council 2020.

Nordic clinical experts verified that disease recurrence would be most likely within 2-3 years of the resection, and that patients who have remained disease-free for 3 years or more can be considered "cured" (Danish clinical expert 2021, Norwegian KOL interview 2021a, Norwegian KOL interview 2021b, Swedish KOL interview 2021a, Swedish KOL interview 2021b). After 3 years patients are no longer followed up and hence the cost-effectiveness model considers the option that patients remaining in the pre-recurrence stage for more than 3 years may be considered "cured" and will no longer incur any disease management costs.

8.5.1.2 Disease management costs in the post-recurrence health state

The Swedish clinical experts specified disease management costs associated with patients in the post-recurrence health state is presented in Table 28. As for the pre-recurrence health state, physician visits are considered separately from test costs and frequencies.

Table 28: Disease management resource use and costs for patients in the post-recurrence health state

Costs	Frequency per month	Unit costs (DKK)	Reference
Oncologist visit	0.42	1456.62	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 according to Medicine council 2020.
Thoracic surgeon	-	1456.62	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 according to Medicine council 2020.
CT Scan (chest and other)	0.33	2007	Sundhedsdatastyrelsen (2021). Interactive DRG: 30PR06 CT-scanning, kompliceret (UXCD10) CT-skanning af øvre abdomen (DK229) Sygdom i øsofagus UNS. Available at: http://interaktivdrg.sundhedsdata.dk/
Blood cell count	1.17	460	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

Costs	Frequency per month	Unit costs (DKK)	Reference
Renal function test	0.67	261	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	0.67	213	Rigshospitalets Labportal (2021). Test code for hepatic tests included (codes): NPU19651, NPU19654, NPU27783, NPU19673, NPU01370, NPU03278. https://labportal.rh.dk/Labportal.asp
Oncology nurse visit	1	583.87	Kommunernes og Regionernes Løndatakontor 2021, Sygeplejersker. bruttolön APR 2021 (41405DKK). available from: https://krl.dk/#/sirka Calculated: salary/hours per month and multiplied by two according to Medicine council 2020.

8.5.2 Drug acquisition costs for the intervention

Table 29 outlines the drug acquisition costs used in the base case model for the intervention. The dose of nivolumab is the recommended dose for this indication as approved by EMA and is based on the CheckMate 577 study protocol; 240 mg every 2 weeks over 30 minutes or 480 mg every 4 weeks over 30 minutes for the first 16 weeks followed by 480 mg every 4 weeks over 30 minutes. The maximum duration of treatment is 12 months.

Pack prices for nivolumab are sourced from Medicinpriser.dk.

Table 29: Drug acquisition costs used for nivolumab in the base-case model

Treatment	Administration			Cost per dose (DKK)	Reference
	Dose	Unit	Frequency (weeks)		
Nivolumab week 1-16	240	mg	2	22 567.94	Checkmate 577
Nivolumab week 17-52	480	mg	4	45 135.88	Medicinpriser.dk (2021)

8.5.3 Subsequent treatment costs

The cost-effectiveness model includes the cost associated with subsequent treatment for all patients who transition to the post-recurrence health state. This is modelled as a one-off treatment cost for a proportion of patients in this state. Swedish clinical experts confirmed that (palliative) chemotherapy would be the standard subsequent treatment following tumour recurrence. They further estimated that around 80% of all patients would be in sufficiently good physical condition to receive this type of treatment (Norwegian KOL interview 2021a, Norwegian KOL interview 2021b, Swedish KOL interview 2021a, Swedish KOL interview 2021b).

The distribution between different chemotherapy regimens and the duration of systemic treatment was obtained from the CheckMate 577 trial. Systemic chemotherapy was the most frequent form of subsequent therapy received by patients on recurrence in both the nivolumab and W&W arms.

The duration for each subsequent therapy was obtained from the Danish treatment guidelines for the indication. The distribution between different chemotherapy regimens used in the model is shown in Table 30. In the CheckMate 577 trial, there were minor differences in the types of treatments received in the two study arms. However, in the economic model the distribution is identical for both treatment arms to make the two arms more comparable.

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Table 30: Subsequent treatments in the base case model

Costs	Nivolumab	W&W	References
Systemic therapy	80.0%	80.0%	[redacted]
5FU + CIS	11.7%	11.7%	[redacted]
CAP + OX	8.7%	8.7%	[redacted]
FOLFOX	79.6%	79.6%	[redacted]

Treatment dosing of subsequent treatments is presented in Table 31 and is based on guidelines for esophagael cancer in Nationella Regimbiblioteket (Nationella regimbiblioteket 2021c, Nationella regimbiblioteket 2021a, Nationella regimbiblioteket 2021b). Drug acquisition costs were based upon pharmacy purchasing price (PPP) excluding VAT. Drug costs were obtained from Medicinpriser.dk (Medicinpriser.dk 2021), using the lowest available price per mg for the package size. In the base case model, subsequent treatment was provided for 6.4 months which is consistent with the median progression-free survival observed in CheckMate 649 and KEYNOTE 590 (Kato 2020, Clinicaltrials.gov 2021).

Table 31:Drug acquisition costs used for the subsequent treatment in the base case model

Treatment	Posology		Vial / package information		Unit cost (DKK)	References
	Dose (mg/m^2)	Administration per cycle	Size	Strength		
5FU + Cis						
5-Fluorouracil	3750	1 per 21 days	50 mg/ml	10 ml	70	Nationella Regimbiblioteket Medicinpriser.dk (2021) https://www.medicinpriser.dk/Default.aspx?id=15&vnr=068671
			50 mg/ml	50 ml	200	Nationella Regimbiblioteket Medicinpriser.dk (2021) https://www.medicinpriser.dk/Default.aspx?id=15&vnr=382001
			50 mg/ml	100 ml	400	Nationella Regimbiblioteket Medicinpriser.dk (2021) https://www.medicinpriser.dk/Default.aspx?id=15&vnr=565141
Cisplatin	100	1 per 21 days	1 mg/ml	50 ml	100	Nationella Regimbiblioteket Medicinpriser.dk (2021) https://www.medicinpriser.dk/Default.aspx?id=15&vnr=598049
			1 mg/ml	100 ml	200	Nationella Regimbiblioteket Medicinpriser.dk (2021) https://www.medicinpriser.dk/Default.aspx?id=15&vnr=548680
CAP + OX						

Treatment	Posology		Vial / package information		Unit cost (DKK)	References
	Dose (mg/m^2)	Administration per cycle	Size	Strength		
Capacitabine	1000	27 per 21 days	150 mg	60 tablets	193.50	Nationella Regimbiblioteket Medicinpriser.dk (2021) https://www.medicinpriser.dk/Default.aspx?id=15&vnr=161150
			500 mg	120 tablets	250	Nationella Regimbiblioteket Medicinpriser.dk (2021) https://www.medicinpriser.dk/Default.aspx?id=15&vnr=581539
Oxaliplatin	130	1 per 21 days	5 mg/ml	10 ml	145	Nationella Regimbiblioteket Medicinpriser.dk (2021) https://www.medicinpriser.dk/Default.aspx?id=15&vnr=099957
			5 mg/ml	20 ml	240	Nationella Regimbiblioteket Medicinpriser.dk (2021) https://www.medicinpriser.dk/Default.aspx?id=15&vnr=483681
			5 mg/ml	40 ml	480	Nationella Regimbiblioteket Medicinpriser.dk (2021) https://www.medicinpriser.dk/Default.aspx?id=15&vnr=559404
FOLFOX						
5-Fluorouracil	2000	1 per 14 days	50 mg/ml	10 ml	70	Nationella Regimbiblioteket Medicinpriser.dk (2021) https://www.medicinpriser.dk/Default.aspx?id=15&vnr=068671
			50 mg/ml	50 ml	200	Nationella Regimbiblioteket Medicinpriser.dk (2021) https://www.medicinpriser.dk/Default.aspx?id=15&vnr=382001
			50 mg/ml	100 ml	400	Nationella Regimbiblioteket Medicinpriser.dk (2021) https://www.medicinpriser.dk/Default.aspx?id=15&vnr=565141
Oxaliplatin	85	1 per 14 days	5 mg/ml	10 ml	145	Nationella Regimbiblioteket Medicinpriser.dk (2021) https://www.medicinpriser.dk/Default.aspx?id=15&vnr=099957
			5 mg/ml	10 ml	240	Nationella Regimbiblioteket Medicinpriser.dk (2021) https://www.medicinpriser.dk/Default.aspx?id=15&vnr=483681
			5 mg/ml	20 ml	480	Nationella Regimbiblioteket Medicinpriser.dk (2021) https://www.medicinpriser.dk/Default.aspx?id=15&vnr=559404

Treatment	Posology		Vial / package information		Unit cost (DKK)	References
	Dose (mg/m^2)	Administration per cycle	Size	Strength		
Calcium folinate	200	1 per 14 days	10 mg/ml	10 ml	111	Nationella Regimbiblioteket Medicinpriser.dk (2021) https://medicinpriser.dk/Default.aspx?id=15&vnr=489899
			10 mg/ml	35 ml	222	Nationella Regimbiblioteket Medicinpriser.dk (2021) https://medicinpriser.dk/Default.aspx?id=15&vnr=563008

8.5.4 Administration costs

Table 32 outlines the administration costs for the IV treatments included in the model. The administration costs were sourced from Sundhedsdatastyrelsen (Sundhedsdatastyrelsen 2021).

Table 32: Administration cost per included IV treatments

Treatment	Name of resource	Unit costs (DKK)	Reference
Nivolumab, 5FU + CIS, CAP + OX & FOLFOX	Administration cost for treatment	5297	Sundhedsdatastyrelsen (2021). Interactive DRG: 06MA11 (BWAA60) Medicingivning ved intravenøs injektion, (DK229) Sygdom i øsofagus UNS. Available at: http://interaktivdrg.sundhedsdata.dk/

8.5.5 Drug monitoring costs

Table 33 outlines the treatment monitoring costs associated with nivolumab in the base case model, which are in addition to the disease management costs for pre- and post-recurrence presented in Section 8.5.1. The resource use required per month was sourced from Swedish KOL. Monitoring costs for nivolumab are only applied for the first year in the model as nivolumab has a maximum treatment duration of 1-year.

Table 33: Monitoring costs associated with nivolumab, 5FU+CIS, CAP+OX and FOLFOX

Treatment	Frequency per cycle (nivolumab)	Unit costs (DKK)	Reference
Oncologist visit	0.375	1456.62	[redacted] 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 according to Medicine council 2020.
Full blood cell count	2.00	460	[redacted] 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 according to Medicine council 2020.
Renal function test	2.00	261	[redacted] 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	2.00	213	[redacted] 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
CT scan	0.125	2007	[redacted] Sundhedsdatastyrelsen (2021). Interactive DRG: 30PR06 CT-scanning, kompliceret (UXCD10) CT-skanning af øvre abdomen (DK229) Sygdom i øsofagus UNS. Available at: http://interaktivdrg.sundhedsdata.dk/

8.5.6 Adverse events and adverse-event costs

Any adverse events associated with adjuvant EC and GEJC treatment occurring for ≥5% of patients in CheckMate 577 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. Swedish experts were contacted to validate how each adverse event of grade 3 – 4 would be treated within a Swedish clinical context. It was assumed that this is applicable to a Danish setting. Table 34 outlines the unit costs associated with the treatment of adverse events included in the base case model (included adverse events are outlined in Table 20 above). The unit costs were sourced from Kommunernes og Regionernes Løndatakontor (Kommunernes og Regionernes Løndatakontor 2021) and the interactive DRG grouper by Sundhedsdatastyrelsen (Sundhedsdatastyrelsen 2021).

For a scenario analysis, DRG rates (Sundhedsdatastyrelsen 2021) have been applied for all adverse events treatment and monitoring, which would consider a more comprehensive treatment and add an assumption of additional cost to the Swedish clinical expert feedback. These rates are presented in Table 35.

Table 34: Grade 3+ AE occurring in >5% of patients in Checkmate 577 included in the model, and related treatment costs: base case

Adverse Event	Resource use per event	Share of patients that should be considered for the treatment	Unit cost per event (DKK)	Reference
Fatigue	1 oncology visit	100%	1456.62	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 according to Medicine council 2020.
Diarrhoea	1 oncologist visit	90%	1456.62	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 according to Medicine council 2020.
	1 visit to emergency department	10%	5130	Sundhedsdatastyrelsen (2021). Interactive DRG: 06MA11 Malabsorption og betændelse i spiserør, mave og tarm, pat. mindst 18 år, u. kompl. bidiag. (FB5258) Andre specificerede funktioner relateret til afføring (DK229) Sygdom i øsofagus UNS. Available at: http://interaktivdrg.sundhedsdata.dk/
Pruritus	-	-	1456.62	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 according to Medicine council 2020.
Rash	1 oncology visit	100%	1456.62	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 according to Medicine council 2020.
Arthralgia	1 oncology visit	100%	1456.62	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 according to Medicine council 2020.
Aspartate aminotransferase increased	1 oncology visit. If grade 4, stop treatment.	100%	1456.62	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 according to Medicine council 2020.

Table 35: Grade 3+ AE occurring in >5% of patients in Checkmate 577 included in the model, and related treatment costs: scenario analysis per DRG rates

Adverse Event	Resource use per event	Share of patients that should be considered for the treatment	Unit cost per event (DKK)	Reference
Fatigue	1 hospital visit treatment	100%	5130	Sundhedsdatastyrelsen (2021). Interactive DRG: 06MA11 Malabsorption og betændelse i spiserør, mave og tarm, pat. mindst 18 år, u. kompl. bidiag. (BZFD0)patient alene (DK229) Sygdom i øsofagus UNS. Available at: http://interaktivdrg.sundhedsdata.dk/
Diarrhoea	1 hospital visit treatment	100%	5130	Sundhedsdatastyrelsen (2021). Interactive DRG: 06MA11 Malabsorption og betændelse i spiserør, mave og tarm, pat. mindst 18 år, u. kompl. bidiag. (FB5258) Andre specificerede funktioner relateret til afføring (DK229) Sygdom i øsofagus UNS. Available at: http://interaktivdrg.sundhedsdata.dk/
Pruritus	1 hospital visit treatment	100%	5130	Sundhedsdatastyrelsen (2021). Interactive DRG: 06MA11 Malabsorption og betændelse i spiserør, mave og tarm, pat. mindst 18 år, u. kompl. bidiag. (BNXY) Interv. med rel.til hud og underhud ikke klass. andetsteds (DK229) Sygdom i øsofagus UNS. Available at: http://interaktivdrg.sundhedsdata.dk/
Rash	1 hospital visit treatment	100%	5130	Sundhedsdatastyrelsen (2021). Interactive DRG: 06MA11 Malabsorption og betændelse i spiserør, mave og tarm, pat. mindst 18 år, u. kompl. bidiag. (BNXY) Interv. med rel.til hud og underhud ikke klass. andetsteds (DK229) Sygdom i øsofagus UNS. Available at: http://interaktivdrg.sundhedsdata.dk/
Arthralgia	1 hospital visit treatment	100%	5130	Sundhedsdatastyrelsen (2021). Interactive DRG: 06MA11 Malabsorption og betændelse i spiserør, mave og tarm, pat. mindst 18 år, u. kompl. bidiag. (BLHN)Medikamentel lokalbeh. af lidelser i muskler, led og knogler (DK229) Sygdom i øsofagus UNS. Available at: http://interaktivdrg.sundhedsdata.dk/
Aspartate aminotransferase increased	1 hospital visit treatment	100%	5130	Sundhedsdatastyrelsen (2021). Interactive DRG: 06MA11 Malabsorption og betændelse i spiserør, mave og tarm, pat. mindst 18 år, u. kompl. bidiag. (DK769) Liver disease UNS (DK229) Sygdom i øsofagus UNS. Available at: http://interaktivdrg.sundhedsdata.dk/

8.5.7 Terminal care costs

The model includes specific end-of-life costs, see Table 36. These enter into the analysis as a one-time cost when a patient dies, to capture the average costs associated with terminal care in Denmark. This cost was included to capture costs arising from specific treatment costs at the end of life and it was assumed to be identical regardless

of prior treatments. A one-time cost of 60 340 DKK was used, sourced from Sundhedsdatastyrelsen [DRG code 06MA11: (BXBA) Specialiseret palliativ indsats in (DK229) Sygdom i øsofagus UNS, for 30 days] ((Sundhedsdatastyrelsen 2021).

Table 36: Cost for terminal care

Resource	Frequency	Cost (DKK)	Reference
Terminal Care	For 30 days	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/

Abbreviation: DKK, Danish kroner

8.5.8 Patient costs

Patient costs for transportation and time were included in this analysis for every drug administration. These are presented in Table 37. For adjuvant treatment with nivolumab, the frequency of administration for nivolumab was used since this drug is given more frequently to the patient. Given this, patients were expected to visit a treatment clinic every 14 days, a frequency of 2 appointments per model cycle. The transportation cost per visit was estimated to DKK 100, in line with DMC guidelines (Medicinrådet 2021).

