Medicinrådet

Bilag til Medicinrådets vurdering af durvalumab i kombination med FLOT kemoterapi som perioperativ behandling til resektabelt adenokarcinom i mavesæk eller mavemund

FLOT består af 5-fluorouracil, leucovorin, oxaliplatin og docetaxel

Vers. 1.0

Bilagsoversigt

1. Ansøgers notat til Rådet vedr. durvalumab i kombination med FLOT kemoterapi
2. Amgros' forhandlingsnotat vedr. durvalumab i kombination med FLOT kemoterapi
3. Ansøgning vedr. durvalumab i kombination med FLOT kemoterapi

Medicinrådet
Dampfærgevej 21-23, 3. sal
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28.05.2026

Note on DMC draft assessment report regarding Imfinzi (durvalumab) in combination with FLOT chemotherapy as neoadjuvant and adjuvant treatment, followed by adjuvant Imfinzi monotherapy, for the treatment of adults with resectable gastric or gastro-oesophageal junction (GEJ) adenocarcinoma.

AstraZeneca would like to thank the DMC for the evaluation of Imfinzi and appreciate the opportunity to comment on the draft assessment report.

Gastric and gastroesophageal junction (GEJ) adenocarcinoma are associated with substantial morbidity and mortality. Even in the resectable setting, these are aggressive cancers, and many patients remain at risk of recurrence despite treatment with curative intent. Prognosis is particular poor with less than 50% of patients alive after 5 years after curative-intent resection and around 50% experience recurrence. Due to the poor prognosis, it is essential to improve treatment outcomes in the perioperative setting for patients with gastric and GEJ cancer.

Surgery remains the primary goal in a curative setting for patients with gastric and GEJ cancer. However, surgery is a major and life-altering procedure that can have a profound impact on patients' quality of life in both short and long term, due to the lasting effects of partial or total stomach removal on food intake, digestion, nutrition, and general function. This underlines the importance of the benefit patients derive from perioperative systemic treatment and surgery, so that more patients achieve durable long-term disease control after undergoing such intensive therapy.

To improve outcomes around surgery, eligible patients receive perioperative FLOT (fluorouracil, leucovorin, oxaliplatin and docetaxel) in Danish clinical practice as the DMC also states in the assessment report. Despite improved outcomes with FLOT, recurrence remains a challenge. In MATTERHORN, despite perioperative FLOT, more than one-third of patients in the placebo + FLOT arm had experienced an event by 18 months, underlining the persistent risk of progression, recurrence, or death despite current standard perioperative treatment.

Overall, the DMC recognize the clinically relevant efficacy results from the MATTERHORN study, a phase III, multinational, double-blinded, randomized, placebo-controlled head-to-head study comparing durvalumab + FLOT (D + FLOT) to FLOT chemotherapy. It is important to highlight, that MATTERHORN included patients from three of the four treatment sites in Denmark, which strengthens the applicability to Danish clinical practice.

The DMC highlights that the MATTERHORN population differs slightly from Danish practice, including af higher proportion of patients with performance status 0 and a different distribution between gastric and GEJ tumors. Although AstraZeneca recognizes this, it does not undermine the validity of the study in a Danish setting. To support this, the forest plot analyses for event-free survival (EFS) and overall survival (OS) do not suggest heterogeneity of treatment effect according to tumor location or ECOG performance status.

AstraZeneca notes that perioperative treatment completion rates in MATTERHORN were higher than those the DMC reported from the Danish real-world analysis by Egebjerg et al. However, these differences should be interpreted in context. First, they do not affect the relevance of the randomized comparison. Second, the relevant population for this appraisal is patients who are considered fit for perioperative FLOT in current Danish practice. Third, the Danish real-world data cited reflect an earlier implementation period for perioperative FLOT.

Mature data are available from MATTERHORN for both EFS and OS. For the primary key endpoint, EFS, D + FLOT reduced the risk of an event by 29% compared with FLOT alone, and the DMC highlights that the estimated number needed to treat is 8 to prevent one EFS event within 3 years. In a perioperative setting where the objective is cure and prevention of relapse, this represents a clinically important treatment effect. These findings may also be viewed in the broader context of previous DMC decisions in curative-intent immunotherapy settings, where similar absolute benefits have been considered clinically meaningful. Looking at the positive DMC decision on pembrolizumab in combination with

chemotherapy for the treatment of perioperative triple-negative breast cancer, data on EFS showed numbers needed to treat of 13 patients to prevent one EFS event within 3 years[1].

An overall survival benefit has been confirmed in the MATTERHORN study. At the latest data cut, the hazard ratio for death was 0.78 (95% CI 0.63–0.96), with a 36-month OS rate of 68.6% versus 61.9%, corresponding to an absolute difference of 6.7 percentage points. The DMC highlights the estimated number needed to treat is 15 to avoid one death within 3 years. Comparing these data to the positive DMC decision on pembrolizumab in combination with chemotherapy for the treatment of perioperative triple-negative breast cancer, data on OS showed numbers needed to treat of 36 patients to avoid one death within 3 years[2].

While the DMC draft report notes uncertainty regarding the proportional hazards assumption, this should not diminish the relevance of the observed absolute landmark benefit. In immuno-oncology, delayed separation of survival curves is well recognized and biologically plausible. Given that approximately 90% in each arm attained R0 resection and both arms received intensive perioperative therapy FLOT +/- durvalumab, early hazards are expected to be similar across arms, with any incremental survival advantage manifesting subsequently, based on the IO long-term effect. In this context, the observed absolute improvement in 36-month overall survival is clinically relevant.

The DMC highlights the uncertainty around D + FLOT as a perioperative treatment and that the MATTERHORN study does not allow a full separation of the relative contribution of the neoadjuvant and adjuvant phase. AstraZeneca accepts that the contribution from the individual treatment phases cannot be fully separated. However, the study reflects real-world perioperative practice where both phases work synergistically. This is an inherent feature of perioperative treatment strategies and therefore does not reduce the relevance of the results. The clinically relevant question is whether the overall perioperative regimen, as studied, improves outcomes compared with perioperative FLOT alone. Nevertheless, the pathological complete response (pCR) observed in the MATTERHORN study, which is assessed before adjuvant treatment, reflects the effect of the neoadjuvant phase shows 19.2% of patients treated with D + FLOT compared with 7.2% with FLOT alone (OR 3.08) achieved pCR.

The DMC states in the draft assessment report that durvalumab, as a checkpoint inhibitor, carries a risk of immune-mediated adverse events, sometimes serious or long-lasting. Immune-mediated adverse events are well documented in prescribing information and are routinely managed in clinical practice. The MATTERHORN study showed immune-mediated adverse events occurred more often with D + FLOT than placebo + FLOT (23% vs 7% for any grade; 7% vs 4% for Grade 3/4), but the safety results did not show excess severe toxicity or new safety concerns beyond the known profile. Importantly, the addition of durvalumab did not hinder surgery rates, delay treatment, or reduce overall health-related quality of life (HRQoL).

AstraZeneca finds that adding durvalumab to perioperative FLOT improves survival in resectable gastric or GEJ adenocarcinoma compared to FLOT alone. The regimen increases pCR, offers meaningful EFS gains, and OS benefit, all without affecting surgery or worsening HRQoL. These outcomes support perioperative durvalumab with FLOT as a new standard of care for patients with resectable gastric or GEJ adenocarcinoma. Enhancing long-term benefits for more patients is crucial in the context of intensive treatment and major surgery. While the uncertainties identified in the draft assessment report should be acknowledged, they should not outweigh the totality of evidence demonstrating meaningful patient benefit and direct relevance to Danish clinical practice.

Kind regards,

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[1] https://filer.medicinraadet.dk/media/tqmarlxl/medicinradets-anbefaling-vedr-pembro-kemo-som-neoadjuv-adjuv-behandling-af-tnbc-vers-2-1x.pdf
[2] https://filer.medicinraadet.dk/media/tqmarlxl/medicinradets-anbefaling-vedr-pembro-kemo-som-neoadjuv-adjuv-behandling-af-tnbc-vers-2-1x.pdf

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28.05.2026

LSC/DBS

Forhandlingsnotat

Dato for vurdering i Medicinrådet	24.06.2026
Leverandør	AstraZeneca
Lægemiddel	Imfinzi (durvalumab)
Ansøgt indikation	Durvalumab i kombination med FLOT-kemoterapi som neoadjuverende og adjuverende behandling, efterfulgt af adjuverende monoterapi med durvalumab, er indiceret til behandling af voksne med operabelt adenokarcinom i ventriklen eller den gastroesophageale overgang
Nyt lægemiddel / indikationsudvidelse	Indikationsudvidelse

Prisinformation

Amgros har følgende pris på Imfinzi:

Tabel 1: Aftalepris

Lægemiddel	Styrke (pakning)	AIP (DKK)	Nuværende SAIP (DKK)	Nuværende rabat ift. AIP
Imfinzi	50 mg/ml (2,4 ml)	4.005,90	[redacted]	[redacted]
Imfinzi	50 mg/ml (10 ml)	16.588,06	[redacted]	[redacted]

Aftaleforhold

Imfinzi indgår i udbuddet på immunterapi. Amgros har en eksisterende aftale på Imfinzi. Aftalen gælder til den 31.12.2026 med mulighed for at forlænge i 12 måneder. Der er inkluderet mulighed for prisregulering i aftalen.

Konkurrencesituationen

Den nuværende standardbehandling af operabelt adenokarcinom i ventriklen eller den gastroesophageale overgang består af perioperativ FLOT alene. Patienter bliver tilbudt op til 8 doser af FLOT: 4 doser forud for operation (neoadjuverende) og 4 efter operation (adjuverende), jf. *Medicinrådets vurdering af durvalumab i kombination med FLOT kemoterapi som perioperativ behandling til resektabelt adenokarcinom i mavesæk eller mavemund*. Imfinzi gives derfor som tillæg til nuværende standardbehandling.

Tabel 2 viser lægemiddeludgiften til Imfinzi for et behandlingsforløb på 48 uger, jf. Medicinrådets tværgående omkostningsanalyse vedr. PD-(L)1-hæmmere. Der er ikke medregnet lægemiddeludgifter til kemoterapi, da disse udgør en mindre del af den samlede lægemiddeludgift.

Tabel 2: Lægemiddeludgifter pr. patient

Lægemiddel	Styrke (pakning)	Dosering	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift pr. 48 uger (SAIP, DKK)
Imfinzi	50 mg/ml (10 ml)	Neoadjuverende: 1.500 mg hver 4. uge i 2 serier, i.v. Adjuverende: 1.500 mg hver 4. uge i op til 12 serier, i.v.	[redacted]	[redacted]

Status fra andre lande

Tabel 3: Status fra andre lande

Land	Status	Link
Norge	Anbefalet	Link til vurdering
Sverige	Anbefalet	Link til vurdering
England	Under vurdering	Link til status

Opsummering

Imfinzi indgår i udbuddet på immunterapier. Leverandøren har derfor kun mulighed for at sænke deres pris ved en aktivering af prisreguleringsmekanismen.

[redacted]

Application for the assessment of durvalumab (Imfinzi) in combination with FLOT chemotherapy as neoadjuvant and adjuvant treatment, followed by adjuvant Imfinzi monotherapy, for the treatment of adults with resectable gastric or gastro-oesophageal junction adenocarcinoma

Color scheme for text highlighting	
Color of highlighted text	Definition of highlighted text
	Confidential information
[Other]	[Definition of color-code]

Contact information

Contact information	
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Table of contents

Tables and Figures

Abbreviations

Abbreviation	Explanation
AE	Adverse event
AJCC	American Joint Committee on Cancer
ALK	Anaplastic lymphoma kinase
BICR	Blinded Independent Central Review
CI	Confidence interval
COVID-19	coronavirus-19
CT	Computed tomography
CTCAE	Common terminology criteria for adverse events
DCO	Data cut-off
DECG	Danish EsophagoGastric Cancer database
DFS	Disease free survival
ECG	Electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EFS	Event free survival
EGFR	Epidermal growth factor receptor
EMA	European Medicines Agency
EORTC	European Organization for Research and Treatment of Cancer
ESMO	European Society of Medical Oncology
FA	Final analysis
FAS	Full analysis set
FLOT	5-fluorouracil, leucovorin, oxaliplatin, docetaxel

GC	Gastric adenocarcinomas
GC/GEJ	Gastric or gastro-oesophageal junction adenocarcinoma
GEC	Gastro-esophageal cancer
GEJC	Gastro-oesophageal junction adenocarcinomas
HER2	Human Epidermal Growth Factor receptor 2
HR	Hazard ratio
HRQoL	Health-related quality of life
IA	Interim analysis
IEMT	important events of medical terminology
imAE	immune mediated adverse events
IP	investigational product
ITT	Intention to treat
KM	Kaplan-Meier
MDT	Multidisciplinary team
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed model for repeated measures
N/A	Not applicable/available
NC	Not calculated
NSCLC	Non small cell lung cancer
OS	Overall survival
PC	Peritoneal carcinomatosis
pCR	Pathological complete response rate
PD-L1	Programmed death-ligand 1
PFS	Progression-free survival
PS	Performance status
PT	Preferred term
Q2W	Every two weeks
Q4W	Every four weeks
QLQ-C30	30-item Quality of Life Questionnaire
RECIST	Response Evaluation Criteria in Solid Tumours
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Safety analysis set
SoC	Standard of care
TAP	Tumour area positivity score

1. Regulatory information on the medicine

Overview of the medicine	
Proprietary name	Imfinzi
Generic name	Durvalumab
Therapeutic indication as defined by EMA	Imfinzi in combination with FLOT chemotherapy as neoadjuvant and adjuvant treatment, followed by adjuvant Imfinzi monotherapy, is indicated for the treatment of adults with resectable gastric or gastro-oesophageal junction adenocarcinoma
Marketing authorization holder in Denmark	AstraZeneca
ATC code	L01FF03
Combination therapy and/or co-medication	FLOT (5-fluorouracil, leucovorin, oxaliplatin, docetaxel)
(Expected) Date of EC approval	March 2026
Has the medicine received a conditional marketing authorization?	No
Accelerated assessment in the European Medicines Agency (EMA)	No
Orphan drug designation (include date)	No
Other therapeutic indications approved by EMA	**Non-Small Cell Lung Cancer (NSCLC)** Durvalumab as monotherapy is indicated for the treatment of locally advanced, unresectable non small cell lung cancer (NSCLC) in adults whose tumours express PD-L1 on ≥ 1% of tumour cells and whose disease has not progressed following platinum based chemoradiation therapy – PACIFIC. Durvalumab in combination with tremelimumab and platinum-based chemotherapy is indicated for the first-line treatment of adults with metastatic NSCLC with no sensitising epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) mutations – POSEIDON. Imfinzi (durvalumab) in combination with platinum-based chemotherapy as neoadjuvant treatment followed by Imfinzi (durvalumab) as monotherapy, as adjuvant treatment, for the treatment of adults with resectable NSCLC at high risk of

Overview of the medicine	
	recurrence and no EGFR mutations or ALK rearrangements - AEGEAN **Small Cell Lung Cancer (SCLC)** Durvalumab in combination with etoposide and either carboplatin or cisplatin is indicated for the first-line treatment of adults with extensive-stage small cell lung cancer (ES SCLC) - CASPIAN. Durvalumab as a consolidation treatment for patients with limited-stage small cell lung cancer (LS-SCLC) who have not progressed following platinum-based chemoradiotherapy – ADRIATIC. **Biliary Tract Cancer (BTC)** Durvalumab in combination with gemcitabine and cisplatin is indicated for the first line treatment of adults with unresectable or metastatic biliary tract cancer (BTC) - TOPAZ. **Hepatocellular Carcinoma (HCC)** Durvalumab as monotherapy is indicated for the first line treatment of adults with advanced or unresectable hepatocellular carcinoma (HCC) - HIMALAYA. Durvalumab in combination with tremelimumab is indicated for the first line treatment of adults with advanced or unresectable HCC - HIMALAYA. **Endometrial cancer** Durvalumab in combination with carboplatin and paclitaxel is indicated for the first-line treatment of adults with primary advanced or recurrent endometrial cancer who are candidates for systemic therapy, followed by maintenance treatment with: durvalumab as monotherapy in endometrial cancer that is mismatch repair deficient (dMMR) and durvalumab in combination with olaparib in endometrial cancer that is mismatch repair proficient (pMMR) – DUO-E. **Bladder cancer** Durvalumab in combination with gemcitabine+cisplatin for neoadjuvant treatment followed by durvalumab alone for adjuvant treatment in patients with muscle-invasive bladder cancer (MIBC) - NIAGARA
Other indications that have been evaluated by the DMC (yes/no)	**<u>Recommendations on:</u>** **Non-Small Cell Lung Cancer (NSCLC)** Durvalumab as monotherapy is indicated for the treatment of locally advanced, unresectable NSCLC in adults whose tumours express PD-L1 on ≥ 1% of tumour cells and whose disease has not progressed following platinum-based chemoradiation therapy - PACIFIC **Biliary Tract Cancer (BTC)**

Overview of the medicine	
	Durvalumab in combination with gemcitabine and cisplatin is indicated for the first-line treatment of adults with unresectable or metastatic BTC – TOPAZ. **Small Cell Lung Cancer (SCLC)** Durvalumab in combination with etoposide and either carboplatin or cisplatin is indicated for the first-line treatment of adults with ES SCLC – CASPIAN. Durvalumab as monotherapy for the treatment of adults with LS-SCLC whose disease has not progressed following platinum-based chemoradiation therapy – ADRIATIC **Hepatocellular Carcinoma (HCC)** Durvalumab in combination with tremelimumab is indicated for the first line treatment of adults with advanced or unresectable HCC – HIMALAYA. **Endometrial cancer** Durvalumab in combination with carboplatin and paclitaxel (chemotherapy medicines) for initial treatment of the disease. For maintenance treatment, it is used on its own when the cancer is dMMR. – DUO-E **<u>Negative recommendations on:</u>** **Non-small cell lung cancer** Imfinzi (durvalumab) in combination with platinum-based chemotherapy as neoadjuvant treatment followed by Imfinzi (durvalumab) as monotherapy, as adjuvant treatment, for the treatment of adults with resectable NSCLC at high risk of recurrence and no EGFR mutations or ALK rearrangements – AEGEAN **Bladder cancer** Durvalumab in combination with gemcitabine+cisplatin for neoadjuvant treatment followed by durvalumab alone for adjuvant treatment in patients with MIBC – NIAGARA
Joint Nordic assessment (JNHB)	Are the current treatment practices similar across the Nordic countries (DK, FI, IS, NO, SE)? Yes, but the reimbursement processes are different in the Nordic countries. In Sweden and Norway, most new PD(L)1s indications are approved shortly after EC decision without HTA assessment. Is the product suitable for a joint Nordic assessment? No If no, why not? See above
Dispensing group	BEGR
Packaging – types, sizes/number of units and concentrations	Vial of 2.4 ml and 10 ml. 50 mg/ml

2. Summary table

Summary	
Indication relevant for the assessment	Imfinzi in combination with 5-fluorouracil/leucovorin/oxaliplatin/docetaxel (FLOT) chemotherapy as neoadjuvant and adjuvant treatment, followed by adjuvant Imfinzi monotherapy, is indicated for the treatment of adults with resectable gastric or gastro-oesophageal junction adenocarcinoma *(GC/GEJC)
Dosage regiment and administration	**Neoadjuvant:** Two cycles of 4-weeks, consisting of durvalumab 1500 mg IV Q4W in combination with FLOT Q2W - *Surgery* - **Adjuvant**: Two cycles of 4-weeks, consisting of durvalumab 1500 mg IV Q4W in combination with FLOT Q2W followed by 10 cycles of durvalumab 1500 mg IV Q4W as monotherapy. A total of 14 cycles of durvalumab (1)
Choice of comparator	Perioperative FLOT (5-fluorouracil, leucovorin, oxaliplatin, docetaxel) Q2W. Patients can receive up to 8 doses of FLOT in total: 4 doses of in the neoadjuvant setting and 4 doses in the adjuvant setting. (1)
Prognosis with current treatment (comparator)	Perioperative chemotherapy with FLOT (administered both as neoadjuvant and adjuvant treatment) is considered the preferred approach and standard of care (SoC) for patients with resectable GC/GEJC. This recommendation is supported by clinical data, including results from the FLOT4-AIO trial (GC/GEJC) (2) However, despite the curative intent of surgery, recurrence rates remain high, and long-term survival is poor. In the FLOT4-AIO trial, 5-year overall survival [OS] in the perioperative FLOT arm was approximately 45%, and the majority of patients experienced disease progression, recurrence or death within three years (median disease-free survival [DFS]: 30 months). (2)
Type of evidence for the clinical evaluation	Head-to-head study, between Durvalumab + FLOT vs. placebo + FLOT (MATTERHORN-study) (1)
Most important efficacy endpoints (Difference/gain compared to comparator)	**Event-free survival** (primary endpoint): HR 0.71 (95% CI 0.58–0.86), p<0.001; median EFS not reached vs 32.8 months; 2-year EFS 70.4% vs 58.5% (absolute gain 8.9%). (3) **Overall survival** (key secondary endpoint) met statistical significance: HR 0.78 (95% CI [0.63–0.96]); median OS not reached in the durvalumab arm at data cut; curves separated from ~13 months. (4) **Pathological complete response rate** (Key secondary endpoint) showed statistically significant improvement in pCR rate per central pathological review: odds ratio: 3.08 [95% CI: 2.03, 4.67]; p < 0.001. (3) **Disease free survival** (secondary endpoint) indicated an

Summary	
	improvement in DFS in the durvalumab arm compared to the placebo arm, with a HR of 0.70 (95% CI: 0.53, 0.93). There was a clear and sustained separation in the DFS KM curves at approximately 14 months (3)
Most important serious adverse events for the intervention and comparator	Serious adverse events (SAEs) and clinically important safety signals: - Durvalumab + FLOT (intervention): Grade 3–4 AEs 71.6%; SAEs 48.2%; AE-related discontinuations 29.9%; deaths 4.8%; immune-mediated AEs (any grade) 23.2%. - Placebo + FLOT (comparator): Grade 3–4 AEs 71.2%; SAEs 44.1%; AE-related discontinuations 22.8%; deaths 4.3%; immune-mediated AEs (any grade) 7.2%. (1) - The most prevalent SAE : pneumonia 2.9 % vers 3.4 %, (1) - Notable categories (both arms, FLOT-driven): neutropenia/infections, gastrointestinal toxicities (e.g., diarrhoea), neuropathy (oxaliplatin), and mucositis
Impact on health-related quality of life	EORTC QLQ-C30 in MATTERHORN, average of all visits: difference in change from baseline between the durvalumab arm vs. the placebo arm: 0.4 (-1.67 to 2.53), p-value: 0.686, no clinically meaningful differences observed. (5)
Type of economic analysis that is submitted	N/A
Data sources used to model the clinical effects	N/A
Data sources used to model the health-related quality of life	N/A
Life years gained	N/A
QALYs gained	N/A
Incremental costs	N/A
ICER (DKK/QALY)	N/A
Uncertainty associated with the ICER estimate	N/A
Number of eligible patients in Denmark	GC/GEJC patients relevant for resection: 322 New patients relevant for treatment with durvalumab + FLOT: 182
Budget impact (in year 5)	N/A

3. The patient population, intervention, choice of comparator(s) and relevant outcomes

3.1 The medical condition

Gastro-oesophageal cancer (GEC) is an umbrella term for cancers located near or within the stomach. This includes cancers of the distal oesophagus, gastric adenocarcinomas (GC) and gastro-oesophageal junction adenocarcinomas (GEJC). Due to the asymptomatic manifestation and poor prognosis, GEC is a type of cancer that should be treated perioperatively to maximize the chance of cure and, where cure is not achievable, to extend time to progression and death.

Collectively, stomach cancer is the fifth most common cancer and the fifth leading cause of cancer mortality globally (2022), with the highest incidence and mortality in eastern Asia (6). In Denmark, oesophageal and GCs together constitute the eighth most common cancer. The median age at diagnosis is approximately 70 years, with a male predominance. (7)

Early GC/GEJC accounts for approximately 30% of cases and is frequently asymptomatic or manifests non-specific symptoms (6, 8-12). Due to the asymptomatic course of the disease, GC/GEJC is diagnosed in the advanced setting in 70% of cases with features including dyspepsia, epigastric pain, early satiety, weight loss, anorexia, iron-deficiency anemia, nausea/vomiting, bleeding, obstruction (especially antral/pyloric), and dysphagia (GEJC) (13-18). No national screening programs exists in Denmark, but more tailored approach is recommended, which restricts screening to those with known risk factors such as Barett's oesophagus (19).

