

Single Technology Appraisal

Durvalumab in combination for neoadjuvant and adjuvant treatment of resectable gastric and gastro-oesophageal junction cancer [ID6374]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL- Streamlined

Durvalumab in combination for neoadjuvant and adjuvant treatment of resectable gastric and gastro-oesophageal junction cancer [ID6374]

Contents:

The following documents are made available to stakeholders:

Access the [final scope and final stakeholder list](#) on the NICE website.

1. [**Company submission from AstraZeneca:**](#)
 - a. [Full submission](#)
 - b. [Summary of Information for Patients \(SIP\)](#)
2. [**Clarification questions and company responses**](#)
3. [**Patient group, professional group, and NHS organisation submission from:**](#)
 - [Stomach Cancer UK](#)
4. [**Expert personal perspectives from:**](#)
 - a. [Professor Wasat Mansoor, clinical expert - Professor of Medical Oncology – nominated by AstraZeneca](#)
 - b. [Mr Piers Boshier, clinical expert – Clinical Assistant Professor / Consultant UGI Surgeon - nominated by Gastric Cancer UK \(operating as Stomach Cancer UK\)](#)
 - c. [Sheena Dewan, patient expert - Executive Director, Founder - nominated by Gastric Cancer UK \(operating as Stomach Cancer UK\)](#)
 - d. [Chloe Stirling, patient expert - nominated by Gastric Cancer UK \(operating as Stomach Cancer UK\)](#)
5. [**External Assessment Report prepared by Liverpool Reviews and Implementation Group \(LRIG\)**](#)
6. [**Company Addendum**](#)
7. [**External Assessment Group response to factual accuracy check of EAR**](#)
8. [**External Assessment Group response to Company Addendum**](#)
9. [**Further Clarification Comments from Clinical Expert Professor Wasat Mansoor following a request by the Chair**](#)

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

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Single technology appraisal

Durvalumab in combination for neoadjuvant and adjuvant treatment of resectable gastric and gastro-oesophageal junction cancer [ID6374]

Company evidence submission

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Company evidence submission template for durvalumab in combination for neoadjuvant and adjuvant treatment of resectable gastric and gastro-oesophageal junction cancer [ID6374]

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Abbreviations

Acronym	Definition
ADCC	Antibody-Dependent Cell-mediated Cytotoxicity
AIC	Akaike Information Criterion
AJCC	American Joint Committee on Cancer
ALT	Alanine Aminotransferase
ASCO	American Society of Clinical Oncology
AST	Aspartate Aminotransferase
BIC	Bayesian Information Criterion
BICR	Blinded Independent Central Review
BNF	British National Formulary
BRCA	Breast Cancer gene (BRCA1 or BRCA2)
BSA	Body Surface Area
BTC	Biliary Tract Cancer
CDSR	Cochrane Database of Systematic Reviews
CEM	Cost-Effectiveness Model
CENTRAL	Cochrane Central Register of Controlled Trials
COVID	Coronavirus Disease
CRD	Centre for Reviews and Dissemination
CRT	Chemoradiotherapy
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CTLA	Cytotoxic T-Lymphocyte Antigen
D-FLOT	Durvalumab plus FLOT
DCO	Data Cut-Off
DFS	Disease-Free Survival
DHSC	Department of Health and Social Care
DSA	Deterministic Sensitivity Analysis
DSS	Disease-Specific Survival
DSU	Decision Support Unit
EAG	Evidence Assessment Group
ECF	Epirubicin, Cisplatin, and Fluorouracil
ECOG	Eastern Cooperative Oncology Group (performance status)
ECX	Epirubicin, Cisplatin, and Capecitabine
EFS	Event-Free Survival
EGFR	Epidermal Growth Factor Receptor

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EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
EPI	Epidemiology
ESMO	European Society for Medical Oncology
ESOPEC	Randomised trial of perioperative chemotherapy comparing FLOT with ECF/ECX for resectable oesophagogastric adenocarcinoma
FAS	Full Analysis Set
FDA	Food and Drug Administration
FLOT	5-fluorouracil, Leucovorin, Oxaliplatin, Docetaxel (chemotherapy regimen)
FOLFOX	Folinic Acid, Fluorouracil, and Oxaliplatin (chemotherapy regimen)
GC	Gastric Cancer
GLOBOCAN	Global Cancer Observatory (IARC database)
GOA	Gastro-Oesophageal Adenocarcinoma
GOC	Gastric and Oesophageal Cancer (or Cancer)
GOJ	Gastro-Oesophageal Junction
GOJC	Gastro-Oesophageal Junction Cancer
GPM	General Population Mortality
HBV	Hepatitis B Virus
HCC	Hepatocellular Carcinoma
HCRU	Health Care Resource Utilisation
HIV	Human Immunodeficiency Virus
HRG	Healthcare Resource Group
HSUV	Health State Utility Value
HTA	Health Technology Assessment
ICD	International Classification of Diseases
ICER	Incremental Cost-Effectiveness Ratio
IHE	Institute of Health Economics
IPD	Individual Patient Data
IRT	Interactive Response Technology
ITT	Intention-To-Treat
IV	Intravenous
JACCRO	Japan Clinical Cancer Research Organization
KEYNOTE	Series of pivotal pembrolizumab clinical trials
LYG	Life Years Gained
MEDLINE	Medical Literature Analysis and Retrieval System Online
MFS	Metastasis-Free Survival
MHRA	Medicines and Healthcare products Regulatory Agency (UK)
MIBC	Muscle-Invasive Bladder Cancer or Medical Information and Benefit Communication

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MMRM	Mixed Model for Repeated Measures
MRI	Magnetic Resonance Imaging
MSI	Microsatellite Instability
MTP	Multiple Testing Procedure
NCCN	National Comprehensive Cancer Network
NHB	Net Health Benefit
NHS	National Health Service
NHSCII	NHS Cancer Intelligence and Insight
NICE	National Institute for Health and Care Excellence
NOGCA	National Oesophago-Gastric Cancer Audit
NSCLC	Non-Small Cell Lung Cancer
OECD	Organisation for Economic Cooperation and Development
OS	Overall Survival
PAR	Public Assessment Report
pCR	Pathological Complete Response
PFS	Progression-Free Survival
PMG	Procedural Manual Guidance
PRO	Patient-Reported Outcome
PRS	Post-recurrence Survival
PSA	Probabilistic Sensitivity Analysis
PSM	Propensity Score Matching
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	Quality-Adjusted Life Year
QLQ	Quality of Life Questionnaire (e.g., EORTC QLQ-C30)
QXW	Every 'X' weeks
RCT	Randomised Controlled Trial
RDI	Relative Dose Intensity
RECIST	Response Evaluation Criteria in Solid Tumours
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System (software)
SCC	Squamous Cell Carcinoma
SCLC	Small Cell Lung Cancer
SEER	Surveillance, Epidemiology, and End Results (database)
SLR	Systematic Literature Review
SmPC	Summary of Product Characteristics
SMR	Standardised Mortality Ratio

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STM	State Transition Model
TAP	Tumour Area Positivity
TEAE	Treatment-Emergent Adverse Event
TFR	Time to First Recurrence
TNM	Tumour, Node, Metastasis
TSD	Technical Support Document
TTD	Time To Discontinuation
WBC	White Blood Cell
WHO	World Health Organization
WTP	Willingness To Pay
XELOX	Capecitabine (Xeloda) and Oxaliplatin

1 Decision problem, description of the technology and clinical care pathway

1.1 *Decision problem*

This submission is aligned with the anticipated marketing authorisation for durvalumab for the indication under consideration: [REDACTED]

[REDACTED]; together referred to as gastric/gastro-oesophageal junction adenocarcinoma (GOA) throughout this submission.

The decision problem addressed in this submission, which is presented in Table 1, is broadly consistent with the National Institute for Health and Care Excellence (NICE) final scope for this appraisal. Any differences between the decision problem addressed and the NICE final scope are also outlined in Table 1.

The current standard of care (SoC) for patients with resectable GOA being treated with curative intent consists of perioperative FLOT chemotherapy, administered both prior to (neoadjuvant) and following (adjuvant) radical surgery.¹⁻⁴ Despite the improved clinical outcomes associated with perioperative FLOT chemotherapy in resectable GOA, overall patient outcomes remain suboptimal and substantial unmet medical needs persist (Section 1.3.5). As detailed in Table 1 and further in Section 1.3.5, durvalumab is expected to be used in combination with FLOT chemotherapy as a perioperative treatment for patients with resectable GOA. Together, this combination is termed perioperative D-FLOT. Perioperative D-FLOT has the potential to address these unmet needs and further improve outcomes for patients with resectable GOA, as demonstrated by the results of the MATTERHORN trial (see Section 2.6). UK clinical experts stated that perioperative D-FLOT will represent a practice-changing treatment and expect this combination therapy to become the future SoC for patients with resectable GOA treated with curative intent.⁵

Table 1. The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with resectable gastric or gastro-oesophageal junction adenocarcinoma	Adults with resectable gastric or gastro-oesophageal junction adenocarcinoma	N/A
Intervention	Durvalumab with chemotherapy (FLOT) before surgery (neoadjuvant) and after surgery (adjuvant), then adjuvant durvalumab monotherapy	Durvalumab with chemotherapy (FLOT) before surgery (neoadjuvant) and after surgery (adjuvant), then adjuvant durvalumab monotherapy	N/A
Comparator(s)	Established clinical management without durvalumab, including but not limited to: - Chemotherapy (FLOT), before and after surgery - For people with gastro-oesophageal junction adenocarcinoma: - Nivolumab, after surgery in adults who have residual disease after previous neoadjuvant chemoradiotherapy	FLOT chemotherapy, before and after surgery (perioperative FLOT chemotherapy)	Relevant comparator: FLOT chemotherapy, before and after surgery (perioperative FLOT chemotherapy) Perioperative FLOT represents the current SoC in the UK, in line with guidelines from the European Society of Medical Oncology (ESMO). This is further supported by feedback from UK clinical experts, who validated that perioperative FLOT chemotherapy is the SoC for all resectable patients fit enough to receive it and that most of the criteria for surgery eligibility are aligned with the FLOT eligibility criteria.^{2, 3, 5, 6} As such, the majority of patients with resectable GOA are eligible for and should be treated with the SoC, perioperative FLOT chemotherapy. As demonstrated in the FLOT4 and ESOPEC trials, perioperative FLOT is associated with superior efficacy compared to other perioperative chemotherapies (i.e., epirubicin, cisplatin and fluorouracil [ECF]/epirubicin, cisplatin and capecitabine [ECX]), or chemoradiotherapies (CRT), and is therefore the preferred treatment option for FLOT-eligible patients.⁷ As detailed above, the technology being appraised is perioperative durvalumab with FLOT chemotherapy (perioperative D-FLOT). Therefore, by definition, the population

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			of interest to this submission represents patients with resectable GOA who are eligible for surgery and a perioperative treatment regimen (at the time of treatment decision) and are able to tolerate FLOT chemotherapy. Regimens intended for patients who are not deemed to be eligible for perioperative FLOT chemotherapy are not considered relevant comparators. These patients represent a distinct patient population to the target population of this submission. As such, the only relevant comparator to perioperative D-FLOT in this setting is perioperative FLOT chemotherapy <i>Not relevant comparator: Nivolumab, after surgery in adults who have residual disease after previous neoadjuvant CRT (for people with gastro-oesophageal junction adenocarcinoma and squamous cell carcinoma [SCC])</i> Nivolumab is licenced and recommended by NICE for use as an adjuvant treatment for patients with completely resected Stage II–III oesophageal cancer/GOJC who have evidence of residual pathologic disease and have received prior neoadjuvant CRT (TA746).^{8, 9} According to UK clinical experts, CRT is mostly used for patients who are not eligible for surgery, therefore it was not included in the final scope. Neoadjuvant CRT followed by surgery is only recommended as a treatment option for patients not suitable for perioperative FLOT. This is based on results of the ESOPEC trial, which demonstrated improved outcomes for patients receiving perioperative FLOT versus neoadjuvant CRT. UK clinical experts unanimously agreed that it is very rare that patients who are ineligible for perioperative FLOT chemotherapy, and therefore receive neoadjuvant CRT, are able to tolerate surgery.⁵ Due to the requirement to receive CRT followed by surgery prior to nivolumab, it follows that adjuvant nivolumab is only an option for patients with GOJC who are not eligible for FLOT but can undergo surgery, meaning the population of patients receiving adjuvant

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			nivolumab in UK clinical practice is negligible. As such, adjuvant nivolumab is not a relevant comparator according to UK clinical experts advice.⁵ The clinical experts also added that nivolumab is primarily used in patients with oesophageal SCC rather than gastro-oesophageal junction adenocarcinoma.⁵ This positioning is reinforced by the latest data from the CheckMate-577 trial.¹⁰ Data from the final OS analysis of CheckMate-577 show a less pronounced OS benefit in the adenocarcinoma subgroup (HR 0.92 [CI 95% 0.73-1.15]) vs. the SCC subgroup (HR 0.72 [CI 95% 0.51-1.03]). The OS benefit was less pronounced in the gastroesophageal junction subgroup (HR 1.14 [CI 95% 0.83-1.56]) vs the oesophageal subgroup (HR 0.69 [CI 95% 0.54-0.88]). UK clinical experts additionally commented that CRT and nivolumab are anticipated to be removed as options from the ESMO guidelines as part of the next update.⁵ Consequently, in order to align the submission with the current treatment pathway in the UK, adjuvant nivolumab is not a relevant comparator in this appraisal.⁸
Outcomes	The outcome measures to be considered include: • Overall survival (OS) • Event-free survival (EFS) • Response rate • Adverse effects (AEs) of treatment • Health-related quality of life (HRQoL)	The outcomes included in this submission are: • OS • EFS • Pathological complete response (pCR) • Surgical outcomes • Disease-free survival (DFS) • Disease-specific survival (DSS) • Metastasis-free survival (MFS)	All outcomes outlined in the final scope are presented in the Company submission. The Company have provided some additional outcome measures, in line with the endpoints reported in the MATTERHORN trial (see Section 2.4.2). These include: pCR, surgical outcomes, pathological downstaging, DFS, DSS and MFS.

		• Pathological downstaging • AEs • HRQoL	
Subgroups to be considered	If evidence allows, results by level of programmed death ligand-1 (PD-L1) expression will be considered	Subgroup analyses for the clinical endpoints of EFS and OS, including by PD-L1 expression level (tumour area positivity [TAP] $\geq 1\%$ vs TAP $< 1\%$) are provided in Section 2.8.	Results of subgroup analyses from MATTERHORN demonstrate a consistent treatment benefit regardless of PD-L1 expression level. Clinical experts validated that PD-L1 expression is not routinely tested in all patients with resectable GOA and does not determine their treatment decisions for patients with resectable GOA.⁵ As such, D-FLOT would be offered to all patients in clinical practice, regardless of their characteristics. Since PD-L1 expression will not inform treatment decision or cost-effectiveness decisions, economic subgroup analyses based on PD-L1 expression have not been explored.

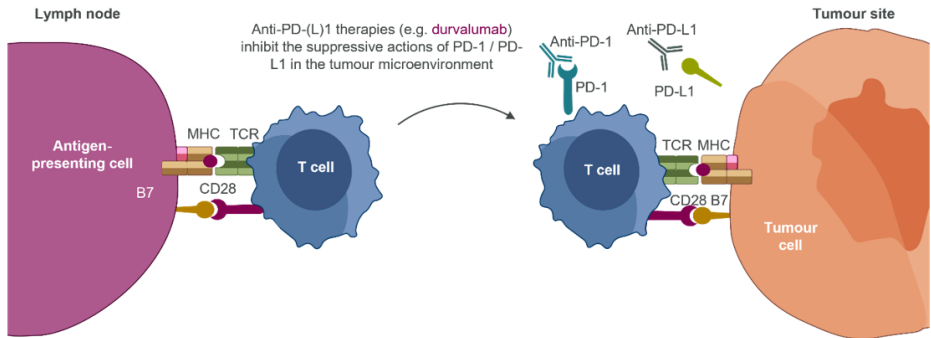
Abbreviations: AE: adverse effect; CI: confidence interval; CRT: chemoradiotherapy; DFS: disease-free survival; D-FLOT: durvalumab + FLOT; DSS: disease-specific survival; EFS: event-free survival; ECF: epirubicin, cisplatin and fluorouracil; ECX: epirubicin, cisplatin and capecitabine; EMA: European Medicines Agency; EPI: epirubicin; ESMO: European Society of Medical Oncology; FLOT: 5-fluorouracil, leucovorin, oxaliplatin and docetaxel; GOA: gastro-oesophageal adenocarcinoma; GOJC: gastro-oesophageal junction cancer; HR: hazard ratio; HRQoL: health-related quality of life; ITT: intention to treat; MFS: metastasis-free survival; NICE: National Institute for Health and Care Excellence; OS: overall survival; pCR: pathological complete response; PD-L1: programmed death ligand-1; SCC: squamous cell carcinoma; SoC: standard of care; TAP: tumour area proportion; UK: United Kingdom.

1.2 Description of the technology being evaluated

A summary of the mechanism of action, marketing authorisation status, costs and administration requirements associated with durvalumab are presented in Table 2.

The draft SmPC and UK public assessment report (PAR) for durvalumab in the indication of relevance to this submission are provided in the reference pack accompanying this submission (see Appendix A).

Table 2. Technology being evaluated

UK approved name and brand name	Durvalumab (IMFINZI®)
Mechanism of action	Durvalumab, a high-affinity immunotherapy, is an anti-programmed cell death ligand 1 (PD-L1) IgGk1 monoclonal antibody which selectively blocks the interaction of PD-L1 with PD-1 and CD80. PD-L1 is a protein that helps cancer cells to evade detection and elimination by the immune system. Durvalumab binds to and inhibits PD-L1, thus enabling the immune system to find and attack cancer cells (Figure 1).¹¹ Figure 1. Durvalumab mechanism of action: PD-L1 blockade  Source: Buchbinder 2016.¹²
Marketing authorisation/CE mark status	The marketing authorisation for durvalumab in this indication is currently pending, and is anticipated to be granted by the Medicines and Healthcare Products Regulatory Agency (MHRA) in [REDACTED]
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Indication of interest to this evaluation: - Anticipated license wording: [REDACTED] Other current indications for durvalumab:¹³ Muscle invasive bladder cancer (MIBC): - Durvalumab in combination with gemcitabine and cisplatin as neoadjuvant treatment, followed by durvalumab as monotherapy adjuvant treatment after radical cystectomy, is indicated for the treatment of adults with MIBC Endometrial cancer (EC): - Durvalumab in combination with carboplatin and paclitaxel is indicated for the first-line treatment of adults with primary advanced or recurrent EC who are candidates for systemic therapy, followed by maintenance treatment with durvalumab as monotherapy in EC that is mismatch repair deficient or durvalumab in combination with olaparib in EC that is mismatch repair proficient.

	Non-small cell lung cancer (NSCLC) - Durvalumab as monotherapy for the treatment of locally advanced, unresectable NSCLC in adults whose tumours express PD-L1 on $\geq 1\%$ of tumour cells and whose disease has not progressed following platinum-based chemoradiation therapy. - Durvalumab in combination with platinum-based chemotherapy as neoadjuvant treatment, followed by durvalumab as monotherapy after surgery, for the treatment of adults with resectable (tumours ≥ 4 cm and/or node positive) NSCLC with no known epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase rearrangements. Small cell lung cancer (SCLC) - Durvalumab is indicated in combination with etoposide and either carboplatin or cisplatin for the first-line treatment of adults with extensive-stage SCLC. Biliary tract cancer (BTC) - Durvalumab is indicated in combination with gemcitabine and cisplatin for the first-line treatment of adults with locally advanced, unresectable or metastatic BTC. Hepatocellular carcinoma (HCC) - Durvalumab is indicated in combination with tremelimumab for the first-line treatment of adults with advanced or unresectable HCC. Contraindications include hypersensitivity to the active substance or to any of the excipients.
Method of administration and dosage	Durvalumab is available as a sterile concentrate for solution for intravenous infusion in 2.4 mL or 10 mL vials (containing 120 mg and 500 mg of durvalumab, respectively). Durvalumab should be administered over one hour through an intravenous line containing a sterile, low-protein binding in-line filter (pore size 0.2 or 0.22 micron); other medicinal products should not be co-administered through the same infusion. The licensed dose of durvalumab is 1,500mg every four weeks for two cycles in the neoadjuvant phase, followed by 12 cycles in the adjuvant phase.
Additional tests or investigations	No additional tests or investigations will be required to prescribe durvalumab in this indication.
List price and average cost of a course of treatment	The list prices for the available formulations of durvalumab are:¹⁴ 120mg/2.4mL concentrate for solution for infusion vials: £592.00 per vial 500mg/10mL concentrate for solution for infusion vials: £2,466.00 per vial The average costs for a course of treatment with durvalumab (consisting of two cycles in the neoadjuvant phase, followed by 12 cycles in the adjuvant phase) are: 500mg/10mL formulation: £103,572 per course
Patient access scheme (if applicable)	This submission includes a confidential commercial access agreement for durvalumab: 120mg/2.4mL concentrate for solution for infusion vials: £[REDACTED] per vial 500mg/10mL concentrate for solution for infusion vials: £[REDACTED] per vial

Abbreviations: CD80: cluster of differentiation 80; IgG: immunoglobulin; MHRA: Medicines and Healthcare Products Regulatory Agency; PD-L1: programmed cell death ligand 1; SmPC: summary of product characteristics.

1.3 **Health condition and position of the technology in the treatment pathway**

Gastro-oesophageal cancer (GOC; comprising gastric cancer [GC] and gastro-oesophageal junction cancer [GOJC]) is the fifth most common cancer worldwide.¹⁵ In the UK, it was the 18th most common cancer between 2017–2019, accounting for 2% of all cancer deaths¹⁶

- GOC is an umbrella term for cancers located near or within the stomach. GC originates in the non-cardia sections of the stomach, while GOJC originates at the gastro-oesophageal junction (GOJ), where the oesophagus joins the gastric cardia¹⁷
- The development of GOC is influenced by a combination of genetic, environmental, and lifestyle factors, many of which contribute to chronic inflammation and cellular changes in the stomach lining¹⁸
- The majority (~90%) of GOC are adenocarcinomas, which develop from mucus-producing cells in the inner lining of the stomach^{19, 20}
- In this submission, the population of interest are adults with resectable GOA. Approximately 1,700 patients will be diagnosed with resectable GOA every year in the UK

The current SoC for patients with resectable GOA is curative intent treatment consisting of surgery alongside perioperative FLOT chemotherapy

- Radical surgery with curative intent represents the primary treatment for patients with resectable GOA^{3, 6}
- The addition of chemotherapy before and after surgery (i.e., perioperative) reduces the risk of disease recurrence and improves the chances of cure for patients with GOA^{3, 6}
- The European Society for Medical Oncology (ESMO) guidelines recommend radical surgery with curative intent alongside perioperative FLOT chemotherapy for patients with resectable GOA who are eligible for perioperative FLOT chemotherapy.^{3, 5, 6} This is based on evidence demonstrating the superior efficacy of perioperative FLOT chemotherapy vs. other chemotherapy regimens or neoadjuvant chemoradiotherapy (CRT)^{2-4, 6, 7, 21}
- UK clinical experts validated that perioperative FLOT chemotherapy represents the current SoC for patients with resectable GOA in UK clinical practice⁵
 - As the SoC therapy in the UK, all patients with resectable GOA who are eligible to receive perioperative FLOT chemotherapy should be offered this regimen

The long-term outcomes for patients with GOA are poor, with disease progression and recurrence significantly impacting patient survival and quality of life (QoL)

- Despite the curative intent of surgery, long-term outcomes for patients with GOA remain suboptimal. The FLOT4 trial reported a 5-year overall survival (OS) of approximately 45%.⁷ Over half of patients receiving the current SoC in UK clinical practice (perioperative FLOT chemotherapy) experience disease recurrence, progression, or death within three years (median disease-free survival [DFS]: 30 months)^{7, 22, 23}
- Disease recurrence in GOA significantly impacts patient survival and health-related quality of life
 - Median OS after recurrence to metastatic GC is between 12–18 months with platinum-based chemotherapy regimens, with novel therapies offering only a modest additional life-prolonging effect²⁴⁻²⁷
- GOA is also associated with a substantial economic burden for healthcare systems, estimated at ~£740 million to the UK economy.²⁸ This economic burden increases with disease progression, reflecting the need for effective early treatment interventions²⁹

In the resectable GOA setting, perioperative IO therapies, which prime anti-tumour immunity in the neoadjuvant phase and sustain immunosurveillance in the adjuvant phase, provide an opportunity to reduce the risk of disease progression and recurrence without impacting patients' QoL

- Even following the introduction of perioperative FLOT, survival rates remain low and the risk of the disease returning remains high.³⁰⁻³² Novel treatment options which improve patient outcomes are needed, especially within the resectable disease setting which represents the last opportunity for treatment with curative intent
- Currently, IO therapies are only available once disease becomes advanced, at which point they deliver modest life-prolonging benefit and cure is no longer achievable^{3, 6, 21, 33, 34}
- As such, there is a clear unmet need for the introduction of more effective interventions, such as durvalumab, at an earlier disease stage where the disease can be treated with curative intent

Perioperative D-FLOT would represent a step change in the treatment of GOA, providing patients with an increased chance of disease cure and protection from the physical and psychological burden associated with disease recurrence or progression

- Durvalumab is a high-affinity, human immunoglobulin G kappa (IgG1κ) monoclonal antibody that selectively blocks the interaction of PD-L1 with programmed death receptor 1 (PD-1) and cluster of differentiation 80 (CD80) (B7.1)³⁵
- In UK clinical practice, durvalumab is [REDACTED]
[REDACTED]
[REDACTED]
- Durvalumab (in combination with perioperative FLOT) represents the first and only IO treatment regimen that has shown improvements vs. perioperative FLOT in the resectable GOA setting³⁶
- The use of perioperative D-FLOT is particularly efficacious, compared to perioperative FLOT chemotherapy alone, due to the synergistic interaction of durvalumab with FLOT, facilitating immune priming before surgery and maintaining immunosurveillance following it³⁷⁻⁴⁴
- This was reflected in the results of the MATTERHORN trial; D-FLOT demonstrated significant improvements in survival and response outcomes without decreasing the number of patients able to undergo curative intent surgery, owing to a tolerable safety profile.³⁶ These findings reflect that if recommended, perioperative D-FLOT would represent a highly valued and impactful treatment option for patients with resectable GOA

1.3.1 Disease overview

Classification of GC and GOJC

Within the gastro-oesophageal tract, tumours can arise in various locations, including the oesophagus, GOJ, and stomach.¹⁷ This appraisal focuses on tumours located near or within the stomach, referred to as GOC. GOC is an umbrella term for cancers located near or within the stomach.¹⁷ It is a heterogeneous group of cancers with distinct histological, anatomical, and molecular features, making accurate classification critical for diagnosis, prognosis, and treatment.¹⁷

GOC is classified into two main types based on the anatomical origin of its development in the stomach:

- **GC:** cancer that originates in the non-cardia sections of the stomach, which include the fundus, body, antrum and pylorus, comprising the lower parts of the stomach.
- **GOJC:** cancer that originates at the gastro-oesophageal junction, where the oesophagus joins the gastric cardia.¹⁷

From a histological perspective, these tumours can be classified as adenocarcinomas, squamous cell carcinomas (SCCs), and other rare types of stomach cancer.¹⁹ The majority of GOC are adenocarcinomas, which develop from mucus-producing cells in the inner lining of the stomach.¹⁹ The Company evidence submission template for durvalumab in combination for neoadjuvant and adjuvant treatment of resectable gastric and gastro-oesophageal junction cancer [ID6374]

focus of this appraisal is on gastro-oesophageal **adenocarcinomas** (GOAs), which exclude tumours located elsewhere (such as oesophageal carcinomas) or those with other histology (such as SCC and other rare subtypes).

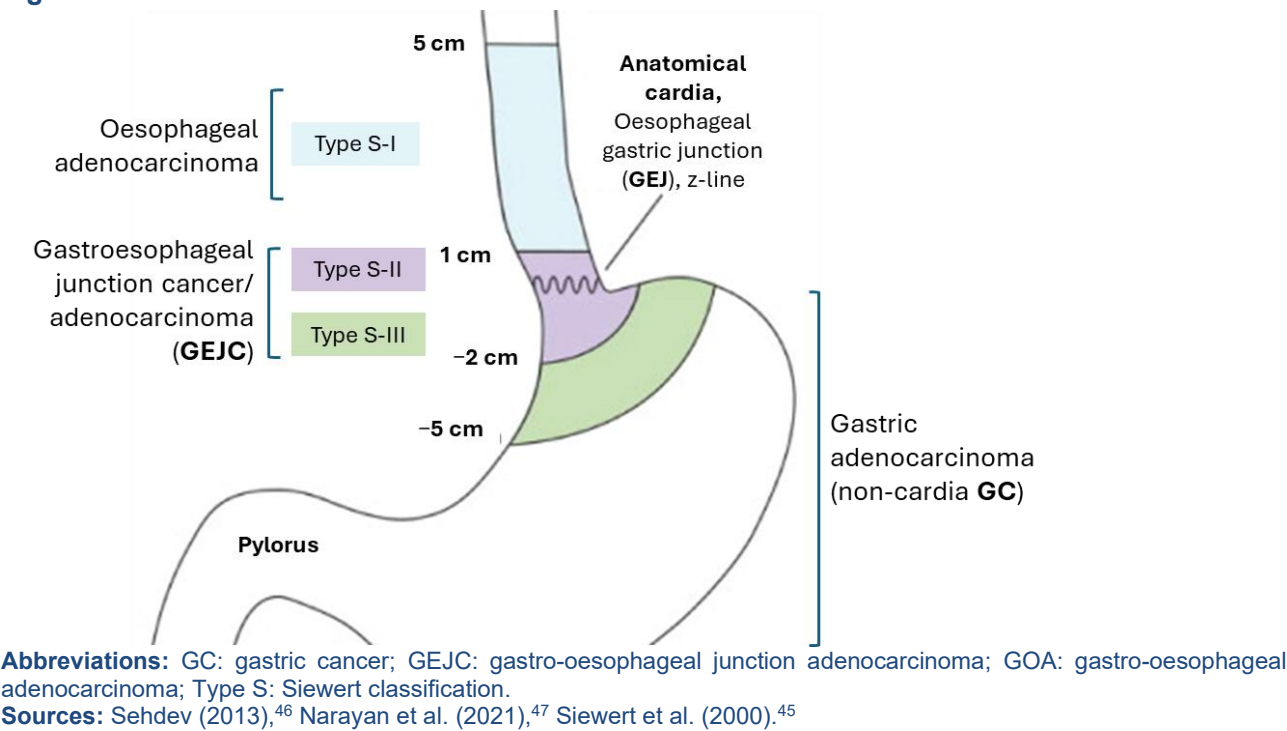
Siewert classification system

GOJC adenocarcinomas are further classified into three subtypes according to the proximity of the tumour epicentre to the cardia using the Siewert classification system (Figure 2):⁴⁵

- Type I adenocarcinomas are located ≥ 1 cm above the GOJ and are typically considered adenocarcinomas of the distal oesophagus that may infiltrate the GOJ from above. Patients with Type I adenocarcinomas are treated as gastric adenocarcinomas or oesophageal carcinomas
- Type II adenocarcinomas are considered ‘true’ carcinomas of the cardia arising immediately at the oesophagogastric junction (1–2 cm below the GOJ). Patients with Type II adenocarcinomas are treated as gastric adenocarcinomas
- Type III are subcardial gastric carcinomas that infiltrate the oesophagogastric junction and distal oesophagus from below (≥ 2 cm below the GOJ). Patients with Type III adenocarcinomas are also treated as gastric adenocarcinomas

In this submission, the population of interest is **adults with resectable GOA** (as per the MATTERHORN trial, detailed in Section 2.3.1). The term “resectable” is used to describe cancer that is localised and can be removed by surgery which is usually in the earlier stages of cancer.

Figure 2. GOA classification



Disease staging

The American Joint Cancer Committee (AJCC)/Union for International Cancer Control (UICC) TNM classification system is the internationally accepted standard for cancer staging and is a major factor influencing prognosis and treatment decisions.^{2, 21} This stages tumours based on their size (T), the extent the cancer has spread into the lymph nodes (N) and the presence of metastasis (M).⁴⁸

Disease pathophysiology and risk factors

The pathophysiology of GOA is complex and multifactorial. The development of these cancers is influenced by a combination of genetic, environmental, and lifestyle factors, many of which contribute to chronic inflammation and cellular changes in the stomach lining.¹⁸ Of note, the pathophysiology and associated risk factors are known to differ for cardia and non-cardia cancers.

Infection with *Helicobacter pylori* (*H. pylori*) is strongly implicated in the aetiology of non-cardia GC.¹⁷ *H. pylori* is a gram-negative bacteria that colonises the gastric mucosa and is the primary cause of chronic gastritis (inflammation of the stomach lining).⁴⁹ This inflammation, along with the resulting immune response and release of various bacterial cytotoxins, can induce cellular changes in the gastric lining, causing abnormal cell proliferation and the development of non-cardia cancer.⁴⁹⁻⁵² Recent estimates attribute approximately 89% of GC cases, and 6.2% of all cancers worldwide to *H. pylori* infection.^{49, 53} Other risk factors such as obesity, tobacco smoking, high salt intake and heavy alcohol consumption have also been associated with an increased risk for GC.⁵⁴ Risk factors for cardia GC include obesity, high fat intake and gastro-oesophageal reflux disease.^{6, 54}

1.3.2 Epidemiology

Data on the epidemiology of GC or GOJC specifically in the UK are scarce, however, a number of studies have reported the epidemiology of GOC (which includes GOA), which are detailed below. These epidemiology data are presented for GOC as a group, consisting of GC, GOJC or as oesophageal cancer (OC) and so should be interpreted in the context of how they were classified.

Collectively, GOC is the fifth most common cancer type, and was the fourth leading cause of cancer-related deaths globally in 2022.⁵⁵ GOC was the 18th most common cancer in the UK, accounting for 2% of all cancer deaths between 2017–2019.¹⁶ Each year in the UK there are approximately 6,500 new cases of GOC (~2,300 in women and ~4,200 in men).¹⁶ As of 2022, the age-standardised incidence rate of GOC in the UK was 3.6 patients per 100,00 individuals.⁵⁵ The UK age-standardised five-year prevalence rate of GOC in 2022 was 11.4 patients per 100,00 individuals.⁵⁵

Globally, over the past 50 years rates of GC have declined, which is attributed to a decrease in *H. pylori* prevalence as well as improvements in the preservation and storage of foods.⁵⁶ In contrast, GOJC incidence has been rising in areas where risk factors such as obesity, gastro-oesophageal reflux disease and Barrett oesophagus are more prevalent.⁵⁷ Notably, in England, GOC incidence rates are 99% and 84% higher among females and males, respectively, in the most deprived quintile compared with the least (2013–2017), suggesting that there is a link between GOC and deprivation.¹⁶ The incidence of GC and GOJC has also been reported to vary between ethnic groups within the UK.⁵⁸

The majority of GOCs (~90%) are classed as adenocarcinomas. However, there are limited recent data that inform the epidemiology of GOA in UK clinical practice specifically.²⁰ Based on data collected from between 2004–2006, the annual incidence of GOA was estimated at 5.4 patients per 100,000.⁵⁹ The budget impact model designed for this submission indicates that as of 2025, around 3,250 patients will receive a diagnosis of GOA annually in the UK, of which 1,700 are estimated to have resectable disease.

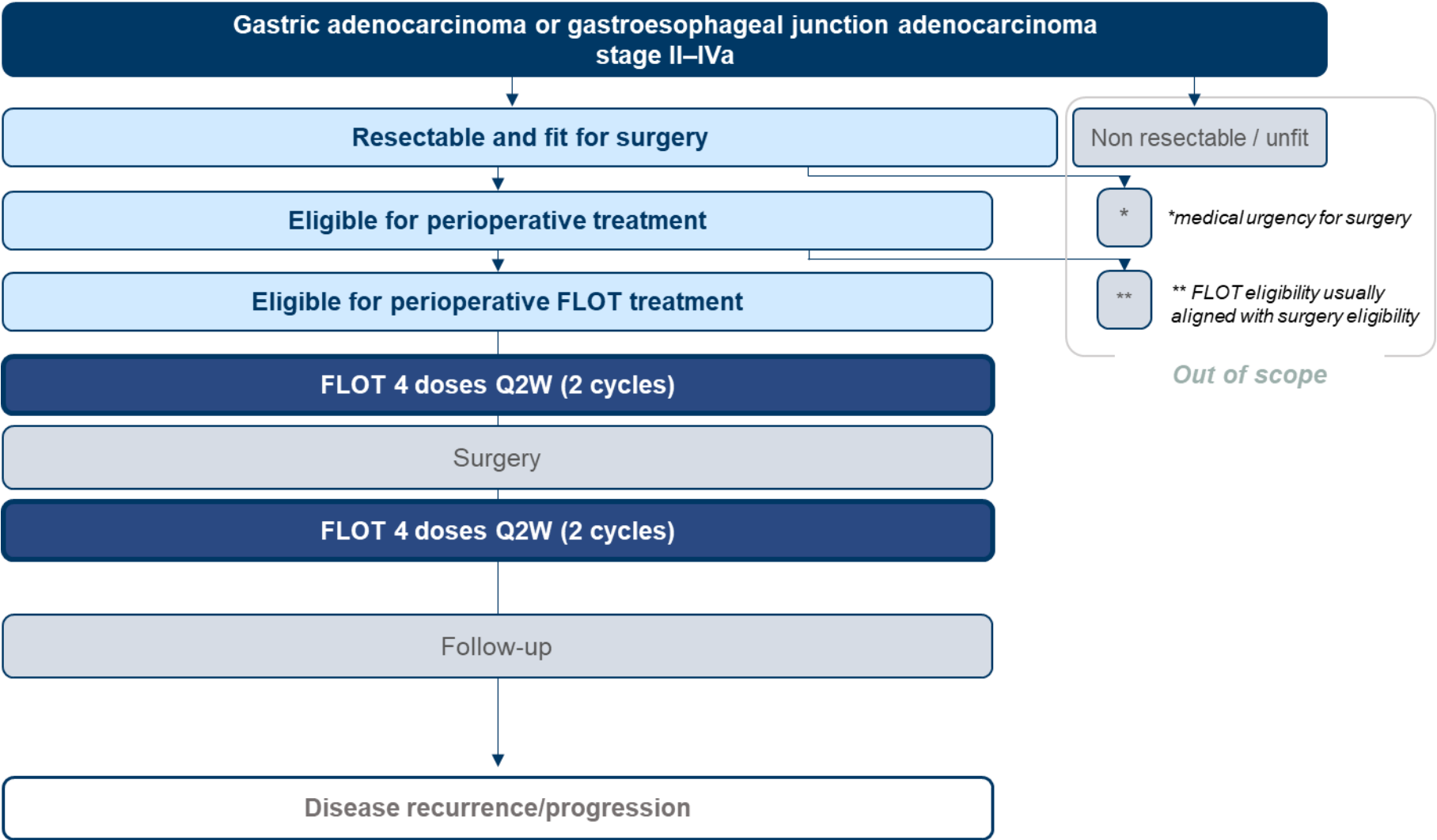
1.3.3 *Clinical management of resectable GOA*

This section focuses on ESMO guidelines (published in 2022 for GC and in 2025 for oesophageal cancer, including GOJC) and recent clinical evidence supporting treatment recommendations to provide an accurate, and up-to-date representation of UK clinical practice for the treatment of GOA.^{3, 6} UK clinical experts consulted by the Company confirmed that they use the ESMO guidelines to inform clinical management of GC and GOJC and validated that these are the most relevant treatment guidelines in the UK.⁵ NICE has published guidelines for the assessment and management of oesophago-gastric cancer in adults (NG83), however these were published in 2018 and since then, the GOA treatment pathway has changed and novel treatment regimens are used in UK clinical practice that NG83 does not yet cover.¹

Treatment for GOA depends on the size, type, location and stage of the tumour, with the guidelines recommending a combination of surgery, chemotherapy and/or radiotherapy.^{3, 6} The treatment pathway for patients with resectable GOA in UK clinical practice, based on ESMO guidelines and supplemented with insight from UK clinical experts, is summarised in Figure 3.^{3, 5, 6} UK clinical experts validated that both GC and GOJC are treated similarly in UK clinical practice, with the only difference related to the surgical approach offered to patients.⁵

The positioning of D-FLOT within the GOA treatment pathway is detailed in Section 1.3.6.

Figure 3. Clinical management of GOA in UK clinical practice



Abbreviations: FLOT: 5-fluorouracil, leucovorin, oxaliplatin, and docetaxel; GOA: gastro-oesophageal adenocarcinoma; Q2W: biweekly.
Source: Figure adapted from ESMO Clinical Practice Guideline: Gastrointestinal Cancers (2022) and ESMO Clinical Practice Guideline: Oesophageal Cancer (2025).^{3, 6}

As detailed in Figure 3, treatments indicated for patients who are ineligible for surgery and/or perioperative FLOT chemotherapy represent a different patient population to the one targeted by this submission and therefore are out of the scope of this appraisal (see Section 1.1). This includes neoadjuvant CRT, which was unanimously validated by UK clinical experts as being used for patients ineligible for perioperative FLOT chemotherapy.⁵ Adjuvant nivolumab is currently reimbursed for patients with GOJC who have received prior neoadjuvant CRT (TA746). Due to the requirement to receive neoadjuvant CRT prior to nivolumab, it follows that adjuvant nivolumab is only an option for patients with GOJC who are not eligible for FLOT.^{8,9} As such, patients receiving neoadjuvant CRT followed by adjuvant nivolumab represent a separate population to patients who will be candidates for D-FLOT. Additionally, clinical experts validated that nivolumab is primarily used for patients with SCC disease, rather than adenocarcinoma.⁵ As further detailed in Section 1.1, adjuvant nivolumab is therefore out of scope of this appraisal.

Subsequently, in order to align this submission with the current treatment pathway in UK clinical practice, the discussion below focuses on the treatment options for patients who are eligible for surgery and perioperative FLOT chemotherapy.

Clinical management of resectable GOA

As detailed in Section 1.1, the technology being appraised is perioperative durvalumab with FLOT chemotherapy (perioperative D-FLOT) and therefore, by definition, the population of interest to this submission represents patients that are suitable for a perioperative treatment regimen (at the time of treatment decision) and are eligible for FLOT chemotherapy.

Surgical treatment

Radical surgery with curative intent represents the primary treatment option for patients with resectable GOA, and at present, is the only treatment option that offers patients with resectable GOA disease the potential for cure.^{3,6} As validated by UK clinical experts, from the surgical perspective, GC and GOJC are approached slightly differently depending on the location of patients' tumours.⁵

Perioperative FLOT chemotherapy

Alongside surgery, the addition of therapeutic approaches, such as perioperative chemotherapy with a platinum and fluoropyrimidine combination, can reduce the risk of disease recurrence and improve the chances of cure following surgery in patients with resectable GOA.^{1,2,6} Several randomised trials have demonstrated the benefits of perioperative chemotherapy over other approaches.^{4,7,60-63} Consequently, the ESMO guidelines recommend the use of perioperative chemotherapy alongside surgery.^{3,6}

Specifically, the ESMO guidelines recommend perioperative FLOT chemotherapy as the SoC for patients with resectable GOA.^{3,6} This was validated by UK clinical experts, who stated that all patients eligible for FLOT should be offered it in clinical practice.⁵ Perioperative FLOT chemotherapy was established as the SoC perioperative chemotherapy regimen following improved results versus other regimens in several clinical trials.^{4,7} The Phase II/III FLOT4 trial reported improved OS for perioperative FLOT compared to perioperative ECX (epirubicin, Cisplatin and Capecitabine)/ECF (epirubicin, Cisplatin and 5-Fluorouracil) in patients with resectable GC (OS increased from median 35 months to 50 months).⁷ The ESOPEC trial also demonstrated significant improvements in OS and PFS for perioperative FLOT compared with neoadjuvant CRT in patients with oesophageal adenocarcinoma, including those with GOJC.⁴ UK clinical experts also validated that FOLFOX (leucovorin, fluorouracil and oxaplatin) is no longer used in clinical practice (unless patients are unable to tolerate FLOT) due to the improved efficacy of FLOT chemotherapy and that CRT is only used in patients who are unfit to receive surgery.⁵

Summary of relevant comparator

For the reasons outlined above, and as validated by UK clinical experts, all patients with resectable GOA who are eligible for perioperative FLOT should be offered this regimen.⁵ Only patients who are eligible for surgery and perioperative FLOT chemotherapy would be expected to be eligible for perioperative D-FLOT in UK clinical practice (see Section 1.3.6). Therefore, for the purposes of decision making in this appraisal, perioperative FLOT chemotherapy is the only relevant comparator to perioperative D-FLOT in the resectable GOA setting.

Biomarkers in GOA

The identification of biomarkers that influence the survival and proliferation of GOA tumours are important for establishing disease prognosis.⁶⁴ In the last decade, several key biomarkers have emerged in advanced GOA, including human epidermal growth factor 2 (HER2), microsatellite instability (MSI), and PD-1/PD-L1.^{2, 3} However, the ESMO guidelines for GC or GOJC do not currently recommend treatments based on biomarkers in patients with early-stage GOA.^{3, 6} This is in line with feedback from UK clinical experts, who confirmed that PD-L1 expression and MSI status are not treatment-influencing biomarkers in the resectable GOA setting and biomarking testing is not performed routinely across centres in UK.⁵

Emerging treatments in the resectable GOA setting

As discussed further in Section 1.3.3, the addition of perioperative FLOT chemotherapy to surgery has significantly improved the prognosis for patients with GOA.³⁸ However, the risk of disease recurrence remains high, and long-term survival continues to be suboptimal.³⁸ As a result, the development of novel efficacious treatment options is required. While targeted therapies and IO therapies have been established as treatment options for advanced/metastatic GOA, there is a distinct lack of novel treatments in the resectable GOA setting. Perioperative treatments that utilise the same IO therapy before and after surgery have the potential to improve patient outcomes by priming anti-tumour immunity in the neoadjuvant setting and sustaining immunosurveillance and eliminating micro-metastatic disease in the adjuvant setting.⁴⁴ This will therefore improve the likelihood of achieving long-term disease control and minimise the risk of recurrence.

There is currently a paucity of global Phase III clinical trials investigating novel therapies for patients with resectable GOA. Recent trials of IOs in resectable GOA have failed to demonstrate statistically significant benefits in clinically important endpoints. For example, KEYNOTE-585 (which evaluated a perioperative approach primarily using cisplatin-based chemotherapy combined with pembrolizumab) showed improved pathological complete response (pCR) rate but did not achieve the primary endpoint of a significant event-free survival benefit.³³ Similarly, the ATTRACTION-5 trial, which assessed adjuvant nivolumab plus chemotherapy, failed to demonstrate an increase in relapse-free survival compared to chemotherapy alone.⁶⁵

With other trials of IOs in resectable GOA having failed to show a significant and clinically meaningful benefit, durvalumab combined with perioperative FLOT, represents the first and only IO treatment regimen to show improvements in the resectable GOA setting (Section 2.6).³⁶ These findings suggest that a treatment regimen that combines an IO therapy with the current SoC chemotherapy specifically (perioperative FLOT) is critical for improving the outcomes for patients with resectable GOA.

1.3.4 Burden of disease

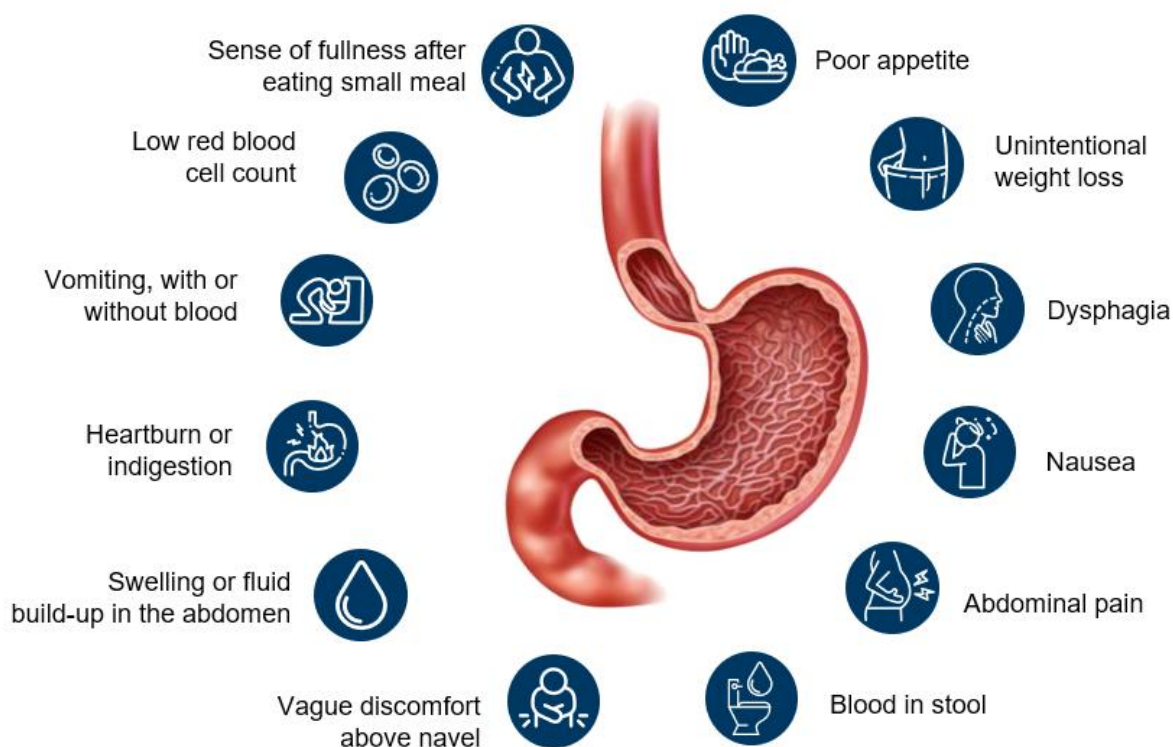
Clinical burden of resectable GOA

Symptom burden

Many of the symptoms of GC and GOJC overlap with those of other gastrointestinal disorders and generally present late in disease progression.^{28, 66-68} Patients with early stage GOA may therefore have vague, minimal or no symptoms and as a result, patients frequently experience delays in presentation and subsequent diagnosis; by this point, patients are commonly diagnosed with advanced disease and have a poor prognosis.^{28, 66-68} Based on 2025 data from the Cancer Research UK Rapid Cancer Registration Database (RCRD), assuming patients with anatomic Stage I–III disease can receive surgery, 36.3% of patients in UK clinical practice are diagnosed with resectable GOA, compared to 31.4% with Stage IV, advanced disease (the remaining 32.3% of patients' stage is unknown).⁶⁹ Despite generally presenting late in disease progression, these data demonstrate that a substantial proportion of patients are diagnosed with resectable disease in UK clinical practice, reflecting that this represents an important point at which to treat patients and prevent their disease progressing to advanced stages.⁶⁹

Advanced GC is associated with multiple synergistic or concomitant disease-related symptoms including loss of appetite, dysphagia, reflux and fatigue (Figure 4).^{28, 70-72} As GOA progresses, these symptoms worsen, often leading to severe manifestations such as weight loss, abdominal pain, and gastric obstruction.²⁸ These symptoms reflect the importance of preventing disease progression to advanced cancer, as well as the implementation of effective treatment strategies as early as possible in the treatment management pathway.

Figure 4. Symptoms of GOA



Abbreviations: GOA: gastro-oesophageal adenocarcinoma.

Sources: American Cancer Society (2023),⁷⁰ Maconi et al. (2008).⁷¹

Prognosis and mortality

As noted in Section 1.3.2, GOA is a significant contributor to cancer morbidity and mortality in the UK, and globally.⁵⁵ It is predicted that just 16.7% of people in England survive GOC for ten years or more, with an age-standardised mortality rate of 2.3 deaths per 100,000 individuals in the UK, thus reflecting the need for novel treatment options that improve patients' prognoses.^{16, 55}

Prognosis for patients with GOA is also dependent on disease stage at diagnosis.⁷³ Based on data from the National Cancer Institute Surveillance, Epidemiology and End Results (SEER) database (collected between 2014–2020), the 5-year survival rate for patients with localised GOA at diagnosis is 75.4%, which decreases to 35.8% for patients diagnosed with regional disease and 7.0% for those diagnosed with distant disease.^{73, 74} This underlines the importance of effective treatment options for GOA as early as possible in the treatment pathway, that can prevent or delay disease progression, ultimately improving long-term prognosis and outcomes.

Impact of disease recurrence and progression

Despite the curative intent of surgery, disease recurrence remains a significant challenge for patients with GOA. In the FLOT4 study, over half of patients treated with perioperative FLOT experienced disease progression, recurrence or death within three years, with a median DFS of 30 months reported in the FLOT arm.⁷

Disease recurrence in GOA significantly influences both patient survival and quality of life. Exemplifying this, following recurrence to metastatic disease, median OS for patients with GC is estimated to be between 12–18 months when receiving platinum-based chemotherapy regimens, with novel therapies offering only a modest life-prolonging effect on top of this.²⁴⁻²⁷ Of note, once the cancer has recurred, treatment is no longer of curative intent, leaving only treatments that aim to delay disease progression and subsequently death.^{2, 6} Consequently, it is critical that patients have the option of effective treatments in the resectable GOA setting that prevent disease recurrence, thereby avoiding the increased burden of disease associated with advanced GOA. The quality of life impact of GOA is discussed further in the following sections.

Humanistic burden of resectable GOA

Impact on patients

The HRQoL of patients with GOA is impacted by several factors, including disease stage, symptoms, and treatment choices. Notably, surgery can impact patients' QoL, however, this effect is often transient.⁷⁵ As shown in Section 2.6.7 of this submission, patients receiving perioperative FLOT chemotherapy often experience an initial decline in their HRQoL at the neoadjuvant treatment/surgery stage, before their HRQoL then returns to baseline.⁷⁵ Patients with early stage GOA may have minimal or no symptoms, while the severe manifestations that develop as the disease progresses, such as weight loss and gastric obstruction can detrimentally impact patients' overall QoL.²⁸ Unlike the transient HRQoL detriment associated with surgery, the HRQoL detriment associated with disease progression is permanent and is often more severe.⁷⁶

Beyond physical symptoms, anxiety and depression are also prevalent challenges for patients with GOA, which become more pronounced as the disease advances and exacerbates the strain on patients' overall well-being.⁷⁷ Across-sectional study of 566 patients with GOA using the EuroQol-5 dimensions-5 levels (EQ-5D-5L) utility instrument found that anxiety and depression are the second most reported problem impacting patient HRQoL, increasing from 22.8% in early-stage GC to 47.7% of patients with advanced-stage GC.⁷⁷ Novel, efficacious treatments are therefore needed in the resectable GOA disease setting to prevent disease progression and the associated negative impact it has on patients' HRQoL.

Company evidence submission template for durvalumab in combination for neoadjuvant and adjuvant treatment of resectable gastric and gastro-oesophageal junction cancer [ID6374]

As GOA progresses, patients experience increasingly significant reductions in HRQoL, in line with the worsening physical and emotional symptoms.⁷⁶ Moreover, disease recurrence, and the fear of it, further diminish patients' HRQoL.⁷⁸ A cross-sectional survey of 326 adults reported that patients with recurrent GC undergoing treatment with chemotherapy had a utility value of 0.399, which was markedly lower than early GC with surgery (utility of 0.767).⁷⁸ This highlights the substantial impact of recurrence on patient QoL and the need for innovative treatments that both delay disease recurrence and maintain HRQoL.⁷⁹

Impact on families and caregivers

The negative HRQoL impact of GOA extends beyond patients themselves, also affecting their caregivers, many of whom will be members of the patients' family.⁸⁰ GOA is associated with a considerable caregiver burden, with patients requiring supportive needs including those related to disruption to the digestive system, the requirement for a modified diet and extreme changes in weight.⁸¹⁻⁸³

A systematic review of caregivers of individuals with upper gastrointestinal cancers (including cancers of the stomach), identified substantial emotional distress among caregivers, including reporting feelings of helplessness, distress, anger, fear, and loneliness.⁸¹⁻⁸³ Caregivers also faced numerous disruptions to daily routines and meals, which impacted their psychological well-being.^{81, 83-86} Dietary restrictions and mealtimes were a particular source of distress for caregivers who were responsible for monitoring the patient's weight.^{81, 85, 87-89}

Additionally, based on a 2022 retrospective medical chart review of N=54 patients with advanced GOC, UK-based caregivers are reported to provide an average of 42 hours of physical and emotional support per week, outlining the intense strain on these individuals.⁸⁰ This subsequently translates into productivity losses for the caregivers (working hours are reduced by an average of 83 hours per month in the UK), which is especially pronounced in patients undergoing intensive cancer treatment.^{80, 90, 91} There is therefore a need for efficacious and curative treatments earlier in the GOA treatment pathway, to not only preserve the QoL of patients, but also mitigate the potential impacts on their caregivers.

Economic burden of resectable GOA

On top of the substantial clinical and humanistic burden of disease, GOA imposes a notable economic burden, associated with both direct and indirect costs which increase as the disease progresses.^{28, 29} Globally, GOA is associated with one of the highest economic burdens of all cancers, with the total estimated annual cost to the UK economy specifically being ~£740 million (based on data collected in 2017).²⁸

Direct economic burden

The direct costs of managing GOA (e.g., hospitalisation, treatment and medical care costs) form a substantial part of the total costs. In particular, cancer-specific treatment is estimated to account for 10% of the total direct costs associated with the disease.^{92, 93} In a cost-utility analysis of N=398 patients with GC in the UK which followed patients between 2006 and 2018, the average costs of treatment were similar across disease stage (22,434€, 23,498€, 22,445€ and 22,032€ for patients with Stage I–IV disease, respectively); however, the incremental cost-effectiveness ratios (ICERs) for best supportive care substantially increase with advancing disease stage (8,335€, 8,952€, 11,317€ and 25,669€ for patients with Stage I–IV disease, respectively). The lower ICERs for patients with early disease reflect the need for and potential benefit of early and effective treatment options that can reduce the risk of disease progression and recurrence, thereby minimising the economic burden GOA has on healthcare systems.⁹⁴

Hospitalisation is another key driver of the direct costs associated with GOA. In a study of patients with GC requiring systemic therapy between January 2011–July 2017, 68.9% of patients with advanced GC and 64.8% of those with metastatic GC had at least one cancer-related hospitalisation, with an average stay of ~14.4 days.⁹⁵ Between 2021–2022 in England there were 23,013 finished consultant episodes, and 18,788 hospital admissions for malignant neoplasms of the lower third of the oesophagus, demonstrating the substantial healthcare resource use (HCRU) burden that GOCs can place on healthcare systems.⁹⁶

Novel, effective treatment regimens will help to mitigate this economic burden by preventing disease progression and recurrence and their associated direct costs.

Indirect economic burden

Beyond direct healthcare costs, the broader socioeconomic impact of GOA is considerable. A medical chart review and survey of N=419 patients with advanced HER2-negative GOA/oesophageal cancer conducted across several countries reported significant employment and financial impacts:⁸⁰

- Over 77% of patients were unemployed, on long-term sick leave or retired due to cancer
- Those who remained employed experienced a 44% overall work impairment, alongside substantial income loss averaging approximately £33,000 annually
- The financial strain extended to caregivers, with 19% reporting income reductions due to time spent on illness-related activities and subsequent productivity losses
- The reduced work productivity and income loss has also been associated with reduced well-being and impaired quality of life

In the UK specifically, it has been estimated that the average out of pocket expenses for GOC patients are £212 per month, while their caregivers also provide an average of £230 per month of financial support to their patients.⁸⁰

An additional population-based cohort study assessed the direct and indirect costs of GC (N=30,659) and OC (N=18,191) between 2007 and 2014, and demonstrated that the mean indirect costs caused by mortality in the first three years following diagnosis accounted for 63.0% and 74.2% of the overall mean costs of GC and OC, respectively.⁹⁷ These data reflect the substantial financial burden of death due to GOA.

Overall, advanced GOA leads to major morbidity and resource use, with significant employment challenges and financial burdens affecting both patients and caregivers.⁸⁰ The introduction of an efficacious treatment option that delays or prevents disease progression would minimise the socioeconomic impact of GOA.

1.3.5 Unmet need

Clinical unmet need

As noted in Section 1.3.4, despite the curative intent of surgery disease recurrence remains a significant challenge for patients with GOA. Most patients with clinical Stages II and III GC experience disease recurrence within two years following curative resection plus chemotherapy and the majority of patients ultimately die due to their cancer returning or progressing, making disease recurrence the leading cause of death in these patients.^{31, 32, 98, 99}

Even following the introduction of current SoC for patients with resectable GOA, perioperative FLOT, the disease survival rates for GOA remain low, and the risk of recurrence remains high.³⁰⁻³² In the FLOT4 study, patients that received perioperative FLOT had an estimated 5-year OS of 45%, with over half of patients (54%) experiencing disease recurrence, progression or death within 30 months.⁷ As such, whilst perioperative FLOT offers a meaningful efficacy advancement over previous treatment strategies, these data demonstrate that there still remains a significant need for improvement in patient outcomes.⁷ This unmet need for more effective treatments for resectable GOA was confirmed by UK clinical experts.

Notably, following disease recurrence and progression to metastatic disease, patients are no longer able to receive treatments with curative intent.³⁸ Once patients' disease progresses to the advanced/metastatic stage, systemic/IO anti-cancer therapy aim is only to extend survival and not cure patients' disease.^{3, 6, 21} As noted in Section 1.3.3, perioperative treatments that utilise the same IO therapy before and after surgery are necessary to improve patient outcomes, as they facilitate the priming of anti-tumour immunity in the neoadjuvant setting and sustain immunosurveillance in the adjuvant setting, thus eliminating residual disease.⁴⁴

As such, there is an unmet need for novel effective perioperative treatment options, especially in the resectable disease setting before patients' disease advances and can no longer be cured. Such treatments should not impair patients' ability to undergo curative-intent surgery by negatively impacting the tolerability of their perioperative treatment or recovery from surgery.

Humanistic unmet need

As first outlined in Section 1.3.4, advanced GOA has a significant, debilitating impact on patient and caregivers' HRQoL, with increasing burden associated with disease progression.^{28, 76, 77, 81, 100} In particular, patients experience anxiety and fear around experiencing disease recurrence, which negatively impacts their HRQoL.⁷⁸ There is therefore a clear unmet need for novel efficacious treatment regimens which prevent or delay disease progression and recurrence, and subsequently the humanistic burden associated with this, whilst having minimal additional treatment/toxicity-related impact on the HRQoL of the patient.

Economic unmet need

As highlighted in Section 1.3.4, the economic burden associated with GOA is substantial, with costs increasing as the disease progresses; these include direct healthcare costs, as well as broader indirect costs resulting from the impact on patients and their caregivers.^{28, 29, 81, 83-86} Early and effective treatment with curative intent may reduce the risk of patients' disease recurring and improve the chances of them remaining disease-free, thereby reducing the high economic burden on healthcare systems. As such, there is an unmet need for more effective treatments in the resectable GOA setting, that delay or prevent disease progression and subsequently reduce the high economic burden associated with managing advanced GOA.

Summary

To conclude, despite the introduction of the current SoC, perioperative FLOT chemotherapy, there remains a clear unmet need for novel, efficacious and tolerable regimens in the resectable GOA disease setting that are able to prevent or delay both disease progression and recurrence without detrimentally impacting patients' HRQoL.

Perioperative IO therapies, which prime anti-tumour immunity in the neoadjuvant phase and sustain immunosurveillance in the adjuvant phase, provide a critical opportunity to further improve survival outcomes in this population. At present, IO therapies are only available once disease becomes advanced, at which point they deliver modest life-prolonging benefit and cure is no longer achievable.^{3, 6, 21} The Company evidence submission template for durvalumab in combination for neoadjuvant and adjuvant treatment of resectable gastric and gastro-oesophageal junction cancer [ID6374]

resectable GOA setting therefore represents the last juncture at which treatment can be offered with curative intent.

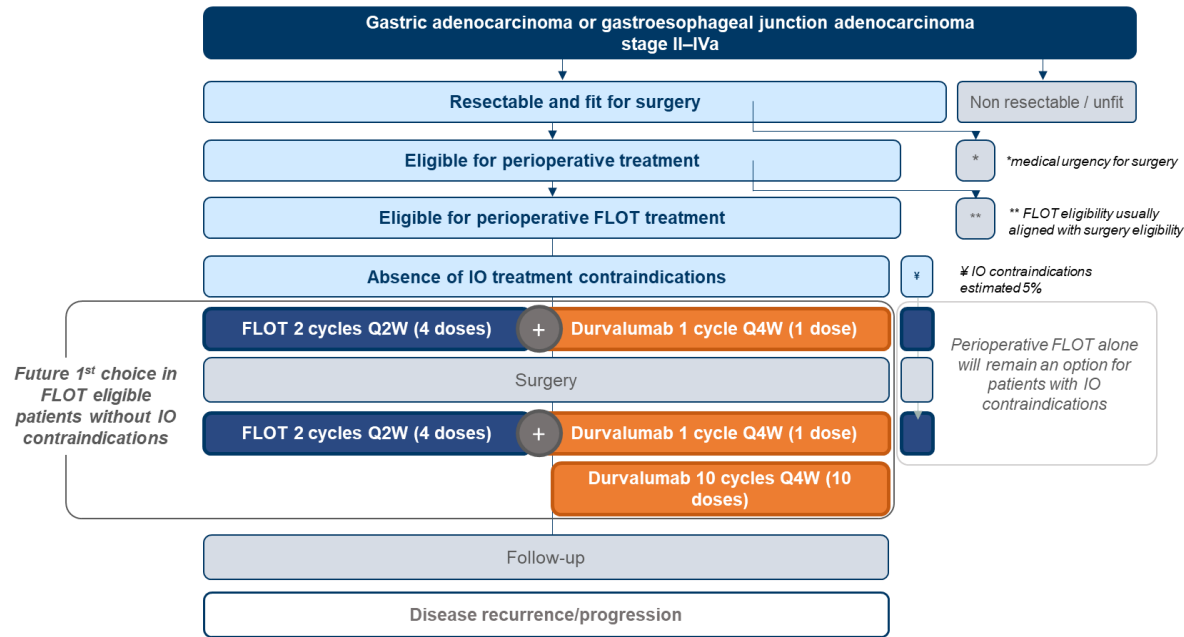
The perioperative use of durvalumab in combination with FLOT chemotherapy has the potential to address this unmet need and would constitute a practice-changing regimen with high value to both patients and their clinicians.

1.3.6 Positioning of durvalumab in the treatment pathway

Durvalumab is a high-affinity, human IgG1κ monoclonal antibody that selectively blocks the interaction of PD-L1 with PD-1 and CD80 (B7.1).³⁵ Expression of PD-L1 is an adaptive immune response that helps tumours evade detection and elimination by the immune system through blocking T cell function, activation, proliferation and cytokine production.³⁵ The inhibition of PD-L1 and blockade of PD-L1/PD-1 and PD-L1/CD80 communication by durvalumab enhances anti-tumour responses and increases T cell activation (see Figure 1 in Section 1.2).^{11, 35} Durvalumab has been engineered to reduce antibody-dependent cellular cytotoxicity (ADCC) on effector T cells following the expression of PD-L1 on activated T cells, thereby preventing T cell depletion.^{101, 102} As detailed in Table 2, durvalumab is already approved and used for a range of indications in UK clinical practice, including muscle invasive bladder cancer (MIBC), endometrial cancer (EC), non-small cell lung cancer (NSCLC), small cell lung cancer (SCLC), biliary tract cancer (BTC) and hepatocellular carcinoma (HCC).¹³

As detailed above, the current SoC for patients with resectable GOA consists of perioperative FLOT chemotherapy.¹ In alignment with UK clinical expert feedback, and its anticipated marketing authorisation, durvalumab is anticipated to be used (Figure 5). As supported by UK clinical experts, perioperative D-FLOT is anticipated to displace perioperative FLOT chemotherapy alone as the SoC in this patient population.⁵

Figure 5. Anticipated positioning of durvalumab as a neoadjuvant and adjuvant treatment for patients with GOA



Abbreviations: FLOT: 5-fluorouracil, leucovorin, oxaliplatin, and docetaxel; GOA: gastro-oesophageal adenocarcinoma; IO: immuno-oncology; Q2W: biweekly; Q4W: monthly.

Source: Figure adapted from ESMO Clinical Practice Guideline: Gastrointestinal Cancers (2022).⁶

Added value of perioperative D-FLOT

As noted in Section 1.3.5, despite the introduction of perioperative FLOT chemotherapy, the disease survival rates for GOA remain low and the risk of recurrence remains high, reflecting the unmet need for novel treatment options such as perioperative D-FLOT that are more effective than perioperative FLOT chemotherapy alone.³⁰⁻³² If recommended, durvalumab would become the first IO treatment to be used with curative intent in combination with the current SoC for patients with resectable GOA. The ability of perioperative IO treatment to prime antitumor immunity before surgery and to maintain immunosurveillance following it, together with the synergistic interaction of durvalumab and FLOT, confers superior efficacy of perioperative D-FLOT versus perioperative FLOT chemotherapy alone..³⁷⁻⁴⁴

As detailed in Section 2.6, in the MATTERHORN trial, D-FLOT demonstrated significantly improved event-free survival (EFS) and pCR rates compared to perioperative FLOT chemotherapy alone, as well as clinically superior OS.³⁶ These results make D-FLOT the first and only IO treatment that has shown improvements vs. the current SoC in the resectable GOA setting. Moreover, perioperative D-FLOT demonstrated a tolerable and manageable safety profile (detailed in Section 2.11), consistent with the known safety profiles of the individual treatment agents and did not compromise patients' HRQoL (Section 2.6.7).³⁶ Critically, perioperative D-FLOT did not preclude patients from receiving surgery or from continuing to receive the planned adjuvant treatment after recovering from on-study surgery (Section 2.6.4).³⁶ UK clinical experts considered that the benefits observed in MATTERHORN trial as practice-changing results, and therefore suggested that perioperative D-FLOT would displace perioperative FLOT chemotherapy as the SoC treatment regimen in clinical practice.⁵

The potential of perioperative D-FLOT is further supported by the recent granting of Priority Review for durvalumab by the Food and Drug Administration (FDA).¹⁰³ The FDA grants Priority Review for medicines that, if approved, would offer significant improvements over available options by demonstrating safety or efficacy improvements, preventing serious conditions or enhancing patient compliance.¹⁰⁴ In addition, durvalumab was also granted Breakthrough Therapy Designation by the FDA in the GOA setting, which accelerates the development and regulatory review of potential new medicines intended to treat a serious condition and address a significant unmet medical need.^{103, 105} This precedent from the FDA reflects that perioperative D-FLOT is anticipated to represent a highly impactful treatment option for patients in the GOA disease setting that will meet the critical unmet needs outlined in Section 1.3.5.

1.4 Equality considerations

As noted in Section 1.3.1, a variety of factors increase the likelihood of developing GOA, including both genetic and environmental factors. Environmental factors, smoking, a diet high in salt, being overweight and a high alcohol intake all increase the risk of developing GOA.^{51, 106, 107} Many of these environmental factors are more prevalent in individuals from a lower socioeconomic background.¹⁰⁸ As noted in Section 1.3.2, in England, GOC incidence rates are almost twice as high in the most deprived quintile compared with the least (2013–2017), suggesting that there is a link between GOA and deprivation.¹⁶

The availability of an effective treatment for GOA would help to benefit these individuals and narrow existing health inequalities related to the impact of GOA on populations from different socioeconomic backgrounds.

2 Clinical effectiveness

MATTERHORN, the pivotal trial for durvalumab in this indication, provides robust evidence for the clinical efficacy and safety of perioperative D-FLOT for patients with resectable GOA

- MATTERHORN is a global, Phase III, randomised, multi-centre, double-blind, placebo-controlled trial examining the efficacy and safety of durvalumab in combination with FLOT chemotherapy as neoadjuvant and adjuvant treatment, followed by adjuvant durvalumab monotherapy for the treatment of adults with resectable GOA (N=948)¹⁰⁹
- The population enrolled in the MATTERHORN trial is broadly generalisable to UK clinical practice, as validated by UK-based clinical experts. Eight of the trial sites were based in the UK, enrolling █ patients, underpinning the generalisability of MATTERHORN^{5, 36}
- The control arm of the MATTERHORN trial (placebo + perioperative FLOT) is representative of the SoC for patients with GOA in UK clinical practice, as validated by UK clinical experts, providing direct evidence for D-FLOT vs. the relevant comparator⁵

Perioperative D-FLOT demonstrated a statistically significant improvement in EFS compared to placebo + FLOT, meeting the primary objective of the MATTERHORN trial

- At data cut-off 2 (DCO2; 20th December 2024), with an overall maturity of 40.6%, perioperative D-FLOT demonstrated a statistically significant improvement in the primary efficacy endpoint, EFS, vs. placebo + FLOT (HR: 0.71; 95% confidence interval [CI]: 0.58, 0.86; $p < 0.001$)¹⁰⁹
- The estimated EFS rates at 12 months (█ vs. █ for the D-FLOT and control arms, respectively) and 24 months (67.4% vs. 58.5%, respectively) reflect the sustained benefits of D-FLOT vs placebo + FLOT over time¹⁰⁹
- The EFS benefit of D-FLOT compared to placebo + FLOT was observed consistently across all pre-specified subgroups, supporting the treatment benefit across the resectable GOA patient population¹⁰⁹
- The improvement in EFS observed with D-FLOT is clinically significant, as it aligns with the treatment goal for resectable GOA (as established in previous NICE appraisals) and was unanimously considered 'practice changing' by UK clinical experts consulted by the company^{110, 111}

Clinically meaningful improvements were observed across all endpoints with D-FLOT vs. placebo + FLOT, providing further support for the clinical benefits associated with durvalumab

- At the December 2024 DCO, with an OS data maturity of 33.9%, there was a strong trend toward improved OS for patients in the D-FLOT arm vs. the control arm (HR: 0.78 [95% CI: 0.62, 0.97]; 2-sided p -value=0.025)³⁶
 - This trend was sustained over time, as shown by a numerical improvement in the proportion of patients who were alive at 18 months, 24 months, 30 months, and 36 months post-randomisation
 - Subsequent OS data from DCO3, recently presented at ESMO 2025, were consistent with data from DCO2 and demonstrated a statistically significant OS benefit in favour of D-FLOT vs perioperative FLOT (HR: 0.78; 95% CI: 0.63, 0.96; $p=0.021$)^{36, 112}
- In addition, D-FLOT demonstrated statistically significant improvements in pCR rate (per central pathological review) at the interim analysis (IA; DCO1: 1st February 2023) as well as improvements in other secondary endpoints of DSS and MFS vs. placebo + FLOT at the December 2024 DCO³⁶
- An improvement in pathological downstaging was observed, with more patients in the D-FLOT arm achieving ypT downstaging and N0 (█ and █ respectively) compared with placebo + FLOT (█ and █, respectively)³⁶

The addition of durvalumab to FLOT did not adversely affect patient function, symptom burden or overall HRQoL

- EORTC QLQ-C30 and EORTC QLQ-STO22 + IL38 results show that treatment in the D-FLOT arm did not adversely affect patient function and symptom burden when compared with the control arm³⁶

Perioperative D-FLOT is both tolerable and manageable, with the MATTERHORN trial demonstrating a favourable benefit-risk profile of D-FLOT compared to placebo + FLOT

- At DCO2, the nature and incidence of adverse events (AEs) of maximum Grade 3 or 4 for the overall study were comparable across arms.³⁶ AEs that were reported at a higher frequency in the D-FLOT arm were consistent with the known adverse drug reactions of durvalumab (e.g., rash and pruritus) and were generally of low severity (Grade 1 or 2)³⁶
- Critically, the addition of neoadjuvant durvalumab to FLOT did not impact the ability of patients to undergo and complete surgery compared to placebo + FLOT. Additionally, similar percentages of patients in each treatment arm initiated and completed adjuvant therapy (■■■% and ■■■% in the D-FLOT arm, respectively, compared to ■■■% and ■■■%, respectively, in the control arm)³⁶
- The safety data from MATTERHORN suggest no concerns and that D-FLOT is a tolerable and manageable treatment. UK clinical experts validated that they are familiar with AEs from both durvalumab and FLOT⁵

Conclusions

- D-FLOT, the first perioperative IO regimen combined with chemotherapy to show clinically meaningful and statistically significant improvement in EFS (and OS at DCO3) in resectable GOA, addresses the unmet need in this population by providing a highly-valued, efficacious and tolerable treatment that increases the likelihood of cure in the resectable GOA setting^{109, 112}
- Based on the totality of the data from the MATTERHORN trial, perioperative D-FLOT would represent a practice-changing innovation in the treatment of resectable GOA in the UK, as validated by UK clinical experts⁵

2.1 Identification and selection of relevant studies

A systematic literature review (SLR) was conducted to identify published clinical efficacy and safety data for durvalumab and potentially relevant comparators for the treatment of resectable GOA (before or after surgical resection of the primary tumour) in adult patients. Searches of electronic databases were performed on Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Database of Systematic Reviews (CDSR), Embase and MEDLINE. Hand-searching of conference proceedings, clinical trial registries and reference lists was also performed. The SLR was originally run in November 2024 with a subsequent update in June 2025.

In order to build on the methodology accepted by NICE in the appraisal of olaparib as a maintenance treatment for breast cancer gene (BRCA) mutation-positive advanced ovarian, fallopian tube or peritoneal cancer after response to first-line platinum-based chemotherapy (TA962), the June 2025 update to the SLR was conducted using assistance from artificial intelligence (AI).¹¹³ The Company engaged with NICE and the EAG ahead of submitting this AI-assisted SLR and the approach was in line with the NICE position statement on AI.¹¹⁴ Full methodological details and results of the SLR can be found in Appendix B.

The electronic database searches identified 3,646 articles, of which 56 publications reporting on 13 unique studies were deemed relevant for extraction and included in the SLR. Of these studies, the MATTERHORN trial is the only study that provides clinical evidence for durvalumab in combination with FLOT chemotherapy as neoadjuvant and adjuvant treatment, followed by adjuvant durvalumab monotherapy for the treatment of patients with resectable GOA, which is the focus of this submission.^{115, 116} A summary of the MATTERHORN trial design, efficacy and safety results is provided in the following sections.

2.2 List of relevant clinical effectiveness evidence

As noted in Section 2.1, the only study relevant to this submission identified in the clinical SLR was the MATTERHORN clinical trial (NCT04592913).^{36, 109}

MATTERHORN is a global Phase III, randomised, multi-centre, double-blind, placebo-controlled trial examining the efficacy and safety of durvalumab in combination with FLOT chemotherapy as neoadjuvant and adjuvant treatment, followed by adjuvant durvalumab monotherapy for the treatment of adults with resectable GOA.^{115, 116} The study commenced in November 2020 and is ongoing at the time of this submission. The data presented in this submission are based on DCO2 of the trial (20th December 2024 data cut-off).³⁶

A summary of the MATTERHORN trial is presented in Table 3.

Table 3. Clinical effectiveness evidence

Study	MATTERHORN (NCT04592913)^{36, 109}
Study design	Global Phase III, randomised, multi-centre, double-blind, placebo-controlled trial
Population	Adults with resectable GOA ^a
Intervention(s)	• Durvalumab: 1,500 mg on Day 1 every four weeks (Q4W) for 2 cycles as neoadjuvant therapy; 1,500 mg on Day 1 Q4W for a maximum of 12 cycles as adjuvant therapy^b • FLOT chemotherapy: on Days 1 and 15 of each 4-week cycle for 2 cycles as neoadjuvant therapy; on Days 1 and 15 Q4W for 2 cycles as adjuvant therapy
Comparator(s)	• Placebo: on Day 1 Q4W for 2 cycles in the neoadjuvant period; on Day 1 Q4W for a maximum of 12 cycles in the adjuvant period^b • FLOT chemotherapy: on Days 1 and 15 of each 4-week cycle for 2 cycles as neoadjuvant therapy; on Days 1 and 15 Q4W for 2 cycles as adjuvant therapy
Indicate if study supports application for marketing authorisation	Yes
Indicate if study used in the economic model	Yes
Rationale if study not used in model	N/A
Reported outcomes specified in the decision problem	A summary of reported outcomes specified in the decision problem is provided below, with full details in the CSR. Outcomes that have been highlighted in bold are included in the economic model: • Overall survival (OS) • Event-free survival (EFS) • Response rate ○ Pathological complete response (pCR) • Adverse effects of treatment • HRQoL ○ Time to deterioration and change from baseline in EORTC QLQ-C30 and EORTC QLQ-STO22 + IL38, in the PRO analysis set
All other reported outcomes	The following outcomes (not specified in the decision problem) are also presented in this submission for completeness: • Pathological downstaging • Surgical outcomes ○ Surgical rate ○ R0 resection rate • Disease-free survival (DFS) • Disease-specific survival (DSS) • Metastasis-free survival (MFS)

Footnotes: ^a Stages II to IV as per the AJCC 8th edition.⁴⁸ ^b If a patient's weight fell to 30 kg or below (≤ 30 kg), the patient received weight-based dosing equivalent to 20 mg/kg of durvalumab/placebo Q4W after consultation between the Investigator and Sponsor, until the patient's weight improved to > 30 kg, at which point the patient started receiving the fixed dosing of durvalumab/placebo 1500 mg Q4W.

Abbreviations: CSR: Clinical Study Report; DFS: Disease-free survival; DFS24/36: Disease-free survival at 24 or 36 months; DSS: Disease-specific survival; EFS: Event-free survival; EFS24/36: Event-free survival at 24 or 36 months; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EORTC QLQ-STO22: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Stomach 22; FLOT: 5-fluorouracil, leucovorin, oxaliplatin, and docetaxel; GOA: Gastro-oesophageal adenocarcinoma; HRQoL: Health-related quality of life; IL38: Interleukin 38; MFS: Metastasis-free survival; OS: Overall survival; OS24/36: Overall survival at 24 or 36 months; pCR: Pathological complete response; PRO: Patient-reported outcomes; Q4W: Every 4 weeks; R0 resection: Microscopically margin-negative resection.

Source: AstraZeneca Data on File (MATTERHORN Clinical Study Report).³⁶ Janjigian et al. 2025.¹⁰⁹

2.3 Summary of methodology of the relevant clinical effectiveness evidence

2.3.1 Trial design

MATTERHORN (NCT04592913) is a global Phase III, randomised, multi-centre, double-blind, placebo-controlled trial examining the efficacy and safety of durvalumab in combination with FLOT chemotherapy as neoadjuvant and adjuvant treatment, followed by adjuvant durvalumab monotherapy for the treatment of adults with resectable GOA.^{115, 116}

Patients eligible for inclusion in the MATTERHORN trial were aged ≥ 18 years old at the time of screening, had histologically documented resectable Stage II through IVA (according to the AJCC TNM staging 8th edition) gastric/GOJ adenocarcinoma, had not received anti-cancer therapy for their current malignancy, had an ECOG score of 0 or 1, and adequate organ and marrow function.¹¹⁷

A total of 1,258 patients were screened at ■ sites, and 948 patients were randomised to treatment at 147 study sites across 20 countries in North and South America, Asia and Europe, including UK centres (8 sites [Addenbrookes Hospital, University of Dundee Hospital, Beatson Weast of Scotland Cancer Centre Glasgow, Leicester Royal Infirmary, University Collage of London Hospital, Royal Marsden Hospital, The Christie Hospital, Oxford University Churchill Hospital]; ■ patients).^{36, 116} Patients were randomised on a 1:1 basis to either treatment arm:

- D-FLOT arm (N=474): Durvalumab 1,500 mg on Day 1 + FLOT (consisting of FLOT chemotherapy 5-fluorouracil [FU], leucovorin, oxaliplatin and docetaxel) on Days 1 and 15 Q4W for 4 cycles (1 dose of durvalumab and 2 doses of FLOT per cycle; 2 cycles in the neoadjuvant phase + 2 cycles in the adjuvant phase), followed by durvalumab 1,500 mg Q4W for 10 additional cycles (1 dose per cycle)
- Control arm (N=474): Placebo on Day 1 + FLOT on Days 1 and 15 Q4W for 4 cycles (1 dose of placebo and 2 doses of FLOT per cycle; 2 cycles in the neoadjuvant phase + 2 cycles in the adjuvant phase), followed by placebo Q4W for 10 additional cycles (1 dose per cycle)

A summary of the MATTERHORN trial design is presented in Figure 6.