It was further assumed that every administration would require 2 hours of patient time, including the time of transportation. This means that 4 hours of the patient's time would be required per model cycle. The unit cost for patient time was estimated to DKK 179, in line with DMC guidelines (Medicinrådet 2021).

The frequency of visits in the post-recurrence state was based upon the number of visits required for treatment with FOLFOX, the most common post-recurrence treatment (see section 8.5.3). This meant that 2 visits and 4 hours per model cycle were used in the post-recurrence health-state as well.

Table 37: Patient costs

Cost type	Frequency per cycle (pre-recurrence)	Frequency per cycle (post-recurrence)	Unit cost (DKK, per hour/visit)	Source
Patient time cost	4	4	179	Medicinrådet (2020), *Værdisætning af enhedsomkostninger*
Transportation cost	2	2	100	Medicinrådet (2020), *Værdisætning af enhedsomkostninger*

8.6 Results

8.6.1 Base case results

Base case results were generated in the economic model using deterministic analysis. The base case analysis shows that adjuvant treatment with nivolumab is associated with substantial increases in both overall and disease-free survival. The expected survival over time by treatment arm for the base case is presented in Table 38.

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Table 38 Survival outcomes by treatment and time, base case analysis

Survival outcome	W&W	Nivolumab	Nivolumab vs. W&W (percentage points)
Survival to 6 months	[redacted]	[redacted]	[redacted]
Survival to 1 year	[redacted]	[redacted]	[redacted]
Survival to 5 years	[redacted]	[redacted]	[redacted]
Survival to 10 years	[redacted]	[redacted]	[redacted]
Survival to 15 years	[redacted]	[redacted]	[redacted]
Disease-free survival to 6 months	[redacted]	[redacted]	[redacted]
Disease-free survival to 1 year	[redacted]	[redacted]	[redacted]
Disease-free survival to 5 years	[redacted]	[redacted]	[redacted]
Disease-free survival to 10 years	[redacted]	[redacted]	[redacted]
Disease-free survival to 15 years	[redacted]	[redacted]	[redacted]

Abbreviations: W&W: watch and wait

In the base case, adjuvant nivolumab treatment is associated with a total cost of DKK [redacted], compared to DKK [redacted] for W&W. The cost increase stems almost entirely from the increased costs for drug acquisition and administration; the total costs for post-recurrence management, subsequent treatment and terminal care are lower than for W&W. Total costs for each treatment arm are presented in Table 39, including a breakdown of costs into different categories.

Table 39: Total costs for adjuvant nivolumab treatment compared to W&W, base case results

	W&W (DKK)	Nivolumab (DKK)	Nivolumab vs. W&W (DKK)
Total Costs	[redacted]	[redacted]	[redacted]
Treatment costs	[redacted]	[redacted]	[redacted]
Monitoring costs	[redacted]	[redacted]	[redacted]
Adverse event costs	[redacted]	[redacted]	[redacted]
Recurrence free disease related costs	[redacted]	[redacted]	[redacted]
Post-recurrence disease related costs	[redacted]	[redacted]	[redacted]
Subsequent treatment costs	[redacted]	[redacted]	[redacted]
Terminal care costs	[redacted]	[redacted]	[redacted]
Patient costs	[redacted]	[redacted]	[redacted]

Abbreviations: DKK: Danish kroner; W&W: watch and wait

Total QALYs and LYs are presented in Table 40. When discounted at 3.5%, adjuvant nivolumab is associated with [redacted] QALYs compared to [redacted] when patients are treated through W&W, a total increase by [redacted]. For LYs, the equivalent values are [redacted] for nivolumab and [redacted] for W&W, an increase by [redacted] LYs. [redacted]

[redacted]

Table 40: Total QALY and LY for adjuvant nivolumab treatment compared to W&W, base case results

Effectiveness	W&W	Nivolumab	Nivolumab vs. W&W
Total QALYs	[redacted]	[redacted]	[redacted]
QALYs pre recurrence	[redacted]	[redacted]	[redacted]
QALYs post recurrence	[redacted]	[redacted]	[redacted]
Total LYs	[redacted]	[redacted]	[redacted]
LYs pre-recurrence	[redacted]	[redacted]	[redacted]
LYs post-recurrence	[redacted]	[redacted]	[redacted]

Abbreviations: LY: life year, QALY: quality-adjusted life year; W&W: watch and wait

For the base case settings, adjuvant treatment with nivolumab, incremental costs were estimated to DKK[redacted], and treatment was associated with an increase of [redacted] QALYs. This resulted in an incremental cost-effectiveness ratio (ICER) of DKK[redacted] per QALY. The cost-effectiveness is summarised in Table 41.

Table 41: Summary of cost-effectiveness results, base case analysis

Outcome	W&W	Nivolumab	Difference
Total costs (DKK)	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]
ICER (DKK)			
		[redacted]	

Abbreviations: DKK: Danish kroner; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; W&W: watch and wait

8.7 Sensitivity analyses

8.7.1 Deterministic sensitivity analyses

Table 42 summarizes the deterministic sensitivity analyses for adjuvant nivolumab versus W&W. Figure 27 illustrates the magnitude for which the ICER changes when each input was varied. The ICERs from the sensitivity analyses were compared to the base case ICER to determine the absolute and proportional change. The parameters with the greatest impact upon the ICER were the cost of subsequent treatment for both W&W and nivolumab, the monitoring cost for nivolumab treatment, and the utility values for the pre-recurrence state.

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Table 42: Deterministic sensitivity analysis of adjuvant treatment with nivolumab versus W&W:

	Parameter	SE	Upper bound of 95% CI	Lower bound of 95% CI	ICER if parameter set to upper bound (DKK)	ICER if parameter set to lower bound (DKK)	Difference (DKK)
Cost of subsequent treatment surveillance (DKK)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost of subsequent treatment nivolumab (DKK)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Utility pre-recurrence (monthly)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Monitoring cost nivolumab (DKK)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Utility post-recurrence (Monthly)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost of terminal care (DKK)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost disease management post-recurrence (DKK)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost disease management pre-recurrence (DKK)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Disutility adverse event nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Disutility adverse event surveillance	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost of managing adverse events nivolumab (DKK)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost of managing adverse events surveillance (DKK)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI: confidence interval; DKK: Danish kroner; ICER: incremental cost-effectiveness analysis; SE: standard error

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8.7.2 Probabilistic sensitivity analyses

Probabilistic sensitivity analysis was performed to assess the sensitivity of the results in regards to parametric uncertainty. Monte-Carlo simulation with 1000 iterations was used for the PSA. New parameter values were sampled from the posterior distributions for efficacy (multivariate normal), safety (beta), utility (beta), and costs (gamma) for each iteration of the model. For the sake of brevity, the parametric input values are not shown here, but can be found in the 'Model parameters' sheet of the health economic model.

The results of the PSA are presented in Table 43. The results from the PSA are closely aligned to the deterministic results (section 8.6.1); the ICER for the PSA is [redacted], compared to [redacted] for the deterministic results.

The result of the cost-effectiveness analyses is presented in a cost-effectiveness plane in [redacted]. The cost-effectiveness acceptability curve (CEAC) is shown in [redacted].

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Table 43: Base case results for probabilistic sensitivity analysis

Outcome	W&W mean	95% CI	Nivolumab mean	95% CI	Nivolumab vs W&W
Incremental cost per QALY gained	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incremental cost per recurrence free life year gained	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Costs					
Total Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Monitoring costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse event costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Recurrence free disease related costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post-recurrence disease related costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent treatment costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Terminal care costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patient costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Effectiveness					
Total QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs pre recurrence	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs post recurrence	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total LYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LYs pre-recurrence	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LYs post-recurrence	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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Outcome	W&W mean	95% CI	Nivolumab mean	95% CI	Nivolumab vs W&W
Survival outcomes					
Survival to 6 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Survival to 1 year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Survival to 5 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Survival to 10 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Survival to 15 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Disease-free survival to 6 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Disease-free survival to 1 year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Disease-free survival to 5 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Disease-free survival to 10 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Disease-free survival to 15 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI: Confidence interval; QALY: quality-adjusted life year; W&W watch and wait

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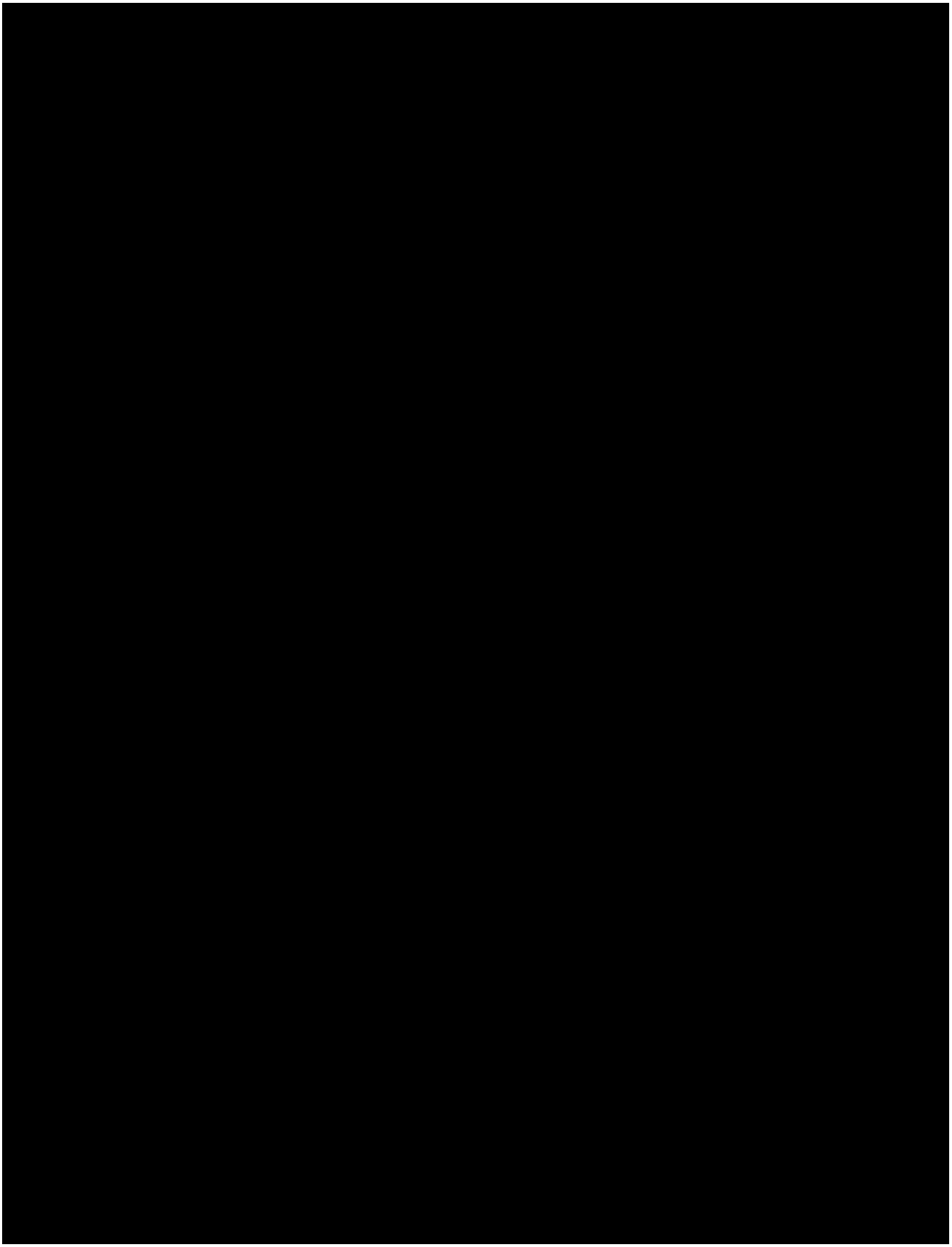

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8.7.3 Scenario analyses

The results from the scenario analyses is presented in Table 44. These analyses were undertaken to investigate the effect of certain model inputs on costs and outcomes. The main outcome was the ICER, traditionally the main indicator of the cost-effectiveness of a treatment.

Reducing the time horizon of the analysis has a significant impact upon the cost-effectiveness of adjuvant nivolumab treatment, as is expected for an intervention which decreases the risk of disease recurrence. This analysis also shows that the time horizon and choice of curve for DFS extrapolations are important drivers of the model. By contrast, alternative data sources for the post-recurrence survival have a much more limited impact on the results.

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Table 44: Results for scenario analysis

Scenario	Incremental cost (DKK)	Incremental QALYs	ICER per QALY (DKK)
Base case	[redacted]	[redacted]	[redacted]
Discount rate 0%	[redacted]	[redacted]	[redacted]
Risk of recurrence reduced to zero after 5 years	[redacted]	[redacted]	[redacted]
Risk of recurrence reduced to zero after 10 years	[redacted]	[redacted]	[redacted]
Risk of recurrence never reduced to zero	[redacted]	[redacted]	[redacted]
Duration of treatment based upon DFS	[redacted]	[redacted]	[redacted]
Alternative approach to estimate post-recurrence survival: meta-analysis of first line EC trials	[redacted]	[redacted]	[redacted]
Background mortality permanently elevated	[redacted]	[redacted]	[redacted]
Background mortality based upon general population survival only	[redacted]	[redacted]	[redacted]
No age-adjusted utilities	[redacted]	[redacted]	[redacted]
Treatment cap: 24 months	[redacted]	[redacted]	[redacted]
Weight-based dosing †	[redacted]	[redacted]	[redacted]
Drug wastage excluded (vial sharing) †	[redacted]	[redacted]	[redacted]
Alternative costs for adverse events	[redacted]	[redacted]	[redacted]
Time horizon: 20 years	[redacted]	[redacted]	[redacted]
Time horizon: 10 years	[redacted]	[redacted]	[redacted]
Starting age: 62 years	[redacted]	[redacted]	[redacted]
Transition to post-recurrence based upon TTR	[redacted]	[redacted]	[redacted]
DFS extrapolation: **Nivolumab: Spline odds 2-knots** **Surveillance: Spline odds 1-knot**	[redacted]	[redacted]	[redacted]
DFS extrapolation: **Nivolumab: generalized F-distribution** **Surveillance: Generalized F-distribution**	[redacted]	[redacted]	[redacted]

† When patient weight is 80 kg, weight-based nivolumab dosing is identical to flat dose.

9. Budget impact analysis

A budget impact analysis was performed for expected cost of adjuvant nivolumab treatment. The economic model described in section 0 was used for estimating total costs. The increased expected survival from treatment with nivolumab is captured within this analysis. However, unlike the cost-effectiveness analysis, the discount rate for costs were set to 0% for the budget impact analysis, and patient costs were excluded.

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

9.1 Number of patients

The number of patients eligible for treatment with adjuvant nivolumab in Denmark was estimated to [redacted] patients annually (for more details, see section 5.1.6). [redacted]

The total number of patients receiving each treatment if adjuvant nivolumab is recommended as standard treatment is presented in Table 45. If adjuvant nivolumab is not recommended, all patients are assumed to be treated with W&W. The number of patients per year and treatment in this scenario is presented in Table 46.

Table 45: Number of incident patients expected to be treated over the next five-year period - if adjuvant nivolumab is recommended as standard treatment

	Year 1	Year 2	Year 3	Year 4	Year 5
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
W&W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total number of patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: W&W: watch and wait

Table 46: Number of incident patients expected to be treated over the next five-year period - if adjuvant nivolumab is NOT recommended as standard treatment

	Year 1	Year 2	Year 3	Year 4	Year 5
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
W&W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total number of patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: W&W: watch and wait

9.2 Cost per patient treated

The total cost per patient treated with adjuvant nivolumab for years 1-5 is presented in Table 47. This table also presents a breakdown of the total costs into its different components. An equivalent table outlining the per patient costs for patients treated with W&W is presented in Table 48.

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Table 47: Cost per patient and year for patients treated with adjuvant nivolumab, years 1-5

Resource type	Year 1	Year 2	Year 3	Year 4	Year 5
Drug acquisition costs (DKK)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Monitoring costs (DKK)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse event costs (DKK)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Recurrence-free disease-related costs (DKK)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post-recurrence disease-related costs (DKK)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent treatment costs (DKK)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Terminal care costs (DKK)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Productivity/Other costs (DKK) †	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total cost (DKK)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

† Indirect treatment costs include the costs of patient time and transportation. These have been excluded from the budget impact analysis

Abbreviations: AE: adverse events; DKK, Danish kroner; PD: progressed disease; PF: progression-free disease

Table 48: Cost per patient and year for patients treated with W&W, years 1-5

Resource type	Year 1	Year 2	Year 3	Year 4	Year 5
Drug acquisition costs (DKK)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Monitoring costs (DKK)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse event costs (DKK)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Recurrence-free disease-related costs (DKK)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post-recurrence disease-related costs (DKK)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent treatment costs (DKK)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Terminal care costs (DKK)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Productivity/Other costs (DKK) †	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total cost (DKK)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

† Indirect treatment costs include the costs of patient time and transportation. These have been excluded from the budget impact analysis

Abbreviations: DKK, Danish kroner; W&W: watch and wait

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9.3 Budget impact

The total expected cost for a scenario where adjuvant nivolumab is recommended as standard treatment is presented in Table 49. The total expected cost for a scenario where adjuvant nivolumab is NOT recommended is presented in Table 50. The resulting budget impact if adjuvant nivolumab is recommended is the difference in costs between these two scenarios. The expected budget impact from a recommendation of adjuvant nivolumab is presented in Table 51.