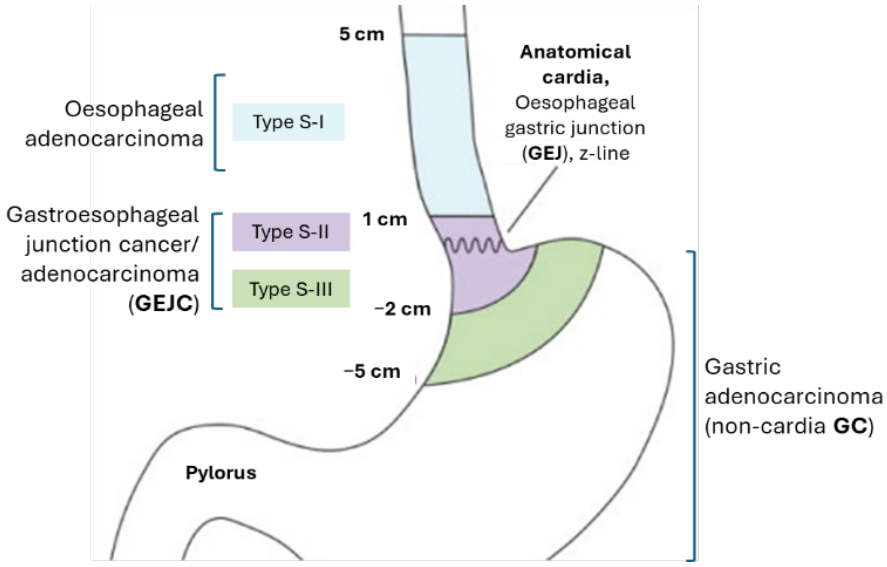
Risk profiles differ by anatomical site with non-cardia GC links mainly to helicobacter pylori, while GEJC is associated with obesity, high-fat intake, and gastro-oesophageal reflux disease (13, 20). Tobacco, high salt intake, and heavy alcohol use further increase the risk (20). Denmark seems to be among the countries with lowest helicobacter pylori prevalence, also reflected in the higher incidence of GEJC (21).

Disease heterogeneity—by anatomy (GC vs GEJC), histology (e.g., Laurén intestinal/diffuse), and molecular subtype (e.g., EBV+, MSI-high, chromosomal instability)—necessitates accurate classification for diagnosis, staging, outcome prediction, and treatment selection. Danish national guidelines classify upper GI tumours per WHO Digestive System Tumours and stage using UICC/AJCC TNM (8th edition), staged as gastric or oesophageal cancer based on tumour epicentre relative to the cardia (Siewert I-III, Figure 1) (22).

For patients undergoing curative treatment the disease substantially impairs patients' functional ability and health-related quality of life (HRQoL) through a combination of the devastating surgical procedure, eating disabilities, and multisystem complications (23). Major surgery, often involving extensive resection, can lead to prolonged recovery, chronic pain, fatigue, reduced mobility, and body image disturbance, all of which limit daily activities and participation in work, caregiving, and social roles. Postoperative eating disabilities, including dysphagia, early satiety, malabsorption, dumping syndrome, and chronic nausea, drive unintentional weight loss, sarcopenia, and nutritional deficiencies, undermining energy, physical functioning, and psychological well-being. Given the substantial post-surgical effects described above, it is essential to provide close, coordinated, cross-functional support, including dieticians and physiotherapist, to optimise recovery and ensure the best possible outcome for the patients. Improving standard of care is critical to enhance prognosis and reduce mortality in this population, reinforcing the rationale for advancing perioperative management. (24, 25)

GC/GEJC undergoing curative resection is associated with a high risk of recurrence and poor prognosis. Most recurrences occur within the first two to three years after curative-intent resection, consistent with registry and trial observations in resectable GC/GEJC (26, 27). Among patients who recur, survival after recurrence is short and only a subset receive systemic therapy post-recurrence, underscoring the disease's aggressive trajectory and care pathway limitations (26). Mortality following surgery remains substantial, reflecting poor post-relapse outcomes (26, 27). The 3 years overall survival (OS) for GC/GEJC cancer patients in Denmark is less than 40% (7) and for those patients undergoing curative resection less than [redacted]% is alive after 3 years (27).

Figure 1 GC/GEJC classification (28-30)



3.2 Patient population

The relevant population for this application is patients who are eligible for perioperative FLOT according to Danish clinical practice. That is adults with resectable stage II–IVa (staged by AJCC/UICC 8th edition as clinical Stage II–IVA, M0, defined as: T2–T4 with any nodal status (N0–N3), M0; or T0–T4 with node-positive disease (N1–N3), M0) GC or GEJC, without evidence of metastasis, no prior systemic therapy, and ECOG performance status 0–1. (22, 31)

According to the Danish EsophagoGastric Cancer (DEGC) Database, 953 patients were diagnosed with GC or GEJC in 2024 (643 GEJ; 310 gastric), with a slight increase in incidence over the past 5 years (Table 1). Approximately one third underwent curative resection, comprising 234 GEJC cases (36.4%) and 88 GC cases (28.4%). Danish resected cohorts have a median age of 68 years), are predominantly male, and primarily exhibit intestinal histology (7, 27).

Table 1 Incidence and prevalence in the past 5 years (7, 32)

Year	2020	2021	2022	2023	2024
Incidence in Denmark (GEJC/GC)*	626/227	674/234	584/276	600/285	643/310
Prevalence in Denmark**	2562	2830	2919	3119	N/A
Global prevalence	N/A	N/A	N/A	N/A	N/A

* Data from the Danish Esophago-gastric Cancer Database (DECG). **Prevalence data from NORDCAN entity: stomach ICD-10 code C16 including C16.0 cardia.

The relevant population for this application comprises patients with resectable GC and GEJC adenocarcinoma who are eligible for perioperative FLOT: neoadjuvant FLOT followed by curative-intent surgery and subsequent adjuvant FLOT. In the latest 2023/2024 yearly report, the DEGC database reports 322 GC/GEJ (234 GEJC and 88 GC) patients underwent resection (7). Data from a retrospective, population-based Danish study (CASTOR study) (2019–2023) showed that [redacted]% of resected patients with GC/GEJ adenocarcinoma stage T2-T4a received neoadjuvant FLOT (see Appendix K for further description of the CASTOR study) (27). The MATTERHORN study showed that adding durvalumab to FLOT did not alter the proportion of patients who attempted or completed surgery, nor the timing of surgery initiation (3). Furthermore, exposure to and delivery of FLOT (neoadjuvant and adjuvant) were comparable between treatment arms, indicating no adverse impact of durvalumab on chemotherapy adherence (5). Accordingly, patients eligible for FLOT are expected to tolerate durvalumab addition, unless contraindicated to immunotherapy. Hence, the estimated number of patients eligible for treatment is approx. [redacted] GC/GEJC each year ([redacted]% of 322 GC/GEJ patients) (Table 2).

Table 2 Estimated number of patients eligible for treatment (7, 27)

Year	Year 1	Year 2	Year 3	Year 4	Year 5
Number of patients in Denmark who are eligible for treatment in the coming years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

3.3 Current treatment options

In Denmark, the standard curative pathway for resectable GC/GEJ adenocarcinoma is a surgery-centered, perioperative chemotherapy approach with FLOT for medically fit patients (ECOG 0–1) and stage II–IVa, M0 disease, aligned with ESMO and NCCN guidance and is reflected in DECG clinical guidelines (33-35). Per Danish DECG guidance: "*Operable patients with resectable tumours (>T1N0M0) should be offered resection, preceded by an assessment for pre-operative oncological treatment (Level A)*." In practice, resectability is established by the multidisciplinary team (MDT) based on the absence of distant metastasis (M0) and the feasibility of achieving an R0 resection (31).

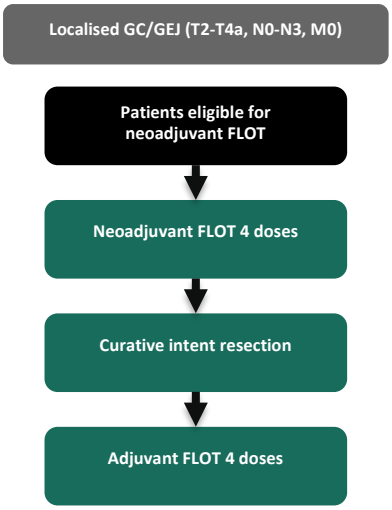
For GEJC, perioperative FLOT is preferred over routine chemoradiotherapy. The ESOPEC randomized phase III trial demonstrated improved OS with perioperative FLOT compared with neoadjuvant chemoradiotherapy (CROSS), reinforcing FLOT as the preferred perioperative approach for GEJC. Consistent with this, Danish DECG clinical guidance, aligned with ESMO, recommends perioperative FLOT for resectable oesophageal or GC (stage I with nodal involvement through stage II–IV, all M0). Preoperative chemoradiotherapy (CROSS) is reserved for a smaller subset of GEJC (primarily Siewert I/II) who are not suitable candidates for perioperative FLOT. Data from the CASTOR study (Danish population-based study) shows increasing adoption of perioperative FLOT and improving survival across diagnosis years, survival has improved across those years, and there is meaningful drop-off with median survival increasing from ~[redacted] months (2017–2018) to ~[redacted] months (2021–2022) in the national registry (see Appendix K for further description of the CASTOR study). (27) This aligns with MDT practice and highlights the value of regimens that preserve surgical feasibility and maintain event-free survival (EFS) even where adjuvant intensity is imperfect (27).

Surgery remains the definitive modality and is planned after restaging to confirm operability. The surgical approach is radical subtotal or total gastrectomy for GC and oesophagectomy for GEJC. Given the demands and potential consequence of perioperative therapy and major resection, careful multidisciplinary preoperative assessment is essential. (31) Per Danish guidance, surgery should occur 4–8 weeks after completion of neoadjuvant FLOT. Frail but operable patients unsuitable for neoadjuvant FLOT may proceed directly to surgery, with adjuvant chemotherapy considered post-operatively if feasible, in line with Danish clinical practice. (31)

Despite optimized perioperative care with FLOT as standard of care, prognosis remains poor with less than 50% of patients alive 5 years after curative-intent resection, and around 50% experience recurrence (27, 36-38) with the risk being particularly high within the first two years post-resection (39). While local recurrence is relatively uncommon distant metastasis, particularly in other organs or peritoneal carcinomatosis (PC), are prevalent and concerning and are associated with poor prognosis, high mortality and low quality of life (40, 41). Data from the CASTOR study shows that survival after recurrence is short; about [redacted]% alive at 12 months after recurrence, underscoring the need for strategies that delay or prevent recurrence (27). In a curative-intent pathway, earlier reductions in events and distant recurrence may have implications for avoided downstream costs and resource use (27).

Adjuvant nivolumab is approved and reimbursed by the Danish Medicine Council only for patients with resected oesophageal (squamous cell carcinoma) or GEJC who received neoadjuvant chemoradiotherapy and have residual pathological disease (42). This is based on CheckMate-577, which showed a statistically significant and clinically meaningful improvement in disease-free survival (DFS) versus placebo; OS at 5 years was numerically longer but not statistically significant, with signals favouring PD-L1 CPS ≥1, oesophageal over GEJ location, and squamous histology over adenocarcinoma (43). Therefore, adjuvant nivolumab does not apply to adenocarcinomas managed with a perioperative FLOT pathway, based on superior survival with perioperative chemotherapy (FLOT) versus neoadjuvant chemoradiotherapy in resectable oesophagogastric adenocarcinoma reported in the ESOPEC study, establishing FLOT as the default perioperative strategy for adenocarcinoma (Figure 2) (44).

Figure 2 Treatment algorithm for curative-intent treatment of GC/GEJ (22)



Adapted based on the Danish clinical guidelines

3.4 The intervention

Durvalumab is a high-affinity, human recombinant IgGκ monoclonal antibody that selectively blocks programmed death-ligand 1 (PD-L1) from binding to its receptors PD-1 and CD80 (B7.1) (45). PD-L1 is frequently overexpressed on tumour cells and

antigen-presenting cells in the tumour microenvironment, where PD-L1/PD-1 and PD-L1/CD80 interactions downregulate T-cell activation and effector function. By inhibiting these interactions, durvalumab prevents PD-L1–mediated immune suppression, thereby restoring cytotoxic T-cell activity, proliferation, and cytokine production against PD-L1–expressing tumour cells. (45, 46)

The combination of immune checkpoint inhibitors (anti PD-1/PD-L1) and chemotherapy has demonstrated significant anti-tumour activity in multiple tumour types, including GC/GEJC, for which the anti-PDL-1/PD-1 monoclonal antibodies have become standard components in systemic therapy for unresectable locally advanced, recurrent, or metastatic disease. (47-53) The potential benefits of combining IO therapy with platinum-based chemotherapy are also supported by non-clinical data which indicates that cytotoxic chemotherapy enhances anti-tumour immunity. (54, 55) Fluorouracil and platinum counteract tumour immuno-suppressive effects by killing tumour cells, regulatory T cells, and myeloid-derived suppressor cells through release of neo-antigens. (54, 56-58) Taxanes such as paclitaxel and docetaxel are known to increase CD8+ T-cell mobilisation and inhibit immuno-suppressive cells. (59)

The combination of anti-PD-L1 therapies such as durvalumab with perioperative FLOT chemotherapy have demonstrated increased efficacy and improved clinical outcomes in patients with resectable GC/GEJC (1). ESMO-MCBS v2.0 (08 Jan 2026) denoted a high magnitude of clinical benefit with Grade A for perioperative durvalumab + FLOT (MATTERHORN), driven by 2-year EFS 70.4% vs 58.5% (absolute +8.9%; median EFS gain ≈13.4 months) (1, 60).

Overview of the intervention is presented in Table 4 and the treatment schedule is illustrated in Figure 3.

Figure 3 Treatment schedule as per MATTERHORN trial (5)

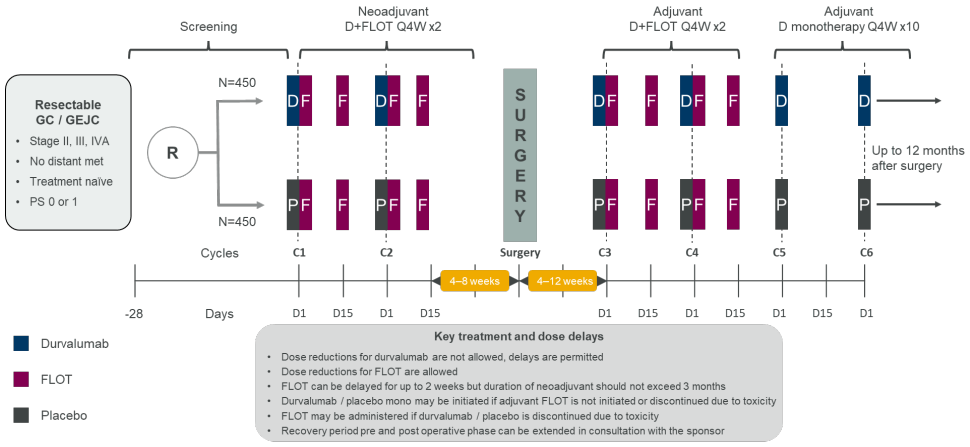


Table 3 Overview of the intervention

Overview of intervention	
Indication relevant for the assessment	Gastric (GC) or gastro-oesophageal junction adenocarcinoma (GEJC): Imfinzi in combination with FLOT chemotherapy as neoadjuvant and adjuvant treatment, followed by adjuvant Imfinzi monotherapy, is indicated for the treatment of adults with resectable gastric or gastro-oesophageal junction adenocarcinoma
ATMP	N/A
Method of administration	IMFINZI and FLOT administered as intravenous infusions in oncology day units at centralized upper GI centers
Dosing	**Neoadjuvant:** Two cycles of 4-weeks, consisting of durvalumab 1500 mg IV Q4W in combination with FLOT Q2W *Surgery: Curative intended resection* **Adjuvant**: Two cycles of 4-weeks, consisting of durvalumab 1500 mg IV Q4W in combination with FLOT Q2W followed by 10 cycles of durvalumab 1500 mg IV Q4W as monotherapy. A total of up to 14 cycles of durvalumab (1) Durvalumab is infused over 60 minutes +/- 10 minutes. FLOT is to be administered intravenously per local protocol. Durvalumab is to be administered prior to the administration of FLOT within the same day.
Dosing in the health economic model (including relative dose intensity)	N/A
Should the medicine be administered with other medicines?	Yes. IMFINZI is co-administered with FLOT in neoadjuvant and early adjuvant phases; IMFINZI monotherapy follows in late adjuvant
Treatment duration / criteria for end of treatment	Duration: ~8 weeks neoadjuvant, surgery, ~8 weeks adjuvant combination, ~40 weeks IMFINZI monotherapy. End of treatment: Completion of planned cycles; unacceptable toxicity; disease progression/recurrence; patient/MDT decision. If adjuvant FLOT is not initiated or stopped, IMFINZI monotherapy may continue per protocol.
Necessary monitoring, both during administration and during the treatment period	*Necessary monitoring, both during administration and during the treatment period.* Routine Danish monitoring: Baseline/staging: CT ± PET-CT; endoscopy/biopsy; MDT; reflex biomarkers (MMR/MSI, HER2 ± ISH, PD-L1)

Overview of intervention	
	Per cycle: CBC/diff; renal/hepatic panels; thyroid (TSH, free T4) periodically; glucose; CRP; LDH; albumin; urinalysis as indicated irAE surveillance (IMFINZI): dermatologic, endocrine, hepatic, pulmonary, GI; grade-based steroid algorithms; IO hold/discontinue per protocol (5) FLOT toxicity: neutropenia/infections (G-CSF), diarrhoea (5-FU adjust), neuropathy (oxaliplatin ± docetaxel omission), mucositis, nausea/vomiting Surgical readiness: pre-op restaging; anaesthesia clearance; nutrition/ERAS; operability preserved Post-op/adjuvant: timelines to adjuvant; adherence/dose intensity tracking; MDT review for delays
Need for diagnostics or other tests (e.g. companion diagnostics). How are these included in the model?	No additional non-routine diagnostics required. Standard Danish reflex biomarker testing and staging suffice.
Package size(s)	50 mg/ml in vials of 2.4 ml or 10 ml

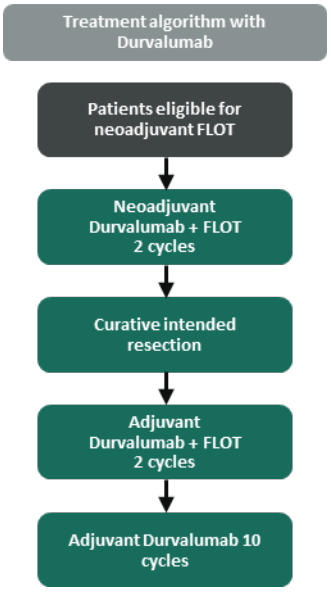
3.4.1 Description of ATMP

N/A.

3.4.2 The intervention in relation to Danish clinical practice

Perioperative FLOT is the SoC for patients with resectable stage II–IVa GC or GEJC, in good performance status (ECOG PS 0–1) (22). Durvalumab is expected to be administered as an add-on to the current Danish clinical practice, perioperative FLOT (Figure 4). The MATTERHORN regimen is designed to integrate directly into the existing Danish perioperative pathway without altering the standard timing of surgery or adjuvant treatment as demonstrated in MATTERHORN.

Figure 4 Expected treatment algorithm with durvalumab



Footnote: Treatment schedule: NEOADJUVANT: Two cycles of 4-weeks, consisting of durvalumab 1500 mg IV Q4W in combination with FLOT Q2W – SURGERY - ADJUVANT: Two cycles of 4-weeks, consisting of durvalumab 1500 mg IV Q4W in combination with FLOT Q2W followed by 10 cycles of durvalumab 1500 mg IV Q4W as monotherapy. A total of 14 cycles of durvalumab (1)

3.5 Choice of comparator(s)

Perioperative FLOT is the established backbone of care in Denmark for patients with resectable GC or GEJC, with international guidelines and the ESOPEC trial supporting its use; Danish clinical practice guidelines reflect routine adoption of FLOT. The CASTOR study treatment pattern outputs (2019–2024) confirm perioperative FLOT as the real-world backbone in Denmark, supporting placebo + FLOT as the appropriate comparator (see Appendix K). (27) Aligned to this standard, MATTERHORN randomizes durvalumab + FLOT versus placebo + FLOT followed by monotherapy durvalumab or placebo after completion of adjuvant FLOT. (1, 33, 34)

Perioperative FLOT was therefore selected as the appropriate comparator. In MATTERHORN, the FLOT combination was administered together with durvalumab in the investigational arm (durvalumab arm) and with placebo (placebo arm) in the comparator arm, reflecting a comparison relevant to Danish clinical practice and in line with the guideline recommendations (22).

The comparator, which is 4 medicines in combination, is presented in Table 4.

Table 4 Overview of comparator – Perioperative FLOT (1)

Overview of comparator	5-FU	Leucovorin (folic acid)	Oxaliplatin	Docetaxel
Generic name	Fluorouracil	Leucovorin calcium	Oxaliplatin	Docetaxel
ATC code	L01BC02	V03AF03	L01XA03	L01CD02
Mechanism of action	Antimetabolite; pyrimidine analogue that inhibits thymidylate synthase and interferes with RNA/DNA synthesis, leading to cytotoxicity in rapidly dividing cells.	Reduced folate that stabilizes the binding of 5-FU to thymidylate synthase, enhancing 5-FU cytotoxicity	Platinum-based DNA crosslinker causing inter- and intra-strand crosslinks, leading to apoptosis.	Taxane that stabilizes microtubules, inhibiting depolymerization and mitosis, leading to apoptosis.
Method of administration	Intravenous infusion per local protocol	Intravenous infusion per local protocol	Intravenous infusion per local protocol	Intravenous infusion per local protocol
Dosing	2600 mg/m2	200 mg/m2	85 mg/m2	50 mg/m2
Dosing in the health economic model (including relative dose intensity)	N/A	N/A	N/A	N/A
Should the medicine be administered with other medicines?	Part of the FLOT regimen with docetaxel, oxaliplatin, and leucovorin	Part of the FLOT regimen with 5-FU, docetaxel, and oxaliplatin	Part of the FLOT regimen with 5-FU, leucovorin, and docetaxel	Part of the FLOT regimen with 5-FU, leucovorin, and oxaliplatin
Treatment duration/ criteria for end of treatment	Neoadjuvant therapy: Q2W for up to 8 weeks Adjuvant therapy: Q2W for up to 8 weeks Dose modifications for individual FLOT components were allowed per local practice to manage toxicity. If FLOT was discontinued in the neoadjuvant or adjuvant phase due to adverse events, durvalumab or placebo could continue as monotherapy (5)			

Overview of comparator	5-FU	Leucovorin (folic acid)	Oxaliplatin	Docetaxel
Need for diagnostics or other tests (i.e. companion diagnostics)	No	No	No	No
Package size(s)	50 mg/ml in a vial of 10, 50 or 100 ml	10 mg/ml in a vial of 10, 35 or 100 ml	5 mg/ml in a vial of 10, 20 or 40 ml	20mg/ml in a vial of 1, 4 or 8 ml

3.6 Cost-effectiveness of the comparator(s)

Perioperative FLOT has not previously been evaluated by the DMC. The FLOT regimen comprises four components that are off-patent and face generic competition in the Danish market. Therefore, it is reasonable to assume that the regimen's marginal cost is minimal, and, at generic pricing, FLOT can be considered cost-effective.

3.7 Relevant efficacy outcomes

3.7.1 Definition of efficacy outcomes included in the application

The efficacy outcomes relevant for this application were sourced from the pivotal clinical trial MATTERHORN and are presented in Table 5 (1).