Patients were stratified according to the following factors: geographic region (Asia vs. non-Asia), clinical lymph node status (positive vs. negative) and PD-L1 expression status (Tumour Area Positivity [TAP] $< 1\%$ vs. $\geq 1\%$).¹¹⁷

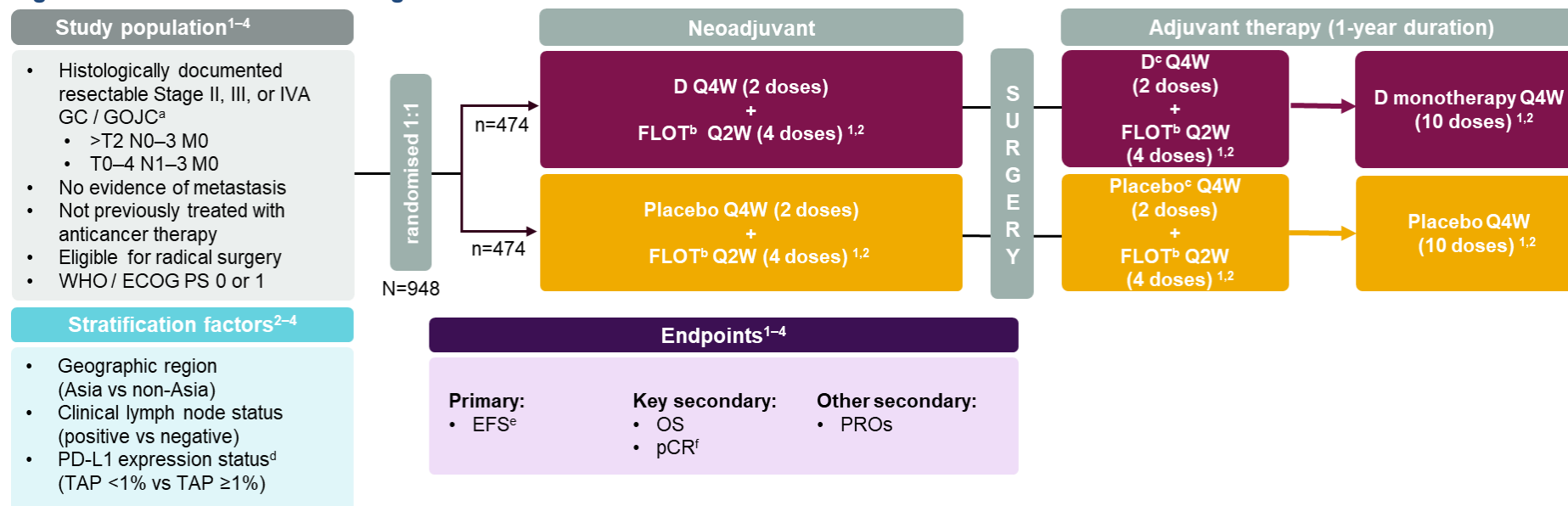
As shown in Figure 6, the MATTERHORN trial consisted of three phases in the overall treatment period: a neoadjuvant period, surgery, and an adjuvant period. Neoadjuvant therapy began following the completion of the screening period and randomisation, with surgery scheduled 4–8 weeks after the final dose of neoadjuvant therapy.³⁶ The surgery performed was gastrectomy or gastro-oesophagectomy with at least D1 lymphadenectomy (D2 lymphadenectomy recommended), as determined by the attending Company evidence submission template for durvalumab in combination for neoadjuvant and adjuvant treatment of resectable gastric and gastro-oesophageal junction cancer [ID6374]

surgeon based on the intraoperative findings. Adjuvant therapy was initiated 4–12 weeks post-surgery (based on the patient's recovery period).³⁶ Crossover between treatment arms was not permitted within the study.³⁶

Across both the D-FLOT and control arms, treatment continued in the adjuvant period for up to a maximum of 12 cycles (2 cycles of durvalumab/placebo in combination with FLOT and 10 additional cycles of durvalumab/placebo monotherapy), or until progression or recurrence of disease, unacceptable toxicity, withdrawal of consent, or if another discontinuation criterion was met.^{36, 118} Adjuvant therapy could be discontinued at the investigator's discretion, including the discontinuation of adjuvant durvalumab and/or FLOT. Treatment was therefore continued until completion of 12 cycles or up to one year from the start of adjuvant therapy, unless early discontinuation occurred for any of the reasons above.³⁶

As described above, the control arm of MATTERHORN (placebo + perioperative FLOT) is representative of SoC treatment for patients with resectable GOA in UK clinical practice. Consequently, based on the results of the MATTERHORN trial, durvalumab represents the first and only IO trial to demonstrate a positive perioperative outcome vs. SoC in GOA.^{2, 4-7}

Figure 6. MATTERHORN trial design



Footnotes: FLOT chemotherapy comprised 5-fluorouracil 2,600 mg/m², leucovorin 200 mg/m², oxaliplatin 85 mg/m² and docetaxel 50 mg/m².

^bNot in multiple testing procedure; ^cNeoadjuvant baseline scan: within 28 days pre-randomisation (RECIST 1.1 baseline; ^dPre-surgery scan: within 4 weeks post-neoadjuvant; if no surgery, follow-up scans every 12 ± 1 weeks until progression/recurrence.; ^eAdjuvant baseline scan: ≥4 weeks post-surgery, ideally ≤28 days before starting adjuvant therapy;

^fAdjuvant follow-up scans: every 12 ± 1 weeks for 2 years, then every 24 ± 1 weeks until progression/recurrence or study end; biopsy confirmation where feasible.

Abbreviations: AE: adverse event; DFS: disease free survival; ECOG PS: Eastern Cooperative Oncology Group Performance Status; EFS: event-free survival; GOA: gastro-oesophageal adenocarcinoma; ITT: intention-to-treat; LATAM: Latin America; LN: lymph node; OS: overall survival; pCR: pathological complete response; PRO: patient reported outcome; PD-L1: programmed death-ligand 1; QXW: every X weeks; 1^o: primary; 2^o: secondary.

Source: Janjigian et al. (ASCO 2025).¹¹⁹

2.3.2 Trial methodology

A summary of the methodology and trial design of MATTERHORN is presented in Table 4.

Table 4: MATTERHORN trial design and methodology

Trial name	MATTERHORN (NCT04592913)
Location	A total of ■ study sites (across 20 countries) screened patients for the study: Argentina (6 sites), Belgium (5 sites), Brazil (7 sites), Canada (6 sites), Chile (5 sites), Denmark (3 sites), France (12 sites), Germany (12 sites), Hungary (5 sites), Japan (16 sites), Netherlands (3 sites), Peru (5 sites), Poland (8 sites), Republic of Korea (6 sites), Russian Federation (7 sites), Spain (10 sites), Taiwan (6 sites), Turkey (6 sites), UK (8 sites), and US (11 sites)
Trial design	MATTERHORN is a global Phase III, randomised, multi-centre, double-blind, placebo-controlled trial examining the efficacy and safety of durvalumab in combination with FLOT chemotherapy as neoadjuvant and adjuvant treatment, followed by adjuvant durvalumab monotherapy for the treatment of adults with resectable GOA
Key Inclusion/exclusion criteria	Inclusion criteria: • Aged ≥18 years at the time of screening^a • Histologically documented resectable Stage II through IVA (according to the AJCC TNM staging 8th edition) gastric/GOJ adenocarcinoma. GOJC includes Siewert^b type 2 and 3 tumours (and type 1 if the patient was intended to be treated in the same way as for Siewert^b type 2 and 3 tumours) • Had not received anti-cancer therapy (e.g., chemotherapy, radiation therapy, or chemoradiation therapy) for the current malignancy • Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1 at enrolment and randomisation • Adequate organ and marrow function as defined by: • Haemoglobin ≥9.0 g/dL • Absolute neutrophil count ≥1.5 x 10⁹/L • Platelet count ≥100 x 10⁹/L • Serum bilirubin ≤1.5 × the upper limit of normal (ULN). This will not apply to patients with confirmed Gilbert's syndrome, who will be allowed in consultation with their physician. • Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤2.5 × ULN • Measured creatinine clearance (CL) >50 mL/min or Calculated creatinine clearance (CL) >50 mL/min as determined by Cockcroft-Gault (using actual body weight) • Availability of a tumour sample before trial enrolment for the assessment of PD-L1 expression Full inclusion criteria for the MATTERHORN trial can be found in the protocol in the reference pack accompanying this submission.¹¹⁷ Exclusion criteria: • Medical conditions:

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	○ Patients with peritoneal dissemination (including tumour cells in peritoneal fluid) or distant metastasis ○ Patients with squamous cell or adenosquamous cell carcinoma or GI stromal tumour ○ History of allogeneic organ transplantation • Active or prior documented autoimmune or inflammatory disorders • Uncontrolled intercurrent illness • History of another primary malignancy^c • History of active primary immunodeficiency • Active infection including tuberculosis (clinical evaluation that includes clinical history, physical examination and radiographic findings, and tuberculosis testing in line with local practice), hepatitis B (known positive HBV surface antigen (HBsAg) result), hepatitis C, or human immunodeficiency virus (positive HIV 1/2 antibodies) • Mean QT interval corrected for heart rate using Fridericia's formula (QTcF) ≥ 470 ms calculated from 3 ECGs (within 15 minutes at 5 minutes apart) • Known allergy or hypersensitivity to any of the study drugs or any of the study drug excipients Full exclusion criteria for the MATTERHORN trial, including details on prior/concurrent therapy, prior/concurrent clinical study experience and other exclusions can be found in the protocol in the reference pack accompanying this submission.¹¹⁷
Intervention	• Durvalumab: 1,500 mg on Day 1 Q4W for 2 cycles as neoadjuvant therapy; 1,500 mg on Day 1 Q4W for a maximum of 12 cycles as adjuvant therapy^d • FLOT chemotherapy: on Days 1 and 15 of each 4-week cycle for 2 cycles as neoadjuvant therapy; on Days 1 and 15 Q4W for 2 cycles as adjuvant therapy
Comparator	• Placebo: on Day 1 Q4W for 2 cycles in the neoadjuvant period; on Day 1 Q4W for a maximum of 12 cycles in the adjuvant period^d • FLOT chemotherapy: on Days 1 and 15 of each 4-week cycle for 2 cycles as neoadjuvant therapy; on Days 1 and 15 Q4W for 2 cycles as adjuvant therapy
Method of study drug administration	• Durvalumab: administered intravenously • Placebo: administered intravenously • FLOT chemotherapy: administered intravenously
Primary outcomes	• EFS
Key secondary outcomes	• OS • pCR
Other secondary outcomes	• Surgery rate • R0 resection rate • MFS • DFS • DSS • EFS24 and EFS36

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	• OS24 and OS36 • DFS24 and DFS26 • HRQoL ◦ Time to deterioration and change from baseline in EORTC QLQ-C30 and EORTC QLQ-STO22 + IL38, in the PRO analysis set • Safety and tolerability analyses
Pre-planned subgroups	• Sex • Age at randomisation • Geographic region (Asian vs. non-Asian) • Clinical lymph node status • ECOG PS • PD-L1 expression level (TAP <1% vs. ≥1%) • Primary tumour location at screening
Duration of study and follow-up	The first subject was enrolled on 17 th November 2020, with the latest data coming from DCO2 (20 th December 2024). At DCO2, the median duration of follow up was 31.5 months (interquartile range: 26.7, 36.6). The MATTERHORN trial is ongoing.

Footnotes: ^a In Japan, patients <20 years old at the time of screening required a written informed consent from the patient and his or her legally acceptable representative. ^b Siewert classification: Type 1 = adenocarcinoma of the lower oesophagus with the centre located within 1–5 cm above the anatomic GOJ; Type 2 = true carcinoma of the cardia at the GOJ, with the tumour centre within 1 cm above and 2 cm below the GOJ; Type 3 = subcardial carcinoma with the tumour centre between 2 and 5 cm below GOJ, which infiltrates the GOJ and lower oesophagus from below. ^c Except for: malignancy treated with curative intent and with no known active disease ≥5 years before the first dose of IP and of low potential risk for recurrence, adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease and adequately treated carcinoma in situ without evidence of disease. ^d If a patient's weight fell to 30 kg or below (≤ 30 kg), the patient received weight-based dosing equivalent to 20 mg/kg of durvalumab/placebo Q4W after consultation between the Investigator and Sponsor, until the patient's weight improved to > 30 kg, at which point the patient started receiving the fixed dosing of durvalumab/placebo 1500 mg Q4W.

Abbreviations: AJCC: American Joint Committee on Cancer; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; CL: Creatinine clearance; DFS: Disease-free survival; DCO: Data cutoff; DSS: Disease-specific survival; ECOG PS: Eastern Cooperative Oncology Group Performance Status; EFS: Event-free survival; EFS24/36: Event-free survival at 24/36 months; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EORTC QLQ-STO22: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Stomach 22; FLOT: 5-fluorouracil, leucovorin, oxaliplatin, and docetaxel; GC: Gastric cancer; GOJ: Gastroesophageal junction; GOJC: Gastroesophageal junction cancer; GI: Gastrointestinal; HBsAg: Hepatitis B surface antigen; HBV: Hepatitis B virus; HIV: Human immunodeficiency virus; HRQoL: Health-related quality of life; IL38: Interleukin 38; IP: Investigational product; MFS: Metastasis-free survival; OS: Overall survival; OS24/36: Overall survival at 24/36 months; pCR: Pathological complete response; PD-L1: Programmed death-ligand 1; PRO: Patient-reported outcome; Q4W: Every 4 weeks; QTcF: Corrected QT interval by Fridericia's formula; R0: Complete tumour resection with negative margins; TAP: Tumour area positivity; TNM: Tumour, node, metastasis; ULN: Upper limit of normal. **Source:** AstraZeneca. Data on File. MATTERHORN Clinical Study Protocol (2024).¹¹⁷ AstraZeneca. Data on File. MATTERHORN Clinical Study Report (December 2024 DCO).³⁶

2.3.3 Baseline characteristics

The key baseline and disease characteristics of patients in the final analysis set (FAS) are summarised in Table 5.

The median age of patients in MATTERHORN was 62 years.¹⁰⁹ The majority of patients in the FAS were male (71.9%), White (67.8%), and from non-Asia geographic regions (81% overall and 81% in each treatment arm) aligning with the demographic distribution observed in UK clinical practice for patients with resectable GOA. Black patients (1.1%) were slightly underrepresented in the trial

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compared to UK clinical practice.¹⁰⁹ According to the National Oesophago-Gastric Cancer Audit (NOGCA), Black and Black British patients constitute fewer than 1% of those with oesophageal adenocarcinoma and approximately 4% of those with gastric cancer.⁶⁷

With regards to disease characteristics, the primary tumour location was gastric in 67.5% of patients overall (68.4% vs. 66.7% patients in the D-FLOT and control treatment arms, respectively). For the 32.5% of patients with primary tumour location in the gastro-oesophageal junction, 10.4% were categorised as Siewert Type 1, 14.8% were Siewert Type 2, and 7.3% were Siewert Type 3.¹⁰⁹ The majority of patients primary tumours were Stage T3 (66.2%), with 24.7% of patients having Stage T4 tumours.¹⁰⁹

The study enrolled patients regardless of PD-L1 expression level. PD-L1 testing was required per protocol, with the results showing that 90.0% of patients in the FAS population had tumours expressing TAP $\geq 1\%$ and the remaining 10.0% of patients had tumours expressing TAP $< 1\%$. This proportion was similar between treatment arms (9.9% vs. 10.1% and 90.1% vs. 89.9% in the D-FLOT and control arms, respectively).¹⁰⁹ Of note, as detailed in Section 1.3.3, PD-L1 testing does not inform treatment decisions for patients with resectable GOA in the UK as per the ESMO guidelines, and PD-L1 testing is not routinely performed across all UK centres.⁵ Accordingly, subgroup analyses by PD-L1 expression are presented for completeness rather than to inform treatment selection.

Clinical validation received by the Company indicated that overall, the baseline characteristics of patients enrolled in MATTERHORN were representative of patients with resectable GOA receiving FLOT in the UK, which is underscored by the inclusion of ■ patients from 8 different UK sites.⁵ Key baseline characteristics of the UK MATTERHORN trial population were: mean age: ■ years; median age: ■ years (range ■); male: ■ PD-L1 $< 1\%$: ■ and PD-L1 $\geq 1\%$: ■. These characteristics are aligned with the overall clinical trial population and represent the candidate cohort for receiving D-FLOT in the UK.

Additionally, the baseline characteristics were generally well balanced across the D-FLOT and control treatment arms, with minor imbalances (5% to $< 10\%$ difference) observed for sex (females: 31.2% vs. 24.9%, by respective treatment arm), age (< 50 years: 18.1% vs. 12.0%, by respective treatment arm), and ECOG PS (PS of 1: 28.9% vs. 22.8%).¹⁰⁹

Table 5. Baseline patient demographics and disease characteristics in MATTERHORN (FAS; December 2024 DCO)

Characteristic	Durvalumab (N=474)	Control (N=474)	Total (N=948)
Age			
Median (range)	62 (26–84)	63 (28–83)	62 (26–84)
Distribution, n (%)			
<50 yr	86 (18.1%)	57 (12.0%)	143 (15.1%)
≥ 50 to <65 yr	205 (43.2%)	208 (43.9%)	413 (43.6%)
≥ 65 to <75 yr	146 (30.8%)	166 (35.0%)	312 (32.9%)
≥ 75 yr	37 (7.8%)	43 (9.1%)	80 (8.4%)
Sex, n (%)			
Male	326 (68.8%)	356 (75.1%)	682 (71.9%)
Female	148 (31.2%)	118 (24.9%)	266 (28.1%)

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Characteristic	Durvalumab (N=474)	Control (N=474)	Total (N=948)
Region, n (%)^a			
Asia	90 (19.0%)	90 (19.0%)	180 (19.0%)
Rest of the world	384 (81.0%)	384 (81.0%)	768 (81.0%)
Race or ethnic group, n (%)^b			
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%)
ECOG performance status, n (%)			
0	337 (71.1%)	366 (77.2%)	703 (74.2%)
1	137 (28.9%)	108 (22.8%)	245 (25.8%)
Primary tumour location, n (%)^c			
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%)
Primary tumour stage, n (%)^d			
Non-T4	357 (75.3%)	357 (75.3%)	714 (75.3%)
T0	1 (0.2%)	0	1 (0.1%)
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%)
T4	117 (24.7%)	117 (24.7%)	234 (24.7%)
T4a	101 (21.3%)	103 (21.7%)	204 (21.5%)
T4b	16 (3.4%)	14 (3.0%)	30 (3.2%)
Positive clinical lymph-node status, n (%)^e	329 (69.4%)	330 (69.6%)	659 (69.5%)
PD-L1 expression, according to TAP, n (%)^f			
<1%	48 (10.1%)	47 (9.9%)	95 (10.0%)
≥1%	426 (89.9%)	427 (90.1%)	853 (90.0%)
Microsatellite instability status, n (%)^g			
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%)
Data missing	79 (16.7%)	88 (18.6%)	167 (17.6%)
Histologic type, n (%)			

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Characteristic	Durvalumab (N=474)	Control (N=474)	Total (N=948)
Intestinal	245 (51.7%)	238 (50.2%)	483 (50.9%)
Diffuse	130 (27.4%)	119 (25.1%)	249 (26.3%)
Unspecified adenocarcinoma or mixed or other	99 (20.9%)	117 (24.7%)	216 (22.8%)

Footnotes: ^a Geographic region is as recorded on the IRT/RTSM. ^b Race or ethnic group was reported by the patient. The category “Other” included any patient-reported race or ethnic group that did not fit in any of the categories specified on the basis of definitions from the FDA. ^c Siewert type 1 indicates an adenocarcinoma of the lower oesophagus with the centre located within 1 to 5 cm above the anatomical gastro-oesophageal junction; Siewert type 2 indicates a true carcinoma of the cardia at the gastro-oesophageal junction, with the tumour centre within 1 cm above and 2 cm below the gastro-oesophageal junction; and Siewert type 3 indicates a subcardial carcinoma with the tumour centre between 2 cm and 5 cm below the gastro-oesophageal junction, which infiltrates the gastro-oesophageal junction and lower oesophagus from below. ^d Tumour staging was performed according to the eighth edition of the American Joint Committee on Cancer AJCC Cancer Staging Manual.⁴⁸ ^e The lymph-node status was recorded at randomisation with the use of the interactive response technology system or the randomisation and trial supply management system. ^f PD-L1 expression (assessed according to the TAP score, which is determined by visual aggregation and estimation of the area covered by PD-L1 positive tumour cells and tumour-associated immune cells relative to the total tumour area on the immunohistochemical slide) was measured by the VENTANA PD-L1 (SP263) CDx assay and recorded at randomisation with the use of the interactive response technology system, randomisation and trial supply management system, or an electronic case-report form or with data from an external vendor from samples collected on or before randomisation. ^g Microsatellite instability was measured by a clinical trial assay based on FoundationOne CDx in a research use only capacity.

Abbreviations: AJCC: American Joint Committee on Cancer; CDx: companion diagnostics; ECOG: Eastern Cooperative Oncology Group; FLOT: fluorouracil, leucovorin, oxaliplatin, and docetaxel; FDA: Food and Drug Administration; IRT: interactive response technology; PD-L1: programmed death-ligand 1; RTSM: randomisation and trial supply management; TAP score: Tumour Area Positivity score.

Source: Janjigian *et al.* (2025).¹⁰⁹

2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

2.4.1 Study populations and patient disposition

The study populations used for the analysis of outcomes from the MATTERHORN trial are detailed below:¹¹⁷

- **Full analysis set (FAS; N=948):** Includes all randomised patients with treatment arms assigned in accordance with the randomisation, regardless of the treatment received. Patients who were randomised but did not subsequently go on to receive study treatment are included in the analysis in the treatment arm to which they were randomised. Unless otherwise specified, the FAS was used for demography and baseline characteristics, and all efficacy analyses, except those involving DFS endpoints.
- **Safety analysis set (SAS; N=944):** Includes all randomised patients who received at least one dose of study treatment. This population was used to assess the tolerability of D-FLOT through AEs, laboratory parameters, vital signs, electrocardiograms (ECGs), WHO/ECOG PS.
- **R0 resected analysis set (N=662):** Includes all patients in the FAS who had surgical resection that was defined as an R0 resection based on local pathology assessments and who had no evidence of disease at adjuvant baseline scan after surgery (per Response Evaluation Criteria In Solid Tumours [RECIST] 1.1 by the investigator). This population was used for DFS analyses.

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- **PRO analysis set (N=■):** Includes all patients from the FAS, except for patients for whom “reason patient did not complete questionnaire” is: “relevant language version not available”, “illiterate” or “cannot use device due to physical limitations”.

Unless otherwise stated, the safety and efficacy analyses presented in this submission are informed by DCO2 (December 2024 DCO) of the MATTERHORN trial.³⁶

Patient disposition

The disposition of all patients in the MATTERHORN trial, as of DCO2 (December 2024), is presented in Table 6. At this DCO, all patients in both arms had completed (or discontinued) adjuvant treatment and had also completed the safety follow-up period.

Overall, there were no imbalances in disposition between the treatment arms; similar numbers of patients in both arms reached surgery, reached the adjuvant phase, and completed adjuvant treatment.

Of note, the majority of patients in both treatment arms underwent surgery (90.9% in the D-FLOT arm and 90.3% in the control arm) and completed surgery (86.9% and 84.4%, respectively), demonstrating that the addition of durvalumab to FLOT chemotherapy did not detrimentally affect the proportion of patients undergoing and completing curative intent surgery.^{36, 109}

Additionally, the addition of durvalumab did not impact the delivery of FLOT chemotherapy. As described in 2.11.1, median duration of treatment was 12.7 months in the D-FLOT arm and 12.5 months in the control arm.¹⁰⁹ In the neoadjuvant phase, ■% patients in the D + FLOT arm and ■% patients in the control arm completed the 4 neoadjuvant doses of any FLOT.³⁶ Following surgery, in the adjuvant phase, 97.0% in the D + FLOT arm and 98.3% patients in the control arm received any adjuvant FLOT treatment, and ■% patients in the D + FLOT arm and ■% patients in the control arm received the 4 planned adjuvant doses of FLOT, confirming that durvalumab did not compromise FLOT administration.^{36, 109}

Table 6. Patient disposition in MATTERHORN (all patients, December 2024 DCO)

Study period	D-FLOT arm	Control arm	Total
Pre-treatment			
Enrolled ^a	■	■	■
Randomized ^b	■	■	■
Overall			
FAS ^{b,c,d}	474	474	948
Patients who received treatment ^{b,d}	■	■	944
Patients who did not receive treatment ^d	■	■	■
Neoadjuvant			
Patients who received treatment in neoadjuvant ^{b,d}	■	■	■
Patients who did not receive treatment neoadjuvant ^d	■	■	■
Any neoadjuvant durvalumab/placebo ^e	■	■	■
Received/completed all neoadjuvant D-FLOT/placebo ^e	■	■	■
Discontinued neoadjuvant D-FLOT/placebo ^e	■	■	■
Any neoadjuvant FLOT ^{b,e}	■	■	■
Completed 4 neoadjuvant. doses of any FLOT ^e	■	■	■
Discontinued ≥1 FLOT neoadjuvant ^{e,f}	■	■	■
Discontinued all FLOT neoadjuvant ^{e,f}	■	■	■
Discontinued D-FLOT/placebo + all FLOT neoadjuvant. ^{ef}	■	■	■
Surgery			
Attempted surgery ^d	431 (90.9)	428 (90.3)	859 (90.6)
Did not undergo surgery ^d	43 (9.1)	46 (9.7)	89 (9.4)
Completed surgery ^d	412 (86.9)	400 (84.4)	812 (85.7)
Did not complete surgery ^{dg}	19 (4.0)	28 (5.9)	47 (5.0)
On-study surgery, no adjuvant treatment ^d	■	■	■
Adjuvant			
Any adjuvant treatment ^d	■	■	■
Any adjuvant D-FLOT/placebo ^e	■	■	■
Ongoing adjuvant D-FLOT/placebo at DCO ^e	■	■	■
Completed all adjuvant D-FLOT/placebo ^{e,h}	■	■	■
Discontinued adjuvant D-FLOT/placebo ^e	■	■	■
Any adjuvant FLOT ^e	■	■	■
Ongoing adjuvant FLOT at DCO ^e	■	■	■
Completed 4 adjuvant FLOT doses ^e	■	■	■
Discontinued at least 1 component of adjuvant FLOT adjuvant ^{e,f}	■	■	■
Discontinued all FLOT adjuvant ^{e,f}	■	■	■
Discontinued D-FLOT/placebo + all FLOT adjuvant ^{e,f}	■	■	■
Any adjuvant mono D-FLOT/placebo ^e	■	■	■
Discontinued adjuvant mono D-FLOT/placebo ^{e,h}	■	■	■
Overall treatment			
Completed all D-FLOT/placebo + FLOT ⁱ	■	■	■

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Follow-up			
Continuing study off treatment at DCO ^{d,j}			

Footnotes: ^a Informed consent received. ^b A patient was randomised twice in error. ^c FAS: all randomised patients. ^d Percentages are calculated from number of patients in the FAS. ^e Percentages from number of patients who received treatment in the treatment period. ^f Reasons not mutually exclusive for patients with multiple reasons, counted only once per category. ^g Refer to Table 14.3.1.5 of the CSR for details. ^h See full CSR for details. ⁱ Completed all treatments. ^j At data cut-off.

Abbreviations: DCO: data cut-off; D-FLOT: durvalumab + FLOT; FLOT: 5-fluorouracil, leucovorin, oxaliplatin, and docetaxel.

Source: AstraZeneca Data on File (MATTERHORN Clinical Study Report; Table 11, P98).³⁶ Janjigian et al. 2025.¹⁰⁹

2.4.2 Statistical analysis

A summary of the statistical analysis methods used in the MATTERHORN trial are presented in Table 7.

Table 7 Statistical methods for the primary analysis

Trial name	MATTERHORN (NCT04592913)
Hypothesis objective	The primary objective of the MATTERHORN trial was to assess the efficacy of D-FLOT compared to placebo + FLOT in terms of EFS, according to RECIST 1.1 per blinded independent central review (BICR) and/or locally by pathology testing in patients with resectable GOA. ¹¹⁷ The null hypothesis was that there is no difference between D-FLOT and placebo + FLOT.
Statistical analysis	- Descriptive statistics were used for all variables, as appropriate, and are presented by treatment arm. Continuous variables were summarised by the number of observations, mean, standard deviation, median, minimum, and maximum. Categorical variables were summarised by frequency counts and percentages for each category. Unless otherwise stated, percentages were calculated out of the population total for the corresponding treatment arm.¹¹⁷ - Unless otherwise specified, efficacy and PRO data are summarised and analysed based on the FAS. DFS endpoints are summarised and analysed based on the R0 resection analysis set. Safety data are summarised based on the SAS.¹¹⁷ - Results of all statistical analysis are presented using 95% CIs and 2-sided p-value, unless otherwise stated. Primary endpoint (EFS)¹¹⁷ - The primary analysis of EFS was performed using a stratified log-rank test on data according to RECIST 1.1 per BICR assessment and/or locally by pathology testing. Stratification variables for generation of the p-value were geographic region, clinical lymph node status, and PD-L1 expression status - HRs were estimated from stratified Cox proportional hazards (PH) model and the CIs calculated using a profile likelihood approach - Kaplan-Meier (KM) plots were presented by treatment arm and were used to estimate the median EFS - Sensitivity analyses of EFS were performed using Investigator assessments according to RECIST 1.1 in place of BICR assessments, and by applying a censoring rule for two consecutive missed visits - Subgroup analyses were conducted in the following (but not limited to) subgroups of the FAS: - Sex (male vs female)

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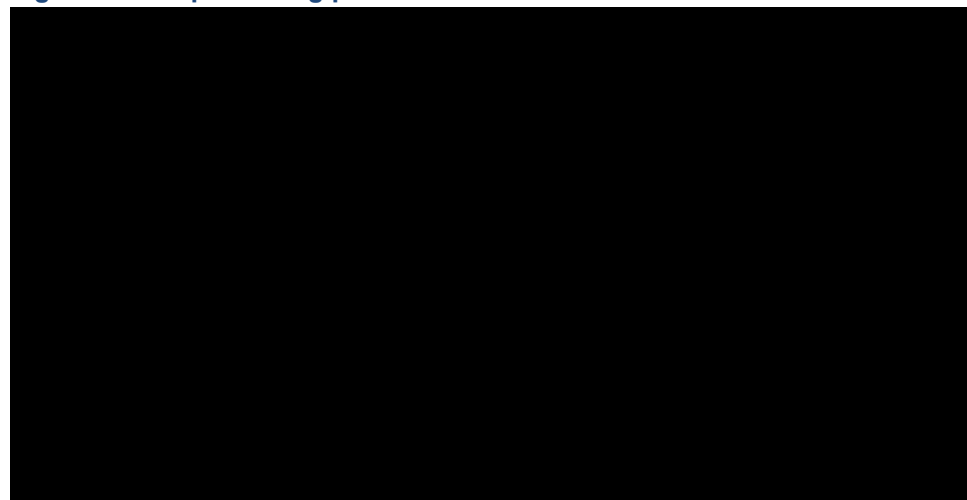
	○ Age at randomisation (<65 vs ≥65 years of age) ○ Geographic region (Asia vs non-Asia) ○ Clinical lymph node status (positive vs negative) ○ PD-L1 expression status (TAP ≥1% vs TAP <1%) (for all prespecified cutoff thresholds which are defined prospectively or during the course of exploratory analysis) Secondary endpoints¹¹⁷ • OS ○ Analysed using a stratified log-rank test • pCR rate ○ Analysed using a stratified Cochran-Mantel-Haenszel test • Full details for all other secondary endpoints and HRQoL endpoints are provided in the protocol alongside this submission¹¹⁷ Safety analyses¹¹⁷ • Full details of the AE analyses are provided in the protocol alongside this submission¹¹⁷
Sample size, power calculation	• The study planned to screen approximately 1,125 patients in order to randomise approximately 900 patients in a 1:1 ratio to either durvalumab or placebo arms.¹¹⁷ • The 5% alpha (2-sided) was split between analyses of pCR (0.1%) and EFS (4.9%).¹¹⁷ The 4.9% (2-sided) alpha allocation for the EFS analysis was controlled at interim (IA) and final analysis (FA) timepoints by using the Lan-DeMets spending function that approximates the O'Brien-Fleming approach, where the significance level applied depends upon the actual proportion of information (i.e., information fraction) available.¹²⁰ • With approximately 461 EFS events at the FA, the study was planned to have approximately 85% power to show a statistically significant difference in EFS at the 4.20% significance level (2-sided), assuming the true treatment effect is a HR of 0.75 for the primary treatment comparison of D-FLOT and control arms; this translates to an approximate 10-month improvement in median EFS over an assumed 30-month median EFS for the D-FLOT arm, assuming EFS is exponentially distributed.¹¹⁷
Data management, patient withdrawals	Data management • Any genotype data generated in this study were stored at a secure system at AstraZeneca and/or designated organisations to analyse the samples¹¹⁷

	- AstraZeneca and its designated organisations could share summary results (such as genetic differences from groups of individuals with a disease) from this genetic research with other researchers, such as hospitals, academic organisations or health insurance companies.¹¹⁷ - This could be done by placing the results in scientific databases, where they can be combined with the results of similar studies to learn even more about health and disease. The researchers could only use this information for health-related research purposes. Researchers may have seen summary results, but they did not see individual patient data or any personal identifiers¹¹⁷ - Some or all of the clinical datasets from the main study may have been merged with the genetic data in a suitable secure environment separate from the clinical database¹¹⁷ Patient withdrawal - Patients were free at any time to withdraw from the study at any time, without prejudice to further treatment. - Patients who withdraw consent for further participation in the study did not receive any further investigational product or further study observation, with the exception of follow-up for survival and request for additional subsequent treatment information, which continued until the end of the study, unless the patient had expressly withdrawn their consent to survival follow-up. Note that the patient may have been offered additional tests or tapering of treatment to withdraw safely. - A patient who withdrew consent was always be asked about the reason(s) for withdrawal and the presence of any AE. The Investigator will follow up AEs outside of the clinical study. - If a patient withdrew consent, they were specifically asked if they were withdrawing consent to: - All further participation in the study including any further follow-up - The use of any samples
Multiplicity	- A total of three DCOs were planned for MATTERHORN. To maintain strong control of the overall 5% type I error rate (2-sided), a multiple testing procedure (MTP) was implemented as detailed below and in Figure 7.¹¹⁷ - Strong control across DCO1, DCO2, and the FA was obtained by allocation of a fixed alpha spend of 0.1% (2-sided) for analysis of pCR (by central pathology review) at DCO1 and spending the remaining alpha=4.9% (2-sided) at DCO2 and FA to analyse EFS and OS. Since the pCR was statistically significant at DCO1, the alpha of 0.1% for pCR was recycled to EFS, so EFS could be tested at an overall alpha of 5% (2-sided). The alpha expenditure for EFS was planned to be spent between DCO2 and FA using the Lan-DeMets spending function that approximates an O'Brien-Fleming approach, with

the exact significance levels to be determined based on the actual information fraction available at the time of analysis.¹²⁰

- OS was only to be tested if EFS was statistically significant. Note that alpha expenditure for OS was planned to be spent between DCO2 and FA by allocating a fixed alpha of 0.01% at DCO2 while spending the remaining alpha at FA.¹¹⁷
- Further information regarding the MTP, including analyses up to DCO3, can be found in the MATTERHORN CSR provided in the reference pack of the submission.³⁶

Figure 7. Multiple testing procedure



Abbreviations: DCO: data cut-off; FA: final analysis; IA: interim analysis

Source: AstraZeneca. Data on File. MATTERHORN Clinical Study Protocol (2024).¹¹⁷

Abbreviations: BICR: Blinded independent central review; CI: Confidence interval; DCO: Data cut-off; DFS: Disease-free survival; EFS: Event-free survival; FAS: Full analysis set; FA: Final analysis; FLOT: 5-fluorouracil, leucovorin, oxaliplatin, and docetaxel; HR: Hazard ratio; HRQoL: Health-related quality of life; IA: Interim analysis; KM: Kaplan-Meier; MFS: Metastasis-free survival; MTP: Multiple testing procedure; OS: Overall survival; pCR: Pathological complete response; PD-L1: Programmed death-ligand 1; PH: Proportional hazards; PRO: Patient-reported outcome; R0: Complete tumour resection with negative margins; RECIST: Response Evaluation Criteria In Solid Tumours; SAS: Safety analysis set; SAP: Statistical analysis plan; TAP: Tumour area positivity.

Source: AstraZeneca. Data on File. MATTERHORN Clinical Study Protocol (2024).¹¹⁷ AstraZeneca Data on File (MATTERHORN Clinical Study Report).³⁶

Definitions of outcome measures

A variety of outcomes were explored in MATTERHORN to explore the efficacy of durvalumab in adult patients with resectable GOA. Definitions for these outcome measures, and the population they were assessed in are presented in Table 8.

Table 8. Primary and secondary endpoints in MATTERHORN

Priority	Endpoint	Endpoint definition	Assessment
Primary efficacy endpoint	EFS	Defined as the time from randomisation to the first of the following (according to RECIST 1.1 per BICR assessment 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	Analysed in the FAS. Assessment according to RECIST 1.1 per BICR ^a and/or locally by pathology testing
Key secondary efficacy endpoints	OS	Defined as the time from the date of randomisation until death due to any cause	Analysed in the FAS
	pCR	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 FAS. Determined by pathology review by central review ^b in accordance with the modified Ryan criteria ¹²¹
Other secondary efficacy endpoints	Surgery rate	Defined as the proportion of patients who undergo gastrectomy or gastro-oesophagectomy	Analysed in the FAS
	R0 resection rate	Defined as the proportion of patients who have confirmed complete resection as assessed by pathology review	Analysed in the FAS. Determined by pathology review by local assessment
	Pathological downstaging	Defined as: a) the proportion of patients who achieved downstaging of the primary tumour at surgery (pathological staging) relative to clinical staging at baseline, and b) the proportion of patients who were downstaged to N0 status at surgery having had node positive status at baseline	Analysed in the FAS
	MFS	Defined as the time from randomisation until the development of metastasis using RECIST 1.1 or death due to any cause	Analysed in the FAS. Assessment according to RECIST 1.1 per Investigator assessment.
	DSS	Defined as the time from randomisation until death due to GOA	Analysed in the FAS
	DFS	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
	HRQoL	Disease-related symptoms, impacts and HRQoL	Time to deterioration and change from baseline in EORTC QLQ-C30 and

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Priority	Endpoint	Endpoint definition	Assessment
			EORTC QLQ-STO22 + IL38, in the PRO analysis set
Safety	AEs, laboratory parameters, vital signs, ECGs, WHO/ECOG PS	Treatment safety and tolerability profile	AEs, physical examinations, vital signs (including blood pressure, pulse, and ECGs), and laboratory findings (including clinical chemistry, haematology, and urinalysis), measured in the SAS

Footnotes: For all efficacy endpoints, comparisons were conducted between the durvalumab and the control arms. Treatment arms were compared based on randomised study treatment, regardless of the treatment actually received. ^a A sensitivity analysis of EFS using Investigator assessments was also conducted. ^b A sensitivity analysis of pCR based on local assessment was also conducted.

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 disease-specific measure to complement QLQ-STO22; MFS: metastasis-free survival; OS: overall survival; pCR: pathological complete response; PRO: patient reported outcome; QLQ-C30: 30-item Core Quality of Life Questionnaire, version 3; QLQ-STO22: 22-item Gastric Cancer Quality of Life Questionnaire; RECIST: Response Evaluation Criteria in Solid Tumours; SAS: safety analysis set.

Source: AstraZeneca (MATTERHORN Clinical Study Report; 2025; Tables 5–6, P75–77, P81–84).³⁶

2.5 Critical appraisal of the relevant clinical effectiveness evidence

Full details of the SLR, including methods and results of the quality assessment, can be found in Appendix B. A summary of the quality assessments conducted based on the University of York Centre for Reviews and Dissemination (CRD) checklist for the MATTERHORN trial is presented in Table 9.¹²²

Table 9. Critical appraisal of the MATTERHORN trial, using the University of York CRD Checklist

Sources (MATTERHORN trial)	Randomisation		Treatment allocation concealment		Blinding of participants and care providers		Blinding of outcome assessors		Similar prognostic factors between groups		
	Was randomisation carried out appropriately?	Details of randomisation	Was the concealment of treatment allocation adequate?	Details of treatment allocation concealment	Were the participants and care providers blind to treatment allocation?	Details of participant /care provider blinding	Were the outcome assessors blind to treatment allocation?	Details of outcome assessor or blinding	Were the groups similar at the outset of the study in terms of prognostic factors?	Details of imbalances in baseline characteristics	
Janjigian 2023; ¹¹⁵ Janjigian 2025; ¹⁰⁹ Al-Batran 2025 ⁷⁵	Yes	Patients were randomised 1:1 in two arms (D-FLOT and Placebo + FLOT)	Yes	-	Yes	Double blind	Yes	Double blind	Yes	-	
	Unexpected imbalances in drop-outs		Reporting of outcome data		Intention to treat analysis		Funding and other details		Additional questions for pre-defined crossover studies		
	Were there any unexpected	If so, give details.	Is there any evidence to suggest that	Details of potentially	Did the analysis use an	Details of analysis methods	Details of study funding	Further quality assess	Is the cros	Does the study design	Is the approach to

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	ed imbalanc es in drop-outs between groups?	Were the imbalanc es explaine d and adjusted for?	the authors measured more outcomes than they reported?	unreport ed outcome s	intention- to-treat analysis? If so, was this appropriat e and were appropriat e methods used to account for missing data?			ment notes	s- over desi gn appr opria te?	allow for the possibilit y of a "carryov er" effect?	statistic al analysis appropri ate?
	Unclear	-	No	-	Yes	-	Astrazene ca	-	NA	NA	Yes

Abbreviations: CRD: Centre for Reviews and Dissemination; D-FLOT: durvalumab with 5-fluorouracil, leucovorin, oxaliplatin and docetaxel; FLOT: 5-fluorouracil, leucovorin, oxaliplatin and docetaxel; NA: not applicable.

2.6 Clinical effectiveness results of the relevant studies

Summary of MATTERHORN data cuts

Three formal analyses of the MATTERHORN trial were prespecified:

- DCO1 (pCR assessment; first IA; 1st February 2023)
- DCO2 (FA of EFS and IA of OS; second IA; 20th December 2024)
- DCO3 (FA of OS; 1st September 2025)

The final data cut-off (DCO3) for OS occurred on 1st September 2025 and results from DCO3 were presented at the ESMO 2025 Congress. Due to timing of data availability from DCO3, DCO1 and DCO2 form the evidence base for this submission. The data from DCO3 demonstrate that outcomes are consistent with the current data package provided, with a statistically significant OS benefit (HR: 0.78; 95% CI: 0.63, 0.96; p=0.021).¹¹²

Efficacy results for the FAS of MATTERHORN from DCO2 (December 2024) are therefore provided in Sections 2.6.1–2.11.8 below, with a focus on the endpoints specified in the decision problem.

2.6.1 Primary efficacy outcome: EFS

The MATTERHORN trial utilises EFS as the primary efficacy endpoint; at DCO2 (December 2024 DCO), the primary objective of the trial was met.¹¹⁷ EFS is aligned with the treatment goals of resectable GOA, as it includes progression events precluding surgery and recurrence events after surgery, both of which are highly relevant events for patients, because of the impact they have on prognosis and HRQoL. EFS provides a direct measure of efficacy across neoadjuvant and adjuvant treatment periods which are not confounded by subsequent therapies following progression or recurrence and there is extensive evidence to demonstrate that it represents a strong surrogate for OS.¹²³

A summary of the EFS data at the December 2024 DCO is presented in Table 10. In total, 385 EFS events (using BICR for RECIST v1.1) had occurred across the two treatment arms in the FAS population (40.6% maturity for EFS),³⁶ with 167 events in the D-FLOT arm and 218 events in the control arm (Table 10).¹⁰⁹ The median duration of follow-up for EFS (in censored patients) was [REDACTED] months (range: [REDACTED] months) in the D-FLOT arm and [REDACTED] months (range: [REDACTED] months) in the control arm.³⁶

The D-FLOT arm demonstrated a clinically meaningful and statistically significant improvement in EFS compared to the control arm (HR: 0.71; 95% CI: 0.58, 0.86; p<0.001); representing a 29% reduction in the risk of an EFS event.¹⁰⁹ Median EFS was not reached (NR) (95% CI: 40.7, not calculated [NC]) in the D-FLOT arm and was 32.8 months (95% CI: 27.9, NC) in the control arm.³⁶

Beginning at approximately three months post randomisation, the EFS Kaplan–Meier curves separated clearly in favour of the D FLOT arm, and this separation persisted throughout the remaining follow up, as shown in Figure 8. This was also reflected in the estimated EFS rates at 12 months ([REDACTED]% vs. [REDACTED]% for the D-FLOT and control arms, respectively), 18 months (73.2% vs. 63.6%, respectively) and 24 months (67.4% vs. 58.5%, respectively). Despite a greater degree of censoring beyond 24 months, the KM estimates of EFS at 30 months ([REDACTED] vs. [REDACTED]) and 36 months

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(████ vs. █████) are supportive of a sustained separation of the EFS curves in favour of the D-FLOT arm through the remaining duration of follow up.

To summarise, at the December 2024 data cut off, MATTERHORN achieved its primary objective: perioperative D-FLOT demonstrated statistically significant and clinically meaningful improvement in EFS versus the control arm in resectable GOA. These findings position durvalumab as the first IO agent combined with perioperative FLOT to demonstrate this level of EFS benefit in this setting.

Table 10. Summary of EFS (using BICR for RECIST v1.1) (FAS, December 2024 DCO)

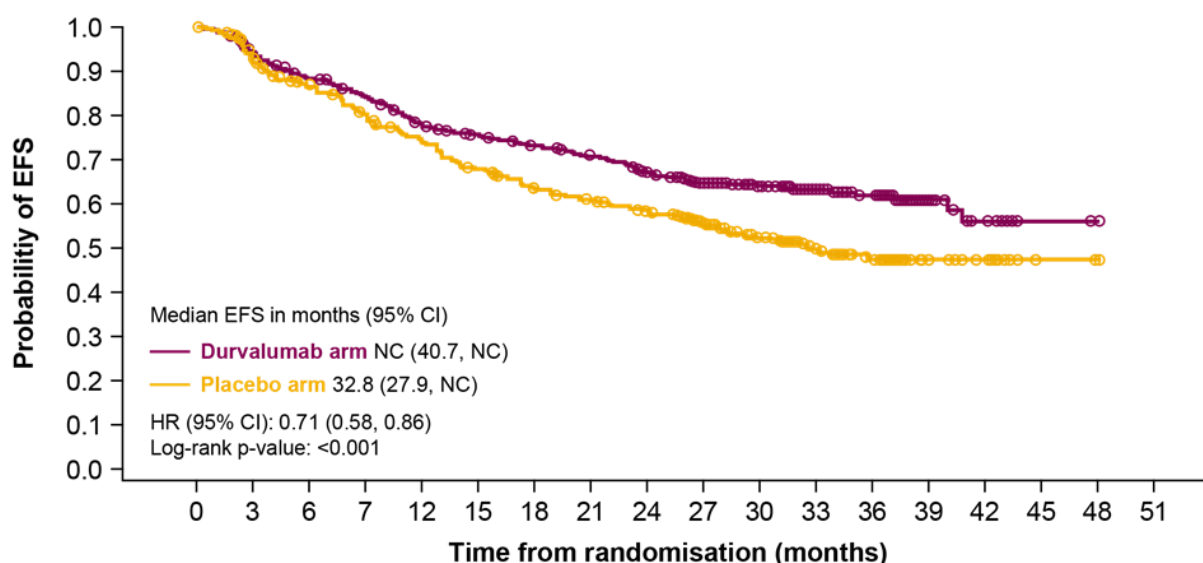
	D-FLOT arm (n=474)	Control arm (n=474)
Events ^a n (%)	167 (35.2)	218 (46.0)
HR ^b	0.71	
95% CI ^b	0.58, 0.86	
2-sided p-value ^c	<0.001	
Median EFS, months ^d (95% CI)	NR (40.7, NC)	32.8 (27.9, NC)
Landmark EFS, %^d (95% CI)		
12 months	██████████	██████████
18 months	73.2 (████████)	63.6 (████████)
24 months	67.4 (████████)	58.5 (████████)
30 months	██████████	██████████
36 months	██████████	██████████
Median duration of follow-up in censored patients, months (range) ^e	31.6 (0.0, 48.1)	31.4 (0.0, 48.1)

Footnotes: ^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 D-FLOT 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. ^e Patients who did not experience an event by the time of analysis were censored at the date of their last evaluable RECIST 1.1 assessment.

Abbreviations: CI: confidence interval; DCO: data cut-off; EFS: event-free survival; HR: hazard ratio; IA: interim analysis; KM: Kaplan-Meier; NC: not calculated; NR: not reached; RECIST: Response Evaluation Criteria in Solid Tumours.

Source: AstraZeneca Data on File (MATTERHORN Clinical Study Report; Table 18, P116–117).³⁶ Janjigian et al. 2025.¹⁰⁹

Figure 8. KM curves for EFS (using BICR for RECIST v1.1) (FAS, December 2024 DCO)



Footnotes: 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.

Abbreviations: BICR: blinded independent central review; CI: confidence interval; DCO: data cut-off; EFS: event-free survival; FAS: full analysis set; HR: hazard ratio; ITT: intention-to-treat; KM: Kaplan-Meier; NC: not calculated; PD-L1: programmed death-ligand 1; RECIST: Response Evaluation Criteria in Solid Tumours.

Source: Janjigian et al. 2025.¹⁰⁹

2.6.2 Key secondary efficacy outcome: OS

At DCO2 (December 2024), OS data had an overall maturity of 33.9%,³⁶ with a similar frequency of deaths across both treatment arms (145 events [30.6%] and 176 events [37.1%] in the D-FLOT and control arms, respectively).¹⁰⁹

Median OS was NR for the D-FLOT treatment arm and 47.2 months (95% CI: 45.1, NR) for the control arm (Table 11). As detailed in Figure 9, at approximately 13 months post-randomisation there was a clear and sustained separation in the KM curves of OS in favour of the D-FLOT arm vs. the control arm.

The trend of improved OS for the D-FLOT arm was sustained over time for the remaining duration of follow-up, as shown by numerical improvements in OS rates in the D-FLOT arm compared to the control arm at 18 months (81.1% vs. 77.1%) and 24 months (75.7% vs. 70.4%) (Table 11). The KM estimates of OS at 30 months (■% vs. ■%) and 36 months (■% vs. ■%) are supportive of a sustained separation of the OS curves that continually increases at each timepoint in favour of the D-FLOT, albeit there is a greater degree of censoring beyond 24 months. The majority of patients in both treatment arms died of the disease under study as determined by the investigator.³⁶

At the interim OS analysis at the December 2024 data cut off (DCO2), the HR indicated a trend toward improved overall survival with D-FLOT versus the control arm (HR 0.78; 95% CI 0.62–0.97; two sided p=0.025), which did not meet the prespecified threshold for statistical significance at that

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cut off ($p < 0.0001$ required). Subsequent OS data from DCO3, recently presented at ESMO 2025, were consistent with data from DCO2 and demonstrated a statistically significant OS benefit in favour of D-FLOT vs perioperative FLOT (HR: 0.78; 95% CI: 0.63, 0.96; $p = 0.021$).^{36, 112}

Table 11. Summary of OS (FAS, December 2024 DCO)

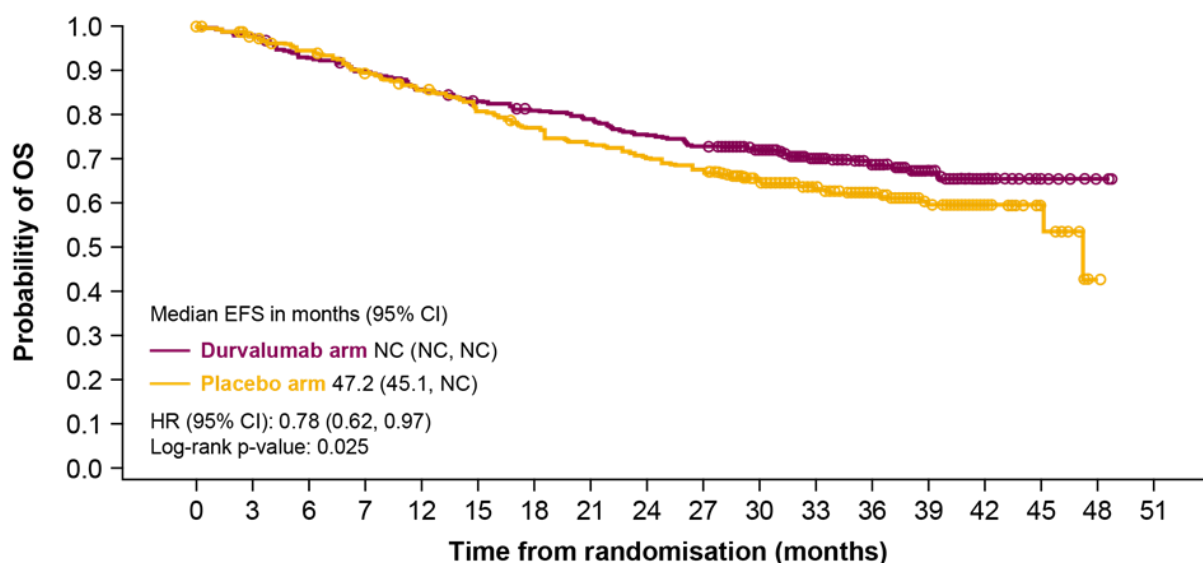
	D-FLOT arm (n=474)	Control arm (n=474)
Total number of deaths, n (%)	145 (30.6)	176 (37.1)
HR ^a	0.78	
95% CI	0.62, 0.97	
2-sided p-value ^b	0.025	
Median OS, ^c months (95% CI)	NR (NC, NC)	47.2 (45.1, NC)
Landmark OS,^c % (95% CI)		
12 months	██████████	██████████
18 months	81.1 (██████████)	77.1 (██████████)
24 months	75.7 (██████████)	70.4 (██████████)
30 months	██████████	██████████
36 months	██████████	██████████

Footnotes: The threshold to declare statistical significance at the December 2024 DCO was $p < 0.0001$, with a fixed alpha spend of 0.01% (2-sided) allocated for the interim analysis of OS. ^a 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 D-FLOT arm. The CI is calculated using a profile likelihood approach. ^b Derived using a stratified log-rank test adjusted for geographic region, clinical lymph node status, and PD-L1 expression status at randomisation. ^c Calculated using the KM technique.

Abbreviations: CI: confidence interval; DCO: data cut-off; FAS: full analysis set; HR: hazard ratio; IA: interim analysis; KM: Kaplan-Meier; NC: not calculated; NR: not reached; OS: overall survival; RECIST: Response Evaluation Criteria in Solid Tumours.

Source: AstraZeneca Data on File (MATTERHORN Clinical Study Report; Table 20, P127).³⁶ Janjigian et al. 2025.¹⁰⁹

Figure 9. KM curves for OS (FAS, December 2024 DCO)



Footnotes: 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 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.

Abbreviations: CI: confidence interval; DCO: data cut-off; FAS: full analysis set; HR: hazard ratio; IA: interim analysis; NC: not calculated; OS: overall survival.

Source: Janjigian et al. 2025.¹⁰⁹

2.6.3 Key secondary efficacy outcome: pCR

pCR is a clinically-relevant and patient-relevant endpoint that reflects tumour eradication in response to neoadjuvant treatment. Residual disease post-surgery is a prognostic indicator of OS in patients with resectable GOA, and pCR rate has been shown to correlate with improved survival outcomes in this patient population.^{124, 125}

In MATTERHORN, pCR was defined as the proportion of patients who have no residual visible tumour in the resected specimens and as determined by pathology review. At DCO1 (01 February 2023), the MATTERHORN study met the prespecified boundary for the key secondary endpoint of pCR rate per central pathology review, demonstrating that treatment with D-FLOT prior to surgery resulted in a statistically significant improvement in pCR rate compared with FLOT alone.¹⁰⁹

At DCO1, the proportion of patients achieving pCR was 19.2% (95% CI: 15.8, 23.0) in the D-FLOT group and 7.2% (95% CI: 5.0, 9.9) in the control group (odds ratio [OR]: 3.1 [95% CI: 2.0, 4.7]; $p < 0.001$), corresponding to an absolute difference of 12.0% and a 2.7-fold higher likelihood of achieving pCR in the D-FLOT arm compared with the control arm (Table 12).¹⁰⁹ These data demonstrate that treatment with perioperative D-FLOT prior to surgery resulted in a statistically significant and clinically meaningful improvement in pCR rate compared with the control arm.

Table 12. pCR rate assessed by central review (FAS, February 2023 DCO)

	D-FLOT arm (n=474)	Control arm (n=474)
Number of patients with response, ^a n	91	34

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	D-FLOT arm (n=474)	Control arm (n=474)
Response rate, (%)	19.2	7.2
95% CI ^b	15.8, 23.0	5.0, 9.9
Difference in response rate, ^c (%)	12.0	
Comparison between groups^d		
OR	3.1	
95% CI	2.0, 4.7	
2-sided p-value	<0.001	

Footnotes: An odds ratio >1 favours the D-FLOT 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 = D-FLOT arm response rate – control 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.

Abbreviations: CI: confidence interval; DCO: data cut-off; FAS: full analysis set; OR: odds ratio; pCR: pathological complete response.

Source: Janjigian et al. 2025.¹⁰⁹

2.6.4 Other secondary efficacy outcomes: Surgical outcomes

As surgery remains the cornerstone of curative-intent treatment in GOA, it is critical that perioperative therapies do not compromise the ability for patients to receive surgery, nor impair surgical outcomes. As such, it is crucial to assess the absence of a negative impact that any regimen may have on surgery, such as by delaying or complicating surgery, or by adding toxicity that reduces the likelihood of completing the full perioperative treatment regimen.

In MATTERHORN, treatment with D-FLOT prior to surgery did not impact the proportion of patients who underwent and completed surgery, nor did it impact the feasibility or timing of surgery compared to the control arm.³⁶ The proportion of patients in the FAS with attempted surgery (90.9% in the D-FLOT arm vs 90.3% in the control arm) and proportion of patients with completed surgery (86.9% in the D-FLOT arm vs 84.4% in the control arm; OR: ■■■) was similar between treatment arms (Table 13).³⁶ Reasons for not undergoing surgery (including higher disease progression in the control arm as detailed in Table 13) were consistent with the expectations of UK clinical experts, suggesting D-FLOT does not preclude, and may even promote, access to curative surgery.⁵

The number of surgical delays (i.e., any surgery attempted more than 8 weeks [56 days] after the end of neoadjuvant treatment) was comparable between treatment arms: 48 (10.1%) patients in the D-FLOT arm and 51 (10.8%) patients in the control arm experienced a surgical delay.³⁶ The most common reasons for surgical delay were logistical reasons (28 [5.9%] vs. 31 [6.5%] patients, respectively) and AE (11 [2.3%] vs. 12 [2.5%] patients, respectively).³⁶ Most surgical delays reported were <2 weeks in duration in both treatment arms.³⁶

Table 13. Summary of patients undergoing surgery (FAS, December 2024 DCO)

	D-FLOT arm (n=474)	Control arm (n=474)
Patients who did not attempt surgery, n (%)	43 (9.1)	46 (9.7)
Patient decision	■■■	■■■
Unfit for surgery (e.g., ECOG PS decline)	■■■	■■■
Adverse event	■■■	■■■

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Disease progression		
Death		
Study discontinuation		
Investigator decision to not perform surgery		
Other		
Patients with attempted/performed surgery, n (%)	431 (90.9)	428 (90.3)
Patients whose surgery was attempted but not completed, n (%)		
Peritoneal dissemination		
Distant metastases		
Other ^a		
Patients who completed surgery	412 (86.9)	400 (84.4)
Distal gastrectomy		
Subtotal gastrectomy		
Total gastrectomy		
Gastro-oesophagectomy		
Surgery rate (%)	86.9	84.4
95% CI ^b		
Difference in surgery rate (%) ^c		
Comparison between arms ^d		
OR ^e		
95% CI		
Type of surgical procedure and extent of resection		
Surgery laparotomy or laparoscopy ^f		
Laparotomy		
Laparoscopy		
Type of lymphadenectomy performed ^f		
D1		
D2/D3		
Missing		
Participants who completed surgery ^f		
R0	377 (91.5)	369 (92.3)
R1		
R2		
Missing		1
Surgical delays		
Patients with no surgical delay		
Patients with any surgical delay ^g	48 (10.1)	51 (10.8)
Unresolved toxicity from previous study treatments	2 (0.4)	2 (0.4)
Chemotherapy	2 (0.4)	1 (0.2)
Durvalumab/placebo	0	1 (0.2)

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Logistical reasons	28 (5.9)	31 (6.5)
AE	11 (2.3)	12 (2.5)
Other	7 (1.5)	6 (1.3)
Duration of delay to on-study surgery		
<2 weeks	████	████
2 to <4 weeks	████	████
4 to <6 weeks	████	████
≥6 weeks	████	████
Reason for delay for Cycle 3 Day 1 dose (initiation of adjuvant treatment)^{h,i}		
AE	████	████
Logistic	████	████
Patient decision	████	████
Laboratory abnormality not reported as an AE	█	████
Other	████	████

Footnotes: A surgical delay is defined as any surgery starting more than 8 weeks (56 days) after the end of neoadjuvant treatment. An odds ratio > 1 favours the D-FLOT arm. ^a Includes 9 patients with inoperable disease. ^b CIs for response rate are calculated using Clopper-Pearson exact method. ^c Difference in response rate = durvalumab response rate – placebo 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. ^e Not part of the multiple testing procedure. ^f Only patients who have completed surgery were used for the denominator when calculating percentages. ^g Reasons for surgical delay are not mutually exclusive for patients with multiple reasons per delay although are counted only once per category. ^h Cycle 3 Day 1 dose is considered delayed if all study drugs have been started after 12 weeks (84 days) post-surgery. ⁱ Reasons for dose delays are not mutually exclusive for subjects with multiple delays although counted only once per category.

Abbreviations: AE: Adverse event; CI: Confidence interval; D1: Limited lymphadenectomy; D2: Standard lymphadenectomy; D3: Extended lymphadenectomy; DCO: data cut-off; ECOG PS: Eastern Cooperative Oncology Group Performance Status; FAS: final analysis set; R0: Complete tumour resection with negative margins; OR: odds ratio; PD-L1: programmed death-ligand 1; R1: Microscopically positive resection margin; R2: Macroscopically positive resection margin.

Source: AstraZeneca Data on File (MATTERHORN Clinical Study Report; Table 25, P138).³⁶

2.6.5 Other secondary efficacy outcomes: MFS and DSS

EFS (the primary efficacy endpoint of the MATTERHORN trial) and OS (a key secondary efficacy endpoint in MATTERHORN) represent the key survival outcomes to assess the clinical benefit of D-FLOT in this indication. However, other relevant survival outcomes were explored in the MATTERHORN trial to provide a multidimensional assessment of efficacy and promote the robust characterisation of the clinical benefit of D-FLOT in resectable GOA.

A summary of MFS and DSS at DCO2 (December 2024) is provided below and a summary of DFS is provided in Appendix K.1 for completeness. The joint evaluation of these endpoints reduces uncertainty by providing convergent evidence across multiple clinically meaningful outcomes. Overall, the results of these analyses provide further support for the clinical benefits associated with D-FLOT, with clinically meaningful improvements across all endpoints vs. FLOT alone.³⁶

MFS

As detailed in Section 1.3.4, once GOA progresses to advanced or metastatic disease, treatment is no longer offered with curative intent and prognosis worsens compared to early-stage GOA. ⁷³

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⁷⁴ Accordingly, preventing or delaying metastatic spread is a key therapeutic objective in the resectable setting..

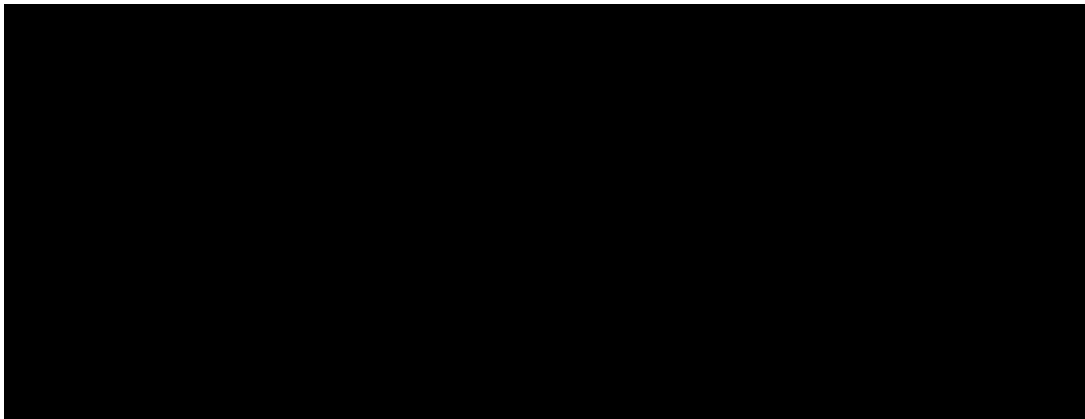
At DCO2 (December 2024 DCO), there were █ (█%) patients in the D-FLOT arm and █ (█%) patients in the control arm with MFS events per Investigator assessment (Table 14).³⁶ The HR was █ (95% CI: █), representing a clinically meaningful █% reduction in the risk of distant metastases or death due to any cause compared with control. The MFS benefit in the D-FLOT arm was sustained over time, as supported by the greater proportion of patients randomised to receive D-FLOT who were alive and metastasis-free based on KM estimates at 12, 18, 24, 30, and 36 months post-randomisation compared to patients in the control arm (Figure 10).³⁶

Table 14: Summary of MFS (FAS); December 2024 DCO

	D-FLOT arm (N=474)	Control arm (N=474)
Total MFS events, ^a n (%)	█	█
MFS HR ^e	█	
95% CI	█	
Median MFS, ^b months (95% CI)	█	█
Landmark MFS, ^b % (95% CI)		
12 months	█	█
18 months	█	█
24 months	█	█
30 months	█	█
36 months	█	█

Footnotes: MFS is the time from date of randomisation until the earliest date of metastasis or death due to any cause. ^a MFS Events signify occurrence of a new lesion outside of local regional tumour locations identified by RECIST 1.1 assessment by investigator. ^b Calculated using the KM technique.
Abbreviations: CI: confidence interval; DCO: data cut-off; HR: hazard ratio; KM: Kaplan-Meier; MFS: metastasis-free survival; NC: not calculated.
Source: AstraZeneca Data on File (MATTERHORN Clinical Study Report; 2025; Table 27, P144).³⁶

Figure 10. KM curves for MFS (FAS; December 2024 DCO)



Footnotes: Circle symbol indicates a censored observation. The HR and its CI were 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 D-FLOT arm. The p-value is not adjusted for multiplicity.
Abbreviations: CI: confidence interval; DCO: data cut-off; FAS: final analysis set; HR: hazard ratio; MFS: metastasis-free survival; NC: not calculated.
Source: AstraZeneca Data on File (MATTERHORN Clinical Study Report; Figure 14, P145).³⁶

DSS

DSS is a clinically meaningful endpoint as it directly evaluates the effect of therapy on mortality attributable to GOA, independent of deaths from other causes. This endpoint provides a focused assessment of the capacity of D-FLOT to reduce or delay disease-related mortality. In the MATTERHORN trial, DSS measures the time from randomisation until death due to GOA.³⁶

At DCO2 (December 2024 DCO), █(█%) patients in the D-FLOT arm and █(█%) patients in the control arm had died due to the disease (Table 15).³⁶ The HR was █(95% CI: █), representing a clinically meaningful █% reduction in the risk of death due to GOA compared with control. DSS benefit in the D-FLOT arm was sustained over time, as supported by the greater proportion of patients randomised to receive D-FLOT who had not experienced death due to the disease based on KM estimates at 12, 18, 24, 30, and 36 months post-randomisation compared to patients in the control arm (Figure 11).³⁶

Table 15. Summary of DSS (FAS); December 2024 DCO

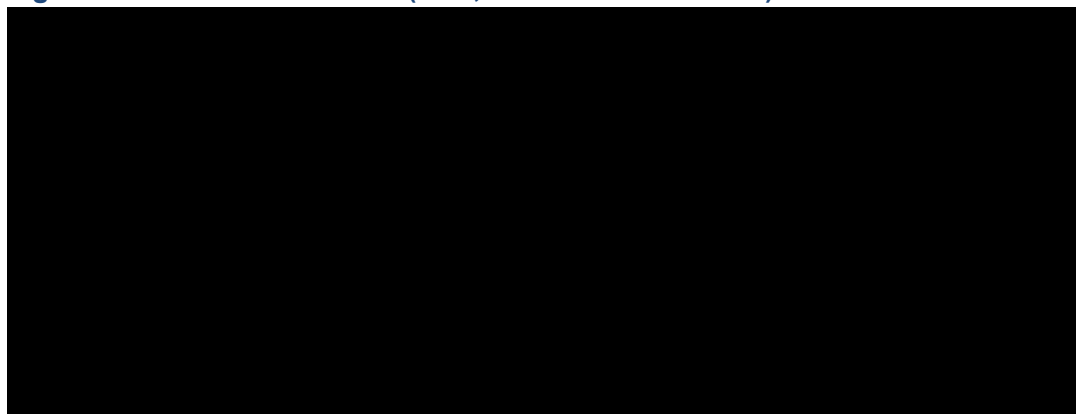
	D-FLOT arm (N=474)	Control arm (N=474)
Total DSS events, ^b n (%)	█	█
DSS HR ^c	█	
95% CI	█	
Median DSS, ^a months (95% CI)	█	█
Landmark DSS, ^a % (95% CI)		
12 months	█	█
18 months	█	█
24 months	█	█
30 months	█	█
36 months	█	█

Footnotes: DSS is defined as the time from date of randomisation until date of death due to GOA (any recorded deaths which are related to the disease under investigation). ^a Calculated using the KM technique. ^b Events are defined as deaths due to GOA (any recorded deaths that are related to the disease under investigation). ^c 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 D-FLOT arm. The CI is calculated using a profile likelihood approach.

Abbreviations: CI: confidence interval; DCO: data cut-off; DSS: disease-specific survival; HR: hazard ratio; KM: Kaplan-Meier; NC: not calculated; PD-L1: programmed death-ligand 1; RECIST: Response Evaluation Criteria in Solid Tumours.

Source: AstraZeneca Data on File (MATTERHORN Clinical Study Report; 2025; Table 28, P146).³⁶

Figure 11. KM curves for DSS (FAS; December 2024 DCO)



Footnotes: Circle symbol indicates a censored observation. Any patient not known to have died from GOA at the time of analysis were censored based on the last recorded date on which the patient was known to be alive. The HR and its CI were 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 D-FLOT arm. The p-value is not adjusted for multiplicity.

Abbreviations: CI: confidence interval; DCO: data cut-off; DSS: disease-specific survival; FAS: final analysis set; HR: hazard ratio; NC: not calculated.

Source: AstraZeneca Data on File (MATTERHORN Clinical Study Report; Figure 15, P147).³⁶

2.6.6 Exploratory efficacy outcomes: Pathological downstaging

Pathological downstaging was evaluated as an exploratory outcome in MATTERHORN, with analyses at the December 2024 DCO presented in Table 16.³⁶ This endpoint quantifies the proportion of patients whose tumour stage decreases after neoadjuvant D FLOT and may reflect improved treatment response versus placebo plus FLOT.. Clinical validation further supports pathological downstaging as a meaningful indicator of treatment response, reflecting tumour regression even without pCR. Although conversion from inoperable to operable disease was not evaluated within the study population (as all patients were surgical candidates at study enrolment), clinical experts highlighted the potential value of downstaging, particularly in patients with bulky tumours who may otherwise be unsuitable for resection.

A greater proportion of patients in the D-FLOT arm achieved downstaging of the primary tumour (ypT; pathological staging in relation to clinical staging at baseline) at surgery compared with the control arm (■ [■%] vs ■ [■%], respectively). A greater proportion of patients who had a node positive status at baseline in the D-FLOT arm (ypN) were downstaged to N0 status compared with the control arm (■ [■%] vs ■ [■%], respectively).

Overall, the results show that D-FLOT treatment is associated with increased rates of pathological downstaging at both the ypT and ypN levels compared with the control. These results reinforce the utility of pathological downstaging as a quantitative endpoint for assessing neoadjuvant treatment response in patients with GOA.

Table 16. Pathological assessment of disease post-surgery according to investigator in patients who attempted surgery (FAS; December 2024 DCO)

	D-FLOT arm (N=474)	Control arm (N=474)
ypT staging at surgery	431 (90.9)	428 (90.3)
Downstaging	■	■
No change	■	■
Upstaging	■	■

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	D-FLOT arm (N=474)	Control arm (N=474)
Missing	██████	██████
Did not undergo surgery	██████	██████
ypN staging at surgery	██████	██████
Downstaged N0	██████	██████
Persistent N0	██████	██████
Persistent N+ or upstaged N+	██████	██████
Missing	██████	██████
Did not undergo surgery	██████	██████

Footnotes: Downstaged N0: positive N stage at baseline while N0 at surgery. Persistent N0: N0 at baseline and N0 at surgery. Persistent N+ or upstaged N+: N+ at baseline and N+ at surgery or N0 at baseline while N+ at surgery.

Abbreviations: CI: Confidence interval; DCO: Data cut-off; FAS: Full analysis set; N0: No regional lymph node metastasis; N+: Regional lymph node metastasis present; ypN: Pathological lymph node stage after preoperative therapy; ypT: Pathological staging in relation to clinical staging at baseline.

Source: AstraZeneca Data on File (MATTERHORN Clinical Study Report; 2025; Table 24, P137).³⁶

2.6.7 Patient reported outcomes: Health-related quality of life (HRQoL)

As detailed in Section 1.3.4, GOA can have a substantial impact on patients' daily lives and HRQoL, which worsens as the disease progresses.²⁸ Disease recurrence and accompanying fear of disease recurrence in particular have a detrimental impact on HRQoL, outlining the unmet need for treatments that prevent or delay progression.⁷⁸ Patient-reported outcomes (PROs) included as secondary endpoints in MATTERHORN were assessed using the EORTC QLQ-C30, EORTC QLQ-STO22 + IL38 and EQ-5D-5L questionnaires.

At the time of DCO2 (December 2024 DCO), the overall compliance rates for the completion of the EORTC QLQ-C30 and QLQ-STO22 + IL38 questionnaires were >90% in both treatment arms at baseline and generally remained above 80% to the end of the adjuvant period.⁷⁵

EORTC QLQ-C30

The EORTC-QLQ-C30 is an internationally validated HRQoL questionnaire for cancer, and is designed to measure cancer patients' physical, psychological and social functions, comprising both multi-item scales and single items.¹¹⁷ A clinically meaningful change from baseline in EORTC QLQ-C30 subscales/scores was defined as an absolute change in score of ≥10 points.¹¹⁷ The pre-specified domains/scales for analysis were:

- Global health status/QoL (1 item scale)
- Physical function (5 item scale)
- Role function (2 item scale)
- Fatigue (3 item scale)
- Appetite loss (1 item scale)

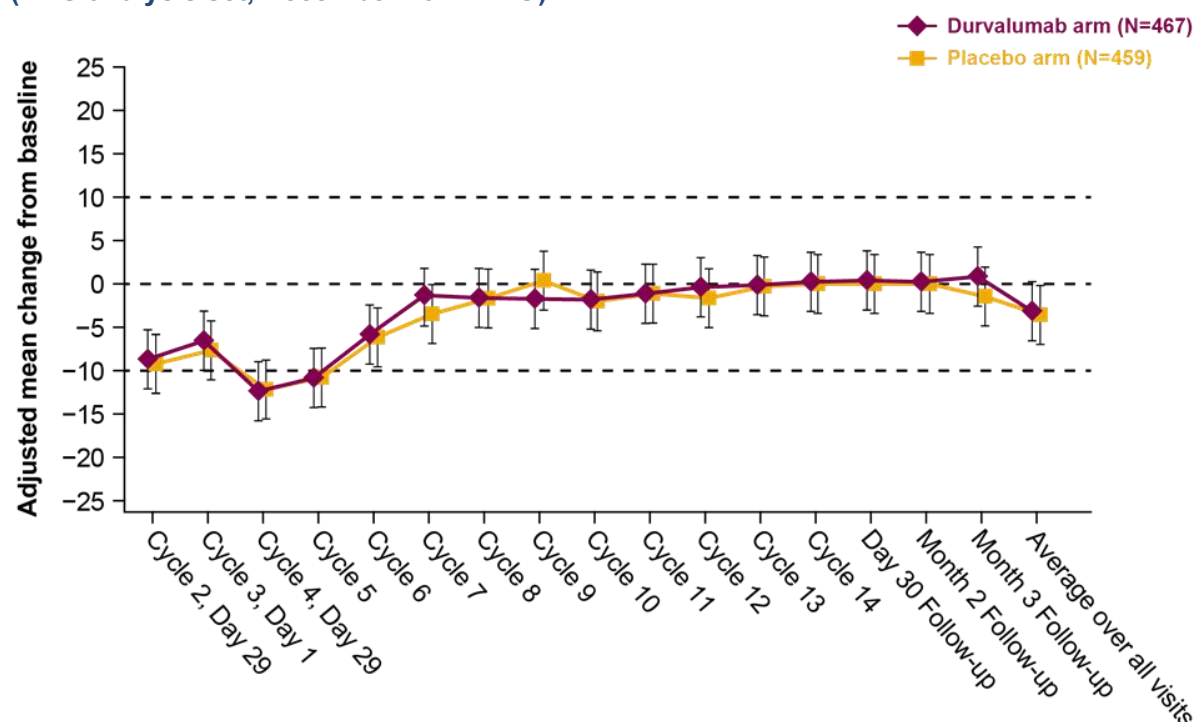
Based on mixed-effect model for repeated measures (MMRM) analyses, there were no meaningful differences between arms in changes from baseline for any functional domain or symptom scale at all timepoints evaluated during the neoadjuvant, adjuvant and follow-up periods. In both arms,

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meaningful deterioration in the QLQ-C30 score of global health status/QoL was observed (Figure 12), with similar trends for physical functioning, role functioning, fatigue, and appetite loss (Appendix K.3).^{36, 75}

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.⁷⁵ The declines were comparable between treatment arms, and none of the associated scales or symptoms showed sustained meaningful deterioration over time.

Figure 12. EORTC QLQ-C30 QoL score change from baseline, plot of the adjusted mean (PRO analysis set, December 2024 DCO)



Footnotes: The analysis was performed using a MMRM analysis of change from baseline global health status/QoL score for all post-baseline visits up to the last scheduled visit where ≥ 20 patients on each treatment arm have a score. Treatment, visit, and treatment-by-visit interaction were included as categorical variables, and the baseline score and baseline score-by-visit interaction were included as covariates.

Abbreviations: EORTC: European Organisation for Research and Treatment of Cancer; MMRM: mixed model for repeated measures; PRO: patient reported outcome; QLQ-C30: 30-Item Core Quality of Life Questionnaire; QoL: Quality of Life.

Source: Al-Batran et al. 2025.⁷⁵

EORTC QLQ-STO22 + IL38

The EORTC QLQ-STO22 + IL38 questionnaire is a gastric cancer-specific module designed to be used alongside the EORTC QLQ-C30 to assess HRQoL in patients with GC.¹²⁶ It comprises 22 items that evaluate disease- and treatment-related symptoms and concerns, including dysphagia, pain, reflux, eating restrictions, anxiety, and body image.¹²⁶

A clinically meaningful change from baseline in EORTC QLQ-STO22 subscale scores is defined as an absolute change of ≥ 10 points. Specific symptom-related assessments associated with IL-38 levels include single-item measures of weight loss and difficulty swallowing. These items are scored on standard ordinal scales, with higher scores reflecting increased symptom burden. The pre-specified domains/scales for analysis were:

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- Dysphagia (4 item scale)
- Pain (3 item scale)
- Reflux (3 item scale)
- Eating restrictions (5 item scale)
- Anxiety (3 item scale)
- Dry mouth (1 item scale)
- Taste (1 item scale)
- Hair loss (1 or 2 item scale)
- Body image (1 item scale)
- IL-38: difficulty swallowing (1 item scale)
- IL-38: weight loss (1 item scale)

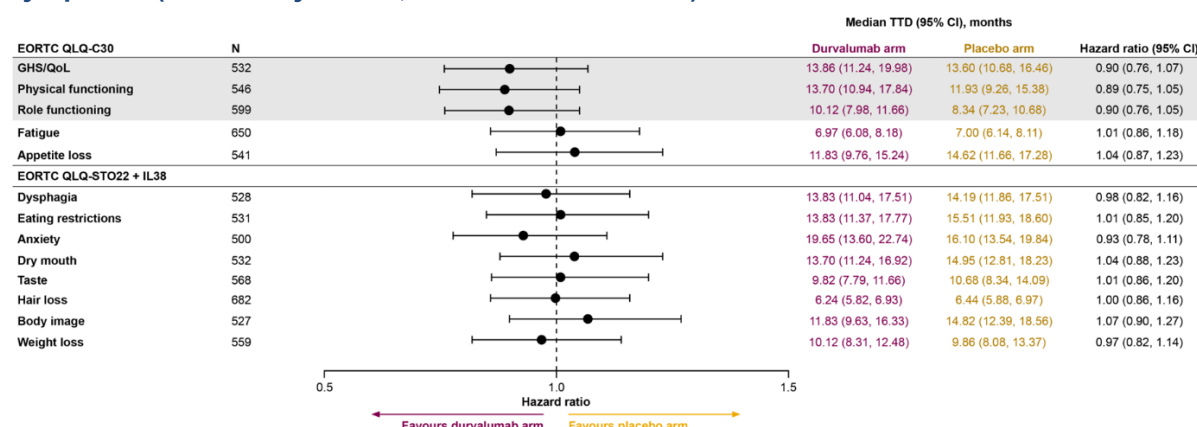
In MMRM analyses, there were [REDACTED] between arms in changes from baseline for any symptom scale of the EORTC QLQ-STO22 + IL38 at all timepoints evaluated during the neoadjuvant, adjuvant and follow-up periods. In both arms, [REDACTED] was reported for the EORTC QLQ-STO22 symptom scales of eating restrictions (Cycles 3 to 5), dry mouth (Cycles 2, 4 and 5), taste (Cycles 2 to 7), hair loss (Cycles 2 to 9), body image (Cycles 2 to 8), and weight loss (Cycles 3 to 5), with [REDACTED] observed in other domains (Appendix K.3). These [REDACTED] were followed by a return to baseline or [REDACTED] levels. These effects were generally considered to be associated with the administration of FLOT chemotherapy.³⁶

[REDACTED] were comparable between treatment arms. Only taste and hair loss showed sustained, meaningful deterioration over time in both groups. In contrast, anxiety (the most impaired symptom at baseline) showed [REDACTED] from Cycle 10 onward, with [REDACTED] observed between treatment arms (Appendix K.3).³⁶

Time to deterioration in EORTC QLQ-C30 and EORTC QLQ-STO22 + IL38

A summary of time to confirmed deterioration across all functional domains and symptom scales of the EORTC QLQ-C30 and EORTC QLQ-STO22 + IL38 is presented in Figure 13. There was no meaningful difference in the time to deterioration between treatment arms in any of the prespecified functional domains or symptom scales of the EORTC QLQ-C30 and EORTC QLQ-STO22 + IL38.⁷⁵

Figure 13. Forest plot for time to confirmed deterioration in primary PRO domains and symptoms (PRO Analysis Set, December 2024 DCO)



Footnotes: TTD is defined as the time from randomisation until date of first clinically meaningful symptom deterioration confirmed at the next consecutive scheduled visit or followed by death (by any cause) without deterioration. An increase ≥ 10 in symptom scales/item scores, or a decrease ≥ 10 in score of global health status/QoL and function scales, from neoadjuvant baseline, indicates clinically relevant deterioration. The HR and its CI were estimated from a Cox proportional hazards model, adjusted for geographical region, clinical lymph node status and PD-L1 expression. An HR < 1 favours the D-FLOT arm.

Abbreviations: CI: confidence interval; HR: hazard ratio; PRO: patient reported outcome; TTD: time to deterioration.

Source: Al-Batran et al. 2025.⁷⁵

2.7 Subsequent treatments used in the relevant studies

At DCO2 (20th December 2024), the proportion of FAS population patients who had received a subsequent anti-cancer therapy was 27.7% (Table 17). A smaller proportion of patients had received at least one anti-cancer therapy post-study treatment discontinuation in the D-FLOT arm vs. the control arm, 23.0% vs. 32.3%, respectively.¹⁰⁹

A lower number of patients in the D-FLOT arm used subsequent IO therapy (14.7%) than in the control arm (29.4%), with the highest proportion receiving immunotherapy + cytotoxic chemotherapy (Table 17). Clinical experts consulted as part of this submission validated that the subsequent treatments received by patients in the MATTERHORN trial were generally reflective of UK clinical practice.⁵

Table 17. Subsequent therapy after discontinuation (FAS, December 2024 DCO)

Post-discontinuation disease-related anticancer therapy regimen ^a	D-FLOT arm (n=474)	Control arm (n=474)
Participants with post-discontinuation disease-related anticancer therapy, n (%)	109 (23.0)	153 (32.3)
	n1=109	n1=153
Systemic therapy, n (%)	105 (96.3)	145 (94.8)
Cytotoxic chemotherapy	103 (94.5)	140 (91.5)
Antiangiogenic therapy	21 (19.3)	28 (18.3)
Targeted therapy	12 (11.0)	14 (9.2)
Immunotherapy	16 (14.7)	45 (29.4)
Immunotherapy only	2 (1.8)	5 (3.3)

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Post-discontinuation disease-related anticancer therapy regimen ^a	D-FLOT arm (n=474)	Control arm (n=474)
Immunotherapy plus cytotoxic chemotherapy	8 (7.3)	23 (15.0)
Immunotherapy plus targeted therapy plus cytotoxic chemotherapy	3 (2.8)	3 (2.0)
Immunotherapy plus other	3 (2.8)	14 (9.2)
Other, n (%)	2 (1.8)	6 (3.9)
Radiotherapy, n (%)	17 (15.6)	25 (16.3)
Concomitant chemoradiotherapy	5 (4.6)	8 (5.2)
Palliative therapy	9 (8.3)	16 (10.5)

Footnotes: N denotes the number of participants in treatment group, n1 denotes the number of participants with post-discontinuation disease-related anticancer therapy, and n denotes the number of participants receiving regimen. ^a Therapies post-discontinuation of trial treatment. Participants may be counted in more than one anticancer therapy.

Abbreviations: DCO: data cut-off; FLOT: fluorouracil, leucovorin, oxaliplatin, and docetaxel.

Source: Janjigian et al. 2025.¹⁰⁹

2.8 Subgroup analysis

As detailed in Table 4, at DCO2 (December 2024 DCO) subgroup analyses were explored for the primary endpoint of EFS and the key secondary endpoint OS, to assess the consistency of the clinical benefits of D-FLOT compared to placebo + FLOT across potential or expected clinically-relevant subgroups. These subgroups included sex, age at randomisation, geographic region, clinical lymph node status, ECOG PS, PD-L1 expression level, and primary tumour location.