Table 49: Cost per year if adjuvant nivolumab is accepted as standard treatment (DKK)

Treatment	Year 1	Year 2	Year 3	Year 4	Year 5
Nivolumab					
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]
Total cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
W&W					
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]
Total cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total if accepted as standard treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: DKK, Danish kroner; W&W: watch and wait

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Table 50: Cost per year if adjuvant nivolumab is NOT accepted as standard treatment (DKK)

Treatment	Year 1	Year 2	Year 3	Year 4	Year 5
Nivolumab					
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	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
W&W					
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]
Total cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total if accepted as standard treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: DKK, Danish kroner; W&W: watch and wait

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Table 51: Expected annual budget impact if adjuvant nivolumab 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 (DKK)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: DKK, Danish kroner

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10. Discussion on the submitted documentation

The reported results of adjuvant nivolumab in adults with resected EC or GEJC who have residual pathologic disease following prior neoadjuvant CRT are considered to be relevant. Despite resection and pre-operative CRT options available to patients with stage II or III EC or GEJC, many patients do not obtain a pathologic complete response (pCR) and are at high risk of recurrence and mortality despite intensive treatment strategies. Currently there is no active treatment but only watch and wait for patients with residual disease following prior CRT and complete resection.

This analysis shows that adjuvant nivolumab is an effective treatment option for patients with residual disease following prior CRT and complete resection. Compared to observation/ watch and wait, adjuvant nivolumab is expected to yield an additional [redacted] per patient. The expected cost for this is [redacted] per patient. The resulting ICER gained is [redacted] All the analyses presented for the base case and scenarios are based upon list prices for the acquisition costs of nivolumab. The analyses are based on best practice methods and according to the guidance provided by the DMC methods guidance. The standard three-health state model structure is consistent with the approaches adopted in economic evaluations and technology appraisals with nivolumab.

The findings from the cost-effectiveness analysis are supported by the results from probabilistic and one-way sensitivity analyses. Subsequent drug acquisition costs is the biggest driver of cost-effectiveness. The utility values applied to the pre-progression and post-progression health states also impact the results. Some uncertainty about the expected utility values for these patients persist, although feedback from clinical experts suggest that the utility values for patients with residual disease following prior CRT and complete resection is relatively high. In this evaluation utility values are based upon observed data from CheckMate 577, and identical utility values have been applied to both the treatment and comparator arms, subject to disease status.

Scenario analyses show that the findings from the evaluation is most sensitive towards changes in the time horizon, discount rate, and the time point beyond which is assumed that no disease recurrence is possible. However, clinical expert feedback suggest that disease recurrence beyond three years is unlikely. Therefor it also makes sense that the time horizon of the analysis is important; any time horizon shorter than a full lifetime (30 years in the base case analysis) essentially cuts short the expected survival benefits for otherwise healthy patients.

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11. List of experts

[redacted]

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Appendix A: Literature search for efficacy and safety of intervention and comparator(s)

A systematic literature review (SLR) was conducted to identify and summarize the clinical efficacy and safety of treatments used in EC and GEJC. The main objective was to identify all clinical evidence published on existing adjuvant therapies. However, as current clinical guidelines recommend treating patients with neoadjuvant and perioperative therapies, the second objective was to identify all relevant randomized evidence on existing neoadjuvant and perioperative therapies.

The submission and cost-effectiveness model includes the results of the CheckMate 577, which includes the relevant comparator for Denmark, placebo i.e., watch and wait. Therefore, the outcomes of the literature review of efficacy and safety have not been used in the clinical and economic sections of the dossier as it will not provide additional relevant documentation. As a systematic literature review (SLR) had previously been conducted in relation to CheckMate 577—to support health technology assessments for different country settings—the processes and outcomes of the SLR have been included for reference.

For more comprehensive overview of the SLR, please see the clinical SLR document attached with this submission.

Search strategy

The selected databases and search engines used to collect clinical evidence are presented in Table 52. The Embase and Medline databases were searched by means of the ProQuest engine. This search engine allows for these databases to be searched simultaneously and removes duplicates between databases. The CENTRAL database was searched by means of the advanced search function on the Cochrane Library homepage.

Table 52: Databases included in the search

Database	Search engine	Phase 1	Phase 2	
		Search date*	Search date	Results
Embase	ProQuest	13 August 2019	30 November 2020	740
Medline (in-Process)	ProQuest	13 August 2019	30 November 2020	
CENTRAL	Cochrane Library	13 August 2019	30 November 2020	237
Total				977

A search of the following proceedings from the previous 2 years (2018-2020) was conducted:

- American Society of Clinical Oncology (ASCO) Annual Meeting
- ASCO Gastrointestinal Cancers (GI) Meeting
- European Society for Medical Oncology (ESMO) Annual Meeting
- American Association for Cancer Research (AACR) Annual Meeting

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The searches for conference proceedings were independent of that conducted for peer-reviewed publications. Conference proceedings that were indexed in Embase were searched electronically, using the same search strategy as for the peer-reviewed publications. Conferences that were not indexed in Embase were "hand-searched" using EC and GEJC search terms in whichever format was provided by the conference (e.g. PDF booklet, online search portal).

The search strategies used are detailed below in the tables below.

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Table 53: Embase and Medline search strategy (ProQuest)

ID	Search terms	Hits
S1	(MESH.EXACT("Esophageal Neoplasms"))	50944*
S2	TI,AB(Esoph* NEAR/3 (cancer or neoplas* or carcinoma* or adenocarcinoma))	107858*
S3	TI,AB((Oesoph* OR gastroesoph*) NEAR/3 (cancer or neoplas* or carcinoma* or adenocarcinoma))	27451*
S4	(EMB.EXACT.EXPLODE("esophagus cancer"))	75056*
S5	TI,AB(("EG junction" OR "GE junction" OR gastroesoph* OR esophagogastric OR cardio?esoph*) NEAR/3 (cancer or neoplas* or carcinoma* or adenocarcinoma))	8600*
S6	MESH.EXPLODE("Esophagogastric Junction")	9021*
S7	EMB.EXACT("gastroesophageal junction")	5017*
S8	MESH.EXPLODE("Neoplasms")	3391285*
S9	EMB.EXPLODE("malignant neoplasm")	3870132*
S10	S1 OR S2 OR S3 OR S4 OR S5	164243*
S11	S6 OR S7	14038*
S12	S8 OR S9	7261417*
S13	S11 AND S12	5987*
S14	S10 OR S13	165269*
S15	(EMB.EXACT.EXPLODE("cancer adjuvant therapy"))	127846*
S16	(EMB.EXACT("neoadjuvant chemotherapy"))	13842*
S17	(MESH.EXACT("Chemotherapy, Adjuvant"))	41211*
S18	MESH.EXACT("Neoadjuvant Therapy")	21237*
S19	MESH.EXACT("Radiotherapy, Adjuvant")	22577*
S20	TI,AB(Adjuvant or neoadjuvant)	448888*
S21	TI,AB(post OR "pre" OR peri)	3505565*
S22	TI,AB(surgery or resect* or opera* OR perioper* or preoper* OR esophagectomy OR oesophagectomy OR ablation)	5992330*
S23	S15 OR S16 OR S17 OR S18 OR S19 OR S20	515462*
S24	S21 AND S22	744156*
S25	S23 OR S24	1227351*
S26	TI,AB(clinical AND (trial or study or studies))	5035011*
S27	TI,AB(random*) OR TI,AB,IF(placebo*) OR TI,AB(double NEAR/1 blind*)	3038987*
S28	TI,AB("RCT")	62762*
S29	TI,AB((singl* OR doubl* OR treb* or tripl*) NEAR/1 (blind[*3] OR mask[*3]))	428356*
S30	TI,AB(placebo[*1])	540806*
S31	TI,AB(random* NEAR/2 allocated)	75631*

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ID	Search terms	Hits
S32	EMB.EXACT.EXPLODE(“Clinical trial”)	1737706*
S33	EMB.EXACT(“Controlled clinical trial”)	534653*
S34	EMB.EXACT(“Randomized controlled trial”)	677329*
S35	EMB.EXACT.EXPLODE(“Randomization”)	101706*
S36	EMB.EXACT(“Single blind procedure”)	45867*
S37	EMB.EXACT(“Double blind procedure”)	184709*
S38	EMB.EXACT(“Crossover procedure”)	69890*
S39	EMB.EXACT(“Placebo”)	400204*
S40	EMB.EXACT("Multicenter study" OR "Phase 3 clinical trial" OR "Phase 4 clinical trial")	330375*
S41	EMB.EXACT("Prospective study")	677608*
S42	MESH.EXACT.EXPLODE("Randomized Controlled Trials as Topic" OR "Randomized Controlled Trial") OR MESH.EXACT.EXPLODE("Clinical Trials as Topic")	349235*
S43	MESH.EXACT.EXPLODE(“Random Allocation”)	104112*
S44	MESH.EXACT.EXPLODE(“Double-Blind Method”)	161158*
S45	MESH.EXACT.EXPLODE(“Single-Blind Method”)	29370*
S46	MESH.EXACT.EXPLODE(“Placebos”)	35220*
S47	RTYPE("Clinical trial, phase i")	21037*
S48	RTYPE("Clinical trial, phase ii")	33800*
S49	RTYPE("Clinical trial, phase iii")	17554*
S50	RTYPE("Clinical trial, phase iv")	2002°
S51	RTYPE("Controlled clinical trial")	93951*
S52	RTYPE("Randomized controlled trial")	518956*
S53	RTYPE("Multicenter study")	283706*
S54	RTYPE("Clinical trial")	603902*
S55	TI,AB("Case control") OR TI,AB(case control NEAR/1 (study OR studies))	306996*
S56	Cohort NEAR/1 (study OR studies)	819886*
S57	TI,AB(Cohort analys*)	709786*
S58	TI,AB(Follow up NEAR/1 (study OR studies))	139662*
S59	TI,AB(Observational NEAR/1 (study OR studies))	347640*
S60	TI,AB(Longitudinal)	605132*
S61	TI,AB(Retrospective)	1485214*
S62	EMB.EXACT("Clinical study")	313032*
S63	EMB.EXACT("Longitudinal study")	160787*
S64	EMB.EXACT("Retrospective study")	1017625*
S65	EMB.EXACT("Prospective study") NOT EMB.EXACT("Randomized controlled trials")	677608*
S66	EMB.EXACT("Cohort analysis")	670867*

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ID	Search terms	Hits
S67	MESH.EXACT.EXPLODE("Case control studies")	292025*
S68	MESH.EXACT.EXPLODE("Cohort studies")	2060699*
S69	S26 or S27 or S28 or S29 or S30 or S31 or S32 or S33 or S34 or S35 or S36 or S37 or S38 or S39 or S40 or S41 or S42 or S43 or S44 or S45 or S46 or S47 or S48 or S49 or S50 or S51 or S52 or S53 or S54 or S55 or S56 or S57 or S58 or S59 or S60 or S61 or S62 or S63 or S64 or S65 or S66 or S67 or S68	12624782*
S70	TI,AB(case NEAR/1 (stud* OR report))	1787873*
S71	EMB.EXACT("Case study")	131011*
S72	EMB.EXACT("Abstract report" OR "Letter")	1174795*
S73	RTYPE("Case reports")	2137989*
S74	RTYPE("Letter")	2259298*
S75	RTYPE("Historical article")	361188*
S76	PSTYPE("Conference proceedings")	4327°
S77	RTYPE("Conference abstract")	3904873*
S78	RTYPE("Editorial")	1224916*
S79	RTYPE("Note")	827014*
S80	S70 or S71 or S72 or S73 or S74 or S75 or S76 or S77 or S78 or S79	11789738*
S81	S69 NOT S80	10069776*
S82	S14 AND S25 AND S81	8783*
S83	S82 AND PD(>20190813)	**740°**

* Duplicates are removed from the search but included in the result count.

°Duplicates are removed from the search and from the result count.

Search date: 30-11-2020

Hits per database: Embase (n=667), Medline (n=472)

Table 54: CENTRAL search strategy

ID	Search	Hits
#1	MeSH descriptor: [Esophageal Neoplasms] this term only	1567
#2	(Esoph* NEAR/3 (cancer or neoplas* or carcinoma* or adenocarcinoma)):ti,ab,kw	4905
#3	((Oesoph* OR gastroesoph*) NEAR/3 (cancer or neoplas* or carcinoma* or adenocarcinoma)):ti,ab,kw	1485
#4	(("EG junction" OR "GE junction" OR gastroesoph* OR esophagogastric OR cardio?esoph*) NEAR/3 (cancer or neoplas* or carcinoma* or adenocarcinoma)):ti,ab,kw	901
#5	MeSH descriptor: [Esophagogastric Junction] explode all trees	442
#6	MeSH descriptor: [Neoplasms] explode all trees	79238
#7	#1 OR #2 OR #3 OR #4	5574
#8	#5 AND #6	144
#9	#7 OR #8	5582

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ID	Search	Hits
#10	MeSH descriptor: [Chemotherapy, Adjuvant] this term only	3835
#11	MeSH descriptor: [Neoadjuvant Therapy] this term only	1154
#12	MeSH descriptor: [Radiotherapy, Adjuvant] this term only	941
#13	(Adjuvant):TI,AB,KW	31068
#14	(neoadjuvant):TI,AB,KW	8560
#15	(post OR "pre" OR peri):TI,AB,KW	229025
#16	(surgery or resect* or opera* OR perioper* or preoper* OR esophagectomy OR oesophagectomy OR ablation):TI,AB,KW	268757
#17	#10 OR #11 OR #12 OR #13 OR #14	35115
#18	#15 AND #16	58312
#19	#17 OR #18	90012
#20	#9 AND #19 in CENTRAL and publication date from Aug 2019 to present	**237**

Table 55: Conference proceedings search strategy (EMBASE)

#	Search terms	Number of hits
S1	(MESH.EXACT("Esophageal Neoplasms"))	0°
S2	TI,AB(Esoph* NEAR/3 (cancer or neoplas* or carcinoma* or adenocarcinoma))	64091*
S3	TI,AB((Oesoph* OR gastroesoph*) NEAR/3 (cancer or neoplas* or carcinoma* or adenocarcinoma))	16950*
S4	(EMB.EXACT.EXPLODE("esophagus cancer"))	75056*
S5	TI,AB(("EG junction" OR "GE junction" OR gastroesoph* OR esophagogastric OR cardio?esoph*) NEAR/3 (cancer or neoplas* or carcinoma* or adenocarcinoma))	5491*
S6	MESH.EXPLODE("Esophagogastric Junction")	0°
S7	EMB.EXACT("gastroesophageal junction")	5017*
S8	MESH.EXPLODE("Neoplasms")	0°
S9	EMB.EXPLODE("malignant neoplasm")	3870132*
S10	S1 OR S2 OR S3 OR S4 OR S5	97537*
S11	S6 OR S7	5017*
S12	S8 OR S9	3870132*
S13	S11 AND S12	2705°
S14	S10 OR S13	98025*
S15	(EMB.EXACT.EXPLODE("cancer adjuvant therapy"))	127846*
S16	(EMB.EXACT("neoadjuvant chemotherapy"))	13842*
S17	(MESH.EXACT("Chemotherapy, Adjuvant"))	0°
S18	MESH.EXACT("Neoadjuvant Therapy")	0°
S19	MESH.EXACT("Radiotherapy, Adjuvant")	0°
S20	TI,AB(Adjuvant or neoadjuvant)	274512*