Table 5 Efficacy outcome measures relevant for the application (1)

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
Overall survival (OS) [MATTERHORN, OS ESMO] (4)	DCO3, 1st September 2025. The median follow-up for overall survival was 43.0 months in Durvalumab arm and 42.9 months in placebo arm	Defined as the time from the date of randomisation until death due to any cause	Analysed in the FAS
Event-free survival (EFS) [MATTERHORN] (1)	DCO2, 20th December 2024. Median follow-up for Event-free survival was 31.6 months in the	Defined as the time from randomisation to the first of the following (according to RECIST 1.1 per BICR assessment	Analysed in the FAS. Assessment according to RECIST 1.1 per BICR and/or locally by pathology testing

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
	durvalumab arm and 31.4 in the placebo arm	and/or locally by pathology testing): a) progression that precludes surgery or requires non-protocol therapy, b) local or distant recurrence or progression of disease, or c) death due to any cause	
Pathological complete response (pCR) [MATTERHORN] (3)	DCO1, 1st February 2023. DCO1 was performed after all patients had been randomized and undergone surgical resection or been precluded from surgery. This occurred approximately 29 months after randomization of the first patient	Defined as the proportion of patients who have no residual visible tumour in the resected specimens and as determined by pathology review	Analysed in the full analysis set (FAS). Determined by pathology review by central review in accordance with the modified Ryan criteria (61)
Disease free survival (DFS) [MATTERHORN] (3)	DCO2, 20th December 2024. Median follow-up for Event-free survival was 31.6 months in the Durvalumab arm and 31.4 in the placebo arm	Defined as the time from first post-surgery scan until disease recurrence, using RECIST 1.1, or death due to any cause	Analysed in the R0 resected analysis set. Assessment according to RECIST 1.1. per investigator assessment

* Time point for data collection used in analysis (follow up time for time-to-event measures)

Validity of outcomes

According to European Medicines Agency (EMA) guidelines on the evaluation of anticancer medicinal products. EFS as a primary endpoint is especially accepted in neoadjuvant and adjuvant settings or in treatments with potentially curative intent, and when there is a high likelihood of early events. (62)

EFS was preferred over PFS as PFS is often used as endpoint in clinical trials involving patients with advanced/metastatic disease, where an event is defined as disease

progression or death. EFS is a broader endpoint more suitable for the perioperative curative-intent GC/GEJC setting as it also captures other clinically relevant failures across the perioperative pathway (e.g. inability to proceed with planned surgery). (62-65)

OS remains gold standard in anti-cancer trials where the aim is to prolong survival (66). However, EFS can provide earlier indications of treatment efficacy, especially in settings where long-term survival data may take extended periods to mature (66). Therefore, when appropriately defined and justified, EFS serves as a meaningful endpoint in the assessment of anticancer therapies.

4. Health economic analysis

N/A, this application is intended for the 14-week process, hence no health economic analysis has been conducted.

4.1 Model structure

N/A.

4.2 Model features

N/A.

Table 6 Features of the economic model

Model features	Description	Justification
N/A.	N/A.	N/A.

5. Overview of literature

5.1 Literature used for the clinical assessment

The main analysis of the application is based on a within-trial comparison; as such, no SLR was done. The literature used is presented in Table 7.

Table 7 Relevant literature included in the assessment of efficacy and safety

Reference (Full citation incl. reference number)*	Trial name*	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Used in comparison of*
Y Janjigian YY, Al-Batran SE, Wainberg ZA, Muro K, Molena D, Van Cutsem E, Hyung WJ; MATTERHORN Investigators. Perioperative durvalumab in gastric and gastroesophageal junction cancer. N Engl J Med. June 1st 2025;393:217-230. doi:10.1056/NEJMoa2503701. (1)	MATTERHORN	NCT04592913	Start (Actual): 17/11/2020 Completion (Estimated): 27/09/2027 Data cut-off DCO1 (IA1): 1/2/2023 DCO2 (IA2): 20/12/2024 DCO3 final analysis: 1/9/2025	Durvalumab + FLOT versus placebo + FLOT, for GC/GEJC patients with resectable adenocarcinoma with clinical Stage II–IVA; >T2 N0–3 M0 or T0–4 N1–3 M0
MATTERHORN final OS Congress abstract ESMO 2025 (4)				
Clinical Study Report AstraZeneca Durvalumab-D910GC00001, Data on file, May 15th 2025th 2025 (5)				
Clinical Study Report AstraZeneca Durvalumab Final OS analysis, Data on file, November 20th 2025 (67-69)				

5.2 Literature used for the assessment of health-related quality of life

Health-related quality of life was measured in the MATTERHORN trial, and this will be presented in this application.

Table 8 Relevant literature included for (documentation of) health-related quality of life (see section 10)

Reference (Full citation incl. reference number)	Health state/Disutility	Reference to where in the application the data is described/applied
Clinical Study Report AstraZeneca Durvalumab-D910GC00001, Data on file, May 15th 2025 (5)	N/A	Section 10.1, comparative analysis on EORTC QLQ-C30 between durvalumab + FLOT vs. placebo + FLOT.

5.3 Literature used for inputs for the health economic model

No health economic analysis was performed for this submission.

Table 9 Relevant literature used for input to the health economic model

Reference (Full citation incl. reference number)	Input/estimate	Method of identification	Reference to where in the application the data is described/applied
N/A	N/A	N/A	N/A

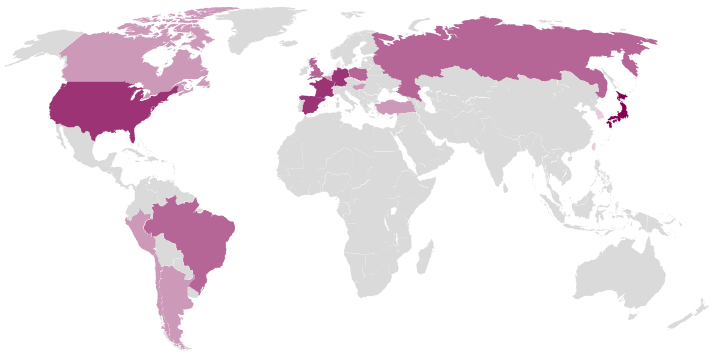
6. Efficacy

6.1 Efficacy of durvalumab + FLOT as perioperative treatment compared to FLOT as perioperative treatment for patients with resectable, locally advanced GC/GEJC (stage II-IVa), ECOG 0-1, eligible for curative-intent surgery

6.1.1 Relevant studies

MATTERHORN is a global, multi-centre clinical study which sought to include patients reflective of the international resectable GC/GEJC clinical population. To this end, patients were randomised to treatment at 159 study sites across 20 countries in North and South America, Europe and Asia, including 3 out of 4 treatment sites in Denmark (Rigshospitalet, Odense University Hospital and Aalborg University Hospital)(Figure 5). 948 patients were randomised into two arms: durvalumab + FLOT or placebo + FLOT (1). Neoadjuvant therapy started after screening and randomization; surgery was performed 4–8 weeks after the last neoadjuvant dose. Adjuvant treatment began 4–12 weeks post-surgery. Crossover between arms was not permitted. (3, 5)

Figure 5 Numbers of trial centres participating in MATTERHORN. (5).



Countries	Number of trial centres
Japan	16
France	12
Germany	12
US	11
Spain	10
Poland	8
UK	8
Brazil	7
Russian Federation	7
Argentina	6
Canada	6
Republic of Korea	6
Taiwan	6
Turkey	6
Belgium	5
Chile	5
Hungary	5
Peru	5
Denmark	3
Netherlands	3

Rationale and design: MATTERHORN is a global, multicentre, phase III, randomized, double-blind, placebo-controlled study including Danish patients designed to test perioperative durvalumab added to a uniform FLOT backbone in resectable GC or GEJC (Stage II–IVa: M0 (T2–T4 any N [N0–N3] M0, or T0–T4 with N+ [N1–N3] M0)) with curative intent. Adults (≥18 years), treatment-naïve, ECOG PS 0–1, with histologically

confirmed adenocarcinoma and MDT-confirmed resectability, were eligible. Patients had to be candidates for standard perioperative FLOT, have adequate organ function (haematologic, hepatic, renal) and surgical intent for R0 resection, with exclusion of uncontrolled comorbidity that would preclude chemotherapy, immunotherapy, or major resection. Randomization was stratified by PD-L1 expression using VENTANA SP263 TAP (≥1% vs <1%), clinical nodal status (cN+ vs cN0), tumour location (gastric vs GEJ), and geographic region to balance biology and practice patterns across arms. RECIST 1.1 staging scans were mandated at baseline (≤28 days pre-randomization), pre-surgery (≤4 weeks after the last neoadjuvant FLOT dose), and at adjuvant baseline (≥4 weeks post-surgery), followed by scheduled assessments every 12 weeks (±1 week) for 2 years and every 24 weeks (±1 week) thereafter until recurrence/progression (see Figure 6 and Table 10). Pathology review (modified Ryan criteria) provided centralized assessment of pCR and local confirmation of R0 status. FLOT dose modifications/omissions (e.g., oxaliplatin/docetaxel for neuropathy; 5-FU adjustments for diarrhoea; G-CSF per centre practice) were permitted per protocol; durvalumab dose reductions were not allowed, but treatment holds or discontinuations were protocol-guided. If post-operative FLOT was not initiated or was discontinued due to toxicity, continuation of durvalumab/placebo monotherapy was allowed. (1, 5)

The statistical plan prespecified three formal analyses with strong type I error control (2-sided 5%): DCO1 pCR (alpha 0.1%; met with OR 3.08), DCO2 interim EFS/OS (EFS HR 0.71; OS tested per multiple testing procedure allocating a fixed alpha of 0.01%), and DCO3 final OS analysis with the remaining alpha of 4.99% at FA.

The rationale for the perioperative design of MATTERHORN is to provide direct tumour response improvement in the neoadjuvant phase and to promote a reduced rate of disease recurrence and micrometastases after surgery (adjuvant phase). The one-year duration of durvalumab therapy during the adjuvant phase was selected to ensure ongoing inhibition of the PD-1/PD-L1 pathway, which is important to counter the PD-L1-mediated suppression of antitumour T-cell activity in this phase. (5) Since durvalumab clearance is expected to cause a significant waning of PD-1/PD-L1 axis inhibition after surgery in the absence of continued exposure, adjuvant durvalumab was continued as a single agent after completion of adjuvant FLOT chemotherapy. This approach was intended to counter this mechanism of resistance, maintain durable checkpoint blockade and long-term antitumour immunity, and ultimately eradicate or maintain effective control of micrometastatic disease. (5) The one-year duration aligns with the highest risk window for recurrence and is consistent with durvalumab use in other indications (66, 70) and with immuno-oncology trials in resectable oesophageal/GC/GEJC (e.g., CheckMate-577, KEYNOTE-585, ATTRACTION-5) (43, 71, 72).

As per DMC guidance, results from the ITT population have been presented, unless otherwise specified. An overview of the MATTERHORN study is presented in Figure 6 and Table 10. MATTERHORN is described in further detail in Appendix A.

Figure 6 Overview of the MATTERHORN Study Design (1, 5)

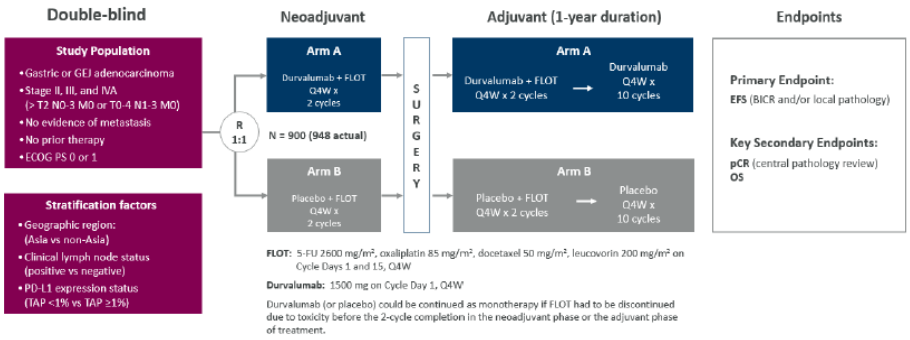


Table 10 Overview of study design for studies included in the comparison (1)

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up time
MATTERHORN; global, multicentre phase III study NCT04592913 (Janjigian YY, Al-Batran SE, Wainberg ZA, et al. Perioperative Durvalumab in Gastric and Gastroesophageal Junction Cancer. New England Journal of Medicine. 2025;393(3):217-230. doi:10.1056/nejmoa2503701) (1)	Randomized, double-blind, placebo-controlled, multicenter, global, phase III perioperative study of durvalumab + FLOT versus placebo + FLOT in resectable GC/GEJC. Stratified by PD-L1 TAP, clinical nodal status, site (gastric vs GEJ), and region.	From randomization until EFS interim analysis (DCO2; ~31 months; 40.6% EFS maturity) and to OS final analysis (FA) planned at ~51% maturity or ~3 years after last-patient-randomized (whichever first).	Adults (≥18 years) with histologically confirmed adenocarcinoma; resectable Stage II–IVa; ECOG 0–1; MDT eligible for curative-intent surgery.	Durvalumab 1500 mg Q4W + FLOT Q2W ×2 (neoadjuvant) → surgery → durvalumab 1500 mg Q4W + FLOT Q2W ×2 (adjuvant) → durvalumab 1500 mg Q4W ×10 (monotherapy); maximum 14 durvalumab cycles.	Matching placebo + FLOT on identical perioperative schedule.	Overall survival (OS): The median duration of follow-up in all patients was 39.1 months at DCO3, 1st of September 2025 . (73) Event-free survival (EFS): The median duration of follow-up for EFS (in censored patients) was 31.6 months (range: 0.03–48.10 months) in the durvalumab arm and 31.4 months (range: 0.03–48.07 months) in the placebo arm at DCO2, 20th December 2024. (3, 5) Pathological complete response rate (pCR): DCO1 (1st February 2023. (3, 5) Disease free survival (DFS): DCO2, 20th December 2024. (3, 5) For further description of outcomes in the MATTERHORN study please see Appendix A.

6.1.2 Comparability of studies

MATTERHORN is a head-to-head study between the intervention and comparator for this application. The control arm of the MATTERHORN study (placebo + FLOT) is representative of SoC in Denmark (22). The comparative effectiveness of perioperative durvalumab + FLOT vs. SoC can therefore be assessed based on the evidence from the MATTERHORN study.

6.1.2.1 Comparability of patients across studies

The baseline demographics and disease characteristics were largely balanced between the intervention arm, durvalumab + FLOT, and the comparator arm placebo + FLOT (Table 11). The median age was 62 years and 71.9% were male. Enrolment was global and balanced by stratification, with around 80% of participants from non-Asia regions. Primary tumour location was gastric in about 68% of patients and gastro-oesophageal junction in about 32% (including Siewert Types I–III). Clinical nodal status at baseline was mostly positive, with roughly 70% node-positive. By AJCC 8th edition staging, most patients were Stage III at baseline. A substantial proportion were PD-L1 positive, defined as TAP ≥1% (90%). (5)

Table 11 Baseline characteristics of patients in MATTERHORN study included for the comparative analysis of efficacy and safety (Full analysis set) (5)

		MATTERHORN		
		Durvalumab + FLOT (n = 474)	**Placebo + FLOT (n = 474)**	**Total (n = 948)**
Age (years)	Median (range)	62.0 (26, 84)	63.0 (28, 83)	62.0 (26, 84)
Age group (years) – no. (%)	≥ 75	37 (7.8)	43 (9.1)	80 (8.4)
Sex — no. (%)	Male	326 (68.8)	356 (75.1)	682 (71.9)
	Female	148 (31.2)	118 (24.9)	266 (28.1)
Region — no. (%)	Non-Asia	271 (79.9)	249 (77.1)	520 (78.5)
	Asia	68 (20.1)	74 (22.9)	142 (21.5)
Race — no. (%)	White	321 (67.7)	322 (67.9)	643 (67.8)
	Asian	96 (20.3)	97 (20.5)	193 (20.4)
	American Indian or Alaska Native	18 (3.8)	20 (4.2)	38 (4.0)
	Black or African American	7 (1.5)	3 (0.6)	10 (1.1)
	Other	8 (1.7)	8 (1.7)	16 (1.7)
	Not reported	24 (5.1)	24 (5.1)	48 (5.1)

		MATTERHORN		
		Durvalumab + FLOT (n = 474)	Placebo + FLOT (n = 474)	Total (n = 948)
Ethnic group, no. (%)	Hispanic or Latino	89 (18.8)	101 (21.3)	190 (20.0)
	Not Hispanic or Latino	385 (81.2)	373 (78.7)	758 (80.0)
Weight group (kg), no. (%)	< 70	200 (42.2)	212 (44.7)	412 (43.5)
	≥ 70 - ≤ 90	200 (42.2)	192 (40.5)	392 (41.4)
	> 90	74 (15.6)	70 (14.8)	144 (15.2)
Geographic region, no. (%)	Asia	90 (19.0)	90 (19.0)	180 (19.0)
	Non-Asia	384 (81.0)	384 (81.0)	768 (81.0)
ECOG performance status – no. (%)	0 (normal activity)	337 (71.1)	366 (77.2)	703 (74.2)
	1 (restricted activity)	137 (28.9)	108 (22.8)	245 (25.8)
Clinical lymph node status, no. (%)	Positive	329 (69.4)	330 (69.6)	659 (69.5)
	Negative	145 (30.6)	144 (30.4)	289 (30.5)
Microsatellite instability status, no. (%)	High	25 (5.3)	24 (5.1)	49 (5.2)
	Not-high	301 (63.5)	310 (65.4)	611 (64.5)
	Not evaluable	69 (14.6)	52 (11.0)	121 (12.8)
	Missing	79 (16.7)	88 (18.6)	167 (17.6)
PD-L1 expression level, no. (%)	TAP ≥ 1%	426 (89.9)	427 (90.1)	853 (90.0)
	TAP < 1%	48 (10.1)	47 (9.9)	95 (10.0)
Primary tumor location ‑ no. (%)	Gastric	324 (68.4)	316 (66.7)	640 (67.5)
	Gastro-oesophageal junction	150 (31.6)	158 (33.3)	308 (32.5)
	Siewert Type 1	44 (9.3)	55 (11.6)	99 (10.4)
	Siewert Type 2	72 (15.2)	68 (14.3)	140 (14.8)
	Siewert Type 3	34 (7.2)	35 (7.4)	69 (7.3)
Histology type – no. (%)	Intestinal type	245 (51.7)	238 (50.2)	483 (50.9)
	Diffuse type	130 (27.4)	119 (25.1)	249 (26.3)

		MATTERHORN		
		Durvalumab + FLOT (n = 474)	Placebo + FLOT (n = 474)	Total (n = 948)
	Indeterminate type	99 (20.9)	117 (24.7)	216 (22.8)
TNM classification	T0	1 (0.2)	0	1 (0.1)
Primary tumor – no. (%)				
	Tis	1 (0.2)	0	1 (0.1)
	T1	7 (1.5)	4 (0.8)	11 (1.2)
	T2	41 (8.6)	32 (6.8)	73 (7.7)
	T3	307 (64.8)	321 (67.7)	628 (66.2)
	T4a	101 (21.3)	103 (21.7)	204 (21.5)
	T4b	16 (3.4)	14 (3.0)	30 (3.2)
Regional lymph nodes – no. (%)	N0	137 (28.9)	140 (29.5)	277 (29.2)
	N1	212 (44.7)	199 (42.0)	411 (43.4)
	N2	103 (21.7)	116 (24.5)	219 (23.1)
	N3a	16 (3.4)	15 (3.2)	31 (3.3)
	N3b	3 (0.6)	3 (0.6)	6 (0.6)
	Missing	3 (0.6)	1 (0.2)	4 (0.4)
Distant metastases – no. (%)	M0	474 (100)	473 (99.8)	947 (99.9)
	Missing	0	1 (0.2)	1 (0.1)
AJCC staging 8th edition – no. (%)	Stage IIA	37 (7.8)	25 (5.3)	62 (6.5)
	Stage IIB	109 (23.0)	108 (22.8)	217 (22.9)
	Stage III	287 (60.5)	298 (62.9)	585 (61.7)
	Stage IVA	41 (8.6)	42 (8.9)	83 (8.8)
	Missing	0	1 (0.2)	1 (0.1)

6.1.3 Comparability of the study population(s) with Danish patients eligible for treatment

The MATTERHORN trial population, including patients enrolled at three Danish treatment centers, is assumed to be representative of Danish patients with GC/GEJC undergoing surgical resection. Inclusion of Danish participants supports the applicability of the study's perioperative findings to routine practice in Denmark. Patient and disease characteristics for the Danish patient population eligible for adding perioperative immunotherapy to standard perioperative FLOT treatment are extracted from Real-world data on resected GC/GEJC patients diagnosed 2019-2024, when FLOT was available for Danish patients (CASTOR study, Appendix K) (27). (Table 12).

The CASTOR study of Danish GC/GEJC patients undergoing resection (2019–2024), shows that resected GC/GEJC patients had a median age of approximately [redacted] years and were predominantly male (~[redacted]%). Compared with MATTERHORN, CASTOR data indicates a higher proportion of GEJC cases (Denmark [redacted]% vs MATTERHORN 32%), a greater prevalence of intestinal histology (Denmark [redacted]% vs MATTERHORN 52%), and fewer diffuse-type tumours (Denmark [redacted]% vs MATTERHORN 27%) (27). These baseline differences do not translate into variations in efficacy: MATTERHORN subgroup analyses showed consistent benefit on both EFS and OS across sex, age, primary site (GC/GEJ), ECOG PS, and histology (including intestinal and diffuse), with no detrimental signals in any subgroup, as presented in the OS subgroup analysis (see 6.1.4.1.1; Figure 8) and EFS subgroup analysis (see 6.1.4.2.1; Figure 10)), however, the MATTERHORN study was not powered for individual subgroup comparisons.

Aligned with MATTERHORN, GC/GEJ patients undergoing surgery in Denmark show a predominance of locally advanced (Stage III/IVA). Real world data from CASTOR and DECG yearly report (year 2024) further support the robustness of perioperative FLOT and surgery treatment (7, 27). With median intervals of ~[redacted] months to surgery (27) (4-8 weeks in MATTERHORN (1)) and ~[redacted] months to adjuvant therapy (27) (4-12 weeks in MATTERHORN (1)), high-quality- resections with D2 lymphadenectomy as standard, and low 90-day postoperative mortality (7). To sum up; Danish registry and CASTOR data support external validity and suggest readiness to implement durvalumab + FLOT in a perioperative setting without systemic pathway changes, while maintaining surgical quality comparable to the MATTERHORN study.

Data on performance status is not reported in the CASTOR data (see Appendix K). According to the Danish clinical guideline, patients should be in a general clinical condition such that treatment is not expected to result in serious adverse events or compromise curatively intended surgery, typically corresponding to a performance status of 0–1 and the absence of significant comorbidities. (22, 27)

Table 12 Characteristics in the relevant Danish population and in the health economic model (7, 27)

	Value in Danish population	Value in MATTERHORN study	Value used in health economic model (reference if relevant)
Age median (years)	[redacted]	62	NA
Sex Male (%)	[redacted]	68.8	NA
GC/GEJC (%)	[redacted]	68.4 / 31.6	NA
Histological classification (%) Intestinal	[redacted]	51.7	NA
Diffuse	[redacted]	27.4	NA
Other	[redacted]	20.9	NA
dMMR	[redacted]	5.3	NA
AAJC stage (GC/GEJC %)			
I	[redacted]		NA
II	[redacted]	30.8	NA
III/IVa	[redacted]	69.1	NA

6.1.4 Efficacy – results per MATTERHORN

As per DMC guidance, data from ITT population will be presented from MATTERHORN, with the exception of subgroup analysis for OS, EFS, and DFS.

The MATTERHORN study was not designed to assess the standalone contribution of neoadjuvant or adjuvant durvalumab + FLOT, nor of adjuvant durvalumab monotherapy. Instead MATTERHORN was designed to assess treatment with neoadjuvant and adjuvant durvalumab + FLOT followed by adjuvant durvalumab monotherapy as a perioperative regime vs. perioperative FLOT monotherapy in resectable GC/GEJC. (3) The clinical benefit of durvalumab in resectable GC/GEJC can therefore only be assessed as the entire perioperative regimen, and there is no evidence to support the use of the neoadjuvant or adjuvant regimen alone. (3) Hence, given the study design closely reflects Danish clinical practice and the FLOT regimen employed in MATTERHORN is concordant with Danish clinical guidelines (22), the perioperative efficacy outcomes observed in the study should be expected to be generalizable to patients treated in Denmark. The totality of data from the study, including secondary endpoints such as pCR (reflecting the effect of treatment in the neoadjuvant period) and DFS (assessing benefit from the time

of surgery in patients who would receive adjuvant therapy), allow a robust characterisation of the benefit of the entire perioperative durvalumab + FLOT regimen.