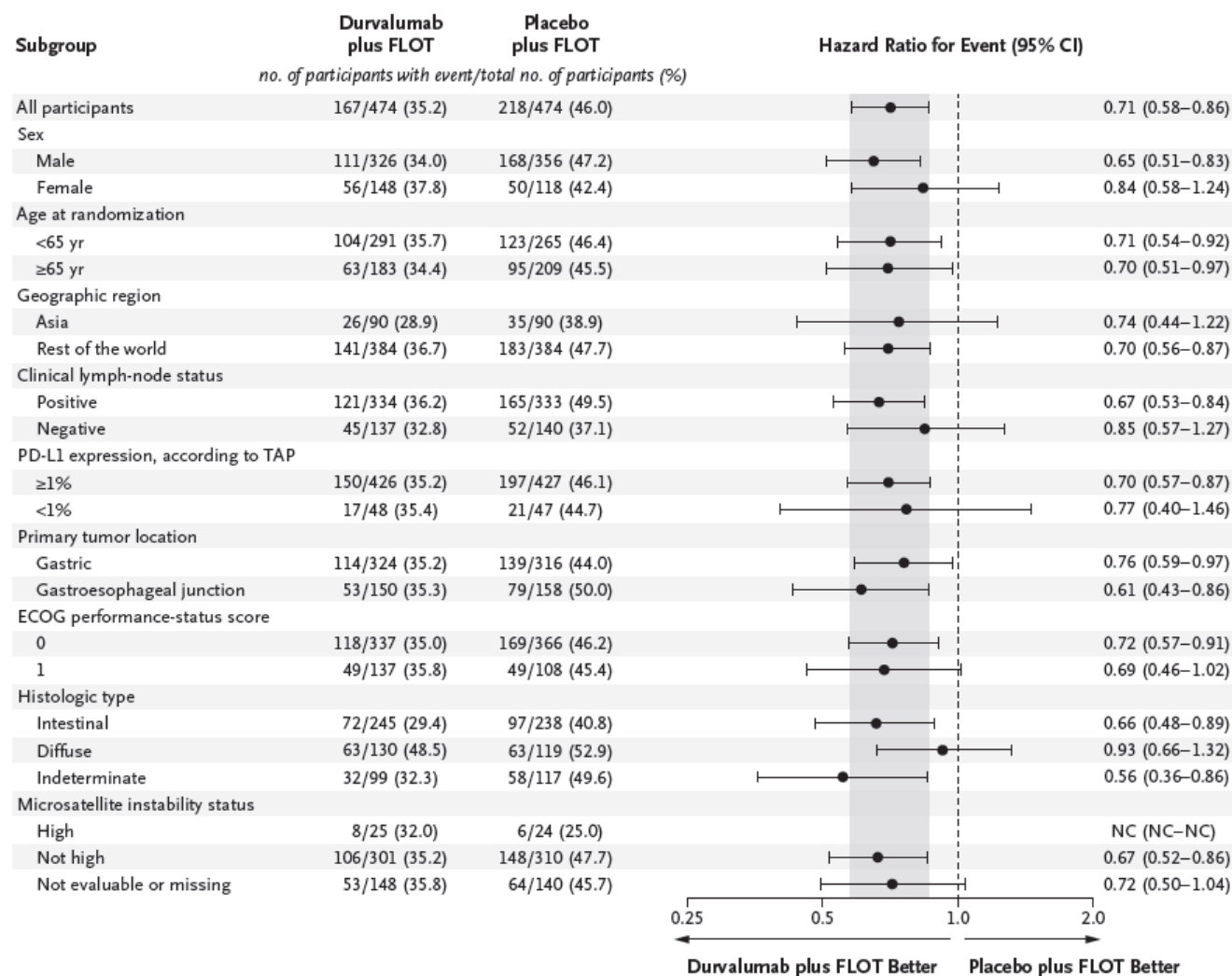
It should be noted, however, that the study was not powered for individual subgroup comparisons, and no multiplicity adjustments were made. As expected in a subgroup analysis, a degree of variability was observed across all subgroups, particularly in the subgroups with a smaller number of patients and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

2.8.1 EFS

At the December 2024 DCO, the estimated HRs for EFS were in favour of the D-FLOT arm compared with the control arm across all pre-specified subgroups (HRs for D-FLOT arm vs. control arm <1), indicating improvements in EFS across subgroups (Figure 14). Clinical expert consultations indicated that the observed efficacy and safety profile of D-FLOT supports its use in all eligible patients, with no subgroups excluded from clinical consideration.⁵ Although the EFS benefit for D-FLOT was not statistically significant in all subgroups, this is likely attributable to the study not being powered for individual subgroup comparisons and to the limited patient numbers and low event rates in certain subgroups.

Of note, subgroup analyses of PD-L1 expression status were highly consistent with the whole patient population (all patients HR: 0.71, tumour area positivity ≥1% HR: 0.70, tumour area positivity <1% HR: 0.77), highlighting that PD-L1 expression is not anticipated to substantially impact the efficacy of D-FLOT.³⁶ This is aligned with UK clinical expert feedback, which suggested that D-FLOT should be recommended and used in patients regardless of their PD-L1 expression status.⁵

Figure 14. EFS subgroup analysis (using BICR for RECIST v1.1) (FAS, December 2024 DCO)



Footnotes: Median EFS calculated using the KM technique. HRs calculated using a stratified Cox proportional hazards for the ITT population and unstratified Cox proportional hazards for subgroups. *Groups are pre-defined IEMTs and not part of the SAP.

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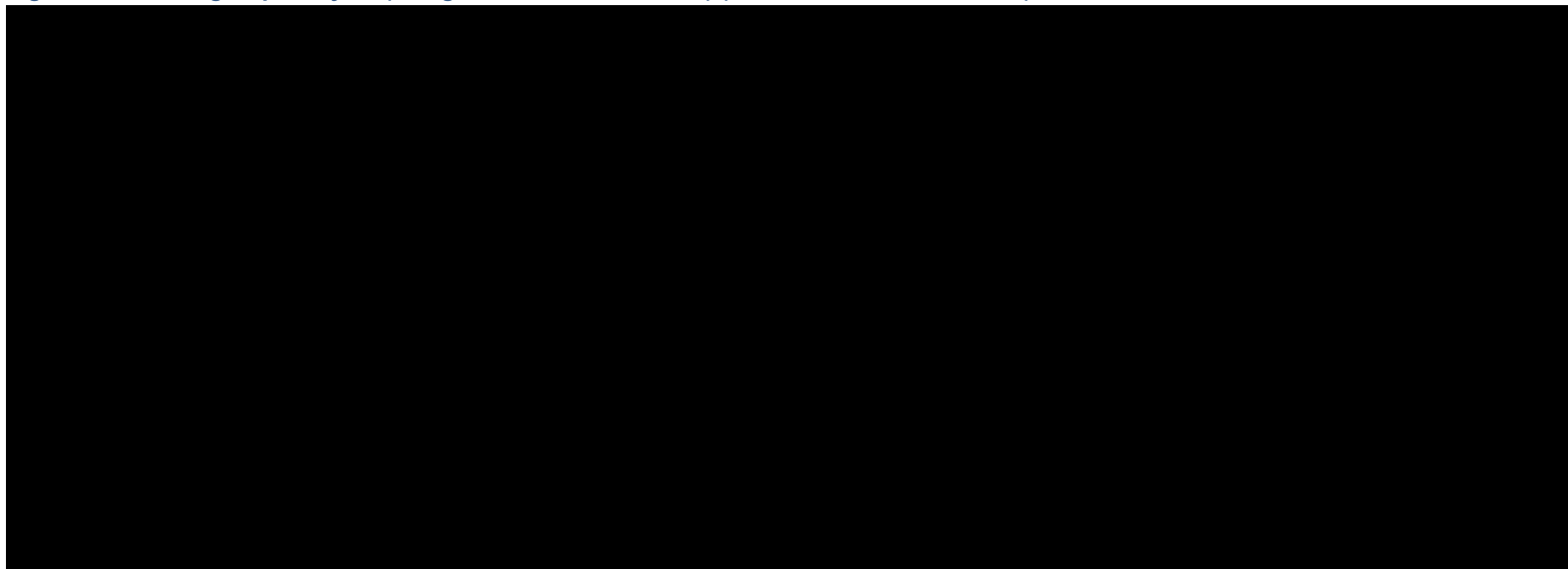
Abbreviations: BICR: blinded independent central review; CI: confidence interval; DCO: data cut-off; ECOG PS: Eastern Cooperative Oncology Group Performance Status; EFS: event-free survival; FAS: full analysis set; GOJ: gastro-oesophageal junction; HR: hazard ratio; IA: interim analysis; IEMTs: important events of medical terminology; ITT: intention-to-treat; KM: Kaplan-Meier; PD-L1: programmed death-ligand 1; RECIST: Response Evaluation Criteria in Solid Tumour; SAP: statistical analysis plan; TAP: tumour area positivity score.

Source: Janjigian et al. 2025.¹⁰⁹

2.8.2 OS

As seen in the main OS analysis in the FAS, there was trend towards improved OS for patients in the D-FLOT arm compared to the control arm across all pre-specified subgroups analysed (Figure 15). Subsequent subgroup analyses of the OS data from DCO3, recently presented at ESMO 2025, were consistent with DCO2, with HRs showing a numerical benefit in favour of D-FLOT across all clinically relevant pre-specified subgroups and a statistically significant benefit in some subgroups.¹¹² The study was not powered for individual subgroup comparisons, and observed variability in subgroups with limited patient numbers or low event rates may account for the absence of statistical significance in some subgroups.

Figure 15. OS subgroup analysis (using BICR for RECIST v1.1) (FAS, December 2024 DCO)



Footnotes: CI was calculated using a profile likelihood approach. The size of circle is proportional to the number of events. Grey band represents the 95% CI for the all-patients HR. Patients provide a tumour tissue sample at screening to determine PD-L1 expression level using the TAP scoring method.

Abbreviations: BICR: blinded independent central review; CI: confidence interval; DCO: data cut-off; ECOG PS: Eastern Cooperative Oncology Group Performance Status; FAS: full analysis set; GOJ: gastro-oesophageal junction; HR: hazard ratio; KM: Kaplan-Meier; OS: overall survival; PD-L1: programmed death-ligand 1; RECIST: Response Evaluation Criteria in Solid Tumour; TAP: tumour area positivity score.

Source: AstraZeneca Data on File (MATTERHORN Clinical Study Report; 2025; Figure 10, P129).³⁶

2.9 *Meta-analysis*

This section is not applicable as no pooling of trials was undertaken.

2.10 *Indirect and mixed treatment comparisons*

As described in Section 2.3.1, the control arm of the MATTERHORN trial (placebo + perioperative FLOT) is representative of the SoC in this indication in UK clinical practice and UK clinical experts unanimously agreed that it represents the only comparator to D-FLOT in this appraisal.⁵ Given this, the MATTERHORN trial provides a clinically relevant comparator for evaluating durvalumab when administered perioperatively in combination with FLOT. The comparative effectiveness of perioperative D-FLOT vs. SoC can therefore be assessed based on direct evidence from the MATTERHORN trial and no indirect comparisons are required.

2.11 *Adverse reactions*

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

At the time of the December 2024 DCO, 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 SAS, comprising 944 patients who received at least one dose of study treatment (n=475 patients in the D-FLOT arm and n=469 patients in the control arm). Unless otherwise stated, safety data presented below are for the overall study period.

2.11.1 *Treatment exposure*

The duration of treatment exposure at the time of the December 2024 DCO is summarised below.³⁶ All patients in both treatment arms had completed (or discontinued) adjuvant treatment and had also completed the safety follow-up period; all patients remaining in the study are in survival follow-up.¹⁰⁹

Durvalumab or placebo

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

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

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 (median total duration of exposure to durvalumab vs. placebo was ■■■ months in both arms).³⁶

The mean relative dose intensity (RDI) was ■■■% for durvalumab and ■■■% for placebo (for patients with dosing in both the neoadjuvant and adjuvant periods).³⁶

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FLOT

The exposure to any FLOT chemotherapy in the overall study was similar across both arms. The median actual duration of exposure to any FLOT component was 3.68 months in each arm.

- In the **neoadjuvant period**, the median actual duration of exposure to any FLOT was the same in both arms (■■■ months)
- In the **adjuvant period**, the median actual duration of exposure to any FLOT was the same in both arms (■■■ months)

Number of treatment cycles (durvalumab, placebo and FLOT)

A summary of the number of treatment cycles in the SAS received is provided in Table 18.³⁶

- In the **neoadjuvant period**, the median number of treatment cycles was 2.0 in both arms. Each cycle comprised 1 dose of durvalumab or placebo and 2 doses of FLOT. The median number of cycles received of any FLOT were 2.0 in both arms.¹¹⁹
- In the **adjuvant period**, the median number of treatment cycles was 12.0 in both arms. Each cycle comprised 1 dose of durvalumab or placebo.¹¹⁹ The median number of cycles received of any FLOT was in both arms.¹⁰⁹

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.¹⁰⁹

Table 18. Number of treatment cycles received in the MATTERHORN trial (SAS, December 2024 DCO)

	D-FLOT (n=475)		Control + FLOT (n=469)	
	Durvalumab	FLOT	Placebo	FLOT
Median number of neoadjuvant cycles ^a	2.0	2.0	2.0	2.0
Median number of adjuvant cycles ^b	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	■■■	■■■■■	■■■	■■■■■
Cycle 1 Day 15	■■■	■■■■■	■■■	■■■■■
2 cycles	461 (97)	462 (97.3)	451 (96)	452 (96)
Cycle 1 Day 1	■■■	■■■■■	■■■	■■■■■
Cycle 1 Day 15	■■■	■■■■■	■■■	■■■■■
Number of adjuvant cycles, n (%)				
≥1 cycle	361 (76)	354 (75)	349 (74)	345 (74)
≥2 cycles	348 (73)	318 (67)	336 (72)	319 (68)
≥3 cycles ^c	343 (72)	N/A	331 (71)	N/A
12 cycles	246 (52)	N/A	240 (51)	N/A

Footnotes: ^a Median number of FLOT treatment cycles is reported in terms of full cycles, each comprising two FLOT administrations on Days 1 and 15. The CSR reports values based on individual administrations rather than full cycles; ^b 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. ^c Only applicable for durvalumab and placebo (maximum cycles of adjuvant FLOT is 2 cycles [4 doses])

Abbreviations: DCO: data cut-off; FLOT: 5-fluorouracil, leucovorin, oxaliplatin, and docetaxel; N/A: not available; SAS: safety analysis set.

Sources: AstraZeneca Data on File (MATTERHORN Clinical Study Report; Table 37, P178–179),³⁶ Janjigian et al. ASCO 2025.¹¹⁹

2.11.2 Dose interruptions, delays and reductions

Dose interruptions, delays, and reductions for durvalumab, placebo, and FLOT are reported in Appendix K.4 for the overall study, neoadjuvant and adjuvant phases, and for adjuvant monotherapy with durvalumab or FLOT. UK clinical experts validated that in clinical practice, if patients are struggling to tolerate FLOT chemotherapy, it is common for them to have their dose reduced, rather than switching to an alternate chemotherapy regimen.

2.11.3 Overview of AEs in MATTERHORN

The incidences of AEs of any cause and possibly related to treatment at the time of DCO2 (December 2024) across the overall treatment period are summarised below and in Appendix K.4.

³⁶ An overview of AEs leading to dose modifications, common AEs, SAEs and TEAEs with an outcome of death is provided in the subsequent sections.

In summary:

- The majority of patients reported an AE of any cause (99.2% vs. 98.7% in the durvalumab vs. control arms, respectively)¹⁰⁹
- Similar proportions of patients experienced a maximum Grade 3 or 4 AE of any cause in each arm (71.6% vs. 71.2% in the D-FLOT and control arms, respectively).¹⁰⁹ SAEs were reported by 48.2% and 44.1% of patients in the D-FLOT and control arms, respectively¹⁰⁹
- Maximum Grade 3 or 4 AEs possibly related to any study treatment (i.e., treatment-related AEs [TRAEs]) occurred in similar proportions in both arms (59.6% vs 59.1% in the D-FLOT and control arms, respectively).¹⁰⁹ Maximum Grade 3 or 4 AEs possibly related to durvalumab or placebo were similar in each arm (████% vs. █████% in the D-FLOT and control arms, respectively), and were lower than the maximum Grade 3 or 4 AEs possibility related to FLOT (at least one component) (████% vs. █████%), which were also similar between arms³⁶
- A lower proportion of patients experienced maximum Grade 3–4 AEs, AEs leading to discontinuation and infusion-related reactions in the adjuvant monotherapy period [durvalumab/placebo monotherapy] compared to the neoadjuvant and overall adjuvant periods, which include FLOT treatment.³⁶ This suggests that FLOT may contribute to the AEs experienced in the neoadjuvant and overall adjuvant periods
- The proportion of patients with AEs leading to discontinuation of any study treatment was higher in the D-FLOT arm vs. the control arm (29.9% vs. 22.8%)¹⁰⁹
- As may be expected, the proportion of patients with immune-mediated AEs was higher in the D-FLOT arm vs. the control arm (23.2% vs. 7.2%).¹⁰⁹ These were mostly low grade and were

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generally manageable and/or reversible with appropriate medical management per standard management guidelines

- AEs leading to surgery not being performed were rare, and similar in both arms (0.6% in the D-FLOT arm vs. 0.4% in the control arm)¹⁰⁹

Overall, durvalumab in combination with FLOT chemotherapy as neoadjuvant and adjuvant treatment followed by adjuvant durvalumab monotherapy demonstrated a tolerable and manageable safety profile, consistent with the established safety profile of the individual agents and resectable GOA.³⁶ The most frequently reported AEs in the overall study were aligned with the known toxicities of FLOT, and were similar across the two treatment arms. The combination of durvalumab and FLOT did not result in an increased frequency or severity of known chemotherapy-related toxicities or known durvalumab-related toxicities.³⁶

No new safety concerns were identified for durvalumab when given in combination with FLOT chemotherapy. In addition, the nature and severity of AEs reported for the D-FLOT arm during the adjuvant monotherapy period were consistent with the established safety profile of durvalumab monotherapy.¹⁰⁹

2.11.4 Common AEs

In the overall treatment period, the most frequently reported AEs (reported by >20% of patients in either arm) in both arms for the overall study were nausea, neutropenia, alopecia, decreased appetite, fatigue, vomiting, anaemia, neutrophil count decreased, peripheral sensory neuropathy (known adverse drug reactions of FLOT chemotherapy); diarrhoea and abdominal pain (known adverse drug reactions of both durvalumab and FLOT chemotherapy (Table 19). The frequency of these AEs was similar between treatment arms.

The AEs reported more frequently in the D-FLOT arm vs. the control arm (>5% difference between arms) were rash (13.7% vs. 7.2%, respectively), pruritus (10.7% vs. 5.3%, respectively), and pyrexia (20.0% vs. 15.1%, respectively) (Table 19). These AEs were mostly low grade in severity (Grade 1 or 2) and are consistent with the known adverse drug reactions of durvalumab.

Table 19. Summary of most common all-cause AEs of any Grade (reported in ≥10% of patients in any treatment arm) in the overall treatment period (SAS, December 2024 DCO)

AE (MedDRA preferred term)	Number (%) of patients ^a	
	D-FLOT arm (n=475)	Control arm (n=469)
Patients with any AE, n (%)	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)

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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)

Footnotes: 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 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). PTs are presented by order of decreasing frequency in the D-FLOT arm. ^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.

Abbreviations: AE: adverse event; COVID-19: coronavirus-19; CTCAE: Common Terminology Criteria for Adverse Events; DCO: data cut-off; EFS: event-free survival; IP: investigational product; MedDRA: Medical Dictionary for Regulatory Activities; PT: preferred term; SAS: safety analysis set.

Source: Janjigian et al. 2025.¹⁰⁹

2.11.5 Maximum Grade 3 or 4 AEs

For the overall study, a similar proportion of patients in the D-FLOT and control arms had one or more AEs of maximum Grade 3 or 4 (71.6% vs. 71.2%, by treatment arm, respectively) (Table 20).¹⁰⁹ The nature and incidence of AEs of maximum Grade 3 or 4 for the overall study were comparable and balanced between the arms (<5% difference between arms).¹⁰⁹

Table 20. 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, December 2024 DCO)

	Number (%) of patients ^a	
AE (MedDRA preferred term)	D-FLOT arm (n=475)	Control 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: ^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.

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Abbreviations: AE: adverse event; COVID-19: coronavirus-19; CTCAE: Common Terminology Criteria for Adverse Events; DCO: data cut-off; EFS: event-free survival; IP: investigational product; MedDRA: Medical Dictionary for Regulatory Activities; PT: preferred term; SAS: safety analysis set.
Source: Janjigian et al. 2025.¹⁰⁹

2.11.6 Serious AEs

At the time of the December 2024 DCO, SAEs of any cause occurring in the overall treatment period were reported in 48.2% of patients in the D-FLOT arm and 44.1% of patients in the control arm.³⁶ The SAEs reported were consistent with the disease under investigation, as well as the established safety profile of the individual agents, durvalumab and FLOT chemotherapy.

The most common SAE in both treatment arms was pneumonia, occurring in ■■■% and ■■■% of patients in the D-FLOT and control arms, respectively.³⁶

Table 21. Summary of most common SAEs (reported in ≥1% of patients in any treatment arm) in the overall treatment period (SAS, December 2024 DCO)

	Number (%) of patients ^a	
AE (MedDRA preferred term)	D-FLOT arm (n=475)	Control arm (n=469)
Patients with any SAE, n (%)	229 (48.2)	207 (44.1)
Pneumonia	■■■	■■■
Febrile neutropenia	■■■	■■■
Neutropenia	■■■	■■■
Vomiting	■■■	■■■
COVID-19	■■■	■■■
Diarrhoea	■■■	■■■
Pyrexia	■■■	■■■
Pulmonary embolism	■■■	■■■
Septic shock	■■■	■■■
Gastrointestinal anastomotic leak	■■■	■■■
Ileus	■■■	■■■
Device related infection	■■■	■■■
Dysphagia	■■■	■■■
Nausea	■■■	■■■
Abdominal pain	■■■	■■■
Anaemia	■■■	■■■
Colitis	■■■	■■■
Sepsis	■■■	■■■
Decreased appetite	■■■	■■■
Pneumonia aspiration	■■■	■■■
Intestinal obstruction	■■■	■■■
Neutrophil count decreased	■■■	■■■
Failure to anastomose	■■■	■■■

Footnotes: 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 D-FLOT arm by PT. Patients with multiple events in the same PT are counted only once in that PT.

Abbreviations: AE: adverse event; COVID-19: coronavirus-19; CTCAE: Common Terminology Criteria for Adverse Events; DCO: data cut-off; EFS: event-free survival; IP: investigational product; MedDRA: Medical Dictionary for Regulatory Activities; PT: preferred term; SAS: safety analysis set.

Source: AstraZeneca Data on File (MATTERHORN Clinical Study Report; Table 57, P251–252).³⁶ Janjigian et al. 2025.¹⁰⁹

2.11.7 Deaths

At the December 2024 DCO, in the overall study, the proportion of deaths reported in each arm for the FAS were 145 (30.6%) patients in the D-FLOT arm and 176 (37.1%) patients in the control arm.¹⁰⁹

In the overall study, a total of 24 participants (5.1%) in the D-FLOT arm and 20 participants (4.3%) in the control arm had adverse events that led to death.¹⁰⁹ AEs with an outcome of death possibly related to any study treatment were uncommon, with occurrences in 3 participants (0.6%) and 2 participants (0.2%) in the D-FLOT and control arms, respectively.³⁶

Table 22. Summary of deaths in overall study (SAS; December 2024 DCO)

Category, n (%)	D-FLOT arm (n=475)	Control arm (n=474)
Total number of deaths	145 (30.6)	176 (37.1)
Safety analysis set, n	475	469
AE with outcome of death	24 (5.1)	20 (4.3)
Possibly related to durvalumab or placebo	3 (0.6)	1 (0.2)
Possibly related to FLOT	3 (0.6)	2 (0.4)

Abbreviations: AE: adverse event; DCO: data cut-off; FAS: full analysis set; FLOT: 5-fluorouracil, leucovorin, oxaliplatin, and docetaxel; GC: gastric cancer; GOJC: gastro-oesophageal junction cancer; IA: interim analysis; SAE: serious adverse event; TEAE: treatment-emergent adverse event.

Source: AstraZeneca Data on File (MATTERHORN Clinical Study Report; Table 53, P245).³⁶ Janjigian et al. 2025.¹⁰⁹

2.11.8 AEs leading to dose modification

For the overall study at the December 2024 DCO, the proportions of patients with AEs leading to dose delays or infusion interruptions of durvalumab or placebo were █% in the D-FLOT arm vs. █% in the control arm.³⁶ The most frequently reported AEs (>5% of patients in either arm) leading to infusion interruption/delay of durvalumab or placebo were neutropenia (█% vs. █%), neutrophil count decreased (█% vs. █%), and COVID-19 (█% vs. █%) (in the D-FLOT arm and control arm, respectively).³⁶ A summary of AEs leading to dose delays and modifications in the overall study period is presented in Table 20.

The proportions of patients with AEs leading to delay in starting adjuvant treatment were █% in the D-FLOT arm vs. █% in the control arm, and those with AEs preventing the start of adjuvant therapy after completed surgery were █% in the D-FLOT arm vs. █% in the control arm, with no specific trends were observed.³⁶

Table 23. Summary of AEs in the overall study leading to dose modifications (SAS, December 2024 DCO)

	Number (%) of patients	
	D-FLOT arm (n=475)	Control arm (n=469)
AEs leading to dose modification in the overall study period		
Any AE leading to durvalumab or placebo dose delay ^a	██████	██████
Neutropenia	██████	██████
Neutrophil count decreased	██████	██████
COVID-19	██████	██████
Any AE leading to FLOT dose delay or interruption ^a	██████	██████
Neutrophil count decreased	██████	██████
Diarrhoea	██████	██████
Any AE leading to FLOT dose delay ^a	██████	██████
Neutropenia	██████	██████
Neutrophil count decreased	██████	██████
Any AE leading to FLOT dose reduction ^a	██████	██████
Neutropenia	██████	██████
Diarrhoea	██████	██████
Neutrophil count decreased	██████	██████
Nausea	██████	██████

Footnotes: ^a The most frequently reported AEs (>5% in either arm) leading to dose modification.

Abbreviations: AE: adverse event; D-FLOT: durvalumab plus FLOT; FLOT: 5-fluorouracil, leucovorin, oxaliplatin and docetaxel.

Source: AstraZeneca Data on File (MATTERHORN Clinical Study Report).³⁶

2.12 Ongoing studies

The final data cut-off (DCO3) for OS occurred on 1st September 2025 and results from DCO3 were presented at the ESMO 2025 Congress. Due to timing of data availability from DCO3, DCO1 and DCO2 form the evidence base for this submission. The findings from DCO3 show that outcomes are consistent with the current data package provided and demonstrate a statistically significant OS benefit for D-FLOT vs perioperative FLOT (HR: 0.78; 95% CI: 0.63, 0.96; p=0.021).^{36, 112}

There are no further ongoing trials that are of relevance to perioperative D-FLOT in the target indication.

2.13 Interpretation of clinical effectiveness and safety evidence

2.13.1 Principal findings from the clinical evidence base

The pivotal evidence base for D-FLOT is provided by the MATTERHORN trial, a global Phase III, randomised, multi-centre, double-blind, placebo-controlled trial examining the efficacy and safety of durvalumab in combination with FLOT chemotherapy as neoadjuvant and adjuvant treatment, followed by adjuvant durvalumab monotherapy for the treatment of adults with resectable GOA.^{115, 116}

The data presented in this submission are from DCO1 (1st February 2023 DCO) for pCR data, and DCO2 (20th December 2024 DCO) for all remaining endpoints.³⁶ The final data cut-off for OS (DCO3) occurred on 1st September 2025 and results from DCO3 were presented at the ESMO 2025 Congress; due to timing of data availability from DCO3, this submission is based on data from DCO1 and DCO2.^{109, 112}

Efficacy

At the time of the December 2024 DCO, and overall data maturity of 40.6%, the MATTERHORN trial met its primary endpoint, demonstrating a clinically meaningful and statistically significant improvement in EFS in the D-FLOT arm compared with the control arm (HR: 0.71; 95% CI: 0.58, 0.86; $p < 0.001$), representing a 29% reduction in the risk of an EFS event.³⁶ UK clinical experts validated that these results are clinically meaningful and demonstrate the potential of D-FLOT to represent a treatment that would displace perioperative FLOT chemotherapy alone as the current SoC in clinical practice.⁵

The benefit of D-FLOT is additionally supported by secondary endpoints. At the December 2024 DCO, there was a strong trend towards improved OS in patients that received D-FLOT compared to control, which was sustained through the follow-up period (HR: 0.78; 95% CI: 0.62, 0.97; 2-sided $p = 0.025$). As noted in Section 2.12, OS data from DCO3 (presented at the ESMO 2025 Congress) are consistent with the current evidence base, including a statistically significant OS benefit of D-FLOT vs the control arm at DCO3 (HR: 0.78; 95% CI: 0.63, 0.96; $p = 0.021$).^{36, 112} These results support the aforementioned survival benefits of D-FLOT compared to perioperative FLOT chemotherapy.

In addition to EFS and OS, the MATTERHORN trial evaluated a wide range of clinically relevant endpoints, including pCR, MFS and DSS, providing a multidimensional assessment of the benefit of D-FLOT compared to perioperative FLOT in patients with resectable GOA. Benefits shown in these endpoints complement those already detailed for EFS and OS. At DCO1, the MATTERHORN trial met the key secondary endpoint of pCR rate showing that treatment with D-FLOT resulted in a statistically significant improvement in pCR rate compared with placebo + FLOT (OR: 3.08 [95% CI: 2.03, 4.67]; $p < 0.001$).³⁶ At DCO2, clinically meaningful and statistically significant improvements in MFS (HR [REDACTED] [95% CI: [REDACTED] and DSS (HR [REDACTED] [95% CI: [REDACTED]) were also observed at the time of DCO2 for the D-FLOT arm compared to the control arm..

An improvement in pathological downstaging was observed, with more patients in the D-FLOT arm achieving ypT downstaging and N0 ([REDACTED]% and [REDACTED]%, respectively) compared with placebo + FLOT ([REDACTED]% and [REDACTED]%, respectively).³⁶ Clinicians validated pathological downstaging as a relevant

measure of treatment response, with particular value in patients with bulky tumours who may otherwise be unsuitable for resection.

With regard to PROs, EORTC QLQ-C30 and EORTC QLQ-STO22 + IL38 results demonstrated that treatment with D-FLOT did not adversely affect patient function and symptom burden.³⁶ The clinically meaningful deterioration compared to baseline observed in both arms during the cycles immediately following surgery, return to non-meaningful levels compared to baseline during the adjuvant period.³⁶ Overall, these PRO data show that the addition of durvalumab to FLOT does not negatively impact patients' HRQoL.³⁶

Safety

At the December 2024 DCO, perioperative D-FLOT demonstrated a tolerable and manageable safety profile and did not preclude patients from undergoing surgery or from continuing to receive their planned adjuvant treatment.³⁶ As surgery remains the cornerstone of curative-intent treatment in GOA, it is critical that the addition of durvalumab to SoC does not compromise surgical feasibility or timing. Importantly, the addition of neoadjuvant durvalumab to FLOT did not impact the ability of patients to undergo and complete surgery compared to placebo + FLOT (90.9% and 90.3%, respectively, attempted surgery and 86.9% and 84.4%, respectively, completed surgery).¹⁰⁹ AEs leading to surgery not being performed were balanced between arms, reported in 0.6% and 0.4% of patients in the D-FLOT and control arms, respectively.³⁶

The nature and incidence of maximum Grade 3/4 AEs were comparable across treatment arms and AEs reported with a higher frequency in the D-FLOT arm were consistent with the known adverse drug reactions of durvalumab (e.g., rash and pruritus) and were generally of low severity (Grade 1 or 2).³⁶ Most commonly reported AEs were neutropenia, neutrophil count decreased, diarrhoea, and nausea which were effectively managed with dose delays and interruptions.³⁶ Treatment discontinuation was observed in 29.9% of patients in the D-FLOT arm and 22.8% of patients in the control arm.³⁶

UK clinical experts agreed that the MATTERHORN safety data indicate that D-FLOT is tolerable, and they are familiar with managing the expected AEs associated with both FLOT chemotherapy and durvalumab. Consequently, these AEs should not pose a challenge for routine clinical services and are anticipated to have minimal impact on patients.⁶ Overall, these data reflect a favourable benefit-risk profile of D-FLOT compared to control + FLOT.

Conclusion

The totality of the evidence from the MATTERHORN trial supports the extensive benefits of D-FLOT over perioperative FLOT chemotherapy to both delay disease progression and prevent recurrence in patients with resectable GOA, while maintaining favourable surgical outcomes and preserving patients' quality of life, thus addressing the existing unmet needs of resectable GOA patients.

2.13.2 Strengths and limitations of the clinical evidence base

Strengths of the clinical evidence base

Robust trial design and generalisability to UK population

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The MATTERHORN trial was robustly designed (double blinded and perioperative FLOT + placebo controlled) and included a large number of patients (N=948), providing sufficient statistical power to detect clinically meaningful differences between treatment arms, evenly distributed between treatment arms (N=474 in both the D-FLOT and control arms).³⁶

The MATTERHORN trial is considered generalisable to the UK clinical practice. The trial included eight centres (32 patients) in the UK and enrolled patients with baseline characteristics that are considered representative of the UK resectable GOA population. The feedback received from the UK-based clinical experts indicate consensus that the MATTERHORN trial population is representative of the standard NHS practice.^{5, 36}

Head-to-head comparison with current SoC

The MATTERHORN trial provides a pivotal head-to-head comparison with the SoC in the UK for patients with resectable GOA, perioperative durvalumab. The effectiveness of perioperative D-FLOT vs. SoC can be assessed based on direct evidence and no indirect comparisons are required. The availability of direct evidence enhances the certainty of the benefit provided by perioperative D-FLOT vs perioperative FLOT, supporting both its evaluation by NICE and its adoption in resectable GOA treatment pathway as the new SoC.

Multidimensional evidence base (pCR, MFS, DSS, safety, HRQoL) and consistency across subgroups

In addition to EFS and OS, the MATTERHORN trial evaluated a wide range of clinically relevant endpoints, including pCR, MFS and DSS, providing a multidimensional assessment of the benefit of D-FLOT compared to perioperative FLOT in patients with resectable GOA. Benefits shown in these endpoints complement those already observed in EFS and OS, offering greater certainty on the value of perioperative durvalumab.

Moreover, EFS and OS benefits were observed across all subgroups, including disease stage at baseline and PD-L1 expression status at baseline, therefore demonstrating the robustness of the benefit of D-FLOT compared to SoC across the resectable GOA patient population.³⁶

Limitations of the clinical evidence base

This submission is informed by DCO2 of the MATTERHORN trial. At DCO2, OS had not yet reached statistical significance, a common challenge in early-stage, curative settings where extended follow up is typically required to demonstrate OS differences. While this does not preclude the primary endpoint results from being practice changing, it may introduce uncertainty during NICE's assessment.

However, this limitation has now been addressed by DCO3, which was recently presented at the ESMO 2025 Congress; with additional follow up versus DCO2, D-FLOT demonstrated a statistically significant OS benefit vs SoC, consistent with the favourable trend observed at DCO2 (HR: 0.78; 95% CI: 0.63, 0.96; p=0.021).^{36, 112}

2.13.3 Conclusions

Unmet need addressed by D-FLOT

The introduction of current SoC, perioperative FLOT chemotherapy, improved the outcomes for patients with resectable GOA.⁷ In spite of this, the outcomes for patients with GOA remain poor, the majority of patients with GC ultimately die due to their cancer returning or progressing. with an estimated 5-year OS of 45%.^{7,31, 32, 98}

Once patients' disease progresses to the advanced/metastatic stage, treatment with curative intent is no longer an option and systemic therapy, including IO treatment offers only a modest life-prolonging effect of weeks to months.^{31, 32, 98} Disease recurrence also has a highly detrimental impact on patients' HRQoL, which worsens as the disease and the severity of symptoms advances.⁷⁶⁻⁷⁸ Disease recurrence therefore remains a significant challenge for patients with GOA and their clinicians. Novel treatment regimens that enhance the efficacy of FLOT and improve long-term disease control in the resectable GOA setting are essential for improving patient survival rates and the chances of disease cure.⁴⁴

The combination of IO therapies with chemotherapy holds particular potential. This lies in the ability of the IO to prime anti-tumour immunity in the neoadjuvant setting and sustain immunosurveillance in the adjuvant setting, improving anti-tumour responses and eliminating micro-metastatic disease.⁴⁴ However, clinical data highlight the challenges of achieving this in practice and the importance of combining IO therapy with the appropriate chemotherapy regimen, perioperative FLOT. As highlighted in Section 1.3.3, recent Phase III clinical trials in the resectable GOA setting, such as KEYNOTE-585 (cisplatin-based chemotherapy plus pembrolizumab) and ATTRACTION-5 (adjuvant nivolumab plus chemotherapy), have not demonstrated statistically significant clinical benefits.^{33, 65}

The compelling results of the MATTERHORN trial make D-FLOT the first and only IO treatment to show meaningful improvements vs. the current SoC in patients with resectable GOA.¹⁰⁹ Perioperative D-FLOT offers the potential to reduce the risk of disease progression and recurrence and therefore increase the chance of cure in this setting.¹⁰⁹ UK clinical experts recognised the MATTERHORN data as clinically meaningful and "practice-changing", highlighting that it is a treatment approach that may also help mitigate the HRQoL burden associated with GOA.⁵

Summary

The results from the MATTERHORN trial have established perioperative durvalumab regimen as a landmark advancement in the management of resectable GOA, validating the hypothesis that perioperative IO therapies in combination with SoC can redefine the treatment paradigm for these patients. Data from the MATTERHORN trial demonstrated that perioperative D-FLOT provides statistically significant and clinically meaningful benefits in EFS and OS (according to DCO3) compared to perioperative FLOT, with the addition of durvalumab to FLOT maintaining patient HRQoL.^{109, 112} Ultimately, perioperative D-FLOT will prevent or delay disease progression and recurrence, without compromising patient HRQoL or their ability to undergo surgery.

The survival benefits demonstrated in the MATTERHORN trial are particularly noteworthy as they were achieved in a direct comparison against the current SoC in the UK, underscoring the additional value that perioperative durvalumab brings to the established treatment approach.³⁶ The robust evidence base from the MATTERHORN trial supports the consideration of perioperative D-

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FLOT as the new SoC for patients with resectable GOA within NHS practice, as also confirmed by UK clinical experts.⁵ **Perioperative D-FLOT has the potential to address a critical unmet need related to poor survival outcomes, disease prognosis and limited efficacious treatments in resectable GOA.**

3 Cost effectiveness

Summary of the cost-effectiveness model

- A semi-Markov state-transition model (STM) was developed to determine the cost-effectiveness of perioperative D-FLOT compared to the current SoC for patients with resectable GOA (perioperative FLOT chemotherapy)
- A time horizon of ■■■ years was used with a one-month cycle length (i.e., 4.35 weeks; with half-cycle correction included) to reflect the lifetime of this patient population
- The model consisted of consisting of three mutually exclusive health states: (i) event-free (EF), (ii) recurred disease (RD), and (iii) death, the occupancy of which was derived from data from the MATTERHORN trial³⁶
- To align with the anticipated curative outcomes for patients with resectable GOA, a five-year cure timepoint was applied to both treatment arms, based on the NICE committee preferred cure assumptions in a previous appraisal in early stage GOJ adenocarcinoma (TA746) and validation from UK clinical experts^{5, 8}
- Extrapolation of the clinical outcomes derived from EFS data (including time to first recurrence [TFR], time to death [TTDeath] and post-recurrence survival [PRS]) using parametric survival analysis was required to assess the cost-effectiveness of perioperative D-FLOT over the model lifetime horizon
 - In line with NICE TSD 14 and 21 (and determined by a combination of statistical goodness of fit, visual fit and clinical plausibility), the generalised gamma distribution was deemed an appropriate curve choice for the base case extrapolation of transition probability (TP)₁, while the Gompertz distribution was deemed most appropriate for TP₂ and log-logistic for TP₃¹²⁷
 - When combining the base case selections TP₁–TP₃ to reconstruct the MATTERHORN OS for perioperative FLOT chemotherapy, the 3-year OS predicted by the model was ■■■%, consistent with the ■■■% reported in the MATTERHORN trial (December 2024 DCO).³⁶ The 5-year model prediction of OS for the perioperative FLOT chemotherapy arm (■■■%) is also closely aligned with the 5-year OS rate of 45.0% in FLOT-4 trial⁷
- Costs included in the model were: drug acquisition/administration costs, surgery costs, healthcare resource use (HCRU), terminal care costs and AE costs. These were sourced from NHS reference costs 2023–2024, British National Formulary (BNF) and drugs and pharmaceutical electronic market information tool (eMIT)¹²⁸⁻¹³¹
- Overall, given it aligns with UK clinical expert validation and NICE recommendations, utilises data from the MATTERHORN, compares D-FLOT to the SoC in clinical practice and was performed from a UK NHS and Personal Social Services (PSS) perspective, this economic model is considered highly appropriate for decision making

Summary of base case cost-effectiveness results

- The probabilistic and deterministic base case ICERs were £12,508/QALY and £12,416/QALY, respectively (including the commercial access agreement discount for durvalumab) for the comparison of perioperative D-FLOT and perioperative FLOT chemotherapy
- Additionally, perioperative D-FLOT was associated with positive incremental life years gained (1.96 LYG and 1.99 LYG for the probabilistic and deterministic base case analyses, respectively) and QALYs (■■■ for both the probabilistic and deterministic analyses) versus perioperative FLOT chemotherapy

Summary of sensitivity and scenario analyses results

- The PSA found the probability of perioperative D-FLOT to be ■ and ■ at a WTP threshold of £20,000 and £30,000 per QALY gained, respectively
- In the DSA, the base case results were found to be robust to uncertainty, with the ICER below ~£20,000 QALY for all model parameters
- Across all scenario analyses performed, the base-case conclusions held, with the ICER for perioperative D-FLOT versus FLOT remaining cost-effective

Conclusion

- Based on an internally and externally validated model that is aligned with UK clinical practice and fit for purpose, the results of the economic analyses demonstrate that perioperative D-FLOT is a cost-effective use of NHS resources.^{5, 132}
- This reflects the improvements in efficacy demonstrated by perioperative D-FLOT versus perioperative FLOT chemotherapy in the MATTERHORN trial (Section 2.6), and demonstrates that perioperative D-FLOT will address the unmet need for a more efficacious and tolerable treatment option that increases the likelihood of cure in the resectable GOA setting³⁶

3.1 Published cost-effectiveness studies

An SLR was conducted to identify published economic evaluations of interventions for patients with resectable GOA, as well as evidence relating to the HRQoL and utility (humanistic burden) and cost/resource use (economic burden) that may be of relevance to this submission. As per Section 2.1, the SLR was originally run in November 2024 with a subsequent update in June 2025.

The update of the SLR was conducted using assistance from AI, building on the methodology accepted in TA962.¹¹³ The Company engaged with NICE and the EAG ahead of submitting this AI-assisted SLR and the approach was in line with the NICE position statement on AI, with the key principles detailed in the NICE position statement adhered to throughout.¹¹⁴ Searches were performed in the MEDLINE, Embase and EconLit databases. Full details of the SLR methodology and results (including identified HRQoL and cost/healthcare resource use [HCRU] studies) are presented in Appendices E, F and G.

A total of 1,712 records across all searches were screened at the title and abstract stage, of which 1,692 records were reviewed at the full-text stage. A total of 1,260 publications were excluded based on title and abstract screening and 432 full-text publications were assessed for eligibility. Of these, a total of 173 publications were excluded, resulting in the inclusion of 268 full-text publications (including the addition of 9 relevant conference publications and HTA reports). Further prioritization criteria were applied which resulted in 83 publications for extraction. In total, publications reporting on economic evaluations (N=16), HCRU and costs (N=24) and HRQoL (N=46) were identified for inclusion and extraction.

3.2 Economic analysis

No relevant economic evaluations comparing perioperative D-FLOT with perioperative FLOT chemotherapy alone from a UK perspective were identified in the economic SLR. As such, a *de novo* cost utility analysis was conducted for the purpose of this evaluation. This model is described in detail below.

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The aim of the economic analysis was to determine the cost-effectiveness of D-FLOT as adjuvant and neoadjuvant treatment, followed by adjuvant durvalumab monotherapy (perioperative D-FLOT) versus current SoC (i.e. perioperative FLOT chemotherapy; as detailed in Section 1.3.3). The analysis was conducted from the perspective of the NHS and PSS.

The economic evaluation was approached as follows, in line with the NICE reference case:¹³²

- Health outcomes were measured in terms of both life years gained (LYG) and QALYs
- The primary outcome measure for the economic evaluation was the incremental cost effectiveness ratio (ICER; cost per QALY gained) for the comparison of perioperative D-FLOT versus perioperative FLOT chemotherapy
- Clinical effectiveness for D-FLOT with perioperative FLOT chemotherapy was measured through the risk of disease recurrence, as well as the risk of death for patients before and after disease recurrence (see Section 3.3)
- All relevant costs were considered, including treatment acquisition costs, administration costs, AEs costs, costs associated with subsequent treatments, healthcare resource use and end-of-life costs (Section 3.5)
- The model used a lifetime time horizon (equivalent to [REDACTED] years). The discount rate was set to 3.5% for both costs and benefits.

3.2.1 Patient population

The population of interest in the model is adult patients with resectable GOA (Stage II to IVA, according to AJCC staging 8th edition). This is aligned with the decision problem for this submission (see Section 1.1), the population enrolled in the MATTERHORN trial (see Section 2.3.1), and the anticipated license wording for perioperative D-FLOT in this indication ([REDACTED]).

A summary of the patient baseline characteristics used in the economic model are presented in Table 24. The characteristics of patients entering the model were based on the baseline characteristics of patients in the FAS of the MATTERHORN trial reported at DCO2 (December 2024).³⁶ Age and sex were included in the model to determine general population mortality and utility inputs. Additionally, mean body weight, height and body surface area (BSA) were included in the model to calculate drug acquisition costs (Section 3.5.1).

Table 24: Summary of baseline characteristics used in the economic model

Characteristics	Population	Source
Mean age at baseline, years (SE)	[REDACTED]	MATTERHORN trial FAS (December 2024 DCO) ³⁶
Proportion of male patients, %	71.9	
Mean body weight, kg (SE)	[REDACTED]	
Mean height, cm (SE)	[REDACTED]	
Mean BSA, m ² (SE)	[REDACTED]	

Abbreviations: BSA: body surface area; DCO: data cut-off; SE: standard error.

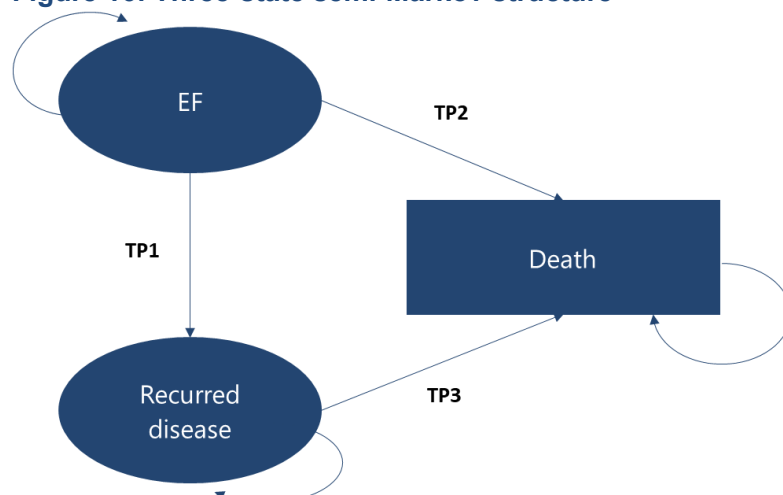
3.2.2 Model structure

Overview of model structure

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A *de novo* semi-Markov STM was built in Microsoft Excel to address the decision problem. The semi-Markov model consisted of three mutually exclusive health states: (i) EF, (ii) RD, and (iii) death (Figure 16). Patients enter the model in the EF health state and are assumed to be treated with either perioperative D-FLOT or perioperative FLOT chemotherapy and remain there until they experience disease recurrence (TP1) or death (TP2). From the RD health state, patients can only transition to the death state (TP3). The occupancy of health states over time was derived from data from the MATTERHORN trial (December 2024 DCO).³⁶

Figure 16: Three-state semi-Markov structure



Abbreviations: EF: event-free; TP: transition probability.

Justification for choice of model structure

A STM was selected because the economic SLR detailed in Section 3.1 indicated that the majority of cost-effectiveness analyses in the resectable GOA disease setting adopted an STM structure (either Markov or semi-Markov models). A separate targeted literature search of previous cost-effectiveness studies submitted to HTA bodies (see Appendix M), which expanded the scope to include neoadjuvant/adjuvant therapies in other cancer types, highlighted that the majority of economic models (16/17 appraisals) in the neoadjuvant/adjuvant and perioperative GOA disease setting were STMs (Markov and semi-Markov models). These appraisals included the NICE appraisal of adjuvant nivolumab in GOJ adenocarcinoma (TA746).⁸ Although adjuvant nivolumab is not a relevant comparator to perioperative D-FLOT in this appraisal it is methodologically appropriate to model GOJ adenocarcinoma and resectable GOA using the same model structure in order to capture all relevant treatment effects.

The predominant usage of STMs in this disease setting is expected because patients have the potential to experience long-term survival and cure.⁸ The selected STM model structure permits the robust modelling of long-term survival while accounting for cure; while the use of a PSM in this context would be subject to additional uncertainty.

Additionally, as detailed in Section 1.3.4, patients with GOA who experience disease recurrence have an increased risk of mortality; the incidence of disease recurrence and time to death events in patients with GOA are therefore linked.⁹⁹ As such, the use of a STM is most appropriate because it allows the relationship between disease mortality and progression to be modelled, unlike a PSM.

Unlike traditional Markov models, a semi-Markov STM allows TPs to vary over time in both the EF and RD health states, reflecting the disease course of resectable GOA. It is implausible that the

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incidence of disease recurrence or death will be constant over time for patients with resectable GOA and therefore a semi-Markov structure, which permits time-variance, was considered the most appropriate modelling approach. The use of a semi-Markov model can improve accuracy and transparency around the mechanisms and processes underpinning the results that are generated using extrapolation and facilitate the conduction of meaningful sensitivity analyses.¹³³ It also removes the necessity for priori assumptions that may be required for a traditional Markov model.

The three-state model was considered appropriate for the decision problem, as both the structure and health states are in line with the clinical pathway in the UK and are consistent with previous NICE TAs in early-stage cancer, including indications similar to GOA, such as oesophageal cancer.^{8, 134-137} Of note, UK clinical experts consulted by the Company confirmed that the three-state semi-Markov model depicted in Figure 16 was an appropriate and sensible structure to model resectable GOA, and was appropriate for a curative intent treatment such as perioperative D-FLOT.⁵

Additionally, the three-state model in this submission relies solely on direct clinical evidence from the MATTERHORN trial, which, as validated by clinical experts, included a patient population that is relevant to UK clinical practice and the decision problem addressed by this submission. MATTERHORN provided efficacy, treatment completion rates, safety, and HRQoL inputs for the health economic model.¹⁰⁹

Features of the economic analysis

Following NICE guidelines, the model was developed from a UK NHS and PSS perspective.¹³⁸ A summary of the key features of the economic analysis for perioperative D-FLOT compared with perioperative FLOT chemotherapy alone is presented below in Table 25.

Table 25: Features of the economic analysis

Factor	Chosen values	Justification
Model structure	A semi-Markov state transition model, with three health states: EF, RD, and death	The approach is in line with the clinical pathway for the patient population and consistent with the previous NICE technology appraisal of adjuvant nivolumab treatment in resectable GOJ adenocarcinoma (TA746). ⁸ While adjuvant nivolumab is not a relevant comparator to perioperative D-FLOT in this indication, the similarity in tumour biology, treatment objectives, and recurrence dynamics of GOJ adenocarcinoma and resectable GOA makes it technically appropriate to model both disease areas using the same structural approach. UK clinical experts consulted by the Company additionally validated that the model structure is appropriate for a curative intent treatment such as perioperative D-FLOT. ⁵
Perspective	UK NHS and PSS	Aligned with NICE Process and Methods guidance [PMG] 36. ¹³⁸
Time horizon	Lifetime (■■■■ years)	The horizon of ■■■■ years is calculated as 100 years – patients' age at baseline (■■■■ years; as per the MATTERHORN trial). ³⁶ Less than 1% of patients in the perioperative D-FLOT arm remain alive at ■■■■ years in the economic analysis so is considered long enough to capture capture all appropriate costs and outcomes.
Cycle length	1 month (4.35 weeks)	This cycle length is considered to be sufficiently granular to accurately capture changes in costs and outcomes over the time horizon.
Half-cycle correction	Applied in the base case analysis	Half-cycle correction was applied to adjust for timing of state transitions throughout the cycle, in line with the recommended best practice. ¹³⁹
Discounting	3.5% for costs and benefits	A UK base case (in line with NICE PMG36). ¹³⁸
Clinical effectiveness – EF	Based on time to first recurrence and time to death as first event from the MATTERHORN perioperative	Time to first recurrence and time to death as first event (i.e. before recurrence) are the clinical outcomes

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	durvalumab and control arms for the model intervention and comparator, respectively	representing the two possible transitions from the EF health state. Together, the events captured by these clinical outcomes represent EFS, which was the primary endpoint in the MATTERHORN trial (see Section 2.3.1). This approach therefore utilises data from the pivotal trial for perioperative D-FLOT (MATTERHORN).
Clinical effectiveness – RD	Based on post-recurrence survival data from the MATTERHORN perioperative durvalumab and control arms for the model intervention and comparator, respectively	Post-recurrence survival represents the only possible transition from the RD health state. This approach utilises data from the pivotal trial for perioperative D-FLOT (MATTERHORN).
Utility – EF	MATTERHORN EQ-5D-5L, mapped onto the UK EQ-5D-3L value set, using the NICE preferred mapping algorithm ¹⁴⁰ and capped at the UK general population utility	This mapping was performed as HRQoL was assessed in the MATTERHORN trial using the UK EQ-5D-5L questionnaire and NICE guidelines indicate that the EQ-5D-3L is the preferred value set to assess HRQoL.¹³⁸ The EF health state utility value from MATTERHORN (■■■■■; based on N=10,387 observations) before disease progression/recurrence was slightly higher than the gender and age-adjusted utility value for the UK general population (0.840), and therefore the EF utility value was capped to the UK general population utility. UK clinical experts confirmed as part of the clinical validation exercises that the GPM-capped EF utility value was reasonable, and consistent with their understanding of quality of life in patients with resectable GOA.⁵
Utility – RD	Aligned with the RD health state utility in the NICE appraisal of nivolumab for the adjuvant treatment of patients with OC or GOJC (TA746) ⁸	Low numbers of EQ-5D-5L observations were recorded after progression or recurrence in the MATTERHORN trial (N=■■■■■). Additionally, it is common that many observations of EQ-5D-5L are recorded soon after patients experience progression or recurrence, and therefore may not capture the full HRQoL impact associated with the worsening of patients' disease over time. Consequently, utility

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		values for the RD health state were instead sourced from a second-line OC population, in line with the Committee-accepted approach in the appraisal of nivolumab for patients with OC or GOJC (TA746). ⁸ Specifically, a value of 0.747 was used for the RD health state in the base case analysis for this appraisal, as per TA746, and the prior NICE appraisal of nivolumab in patients with previously treated resectable advanced/recurrent OC (TA707). ⁸ The use of an RD utility value aligned with previous appraisals in a similar disease area ensures consistency in both the modelling approach and decision-making.
Treatment and healthcare resource use costs	NHS reference costs; BNF; eMIT; PSSRU; ¹²⁸⁻¹³¹ published literature, resource utilisation and costs accepted in previous NICE submissions ^{8, 141} The cost of subsequent therapy received in the RD health state are based on those received in the MATTERHORN trial and supplemented with UK clinical expert validation ⁵	These represent widely used and accepted sources of cost and resource use data in NICE appraisals.
AE rates and costs – EF	MATTERHORN trial (Grade 3-4 with incidence $\geq$ 5% in any treatment arm) for perioperative D-FLOT and perioperative FLOT chemotherapy	This approach utilises data from the pivotal trial for perioperative D-FLOT. The inclusion of AEs experienced during the treatment period only (and not subsequent therapies in RD), as well as the criteria for AE grade and incidence are in line with the recent NICE appraisal of pembrolizumab for patients with advanced GOA (TA997). ¹¹⁰
AE rates and costs – RD	Not included	Not including AEs and costs experienced during the RD health state (when patients are not receiving treatment) is in line with the recent NICE appraisal of pembrolizumab for patients with advanced GOA (TA997). ¹¹⁰

Abbreviations: AE: adverse event; BNF: British National Formulary; EF: event-free; EQ-5D-3L: EuroQol 5-Dimension 3-Level; EQ-5D-5L: EuroQol 5-Dimension 5-Level; FLOT: 5-fluorouracil, leucovorin, oxaliplatin, and docetaxel; GC: gastric cancer; GOJC: gastro-oesophageal junction cancer; gastro-oesophageal; HTA: health technology assessment; HRQoL: health-related quality of life; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; PMG: Process and Methods guide; PSS: Personal Social Services; PSSRU: Personal Social Services Research Unit; RD: recurred disease; TA: technology Appraisal; UK: United Kingdom.

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3.2.3 Intervention technology and comparators

Intervention

The intervention included in the cost-effectiveness model is D-FLOT, as neoadjuvant and adjuvant treatment, followed by adjuvant durvalumab monotherapy, as a treatment for patients with resectable GOA. The treatment protocols for the intervention in the model are consistent with the MATTERHORN trial (see Section 2.3.1), and the draft SmPC-recommended posology (see Appendix A).

Durvalumab is administered as an intravenous infusion over one hour at a fixed dose of 1,500 mg in combination with FLOT chemotherapy every four weeks for up to two cycles prior to surgery (neoadjuvant period), followed by D-FLOT every four weeks for up to two cycles after surgery and then as durvalumab monotherapy every four weeks for 10 additional cycles (adjuvant period). Durvalumab is administered until the patient experiences disease progression, disease recurrence, exhibits unacceptable toxicity, or reaches a maximum of 12 cycles after surgery.

Comparator

In line with the decision problem outlined in Section 1.1, perioperative FLOT chemotherapy alone represents the comparator in this submission, given this regimen reflects the current SoC treatment in UK clinical practice for patients with resectable GOA. Feedback from UK clinical experts confirmed that perioperative FLOT is the only appropriate comparator to perioperative D-FLOT in this setting.⁵

Perioperative FLOT chemotherapy is modelled in line with the MATTERHORN trial (placebo + FLOT control arm) as an intravenous infusion on days one and 15 every four weeks for two cycles as neoadjuvant therapy and for two cycles as adjuvant therapy (up to four cycles).¹¹⁷

3.3 Clinical parameters and variables

3.3.1 Data inputs and assumptions

The economic model is a semi-Markov STM comprising three mutually exclusive health states: EF, RD and death. The MATTERHORN trial (December 2024 DCO) was used as the primary source of clinical data to inform the economic model transition probabilities (Table 26) between each health state.¹⁰⁹ Transition probabilities were derived from parametric survival analyses of individual patient-level (IPD) data from the MATTERHORN trial for both perioperative D-FLOT and perioperative FLOT chemotherapy, consistent with standard approaches for modelling time-to-event outcomes.^{109, 133} The MATTERHORN trial population, intervention and comparator are aligned with those defined in the decision problem, supporting the appropriateness of the trial data for informing the economic analysis.

Specifically, EFS data from the MATTERHORN trial were split into time to first recurrence (TFR) and time to death as first event (TTDeath) to estimate transition probabilities from the EF health state to the RD health state (i.e., EF to RD) and to the death health state (i.e., EF to death), respectively. For RD to death, MATTERHORN post-recurrence survival (PRS) data were utilised.

As such, the clinical outcomes used in the model to calculate the time patients spent in each model health state were as follows:

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- **TFR:** defined as the time from randomisation until recurrence or progression (as per EFS), but with censoring for deaths that occur before recurrence or progression (**TP1**).
- **TTDeath:** defined as time from randomisation to death as a first EFS event, with censoring for all other EFS events (e.g. recurrence or progression) (**TP2**).
- **PRS:** defined as time from first recurrence or progression event to death, in patients who have experienced recurrence or progression as an EFS event (**TP3**).

Table 26: Key clinical inputs and transition probabilities

Transition	Clinical outcomes	Application
EF to RD (TP1)	EFS divided into: • TFR • TTDeath^a	Informed time spent alive and event free
EF to Death (TP2)		
RD to Death (TP3)	PRS ^a	Informed time spent alive after disease recurrence

Footnotes: ^aData constrained by UK general population mortality for TP2 and TP3.¹⁴²

Abbreviations: EF: event-free; EFS: event-free survival; PRS: post-recurrence survival; RD: recurred disease; TFR: time to first recurrence; TP: transition probability; TTDeath: time to death as a first event; UK: United Kingdom.

Extrapolation methods

The follow-up period for MATTERHORN was shorter than the model time horizon (■ years) and therefore extrapolation of the clinical outcomes derived from MATTERHORN (i.e. TFR, TTDeath and PRS) using parametric survival analysis was required to assess the cost-effectiveness of perioperative D-FLOT over a lifetime time horizon.

In accordance with standard practice and guidance from the NICE Decision Support Unit (DSU), the extrapolation of the survival data was conducted using a range of standard parametric survival models including exponential, Weibull, Gompertz, log-normal, log-logistic, generalised gamma and gamma.¹⁴³ Diagnostic tests (including log-cumulative hazard plots, Schoenfeld residuals and quantile-quantile plots) were conducted to assess the proportionality of hazards between treatment arms as well as the suitability of proportional hazard (PH) or accelerated failure time models.

General population mortality

Parametric distributions were constrained to ensure that the hazards of the extrapolations could not be less than the general population mortality (GPM) hazards, using the latest UK life tables (based on data from 2021–2023).¹⁴² The GPM adjustment was applied only to TP2 and TP3.

Selection criterion for best fit survival models

The analytical process consisted of testing the various statistical distributions and assessing their fits over the observed trial period and beyond to ensure reliable projection of the clinical outcomes. The best-fitting distributions were selected in line with NICE DSU guidance on the analysis of survival outcomes for economic evaluations alongside clinical trials.¹⁴⁴ The selection of the most appropriate distributions was based on the following:

- Statistical goodness of fit (Akaike Information Criteria (AIC)/ Bayesian Information Criterion (BIC) of extrapolations to observed KM data from the MATTERHORN trial
- Visual inspection of the curve fit against the observed KM data from the MATTERHORN trial, and visual inspection of the hazard profiles of the observed MATTERHORN data

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- Clinical plausibility and external validation of long-term predictions

Further discussion of curve selection is detailed in Sections 3.3.2, 3.3.3 and 3.3.4.

Cure assumption

According to ESMO GC guidelines, surgical resection of operable GC is potentially curative.⁶ This is supported by published literature, which notes that the OS of patients with OC has doubled in the previous 20 years, owing to earlier diagnosis and treatment advances.^{145, 146} However, these studies also note that the number of patients who can be cured with surgery alone is inadequate and limited, highlighting the need to combine perioperative FLOT with innovative IO therapies in the resectable GOA setting.^{145, 146}

In the NICE appraisal assessing early-stage oesophageal or GOJC (TA746),⁸ the NICE Committee concluded that cure at 5 years was an appropriate assumption in this setting. To align with anticipated clinical outcomes for patients undergoing curative-intent surgery, and consistent with prior NICE precedent for cure in early-stage OC/GOJC,⁸ the model incorporates a 5-year cure timepoint, which is applied to both treatment arms. Specifically, the model assumes that patients who have not experienced an EFS event (i.e. are still in the EF health state) at 5 years are effectively 'cured'. Figure 8 (Section 2.6.1) shows that the EFS KM curves for both the perioperative durvalumab and control arms in the MATTERHORN trial show signs of plateauing after ~18 months, further supporting the applicability of a cure assumption at 5 years in the model.¹⁰⁹

After this timepoint, it is assumed that patients who are still in the EF health state:

- Are no longer at risk of recurrence (TP1 equals zero)
- Are no longer followed up regularly (do not incur HCRU/monitoring costs)
- Have a risk of death that is equal to that of the general population (TP3 equals GPM)
- Feedback from all UK clinical experts consulted by the Company as part of this appraisal validated that a cure assumption at 5 years was both clinically plausible and highly reflective of UK clinical practice, in which very few patients are estimated to experience disease relapse after this time.⁵ One of the experts specified that they discharge patients with GOA if they have not experienced disease relapse after five years, further supporting the cure assumption at 5 years.⁵

Of note, as part of TA746, clinical experts advised that the mortality rate among patients who were assumed to be 'cured' was expected to be higher than the general population, and therefore an SMR of 1.1 was deemed reasonable in that appraisal.⁸ However, clinical experts consulted by the Company as part of this submission confirmed that the SMR of 1.1 utilised in TA746 is conservative, with the true SMR likely to be lower than 1.1 in UK clinical practice.⁵ Reflective of this feedback, in the base case analysis no SMR (specifically, an SMR of 1.0) is applied; the mortality rate among patients who are considered to be cured beyond 5 years is equal to that of the general population. An SMR of 1.1 (based on the value used to adjust GPM in NICE TA746)⁸ is explored in a scenario analysis (see Section 3.11.3). A further scenario analysis, whereby no cure is assumed, has been conducted as part of this appraisal to assess the impact of the wider cure assumption on the ICER (see Section 3.11.3).

The following sections detail the selection of curve choices for TP1, TP2 and TP3 in the economic analysis. Of note, given the underlying cure assumption, extrapolation of TP1 and TP2 was only required to a 5-year horizon, with KM data available for approximately 4 years of follow-up. Company evidence submission template for durvalumab in combination for neoadjuvant and adjuvant treatment of resectable gastric and gastro-oesophageal junction cancer [ID6374]

up (Sections 3.3.2, 3.3.3 and 3.3.4). As such, the primary consideration in model selection was the ability of candidate parametric distributions to provide the best statistical and visual fit to the observed KM data, given the minimal need for long-term extrapolation beyond the observed period (as discussed further in Section 3.7).

3.3.2 *Modelling of time to first recurrence (TP1)*

Derivation of TP1

TFR data from MATTERHORN, derived from EFS (as assessed by BICR) were utilised to derive transition probabilities for the transition from EF to RD (TP1). As detailed in Section 3.3.1, TFR is defined as the time from randomisation until recurrence or progression (as per EFS) with censoring for deaths that occur before recurrence or progression. Events had occurred in ■■■% and ■■■% patients (December 2024 DCO) in the perioperative FLOT chemotherapy and perioperative D-FLOT arms, respectively.³⁶

PH testing

PH testing was undertaken utilising cumulative hazard plots, log-log plots and Schoenfeld statistics. Based on the assessment of the Schoenfeld residual plot (Figure 18) the PH assumption cannot formally be rejected, with a p-value >0.05 (Schoenfeld statistics: p=0.7368). However, the log cumulative hazard plots, log-odds or log-normal lines are not strictly parallel (Figure 17). The CEM therefore considers individual fits for TFR from the MATTERHORN trial (i.e., parametric distributions were fitted separately to the perioperative D-FLOT and perioperative FLOT chemotherapy arms). This is aligned with NICE guidance,¹⁴³ which notes that separate fits require fewer assumptions than combined fits (e.g. PH during post-trial follow-up) and allow, if appropriate, for different parametric models to be applied to each treatment arm.

Standard parametric distributions (i.e., exponential, Weibull, log-normal, log-logistic, Gompertz, generalised gamma, gamma) were fitted separately to the perioperative D-FLOT and perioperative FLOT chemotherapy trial arms. As detailed below, the selection of parametric fits for each arm was based on statistical fit, visual fit, as well as clinical plausibility.

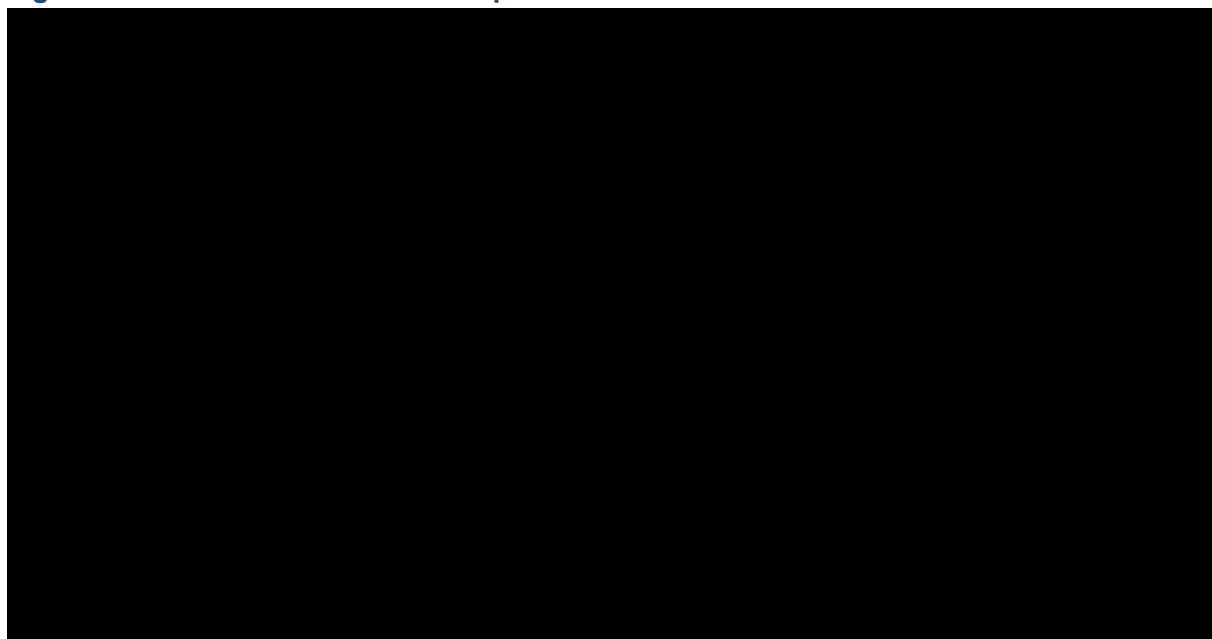
Figure 17. TFR: Log cumulative hazards, log odds and log normal versus log time



Abbreviations: Durva: durvalumab; FLOT: fluorouracil, leucovorin, oxaliplatin and docetaxel; TFR: time to first recurrence.

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Figure 18. TFR: Schoenfeld residual plot



Abbreviations: TFR: time to first recurrence.

Statistical fit

An overview of the AIC scores and BIC scores for each parametric distribution is shown in perioperative D-FLOT (Table 27) and perioperative FLOT chemotherapy (Table 28). Assessment of statistical fit indicated that the generalised gamma distribution provided the best statistically fitting standard parametric curve across AIC/BIC for both treatment arms. The second best fitting curve was the log-normal distribution, based on both AIC and BIC scores.

Table 27: TFR: goodness of fit statistics perioperative D-FLOT (MATTERHORN, FAS)

Model	AIC	AIC rank	BIC	BIC rank
Exponential	██████	5	██████	4
Weibull	██████	6	██████	6
Log-normal	██████	2	██████	2
Log-logistic	██████	4	██████	5
Gompertz	██████	3	██████	3
Generalised gamma	██████	1	██████	1
Gamma	██████	7	██████	7

Footnotes: Bold indicates lowest AIC/BIC value

Abbreviations: AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; FAS: full analysis set; FLOT: Fluorouracil: Leucovorin: Oxaliplatin and Docetaxel; TFR: time to first recurrence.

Table 28: TFR: goodness of fit statistics perioperative FLOT chemotherapy (MATTERHORN, FAS)

Model	AIC	AIC rank	BIC	BIC rank
Exponential		5		5
Weibull		6		6
Log-normal		2		4
Log-logistic		4		3
Gompertz		3		2
Generalised gamma		1		1
Gamma		7		7

Footnotes: Bold indicates lowest AIC/BIC value

Abbreviations: AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; FAS: full analysis set; FLOT: Fluorouracil: Leucovorin: Oxaliplatin and Docetaxel; TFR: time to first recurrence.

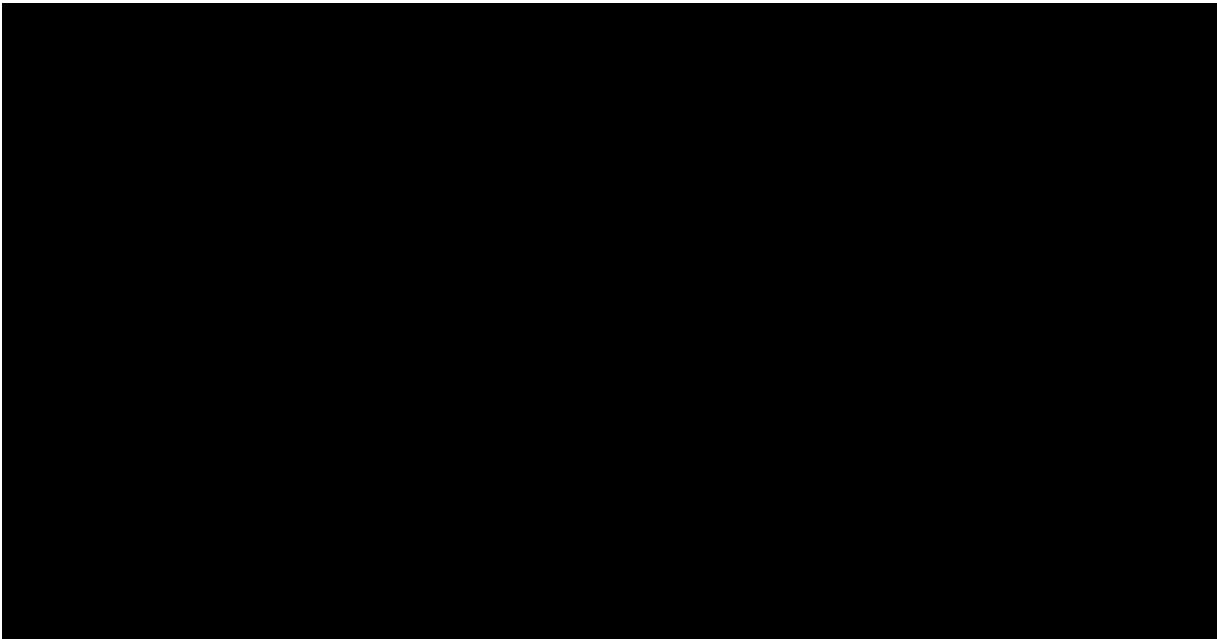
Visual fit

Figure 19 and Figure 20 show the parametric distributions highlighting the visual fit to the observed KM data and long-term predictions for perioperative durvalumab + FLOT and perioperative FLOT chemotherapy, respectively. Survival landmark estimates over a 5-year horizon for each parametric distribution are shown for perioperative durvalumab + FLOT (in Table 29) and perioperative FLOT chemotherapy (in Table 30). These estimates are provided up to 60 months (5 years) due to the underlying 5-year cure assumption detailed in Section 3.3.1.

In terms of visual fit against the KM curves (Figure 19 and Figure 20), the generalised gamma and the log-normal demonstrated the closest alignment.. In the perioperative D-FLOT arm, the Gompertz distribution produced extrapolations broadly consistent with those of the generalised gamma, whereas other distributions tended to underestimate survival from approximately 30 months onwards. The KM curves for perioperative D-FLOT in Figure 19 begin to plateau after approximately 40 months.

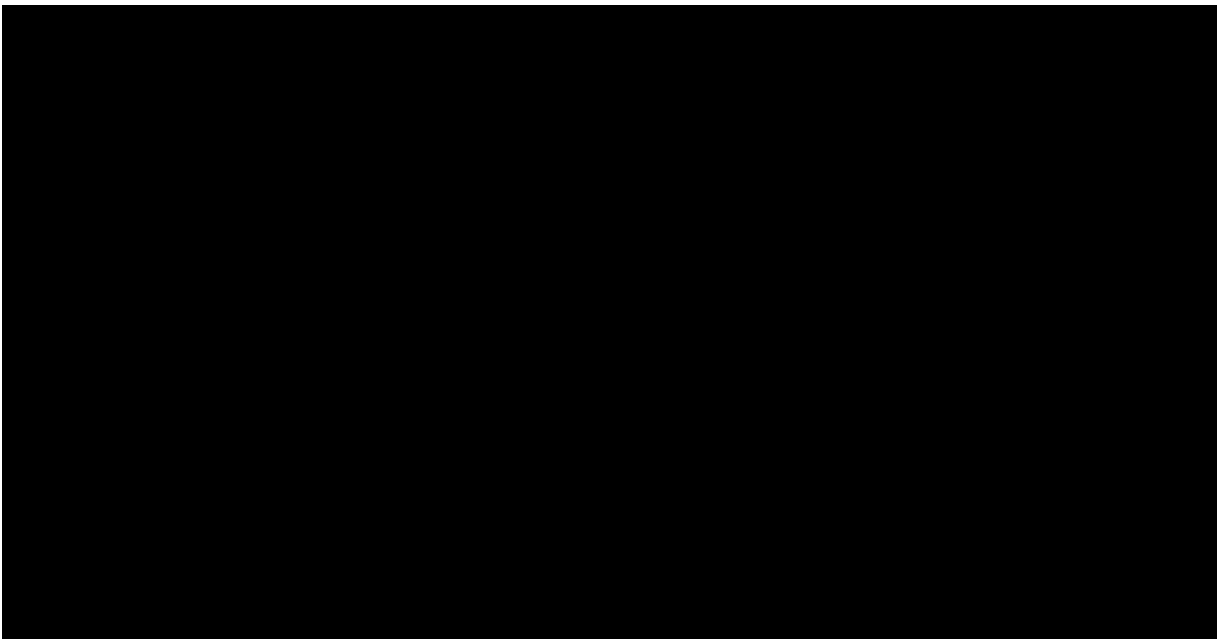
In the perioperative FLOT chemotherapy arm, the predictions using the Gompertz distribution were again consistent with the generalised gamma predictions, with other distributions underestimating survival from approximately 36 months onwards. The KM curves for perioperative FLOT chemotherapy in Figure 20 plateau after approximately 36 months.

Figure 19: TFR: observed vs. predicted for perioperative D-FLOT (MATTERHORN, FAS)



Abbreviations: FAS: full analysis set; FLOT: Fluorouracil: Leucovorin: Oxaliplatin and Docetaxel; KM: Kaplan-Meier; TFR: time to first recurrence.

Figure 20: TFR: observed vs. predicted for perioperative FLOT chemotherapy (MATTERHORN, FAS)



Abbreviations: FAS: full analysis set; FLOT: Fluorouracil: Leucovorin: Oxaliplatin and Docetaxel; KM: Kaplan-Meier; TFR: time to first recurrence.

Table 29: TFR: predictions for perioperative D-FLOT (MATTERHORN, FAS)

Model	1 year	2 years	3 years	5 years

MATTERHORN KM for perioperative D-FLOT				
Exponential				
Weibull				
Log-normal				
Log-logistic				
Gompertz				
Generalised gamma				
Gamma				

Abbreviations: FAS: full analysis set; FLOT: Fluorouracil: Leucovorin: Oxaliplatin and Docetaxel; KM: Kaplan-Meier; TFR: time to first recurrence.

Table 30: TFR: predictions perioperative FLOT chemotherapy (MATTERHORN, FAS)

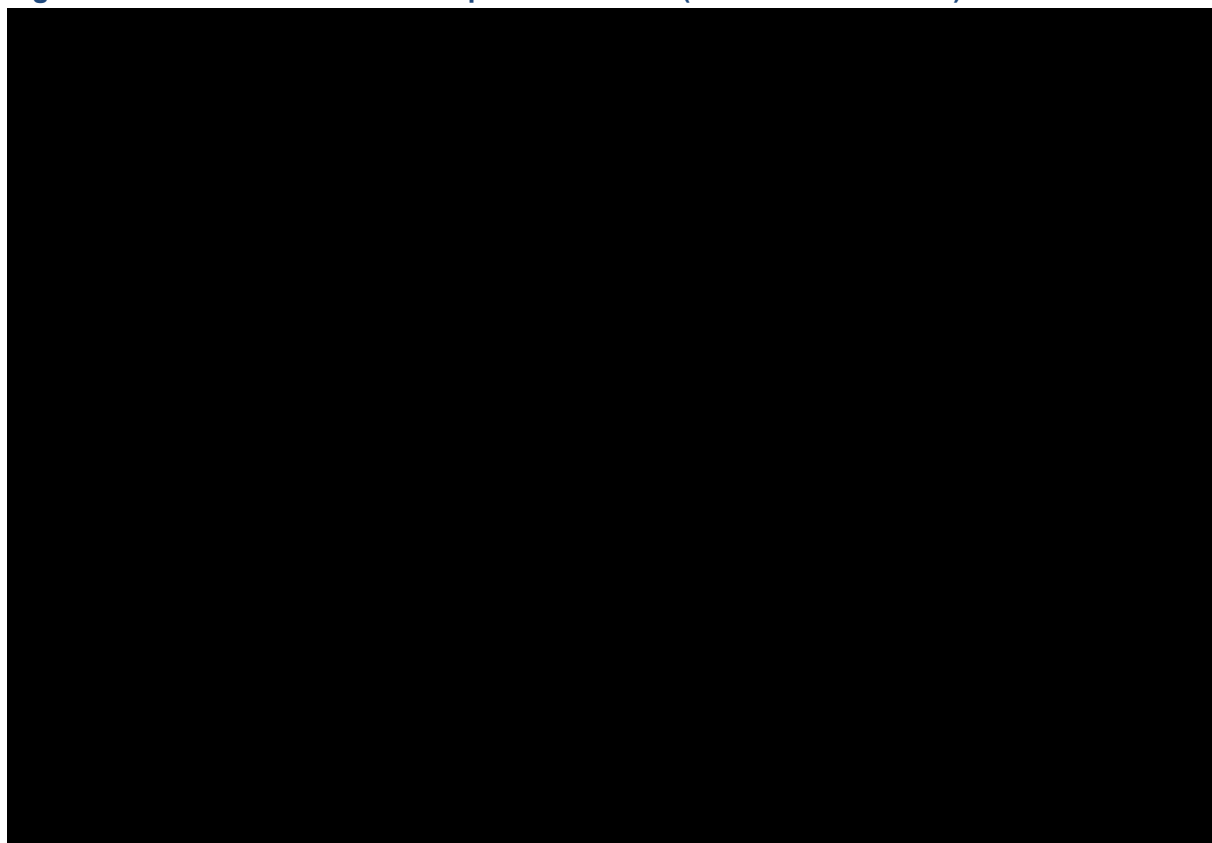
Model	1 year	2 years	3 years	5 years
MATTERHORN KM for perioperative FLOT chemotherapy				
Exponential				
Weibull				
Log-normal				
Log-logistic				
Gompertz				
Generalised gamma				
Gamma				

Abbreviations: FAS: full analysis set; FLOT: Fluorouracil: Leucovorin: Oxaliplatin and Docetaxel; KM: Kaplan-Meier; TFR: time to first recurrence.

Hazard profiles

As shown in Figure 21, the log-normal and the generalised gamma distribution were able to best capture the behaviour of the observed hazards for both treatment arms. The smoothed hazards for both treatment arms in the MATTERHORN trial are observed to decrease over time. Whilst a small uptick is observed in the D-FLOT arm, this is informed by a small number at risk at maximum follow up, and therefore the tail of the hazard should be interpreted with caution.

Figure 21. TFR: Predicted hazards per distribution (MATTERHORN FAS)



Abbreviations: FAS: full analysis set; FLOT: Fluorouracil: Leucovorin: Oxaliplatin and Docetaxel; KM: Kaplan-Meier; TFR: time to first recurrence.

Clinical validation

There was no clear consensus among clinical experts consulted by the Company on the most clinically plausible curve to extrapolate TP1 within the model, however, clinicians stated preference for a curve with a plateau in both arms.⁵

Base case selection

Given the underlying cure assumption, extrapolation of outcomes was only required to a 5-year horizon. As such, with KM data available for approximately █ years of follow-up and the absence of a clear consensus among clinical experts, the primary consideration in model selection for TP1 was the ability of candidate parametric distributions to provide the best statistical and visual fit to the observed KM data. Of note, NICE TSD 14 states that *“fitting different types of parametric model to different treatment arms would require substantial justification, as different models allow very different shaped distributions”*; following assessment of statistical fit, visual fit, and hazard profiles (as well as clinical plausibility), it was considered most appropriate to select the same extrapolation curves across both the intervention and comparator arm for TP1.¹²⁷

Accordingly, the generalised gamma distribution was selected as the base case model for extrapolation of TFR in both treatment arms, reflecting strong statistical and visual alignment with the observed KM data (as well as the observed hazard profiles) for both treatment arms.

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The log-normal distribution, which reflects a more pessimistic estimate of TP1 for both perioperative D-FLOT and perioperative FLOT chemotherapy, was explored in a scenario analysis (Section 3.11.3).