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#	Search terms	Number of hits
S21	TI,AB(post OR "pre" OR peri)	2171508*
S22	TI,AB(surgery or resect* or opera* OR perioper* or preoper* OR esophagectomy OR oesophagectomy OR ablation)	3536141*
S23	S15 OR S16 OR S17 OR S18 OR S19 OR S20	312810*
S24	S21 AND S22	490317*
S25	S23 OR S24	780607*
S26	TI,AB(clinical AND (trial or study or studies))	3054806*
S27	TI,AB(random*) OR TI,AB,IF(placebo*) OR TI,AB(double NEAR/1 blind*)	1762758*
S28	TI,AB("RCT")	40071*
S29	TI,AB((singl* OR doubl* OR treb* or tripl*) NEAR/1 (blind[*3] OR mask[*3]))	251574*
S30	TI,AB(placebo[*1])	321365*
S31	TI,AB(random* NEAR/2 allocated)	41980*
S32	EMB.EXACT.EXPLODE("Clinical trial")	1737706*
S33	EMB.EXACT("Controlled clinical trial")	534653*
S34	EMB.EXACT("Randomized controlled trial")	677329*
S35	EMB.EXACT.EXPLODE("Randomization")	101706*
S36	EMB.EXACT("Single blind procedure")	45867*
S37	EMB.EXACT("Double blind procedure")	184709*
S38	EMB.EXACT("Crossover procedure")	69890*
S39	EMB.EXACT("Placebo")	400204*
S40	EMB.EXACT("Multicenter study" OR "Phase 3 clinical trial" OR "Phase 4 clinical trial")	330375*
S41	EMB.EXACT("Prospective study")	677608*
S42	MESH.EXACT.EXPLODE("Randomized Controlled Trials as Topic" OR "Randomized Controlled Trial") OR MESH.EXACT.EXPLODE("Clinical Trials as Topic")	0°
S43	MESH.EXACT.EXPLODE("Random Allocation")	0°
S44	MESH.EXACT.EXPLODE("Double-Blind Method")	0°
S45	MESH.EXACT.EXPLODE("Single-Blind Method")	0°
S46	MESH.EXACT.EXPLODE("Placebos")	0°
S47	RTYPE("Clinical trial, phase i")	0°
S48	RTYPE("Clinical trial, phase ii")	0°
S49	RTYPE("Clinical trial, phase iii")	0°
S50	RTYPE("Clinical trial, phase iv")	0°
S51	RTYPE("Controlled clinical trial")	0°
S52	RTYPE("Randomized controlled trial")	0°
S53	RTYPE("Multicenter study")	0°
S54	RTYPE("Clinical trial")	0°

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#	Search terms	Number of hits
S55	TI,AB("Case control") OR TI,AB(case control NEAR/1 (study OR studies))	174793*
S56	Cohort NEAR/1 (study OR studies)	376240*
S57	TI,AB(Cohort analys*)	461506*
S58	TI,AB(Follow up NEAR/1 (study OR studies))	82219*
S59	TI,AB(Observational NEAR/1 (study OR studies))	213282*
S60	TI,AB(Longitudinal)	351583*
S61	TI,AB(Retrospective)	928833*
S62	EMB.EXACT("Clinical study")	313032*
S63	EMB.EXACT("Longitudinal study")	160787*
S64	EMB.EXACT("Retrospective study")	1017625*
S65	EMB.EXACT("Prospective study") NOT EMB.EXACT("Randomized controlled trials")	677608*
S66	EMB.EXACT("Cohort analysis")	670867*
S67	MESH.EXACT.EXPLODE("Case control studies")	0°
S68	MESH.EXACT.EXPLODE("Cohort studies")	0°
S69	S26 or S27 or S28 or S29 or S30 or S31 or S32 or S33 or S34 or S35 or S36 or S37 or S38 or S39 or S40 or S41 or S42 or S43 or S44 or S45 or S46 or S47 or S48 or S49 or S50 or S51 or S52 or S53 or S54 or S55 or S56 or S57 or S58 or S59 or S60 or S61 or S62 or S63 or S64 or S65 or S66 or S67 or S68	7182109*
S70	S14 AND S25 AND S69	7563*
S71	CFTI("Annual Meeting of the American Society of Clinical Oncology" OR "Gastrointestinal Cancers Symposium" OR "Congress of European Society for Medical Oncology" OR "Annual Meeting of the American Association for Cancer Research")	111006*
S72	S70 AND S71	493°
S73	S72 AND PD(>20180101)	**170°**

* Duplicates are removed from the search but included in the result count.

° Duplicates are removed from the search and from the result count.

Search date: 30-11-2020

Table 56: ESMO Annual Meeting search strategy – Hand searches

#	Search terms	Limits	Number of hits
1	esophageal	Limits: -Keywords -Congress 2020	43
2	Esophageal		11
3	gastroesophageal		33
4	esophagogastric		19
Total			**106**

Link sources: https://oncologypro.esmo.org/meeting-resources/esmo-virtual-congress-2020; date searched: 30-11-2020

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Table 57: AACR Annual meeting search strategy – Hand searches

#	Search terms	Limits	Number of hits
1	esophageal cancer	-Search *all* in full-text or abstract or title -Include meeting abstracts	2019: 6 2020: 3
2	oesophageal carcinoma		2019: 2 2020: 2
3	esophageal cancer		2019: 84 2020: 62
4	esophageal carcinoma		2019: 47 2020: 24
5	gastroesophageal junction		2019: 4 2020: 5
7	esophagogastric junction		2019: 1 2020: 1
Total			**241**

Link sources: https://cancerres.aacrjournals.org/content/79/13_Supplement; https://cancerres.aacrjournals.org/content/80/16_Supplement; date searched: 30-11-2020

The scope of this literature review was defined by the criteria for relevant population, intervention, comparators, outcomes and study design (PICOS). These eligibility criteria are specified in Table 58. The scope as defined by the eligibility criteria is used a guide for developing search strategies. For a publication to be included it had to match the criteria from each of the PICOS components. Any study that did not match the criteria in at least one of the PICOS components was excluded.

Table 58: Eligibility criteria for the SLR

	Inclusion criteria	Exclusion criteria
Population (P)	• Patients with local/ locoregional resectable EC or GEJC • Patients who are eligible to receive surgery and have had surgery to remove or shrink tumor • Adults (≥18 years of age)	• Patients with metastases • Pediatrics or adolescents (<18 years of age)

Interventions (I)	• Any neoadjuvant (preoperative), perioperative or adjuvant therapy
	  ○ Systemic treatment
	  ○ Radiotherapy
	  ○ Chemoradiation
		• Any treatment that is not preoperative, perioperative or postoperative, as listed in the inclusion criteria

Comparators (C)	• Any neoadjuvant, perioperative or adjuvant therapy • Surgery only • Placebo	• Any treatment that is not preoperative, perioperative or postoperative, as listed in the inclusion criteria
Outcomes (O)*	• OS • OS at 1, 2, 3 years • PFS	• Studies that do not report any of the outcomes of interest specified in the inclusion criteria

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	• DFS (or time to recurrence/relapse) • ORR • CR • PR • Safety outcomes	
Study design (S)	• RCTs** • Non-randomized prospective interventional trials*** • Observational studies*** (prospective or retrospective)	• Case reports • Systematic literature reviews and meta-analyses**** • Studies which do not have as primary objective to study treatment efficacy/safety
Publication date	• No Restriction	• N/A
Language	• English	• Non-English

Systematic selection of studies

Abstract/title review of all references were performed in double and independently by two reviewers. Any discrepancies were resolved by a third reviewer. The same process was applied for articles that were selected for full-text review. During both title/abstract and full-text screening phase, articles that were excluded were documented with reasons for their exclusion according to the pre-defined criteria. The result of the selection phase was a final list of articles that were included for data extraction and reporting.

Searches of conference proceedings were performed by a single reviewer and checked by a second reviewer. Conference abstracts which met the eligibility criteria were collated in a Microsoft Excel database and matched up to included peer-reviewed publications where relevant to determine if any additional information was provided. If the data presented in a conference abstract was available from a peer-reviewed publication the conferences abstract was excluded. If duplicate data were presented in multiple conference abstracts, only the most recent abstract was included.

The study flow diagram is provided in Figure 30.

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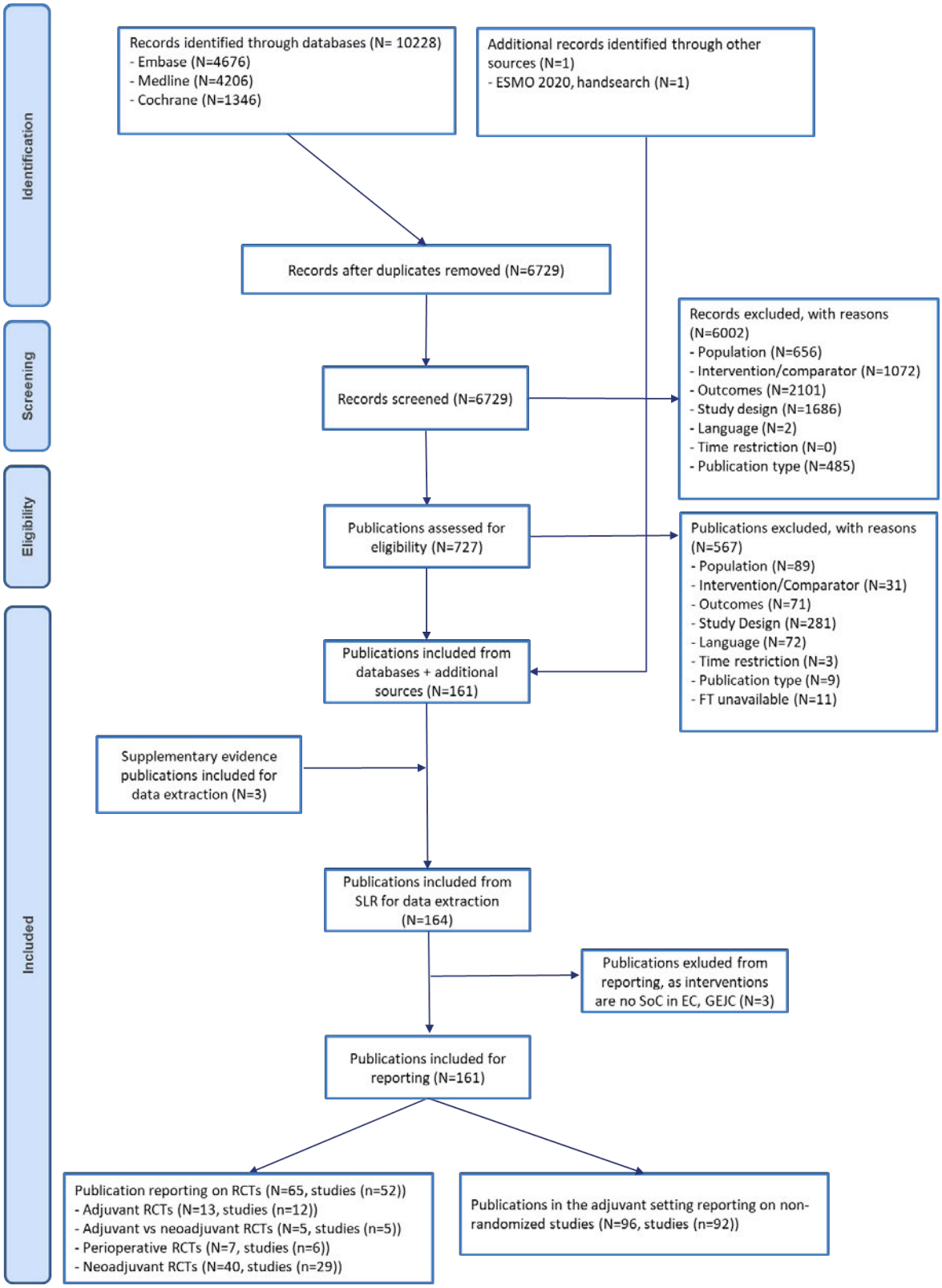
Figure 30: PRISMA flow diagram for studies assessing treatments for EC and GEJC



A total of 10,228 publications were identified via the search engine databases (see Figure 30) during the original and update searches. Following the removal of duplicates (N=3,449), the title and abstracts of 6,729 were screened for eligibility. After excluding 6,002 publications based on title and abstract screening, 727 publications were eligible for full-text screening based on the pre-specified criteria. A total of 567 publications were excluded after full-text screening. Reason for exclusion were due to ineligibility of population (N=89), intervention/comparator (N=31), outcomes (N=71), study design (N=271), language (N=72), time restriction (N=3), publication type (N=9) and publication unavailable (N=11). In addition to the search engine databases, one abstract from ESMO 2020 was identified via a hand search and included in this SLR. Therefore, a total of 161 publications from database searches were considered relevant for this clinical SLR. On top of these 161 publications three additional publications were included as supplementary evidence. This resulted in a total of 164 publications relevant for data extraction. All 164 publications have been extracted, however for reporting purposes three publications have been excluded as they report on RCTs that assess interventions (i.e. statins and low molecular weight heparins) that are not considered to be relevant treatment options in EC and GEJC at the moment. As a result, a total of 161 publications are included in this report. Of these, 65 publications report on RCTs in the adjuvant, perioperative and neoadjuvant setting and 96 publications report on non-randomized studies in the adjuvant setting.

Quality assessment

According to the National Institute for Health and Care Excellence (NICE) requirements, as part of any SLR, RCTs should be subjected to a Quality Assessment (QA) using a recommended checklist. The QA checklist for RCTs from the Centre for Reviews and Dissemination (CRD) Guidance for Undertaking Reviews in Health Care (2009) was applied for QA. One reviewer conducted the QA of included articles; a second reviewer checked the accuracy of QA performed for all relevant articles. There was no QA conducted for the non-randomized prospective interventional studies or for conference proceedings.

Unpublished data

N/A

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Appendix B: Main characteristics of included studies

Trial name: CheckMate 577	NCT number: NCT02743494
Objective	The primary objective of this study is to compare DFS of nivolumab versus placebo in subjects with resected EC or GEJC.
Publications – title, author, journal, year	• Kelly RJ, Ajani JA, Kuzdzal J, et al. LBA9_PR Adjuvant nivolumab in resected esophageal or gastroesophageal junction cancer (EC/GEJC) following neoadjuvant chemoradiation therapy (CRT): First results of the CheckMate 577 study. Ann Oncol. 2020;31(suppl4):S1193–S1194. • Kelly RJ, Ajani JA, Kuzdzal J, et al. Adjuvant nivolumab in resected esophageal or gastroesophageal junction cancer. N Engl J Med. 2021;384(13):1191–1203.
Study type and design	CheckMate 577 was a global Phase 3, randomised, double-blind, placebo-controlled trial. The study was conducted at 170 study locations across 29 countries, including at one site in Denmark. Patients were randomised in a 2:1 ratio to receive either nivolumab or placebo monotherapy. Randomisation was stratified by tumour cell PD-L1 expression (≥1% vs. <1% or indeterminate or could not be evaluated), pathological lymph node status (positive ≥ypN1 vs. negative ypN0) and histology (adenocarcinoma vs. squamous).
Sample size (n)	794 randomised patients
Main inclusion and exclusion criteria	Inclusion Criteria: • Diagnosed with Stage II/III carcinoma of the esophagus or gastroesophageal junction • Completed pre-operative chemo radiotherapy followed by surgery • Diagnosed with residual pathologic disease after being surgically rendered free of disease with negative margins following complete resection Exclusion Criteria: • Diagnosed with cervical esophageal carcinoma • Diagnosed with Stage IV resectable disease • Did not receive concurrent chemoradiotherapy prior to surgery • Participants who have received a live/attenuated vaccine within 30 days of the first treatment
Intervention	Nivolumab 240 mg intravenous (IV) infusion over 30 minutes every 2 weeks (Q2W) for 16 weeks (Cycles 1-8) followed by nivolumab 480 mg IV infusion over 30 minutes every 4 weeks (Q4W) beginning at Week 17 (2 weeks after the 8th dose) [Cycles 9-17] for a total duration of 1 year.
Comparator(s)	Subjects randomised to the placebo arm received placebo IV infusion over 30 minutes according to the same dosing schedule as nivolumab
Follow-up time	Preliminary analysis: median follow-up 24.4 months (data cut-off, July 3, 2020) Follow-up, ad hoc analysis: median follow-up 32.2 months (data cut-off, February 18, 2021)