Collectively, the efficacy results in this study demonstrate that durvalumab given in combination with FLOT chemotherapy as neoadjuvant and adjuvant treatment, followed by durvalumab monotherapy, resulted in a substantial enhancement of pathological regression and a clinically meaningful improvement of overall disease control and long-term clinical outcomes in patients with resectable GC/GEJC, as compared to placebo + FLOT. Data from the CASTOR study shows that most EFS-from-surgery occurring within the first [redacted] months post-resection. This directly overlaps with the perioperative window where MATTERHORN demonstrated a significant EFS improvement (HR 0.71; 2-year EFS 70.4% vs 58.5%), indicating that early event reduction is clinically relevant in Denmark and likely to lower perioperative pathway failures. (1, 5, 27)

This assessment includes the primary endpoint, EFS and the three secondary endpoints OS, pCR and DFS.

6.1.4.1 Overall survival

Data from the CASTOR study shows overall survival from surgery declines over [redacted] months, with short survival after recurrence, highlighting substantial mortality in routine practice. The OS benefit in MATTERHORN's (HR 0.78) is therefore relevant to Denmark and suggests that fewer patients will experience prolonged high-intensity care following early perioperative events. (27) At DCO3 (1st September 2025), the FA of OS was conducted with an overall data maturity of 37.1%. At DCO3, 160 (33.8%) patients had died due to any cause in the durvalumab arm vs 192 (40.5%) patients in the placebo arm (Table 13**)**. The median duration of follow-up in all patients was 39.1 months at DCO3. (73)

MATTERHORN demonstrated that treatment with durvalumab in combination with perioperative FLOT resulted in a statistically significant and clinically meaningful improvement in OS compared with placebo and perioperative FLOT. Median OS was not reached in the durvalumab arm nor the placebo arm for the ITT population. The HR was 0.78 (95% CI: 0.63, 0.96; 2-sided p-value = 0.021), representing a 22% reduction in the risk of death due to any cause in the durvalumab arm compared to the placebo arm. (73) When assessing the log-log plot for OS at DCO3, the curves are indistinguishable through approximately 13 months (log(time) ≈ 2.5 on the natural-log scale), consistent with the KM curve (see Figure 15) (73). Beyond roughly 13 months, the log-log curves appear approximately parallel without crossing of the curve, indicating that the proportional hazards assumption appears reasonable for the interval >12 months. Over the entire follow-up, however, the proportional hazards assumption could not be satisfied due to the early non-proportionality. The Cox model's hazard ratio can be interpreted as a time-averaged (event-time–weighted) effect over the observed follow-up, which still demonstrates a meaningful survival improvement in the durvalumab arm.

Consistent with the pattern observed in the log-log plot, piecewise Cox analyses (DCO2) indicated no evidence of benefit during months 0–12 (hazard ratio [HR] for death, 0.99;

95% CI, 0.70–1.39) and a subsequently larger effect beyond 12 months (HR, 0.67; 95% CI, 0.50–0.90) (3).

After approximately 13 months post-randomization, there was a clear and sustained separation in the KM curves of OS in favour of the durvalumab arm vs the placebo arm (Figure 7). Given that approximately 90% in each arm attained R0 resection and both arms received intensive perioperative therapy FLOT +/- durvalumab, early hazards could be expected to be similar across arms, with any incremental survival advantage manifesting subsequently, based on the IO long-term effect(3). The OS benefit in the durvalumab arm was sustained over time, as shown by a numerical improvement in the proportion of patients who were alive based on KM estimates in the durvalumab arm compared to the placebo arm at 18 months (81.1% vs 77.1%), 24 months (75.5% vs 70.4%), 30 months (71.8% vs 64.7%), and 36 months (68.6% vs 61.9%) post-randomization (in the durvalumab arm and placebo arm, respectively) (Table 13). (73)

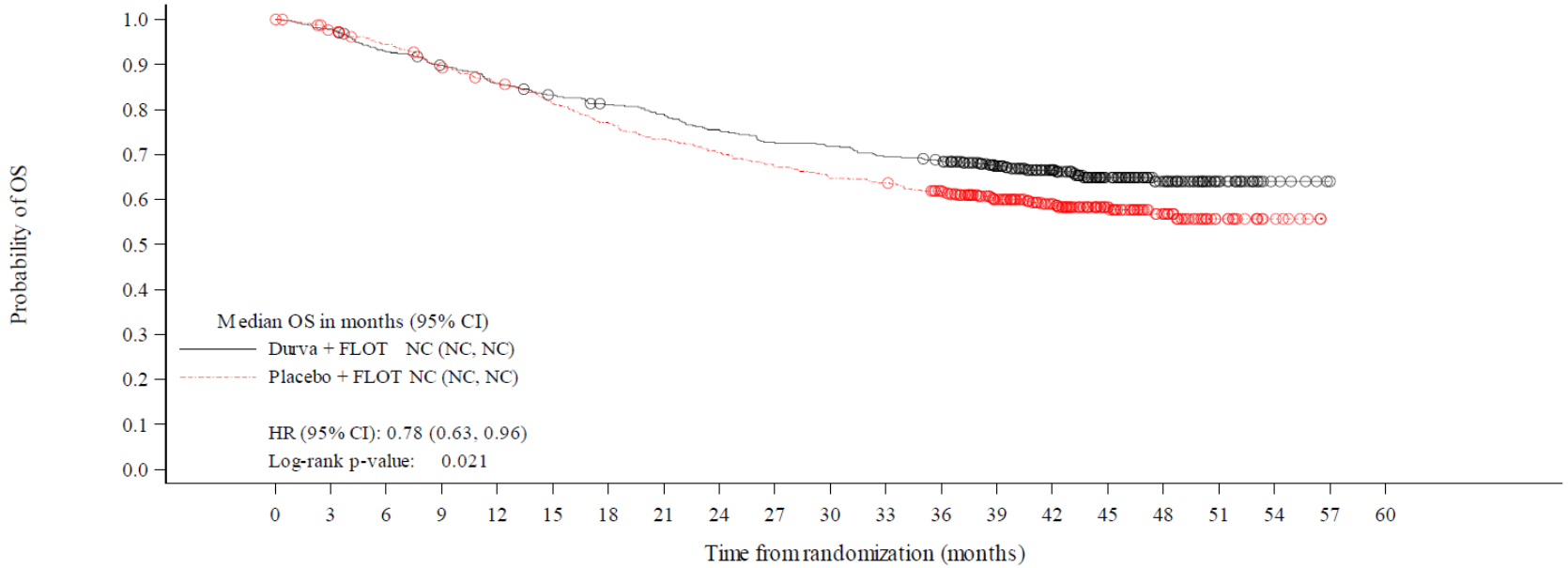
Data from the CASTOR study shows that OS in resected cohorts declines over [redacted] months in routine care. Specifically, OS from surgery is approximately [redacted] % at [redacted] months (95% CI [redacted]), [redacted] % at [redacted] months (95% CI [redacted]), and [redacted] % at [redacted] months (95% CI [redacted]). (27) This trajectory is consistent with the mortality burden seen in the placebo arm and is mitigated by the OS separation observed in MATTERHORN (HR 0.78). (73)

Table 13 Summary of OS (FAS, DCO3, unless otherwise specified) (73)

	Durvalumab arm (n=474)	Placebo arm (n=474)
Events n (%)	160 (33.8)	192 (40.5)
HR (95% CI)	0.78 (0.63, 0.96)	
2-sided p-value	0.021	
Median OS, months (95% CI)	NC (NC – NC)	NC (NC – NC)
Piecewise HR (FAS, DCO2*)		
0 to 12 months, events (%)	67/474 (14.1)	67/474 (14.1)
HR (95% CI)	0.99 (0.70, 1.39)	
≥ 12 months, events	78/403 (19.4)	109/395 (27.6)
HR (95% CI)	0.67 (0.50, 0.90)	
Landmark OS		
12 months, % (95% CI)	85.8 (82.3, 88.6)	85.6 (82.1, 88.5)
- *HR (95% CI)*	0.98 (0.72–1.34)	

18 months, % (95% CI)	81.1 (77.3, 84.4)	77.1 (73.0, 80.7)
- *HR (95% CI)*	0.81 (0.62–1.05)	
24 months, % (95% CI)	75.5 (71.4, 79.1)	70.4 (66.0, 74.3)
- *HR (95% CI)*	0.80 (0.63–1.01)	
30 months, % (95% CI)	71.8 (67.5, 75.7)	64.7 (60.2, 68.9)
- *HR (95% CI)*	0.76 (0.61–0.95)	
36 months, % (95% CI)	68.6 (64.2, 72.6)	61.9 (57.3, 66.2)
- *HR (95% CI)*	0.79 (0.64–0.97)	
Median duration of follow-up in all patients, month (range)	39.06 (0.03, 57.00)	
Median duration of follow-up in censored patients, months (range)	42.99 (0.03, 57.00)	

Figure 7 KM curves for OS (FAS, DCO3) (73)



Number of subjects at risk Month	000	003	006	009	012	015	018	021	024	027	030	033	036	039	042	045	048	051	054	057	060	Number of randomized subjects/ number of events
Durva + FLOT	474	464	438	422	403	389	377	367	351	338	334	323	316	255	182	112	71	29	6	1	0	474/160
Placebo + FLOT	474	457	439	414	395	374	355	338	324	310	298	293	278	221	167	99	61	23	7	0	0	474/192

Foodnote: Circle symbol indicates a censored observation. The HR and its CI are estimated from a Cox proportional hazards model, adjusted for geographic region, clinical lymph node status, and PD-L1 expression level. The CI for the HR is calculated using a profile likelihood approach. An HR < 1 favors the Durvalumab arm. The 2-sided p-value is calculated using a stratified log-rank test, adjusting for geographic region, clinical lymph node status, and PD-L1 expression level.

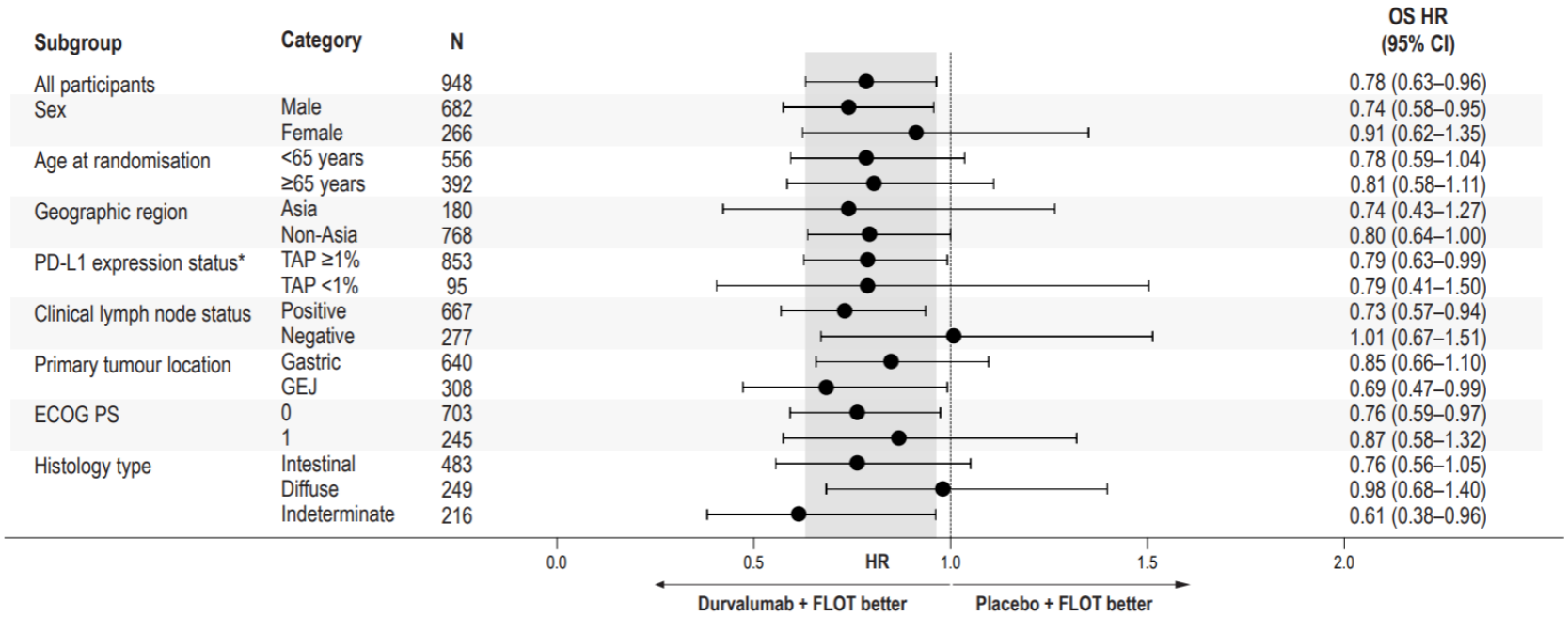
6.1.4.1.1 Subgroup analysis for overall survival

The OS benefit in the durvalumab arm compared to the placebo arm was observed to be consistent across the prespecified subgroups, including sex, age, geographic region, primary tumour location (gastric vs gastro-oesophageal junction), clinical lymph node status, ECOG PS, and regardless of PD-L1 expression level (i.e, the prespecified TAP 1% cut-off) (Figure 8). (4)

Histology subgroup analysis was assessed in a post hoc analysis per local laboratory. Diffuse-type histology is associated with an inferior prognosis compared with intestinal-type (20). Accordingly, the lower prevalence of diffuse histology in Danish resected cohorts relative to MATTERHORN (approximately [redacted] % vs 27.4%, see Table 12) implies a higher proportion of intestinal-type disease in Denmark, which is generally more amenable to perioperative chemotherapy (see Figure 8). This difference supports the expectation that the overall survival benefit observed with perioperative durvalumab plus FLOT is likely to translate to clinical benefit in Danish practice. (27, 67)

Since the 95% CI of the all the subgroups includes the point estimate of OS in the FAS (HR = 0.78), OS results for the subgroups are not considered significantly different from those of the FAS population. (73) It should be noted, however, that the study was not powered for individual subgroup comparisons, and no multiplicity adjustments were made.

Figure 8 OS in key subgroups (4)



*Measured by immunohistochemistry using the investigational VENTANA PD-L1 (SP263) Assay (Roche Diagnostics) and recorded at randomisation on the Interactive Response Technology System, Randomisation and Trial Supply Management, Electronic Case Report Form or from external vendor data from samples collected on or before randomisation. Participants provided a tumour tissue sample at screening to determine PD-L1 status using the TAP scoring method.
Data cut-off: 01 September 2025. The analysis was performed using a Cox proportional hazards model with treatment as the only covariate. An HR <1 favours durvalumab + FLOT. The CI was calculated using a profile likelihood approach. The grey band represents the 95% CI for the intention to treat HR.

6.1.4.2 Event-free survival

A DCO2 (20th December 2024), 385 EFS events (using BICR for RECIST v1.1) had occurred across the two treatment arms in the FAS population (3) with 167 events in the durvalumab arm and 218 events in the placebo arm (Table 14) (3), equivalent to 40.6% maturity for EFS. The median duration of follow-up for EFS (in censored patients) was 31.6 months (range: 0.03–48.10 months) in the durvalumab arm and 31.4 months (range: 0.03–48.07 months) in the placebo arm. (3, 5)

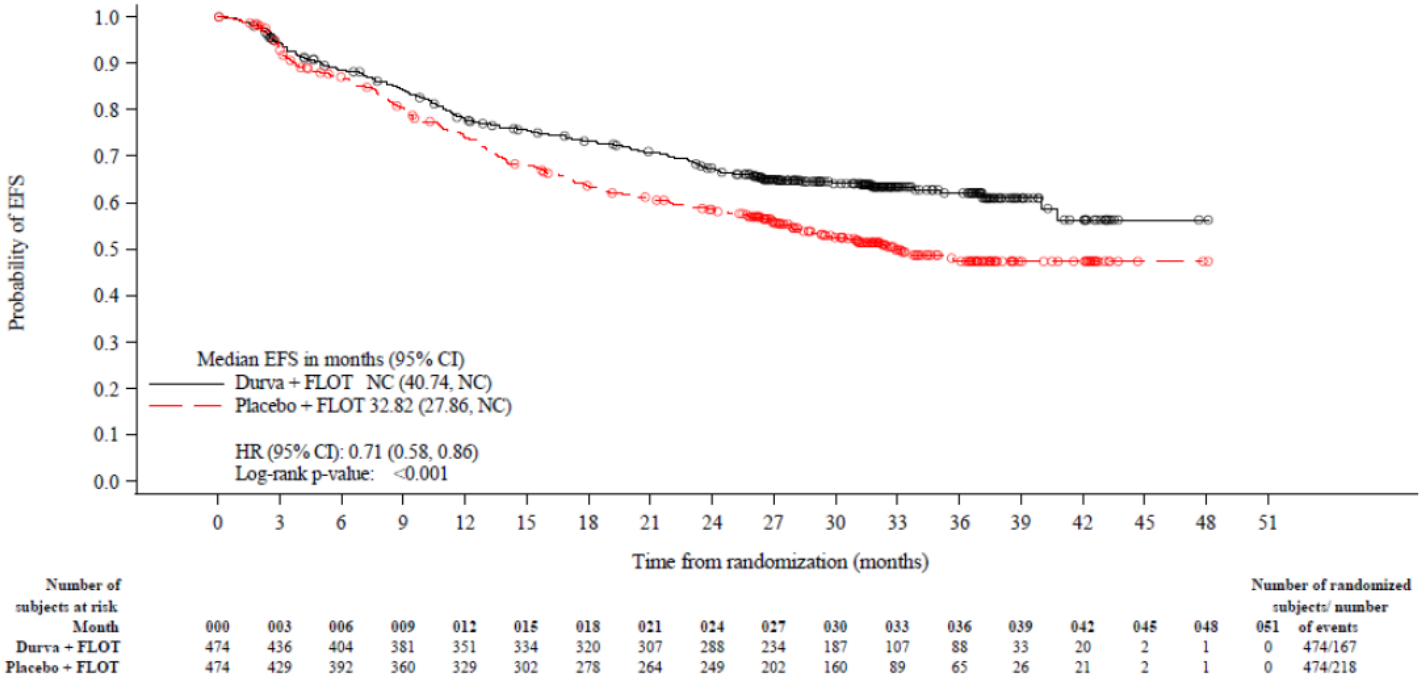
A clinically meaningful and statistically significant improvement in EFS was demonstrated in the durvalumab arm compared with the placebo arm (HR: 0.71; 95% CI: 0.58, 0.86; p<0.001) (3). Median EFS was not reached (95% CI: 40.7 months, NC) in the durvalumab arm and was 32.8 months (95% CI: 27.9 months, NC) in the placebo arm (3).

After approximately three months post-randomisation, there was clear and sustained separation of the EFS Kaplan-Meier (KM) curves through the remaining duration of follow-up that favoured the durvalumab arm (Figure 9) (3).

This was also reflected in the estimated EFS rates at 18 months (73.2% vs. 63.6%, for the durvalumab and placebo arms respectively) and 24 months (67.4% vs. 58.5%, respectively) (3).

The results of the primary EFS analysis were robust, with consistent results observed across all pre-specified sensitivity analyses as demonstrated in the subgroup analyses presented in Figure 10. Additionally, Durvalumab plus FLOT reduced distant recurrence/progression by almost 7 percentage points (23.3% with placebo + FLOT versus 16.5% with durvalumab + FLOT) and given that most recurrences are distant and typically lead to fatal outcomes, this reduction is clinically meaningful and directly addresses the principal driver of mortality in resectable GC/GEJC. (3)

Figure 9 KM curves for EFS (using BICR for RECIST v1.1) (FAS, DCO2) (3, 5)



Number of subjects at risk Month	000	003	006	009	012	015	018	021	024	027	030	033	036	039	042	045	048	051	Number of randomized subjects/ number of events
Durva + FLOT	474	436	404	381	351	334	320	307	288	234	187	107	88	33	20	2	1	0	474/167
Placebo + FLOT	474	429	392	360	329	302	278	264	249	202	160	89	65	26	21	2	1	0	474/218

Footnotes: DCO: 10th December 2024. Circle indicates a censored observation. Events are defined as the earliest of RECIST 1.1 events, non-RECIST 1.1 events, or deaths of any cause as defined in the SAP. Analysis is based on BICR assessments and/or locally by pathology testing if clinically required. The HR and its CI are estimated from a Cox proportional hazards model, adjusted for geographic region, clinical lymph node status, and PD-L1 expression level. The CI for the HR is calculated using a profile likelihood approach. An HR <1 favours the durvalumab arm. The 2-sided p-value is calculated using a stratified log-rank test, adjusting for geographic region, clinical lymph node status, and PD-L1 expression level.

Table 14 Summary of EFS (using BICR for RECIST v1.1) (FAS, DCO2) (3, 5)

	Durvalumab arm (n=474)	Placebo arm (n=474)
Events[a] n (%)	167 (35.2)	218 (46.0)
HR[b]	0.71	
95% CI[b]	0.58, 0.86	
2-sided p-value[c]	<0.001	
Median EFS, months[d] (95% CI)	NC (40.7, NC)	32.8 (27.9, NC)
Landmark EFS, %[d] (95% CI)		
18 months, % (95% CI)	73.2 (68.9, 77.0)	63.6 (59.0, 67.9)
24 months, % (95% CI)	67.4 (62.9, 71.6)	58.5 (53.8, 63.0)
36 months, % (95% CI)	61.99 (57.0, 66.6)	52.48 (41.8, 52.5)
Median duration of follow-up in censored patients, months (range)	31.64 (0.03–48.10)	31.44 (0.03–48.07)

Footnotes: DCO: 10th December 2024. [a] Events are defined as the earliest of RECIST 1.1 events, non-RECIST 1.1 events or deaths of any cause as defined in the SAP. Events are according to RECIST 1.1 per BICR assessment and/or local pathology testing. [b] Estimated from a stratified Cox proportional hazards model stratified by geographic region, clinical lymph node status and PD-L1 expression level at randomisation. An HR <1 favours the durvalumab arm. The corresponding CI was calculated using the profile likelihood approach. [c] Derived using a stratified log-rank test adjusted for geographic region, clinical lymph node status, and PDL1 expression status at randomisation. [d] Calculated using the KM technique. Based on a Lan-DeMets alpha spending function with O'Brien Fleming boundary calculated using the actual number of events at DCO2, the p-value boundary for declaring statistical significance of EFS was p <0.0239.