3.3.3 *Modelling of time to death as first event (TP2)*

Derivation of TP2

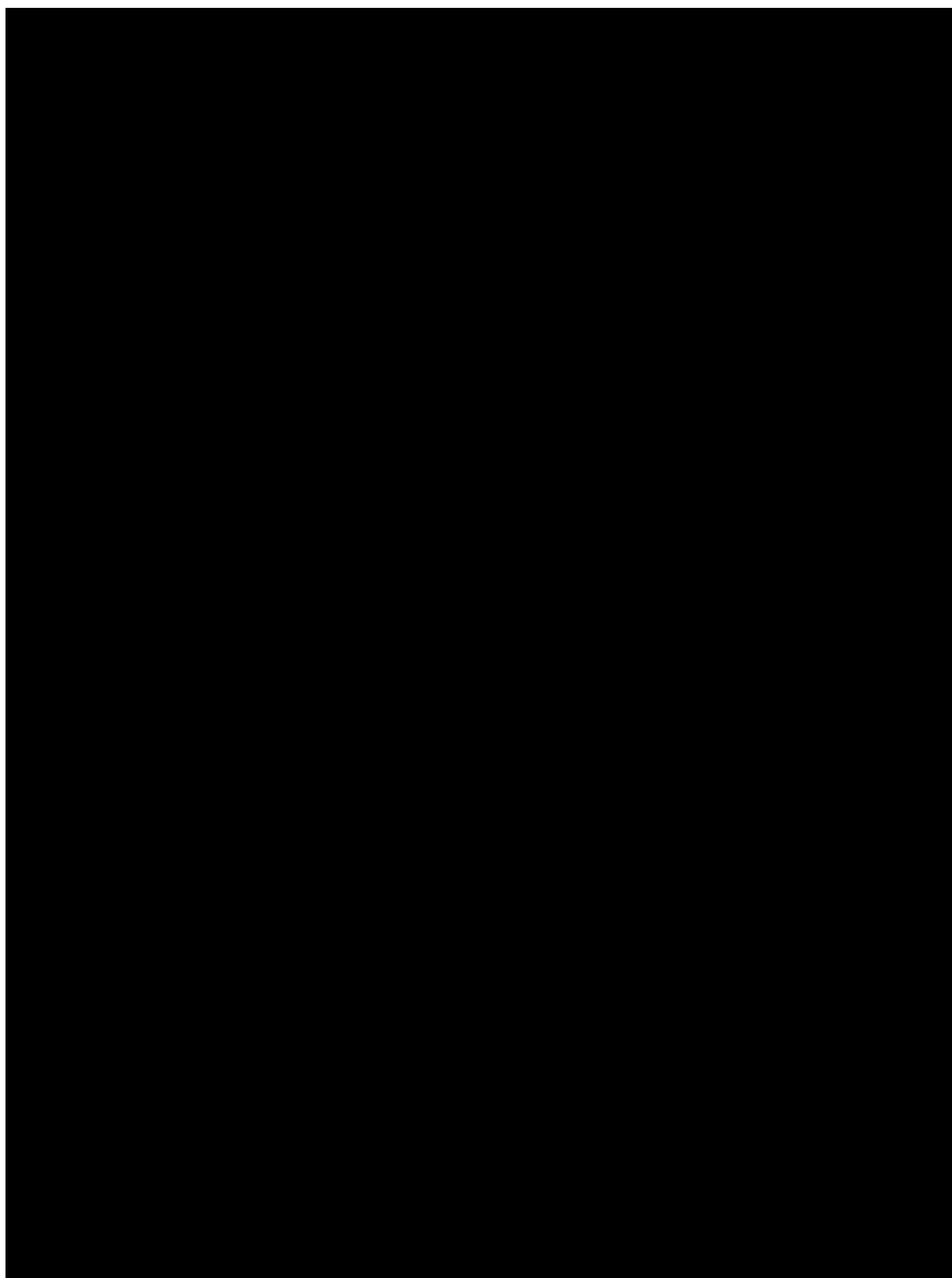
TTDeath as first event from MATTERHORN, derived from EFS (as assessed by a BICR) were utilised to derive transition probabilities for the transition from EF to Death (TP2). As detailed in Section 3.3.1, TTDeath is defined as the time from randomisation to death as a first EFS event, with censoring for all other EFS events (e.g. recurrence or progression). Events had occurred in █% and █% of patients (December 2024 DCO) in the perioperative FLOT chemotherapy and perioperative D-FLOT arms, respectively.³⁶

PH testing

PH testing was undertaken similarly to TP1, by utilising cumulative hazard plots, log-log plots and Schoenfeld statistics. Based on the assessment of the Schoenfeld residual plot (as presented in Figure 23), the PH assumption cannot formally be rejected, with a p-value >0.05 (Schoenfeld statistics: █). However, the log cumulative hazard plots, log-odds or log-normal lines are not strictly parallel. The CEM therefore also considers individual fits for TTDeath from the MATTERHORN trial. This is aligned with NICE guidance on the use of parametric models (detailed in Section 3.3.2).¹⁴³

Specifically, standard parametric distributions (i.e. exponential, Weibull, log-normal, log-logistic, Gompertz, generalised gamma, gamma) were fitted separately on the perioperative D-FLOT and perioperative FLOT chemotherapy trial arms. As detailed below, the selection of parametric fits for each arm was based on statistical fit, visual fit, as well as clinical plausibility.

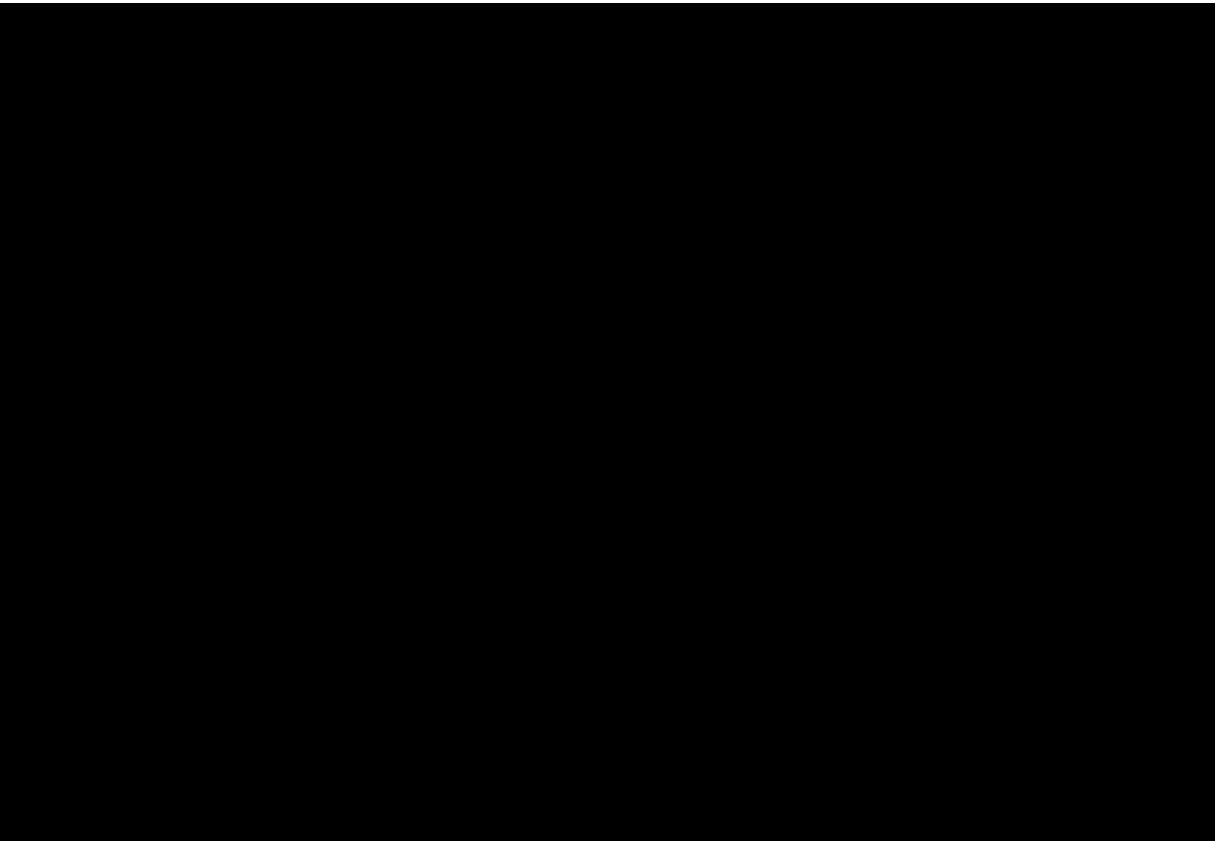
Figure 22: TTDeath: Log cumulative hazards, log odds and log normal versus log time



Abbreviations: Durva: durvalumab; FLOT: fluorouracil, leucovorin, oxaliplatin and docetaxel; TP2: transition probability 2.

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Figure 23: TTDeath: Schoenfeld residual plot



Abbreviations: TP2: transition probability 2.

Statistical fit

An overview of the AIC scores and BIC scores are shown for perioperative D-FLOT (Table 31) and perioperative FLOT chemotherapy (Table 32). Following an assessment of statistical goodness of fit, the log-normal distribution (for perioperative D-FLOT) and the exponential distribution (for perioperative FLOT chemotherapy) were associated with the best statistical fits based on AIC and BIC criteria. It should be noted that all other distributions fell within five AIC points of the best-fitting curve, indicating that each provides a reasonable statistical fit to the data.

Table 31: TTDeath: goodness of fit statistics perioperative D-FLOT (MATTERHORN, FAS)

Model	AIC	AIC rank	BIC	BIC rank
Exponential	■	7	■	2
Weibull	■	5	■	5
Log-normal	■	1	■	1
Log-logistic	■	4	■	4
Gompertz	■	3	■	3
Generalised gamma	■	2	■	7
Gamma	■	6	■	6

Footnotes: Bold indicates lowest AIC/BIC value
Abbreviations: AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; FAS: full analysis set; FLOT: Fluorouracil: Leucovorin: Oxaliplatin and Docetaxel; TTDeath: time to Death at first event.

Table 32: TTDeath: goodness of fit statistics perioperative FLOT chemotherapy (MATTERHORN, FAS)

Model	AIC	AIC rank	BIC	BIC rank
Exponential	■	1	■	1
Weibull	■	5	■	5
Log-normal	■	2	■	2
Log-logistic	■	3	■	3
Gompertz	■	4	■	4
Generalised gamma	■	6	■	6
Gamma	■	5	■	5

Footnotes: Bold indicates lowest AIC/BIC value

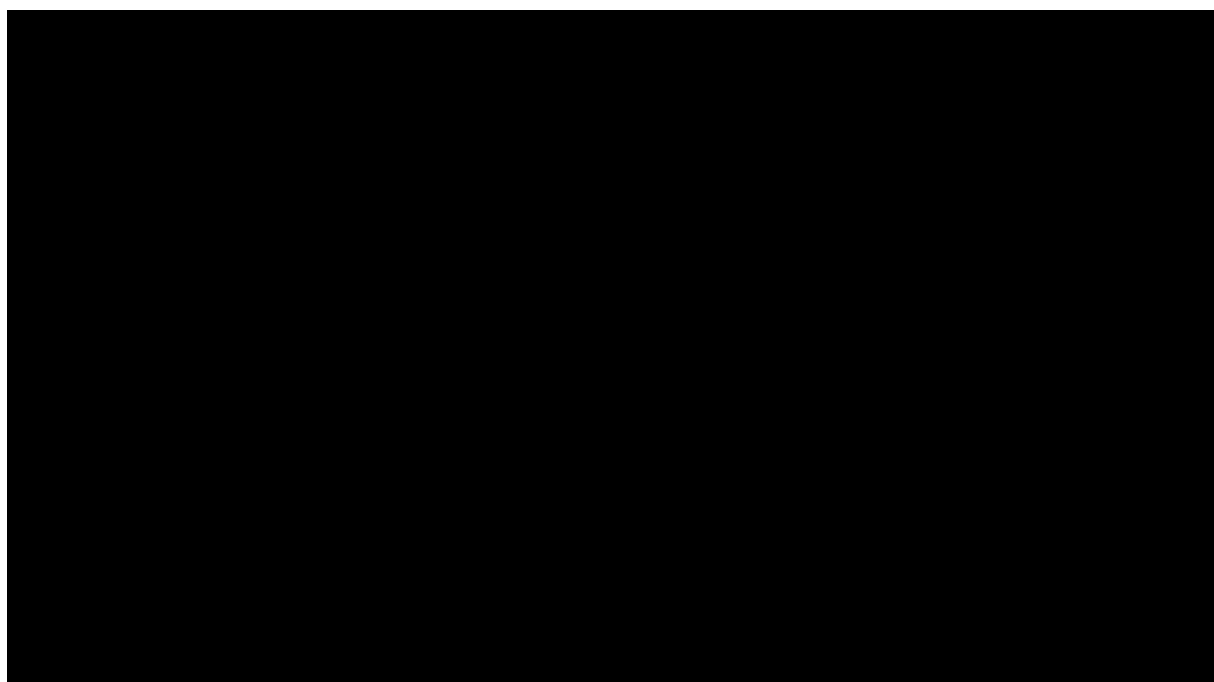
Abbreviations: AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; FAS: full analysis set; FLOT: Fluorouracil: Leucovorin: Oxaliplatin and Docetaxel; TTDeath: time to Death at first event.

Visual fit

Figure 24 and Figure 25 show the parametric distributions (adjusted for general population mortality) highlighting the visual fit to the KM data and long-term predictions for perioperative D-FLOT and perioperative FLOT chemotherapy, respectively. Survival landmark estimates over a 5-year time horizon) for each parametric distribution are shown for perioperative durvalumab + FLOT (in Table 33) and perioperative FLOT chemotherapy (in Table 34). These estimates are provided up to 60 months (5 years) due to the underlying 5-year cure assumption detailed in Section 3.3.1.

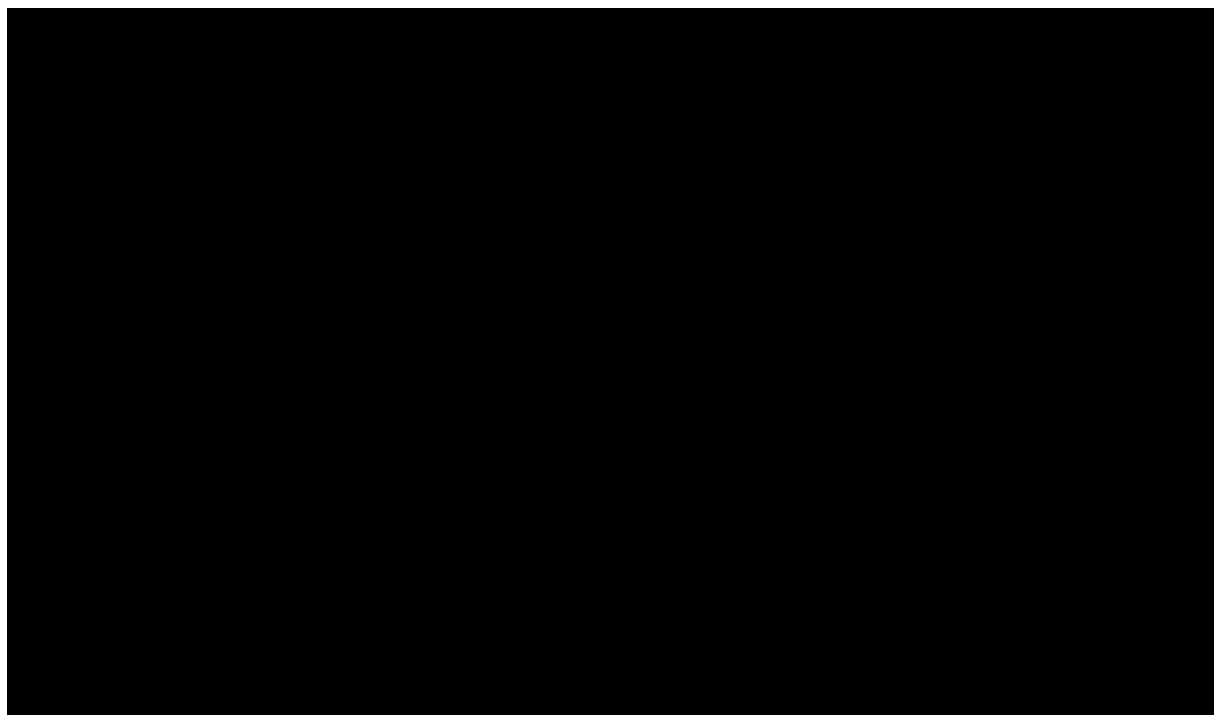
In terms of visual fit against the KM curves (Figure 19 and Figure 20), all curve choices demonstrated good visual fit to the KM data, with very little difference in estimates of TTDeath over the 5 years (pre-cure assumption) across all curves, for both treatment arms. All curves predicted landmark survival similar to the observed survival, although of note, the Gompertz curve provided 3-year estimates of TTDeath (■) which were most closely aligned to the observed MATTERHORN KM curve for perioperative D-FLOT (■).

Figure 24: TTDeath: observed vs. predicted for perioperative D-FLOT (MATTERHORN, FAS) – adjusted for general population mortality



Abbreviations: FAS: full analysis set; FLOT: Fluorouracil: Leucovorin: Oxaliplatin and Docetaxel; KM: Kaplan-Meier; TTDeath: time to Death at first event.

Figure 25: TTDeath: observed vs. predicted for perioperative FLOT chemotherapy (MATTERHORN, FAS) – adjusted for general population mortality



Abbreviations: FAS: full analysis set; FLOT: Fluorouracil: Leucovorin: Oxaliplatin and Docetaxel; KM: Kaplan-Meier; TTDeath: time to Death at first event.

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Table 33: TTDeath: predictions for perioperative D-FLOT (MATTERHORN, FAS) – adjusted for general population mortality

Model	1 year	2 years	3 years	5 years
MATTERHORN KM for perioperative D-FLOT	■	■	■	■
Exponential	■	■	■	■
Weibull	■	■	■	■
Log-normal	■	■	■	■
Log-logistic	■	■	■	■
Gompertz	■	■	■	■
Generalised gamma	■	■	■	■
Gamma	■	■	■	■

Abbreviations: AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; FAS: full analysis set; FLOT: Fluorouracil: Leucovorin: Oxaliplatin and Docetaxel; KM: Kaplan-Meier; TTDeath: time to Death at first event.

Table 34: TTDeath: predictions perioperative FLOT chemotherapy (MATTERHORN, FAS) – adjusted for general population mortality

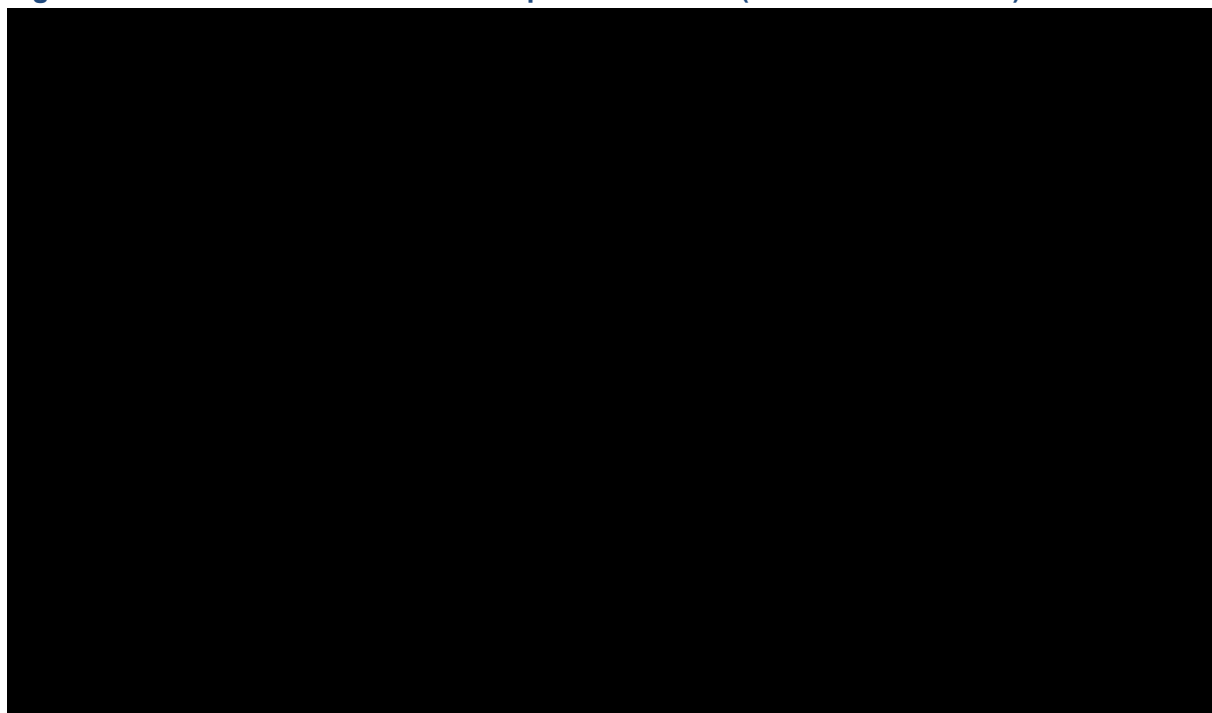
Model	1 year	2 years	3 years	5 years
MATTERHORN KM for perioperative FLOT chemotherapy	■	■	■	■
Exponential	■	■	■	■
Weibull	■	■	■	■
Log-normal	■	■	■	■
Log-logistic	■	■	■	■
Gompertz	■	■	■	■
Generalised gamma	■	■	■	■
Gamma	■	■	■	■

Abbreviations: AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; FAS: full analysis set; FLOT: Fluorouracil: Leucovorin: Oxaliplatin and Docetaxel; KM: Kaplan-Meier; TTDeath: time to Death at first event.

Hazard profiles

Figure 21 presents the predicted hazards for each curve choice for the intervention and comparator. As shown, the observed hazards for both arms gradually decrease over time. The Gompertz distribution was able to best capture the behaviour of the observed hazards, particularly for the perioperative D-FLOT arm. The FLOT arm shows hazards that plateau and then decline. Because only a small number of patients remain at risk toward the end of follow-up, the late period hazard estimates should be interpreted with caution.

Figure 26: TTDeath: Predicted hazards per distribution (MATTERHORN FAS)



Abbreviations: FAS: full analysis set; FLOT: Fluorouracil: Leucovorin: Oxaliplatin and Docetaxel; KM: Kaplan-Meier; TTDeath: time to Death at first event.

Clinical validation

There was no clear consensus among clinical experts consulted by the Company for the curve selection for TP2.⁵ Several curves were raised by clinical experts as most clinically plausible across both arms, including the log-normal, log-logistic, Gompertz, generalised gamma and Weibull.

Base case selection

As detailed above, all curve choices provided a similar level of statistical and visual fit to the observed KM data. No clear consensus was reached among clinical experts regarding the most clinically plausible curve choice, with several parametric models noted as providing clinically plausible long-term estimates across both arms. As such, given the hazard profile of the Gompertz curve was able to best capture the behaviour of the observed hazards for both the perioperative D-FLOT and perioperative FLOT arms, and given the close alignment of TTDeath estimates in the perioperative D-FLOT arm (at 3 years; Gompertz: ■■■%; MATTERHORN KM: ■■■%), as well as in the perioperative FLOT arm (at 3 years; Gompertz: ■■■%; MATTERHORN KM: ■■■%), the Gompertz distribution was selected for the extrapolation of TTDeath for both arms in the base case analysis. Of note, the selection of the Gompertz distribution for both arms is in line with NICE TSD 14 which states that “*substantial justification*” would be required to fit different types of parametric models to different treatment arms.¹²⁷

The generalised gamma distribution, which predicts higher 5-year TTDeath estimates for perioperative FLOT chemotherapy (but not perioperative D-FLOT) than the Gompertz distribution, was explored in a more conservative scenario analysis (Section 3.11.3).

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Assessment of predicted EFS from TP1 and TP2

Perioperative FLOT chemotherapy

When combining the base case selections of generalised gamma for TP1 and Gompertz for TP2 to reconstruct the MATTERHORN EFS for perioperative FLOT chemotherapy, the 3-year EFS predicted by the model was █%, which is consistent with, and falls within the 95% CIs for the 3-year EFS reported in the MATTERHORN trial (December 2024 DCO; █%; 95% CI: █%).³⁶ At 5 years, using the base case extrapolations for TP1–TP2, the model provides a plausible EFS extrapolation, predicting an EFS of █% for the perioperative FLOT chemotherapy arm which is consistent with the 5-year DFS/EFS for perioperative FLOT chemotherapy in the aforementioned FLOT4 trial (~41%) (see Section 1.3.3).⁷

Perioperative D-FLOT

For perioperative D-FLOT, the 3-year EFS predicted by the model was █%, which is highly consistent with, and falls within the 95% CIs for the 3-year EFS reported in MATTERHORN of █% (95% CI: █%) (December 2024 DCO; detailed in Section 2.6.1).³⁶ At 5 years, using the base case extrapolations for TP1–TP2, the model predicts an EFS of █% for perioperative D-FLOT.

3.3.4 *Modelling of post-recurrence survival (TP3)*

Derivation of TP3

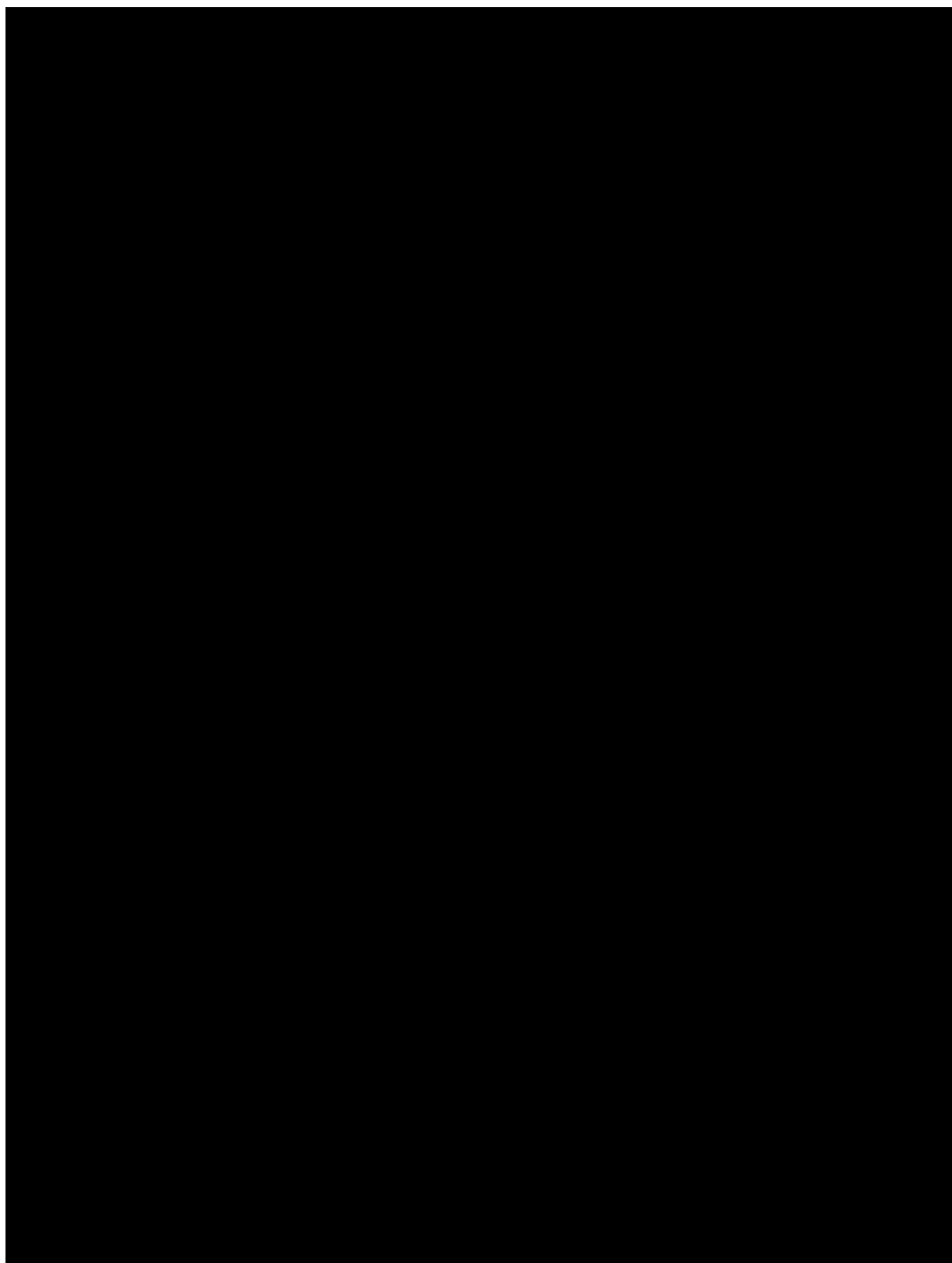
PRS data from MATTERHORN, derived from the time from first recurrence or progression (as an EFS event, as assessed by BICR) to death in those patients who experienced recurrence or progression as an EFS event, were utilised to derive transition probabilities for the transition from RD to Death. Of those patients included in the analysis of post-recurrence survival at the December 2024 DCO (N=█ in the perioperative durvalumab arm and N=█ in the control arm), events had occurred in █% and █% patients in the perioperative durvalumab and control arms, respectively.³⁶

PH testing

PH testing was undertaken similarly to TP1 and TP2, by utilising cumulative hazard plots, log-log plots and Schoenfeld statistics. Based on the assessment of the Schoenfeld residual plot (as presented in Figure 28), the PH assumption cannot formally be rejected, with a p-value >0.05 (Schoenfeld statistics: █). However, the log cumulative hazard plots, log-odds or log-normal lines are not strictly parallel. The CEM therefore also considers individual fits for PRS, in alignment with NICE guidance.¹⁴³

Specifically, standard parametric models (i.e. exponential, Weibull, log-normal, log-logistic, Gompertz, generalised gamma, gamma) were fitted to the perioperative D-FLOT and perioperative FLOT chemotherapy arms. As detailed below, the selection of parametric fits for each arm was based on statistical fit, visual fit, as well as clinical plausibility.

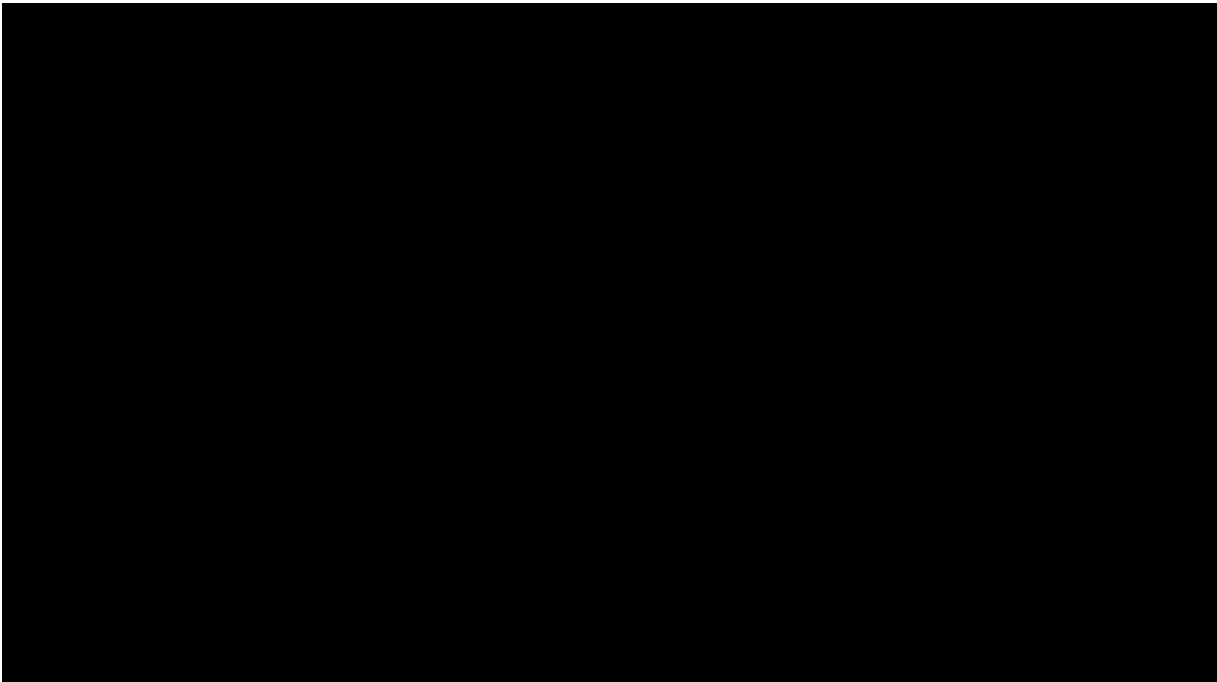
Figure 27: PRS: Log cumulative hazards, log odds and log normal versus log time



Abbreviations: Durva: durvalumab; FLOT: fluorouracil, leucovorin, oxaliplatin and docetaxel; PRS: post-recurrence survival.

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Figure 28: PRS: Schoenfeld residual plot



Abbreviations: PRS: post-recurrence survival.

Statistical fit

An overview of the AIC scores and BIC scores for perioperative D-FLOT and for perioperative FLOT chemotherapy are presented in Table 35 and Table 36, respectively. All distributions (excluding log-normal for AIC/BIC and generalised gamma for BIC) resulted in AIC/BIC statistics that were within 5 points of each other in the perioperative D-FLOT arm, reflecting that they provide a reasonably good statistical fit to the data. Furthermore, in the perioperative FLOT chemotherapy arm, all distributions (bar generalised gamma for BIC) resulted in AIC/BIC statistics that were within 5 points of each other.

The exponential distribution was initially considered as the curve with the best statistical fit (lowest AIC and BIC for perioperative D-FLOT; lowest BIC for the perioperative FLOT chemotherapy arm). However, the exponential extrapolation assumes that the risk of post-recurrence survival remains constant over time. This does not reflect the observed hazards in the MATTERHORN trial (see Figure 31), and is not aligned with modelling approaches previously applied to OS in first-line advanced GOA (NICE TA983, TA997, and TA857),^{138, 141, 147} In these appraisals, models allowing for time-varying hazards were preferred.

In the perioperative FLOT chemotherapy arm, the log-logistic distribution provided the best statistical fit, based on AIC statistics.

Table 35: PRS: goodness of fit statistics perioperative D-FLOT (MATTERHORN, FAS)

Model	AIC	AIC rank	BIC	BIC rank
Exponential	████	1	████	1
Weibull	████	3	████	3
Log-normal	████	7	████	7
Log-logistic	████	5	████	5

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Model	AIC	AIC rank	BIC	BIC rank
Gompertz	■	4	■	4
Generalised gamma	■	6	■	6
Gamma	■	2	■	2

Footnotes: Bold indicates lowest AIC/BIC value

Abbreviations: AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; FAS: full analysis set; FLOT: Fluorouracil: Leucovorin: Oxaliplatin and Docetaxel; PRS: post-recurrence survival.

Table 36: PRS: goodness of fit statistics perioperative FLOT chemotherapy (MATTERHORN, FAS)

Model	AIC	AIC rank	BIC	BIC rank
Exponential	■	2	■	1
Weibull	■	6	■	5
Log-normal	■	3	■	4
Log-logistic	■	1	■	2
Gompertz	■	4	■	3
Generalised gamma	■	5	■	7
Gamma	■	7	■	6

Footnotes: Bold indicates lowest AIC/BIC value

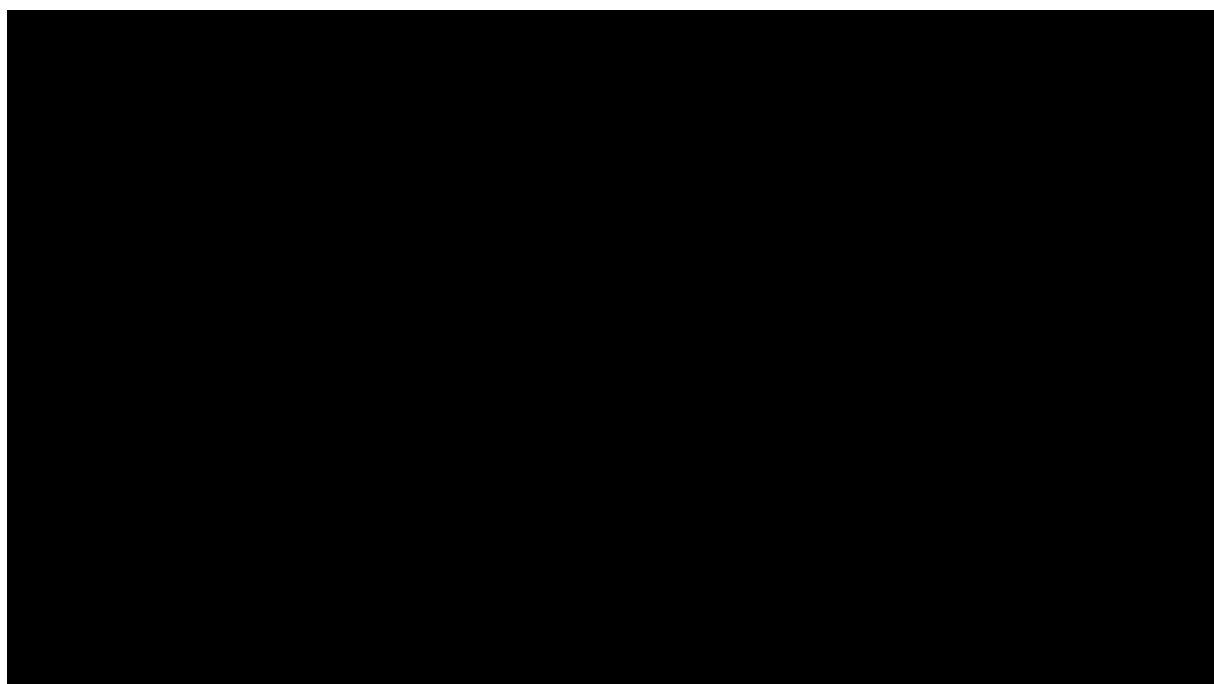
Abbreviations: AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; FAS: full analysis set; FLOT: Fluorouracil: Leucovorin: Oxaliplatin and Docetaxel; PRS: post-recurrence survival.

Visual fit

Figure 29 and Figure 30 present the parametric distributions (adjusted for general population mortality) and fit to the KM data and long-term predictions for perioperative D-FLOT and perioperative FLOT chemotherapy, respectively. These KM extrapolations are provided up to 60 months (5 years) due to the underlying 5-year cure assumption detailed in Section 3.3.1.

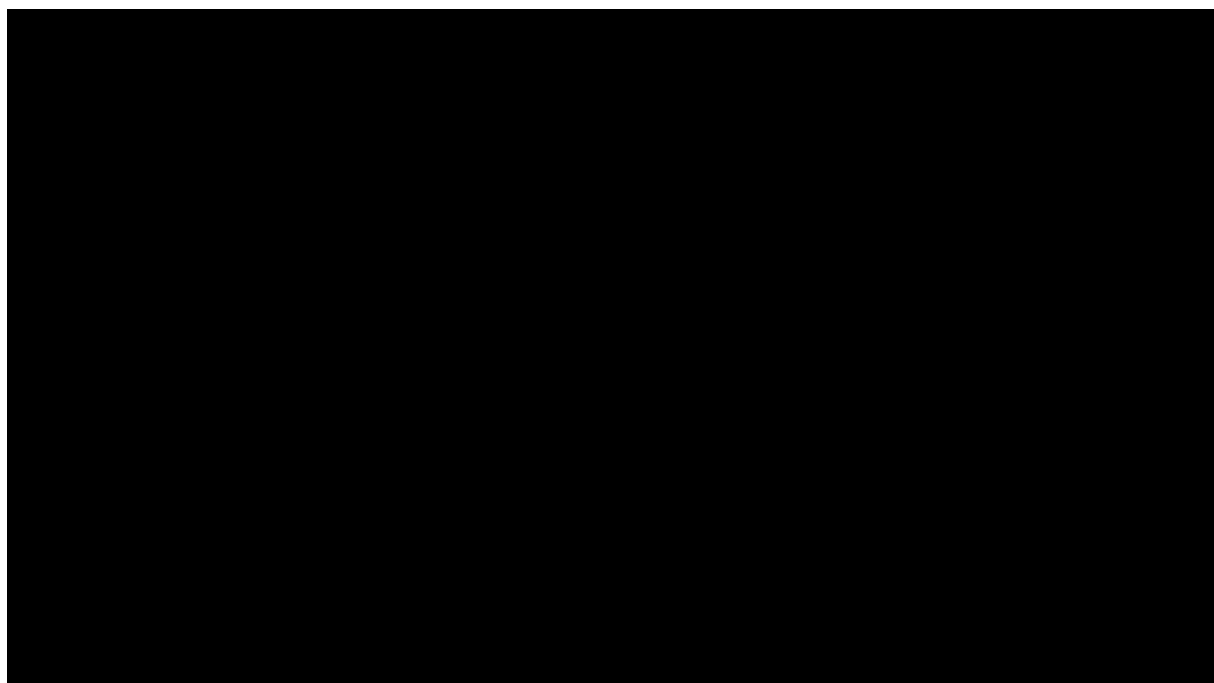
The log-logistic distribution (associated with the best AIC for the perioperative FLOT arm and within three points of the AIC of the best fitting curve in the perioperative D-FLOT arm) provided a reasonable fit to both the observed survival and the hazard functions (see below) in the perioperative D-FLOT arm.

Figure 29: PRS: observed vs. predicted for perioperative D-FLOT (MATTERHORN, FAS) – adjusted for general population mortality



Abbreviations: FAS: full analysis set; KM: Kaplan-Meier; FLOT: Fluorouracil: Leucovorin: Oxaliplatin and Docetaxel; PRS: post-recurrence survival.

Figure 30: PRS: observed vs. predicted for perioperative FLOT chemotherapy (MATTERHORN, FAS) – adjusted for general population mortality



Abbreviations: FAS: full analysis set; KM: Kaplan-Meier; FLOT: Fluorouracil: Leucovorin: Oxaliplatin and Docetaxel; PRS: post-recurrence survival.

Table 37: PRS: predictions for perioperative D-FLOT (MATTERHORN, FAS) – adjusted for general population mortality

Model	1 year	2 years	3 years	5 years
MATTERHORN KM for perioperative D-FLOT	■	■	■	■
Exponential	■	■	■	■
Weibull	■	■	■	■
Log-normal	■	■	■	■
Log-logistic	■	■	■	■
Gompertz	■	■	■	■
Generalised gamma	■	■	■	■
Gamma	■	■	■	■

Abbreviations: AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; FAS: full analysis set; FLOT: Fluorouracil: Leucovorin: Oxaliplatin and Docetaxel; KM: Kaplan-Meier; PRS: post-recurrence survival.

Table 38: PRS: predictions perioperative FLOT chemotherapy (MATTERHORN, FAS) – adjusted for general population mortality

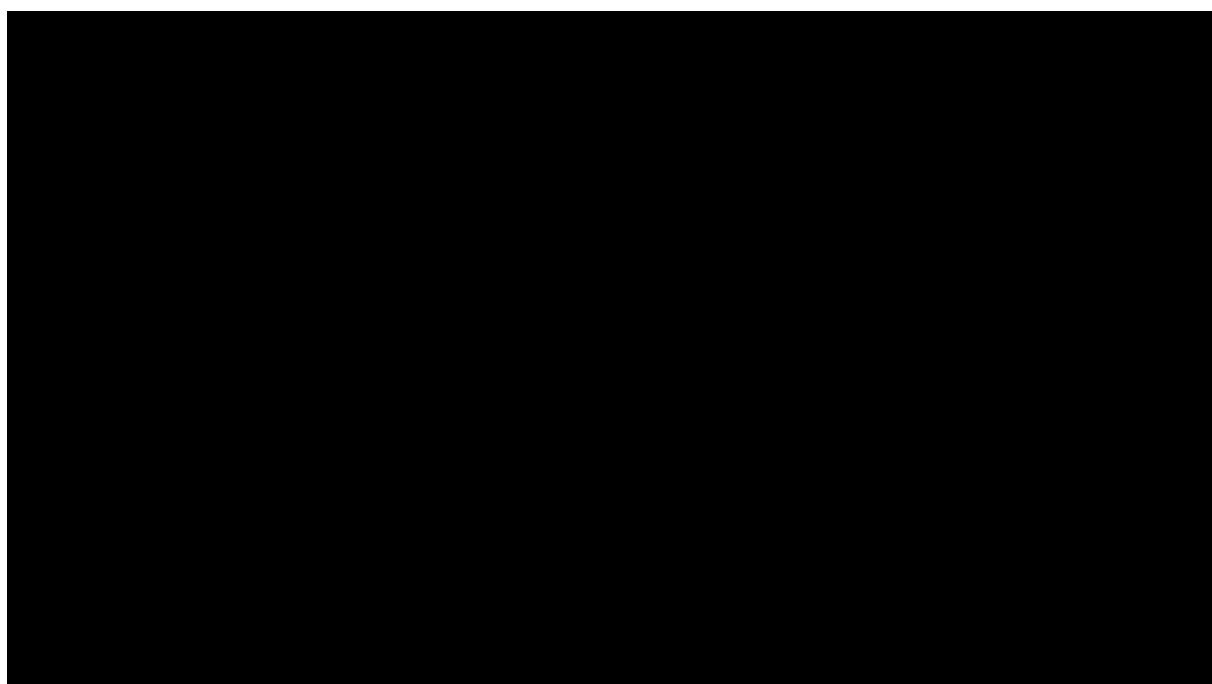
Model	1 year	2 years	3 years	5 years
MATTERHORN KM for perioperative FLOT chemotherapy	■	■	■	■
Exponential	■	■	■	■
Weibull	■	■	■	■
Log-normal	■	■	■	■
Log-logistic	■	■	■	■
Gompertz	■	■	■	■
Generalised gamma	■	■	■	■
Gamma	■	■	■	■

Abbreviations: AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; FAS: full analysis set; FLOT: Fluorouracil: Leucovorin: Oxaliplatin and Docetaxel; KM: Kaplan-Meier; PRS: post-recurrence survival.

Hazard profiles

As shown in Figure 31, the log-normal and the log-logistic distributions were able to best capture the behaviour of the observed hazards for both treatment arms. Both distributions were able to capture an initial increase in hazards followed by a gradual decrease in hazards over time.

Figure 31: PRS: Predicted hazards per distribution (MATTERHORN FAS)



Abbreviations: FAS: full analysis set; FLOT: Fluorouracil: Leucovorin: Oxaliplatin and Docetaxel; KM: Kaplan-Meier; PRS: post-recurrence survival.

Clinical validation

There was no clear consensus among clinical experts consulted by the Company for the TP3 curve selection. Several curves were discussed by clinical experts as most clinically plausible across both arms, including the log-logistic, generalised gamma and Gompertz.

Base case selection

Given its stronger alignment with both statistical and clinical considerations, the log-logistic distribution was selected as the most appropriate model for extrapolation of PRS in both treatment arms in the base case. The log-logistic distribution offered an acceptable statistical fit across both treatment arms (within five points of the best fitting exponential AIC/BIC), a reasonable visual fit to the observed KM data and hazards. Statistical and visual fit to the observed KM data were considered the important criterion given the maturity of the available KM data for PRS. As detailed above, the log-logistic predicted 5-year PRS for perioperative FLOT chemotherapy which is in line with recently published literature.¹⁴⁸ Of note, in line with TP1 and TP2, the selection of the log-logistic distribution for both arms is in line with guidance in NICE TSD 14 relating to the “*substantial justification*” required to fit different types of parametric models to different treatment arms.¹²⁷

While the exponential does not reflect the observed hazards from the MATTERHORN trial, as the best statistically fitting curve across both treatment arms, the selection of the exponential distribution for TP3 was explored in a scenario analysis, as presented in Section 3.11.3.

Assessment of predicted OS from TP1, TP2 and TP3

Perioperative FLOT chemotherapy

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When combining the base case selections of generalised gamma for TP1, Gompertz for TP2 and log-logistic for TP3 to reconstruct the MATTERHORN OS for perioperative FLOT chemotherapy, the 3-year OS predicted by the model was █%, which is consistent with, and falls within the 95% CIs for the 3-year OS reported in the MATTERHORN trial (December 2024 DCO; █%; 95% CI: █).³⁶ Similarly, the 5-year model prediction of OS for the perioperative FLOT chemotherapy arm (█%) is closely aligned with the 5-year OS rate of 45.0% in FLOT-4 trial.⁷

Perioperative D-FLOT

For perioperative D-FLOT, the 3-year OS predicted by the model was █%, which is highly consistent with the █% (95% CI: █) 3-year OS rate reported in the MATTERHORN trial (December 2024 DCO; detailed in Section 2.6.2).³⁶ At 5 years, using the base case extrapolations for TP1–TP3, the model predicts an OS of █% for perioperative D-FLOT.

These findings further validate the selection of parametric distributions for TP1–TP3, demonstrating that the EFS and OS long-term predictions from the model align closely with outcomes observed in the MATTERHORN trial and remain consistent with published literature.⁷

3.3.5 AEs

The economic model considers Grade ≥3 AEs that occurred in at least 5% of patients in either arm of the MATTERHORN trial. The 5% cut-off was selected to capture AEs that would impact patients consistently enough to have validity in a real-world setting where AEs are potentially monitored in a less strict manner compared with a clinical trial setting. As detailed in Section 2.11, the addition of durvalumab to FLOT did not result in an overall increase in the incidence of Grade ≥3 AEs compared with FLOT alone.

The AE rates included in the economic model are presented in Table 39. The disutilities associated with AEs are presented in Section 3.4.4, and the costs associated with the management of AEs are presented in Section 3.5.3.

Table 39: Treatment-emergent Grade 3/4 adverse event frequencies (as per MATTERHORN SAS; December 2024 DCO)

Adverse event	Perioperative D-FLOT	Perioperative FLOT chemotherapy
Neutropenia	█	█
Neutrophil Count Decreased	█	█
Diarrhoea	█	█
WBC-count decreased	█	█
Anaemia	█	█

Abbreviations: FLOT: Fluorouracil, Leucovorin, Oxaliplatin and Docetaxel; SAS: safety analysis set; WBC: white blood cell.

3.4 Measurement and valuation of health effects

3.4.1 Health-related quality-of-life data from clinical trials

As detailed in Section 2.6.7, to capture the impact of treatment on patients' QoL in the durvalumab and control arms, HRQoL was assessed in the MATTERHORN trial using several measures, including the EQ-5D-5L questionnaire.³⁶

EQ-5D-5L questionnaires were administered at baseline and at Week 4 (neoadjuvant phase: Cycle 2), at the first treatment visit during the adjuvant treatment period, at Week 4 of the adjuvant treatment, and then every 4 weeks between Weeks 8 and 44 of the adjuvant treatment period, unless dosing had been held for toxicity periods. After the last dose of study treatment, EQ-5D-5L questionnaires were administered 30 days after the last dose, at 2 and 3 months after the last dose, and then at every scheduled assessment visit.¹¹⁷

Compliance with EQ-5D-5L completion was high and consistent across study visits. At each timepoint, the proportion of received and evaluable forms relative to expected forms was [REDACTED], with overall compliance rates [REDACTED] to those observed for the EORTC QLQ-C30 (see Section 2.6.7).

3.4.2 Mapping

In accordance with NICE guidance (PMG36),¹³⁸ the EQ-5D-5L responses collected in the MATTERHORN trial were mapped to EQ-5D-3L-derived UK utility values using the Policy Research Unit in Economic Methods of Evaluation of Health and Care Interventions (EERPU) dataset (Hernández Alava *et al.* 2020),¹⁴⁹ by applying the mapping function developed by Hernández Alava *et al.* 2017.¹⁴⁰ The scores were derived from the FAS of the MATTERHORN trial (December 2024 DCO) and consisted of all completed EQ-5D-5L measures (i.e., excluding EQ-5D-5L observations with any missing domain responses). The resulting utility values derived from the mapping for perioperative D-FLOT and perioperative FLOT chemotherapy alone are presented in Section 3.4.5.

A mixed model for repeated measures (MMRM) method was used to estimate the statistical relationship between utilities and health state (defined by recurrence or treatment status). Further details of the utility mapping can be found in Appendix L.

In the MATTERHORN trial, a total of [REDACTED] EQ-5D-5L observations from n=[REDACTED] patients were collected. Of these:

- [REDACTED] observations were documented before progression or recurrence
- [REDACTED] observations were documented after progression or recurrence
- [REDACTED] observations were recorded after censoring for recurrence

The marginal (least square) means from the MMRM were [REDACTED] for the pre-recurrence period and [REDACTED] for the post-recurrence period. These estimates were based on the model including a term for recurrence status only (as this was the best fitting model in terms AIC). Since treatment status was not included in the best fitting model, the utilities applied in the model were specific to health-state rather than treatment-specific.

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3.4.3 Health-related quality-of-life studies

The SLR detailed in Section 3.1 also identified evidence on HRQoL, PROs and utilities in patients with resectable GOA (Appendix F). The HRQoL SLR was conducted in June 2025, as part of the economic evaluation SLR.

In total, 46 records reporting on the HRQoL of patients with resectable GOA were captured in the HRQoL SLR.

3.4.4 Adverse reactions

In order to account for the impact of AEs on patients' HRQoL, the model included disutility values for maximum Grade 3/4 AEs (any cause) that occurred in $\geq 5\%$ of patients in either treatment arm in the MATTERHORN trial. The total mean QALY loss associated with AEs for each treatment was determined by calculating the treatment-specific AE frequencies, the mean utility decrements related to these AEs, and the assumed duration of AEs (1 month [30.4 days], equivalent to a single model cycle). This total QALY loss was applied as a one-off decrement in the first model cycle.

Disutility values for AEs were sourced from Nafees *et al.* 2008,¹⁵⁰ Doyle *et al.* 2008,¹⁵¹ and Swinburn *et al.*¹⁵² 2010, in line with recent NICE appraisals of pembrolizumab (TA997) and nivolumab (TA857) as treatments for patients with first-line advanced HER2-negative GOA.^{110, 141} For the AEs 'neutrophil count decreased' and 'white blood cell count decreased', the utility decrement was assumed to be the same as 'neutropenia'.

A summary of the AE disutilities included in the base case economic analysis are presented in Table 40. The proportion of patients experiencing these AEs in the model are described in Section 3.5.3.

Table 40: Summary of AE disutilities included in the economic model (based on any cause Grade 3/4 AEs experienced by $\geq 5\%$ of patients in either treatment arm in the MATTERHORN SAS [December 2024 DCO])

Adverse event	Utility decrement (SE)	Decrement sources
Neutropenia	-0.090 (0.015)	Nafees <i>et al.</i> (2008). ¹⁵⁰ As per NICE TA997 ¹¹⁰ and TA857 ¹⁴¹
Neutrophil count decreased	-0.090 (0.015)	Assumed the same as neutropenia
Diarrhoea	-0.047 (0.009)	Doyle <i>et al.</i> (2008). ¹⁵¹ As per NICE TA997 ¹¹⁰ and TA857 ¹⁴¹
White blood cell count decreased	-0.090 (0.015)	Assumed the same as neutropenia
Anaemia	-0.115 (0.023)	Swinburn <i>et al.</i> (2010). ¹⁵² As per NICE TA997 ¹¹⁰ and TA857 ¹⁴¹

Abbreviations: AE: adverse event; SAS: safety analysis set; SE: standard error; TA: technology appraisal.

3.4.5 Health-related quality-of-life data used in the cost-effectiveness analysis

For the EF health state, MATTERHORN EQ-5D-3L utilities were preferred over utility sources in the SLR, as they directly align with the source of efficacy data and the population in the decision problem. Notably however, the utility value for the EF health state from MATTERHORN (0.840) was slightly higher than the gender- and age-adjusted utility value for the UK general population (0.840).¹⁴⁰ As such, in line with the approach accepted by NICE in TA746, the EF utility value was capped to the UK general population utility in the base case.^{8, 140} A scenario was explored in Section 3.11.3 in which this population cap was excluded. UK clinical experts confirmed as part of the clinical validation exercises that the GPM-capped EF utility value was reasonable, and consistent with their understanding of quality of life in patients with resectable GOA.⁵

In the MATTERHORN trial there were low number of observations of EQ-5D-5L following progression or recurrence (N=10; substantially lower than the 100 observations before disease progression/recurrence). Additionally, it is common that many observations of EQ-5D-5L are recorded soon after patients experience progression or recurrence and therefore may not capture the full HRQoL impact associated with the worsening of patients' disease. Consequently, an alternative RD utility value of 0.747 was selected in the base case analysis. This approach is aligned to the value for the RD health state accepted by NICE in the appraisal of nivolumab for patients with OC or GOJC (TA746), and additionally used in the NICE appraisal of nivolumab in patients with previously treated resectable advanced/recurrent OC (TA707).⁸ The use of an RD utility value aligned with previous appraisals in a similar disease area ensures consistency in both the modelling approach and decision-making. For completeness, a scenario analysis using an RD utility value derived from MATTERHORN (with the decrement associated with recurred disease based on the MMRM (0.747) removed from the general population-capped EF state utility value [0.840–0.747]), was explored (see Section 3.11.3).

A summary of the health state utility values used in the base case analysis is provided in Table 41. Of note, these utility values were treatment-independent. In line with NICE PMG36 these utility values were age-adjusted throughout the model time horizon in the base case; a scenario analysis exploring the exclusion of age-adjusted utility decrements is presented in Section 3.11.3.¹³⁸

Table 41: Summary of health state utility values for perioperative D-FLOT and perioperative FLOT used in the base case economic analysis

Health state	Utility	SE	Source
EF	0.840	0.005 ^a	EQ-5D-5L values from MATTERHORN mapped to EQ-5D-3L as outlined in Section 3.4.2, capped to UK general population utility ³⁶
RD	0.747	0.015	Aligned with the RD health state utility in the NICE appraisal of nivolumab for the adjuvant treatment of patients with OC or GOJC (TA746) ⁸

Footnotes: ^a The SE for the EF health state related to the general population utility uncapped value of [REDACTED].
Abbreviations: CI: confidence interval; EF: event-free; EQ-5D-5L: EuroQol five dimensions five levels; EQ-5D-3L: EuroQol five dimensions three levels; GOJC: gastro-oesophageal cancer; OC: oesophageal cancer; RD: recurred disease; standard error.

3.5 Cost and healthcare resource use identification, measurement and valuation

The economic SLR detailed in Section 3.1 also identified cost and HCRU studies associated with resectable GOA in the UK. Of the studies included in the SLR that were eligible for data extraction and reporting, N=24 publications were identified that reported cost/HCRU data. Full details of the SLR search strategy, study selection process and results are reported in Appendix G.

The health economic analysis was conducted from the perspective of the NHS and PSS in England and as such, only included costs that would be incurred by the health system. Appropriate sources of unit costs, such as NHS reference costs 2023–2024, British National Formulary (BNF) and drugs and pharmaceutical electronic market information tool (eMIT) costs were used for cost inputs in the model.¹²⁸⁻¹³¹ The model cost year was 2024 and any costs from earlier years were inflated to the 2024 price levels using the NHSCII pay and price indices published by the PSSRU.¹²⁹

Specifically, the following cost components were considered in the model:

- Drug acquisition and administration costs for the intervention, comparator and subsequent therapies
- Surgery costs
- Healthcare resource use (HCRU)
- Terminal care costs
- AE management costs

3.5.1 Intervention and comparators' costs and resource use

Drug acquisition costs

Drug dosing regimens per model cycle are presented in Figure 32 for the intervention and comparators in the EF health state. The dose per treatment cycle was calculated based on the

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dose per administration, the number of administrations per treatment cycle and relative dose intensity (RDI).

Treatment acquisition costs in the EF health state were calculated based on treatment completion rates from MATTERHORN (i.e. proportion of patients completing ≥ 1 , ≥ 2 etc. treatment cycles) and the cost per treatment cycle.³⁶ See Appendix K.5 for treatment completion rates for each treatment component. Treatment acquisition costs were applied within the corresponding model cycles by mapping the timing of treatment cycles to the 1-month model cycles.

In the model, adjuvant treatment cycles started at a pre-defined timepoint, to enable the model to account for the gap between neoadjuvant and adjuvant treatment during which time patients would undergo surgical resection. In the MATTERHORN trial, median time to adjuvant treatment initiation was ■■■ months and ■■■ months in the perioperative D-FLOT arm and perioperative FLOT chemotherapy arms, respectively.³⁶ For simplicity, and to align with the model cycle length (i.e. 1 month), the timepoint at which adjuvant treatment cycles started in the model was rounded to 5 months in both arms. This translates into a 3-month gap between the end of neoadjuvant treatment and the start of adjuvant treatment, during which time no treatment acquisition or administration costs were incurred in the model.

Figure 32: Dosing regimen per cycle in the EF health state

Treatment		Dose per administration		Frequency (per treatment cycle)	Treatment cycle length (days)	RDI ^a	Max number of administrations	
							Neoadjuvant	Adjuvant
Perioperative durvalumab (+ FLOT chemotherapy)	Durvalumab	1,500	mg	1	28	■	2	2
	5-FU	2,600	mg/m ²	2	28	■	2	2
	Oxaliplatin	85	mg/m ²	2	28	■	2	2
	Leucovorin	200	mg/m ²	2	28	■	2	2
	Docetaxel	50	mg/m ²	2	28	■	2	2
Perioperative FLOT chemotherapy	5-FU	2,600	mg/m ²	2	28	■	2	2
	Oxaliplatin	85	mg/m ²	2	28	■	2	2
	Leucovorin	200	mg/m ²	2	28	■	2	2
	Docetaxel	50	mg/m ²	2	28	■	2	2
Perioperative durvalumab (monotherapy)	Durvalumab	1,500	mg	1	28	■	-	10

Footnotes: ^a RDI was informed by data from the MATTERHORN trial.³⁶

Abbreviations: 5-FU: 5-fluorouracil; comb: combination; EF: event free; FLOT: Fluorouracil, Leucovorin, Oxaliplatin and Docetaxel; RDI: relative dose intensity.

Average dosages for FLOT chemotherapy components were calculated using an average BSA of ■ m², obtained from the MATTERHORN population combined with the Gehan and George formula.¹⁵³ For the base case analysis, vial sharing for IV chemotherapy was assumed and therefore no wastage costs were included. A scenario analysis is presented to explore the impact of no vial wastage cost considered (see Section 3.11.3).

Unit acquisition costs for the intervention and relevant comparators were sourced from the British National Formulary (BNF 2025),¹⁵⁴ and the electronic market information tool (eMIT) databases and are displayed in Table 42.^{155, 156} Drug acquisition costs were calculated based on the dosing schedule for each treatment, with doses determined according to the licensed regimen and dose type (either kg, mg/m² or a flat dose). Costs were derived by applying

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the relevant unit price (where applicable, both list and prices reflecting the commercial access arrangement for durvalumab are used and presented) to the required number of vials per administration. To align with clinical practice, the lowest-cost option for each required dosage was used.

Table 42: Unit acquisition costs

Treatment	Dose per vial (mg)	Pack size	Cost per pack	Discounted price per pack	Discount	Source
Durvalumab	120	1 vial	£592.00	████	████	BNF 2025 (via NICE) ¹⁵⁴
	500	1 vial	£2,466.00	████	████	BNF 2025 (via NICE) ¹⁵⁴
5-FU (2.5%)	2500	1 vial	£4.082	N/A	N/A	eMIT ¹⁵⁶
5-FU (5%)	2500	1 vial	£4.621	N/A	N/A	eMIT ¹⁵⁶
5-FU (5%)	5000	1 vial	£6.269	N/A	N/A	eMIT ¹⁵⁶
Oxaliplatin	50	1 vial	£6.482	N/A	N/A	eMIT ¹⁵⁶
	100	1 vial	£14.269	N/A	N/A	eMIT ¹⁵⁶
	200	1 vial	£11.312	N/A	N/A	eMIT ¹⁵⁶
Leucovorin	100	10 vials	£27.633	N/A	N/A	eMIT ¹⁵⁶
	300	1 vial	£15.800	N/A	N/A	eMIT ¹⁵⁶
	350	10 vials	£60.966	N/A	N/A	eMIT ¹⁵⁶
Docetaxel	20	1 vial	£4.486	N/A	N/A	eMIT ¹⁵⁶
	80	1 vial	£9.732	N/A	N/A	eMIT ¹⁵⁶
	160	1 vial	£19.702	N/A	N/A	eMIT ¹⁵⁶

Abbreviations: 5-FU: 5-fluorouracil; BNF: British National Formulary; eMIT: electronic market information tool; NICE: National Institute for Health and Care Excellence.

Subsequent treatments

The model estimates the cost of subsequent lines of treatment after disease recurrence, accounting for costs based on the proportion of patients receiving further therapies following disease recurrence, the distribution of treatments used, and the duration of treatment. Based on MATTERHORN data on subsequent treatments received by patients who had experienced progression/recurrence (i.e. non-death event) as an EFS event, [REDACTED] and [REDACTED] patients in the perioperative D-FLOT and perioperative FLOT chemotherapy arms, respectively, received subsequent therapy after disease recurrence.³⁶

The types of systemic therapy received by patients in the MATTERHORN trial (across all lines) included: cytotoxic chemotherapy, targeted therapy, and immunotherapy.³⁶ The individual treatment agents included in the model within each of these categories were selected based on those commonly received in MATTERHORN,³⁶ and supplemented with UK clinical expert validation.⁵

UK clinical experts consulted by the Company as part of this submission were presented the distribution of subsequent treatments received in each arm of the MATTERHORN trial. Validation received from the clinical experts highlighted that retreatment with IO therapy is likely following prior D-FLOT treatment, though is dependent on when patients relapse with D-FLOT.⁵ Experts also noted that ramucirumab is not used in UK clinical practice, while irinotecan is used more widely (estimated at between 10–20%) following IO treatment.⁵ As such, irinotecan replaced ramucirumab as a subsequent treatment option to align to UK clinical practice. The distribution of irinotecan was aligned to the use of ramucirumab in the MATTERHORN trial.³⁶ This minor change represents the only difference between the modelled efficacy data and the subsequent treatment costs included in the model.

The drug dosing regimens by for each subsequent treatment are detailed in Table 43. Monthly doses were determined based on the dose per administration, the number of administrations, and the duration of each treatment cycle for the respective therapies. The RDI for all subsequent treatments was assumed to be 100%.

Table 43: Dosing regimen per cycle in subsequent health state

Treatment	Target dose	Frequency (per treatment cycle)	Treatment cycle length	RDI
Cytotoxicity chemotherapy				
Oxaliplatin	130 mg/m ²	1	21	100%
Cisplatin	80 mg/m ²	1	21	100%
5-FU	800 mg/m ²	5	21	100%
Capecitabine	1,000 mg/m ²	28	21	100%
Irinotecan	350 mg/kg	1	21	100%
Targeted therapy				
Trastuzumab (loading dose)	8 mg/kg	1	NA	100%
Trastuzumab (maintenance dose)	6 mg/kg	1	21	100%

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IO monotherapy				
Nivolumab (1)	360 mg	1	21	100%
Nivolumab (2)	240 mg	1	14	100%
Pembrolizumab	200 mg	1	21	100%

Abbreviations: 5-FU: 5-fluorouracil; IO: immune-oncology; RDI: relative dose intensity.

For IV treatments, average dosages were calculated assuming a BSA of 1.73 m^2 , estimated using the Gehan and George formula and based on mean values from the MATTERHORN trial population.¹⁵³ In the base case analysis, vial-sharing was assumed for IV chemotherapy, therefore associated vial wastage costs were not considered.

Unit acquisition costs were sourced from the BNF and eMIT databases and presented in Table 44.¹⁵⁶ These costs represent UK list prices.

Table 44: Unit acquisition costs (subsequent therapies)

Treatment	Dose per vial (mg)	Pack size	Cost per pack	Cost per mg	Source
Cisplatin	10	1 vial(s)	£3.67	£0.37	eMIT ¹⁵⁶
	50	1 vial(s)	£19.69	£0.39	
	100	1 vial(s)	£37.34	£0.37	
Nivolumab	40	1 vial(s)	£439.00	£10.98	
	100	1 vial(s)	£1,097.00	£10.97	
	120	1 vial(s)	£1,317.00	£10.98	
	240	1 vial(s)	£2,633.00	£10.97	
Pembrolizumab	100	1 vial(s)	£2,630.00	£26.30	
Capecitabine	150	60 tablets	£4.83	<£0.01	
	300	60 tablets	£7.40	<£0.01	
	500	120 tablets	£20.13	<£0.01	
Irinotecan	100	1 vial(s)	£5.95	£0.06	
	500	1 vial(s)	£26.60	£0.05	
Trastuzumab	150	1 vial(s)	£366.00	£2.44	
	420	1 vial(s)	£1,025.65	£2.44	

Abbreviations: eMIT: electronic market information tool.

The base case analysis considered patients who had experienced progression/recurrence (i.e. non-death event) as an EFS event (see Table 45).³⁶ As detailed previously, the number and proportion of patients receiving subsequent therapy in each treatment category was based on data from MATTERHORN, and amended to reflect UK clinical practice. A scenario analysis was conducted whereby MATTERHORN data (amended to reflect UK clinical practice; including irinotecan in place of ramucirumab) were used to account for the cost of all subsequent therapy received (regardless of whether it was received before/after progression; see Section 3.11.3). In this scenario, the data are only adjusted with respect to costs, and the efficacy of the treatments were not changed.

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The treatment categories in Table 45 are not mutually exclusive. To ensure that each treatment agent was counted only once, the proportion of patients receiving each agent was calculated individually, regardless of whether the agent was administered as monotherapy or in combination. For instance, all chemotherapy agents were grouped under the cytotoxic chemotherapy category, even when used in combination with immunotherapy and/or targeted therapies. Similarly, immunotherapy was represented by a single category that included all use of nivolumab and pembrolizumab, without distinguishing between combination regimens.

For the time spent on each subsequent therapy, median PFS data from the pivotal trials (as reported in the respective EMA labels) of each regimen were used. CheckMate-649 (CM649), and KEYNOTE-859 (KN859), were the main trials used to inform the duration of subsequent therapies, i.e. pivotal trials for IO with chemotherapy (nivolumab [CM649], pembrolizumab [KN859]).^{157, 158} For the duration of cytotoxic chemotherapy, KN859 was preferred to CM649 since the chemotherapy regimens in KN859 better match the chemotherapy regimens included in the model.^{157, 158}

A lump-sum subsequent treatment cost was calculated for each arm based on the total cost across each subsequent therapy, weighted according to the distribution of subsequent therapies in each arm. This lump-sum cost was applied to patients entering the RD health state in each cycle.

Table 45: Distribution and average treatment duration of subsequent treatments

Regimen	Perioperative D-FLOT	Perioperative FLOT	Duration (months)	Source for duration
Cytotoxic chemotherapy				
Oxaliplatin	■	■	5.6	mPFS in the placebo arm of KN859 ¹⁵⁷
Cisplatin	■	■	5.6	mPFS in the placebo arm of KN859 ¹⁵⁷
5-FU	■	■	5.6	mPFS in the placebo arm of KN859 ¹⁵⁷
Capecitabine	■	■	5.6	mPFS in the placebo arm of KN859 ¹⁵⁷
Irinotecan	■	■	2.2	mPFS in the irinotecan arm in Ochenduszko, <i>et al.</i> 2017 ¹⁵⁹
Targeted therapy				
Trastuzumab	■	■	6.7	mPFS in the trastuzumab arm of ToGA ¹⁶⁰
IO monotherapy				
Nivolumab	■	■	8.3	mPFS in the nivolumab arm of CM649 ¹⁵⁸

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Pembrolizumab	■	■	6.9	mPFS in the pembrolizumab arm of KN859 ¹⁵⁷

Abbreviations: 5-FU: 5-fluorouracil; IO: immune-oncology; mPFS: median progression-free survival; FLOT: Fluorouracil, Leucovorin, Oxaliplatin and Docetaxel.

Treatment administration costs

Drug administration costs (Table 45) were applied per administration for drugs given intravenously. Administration costs for the EF and RD health states costs were calculated similarly to the approach adopted for the associated drug acquisition costs (EF or subsequent). Unit costs for drug administration were based on NHS Reference Costs 2023/2024.¹ For the first treatment cycle, a cost of £418.29 was applied for simple chemotherapies and £570.43 for complex chemotherapies. For all subsequent cycles, a cost of £426.15 was applied. For oral therapies, no administration cost was assumed, in line with previous NICE appraisals. For regimens with multiple components (e.g. FLOT in EF, combination therapies in RD), a single drug administration cost was applied per administration, covering all components given simultaneously.

Table 46. Treatment administration costs

Administration type	Costs (per administration)
IV, simple chemotherapy	£418.29
IV, subsequent dose(s)	£426.15
IV, complex chemotherapy	£570.43
Oral therapies	£0.00

Abbreviations: IV: intravenous

Cost of surgery

A one-time cost of surgical resection (total gastrectomy) was considered in the model for a proportion of patients in the EF health state to reflect the possibility that not all patients might receive surgery following neoadjuvant treatment. The proportion of patients that receive surgery was sourced from the MATTERHORN study (Section 2.6.4). The unit costs of surgery (total gastrectomy) were obtained from NHS Reference Costs 2023/2024.¹¹⁰ The surgery cost input and resulting cost calculations are presented in Table 47.

Table 47: Surgery costs

	Perioperative D-FLOT	Perioperative FLOT chemotherapy
Unit cost of surgery ^a	£17,737.32	
Proportion of patients with attempted/performed surgery	90.9%	90.3%
Cost of surgery by treatment arm ^b	£16,128	£16,016

Footnotes: ^a Unit costs of surgery (total gastrectomy) were sourced from the NHS Reference costs 2023/2024: FF01A-C Very Complex, Oesophageal, Stomach or Duodenum Procedures, 19 years and over, with CC score 0-6+ (weighted average – elective inpatients) in line with NG83;^{1, 110} ^b Costs of surgery by treatment were estimated by weighting the unit costs for surgery based on the proportion of patients receiving surgery.

Abbreviations: FLOT: Fluorouracil, Leucovorin, Oxaliplatin and Docetaxel; NHS: National Health Service.

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3.5.2 Health-state unit costs and resource use

Healthcare resource use and costs

HCRU inputs relating to clinical visits, hospitalisation, and imaging for each of the model health states were sourced from NICE TA746, and supplemented with clinical expert validation (Table 48).^{5, 8} TA746 included estimates of resource use and costs associated with managing patients with resected oesophageal cancer/GOJC during and after adjuvant therapy, and after disease progression, and were therefore generally deemed applicable to this indication.⁸

In line with TA746, the HCRU in the RD health state included clinical consultations, which were accounted separately from oncologist visits.⁸ However, in order to best reflect clinical practice, following feedback received from UK clinical experts, the frequency of oncologist visits in the RD health state was adjusted to be equivalent to the frequency of visits in the EF health state, differing to TA746 in which oncologist visits were only assumed to occur for patients in the EF health state.⁵ All other healthcare resource use estimates are equivalent to those estimated in TA746, multiplied by four, given the monthly cycle length of the model in this submission (see Table 48).⁸

Unit costs for HCRU were sourced from NHS Reference costs 2023/2024, and are presented in Table 49.¹³¹ A summary of the total health state costs per cycle is provided in Table 50.

Table 48: Healthcare resource use by health state

Resource item	Frequency per month	
	EF	RD
Oncologist	0.361	0.361
CT scan/MRI	0.361	0.400
Clinical consultation	0.000	0.665
Hospitalisation	0.000	0.413
Palliative care specialist care	0.000	1.561
Full blood count	0.000	0.961
Renal function test	0.000	0.739
Hepatic function test	0.000	0.704

Abbreviations: CT: computed tomography; EF: event-free; MRI: magnetic resonance imaging; RD: recurred disease.

Table 49: Healthcare resource unit costs

Resource item	Unit cost	Source
Oncologist	£336.59	Healthcare costing standards for England (2016); Costing year 2018/2019, inflated to 2023/2024 prices ¹⁶¹
CT scan/MRI	£132.24	NHS Reference costs 2023/2024: CT (weighted average of direct access, outpatient and other costs; RD20A, RD21A, RD22Z, RD23Z, RD24Z, RD25Z, RD26Z, RD27Z) ¹³¹
Clinical consultation	£290.07	NHS Reference costs 2023/2024: Medical Oncology (weighted average of consultant led and non-consultant led; WF01A, WF01B, WF01C, WF01D, WF02A, WF02B, WF02C, WF02D) ¹³¹

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Hospitalisation	£1,044.00	NHS Reference costs 2023/2024: Malignant GI Tract Disorders (weighted average of elective inpatients) FD11A, FD11B, FD11C, FD11D, FD11E, DF11F, F11G, FD11H, FD11J, FD11K) ¹³¹
Palliative care specialist care	£69.00	NHS Reference costs 2023/2024: PSSRU 2024 – Specialist Nursing, Palliative/Respite Care, Adult, Non-face-to-face ¹³¹
Full blood count	£4.43	NHS Reference costs 2023/2024: Hematology; DAPS05 chemical pathology service ¹³¹
Renal function test	£1.46	NHS Reference costs 2023/2024: Clinical Biochemistry; DAPS04 chemical pathology service ¹³¹
Hepatic function test	£1.46	NHS Reference costs 2023/2024: Clinical Biochemistry; DAPS04 chemical pathology service ¹³¹

Abbreviations: CT: computed tomography; MRI: magnetic resonance imaging; GI: Gastrointestinal; NHS: National Health Service

Table 50: Total healthcare resource use cost per cycle

Resource item	Cost per cycle
EF	£169.20
RD	£912.69

Abbreviations: EF: event-free; RD: recurred disease

A one-time terminal care cost was applied to all patients in the model upon transition to death, in order to capture end-of-life healthcare costs (see Table 51).

Table 51: Terminal care cost

	Unit cost	Source
Terminal care	£9,483.97	Georgiou <i>et al.</i> (2014). ¹⁶² As per NICE TA746. ⁸ Costing year 2010/2011, inflated to 2023/2024 prices

Abbreviations: NICE: National Institute for health and Care Excellence; TA: technology appraisal.

3.5.3 Adverse reaction unit costs and resource use

Costs for maximum Grade 3 or 4 AEs (any cause) occurring in $\geq 5\%$ of patients in any treatment arm were included in the model. For perioperative D-FLOT and perioperative FLOT chemotherapy, AE frequencies, as presented in Section 3.3.5, were obtained from the MATTERHORN trial (December 2024 DCO).

The costs of managing AEs were sourced from the NHS Reference Costs 2023/2024, as a weighted average of total treatment costs for each AE considered (see Table 52).¹³¹ The AE costs were applied as a one-off cost in the first cycle of the model (see Table 53); for each AE an average duration of one month was assumed.

Table 52: AE unit costs

Adverse event	Unit cost	Source
Neutropenia	£2,402.12	NHS Reference costs 2023/2024: Total HRGs Weighted average SA35A-E. ¹³¹ As per NICE TA997. ¹¹⁰
Neutrophil Count Decreased	£2,402.12	Assumed equal to neutropenia

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Diarrhoea	£508.69	NHS Reference costs 2023/2024: Non-elective short stay. FD10M. ¹³¹ Non-Malignant Gastrointestinal Tract Disorders without Interventions, with CC Score 0. As per NICE TA997. ¹¹⁰
WBC-count decreased	£2,402.12	Assumed equal to neutropenia
Anaemia	£766.75	NHS Reference costs 2023/2024: Non-elective short stay. ¹³¹ Weighted average of SA01G-K. As per NICE TA997. ¹¹⁰

Abbreviations: AE: adverse event; HRG: HealthCare Resource Group; NICE: National Institute of Health and Care Excellence; NHS: National Health Service; WBC: white blood cell; TA: technology appraisal.

Table 53: Total AE (one-off) costs

Treatment arm	Total cost (one-off)
Perioperative D-FLOT	£1,178.64
Perioperative FLOT chemotherapy	£1,283.47

Abbreviations: AE: adverse events; FLOT: Fluorouracil, Leucovorin, Oxaliplatin and Docetaxel.

3.6 Severity

No severity modifier is applicable for this appraisal.

3.7 Uncertainty

Parameter uncertainty in the model was assessed via probabilistic (PSA) and deterministic sensitivity analyses (DSA), the results of which are presented in Section 3.11.1 and Section 3.11.2, respectively. In addition, key assumptions in the model were explored in several scenario analyses, the results of which are presented in Section 3.11.3.

3.8 Managed access proposal

This submission does not include a proposal for managed access.

The final data cut-off for OS (DCO3) in the MATTERHORN trial occurred on 1st September 2025 and results from DCO3 were presented at the ESMO 2025 Congress. Due to timing of data availability from DCO3, this submission is based on data from DCO1 and DCO2.¹¹² The findings from DCO3 indicate that outcomes are consistent with the current data package provided and demonstrate a statistically significant OS benefit in favour of D-FLOT vs perioperative FLOT (HR: 0.78; 95% CI: 0.63, 0.96; p=0.021).^{36, 112} No further formal analyses of the MATTERHORN trial are planned.

Across all scenarios explored in Section 3.11.3, which utilise the EFS and OS data from DCO2, perioperative D-FLOT is cost-effective compared to perioperative FLOT chemotherapy. Therefore, despite any perceived uncertainty, the base case cost-effectiveness results are highly robust and expected to remain cost-effective when data from DCO3 are incorporated.

For these reasons, the data from MATTERHORN are anticipated to provide sufficient certainty for a recommendation via routine commissioning and is not expected to be a candidate for managed access.

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3.9 Summary of base case analysis inputs and assumptions

3.9.1 Summary of base case analysis inputs

A summary of inputs used in the base case analysis is presented in Table 54.

Table 54: Summary of variables applied in the economic model

Variable	Value		Reference to section in submission
Model settings			
Discount rate (costs and benefits)	3.5%		Section 3.2.2
Time horizon	█ years		
Patient baseline characteristics			
Mean age, years (SE)	██████		Section 3.2.1
Proportion of male patients (%)	71.9		
Mean body weight, kg (SE)	██████		
Mean height, cm (SE)	██████		
Mean BSA, m² (SE)	██████		
Survival curve			
Transition probability	Perioperative D-FLOT	Perioperative FLOT chemotherapy	Section 3.3
TP1 (TFR)	Generalised gamma	Generalised gamma	
TP2 (TTDeath)	Gompertz	Gompertz	
TP3 (PRS)	Log-logistic	Log-logistic	
AEs			
Adverse event	Perioperative D-FLOT	Perioperative FLOT chemotherapy	Section 3.4.4
Neutropenia	██	██	
Neutrophil Count Decreased	██	██	
Diarrhoea	██	██	
WBC-count decreased	██	██	
Anaemia	██	██	
Utility inputs			
EF	0.840		Section 3.4.5
RD	0.747		
Adverse event disutility			
	Utility decrement	Duration of AE (days)	Section 3.4.4
Neutropenia	-0.090 (0.015)	30.4	
Neutrophil Count Decreased	-0.090 (0.015)	30.4	
Diarrhoea	-0.047 (0.009)	30.4	

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White blood cell count decreased	-0.090 (0.015)	30.4		
Anaemia	-0.115 (0.023)	30.4		
Resource use				
Cost of surgery, perioperative D-FLOT	£16,128		Section 3.5.2	
Cost of surgery, perioperative FLOT chemotherapy	£16,016			
Total healthcare resource use per cycle, EF	£169.20			
Total healthcare resource use per cycle, RD	£912.69			
Terminal care cost (one-off)	£9,483.97			
	Frequency per month			
Resource item	EF	RD		Unit cost
Oncologist	0.361	0.361		£336.59
CT scan/MRI	0.361	0.400		£132.24
Clinical consultation	0.000	0.665		£290.07
Hospitalisation	0.000	0.413		£1,044.00
Palliative care specialist care	0.000	1.561		£69.00
Full blood count	0.000	0.961		£4.43
Renal function test	0.000	0.704		£1.46
Hepatic function test	0.000	0.739		£1.46
Drug acquisition costs				
Treatment	Cost per pack		Section 3.5.1	
Durvalumab (list price; 120mg)	£592.000			
Durvalumab (list price; 500 mg)	£2,466.00			
5-FU (2.5%)	£4.082			
5-FU (5%)	£4.621			
5-FU (5%)	£6.269			
Oxaliplatin	£6.482			
	£14.269			
	£11.312			
Leucovorin	£27.633			
	£15.800			
	£60.966			
Docetaxel	£4.486			
	£9.732			
	£19.702			
Subsequent treatments				
Regimen	Perioperative D-FLOT	Perioperative FLOT chemotherapy	Section 3.5.1	

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Cytotoxic chemotherapy			
Oxaliplatin	████	████	
Cisplatin	████	████	
5-FU	████	████	
Capecitabine	████	████	
Irinotecan	████	████	
Targeted therapy			
Trastuzumab	████	████	
IO monotherapy			
Nivolumab	████	████	
Pembrolizumab	████	████	
Administration costs (per admin)			
IV, simple chemotherapy	£418.29		Section 3.5.2
IV, subsequent dose(s)	£426.15		
IV, complex chemotherapy	£570.43		
Oral therapies	£0.00		
AE costs			
Total one-off AE cost, perioperative D-FLOT	£1,178.64		Section 3.5.3
Total one-off AE cost, perioperative FLOT chemotherapy	£1,283.47		

Footnotes: Please note that full details of the uncertainty associated with each parameter can be found on the 'parameters' tab on the CEM.

Abbreviations: AE: adverse event; BSA: body surface area; CT: computed tomography; EF: event-free; FLOT: Fluorouracil, Leucovorin, Oxaliplatin and Docetaxel; MRI: magnetic resonance imaging; RD: recurred disease; SE: standard error; TP: transition probability.

3.9.2 Assumptions

A summary of the key assumptions utilised in the base case economic analysis can be found in Table 55.

Table 55: Summary of assumptions in the economic analysis

Parameter	Assumption	Justification
Clinical parameters	Survival outcomes from MATTERHORN were extrapolated over the entire time horizon, assuming that some patients may be 'cured' if they remain EF after five years	As detailed in Section 3.3.1, according to ESMO guidelines, surgical resection of operable GC is potentially curative.⁶ To reflect the expected clinical outcomes for patients with resectable GOA receiving surgery with curative intent, the model includes the possibility that patients will be considered 'cured' if they have not experienced recurrence (or died) after a specified time period. A five year cure timepoint was applied, based on the NICE committee preferred cure assumptions used in a previous appraisal in early stage oesophageal or GOJC (TA746).⁸ By this timepoint, patients who are disease/event-free are expected to have a low risk of recurrence and to have been discharged from care. UK clinical experts confirmed that the five year cure assumption included in the base case is reflective of UK clinical practice, in which patients are often discharged from practice after 5 years of being EF and very few patients are estimated to experience disease relapse in this time.⁵ The impact of alternative cure assumptions, after either three years or seven years and additionally not including a cure assumption were explored in a scenario analysis (Section 3.11.3). Figure 8 (Section 2.6.1) shows that the EFS KM curves for both the perioperative durvalumab and control arms in the MATTERHORN trial show signs of plateauing after ~40 months, suggesting that patients who remain EF after approximately three years are likely to be cured.¹⁰⁹
Subsequent treatment	Treatment in RD	The distribution of subsequent therapies across treatment arms was informed by data from the MATTERHORN trial detailing the subsequent therapies received by patients who had experienced progression/recurrence (i.e., non-death event) as an EFS event and supplemented by UK clinical expert validation. ⁵ In a scenario analysis, published data from the MATTERHORN trial were used to account for treatments costs of subsequent therapy for all patients who received it (regardless of whether it was received before/after progression).
Vial sharing	Vial sharing included for IV treatments	Vial sharing for IV treatments was assumed in the model base case, reflecting how NHS resources

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		are used in clinical practice, whereby vial sharing for high-cost oncology drugs is common to minimise wastage. ¹⁶³ The impact of vial sharing for FLOT chemotherapy would be equivalent between the intervention and comparator arms. As such, the effect of vial sharing only impacts subsequent treatments. Vial sharing has been included in the base case to account for this, and the impact of excluding vial sharing has been explored in a scenario in Section 3.11.3.
Time on treatment	Time on treatment in EF was based on MATTERHORN treatment completion rates for durvalumab and FLOT components	Not all patients completed the maximum number of treatment cycles in the neoadjuvant and adjuvant phase in MATTERHORN. ³⁶ Data on treatment completion per cycle, separately for the durvalumab and FLOT components from MATTERHORN trial were therefore utilised to capture patients who did not complete their treatment regimens. ³⁶
Utility values	Treatment-independent utilities	The health state utility values were assumed to be the same across treatments (i.e., utilities are not treatment-specific), because, as detailed in Section 3.4.5, treatment status was not included in the best fitting model. This is also in alignment with the PRO data from the MATTERHORN trial reported in Section 2.6.7, which showed that treatment with D-FLOT did not adversely affect overall HRQoL vs placebo + FLOT. ⁷⁵
	Age-adjusted utility decrements included	In the base case analyses, age-adjusted utility decrements were applied in line with the NICE reference case (PMG36). ¹³⁸ The impact of excluding age-adjusted utility decrements has been explored in a scenario in Section 3.11.3.