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Trial name: CheckMate 577	NCT number: NCT02743494
Is the study used in the health economic model?	Yes
Primary, secondary and exploratory endpoints	**Endpoints included in this application:** The primary endpoint in the study was disease-free survival (DFS), which was defined as the time between the date of randomisation and the first date of recurrence or death, whichever occurred first, prior to subsequent anticancer therapy. Exploratory endpoints include distant metastasis-free survival (DMFS), safety and tolerability, and health-related quality of life (HRQoL) as assessed by the European Quality of life-5 Dimensions questionnaire (EQ-5D-3L), and Functional assessment of Cancer Therapy-Esophageal (FACT-E). **Other endpoints:** Overall survival was a secondary endpoint but results are not included in this application as the OS data were not mature and did not meet the pre-specified boundary for declaring statistical significance of 0.003 at the time of the prespecified interim analysis of the primary endpoint. OS data are expected in 2022. Other exploratory endpoints included immunogenecity, PK/exposure response, Esophageal Cancer Subscale (ECS), and FACT-G7, and PFS2; results are not included in this application.
Method of analysis	For the DFS primary endpoint, at least 440 events were required to achieve approximately 91% power to detect an average hazard ratio of 0.72 at a two-sided α of 0.05. Pre-specified interim analysis was triggered when at least 85% of the 440 events were observed; the boundary for statistical significance at this interim analysis was P<0.036. DFS was compared between treatment arms using the two-sided log rank test, stratified by the three randomisation stratification factors (see section 4.3.1 for stratification factors). The hazard ratio with its corresponding two-sided 100 x (1-adjusted α) CIs was estimated using a stratified Cox proportional hazards model with treatment arm as the only covariate in the model. The Kaplan-Meier method was used to estimate and plot DFS for both treatment arms, a two-sided 95% CI for median DFS was also calculated using both the Kaplan-Meier method as well as the log-log transformation method (Kelly 2021). For the analysis of patient-reported outcomes, longitudinal mixed model analysis was used to compare the least squares mean differences between treatment groups (Kelly 2021).
Subgroup analyses	Prespecified subgroups included age, sex, race, region, disease type, disease stage at initial diagnosis, histological grade, lymph node status, pathologic tumour status, time from beginning neoadjuvant CRT to complete resection, time from complete resection to randomisation, HER-2 status, and PD-L1 status.
Other relevant information	n/a

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

N/A

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Appendix D: Efficacy and safety results per study

Definition, validity and clinical relevance of included outcome measures

Efficacy

[redacted]

Safety

[redacted]

PROs

[redacted]

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Results per study

Table A3a Results of CheckMate577 (NCT02743494)

Outcome	Study arm	N	Result (CI)	Estimated relative difference in effect			Description of methods used for estimation	References
				Difference	95% CI	*P* value		
[redacted]								
Median DFS (median 24.4 months follow-up)	Nivolumab	532	22.4 (16.6–34.0) months	HR: 0.69	96.4% CI: 0.56–0.86	<0.001	Median DFS in the ITT population was computed using the K-M estimate and a 95% CI for the median was computed based on a log-log transformation of the survivor function. The HR for DFS with its corresponding alpha-adjusted 2-sided 96.4% confidence interval (CI) was estimated via a stratified Cox model with treatment arm as the only covariate in the model. Adjustment on the CI was based on the actual alpha level.	Kelly et al. 2021
	Placebo	262	11.0 (8.3–14.3) months					
6-month DFS	Nivolumab	532	72% (68–76)	-	-	-	DFS rates at 6 months in the ITT population for each treatment arm were derived from the K-M estimate and their corresponding CIs were derived based on the Greenwood formula for variance derivation and on	Kelly et al. 2021
	Placebo	262	63% (57–69)					

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Outcome	Study arm	N	Result (CI)	Estimated relative difference in effect			Description of methods used for estimation	References
				Difference	95% CI	*P* value		
							log-log transformation applied on the survivor function.	
Median DMFS (median 24.4 months follow-up)	Nivolumab	532	28.3 (21.3–NE) months	HR: 0.74	0.60–0.92	-	DMFS for each treatment arm was estimated and plotted using the K-M product-limit method. Median survival time was computed using the K-M estimate and a 95% CI for the median was computed based on a log-log transformation of the survivor function. The HR for DMFS with its corresponding 2-sided 95% CI was estimated via a stratified Cox model with treatment arm as the only covariate in the model.	Kelly et al. 2021
	Placebo	262	17.6 (12.5–25.4) months					
Median OS	Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Placebo	[redacted]	[redacted]					
Any AEs, n (%) (median 24.4 months follow-up)	Nivolumab	532	510 (96)	-	-	-	Safety analyses were performed in all treated subjects. Descriptive statistics of safety were presented using NCI CTCAE version 4 by treatment group.	Kelly et al. 2021
	Placebo	260	243 (93)					

Outcome	Study arm	N	Result (CI)	Estimated relative difference in effect			Description of methods used for estimation	References
				Difference	95% CI	*P* value		
[redacted]								
Any Grade 3 or 4 AEs, n (%) (median 24.4 months follow-up)	Nivolumab	532	183 (34)	-	-	-		Kelly et al. 2021
	Placebo	260	84 (20)					
[redacted]								
Any TRAEs, n (%) (median 24.4 months follow-up)	Nivolumab	532	376 (71)	-	-	-		Kelly et al. 2021
	Placebo	260	119 (46)					
[redacted]								

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Outcome	Study arm	N	Result (CI)	Estimated relative difference in effect			Description of methods used for estimation	References
				Difference	95% CI	*P* value		
Any treatment-related Grade 3 or 4 AEs, n (%) (median 24.4 months follow-up)	Nivolumab	532	71 (13)	-	-	-		Kelly et al. 2021
	Placebo	260	15 (6)					
[redacted]								

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Appendix E: Safety data for intervention and comparator(s)

The safety data for the intervention and the comparators are described in Appendix D.

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Appendix F: Comparative analysis of efficacy and safety

N/A

Appendix G: Extrapolation

To determine the most appropriate parametric function to extrapolate DFS, alternative methods of parametric analyses were explored. These included:

- **Standard parametric models** (7 parametric models in total): standard parametric models included exponential, weibull, gompertz, log-logistic, log normal, gamma, and generalized gamma
- **Spline parametric models** (15 parametric models in total): spline models are "structurally flexible" extensions of the standard parametric distributions. They are similar to piecewise models as they are flexible mathematical functions defined by piecewise polynomials joined at points on the x-axis (time) known as knots. Spline models were fit on three different scales: hazards, odds, and normal. Within each scale, spline models with up to 5-knots were evaluated.
- **Fractional polynomial models** (10 parametric models in total): Fractional polynomial models, as outlined by Ouwens et al 2010 and Jansen et al 2015, provide an alternative to splines where the hazard functions of the interventions in a trial are modeled using known parametric survival functions or fractional polynomials (Ouwens 2010, Jansen 2015). Second order fractional polynomials allowing p1=0 or 1 and p2=-1, -0.5, 0, 0.5, or 1 were fit (Jansen 2015). In essence, these second order fractional polynomial models are extensions of the Weibull and Gompertz models and allow arc- and bathtub shaped hazard functions, which emulate parametric distributions such as log-logistic and log normal.
- **Piecewise models** (14 parametric models in total): the use of Kaplan-Meier data up to 3-months and 6-months followed by standard parametric models

The formulas used to derive these parametric models are presented in Table 59. The model fits to CheckMate 577 DFS data is presented in Figure 31, Figure 32, Figure 33, Figure 34, Figure 35, Figure 36, and Figure 37.

Table 59: Summary of candidate survival models for disease-free survival

Model description	Model	Characteristic
Standard parametric models		
Exponential	$s(t) = \exp(-\lambda x)$	Constant hazard function; proportional hazards model
Weibull	$S(t) = \exp\left(-\left(\frac{x}{b}\right)^{a}\right)$	Hazard function can increase or decrease monotonically over time; proportional hazards (or accelerated failure time)
Gompertz	$s(t) = \exp\left(-\frac{b}{a}(\exp(ax) - 1)\right)$	Hazard function can increase or decrease monotonically over time; proportional hazards
Log normal	$s(t) = 1 - \Phi\left(\frac{\log(x) - \mu}{\sigma}\right)$	Hazard function increases initially to a maximum before decreasing over time
Log logistic	$s(t) = 1 - \frac{1}{1 + \left(\frac{x}{\alpha}\right)^{-\beta}}$	Hazard function can be non-monotonic with respect to time; accelerated failure time. Log-logistic models often result in long tails in the survivor function

Gamma	$f(t) = \frac{1}{\left(b^a\,\Gamma(a)\right)} t^{(a-1)} e^{-\left(\frac{t}{b}\right)}$	Hazard function can increase or decrease monotonically over time; proportional hazards
Generalized gamma	$f(x) = \lvert Q\rvert (Q^{-2})^{Q^{-2}} \frac{1}{\sigma x \Gamma(Q^{-2})} \exp\left(Q^{-2}(Qw - e^{Qw})\right)$ $x = \exp(\mu + \sigma w)$	Flexible 3-parameter model and can be generalized to the Weibull, exponential, and log-normal distributions
Flexible parametric models (splines)		
Hazards spline	$\ln O\,(x) = s(x,\gamma) + \beta$ $S(x,\gamma) = \gamma_0 + \gamma_1 x + \gamma_2 V_1(x) + \cdots \gamma_{m+1} V_m(x)$ $V(x) = (x-k_j)_+^3 - \lambda_j (x-k_{min})_+^3 - (1-\lambda_j)(x-k_{max})_+^3$ $\lambda_j = \frac{k_{max}-k_j}{k_{max}-k_{min}}$ $(x-a)_+ = \max(0, x-a)$	Up to 5-knot models were fitted to the trial data where the knots were evenly distributed over the time horizon of the study follow-up, based on the default settings of the flexsurv package
Odds spline	$\ln H(x) = s(x,\gamma) + \beta$ $S(x,\gamma) = \gamma_0 + \gamma_1 x + \gamma_2 V_1(x) + \cdots \gamma_{m+1} V_m(x)$ $V(x) = (x-k_j)_+^3 - \lambda_j (x-k_{min})_+^3 - (1-\lambda_j)(x-k_{max})_+^3$ $\lambda_j = \frac{k_{max}-k_j}{k_{max}-k_{min}}$ $(x-a)_+ = \max(0, x-a)$	
Spline with probit link function	$-\Phi^{-1}[S(x)] = s(x,\gamma) + \beta$ $S(x,\gamma) = \gamma_0 + \gamma_1 x + \gamma_2 V_1(x) + \cdots \gamma_{m+1} V_m(x)$ $V(x) = (x-k_j)_+^3 - \lambda_j (x-k_{min})_+^3 - (1-\lambda_j)(x-k_{max})_+^3$ $\lambda_j = \frac{k_{max}-k_j}{k_{max}-k_{min}}$ $(x-a)_+ = \max(0, x-a)$	
Fractional polynomial models		
Fractional polynomials	$\ln h(x) = \mu_0 + t^{p1}\mu_1 + t^{p2}\mu_2$	Fractional polynomial models tested included all combinations of p1={0, 1} and p2={-1, -0.5, 0, 0.5, 1}.

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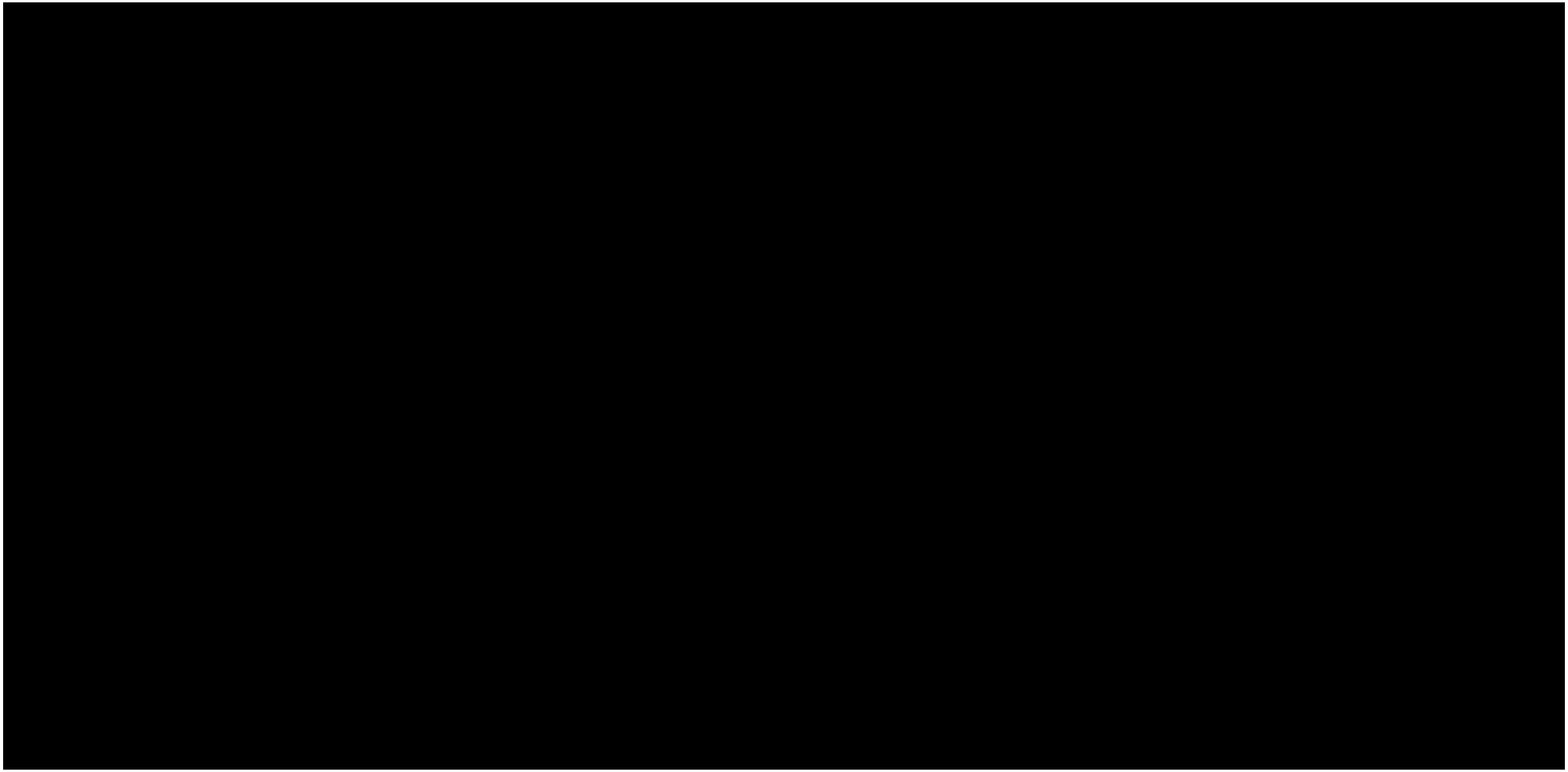

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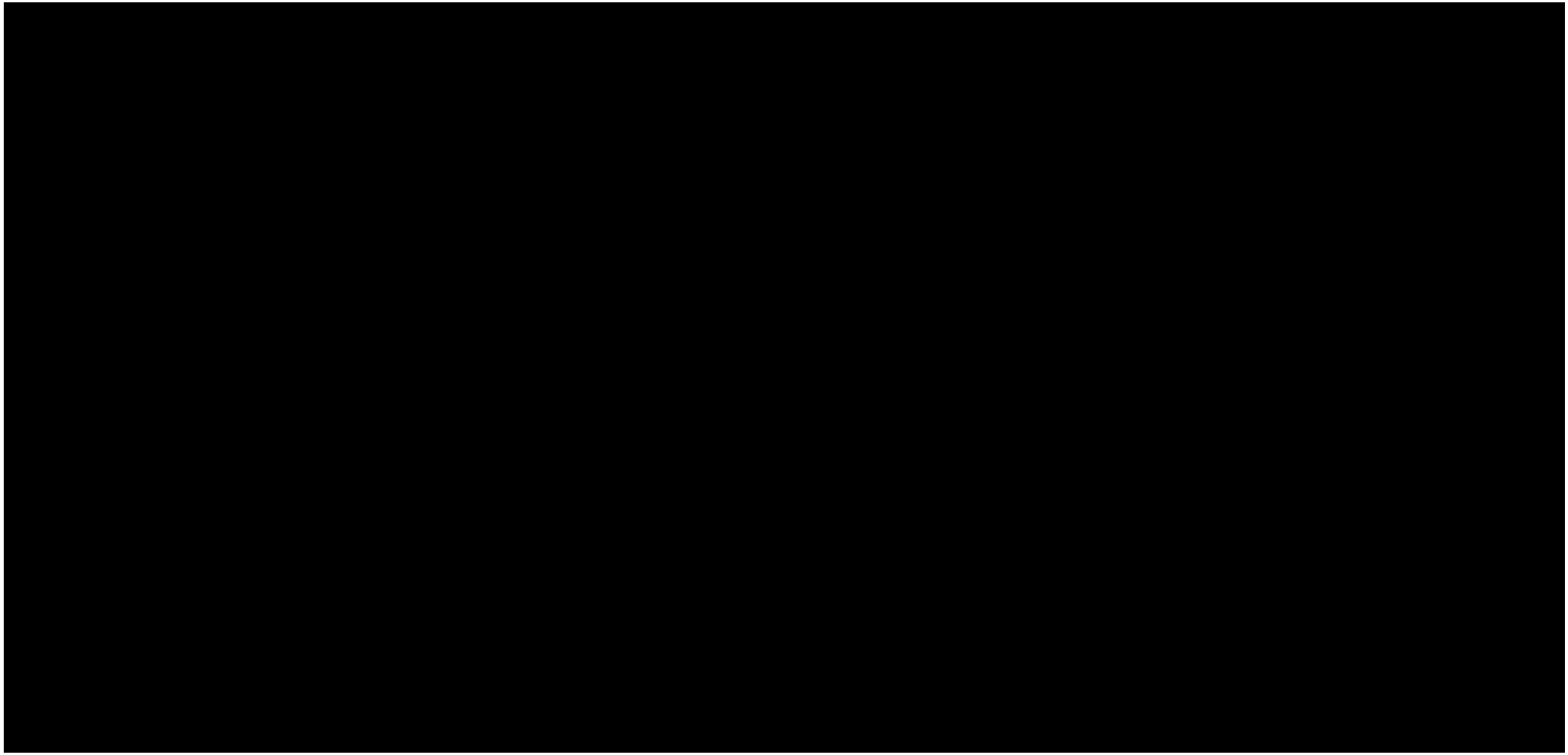