6.1.4.2.1 Subgroup analysis of EFS

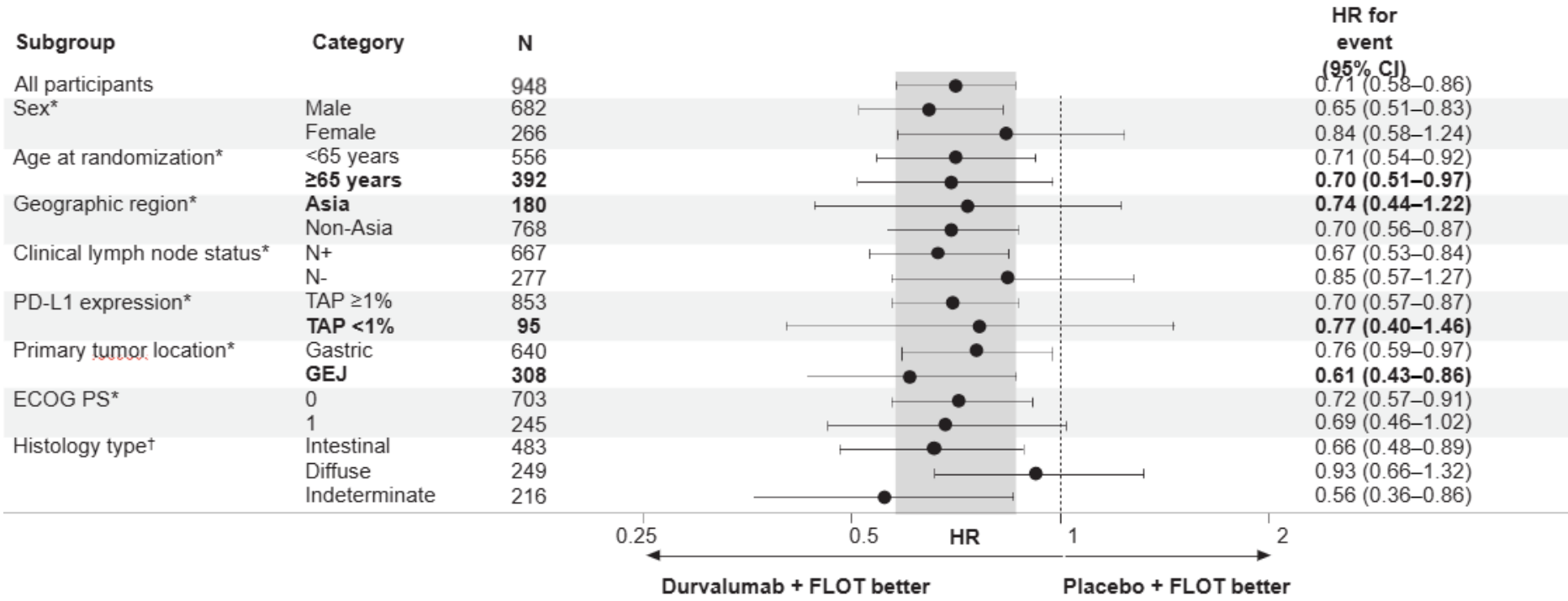
Prespecified subgroup analyses of EFS were performed to evaluate the consistency of the treatment effect across prespecified stratification factors and subgroups, including sex, age at randomisation, geographic region, clinical lymph node status, ECOG PS, PD-L1 expression level (TAP <1% vs. ≥1%), and primary tumour location (Figure 10) (5).

The estimated HRs were in favour of the durvalumab arm compared with the placebo arm (HRs for durvalumab arm vs. placebo arm <1), indicating consistent improvements in EFS across pre-specified subgroups.

HRs in favour of the durvalumab arm were also observed for post-hoc subgroup analyses, including subgroups for PD-L1 expression levels at the prespecified TAP cut-off of 1%, MSI status, primary tumour location (Gastric/GEJC), and histology type (intestinal/diffuse/indeterminate) (3). Diffuse type histology has a worse prognosis than intestinal type histology, in Danish population. The lower proportion of diffuse histology in Danish resected GC/GEJC patients compared to MATTERHORN ([redacted] % vs. 27.4%) favours durvalumab + FLOT in a perioperative setting, due to the inherent worse prognosis of diffuse subtype and supports the expectation that MATTERHORN's EFS signals translate to benefit for Danish patients. (5, 27)

It should be noted, however, that the study was not powered for individual subgroup comparisons, and no multiplicity adjustments were made. As expected in a subgroup analysis, a degree of variability was observed across all subgroups, particularly in the subgroups with a smaller number of patients and with fewer EFS events observed.

Figure 10 EFS in key subgroup (5)

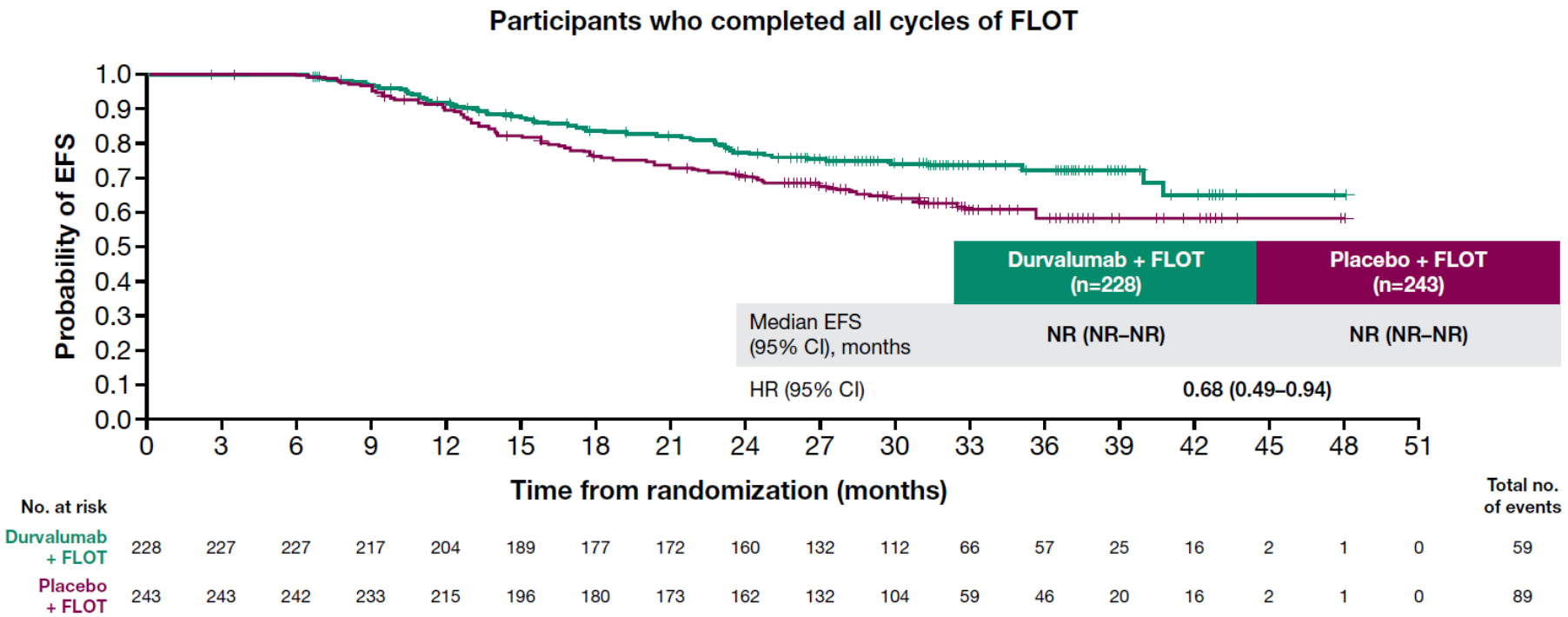


Footnotes: DCO: 20th December 2024. Gray band represents the 95% CI for the all-participants HR. The analysis was performed using a Cox proportional hazards model with treatment as the only covariate. The CI was calculated using a profile likelihood approach. Events were defined as the earliest of RECIST v1.1 events, non-RECIST v1.1 events, or deaths of any cause. Analysis was based on BICR assessment and / or locally by pathology testing if clinically required. *Pre-specified per protocol. †Assessed post hoc per local laboratory.

6.1.4.3 FLOT completion status on EFS

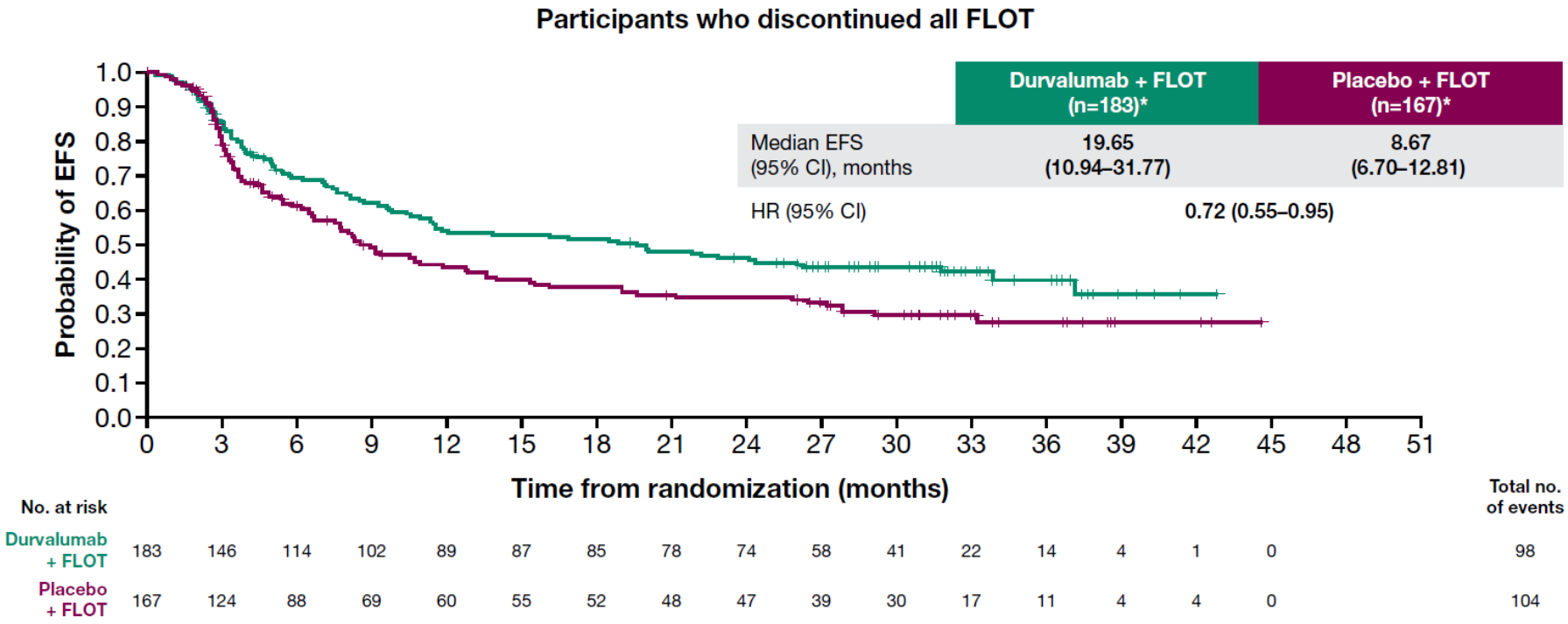
The MATTERHORN protocol prospectively allowed modification of individual FLOT components to reflect real-world practice, recognizing that toxicity profiles and supportive care standards for 5-fluorouracil, leucovorin, oxaliplatin, and docetaxel vary by patient factors and by country (74). Recent data presented at ASCO-GI 2026 showed that durvalumab + FLOT did not compromise FLOT delivery: neoadjuvant completion of ≥1 component 96.0% vs 95.1%; adjuvant 61.5% vs 64.4% (durvalumab vs placebo). AE-related discontinuation of ≥1 FLOT drug occurred in Durvalumab + FLOT 25.5% vs Placebo + FLOT 20.3%; oxaliplatin most frequently stopped; key AEs were peripheral neuropathy and neutropenia. EFS benefit with durvalumab was maintained irrespective of FLOT completion (completed all FLOT HR 0.68 [0.49–0.94]; discontinued 1–3 components HR 0.35 [0.16–0.71]; discontinued all FLOT HR 0.72 [0.55–0.95]). This data shows that adding durvalumab doesn't compromise FLOT use and still improves EFS outcomes even when FLOT components are discontinued - supporting durvalumab + FLOT as a robust perioperative option (see Figure 11 and Figure 12). (69)

Figure 11 EFS was improved with durvalumab + FLOT versus placebo + FLOT, in patients completing all cycles of FLOT (69)



Footnotes: Analyses performed in the intention-to-treat analysis set (all randomized participants, regardless of treatment received). HRs show durvalumab + FLOT versus placebo + FLOT, with an HR <1 favouring durvalumab + FLOT. *Includes 62 participants in the durvalumab + FLOT arm and 70 participants in the placebo + FLOT arm who did not complete surgery.

Figure 12 EFS was improved with durvalumab + FLOT versus placebo + FLOT, in patients who discontinued all FLOT (69)



Footnotes: Analyses performed in the intention-to-treat analysis set (all randomized participants, regardless of treatment received). HRs show durvalumab + FLOT versus placebo + FLOT, with an HR <1 favouring durvalumab + FLOT. *Includes 62 participants in the durvalumab + FLOT arm and 70 participants in the placebo + FLOT arm who did not complete surgery.

6.1.4.4 Pathological complete response rate

At DCO1 (1st February 2023), MATTERHORN met the prespecified boundary for declaring a statistically significant improvement in pCR rate per central pathological review (according to CAP-modified Ryan tumour regression score of 0, indicating no viable tumour cells in the resected specimen and nodes) (75, 76). Results demonstrated that treatment with durvalumab + FLOT prior to surgery resulted in a statistically significant improvement in pCR rate compared with the placebo + FLOT.

The pCR rate per central pathology review was 19.2% (95% CI: 15.75 to 23.04) in the durvalumab arm and 7.2% (95% CI: 5.02 to 9.88) in the placebo arm, which corresponded to an absolute between-arm difference in pCR rate of 12.0% (odds ratio: 3.08 [95% CI: 2.03, 4.67]; p < 0.001; Table 16) (77).

Table 15 pCR rate assessed by central review (FAS, DCO1) (3)

	Durvalumab arm (n=474)	Placebo arm (n=474)
Number of patients with response,[a] n	91	34
Response rate, (%)	19.2	7.2
95% CI[b]	15.7, 23.0	5.0, 9.9
Difference in response rate,[c] (%)	12.0	
Comparison between groups[d]		
Odds Ratio	3.08	
95% CI	2.0, 4.7	
2-sided p-value	<0.001	

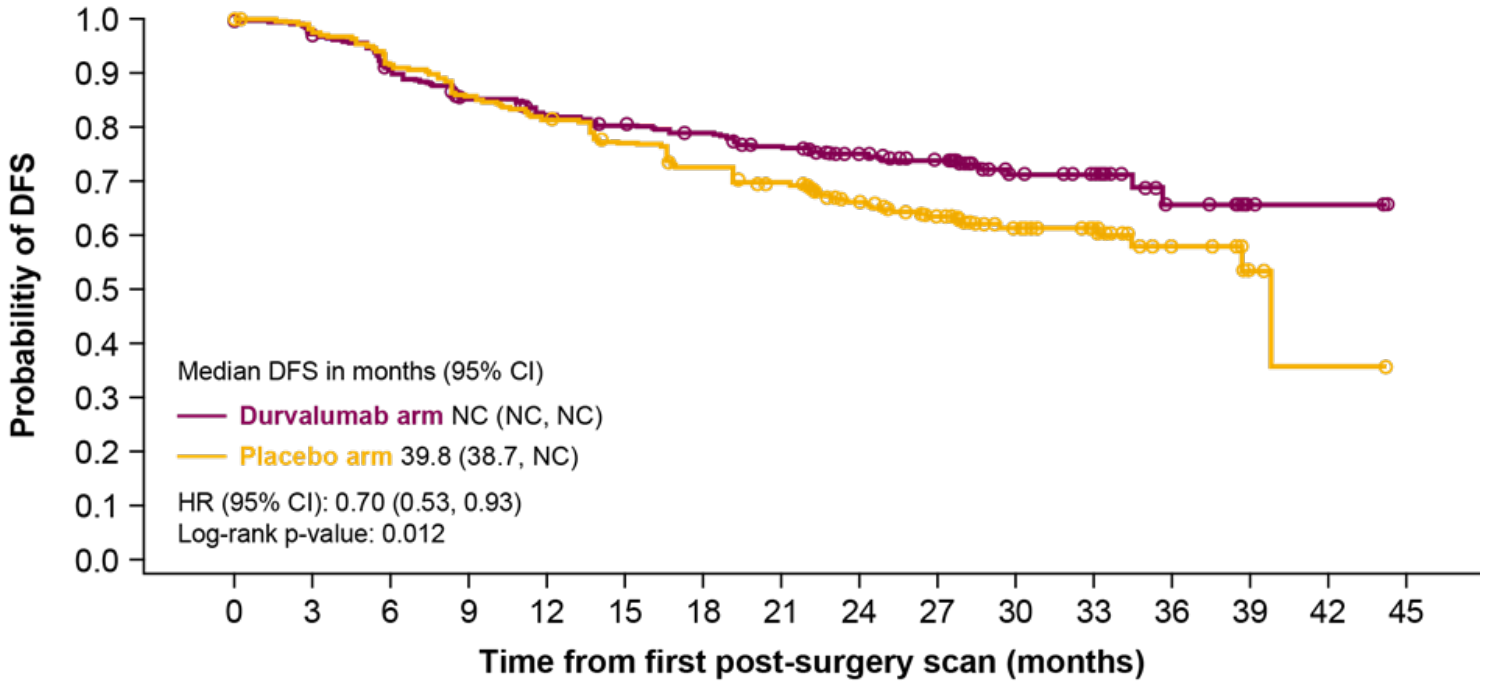
Footnotes: DCO: 1st February 2023. An odds ratio >1 favours the durvalumab arm. [a] Patients achieved pCR if there was no residual viable tumour cells found at primary tumour and resected lymph nodes at the time of resection, meaning a pathological regression of -100%, based on central assessment. [b] CIs for response rate are calculated using Clopper- Pearson exact method. [c] Difference in response rate = durvalumab arm response rate – placebo arm response rate. [d] The analysis was performed using a stratified Cochran-Mantel-Haenszel test. The stratification factors include geographic region, clinical lymph node status, and PD-L1 expression level at randomisation.

6.1.4.5 Disease free survival

A total of 339 patients in the durvalumab arm and 323 patients in the placebo arm had R0 resection and no measurable disease at adjuvant baseline and were included in the R0 Resected Analysis Set for analysis of DFS in the adjuvant period. (3)

At DCO2 (20th December 2024), DFS data had a 31.6% overall maturity, with 90 (26.5%) patients in the durvalumab arm and 119 (36.8%) patients in the placebo arm with DFS events (3, 5). Results indicated an improvement in DFS in the durvalumab arm compared to the placebo arm, with a HR of 0.70 (95% CI: 0.53, 0.93), representing a 30% reduction in the risk of disease recurrence or death due to any cause in the durvalumab arm (3, 5). There was a clear and sustained separation in the DFS KM curves at approximately 14 months post-adjuvant baseline that favoured the durvalumab arm, supported by the greater proportion of patients in the durvalumab arm who were alive and recurrence-free compared to the placebo arm at 18 months (79.1% and 72.8%, respectively), 24 months (75.2% and 66.2%, respectively), and 36 months (65.8% and 58.1%, respectively) Figure 13. (3, 5)

Figure 13 KM plot of DFS (R0 resected analysis set, DCO2) (3, 5)



Footnotes: DCO: 20th December 2024. DFS is the time from date of first post-surgery scan until an event in patients who had margin-negative surgery (R0) and no evidence of disease at the adjuvant baseline scan. A circle symbol indicates a censored observation. Patients who are alive and disease free at time of analysis are censored at date last known alive and without DFS event. If a patient died between first post-surgery scan and next scheduled RECIST 1.1 scan, this was considered an event. The HR and its CI are estimated from a Cox proportional hazards model, adjusted for geographic region, clinical lymph node status, and PD-L1 expression level. The CI for the HR is calculated using a profile likelihood approach. An HR <1 favours the durvalumab arm. The p-value is not adjusted for multiplicity.

Table 16 Summary of DFS (R0 resected analysis set, DCO2) (3, 5)

	Durvalumab arm	Placebo arm
Total DFS events,[a] n (%)	90/339 (26.5)	119/323 (36.8)
DFS HR[b]	0.70	
95% CI	0.53, 0.93	
Median DFS,c months (95% CI)	NC (NC, NC)	39.8 (38.7, NC)
Landmark DFS,[c] % (95% CI)		
18 months	79.1 (74.3, 83.1)	72.8 (67.6, 77.3)
24 months	75.2 (70.2, 79.5)	66.2 (60.6, 71.2)
36 months	65.8 (55.7, 74.0)	58.1 (50.4, 65.0)

Footnotes: DCO: 20th December 2024. N values for each analysis are provided in the relevant publication or CSR. DFS is the time from date of first post-surgery scan until an event in patients who had margin-negative surgery (R0) and no evidence of disease at the adjuvant baseline scan. MFS is the time from date of randomisation until the earliest date of metastasis or death due to any cause. DSS is defined as the time from date of randomisation until date of death due to GC/GEJC (any recorded deaths which are related to the disease under investigation). a DFS events are defined as disease recurrence by RECIST 1.1 by investigator, death due to any cause, or death between first post-surgery scan and next RECIST 1.1 scan. b The analysis was performed using a stratified Cox proportional hazards model, adjusting for geographic region, clinical lymph node status, and PD-L1 expression level. An HR <1 favours the durvalumab arm. The CI is calculated using a profile likelihood approach. c Calculated using the KM technique.

6.1.4.6 Surgical feasibility and pathway integrity

Surgery was attempted in approximately 91% of patients in both treatment arms, with completion in 86.9% in the durvalumab arm versus 84.4% in the placebo arm. Delays to surgery >8 weeks occurred in ~10% in each arm (most delays <2 weeks). Delayed start of adjuvant therapy (>12 weeks post-operatively) occurred in 2.3% versus 4.6%, respectively; median 42 days from last neoadjuvant to surgery and 56 days to adjuvant in both arms. EFS benefit with durvalumab was consistent by tumour location, margin, and lymphadenectomy type (see Table 17). In conclusion, these data indicate that adding durvalumab did not delay surgery, compromise initiation of adjuvant therapy, or increase perioperative risk; perioperative FLOT delivery was comparable between arms, and the EFS benefit was maintained across key surgical subgroups—supporting feasibility for routine perioperative use. (5, 68)

Importantly, treatment with durvalumab + FLOT did not influence the ability of patients to undergo curative surgery compared to treatment with placebo + FLOT. The proportion of patients in the FAS with completed surgery was similar between treatment arms (86.9% in the durvalumab arm vs 84.4% in the placebo arm). Among the participants in

whom surgery was completed, 377 of 412 participants (91.5%) in the durvalumab arm and 369 of 400 participants (92.3%) in the placebo arm had R0 resection. (3, 5)

Table 17 Surgical outcomes (DCO2) (3, 68)

	Durvalumab arm (n=474)*	Placebo arm (n=474)*
Received any neoadjuvant treatment, n (%)	474 (100)	470 (99.2)
Completed durvalumab or placebo	458 (96.6)	449 (94.7)
Completed all FLOT	448 (94.5)	437 (92.2)
Attempted surgery, n (%)	431 (90.9)	428 (90.3)
Completed surgery, n (%)	412 (86.9)	400 (84.4)
Type of surgery†, n (%)		
Distal gastrectomy	38 (8.0)	38 (8.0)
Subtotal gastrectomy	79 (16.7)	72 (15.2)
Total gastrectomy	168 (35.4)	166 (35.0)
Gastroesophagectomy	127 (26.8)	124 (26.2)
Surgery attempted but not completed, n (%)	19 (4.0)	28 (5.9)
Did not undergo surgery, n (%)	43 (9.1)	46 (9.7)
Resection margin‡, n (%)		
R0	377 (91.5)	369 (92.3)
R1†	23 (5.6)	21 (5.3)
R2†	11 (2.7)	10 (2.5)
Type of lymphadenectomy, n (%)		
D1	36 (8.7)	26 (6.5)
D2 / D3	375 (91.0)	373 (93.3)
Missing	1 (0.2)	1 (0.3)
Received any adjuvant treatment, n (%)	364 (76.8)	352 (74.3)
Completed durvalumab or placebo	248 (52.3)	245 (51.7)
Completed all FLOT	229 (48.3)	245 (51.7)

*ITT analysis set (all randomized participants, regardless of treatment received). †Data not reported in (3)

6.1.4.7 Subsequent anticancer treatment

At DCO3, the proportion of patients who has received at least one subsequent anticancer therapy was 27.4% (23.2% in the durvalumab arm and 31.6% in the placebo arm). A lower number of patients received subsequent immunotherapy (3.8% in the durvalumab arm and 10.5% in the placebo arm). The most common anticancer therapies administered are presented in Table 18. (73)

Table 18 Post-discontinuation disease-related anti-cancer therapy (73)

Anticancer therapy	Durvalumab arm (N = 474)	Placebo arm (N = 474)
Cytotoxic chemo – no. (%)	109 (23.0)	148 (31.2)
Antiangiogenic therapy – no. (%)	22 (4.6)	32 (6.8)
Targeted therapy – no. (%)	13 (2.7)	16 (3.4)
Immunotherapy – no. (%)	18 (3.8)	50 (10.5)

7. Comparative analyses of efficacy

7.1.1 Differences in definitions of outcomes between studies

N/A, comparison between durvalumab vs. SoC has been based on MATTERHORN, a head-to-head study.