Abbreviations: EFS: event-free survival; EF: event-free; FLOT: 5-fluorouracil, leucovorin, oxaliplatin, and docetaxel; GC: gastric cancer; GOJC: gastro-oesophageal junction cancer; IV: intravenous; NICE: National Institute for Health and Care Excellence; OC: oesophageal cancer; RD: recurred disease; SMR: standardised mortality ratio; TFR: time to first recurrence; TP: transition probability; TTDeath: time to death.

3.10 Base case results

Results of the economic analysis are presented in the following sections.

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3.10.1 Base case incremental cost-effectiveness analysis results

The probabilistic base case cost-effectiveness results for perioperative D-FLOT versus perioperative FLOT chemotherapy are presented in Table 56. The deterministic base case cost-effectiveness results are presented in Table 57. All results presented throughout Section 3.10.1 to 3.11.3 include the commercial access agreement price for durvalumab (detailed in Section 3.5.2).

The probabilistic base case cost-effectiveness results show the total costs associated with perioperative D-FLOT are estimated to be £[REDACTED], compared with £[REDACTED] for patients treated with perioperative FLOT chemotherapy (incremental cost of £[REDACTED]). The total QALYs are estimated to be higher for patients receiving perioperative D-FLOT versus perioperative FLOT chemotherapy ([REDACTED] versus [REDACTED]; incremental QALYs: [REDACTED]), resulting in an ICER for perioperative D-FLOT of £12,508 per QALY gained versus perioperative FLOT chemotherapy.

The probabilistic base case cost-effectiveness results are consistent with the deterministic results. In the deterministic base case analysis, perioperative D-FLOT was associated with [REDACTED] more QALYs and increased total costs of £[REDACTED] in comparison to perioperative FLOT chemotherapy, resulting in an ICER of £12,416 per QALY gained versus perioperative FLOT chemotherapy alone, therefore suggesting that the deterministic base case may be conservative. The incremental net health benefit (NHB) at a willingness-to-pay threshold of £30,000 per QALY is 0.94.

Taken together, the deterministic and probabilistic results demonstrate that perioperative D-FLOT represents a cost-effective use of NHS resources in the UK.

Table 56: Probabilistic base case results

Intervention	Total Costs	Total LYs	Total QALYs	Incremental Costs	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Perioperative D-FLOT	[REDACTED]	9.44	[REDACTED]	–	–	–	–
Perioperative FLOT chemotherapy	[REDACTED]	7.48	[REDACTED]	[REDACTED]	1.96	[REDACTED]	£12,508

Abbreviations: D-FLOT: durvalumab plus FLOT; FLOT: fluorouracil, leucovorin, oxaliplatin and docetaxel; ICER: incremental cost-effectiveness ratio; LY: life years; NHB: net health benefit; QALYs: quality-adjusted life years.

Table 57: Deterministic base case results

Intervention	Total Costs	Total LYs	Total QALYs	Incremental Costs	Incremental LYs	Incremental QALYs	ICER (£/QALY)	Incremental NHB at £30,000
Perioperative D-FLOT	■	9.54	■	–	–	–	–	–
Perioperative FLOT chemotherapy	■	7.55	■	■	1.99	■	£12,416	0.94

Abbreviations: D-FLOT: durvalumab plus FLOT; FLOT: fluorouracil, leucovorin, oxaliplatin and docetaxel; ICER: incremental cost-effectiveness ratio; LY: life years; NHB: net health benefit; QALYs: quality-adjusted life years.

3.11 Exploring uncertainty

3.11.1 Probabilistic sensitivity analysis

A probabilistic sensitivity analysis (PSA) was conducted in order to assess the impact of parameter uncertainty on the results of the CEM. The PSA was run for 1,000 iterations and in each iteration model inputs for all parameters were randomly drawn from specified distributions. Where possible the 95% CIs or SEs associated with each parameter were used to define the distribution, otherwise it was assumed that the standard error of the parameter would be 10% of the mean value.

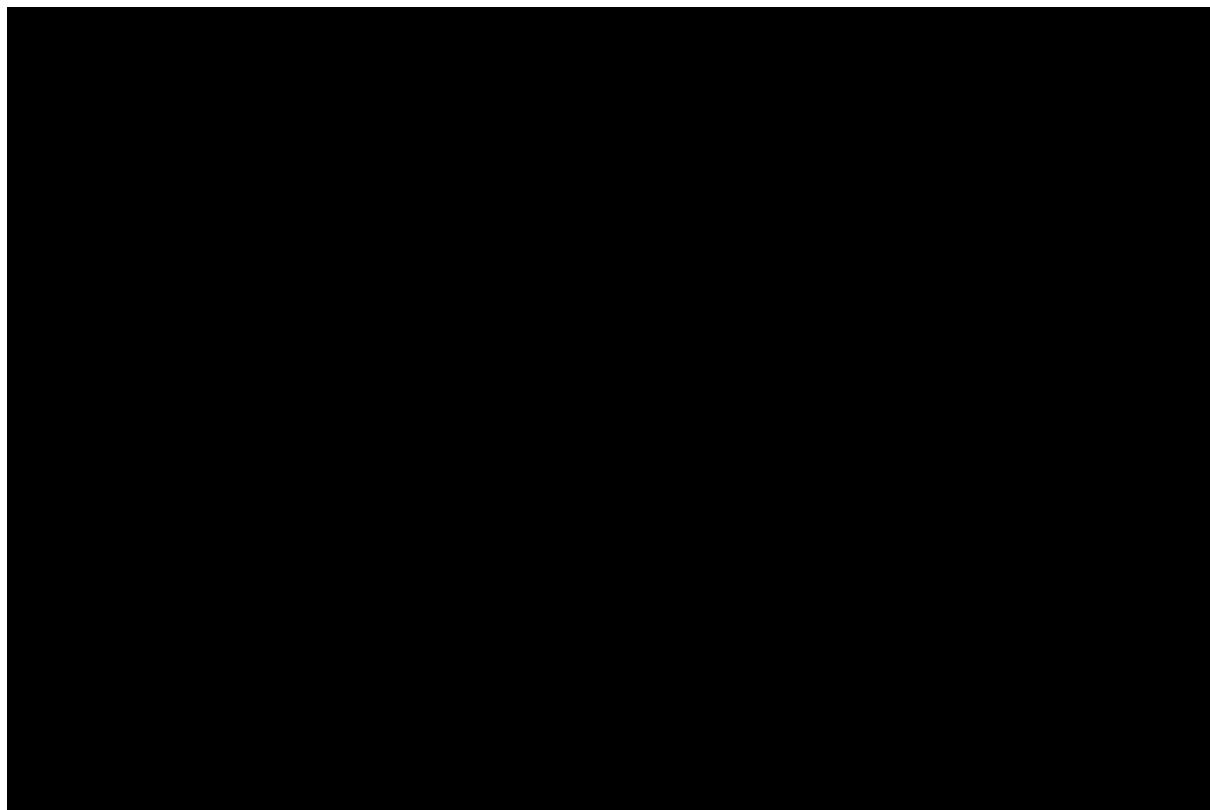
An ICER convergence plot for the PSA is presented in Figure 33, which demonstrated that the cumulative ICER stabilised after approximately 200 iterations. The probabilistic cost-effectiveness planes for perioperative D-FLOT versus perioperative FLOT chemotherapy alone are presented in

Figure 34.

The cost-effectiveness acceptability plots are presented in

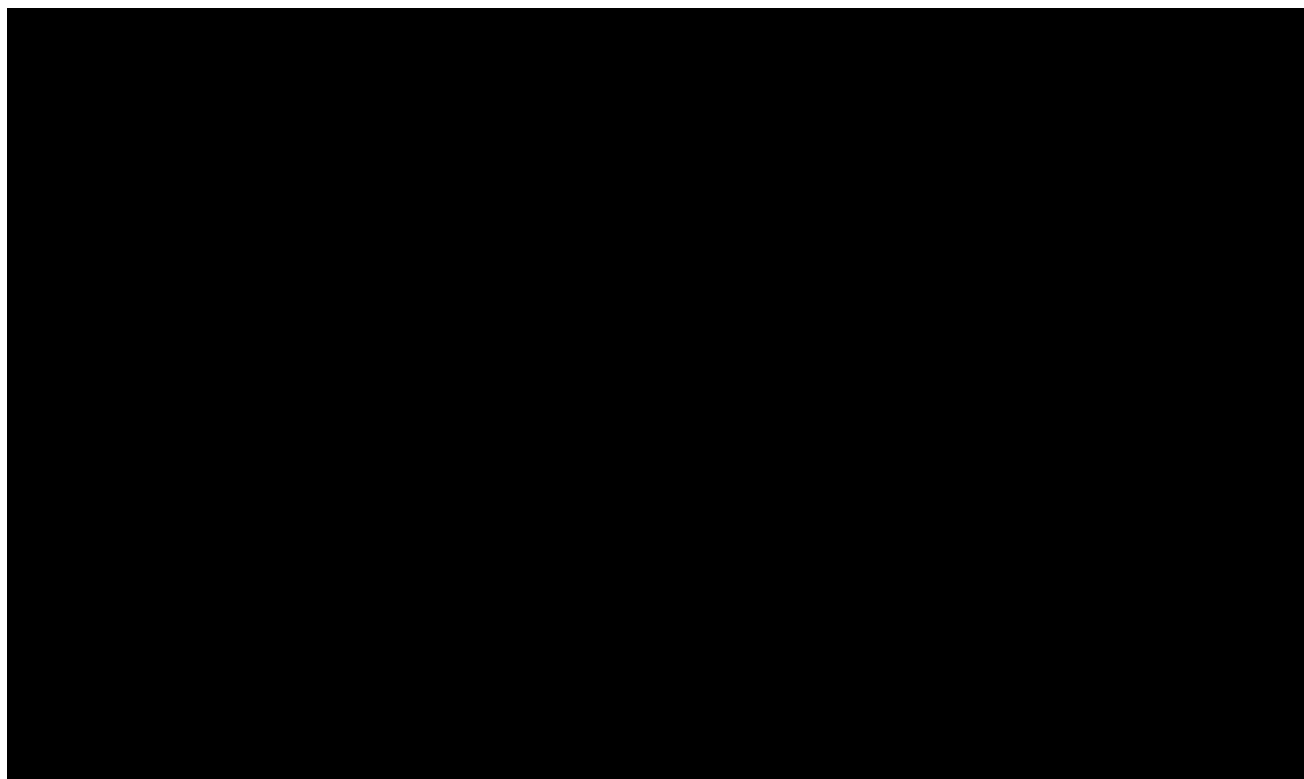
Figure 35; the PSA found the probability of perioperative D-FLOT being a cost-effective use of NHS resources to be ■ and ■ at a WTP threshold of £20,000 and £30,000 per QALY gained, respectively.

Figure 33: Convergence plot



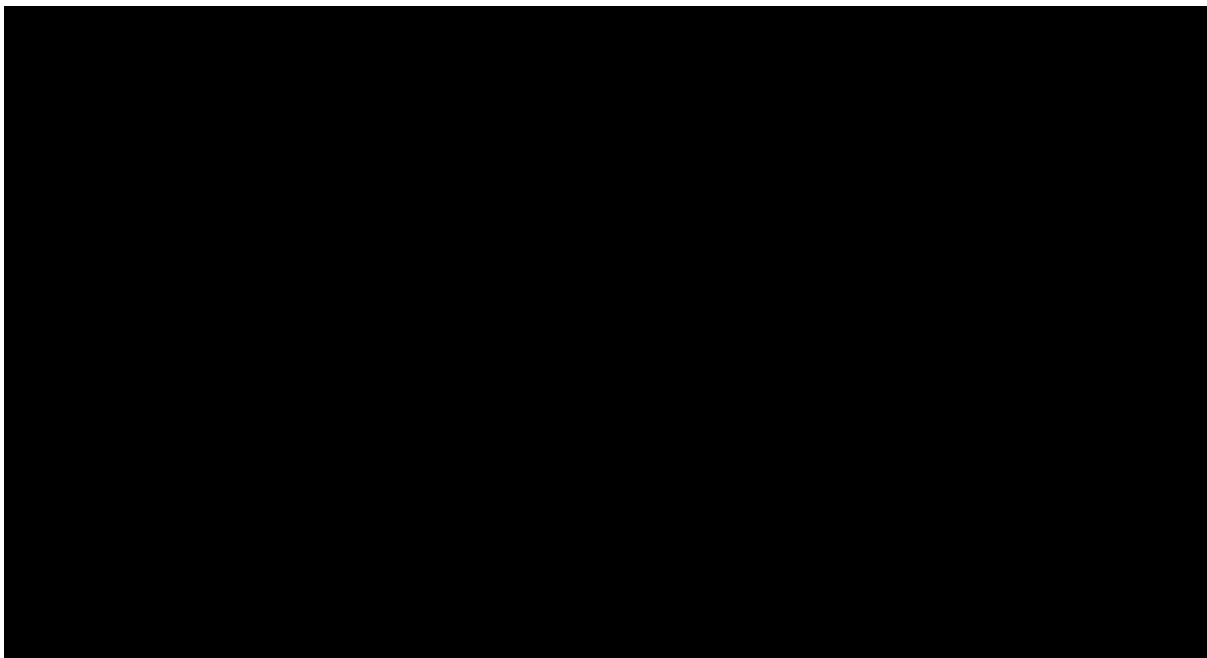
Abbreviations: ICER: incremental cost-effectiveness ratio; PSA: probabilistic sensitivity analysis.

Figure 34: Probabilistic cost-effectiveness plane



Abbreviations: FLOT: fluorouracil, leucovorin, oxaliplatin and docetaxel; QALYs: quality adjusted life years.

Figure 35: Cost-effectiveness acceptability curve



Abbreviations: FLOT: fluorouracil, leucovorin, oxaliplatin and docetaxel.

3.11.2 **Deterministic sensitivity analysis**

In order to assess the robustness of the base case cost-effectiveness results, a deterministic sensitivity analysis (DSA) was conducted by varying the input for each parameter in the model, whilst keeping all other inputs the same. In the DSA, the base-case inputs for parameters were varied using the 95% CIs where available. In the absence of 95% CIs, upper and lower bounds were calculated assuming a SE of 10%.

A tornado diagram showing the top 10 most influential parameters on the ICER for perioperative D-FLOT versus perioperative FLOT chemotherapy is presented in Figure 36. Overall, all variables tested had a minimal impact on the ICER and on the cost-effectiveness conclusions; the ICER upper bounds of all variables remained below ~£20,000/QALY, reflecting the robustness of the base case results and the minimal uncertainty regarding perioperative D-FLOT being a cost-effective use of NHS resources in this population.

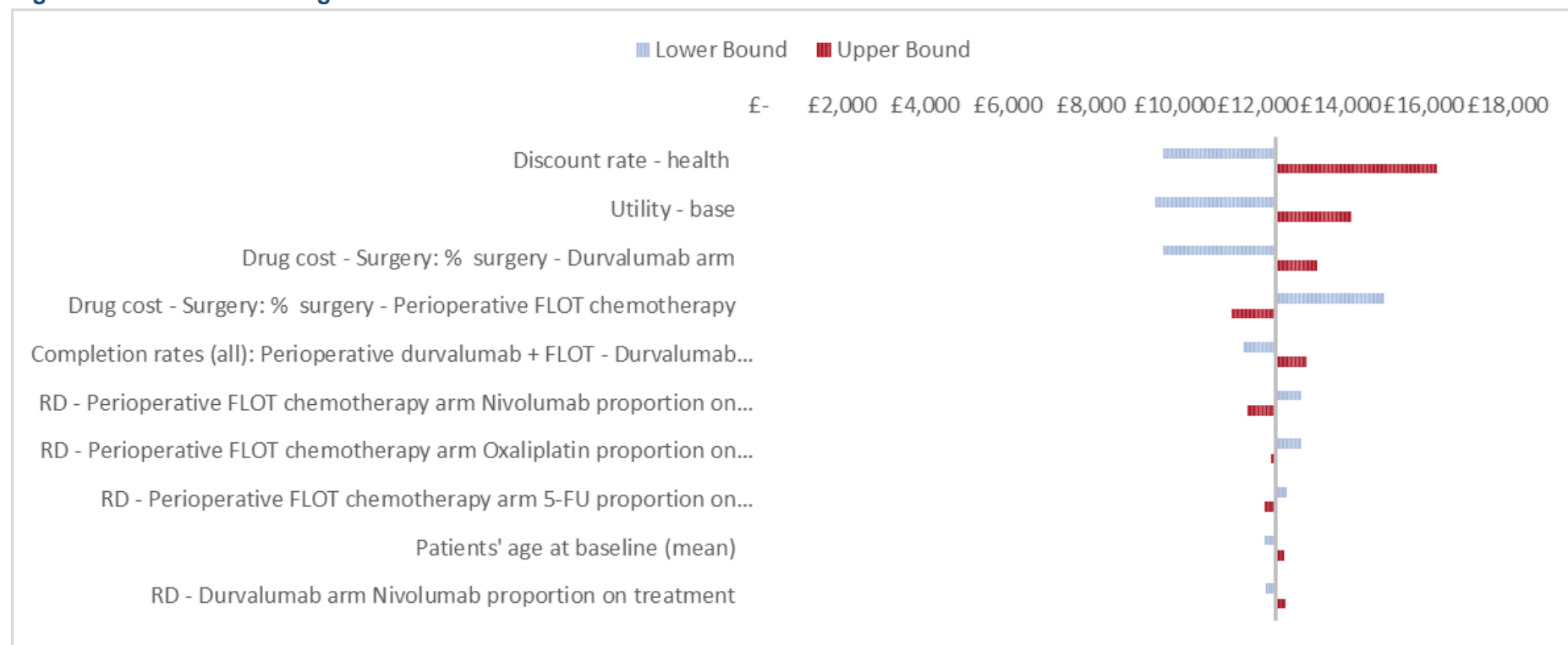
The ICER was found to be most sensitive to the discount rate for all costs and benefits. When varying the discount rate between 1.5% and 6.0%, the ICER varied between £9,710/QALY and £16,308/QALY, highlighting that the greatest driver of the ICER did not preclude perioperative D-FLOT from being cost-effective compared to perioperative FLOT chemotherapy. In the base case, a discount of 3.5% was applied in line with NICE PMG36 and therefore, this should be considered to represent a minimal source of uncertainty.¹³⁸

The variable with the second greatest impact on the ICER was the utility value for the EF health state, which when varied between [REDACTED] and [REDACTED], resulted in ICERs of £9,516/QALY and £14,247/QALY, respectively. As noted in Section 3.4.5, the utility value used in the base case (0.840) was derived from the EQ-5D-5L data from the MATTERHORN trial, mapped onto the UK EQ-5D-3L value set ([REDACTED]), using the NICE preferred mapping algorithm and capped at the UK general population utility, given it was slightly higher than the age-adjusted general population.¹⁴⁰ UK clinical experts validated that the GPM-capped EF utility value was reasonable, and consistent with their understanding of QoL in patients with resectable GOA.⁵ To further explore any uncertainty around the EF utility value, a scenario analysis was explored using the uncapped utility value, derived from the MATTERHORN trial (Section 3.11.3), which had a minimal impact on the ICER.

The proportion of patients receiving surgery in the D-FLOT and perioperative FLOT chemotherapy arms had the next greatest impact on the ICER. As detailed in Section 3.5.1, a one-time cost of surgical resection was in the base case for patients in the EF health state ([REDACTED]% and [REDACTED]% in the D-FLOT and perioperative FLOT chemotherapy arms, respectively), to reflect the possibility that not all patients might receive surgery following neoadjuvant treatment. The overall impact of the proportion of patients receiving surgery was still minimal, with the ICER varying within £9,719/QALY and £13,408/QALY across the D-FLOT arm and between £11,367/QALY and £15,047/QALY in the perioperative FLOT chemotherapy arm. Moreover, because the data from MATTERHORN showed that D-FLOT did not impact the ability of patients to undergo surgery (see Section 2.6.4) the proportion of patients receiving surgery is not expected to differ substantially for patients receiving either treatment, and so it lacks face validity to change the proportion of patients receiving surgery in one arm, without changing the other.

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Figure 36: DSA tornado diagram



Abbreviations: DSA: deterministic sensitivity analyses; FLOT: FLOT: fluorouracil, leucovorin, oxaliplatin and docetaxel; 5-FU: 5-fluorouracil; RD: recurred disease.

3.11.3 Scenario analysis

As described in Section 3.11, scenario analyses were conducted to explore the impact of structural assumptions and alternative inputs on the results of the cost-effectiveness model. A complete list of the scenario analyses explored along with the rationale for their selection is provided Table 58.

Table 58: Summary of scenario analyses

Model element	Base case	Scenario analysis	Justification
SMR	1.0	1: 1.1	Clinical experts consulted by the Company as part of this submission validated that the SMR of 1.1 accepted by NICE in the appraisal of nivolumab for early oesophageal or GOJC (TA746) is conservative, with the true SMR likely to be lower than 1.1 in UK clinical practice. ^{5, 8} A conservative scenario has been performed with an SMR of 1.1, to explore the impact of the SMR value on the ICER.
Cure assumption	5 years	2: No cure assumption	In the base case, cure was assumed after patients had been event-free for 5 years, in line with UK clinical expert validation and TA746. ^{5, 8} An alternative scenario was included where no cure assumption was applied, to assess the impact of this on the ICER.
TP1	Generalised gamma	3: Log-normal	The use of the log-normal distribution for TP1 was explored in a scenario, given this reflects the second best statistically fitting curve choice. The log-normal reflects a more pessimistic estimate of TP1 for both perioperative D-FLOT and perioperative FLOT chemotherapy.
TP2	Gompertz	4: Generalised gamma	The use of the generalised gamma distribution for TP2 was explored in a scenario to assess the impact of utilising an alternative, more pessimistic parametric distribution for TP2.
TP3	Log-logistic	5: Exponential	Though it does not reflect the observed hazards from the MATTERHORN trial, as the best statistically

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Model element	Base case	Scenario analysis	Justification
			fitting curve across both treatment arms, the selection of the exponential distribution for TP3 was explored in a scenario analysis.
Subsequent treatments	The distribution of subsequent therapies informed by the MATTERHORN trial for patients who had experienced progression/recurrence (i.e., non-death event) as an EFS event and supplemented by UK clinical expert validation. ⁵	6: All subsequent treatments included, regardless of whether they were received before/after progression	Though the base case approach of including subsequent treatments for patients who had experienced progression and recurrence was aligned with validation from UK clinical experts, this scenario was conducted to explore the impact of this assumption on the ICER.
Utility values	UK general population utility cap applied (EF utility value: 0.840)	7a: UK general population utility cap excluded (EF utility value: [REDACTED])	The utility value for the EF health state derived from MATTERHORN ([REDACTED]) was higher than the gender- and age-adjusted utility value for the UK general population (0.840).¹⁴⁰ As such, the EF utility value was capped to the UK general population utility in the base case. This scenario explored the impact of not capping the EF utility to the UK general population and using the utility value derived directly from the MATTERHORN trial.
	RD utility value: 0.747, based on TA746 ⁸	7b: RD utility value: [REDACTED], based on the data from MATTERHORN	Low numbers of EQ-5D-5L observations were recorded after progression or recurrence in the MATTERHORN trial (N=[REDACTED]). Consequently, in the base case, utility values for the RD health state were instead sourced from TA746.⁸ For completeness, a scenario analysis using an RD utility value derived from MATTERHORN (with the decrement associated with recurred disease based on the MMRM ([REDACTED]) removed from the general population-capped EF state utility value [0.840–[REDACTED]]), was explored.

Model element	Base case	Scenario analysis	Justification
	Age-adjusted utility decrements included	7c: Age-unadjusted utility decrements excluded	In the base case, analyses age-adjusted utility decrements were applied in line with the NICE reference case (PMG36). ¹³⁸ The impact of excluding age-adjusted utility decrements has been explored in a scenario analysis.
Vial sharing	Included	8: Excluded	In the base case analysis, vial sharing was included, reflecting how NHS resources are used in clinical practice, whereby vial sharing for high-cost oncology drugs is common to minimise wastage. ¹⁶³ This scenario explores the impact of excluding vial wastage on the ICER.
Time horizon	■ years	9: 30 years	This scenario was conducted to explore the impact of using a shorter model time horizon.
Discounting costs/effects	3.5%	10: 1.5%	In the base case, a discount of costs/effect of 3.5% was applied in line with NICE PMG36. ¹³⁸ This scenario explores the impact of reducing this discount on the ICER.

Abbreviations: D-FLOT: durvalumab with 5-fluorouracil, leucovorin, oxaliplatin and docetaxel; EFS: event-free survival; EF: event-free; FLOT: 5-fluorouracil, leucovorin, oxaliplatin and docetaxel; ICER: incremental cost-effectiveness ratio; MATTERHORN: name of the phase III trial referenced; MMRM: mixed model for repeated measures; NHS: National Health Service; RD: recurred disease; SMR: standardised mortality ratio; TA: technology appraisal; TP1: first transition probability; TP2: second transition probability; TP3: third transition probability; UK: United Kingdom.

A summary of the deterministic results of these scenario analyses are presented in Table 59, inclusive of the commercial access agreement for D-FLOT. In these analyses the conclusions of the base case analysis were unchanged, with the ICER for the comparison of perioperative D-FLOT and perioperative FLOT chemotherapy being cost-effective (ICER range: £9,310–13,742 per QALY) across the full range of scenario analyses conducted, demonstrating the minimal uncertainty and robustness associated with the base case results. The ICER was most sensitive to using the exponential distribution for TP3 (base case: log-logistic), however the results of this scenario favour perioperative D-FLOT, with the ICER decreasing by £3,106 per QALY compared to the base case. All scenarios demonstrated positive incremental QALYs (range: ■) in favour of perioperative D-FLOT.³⁶

Table 59: Summary of scenario analysis results – deterministic

Scenario		Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Base case		████	██	£12,416
1	SMR of 1.1	████	██	£12,725
2	No cure assumption	████	██	£11,182
3	Use log-normal distribution for TP1	████	██	£11,769
4	Use generalised gamma distribution for TP2	████	██	£13,742
5	Use exponential distribution for TP3	████	██	£9,310
6	All subsequent treatments included, regardless of whether they were received before or after progression	████	██	£12,766
7a	UK general population utility cap excluded (EF utility value: █████)	████	██	£12,453
7b	RD utility value set to █████, based on the data from MATTERHORN	████	██	£12,497
7c	Age-adjusted utility decrements excluded	████	██	£11,678
8	Vial sharing excluded	████	██	£12,183
9	30-year time horizon	████	██	£12,610
10	Annual discount rate of 1.5%	████	██	£9,657

Abbreviations: EF: event-free; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; RD: recurred disease; SMR: standardised mortality ratio; TP: transition probability.

3.12 Subgroup analysis

For the reasons detailed in Section 1.1, no subgroups were considered in this appraisal, and therefore no cost-effectiveness analyses were conducted for specific subgroups.

3.13 Benefits not captured in the QALY calculation

HRQoL burden associated with disease progression and metastatic GOA

Disease progression and recurrence diminish the HRQoL of patients with GOA, and the fear of disease recurrence following surgery also negatively impacts patients' daily lives (Section 1.3.4).⁷⁶ A systematic review of 12 studies reported that the utility scores of patients with GC decline with disease stage due to the worsening symptom burden and severe manifestations such as abdominal pain, and gastric obstruction that arise as the disease progresses (as detailed in Section 1.3.4).^{28, 76} Additionally, 24.8% more patients with advanced GC report anxiety/depression than those with early stage disease.⁷⁷

UK clinical experts validated that the utility values used in the base case analyses reflect the clinical reality of patients with GOA.⁵ However, as noted detailed above, disease recurrence drastically impacts patient QoL, and patients may experience decreases utility at different points of their disease journey. As such, at disease recurrence, patients in the RD state may have lower utility than the utility values used in the model and subsequently, by reducing the risk of disease recurrence, progression or death, the QALY benefit associated with D-FLOT could be slightly underestimated.

Value of hope

Value of hope is conceived as patient risk-seeking preferences based on a potential substantial benefit.¹⁶⁴ This is particularly important for patients with resectable GOA who undergo neoadjuvant chemotherapy and surgery. Even following the introduction of perioperative FLOT, the disease survival rates for GOA remain low, and the risk of disease recurrence remains high.³⁰⁻³² If recommended, durvalumab would become the first IO treatment to be used in combination with the current SoC (perioperative FLOT) for patients with resectable GOA and will be administered with curative intent for all eligible patients, representing a step-change in the management of this disease.

D-FLOT is administered at the last opportunity for cure in resectable GOA, so there are substantial benefits and hope for both patients and their families from knowing that D-FLOT increases the chance of cure and decreases the risk of recurrence following surgery. Whilst the health benefits of the reduction of risk in recurrence will be captured in the QALY, this hope also enhances the ability of patients and their families to cope with difficult circumstances and promotes a more positive emotional state.

Moreover, treatment-independent HSUVs have been used in the model, as outlined in Section 3.4.5. Because of this, the increased hope, and therefore HRQoL that patients will experience with D-FLOT compared to perioperative FLOT chemotherapy, owing to the improved outcomes and reduction in risk of disease recurrence associated with D-FLOT are not captured in the utility values. The HRQoL benefits associated with the value of hope are therefore not fully captured in the QALY calculations.

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Reduction in caregiver burden

The economic model also underestimates the benefits for the carers of patients with GOA in the RD health state. As detailed in Section 1.3.4, advanced/recurrent GOA is associated with a substantial disease burden, with patients requiring substantial supportive needs including those related to disruption to the digestive system, the requirement for a modified diet and extreme changes in weight.⁸¹⁻⁸³ Due to the considerable supportive needs for patients with GOA, informal caregivers play a critical role for patients with GOA and face high levels of caregiver burden including anxiety, depression and fear of disease recurrence.⁸¹⁻⁸³

The subsequent productivity losses associated with providing patients an average of 42 hours of support weekly (and the costs associated with this) are not captured in the QALY calculations.⁸⁰ The caregiver burden associated with GOA is especially pronounced in patients undergoing intensive treatment and in those with advanced disease.^{90, 91} If reimbursed, durvalumab may prevent patients' disease progression to advanced disease, meaning such intensive treatment can be avoided. Preventing the progression/recurrence of patients' disease and reducing their symptom burden will also allow them to be more independent, so less caregiver time is required. As such, the benefits of perioperative D-FLOT compared to perioperative FLOT chemotherapy may be underestimated in the economic model.

3.14 Validation

3.14.1 Validation of cost-effectiveness analysis

Internal validity

Model validations were performed in alignment with best practices.¹⁶⁵ This validation process included the assessment of model design, verification of calculation logic and formula integrity, and stress-testing with extreme values. Any discrepancies or errors identified during the validation process were promptly corrected and integrated into the final model.

Further quality-control procedures for verification of input data and coding were performed by health economists not involved in the model development. This validation exercise focused on assessing the model's conceptual validity, by examining structure, logic, and causal relationships, as well as its technical implementation. Overall, this additional validation further strengthens confidence in the model's technical robustness and conceptual validity.

External validity

Following internal validation, an independent review was conducted by a third-party health economics and outcomes research consultancy in July 2025. This validation exercise focused on assessing the model's conceptual validity; examining structure, logic, and causal relationships, as well as its technical implementation. Overall, this additional validation further strengthens confidence in the model's technical robustness and conceptual validity.

Clinical feedback was also used to validate key inputs and assumptions utilised in the model, including the use of a cure assumption, utility values, subsequent treatment choices and monitoring frequencies.

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Model prediction validation

As detailed in Section 3.3.1, EFS and OS were not explicit inputs in the cost-effectiveness analysis but outcomes that could be predicted by the model based on the time spent across the (non-death) health states. In order to validate the long-term predictions from the model, data were compared against the MATTERHORN trial EFS and OS, as well as external data reporting long-term estimates of EFS, and OS for perioperative FLOT chemotherapy, with the findings of this validation presented in Section 3.3.^{7, 36} Using the base case extrapolations for TP1–TP2, (generalised gamma and Gompertz, respectively), the model prediction of EFS at three years in the perioperative FLOT chemotherapy arm (■■■%) is highly aligned with the three year EFS for the control arm of the MATTERHORN trial (December 2024 DCO: ■■■%).³⁶ Additionally, the 3-year OS predicted by the model was ■■■% and ■■■% in the perioperative D-FLOT and perioperative FLOT chemotherapy arms, respectively, which is highly consistent and within the confidence intervals of the ■■■% (95% CI: ■■■■■) and ■■■% (95% CI: ■■■■■) reported in the MATTERHORN trial December 2024 DCO for each arm, respectively.³⁶

These model prediction validations therefore further validate the selection of parametric distributions for TP1–TP3, demonstrating that the EFS and OS long-term predictions from the model align closely with outcomes observed in the MATTERHORN trial and remain consistent with published literature.⁷

3.15 Interpretation and conclusions of economic evidence

3.15.1 Summary of the cost-effectiveness evidence

A *de novo* economic model was developed to evaluate the cost-effectiveness of perioperative D-FLOT for patients with resectable GOA. The model comprehensively considered all relevant costs, resources, and outcomes from a UK NHS and PSS healthcare perspective. A three-state semi-Markov STM was developed, which followed a cohort of patients over a lifetime (■■■ year) horizon. The model structure was aligned to the structure used in the recent NICE appraisal of adjuvant nivolumab in GOJ adenocarcinoma (TA746) as detailed in Section 3.2.2.⁸ UK clinical experts consulted by the Company confirmed that the model structure was appropriate to model resectable GOA, and was appropriate for a curative intent treatment such as perioperative D-FLOT.⁵

UK clinical experts also validated that the comparator included in the model, perioperative FLOT chemotherapy, represents the SoC for patients with resectable GOA in UK clinical practice and is the only appropriate comparator to perioperative D-FLOT in this setting.⁵ Additionally, the model in this submission relies solely on direct clinical evidence from the MATTERHORN trial, which, as validated by clinical experts, included a patient population that is relevant to UK clinical practice and the decision problem addressed by this submission.⁵

As detailed in Section 2, the MATTERHORN trial demonstrated the efficacy and tolerability of perioperative D-FLOT compared to perioperative FLOT chemotherapy (the current SoC).^{5, 36} Based on the results of the trial, perioperative D-FLOT represents the only IO regimen to successfully demonstrate a statistically significant benefit in EFS compared to perioperative FLOT chemotherapy (HR: 0.71; 95% CI: 0.58, 0.86; $p < 0.001$) in the resectable GOA setting.³⁶ Perioperative D-FLOT also demonstrated improved OS at DCO2 (HR: 0.78).³⁶ As noted in Section 2.12, OS data from DCO3 (presented at the ESMO 2025 Congress) are consistent with the current evidence base, including a statistically significant OS benefit of D-FLOT vs the control arm at DCO3

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(HR: 0.78; 95% CI: 0.63, 0.96; $p=0.021$).^{36, 112} UK clinical experts commented that these results demonstrate the potential of D-FLOT to represent a practice-changing treatment that would displace perioperative FLOT chemotherapy alone as the current SoC in clinical practice.⁵ In MATTERHORN, D-FLOT additionally demonstrated a tolerable and manageable safety profile and did not preclude patients from undergoing surgery or from continuing to receive their planned adjuvant treatment.³⁶

These improved efficacy results compared to perioperative FLOT chemotherapy were reflected in the base case economic analysis, where durvalumab was associated with 1.96 LYG and ■■■ QALYS gained compared to perioperative FLOT chemotherapy in the probabilistic analysis. Perioperative D-FLOT was also associated with lower costs within the RD health state compared to perioperative FLOT chemotherapy (as detailed in Appendix H.2), thus offsetting the greater cost of D-FLOT in the EF health state.

Overall, the probabilistic and deterministic base case ICERs presented in Section 3.10.1 (£12,508/QALY and £12,416/QALY, respectively [including commercial access agreement for durvalumab]) for the comparison of perioperative D-FLOT and perioperative FLOT chemotherapy demonstrate that perioperative D-FLOT represents a cost-effective use of NHS resources for patients with resectable GOA.

The PSA found the probability of perioperative D-FLOT to be ■■■ and ■■■ at a WTP threshold of £20,000 and £30,000 per QALY gained, respectively. In the DSA, the base case results were found to be robust to uncertainty, with the ICER remaining below ~£20,000/QALY for all model parameters. The results were most sensitive to the discount rate, HSUV in the EF health state and proportion of patients receiving surgery in either treatment arm, however, perioperative D-FLOT remained cost-effective when using the upper bound of each of these variables, reflecting the certainty in the base case results.

Scenario analyses conducted to address sources of uncertainty in the model additionally demonstrated that variations in the ICER were minimal across the full range of scenario analyses conducted (ICER range: £9,310–13,742 per QALY), thus reflecting the minimal uncertainty and robustness associated with the base case results.

As detailed further in Section 3.13, the economic results presented in this submission omit certain key benefits associated with D-FLOT that cannot be captured in the QALY calculations. These include the value of hope associated with providing an effective treatment option for patients with resectable GOA, the full extent of the reduction in HRQoL associated with disease progression/recurrence and the reduction in caregiver burden associated with D-FLOT, which both mean that the base case results likely represent a conservative estimate of the true cost-effectiveness of perioperative D-FLOT in UK clinical practice.

3.15.2 Strengths

This cost-effectiveness analysis has several strengths. Notably, it includes the clinical and HRQoL data from the MATTERHORN RCT, which provides direct head-to-head evidence comparing perioperative D-FLOT with the SoC treatment in UK clinical practice, perioperative FLOT chemotherapy.³⁶ UK clinical experts validated that the MATTERHORN trial included both a patient population and comparator relevant to UK clinical practice and the decision problem addressed by this submission, considering the results of the trial to be “practice changing”.⁵

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Additionally, as detailed above, extensive sensitivity and scenario analyses were conducted to assess the robustness of the base case analysis. In summary, the results and cost-effectiveness conclusions of these analyses were highly consistent with the base case; thus reflecting the certainty in the key model parameters.

Furthermore, the model closely aligns to the NICE reference case, by adopting an NHS and PSS perspective as well as utilising a lifetime time horizon to ensure all costs and QALY gains associated with D-FLOT and perioperative FLOT chemotherapy are fully captured.¹³² In line with PMG36, discounting of costs and benefits was applied at a rate of 3.5% per annum.¹³²

Finally, as detailed in Section 3.14.1, the model underwent internal and external validation to ensure it was robust and aligned with UK clinical practice.⁵ Overall, UK clinical experts validated that the model structure, comparator (perioperative FLOT chemotherapy), utility values and cure assumption were appropriate and in line with UK clinical practice.⁵ In addition to this, several adaptations were made to the model to further align the model to feedback from UK clinical experts, such as by including irinotecan as a subsequent treatment in place of ramucirumab, and accounting for oncologist visits in the RD health state.⁵ As a result, the model is anticipated to be highly reflective of UK clinical practice and to accurately capture the benefits associated with perioperative D-FLOT compared to perioperative FLOT chemotherapy.

Additionally, the EFS and OS predictions from the model are highly aligned with the MATTERHORN trial and published literature.⁷ This reflects that the model has the ability to accurately predict the long term EFS and OS outcomes of patients with resectable GOA receiving perioperative D-FLOT or perioperative FLOT chemotherapy.

3.15.3 Limitations

A potential limitation of these analyses is the need to extrapolate data from the MATTERHORN trial. Long-term extrapolations of data from MATTERHORN were required (in line with NICE TSD 14) due to the median follow-up of the trial being shorter than the ■■■ year model lifetime horizon.¹²⁷ However, any uncertainty in these long-term extrapolations was explored in scenario analyses presented in Section 3.11.3, whereby alternative parametric distributions were selected for each transition probability. The results of these scenarios showed that the base case results were robust to variations in the choice of parametric distribution, and thus providing certainty in the base case extrapolations. Additionally, UK clinical expert validation was used to support the selection of the parametric distributions, as noted in Section 3.3, to ensure the predictions accurately reflect the efficacy of perioperative D-FLOT and perioperative FLOT chemotherapy.

Additionally, the need to extrapolate the data from the MATTERHORN trial reflects the nature of resectable GOA where treatment can substantially improve survival and, can lead to cure, allowing patients to survive for many more years.⁶ The 5-year cure assumption, applied in line with TA746, mitigates any uncertainty associated with this relative immaturity however, as after this timepoint, any patients who have not experienced an EFS event in the model are no longer at risk of recurrence or death, meaning TFR and TTDeath data do not require extrapolation beyond the 5-year timepoint.⁸ Subsequently, any uncertainty in the TFR or TTDeath data in the model is mitigated and therefore does not impact the conclusions of the economic analyses. This approach was considered highly reflective of UK clinical practice by clinical experts, and the assumption of cure is also supported by published literature, as noted in Section 3.3.1.^{145, 146}

3.15.4 Conclusion

Despite the improvement in patient outcomes with the introduction of perioperative FLOT chemotherapy compared to previous regimens, outcomes for patients with GOA remain poor, with an estimated 5-year OS of 45%.⁷ Additionally, currently, IO-based treatment regimens are only available once patients' disease advances and recurs, at which point there is a very limited possibility of achieving disease cure, with treatment being largely palliative. Novel treatment regimens for patients with resectable GOA that enhance the efficacy of FLOT and improve long-term disease control are essential for improving patient survival rates and the chances of cure.⁴⁴ Combining IO therapies with perioperative FLOT chemotherapy holds particular promise in addressing these unmet needs for patients with resectable GOA by priming anti-tumour immunity in the neoadjuvant setting and sustaining immunosurveillance in the adjuvant setting.⁴⁴

Overall, the probabilistic and deterministic base case ICERs presented for the comparison of D-FLOT and perioperative FLOT chemotherapy demonstrate perioperative D-FLOT to be a cost-effective use of NHS resources for the treatment of patients with resectable GOA. Ultimately, as shown by the results of the MATTERHORN trial, perioperative D-FLOT will prevent or delay disease progression and recurrence, without compromising patient HRQoL or their ability to undergo surgery, making it a highly impactful and efficacious treatment regimen. If recommended, perioperative D-FLOT will subsequently address the significant unmet needs within the resectable GOA disease setting, disease setting, and represent a treatment option that will increase the chance of patients being cured from their disease.

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Summary of Information for Patients (SIP)

November 2025

File name	Version	Contains confidential information	Date
ID6374_Durvalumab GCGOJC NICE SIP [noCON]_051025	N/A	No	5 th November 2025

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the [Health Technology Assessment International – Patient & Citizens Involvement Group](#) (HTAi PCIG). Information about the development is available in an open-access [JTAHC journal article](#)

SECTION 1: Submission summary

Please note: Further explanations for the words and phrases highlighted in **black bold text** are provided in the glossary ([Section 4b](#)). Cross-references to other sections are highlighted in [blue](#).

1a) Name of the medicine (generic and brand name):

Generic name: Durvalumab

Brand name: IMFINZI®

1b) Population this treatment will be used by: Please outline the main patient population that is being appraised by NICE:

This medicine is under consideration for the treatment of adults with **resectable gastro-oesophageal adenocarcinoma** (GOA), which comprises patients with **gastric cancer** (GC) and **gastro-oesophageal junction cancer** (GOJC). Further information on GOA is provided in [Section 2a](#).

1c) Authorisation: Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state

this, and reference the section of the company submission with the anticipated dates for approval.

The **marketing authorisation** for durvalumab from the **Medicines and Healthcare products Regulatory Agency (MHRA)** is pending. The anticipated dates for approval can be found in the Company Evidence Submission in Section 1.1.

1d) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

AstraZeneca provided the following support to relevant patient groups in the UK in the last 12 months.

As a member of the Association of the British Pharmaceutical Industry (ABPI), AstraZeneca is required to publish information about relationships with patient organisations, annually, known as transfer of value (TOV) as presented in [Table 1](#). Any contributions or fees shall be used exclusively as per the letter of request from the patient organisation or as outlined in the contracted service agreement, and do not obligate the patient organisation to purchase, use, recommend or arrange for the use of any product of AstraZeneca or any of its affiliates.

Table 1: Summary of support provided by AstraZeneca to relevant patient groups

Patient group	Engagement/activity	Reason for engagement/activity	Financial support provided
British Liver Trust	Provided financial support to the organisation to assist with delivery of patient education and disease awareness initiatives related to liver health	To support activities that improve patient awareness and understanding of liver disease within the gastrointestinal area	Yes – financial support provided in the form of a grant and consultancy fees.
AMMF (The Cholangiocarcinoma Charity)	Provided financial support to the organisation to assist with the development of patient information and awareness materials for cholangiocarcinoma	To support initiatives aimed at improving patient understanding and disease awareness for cholangiocarcinoma	Yes – financial support provided in the form of sponsorship.

GC/GOJC (including OC) patient groups	No direct engagement or collaboration in the UK in the past 12 months	N/A	None

Abbreviations: AMMF: Alan Morement Memorial Fund (The Cholangiocarcinoma Charity); GC: gastric cancer; GI: gastrointestinal; GOJC: gastro-oesophageal junction cancer; OC: oesophageal cancer; UK: United Kingdom.

SECTION 2: Current landscape

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

What is GOA?

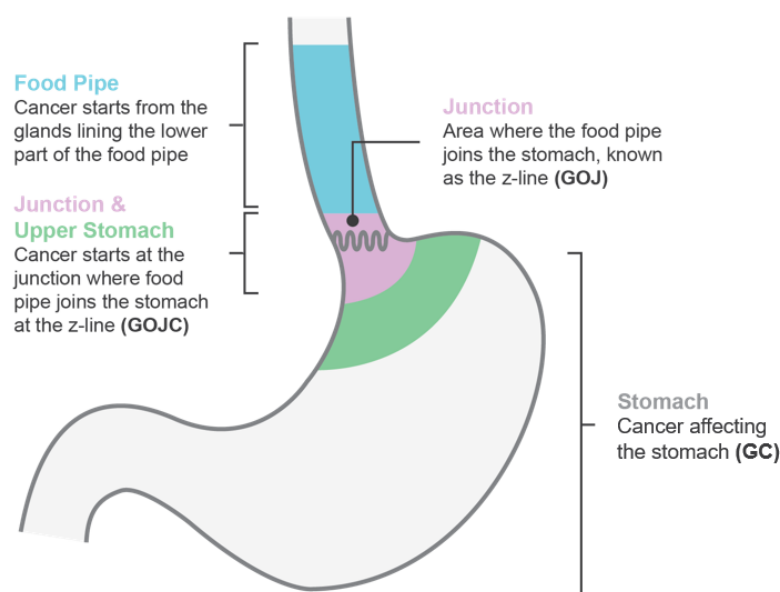
Cancers that form in the stomach and cancers that form close to where the food pipe (oesophagus) meets the stomach are together called **gastro-oesophageal cancers**.¹ Gastro-oesophageal cancers are grouped into two main types based on where they start in the stomach (Figure 1):¹

- GC: Starts in the lower or middle parts of the stomach, away from where it connects to the food pipe
- GOJC: Starts where the food pipe and the upper part of the stomach meet

GC and GOJC cancers can be further categorised based on the cell type they come from. The most common type of these cancers begin in the cells of the stomach lining that produce mucus.² These cancers are called **adenocarcinomas**. Gastro-oesophageal cancers originating from cells that produce mucus are collectively termed GOA.

The population of interest to the submission is adults with resectable GOA. 'Resectable' means that the cancer has not spread beyond the stomach and can be removed by surgery. Surgery can **cure** patients of their cancer. This means that there are no traces of the cancer left and the cancer is not expected to come back.³

Figure 1. GOA classification



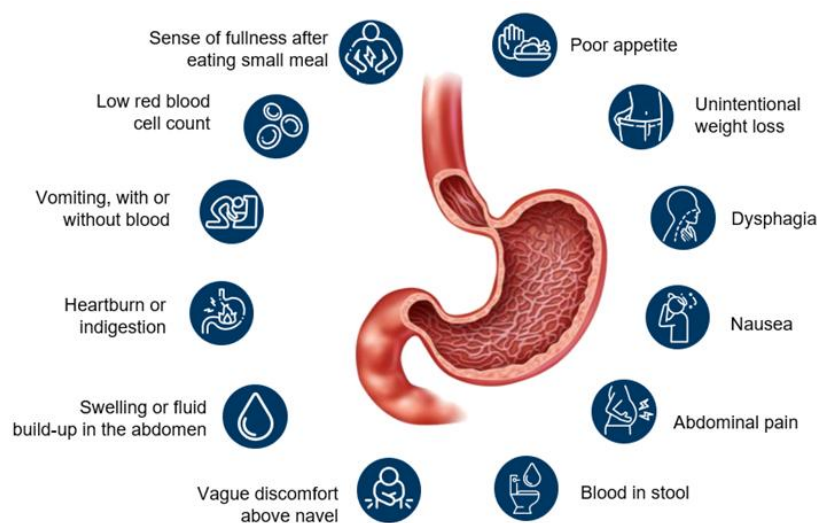
Abbreviations: GC: gastric cancer; GOA: gastric/gastro-oesophageal junction adenocarcinoma; GOJ: gastro-oesophageal junction; GOJC: gastro-oesophageal junction cancer.

Sources: Sehdev (2013),⁴ Narayan et al. (2021),⁵ Siewert et al. (2000).⁶

What are the signs and symptoms of GOA?

At an early stage, there are often no clear **symptoms** of GOA. This means that patients may not know they have the disease until it has progressed and spread.^{7, 8} Once the cancer has spread, symptoms may appear. These symptoms can include weight loss, stomach pain, and blockages in the stomach which make it hard to eat or digest food. As GOA further progresses, these symptoms can worsen and so it is important to identify and treat these cancers as early as possible.⁹⁻¹² The symptoms of GOA are summarised in Figure 2.

Figure 2. Symptoms of GOA



Abbreviations: GC: gastric cancer; GOJC: gastro-oesophageal junction cancer.

Sources: American Cancer Society (2023),⁹ Maconi et al. (2008).¹¹

How common is GOA?

There is limited data about the rates of GOA specifically. However, several studies have reported the rates for gastro-oesophageal cancers collectively.

Between 2017–2019 in the UK, gastro-oesophageal cancer was the 18th most common cancer and accounted for 2% of all cancer deaths. This means that 1 in 50 deaths from cancer in the UK were caused by gastro-oesophageal cancer.¹³ Each year in the UK there are approximately 6,500 people are diagnosed with gastro-oesophageal cancer (~2,300 in women and ~4,200 in men).¹³ The rate at which GC specifically occurs increases with age, plateauing between 55–80 years.¹⁴

As noted above, this submission focusses on adenocarcinomas. Adenocarcinomas are the most common form of gastro-oesophageal cancers. Around 9 out of 10 gastro-oesophageal cancers are classed as adenocarcinomas.¹⁵ Based on data collected from between 2004–2006, one study estimated that about 5 people per 100,000 are diagnosed with GOA each year.¹⁶

What is the impact of GOA on survival?

GOA is the cause of many deaths in the UK and worldwide. It is predicted that just 16.7% (under 2 in 10) of people in England survive stomach cancer for ten years or more after they are diagnosed.¹⁷ Survival rates decrease as the disease spreads throughout the body. This shows that using effective treatments early for GOA is important. Using treatments early has the potential to prevent or delay the disease getting worse.^{18, 19}

Surgery can cure some patients of their cancer. However, for many patients with GOA the disease can return. This is called disease **recurrence**.²⁰ Patients who have disease that recurs often have worse outcomes. It is therefore important that patients receive treatments that are able to stop the disease from coming back (i.e. recurring).²¹

What is the impact of GOA on patient and carer wellbeing?

Cancers such as GOA can have a negative impact on patients' **quality of life (QoL)**. Quality of life is a measure of a person's wellbeing. GOA can also affect the wellbeing of people who care for patients with GOA. The impact of GOA on patient and carer wellbeing is discussed further in [Section 2d](#).

What are the economic impacts of GOA?

GOA is also associated with costs to healthcare systems and society. It is costly to treat patients in hospitals, including hospital stays and treatments. GOA also affects people's ability to work and live their daily lives. Costs therefore also include time off work and support for daily living.¹⁰ As the cancer becomes worse, the financial impact usually increases.¹⁰

GOA is among the most costly types of cancer to manage globally. In the UK, managing GC and GOJC cost the economy about £740 million in one year (based on 2017 data).¹⁰ In addition, many patients have serious side effects and often need care from family or friends. This can mean that carers have to take time off work or reduce their hours, leading to a loss of income and extra financial strain for both families and society.

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

How is GOA diagnosed?

To diagnose GOA, doctors usually use **gastroscopy** (a type of **endoscopy**). A gastroscope is a thin, flexible tube with a camera that is passed into the stomach to look for signs of cancer.²² During this procedure, the doctor may also take small samples of tissue (**biopsies**) for examination in a laboratory to confirm if cancer is present.²²

If GOA is presented, the **Siewert classification system** is used to classify the cancer depending on how close the tumour is to the top part of the stomach (the **cardia**).⁶

- Type I: Starts in the upper part of the food pipe (oesophagus), at least 1 centimetre (cm) above where it joins the stomach
- Type II: Starts at the junction where the oesophagus meets the stomach, anywhere from 1 cm to 2 cm below this point. Because it is located exactly at the join, it is often called "junctional" or "cardia" cancer
- Type III: Starts in the lower part of the stomach, at least 2 cm below where the oesophagus and stomach join

How is GOA staged?

After GOA is diagnosed, doctors determine the **stage** of the cancer to understand how advanced it is and to guide treatment decisions.²² Staging usually involves imaging tests to see whether the cancer has grown into nearby organs or lymph nodes, or spread to distant parts of the body.²²

The stage is usually based on the size of the tumour, whether it has spread into **the lymph nodes** and the presence of **metastases**. The stage of the cancer is described using numbers from I (early, localised cancer) to IV (advanced cancer that has spread).^{23, 24}

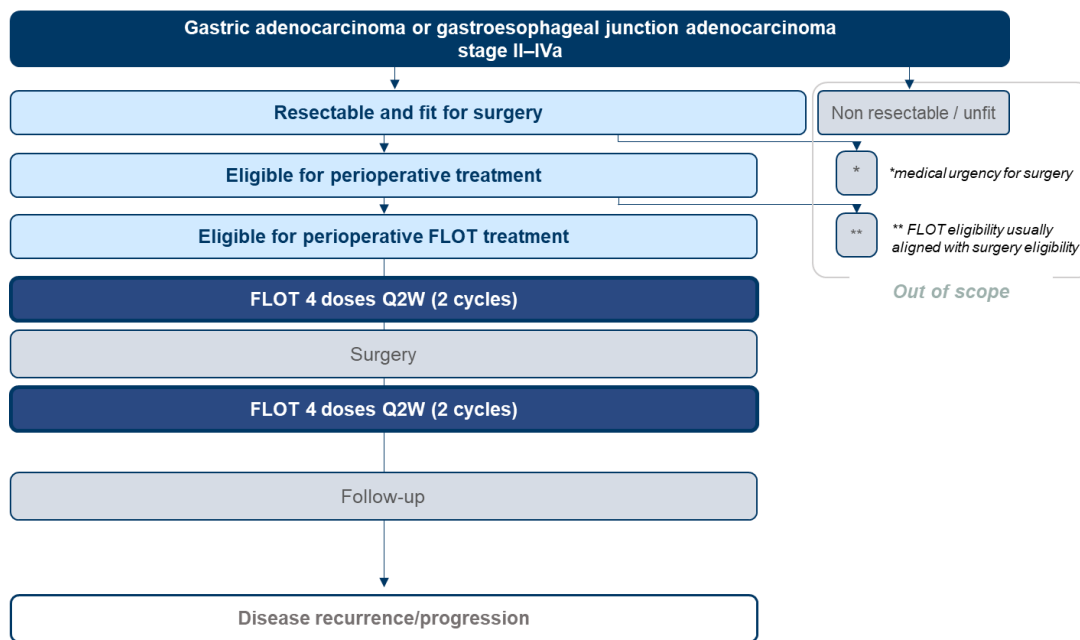
2c) Current treatment options

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.
- Please also consider:
 - if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
 - are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

Treatment for GOA depends on the size, type, location and stage of the tumour, with guidelines recommending a combination of surgery, **chemotherapy** and/or **radiotherapy**.²⁵ The treatment guidelines of most relevance to GOA are the European Society for Medical Oncology (ESMO) guidelines (published in 2022 for GC and in 2025 for oesophageal cancer, including GOJC).^{3, 26} A summary of the treatment pathway for GOA is presented in Figure 3.^{3, 26}

Figure 3. Clinical management of GOA in UK clinical practice



Abbreviations: FLOT: 5-fluorouracil, leucovorin, oxaliplatin, and docetaxel; GOA: gastro-oesophageal adenocarcinoma; Q2W: biweekly.

Source: Figure adapted from ESMO Clinical Practice Guideline: Gastrointestinal Cancers (2022) and ESMO Clinical Practice Guideline: Oesophageal Cancer (2025).^{3, 26}

How is resectable GOA treated in the UK?

The main treatment option for patients with resectable GOA is surgery. The goal of surgery is curing the cancer.^{3, 26} To reduce the risk of disease recurrence and improve the chances of cure, treatment guidelines also recommend the addition of **perioperative** chemotherapy.^{3, 26} Perioperative means that patients receive the therapy both before (**neoadjuvant**) and after (**adjuvant**) surgery.

The treatment guidelines recommend a combination of chemotherapies (5-fluorouracil/leucovorin/oxaliplatin/docetaxel) called **FLOT** as the perioperative chemotherapy option for patients with GOA. This recommendation is based on **clinical trial** results that show perioperative FLOT improves patient survival compared to other chemotherapy treatments.^{3, 20, 26} Perioperative FLOT is therefore the standard of care for all patients who are able to receive this regimen. Patients who are able to receive perioperative FLOT are the focus of this submission. Perioperative FLOT is considered the only comparator in this submission.

Other perioperative chemotherapy regimens may be used in patients who cannot tolerate FLOT. In addition, **chemoradiotherapy** (CRT) is an option for certain patients, particularly those with GOJC, as recognised in the ESMO guidelines.^{3, 27} However, CRT is used in patients who are not eligible for surgery. Neoadjuvant CRT followed by surgery may be used in patients not suitable for perioperative FLOT. After neoadjuvant CRT and surgery, patients may go on to receive **nivolumab** (an immunotherapy) as adjuvant treatment if they have residual disease after surgery. However, these patients are not the focus of this submission, as they would not be suitable to receive perioperative FLOT chemotherapy.

How is advanced GOA treated in the UK?

As described in [Section 2a](#), patients with GOA have high rates of disease recurrence and disease progression.²⁸⁻³⁰ In these cases, the disease is hard to treat as many patients are often not suitable for further surgery.³¹ For patients with advanced or **metastatic** GOA that cannot be removed by surgery, curing the disease is no longer possible. For these patients, **palliative** management is recommended to provide symptom relief and enhance their QoL.²⁶

Targeted treatments (including trastuzumab) and **immuno-oncology therapies** (including nivolumab and pembrolizumab) have recently emerged as treatment options for advanced GOA.^{25, 32-34} However, in the advanced setting, these treatments offer a limited benefit and may only extend survival by a few weeks or months.^{23, 26, 35} Immuno-oncology therapies are currently only recommended for patients whose disease has progressed, meaning they are not used alongside perioperative FLOT in UK clinical practice.

Need for novel efficacious treatment options

Despite the goal of surgery being to cure the disease, the long-term outcomes for patients with resectable GOA who receive perioperative FLOT (the SoC) remain poor. Just under 1 in 2 patients remain alive at 5 years.²⁰ The early GOA setting is the last chance for patients to be treated with the possibility of cure. Therefore, new treatments that stop disease progression and recurrence, and ultimately death from the disease, are needed in this curable disease setting.

There is a clear unmet need for more effective treatments, like durvalumab, at an earlier disease stage where patients' disease can be potentially cured with treatment. The combination of durvalumab with the current recommended treatment option, perioperative FLOT (together termed "perioperative D-FLOT"), would increase the chance of cure and reduce the risk of disease progression/recurrence. As a result, perioperative D-FLOT would be highly valued by patients and clinicians.

2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

Impact on patients

The health-related quality of life (**HRQoL**) of patients with GOA is impacted by several factors, including disease stage, symptoms, and treatment choices. Patients with early-stage GOA may have minimal or no symptoms. However, as the disease progresses, patients experience more severe complications, such as weight loss and gastric obstruction. These can have a substantial negative impact on patients' overall HRQoL.¹⁰ Supporting this, a **systematic review** of studies that investigated the HRQoL of patients with GC showed patients experience increasingly significant reductions in HRQoL with disease progression, in line with the worsening physical and emotional symptoms.³⁶

Anxiety and depression are common challenges for patients with GOA. These often worsen as the disease advances and further increases the strain on patients' overall wellbeing.³⁷ One study using the EuroQol-5 dimensions-5 levels (**EQ-5D-5L**) **utility** instrument demonstrated that 23% of patients with early-stage GC and 48% of patients with advanced-stage GC reported anxiety or depression.³⁷ In another study, patients with early GC receiving surgery had higher HRQoL than patients with recurrent GC, reflecting that disease recurrence also has negative effect on daily lives.³⁸ Furthermore, disease recurrence, and the fear of it, have been shown to further impact patients' HRQoL.³⁸ It is critical that treatments are introduced that prevent disease progression and recurrence, and the subsequent negative impact this has on patient HRQoL.

Impact on families and caregivers

The carers of patients with GOA are also impacted by the disease. On average, the caregivers of patients with GOA in the UK are reported to provide 42 hours of physical and emotional support per week. This shows the time and energy invested by these individuals.³⁹ On top of the time dedicated to providing support, studies show that caregivers also face numerous disruptions to daily routines and meals, which impact their psychological wellbeing.⁴⁰⁻⁴⁴

There is also an emotional burden of the disease on caregivers. The caregivers of patients with GOA frequently experience emotional distress, including reporting feelings of helplessness, distress, anger, fear, and loneliness.^{40, 44, 45} The fear of cancer recurrence is also expected to negatively impact caregivers, who often have high levels of anxiety about a loved one's cancer returning.⁴⁶

There is therefore a need for effective and curative treatments in the GOA treatment pathway, to not only preserve the QoL of patients, but also prevent the impacts of the disease on their caregivers.

SECTION 3: The treatment

3a) How does the new treatment work?

What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

What is durvalumab and how does it work?

Durvalumab is a type of **immunotherapy**, known as a **checkpoint inhibitor**. This means that durvalumab works by helping the **immune system** to recognise and destroy cancer cells. It does this by blocking the system that helps cancer cells disguise themselves and hide from the immune system.⁴⁷

More information on durvalumab is provided in the Summary of Product Characteristics (SmPC): [Durvalumab SmPC \(August 2025\)](#).⁴⁸ As the marketing authorisation for durvalumab in patients with resectable GOA is pending, the SmPC linked here does not yet include information specific to GOA.

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

- **Yes / No**

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.

Durvalumab is expected to be used in combination with perioperative FLOT chemotherapy (perioperative D-FLOT) as a neoadjuvant (before surgery) and adjuvant (after surgery) treatment for patients with resectable GOA.

As noted in [Section 2c](#), clinical guidelines state that patients receiving surgery to remove their GOA tumours should be offered chemotherapy before and after their surgery.^{3, 26} Several clinical trials have shown that perioperative FLOT chemotherapy is more effective than other chemotherapy treatments in improving patient survival and because of this, perioperative FLOT is the standard of care in this disease setting.^{20, 49-53}

FLOT chemotherapy uses four medicines (fluorouracil, leucovorin, oxaliplatin, and docetaxel) that work together to stop cancer cells from growing and spreading by damaging their DNA and blocking their ability to divide. This helps shrink the tumour and slow down the disease.⁵⁴

Combining durvalumab with perioperative FLOT chemotherapy can improve treatment effectiveness. The two therapies work in different but complementary ways. FLOT chemotherapy works to reduce the size of the tumour and durvalumab supports the body's immune system to recognise and destroy cancer cells that remain.⁵⁵⁻⁵⁷ As a result,

perioperative D-FLOT has been shown to further improve patient outcomes and reduce the risk of disease progression or recurrence compared to perioperative FLOT alone.⁵⁵

Crucially, if recommended, perioperative durvalumab would represent the first and only immuno-oncology treatment that can be used in combination with perioperative FLOT, and would provide patients with an increased chance of disease cure.

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for.

How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?

How is durvalumab and FLOT chemotherapy taken?

Durvalumab is delivered as a fluid into the vein (**intravenous infusion**) for over one hour and is available in 2.4mL or 10mL vials.

FLOT chemotherapy is also administered **intravenously** into your bloodstream in treatment cycles. Each cycle lasts for two weeks, and patients usually have eight cycles of FLOT in total. FLOT comprises of a combination of four chemotherapy drugs:

- 5-Fluorouracil at a dose of 2,600 mg/m²
- Leucovorin at a dose of 200 mg/m²
- Oxaliplatin at a dose of 85 mg/m²
- Docetaxel at a dose of 50 mg/m²

During the combination portion of treatment, durvalumab is administered first; the FLOT infusion starts approximately one hour (maximum two hours) after the end of the durvalumab infusion. For all other administrations (including neoadjuvant and adjuvant treatment), FLOT is given immediately after the durvalumab infusion had finished.

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

Studies of durvalumab in GOA

The clinical evidence for perioperative D-FLOT for the treatment of patients with GOA is from the ongoing **Phase III MATTERHORN** clinical trial.⁵⁵ The trial investigated how well durvalumab works in combination with perioperative FLOT, followed by adjuvant durvalumab alone, compared to patients receiving a **placebo + FLOT**.⁵⁵ MATTERHORN

also assessed the safety of perioperative D-FLOT compared to placebo + FLOT and the impact each regimen has on QoL.⁵⁵

MATTERHORN was a **double-blind study**. This means that neither the patient nor the doctor knew which treatment regimen each patient was receiving. This helped to reduce **bias** in the study.

Who was included in the MATTERHORN trial?

MATTERHORN was a global trial carried out in 20 countries.⁵⁵ It included adults aged 18 years or older who had resectable GOA and had not yet received any treatment for their cancer.⁵⁵ Patients were excluded from the trial if they had certain medical conditions, including **autoimmune** or **inflammatory disorders**, history of another cancer, active infection or allergy to any of the study treatments.⁵⁵

The study included 948 patients who were randomly allocated to one of two groups.⁵⁵

- Perioperative D-FLOT arm (474 patients): Patients receiving D-FLOT before and after surgery
- Control arm (474 patients): Patients receiving placebo + FLOT before and after surgery

The first patient was enrolled in the MATTERHORN trial on 17th November 2020. Data in this submission are informed by the first (1st February 2023) and second data cut-offs (20th December 2024).⁵⁵ A final data cut-off for overall survival was conducted on 1st September 2025 – the overall findings at this final analysis are similar to those seen in the earlier analyses.⁵⁸ UK clinical experts interviews by AstraZeneca validated that the patients who took part in the MATTERHORN trial were reflective of patients with resectable GOA in the UK.⁵⁹

More information

More information about the MATTERHORN trial can be found here:

- Janjigian, *et al.* 2025.⁵⁵
- ClinicalTrials.gov ([Assessing Durvalumab and FLOT Chemotherapy in Resectable Gastric and Gastroesophageal Junction Cancer \[NCT04592913\]](https://clinicaltrials.gov/ct2/show/study/NCT04592913))⁵⁵

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

How was the efficacy of perioperative D-FLOT measured?

In the MATTERHORN trial, the main measure that was used to assess the efficacy of the treatment regimens was **event-free survival (EFS)**. EFS is the time between the start of the trial and patients experiencing one of the following:

- Signs that their cancer has started to grow again (i.e., the time before the disease progresses)
- Signs that their cancer has returned in the same place or elsewhere in the body (i.e., the time before disease recurrence)
- Death, due to any cause (i.e., the time before patients die if they do not experience disease progression or recurrence)

Other efficacy measures in the MATTERHORN trial included:

- **Overall survival (OS)**: The time between the start of the trial and death due to any cause
- **Pathological complete response (pCR)**: The proportion of patients who have no remaining visible tumour in their surgically removed tissue sample

As the MATTERHORN trial directly compared perioperative D-FLOT with the current preferred chemotherapy regimen for patients with GOA (perioperative FLOT), all the evidence informing the effectiveness of perioperative D-FLOT and the comparator is from the MATTERHORN trial.

EFS

At the second data cut-off, patients in the perioperative D-FLOT arm had a 29% reduction in the risk of experiencing an EFS event (see details of this endpoint outlined above) compared to the control arm.⁵⁵ After 24 months of treatment, 67.4% of patients in the perioperative D-FLOT arm had not experienced an EFS event, compared to 58.5% of patients in the control arm.⁵⁵ This means that at 24 months, nine more patients out of every 100 receiving D-FLOT had not experienced return or progression of their disease, or death, compared to the control.⁵⁵ The reduced risk of an EFS event was clinically meaningful and **statistically significant**.

Statistically significant means that these results are most likely to be because of the treatment and are unlikely to have been due to chance. **Clinically meaningful** means that these results are impactful for patients. These data indicate that patients receiving perioperative D-FLOT are less likely to experience disease progression, recurrence or death compared to placebo + FLOT.

OS

At the second data cut-off, patients who were receiving perioperative D-FLOT in the MATTERHORN trial had improved survival outcomes compared to those receiving placebo + FLOT. Specifically, patients receiving perioperative D-FLOT lived, on average, longer than those who received placebo + FLOT and had a 22% reduction in their risk of dying.⁵⁵ After 24 months, five more patients out of every 100 were alive in the perioperative D-FLOT arm (75.7%) compared to the control arm (70.4%).⁵⁵ OS data from the third data cut-off were

recently published.⁵⁸ These data are very similar to the data from the second data cut-off.⁵⁸ Patients receiving perioperative D-FLOT had a 22% reduction in their risk of dying than patients receiving placebo + FLOT but the reduced risk of dying was statistically significant.⁵⁸

pCR

Treatment with perioperative D-FLOT resulted in a statistically significant improvement in pCR rates compared with placebo + FLOT.⁵⁵ In total, approximately one in five patients (19.2%) receiving perioperative D-FLOT achieved pCR (i.e. had no remaining visible cancer cells in their surgically-removed tissues), while less than one in 10 patients (7.2%) receiving placebo + FLOT achieved the same.⁵⁵ This data reflects that by combining durvalumab with perioperative FLOT chemotherapy, cancerous cells are more effectively killed. As a result, patients are more likely to live longer without their disease returning.

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as **patient reported outcomes (PROs)**.

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

How was quality of life measured?

The MATTERHORN trial measured patient QoL using various different questionnaires, including:

- **EORTC-QLQ-C30:** The EORTC-QLQ-C30 is a specific measure for QoL in people living with cancer, and was used in the MATTERHORN trial to assess patients' physical, psychological and social functions.⁵⁵
- **EORTC QLQ-STO22 + IL38:** The EORTC QLQ-STO22 + IL38 questionnaire is specific to GC. It assessed disease and treatment-related symptoms in patients in the MATTERHORN trial, including pain, eating restrictions, anxiety and body image.⁶⁰
- **EuroQol Five Dimension Five Level Questionnaire (EQ-5D-5L):** The EQ-5D-5L is a generic tool to measure how many patients experienced improvements in QoL. Patients are asked questions about whether they are experiencing problems with mobility, self-care, performing usual activities, pain and discomfort, and anxiety and depression.⁶¹

QoL impact

In MATTERHORN, patients in the perioperative D-FLOT and the control arms reported similar QoL, and there were similar findings between treatments for the specific measures of physical functioning, tiredness and appetite loss.⁶² Additionally, there was no

meaningful difference in the time to a decrease in QoL between treatment arms in any of the symptom categories of the EORTC QLQ-C30 and EORTC QLQ-STO22 + IL38.⁶²

Overall, the similar QoL scores between the treatment arms shows that the addition of durvalumab to perioperative FLOT chemotherapy does not negatively impact patients' QoL.

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

What are the side effects?

Every medicine has the potential to result in side effects, and the same medicine can produce different effects in different people. Overall, the medicines used in the MATTERHORN trial (durvalumab and FLOT chemotherapy) showed a manageable **safety profile** that was in line with what is already known about each of the individual medicines.⁵⁵

In the MATTERHORN trial, a similar number of patients experienced side effects and serious side effects in the perioperative D-FLOT and control treatment arms. No new safety concerns were identified for durvalumab when given in combination with perioperative FLOT chemotherapy.⁵⁵

The most common side effects in MATTERHORN (reported by at least 1 in 5 patients in either treatment arm) were nausea, low white blood cell count, hair loss, decreased appetite, fatigue, vomiting, anaemia, loss of feeling in hands or feet, diarrhoea and abdominal pain. These side effects are consistent with the known side effects of FLOT chemotherapy.⁵⁵

The side effects that were reported more in patients receiving perioperative D-FLOT than placebo + FLOT (at least a 5% difference) were rash, itchiness and fever.⁵⁵ However, these side effects were not severe and were consistent with the known side effects of durvalumab.⁵⁵

A complete list of all potential side effects associated with durvalumab, including rare side effects, can be found in the [Patient Information Leaflet \(durvalumab\)](#).⁶³ As the marketing authorisation for durvalumab in patients with resectable GOA is pending, the Patient Information Leaflet linked here does not include information specific to GOA.

Managing side effects

Clinicians are familiar with the side effects that durvalumab and perioperative FLOT chemotherapy can cause. They are therefore experienced in managing the side effects and helping patients tolerate the treatments. Side effects were effectively managed in MATTERHORN by interrupting the dose or delaying the next dose of perioperative D-FLOT or placebo + FLOT.⁵⁵

Slightly more patients had side effects that led to them stopping treatment in the perioperative D-FLOT arm compared to the control arm, but side effects leading to surgery not being performed were rare across both treatment arms.⁵⁵ The addition of neoadjuvant durvalumab to FLOT did not impact the ability of patients to undergo or complete surgery compared with placebo + FLOT.⁵⁵ Rates of surgery, timing to surgery, and perioperative outcomes were comparable across treatment arms.⁵⁵ These findings suggest that including D-FLOT does not prevent patients from having potentially curative surgery.

Overall, the safety data from the MATTERHORN trial reflect that the safety profile of perioperative D-FLOT is both tolerable and manageable for patients.

3h) Summary of key benefits of treatment for patients

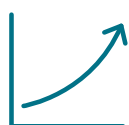
Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration.

As detailed in [Section 2c](#), even though surgery aims to cure patients' GOA, the outcomes for patients receiving perioperative FLOT remain poor, with less than half (45%) of patients receiving it remaining alive five years after treatment.²⁰ New, effective treatment options are required for patients with resectable GOA, as this is the last opportunity for treatment with the possibility of curing the disease. There is therefore an unmet need for treatments that decrease the risk of patients' disease returning or progressing and increase the likelihood of cure.

The availability of an immuno-oncology therapy, such as durvalumab, for resectable gastric cancer would help improve patient outcomes and increase the chances of cure.

The key benefits of perioperative D-FLOT to patients with resectable GOA include:



Improved efficacy and increased chance of cure compared to SoC

- As shown in [Section 3e](#), in the MATTERHORN trial, patients in the perioperative D-FLOT arm had significantly improved EFS, OS (based on the third data cut-off) and pCR than patients in the control arm. This

reflects that the addition of durvalumab prevents or delays disease progression, recurrence and death.⁵⁵

- Patients receiving D-FLOT are more likely to live longer and have a greater chance of their disease being cured than patients receiving perioperative FLOT chemotherapy alone.

Manageable safety profile that does not impact surgery



- In the MATTERHORN trial, perioperative D-FLOT was shown to be tolerable and manageable. The safety profile was in line with what is already known about each of the individual medicines. Side effects were well managed by adjusting or delaying treatment doses when needed ([Section 3g](#)).⁵⁵
- Side effects leading to surgery not being performed were rare across both the perioperative D-FLOT and control arms. This reflects that patients' ability to receive potentially curative surgery was not impacted by adding durvalumab to perioperative FLOT chemotherapy.⁵⁵

No negative impact on HRQoL



- There was no meaningful difference in the time to decline in HRQoL between treatment arms across any questionnaires used in the MATTERHORN trial.⁶²
- The similar QoL scores between patients receiving perioperative D-FLOT and placebo + FLOT show that the addition of durvalumab to perioperative FLOT chemotherapy does not negatively impact patients' QoL ([Section 3f](#)).⁶²

First immuno-oncology treatment option in the resectable GOA setting



- As outlined above, immuno-oncology treatments are needed in the resectable GOA setting to improve patient outcomes and the chances of disease cure.
- Durvalumab represents the first and only immuno-oncology treatment to demonstrate a statistically significant benefit in EFS in resectable GOA. Perioperative D-FLOT is anticipated to be a highly valued and practice-changing treatment option for patients with GOA.⁶⁴

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration.
- What is the impact of any disadvantages highlighted compared with current treatments.

Side effects

As with most cancer treatments, patients may experience side effects while receiving treatment which can impact their QoL.

However, based on the MATTERHORN trial, the side effects of perioperative D-FLOT are generally manageable and in line with what is already known about each of the individual medicines.⁵⁵ This means that if patients experience side effects, their clinicians are likely to know the most effective way to control them. The side effects associated with perioperative D-FLOT also rarely meant that patients were unable to continue to receive surgery to remove their cancer. Full details on the side effects of perioperative D-FLOT are provided in [Section 3g](#).

Overall, the improved efficacy benefits of perioperative D-FLOT compared to perioperative FLOT alone are likely to outweigh any negative impacts associated with side effects.

3j) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

How the model reflects GOA

A **health economic model** was designed to represent the key features of the experience of a patient with GOA and to reflect clinical practice in the UK. To do this, a **semi-Markov model** was chosen, as it is a commonly used tool for modelling treatments in the perioperative GOA disease setting.⁴⁶ The model consisted of three health states that a patient could be in:

- Event-free (EF) state: Patients have not experienced disease recurrence or death
- Recurred disease (RD): Patients have experienced disease recurrence
- Death

Modelling how much durvalumab extends life

Using the model, the economic analysis considered whether and to what extent durvalumab extends patient survival before and after disease recurrence. The results from the second data cut-off (December 2024) of the MATTERHORN trial were used to inform the model. However, the economic model simulates patients for the rest of their lifetime. This represents a considerably longer period of time than the length of the MATTERHORN trial. Therefore, the model uses extrapolations of MATTERHORN data to predict patients' long-term outcomes.

Additionally, because the aim of treatment is to cure patients, the model included a 5-year 'cure' timepoint. If patients in the model reached this timepoint and had not experienced an EFS event ([Section 3e](#)) patients were assumed to be 'cured' of their cancer. These patients in the model were then no longer considered at risk of disease recurrence.

Modelling how much durvalumab improves HRQoL

QoL data in the model for patients who had not experienced disease recurrence or death (EF state) were assumed to be the same as that of the general population in the UK (i.e., those without GOA). QoL data for patients who had experienced a disease recurrence (RD stage) was based on data from previous NICE assessment of a treatment in this disease area. This is because low numbers of patients in the MATTERHORN trial had reached the RD stage, and therefore limited QoL data was collected in MATTERHORN for the RD state specifically.⁴⁶ These QoL data were then converted into health **utility** inputs to inform the economic model.

Additionally, a **utility decrement** was applied to account for the differences in the side effects experienced by patients receiving perioperative D-FLOT or placebo + FLOT (as discussed in [Section 3g](#)).

Modelling the costs of managing GOA with durvalumab

Various costs were included in the model to reflect the differences in the costs paid by the NHS associated with perioperative D-FLOT compared to placebo + FLOT in patients with GOA in UK clinical practice. These included:

- The cost of the medicine itself and how much it costs to administer the medicine
- The cost of starting treatment and the cost of monitoring the patients during treatment
- The cost of side effects that happen during treatment
- The cost of additional treatments patients receive after disease progression, including end-of-life treatments

Uncertainty

Although data from the MATTERHORN trial were used in the model, there is uncertainty around how long people would remain free from disease recurrence with each treatment, as data are only available for a certain duration of follow-up. Predictions on how long people would remain alive were used and additional scenarios in the model were explored to

minimise this uncertainty. Of note, because of the 5-year 'cure' timepoint included in the model, these predictions were only required for up to 5 years, which reduces the uncertainty.

Benefits of durvalumab not captured in the economic analysis

Treatment with perioperative D-FLOT may have many different positive impacts for patients with GOA. The model aims to capture as many of these benefits as possible, but there are other benefits that could not be fully captured, as described below.

QoL impact associated with disease progression and metastatic GOA

As discussed in [Section 2d](#), patients with GOA experience a decline in HRQoL as their disease progresses and/or recurs, which leads to greater anxiety, depression, and symptom burden.^{36, 38} The health state utility values used in the model to measure patient QoL in the RD health state may not fully capture the HRQoL burden caused by disease progression and recurrence.

UK clinical experts confirmed that the utility values used in the model reflect the reality of patients with GOA. However, patients may experience decreased utility at different points in their disease journey, as disease recurrence can have a major impact on quality of life. This means that patients may feel worse than the model assumes at certain stages of their disease journey. As a result, the benefits of D-FLOT in improving quality of life and survival may be slightly underestimated.

Value of hope

The value of hope reflects patients' willingness to accept risk, based on the possibility of receiving a substantial benefit with their treatment.⁶⁵ This is particularly important for patients with resectable GOA who receive both neoadjuvant chemotherapy and surgery. Even with perioperative FLOT, survival remains limited, and the risk of recurrence is high.²⁰

If recommended, durvalumab would become the first immunotherapy added to the current standard of care, with the aim of curing all patients who can receive it. This would represent a major step forward in managing GOA. D-FLOT is given at the last opportunity for cure in resectable GOA. This offers substantial hope for patients and their families by increasing the chance of cure and reducing the chance of recurrence after surgery. This hope helps patients and their families cope with the disease and improves emotional well-being. These benefits are not captured in the model. As a result, the overall value of hope associated with D-FLOT is not fully reflected in the model.

Reduced caregiver burden

The negative QoL impact of GOA extends beyond the patients themselves and also causes caregivers to feel emotional distress, anger, fear and loneliness ([Section 2d](#)).^{40, 44, 45} The caregiver burden is particularly strong in patients with advanced cancer.^{66, 67} If available, perioperative D-FLOT would reduce the likelihood of advanced cancer among patients diagnosed with GOA – protecting both patients and their caregivers from the substantial psychical and psychological burden associated with disease progression. The benefits to caregivers associated with perioperative D-FLOT is not included in the economic model.

Therefore, the total benefits of perioperative D-FLOT compared to perioperative FLOT chemotherapy may be underestimated in the economic analysis.

3k) Innovation

NICE considers how innovative a new treatment is when making its recommendations.

If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

Durvalumab is an innovative immuno-oncology therapy representing a practice-changing step forward in the treatment of resectable GOA

Even following the introduction of perioperative FLOT (the current SoC for patients with early GOA), disease survival rates remain low and the risk of patients' disease returning remains high.²⁹⁻³¹ There is an unmet need for new treatment options in the resectable disease setting before the disease advances and is no longer able to be treated with the possibility of curing the disease.

Currently, immuno-oncology therapies are only recommended once patients' disease becomes advanced. At this point, these treatments are only able to extend survival by just weeks to months.^{23, 26, 35} If recommended, durvalumab would become the first immuno-oncology treatment for patients with resectable GOA (perioperative FLOT). Perioperative D-FLOT has the potential to decrease the risk of disease recurrence and increase the chances of achieving cure compared to perioperative FLOT alone. The addition of durvalumab to perioperative FLOT would represent a step-change in the treatment of resectable GOA.

In the MATTERHORN trial, perioperative D-FLOT demonstrated significant improvements in survival and response outcomes, and has a tolerable safety profile that does not prevent patients from receiving surgery. It would represent a highly valued, innovative and impactful treatment option for patients with resectable GOA.⁶⁸

3l) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.

Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics

More information on how NICE deals with equality issues can be found in the NICE equality scheme.

Find more general information about the Equality Act and equalities issues here.

A variety of factors increase the risk of developing GOA, including environmental factors such as smoking, being overweight and a high alcohol or high salt intake all increase the risk of developing GOA.⁶⁹⁻⁷¹ Many of these environmental factors are more prevalent in individuals from a lower socioeconomic background.⁷² For example, people living in the most deprived areas of England are almost twice as likely to develop stomach cancer as those in the most well-off areas (based on data from 2013 to 2017), suggesting that there is a link between stomach cancer and deprivation.¹³

The availability of an effective treatment for GOA would help to benefit these individuals and reduce existing health inequalities related to the impact of GOA on populations from different socioeconomic backgrounds.

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc.

Where possible, please provide open access materials or provide copies that patients can access.

Further information on GOA:

- A UK based charity dedicated to providing healthcare, information, and financial support to those affected by cancer. [MacMillan Cancer Support](#).
- Cancer Research UK's information and guidance related to stomach cancer, including GOA. [What is stomach cancer? | Cancer Research UK](#).
- Information and guidance from the NHS relating to stomach cancer. [What is stomach cancer? - NHS](#).

Further information on NICE and the role of patients:

- Public Involvement at NICE: [Public involvement | NICE and the public | NICE Communities | About | NICE](#)
- NICE's guides and templates for patient involvement in HTAs: [Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector \(VCS\) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE](#)
- EUPATI guidance on patient involvement in NICE: <https://www.eupati.eu/guidance-patient-involvement/>
- EFPIA – Working together with patient groups: <https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf>
- National Health Council Value Initiative: <https://nationalhealthcouncil.org/issue/value/>
- INAHTA: <https://www.inahta.org>

- European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: [Health technology assessment: an introduction to objectives, role of evidence, and structure in Europe](#)

4b) Glossary of terms

This glossary explains terms highlighted in **black bold text** in this summary of information for patients. At times, an explanation for a term might mean you need to read other terms to understand the original terms.

Adenocarcinoma	A type of cancer that starts in the cells that make mucus or other fluids, called glandular cells.
Adjuvant	A treatment given after the main treatment (such as surgery) to lower the chance of the cancer coming back.
Autoimmune	A condition where a person's immune system mistakenly attacks their own body, as if it were fighting an infection.
Bias	In a scientific research study or clinical trial, a flaw in the study design or the method of collecting or interpreting information. Biases can lead to incorrect conclusions about what the study or clinical trial showed.
Biopsy	A medical procedure where a small sample of tissue, cells, or fluid is removed from the body for examination.
Cardia	The area at the top of the stomach where it connects to the food pipe (oesophagus).
Checkpoint inhibitor	A type of medication used in cancer treatment that helps the immune system recognise and attack cancer cells more effectively.