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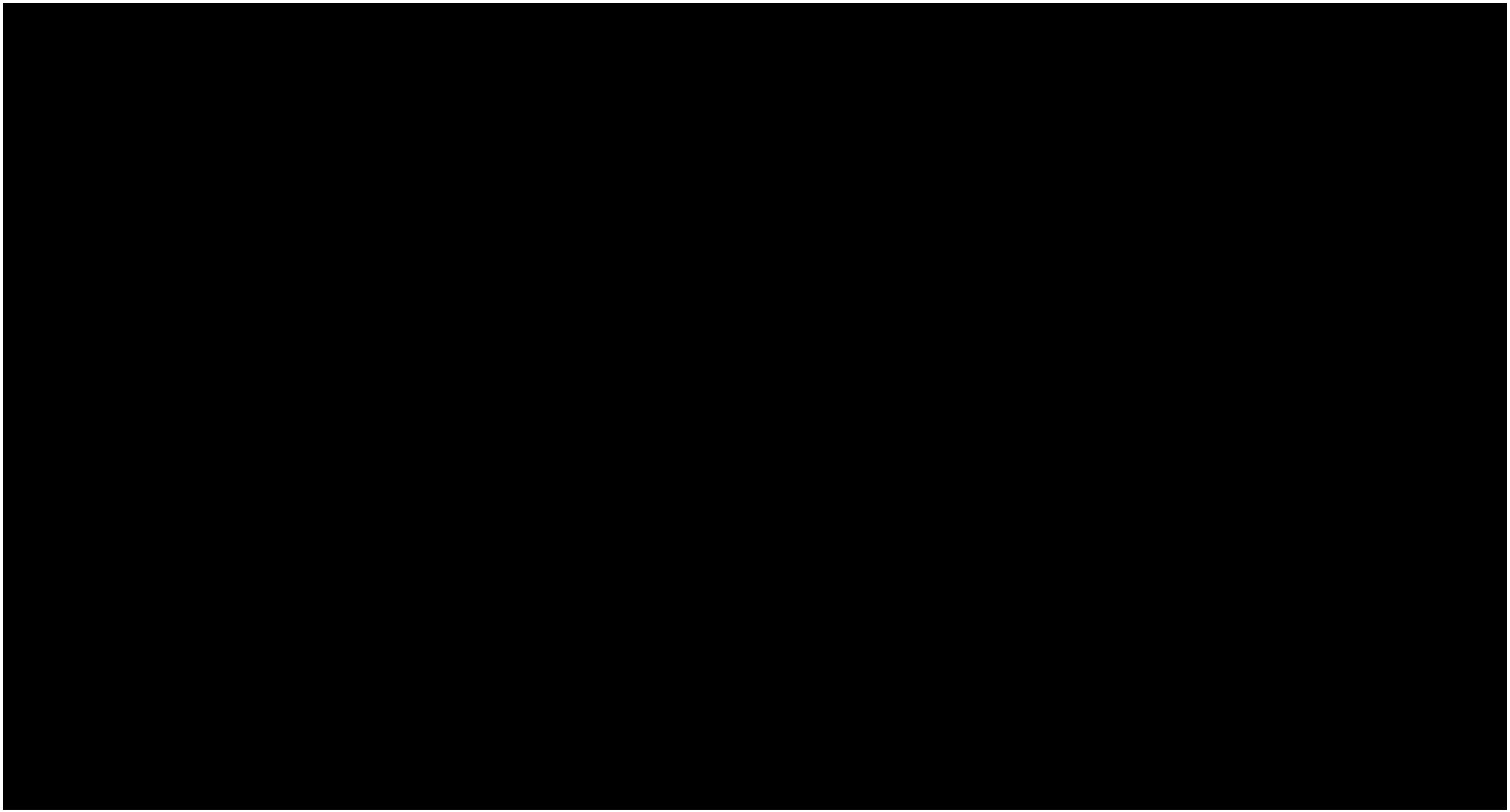

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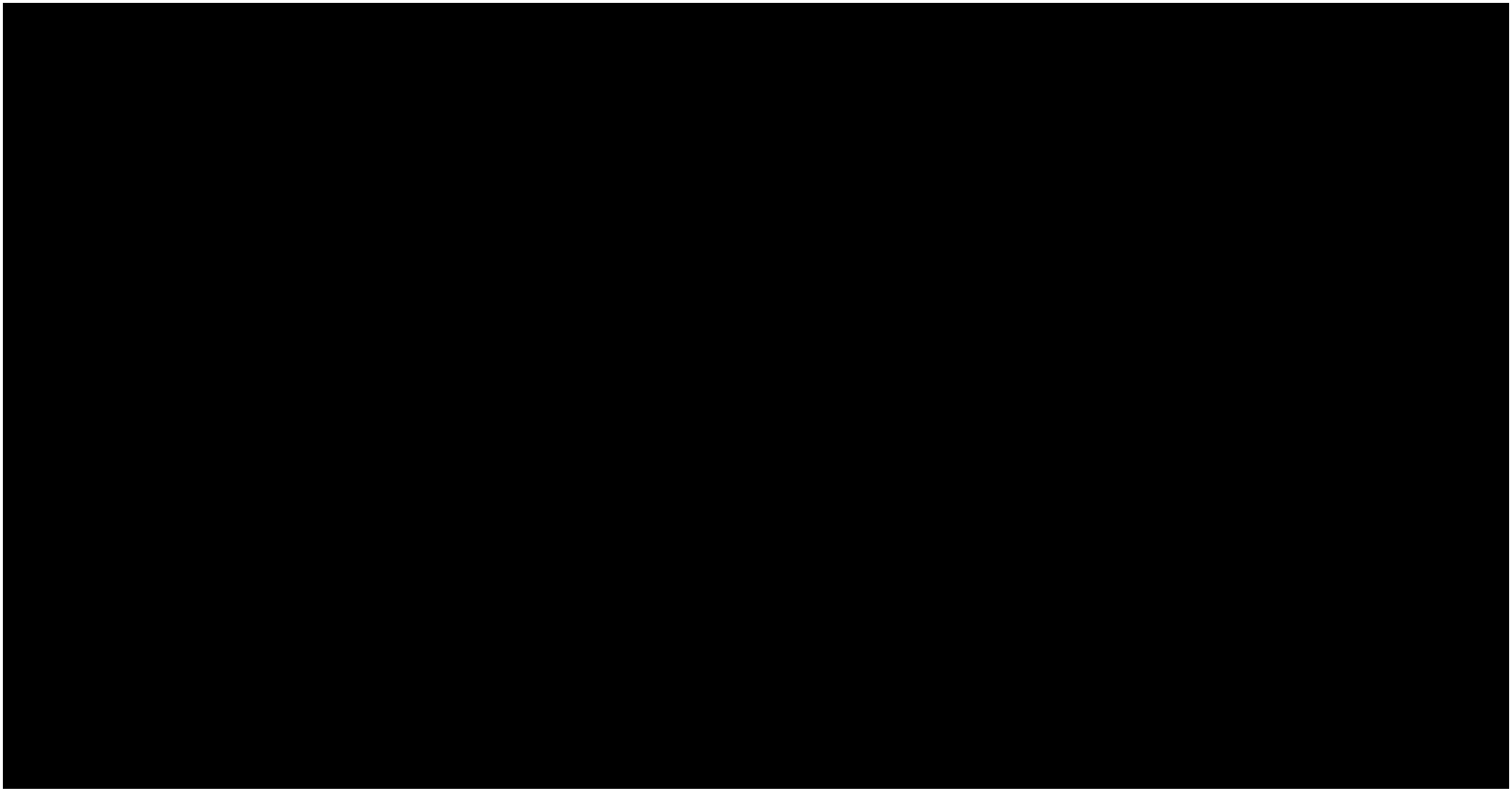

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Appendix H: Literature search for HRQoL data

HRQoL data were identified as part of a SLR conducted to collect economic evidence as input for the development of cost-effective models for adjuvant nivolumab in resectable EC or GEJC patients. For a comprehensive description of the SLR, please see the economic SLR document attached with this submission.

Search strategy

The selected databases to collect economic evidence are presented in Table 60. The Embase, Medline and EconLit databases were searched by means of the ProQuest engine. This search engine allows for these databases to be searched simultaneously and removes duplicates between databases. The search in the NHS EED and HTA databases were considered for phase I, but not for phase II, given that these databases have not been updated since the original search.

Table 60: Economic SLR databases

		Phase 1	Phase 2
Database	**Search engine**	**Search date***	**Search date**
Embase	ProQuest	26 September 2019	30 November/ 1 December 2020
Medline (in-Process)	ProQuest	26 September 2019	30 November/ 1 December 2020
EconLit	ProQuest	26 September 2019	30 November/ 1 December 2020
NHS EED**	CRD	26 September 2019	N/A
HTA***	CRD	26 September 2019	N/A

* No time restriction was used during the original searches ** The NHS EED database is no longer updated since 31 March 2015. Therefore, no update search was required in phase II. *** The HTA database is no longer updated since 31 March 2018. Therefore, no update search was required in phase II.

Abbreviations: CRD: Centre for Reviews and Dissemination; HTA: Health Technology Assessment; N/A: Not Applicable, NHS EED: National Health Service Economic Evaluation Database

A search of the following proceedings from the previous 2 years (2018-2020) was conducted:

- American Society of Clinical Oncology (ASCO) Annual Meeting
- ASCO Gastrointestinal Cancers (GI) Meeting
- European Society for Medical Oncology (ESMO) Annual Meeting
- American Association for Cancer Research (AACR) Annual Meeting
- International Society for Pharmacoeconomics and Outcomes (ISPOR) EU and US Annual Meetings

The searches for conference proceedings were independent of those conducted for peer-reviewed publications. Conference proceedings that are indexed in Embase were searched electronically, using the same search strategy as for the peer-reviewed publications. Conferences that were not indexed in Embase were "hand-searched" using EC, GEJC and search terms in whichever format was provided by the conference (e.g. PDF booklet, online search portal).

Additional searches were performed on the websites of HTA authorities to retrieve critical appraisals and key learnings from previous assessments. To identify relevant articles, search terms for EC, GEJC and GC were used in the website's search engines. HTA authorities considered for inclusion in the SLR were:

- National Institute of Health and Care Excellence (NICE)
- Scottish Medicines Consortium (SMC)
- Haute Autorité de Santé (HAS)
- Canadian Agency for Drugs and Technologies in Health (CADTH)
- Pharmaceutical Benefits Advisory Committee (PBAC)

Please see the economic SLR document for the full search strings used to identify relevant HRQoL data.

The scope of this literature review was defined by the criteria for relevant population, intervention, comparators, outcomes and study design (PICOS). These eligibility criteria are specified in Table 61. The scope, as defined by the eligibility criteria, is used as a guide for developing search strategies. For a publication to be included it had to match the criteria from each of the PICOS components. Any study that did not match the criteria in at least one of the PICOS components was excluded.

Table 61: PICOS criteria

	Inclusion criteria	Exclusion criteria
Population (P)	• Patients with local/ locoregional resectable EC, GEJC and GC* • Patients who are eligible to receive surgery and have had surgery to remove or shrink tumor Adults (≥18 years of age)	• Patients with metastases • Pediatrics or adolescents (<18 years of age)
Interventions (I)	N/A	N/A
Comparators (C)	N/A	N/A

Outcomes (O)	**Economic models**
	• (Incremental) QALYs
	• (Incremental) LY
	• Cost/QALY
	• Cost/LY
	• Cost-benefit
	• Net present benefit
	Resource use and costs
	• Frequency of resource use
	  ○ Hospitalization/ Inpatient days
	  ○ ER visits
	  ○ Outpatient visits
	• Medication use
	• Cost per visits
	• Cost per treatment
	• Indirect costs
	• Societal costs
	Utilities/HRQoL
	• Utilities
	• QoL questionnaire results that can be mapped to utilities
		• Studies that do not report any of the outcomes of interest specified in the inclusion criteria

Study design (S)	**Economic models** • Cost-effectiveness models	• Systematic reviews** • Study designs other than specified in the inclusion criteria

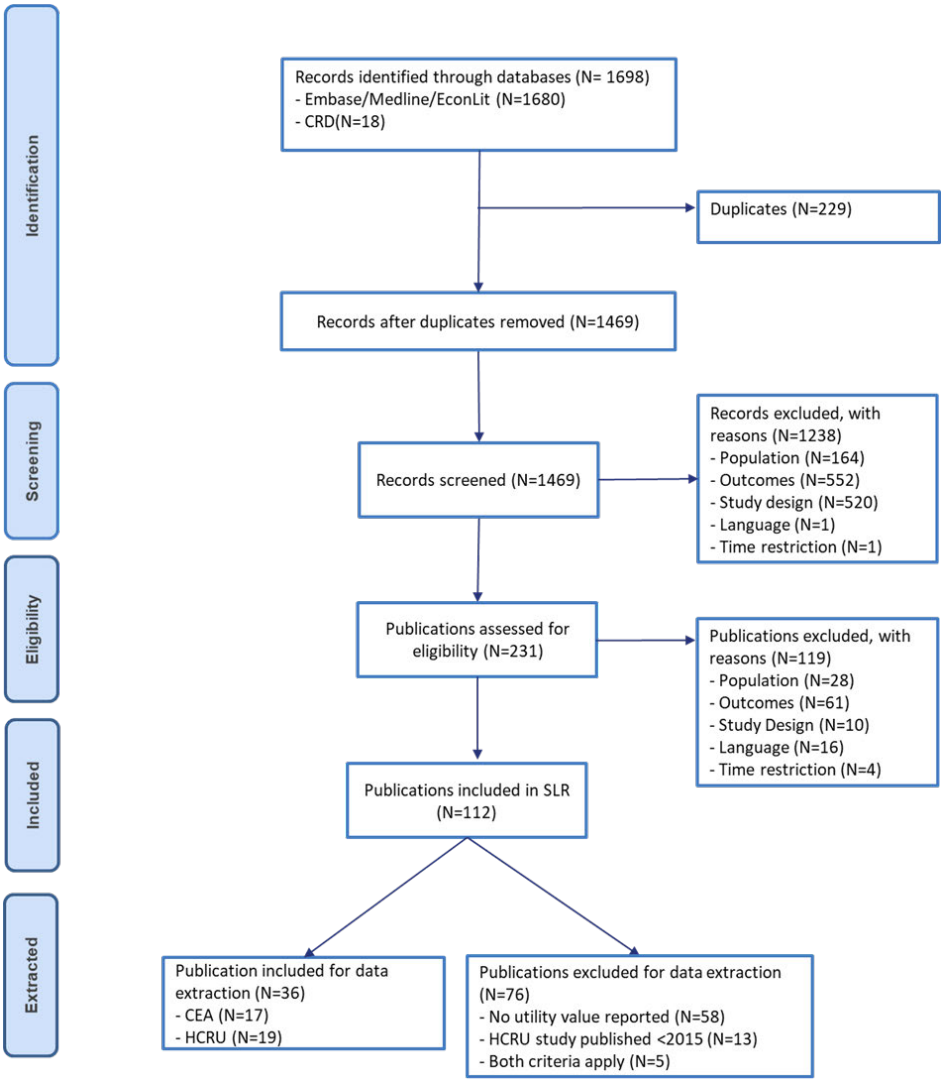
	• Cost-utility models • Cost-benefit models • Budget impact models **Resource use and costs & utilities/HRQoL** <u>Economic models</u> • Cost-effectiveness models • Cost-utility models • Cost-benefit models • Budget impact models <u>Observational studies</u> • Non-randomized study • Single arm study • Follow-up study • Disease registry • Patient chart analysis • Database analysis	
		•
Publication date	No restriction	N/A
Language	• English	• Non-English

* Publications on economic models in resectable GC were eligible for inclusion. HCRU and utility studies for GC were not eligible for inclusion. **Systematic literature reviews were not included for data extraction but references of the five most recent (date)/relevant (impact factor journal) have been screened to check for any missed references.