7.1.2 Method of synthesis

N/A, head-to-head study.

7.1.3 Results from the comparative analysis

Table 19 Results from the comparative analysis of perioperative durvalumab + FLOT vs. placebo + FLOT for GC/GEJC cancer patients (5, 73)

Outcome measure	Durvalumab + FLOT (n = 474)	Placebo + FLOT (n=474)	Result
Overall survival	NC (NC – NC)	NC (NC – NC)	Absolute diff: NC HR: 0.78 (95% CI: 0.63, 0.96)
Overall survival, 12-month landmark	85.8% (95% CI: 82.3, 88.6)	85.6% (95% CI: 82.1, 88.5)	Absolute diff: 0.2% HR: 0.98 (95% CI: 0.72-1.34)
Overall survival, 18-month landmark	81.1% (95% CI: 77.3, 84.4)	77.1% (95% CI: 73.0, 80.7)	Absolute diff: 4.0% HR: 0.81 (95% CI: 0.62-1.05)
Overall survival, 24-month landmark	75.5% (95% CI: 71.4, 79.1)	70.4% (95% CI: 66.0, 74.3)	Absolute diff: 5.1% HR: 0.80 (95% CI: 0.63-1.01)
Overall survival, 30-month landmark	71.8% (95% CI: 67.5, 75.7)	64.7% (95% CI: 60.2, 68.9)	Absolute diff: 7.1% HR: 0.76 (95% CI: 0.63-1.01)
Overall survival, 36-month landmark	68.6% (95% CI: 64.2, 72.6)	61.9% (95% CI: 57.3, 66.2)	Absolute diff: 6.6% HR: 0.79 (95% CI: 0.64-0.97)

Outcome measure	Durvalumab + FLOT (n = 474)	Placebo + FLOT (n=474)	Result
Event-free survival	Median: NC (95% CI: 40.7, NC)	32.8 months (95% CI: 27.9, NC)	Absolute diff: NC HR: 0.71 (95% CI: 0.58, 0.86)
Event-free survival, 18-month landmark, %	73.2% (95% CI: 68.9, 77.0)	63.6% (95% CI: 59.0, 67.9)	Absolute diff: 9.6%
Event-free survival, 24-month landmark	67.4% (95% CI: 62.9, 71.6)	58.5% (95% CI: 53.8, 63.0)	Absolute diff: 8.9%

7.1.4 Efficacy – results per [outcome measure]

N/A, head-to-head study used for comparison, hence the comparative results are presented in section 6.1.

8. Modelling of efficacy in the health economic analysis

N/A.

8.1 Presentation of efficacy data from the clinical documentation used in the model

N/A.

8.1.1 Extrapolation of efficacy data

N/A.

8.1.1.1 Extrapolation of [effect measure 1]

N/A.

Table 20 Summary of assumptions associated with extrapolation of [effect measure]

Method/approach	Description/assumption
N/A.	N/A.

8.1.2 Calculation of transition probabilities

N/A.

Table 21 Transitions in the health economic model

Health state (from)	Health state (to)	Description of method	Reference
N/A.	N/A.	N/A.	N/A.

8.2 Presentation of efficacy data from [additional documentation]

N/A.

8.3 Modelling effects of subsequent treatments

N/A.

8.4 Other assumptions regarding efficacy in the model

N/A.

8.5 Overview of modelled average treatment length and time in model health state

N/A.

Table 22 Estimates in the model

	Modelled average [effect measure] (reference in Excel)	Modelled median [effect measure] (reference in Excel)	Observed median from relevant study
N/A.	N/A.	N/A.	N/A.

Table 23 Overview of modelled average treatment length and time in model health state, undiscounted and not adjusted for half cycle correction (adjust the table according to the model)

Treatment	Treatment length [months]	Health state 1 [months]	Health state 2 [months]
N/A.	N/A.	N/A.	N/A.

9. Safety

9.1 Safety data from the clinical documentation

Safety and tolerability were assessed in the MATTERHORN study in terms of AEs (including serious AEs [SAEs]), deaths, clinical laboratory evaluation, vital signs, electrocardiograms (ECGs) and treatment exposure (1).

At the time of DCO2 (10th December 2024), all patients had completed the safety follow-up period (≥90 days from the last dose of study drug). All safety analyses were conducted based on the safety analysis set (SAS). The SAS includes all randomised patients who received at least one dose of study treatment. This analysis set comprises of 944 patients who received at least one dose of study treatment (n=475[1] patients in the durvalumab arm and n=469 patients in the placebo arm)(5).

The median actual duration of exposure to study treatment (durvalumab or placebo) for the overall study was similar between treatment arms: 12.7 months in the durvalumab arm and 12.5 months in the placebo arm. (3)

- In the **neoadjuvant period**, the median actual duration of exposure to durvalumab or placebo was the same in both arms (1.84 months) (5)
- In the **adjuvant period**, the median actual duration of exposure to durvalumab or placebo was the same in both arms (11.04 months) (5)

After accounting for dose delays, there were no notable differences between the two arms in the total duration of exposure to durvalumab/placebo for the overall treatment period. The median total duration of exposure to durvalumab vs. placebo was the same in both arms (12.88 months). (5)

Overall, the duration of exposure to durvalumab/placebo and FLOT was comparable between treatment arms in the individual treatment periods of the MATTERHORN study, and the addition of durvalumab did not affect the administration of FLOT (Table 24). (3)

Table 24 Number of treatment cycles received in the MATTERHORN trial (SAS, DCO2) (3, 5)

[1] In addition, 1 patient was randomized to the Placebo + FLOT arm but received both placebo and durvalumab and therefore was included in the D + FLOT arm for the purpose of the Safety Analysis Set.

	Durvalumab + FLOT (n=475)		Placebo + FLOT (n=469)	
	Durvalumab	**FLOT**	**Placebo**	**FLOT**
Median number of neoadjuvant cycles	2.0	2.0	2.0	2.0
Median number of adjuvant cycles*	12.0	2.0	12.0	2.0
Number of neoadjuvant cycles, n (%)				
⩾1 cycle	475 (100)	475 (100)	469 (100)	469 (100)
Cycle 1 Day 1	N/A	475 (100)	NA	469 (100)
Cycle 1 Day 15	N/A	469 (98.7)	NA	459 (97.9)
2 cycles	461 (97.1)	462 (97.3)	451 (96.2)	452 (96.4)
Cycle 1 Day 1	N/A	462 (97.3)	NA	452 (96.4)
Cycle 1 Day 15	N/A	456 (96.0)	NA	446 (95.1)
Number of adjuvant cycles, n (%)				
⩾1 cycle	361 (76.0)	354 (74.5)	349 (74.4)	345 (73.6)
⩾2 cycles	348 (73.3)	318 (66.9)	336 (71.6)	319 (68.0)
⩾3 cycles*	343 (72.2)	N/A	331 (70.6)	N/A
12 cycles	246 (51.8)	N/A	240 (51.2)	N/A

Footnotes: DCO: 10th December 2024. *Start of adjuvant monotherapy. A cycle equals 28 days. Patients were counted as having received a cycle of therapy as soon as the infusion was started. If a cycle was prolonged due to toxicity, this was counted as 1 cycle. A cycle was counted if treatment was started, even if the full dose was not delivered. Rows are cumulative, and patients are included if they received treatment up to that number of cycles. Percentages are based on the total number of patients per treatment arm.
Abbreviations: DCO: data cut-off; FLOT: 5-fluorouracil, leucovorin, oxaliplatin, and docetaxel; N/A: not available; SAS: safety analysis set.

The majority of patients reported at least one AE (99.2% in the durvalumab arm vs 98.7% in the placebo arm). The most frequently reported AEs in the durvalumab arm and placebo arm (> 20% of patients in either treatment arm) were nausea, neutropenia, alopecia, decreased appetite, fatigue, vomiting, anaemia, neutrophil count decreased, and peripheral sensory neuropathy (known adverse drug reactions of FLOT chemotherapy); and diarrhoea and abdominal pain (known adverse drug reactions of both durvalumab and FLOT). (3, 5)

The AEs reported more frequently in the durvalumab arm vs the placebo arm (> 5% difference between arms) were pyrexia (20.0% vs 15.1%), rash (13.7% vs 7.2%), and pruritus (10.7% vs 5.3%), all of which are known adverse drug reactions of both durvalumab and FLOT and were mostly low grade in severity (Appendix E, Table 52). (3, 5)

SAEs of any cause were reported in 48.2% of patients in the durvalumab arm and 44.1% of patients in the placebo arm in the overall treatment period (3). The SAEs reported were consistent with the disease under investigation, as well as the established safety profile of the individual agents, durvalumab and FLOT. SAEs related to study drug were

primarily associated with FLOT during the neoadjuvant and the adjuvant phase. In the adjuvant monotherapy period, overall SAE rates were similar between arms (14.5% in each arm), and SAEs related to durvalumab or placebo occurred in 3.2% versus 1.8%, respectively (section 9.1.3 and Appendix E). (3, 5)

The nature and incidence of adverse events (AEs) of maximum Grade 3 or 4 for the overall study were comparable across arms (71.6% in the durvalumab arm vs. 71.2% in the placebo arm). Overall, a lower proportion of Grade 3 or 4 AEs possibly related to study treatment were attributed to durvalumab or placebo (14.1% vs. 12.4% in the respective treatment arms) compared to FLOT (57.3% vs. 57.1%), with similar rates reported in both arms (5). AEs max grade 3-4 related to study drug were majority related to FLOT both in the neoadjuvant phase and the adjuvant phase, and in the adjuvant monotherapy period similar frequencies were reported in both arms 5.5% vs 5.7% for addition of durvalumab or placebo, respectively. (3, 5) Additional details in section 9.1.2.

Dose reductions occurred in 41.9% of patients in the durvalumab arm and 39.4% in the placebo arm; these reflect adjustments to FLOT components as per protocol, as durvalumab is administered at a fixed dose. The most frequently reported AEs leading to dose modification overall (neutropenia and neutrophil count decreased) reflect the known safety profile of FLOT. (3, 5)

The proportions of patients with AEs leading to discontinuation of any study treatment during the overall study were higher in the durvalumab arm vs the placebo arm (29.9% vs 22.8% of patients, respectively), including those that led to discontinuation of durvalumab/placebo (10.1% vs 6.4% of patients, respectively) and those that led to discontinuation of any FLOT (25.5% vs 20.3% of patients, respectively). (3, 5)

During the overall study, TEAEs with outcome of death occurred in 24 (5.1%) patients in the durvalumab arm vs 20 (4.3%) patients in the placebo arm, the majority of which were assessed as unrelated to any study treatment by the investigator. Treatment-emergent AEs with outcome of death were assessed by the investigator as possibly related to any study treatment for 6 (1.3%) vs 2 (0.4%) patients, by respective treatment arm. (3, 5)

Immune-mediated adverse events will be described in the following section.

Table 25 Overview of safety events observed in MATTERHORN, (SAS, DCO2) (3, 5)

	Durvalumab + FLOT (N=475) (3, 5)	Placebo + FLOT (N=469) (3, 5)	Difference, % (95 % CI)
Number of adverse events, n	NA	NA	NA
Number and proportion of patients with ≥1 adverse events, n (%)	471/475 (99.2%)	463/469 (98.7%)	0.4% (-0.9%;1.7%)
Number of serious adverse events*, n	NA	NA	NA

Number and proportion of patients with ≥ 1 serious adverse events*, n (%)	229/475 (48.2%)	207/469 (44.1%)	4.1% (-2.3%;10.4%)
Number of CTCAE grade ≥ 3 events, n	NA	NA	NA
Number and proportion of patients with ≥ 1 CTCAE grade ≥ 3 events§, n (%)	367/475 (77.3%)	356/469 (75.9%)	1.4% (-4.0%;6.8%)
Number of adverse reactions, n	NA	NA	NA
Number and proportion of patients with ≥ 1 adverse reactions, n (%)	NA	NA	NA
Number and proportion of patients who had a dose reduction, n (%)	199/475 (41.9%)	185/469 (39.4%)	2.45% (-3.8%;8.7%)
Number and proportion of patients who discontinue treatment regardless of reason, n (%)	NA	NA	NA
Number and proportion of patients who discontinue treatment due to adverse events, n (%)	142/475 (29.9%)	107/469 (22.8%)	7.1% (1.5%;12.7%)
Number and proportion of patients with any treatment emergent AE with outcome of death, n (%) **	23/475 (4.8)	20/469 (4.3)	NA

* A serious adverse event is an event or reaction that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect (see the ICH's complete definition).
**Includes AEs with an onset date on or after the date of first dose or pre-treatment AEs that increased in severity and resulted in an outcome of death on or after the first dose up to and including 90 days following the last dose of IP, or until initiation of first subsequent anti-cancer therapy (whichever occurs first).
§ CTCAE v. 5.0 must be used if available.

9.1.1 Immune mediated adverse events

In the overall study, as expected, the proportion of patients with immune mediated adverse events (imAEs) was higher in the durvalumab arm (23.2%) compared to the placebo arm (7.2%) (see Table 51 in Appendix E).

The majority of imAEs were CTCAE Grade 1 or 2 in severity; 34 (7.2%) patients in the durvalumab arm and 17 (3.6%) patients in the Placebo arm had imAEs of maximum CTCAE Grade 3 or 4. The imAEs were generally manageable and/or reversible with appropriate medical management per standard treatment guidelines, which included the use of steroids, other immunosuppressants, or endocrine therapy, withholding durvalumab until the event resolved, or permanent discontinuation of durvalumab. There was a low frequency of patients with imAEs leading to discontinuation of any study treatment for the overall study (5.1% vs 3.0% in the durvalumab arm vs placebo arm, respectively) (see Table 51 in Appendix E).

As expected, immune-mediated AEs were more frequent with durvalumab + FLOT vs placebo + FLOT (23.2% vs 7.2%) and were predominantly low grade and manageable with standard care. The 7.2% imAE rate in the placebo arm underscores the value of a placebo-controlled design to differentiate checkpoint-related toxicity from background events linked to chemotherapy, perioperative stress, or comorbidities.

9.1.2 Adverse events of CTCAE Grade 3 or 4

Across the overall study, a similar proportion of patients in the durvalumab and placebo arms had one or more AEs of maximum Grade 3 or 4 reported in ≥5% of patients in any treatment arm (71.6% vs. 71.2%, respectively). Grade 3-4 AEs observed in ≥5% of patients in any treatment arm were limited to anaemia, white blood cell counts decreased, diarrhoea, neutrophil count decreased, and neutropenia (Table 26). A full list of common AEs is provided in Table 52 in Appendix E. (78) The nature and incidence of AEs of maximum Grade 3 or 4 were comparable and balanced between the arms, with differences <5% for individual events (78).

Table 26 Summary of most common AEs of CTCAE Grade 3 or 4 (reported in ≥5% of patients in any treatment arm) in the overall treatment period (SAS, DCO2) (3)

AE (MedDRA preferred term)	Number (%) of patients[a]	
	Durvalumab arm (n=475)	Placebo arm (n=469)
Patients with AE of maximum Grade 3 or 4, n (%)	340 (71.6)	334 (71.2)
Neutropenia	101 (21.3)	104 (22.2)
Neutrophil count decreased	93 (19.6)	105 (22.4)
Diarrhoea	30 (6.3)	28 (6.0)
White blood cell count decreased	25 (5.3)	28 (6.0)
Anaemia	24 (5.1)	24 (5.1)

Footnotes: *DCO: 10th December 2024.* [a] Patients with multiple AEs of maximum CTCAE Grade 3 or 4 are counted once for each PT. Number (%) of patients with AEs of maximum CTCAE Grade 3 or 4, sorted alphabetically by PT. Includes AEs in the overall treatment period, with onset date on or after date of first IP dose or pre-treatment AEs that increase in severity on or after the date of first IP dose up to and including 90 days following the date of last IP dose or until the date of initiation of the first subsequent anti-cancer therapy (whichever occurs first). Excludes any patients with any AE of Grade 5.

9.1.3 Serious adverse events (SAEs)

At the time of DCO2 (20th December 2024), SAEs of any cause occurring in the overall treatment period were reported in 48.2% of patients in the durvalumab arm and 44.1% of patients in the placebo arm (3). The SAEs reported were consistent with the disease under investigation, as well as the established safety profile of the individual agents, durvalumab and FLOT.

The most common SAE in both treatment arms was pneumonia, occurring in 2.9% and 3.4% of patients in the durvalumab and placebo arms, respectively (3). Reported SAEs only occurred in less than 5%, hence Table 27 has not been populated. Please refer to Appendix E for full report of SAEs in MATTERHORN.

Table 27 Serious adverse events, ≥ 5% frequency in MATTERHORN, (SAS, DCO2) (5)

Adverse events	Durvalumab + FLOT (N=475) (source)		Placebo + FLOT (N=469) (source)	
	Number of patients with adverse events	Number of adverse events	Number of patients with adverse events	Number of adverse events
Adverse event, n (%)	N/A	N/A	N/A	N/A

* A serious adverse event is an event or reaction that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect (see the ICH's complete definition).

As no health economic analysis was conducted Table 28, is not applicable.

Table 28 Adverse events used in the health economic model

Adverse events	Intervention	Comparator		
	Frequency used in economic model for intervention	Frequency used in economic model for comparator	Source	Justification
NA	N/A	N/A	N/A	N/A

9.2 Safety data from external literature applied in the health economic model

N/A.

Table 29 Adverse events that appear in more than X % of patients

Adverse events	Intervention (N=x)			Comparator (N=x)			Difference, % (95 % CI)	
	Number of patients with adverse events	Number of adverse events	Frequency used in economic model for intervention	Number of patients with adverse events	Number of adverse events	Frequency used in economic model for comparator	Number of patients with adverse events	Number of adverse events
Adverse event, n	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

10. Documentation of health-related quality of life (HRQoL)

To compare the impact on HRQoL of adding durvalumab to the perioperative FLOT regimen, data on the European Organization for Research and Treatment of Cancer (EORTC) 30-item Quality of Life Questionnaire (QLQ-C30) has been presented in the subsequent section. Data was collected in the MATTERHORN study. (1) As this application does not contain a health economic analysis, the documentation for HRQoL will only be presented for the EORTC QLQ-C30-instrument.

Table 30 Overview of included HRQoL instruments

Measuring instrument	Source	Utilization
EORTC QLQ-C30	MATTERHORN (1)	Comparative analysis of impact on HRQoL

10.1 Presentation of the health-related quality of life, EORTC QLQ-C30

10.1.1 Study design and measuring instrument

In MATTERHORN, assessment of the impact on HRQoL was conducted using the EORTC QLQ-C30-instrument (1). The EORTC QLQ-C30 is a questionnaire that assesses the quality of life of cancer patients; as well as assessing global health status and HRQoL, it assesses important functioning domains (e.g. physical, emotional and role) and common cancer symptoms (e.g. fatigue, pain, nausea/vomiting and appetite loss). All EORTC QLQ-C30 domains range in score from 0 to 100; higher scores on HRQoL and functioning scales indicate better HRQoL/functioning, whereas higher scores on symptom scales indicate a worse symptom severity. A clinically meaningful change from baseline in EORTC QLQ-C30 subscales/scores was defined as an absolute change in score of ≥10 points. (5)

10.1.2 Data collection

HRQoL data collection was conducted throughout the MATTERHORN trial. During the dosing of the investigational drug, data was collected in the neoadjuvant and adjuvant phase, in the neoadjuvant phase Q4W at the start of each cycle and in the adjuvant phase Q4W at the start of each cycle until cycle 14. Following the last dose of the investigational drug, subjects were followed up at day 30 (+/-3 days), month 2 and 3, and at every scheduled scan visit relative to the scan schedule.

PRO questionnaires were administered via a site-based electronic tablet PRO device and should be completed prior to treatment administration and ideally before any discussions of health status to avoid biasing the patient's responses to the questions. As feasible, site staff should also ensure that PRO questionnaires are completed prior to

other study procedures, such as collection of laboratory samples, to further minimize bias. (74)

At the time of DCO2 (20th December 2024), the overall compliance rates for the completion of the EORTC QLQ-C30 were >90% in both treatment arms at baseline and generally remained above 80% to the end of the adjuvant period (Table 31) (5).

Table 31 Pattern of missing data and completion for EORTC QLQ-C30 in MATTERHORN, both treatment arms (5)

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
	Number of patients at randomization	Number of patients for whom data is missing (% of patients at randomization)	Number of patients "at risk" at time point X	Number of patients who completed (% of patients expected to complete)
Baseline	D+FLOT, N=467 Pbo+FLOT, N=459	D+FLOT: 42 (9.0%) Pbo+FLOT: 31 (6.8%)	D+FLOT: 467 Pbo+FLOT: 455	D+FLOT: 425 (91.0%) Pbo+FLOT: 428 (94.1%)
Cycle 2, Day 29	D+FLOT, N=467 Pbo+FLOT, N=459	D+FLOT: 39 (8.4%) Pbo+FLOT: 52 (11.3%)	D+FLOT: 467 Pbo+FLOT: 455	D+FLOT: 428 (91.6%) Pbo+FLOT: 407 (89.5%)
Cycle 3, Day 1	D+FLOT, N=467 Pbo+FLOT, N=459	D+FLOT: 174 (37.3%) Pbo+FLOT: 183 (39.9%)	D+FLOT: 358 Pbo+FLOT: 338	D+FLOT: 293 (81.8%) Pbo+FLOT: 276 (81.7%)
Cycle 4, Day 29	D+FLOT, N=467 Pbo+FLOT, N=459	D+FLOT: 177 (37.9%) Pbo+FLOT: 184 (40.1%)	D+FLOT: 344 Pbo+FLOT: 326	D+FLOT: 290 (84.3%) Pbo+FLOT: 275 (84.4%)
Cycle 5	D+FLOT, N=467 Pbo+FLOT, N=459	D+FLOT: 205 (43.9%) Pbo+FLOT: 201 (43.8%)	D+FLOT: 337 Pbo+FLOT: 319	D+FLOT: 262 (77.7%) Pbo+FLOT: 258 (80.9%)
Cycle 6	D+FLOT, N=467 Pbo+FLOT, N=459	D+FLOT: 179 (38.3%) Pbo+FLOT: 185 (40.3%)	D+FLOT: 333 Pbo+FLOT: 309	D+FLOT: 288 (86.5%) Pbo+FLOT: 274 (88.7%)

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
Cycle 7	D+FLOT, N=467 Pbo+FLOT, N=459	D+FLOT: 184 (39.4%) Pbo+FLOT: 195 (42.5%)	D+FLOT: 319 Pbo+FLOT: 299	D+FLOT: 283 (88.7%) Pbo+FLOT: 264 (88.3%)
Cycle 8	D+FLOT, N=467 Pbo+FLOT, N=459	D+FLOT: 182 (39.0%) Pbo+FLOT: 192 (41.8%)	D+FLOT: 312 Pbo+FLOT: 296	D+FLOT: 285 (91.3%) Pbo+FLOT: 267 (90.2%)
Cycle 9	D+FLOT, N=467 Pbo+FLOT, N=459	D+FLOT: 199 (42.6%) Pbo+FLOT: 201 (43.8%)	D+FLOT: 296 Pbo+FLOT: 285	D+FLOT: 268 (90.5%) Pbo+FLOT: 258 (90.5%)
Cycle 10	D+FLOT, N=467 Pbo+FLOT, N=459	D+FLOT: 209 (44.8%) Pbo+FLOT: 204 (44.4%)	D+FLOT: 282 Pbo+FLOT: 274	D+FLOT: 258 (91.5%) Pbo+FLOT: 255 (93.1%)
Cycle 11	D+FLOT, N=467 Pbo+FLOT, N=459	D+FLOT: 209 (44.8%) Pbo+FLOT: 220 (47.9%)	D+FLOT: 276 Pbo+FLOT: 267	D+FLOT: 258 (93.5%) Pbo+FLOT: 239 (89.5%)
Cycle 12	D+FLOT, N=467 Pbo+FLOT, N=459	D+FLOT: 217 (46.5%) Pbo+FLOT: 227 (49.5%)	D+FLOT: 270 Pbo+FLOT: 258	D+FLOT: 250 (92.6%) Pbo+FLOT: 232 (89.9%)
Cycle 13	D+FLOT, N=467 Pbo+FLOT, N=459	D+FLOT: 231 (49.5%) Pbo+FLOT: 238 (51.9%)	D+FLOT: 263 Pbo+FLOT: 250	D+FLOT: 236 (89.7%) Pbo+FLOT: 221 (88.4%)
Cycle 14	D+FLOT, N=467 Pbo+FLOT, N=459	D+FLOT: 216 (46.3%) Pbo+FLOT: 228 (49.7%)	D+FLOT: 259 Pbo+FLOT: 243	D+FLOT: 251 (96.9%) Pbo+FLOT: 231 (95.1%)
Day 30 Follow-up	D+FLOT, N=467 Pbo+FLOT, N=459	D+FLOT: 219 (46.9%) Pbo+FLOT: 228 (49.7%)	D+FLOT: 447 Pbo+FLOT: 434	D+FLOT: 248 (55.5%) Pbo+FLOT: 231 (53.2%)
Month 2 Follow-up	D+FLOT, N=467 Pbo+FLOT, N=459	D+FLOT: 229 (49.0%)	D+FLOT: 428 Pbo+FLOT: 419	D+FLOT: 238 (55.6%)