Chemotherapy	A type of cancer treatment that uses powerful drugs to kill or slow the growth of cancer cells.
Chemoradiotherapy	A type of cancer treatment that combines chemotherapy and radiotherapy. The chemotherapy drugs make cancer cells more sensitive to radiation, helping the radiotherapy work more effectively to kill cancer cells.
Clinically meaningful	A result in a study that is impactful for patients.
Clinical trial/clinical study	A type of research study that tests how well new medical approaches work in people. These studies test new methods of screening, prevention, diagnosis or treatment of a disease. Also called a clinical study.
Double-blind study	A type of clinical trial where neither the patient nor the doctor knows who is getting the real treatment and who is getting a placebo, to reduce bias.
Endoscopy	A medical procedure that allows doctors to look inside your body using a long, thin, flexible tube called an endoscope.
EORTC-QLQ-C30	A general questionnaire used to measure quality of life in cancer patients. Used in the MATTERHORN trial to measure patient health status.
EORTC QLQ-STO22 + IL38	A questionnaire that is GC-specific, designed to be used alongside the EORTC QLQ-C30 to assess HRQoL in patients with GC.

EQ-5D-5L	A questionnaire that asks about a person's health and quality of life in five main areas, such as mobility, self-care, and pain.
Event-free survival	EFS is the time between the start of the trial and patients experiencing one of the following: - Signs that their cancer has started to grow again (i.e., the time before the disease progresses) before surgery - Signs that their cancer has returned in the same place or elsewhere in the body (i.e., the time before disease recurrence) - Death, due to any cause (i.e., the time before patients die if they do not experience disease progression or recurrence)
Extrapolations	Information or data that are used to make informed estimates or predictions about situations where direct results are not available.
FLOT chemotherapy	FLOT chemotherapy uses four medicines (fluorouracil, leucovorin, oxaliplatin, and docetaxel) that work together to stop cancer cells from growing and spreading by damaging their DNA and blocking their ability to divide.
Gastric cancer	Cancer that starts in the stomach.
Gastro-oesophageal adenocarcinoma	Gastro-oesophageal cancers that specifically originate from the cells that make mucus or other fluid (glandular cells).
Gastro-oesophageal junction cancer	Cancer that develops where the food pipe (oesophagus) meets the stomach.
Gastro-oesophageal cancers	A group of cancers that start in the food pipe (oesophagus), the stomach, or where the two meet (the gastro-oesophageal junction).

Gastroscopy	A specific type of endoscopy that examines the inside of your stomach and the upper part of your small intestine.
Health economic model	A way to predict the costs and effects of a technology over time or in patient groups not covered in a clinical trial.
Health-related quality of life	Refers to how well a person feels and functions in their daily life because of their health. It covers aspects like physical ability, mental wellbeing, social relationships, and overall enjoyment of life.
Immune system	A complex network of cells, tissues, organs and the substances they make that helps the body fight infections and other diseases.
Immuno-oncology therapies	Treatments that help the immune system recognise and attack cancer cells.
Immunotherapy	A treatment that help the immune system fight diseases like cancer.
Indirect treatment comparisons	A type of comparison done in evaluation of new medicines to compare the outcomes of treatments studied in different clinical trials. This type of comparison is indirect as the treatments were studied in different trials.
Inflammatory disorders	Conditions where parts of the body become swollen, red, or sore due to the immune system reacting too strongly, sometimes lasting a long time.
Intravenous infusion	Medicine or fluids given directly into a patient's vein through a needle or tube.

Lymph nodes	Small, bean-shaped glands that are part of the immune system and help the body fight infection. Cancer can spread to lymph nodes.
Marketing authorisation	The legal approval by a regulatory body that allows a medicine to be given to patients in a particular country.
Medicines and Healthcare products Regulatory Agency	The regulatory body that evaluates, approves and supervises medicines throughout the UK.
Metastases	Additional cancerous growths that form when cancer cells break away from their original location and establish new cancer tumours in distant parts of the body.
Metastatic	Cancer that has spread from its original location (the primary cancer) to other parts of the body.
Neoadjuvant	A treatment given before the main treatment (such as surgery) to help shrink the tumour and make the main treatment more effective.
Overall survival	The length of time from either the date of diagnosis or the start of treatment for a disease, such as cancer, that patients diagnosed with the disease are still alive. In a clinical trial, measuring the OS is one way to see how well a new treatment works.
Palliative	Care or treatment that relieves pain, symptoms and stress caused by serious illness. Palliative reflects care or treatment that focuses on optimising quality of life, rather than curing the illness.

Pathological complete response	The proportion of patients who have no remaining visible tumour in their surgically removed tissues.
Pathological downstaging	A situation where the cancer appears to be at a lower stage (less advanced) when examined under the microscope after treatment than it was thought to be before treatment. This often happens when therapies given before surgery (such as chemotherapy or radiation) shrink or eliminate the tumour, leading to less cancer being found in the tissue sample.
Perioperative	The period of time around surgery, including before, during, and after the operation.
Placebo	A treatment that appears real, but that does not treat the disease. It is used in clinical trials to compare treatments to.
Phase III (clinical trial)	A study that tests the safety and how well a new treatment works compared with a standard treatment. In most cases, treatments move into Phase 3 clinical trials only after they meet the goals of Phase 1 and Phase 2 clinical trials. Phase 3 clinical trials may include hundreds of people.
Quality of life	The overall enjoyment of life. Many clinical trials assess the effects of a disease and its treatment on the quality of life of patients. These studies measure aspects of a patient's sense of well-being and their ability to carry out activities of daily living.
Radiotherapy	A treatment that uses high-energy radiation, like X-rays, to kill or damage cancer cells.
Recurrence	When the cancer or disease has returned after a period of remission.

Resectable	Describes a tumour that can be removed with surgery.
Safety profile	Information about the side effects and risks associated with a treatment.
Semi-Markov model	A mathematical way to predict how patients move between different health states over time and how this affects costs and outcomes.
Side effects	Unwanted effects of a drug or treatment.
Siewert classification system	A system used to describe where cancers around the area where the food pipe (oesophagus) and stomach meet are located.
Stage	Describes the size of the cancer and the extent of spread throughout the body.
Statistically significant	A result in a study that is unlikely to have happened by chance, showing that the findings are probably real.
Systematic review	A type of research that looks at all the available studies on a certain topic to summarise what is known about it.
Symptoms	A feeling or experience, like pain, nausea, or fatigue, that indicates a potential disease or condition.
Utility	A number used in health care to show how good or bad a particular health state is, often used for measuring quality of life.

Utility decrement	A drop or loss in the quality of life, as measured by a lower utility value, due to illness or side effects.

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:	
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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Durvalumab in combination for neoadjuvant and adjuvant treatment of resectable gastric and gastro-oesophageal junction cancer [ID6374]

Clarification questions

November 2025

File name	Version	Contains confidential information	Date
ID6374-Durvalumab- GGOJ-cancer_EAG Clarification Question Response [NoCON]	1.0	No	12 th December 2025

Section A: Clarification on effectiveness data

MATTERHORN trial

A1. Please provide responses to the following clarification questions on MATTERHORN patient disposition presented in CS Table 6:

- i. Did patients who had surgery, but no adjuvant treatment with FLOT (combination 5-fluorouracil, leucovorin, oxaliplatin and docetaxel) or D-FLOT (durvalumab in combination with FLOT) receive anything else instead of the adjuvant treatment?**

According to the clinical study protocol and the anticipated license for durvalumab, D-FLOT is a perioperative treatment, with durvalumab in combination with FLOT followed by durvalumab monotherapy given in the adjuvant period.¹ The goal of treating resectable gastroesophageal adenocarcinoma (GOA) is to improve long-term outcomes and reduce the risk of recurrence, and achieving this requires an effective and comprehensive approach combined with surgery to provide continued protection.

Per the clinical study protocol, a patient will only **not** receive any further investigational product (IP; durvalumab or FLOT) in the adjuvant period if any of the following occur:¹

- Withdrawal of consent
- Adverse events (AEs) that meets criteria for discontinuation or contraindicates further dosing
- Becoming pregnant
- Non-compliance with the study protocol
- Initiation of alternative anti-cancer therapy including another investigational agent
- Clinical progression/recurrence and Investigator determination that the patient is no longer benefiting from treatment
- RECIST 1.1-defined progression disease that precludes the patient from radical surgery or requires non-protocol therapy as adjuvant treatment
- Discovery of peritoneal dissemination or distant metastasis (pathology confirmation) during surgery that the radical resection cannot be completed and local/distant recurrence or progression of disease by RECIST.

Therefore, these patients will be identified as permanently discontinued from further IP treatment, regardless of the reason and will enter the follow-up period.¹

An overview of patients who completed surgery but did not receive any adjuvant treatment, and the reasons for this, is provided in Table 1.² In total, ■ patients (■) in the MATTERHORN trial completed surgery but did not receive any IP treatment in the adjuvant period (■ patients each in the D-FLOT and the control treatment arms).² However, the majority of these patients would not have been able and/or suitable to receive a non-IP treatment in the adjuvant setting, as discussed in the following paragraphs.²

Of the █ patients who completed surgery but did not receive any IP adjuvant treatment, █ patients (█) did not receive any adjuvant treatment due to death; these patients would therefore not be able to receive any alternative treatment.²

A total of █ patients (█) completed surgery and were still alive but did not receive any IP treatment in the adjuvant phase.² Of these patients, █ patients did not receive any study adjuvant treatment due to worsening of the condition (n=█) or disease progression (n=█); these patients could receive subsequent therapy as first therapy post-progression/recurrence (i.e., not as an alternative adjuvant therapy).²

█ patients (█%) did not receive any adjuvant IP treatment due to AEs, subject or investigator decision.² These patients would be eligible to receive non-IP treatment in the adjuvant setting as subsequent therapy. However, per the MATTERHORN clinical study protocol, patients had to recover from toxic effects of previous treatment before continuing with adjuvant therapy.¹ Therefore, some patients who did not receive any adjuvant treatment due to AEs (n=█) or investigator decision (n=█) may be considered unsuitable for adjuvant therapy in general, as reasons for not receiving any study adjuvant therapy may preclude some patients from receiving non-IP treatment in the adjuvant setting.² Therefore, the number of patients actually receiving non-IP/subsequent therapy as an adjuvant treatment represents a minority of the patients in the MATTERHORN trial.

Data on the subsequent therapies received in the MATTERHORN trial were presented in the CS (Table 17; Section 2.7), and further discussion on these data are provided in response to Clarification Question A1.

Table 1: Patients who completed surgery but did not receive treatment in the adjuvant period

	D-FLOT arm (n=474)	Control arm (n=474)	Total (n=948)
Patients who completed surgery but did not receive treatment in the adjuvant period	█	█	█
Subject decision	█	█	█
Adverse event	█	█	█
Condition under investigation worsened	█	█	█
Subjective disease progression	█	█	█
Investigator decision	█	█	█
Death	█	█	█

Abbreviations: D: durvalumab; FLOT: 5-fluorouracil, leucovorin, oxaliplatin, and docetaxel.

Source: AstraZeneca Data on File (MATTERHORN Tables, figures and listings, Table 14.1.1)²

ii. Were people who completed 4 adjuvant FLOT doses only supposed to get 2 adjuvant FLOT doses according to protocol?

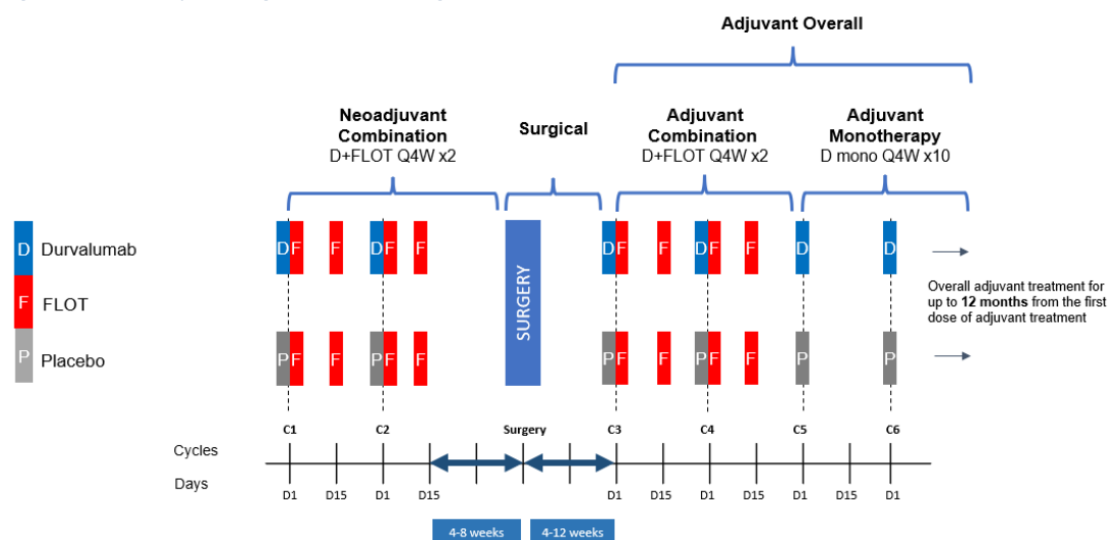
What were the reasons recorded for offering 4 adjuvant FLOT doses?

Per the Clinical Study Protocol, patients were planned to receive two cycles of neoadjuvant FLOT (in combination with placebo or durvalumab) and two cycles of adjuvant FLOT (in combination with placebo or durvalumab).¹ FLOT is administered on Days 1 and 15 of each cycle (i.e., there are two doses of FLOT per cycle). As such, two cycles of adjuvant FLOT equates to four doses of FLOT.¹ Therefore, patients who receive four doses of adjuvant FLOT received two cycles of adjuvant FLOT, in line with the study protocol.¹

The dosing schedule for perioperative FLOT in the MATTERHORN trial is aligned with UK clinical practice and represent the current standard of care for patients with GOA.

An overview of the study design and dosing schedule is presented in Figure 1.

Figure 1: Study design and dosing schedule



Abbreviations: CX: Cycle X; D: durvalumab; DX: Day X; F: FLOT; FLOT: 5-fluorouracil, leucovorin, oxaliplatin, and docetaxel; P: placebo; Q4W: once every 4 weeks.

Source: AstraZeneca Data on File (MATTERHORN Clinical Study Report)³

- iii. **Are the data presented for people continuing “study off treatment at DCO [data cut-off]” the data for the number and proportion of people of people who are still being followed up at this DCO?**
How are people not included in these proportions accounted for? Are people censored from this proportion when they die or are lost to follow-up?

The data presented for patients “continuing study off treatment at DCO” in Table 6 of the CS (Section 2.4.1) refers to the proportion of patients in the full analysis set (FAS) that had completed (or discontinued) treatment but remained in the study. As described in A.1 Part i), per the Clinical Study Protocol, discontinuation of study treatment did not impact the patient’s participation in the trial and all patients are followed for survival until the end of the study.¹ Patients no longer in the study (i.e., deceased, lost to follow-up, withdrawn from study etc.) are not included in this proportion.¹

At DCO2, all patients remaining in the study in both treatment arms had completed (or discontinued) adjuvant treatment and were in the survival follow-up period.³ As presented in the CS (Table 6; Section 2.4.1), ■ patients (■) and ■ patients (■) in the D-FLOT arm and the control arm, respectively, remained in the study but were off treatment (‘continuing study off treatment’).³ The patients excluded from this number are those that had terminated study participation; in the D-FLOT arm, ■ patients (■) had terminated study participation and ■ patients (■) in the control arm had terminated study participation.³ An overview of reasons for termination of study participation and the number of patients for each reason is presented in Table 2.

Table 2: Reasons for study termination

	D-FLOT arm (n=474)	Control arm (n=474)
Patients who terminated study	■	■
Failure to meet inclusion/exclusion criteria	■	■
Withdrawal by parent/guardian	■	■
Death	■	■
Withdrawal by subject	■	■

Abbreviations: D: durvalumab; FLOT: 5-fluorouracil, leucovorin, oxaliplatin, and docetaxel.

Source: AstraZeneca Data on File (MATTERHORN Tables, figures and listings, Table 14.1.1)²

- iv. **The EAG is aware that Table 6 is sourced from Table 11 of the Clinical Study Report (CSR). In Table 11 of the CSR, there are no references to the combination “D-FLOT” regimen. The EAG considers it is likely that all uses of “D-FLOT” in Table 6 of the CS should be replaced with “durvalumab”. Please confirm (or refute) that all uses of ‘D-FLOT’ in CS Table 6 should be replaced with ‘durvalumab’.**

The EAG are correct that all uses of ‘D-FLOT’ in Table 6 of the CS (Section 2.4.1) should be replaced with ‘durvalumab’, in line with Table 11 in the CSR.³

A2. Please clarify if subsequent anti-cancer therapy after discontinuation reported in CS, Table 17 relates to therapy received only following adjuvant treatment with D-FLOT or FLOT or if this also includes patients who did not receive any adjuvant treatment with D-FLOT or FLOT.

If the data in Table 17 include patients who did not receive adjuvant treatment with D-FLOT or FLOT, please present data separately for patients who (i.) did not receive adjuvant treatment with D-FLOT or FLOT and (ii.) received adjuvant treatment with D-FLOT or FLOT.

Table 17 of the CS (Section 2.7) reports the proportion of patients in the FAS who received any post-discontinuation disease-related anti-cancer therapy, and the distribution of subsequent therapies received by these patients.³ These data are for all patients in the FAS and are therefore regardless of whether a patient received IP adjuvant treatment; the data include patients who did not receive any adjuvant treatment with D-FLOT or placebo + FLOT.³ Data on the proportion of the distribution of subsequent treatments specifically for patients who did not receive any adjuvant therapy are not available.

In the FAS population, 27.6% of patients (n=262) received at least one subsequent anti-cancer (CS, Table 17; Section 2.7). Most patients (n=■) who initiated post-discontinuation subsequent therapy did so following documented disease progression or recurrence (CS, Section 3.5.1), rather than as an adjuvant non-IP treatment.³ It is important to note that, given the predominance of post-progression interventions, a smaller proportion of patients in the D-FLOT arm required anti-cancer therapy after IP treatment discontinuation compared with the control arm (23.0% vs 32.3%).³

As outlined in response to Clarification Question A1 part i), █ patients in the MATTERHORN trial completed surgery but did not receive any adjuvant therapy.² Of these, █ patients did not receive adjuvant IP treatment due to death so would not receive any subsequent therapy, and a further █ patients did not receive adjuvant IP therapy due to worsening of the condition or disease progression; these patients received subsequent therapies consistent with the approach used for MATTERHORN patients who had received adjuvant IP therapy and required further treatment.² █ patients did not receive adjuvant IP therapy due to AEs or investigator decision; the reasons for these patients not receiving study adjuvant therapy may preclude them from receiving alternative adjuvant therapy.² Therefore, the number of patients receiving a non-IP adjuvant therapy will represent a minority of the patients in the MATTERHORN trial.

A3. Please provide the MATTERHORN trial Statistical Analysis Plan (SAP).

The statistical analysis plan (SAP) for the MATTERHORN trial has been provided in the reference pack alongside this response.⁴

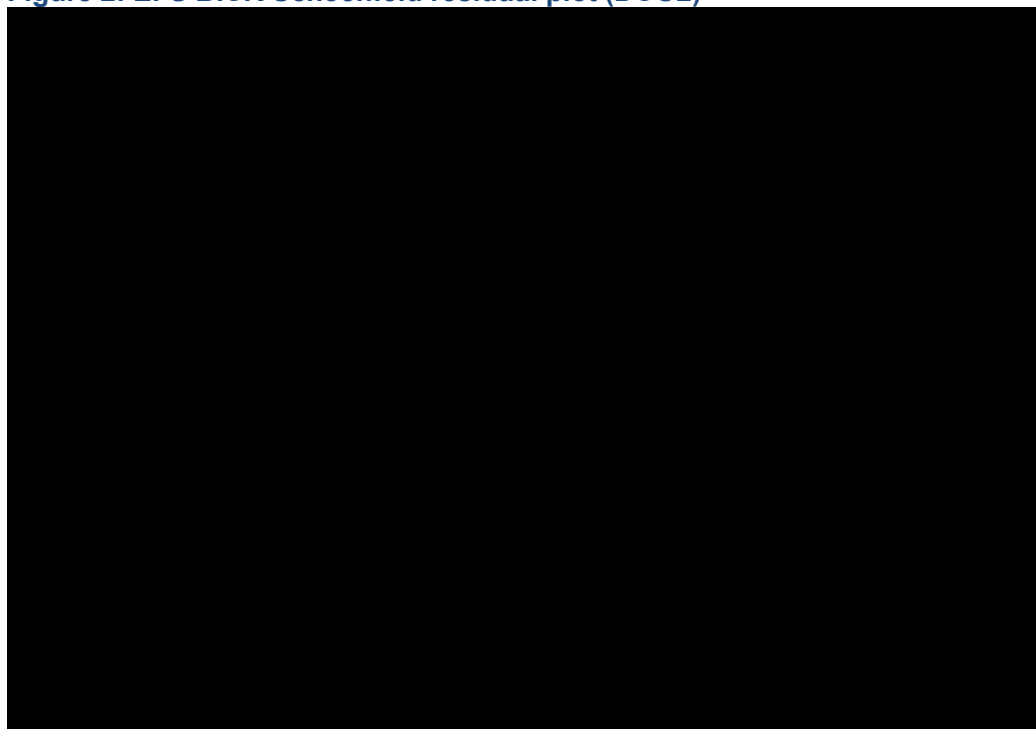
A4. Please provide an assessment of the proportional hazards (PH) assumption for event-free survival (EFS) and overall survival (OS) for DCO2 and DCO3.

Event-free survival (EFS)

DCO2 was the final analysis for EFS (discussed in response to Clarification Questions A6 and A7), so assessment of the proportional hazards (PH) assumption for EFS is presented for DCO2 only.² PH testing was undertaken utilising log cumulative hazard plots and Schoenfeld residual plots. Based on the assessment of the Schoenfeld residual plots (Figure 2), the PH assumption cannot be formally rejected with a p-value >0.05 (Schoenfeld statistic: p=█).

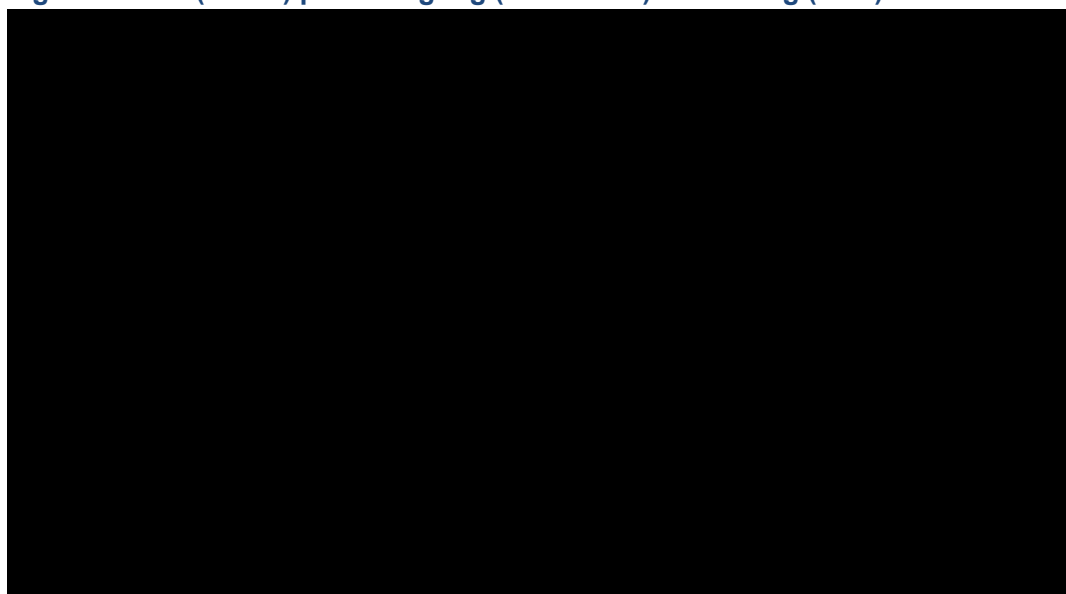
The log cumulative hazard plots for EFS for DCO2 are presented in Figure 3. The log cumulative hazard plots show an early crossing of curves, however by approximately 3 months (after log(1)), the curves become parallel. As concluded in Janjigian, *et al.* 2025, PH assumption was deemed to be satisfied for EFS.⁵

Figure 2: EFS BICR Schoenfeld residual plot (DCO2)



Abbreviations: BICR: Blinded independent central review; DCO: data cut off; EFS: event-free survival.

Figure 3: EFS (DCO2) plot of log-log (event time) versus log (time)



Abbreviations: D: durvalumab; DCO: data cut off; EFS: event-free survival; FLOT: 5-fluorouracil, leucovorin, oxaliplatin and docetaxel.

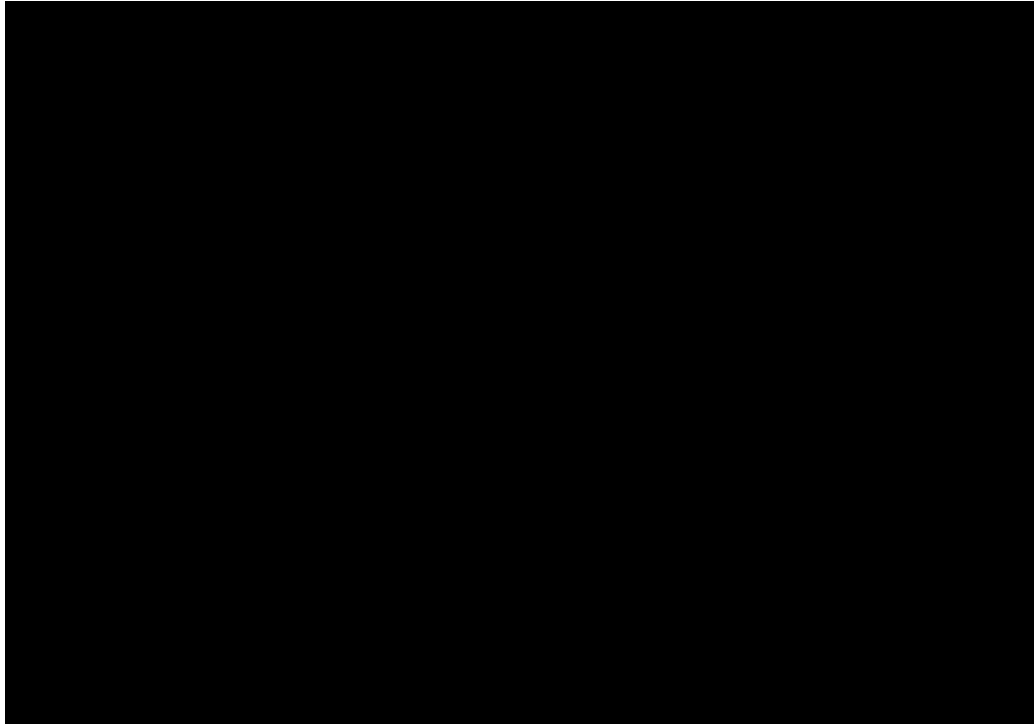
Overall survival (OS)

The Schoenfeld residual plots for OS for both DCO2 and DCO3 are presented in Figure 4 and Figure 5, respectively. Based on the assessment of the Schoenfeld residual plots the PH assumption cannot be formally rejected with a p-value >0.05 across both data cut-offs (Schoenfeld statistic: $p=$ ■■■■, $p=$ ■■■■, respectively).

The log cumulative hazard plots for OS for DCO2 (Figure 6) and DCO3 (Figure 7) are presented below. The log cumulative hazard plots at both DCOs are not strictly parallel up until approximately

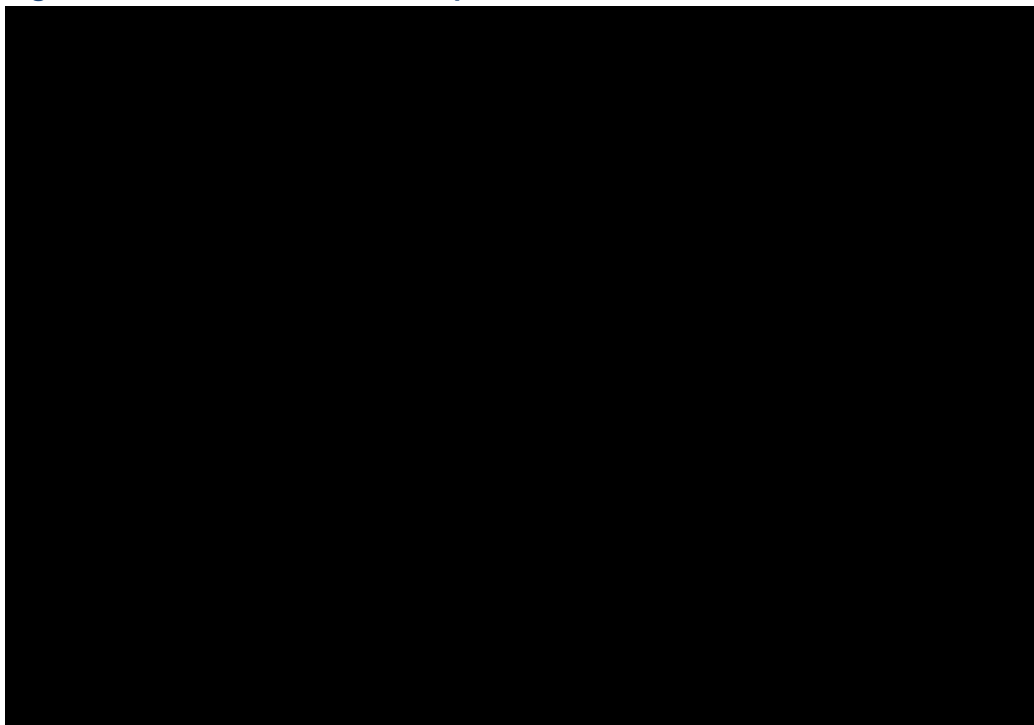
12 months, characterised by the late separation of the Kaplan-Meier (KM) curves. Curves do however become more parallel, indicative of sustained separation, after the 12-month timepoint. As concluded in Janjigian, *et al.* 2025 (based on DCO2), the PH assumption is not satisfied due to this late separation.⁵ Based on the evaluation of the log cumulative hazard plots, the PH assumption can be formally rejected. With the same late separation apparent at DCO3, the conclusion of non-PH is consistent across both DCOs.

Figure 4: OS Schoenfeld residual plot (DCO2)



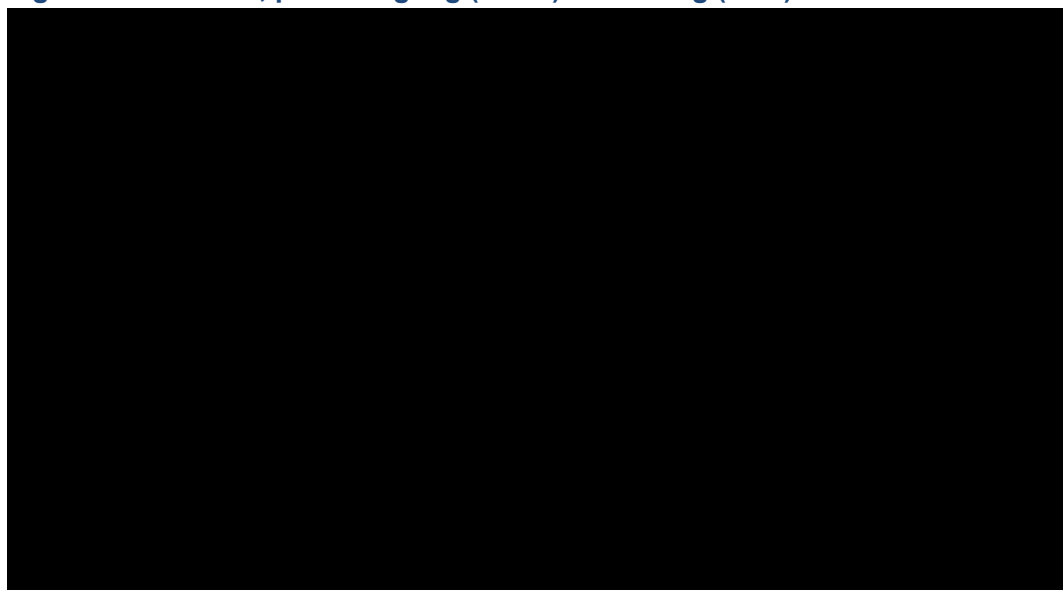
Abbreviations: DCO: data cut off; OS: overall survival.

Figure 5: OS Schoenfeld residual plot DCO3



Abbreviations: DCO: data cut off; OS: overall survival

Figure 6: DCO2 OS, plot of log-log (event) versus log (time)



Abbreviations: D: durvalumab; DCO: data cut off; FLOT: 5-fluorouracil, leucovorin, oxaliplatin and docetaxel; OS: overall survival.

Figure 7: DCO3 OS, plot of log-log (event) versus log (time)



Abbreviations: D: durvalumab; DCO: data cut off; FLOT: 5-fluorouracil, leucovorin, oxaliplatin and docetaxel; OS: overall survival.

A5. Please clarify whether in the MATTERHORN trial it was pre-specified that:

- i. R0 (confirmed complete, microscopically-negative) resection rate would be determined by pathology review by local assessment (rather than by central assessment).**

It was pre-specified in the MATTERHORN clinical study protocol that R0 resection rate would be determined by pathology review by local assessment.¹ Page 15 of the protocol provides the definition of R0 resection rate, stating “*R0 resection (complete resection) rate is the proportion of patients who have a confirmed complete resection as assessed by pathology review*”. This definition was also provided in the CS, Section 2.4.2 (Table 8). Page 79 of the protocol states that

*“Pathology review for determination of staging after surgery will be performed by **local assessment**” (bold emphasis added).¹*

- ii. **Metastasis-free survival and disease-free survival would be assessed according to RECIST 1.1 per investigator-assessment (rather than by blinded independent central review-assessment).**

According to the MATTERHORN Clinical Study Protocol, both metastasis-free survival (MFS) and disease-free survival (DFS) were assessed using RECIST 1.1, however investigator or BICR assessment was not pre-specified. The definitions of MFS and DFS are presented on Page 113 of the clinical study protocol.^{1, 3}

Please provide reference to the SAP or protocol (including page numbers) where these pre-specifications were documented.

References to the page numbers in the clinical study protocol have been provided in response to the questions above.

A6. Please comment on apparently contradictory statements on analysis of EFS. The CS, Table 7 states, ‘The alpha expenditure for EFS was planned to be spent between DCO2 and [final analysis] using the Lan-DeMets spending function’ whereas CS, page 57 states that the final analysis of EFS was conducted at DCO2.

The information provided in the CS regarding the pre-planned final analysis of EFS was based on the MATTERHORN clinical study protocol which outlines the prespecified analysis plan for the MATTERHORN trial.¹ However, at DCO2, the boundary for declaring statistical significance for EFS was met and the MATTERHORN trial achieved its primary endpoint, demonstrating a statistically significant EFS benefit for the D-FLOT arm versus the control arm.³ As outlined in the CSR, since a statistically significant EFS benefit was demonstrated at DCO2, this became the final analysis for EFS.³ This DCO remained the interim analysis for OS, with final OS analysis being conducted at DCO3.⁶

A summary of the data cuts from the MATTERHORN trial are presented below:

- DCO1 (pCR assessment; first interim analysis; 1st February 2023)
- DCO2 (pre-planned interim analysis of EFS and OS, but became the final analysis of EFS having met the boundary for declaring statistical significance at this DCO; second interim analysis; 20th December 2024)
- DCO3 (final analysis of OS; 1st September 2025)

A7. In CS, Table 7, it is stated that “With approximately 461 EFS events at the [final analysis], the study was planned to have approximately 85% power”. On page 57 of the CS, it is stated that the final analysis of EFS was conducted at DCO2. Table 10 of the CS reports that only 385 events had occurred at the time

of DCO2. Please clarify whether DCO2 is the final analysis for EFS, and if this is the case, why the number of EFS events observed is less than the number required to power the study. If DCO2 is not the final analysis, please provide results for EFS at DCO3.

As outlined in response to Clarification Question A6, as the MATTERHORN trial met its primary endpoint at DCO2 and demonstrated a statistically significant EFS benefit for the D-FLOT arm versus the control arm, DCO2 became the final analysis for EFS (as outlined in the CSR).³ Although this subsequently became the final analysis for EFS, this was the pre-specified interim analysis for EFS which was planned when approximately 369 events had occurred.³ This explains why the number of EFS events does not match the pre-specified number of events for DCO3.⁶

Clinical effectiveness review methods

A8. Please clarify if any records were excluded from the clinical SLR solely on the basis of the following criteria listed in CS, Appendix B.1.2:

- i. being a phase I or II clinical trial?**
- ii. a clinical trial that was terminated early?**

The eligibility criteria for inclusion in the clinical systematic literature review (SLR) are presented in Table 6 of the CS Appendices (Appendix B.1.2). As outlined in these eligibility criteria, the only study design inclusion criteria was any randomised controlled trials. Phase I or II clinical trials or clinical trials that terminated early were not excluded from the clinical SLR.

As outlined in Appendix B.1.2 of the CS Appendices, due to the volume of evidence identified after full-text screening, further eligibility criteria were applied to prioritise articles for data extraction; however, these criteria did not influence the inclusion of studies in the SLR.

Of the records included in the SLR, articles must have met the following criteria to be extracted:

- Reporting on a study that includes at least one neoadjuvant and/or adjuvant treatment arm (i.e., studies comparing only different surgical procedures were not extracted)
- **Reporting on a Phase III study**
- Reporting results for patients with GC, GOJC or GOA (i.e., publications reporting on a mixed population of GOJC/OC were not extracted if results were not separated)

Studies were also deprioritised for extraction if characterised by one or more of the following:

- **Trial terminated early**
- Reported relevant details/outcomes that were captured in another publication that was already extracted, including ad-hoc analyses involving relevant outcomes (e.g., association of outcome with factors other than treatment)
- Study was published 25 or more years ago.

Of the studies included in the SLR, 244 were deprioritised for data extraction (as presented in CS Appendix B.1.3, Figure 2). Of these, data extraction was not completed for 62 studies due to not being a Phase 3 trial (or it was unclear) and for 2 studies as the trial terminated early. None of the studies deprioritised for data extraction were considered relevant to the decision problem for this appraisal (i.e., no studies provided evidence for perioperative D-FLOT versus perioperative FLOT chemotherapy in the relevant population).

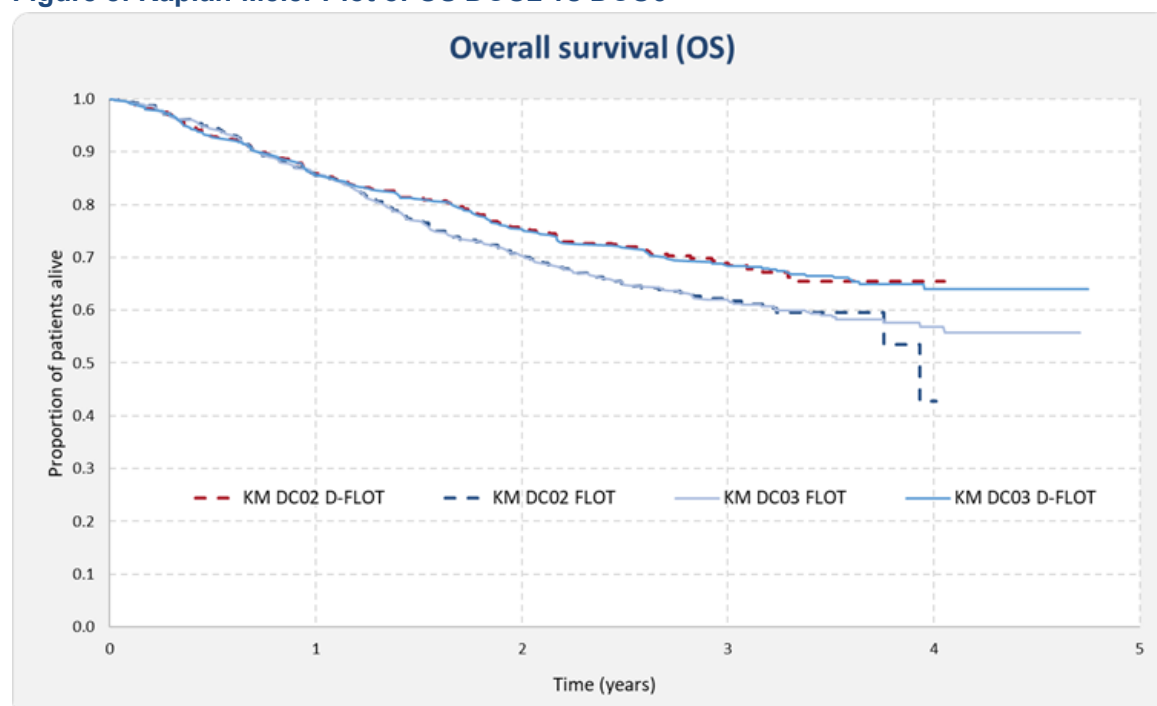
Section B: Clarification on cost effectiveness data

B1. Priority question. Please select distributions for time to first recurrence (TFR, also referred to as TP1), time from randomisation to death as a first event (TTDeath, also referred to as TP2), post-recurrence survival (PRS, also referred to as TP3) such that modelled OS, TP1, TP2 and TP3 align with OS, TP1, TP2 and TP3 as reported at DCO3. If this is not possible, please present a partitioned survival model using OS and EFS from DCO3.

During the Clarification Call with the EAG and the Company, the EAG confirmed that the focus of this question was for the Company to ensure that the modelled OS is aligned with the OS KM curves from the MATTERHORN trial. The EAG also commented that modelled transition probabilities (TPs) do not align with the TPs reported at DCO3, however the TPs were not updated during the latest DCO. While OS is not included as an input in the model, observed OS data can be used for validation of the predicted results. The Company maintains the position that the modelled TPs based on DCO2 data provide a good fit to the observed OS data (at DCO2 and also DCO3).

As presented in the CS, OS data from DCO2 are consistent with data from DCO3, as evidenced by a stable HR across the data cuts.^{3, 6} Furthermore, the KM curves from both data cuts have highly aligned trajectories, as demonstrated by the overlaid KM curves presented in Figure 8 and the reported landmarks presented in Table 3.^{3, 6} At DCO2, there was a strong trend towards improved OS in patients who received D-FLOT compared to patients in the control arm, which was sustained through the follow-up period (HR: 0.78; 95% CI: 0.62, 0.97; 2-sided p=0.025).⁵ OS data from DCO3 are consistent with the current evidence base, with D-FLOT demonstrating a statistically significant OS benefit versus the control arm (HR: 0.78; 95% CI: 0.63, 0.96; p=0.021). DCO3 occurred approximately eight months after DCO2 and provides 3.3% additional data maturity, hence the consistency between data cuts. At DCO3, OS was evaluated using the remaining alpha of 4.99%, whereas a fixed alpha of 0.01% had been allocated to OS testing at DCO2. Consequently, statistical significance was achieved only at DCO3.^{3, 6} This concordance supports the use of DCO2 data to inform the model. Furthermore, given the consistency between OS results at DCO2 and DCO3, validation of modelled OS against either data cut-off at landmark time-points provides confidence in the robustness of the model predictions.

Figure 8: Kaplan-Meier Plot of OS DCO2 vs DCO3



Abbreviations: D: durvalumab; DCO: data cut off; FLOT: 5-fluorouracil, leucovorin, oxaliplatin and docetaxel; OS: overall survival.

Source: Janjigian, *et al.* 2025;⁵ Taberno, *et al.* Presented at ESMO 2025.⁶

The TPs selected for the base case that inform modelled OS were selected in line with NICE Decision Support Unit (DSU) guidance on the analysis of survival outcomes for economic evaluations alongside clinical trials, including validation with UK clinical experts.^{7, 8} The resulting extrapolations are aligned with established expectations for patients treated with FLOT chemotherapy, supporting the credibility of the base case survival projections.

A comparison of the modelled OS (when combining the base case selections of generalised gamma for TP1, Gompertz for TP2 and log-logistic for TP3 to reconstruct the OS extrapolation) versus data from the MATTERHORN trial and FLOT-4 trial is presented in Table 3.

For perioperative FLOT chemotherapy, the 3-year OS predicted by the model was ■■■, which is consistent with, and falls within the 95% CIs for the 3-year OS reported in the MATTERHORN trial at DCO2 (■■■% [95% CI: ■■■]) and at DCO3 (■■■ [95% CI: ■■■]).³ Similarly, the 5-year model prediction of OS for the perioperative FLOT chemotherapy arm (■■■) is closely aligned with the 5-year OS rate of 45.0% in FLOT-4 trial.^{3, 9} As such, the cost-effectiveness model can be considered as appropriately predicting OS for the control arm, based on the MATTERHORN trial and other published sources of long-term OS for perioperative FLOT.

For perioperative D-FLOT, the model predicted a 3-year OS of ■■■, which is consistent with the 3-year OS observed in the MATTERHORN trial at DCO2 (■■■% [95% CI: ■■■]) and at DCO3 (■■■% [95% CI: ■■■]).

Table 3: Modelled OS versus OS from MATTERHORN and FLOT-4 for D-FLOT and the control arm

	2-year	3-year	5-year
D-FLOT			
Modelled, %	■■■	■■■	■■■

MATTERHORN DCO2, % (95% CI)	75.7 [REDACTED]	[REDACTED]	NR
MATTERHORN DCO3, % (95% CI)	75.5 [REDACTED]	[REDACTED]	NR
FLOT			
Modelled, %	[REDACTED]	[REDACTED]	[REDACTED]
MATTERHORN DCO2, % (95% CI)	70.4 [REDACTED]	[REDACTED]	NR
MATTERHORN DCO3, % (95% CI)	70.4 [REDACTED]	[REDACTED]	NR
FLOT-4, % (95% CI)	68 (63, 73)	57 (52, 62)	45.0 (38, 51)

Abbreviations: CI: confidence interval; D: durvalumab; FLOT: 5-fluorouracil, leucovorin, oxaliplatin and docetaxel; OS: overall survival.

Source: Al-batran, *et al.* 2019;⁹ AstraZeneca Data on File (MATTERHORN Clinical Study Report; DCO2);³ Janjigian, *et al.* 2025.⁵

In response to the EAG's request for a partitioned survival model (PSM), it is not appropriate to model resectable GOA using a PSM model. The use of a PSM in this setting would be associated with substantial limitations – most notably, the absence of a structural link between EFS and OS, unlike the semi-Markov Model in the CS. EFS and OS are structurally linked for patients with resectable GOA, given that as noted in Section 1.3.4 of the CS, disease recurrence and progression significantly influence survival.¹⁰⁻¹³ An STM inherently allows this relationship to be modelled; patients who transition to the recurred disease (RD) health state experience substantially poorer survival compared to those who remain event-free (EF). The structure of the STM enables explicit representation of a “cure” pathway that aligns with expected patient outcomes and established appraisal practice. Specifically, patients deemed cured are no longer at risk of recurrence (modelled via TP1), and their subsequent mortality is assumed to be comparable to that of the general population (modelled via TP2). This approach is consistent with previous evaluations in similar settings, including TA746. In contrast, a PSM would assume that the two endpoints are independent.

As detailed in Section 3.2.2 of the CS, this structure was selected based on the results of the economic SLR, which indicated that the majority of cost-effectiveness analyses in the resectable GOA disease setting adopted an STM structure (either Markov or semi-Markov models). Further to this, in a separate targeted literature search of previous cost-effectiveness studies submitted to HTA bodies (see Appendix M of the CS), 16/17 appraisals in the neoadjuvant/adjuvant and perioperative GOA disease setting were STMs (Markov and semi-Markov models), including the recent NICE appraisal of adjuvant nivolumab in GOJ adenocarcinoma (TA746).¹⁴

While a PSM directly uses OS data directly and may therefore achieve a close fit to observed OS, the STM used in this analysis already provides a reasonable prediction of OS. Where discrepancies between STM predicted OS and observed OS are present, for example, a slightly lower predicted 3-year OS than the observed landmark - they remain within the 95% CIs and occur consistently across both arms. Accordingly, these differences are not expected to materially affect incremental outcomes.

Finally, the semi-Markov STM structure adopted in the Company economic model has been validated extensively by UK clinical experts, who confirmed that it is appropriate for a curative-intent treatment such as perioperative D-FLOT.⁷ Given this, there is no clear rationale to consider an alternative model structure in this indication.

B2. Please provide justification as to why the company consider the PRS utility value (0.747, as reported in CS, Table 25) is representative of symptom burden in recurrent disease. Clinical advice to EAG is the symptom burden progressive disease is significant and could result in people experiencing lower utility than used for PRS in the CS. The EAG also note that the company stated in CS, Section 1.3.4 (page 28) that: “A cross-sectional survey of 326 adults reported that patients with recurrent GC [gastric cancer] undergoing treatment with chemotherapy had a utility value of 0.399, which was markedly lower than early GC with surgery (utility of 0.767).”

The utility values derived from the MATTERHORN trial underwent clinician validation and expert opinion indicated that the utility associated with the progressed disease (PD) health state is likely lower than the values from the MATTERHORN trial.⁷ As such, a lower utility value of 0.747 was selected for use in the base case as it aligned with the recurrent disease utility value selected in TA746.¹⁴ However, the Company recognise that the utility value of 0.747 for PRS may not fully capture the utility decrement associated with progressed disease.

Based on the published literature and feedback from clinical experts interviewed by the Company, as GOA progresses, patients experience increasingly significant reductions in health-related quality of life (HRQoL), in line with the worsening physical and emotional symptoms.¹⁵ Moreover, disease recurrence, and the fear of it, further diminish patients' HRQoL.¹⁶ In the cross-sectional survey highlighted by the EAG above, patients with recurrent GC receiving chemotherapy exhibited a utility of 0.399, far lower than the 0.767 observed in early GC managed with surgery.¹⁶ The Company agree with the EAG that a PD value of 0.399 may better reflect clinical advice to the EAG, as well as the feedback received by the Company regarding the considerable symptom burden associated with recurrent disease.

The progressed-disease utility value used in the company's base case is therefore a conservative estimate of the quality-of-life decrement associated with progression; the true decrement is likely substantially higher.

Using a PD utility of 0.399 in a scenario analysis to better reflect symptom burden in recurrent disease resulted in an ICER of £11,629, indicating improved cost-effectiveness when utility values more accurately capture patient burden.

Table 4: Scenario analysis using a PD utility value of 0.399

Technologies	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER (£)
Base case: PD utility of 0.747	-	-	████	██	£12,416
Scenario analysis: PD utility of 0.399					
Perioperative D-FLOT	████	██	-	-	-
Perioperative FLOT chemotherapy	████	██	████	██	£11,629

Abbreviations: D: durvalumab; FLOT: 5-fluorouracil, leucovorin, oxaliplatin and docetaxel; ICER: incremental cost-effectiveness ratio; incr.: incremental; QALY: quality-adjusted life year; PD: progressed disease.

Section C: Textual clarification and additional points

C1. Please provide, with supporting evidence (relevant references), an estimate of PD-L1 status (Tumour Area Positivity [TAP] equal or greater than 1% and TAP less than 1%) in people with resectable gastric or gastro-oesophageal junction adenocarcinoma in the UK. The EAG note that in the MATTERHORN trial, 90.0% of patients had tumours expressing (TAP equal or greater than 1%) PD-L1 and 10.0% had tumours expressing below the ‘positive’ threshold (TAP less than 1%).

PD-L1 status was a prespecified stratification factor in MATTERHORN (Combined Positive Score [CPS] PD-L1 expression status using Tumour Area Positivity (TAP), TAP $\geq 1\%$ vs TAP $< 1\%$), and all efficacy endpoints were prospectively assessed within PD-L1 subgroups.¹ Incorporating PD-L1 as a stratification factor is common practice in recent anti-PD(L)1 trials across tumour types, even when PD-L1 does not guide routine clinical decision making.⁷ It is important to note that TAP is not the most common approach to PD-L1 assessment in the UK, where laboratories typically report PD-L1 as CPS. As a result, UK real world data aligned specifically to TAP $\geq 1\%$ versus TAP $< 1\%$ in resectable gastric or gastroesophageal junction adenocarcinoma are not available.

In MATTERHORN, tumour samples were collected prior to randomisation.³ Furthermore, the trial permitted enrolment of both PD-L1-positive and PD-L1-negative tumours, so there is no reason to suggest the study population was enriched toward PD-L1-positive or negative patients.³ As PD-L1 testing is not routinely performed in early-stage disease in most centres given it does not influence perioperative treatment selection, preselection of patients into the MATTERHORN trial based on PD-L1 status is unlikely.^{7, 17} PD-L1 expression of patients in MATTERHORN is as expected based on findings in other contemporary studies in GC/GOJC.^{5, 17, 18}

Moreover, the representativeness of the population in MATTERHORN was validated with UK clinical experts consulted by the Company, who considered the observed proportion of PD-L1-positive and negative tumours as plausible for UK practice, while noting that PD-L1 testing is generally not undertaken in early-stage disease because it does not direct treatment decisions; ESMO guidelines recommend PD-L1 testing only in advanced or metastatic disease and not in the resectable setting.^{7, 19, 20}

Furthermore, subgroup analyses from MATTERHORN (CS, Section 2.8) demonstrate that D-FLOT demonstrates a clinical benefit versus placebo + FLOT regardless of PD-L1 status.⁵ For both OS and EFS, the clinical benefit observed in PD-L1 subgroups was highly consistent with the intent-to-treat (ITT) population, highlighting that PD-L1 expression is not anticipated to impact the efficacy of D-FLOT.^{3, 5} Results for the OS subgroup analysis were consistent at DCO3, with a HR of 0.79 (95% CIs: 0.63, 0.99) for the TAP $\geq 1\%$ subgroup and a HR of 0.79 (95% CIs: 0.41, 1.50) for the TAP $< 1\%$ subgroup.^{5, 6} It should be noted that the study was not powered for individual subgroup comparisons and a degree of variability was observed across the subgroups due to small patient numbers and numbers of events.³

PD-L1 expression is not anticipated to influence treatment decisions in resectable GOA, as confirmed by UK clinical experts, and the unmet need for an effective treatment exists across the

GOA population. As such, the precise UK distribution of PD-L1 by TAP is not decision critical for this appraisal.

C2. Please clarify the planning, application and performance of all AI tools used for selection, data extraction and quality assessment both SLRs (including DistillerSR Artificial Intelligence SYstem (DAISY), ChatGPT (5.0) in Agent mode and any other tools used) in the format recommended in the RAISE (1) reporting standard. Please use the RAISE checklist for the SLRs conducted to identify clinical effectiveness evidence and to identify published economic evaluations, evidence relating to the HRQoL and utility (humanistic burden) and cost/resource use (economic burden).

An overview of the AI tools used in the clinical and economic SLRs in line with the RAISE reporting standards (presented in Table 1 of Flemyng *et al.* [2025]) is presented below.²¹

Table 5: Clinical Systematic Literature Review, Screening

Topic	Company response
Name of tool	DistillerSR (DAISY)
Version of tool	NA – not given
Date used	15 October 2025 and earlier
Purpose for using the tool	This tool is used for data annotation (i.e., classification and annotation) in literature reviews. Functionality is underpinned by natural language processing (NLP) that detects similarities within and differences between categories of references based on titles and abstracts. Through training and validation on the adjudicated decisions for title/abstract screening in the original search results, the tool “learns” patterns based on annotations performed by human reviewers and the classifiers are then used to screen unreviewed records.
Evidence for methodologic soundness and validity	Gartlehner <i>et al.</i> (2019) conducted a user study to evaluate the tool for title/abstract screening. ²² Five independent screening teams each screened 2,472 abstracts from a published review, with DistillerSR replacing one of the two human reviewers after initial training. ²² The machine-assisted screening (one human + DAISY) achieved a pooled sensitivity of 78% and specificity of 95%, consistent with traditional single-reviewer screening (78% sensitivity, 94% specificity). ²²
Steps taken to verify content	For HTA-grade SLRs, the intent of any review team is to capture all qualifying studies (i.e., 100% sensitivity) or to minimise loss of sensitivity to the maximum extent possible, even at the expense of sacrificing some specificity. The threshold for optimal sensitivity commonly employed in the literature is $\geq 95\%$. In the present review, sub-optimal sensitivity ($<95\%$) was initially observed, indicating that some qualifying records were being missed. This was due to settings within the DAISY model that control the threshold above which a given study qualifies to be retained (i.e., initial default settings placed this threshold too high). The threshold was subsequently reduced, which effectively reduced the probability of type 2 errors (false negatives, i.e., excluding qualifying studies), but increased the probability of type 1 errors (false positives, i.e., retaining non-qualifying studies; hence suboptimal specificity). This was considered acceptable because it ensured no loss of qualifying studies while increasing the number of ultimately unqualified full texts by only 10%.

Financial or non-financial interests	None
Limitations for using this tool	As this is proprietary software, there is some lack of transparency into the coding and settings that affect the tool's performance. Users also do not have the option of editing the code or some of the settings in order to optimize the tool for the specific project, research question, or other context. However, we did have an opportunity to work directly with the Distiller team to give our feedback on the performance of the classifiers, and the Distiller team was able to revise them accordingly so that we achieved acceptable sensitivity.

Table 6: Clinical Systematic Literature Review, Extraction

Topic	Reply
Name of tool	ChatGPT (Model 5.0, Agent Mode)
Version of tool	Model 5.0
Date used	15 October 2025
Purpose for using the tool	The purpose for using this tool was to extract targeted data from the included studies, which were then checked by a human reviewer.
Evidence for methodologic soundness and validity	Evidence from recent evaluations in epidemiology and health sciences supports using ChatGPT to assist with data extraction, as it can markedly reduce omission and hallucination errors when paired with human verification. For instance, Jensen <i>et al.</i> (2025) had ChatGPT act as a second extractor of clinical studies; the model achieved 92.4% accuracy, with only 5.2% of the extracted data points being false or hallucinated.²³ Omission rate was low, as reflected in a 97% recall in comparisons versus human gold-standard extractions, and the reproducibility was high.²³ Observed error rates (5-10% missed data and 3-5% fabricated data) were comparable to or lower than human error rates in exhaustive manual extraction tasks.²³ Andersen <i>et al.</i> (2025) found no significant difference between ChatGPT and a human in overall data recall and precision.²⁴ They and others concluded that ChatGPT's extraction is sufficiently accurate to replace one of two human extractors in a systematic review, so long as the remaining human reviewer cross-verifies the AI's output.²⁴ This indicates that ChatGPT can draft comprehensive data extractions with minimal omissions, while the human co-reviewer corrects any AI mistakes.²⁴ Nevertheless, the process for extraction described in the protocol for this SLR includes additional safeguards.
Steps taken to verify content	As presented in the CS Appendices, the performance of the AI extractor was acceptable-to-high. These findings are consistent with the literature upon which the prompts and overall validation structure were based. The volume of data points categorized as "completely correct" or "satisfactory" was 94.3%. The volume of extracted data that was completely false (i.e., hallucinated) was 3.2%. Performance was highest for study characteristics (98.9% completely correct or satisfactory) and lowest for outcomes (91.2% completely correct or satisfactory). The AI extractor therefore qualified as a "second reviewer" based on the rubric described in described by Motzfeldt Jensen <i>et al.</i> 2025.²³ This is consistent with its intended use whereby the AI extractor is accompanied by 100% human oversight of all extracted values. Reproducibility between two independent applications of the AI extraction process was high in the present review (i.e., 96.2% concordance between AI extractor #1 and AI extractor #2).
Financial or non-financial interests	None
Limitations for using this tool	The primary limitation is the risk of hallucination, which is inherent in all such tools. In addition, concordance between independent applications of the AI was considerably lower when measuring ability to correctly identify instances where a

	targeted value (i.e., a value explicitly sought for extraction via the prompts given in the methods section [e.g., progression free survival value and duration of follow-up for this outcome]) is not reported (82.4% concordance). This finding is explained by established phenomena whereby large language models seek to validate a user's implied intent that the information being sought is necessarily found in the given material. Both of these limitations were mitigated by full human checks of all values extracted by the AI.

Table 7: Clinical Systematic Literature Review, ROB Assessment

Topic	Reply
Name of tool	ChatGPT (Model 5.0, Agent Mode)
Version of tool	Model 5.0
Date used	15 October 2025
Purpose for using the tool	The purpose for using this tool was to conduct risk of bias and study quality assessment using the ROB1 rubric.
Evidence for methodologic soundness and validity	Lai et al. (2024) tested two LLMs – ChatGPT (GPT-4) and Anthropic Claude – on RoB 2 assessments for 30 RCTs, using a structured prompt and expert consensus as the gold standard. ²⁵ Both models showed high accuracy in reproducing expert judgments, with ChatGPT averaging 84.5% correct and Claude 89.5% correct (p = .01 for difference). ²⁵ Across most RoB domains, agreements with experts were substantial, with many domain-specific Cohen's $\kappa > 0.80$. ²⁵ Overall sensitivity and specificity were high (ChatGPT's sensitivity 0.82, specificity 0.96; Claude's 0.90 and 0.97). ²⁵
Steps taken to verify content	Across 30 clinical trials included in our review and 270 individual points of assessment (30 trials x 9 assessment points per trial), the performance of ChatGPT for conducting risk of bias and study quality assessment using ROB1 for clinical trials was high overall (94% concordance with the human-derived reference standard) but was variable across the individual assessment items. The model performed optimally (i.e., 100% concordance) for items pertaining to randomization, treatment allocation, clinician / patient blinding, and funding; performed acceptably (i.e., 85% to 99% concordance) for items pertaining to assessor blinding, balanced prognostic factors, unexpectedly imbalanced dropouts, and reporting outcomes; and suboptimally (i.e., <85% concordance) for ITT analysis. The literature is mixed with respect to establishing a threshold above which AI performance on risk of bias and study quality assessment should be considered acceptable, but a targeted review of the literature suggests that values above 80% are indicative of an approach that is performing acceptably. Importantly, the model required retraining for the "unexpectedly imbalanced dropouts" item as it initially interpreted any differential (even when expected for example due to higher rates of adverse events) as being due to unexpected reasons. The lower performance on the ITT analysis item was likely due to difficulty in parsing the language indicating an ITT analysis was conducted despite not using the phrase "intent to treat".
Financial or non-financial interests	None
Limitations for using this tool	The primary limitation is the risk of hallucination, which is inherent in all such tools. This was mitigated by full human checks of all values extracted by the AI.

Table 8: Economic Systematic Literature Review, Screening

Topic	Reply

Name of tool	DistillerSR (DAISY)
Version of tool	Not given
Date used	15 October 2025 and earlier
Purpose for using the tool	This tool is used for data annotation (i.e., classification and annotation) in literature reviews. Functionality is underpinned by natural language processing (NLP) that detects similarities within and differences between categories of references based on titles and abstracts. Through training and validation on the adjudicated decisions for title/abstract screening in the original search results, the tool “learns” patterns based on annotations performed by human reviewers and the classifiers are then used to screen unreviewed records.
Evidence for methodologic soundness and validity	Gartlehner et al. (2019) conducted a user study to evaluate the tool for title/abstract screening. ²² Five independent screening teams each screened 2,472 abstracts from a published review, with DistillerSR replacing one of the two human reviewers after initial training. ²² The machine-assisted screening (one human + DAISY) achieved a pooled sensitivity of 78% and specificity of 95%, consistent with traditional single-reviewer screening (78% sensitivity, 94% specificity). ²²
Steps taken to verify content	For HTA-grade SLRs, the intent of any review team is to capture all qualifying studies (i.e., 100% sensitivity) or to minimise loss of sensitivity to the maximum extent possible, even at the expense of sacrificing some specificity. The threshold for optimal sensitivity commonly employed in the literature is $\geq 95\%$. In the present review, sub-optimal sensitivity ($<95\%$) was initially observed, indicating that some qualifying records were being missed. This was due to settings within the DAISY model that control the threshold above which a given study qualifies to be retained (i.e., initial default settings placed this threshold too high). The threshold was subsequently reduced, which effectively reduced the probability of type 2 errors (false negatives, i.e., excluding qualifying studies), but increased the probability of type 1 errors (false positives, i.e., retaining non-qualifying studies; hence suboptimal specificity). This was considered acceptable because it ensured no loss of qualifying studies while increasing the number of ultimately unqualified full texts by only 6%.
Financial or non-financial interests	None
Limitations for using this tool	As this is proprietary software, there is some lack of transparency into the coding and settings that affect the tool’s performance. Users also do not have the option of editing the code or some of the settings in order to optimize the tool for the specific project, research question, or other context. However, we did have an opportunity to work directly with the Distiller team to give our feedback on the performance of the classifiers, and the Distiller team was able to revise them accordingly so that we achieved acceptable sensitivity.

Table 9: Economic Systematic Literature Review, Extraction

Topic	Reply
Name of tool	ChatGPT (Model 5.0, Agent Mode)
Version of tool	Model 5.0
Date used	03 October 2025
Purpose for using the tool	The purpose for using this tool was to extract targeted data from the included studies, which were then checked by a human reviewer.
Evidence for methodologic soundness and validity	Evidence from recent evaluations in epidemiology and health sciences supports using ChatGPT to assist with data extraction, as it can markedly reduce omission and hallucination errors when paired with human verification. For instance, Jensen et al. (2025) had ChatGPT act as a second extractor of clinical studies:

	the model achieved 92.4% accuracy, with only 5.2% of the extracted data points being false or hallucinated.²³ Omission rate was low, as reflected in a 97% recall in comparisons versus human gold-standard extractions, and the reproducibility was high.²³ Observed error rates (5-10% missed data and 3-5% fabricated data) were comparable to or lower than human error rates in exhaustive manual extraction tasks.²³ Andersen et al. (2025) found no significant difference between ChatGPT and a human in overall data recall and precision.²⁴ They and others concluded that ChatGPT's extraction is sufficiently accurate to replace one of two human extractors in a systematic review, so long as the remaining human reviewer cross-verifies the AI's output.²⁴ This indicates that ChatGPT can draft comprehensive data extractions with minimal omissions, while the human co-reviewer corrects any AI mistakes.²⁴ Nevertheless, the process for extraction described in the protocol for this SLR includes additional safeguards.
Steps taken to verify content	Across the publications retained from the second search, the performance of the AI extractor was acceptable-to-high, as presented in the CS Appendices. These findings are consistent with the literature upon which our prompts and overall validation structure were based. The volume of data points categorized as "completely correct" or "satisfactory" was 92.1%. The volume of extracted data that was completely false (i.e., hallucinated) was 4.3%. Performance was highest for study characteristics (98.9% completely correct or satisfactory) and lowest for outcomes (91.2% completely correct or satisfactory). The AI extractor therefore qualified as a "second reviewer" based on the rubric described in the methods. This is consistent with its intended use whereby the AI extractor is accompanied by 100% human oversight of all extracted values. Reproducibility between two independent applications of the AI extraction process was high in the present review (i.e., 95.8% concordance between AI extractor #1 and AI extractor #2).
Financial or non-financial interests	None
Limitations for using this tool	The primary limitation is the risk of hallucination, which is inherent in all such tools. In addition, concordance between independent applications of the AI was considerably lower when measuring ability to correctly identify instances where a targeted value (i.e., a value explicitly sought for extraction via the prompts given in the methods section [e.g., progression free survival value and duration of follow-up for this outcome]) is not reported (72.6% concordance). This finding is explained by established phenomena whereby large language models seek to validate a user's implied intent that the information being sought is necessarily found in the given material. Both of these limitations were mitigated by full human checks of all values extracted by the AI.

Table 10: Economic Systematic Literature Review, ROB Assessment

Topic	Reply
Name of tool	ChatGPT (Model 5.0, Agent Mode)
Version of tool	Model 5.0
Date used	03 October 2025
Purpose for using the tool	The purpose for using this tool was to conduct risk of bias and study quality assessment using the ROB1 rubric.
Evidence for methodologic soundness and validity	Lai et al. (2024) tested two LLMs – ChatGPT (GPT-4) and Anthropic Claude – on RoB 2 assessments for 30 RCTs, using a structured prompt and expert consensus as the gold standard. ²⁵ Both models showed high accuracy in reproducing expert judgments, with ChatGPT averaging 84.5% correct and Claude 89.5% correct ($p = .01$ for difference). ²⁵ Across most RoB domains, agreements with experts were substantial, with many domain-specific Cohen's $\kappa >$

	0.80. ²⁵ Overall sensitivity and specificity were high (ChatGPT's sensitivity 0.82, specificity 0.96; Claude's 0.90 and 0.97). ²⁵
Steps taken to verify content	Across 10 published cost-effectiveness analyses included in our review and 350 individual points of assessment (10 analyses x 35 assessment points per analysis), the performance of ChatGPT for conducting risk of bias and study quality assessment using the Drummond Checklist for cost-effectiveness analyses was acceptable overall (86% concordance with the human-derived reference standard) but was variable across the individual assessment items. The model performed well (i.e., 93% concordance) for items pertaining to study design; performed acceptably (i.e., 84% to 86% concordance) for items pertaining to data collection and analysis / interpretation. The literature is mixed with respect to establishing a threshold above which AI performance on risk of bias and study quality assessment should be considered acceptable, but a brief review of the literature suggests that values above 80% are indicative of an approach that is performing acceptably. The item-level concordance rates were mixed, with somewhat subjective items ascertaining whether model characteristics were “justified” having lower performance than more objective items. For the subjective judgements of whether something was “justified”, there was likely not enough training data for the AI to “understand” what language or latent sentiments in the text constituted a justified versus a not justified variable value. For “details of the methods”, the large language model underpinning the AI may have had difficulty distinguishing the methods for synthesis/meta-analysis from the methods of the overall economic analysis itself. For “quantities separate from unit costs”, the AI may have had difficulty parsing the different ways in which costs and units can be reported separately from one another and perhaps considered their physical proximity in the text as equal to being reported together.
Financial or non-financial interests	None
Limitations for using this tool	The primary limitation is the risk of hallucination, which is inherent in all such tools. This was mitigated by full human checks of all values extracted by the AI.

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Single Technology Appraisal

Durvalumab in combination for neoadjuvant and adjuvant treatment of resectable gastric and gastro-oesophageal junction cancer ID6374

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

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- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1. Your name	
2. Name of organisation	Gastric Cancer UK (operating as Stomach Cancer UK)
3. Job title or position	
4a. Brief description of the organisation (including who funds it). How many members does it have?	Stomach Cancer UK was founded in 2024 and is a UK-based charity focused on improving outcomes for people with gastric and gastro-oesophageal junction cancers. We are a registered charity under the name Gastric Cancer UK (charity number 1213056). The charity provides patient information, advocacy and signposting to patients, caregivers and family members. We engage with policy and decision-making bodies and liaise with clinicians within the NHS and in independent practice. SCUUK is not a membership organisation; we engage with patients, caregivers and clinicians through direct outreach, interviews and digital platforms. We have two full-time members of staff and five trustees. We are funded by public donations and grants from charitable foundations.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] If so, please state the name of the company, amount, and purpose of funding.	No
4c. Do you have any direct or indirect links	No

with, or funding from, the tobacco industry?	
5. How did you gather information about the experiences of patients and carers to include in your submission?	We conducted twelve semi-structured interviews: six with patients/survivors and six with caregivers/family members (four bereaved) via phone, Teams, or WhatsApp. Interviews followed the format of this submission to cover questions 6-13. Where direct quotes are included, the wording was verified with the individual concerned to confirm accuracy. We have used initials instead of full names to preserve anonymity. We were unable to find any UK patients enrolled in the MATTERHORN trial or treated with durvalumab. We spoke to a range of patients and caregivers to discuss their experiences and the addition of durvalumab to FLOT. Participants ranged in age from 30 to 83. Participants were provided with a summary of the MATTERHORN trial findings, including the published abstract in The New England Journal of Medicine, to provide context regarding durvalumab plus FLOT.

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Stomach cancer is one of the six least survivable cancers in the UK (Less Survivable Cancers Taskforce). Most people are diagnosed when cancer is advanced and incurable, but around 40% of those with local and locoregional disease do not survive three years despite surgery and perioperative chemotherapy (FLOT-4 trial). Treatment options are limited after recurrence. Initial symptoms can be non-specific and seem minor compared to the severity of the diagnosis, but they progress swiftly: <i>"A sandwich felt stuck going down one lunchtime. It didn't feel right, so I went to my GP. I was diagnosed with stomach cancer. That was my only symptom. Shock doesn't even describe it."</i> G.J. patient The impact on everyday life is severe, both in terms of symptoms and psychosocial burden. Eating can become difficult, with an inability to tolerate regular food or feeling full after a few mouthfuls. This can feel isolating and frightening. Tasks such as working, cooking and caring for children can quickly become too much to manage. Caregivers may need to give up work to provide assistance with daily tasks. Stomach cancer has traditionally been an illness associated with older men, but incidence is increasing in the under-50s, especially in younger women, many of whom will be both economically active and looking after a young family. (Kim, Tae-Se et al. <i>eClinicalMedicine</i>. 2025;90:103637) <i>"My doctor told me I was too young for cancer."</i> C.S, patient, 30 years old.

	The current standard of care, perioperative FLOT, carries a high treatment burden, which includes neutropenia, infection, peripheral neuropathy (long-term), nausea, vomiting, mucositis, weight loss, fatigue and the psychological strain of intensive therapy without a guaranteed cure. Many patients are willing to endure high toxicity in the hope of a cure. Despite this, recurrence remains high. Total or partial gastrectomy is a major, life-changing surgery because of lifelong changes to eating, nutrition and weight maintenance. Effects of surgery include dumping syndrome, bile reflux, osteoporosis, anaemia, weight loss and fatigue – all of which have a lasting impact on quality of life. There is a profound emotional and psychosocial toll of stomach cancer on patients and caregivers. Hopelessness, anxiety and grief are common at all stages of the disease. Patients with resectable stomach cancer and their caregivers report considerable anxiety and dread around the possibility of recurrence. <i>"I live in constant fear of her cancer coming back. When she was diagnosed, I wanted to die. We have four children, the youngest a baby, and I couldn't see how I would manage. I was useless, so E. had to be brave for me too. If there was anything extra that could take some of the fear away, we would both want it."</i> I.M., caregiver <i>"The years after surgery were like walking through the valley of death, just waiting for it to come back and kill me because I knew the odds. I couldn't plan anything in my business beyond six months, just in case. I didn't start to relax until the three-year mark. Z has never stopped hovering over me, getting worried every time I dump or feel bad."</i> R.D., patient <i>"I was constantly anxious after his surgery. Would it come back? What would happen if it did? Was it [the surgery] all worth it? I lived in limbo for years, unable to see a future. It's been eight years and I'm still watching him like a hawk in case it's back. It's exhausting."</i> Z.D., caregiver

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	All people interviewed had positive things to say about the NHS, and they expressed gratitude and positivity towards the majority of the individuals who provided them with care. However, patients and caregivers perceive a gap between NHS treatment availability and that in some other high- and middle-income countries. Patients recognise that funding decisions must consider cost-effectiveness, but nevertheless experience distress when treatments available elsewhere are not accessible. <i>"Through talking to many patients and survivors in other countries, I've come to realise that the standard of care on the NHS is not the same as standard of care in the rest of the world and that's really sad."</i> G.J. patient

	Awareness of available treatments is high in this community due to international online support groups and high levels of individual research. The perceived disparity in treatment standards evokes strong feelings, ranging from anger and disbelief to anguish and even guilt or shame for not having the money to go private or travel overseas. <i>"When Dad was sick, there were treatments people in other countries could get, but we couldn't here. Dad didn't get a fair chance, and he might still be with us, but I'll never know. I feel guilty that we didn't have the money to get him overseas. Dad would have jumped at the chance to have more treatment at the beginning."</i> R.N., bereaved caregiver Some patients perceive inequity between private provision and NHS access. <i>"It makes me angry to see all the drugs and treatments people can get in other countries when we don't. To get proper care here, you need to have private insurance."</i> R.D., patient <i>"Dad's oncologist was so kind, and the NHS does the best it can, but I'll always wonder if there was something that could have been done that wasn't... I feel like no one cares about stomach cancer. It's different with breast cancer."</i> A.C. bereaved caregiver Our interview subjects were variously aware of or affected by the following NHS differences from international standards of care: delays in the initial availability of immunotherapy for advanced cancer (now resolved); zolbetuximab and ramucirumab were rejected for routine use in first- and second-line settings, respectively, while trifluridine–tipiracil was not routinely commissioned in later-line settings. Those who had loved ones with peritoneal metastasis felt distressed that HIPEC and PIPAC were available in other countries (though we note that efficacy data are insufficient for both these treatments to be standard of care). We add that pembrolizumab + trastuzumab was not approved for HER2+ PDL1+ advanced cancer. Against this backdrop, patients are highly attentive to decisions regarding new treatments in curative-intent and advanced settings.

8. Is there an unmet need for patients with this condition?	<i>"Everything new is for stage IV people only. If you can have surgery, it's just chemo, and if it doesn't work, you're in trouble."</i> R.S., patient There has been no substantive change to the standard of care treatment for resectable gastric cancer in nearly a decade, when perioperative FLOT replaced epirubicin-containing protocols after the FLOT-4 trial (2017). Despite this, recurrence and mortality remain high even after radical surgery and intensive chemotherapy. Targeted therapies and immune checkpoint inhibition have only been accessible to those with stage IV disease, due to a lack of trial data up until now. This means that non-responders, poor and partial responders to chemotherapy on the curative pathway are: a) At risk of being deemed inoperable due to the discovery of peritoneal metastasis before surgery. b) Less likely to achieve R0 (clear margins) resection during gastrectomy, which increases the risk of local recurrence c) More likely to experience distant recurrence after surgery due to micrometastasis not eradicated by chemotherapy. If a patient has a recurrence after perioperative FLOT, treatment options are severely limited. Recurrence is often only detected when patients report symptoms, by which time the disease burden is usually significant. Treatment options at that point are limited in both availability and efficacy. In patients who recur shortly after perioperative FLOT, treatment options are further constrained because prior exposure to taxanes may limit suitability for second-line paclitaxel monotherapy. For GOJ cancers treated with chemoradiation, there is a second-line treatment option with nivolumab, and we are aware that this has been listed as a comparator. However, following the ESOPEC trial, FLOT is now adopted as standard perioperative treatment for resectable GOJ cancers in centres offering contemporary care. Third-line treatments such as irinotecan or irinotecan + 5-FU (FOLFIRI) are only marginally effective. Many recurrences are in the peritoneum, for which prognosis is dismal, with median survival measured in months. HIPEC and PIPAC are not routinely commissioned in the UK and are not the international standard of care. The landscape of high recurrence rates and lack of treatment options, coupled with no changes to the standard of care despite the development of several targeted treatments, shows the unmet need for people with resectable stomach and GOJ cancer.

	In advanced stomach cancer, treatments are increasingly being frontloaded to first-line to prolong survival with demonstrable results. Trastuzumab, nivolumab, pembrolizumab and zolbetuximab (Scotland only) are all available options in first-line treatment alongside chemotherapy for eligible patients. Durvalumab + FLOT represents the first opportunity to incorporate immune checkpoint inhibition into the curative-intent pathway. This directly addresses the unmet need outlined above.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	Interview subjects were consistently positive about the addition of durvalumab to perioperative FLOT. From a patient and caregiver perspective, the principal advantage of durvalumab plus FLOT is the opportunity to reduce the risk of recurrence at the earliest possible stage of treatment, rather than waiting for metastatic disease to develop before accessing immunotherapy. This shift, from treating relapse to preventing it, was seen as both logical and necessary in a cancer with historically poor survival. For patients facing major surgery, the idea that more effective pre-operative treatment could translate into improved surgical outcomes and long-term survival was intuitive and reassuring. <i>“I’d imagine that better treatment before surgery means better surgery and better survival”</i>, R.N., bereaved caregiver The potential to reduce recurrence risk and improve survival without a substantial increase in treatment burden was seen as highly meaningful. <i>“Better survival and the same amount of side effects as chemo. It’s a no-brainer, isn’t it?!”</i> G.J., patient Patients and caregivers placed particular weight on the improvement in pathological complete response (pCR) observed in MATTERHORN (19.2% with durvalumab plus FLOT versus 7.2% with FLOT alone). A complete pathological response was viewed not simply as a statistical endpoint, but as something tangible and emotionally significant. <i>“I had a complete response to chemo. I’d like more people to have the same response and survive... I think this treatment could do that.”</i> R.D., patient. <i>“Complete response matters because it means hope and less fear.”</i> I.M., caregiver Bereaved family expressed a desire that others might avoid the loss they had experienced. <i>“Durvalumab helps more people survive this beast. I miss my dad every day, and I wouldn’t wish his suffering or my loss on anyone.”</i> A.C., bereaved caregiver

	Beyond pCR, patients recognised that D-FLOT demonstrated a clinically meaningful improvement in event-free survival. In a disease where recurrence remains common, even a moderate reduction in recurrence risk is highly significant from a patient perspective. Avoiding or delaying recurrence means more time free from metastatic disease and less exposure to further systemic therapy and the physical and psychological burden of relapse. Patients and caregivers are aware of the intensity of perioperative chemotherapy. The addition of durvalumab does not appear to compromise the delivery of FLOT, with similar completion rates between arms. This strengthened confidence in the treatment, given the perception that improved outcomes were achieved without a meaningful increase in toxicity.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	Interview subjects did not spontaneously identify disadvantages to adding durvalumab to perioperative FLOT; therefore, we prompted discussion of potential concerns. When prompted, they felt that additional treatment would be acceptable given the high risk of recurrence. Length of postoperative treatment: patients acknowledged that treatment after surgery is harder than before, but no one saw this as an insurmountable barrier. Patients noted that, as with chemotherapy alone, treatment could be stopped if toxicity became unacceptable. We note that the completion rates in MATTERHORN were nearly identical across both arms, at around 50%, despite the higher number of treatment cycles. <i>“Chemo was hard after the operation. I put my head down and got on with it but it was hard. Having treatment for longer would be difficult but it doesn’t sound like it was harder than what I did. I would do whatever was necessary because I have so much more I want to do and achieve. My motto for getting through was: ‘The best is yet to come!’. And I bore everyone around me by still saying it all the time!”</i> R.D., patient Regarding side effects, patients acknowledged that immune-related adverse events can be serious, though they understood these to be relatively uncommon and generally manageable when identified early. <i>“Chemo is nasty and you get side effects you just have to live with. I vomited so much they had to stop my post-op chemo. My fingers and toes are still numb years later. The serious immunotherapy side effects are rarer and I think most can be treated.”</i> G.J., patient Longer infusion times during cycles with durvalumab were not seen as a disadvantage or an inconvenience. As a patient organisation, we recognise that adding immunotherapy may expose some individuals who would not otherwise have experienced recurrence to additional toxicity. Immune-related adverse events can be serious. However, patients consistently prioritised reducing the risk of recurrence over concerns about extended treatment duration or additional toxicity.

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	The MATTERHORN trial showed a consistent treatment effect across all subgroups, including those with PD-L1 expression measured by TAP score. There may be a trend towards greater benefit in patients with higher TAP scores, but the overall population benefited regardless of TAP score. From a patient perspective, the potential benefit is available to all eligible patients with resectable gastric and GOJ cancer. Patients who are unsuitable for immune checkpoint inhibition are unlikely to benefit from this treatment. This would include patients with active autoimmune conditions, those requiring systemic immunosuppression, including prior transplant recipients, as well as those with significant underlying hepatic impairment. In these cases, standard perioperative chemotherapy without immunotherapy would remain the more appropriate option. We also note that the trial included only relatively fit patients with ECOG 0-1, whereas in real-world practice, some patients in the UK are frailer. As with the current standard of care, patients must be fit enough to receive perioperative FLOT to be eligible for durvalumab in this setting.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	Stomach cancer has a higher incidence within more deprived populations within the UK. Implementation should ensure that access to the treatment is geographically and socially equitable, taking into account that patients from deprived backgrounds may present later with more advanced loco-regional disease, and that they may have poorer nutritional status and more comorbidities, which could affect fitness for perioperative FLOT, even before the addition of durvalumab. Older patients are often under-represented in clinical trials, especially perioperative trials. Frailty may limit eligibility, but care should be taken to ensure that age alone is not used to deny access, especially if performance status is adequate. Regarding different ethnic and national groups within the UK, adequate care should be taken to ensure equitable access to information and appropriate interpretation services to support informed consent for complex perioperative chemo- and immunotherapy pathways. Additionally, access to centres offering durvalumab + FLOT should not depend on geography or postcode. Implementation should ensure that rural patients do not shoulder a disproportionate travel burden to access treatment.

Other issues

13. Are there any other issues that you would like the committee to consider?	We would ask the committee to consider whether 2L nivolumab following CRT for resectable GOJ cancer represents a clinically appropriate comparator for durvalumab plus FLOT. Following the ESOPEC trial, perioperative FLOT has been adopted as standard curative-intent treatment in centres offering contemporary care for resectable GOJ cancer. Durvalumab plus FLOT is therefore positioned within the perioperative pathway. Second-line nivolumab, by contrast, is used following disease progression. These treatments address different stages of the disease trajectory and different clinical objectives. We would also ask the committee to consider that interventions in the curative-intent setting carry a distinct weight for patients. Individuals undergoing radical surgery and perioperative chemotherapy do so with the expectation of cure. Treatments that reduce the likelihood of relapse in this setting may have a disproportionate impact on long-term outcomes compared with later-line therapies introduced after metastatic progression. Stomach Cancer UK is grateful for the opportunity to make this submission on behalf of gastric and GOJ cancer patients, their caregivers and family members.

Key messages

24. In up to 5 bullet points, please summarise the key messages of your submission.	• Resectable gastric and GOJ cancer carries a high risk of recurrence despite intensive chemotherapy and radical surgery. Patients in the curative pathway know this risk and experience significant fear of relapse. • MATTERHORN demonstrated a meaningful improvement in pCR and EFS with D-FLOT, without compromising chemo completion rates. For patients, improved outcomes without additional treatment burden are highly significant. • D-FLOT reduces the risk of relapse at the point of greatest curative potential. For patients entering treatment with the expectation of cure, reducing that risk carries profound practical and psychological significance. • Gastric cancer has historically seen slower therapeutic innovation than many other solid tumours. Patients are acutely aware of this and place significant weight on decisions that represent meaningful advancement in the curative-intent setting. • D-FLOT is the first immunotherapy-based curative treatment for resectable gastric and GOJ cancer and sets a new international standard. Patients in England should not be excluded from accessing it.