Abbreviations: EC: esophageal cancer; ER: emergency room; GC, gastric cancer; GEJC: gastroesophageal junction cancer; HRQoL: health related quality of life; LY: life year; N/A: not applicable; QALY: quality adjusted life year; QoL: quality of life;

The initial database searches were conducted on the 26th of September 2019, with an update conducted on 30th of November 2020 (Figure 38). A total of 1,698 publications were identified. Following the removal of duplicates (N=229), the title and abstracts of 1,469 were screened for eligibility. After excluding 1,238 publications based on title and abstract screening, 231 were eligible for full-text screening based on the pre-specified criteria. A total of 119 were excluded after full-text screening. Reason for exclusion were due to ineligibility of population (N=28), outcomes (N=61), study design (N=10), language (N=16) and time restriction (N=4). This results in a total of 112 publications relevant for inclusion in this economic SLR. Of these 112 publications, 76 publications were not considered relevant for data extraction because of the following criteria: no utility values reported (N=58), the healthcare resource use and cost study was published prior to 2015 (N=13) or both criteria applied (N=5). Therefore, a total of 36 publications were finally included for data extraction. Of these publications, 17 publications reported on a cost-effectiveness analysis (CEA) and 19 publications on HCRU and costs in the population of interest.

Figure 38: PRISMA diagram



The SLR did not identify any original publications reporting on health state utility values. However, the included economic models present utility data that has been used as input to populate the economic models. Please see the economic SLR document attached to this submission for detailed information on studies identified which presented utility data.

Quality assessment and generalisability of estimates

According to the National Institute for Health and Care Excellence (NICE) requirements, as part of any SLR, economic models should be subjected to a Quality Assessment (QA) using a recommended checklist. The Drummond checklist was applied for QA of economic models. One reviewer conducted the QA of included articles; a second reviewer checked the accuracy of QA performed for all relevant articles.

No explicit QA was conducted for HRQoL values for adverse events. These were sourced from identified literature including international research, hence their generalizability to a Danish setting could be questioned. However, considering the very minor impact that the HRQoL values for adverse events have on this analysis, the effect of using Danish-specific values instead would be negligible. By contrast, the HRQoL values used for disease progression were based upon a Danish value set, in line with DMC guidelines (see Appendix I for more details).

Also, as the cost-effectiveness models included in this submission is including HRQoL values mapped to EQ-5D-5L and is based upon a Danish value set, an elaborated discussion comparing the outcomes of the literature review and the data from the trial, is not meaningful.

Unpublished data

N/A

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Appendix I: Mapping of HRQoL data

The five-level version of the EQ-5D (EQ-5D-5L) is the recommended version to be used for estimation of quality-adjusted life years (QALYs) in the latest Danish guidelines for the economic evaluation of new treatments.(Medicinrådet 11/19/2020, Jensen 2021b) In the absence of EQ-5D-5L data in CheckMate 577, the parametric predictive model (van Hout and Shaw cross-walk) using the EQ-5D-5L Danish value set (Jensen 2021b) was implemented to generate utility estimates based on the existing CheckMate 142 EQ-5D-3L data.

For each EQ-5D-3L assessment, the health state (e.g., 11111 or 33333) was converted into index values by using the value sets mapped from the EQ-5D-5L Danish value set (Jensen 2021b) and applying the parametric predictive model (van Hout and Shaw) method (van Hout).

The index value obtained for each individual assessment was then used in the modelling to estimate the mean utility values within the health states of interest (i.e., pre-/post-progression and on/off treatment).

The results of the utility analysis by health state generated using parametric mapping for Denmark are presented in Table 62

Table 62: Overall, Recurrence-based, and Time-to-event-based LS Mean Estimates (Denmark, Model without Treatment)

	Health State	Overall	
		EQ-5D-3L Value Set	Parametric van Hout 5L Mapping
Overall LS means (95% CI)	All data (overall)	[redacted]	[redacted]
Recurrence models: LS means (95% CI)	Pre-recurrence	[redacted]	[redacted]
	Post- recurrence: overall	[redacted]	[redacted]
	Post- recurrence: distant recurrence	[redacted]	[redacted]
	Post- recurrence: local/ regional recurrence	[redacted]	[redacted]
TTD model: LS means (95% CI)	Overall	[redacted]	[redacted]
	>52 weeks	[redacted]	[redacted]
	27–52 weeks	[redacted]	[redacted]
	5–26 weeks	[redacted]	[redacted]
	≤4 weeks	[redacted]	[redacted]

Abbreviations: CI=confidence internal; LS=least squares; UI=utility index

Table 63: Overall, Recurrence-based, and Time-to-event-based LS Mean Estimates (Denmark, Model with Treatment)

	Health State	Nivolumab		Placebo	
		EQ-5D-3L Value Set	Parametric van Hout 5L Mapping	EQ-5D-3L Value Set	Parametric van Hout 5L Mapping
Overall LS means (95% CI)	All data (overall)	[redacted]	[redacted]	[redacted]	[redacted]
Recurrence models: LS means (95% CI)	Pre-recurrence	[redacted]	[redacted]	[redacted]	[redacted]
	Post- recurrence: overall	[redacted]	[redacted]	[redacted]	[redacted]

	Health State	Nivolumab		Placebo	
		EQ-5D-3L Value Set	Parametric van Hout 5L Mapping	EQ-5D-3L Value Set	Parametric van Hout 5L Mapping
	Post- recurrence: distant recurrence	[redacted]	[redacted]	[redacted]	[redacted]
	Post- recurrence: local/ regional recurrence	[redacted]	[redacted]	[redacted]	[redacted]
TTD model: LS means (95% CI)	Overall	[redacted]	[redacted]	[redacted]	[redacted]
	>52 weeks	[redacted]	[redacted]	[redacted]	[redacted]
	27–52 weeks	[redacted]	[redacted]	[redacted]	[redacted]
	5–26 weeks	[redacted]	[redacted]	[redacted]	[redacted]
	≤4 weeks	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI=confidence internal; LS=least squares; UI=utility index

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Appendix J: Probabilistic sensitivity analyses

See section 8.7.2

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Appendix K: EQ-5D Utility Analyses: Denmark

Please see attached the supplementary appendix document, which presents utility, specific to the Danish setting:

- Appendix K - Utility Analysis v4.0 Denmark

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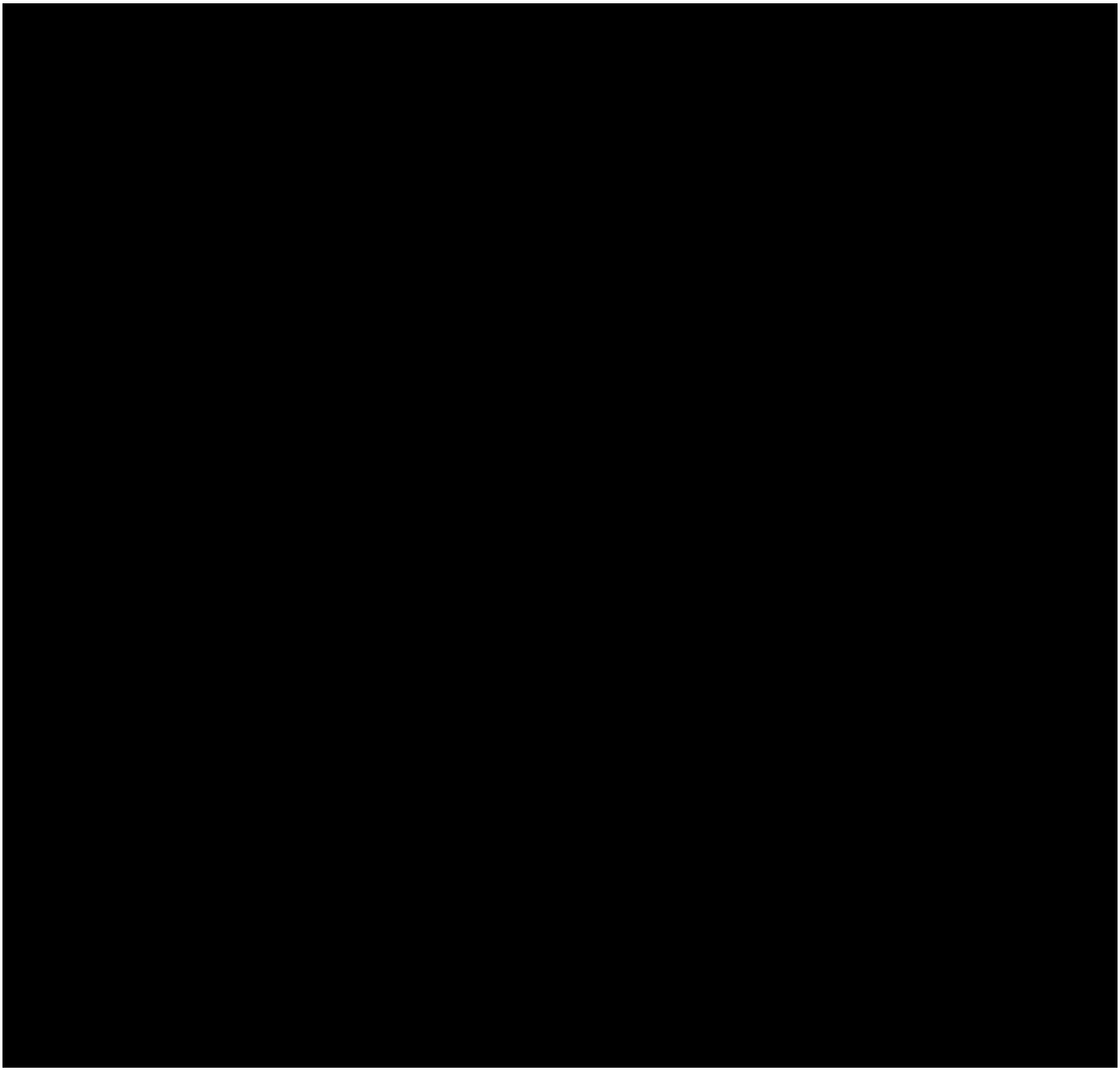
Appendix L: Smoothed Hazard Curves

Presentation of hazards over time are traditionally smoothed as they are used to illustrate trends. Three types of hazard plots were explored for the current analyses: those with default smoothing (described hereafter as default knots; 32 knots with muhaz function in R), less smoothing (described hereafter as increased knots; n/2 knots with muhaz function in R), and unsmoothed (hazards at monthly intervals manually calculated from -log[1-r/n] where r is the number of events in the interval and n is the number at risk at the start of the interval). Unsmoothed hazards and hazards (default knots) are presented in Figure 39 to Figure 42. As piecewise models are fit to data after the specified cut point, resulting smoothed hazards may be different than for smoothed hazards including all data. As such, the hazards for the three-month cut points for the piecewise models for nivolumab and surveillance are presented in Figure 43 and Figure 44, respectively. The hazards for the six-month cut points for the piecewise models are presented for nivolumab and surveillance in Figure 45 and Figure 46, respectively. Figure 47 to Figure 58 presents the smoothed hazard plots of the observed data from the clinical study with plots of the hazard function for all the parametric functions included in the same figure, per treatment arm.



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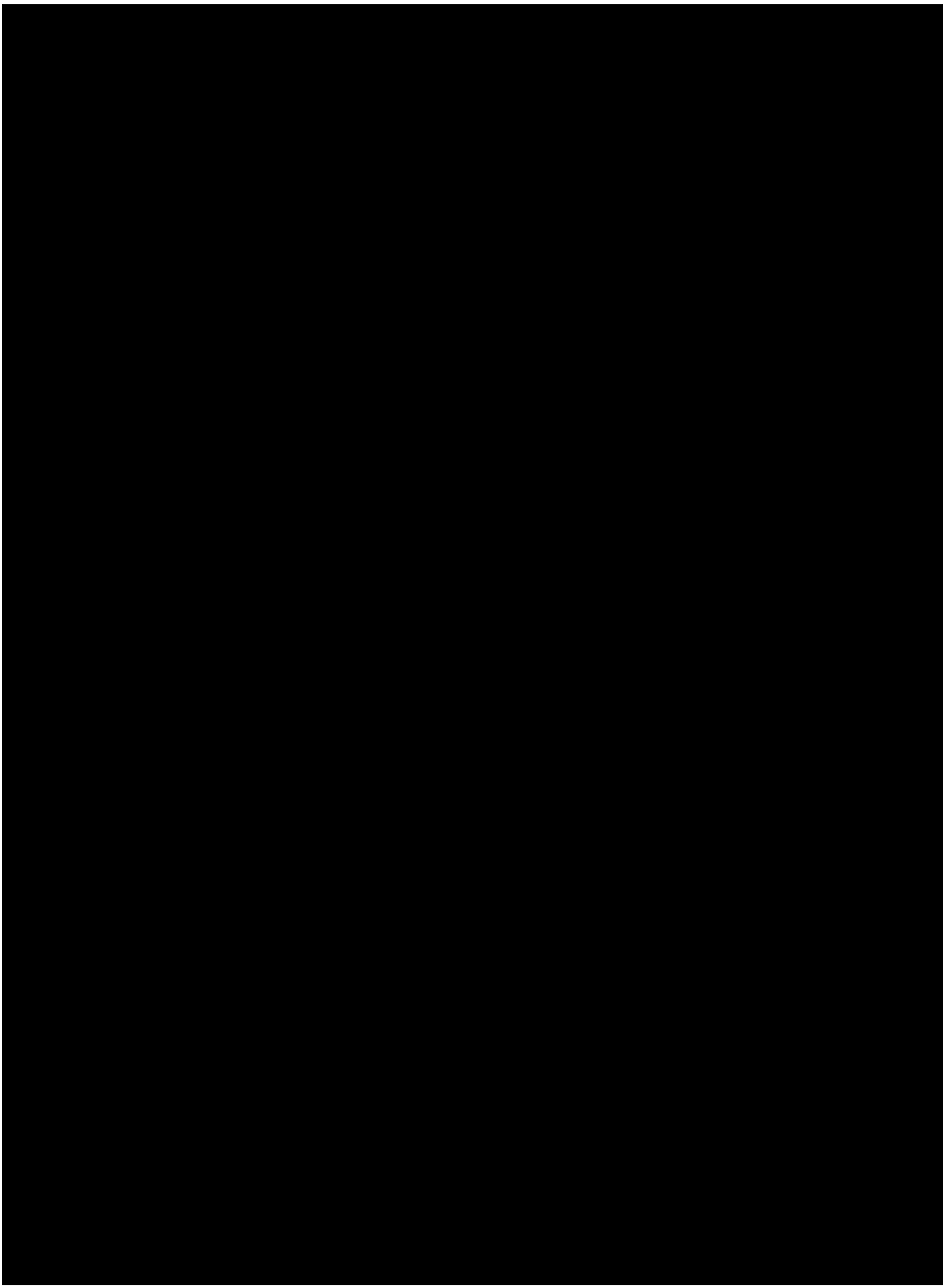

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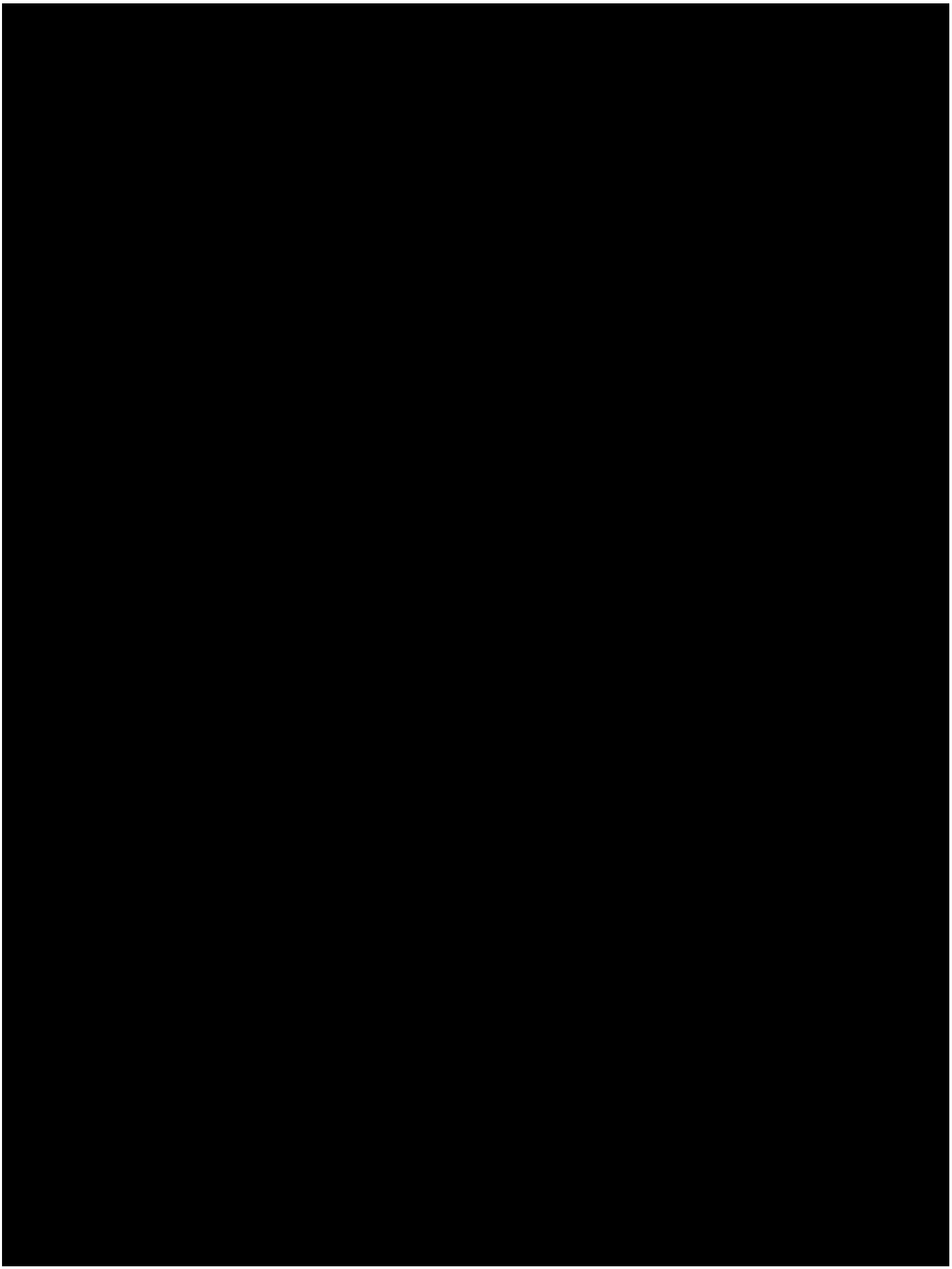