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
		Pbo+FLOT: 221 (48.1%)		Pbo+FLOT: 238 (56.8%)
Month 3 Follow-up	D+FLOT, N=467 Pbo+FLOT, N=459	D+FLOT: 215 (46.0%) Pbo+FLOT: 203 (44.2%)	D+FLOT: 405 Pbo+FLOT: 396	D+FLOT: 252 (62.2%) Pbo+FLOT: 256 (64.6%)

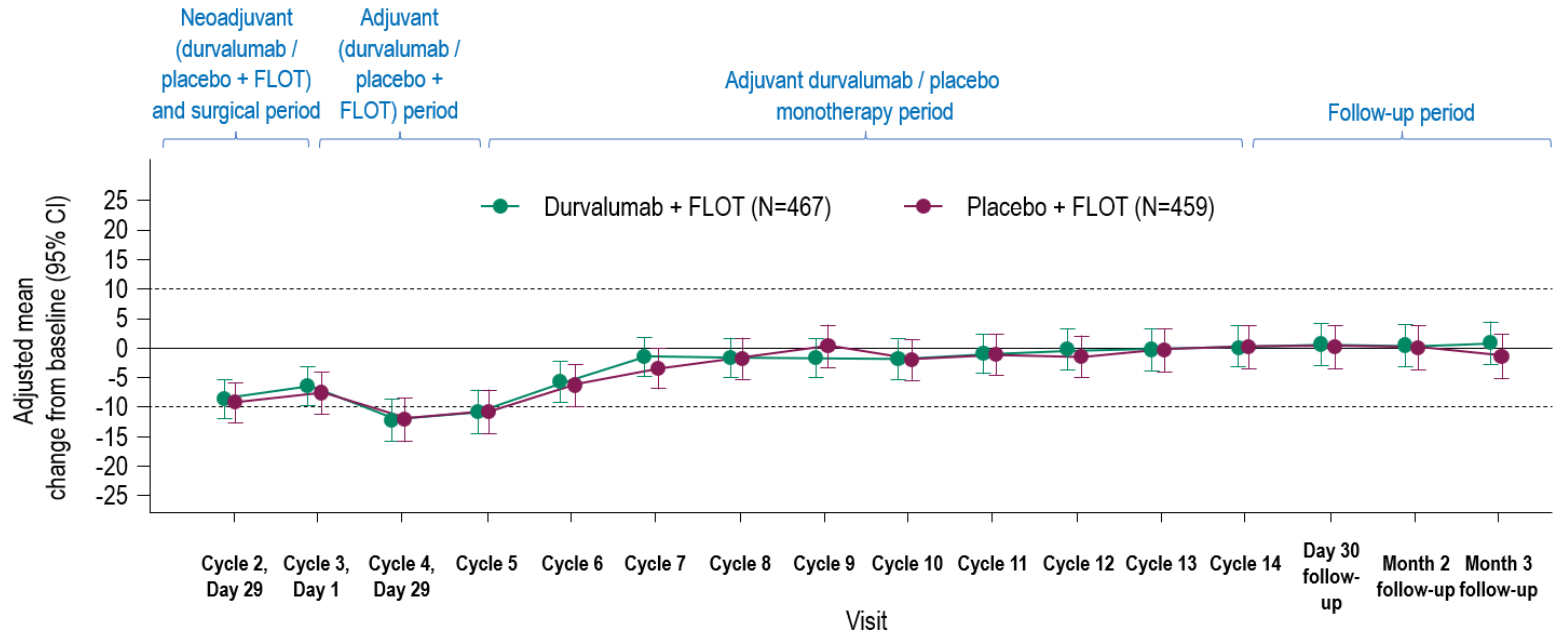
10.1.3 HRQoL results

Based on mixed model for repeated measures (MMRM) analyses, there were no meaningful differences between arms in changes from baseline for any functional domain or symptom scale at all timepoints evaluated during the neoadjuvant, adjuvant and follow-up periods.

In both arms, meaningful deterioration in the QLQ-C30 score of global health status/QoL was observed (Figure 14 and Table 32) (5). These declines occurred primarily during the neoadjuvant phase and were followed by a return to levels that were non-meaningful compared to baseline, reflecting the impact of surgery and FLOT chemotherapy. The declines were comparable between treatment arms, and none of the associated scales or symptoms showed sustained meaningful deterioration over time.

HRQoL and safety data suggest that the clinical benefits described above are achieved without detrimental impacts to safety and HRQoL.

Figure 14 Adjusted mean EORTC QLQ-C30 score, Global Health Status/QoL, change from baseline over time by mixed model for repeated measures analysis (5)



No. of participants at each visit																
Durvalumab + FLOT	400	275	268	243	266	260	262	247	237	238	231	215	231	229	222	233
Placebo + FLOT	389	271	265	250	265	255	258	249	245	232	224	213	222	223	229	246

Table 32 Adjusted mean EORTC QLQ-C30 score, Global Health Status/QoL, change from baseline over time by mixed model for repeated measures analysis (5)

	Intervention		Comparator		Intervention vs. comparator
	N	Mean (SE)	N	Mean (SE)	Difference (95% CI) p-value
Cycle 2	400	-8.5 (1.72)	389	-9.2 (1.76)	0.7 (-2.07 to 3.42), p-value: 0.63
Cycle 3	275	-6.5 (1.73)	271	-7.7 (1.78)	1.2 (-1.61 to 3.99), p-value: 0.405
Cycle 4	268	-12.3 (1.81)	265	-12.2 (1.85)	-0.2 (-3.29 to 2.96), p-value: 0.916
Cycle 5	243	-10.7 (1.84)	250	-10.8 (1.86)	0.1 (-3.08 to 3.36), p-value: 0.932
Cycle 6	266	-5.8 (1.77)	265	-6.2 (1.81)	0.5 (-2.45 to 3.42), p-value: 0.747
Cycle 7	260	-1.4 (1.74)	255	-3.3 (1.78)	1.9 (-0.90 to 4.72), p-value: 0.183
Cycle 8	262	-1.6 (1.71)	258	-1.7 (1.75)	0.1 (-2.57 to 2.74), p-value: 0.949
Cycle 9	247	-1.7 (1.72)	249	0.4 (1.76)	-2.1 (-4.78 to 0.60), p-value: 0.128
Cycle 10	237	-1.7 (1.75)	245	-2 (1.79)	0.2 (-2.61 to 3.06), p-value: 0.874
Cycle 11	238	-1 (1.73)	232	-1.1 (1.78)	0.1 (-2.65 to 2.86), p-value: 0.941
Cycle 12	231	-0.3 (1.77)	224	-1.5 (1.81)	1.3 (-1.65 to 4.23), p-value: 0.39
Cycle 13	215	-0.2 (1.82)	213	-0.3 (1.86)	0.1 (-3.09 to 3.25), p-value: 0.959
Cycle 14	231	0.3 (1.76)	222	0.2 (1.81)	0.1 (-2.81 to 3.02), p-value: 0.943
Day 30 Follow-up	229	0.5 (1.81)	223	0.2 (1.86)	0.4 (-2.79 to 3.51), p-value: 0.82

	Intervention		Comparator		Intervention vs. comparator
Month 2 Follow-up	222	0.3 (1.81)	229	0 (1.85)	0.2 (-2.88 to 3.38), p-value: 0.875
Month 3 Follow-up	233	0.8 (1.84)	246	-1.4 (1.88)	2.3 (-0.99 to 5.53), p-value: 0.172
Average over all visits	410	-3.1 (1.61)	407	-3.5 (1.65)	0.4 (-1.67 to 2.53), p-value: 0.686

10.2 Health state utility values (HSUVs) used in the health economic model

N/A.

10.2.1 HSUV calculation

N/A

10.2.1.1 Mapping

N/A

10.2.2 Disutility calculation

N/A

10.2.3 HSUV results

N/A

Table 33 Overview of health state utility values [and disutilities]

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
HSUVs				
HSUV A	N/A	N/A	N/A	N/A

10.3 Health state utility values measured in other trials than the clinical trials forming the basis for relative efficacy

N/A

10.3.1 Study design

N/A

10.3.2 Data collection

N/A

10.3.3 HRQoL Results

N/A

10.3.4 HSUV and disutility results

N/A

Table 34 Overview of health state utility values [and disutilities] N/A

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
HSUVs				
HSUV A	N/A	N/A	N/A	N/A

Table 35 Overview of literature-based health state utility values

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
HSUV A				
Study 1	N/A	N/A	N/A	N/A

11. Resource use and associated costs

N/A.

11.1 Medicines - intervention and comparator

N/A.

Table 36 Medicines used in the model N/A

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing
[Name of the intervention]	N/A	N/A	N/A	N/A
[Name of the comparator]	N/A	N/A	N/A	N/A

11.2 Medicines– co-administration

N/A.

11.3 Administration costs

N/A.

Table 37 Administration costs used in the model N/A

Administration type	Frequency	Unit cost [DKK]	DRG code	Reference
[E.g. i.v. infusion, subcutaneous infusion]	N/A	N/A	N/A	N/A

11.4 Disease management costs

N/A

Table 38 Disease management costs used in the model N/A

Activity	Frequency	Unit cost [DKK]	DRG code	Reference
[Activity]	N/A	N/A	N/A	N/A

11.5 Costs associated with management of adverse events

N/A

Table 39 Cost associated with management of adverse events N/A

	DRG code	Unit cost/DRG tariff
[Adverse event]	N/A	N/A
[Adverse event]	N/A	N/A

11.6 Subsequent treatment costs

N/A

Table 40 Medicines of subsequent treatments N/A

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing
[Name of the intervention]	N/A	N/A	N/A	N/A

11.7 Patient costs

N/A

Table 41 Patient costs used in the model N/A

Activity	Time spent [minutes, hours, days]
Activity	N/A

11.8 Other costs (e.g. costs for home care nurses, out-patient rehabilitation and palliative care cost)

N/A.

12. Results

N/A.

12.1 Base case overview

N/A

Table 42 Base case overview N/A

Feature	Description
N/A	N/A

12.1.1 Base case results

N/A

Table 43 Base case results, discounted estimates N/A

	[Intervention]	[Comparator]	Difference
Medicine costs	N/A	N/A	N/A

12.2 Sensitivity analyses

12.2.1 Deterministic sensitivity analyses

N/A

Table 44 One-way sensitivity analyses results N/A

	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
Base case	N/A	N/A	N/A	N/A	N/A

12.2.2 Probabilistic sensitivity analyses

N/A

13. Budget impact analysis

N/A

Number of patients (including assumptions of market share)

Table 45 Number of new patients expected to be treated over the next five-year period if the medicine is introduced (adjusted for market share) N/A

	Year 1	Year 2	Year 3	Year 4	Year 5
			N/A		

	Year 1	Year 2	Year 3	Year 4	Year 5
N/A	N/A	N/A	N/A	N/A	N/A

Budget impact

Table 46 Expected budget impact of recommending the medicine for the indication N/A

	Year 1	Year 2	Year 3	Year 4	Year 5
The medicine under consideration is recommended	N/A	N/A	N/A	N/A	N/A
The medicine under consideration is NOT recommended	N/A	N/A	N/A	N/A	N/A
Budget impact of the recommendation	N/A	N/A	N/A	N/A	N/A

14. List of experts

No experts have been consulted.

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Appendix A. Main characteristics of studies included

[Complete Table 46 for each study included. Comply with section 3 of the methods guide.]

Table 47 Main characteristic of studies included (1, 5)

Trial name: MATTERHORN	NCT number: NCT04592913
Objective	This study will evaluate the efficacy, safety and tolerability of Durvalumab + FLOT versus placebo + FLOT, for GC/GEJC patients with resectable adenocarcinoma with clinical Stage II–IVA; >T2 N0–3 M0 or T0–4 N1–3 M0
Publications – title, author, journal, year	MATTERHORN: phase III study of durvalumabplus FLOT chemotherapy in resectablegastric/gastroesophageal junction cancer Yelena Y Janjigian, Eric Van Cutsem, Kei Muro, Zev Wainberg, Salah-EddinAl-Batran, Woo Jin Hyung, Daniela Molena, Michelle Marcovitz, Dario Ruscica, Scott HRobbins, Alejandra Negro & Josep Tabernero Future oncology, 2022
Study type and design	A randomized, double-blind, placebo-controlled, multicenter, global phase III study. Patients were randomized 1:1 using an interactive trial management system to receive durvalumab 1500 mg or placebo every 4 weeks on day 1 plus FLOT every 2 weeks on day 1 and 15 for four cycles (two neoadjuvant cycles and two adjuvant cycles) followed by durvalumab 1500 mg or placebo for 10 additional cycles. Durvalumab or placebo assignment will be masked to both patients and investigators.
Sample size (n)	A total of 948 patients were randomly assigned to the durvalumab + FLOT group (474 patients) or the placebo + FLOT group (474 patients).
Main inclusion criteria	• Patients must be ≥ 18 years of age (≥ 20 years in Japan) • Histologically confirmed, resectable, stage ≥ II GC or GEJC not treated with anti-cancer therapy • Complete surgical resection of the primary tumor must be achievable • WHO/Eastern Cooperative Oncology Group performance status of 0 or 1 • Adequate orhan and marrow function • Availability of tumor sample prior to study entry

Trial name: MATTERHORN		NCT number: NCT04592913
Main exclusion criteria	• Any prior immune-mediated therapy • Peritoneal dissemination or distant metastasis • (Adeno)squamous cell carcinoma, or gastrointestinal stromal tumour • Any concurrent chemotherapy, investigational product, biologic or hormonal therapy for cancer treatment • Contraindication to any of the study drugs	
Intervention	Durvalumab 1500 mg + FLOT (5-fluorouracil, leucovorin, oxaliplatin, docetaxel) administered as an IV infusion. Neoadjuvant: Two cycles of 4-weeks, consisting of durvalumab 1500 mg IV Q4W in combination with FLOT Q2W *Surgery* Adjuvant: Two cycles of 4-weeks, consisting of durvalumab 1500 mg IV Q4W in combination with FLOT Q2W followed by 10 cycles of durvalumab 1500 mg IV Q4W as monotherapy. A total of 14 cycles of durvalumab	
Comparator(s)	Placebo + FLOT (5-fluorouracil, leucovorin, oxaliplatin, docetaxel) Q2W. Patients can receive up to 8 doses of FLOT in total: 4 doses of in the neoadjuvant setting and 4 doses in the adjuvant setting	
Follow-up time	The used data cut-off for EFS in MATTERHORN was 20th of December 2024. The median duration of follow-up for EFS (in censored patients) was 31.6 months (range: 0.03–48.10 months) in the durvalumab arm and 31.4 months (range: 0.03–48.07 months) in the placebo arm. The used data cut-off for OS in MATTERHORN was 1st of September 2025. The median duration of follow-up for OS in all patients was 39.1 months.	
Is the study used in the health economic model?	N/A	
Primary, secondary and exploratory endpoints	**Primary efficacy endpoint**: Event-free survival (EFS). EFS is measured from randomisation to the first occurrence of any of the following, per RECIST 1.1 (BICR) and/or local pathology: (a) progression that precludes surgery or necessitates non-protocol therapy, (b) local or distant recurrence/progression, or (c) death from any cause. The primary analysis is performed in the full analysis set (FAS). A sensitivity analysis of EFS using Investigator assessments was also conducted. **Key secondary efficacy endpoint**: Overall survival (OS), defined as time from randomisation to death from any cause. Analysed in the FAS.	

Key secondary efficacy endpoint: Pathological complete response (pCR), defined as no residual viable tumour in resected specimens by central pathology review according to the modified Ryan criteria. Analysed in the FAS. A sensitivity analysis based on local pathology assessment was also conducted.

Other secondary endpoints

Surgery rate: proportion of randomised patients who undergo gastrectomy or gastro-oesophagectomy. Analysed in the FAS.

R0 resection rate: proportion of patients with confirmed complete (R0) resection by local pathology review. Analysed in the FAS.

Metastasis-free survival (MFS): time from randomisation to development of metastasis per RECIST 1.1 or death from any cause. Analysed in the FAS (Investigator assessment).

Disease-specific survival (DSS): time from randomisation to death due to GC/GEJC. Analysed in the FAS.

Disease-free survival (DFS): time from first post-surgery scan to recurrence per RECIST 1.1 or death from any cause. Analysed in the R0-resected analysis set (Investigator assessment).

Landmark endpoints

EFS24/EFS36: proportions of patients alive and event-free from randomisation to 24 and 36 months, respectively (RECIST 1.1 per BICR and/or local pathology).

OS24/OS36: proportions of patients alive at 24 and 36 months, respectively.

DFS24/DFS36: proportions of patients alive and recurrence-free from first post-surgery scan to 24 and 36 months, respectively (RECIST 1.1).

Analytical sets and stratification

Unless otherwise specified, EFS and OS are analysed in the FAS; DFS is analysed in the R0-resected analysis set. EFS assessment uses RECIST 1.1 (BICR and/or local pathology); DFS assessment uses RECIST 1.1 (Investigator). Prespecified subgroup analyses include PD-L1 expression (e.g., OS, EFS, MFS, DSS, DFS, and pCR by PD-L1 status), with definitions identical to the overall endpoints.

Patient-reported outcomes (HRQoL)

Disease-related symptoms, impacts, and HRQoL are captured as time to deterioration and change from baseline using EORTC QLQ-C30 and QLQ-STO22 plus IL38, analysed in the PRO analysis set.

Safety

Safety and tolerability are assessed in the Safety Analysis Set (SAS) using adverse events (AEs), physical examinations, vital signs (including

blood pressure, pulse, ECGs), WHO/ECOG performance status, and laboratory findings (clinical chemistry, haematology, urinalysis).

Notes

All efficacy comparisons are between the durvalumab and placebo arms, based on randomised treatment (intent-to-treat), irrespective of treatment received.

Sensitivity analyses include EFS by Investigator assessment and pCR by local pathology assessment.

Abbreviations: AE, adverse event; BICR, blinded independent central review; DFS, disease-free survival; DSS, disease-specific survival; EFS, event-free survival; EORTC, European Organisation for Research and Treatment of Cancer; HRQoL, health-related quality of life; IL38, Item Library 38 (2-item add-on to QLQ-STO22); MFS, metastasis-free survival; OS, overall survival; pCR, pathological complete response; PRO, patient-reported outcome; QLQ-C30, 30-item core QoL questionnaire; QLQ-STO22, 22-item gastric cancer module; RECIST, Response Evaluation Criteria in Solid Tumours; SAS, Safety Analysis Set.

Follow-up periods, assessment schedule, and predefined analyses

RECIST and pathology assessment schedule

Neoadjuvant period: RECIST 1.1 at baseline (≤28 days before randomisation) and pre-surgery (≤4 weeks after last neoadjuvant FLOT dose); post-surgical pathology review for staging, EFS and pCR determination.

Adjuvant period: Adjuvant baseline RECIST 1.1 scan ≥4 weeks after radical surgery (preferably ≤28 days before first adjuvant dose); thereafter tumour assessments every 12 weeks (±1 week) for 2 years, then every 24 weeks (±1 week) until progression/recurrence.

Time-to-event outcomes and follow-up

EFS (FAS; RECIST 1.1 per BICR and/or local pathology): interim analysis (DCO2) at ~31 months' median follow-up with 40.6% EFS maturity (385/484 events); EFS achieved statistical significance at DCO2 and is considered final for EFS.

OS (FAS): interim tested at DCO2 with fixed alpha 0.01% (pre-specified boundary not met); final OS analysis (DCO3/FA) pre-defined to occur at ~51% EFS maturity or ~3 years after last patient randomised, whichever occurs first; remaining 2-sided alpha 4.99% allocated to FA.

DFS (R0 subset; RECIST 1.1 per Investigator): analysed post-surgery; assessments follow the adjuvant schedule above.

MFS, DSS: analysed in FAS per RECIST 1.1 (Investigator) and cause-specific death definitions; follow the same 12-/24-week schedule.

pCR and surgery/R0 endpoints

Trial name: MATTERHORN	NCT number: NCT04592913
	pCR: central pathology per modified Ryan criteria; formally tested at DCO1 (alpha 0.1%); met significance and alpha was recycled to EFS/OS. Surgery rate and R0 resection: analysed in FAS; pathology by local assessment; captured up to completion/discontinuation of adjuvant therapy and safety follow-up. **PROs and safety** HRQoL (EORTC QLQ-C30, QLQ-STO22 + IL38): time to deterioration and change from baseline per PRO analysis set at scheduled adjuvant visits (12-/24-week cadence). Safety (SAS): AEs, labs, vitals/ECGs, ECOG PS throughout neoadjuvant, peri-operative, and adjuvant phases; all patients completed adjuvant therapy and safety follow-up by DCO2. Multiplicity and predefined alpha spending Three formal analyses were prespecified (DCO1 pCR; DCO2 EFS/OS; FA OS). Strong type I error control (2-sided 5%) via an MTP: 0.1% alpha at DCO1 (pCR), remaining 4.9% split between DCO2 and FA for EFS/OS using a Lan-DeMets/O'Brien-Fleming approach; OS tested only if EFS significant. At DCO2, EFS was significant (2-sided 2.39% significance level applied for 40.6% maturity); OS will be tested at FA with the remaining 4.99% alpha. All other secondary endpoints/PROs were supportive (no multiplicity adjustment).
Method of analysis	All efficacy data will be assessed on the Full Analysis Set (FAS) including all randomized patients. EFS and OS was summarized using Kaplan-Meyer curves plotted by treatment arm. EFS and OS was analysed using a stratified log-rank test adjusting for the stratification factors of geographic region, clinical lymph noted status and PD-L1 expression status. Safety data was summarized descriptively from the safety analysis set including all randomized patients who have received at least one dose of the study medication.
Subgroup analyses	N/A
Other relevant information	N/A

Appendix B. Efficacy results per study

Results per study

Table 48 Results per study (5, 73)

Results of [trial name (NCT number)]											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
OS, DCO3 1st of September, 2025	D + FLOT	474	NC (NC-NC)	N/A	N/A	NA	HR: 0.78	0.63–0.96	0.021	Overall survival is based on the Kaplan-Meyer estimator and analysed using stratified log-rank test.	(73)
	P + FLOT	474	NC (NC-NC)								
EFS, DCO2 20th of December, 2024	D + FLOT	474	NC (40.74–NC)	N/A	N/A	N/A	HR: 0.71	0.58-0.86	0.001	Same as OS	(5)
	P + FLOT	474	32.82 (27.86-NC)								
pCR, DCO1 1st of February 2023	D + FLOT	474	91 (19.2%) (15.75-23.04)	12.0	N/A	N/A	OR: 3.08	2.03-4.67	<0.001	Pathological complete response rate based on central assessment will be compared using a stratified Cochran-Mantel-Haenszel test.	(5)
	P + FLOT	474	34 (7.2%)								

Results of [trial name (NCT number)]											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
DFS, DCO2 20th of December 2024 (R0 resection)	D + FLOT	339	NC (NC-NC)	N/A	N/A	N/A	HR: 0.70	0.53-0.93	0.012	Same as OS	(5)
	P + FLOT	323	39.75 (38.67-NC)								

Appendix C. Comparative analysis of efficacy

Not applicable, efficacy comparison will be based on MATTERHORN, a head-to-head study between durvalumab + FLOT vs. FLOT.