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Single Technology Appraisal

Durvalumab in combination for neoadjuvant and adjuvant treatment of resectable gastric and gastro-oesophageal junction adenocarcinoma [ID6374]

Clinical expert statement

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Clinical expert statement

Durvalumab in combination for neoadjuvant and adjuvant treatment of resectable gastric and gastro-oesophageal junction adenocarcinoma [ID6374]

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Clinical expert statement

Durvalumab in combination for neoadjuvant and adjuvant treatment of resectable gastric and gastro-oesophageal junction adenocarcinoma [ID6374]

Part 1: Treating resectable gastric or gastro-oesophageal junction adenocarcinoma and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Was Mansoor
2. Name of organisation	Christie Hospital
3. Job title or position	Professor
4. Are you (please tick all that apply)	☒ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with resectable gastric or gastro-oesophageal junction adenocarcinoma? ☒ A specialist in the clinical evidence base for resectable gastric or gastro-oesophageal junction adenocarcinoma or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes

Clinical expert statement

Durvalumab in combination for neoadjuvant and adjuvant treatment of resectable gastric and gastro-oesophageal junction adenocarcinoma [ID6374]

7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	nil
8. What is the main aim of treatment for resectable gastric or gastro-oesophageal junction adenocarcinoma? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	To increase the survival rate for patients with surgically resectable gastric, GOJ and oesophageal adenocarcinomas (stage 2-3c)
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	Approximately 30% of UGI gastric, GOJ or lower oesophagus patients with adenocarcinoma present with stage II-IIIc cancers. This accounts for approximately 2400 patients in the UK who are then amenable to peri-operative treatment assuming they are fit. Pre 2018 (ie pre FLOT) when ECX/ECF chemotherapy was the SOC peri-operative chemo of choice, the 5 year median overall survival was 36% (accounting for approx. 850 patients alive at 5 years). Based on the FLOT4 trial, FLOT became SOC in 2018 and demonstrated improvement in the 5 year survival with FLOT to 46% (equating to approx. 1104 patients). Despite this encouraging improvement in outcomes for these patients with the advent of FLOT, recurrence rates remained common and the long term prognosis still remains poor (less than 50% patients surviving to 5 years). There, therefore, remained an urgent unmet need to improve curative outcomes with this cancer. And improvement in EFS (as per the Matterhorn trial) of > 5% or an improvement in OS of >5% would be considered clinically significant.
10. In your view, is there an unmet need for patients and healthcare professionals in resectable gastric or gastro-oesophageal junction adenocarcinoma?	As stated above, this is a lethal cancer where currently 50% of patients with early disease undergoing curative treatment as still dying. It is undoubtedly an unmet need.
11. How is resectable gastric or gastro-oesophageal junction adenocarcinoma currently treated in the NHS?	As above, with perioperative FLOT chemotherapy and surgery Guidelines currently being used are the ESMO/ Asco guidelines

Clinical expert statement

Durvalumab in combination for neoadjuvant and adjuvant treatment of resectable gastric and gastro-oesophageal junction adenocarcinoma [ID6374]

• Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	D FLOT will remain a peri-operative regimen, however the durvalumab will need to be given once monthly for 12 months once the D FLOT / surgery have been completed. This will mean that the patients will stay with the oncologists for an extra year receiving this Durvalumab treatment where as previously, patients were discharged back to the surgeons for follow up by the surgical team. Patients will receive the treatment as an out patient A greater capacity in oncology may be required.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	The Matterhorn trial , where D FLOT was compared to FLOT, used event free survival as its primary end point and surrogate for OS. The 2 year EFS was significantly better for D FLOT (67.4%) vs FLOT (58.5%). The data is not mature as yet to understand 5 year OS, however the 3 year OS data has been presented and demonstrates data that is once again transformative for patients with early cancer – the OS rates at 36 months are 68.6% for the patients who received D FLOT compared to 61.9% for those who only received FLOT. With a 22% reduction in risk of death, in my view, this is once again an important step up in outcomes improvement and has already changed the global treatment paradigm where D FLOT has widely become the SOC. With almost 7 out of 10

Clinical expert statement

Durvalumab in combination for neoadjuvant and adjuvant treatment of resectable gastric and gastro-oesophageal junction adenocarcinoma [ID6374]

	patients alive at 3 years with the D FLOT regimen regardless of PD-L1 TAP score, I would strongly recommend D FLOT becomes the new SOC regimen in the UK. Health related QOL was not disadvantaged due to the addition of the Durvalumab.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	The outcomes described above seemed to benefit all patients regardless of the PD=L1 TAP score
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	Clinicians will have to be aware of the rare immune toxicities that can arise due to the administration of Durvalumab. Significant toxicities occur in less than 5% of patients.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	In my opinion PD L1 TAP testing is not required as 90% of patients in the trial were positive for this test. The Durvalumab maintenance will stop at 1 year
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? Do the instruments that measure quality of life fully capture all the benefits of the technology or have some	Yes, there will be significantly less patients becoming metastatic and therefore entering the palliative pathway. Significantly more people will be cured. This is not necessarily captured. Also, more patients will receive the intended surgery and therefore theatre slots and surgical time will not be wasted.

Clinical expert statement

been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? - Is the technology a 'step-change' in the management of the condition? - Does the use of the technology address any particular unmet need of the patient population?	Yes As stated above, with a 22% reduction in risk of death, in my view, this is once again an important step up in outcomes improvement and has already changed the global treatment paradigm where D FLOT has widely become the SOC. With almost 7 out of 10 patients alive at 3 years with the D FLOT regimen regardless of PD-L1 TAP score, I would strongly recommend D FLOT becomes the new SOC regimen in the UK.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Clinicians will have to be aware of the immune related toxicities. Serious toxicity occurs in less than 5% of patients
20. Do the clinical trials on the technology reflect current UK clinical practice? - If not, how could the results be extrapolated to the UK setting? - What, in your view, are the most important outcomes, and were they measured in the trials? - If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? - Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Yes, reflects UK practice regarding patient inclusion criteria and practice Both EFS was measure as the primary end point and this is a reasonable surrogate of OS. 3 year OS was also measured All adverse events were as expected
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No except for the possible data emerging from the UK wide EAP
22. How do data on real-world experience compare with the trial data?	As above, data is a good match

Clinical expert statement

Durvalumab in combination for neoadjuvant and adjuvant treatment of resectable gastric and gastro-oesophageal junction adenocarcinoma [ID6374]

23. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.

Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics.

Please state if you think this evaluation could

- exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation
- lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population
- lead to recommendations that have an adverse impact on disabled people.

Please consider whether these issues are different from issues with current care and why.

More information on how NICE deals with equalities issues can be found in the [NICE equality scheme](#).

[Find more general information about the Equality Act and equalities issues here.](#)

No

Clinical expert statement

Durvalumab in combination for neoadjuvant and adjuvant treatment of resectable gastric and gastro-oesophageal junction adenocarcinoma [ID6374]

24. Nivolumab is included as a comparator in the final NICE scope. Nivolumab is recommended for adjuvant treatment of completely resected oesophageal cancer (OC) or gastro-oesophageal junction cancer (GOJC) in adults who have residual disease after previous neoadjuvant chemoradiotherapy (CRT) (TA746). However, the company and the external assessment group (EAG) did not consider nivolumab as an appropriate comparator. Clinical advice to the company is that: • CRT is considered an option only for people ineligible for surgery and neoadjuvant FLOT • it is very rare people with gastro-oesophageal adenocarcinoma (GOA) who receive neoadjuvant CRT can tolerate surgery (and therefore potentially be eligible to receive nivolumab) • nivolumab is primarily used in OC/GOJC patients with squamous cell carcinoma rather than GOA • CRT and nivolumab are anticipated to be removed as treatment options from the next update of the European Society for Medical Oncology (ESMO) guidelines. Is it appropriate not to consider nivolumab as a comparator? Does this reflect what would be observed in clinical practice?	I would agree that the Checkmate 577 trial is not an appropriate comparator. I would agree that CRT, in the context of adenocarcinomas, is only offered when FLOT is not an option. Tri modality therapy has not been used a great deal in the UK in the context of adenocarcinoma due to the strong trial evidence pointing towards the peri-operative approach and due to poor tolerance and because it is widely felt that the CM577 trial benefited the SCC cohort rather than the adenocarcinoma cohort.
25. The company provided subgroup analyses of Durvalumab plus FLOT's (D-FLOT) clinical effectiveness by PD-L1 status stating the results from MATTERHORN demonstrate a consistent treatment	Not aware of any evidence or study assessing PD-L1 status in the group of patients. Would agree with the companies view regarding consistent results regardless of biomarker results.

Clinical expert statement

Durvalumab in combination for neoadjuvant and adjuvant treatment of resectable gastric and gastro-oesophageal junction adenocarcinoma [ID6374]

benefit regardless of PD-L1 expression level. The EAG note if PD-L1 expression affects treatment effectiveness, the proportion of patients with differing levels of PD-L1 expression may affect the results for the overall trial population; therefore generalisability to NHS clinical practice.

The EAG suggest data on the PD-L1 status of UK patients undergoing perioperative treatment for GOA would improve clarity on the generalisability of the overall trial results.

Are you aware of any evidence or study that assesses the PD-L1 status of UK patients undergoing perioperative treatment for GOA?

Clinical expert statement

Durvalumab in combination for neoadjuvant and adjuvant treatment of resectable gastric and gastro-oesophageal junction adenocarcinoma [ID6374]

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Event free survival and the 3 year survival are both significant and would be impactful for our patients

Patients benefited from D FLOT regardless of PD L1 TAP testing

Well designed study representative of the UK population

Durvalumab did not negatively impact on QOL for patients

Maintenance Durvalumab for 12 months will alter the curative pathway – requiring more oncology support

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

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Clinical expert statement

Durvalumab in combination for neoadjuvant and adjuvant treatment of resectable gastric and gastro-oesophageal junction adenocarcinoma [ID6374]

Single Technology Appraisal

Durvalumab in combination for neoadjuvant and adjuvant treatment of resectable gastric and gastro-oesophageal junction adenocarcinoma [ID6374]

Clinical expert statement

Information on completing this form

In [part 1](#) we are asking for your views on this technology. The text boxes will expand as you type.

In [part 2](#) we are asking you to provide 5 summary sentences on the main points contained in this document.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Clinical expert statement

Durvalumab in combination for neoadjuvant and adjuvant treatment of resectable gastric and gastro-oesophageal junction adenocarcinoma [ID6374]

Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See [Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals](#) (section 3.2) for more information.

The deadline for your response is stated in the accompanying email sent with this document. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Clinical expert statement

Durvalumab in combination for neoadjuvant and adjuvant treatment of resectable gastric and gastro-oesophageal junction adenocarcinoma [ID6374]

Part 1: Treating resectable gastric or gastro-oesophageal junction adenocarcinoma and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Piers Boshier
2. Name of organisation	Imperial College London
3. Job title or position	Clinical Associate Professor / Consultant UGI Surgeon
4. Are you (please tick all that apply)	☒ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with resectable gastric or gastro-oesophageal junction adenocarcinoma? ☒ A specialist in the clinical evidence base for resectable gastric or gastro-oesophageal junction adenocarcinoma or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes

Clinical expert statement

Durvalumab in combination for neoadjuvant and adjuvant treatment of resectable gastric and gastro-oesophageal junction adenocarcinoma [ID6374]

7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
8. What is the main aim of treatment for resectable gastric or gastro-oesophageal junction adenocarcinoma? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	To offer the opportunity to cure the disease.
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	- Reduced/stable tumour size - No new metastatic disease (including new lymph node metastasis) - Improvement in associated symptoms (e.g. dysphagia) where relevant
10. In your view, is there an unmet need for patients and healthcare professionals in resectable gastric or gastro-oesophageal junction adenocarcinoma?	Yes - Improvement in standardisation of treatment nationally - Improvement in perioperative outcomes - Improvement of associated quality of life - Improvement in long term survival / rates of disease recurrence
11. How is resectable gastric or gastro-oesophageal junction adenocarcinoma currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	Two primary options 1. Straight to surgery (in selected cases endoscopic resection may be possible) 2. Neoadjuvant chemotherapy + surgery There can be significant variation between centres in regards to the choice of treatment pathways and approach to treatment The technology/treatment may serve as adjunct to standard of care systemic therapies (and surgery) – with the aim of improving patient survival (overall and disease free)

Clinical expert statement

Durvalumab in combination for neoadjuvant and adjuvant treatment of resectable gastric and gastro-oesophageal junction adenocarcinoma [ID6374]

12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	Durvalumab is currently used in the NHS for the treatment of selected advanced cancers, e.g. non-small-cell lung cancer (NSCLC) The proposed treatment would be used within a specialist (UGI oncology) setting Minimal investment would be required to introduce this drug into routine practice.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	The MATTERHORN Trial demonstrated that perioperative Durvalumab (+FLOT/systemic chemotherapy) improved the event free survival of patients with resectable gastric or gastroesophageal junction adenocarcinoma. Survival at 3 years was 69% in the intervention (Durvalumab) group compared to 62% in the control arm. The effect of HRQOL is not clear.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	The survival advantage was consistent across subgroups, regardless of PD-L1 expression or pathologic lymph node status. It was noted that patients who are microsatellite instability–high and PD-L1–positive (expression on ≥ 1) may generally do better with immunotherapy, however this was not felt to be a major driver of the results of the MATTERHORN Trial
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than	There may be a general desire to undertake PD-L1 testing prior to starting treatment (despite no link between response and PD-L1 expression). This is something that is already done routinely in some UK centres. In centres where

Clinical expert statement

Durvalumab in combination for neoadjuvant and adjuvant treatment of resectable gastric and gastro-oesophageal junction adenocarcinoma [ID6374]

current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	'reflex' testing is not performed at diagnosis, PD-L1 testing will result in additional burden on pathology services (e.g. increased pathologist reporting time) and with a potential to introduce a delay in patients starting treatment.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Please see comment above regarding PD-L1. The MATTERHORN Trial did not demonstrate PD-L1 was a significant driver of Durvalumab response.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	No
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? - Is the technology a 'step-change' in the management of the condition? - Does the use of the technology address any particular unmet need of the patient population?	Durvalumab in combination with FLOT/systemic chemotherapy has been shown to improve survival in patient with resectable gastric and GOJ adenocarcinoma. In the context of rapidly evolving field of systemic treatments of gastric cancers this survival benefit is significant – but is arguably cannot be considered a 'step-change'. Durvalumab contributes to improving survival in this patient group which represents an important and on-going unmet need in this field.

Clinical expert statement

Durvalumab in combination for neoadjuvant and adjuvant treatment of resectable gastric and gastro-oesophageal junction adenocarcinoma [ID6374]

19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	This does not seem to be an important factor. Specifically, Durvalumab does not seem to impact on the timing or early outcomes of surgery.
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Clinical trials are broadly reflective of UK practice. Important outcomes including - overall survival, event free survival, toxicity and impact on surgery were measured There were no adverse events that have come to light after the trial.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. How do data on real-world experience compare with the trial data?	Real world experience particularly in the standard of care arm is comparable.
23. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil	No

Clinical expert statement

Durvalumab in combination for neoadjuvant and adjuvant treatment of resectable gastric and gastro-oesophageal junction adenocarcinoma [ID6374]

partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	
24. Nivolumab is included as a comparator in the final NICE scope. Nivolumab is recommended for adjuvant treatment of completely resected oesophageal cancer (OC) or gastro-oesophageal junction cancer (GOJC) in adults who have residual disease after previous neoadjuvant chemoradiotherapy (CRT) (TA746). However, the company and the external assessment group (EAG) did not consider nivolumab as an appropriate comparator. Clinical advice to the company is that: • CRT is considered an option only for people ineligible for surgery and neoadjuvant FLOT	It is appropriate not to consider nivolumab as a comparator - reflecting current clinical practice.

Clinical expert statement

Durvalumab in combination for neoadjuvant and adjuvant treatment of resectable gastric and gastro-oesophageal junction adenocarcinoma [ID6374]

• it is very rare people with gastro-oesophageal adenocarcinoma (GOA) who receive neoadjuvant CRT can tolerate surgery (and therefore potentially be eligible to receive nivolumab) • nivolumab is primarily used in OC/GOJC patients with squamous cell carcinoma rather than GOA • CRT and nivolumab are anticipated to be removed as treatment options from the next update of the European Society for Medical Oncology (ESMO) guidelines. Is it appropriate not to consider nivolumab as a comparator? Does this reflect what would be observed in clinical practice?	
25. The company provided subgroup analyses of Durvalumab plus FLOT's (D-FLOT) clinical effectiveness by PD-L1 status stating the results from MATTERHORN demonstrate a consistent treatment benefit regardless of PD-L1 expression level. The EAG note if PD-L1 expression affects treatment effectiveness, the proportion of patients with differing levels of PD-L1 expression may affect the results for the overall trial population; therefore generalisability to NHS clinical practice. The EAG suggest data on the PD-L1 status of UK patients undergoing perioperative treatment for GOA would improve clarity on the generalisability of the overall trial results.	See comments above. I agree with the EAG that data on the PD-L1 status of UK patients undergoing perioperative treatment for GOA would improve clarity on the generalisability of the overall trial results. I am not aware of any published evidence or study that assesses the PD-L1 status of UK patients undergoing perioperative treatment for GOA. How many centers are undertaking reflex PD-L1 testing at diagnosis so this data would be available at these centres.

Clinical expert statement

Durvalumab in combination for neoadjuvant and adjuvant treatment of resectable gastric and gastro-oesophageal junction adenocarcinoma [ID6374]

Are you aware of any evidence or study that assesses the PD-L1 status of UK patients undergoing perioperative treatment for GOA?	

Clinical expert statement

Durvalumab in combination for neoadjuvant and adjuvant treatment of resectable gastric and gastro-oesophageal junction adenocarcinoma [ID6374]

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

The primary aim of treatment for resectable gastric and gastro-oesophageal junction adenocarcinoma is to achieve cure, typically through surgery combined with perioperative systemic therapy.

Current NHS treatment pathways generally involve either upfront surgery or neoadjuvant chemotherapy followed by surgery, although there is variation in practice between centres.

Evidence from the MATTERHORN trial indicates that adding durvalumab to perioperative FLOT chemotherapy improves overall and event-free survival in patients with resectable gastric and gastro-oesophageal junction adenocarcinoma.

Durvalumab could be implemented within existing specialist oncology pathways with minimal additional infrastructure, although PD-L1 testing may increase demands on pathology services in some centres.

While not necessarily a step-change in treatment, durvalumab represents a meaningful advancement that may improve survival outcomes and help address the ongoing unmet need for better long-term outcomes in this patient population

Thank you for your time.

Clinical expert statement

Durvalumab in combination for neoadjuvant and adjuvant treatment of resectable gastric and gastro-oesophageal junction adenocarcinoma [ID6374]

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Clinical expert statement

Durvalumab in combination for neoadjuvant and adjuvant treatment of resectable gastric and gastro-oesophageal junction adenocarcinoma [ID6374]

Single Technology Appraisal

Durvalumab in combination for neoadjuvant and adjuvant treatment of resectable gastric and gastro-oesophageal junction adenocarcinoma [ID6374]

Patient expert statement

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources

Information on completing this form

In [part 1](#) we are asking you about living with resectable gastric or gastro-oesophageal junction adenocarcinoma or caring for a patient with resectable gastric or gastro-oesophageal junction adenocarcinoma. The text boxes will expand as you type.

In [part 2](#) we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Patient expert statement

Durvalumab in combination for neoadjuvant and adjuvant treatment of resectable gastric and gastro-oesophageal junction adenocarcinoma [ID6374]

Please use this questionnaire with our [hints and tips for patient experts](#). You can also refer to the [Patient Organisation submission guide](#). **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Your response should not be longer than 15 pages.

The deadline for your response is stated in the accompanying email sent with this document. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Patient expert statement

Durvalumab in combination for neoadjuvant and adjuvant treatment of resectable gastric and gastro-oesophageal junction adenocarcinoma [ID6374]

Part 1: Living with this condition or caring for a patient with resectable gastric or gastro-oesophageal junction adenocarcinoma

Table 1 About you, resectable gastric or gastro-oesophageal junction adenocarcinoma, current treatments and equality

1. Your name	Sheena Dewan
2. Are you (please tick all that apply)	☐ A patient with resectable gastric or gastro-oesophageal junction adenocarcinoma? ☐ A patient with experience of the treatment being evaluated? ☒ A carer of a patient with resectable gastric or gastro-oesophageal junction adenocarcinoma ? ☒ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	Gastric Cancer UK (operating as Stomach Cancer UK)
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and do not wish to complete a patient expert statement ☒ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and do not wish to complete this statement ☒ I agree with it and will be completing

Patient expert statement

Durvalumab in combination for neoadjuvant and adjuvant treatment of resectable gastric and gastro-oesophageal junction adenocarcinoma [ID6374]

5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☒ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: ☐ I have completed part 2 of the statement after attending the expert engagement teleconference ☐ I have completed part 2 of the statement but was not able to attend the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with resectable gastric or gastro-oesophageal junction adenocarcinoma ? If you are a carer (for someone with resectable gastric or gastro-oesophageal junction adenocarcinoma) please share your experience of caring for them	When dad told me he was diagnosed with stomach cancer in 2017, I'd never heard of it, so I assumed it wasn't one of the dire ones. The first thing I read was a ranked list of all cancers and their survivability. Reading the list and not seeing stomach cancer until near the bottom... I can't describe the shock, fear and dread of that moment. Dad was a very fit 70-year-old who did high-intensity interval training three times a week. In just weeks before his diagnosis, he lost his appetite and became breathless walking short distances, and once diagnosed, he seemed to get worse each day, until chemo started. I attended all his appointments, including transfusions and chemotherapy. We're so lucky that he had a complete response to chemo, but he wasn't eligible for surgery, being stage IV because of lymph nodes. After a small recurrence, he did have surgery. I stayed at the hospital with him except to sleep and moved in with my parents to help care for him during his recovery. The impact on both my mum and me was extreme. The year between diagnosis and surgery was like being on autopilot, structured around all his appointments, living in

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	fear, knowing he was going to die. Once he had surgery, it was like being in the trenches – relentless. Feeding him a few spoonfuls of food every hour, not knowing if he could eat what we cooked, fighting for each pound of weight he regained and then more chemotherapy, which was much harder for him after surgery. The fear of recurrence was, in some ways, almost worse than when he was diagnosed. The uncertainty about whether it might come back and he might die was, in some ways, harder than the knowledge that he would. Hypervigilance about every symptom, dreading the scans... I wasn't okay for at least three or four years, and my mum still isn't, as she still worries deeply about any symptom or issue my dad has, and whether the cancer has returned. I relied on online support spaces from the beginning, and I'm still a part of those online communities. No one I knew from when dad was diagnosed in 2017 is still alive, not even the people who had been on the curative pathway. I am still in touch with some families, and while I feel grateful, I also feel guilty that my dad is still alive when their loved ones did not survive.
7a. What do you think of the current treatments and care available for resectable gastric or gastro-oesophageal junction adenocarcinoma on the NHS? 7b. How do your views on these current treatments compare to those of other people that you may be aware of?	a) Current care for resectable stomach cancer is delivered by highly trained teams who are committed to their patients. I feel that clinicians do their best with empathy and care, often under significant pressure within the system. However, treatment options have not meaningfully advanced in the past decade. The introduction of FLOT following the 2017 FLOT-4 trial replaced epirubicin-based regimens as the global standard of care, but it was an incremental step rather than a transformative change because recurrence rates remain high despite radical surgery and intensive chemotherapy.

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	NHS implementation was not always swift or consistent – I was personally aware of patients still receiving epirubicin-based chemotherapy several years after FLOT became the international standard. In some cancer alliances, epirubicin regimens are still referenced in treatment materials today, even though global practice has moved on. While there have been advances in options for advanced gastric cancer, some of which are available on the NHS, there has been nothing beyond chemotherapy for the curative path. We need improvement for this lethal cancer now, and improvements need to be implemented swiftly. b) Although my dad’s experience, moving from palliative to curative, was unusual, it has given me a nearly unique perspective of being a caregiver to someone on both pathways and into their survivorship. Over the past nine years, through engagement with many patients and their families, I have heard a wide range of experiences across all stages of disease. There is strong awareness of the treatments available in advanced gastric cancer and of the differences between countries and tumour types. Common views I’ve heard include fear of recurrence, awareness that outcomes remain poor even after surgery and frustration at the limited pace of innovation and approvals for stomach cancer. Many describe gastric cancer as feeling overlooked compared with other solid tumours. NICE’s own published figures indicate that lung cancer has seen 47 approvals between 2015 and 2024. In contrast, gastric cancer has had only two approvals and three rejections over roughly the same period. My views are consistent with these themes. The sense that current treatments are not sufficient, and that relapse remains a constant threat, is widely shared.

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8. If there are disadvantages for patients of current NHS treatments for resectable gastric or gastro-oesophageal junction adenocarcinoma (for example, how they are given or taken, side effects of treatment, and any others) please describe these	FLOT is intensive chemotherapy, which can cause neuropathy, fatigue and neutropenia which brings the risk of dangerous infections. It can be hard to eat due to appetite loss and taste changes. Surgery is life-changing and can take months to recover from. Chemotherapy after surgery can be particularly difficult, with a greater risk of side effects because of surgical recovery and altered nutrition. Neuropathy and changes to eating and digestion can remain for years after treatment has ended. Despite this, the risk of recurrence is still high. All of these issues can have a significant psychosocial, practical and financial burden on patients and families. Even so, the vast majority of patients on the curative pathway are willing to accept these burdens for the chance to survive, given the swift, lethal nature of stomach cancer.
9a. If there are advantages of durvalumab in combination with chemotherapy (FLOT) for neoadjuvant and adjuvant treatment over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? 9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why? 9c. Does durvalumab in combination with chemotherapy (FLOT) for neoadjuvant and adjuvant treatment help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these	a) Advantages Treatment in the MATTERHORN trial with durvalumab + FLOT had similar completion rates to those treated with FLOT alone, which suggests the possibility of improved outcomes without increased toxicity, and without compromising the completion of the current standard of care treatment. The improved pathological complete response rate is tangible evidence that treatment has worked before major surgery and brings a high level of hope for recurrence-free survival. Adding immunotherapy upfront to peri-operative chemotherapy reduces the risk of recurrence, at which point treatment options can be very limited, and for which the prognosis is poor. Improved response to pre-operative treatment reduces the risk of progressive disease before surgery, including peritoneal disease, which is at present essentially unsurvivable.

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	Improved event-free survival means a greater chance of remaining cancer-free for longer. For patients and families, time without recurrence means time without the constant fear of relapse and further treatment. Improved overall survival translates to more time with loved ones, and more opportunity to work, parent and participate fully in society. Knowing that one is receiving the most contemporary, internationally recognised curative-intent treatment also provides psychological reassurance about the quality of care delivered by the NHS. b) Most important advantages For me personally, the most important benefit of optimising perioperative treatment with durvalumab is the potential to reduce recurrence and extend survival in a meaningful way, because this allows people to remain present in their families and communities. My dad was working full-time when he was diagnosed at age 70, and he struggled, but succeeded in working part-time through his treatment. He is now 78 and still working full-time because he loves what he does. He has been able to watch his granddaughter grow up. She was seven when he was diagnosed, and there is every reason to assume he will see her reach adulthood because he is once more in very good health. I recognise my father is not typical for his age in terms of his current health, working status as well as his experience of stomach cancer. But our experiences illustrate what improved survival means in real terms. More time to work, parent, care for

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	grandchildren, while participating in society and living fully. I want more people to be as fortunate as our family has been, and durvalumab can make that possible. c) Addressing disadvantages of current treatment Durvalumab is added to existing NHS treatment rather than replacing it, so it does not remove the burdens of chemotherapy or surgery. Treatment remains intensive, and gastrectomy is life-changing. However, the addition of durvalumab does not appear to worsen overall quality of life for most patients and may improve outcomes. In that sense, it increases the likelihood that the burdens patients already accept in pursuit of a cure translate into longer-term benefit. Recurrence after intensive chemotherapy and radical surgery is devastating for patients and families. Reducing that risk meaningfully changes how those burdens are experienced. Before her death in 2025, A.K., a 40-year-old mother of four, asked me to ensure her views were represented in future drug appraisals. She said, “I would endure any number of side effects if it meant more time with my kids.” For many patients, adding durvalumab does not substantially increase treatment burden, but it may improve the likelihood that those burdens translate into durable survival.
10. If there are disadvantages of durvalumab in combination with chemotherapy (FLOT) for neoadjuvant and adjuvant treatment over current treatments on the NHS please describe these.	Adding durvalumab to FLOT means patients remain in active treatment for longer after radical surgery. Even if tolerable and acceptable, this can prolong the period of feeling like a cancer patient before becoming a survivor. Additional infusion appointments require more travel, more time off work and further disruption to

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For example, are there any risks with durvalumab in combination with chemotherapy (FLOT) for neoadjuvant and adjuvant treatment? If you are concerned about any potential side effects you have heard about, please describe them and explain why	family life, which may exacerbate employment or income pressures that are already present. While my family and many patients I have spoken to regard this as an acceptable trade-off for a better chance of life free from cancer, for some, it may represent a practical barrier. Serious side effects of immunotherapy are uncommon, and most can be medically managed alongside dose reduction or discontinuation. However, some rare side effects, such as thyroid dysfunction, can lead to lifelong issues.
11. Are there any groups of patients who might benefit more from durvalumab in combination with chemotherapy (FLOT) for neoadjuvant and adjuvant treatment or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	Durvalumab + FLOT showed improved event-free and overall survival, regardless of PDL1 status, suggesting a potential benefit for nearly all patients who are fit enough to receive FLOT. Stomach and GOJ cancer is increasing in younger populations. Diffuse and signet-ring subtypes, which can behave aggressively, are more common in younger populations. This population is more likely to be fit, well and economically active and is more likely to resemble the trial population in terms of performance. For this group, reducing the risk of recurrence has profound long-term implications for family life, employment and survival. People who have active auto-immune conditions or who have received organ transplants, as well as those with significant liver disease that impairs their liver function, may not be suitable for treatment with durvalumab.
12. Are there any potential equality issues that should be taken into account when considering resectable	Age (older): It is important that age alone should not be a barrier to treatment. An individual's comorbidities, performance and frailty should be considered instead of

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gastric or gastro-oesophageal junction adenocarcinoma and durvalumab in combination with chemotherapy (FLOT) for neoadjuvant and adjuvant treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	numerical age. My father had direct experience of treatment intensity being influenced primarily by age, despite good baseline fitness. If durvalumab is approved, older but biologically fit patients should not be excluded solely on the basis of age. Age (younger): Gastric and GOJ cancer is rising in younger adults, who may face delays in referral because existing guidelines are weighted toward patients over 55. Younger patients often present after multiple GP visits. Ensuring access to the most effective curative-intent therapy is particularly important in this population, who may otherwise lose decades of potential life. Immigrant communities/country of birth: incidence of gastric cancer is higher in populations from Eastern Europe, East Asia and parts of South America and Africa. It is important that there is sufficient outreach and awareness-building about stomach cancer in these populations and that approval and implementation do not widen disparities in access among communities already at higher risk. Deprivation: gastric and junction cancer has a higher incidence in economically deprived areas of England, such as NW England. Diagnosis is often made later, leading to poorer outcomes. If approved, access to durvalumab plus FLOT should be consistent across Cancer Alliances so that postcode does not determine availability.
13. Are there any other issues that you would like the committee to consider?	I attended the presentation of MATTERHORN data by Dr Yelena Jangigian at ASCO 2025, Chicago (virtually). In seven years of attending gastrointestinal and oncology conferences, I have never seen that level of visible emotion from a presenting

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	investigator, nor heard that degree of spontaneous applause and enthusiasm from an audience of oncologists. The reaction in the room reflected immediate recognition that adding durvalumab to FLOT represents a significant shift in the treatment of resectable gastric and GOJ cancer. It was clear that the global oncology community regarded this as a watershed moment in a disease that has seen limited therapeutic progress. I hope the Committee will take into account the data, the weight of international clinical consensus and the support of patients and caregivers when reaching its decision. Thank you for considering this submission and for conducting this appraisal.

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Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Adding durvalumab to FLOT gives people a better chance of staying cancer-free for longer and living longer, without making it harder to complete treatment.
- A stronger response before surgery means more people are likely to reach surgery and have their cancer fully removed, which is the only route to a possible cure.
- Reducing the risk of recurrence changes everything for patients and families, because relapse after intensive chemotherapy and major surgery is emotionally, psychologically and practically devastating.
- More time without cancer means more time to work, to parent, to care for loved ones and to live an ordinary life again, which matters deeply to patients and families.
- Although treatment with D-FLOT lasts longer and carries some additional risks, most people facing this diagnosis are willing to accept those risks for a better chance of long-term survival, especially when overall quality of life does not appear to be significantly worse.

Thank you for your time.

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Single Technology Appraisal

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Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources

Information on completing this form

In [part 1](#) we are asking you about living with resectable gastric or gastro-oesophageal junction adenocarcinoma or caring for a patient with resectable gastric or gastro-oesophageal junction adenocarcinoma. The text boxes will expand as you type.

In [part 2](#) we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

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Please use this questionnaire with our [hints and tips for patient experts](#). You can also refer to the [Patient Organisation submission guide](#). **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

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Your response should not be longer than 15 pages.

The deadline for your response is stated in the accompanying email sent with this document. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

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Part 1: Living with this condition or caring for a patient with resectable gastric or gastro-oesophageal junction adenocarcinoma

Table 1 About you, resectable gastric or gastro-oesophageal junction adenocarcinoma, current treatments and equality

1. Your name	Chloe Stirling
2. Are you (please tick all that apply)	☒ A patient with resectable gastric or gastro-oesophageal junction adenocarcinoma? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with resectable gastric or gastro-oesophageal junction adenocarcinoma ? ☐ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	Stomach Cancer UK
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and do not wish to complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and do not wish to complete this statement ☐ I agree with it and will be completing

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5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: ☐ I have completed part 2 of the statement after attending the expert engagement teleconference ☐ I have completed part 2 of the statement but was not able to attend the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with resectable gastric or gastro-oesophageal junction adenocarcinoma ? If you are a carer (for someone with resectable gastric or gastro-oesophageal junction adenocarcinoma) please share your experience of caring for them	I was diagnosed in March 2024, at age 28, with signet ring cell adenocarcinoma of the distal stomach. I completed 4 rounds of FLOT chemotherapy, total gastrectomy and a further 4 rounds of FLOT. My pathological staging was ypT1bN0M0. I am no longer receiving any active treatment and remain cancer free at present.
7a. What do you think of the current treatments and care available for resectable gastric or gastro-oesophageal junction adenocarcinoma on the NHS? 7b. How do your views on these current treatments compare to those of other people that you may be aware of?	7a) I believe treatment has improved since the FLOT4 trial, but compared to other cancers there are still fewer options available—particularly when it comes to targeted therapies. At the same time, there is a noticeable increase in gastrointestinal cancers being diagnosed in younger people, and these cases are often more aggressive. Introducing more targeted treatments could make a meaningful difference for this group, helping to downstage the disease and improve their chances of remaining cancer-free without recurrence. 1. Most gastric cancers are diagnosed at stage 3 or later, which contributes to high rates of recurrence and, sadly, mortality. I was fortunate to seek medical advice early, when my symptoms were limited to mild reflux—otherwise, my situation could have been very different.

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	2. I also feel there is a gap in care when it comes to younger patients. Concerns about cancer are not always taken seriously by GPs and healthcare professionals, which can lead to delayed or missed diagnoses, often because younger individuals are perceived as being “too young” for cancer. 7b) I think most people of my age group would agree with my point of view.
8. If there are disadvantages for patients of current NHS treatments for resectable gastric or gastro-oesophageal junction adenocarcinoma (for example, how they are given or taken, side effects of treatment, and any others) please describe these	Current NHS treatments for resectable gastric and gastro-oesophageal junction adenocarcinoma, such as perioperative chemotherapy (commonly the FLOT regimen) combined with surgery, do offer survival benefits, but they come with several disadvantages for patients. One of the main challenges is how treatment is delivered. Patients are required to undergo multiple cycles of chemotherapy both before and after major surgery, which can be physically and emotionally demanding. In practice, a significant proportion of patients are unable to complete all planned chemotherapy cycles, particularly after surgery due to the impact of recovery and reduced physical resilience- from personal experience, I was extremely unwell when I was completing my chemotherapy post-surgery. The side effects of chemotherapy can also be substantial. Common issues include fatigue, nausea, vomiting, loss of appetite, hair loss, and an increased risk of infection due to reduced blood counts. More severe toxicities, such as neutropenia, anaemia, and gastrointestinal symptoms, can occur and may require dose reductions, treatment delays, or discontinuation. These side effects can significantly affect quality of life and a patient’s ability to tolerate treatment. Additionally, the intensity of regimens such as FLOT means that not all patients are suitable candidates, particularly those who are older or less physically fit. This can limit access to the most effective standard treatments.

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	Another key limitation is that chemotherapy is not targeted, meaning it affects both cancerous and healthy cells. This contributes to toxicity and highlights the lack of more personalised or targeted treatment options compared to other cancer types. Overall, while current NHS treatments can be effective, they are often associated with significant toxicity, challenges in completion, and a lack of tailored approaches, all of which can impact patient outcomes and experience.
9a. If there are advantages of durvalumab in combination with chemotherapy (FLOT) for neoadjuvant and adjuvant treatment over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? 9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why? 9c. Does durvalumab in combination with chemotherapy (FLOT) for neoadjuvant and adjuvant treatment help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these	9a) There are several potential advantages of adding Durvalumab to chemotherapy (FLOT) for neoadjuvant and adjuvant treatment, compared to current NHS standard treatments. One of the most important advantages is improved effectiveness. Evidence from the MATTERHORN trial shows that combining durvalumab with FLOT increases event-free survival compared to FLOT alone, meaning patients are more likely to remain cancer-free for longer after treatment. This suggests a reduced risk of recurrence, which is particularly important given the high relapse rates seen with current treatments. For patients, this could translate into significant quality of life benefits. If the cancer is better controlled or eradicated earlier, patients may avoid the physical and emotional impact of recurrence and the need for further intensive treatments. Living without recurrence can allow individuals to return more confidently to normal life, including work, education, and caring responsibilities. Another advantage is the addition of immunotherapy, which works differently from traditional chemotherapy by helping the immune system recognise and attack cancer cells. This more targeted mechanism may improve outcomes without simply increasing chemotherapy intensity. While side effects can still occur,

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	immunotherapy is often perceived as more tolerable for some patients compared to prolonged or repeated chemotherapy alone. The treatment schedule may also offer benefits. In this approach, durvalumab is continued as a single agent after chemotherapy and surgery, which may be less physically demanding than ongoing combination chemotherapy. This could support better recovery after surgery and improve a patient's ability to regain independence, manage self-care, and gradually return to daily routines. Importantly, better disease control and potentially improved survival outcomes can have a wider impact on a person's life. Patients who respond well may be more able to: • return to work or education sooner • maintain financial stability • care for family members or dependents • participate in social and physical activities Finally, introducing durvalumab represents progress towards more personalised and advanced treatment options in this disease area, which has historically had limited innovation compared to other cancers. This may help address an unmet need, particularly for younger patients and those with aggressive disease. Overall, the combination of durvalumab with FLOT has the potential to improve both clinical outcomes and day-to-day quality of life by reducing recurrence risk, supporting recovery, and enabling patients to return more fully to normal life. 9b) The most important advantage is the potential improvement in event-free survival and reduction in recurrence risk. Gastric and gastro-oesophageal cancers are often diagnosed at a later stage, and recurrence rates remain high even after surgery and chemotherapy. A treatment that increases the likelihood of remaining cancer-free for longer is therefore extremely significant. This is important not only from a clinical perspective but also for quality of life. Avoiding recurrence means patients are less likely to need further intensive treatments, experience additional side effects, or face

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	the emotional distress associated with cancer returning. It allows individuals to move forward with their lives, return to work or education, and maintain independence and normality. 9c) Yes, durvalumab in combination with FLOT has the potential to address several of the key disadvantages of current treatment. Firstly, it may improve overall treatment effectiveness, which directly addresses the high rates of recurrence seen with current NHS treatment. By enhancing the body's immune response to cancer, durvalumab may help achieve deeper and more durable responses, reducing the likelihood of relapse. Secondly, the addition of immunotherapy introduces a more targeted treatment approach. This begins to address the current lack of targeted options in this disease area, moving treatment beyond chemotherapy alone and towards more personalised care. Thirdly, the continuation of durvalumab as a single-agent treatment after surgery may be more tolerable for some patients compared to ongoing chemotherapy. This could help patients better recover from surgery, maintain their strength, and improve their ability to carry out daily activities such as self-care, returning to work, or caring for others. Finally, by potentially improving outcomes earlier in the treatment pathway (in the neoadjuvant and adjuvant setting), this approach may reduce the need for further lines of treatment later on, which are often more intensive and associated with greater side effects. Overall, while it does not remove all the challenges associated with treatment, the addition of durvalumab has the potential to meaningfully improve both outcomes and patient experience compared to current standard care.

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10. If there are disadvantages of durvalumab in combination with chemotherapy (FLOT) for neoadjuvant and adjuvant treatment over current treatments on the NHS please describe these. For example, are there any risks with durvalumab in combination with chemotherapy (FLOT) for neoadjuvant and adjuvant treatment? If you are concerned about any potential side effects you have heard about, please describe them and explain why	There are disadvantages with any treatment options, however, the only one I've particularly heard about is the potential for auto immune reactions, which could potentially cause treatment to cease.
11. Are there any groups of patients who might benefit more from durvalumab in combination with chemotherapy (FLOT) for neoadjuvant and adjuvant treatment or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	Patients who may benefit more: • Younger patients and those with aggressive disease: Younger individuals with gastric or gastro-oesophageal junction cancers often present with more aggressive tumours. Combining durvalumab with FLOT in the neoadjuvant/adjuvant setting could help downstage tumours and reduce recurrence risk, improving long-term outcomes. • Patients with PD-L1 positive tumours or high immune activity: Immunotherapy like durvalumab works by enhancing the immune system's ability to attack cancer. Patients whose tumours express PD-L1 or have higher levels of immune infiltration may respond better to this combination, as their immune system is more likely to be activated by the treatment. • Patients fit enough to tolerate intensive treatment: Those with good performance status who can tolerate both chemotherapy and immunotherapy are more likely to complete the treatment course and gain maximum benefit. Patients who may benefit less: • Older or frail patients: Patients with reduced fitness or comorbidities may struggle with the side effects of combined chemotherapy and immunotherapy, making it harder to complete the full course and reducing potential benefit.

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	Patients with low PD-L1 expression or immunologically “cold” tumours: Tumours that are less responsive to immune activation may gain less from durvalumab, as the immunotherapy component may be less effective. Patients with severe autoimmune conditions: Because durvalumab activates the immune system, it may exacerbate pre-existing autoimmune disorders, making it less suitable or requiring careful monitoring.
12. Are there any potential equality issues that should be taken into account when considering resectable gastric or gastro-oesophageal junction adenocarcinoma and durvalumab in combination with chemotherapy (FLOT) for neoadjuvant and adjuvant treatment? Please explain if you think any groups of people with this condition are particularly disadvantage Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	Groups that may be particularly disadvantaged include younger patients (due to delayed diagnosis), older or frail patients (due to reduced tolerance), socioeconomically deprived individuals (due to logistical or financial barriers), patients living far from specialist centers, and those with comorbidities like autoimmune disorders.
13. Are there any other issues that you would like the committee to consider?	No

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Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Current NHS treatments for resectable gastric cancer are intense and can cause serious side effects.
- Many patients experience recurrence even after surgery and chemotherapy.
- Durvalumab with FLOT may reduce the risk of recurrence and improve outcomes.
- This treatment could help patients recover faster and return to daily life.
- Some groups, like older or frail patients, may benefit less, and equality issues must be considered.

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LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Durvalumab in combination for neoadjuvant and adjuvant treatment of resectable gastric and gastro-oesophageal junction adenocarcinoma [ID6374]

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External Assessment Group (EAG) Report

Durvalumab in combination for neoadjuvant and adjuvant treatment of resectable gastric and gastro-oesophageal junction adenocarcinoma [ID6374]

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LIST OF ABBREVIATIONS

AE	adverse event
AI	artificial intelligence
AIC	Akaike Information Criterion
BIC	Bayesian Information Criterion
BICR	blinded independent central review
BNF	British National Formulary
CI	confidence interval
CRD	Centre for Reviews and Dissemination
CRT	chemoradiation therapy
CS	company submission
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DCO	data cut-off
D-FLOT	durvalumab in combination with 5-fluorouracil, leucovorin, oxaliplatin, docetaxel
DFS	disease-free survival
DoR	duration of response
DSS	disease-specific survival
DSU	Decision Support Unit
EAG	External Assessment Group
ECOG PS	Eastern Cooperative Oncology Group performance status
EF	event-free
EFS	event-free survival
EORTC QLQ- STQ22+IL38	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Stomach 22 plus item library 38
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
EQ-5D-3L	European Quality of Life 5-Dimension, 3-Level
EQ-5D-5L	European Quality of Life 5-Dimension, 5-Level
FAS	full analysis set
FLOT	5-fluorouracil, leucovorin, oxaliplatin, docetaxel
GC	gastric cancer
GOA	gastro-oesophageal adenocarcinoma
GOC	gastric oesophageal cancer
GOJ	gastro-oesophageal junction
GOJC	gastro-oesophageal junction cancer
HCRU	healthcare resource use

HR	hazard ratio
HRQoL	health-related quality of life
HRU	healthcare resource utilisation
HTA	health technology assessment
ICER	incremental cost-effectiveness ratio
IV	intravenous
K-M	Kaplan-Meier
MRI	magnetic resonance imaging
MFS	metastasis-free survival
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
OC	oesophageal cancer
OS	overall survival
OWSA	one-way sensitivity analysis
PAS	Patient Access Scheme
pCR	pathological complete response
PD-L1	programmed death ligand-1
PFS	progression-free survival
PH	proportional hazard
PPS	post-progression survival
PRO	patient-reported outcome
PSM	partitioned survival model
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	quality-adjusted life year
QD	once daily
R0	complete surgical resection
R1	microscopic residual tumour
R2	macroscopic residual tumour
RCRD	Rapid Cancer Registration Database
RCT	randomised controlled trial
RD	recurred disease
RDI	relative dose intensity
SAE	serious adverse event
SAS	safety analysis set
SCC	squamous cell carcinoma
SLR	systematic literature review
SoC	standard of care

TAP	tumour area positivity
TFR	time to first recurrence
TTOT	time to end of treatment
WTP	willingness to pay

1 EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the external assessment group (EAG) as being potentially important for decision making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Section 1.3 explains the key issues in more detail. Secondary issues and modelling errors identified by the EAG are explored in sections 1.4 and 1.5. Background information on the condition, technology and evidence, and non-key issues are presented in later sections of the EAG report.

All issues identified represent the EAG's view, not the opinion of NICE.

1.1 Overview of EAG's key issues

Table 1 Summary of the EAG's key issues

ID6374	Summary of issue	Impact on results	Report sections
1	Nivolumab is not a relevant comparator	Unknown	2.3, Table 1
2	PD-L1 status in the MATTERHORN trial and NHS practice	Unknown	2.3, Table 1, 3.2.3 and 3.3.2
3	Cost-effectiveness model structure	Unknown	4.2.2

The key differences between the company's preferred assumptions and the EAG's preferred assumptions are the company choice of a semi-Markov model structure against the EAG preference for a partitioned survival model.

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, the technology is modelled to affect QALYs by:

- Increasing the time patients spend event-free
- increasing survival

Overall, the technology is modelled to affect costs by:

- Increasing treatment costs through the addition of durvalumab to the standard of care (FLOT)
- Reducing the time patients spend in the recurred disease health state

The modelling assumption that has the greatest effect on the ICER is:

- The modelling of overall survival (OS) using surrogate outcomes within a semi-Markov model.

1.3 EAG's key issues

The EAG has identified evidence that the company's modelling of OS using surrogate outcomes within a semi-Markov model is inaccurate. The EAG suggested that the company adopt an alternative, new modelling approach. The company is considering its response to this request.

The EAG critique of the economics is limited by, and therefore focused on, the current model structure. No robust alternative scenarios could be produced at this time. Should the company develop a renewed model that addresses the EAG's concerns, then an expanded critique may be provided.

Issue 1 Nivolumab is not a relevant comparator

Report section	2.3, Table 1
Description of issue and why the EAG has identified it as important	Nivolumab is included as a comparator in the final scope issued by NICE. Nivolumab is recommended by NICE for use as an adjuvant treatment for patients with completely resected Stage II to III OC/GOJC who have evidence of residual pathologic disease and have received prior neoadjuvant CRT. The company consider nivolumab is not a relevant comparator in the current appraisal because: • CRT is considered a treatment option only for patients who are not eligible for surgery and neoadjuvant FLOT • it is very rare that patients with GOA who receive neoadjuvant CRT can tolerate surgery (and therefore potentially be eligible to receive nivolumab) • nivolumab is primarily used in OC/GOJC patients with SCC rather than GOA • CRT and nivolumab are anticipated to be removed as treatment options from the next update of the ESMO guidelines.
What alternative approach has the EAG suggested?	None. The EAG agrees with the company that nivolumab is not a relevant comparator for the reasons provided.
What is the expected effect on the cost-effectiveness estimates?	Unknown.
Could any additional evidence or analyses be provided to resolve this key issue?	No. The EAG agrees that nivolumab is not a relevant comparator for this appraisal.

CRT=chemoradiotherapy; EAG=External Assessment Group; ESMO=European Society for Medical Oncology; FLOT=5-fluorouracil, leucovorin, oxaliplatin, docetaxel; GOA=gastro-oesophageal adenocarcinoma; GOJC=gastro-oesophageal junction cancer; OC=oesophageal cancer; SCC=squamous cell carcinoma

Issue 2 PD-L1 status in the MATTERHORN trial and NHS clinical practice

Report section	2.3, Table 1, 3.2.3 and 3.3.2
Description of issue and why the EAG has identified it as important	It is stated in the final scope issued by NICE that if evidence allows, results by level of PD-L1 expression will be considered. The company has only provided subgroup analyses for the clinical effectiveness of D-FLOT by PD-L1 status, not cost-effectiveness. MATTERHORN trial subgroup results for EFS and OS for PD-L1 expression levels $\geq 1\%$ TAP and $< 1\%$ TAP were presented in the CS. Additional results have been presented in the supplementary appendix to the primary published paper for EFS for expression levels $\geq 5\%$ and $< 5\%$ and $\geq 10\%$ and $< 10\%$. Although results for PD-L1 expression status subgroups were consistent with results for the overall trial population of the MATTERHORN trial, the trial was not powered to detect subgroup differences. Therefore, there is insufficient evidence to determine whether PD-L1 expression status has an important impact on treatment effect. If PD-L1 expression levels do have an important impact on treatment effectiveness, the proportion of patients with differing levels of PD-L1 expression may affect the results for the overall trial population and, therefore, the generalisability of the overall trial results to NHS clinical practice.
What alternative approach has the EAG suggested?	During the clarification process, the EAG asked the company to provide an estimate of the percentage of UK patients with GOA with PD-L1 expression level TAP $\geq 1\%$ and PD-L1 expression level TAP $< 1\%$ (clarification question C1). The company was unable to provide any relevant data.
What is the expected effect on the cost-effectiveness estimates?	Unknown.
Could any additional evidence or analyses be provided to resolve this key issue?	Although the MATTERHORN trial was not powered to assess subgroups by PD-L1 expression level, the point estimates favoured D-FLOT versus FLOT regardless of PD-L1 status. Data on the PD-L1 status of UK patients undergoing perioperative treatment for GOA would improve clarity on the generalisability of the overall trial results.

CS=company submission; D-FLOT=durvalumab in combination with 5-fluorouracil, leucovorin, oxaliplatin, docetaxel; EFS=event-free survival; FLOT=5-fluorouracil, leucovorin, oxaliplatin, docetaxel; GOA=gastro-oesophageal adenocarcinoma; OS=overall survival; PD-L1=programmed death ligand-1; TAP=tumour area positivity

Issue 3 Cost-effectiveness model structure

Report section	4.2.2
Description of issue and why the EAG has identified it as important	The difference in OS is the key determinant of the difference in QALYs between D-FLOT and FLOT in the company model. In the semi-Markov model structure, OS is modelled as a surrogate outcome and does not predict the OS for D-FLOT or FLOT that was demonstrated in the MATTERHORN trial at three years. Any bias towards D-FLOT that occurs from OS modelling at three years is compounded by extrapolation of these curves to predict survival for the remaining lifetime of the model. Distributions cannot be chosen for TP1, TP2 or TP3 that make OS more realistic without making these outcomes to be less in line with MATTERHORN trial outcomes.
What alternative approach has the EAG suggested?	The EAG considers that a PSM would have been a preferable model structure as this would enable curve selection for both EFS and OS that would align with MATTERHORN trial data
What is the expected effect on the cost-effectiveness estimates?	The EAG considers that more accurate modelling of OS may result in a decrease in the QALY gain for D-FLOT when compared to the current analysis. The magnitude of this impact is uncertain.
Could any additional evidence or analyses be provided to resolve this key issue?	The EAG considers that a PSM would provide the best estimates of cost-effectiveness given the evidence available.

D-FLOT=durvalumab in combination with 5-fluorouracil, leucovorin, oxaliplatin, docetaxel; EAG=External Assessment Group; EFS=event-free survival; FLOT=5-fluorouracil, leucovorin, oxaliplatin, docetaxel; OS=overall survival; PSM=partitioned survival model; QALY=quality-adjusted life years; TP=transition probability

1.4 Secondary issues identified by the EAG

The EAG does not have any secondary issues.

1.5 Company's modelling errors identified by the EAG

No modelling errors have been identified by the EAG.

1.6 Summary of EAG's preferred assumptions and resulting ICER

The EAG's preferred assumption would be to remove the cure assumption at five years in terms of its impact on OS (Section 5.2.2). The EAG has not presented analysis using this assumption although the company did so in a scenario analysis.

1.7 Outline of confidential comparator or subsequent treatment prices

The EAG has produced a confidential appendix with confidential prices for comparators and subsequent treatments (Section 5.4).

2 BACKGROUND

This External Assessment Group (EAG) report presents the EAG critique of the company submission (CS) for durvalumab (*Imfinzi*, AstraZeneca) used in combination for neoadjuvant and adjuvant treatment of resectable gastric and gastro-oesophageal junction adenocarcinoma. Durvalumab is used with 5-fluorouracil/leucovorin/oxaliplatin/docetaxel (FLOT) chemotherapy for gastro-oesophageal adenocarcinoma (GOA, which encompasses gastric and gastro-oesophageal junction adenocarcinoma) which is in line with its anticipated marketing authorisation.

In this EAG report, references to the CS are to the company's full evidence submission. Additional evidence was provided by the company in response to the NICE clarification letter.

2.1 Critique of the company's description of underlying health problem

The company presented a description of gastric oesophageal cancer (GOC) in the CS (pp18-19 and Section 1.3.1 to Section 1.3.4).

Gastric oesophageal cancers occur near or within the stomach. This heterogeneous group of cancers are classified by location with gastric cancer (GC) arising in the non-cardia sections of the lower parts of the stomach and gastro-oesophageal junction cancer (GOJC) arising where the oesophagus joins the upper section of the stomach cardia and oesophageal cancer (OC) arising from the oesophagus.

Although GOC cancers can be classed as adenocarcinomas, squamous cell carcinomas (SCC) or other rare types of stomach cancer,¹ the majority (approximately 90%) of GOC are adenocarcinomas that develop from mucus-producing cells.^{1,2}

GOA can be further classified by the location where the carcinomas develop (see CS, Figure 2) relative to the gastric cardia using the Siewert classification system:³

- type I: ≥ 1 cm above the gastric cardia and may arise from the oesophagus
- type II: 1 to 2 cm below the gastro-oesophageal junction involving the gastric cardia
- type III: ≥ 2 cm below the gastro-oesophageal junction.

Siewert type I cancers may be classified as GOA or oesophageal carcinomas whereas all Siewert type II and Siewert type III cancers are classified as GOA.

The company noted (CS, Section 1.3.4) that as symptoms of GOC overlap with those of other gastrointestinal conditions, people's cancer may be diagnosed at a late stage. However, Rapid Cancer Registration Database (RCRD) data suggest that 36.3% of people are diagnosed with resectable GOC in UK clinical practice.^{4, 5}

According to the FLOT4 trial,⁷ after surgery over half of patients treated with perioperative FLOT experienced disease progression, recurrence or death within three years, with a median disease-free survival (DFS) of 30 months reported in the FLOT arm. The company highlighted that (CS, Section 1.3.4):

- once the cancer has recurred, treatment is no longer of curative intent, leaving only treatments that aim to delay disease progression and subsequently death
- following recurrence to metastatic disease, median overall survival (OS) for patients with GC is estimated to be between 12 and 18 months when receiving platinum-based chemotherapy regimens including FLOT⁶⁻⁹
- it is predicted that just 16.7% of people in England survive GOC for ten years or more, with an age-standardised mortality rate of 2.3 deaths per 100,000 individuals in the UK, thus reflecting the need for novel treatment options that improve patients' prognoses.^{16, 55}

The company suggested that risk factors for GOA (CS, Section 1.3.1) include genetic, environmental and lifestyle factors which may contribute to inflammation and changes in cells lining the stomach. The risks and cancer development differ for GOA of the stomach cardia (such as Type II GOA) and non-cardia regions. The company cited evidence¹⁰ that infection with *Helicobacter pylori* is strongly implicated in GC originating in the non-cardia tissue and may contribute to 89% of cases. Other risk factors across GOA include obesity, tobacco smoking, high salt intake and heavy alcohol consumption.¹¹ Risk factors for cancers of the gastric cardia include obesity, high fat intake and gastro-oesophageal reflux disease.^{11,12} The company stated that overall GC is declining due to improved prevention and management of *Helicobacter pylori*, but GOJC has increased due to prevalence of risk factors such as obesity and gastro-oesophageal reflux disease. The incidence of GOC is likely to vary according to deprivation status¹³ and across different ethnic groups in the UK.¹⁴

EAG comment

The EAG considers that the company's description of the underlying health problem in the CS is relevant to the final scope issued by NICE and in line with current biomedical understanding of GOA. The EAG highlights that patients with oesophageal carcinomas are outside the scope of this NICE technology appraisal.

Clinical advice to the EAG is that complete surgical resection (R0) results in superior outcomes compared to cases where it is not achieved and agrees with the company that people with GOA who relapse after attempted re-section surgery tend to have a short OS period following relapse.

The EAG notes that risk factors for GOA vary with social economic status, ethnicity and exposure to *Helicobacter pylori* in people visiting or travelling from outside the UK.

2.2 Critique of the company's overview of current service provision

The company provided a description of management of resectable GOA in the CS (pp18-19, Section 1.1 and Section 1.3.3).

Clinical advice to the company was that people with GC and GOJC are offered similar management except for the surgical approach used in different anatomical locations.⁵ Recommendations in published clinical guidelines^{12,15,16} and clinical advice to the company is that standard of care (SoC) treatment for patients with resectable GOA consists of perioperative FLOT chemotherapy, administered both prior to (neoadjuvant) and following (adjuvant) radical surgery. This treatment pathway is shown in CS, Figure 3.

Durvalumab is expected to be used in combination with FLOT chemotherapy as a perioperative treatment for patients with resectable GOA; this combination is termed perioperative D-FLOT, as shown in CS, Figure 5. The key features of durvalumab are summarised in CS, Table 2. Durvalumab is described as a high-affinity immunotherapy; durvalumab is an anti-programmed cell death ligand 1 (PD-L1) monoclonal antibody which selectively blocks the interaction of PD-L1 with programmed cell death 1 (PD-1) and cluster of differentiation 80 (CD80).

Alternative treatment options for patients with GOC include neoadjuvant chemoradiation therapy (CRT) and adjuvant nivolumab; nivolumab is recommended by NICE for use as an adjuvant treatment for patients with completely resected Stage II to III OC/GOJC who have evidence of residual pathologic disease and have received prior neoadjuvant CRT (TA746).¹⁷ However, CRT and nivolumab are not considered in CS, Figure 5 as the company considered them not to be relevant treatment options based on the following clinical advice to the company (CS, Table 1):

- CRT is considered a treatment option only for patients who are not eligible for surgery and neoadjuvant FLOT¹⁶
- it is very rare that patients with GOA who receive neoadjuvant CRT can tolerate surgery (and therefore potentially be eligible to receive nivolumab)¹⁶
- nivolumab is primarily used in OC/GOJC patients with SCC rather than GOA¹⁶
- CRT and nivolumab are anticipated to be removed as treatment options from the next update of the ESMO guidelines.

EAG comment

Clinical advice to the EAG agreed that the CS provided an accurate description of SoC in NHS practice which has extended beyond care options recommended in the 2018 NICE guideline on oesophago-gastric cancer in adults (NICE guideline 83).¹⁶

2.3 Critique of the company's definition of decision problem

A summary of the NICE final scope¹⁸ and decision problem addressed by the company is presented in Table 1.

Table 1 Summary of decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission and rationale if different from the final NICE scope	EAG comment
Population	Adults with resectable gastric or gastro-oesophageal junction adenocarcinoma	Adults with resectable gastric or gastro-oesophageal junction adenocarcinoma	CS aligned with the final scope issued by NICE
Intervention	Durvalumab with chemotherapy (D-FLOT) before surgery (neoadjuvant) and after surgery (adjuvant), then adjuvant durvalumab monotherapy	D-FLOT before surgery (neoadjuvant) and after surgery (adjuvant), then adjuvant durvalumab monotherapy	CS aligned with the final scope issued by NICE. The EAG notes that marketing authorisation application is in progress.
Comparator(s)	Established clinical management without durvalumab, including but not limited to: - chemotherapy (FLOT), before and after surgery - for people with gastro-oesophageal junction adenocarcinoma: - nivolumab, after surgery in adults who have residual disease after previous neoadjuvant chemoradiotherapy	FLOT chemotherapy, before and after surgery (perioperative FLOT chemotherapy). The company considered that management with nivolumab was not a relevant comparator and did not present evidence for the comparison of durvalumab vs nivolumab in the CS. The company stated highlighted that nivolumab is licenced and recommended by NICE for use as an adjuvant treatment for patients with completely resected to III OC/GOJC who have evidence of residual pathologic disease and have received prior neoadjuvant CRT but clinical advice to the company was that: - CRT is considered a treatment option only for patients who are not eligible for surgery and neoadjuvant FLOT - it is very rare that patients with GOA who receive neoadjuvant CRT can tolerate surgery (and therefore potentially be eligible to receive nivolumab) - nivolumab is primarily used in OC/GOJC patients with SCC rather than GOA	The company considered that perioperative FLOT was the only relevant comparator to durvalumab with FLOT. The EAG agrees that nivolumab is not an appropriate comparator and that the appropriate comparator for this appraisal is perioperative FLOT chemotherapy

	Final scope issued by NICE	Decision problem addressed in the company submission and rationale if different from the final NICE scope	EAG comment
		CRT and nivolumab are anticipated to be removed as treatment options from the next update of the ESMO guidelines.	
Outcomes	The outcome measures to be considered include: - OS - EFS - response rate - AEs of treatment - HRQoL	The outcomes included in the CS are: - OS - EFS - pCR - surgical outcomes - DFS - DSS - MFS - pathological downstaging - AEs - HRQoL Additional outcome measures reported in the MATTERHORN trial are provided in CS, Section 2.4.2.	CS aligned with the final scope issued by NICE
Economic analysis	The reference case stipulates that the - effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and - effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.	The economic model presented by the company is in line with the NICE reference case.	The EAG considers that a partitioned survival model (PSM) would have been a preferable model structure.

	Final scope issued by NICE	Decision problem addressed in the company submission and rationale if different from the final NICE scope	EAG comment
	The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account.		
Subgroups	If evidence allows, results by level of PD-L1 expression will be considered.	Subgroup analyses for the clinical endpoints of EFS and OS, including by PD-L1 expression level (TAP $\geq 1\%$ vs TAP $< 1\%$) are provided in CS, Section 2.8. The company stated that the MATTERHORN trial subgroup analyses results indicate a consistent treatment benefit regardless of PD-L1 expression level. Furthermore, clinical advice to the company suggested that PD-L1 expression is not routinely tested in all patients with resectable GOA and does not determine their treatment decisions for patients with resectable GOA and does not inform treatment offered.	Clinical advice to the EAG is that: • PD-L1 testing is not currently routine for resectable GOA • testing modalities and PD-L1 expression level thresholds for positivity vary • PD-L1 expression status can change over time. The EAG notes that the MATTERHORN trial subgroup analyses results by PD-L1 expression status were limited by the small proportion of patients (10.0%) in the PD-L1 expression level $< 1\%$ subgroup.

AE=adverse event; CRT=chemoradiotherapy; D-FLOT=durvalumab plus 5-fluorouracil, leucovorin, oxaliplatin, docetaxel; DFS=disease-free survival; DSS=disease-specific survival; EFS=event-free survival; ESMO=European Society for Medical Oncology; GOA=gastro-oesophageal adenocarcinoma; GOJC=gastro-oesophageal junction cancer; HRQoL=health-related quality of life; MFS=metastasis-free survival; NHS=National Health Service; OS=overall survival; pCR=pathological complete response; PD-L1=programmed death ligand-1; SCC=squamous cell carcinoma; SoC=standard of care; TAP=tumour area positivity
Source: CS, Table 1

2.4 *Special considerations including issues related to equity or equality*

The company highlighted that GOA disproportionately affects already disadvantaged populations, including people experiencing socioeconomic deprivation, and therefore widens existing health inequalities. The company stated that although global rates of GC have declined, rates of GOJC are increasing, likely due to risk factors such as obesity and gastro-oesophageal reflux disease. Conditions that increase risk of GOA are also associated with underlying inequalities and men are almost twice as likely to develop GOC as women (CS, Section 1.3.1).

EAG comment

The EAG considers the company's description of special considerations to be relevant, sufficiently referenced and to align with current biomedical and sociobiological understanding of cancer risk. The EAG notes that the company has not made specific claims in relation to the D-FLOT addressing these inequalities other than offering effective treatment for a condition that is unequally distributed across different socioeconomic and ethnic groups, and offering people who may otherwise be disadvantaged by the burden of the condition the potential to resume or continue their economic and social activities. Clinical advice to the EAG is that there is potential for variation in access to SoC cancer services across the UK. However, there is no evidence to suggest that the technology itself would introduce further inequalities.

3 CLINICAL EFFECTIVENESS

This section presents a summary and critique of the clinical-effectiveness evidence included in the company's submission. Section 3.1 focuses on the company's review of clinical and safety evidence. Sections 3.2 to 3.3 provide a critique of the included study and clinical-effectiveness analyses. Sections 3.4 to 3.5 highlight why the company did not present any indirect comparisons. The EAG did not conduct any additional work on clinical effectiveness (Section 3.6). Section 3.7 contains the EAG's clinical effectiveness conclusions.

3.1 Critique of the methods of review

The company conducted a SLR to identify published clinical efficacy and safety data for durvalumab and potentially relevant comparators to durvalumab used before or after surgical resection of GOA tumours in adult patients (CS, Section 2.1).

The SLR was informed by searches conducted on 3 November 2024 and updated on 26 June 2025. The original and updated searches were comparable in scope and sources. The update used AI-assisted review processes for evidence selection, data extraction and quality assessment.

The company selected and extracted data from a total of 13 trials (reported in 56 publications) which explored a range of combination therapies (or no treatment) used perioperatively as well as a further 20 trials (reported in 28 publications) of adjuvant only or neoadjuvant only approaches, that is, non-perioperative approaches with surgery. Only one RCT, the MATTERHORN trial (NCT04592913), reported in two publications (Janjigian 2023,¹⁹ Janjigian 2025²⁰) and one conference presentation (Al-Batran 2025²¹), was considered relevant to the decision problem. The MATTERHORN trial is described in the CS (CS, Section 2.2).

EAG comment

The EAG considers that the company's SLR methods were appropriate and it is unlikely that relevant clinical trials of perioperative use of durvalumab in GOA were omitted. Clinical advice to the EAG confirmed this.

An assessment of the company's SLR using the EAG (LRiG) in-house systematic review checklist is summarised in Table 2.

The SLR was informed by searches that were updated on 26 June 2025, within 6 months of the company's evidence submission to NICE. The EAG notes that combined search strategies were presented for Embase and MEDLINE. These databases differ in indexing terms, syntax

and Boolean operators which could affect search results, but the EAG consider it is unlikely that relevant clinical trials were omitted.

Overall, the company SLR appeared sufficiently robust to identify relevant clinical trials. Procedures used in the original SLR were in line with established methodological standards. The updated review used AI-assisted procedures with human oversight for study selection, data extraction and quality assessment. The EAG considers that AI-assisted procedures used for study selection appear to be in line with currently accepted practice. The company's own analysis of the performance of AI and its report of limitations according to RAISE guidelines (company response to clarification question C2) indicated some challenges with data extraction and quality assessment (including AI hallucination). The company's quality assessment procedures, including the tool used and the level of human and AI involvement, were unclear.

Table 2 EAG appraisal of the company's systematic review methods

Review process	EAG response	Note
Was the review question clearly defined in terms of population, interventions, comparators, outcomes and study designs?	Yes	See CS, Section 2.1 and Appendix B1.2 (Table 6)
Were appropriate sources searched?	Yes	See CS, Appendix B.1 and Appendix B.1.1
Was the timespan of the searches appropriate?	Yes	See CS, Appendix B.1 and Appendix B.1.1 (Table 1 to Table 5).
Were appropriate search terms used?	Yes	See CS, Appendix B.1 and Appendix B.1.1.
Were the eligibility criteria appropriate to the decision problem?	Yes	See CS, Section 2.1 and Appendix B1.2 (Table 6) Criteria were sufficiently broad to include evidence on any perioperative therapies used with surgical resection for gastric or gastroesophageal junction cancer in the SLR.
Was study selection applied by two or more reviewers independently?	Partly	See CS, Appendix B.1, Appendix B.1.2 and Appendix B.1.4 The original SLR used two independent reviewers to review records at title and abstract screening and full text screening (but conference proceedings and trial registries were reviewed by a single reviewer). The updated SLR used a single human reviewer (reviewer 1) and an AI tool (DAISY) for title and abstract screening. Application of eligibility criteria at full text stage appear to have been conducted as per the original review. The EAG considers that processes applied by the company are unlikely to have excluded relevant evidence. More detail on the use of AI in this review process is presented in Table 20.

Review process	EAG response	Note
Was data extracted by two or more reviewers independently?	Partly	See CS, Appendix B.1, Appendix B.1.2 (Table 7) and Appendix B.1.4 (Figure 4) For the original SLR, data were extracted by a single reviewer and checked by a second reviewer independently. For the updated SLR, data were extracted by two human reviewers. Consensus was reached between the two human reviewers and this was compared to data extracted by two AI reviewers. The EAG considers that as only the MATTERHORN trial is relevant to the current appraisal, processes applied by the company are unlikely to have excluded or incorrectly extracted relevant data used in the CS. More detail on the use of AI in this review process is presented in Table 20.
Were appropriate criteria used to assess the risk of bias and/or quality of the primary studies?	Yes	See CS, Section 2.5 (Table 9)
Was the quality assessment conducted by two or more reviewers independently?	Yes	See CS, Section 2.5, Appendix B.1.2 and Appendix B1.3 More detail on the use of AI in this review process is presented in Table 20.
Were attempts to synthesise evidence appropriate?	Yes	See CS, Section 2 As the comparative effectiveness of perioperative D-FLOT versus SoC can be assessed based on direct evidence from the MATTERHORN trial, it was not necessary to conduct meta-analyses or indirect treatment comparisons. The EAG agrees that the MATTERHORN trial is the only source of evidence relevant to the current appraisal.

AI=artificial intelligence; CRD=Centre for Reviews and Dissemination; DAISY=DistillerSR Artificial Intelligence System; RCT=randomised controlled trial; SLR=systematic literature review

3.2 Critique of the methods of the trials of the technology of interest

3.2.1 Trials included in the review

The company SLR included only one study, the MATTERHORN trial (NCT04592913), which has been reported in two publications^{19,20} and one conference presentation²¹ (described in CS, Section 2.2).

Data from the MATTERHORN trial provided the primary source of clinical effectiveness evidence in the CS as it was the only study identified that included the population, intervention and comparators specified in the final scope issued by NICE.¹⁸ The MATTERHORN trial data also informed clinical parameters in the economic model.

EAG comment

The EAG agrees with the company that the MATTERHORN trial is relevant to the decision problem.

3.2.2 Trial characteristics

Key characteristics of the trial are presented in Table 3. As reported in the CS (p76), all patients in the trial had completed (or discontinued) adjuvant treatment and completed the safety follow-up. All patients remaining in the study are in survival follow-up (all ■■■; D-FLOT arm, N=■■■; FLOT arm, N=■■■).

Table 3 Key characteristics of the MATTERHORN trial

	MATTERHORN
Role in this evaluation	Primary source of clinical effectiveness evidence and basis of economic model
Study aim	To assess the efficacy and safety of durvalumab in combination with FLOT chemotherapy as neoadjuvant and adjuvant treatment, followed by adjuvant durvalumab monotherapy for the treatment of adults with resectable GOA
Study type	Phase III, 1:1 randomised, multi-centre, double-blind, placebo-controlled trial conducted in multiple centres worldwide. People with GOA in the trial were stratified by geographic region (Asia vs non-Asia), clinical lymph node status (positive vs negative) and PD-L1 expression status (TAP <1% vs ≥1%)
Patient group	Adults (N=948) with resectable GOA (Stage II to IVA)
Key eligibility criteria	• Aged ≥18 years at the time of screening • Histologically documented resectable Stage II through IVA (according to the AJCC TNM staging 8th edition) gastric/GOJ adenocarcinoma. GOJC includes Siewert type II and Siewert type III tumours (and Siewert type 1 tumours if the patient was intended to be treated in the same way as a patient with a Siewert type II or Siewert type III tumour would be treated) • Had not received anti-cancer therapy (e.g., chemotherapy, radiation therapy, or chemoradiation therapy) for the current malignancy • ECOG PS of 0 or 1 at enrolment and randomisation
Intervention	Durvalumab (IV administration): 1500mg on Day 1 Q4W for 2 cycles as neoadjuvant therapy; 1500mg on Day 1 Q4W for a maximum of 12 cycles of adjuvant therapy (2 cycles in combination with FLOT followed by 10 cycles as monotherapy). In combination with FLOT chemotherapy (IV administration): on Days 1 and 15 of each 4-week cycle for 2 cycles as neoadjuvant therapy; on Days 1 and 15 Q4W for 2 cycles as adjuvant therapy.
Comparator	Placebo (IV administration): on Day 1 Q4W for 2 cycles in the neoadjuvant period; on Day 1 Q4W for a maximum of 12 cycles in the adjuvant period (2 cycles in combination with FLOT followed by 10 cycles as monotherapy). In combination with FLOT chemotherapy (IV administration): on Days 1 and 15 of each 4-week cycle for 2 cycles as neoadjuvant therapy; on Days 1 and 15 Q4W for 2 cycles as adjuvant therapy.
Duration	Intervention schedule: surgery was scheduled 4 to 8 weeks after the final dose of neoadjuvant therapy and adjuvant therapy commenced 4 to 12 weeks post-surgery.

	MATTERHORN
	Trial is ongoing. At DCO2 the median duration of follow-up was 31.5 months (IQR: 26.7 to 36.6). At DCO3, the median duration of follow-up was 43.0 months in the D-FLOT arm and 42.9 months in the FLOT arm.
Dates	People with GOA first enrolled: 7 November 2020 DCO1: 1 February 2023 DCO2: 20 December 2024 DCO3: 1 September 2025.
Location	948 patients were randomised to treatment at 147 study sites across 20 countries in North and South America, Asia and Europe. The study sites included 8 UK centres (█ people).
Primary endpoint	EFS
Secondary endpoints	Key (according to CS) • OS • pCR Other: • Surgery rate • R0 resection rate • MFS • DFS • DSS • HRQoL (EQ-5D-5L) • Time to deterioration and change from baseline in EORTC QLQ-C30 and EORTC QLQ-STO22 + IL38, in the PRO analysis set • Safety and tolerability analyses
Subgroup analyses	Subgroup analyses were conducted for EFS and OS to investigate whether treatment effect varies according to various baseline and disease characteristics, including: sex, age at randomisation, geographic region, clinical lymph node status, ECOG PS, PD-L1 expression level and primary tumour location.

AJCC=American Joint Committee on Cancer; DCO=data cut-off; DFS=disease-free survival; DSS=disease specific survival; ECOG PS=Eastern Cooperative Oncology Group performance status; EORTC QLQ-C30= European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EORTC QLQ- STO22+IL38=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Stomach 22 plus item library 38; EQ-5D-5L=European Quality of Life 5-Dimension, 5-Level; GOA=gastro-oesophageal adenocarcinoma; HRQoL=health-related quality of life; IV=intravenous; MFS=metastasis-free survival; OS=overall survival; pCR=pathological complete response; PD-L1=programmed death ligand-1; PRO=patient reported outcome; Q4W=every 4 weeks; R0=complete surgical resection; Stage IVA= locally advanced subclass of stage IV cancer; TAP=tumour area positivity
Source: CS, Table 4 and CS, Section 2.3.3.

EAG comment

The EAG considers that the MATTERHORN trial was designed and implemented appropriately. It had a relevant, clearly stated aim; randomised, multi-centre, double-blind, placebo-controlled design; objectively defined patient characteristics; pre-defined subgroups and appropriate inclusion and exclusion criteria. It is a sizable study with 948 people with GOA randomised and reported median follow-up of over 2.5 years at DCO2, and over 3.5 years at DCO3.

3.2.3 Patient characteristics

The company considered that the MATTERHORN trial patient characteristics (presented in CS, Table 5) were well balanced between treatment arms (CS, Section 2.3.3) with the exception of some minor imbalances (5% to <10% difference), namely that, compared to the FLOT arm, the D-FLOT arm included more females, under 50-year-olds and patients with Eastern Cooperative Oncology Group performance status (ECOG PS 1; i.e., symptomatic, but ambulatory) status (see CS, Section 2.3.3).

EAG comment

The EAG agrees with the company that patient characteristics were well balanced between the MATTERHORN trial treatment arms.

Clinical advice to the company and to the EAG is that baseline characteristics of people enrolled in the MATTERHORN trial were broadly representative of patients with resectable GOA receiving FLOT in the UK. However, clinical advice to the EAG suggested that it was unlikely that approximately 90% of patients would have PD-L1 expression level $\geq 1\%$, as in the MATTERHORN trial. If PD-L1 expression levels have an important treatment effect, then the proportion of patients with differing levels of PD-L1 expression may affect the results for the overall trial population and, therefore, the generalisability of the overall trial results to NHS clinical practice. During the clarification process, the EAG asked the company to provide an estimate of UK patients with GOA with PD-L1 expression level TAP $\geq 1\%$ and PD-L1 expression level TAP $< 1\%$ (clarification question C1). The company responded that UK real world data aligned specifically to TAP $\geq 1\%$ versus TAP $< 1\%$ in resectable GOA are not available. The company also considered PD-L1 expression is not anticipated to influence treatment decisions in resectable GOA and referred to results from subgroup analyses by PD-L1 status presented in the CS. Clinical advice to the EAG is that PD-L1 testing is not currently routine for resectable GOA. See Section 3.3.2 for EAG comment on the subgroup results.

3.2.4 Outcomes

Trial outcomes are summarised in Table 3 and outcomes included at DCO points are presented in Table 7.

EAG comment

The MATTERHORN trial assessed an appropriate range of relevant outcomes (see Table 3), including all outcomes specified in the decision problem. The company economic model incorporated OS and event-free survival (EFS) data.

The EAG highlights that the definition of EFS in the MATTERHORN trial is similar to the definition of DFS in other trials of adjuvant or perioperative therapies. While clinical advice to the EAG considered EFS and DFS to be clinically meaningful outcomes, clinical advice to the EAG also highlighted that a recurrence event identified as part of computed tomography (CT) or magnetic resonance imaging (MRI) surveillance, as in the MATTERHORN trial protocol, may not be associated with symptomatic disease recurrence. The EAG consider that this does not reflect NHS practice, where people present for assessment only after experiencing symptoms. The impact on EFS and OS is uncertain.

3.2.5 Quality assessment

The company quality assessed the MATTERHORN trial using the Centre for Reviews and Dissemination (CRD) Report 4 RCT checklist²² (CS, Table 9). Quality checklist items were graded as adequate except for “unexpected imbalances in drop-outs between groups” which was graded unclear.

The CS did not include a summary of the overall trial quality (the tool used does not produce an overall ‘risk of bias’ assessment) or discussion of the potential impact of elements of quality assessment. Although the company’s quality assessment indicated that groups were “similar at the outset of the study”, the company noted (CS, p43) the following minor differences in baseline characteristics (D-FLOT versus FLOT):

- sex (females: 31.2% vs. 24.9%)
- age (younger than 50 years: 18.1% vs. 12.0%)
- ECOG PS (PS of 1: 28.9% vs. 22.8%).

EAG comment

The EAG agrees that the MATTERHORN trial was well designed and implemented appropriately. It is likely to be of good overall quality.

With regard to the company’s assessment of CRD Report 4 RCT checklist²² item on “unexpected imbalances in drop-outs” the EAG considers that the MATTERHORN trial report does offer some clarity on participant disposition through the trial pathway (including interventions received and clinical assessments undertaken) and on censoring. While some of these data are not direct measures of dropout, the overall similarity in participation and censoring provide confidence that there were not unexpected imbalances in dropouts.

3.2.6 Statistical approach adopted for the analysis of results from the MATTERHORN trial

Generally, the EAG considers that the company used appropriate statistical methods to analyse MATTERHORN trial data. This section of the EAG report presents a summary and

critique of key aspects of the MATTERHORN trial statistical analyses undertaken by the company.

Analysis sets

Definitions for the R0 resected analysis set, full analysis set (FAS), and safety analysis set (SAS) are provided in Table 4.

Table 4 MATTERHORN trial analysis sets

Analysis set	Definition
R0 resected analysis set	All patients in the FAS who had margin-negative or R0 surgical resection following neoadjuvant treatment
FAS	All randomised participants. Participants were included in the analyses according to the treatment they were assigned
SAS	All participants who received at least one dose of study treatment. Participants were analysed according to the treatment that they received

FAS=full analysis set; R0=complete surgical resection; SAS=safety analysis set

Source: MATTERHORN trial protocol, p110²³

The analysis of the secondary efficacy endpoint, disease-free survival (DFS, see Table 5 for definition) was performed for the R0 resected analysis set. All other efficacy and patient reported outcome (PRO) analyses presented in the CS (and in this EAG report) were performed for the FAS. All safety analyses presented in the CS (and in this EAG report) were performed for the SAS.

EAG comment

The trial analysis sets were pre-specified in the trial protocol (trial protocol, p110)²³ and appropriate for the outcomes analysed.

Efficacy endpoint definitions

The MATTERHORN trial primary and secondary efficacy endpoint definitions are provided in Table 5.

Table 5 MATTERHORN trial primary and secondary efficacy endpoint definitions

Endpoint	Priority	Endpoint definition	Assessment
EFS	Primary	Time from randomisation to the first of the following: 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	RECIST 1.1 per BICR assessment ^a and/or locally by pathology testing
OS	Secondary	Time from the date of randomisation until death due to any cause	N/A
pCR	Secondary	Proportion of patients who have no residual visible tumour in the resected specimens	Pathology review by central review ^b in accordance with the modified Ryan criteria ²⁴
Surgery rate	Secondary	Proportion of patients who undergo gastrectomy or gastro-oesophagectomy	N/A
R0 resection rate	Secondary	Proportion of patients who have confirmed complete resection	Pathology review (local assessment)
Pathological downstaging	Secondary ^c	Defined as: a) the proportion of patients who achieved downstaging of the primary tumour at surgery (pathological staging) relative to clinical staging at baseline, and b) the proportion of patients who were downstaged to N0 status at surgery having had node positive status at baseline	N/A
MFS	Secondary	Time from randomisation until the development of metastasis or death due to any cause	RECIST 1.1 (investigator assessment)
DSS	Secondary	Time from randomisation until death due to GOA	N/A
DFS	Secondary	Time from first post-surgery scan until disease recurrence or death due to any cause	RECIST 1.1 (investigator assessment)

^a A sensitivity analysis of EFS using investigator assessments was also conducted.

^b A sensitivity analysis of pCR based on local assessment was also conducted.

^c Referred to as a secondary outcome in Table 8 of the CS, and as an exploratory outcome in Section 2.6.6 of the CS
 BICR=blinded independent central review; DFS=disease-free survival; DSS=disease-specific survival; EFS=event-free survival; GOA=gastro-oesophageal adenocarcinoma; N/A=not applicable; MFS=metastasis-free survival; OS=overall survival; pCR=pathological complete response; RECIST=Response Evaluation Criteria in Solid Tumors; R0=complete surgical resection
 Source: CS, Table 8

EAG comment

The efficacy endpoints and definitions presented in Table 5 were all pre-specified in the trial protocol (trial protocol, p41 and p79), with the following exceptions:

- pathological downstaging was not pre-specified as a trial outcome in the protocol; it is appropriately referred to as an “exploratory outcome” in Section 2.6.6 of the CS
- it was not pre-specified that metastasis-free survival (MSS) and disease-free survival (DFS) would be assessed according to Response Evaluation Criteria in Solid Tumours (RECIST 1.1) per investigator-assessment (rather than by blinded independent central review-assessment); the company confirmed this in response to clarification question A5.

The *post-hoc* nature of these analyses should be considered when interpreting results.

Clinical cut-off dates

A total of three data cut-offs (DCOs) were planned for the MATTERHORN trial:

- DCO1 (1 February 2023): pre-planned interim analysis of pathological complete response (pCR)
- DCO2 (20 December 2024): pre-planned interim analysis of EFS and OS, which became the final analysis of EFS as the boundary for declaring statistical significance was met at this time (see Section 3.3.1)
- DCO3 (1 September 2025): final OS analysis

EAG comment

The interim analyses were pre-specified (trial protocol, p129) and accounted for in the company's multiple testing procedure (see "Multiple testing procedure"). The EAG considers that it was appropriate for the final EFS analysis to take place at DCO2; EFS data are not available from the most recent data-cut (DCO3) of the MATTERHORN trial.

Multiple testing procedure

The company applied a multiple testing procedure to control the overall type 1 error rate for the study at 0.05. The company allocated $\alpha=0.1\%$ (2-sided) for the analysis of pCR at DCO1. The remaining $\alpha=4.9\%$ (2-sided) was allocated to testing EFS at DCO2 and DCO3 if applicable (i.e. if statistical significance was not already achieved at DCO2).

As a statistically significant result was observed for pCR at DCO1 (see Section 3.3.1), the $\alpha=0.1\%$ for pCR was recycled to EFS, so EFS could be tested at an overall α of 5% (2-sided). The allocated α for EFS was planned to be spent between DCO2 and DCO3 using the Lan-DeMets²⁵ spending function that approximates an O'Brien-Fleming²⁶ approach, with the boundaries for statistical significance to be determined based on the number of events that had occurred at the time of analysis. The boundary for declaring statistical significance for EFS at DCO2 was $p<0.0239$. As the boundary was met at this time (see Section 3.3.1), DCO2 became the final EFS analysis.