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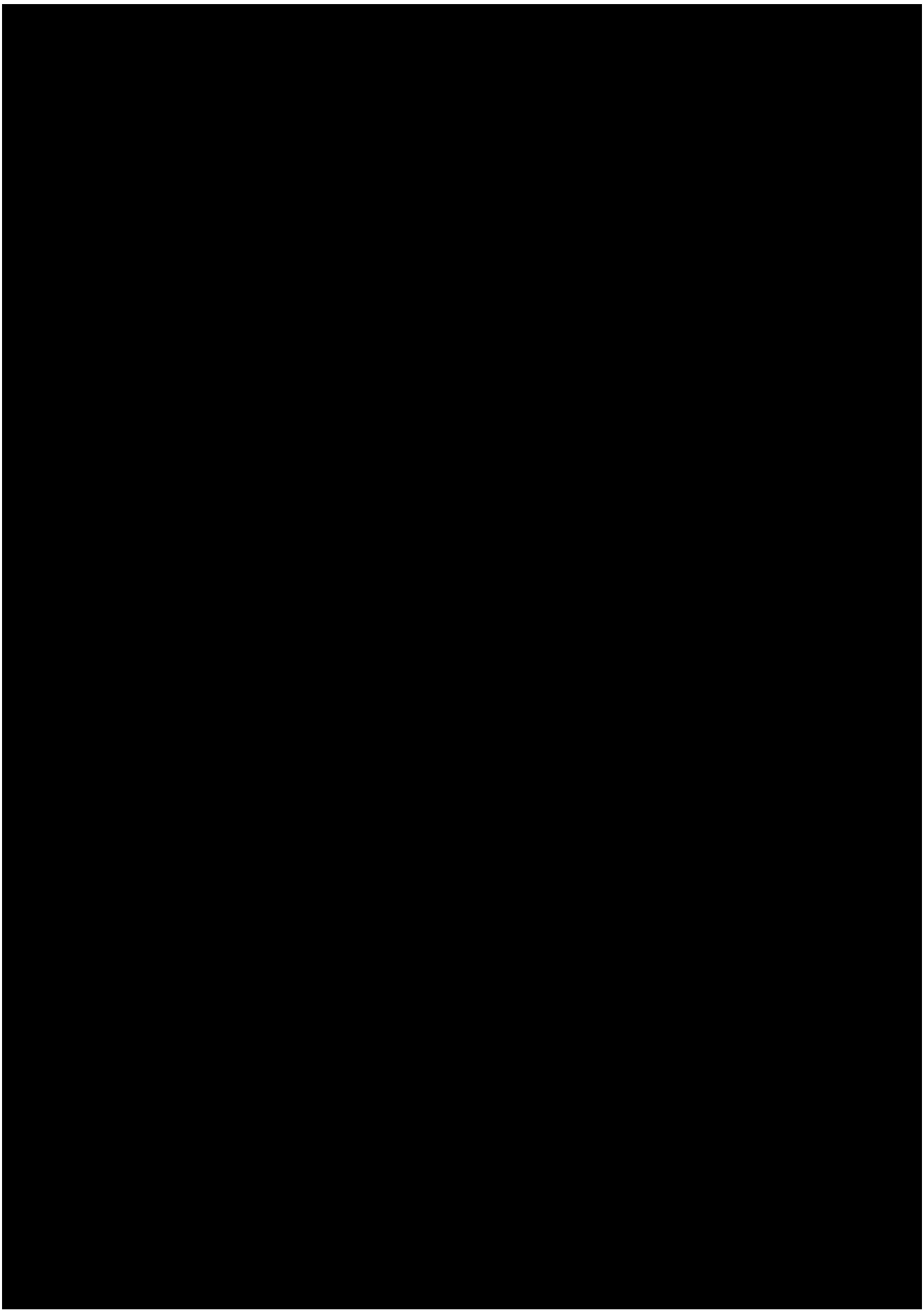

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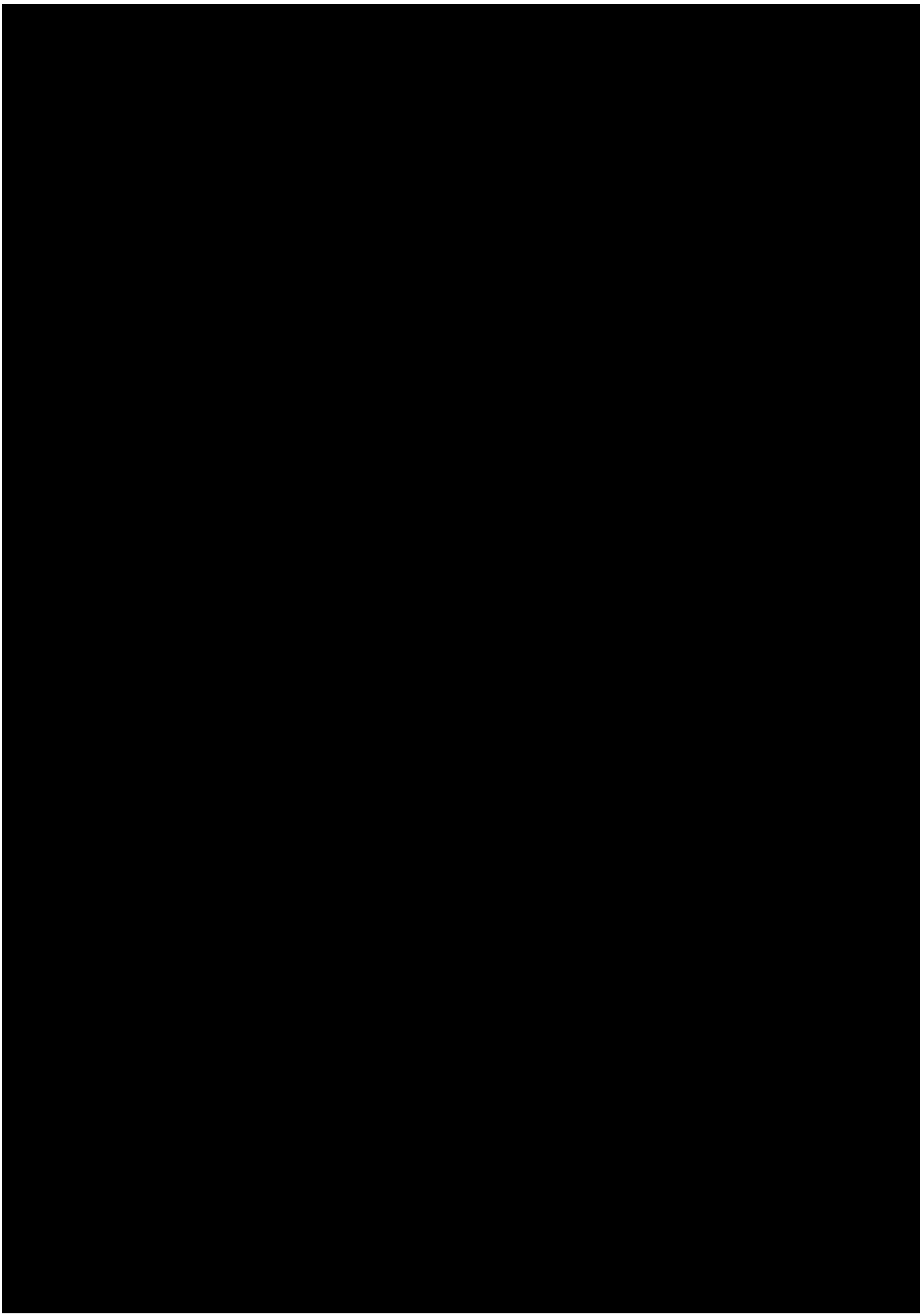

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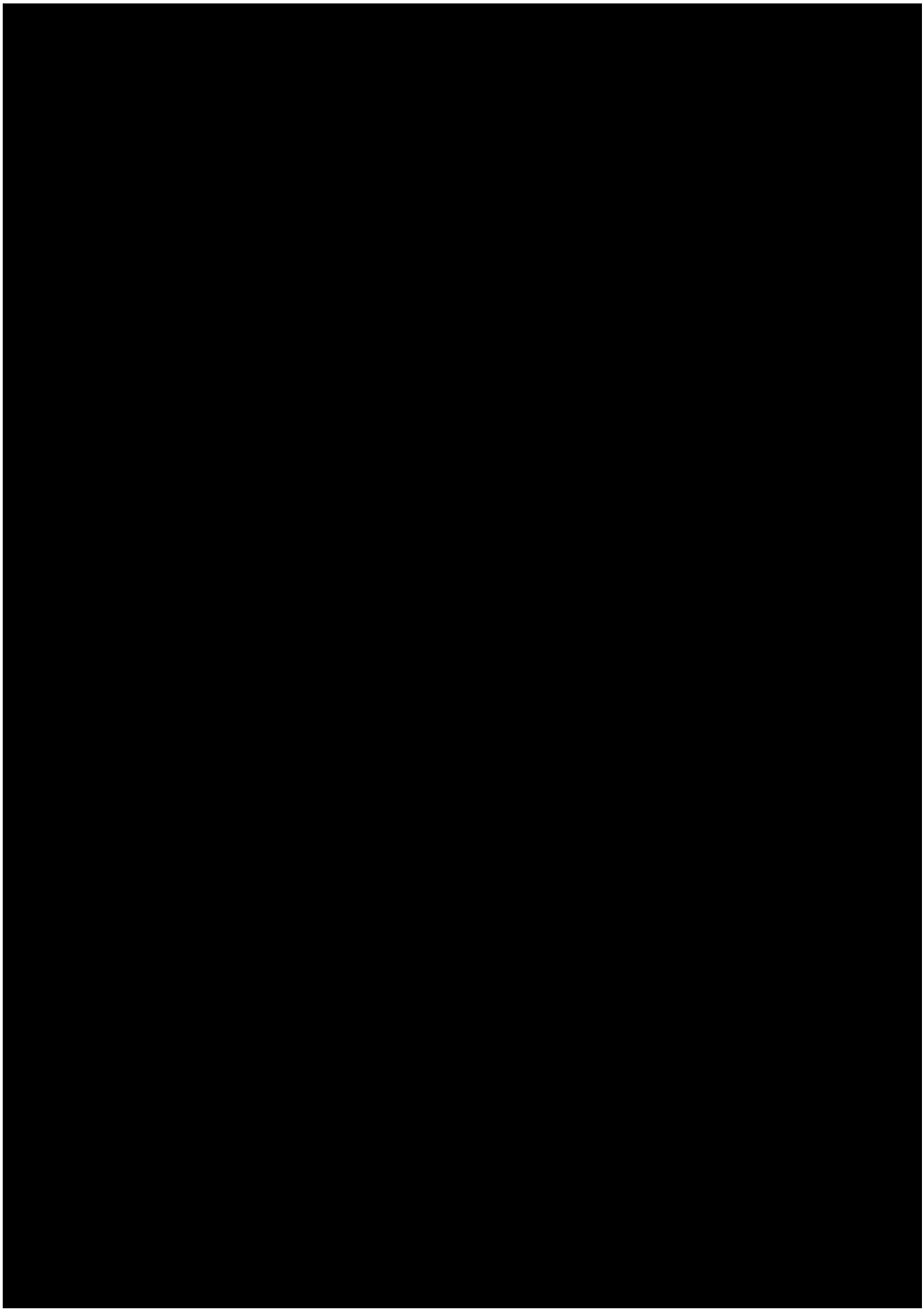

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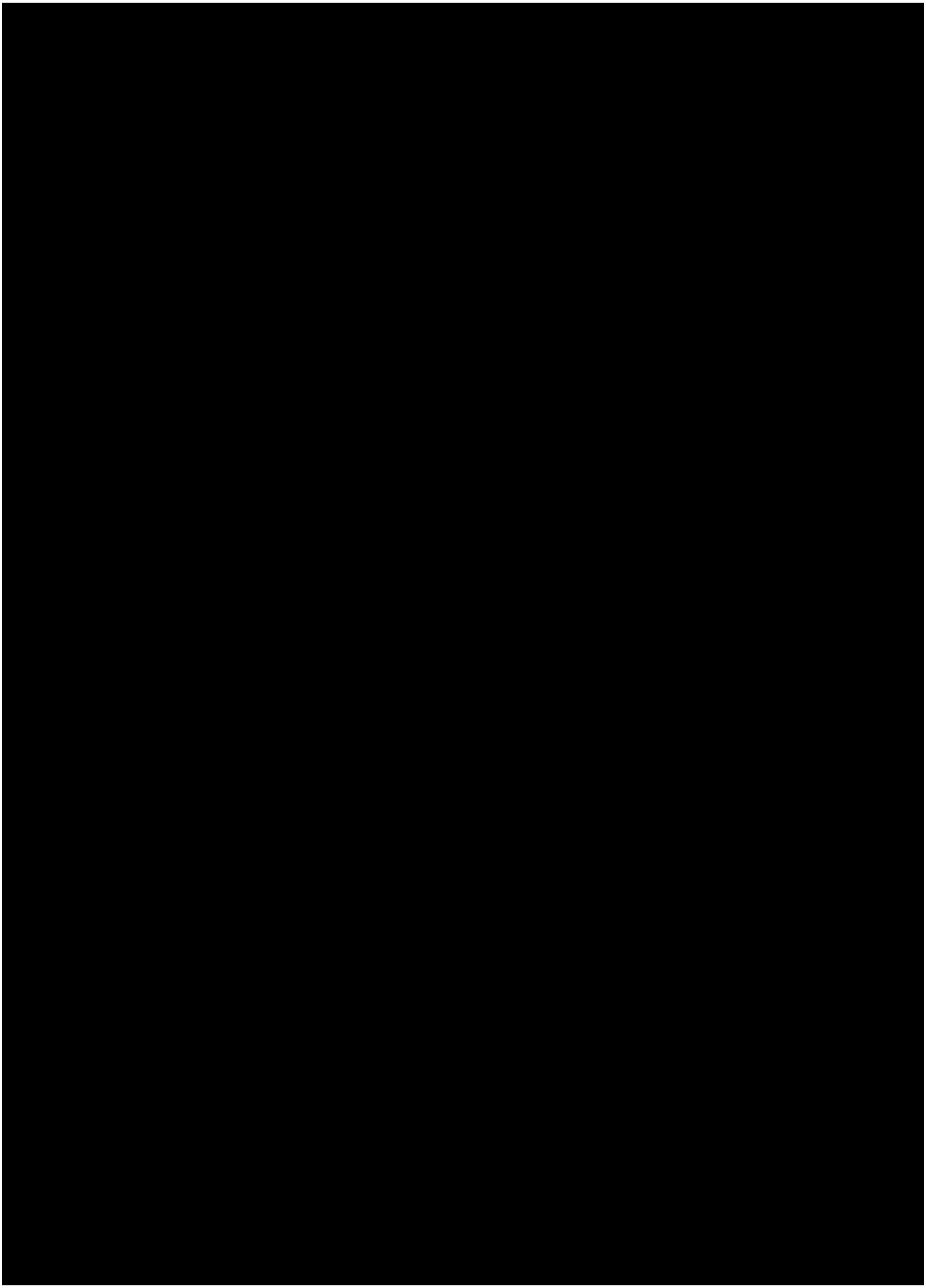

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