Table 49 Comparative analysis of studies comparing [intervention] to [comparator] for patients with [indication]

Outcome		Absolute difference in effect			Relative difference in effect			Method used for quantitative synthesis	Result used in the health economic analysis?
	Studies included in the analysis	Difference	CI	P value	Difference	CI	P value		
N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Appendix D. Extrapolation

N/A.

D.1 Extrapolation of [effect measure 1]

D.1.1 Data input

D.1.2 Model

D.1.3 Proportional hazards

D.1.4 Evaluation of statistical fit (AIC and BIC)

D.1.5 Evaluation of visual fit

D.1.6 Evaluation of hazard functions

D.1.7 Validation and discussion of extrapolated curves

D.1.8 Adjustment of background mortality

D.1.9 Adjustment for treatment switching/cross-over

D.1.10 Waning effect

D.1.11 Cure-point

Appendix E. Serious adverse events

Table 50 Summary of most common SAEs (reported in ≥1% of patients in any treatment arm) in the overall treatment period (SAS, DCO2) (5)

	Number (%) of patients[a]	
AE (MedDRA preferred term)	**Durvalumab arm (n=475)**	**Placebo arm (n=469)**
Patients with any SAE, n (%)	229 (48.2)	207 (44.1)
Pneumonia	14 (2.9)	16 (3.4)
Febrile neutropenia	10 (2.1)	15 (3.2)
Neutropenia	10 (2.1)	4 (0.9)
Vomiting	10 (2.1)	10 (2.1)
COVID-19	9 (1.9)	5 (1.1)
Diarrhoea	9 (1.9)	12 (2.6)
Pyrexia	9 (1.9)	8 (1.7)
Pulmonary embolism	8 (1.7)	4 (0.9)
Septic shock	8 (1.7)	2 (0.4)
Gastrointestinal anastomotic leak	7 (1.5)	3 (0.6)
Ileus	7 (1.5)	2 (0.4)
Device related infection	6 (1.3)	1 (0.2)
Dysphagia	6 (1.3)	4 (0.9)
Nausea	6 (1.3)	2 (0.4)
Abdominal pain	5 (1.1)	2 (0.4)
Anaemia	5 (1.1)	3 (0.6)
Colitis	5 (1.1)	3 (0.6)
Sepsis	5 (1.1)	6 (1.3)
Decreased appetite	4 (0.8)	5 (1.1)
Pneumonia aspiration	3 (0.6)	9 (1.9)
Intestinal obstruction	2 (0.4)	5 (1.1)
Neutrophil count decreased	2 (0.4)	5 (1.1)
Failure to anastomose	1 (0.2)	5 (1.1)

Footnotes: DCO: 10th December 2024. Includes AEs in the overall treatment period, with onset date on or after date of first IP dose or pre-treatment AEs that increase in severity on or after the date of first IP dose up to and

including 90 days following the date of last IP dose or until the date of initiation of the first subsequent anti-cancer therapy (whichever occurs first). Percentages are based on the total numbers of patients in the treatment arm (N). [a] Number (%) of patients with an SAE, sorted by prevalence in durvalumab arm by PT. Patients with multiple events in the same PT are counted only once in that PT.

Table 51 Immune-mediated AEs by Category in the Overall Study (Safety Analysis Set) (5)

	Number (%) of patients	
	Durvalumab arm (N = 475)	Placebo arm (N = 469)
Any imAE	110 (23.2)	34 (7.2)
Any imAE possibly related to any study drug[a]	99 (20.8)	31 (6.6)
Any imAE possibly related to durvalumab or placebo[a]	90 (18.9)	24 (5.1)
Any imAE possibly related to any FLOT (at least 1 component)[a]	19 (4.0)	10 (2.1)
imAEs of maximum CTCAE Grade 3 or 4		
Any imAE of maximum CTCAE Grade 3 or 4[b]	34 (7.2)	17 (3.6)
Any imAE of maximum CTCAE Grade 3 or 4, possibly related to any study drug[a,b]	32 (6.7)	16 (3.4)
Any imAE of maximum CTCAE Grade 3 or 4 possibly related to durvalumab or placebo[a,b]	28 (5.9)	13 (2.8)
Any imAE of maximum CTCAE Grade 3 or 4 possibly related to any FLOT (at least 1 component)[a,b]	8 (1.7)	6 (1.3)
imAEs with an outcome of death (treatment-emergent)		
Any treatment-emergent imAE with outcome death[b]	2 (0.4)	0
Any treatment-emergent imAE with outcome death, possibly related to any study drug[a,b]	2 (0.4)	0
Any treatment-emergent imAE with outcome death, possibly related to durvalumab or placebo[a,b]	2 (0.4)	0
Any treatment-emergent imAE with outcome death, possibly related to any FLOT (at least 1 component)[a,b]	0	0
Serious imAEs		
Any serious imAE	23 (4.8)	13 (2.8)

Any serious imAE possibly related to any study drug[a]	21 (4.4)	12 (2.6)
Any serious imAE possibly related to durvalumab or placebo[a]	20 (4.2)	11 (2.3)
Any serious imAE possibly related to any FLOT (at least 1 component)[a]	2 (0.4)	4 (0.9)
imAEs leading to discontinuation of study treatment		
Any imAE leading to discontinuation of any study drug	24 (5.1)	14 (3.0)
Any imAE leading to discontinuation of durvalumab or placebo	21 (4.4)	13 (2.8)
Any imAE leading to discontinuation of any FLOT (at least 1 component)	9 (1.9)	4 (0.9)
Therapy for imAE		
Received therapy	110 (23.2)	34 (7.2)
Systemic corticosteroids	67 (14.1)	29 (6.2)
High-dose steroids (≥ 40 mg prednisone equivalent)	47 (9.9)	25 (5.3)
Endocrine therapy	52 (10.9)	7 (1.5)
Other immunosuppressants	3 (0.6)	2 (0.4)
imAE outcome[b]		
Resolved	53 (11.2)	24 (5.1)
Resolved with sequelae	2 (0.4)	0
Resolving	17 (3.6)	1 (0.2)
Not resolved	36 (7.6)	9 (1.9)
Resulted in death	2 (0.4)	0

[a] Assessed by the investigator.

[b] If a patient has multiple events within a specific imAE type, then the outcome of the event with the worst outcome is counted. Outcomes from worst to best are death, not resolved, resolving, resolved with sequelae, and resolved. Includes events in the overall study with onset on or after first dose and up to and including 90 days following last dose of study medication or date of subsequent therapy, whichever occurs first.

Table 52 Any AEs Occurring in ≥ 10% of Patients in Either Treatment Arm by PT in the Overall Study (Safety Analysis Set, DCO2)

	Number (%) of patients[a]	
	Durvalumab arm (N = 475)	Placebo arm (N = 469)
Patients with any AE	471 (99.2)	463 (98.7)
Diarrhoea	296 (62.3)	270 (57.6)
Nausea	241 (50.7)	237 (50.5)
Neutropenia	153 (32.2)	155 (33.0)
Alopecia	145 (30.5)	149 (31.8)
Decreased appetite	145 (30.5)	141 (30.1)
Fatigue	137 (28.8)	146 (31.1)
Vomiting	124 (26.1)	120 (25.6)
Anaemia	119 (25.1)	147 (31.3)
Neutrophil count decreased	119 (25.1)	138 (29.4)
Peripheral sensory neuropathy	96 (20.2)	88 (18.8)
Asthenia	95 (20.0)	71 (15.1)
Pyrexia	95 (20.0)	71 (15.1)
COVID-19	85 (17.9)	74 (15.8)
Abdominal pain	82 (17.3)	96 (20.5)
Dysgeusia	78 (16.4)	61 (13.0)
Constipation	77 (16.2)	81 (17.3)
Neuropathy peripheral	73 (15.4)	70 (14.9)
Weight decreased	70 (14.7)	88 (18.8)
Rash	65 (13.7)	34 (7.2)

Stomatitis	60 (12.6)	44 (9.4)
Pruritus	51 (10.7)	25 (5.3)
White blood cell count decreased	46 (9.7)	62 (13.2)
Hypokalaemia	39 (8.2)	53 (11.3)
Epistaxis	38 (8.0)	51 (10.9)

a Number (%) of patients with AEs, sorted by frequency in the D + FLOT arm. Patients with multiple events in the same PT are counted only once in that PT. Patients with AEs in more than 1 PT are counted once in each of those PTs

Appendix F. Health-related quality of life

N/A

Appendix G. Probabilistic sensitivity analysis

N/A.

Table 53 overview of parameters in the PSA

Input parameter	Point estimate	Lower bound	Upper bound	Probability distribution
Probabilities				
N/A	N/A	N/A	N/A	N/A

Appendix H. Literature searches for the clinical assessment

H.1 Efficacy and safety of the intervention and comparator(s)

N/A, application based on head-to-head trial with SoC.

Table 54 Bibliographic databases included in the literature search

Database	Platform/source	Relevant period for the search	Date of search completion
N/A	N/A	N/A	N/A

Table 55 Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search
N/A	N/A.	N/A.	N/A.

Table 56 Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
N/A	N/A	N/A	N/A	**N/A**

H.1.1 Search strategies

N/A.

Table 57 of search strategy table for [name of database]

No.	Query	Results
N/A	N/A	N/A

H.1.2 Systematic selection of studies

N/A.

Table 58 Inclusion and exclusion criteria used for assessment of studies

Clinical effectiveness	Inclusion criteria	Exclusion criteria	Changes, local adaption
N/A	N/A	N/A	N/A

Table 59 Overview of study design for studies included in the analyses

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
N/A	N/A	N/A	N/A	**N/A**	N/A	N/A

H.1.3 Excluded fulltext references

N/A.

H.1.4 Quality assessment

N/A.

H.1.5 Unpublished data

N/A.

Appendix I. Literature searches for health-related quality of life

I.1 Health-related quality-of-life search

N/A.

Table 60 Bibliographic databases included in the literature search

Database	Platform	Relevant period for the search	Date of search completion
N/A	N/A	N/A	N/A

Table 61 Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search
N/A	N/A	N/A	N/A

Table 62 Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
N/A	N/A.	N/A	N/A	N/A

I.1.1 Search strategies

N/A.

Table 63 Search strategy for [name of database]

No.	Query	Results
N/A	N/A	N/A

I.1.2 Quality assessment and generalizability of estimates

N/A.

I.1.3 Unpublished data

N/A.

Appendix J. Literature searches for input to the health economic model

J.1 External literature for input to the health economic model

N/A.

J.1.1 Example: Systematic search for […]

N/A.

Table 64 Sources included in the search

Database	Platform/source	Relevant period for the search	Date of search completion
N/A	N/A	N/A	N/A

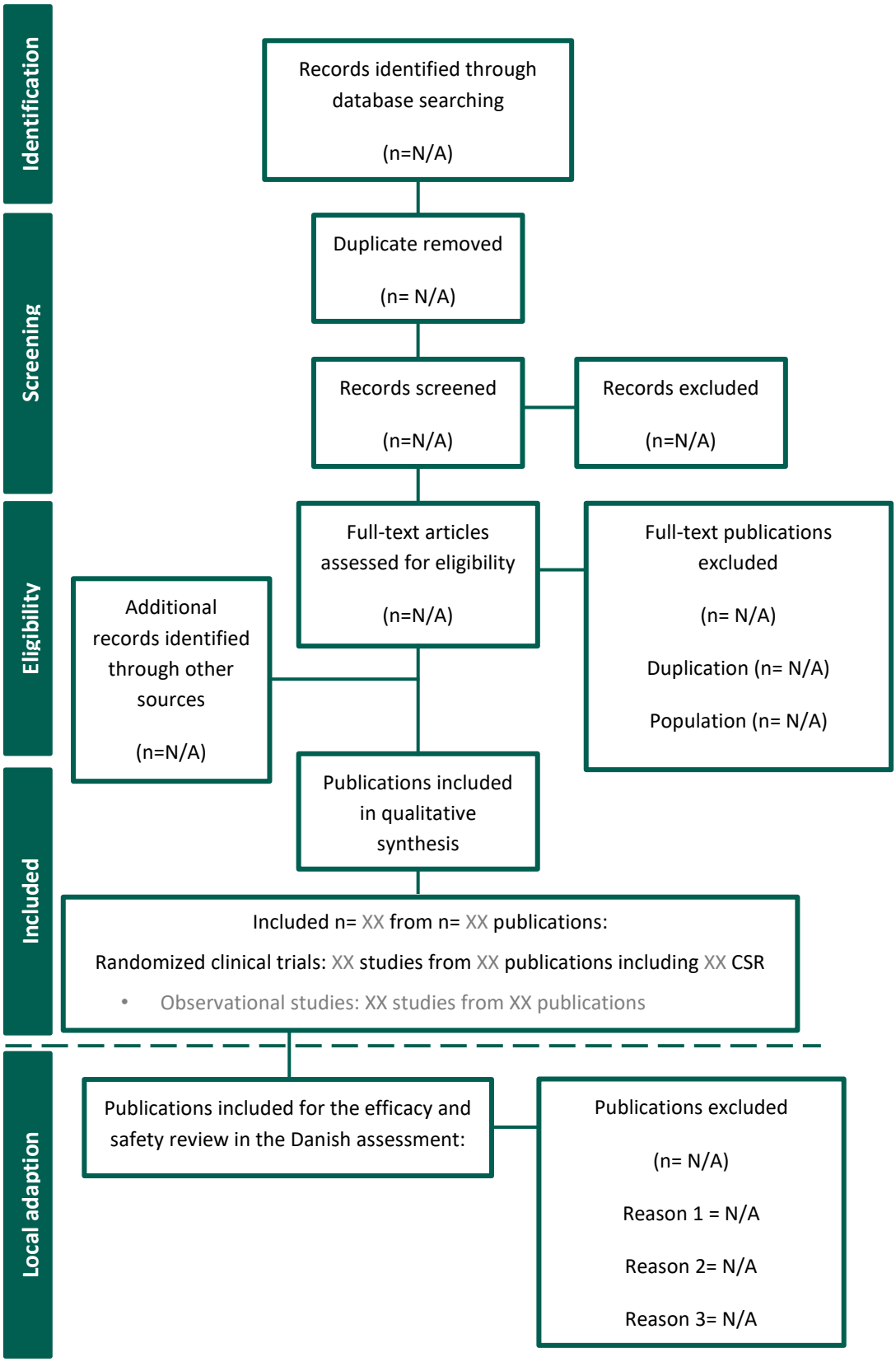
J.1.2 Example: Targeted literature search for [estimates]

N/A.

Table 65 Sources included in the targeted literature search

Source name/ database	Location/source	Search strategy	Date of search
N/A	N/A	N/A	N/A

Example of PRISMA diagram. The diagram is editable and may be used for recording the records flow for the literature searches and for the adaptation of existing SLRs. (N/A)



Appendix K. Real-World evidence

K.1 CASTOR study

K.1.1 Title and purpose

- Real-world evidence to describe patient characteristics, treatment patterns, healthcare resource utilization (HRU) and costs around recurrence, and time-to-event outcomes in resectable gastric and distal esophageal/GEJ adenocarcinoma in Denmark (2019–2024 diagnoses; follow-up to 30th. Nov 2025).
- Data will be published in [redacted] in collaboration with Danish oncologist in an international medical journal.

K.1.2 Background and rationale

- For resectable GC and EC/GEJ, population-based evidence on perioperative practice and economic burden—particularly around recurrence—is limited; nationwide Danish registries enable unbiased inclusion and longitudinal follow-up.

K.1.3 Protocol summary

- Population: Adults (≥18) with histologically confirmed adenocarcinoma of stomach (ICD-10 C16) or distal esophagus/GEJ (ICD-10 C15) diagnosed 1 Jan 2019–31 Dec 2024 in the Danish Cancer Register; resectable at diagnosis (M0; predefined TNM ranges; exclusions: M1, T4b, Tx, Nx, T1aN0M0, T0N0M0, T0).
- Intervention: Real-world perioperative management (e.g., neoadjuvant chemotherapy such as FLOT, surgery, adjuvant therapy), and care at recurrence.
- Comparator: Descriptive; no direct treatment comparison.
- Outcomes: Descriptive characteristics; [redacted]
- Time horizon: Index at diagnosis; surgery [redacted]

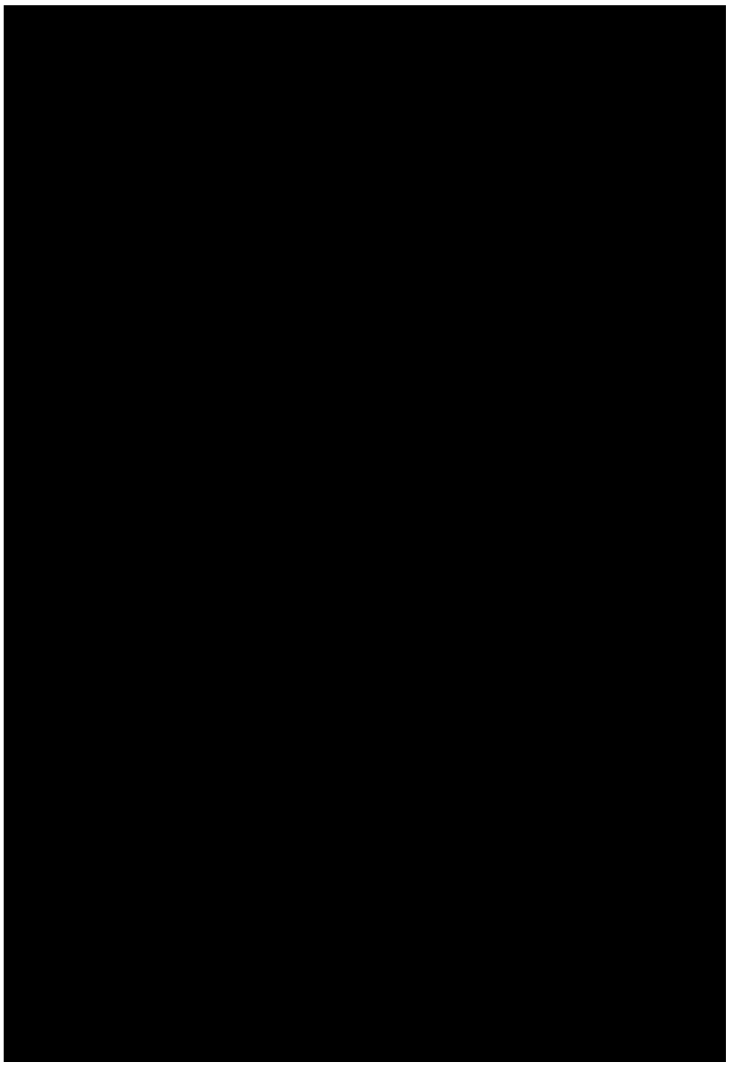
K.1.4 Data and data sources

- Nationwide Danish registries:

- National Patient Register (NPR; incl. DRG-grouped data): diagnoses (ICD-10), procedures (SKS), dates, in/outpatient classification, DRG/DAG costs.
- National Cancer Register (NCR): incident diagnoses, TNM (AJCC), histology (ICD-O-3).
- Pathology Register: SNOMED (e.g., HER2, PD-L1, MMR).
- Hospital Medication Register (from mid-2018): hospital-administered drugs (ATC).
- Registry of Medicinal Product Statistics: dispensed prescriptions (ATC; AUP costs).
- National Health Insurance Registry: primary care contacts and fees.
- Civil Registration/Population Register: demographics, death, migration.

- Data quality and relevance: National coverage; mandatory reporting for hospital contacts; known high completeness in NCR; key variables (diagnoses, procedures, dates) captured prospectively.

Figure 15. [redacted]



K.1.5 Study design

- Design: Retrospective cohort.

K.1.6 Eligibility (in/exclusion)

- Inclusion: [redacted]
- Exclusion: [redacted]

K.1.7 Exposure and variables

- Baseline: [redacted]
- Treatments: [redacted]
- Recurrence algorithm: [redacted]

K.1.8 Outcomes and analyses

- Descriptive analyses: Report data sources, target population, design, and methods. Present patient characteristics and treatment uptake.
- HRU and costs: Monthly per-patient averages for inpatient admissions/outpatient contacts (NPR; DRG/DAG), primary care (fees), prescriptions (AUP). Costs adjusted to 2025 values (healthcare CPI) and converted to EUR; episodes spanning periods prorated; overlapping admissions merged.
- [redacted] Time-to-event: [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]

Appendix L. Proportional hazard plots for OS and EFS

Figure 16. Overall survival, plot of log-log (event) versus log(time), DCO3.

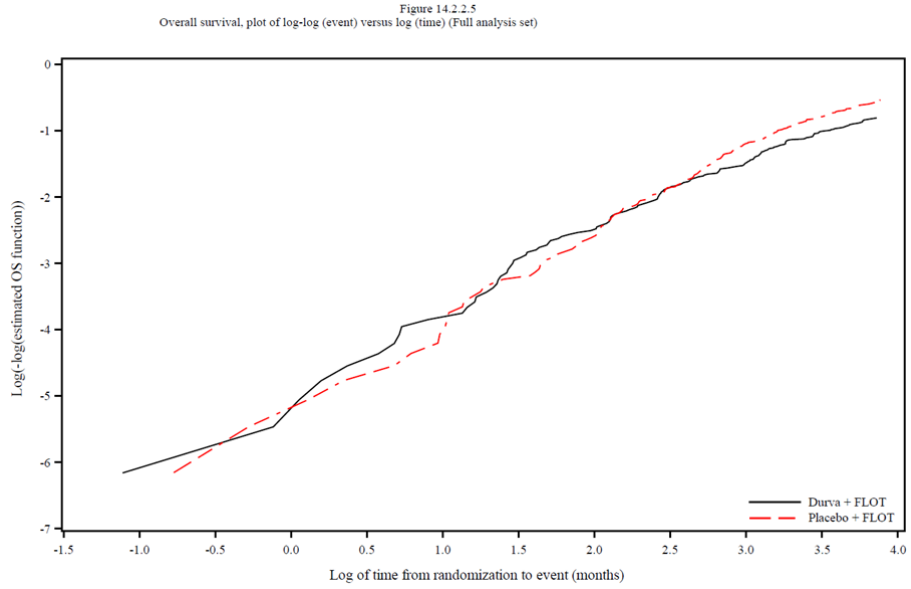
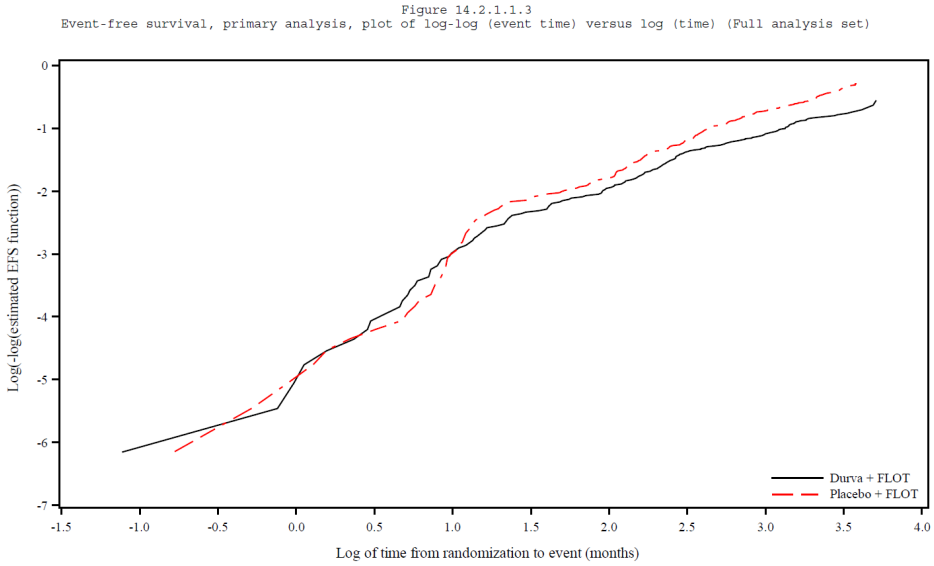


Figure 17. Event free-survival, plot of log-log (event) versus log(time), DCO2.



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