The company planned to test OS if a statistically significant result was observed for EFS. As a statistically significant result was observed at DCO2 for EFS, the full $\alpha=5\%$ was available for OS testing at DCO2 and DCO3. The company pre-specified a fixed α of 0.01% for testing OS at DCO2, with the remaining α (4.99%) to be spent at DCO3.

EAG comment

The multiple testing procedure and alpha-spending function were pre-specified (trial protocol, Section 9.5.7)²³ and applied correctly.

Proportional hazards assumption

The company used Cox proportional hazards (PH) models to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for time-to-event endpoints.

EAG comment

The Cox PH model is only an appropriate method to use if the PH assumption holds, i.e., if the event hazards associated with the intervention and comparator data are proportional over time. The company assessed the validity of the PH assumption for EFS (DCO2) and OS (DCO2 and DCO3). The company considered log cumulative hazard plots, Schoenfeld residual plots and p-values from global Schoenfeld tests to assess PH assumptions (company response to clarification question A4). The results of the company's PH assessments are discussed in Section 3.3.1 of this EAG report.

3.3 Critique of the results of the trials of the technology of interest

3.3.1 MATTERHORN trial efficacy results

A summary of pCR results is provided in Table 6. A summary of EFS, OS, metastasis-free survival (MFS) and disease-specific survival (DSS) results is provided in Table 7.

Table 6 MATTERHORN trial pCR results

Outcome and DCO	D-FLOT (n=474) # patients with response	FLOT (n=474) # patients with response	D-FLOT (n=474) Response rate (95% CI), %	FLOT (n=474) Response rate (95% CI), %	D-FLOT vs FLOT Difference in response rate, %	D-FLOT vs FLOT OR (95% CI)	p-value
pCR (DCO1)	91	34	19.2 (15.8 to 23.0)	7.2 (5.0 to 9.9)	12.0	3.1 (2.0 to 4.7)	<0.001 ^a

^a The p-value boundary for declaring statistical significance of pCR at DCO1 was p<0.001; CI=confidence interval; DCO=data cut-off; OR=odds ratio; pCR=pathological complete response
Source: CS Table 12

Table 7 Summary of MATTERHORN trial EFS, OS, MFS and DSS

Outcome and DCO	D-FLOT (n=474) # events (%)	FLOT (n=474) # events (%)	D-FLOT (n=474) Median (95% CI), months	FLOT (n=474) Median (95% CI), months	HR (95% CI) D-FLOT vs FLOT	p-value
EFS (DCO2)	167 (35.2)	218 (46.0)	NR (40.7 to NC)	32.8 (27.9 to NC)	0.71 (0.58 to 0.86)	<0.001 ^a
OS (DCO2)	145 (30.6)	176 (37.1)	NR (NC to NC)	47.2 (45.1 to NC)	0.78 (0.62 to 0.97)	0.025 ^b
OS (DCO3)	160 (33.8)	192 (40.5)	NR (NR to NR)	NR (NR to NR)	0.78 (0.63 to 0.96)	0.021 ^c
MFS (DCO2)						
DSS (DCO2)						

^a The p-value boundary for declaring statistical significance of EFS at DCO2 was p<0.0239

^b The p-value boundary for declaring statistical significance of OS at DCO2 was p<0.0001

^c The p-value boundary for declaring statistical significance of OS at DCO3 was p<0.0499

^d The reported p-value is nominal only as it is not adjusted for multiplicity

CI=confidence interval; DCO=data cut-off; DSS=disease-specific survival; EFS=event-free survival; HR=hazard ratio; MFS=metastasis-free survival; NC=not calculated; NR=not reached; OS=overall survival

Source: CS Table 10, Table 11, Table 14 and Table 15; MATTERHORN trial CSR, Figure 14 and Figure 15; Tabernero 2025.²⁷

Pathological complete response

At DCO1, the pCR rate was 12.0% higher in the D-FLOT arm than in the FLOT arm (Table 6). The company reported that this treatment effect is statistically significant and clinically meaningful (CS, p61).

EAG comment

The EAG highlights that 'response rate' was listed as a relevant outcome in the final scope issued by NICE.

Event-free survival and overall survival

At DCO2, median follow-up time for EFS at DCO2 (calculated by reverse Kaplan-Meier [K-M] method) was 31.6 months and 31.4 months in the D-FLOT and FLOT arms, respectively. The EFS results at DCO2 (final EFS analysis, Section 3.2.6) indicated a statistically significant treatment effect in favour of D-FLOT (Table 7).

DCO2 OS results also favoured D-FLOT, but the p-value did not meet the pre-specified boundary ($p < 0.0001$) for declaring statistical significance at this time. At DCO3, the OS HR and 95% CI were almost identical to the corresponding results from DCO2; however, at DCO3, additional follow-up data and a higher p-value threshold for declaring statistical significance led to a statistically significant result (Table 7). The EAG has been unable to source the median follow-up specifically for OS (calculated by reverse K-M method) for DCO2. At DCO3, the median duration of follow-up for OS was 43.0 months in the D-FLOT arm and 42.9 months in the FLOT arm.

The company provided EFS (CS, Table 10) and OS rates (CS, Table 11) at 12, 18, 24, 30 and 36 months, and K-M curves for EFS (CS, Figure 8) and OS (CS, Figure 9).

EAG comment

Clinical advice to the EAG is that the EFS and OS results are clinically meaningful.

The company assessed the PH assumption for EFS at DCO2 and OS at DCO2 and DCO3 (clarification question A4), concluding that the PH assumption was valid for each of these analyses. The EAG concurs with the company's assessments and considers the company's use of the Cox PH model to analyse EFS and OS data to be appropriate.

An important issue to consider when interpreting the MATTERHORN trial results is the use of subsequent treatments. Decisions regarding subsequent treatments were made

at the investigator's discretion; investigators remained blinded to patients' original treatment allocation. Patients in the MATTERHORN trial were able to initiate subsequent therapy upon discontinuation of study treatment, which may have occurred prior to patients experiencing progression or recurrence. Therefore, the use of subsequent treatments could potentially impact both EFS and OS.

Subsequent treatments in the MATTERHORN trial included the antiangiogenic drug ramucirumab (CS, Table 17 and the company's Clinical Validation Report, Table 1).¹⁶ Clinical advice to the EAG is that NHS patients would not be eligible to receive ramucirumab following treatment with either D-FLOT or FLOT; ramucirumab is not recommended as a treatment option for patients with advanced GC or GOA who have previously been treated with chemotherapy (NICE TA 378).²⁸ However, clinical advice to the EAG is that ramucirumab is unlikely to be significantly more clinically effective than the subsequent treatments used in NHS clinical practice. In addition, the proportions of patients receiving treatment with ramucirumab were well-balanced between treatment arms. The EAG therefore considers that it is unlikely that EFS and/or OS efficacy estimates were biased by subsequent treatment with ramucirumab.

Finally, the EAG notes that event rates were relatively low for both EFS (DCO2) and OS (DCO2 and DCO3). As the timing of the trial analyses was based on an appropriate sample size and power calculation, the EAG does not consider that further data should be collected. However, the low event rate does mean that it was not possible for the company to calculate either median EFS time or median OS time for the D-FLOT arm at DCO2, or median OS time for either arm at DCO3.

Other efficacy endpoints

The company presented results from the following other efficacy endpoints in the CS:

- MFS at DCO2: see Table 7 and CS, Table 14 and Figure 10
- DSS at DCO2: see Table 4 and CS, Table 15 and Figure 11
- DFS at DCOS, CS Appendix K.1, Table 37
- surgical outcomes at DCO2: see CS, Table 13
- pathological downstaging at DCO2: see CS, Table 16.

At DCO2, both MFS and DSS results favoured D-FLOT; the reported p-values are nominal only as they are not adjusted for multiplicity (see Table 7). The HR for DFS also favoured D-FLOT (HR=0.70, 95% CI: 0.53 to 0.93); no p-value was provided for this outcome in the Appendices to the CS or the CSR.²⁹ Median DFS was not reached in the D-FLOT arm and was 39.8 months in the FLOT arm.

Surgical outcomes (measured at DCO2) were all well balanced between treatment arms. Surgical outcomes included:

- the percentage of patients who did not attempt surgery (D-FLOT arm, 9.1%; FLOT arm, 9.7%), and reasons for not attempting surgery (including patient decision, unfit for surgery, adverse events, disease progression, death, study discontinuation, investigator decision and other reasons; all were well-balanced between treatment arms)
- the percentage of patients whose surgery was attempted but not completed (D-FLOT arm, [REDACTED]; FLOT arm, [REDACTED]) and reasons for not completing surgery (including peritoneal dissemination, distant metastases and other reasons; all were well-balanced between treatment arms)
- type of surgery (i.e. distal gastrectomy, subtotal gastrectomy, total gastrectomy or gastro-oesophagectomy)
- surgical approach (laparotomy or laparoscopy)
- type of lymphadenectomy performed (D1, D2/D3, or unknown)
- extent of resection (R0 [complete surgical resection], R1 [microscopic residual tumour], R2 [macroscopic residual tumour], or unknown); 377 (91.5%) D-FLOT and 369 (92.3%) FLOT patients' surgery was reported as R0
- the percentage of patients with any surgical delay (D-FLOT arm, 10.1%; FLOT arm, 10.8%), reasons for surgical delay and the duration of delay
- reasons for delaying adjuvant treatment initiation (Cycle 3 Day 1 dose)

Pathological downstaging results (measured at DCO2) were presented for both the ypT (pathological tumour stage after pre-operative therapy) and ypN (pathological lymph node stage after pre-operative therapy) classifications of the TNM staging system. Downstaging refers to a decrease (improvement) in tumour stage following neoadjuvant therapy.

For ypT at surgery:

- a higher proportion of patients in the D-FLOT arm achieved downstaging in comparison to the FLOT arm ([REDACTED] versus [REDACTED], respectively)
- a lower proportion of patients in the D-FLOT arm experienced no change in staging in comparison to the FLOT arm ([REDACTED] versus [REDACTED], respectively)
- similar proportions of patients experienced upstaging between treatment arms (D-FLOT, [REDACTED]; FLOT, [REDACTED]) or were missing staging data (D-FLOT, [REDACTED]; FLOT, [REDACTED]).

For ypN staging at surgery:

- higher proportions of patients in the D-FLOT arm had “downstaged N0” status or “persistent N0” status in comparison to the FLOT arm (downstaged N0, [REDACTED] versus [REDACTED]; persistent N0, [REDACTED] versus [REDACTED], respectively)
- a lower proportion of patients in the D-FLOT arm had “persistent N+ or upstaged N+” status in comparison to the FLOT arm ([REDACTED] versus [REDACTED], respectively)
- similar proportions of patients were missing staging data between treatment arms (D-FLOT, [REDACTED]; FLOT, [REDACTED]).

EAG comment

These outcomes were not specified in the final scope issued by NICE or incorporated in the company’s economic model. However, the company provided detailed rationale for presenting each of these outcomes in the CS. In brief:

- the company presented MFS, DSS and DFS to provide “a multidimensional assessment of efficacy” and “convergent evidence across multiple clinically meaningful outcomes” (CS, p64)
- the company presented surgical outcomes to explore whether treatment with D-FLOT might compromise a patient’s ability to undergo surgery or negatively impact surgery; such an assessment is important as “surgery remains the cornerstone of curative-intent treatment in GOA” (CS, p62)
- the company presented pathological downstaging results to explore how patients’ tumour stages change following neoadjuvant therapy; this endpoint is referred to as “a meaningful indicator of treatment response, reflecting tumour regression even without pCR” (CS, p67).

Clinical advice to the EAG is that MFS is not a particularly informative outcome for this type of cancer, because recurrence at the primary tumour site is just as concerning to clinicians as the occurrence of metastasis. As EFS and DFS capture both local recurrence and systemic spread, these outcomes are more informative than MFS. Clinical advice to the EAG is that the data presented for surgical outcomes are particularly informative and reassuring, as all surgical outcomes were well balanced between treatment arms.

The EAG considers that the pathological downstaging results should be considered exploratory in nature only, as this outcome was not pre-specified in the trial protocol.²³ Finally, the EAG considers that the MFS and DSS results would provide stronger evidence of clinical effectiveness if the method of assessment (investigator-assessment) had been pre-specified.

Finally, as for EFS and OS, event rates were relatively low for MFS and DSS. The low event rates means that it was not possible for the company to calculate median MFS

time for the D-FLOT arm, and it was not possible for the company to calculate median DSS for either treatment arm.

3.3.2 MATTERHORN trial subgroup results

The company presented results from subgroup analyses for EFS at DCO2 (CS, Figure 14) and OS at DCO2 (CS, Figure 15) and DCO3²⁷ for the following baseline characteristics:

- sex (male versus female)
- age at randomisation (<65 years versus ≥65 years)
- geographic region (Asia versus rest of the world)
- clinical lymph node status (positive versus negative)
- PD-L1 expression level (tumour area positivity [TAP] ≥1% versus TAP <1%)
- primary tumour location (gastric versus gastroesophageal junction)
- ECOG performance-status score (0 versus 1).

The company also presented results from subgroup analyses for histologic type (intestinal versus diffuse versus indeterminate) for EFS at DCO2 (CS, Figure 14) and OS at DCO3²⁷ and for microsatellite instability status (high versus not high versus not evaluable/missing) for EFS at DCO2 only (CS, Figure 14).

EAG comment

For EFS at DCO2 and OS at DCO2 and DCO3, the reported HRs numerically favoured the D-FLOT arm in comparison to the FLOT arm for almost all subgroups. The only HR that did not favour the D-FLOT arm was the OS HR reported at DCO3 for patients with negative clinical lymph node status (HR=1.01, 95% CI: 0.67 to 1.51). Clinical advice to the EAG is that there is no biological reason that patients with negative clinical lymph node status would experience a different treatment effect to those with positive clinical lymph node status. The EAG also notes that the 95% CI for this treatment effect is wide and considers that the HR indicating no difference between treatments is likely to be due to sampling variation, rather than a true subgroup effect.

The final scope issued by NICE specified that evidence for subgroups defined by PD-L1 expression status would be considered, if available. Results for PD-L1 expression status subgroups (TAP ≥1% and TAP <1%) reported in the CS were consistent with results for the overall patient population of the MATTERHORN trial, for both EFS and OS (see Table 8). However, for the TAP <1% subgroup results, 95% CIs were wide due to the relatively low number of patients in this subgroup. The EAG highlights that the MATTERHORN trial was not powered to detect subgroup differences between

different PD-L1 expression status groups (or between any other subgroups), and therefore there is insufficient evidence to conclusively determine whether PD-L1 expression status has an important impact on treatment effect.

Table 8 Results of PD-L1 expression status subgroup analyses

Outcome, DCO, subgroup	D-FLOT # events / # total (%)	FLOT # events / # total (%)	HR (95% CI) D-FLOT vs FLOT
EFS, DCO2, TAP $\geq$ 1%	150/426 (35.2)	197/427 (46.1)	0.70 (0.57 to 0.87)
EFS, DCO2, TAP <1%	17/48 (35.4)	21/47 (44.7)	0.77 (0.40 to 1.46)
OS, DCO2, TAP $\geq$ 1%			
OS, DCO2, TAP <1%			
OS, DCO3, TAP $\geq$ 1%	NR	NR	0.79 (0.63 to 0.99)
OS, DCO3, TAP <1%	NR	NR	0.79 (0.41 to 1.50)

CI=confidence interval; DCO=data cut-off; EFS=event-free survival; HR=hazard ratio; NR=not reported; OS=overall survival; PD-L1=programmed death ligand-1; TAP=tumour area positivity

Source: CS, Figure 14 and Figure 15; Tabernero 2025²⁷

Clinical advice to the EAG is that subgroup analyses by PD-L1 TAP score using different cut off values may be informative. The EAG identified subgroup results for EFS from the supplementary appendix³⁰ to the MATTERHORN primary published paper.²⁰ These results show the point estimates favoured D-FLOT versus FLOT regardless of PD-L1 status for patients treated with D-FLOT versus FLOT regardless of PD-L1 expression level, using two alternative cut off values (TAP $\geq$ 5% or TAP <5% and TAP $\geq$ 10% or TAP <10%). The EAG reiterates that the MATTERHORN trial was not powered to detect subgroup differences. Furthermore, results from subgroup analyses that used alternative cut off values for PD-L1 TAP score were not presented for OS.

3.3.3 Patient reported outcomes

The company noted (CS, Section 2.6.7) that patient-reported outcomes (PROs) in the MATTERHORN trial PRO analysis set were assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30), European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Stomach 22 plus item library 38 (EORTC QLQ-STO22+IL38) and European Quality of Life 5-Dimension, 5-Level (EQ-5D-5L) questionnaires. PRO data were reported from DCO2 (December 2024). Results for change from baseline and time to deterioration in EORTC QLQ-C30 and EORTC QLQ-STO22+IL38 were reported in the CS; however, results for EQ-5D-5L were not reported.

Questionnaires were completed at baseline, at each cycle and following the completion of treatment. The company reported (CS, p68) that overall compliance rates for questionnaire completion were >90% in both treatment arms at baseline. Completion rates were reported to be “generally” >80% to the end of the adjuvant period.²¹

Change from baseline in EORTC QLQ-C30 and EORTC QLQ-STO22+IL38

Results for change from baseline scores for EORTC QLQ-C30 and EORTC QLQ-STO22 were reported in the CS (CS, Section 2.6.7 and Appendix K.3). The figures presented (CS, Figure 12 and CS, Appendix K.3, Figures 10 to 24) showed the change in scores at each cycle, Day 30 follow-up, 2-months follow-up, 3-months follow-up and as an average over all visits. An absolute change in score of ≥ 10 points is clinically meaningful.

QLQ-C30

In both arms, a clinically meaningful deterioration from baseline was observed at Cycle 4 and Cycle 5 in the QLQ-C30 score of global health status/QoL followed by a return to levels that were non-clinically meaningfully different compared to baseline in subsequent cycles (CS, Figure 12). There were also clinically meaningful deteriorations in physical functioning between Cycles 4 and 5 (CS, Appendix K.3, Figure 10), and role functioning, fatigue and appetite loss between Cycles 3 and 5 (CS, Appendix K.3, Figures 11 to 13) in both arms. These deteriorations were followed by a return to levels that were non-clinically meaningful compared to baseline in both arms. However, there were no statistically significant or clinically meaningful differences between arms at any time point for any of these scores. The company considered (CS, page 69) that deterioration reflected the impact of surgery and FLOT chemotherapy.

QLQ-STO22+IL38

In both arms, [REDACTED] was reported for the EORTC QLQ-STO22 symptom scales of eating restrictions (Cycles 3 to 5), dry mouth (Cycles 2, 4 and 5), taste (Cycles 2 to 7), hair loss (Cycles 2 to 9), body image (Cycles 2 to 8), and weight loss (Cycles 3 to 5) (CS, Appendix K.3, Figure 17, Figures 19 to 22 and Figure 24). These deteriorations were followed by a return to baseline or to [REDACTED] compared to baseline in both arms. The company considered (CS, p70 and CS, Appendix K.3, p113) that deterioration was “generally considered to be associated with the administration of FLOT chemotherapy”. There were [REDACTED] observed in other domains of the EORTC QLQ-STO22. There were [REDACTED] between arms for any symptom scale of the

EORTC QLQ-STO22+IL38 at all timepoints evaluated during the neoadjuvant, adjuvant and follow-up periods.

Time to deterioration in EORTC QLQ-C30 and EORTC QLQ-STO22+IL38

There was no statistically significant or clinically meaningful difference in the time to deterioration between treatment arms for any of the pre-specified functional domains or symptom scales of the EORTC QLQ-C30 and EORTC QLQ-STO22+IL38 (CS, Figure 13).

EAG comment

The EAG observes that the change from baseline data for all scores show almost identical scores for both treatment arms at each time point (CS, Figure 12 and Appendix K.3, Figures 10 to 24). The EAG considers that, alongside the time to deterioration data showing no statistically significant differences between arms (CS, Figure 13), the PRO results showed D-FLOT did not adversely affect health-related quality of life (HRQoL) (symptoms or functioning) when compared with FLOT.

3.3.4 Safety and tolerability

MATTERHORN trial safety and tolerability assessments included the incidence and severity of adverse effects (AEs), serious AEs and AE-attributable deaths. Laboratory parameters, physiological observations, electrocardiogram (ECG) recordings and treatment exposure were also evaluated.

The company reported (CS, Section 2.11) that all patients had completed the safety follow-up period (≥ 90 days from the last dose of study drug) by DCO2 (December 2024). The SAS included 944 participants who received at least one dose of study treatment (D-FLOT arm, N=475; FLOT arm, N=469).

Treatment exposure

The company (CS, Section 2.11.1) reported treatment exposure to be similar between treatment arms (D-FLOT: 12.7 months; placebo-FLOT: 12.5 months), with the same exposure to durvalumab or placebo, and similar exposure to any FLOT chemotherapy across both study arms. The median number of neoadjuvant treatment cycles was 2.0 for both D-FLOT and placebo-FLOT and the median number of adjuvant treatment cycles was 2.0 for both D-FLOT and placebo-FLOT and 12.0 for both durvalumab monotherapy and placebo. Median duration of exposure to any FLOT component was 3.68 months in both MATTERHORN study arms.

Dose interruptions, delay and reduction were reported in CS Appendix K.4.1, Table 38. Clinical advice to the company (CS, p78) was that dose reductions of FLOT would be preferred in people with AEs affecting tolerability of FLOT, rather than switching to an alternative chemotherapy. AEs leading to dose delays or infusion interruptions of durvalumab or placebo (most commonly neutropenia, decreased neutrophil count, COVID-19) were reported to be ■■■% in the D-FLOT arm versus ■■■% in the FLOT arm. Dose reductions were only permitted for components of FLOT (CS, Appendix K4.1, Table 38).

AEs overview

The company provided an overview of the types of AEs experienced by patients in the MATTERHORN trial (CS, Section 2.11.3 and Appendix K.4.1, Table 39). In summary, similar proportions of patients experienced:

- any AE of any cause: D-FLOT, 99.2%; FLOT, 98.7%
- maximum Grade 3 or 4 AEs of any cause (most commonly neutropenia, decreased neutrophil count, diarrhoea, decreased white blood cell count, anaemia): D-FLOT, 71.6%; FLOT, 71.2%
- maximum Grade 3 or 4 AEs possibly related to any study component: D-FLOT, 59.6%; FLOT, 59.1%
- maximum Grade 3 or 4 AEs possibly related to durvalumab or placebo: D-FLOT, ■■■%; FLOT, ■■■%
- serious AEs (most commonly pneumonia, febrile neutropenia, neutropenia, vomiting): D-FLOT, 48.2%; FLOT, 44.1%
- AEs leading to discontinuation of any study treatment: D-FLOT, 29.9%; FLOT, 22.8%
- deaths from AEs: D-FLOT, 5.1%; FLOT, 4.3%
- deaths from AEs possibly related to durvalumab or placebo: D-FLOT, 0.6%; FLOT, 0.2%
- deaths from AEs possibly related to FLOT: D-FLOT, 0.6%; FLOT, 0.4%.

The company (CS, page 78) suggested FLOT may be a large contributor to the AEs experienced in the neoadjuvant and overall adjuvant periods, since there was a lower proportion of AEs leading to discontinuation and infusion-related reactions in the adjuvant monotherapy period (durvalumab or placebo) compared to the neoadjuvant and overall adjuvant periods that included FLOT. Immune-mediated AEs were more common in the D-FLOT arm (23.2%) in comparison to the FLOT arm (7.2%). These were described (CS, p79) as mostly low grade and manageable and/or reversible with appropriate medical management per standard management guidelines.

Common AEs reported in more than 20% of patients in any trial arm were AEs known to be associated with FLOT (nausea, neutropenia, alopecia, decreased appetite, fatigue, vomiting, anaemia, neutrophil count decreased, peripheral sensory neuropathy) or associated with both durvalumab and FLOT (diarrhoea and abdominal pain) (CS, Section 2.11.4 and Table 19). The company highlighted other AEs that are known to be associated with durvalumab and that occurred with >5% difference between arms (but reported by <20% of patients in either arm) were rash, pruritus and pyrexia and that these were mostly low grade in severity (Grade 1 or 2).

EAG comment

The EAG considers that sufficient detail on AEs has been provided in the CS. The EAG agrees with the company what AE associated with the FLOT components of D-FLOT and FLOT regimes make the most significant contribution to AEs reported overall.

Overall, the EAG agrees with the company that no new safety concerns were identified in the MATTERHORN trial and the nature and severity of AEs reported for the D-FLOT arm during the adjuvant monotherapy period were consistent with the established safety profile of durvalumab monotherapy.

3.4 Critique of studies identified and included in the indirect treatment comparison or multiple treatment comparison

The company considered (CS, Section 2.10) that since the comparative effectiveness of perioperative D-FLOT versus SoC can be assessed based on direct evidence from the MATTERHORN trial, no indirect treatment comparison or multiple treatment comparison was required.

EAG comment

The EAG agrees with the company that an indirect treatment comparison or multiple treatment comparison was not required.

3.5 Critique of the indirect comparison or multiple treatment comparison

No indirect treatment comparison or multiple treatment comparison was conducted as none was required.

3.6 Additional work on clinical effectiveness done by the EAG

In its response to clarification question B1, the company referred to OS data from the FLOT4 trial to validate OS associated with FLOT that was generated from its economic

model (see Section 4.2.2). The FLOT trial was also used to inform some of the information cited in the CS, Section 1.3.

Key FLOT4 trial characteristics and a summary of results for the FLOT arm from the FLOT4 trial are presented alongside those from the MATTERHORN trial in Table 9 and Table 10. In both trials, FLOT comprised 5-fluorouracil 2,600mg/m², leucovorin 200mg/m², oxaliplatin 85mg/m² and docetaxel 50mg/m² (administered as four preoperative cycles followed by four postoperative cycles).

The most notable difference in characteristics between trials related to the location where the carcinomas developed (tumour location). This may have contributed to the differences in the proportions of patients who underwent and completed surgery and achieved R0 as well as differences in the median and time-to-event outcomes observed in the FLOT arms of the trials. Differences in subsequent treatment may have also contributed to differences in median and time-to-event outcomes; information on subsequent treatment was not reported in the FLOT4 trial.

Table 9 Comparison of key characteristics from the FLOT4 and MATTERHORN trials

Characteristic	FLOT4	MATTERHORN
Study type	Phase II/III, 1:1 randomised, multi-centre, open-label, controlled trial conducted in Germany.	Phase III, 1:1 randomised, multi-centre, double-blind, placebo-controlled trial conducted in multiple centres worldwide.
Population	Patients with resectable GOA (GC or GOJC).	Patients with resectable GOA (GC or GOJC).
Number of patients in FLOT arm	n=356	n=474
Median age (range), years	62 (54 to 69)	63 (28 to 83)
Male, n (%)	268 (75.2)	356 (75.1)
ECOG PS <1, n (%)	246 (69.1)	366 (77.2)
Tumour location, n (%)	Siewert type 1: 80 (22.5) Siewert type 2 or 3: 118 (33.1) Stomach: 158 (44.4)	Siewert type 1: 55 (11.6) Siewert type 2 or 3: 103 (21.7) Gastric: 316 (66.7)
Note	The trial authors noted that "Siewert type 1 tumours might not involve the junction and might have been classified as oesophageal adenocarcinomas in other studies."	GOJC includes Siewert type II and Siewert type III tumours (and Siewert type 1 tumours if the patient was intended to be treated in the same way as a patient with a Siewert type II or Siewert type III tumour would be treated).

ECOG PS=Eastern Cooperative Oncology Group Performance Status; FLOT=5-fluorouracil, leucovorin, oxaliplatin and docetaxel; GC=gastric cancer; GOA=gastro-oesophageal adenocarcinoma; GOJC=gastro-oesophageal junction cancer

Source: Primary published papers for FLOT4 trial (Al Batran 2019)⁷ and MATTERHORN trial (Janjigian 2025)²⁰

Table 10 Comparison of key results from the FLOT4 and MATTERHORN trials

Outcome	FLOT4 FLOT arm (n=356)	MATTERHORN FLOT arm (n=474)
Median trial follow-up	43 months	31.5 months (DCO2)
Underwent tumour surgery, n (%)	345 (96.9)	428 (90.3)
Completed tumour surgery, n (%)	336 (94.4)	400 (84.4)
Achieved R0, n (%)	301 (84.6)	369 (92.3)
Median DFS (95% CI), months	30 (CIs not reported)	39.8 (38.7 to NC)
Median EFS (95% CI), months	Not measured (but see Note)	32.8 (27.86 to NC)
Median OS (95% CI), months	50 (38.33 to NC)	32.8 (27.9 to NC)
Note	DFS was defined for the ITT population as time from randomisation to disease progression, relapse, or death, i.e., similar to the definition of EFS in the MATTERHORN trial.	DFS was defined for the R0 population as time from first post-surgery scan until disease recurrence or death due to any cause. EFS was defined for the FAS population as time from randomisation to the first of the following: 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.

CI=confidence interval; DCO= data cut off; DFS=disease-free survival; EFS=event-free survival; FAS=full analysis set; FLOT=5-fluorouracil, leucovorin, oxaliplatin and docetaxel; NC=not calculated; OS=overall survival; R0=complete surgical resection

Source: Primary published papers for FLOT4 trial (Al Batran 2019)⁷ and MATTERHORN trial (Janjigian 2025)²⁰

3.7 Conclusions of the clinical-effectiveness section

The company SLR identified one RCT as relevant to the decision problem – the MATTERHORN trial which was well designed and of good overall quality. As the MATTERHORN trial was the only RCT relevant to the decision problem, it was not necessary for the company to conduct any indirect comparisons.

The MATTERHORN trial investigated an intervention (D-FLOT), comparator (FLOT) and population (patients with resectable GOA) relevant to the decision problem. It recruited 948 people and follow-up is ongoing.

The MATTERHORN trial was powered for its primary endpoint (EFS). For secondary outcomes, a multiple testing procedure was used to control the overall type 1 error. There was a statistically significant reduction in EFS at the final EFS analysis (DCO2)

and statistically significant improvement in OS in the final OS analysis (DCO3) among patients treated with D-FLOT compared with FLOT.

Subgroup analyses conducted included those according to PD-L1 expression status, a subgroup analysis specified in the final scope ("if evidence allows"), issued by NICE. Results of the subgroup analyses for EFS and OS were consistent with the overall trial results, but conclusions on the impact of PD-L1 status on treatment effect cannot be made as the subgroup analyses were not sufficiently powered (especially for people in the PD-L1 TAP <1% subgroup who made up only 10% of the overall trial population).

Safety profiles were similar for the D-FLOT and FLOT arms. Adverse effects were likely related to the FLOT therapy common to both treatment groups.

4 COST-EFFECTIVENESS

This section presents a summary and critique of the cost-effectiveness evidence included in the company's submission. Section 4.1 focuses on the company's review of the cost-effectiveness evidence and Section 4.2 covers the company's economic evaluation. The two key components of the cost-effectiveness evidence presented in the CS are (i) a SLR of the cost-effectiveness literature and (ii) a report of the company economic evaluation. The company has provided an electronic copy of their economic model, developed in Microsoft® Excel.

4.1 Critique of the review of cost-effectiveness evidence

The company conducted an SLR to identify and appraise evidence relevant to the decision problem on:

- cost-effectiveness (CS, Appendix E)
- HRQoL utilities (CS, Appendix F)
- healthcare resource use (HCRU) and cost data (CS, Appendix G).

The company selected and extracted data from a total of 83 publications (economic evaluations [N=16], HCRU and costs [N=24] and HRQoL [N=46]). No economic evaluations relevant to the decision problem were identified. None of the extracted studies were used directly within the company model. The SLR methodology for the economic SLR was in line with the clinical effectiveness SLR with EAG comments contained within Table 3 also relevant to this review. Details of the company's SLR methods and results are presented in the CS (Appendix E for cost-effectiveness, Appendix F for HRQoL and Appendix G for cost and health care resource). The EAG appraisal of the SLR methods for the economics review is shown in Table 11.

Table 11 EAG appraisal of the company's SLR methods (economics review)

Review process	EAG response	EAG comment
Was the review question clearly defined in terms of population, interventions, comparators, outcomes and study designs?	Yes	See CS, Section 3.1 and Appendix E.1.2, Table 16
Were appropriate sources searched?	Yes	See CS, Appendix E.1.1
Was the timespan of the searches appropriate?	Yes	See CS, Appendix E.1.1.1
Were appropriate search terms used?	Yes	See CS, Appendix E.1.1 (Tables 12 to 15)
Were the eligibility criteria appropriate to the decision problem?	Partly	See CS, Appendix E.1.2 (Table 16 and page 57) Four deprioritisation criteria were applied to restrict the number of papers to be data extracted. Criterion no.4 meant that the company only extracted data from studies with HRQoL measured using the EQ-5D or EORTC-QLQ instruments. Given the uncertainty in the utility estimates for the recurred disease health state, this restriction may have excluded potential sources of utility estimates (Section 4.2.4).
Was study selection applied by two or more reviewers independently?	Yes,	See CS, Appendix E.1.2 For the initial search, two reviewers assessed the studies for inclusion independently. For the search update, study selection was conducted by AI plus one reviewer (with a second reviewer to deal with discrepancies).
Was data extracted by two or more reviewers independently?	Partly	See CS, Appendix E.1.2 The original search was extracted by one reviewer and checked by a second reviewer. AI was used alongside human reviewers to extract data from studies identified by the search update.
Were appropriate criteria used to assess the risk of bias and/or quality of the primary studies?	Partly	See CS, Appendix E.1.2 The company used the Drummond quality checklist for included economic evaluations. No quality assessment was conducted on the quality of life or costs and resource use studies.
Was the quality assessment conducted by two or more reviewers independently?	No	See CS, Appendix E.1.2 AI was used to assist with the quality assessment alongside a human reviewer.
Were attempts to synthesise evidence appropriate?	Yes	See CS, Appendix E Table 19, Appendix F Tables 22, 23 and 24, Appendix G Tables 25-29 The company summarised economic data in tables and narratively.

AI=artificial intelligence; EORTC-QLQ=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D=European Quality of Life 5-Dimension; HRQoL=health-related quality of life

4.2 Critique of the submitted economic evaluation

4.2.1 NICE reference case checklist

Table 12 NICE reference case checklist

Element of health technology assessment	Reference case	EAG comment on company's submission
Perspective on outcomes	All health effects, whether for patients or, when relevant, carers	QALYs were appropriately used to reflect patient health benefits
Perspective on costs	NHS and PSS	The analysis adopted the NHS and PSS perspective, which is appropriate for the decision problem
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	The company produced a cost-utility analysis
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	A lifetime horizon was used (■■■■ years) which is considered long enough to capture all relevant costs and outcomes for the population included in this decision problem
Synthesis of evidence on health effects	Based on systematic review	The HRQoL systematic review only included studies that used the EQ-5D or the EORTC-QLQ. This may have reduced the options for utility values from additional studies using alternative tools or methodology within the NICE Reference Case framework that were not included.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	Health effects were expressed in QALYs with utility values from studies that used the EQ-5D
Source of data for measurement of health-related quality of life	Reported directly by patients, carers or both	HRQoL was reported directly by patients
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	HRQoL was valued using UK population valuation sets for the EQ-5D
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the people having the health benefit, except in specific circumstances	Additional QALYs had equal weight for all patients
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be	Costs were derived from UK based sources

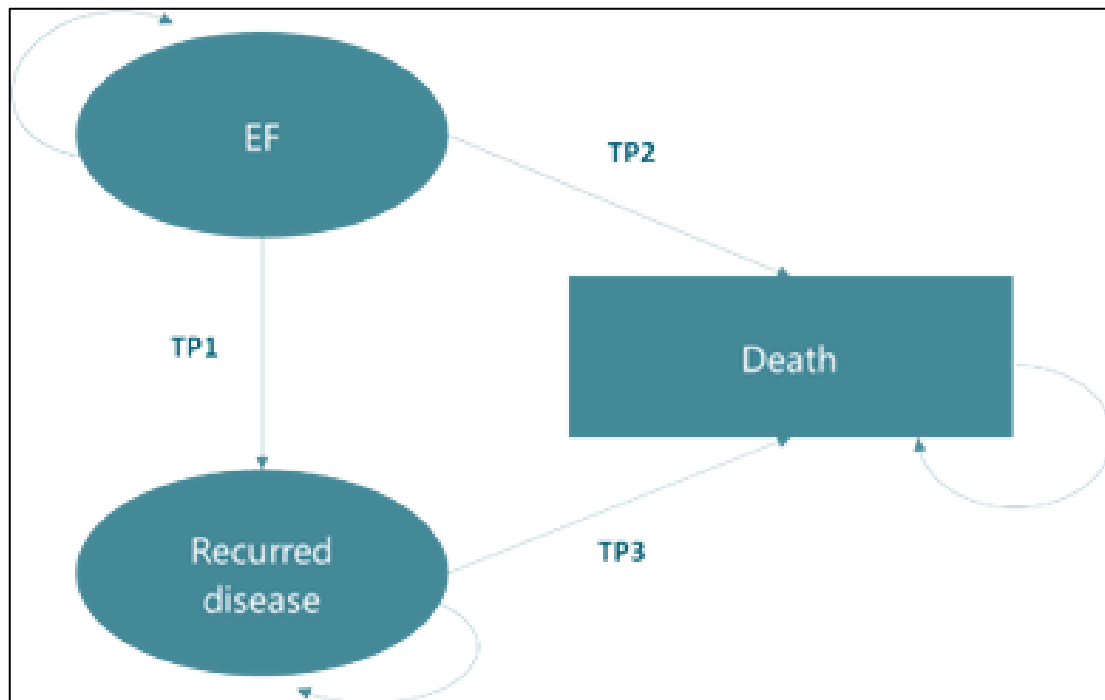
Element of health technology assessment	Reference case	EAG comment on company's submission
	valued using the prices relevant to the NHS and PSS	
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Discounting of 3.5% per annum was applied to costs and benefits

EORTC-QLQ=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D=European Quality of Life 5-Dimension; HRQoL=health-related quality of life; NHS=national health service; PSS=personal social services; QALYs=quality-adjusted life years

4.2.2 Model structure

The company developed a *de novo* semi-Markov model with three health states to evaluate the cost-effectiveness of perioperative D-FLOT to treat adult patients with resectable GOA. Patients enter the model in the event-free (EF) health state. In each model cycle patients may remain in this state or transition to the recurred disease (RD) health state or death. Patients in the recurred disease health state remain in this health state or transition to death but cannot return to the EF health state. The transition probabilities (TP1, TP2, TP3) are based on parametric survival curves fitted to data from the MATTERHORN trial.

The economic model cycle length is 4 weeks and includes a half-cycle correction. The time horizon is ■■■ years (lifetime). The economic model perspective is the NHS and personal social services (PSS).



EF=event-free; TP=transition probability.
Source: CS, Figure 16

Figure 1 Economic model structure

EAG comment

The EAG considers that a partitioned survival model (PSM) would have been a preferable model structure for three reasons.

Firstly, the difference in OS is the key determinant of the difference in QALYs between D-FLOT and FLOT. OS is only modelled indirectly as a surrogate outcome using the company's semi-Markov approach. This is problematic if the OS generated by the model differs from that observed in the MATTERHORN trial, as OS in the model can only be modified by changing other modelled outcomes. A PSM would have allowed direct extrapolation of OS.

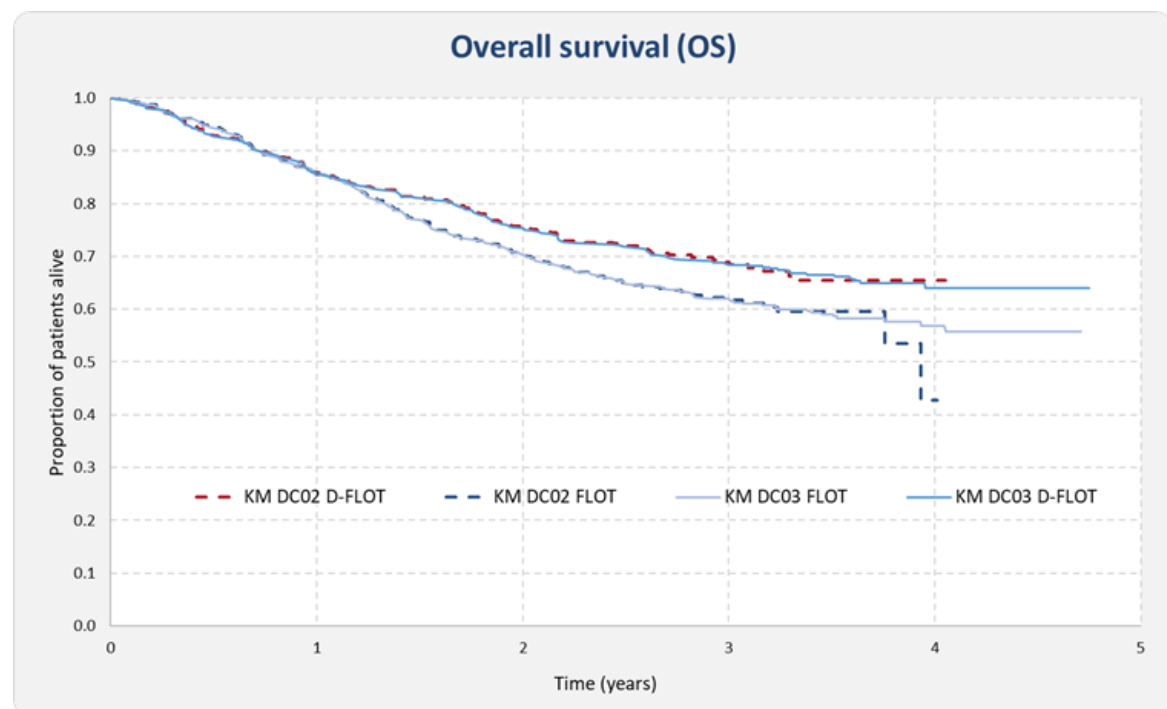
The use of a semi-Markov model structure also meant that the company had to split EFS and OS data from the MATTERHORN trial into three outcomes to populate the model; less data were therefore available to estimate distributions than if a PSM with EFS and OS had been used.

Finally, the semi-Markov model has the implicit assumption that mortality risk after recurrence is independent of how long a person remains recurrence free. The EAG considers that it is likely that patients with recurrence shortly after commencing D-FLOT or FLOT will face a different mortality hazard profile (more likely to die more quickly) compared to patients with disease recurrence several years after resection

followed by adjuvant treatment. Data currently available from the MATTERHORN trial on survival after recurrence may therefore be biased towards patients in the trial who will die more rapidly at progression; using these data means that the model will be systematically underestimating survival for patients at recurrence and OS in the model.

At clarification (question B1), the EAG asked the company to compare OS from the company model to OS from the MATTERHORN trial DCO2 and DCO3 data cuts. If trial and model OS outcomes did not align, the EAG requested that either alternative distributions for TP1, TP2 or TP3 were chosen, such that OS more closely matched MATTERHORN trial OS or, if that could not be done, to produce a PSM instead.

In response to clarification question B1, the company stated that they considered DCO2 and DCO3 OS to be consistent, providing an OS K-M chart to support this position (Figure 2).



D=durvalumab; DCO=data cut off; FLOT=5-fluorouracil, leucovorin, oxaliplatin and docetaxel; OS=overall survival.
Source: Company response to clarification question, Figure 8

Figure 2 Kaplan-Meier plot of OS DCO2 vs DCO3

The company also provided a table summarising OS over five years from the model and MATTERHORN DCO2 and DCO3 trial, as well as for FLOT arm of the FLOT4 trial (Table 13).

Table 13 Modelled OS versus MATTERHORN trial OS and FLOT4 trial FLOT arm OS

	2-year	3-year	5-year
D-FLOT			
Modelled, %	■	■	■
MATTERHORN DCO2, % (95% CI)	75.7 ■	■	NR
MATTERHORN DCO3, % (95% CI)	75.5 ■	■	NR
FLOT			
Modelled, %	■	■	■
MATTERHORN DCO2, % (95% CI)	70.4 ■	■	NR
MATTERHORN DCO3, % (95% CI)	70.4 ■	■	NR
FLOT4, % (95% CI)	68 (63, 73)	57 (52, 62)	45.0 (38, 51)

CI=confidence interval; D=durvalumab; DCO=data cut-off; FLOT=5-fluorouracil, leucovorin, oxaliplatin and docetaxel; NR=not reported; OS=overall survival

Source: Company response to clarification question B1, Table 3

In response to clarification question B1, the company considered that, based on the data presented in Table 13, OS for patients treated with FLOT closely aligned with trial OS (MATTERHORN and FLOT4) and clinical expectations. For patients treated with D-FLOT, the company stated that survival aligned with MATTERHORN trial OS.

The EAG does not consider that a naive comparison of MATTERHORN trial and FLOT4 trial OS is informative due to differences in patient characteristics between the trials highlighted in Section 3.6.1.

As shown in Table 14, whilst at two years the difference between modelled survival and that seen in the MATTERHORN trial favours FLOT, by three years this has changed such that the absolute differences in OS between modelled and observed are ■ for D FLOT and -3.6% for FLOT, leading to a ■ relative modelled difference between patients treated with D-FLOT and FLOT compared with the MATTERHORN trial.

Table 14 Difference in modelled and MATTERHORN trial D-FLOT and FLOT OS

	2-year	3-year	5-year
D-FLOT			
Modelled, %	■	■	■
MATTERHORN DCO3, % (95% CI)	75.5 ■	■	NR
Absolute difference	-1.0%	■	-
FLOT			
Modelled, %	■	■	■
MATTERHORN DCO3, % (95% CI)	70.4 ■	■	NR
Absolute difference	-0.5%	-3.6%	45.0 (38, 51)
D-FLOT minus FLOT			
Modelled	■	■	■
MATTERHORN DCO3, %	■	■	-
Absolute difference	■	■	
Relative difference	■	■	

CI=confidence interval; D=durvalumab; FLOT=5-fluorouracil, leucovorin, oxaliplatin and docetaxel; NR=not reported; OS=overall survival

Source: response to clarification question B1, Table 3

The company model base case estimates a ■ (discounted) life year gain for patients treated with D-FLOT compared to patients treated with FLOT but 95% of this gain comes after three years. That the OS gain for D-FLOT at three years is already modelled to be ■ higher relative to FLOT is therefore concerning (absolute difference ■). As the modelled and MATTERHORN trial OS relative difference between D-FLOT and FLOT grew substantially between years two and three in the model (from ■) the extrapolations beyond three years may be even more biased towards D-FLOT than the difference at three years suggests. As discussed in section 4.2.3, distributions cannot be chosen for TP1, TP2 or TP3 that make OS more realistic without making these outcomes to be less in line with MATTERHORN trial outcomes.

The EAG considers that a PSM would be a better model structure to use. However, in response to clarification question B1, the company stated that a PSM was not suitable for patients with resectable GOA because of the absence of a structural link between EFS and OS and recurred disease results in poorer survival. The company also stated that a PSM would not allow modelling of 'cure' at five years. The EAG does not consider either of these statements to be accurate because:

- regardless of the stage of cancer or treatment options, PSMs with OS and PFS (or EFS) have been used for decision making with the OS curve implicitly including the changing mortality risk facing the proportion of patients with

progressed disease at any point in time; if the company argument holds, then all PSM models are unsuitable for decision making for cancer treatments.

- PSM models can also (and have been) used to model 'cure' in the same way the company has modelled 'cure' in their model – by adjusting the risk of progression to zero and/or by setting mortality risk to zero at a specific time point.

Finally, the company also stated in their response to clarification question B1 that the semi-Markov modelling approach has been used in previous appraisals for the neoadjuvant/adjuvant and perioperative GOA. However, an argument for precedent is not sufficient if the modelling approach used in previous submissions fails to produce robust cost-effectiveness estimates for a current submission.

In summary, the EAG considers that there is no justification for the company having not produced a PSM and that the bias in the OS in favour of D-FLOT produced by the company model cannot be addressed using the current structure.

Population

The modelled patient population is adult patients with resectable GOA. This mirrors the population in the MATTERHORN trial (Table 15).

Table 15 Economic model baseline characteristics (MATTERHORN trial)

Economic model parameter	Mean Value (Cycle 0)	Source
Mean age at baseline, years	■	MATTERHORN trial FAS
Proportion of male patients, %	71.9	
Mean body weight, kg	■	
Mean height, cm	■	
Mean BSA, m ²	■	

BSA=body surface area; FAS=full analysis set
Source: CS, Table 14

EAG comment

The EAG considers the modelled population to appropriately reflect the patients in the MATTERHORN trial.

Interventions and comparators

The economic model compares the cost-effectiveness of D-FLOT as neoadjuvant and adjuvant treatment, followed by adjuvant durvalumab monotherapy versus FLOT as perioperative treatment.

Durvalumab is administered as a fixed-dose of 1500mg as an intravenous (IV) infusion in four-week cycles with FLOT for up to two cycles in the neoadjuvant period and two cycles in the adjuvant period. Monotherapy with durvalumab is continued every four weeks for up to 10 cycles.

FLOT chemotherapy is administered as an IV infusion on day one and day 15 in four-week cycles for two cycles in the neoadjuvant period and two cycles in the adjuvant period (up to a maximum of four neoadjuvant cycles).

EAG comment

The EAG considers the company's approach to include only FLOT as a relevant comparator to be reflective of NHS clinical practice. Further details and EAG comment on nivolumab as a comparator in this patient group are provided in Section 3.2.

4.2.3 Treatment effectiveness and extrapolation

The transition between EF and RD (TP1) is called the time to first recurrence (TFR) and is estimated based on the primary outcome data from the MATTERHORN trial, EFS (as assessed by BICR). The definition of TFR is not the same as EFS in the MATTERHORN trial, but rather the time from randomisation until disease recurrence or progression with censoring for deaths that occur before recurrence or progression. The transition between EF and Death (TP2) is derived from time to death as first event data from the MATTERHORN trial. Post-progression survival (TP3) was based on data from the MATTERHORN trial on time from first recurrence or progression to death.

Patients who remain in the EF health state after five years (60 months) are assumed to be cured within the health economic model. The company stated that this is supported by assumptions in the appraisal of nivolumab for adjuvant treatment of resected oesophageal or GOJC (TA746)¹⁷ and the EFS results for both the D-FLOT and FLOT arms of the MATTERHORN trial which demonstrate signs of a plateau at around ■ months.

After 60 model cycles, the risk of death is equal to that of the general population, there is no risk of transition to recurrent disease and there are no costs attributed to monitoring for progression or any other healthcare resource use.

The company used parametric survival models to estimate the transition probabilities between the three health states (EF, RD & death). The methodology used is the same for each transition probability and treatment arm; exponential, Weibull, Gompertz, log-normal, log-logistic, generalised gamma, and gamma parametric survival model were

fitted to the K-M data from the MATTERHORN trial and the proportional hazards assumption was tested between treatment arms and diagnostic testing conducted to assess the suitability of proportional hazard or accelerated failure time models.

The parametric survival curves were chosen based on their fit to the K-M data from the MATTERHORN trial. Akaike Information Criteria (AIC) and Bayesian Information Criterion (BIC) were used to measure the statistical goodness of fit with visual inspection of both the fit to the trial data and the hazard functions also conducted. Clinical experts examined the plausibility of the extrapolations beyond the observed data into the long-term. Proportional hazard or accelerated failure time models were considered.

The company used the same type of parametric model for both treatment arms. For TP1, generalised gamma distributions were selected. For TP2, Gompertz distributions were selected. The OS of the patients in each treatment arm of the model is a function of the transitions between the three health states.

The mortality rate of the general population is applied within the model to TP2 and TP3 to ensure that the mortality rate of the modelled survival curves does not fall below that of the general population using UK life tables.³¹

EAG comment

The EAG considers the cure assumption in the model to be uncertain. The EAG considers the assumption that patients who remain EF after five years will have a mortality rate equal to that of the general population beyond this point uncertain. This results in 'kinks' in the mortality hazards for both model arms and lacks clinical validity. Whilst at five years patients who are EF may no longer require routine monitoring, it is a significant assumption that patients who have had GOJC, resection surgery and chemotherapy (with or without immunotherapy) will have no excess mortality.

The EAG is satisfied that the company followed appropriate methodology in the selection of the parametric distributions used to estimate T1, T2 and T3. However, the EAG cannot select distributions for T1, T2 or T3 in isolation or in combination that produce OS projections that are closer to MATTERHORN trial DCO3 estimates either without making the OS gap between D-FLOT and FLOT wider than in the company base case (which is already overestimated) or moving estimates of EFS (TP1+TP2) further from EFS seen in the MATTERHORN trial.

Further, the EAG notes the [REDACTED] in the D-FLOT arm of the MATTERHORN trial when compared to the FLOT arm. It is unclear what clinical justification there is for this difference, and none was offered by the company in the CS. It is unclear to the EAG whether this is a statistical artefact of extrapolating a small number of events, in which case, no difference should have been modelled (although this would expand the OS gap between D-FLOT and FLOT) or whether there is a clear clinical justification for modelling a difference. Potentially, it could reflect the use of nivolumab in the FLOT arm being higher than in the D-FLOT arm of the MATTERHORN trial ([REDACTED]) which could also reflect a difference in HER2 and/or PD-L1 status on progression.

4.2.4 Health-related quality of life

In the cost-effectiveness model the utility value for the EF health state was based on the MATTERHORN trial EQ-5D-5L data but, as this value exceeded that of the age-adjusted general population value, in the economic model, the utility values are capped to the values of the general population.

The company states that the utility value for the progressed disease health state (0.747) is taken from the appraisal of nivolumab for adjuvant treatment of resected OC or GOJC (TA746).¹⁷ The original source of this value is unclear, as the committee papers for TA746 state the value was taken from nivolumab for previously treated unresectable advanced or recurrent OC (TA707),³² however the utility values used within this appraisal are redacted in the committee papers.

EAG comment

Clinical advice to the EAG is that the utility value for the progressed disease health state (0.747) does not represent the HRQoL experienced by patients. At the clarification stage, the EAG asked the company to justify that the utility value chosen reflects the HRQoL and symptom burden of people with post-surgical progression of GOA. In the CS (Section 1.3.4), the company discussed a study³³ in adults with recurrent GC undergoing palliative chemotherapy.³³ The study estimates utility values with a standard gamble approach. As part of their response to clarification question B2, the company conducted a scenario analysis using the value from this study (0.399) for the progressed disease health state. This change impacts the FLOT arm more than the D-FLOT arm as there are more patients with recurrent disease in the FLOT arm than in the D-FLOT arm. This, in turn, reduces the ICER. The results of the scenario

analysis presented by the company at the clarification stage are presented in Table 19.

Resources and costs

Drug acquisition costs

The dose per administration, the number of administrations, treatment completion rates and the relative dose intensity are taken from the MATTERHORN trial data. CS, Figure 32 and Table 42 show the estimates used to calculate the drug acquisition costs.

Subsequent treatments

The subsequent treatments modelled are based on the treatments received and the duration of use of these trials, by patients in the MATTERHORN trial. One treatment, ramucirumab is not recommended by NICE nor used in NHS clinical practice. Irinotecan is used in the NHS and therefore the proportion of patients who received ramucirumab in the clinical trial is replaced by irinotecan within the resource use estimates for subsequent treatments. The treatments received upon progression are presented in CS, Table 45.

Drug administration costs

An administration cost for all IV drug treatments is included in the first cycle, with different administration costs based on whether the chemotherapy regime was simple or complex, and different administration cost for subsequent treatment cycles (CS, Table 46), in line with National Cost Collection.³⁴ Only one administration cost was applied to regimens which include multiple IV treatments administered at the same time. Oral therapy administration costs were zero for all model cycles.

Surgery costs

The cost of surgery is applied to people in the EF health state with the cost obtained from National Cost Collection³⁴ costs and the proportion of the people in each arm of the MATTERHORN trial who had surgery after neoadjuvant treatment (CS, Table 47).

Healthcare resource use (HCRU)

The health state resource use estimates were based on a previous STA (TA746)¹⁷ for adjuvant treatment of resected oesophageal or GOJC). The resource use and unit costs are shown in CS, Tables 48 and 49. The company changed one assumption from TA746¹⁷ which is to have the same frequency of oncologists visits for both EF and RD health states.

Terminal care costs

A one-off terminal care cost is applied to each death in the model (CS, Table 51).

AE management costs

A one-off cost per AE event is included in the first model cycle. The mean cost of each AE event is given in Table 53 of the CS.

EAG comment

Clinical advice to the EAG is that the frequency of scans in the MATTERHORN trial and used in the EF health state in the economic model does not reflect UK clinical practice, in which patients are to seek further advice from a healthcare provider if their symptoms recur. The impact of this is unknown as it may impact EFS and OS.

Clinical advice to the EAG is that the replacement of costs of ramucirumab with irinotecan in the subsequent therapy costs is an appropriate reflection of NHS clinical practice. This assumes that all other outcomes (EFS, OS) would not change because of receiving an alternative subsequent therapy.

Clinical advice to the EAG is that there may be a period in which a patient who received durvalumab cannot be prescribed another immunotherapy but, at this time, there is no set rule as to how long that period should be.

It is unclear to the EAG why the subsequent therapies received for patients treated with D-FLOT would be different to those for patients treated with FLOT when based on the MATTERHORN trial patients and clinicians were blinded to adjuvant therapy

The EAG is satisfied with how the company has calculated time on treatment for D-FLOT and FLOT, the administration costs of durvalumab, FLOT and the subsequent therapies within the economic model.

The company base case includes vial sharing of IV chemotherapy. Clinical advice to the EAG is that vial sharing is not consistently practiced in the NHS and so the EAG considers it should not be included in the base case.

5 COST EFFECTIVENESS RESULTS

Section 5.1 summarises the company's cost effectiveness results, section 5.2 presents the EAG's additional work and preferred assumptions, and section 5.3 explores decision modifiers including the company's and EAG's preferred QALY weighting for severity.

5.1 Company's cost effectiveness results

5.1.1 Company's base case

Deterministic base-case results from the company economic model are presented in Table 16 and probabilistic results are presented in Table 17. A disease severity modifier of 1.0 was applied by the company. All results are shown with the commercial access agreement (CAA) price for durvalumab and the list price for all other treatments. Results are taken from the economic model presented with the CS.

Table 16 Company's deterministic base-case cost effectiveness results without severity weighting

	Total costs	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Perioperative FLOT chemotherapy	■	■	=	=	=
Perioperative D-FLOT	■	■	■	■	£12,416

The company considers a disease severity modifier of 1.0 was appropriate.
D-FLOT=durvalumab plus FLOT; FLOT=fluorouracil, leucovorin, oxaliplatin and docetaxel; ICER=incremental cost-effectiveness ratio; QALYs=quality-adjusted life years
Source: CS, Table 57

Table 17 Company's probabilistic base-case cost effectiveness results without severity weighting

	Total costs	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Perioperative FLOT chemotherapy	■	■	=	=	=
Perioperative D-FLOT	■	■	■	■	£12,508

The company considered a disease severity modifier of 1.0 was appropriate.
D-FLOT=durvalumab plus FLOT; FLOT=fluorouracil, leucovorin, oxaliplatin and docetaxel; ICER=incremental cost-effectiveness ratio; QALYs=quality-adjusted life years
Source: CS, Table 56

Company's sensitivity and scenario analyses

Deterministic sensitivity analyses

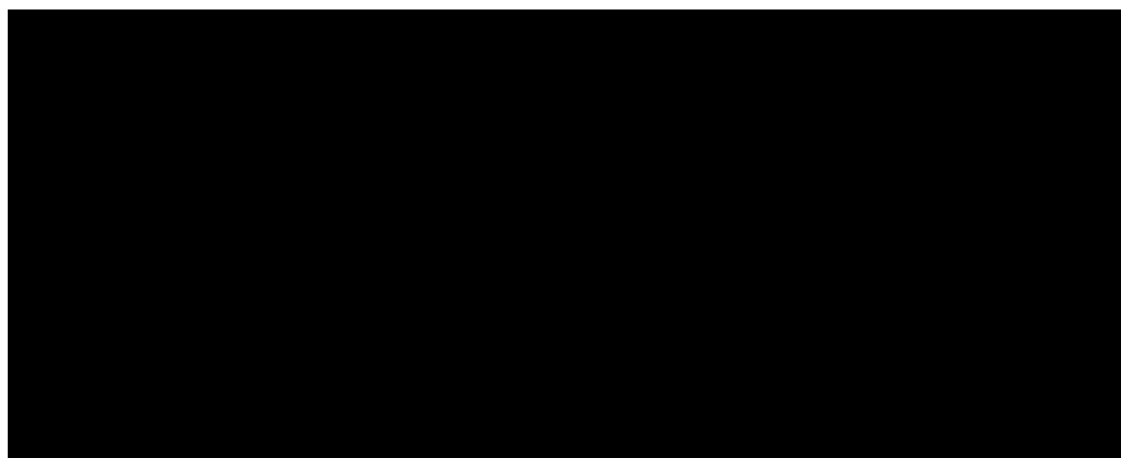
The company undertook a deterministic one-way sensitivity analysis (OWSA) by varying individual parameters. The top ten parameters with the biggest individual impact on the ICER are shown in Table 18 and The company considered a disease severity modifier of 1.0 is appropriate

Figure 3. Based on the results of the OWSA, the economic model was most sensitive to the discount rate for QALYs, the percentage of people who were able to undergo surgery in both arms and the age-related utility value.

Table 18 One-way sensitivity analysis results

Name [Applicable Arm]	Lower ICER	Upper ICER	Difference
Discount rate - health	■	■	■
Utility – base	■	■	■
Drug cost - Surgery: % surgery - Durvalumab arm	■	■	■
Drug cost - Surgery: % surgery - Perioperative FLOT chemotherapy	■	■	■
Completion rates (all): Perioperative durvalumab + FLOT - Durvalumab component	■	■	■
RD - Perioperative FLOT chemotherapy arm Nivolumab proportion on treatment	■	■	■
RD - Perioperative FLOT chemotherapy arm Oxaliplatin proportion on treatment	■	■	■
RD - Perioperative FLOT chemotherapy arm 5-FU proportion on treatment	■	■	■
Patients' age at baseline (mean)	■	■	■
RD - Durvalumab arm Nivolumab proportion on treatment	■	■	■

The company considered a disease severity modifier of 1.0 is appropriate
 FLOT=fluorouracil, leucovorin, oxaliplatin and docetaxel; 5-FU=5-fluorouracil; RD=recurred disease.
 Source: Company economic model



The company considered a disease severity modifier of 1.0 is appropriate

Figure 3 Company base case one-way sensitivity analysis tornado diagram

Source: CS, Figure 36

Durvalumab in combination for neoadjuvant and adjuvant treatment of resectable gastric and GOA [ID6374]

Scenario analyses

The company carried out 10 scenario analyses (Table 19). Most of the scenarios made minimal difference to the ICER, with the biggest impact being if the exponential distribution was used to model TP3 (death following recurrence). As part of their response to clarification question B2, the company presented an additional scenario using a utility value of 0.399 for RD. The results of this scenario are presented in Table 19.

Table 19 Company' deterministic scenario analyses without severity weighting

Scenario	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Base case	██████	███	£12,416
1. SMR of 1.1	██████	███	£12,725
2. No cure assumption	██████	███	£11,182
3. Use log-normal distribution for TP1	██████	███	£11,769
4. Use generalised gamma distribution for TP2	██████	███	£13,742
5. Use exponential distribution for TP3	██████	███	£9,310
6. All subsequent treatments included, regardless of whether they were received before or after progression	██████	███	£12,766
7. UK general population utility cap excluded (EF utility value: █████)	██████	███	£12,453
8. RD utility value set to █████, based on the data from MATTERHORN	██████	███	£12,497
9. Age-adjusted utility decrements excluded	██████	███	£11,678
10. Vial sharing excluded	██████	███	£12,183
11. 30-year time horizon	██████	███	£12,610
12. Annual discount rate of 1.5%	██████	███	£9,657
13. RD utility value of 0.399*	██████	███	£11,629

EF=event-free; ICER=incremental cost effectiveness ratio; QALYs=quality-adjusted life years; RD=recurred disease; SMR=standardised mortality ratio; TP1=transition probability 1; TP2=transition probability 2; TP3=transition probability 3

The company considers a disease severity modifier of 1.0 is appropriate.

* Additional scenario presented in the clarification response

Source: CS, Table 59; response to clarification question B2, Table 4

5.2 EAG's additional analyses

5.2.1 Model validation and face validity check

The EAG conducted model validation and verification in the following areas:

- cross-checking of parameter values against their original data sources, where data were available
- assessment of consistency between the executable model, the descriptions provided in the CS, and the company's clarification response
- cell-by-cell checks to ensure the accuracy and integrity of model programming
- assessment of whether the model outputs were consistent with the model inputs and key outcomes from the trials and what clinical expert advice to the EAG would expect based upon outcomes from the MATTERHORN trial
- reproduction of the base-case results, probabilistic sensitivity analysis (PSA), deterministic sensitivity analyses (DSAs), and scenario analyses presented in the CS using the company's executable model.

The EAG is satisfied that, following these checks, the economic model results accurately represent the assumptions and parameter values specified by the company in the CS and/or at clarification.

5.2.2 EAG's exploratory analyses using company's base case

The EAG has not undertaken any exploratory analyses as given the OS bias in favour of D-FLOT that cannot be rectified in the current model structure (Section 4.2.2), the magnitude and potentially the direction of any analyses may be misleading. However, the exploratory analyses that the EAG would wish to undertake would be limited to a lower utility rate for progressed disease.

5.2.3 EAG's preferred assumptions

The EAG's preferred assumption would be to remove the cure assumption at five years in terms of its impact on OS. As was the case with the exploratory analysis (Section 5.2.2), the EAG has not presented an analysis with the cure assumption removed as it would be potentially misleading given the current overestimate of OS benefit in the model for D-FLOT versus FLOT (Section 4.2.2).

5.3 Decision modifiers

5.3.1 QALY weighting for severity

The company did not consider that a severity modifier should be applied. The EAG agrees a disease severity modifier of 1.0 is appropriate.

5.3.2 *Uncaptured benefits*

The company highlighted several benefits of treating the target population with durvalumab that they considered were not captured in the cost-effectiveness analysis (CS, Section 5.3.2):

- HRQoL burden associated with disease progression and metastatic GOA may be greater than used within the base case of the company model. If this were the case any improvement in the rate of recurrence would have a larger impact on HRQoL and thus increase the number of QALYs gained and reduce the ICER.
- the value of hope of a novel treatment into the pathway for patients with resectable GOA is not accounted for within the company economic model as health state utility values are independent of treatment.
- the caregiver burden with GOA is significant, particularly whilst patients are undergoing intensive treatment and for caregivers of patients with advanced disease.

EAG comment

The EAG agrees that quality of life in the recurred disease state is overestimated. Any impact of hope on a patients' quality of life would presumably have been captured in the MATTERHORN trial. Caregiver burden is an important consideration in economic analysis but without any data on this for patients with GOA and the impact D-FLOT has on this burden, it is not possible to comment on how important a factor it is to the overall cost-effectiveness assessment of D-FLOT.

5.3.3 *Health inequalities*

The company has presented information (CS, Section 1.4, see also EAG report Section 2.4) to suggest that GOA tends to disproportionately impact people experiencing socioeconomic deprivation. This is because environmental factors that increase the risk of developing GOA, such as smoking, high salt diet, being overweight and having a high alcohol intake, occur at a higher rate in people experiencing socioeconomic deprivation.

EAG comment

The EAG considers the evidence presented by the company supports a conclusion that differing GOA disproportionately affects people living in areas of higher deprivation and so an effective treatment for GOA may reduce health inequalities.

5.4 Confidential comparator and subsequent treatment prices

A confidential appendix has been produced by the EAG using confidential prices for the following treatments:

- nivolumab
- pembrolizumab
- trastuzumab

The confidential appendix includes the company deterministic base-case and probabilistic base-case cost-effectiveness results using the confidential prices for the above drugs has been produced by the EAG.

5.5 Conclusions of the cost-effectiveness section

The evidence from the MATTERHORN trial clearly points to D-FLOT producing a survival gain over FLOT. However, the [REDACTED] difference in OS at three years observed in the MATTERHORN trial for patients treated with D-FLOT over FLOT has been extrapolated in the company model into a [REDACTED] (undiscounted) life year gain with >95% of this gain coming via model projections after three years. Unfortunately, this extrapolation is based on OS estimates from the model that are biased in favour of D-FLOT when compared to the OS outcomes from the MATTERHORN trial. The model structure chosen means that model inputs cannot be changed without making the OS bias worse or without introducing biases in other outcomes. Other EAG modelling concerns that have been identified within this report are relatively minor and are likely to improve the cost-effectiveness of D-FLOT, but without the OS being generated by the model being more plausible, it is not possible to robustly explore the magnitude of making any changes to address these concerns. This could be rectified by producing a PSM.

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7 APPENDIX

7.1 EAG appraisal of the company's systematic review methods

Table 20 expands on Table 2 by presenting further information on the EAG appraisal of the company SLR and use of AI tools.

Table 20 EAG appraisal of the company's systematic review methods, including use of AI tools

Review process	EAG response	Note
Was the review question clearly defined in terms of population, interventions, comparators, outcomes and study designs?	Yes	See CS, Section 2.1 and Appendix B1.2 (Table 6)
Were appropriate sources searched?	Yes	See CS, Appendix B.1 and Appendix B.1.1
Was the timespan of the searches appropriate?	Yes	See CS, Appendix B.1 and Appendix B.1.1 (Table 1 to Table 5).
Were appropriate search terms used?	Yes	See CS, Appendix B.1 and Appendix B.1.1.
Were the eligibility criteria appropriate to the decision problem?	Yes	See CS, Section 2.1 and Appendix B1.2 (Table 6) Criteria were sufficiently broad to include evidence on any perioperative therapies used with surgical resection for gastric or gastroesophageal junction cancer in the SLR.
Was study selection applied by two or more reviewers independently?	Partly	See CS, Appendix B.1, Appendix B.1.2 and Appendix B.1.4 The original SLR (searches conducted in November 2024) was updated in June 2025. Review processes differed between the original review and the updated SLR. The original SLR used two independent reviewers to review records at title and abstract screening and full text screening (but conference proceedings and trial registries were reviewed by a single reviewer). The updated SLR used a single human reviewer (reviewer 1) and an AI tool (DistillerSR Artificial Intelligence SYstem - DAISY) trained on the selection process used for the original SLR. All records (title and abstracts) were screened by both reviewer 1 and the AI software and all discrepancies were reviewed by a second human reviewer (reviewer 2). According to the CS, unless stated otherwise, the SLR processes for the updated SLR were the same as for the original SLR. Application of eligibility criteria to records selected at full text stage was presumably conducted by two human reviewers, as per the original review.

Review process	EAG response	Note
		The EAG considers that processes applied by the company are unlikely to have excluded relevant evidence.
Was data extracted by two or more reviewers independently?	Partly	See CS, Appendix B.1, Appendix B.1.2 (Table 7) and Appendix B.1.4 (Figure 4) For the original SLR, data were extracted by a single reviewer and checked by a second reviewer independently. For the updated SLR, data were extracted using an AI platform (ChatGPT Pro 5.0 in Agent mode) instructed by a series of prompts for extraction of study characteristics, intervention, participants and outcomes. The company assessed the performance of AI for data extraction using a process outlined in Motzfeldt Jensen 2025.³⁵ Two human reviewers were involved in setting reference extraction standards (based on data extraction performed for the original SLR), two independent applications of the AI-extraction were used for every study and, according to the CS, there was “100% human oversight” of data extraction, with the AI platform operating in a second reviewer role. The company reported that performance of the AI-platform ranged from 91.2% of data completely correct or satisfactory for outcomes to 98.9% of data completely correct or satisfactory for study characteristics. The EAG considers that as only the MATTERHORN trial is relevant to the current appraisal, processes applied by the company

Review process	EAG response	Note
		are unlikely to have excluded or incorrectly extracted relevant data.
Were appropriate criteria used to assess the risk of bias and/or quality of the primary studies?	Yes	See CS, Section 2.5 (Table 9)
Was the quality assessment conducted by two or more reviewers independently?	Yes	See CS, Section 2.5, Appendix B.1.2 and Appendix B1.3 For the original SLR, the CRD RCT checklist ²² was used. And reported for the 1 RCT. For the updated SLR, the company stated that the Risk of Bias “1” tool (Higgins 2011 ³⁶) was used in an AI-assisted process (ChatGPT Pro 5.0 in Agent mode) instructed by a series of task prompts. Discrepancies between the AI assistant and human reviewer(s) were assessed by a second human reviewer.
Were attempts to synthesise evidence appropriate?	Yes	See CS, Section 2 As the comparative effectiveness of perioperative D-FLOT versus SoC can be assessed based on direct evidence from the MATTERHORN trial, it was not necessary to conduct meta-analyses or indirect treatment comparisons. The EAG agrees that the MATTERHORN trial is the only source of evidence relevant to the current appraisal.

AI=artificial intelligence; CRD=Centre for Reviews and Dissemination; DAISY=DistillerSR Artificial Intelligence System; RCT=randomised controlled trial; SLR=systematic literature review

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Technology appraisal

Durvalumab in combination for neoadjuvant and adjuvant treatment of resectable gastric and gastro-oesophageal junction cancer [ID6374]

Company Addendum

February 2026

File name	Version	Contains confidential information	Date
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1. Introduction

In the Company evidence submission in November 2025, a semi-Markov state-transition model (STM) was developed to determine the cost-effectiveness of durvalumab in combination with 5-fluorouracil/leucovorin/oxaliplatin/docetaxel (perioperative D-FLOT) chemotherapy compared to the current standard of care (SoC) for patients with resectable gastric or gastro-oesophageal junction adenocarcinoma (GOA), perioperative FLOT chemotherapy. An STM was considered the most appropriate model structure for this decision problem, as comprehensively detailed in the Company evidence submission and the Company's response to the External Assessor Group (EAG) clarification questions (CQs). In summary:

- There is extensive precedent for cost-effectiveness modelling via an STM structure (either Markov or semi-Markov models) in the resectable GOA disease setting
- The STM model structure permits the robust modelling of long-term survival
- The STM structure allows the structural relationship between disease mortality and progression to be modelled

The latter points are particularly relevant for modelling treatment in a curative-intent setting, where the possibility of 'cure' can be accounted for in a way that directly reflects expectations for patients' ongoing risk of events (i.e., assumed to be no longer at risk of recurrence [modelled via TP1] and with mortality comparable to that of the general population [modelled via TP2]). Additionally, the semi-Markov STM structure adopted in the Company evidence submission was validated extensively by UK clinical experts, who confirmed that it is appropriate for a curative-intent treatment such as perioperative D-FLOT.¹

However, the EAG considers a partitioned survival model (PSM) to be the preferable model structure for this decision problem, as this allows for direct extrapolation of overall survival (OS) data from the MATTERHORN trial (the pivotal trial in this indication). Whilst the Company maintains that the semi-Markov STM structure adopted in the Company base case was appropriate to robustly determine the cost-effectiveness of D-FLOT versus perioperative FLOT chemotherapy in resectable GOA, the Company has since developed a *de novo* PSM informed by OS and event-free survival (EFS) data from the MATTERHORN trial to meet the EAG's request.

The EFS data informing the PSM are from the final EFS analysis (data cut-off 2 [DCO2]; December 2025) of MATTERHORN, at which point the trial met its primary endpoint, demonstrating a clinically meaningful and statistically significant improvement in EFS in the D-FLOT arm compared with the control arm (hazard ratio [HR]: 0.71; 95% confidence interval [CI]: 0.58, 0.86; $p < 0.001$).² The OS data informing the PSM are from the latest DCO of the MATTERHORN trial (DCO3; final OS analysis; September 2025; see Appendix A).³ Of note, the Company base case was based on OS from DCO2 (December 2024), due to the timing of the submission. At DCO3, OS maturity in the D-FLOT and perioperative FLOT chemotherapy arms were █% and █%, respectively, and a statistically significant OS benefit in favour of D-FLOT versus perioperative FLOT (HR: 0.78; 95% CI: 0.63, 0.96; $p = 0.021$) was demonstrated.^{3,4} As the PSM approach directly models trial data (and thus is more appropriate when more mature data are available), the Company acknowledges that the availability of DCO3 OS data reduces the uncertainty associated with the PSM approach than at the time of the ingoing Company submission (which, due to the timing of the submission, relied on less mature DCO2 data from MATTERHORN).

In response to the request from the EAG, this addendum provides details of a cost-effectiveness analysis of perioperative D-FLOT versus perioperative FLOT chemotherapy using a PSM, and Company evidence submission template for durvalumab in combination for neoadjuvant and adjuvant treatment of resectable gastric and gastro-oesophageal junction cancer [ID6374]

additionally responds to issues detailed in the EAG report to alleviate any remaining uncertainty in the cost-effectiveness analysis. Where applicable, the Company has also utilised assumptions in the PSM to reflect the EAG's preferred assumptions. To streamline the EAG's review, only methods and model inputs that have changed since the Company base case are detailed in Section 2 below. All other model inputs remain in line with the Company base case. For completeness, a table summarising all base case analysis inputs for this alternative cost-effectiveness analysis requested by the EAG is provided in Section 2.5.

Full cost-effectiveness results from this alternative cost-effectiveness analysis of D-FLOT and perioperative FLOT chemotherapy using a PSM are presented in Section 3. The results from this alternative cost-effectiveness analysis are highly aligned with the Company's base case analysis (with the deterministic incremental cost-effectiveness ratio [ICER] within 3.1% of the Company's base case deterministic ICER); the conclusions of the semi-Markov STM and the PSM are therefore consistent with both models demonstrating that perioperative D-FLOT is a cost-effective use of NHS resources in England. Critically, the OS estimates predicted by the PSM are closely aligned with the observed MATTERHORN trial data at Year 3 (<1% in both model arms), thereby addressing the EAG's key concern regarding the semi-Markov modelling approach.

2. Cost-effectiveness methodology

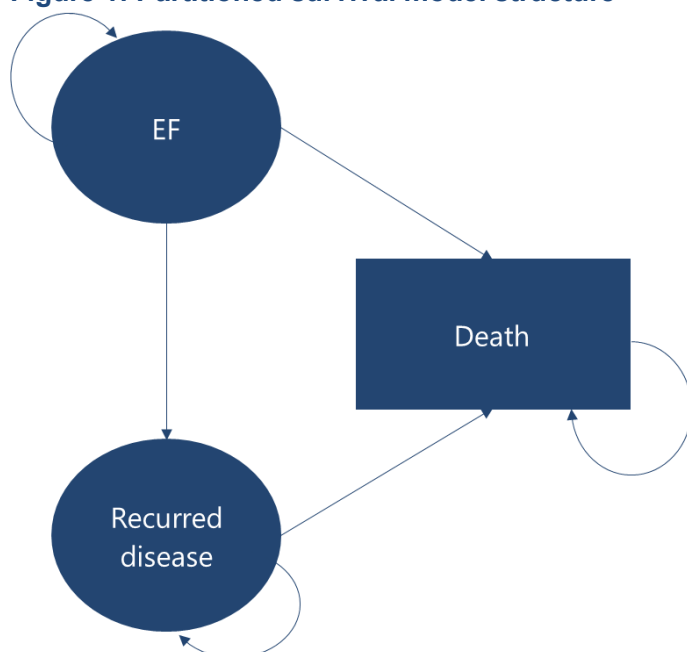
2.1 Model structure

Overview of model structure

At the EAG's request, a *de novo* PSM was built in Microsoft Excel. The PSM consisted of three mutually exclusive health states: (i) event-free (EF), (ii) recurred disease (RD), and (iii) death. The occupancy of health states over time was calculated using EFS and OS survival extrapolations, as described below:

- The proportion of patients occupying the EF state was calculated as the proportion alive and event-free (based on EFS extrapolations)
- The proportion of patients occupying the RD state was calculated as the proportion alive (based on OS extrapolations) minus the proportion of patients alive and EF (based on EFS extrapolations)
- The proportion of patients occupying the death state was calculated as the proportion who had died (based on OS extrapolations)

Figure 1: Partitioned survival model structure



Abbreviations: EF: event-free.

Features of the economic analysis

Following NICE guidelines, the EAG-requested model was developed from a UK NHS and Personal Social Services (PSS) perspective.⁵ A lifetime time horizon (■■■ years) was adopted to capture all relevant costs and outcomes. A cycle length of 1 month (4.35 weeks) and half-cycle correction was applied to adjust for timing of transitions throughout the cycle, in line with the recommended best practice.⁶ In addition, a 3.5% discount rate for costs and benefits was included, in line with NICE PMG36.⁵

2.2 Clinical parameters and variables

2.2.1 Survival inputs and assumptions

In line with the Company base case, the primary source of clinical inputs for the PSM cost-effectiveness model (CEM) requested by the EAG was individual patient-level data (IPD) from MATTERHORN. The MATTERHORN trial population, intervention and comparator are aligned with those defined in the decision problem, supporting the appropriateness of the trial data for informing the economic analysis. Consistent with the Company's base case, EFS data were sourced from the December 2024 DCO (DCO2; the final EFS analysis).² OS data were sourced from the September 2025 (DCO3; final OS analysis), reflecting the availability of updated OS data since submission of the Company's base case.³ For completeness, the OS data from DCO3 of MATTERHORN are presented in Appendix A. As outlined in the Company submission, OS data from DCO2 are highly consistent with data from DCO3, as evidenced by a stable HR across the data cuts.

The proportion of patients in each health state at each model cycle was determined for perioperative D-FLOT and perioperative FLOT chemotherapy from survival probabilities from extrapolations of MATTERHORN EFS and OS data. The follow-up period for MATTERHORN was

shorter than the model time horizon (■■■ years) and therefore extrapolations of the observed EFS and OS data were required.

In accordance with standard practice and guidance from the NICE Decision Support Unit (DSU), the extrapolation of the survival data was conducted using a range of standard parametric survival models including exponential, Weibull, Gompertz, log-normal, log-logistic, generalised gamma and gamma.⁷ Diagnostic tests (including log-cumulative hazard plots, Schoenfeld residuals and quantile-quantile plots) were conducted to assess the proportionality of hazards between treatment arms as well as the suitability of proportional hazard (PH) or accelerated failure time (AFT) models.

General population mortality

Parametric distributions were constrained to ensure that the hazards of the extrapolations could not be less than the general population mortality (GPM) hazards, using the latest UK life tables (based on data from 2021–2023).⁸ In addition, at the point of intersect between the EFS and OS curves, OS was set to the EFS curve to prevent incongruent relationships of EFS and OS.

Selection criterion for best fit survival models

The methodology used for the selection of survival extrapolation models was consistent with that used in the Company evidence submission. Additionally, following the EAG's request for a PSM, additional 1:1 consultations with UK clinical experts (n=2) were conducted to validate the clinical plausibility of long-term survival predictions.⁹

The analytical process consisted of testing the statistical distributions and assessing their fits over the observed trial period and beyond to ensure reliable projection of the clinical outcomes. The best-fitting distributions were selected in line with NICE DSU guidance on the analysis of survival outcomes for economic evaluations alongside clinical trials.⁷ The selection of the most appropriate distributions was based on the following:

- Statistical goodness of fit (Akaike Information Criteria [AIC]/Bayesian Information Criterion [BIC] of extrapolations to observed Kaplan–Meier [KM] data from the MATTERHORN trial
- Visual inspection of the curve fit against the observed KM data from the MATTERHORN trial, and visual inspection of the hazard profiles of the observed MATTERHORN data
- Clinical plausibility of long-term predictions, as validated by clinical experts^{1, 9}

Cure assumption

In the Company's base case, patients who remained in the EF health state after five years (60 months) were assumed to be cured, to reflect the expected clinical outcomes for patients with resectable GOA receiving surgery with curative intent.¹⁰ As noted above, the semi-Markov model permitted cure to be modelled in a way that directly reflects expectations for patients' ongoing risk of events. Specifically, after the 5-year timepoint, it was assumed that patients in either treatment arm who are still in the EF health state are no longer at risk of recurrence, are no longer followed up regularly, and have a risk of death that is equal to that of the general population. As detailed in the Company evidence submission, the five-year timepoint was chosen based on the NICE Committee-preferred cure assumption used in TA746 (a NICE appraisal assessing early-stage oesophageal cancer or GOJC).¹¹ Additionally, UK clinical experts confirmed that a five-year cure assumption was clinically plausible and highly reflective of UK clinical practice in which very few

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patients are estimated to experience disease relapse in this time (reflective of the curative intent of treatment in resectable GOA).¹ The cure assumption employed in the Company's base case was further supported by the hazard profile of the observed EFS data from MATTERHORN (see Figure 6), which clearly demonstrates decreasing hazards over time.

However, the EAG considered the cure assumption to be uncertain. Whilst the Company maintains that patients in this setting have the potential to experience long-term survival and cure,^{10, 12} in line with EAG preference, the assumption of cure has been removed from the alternative base case analysis. As such, given clinical advice to the Company that cure is clinically plausible in this setting, the alternative base case as per the EAG's request is conservative in terms of resulting survival projections for both trial arms. Thus, as detailed in Section 3.2.3, two scenarios in which the five-year cure assumption was reinstated were conducted:

- One scenario analysis applied a cure assumption with no standardised mortality ratio (SMR), in line with the Company's base case, and reflective of clinical advice to the Company¹
- One scenario analysis applied a cure assumption with an SMR of 1.1 to address the EAG's concern regarding excess mortality. An SMR of 1.1 was chosen to align with Committee preference and clinical expert advice to the Committee in TA746¹¹

Event-free survival

EFS data used in the model from the MATTERHORN trial are from DCO2 (December 2024; the final EFS analysis).²

PH testing

In line with the Company base case, PH testing was undertaken using cumulative hazard plots, log-log plots and Schoenfeld statistics. Based on the assessment of the Schoenfeld residual plot (Figure 3) the PH assumption cannot formally be rejected, with a p-value >0.05 (Schoenfeld statistics: p=■■■■). However, the log cumulative hazard plots, log-odds or log-normal lines are not strictly parallel (Figure 2). The CEM therefore considers individual fits for EFS from the MATTERHORN trial (i.e., parametric distributions were fitted separately to the perioperative D-FLOT and perioperative FLOT chemotherapy arms). This is aligned with NICE guidance,⁷ which notes that separate fits require fewer assumptions than combined fits (e.g. PH during post-trial follow-up) and allow, if appropriate, for different parametric models to be applied to each treatment arm.

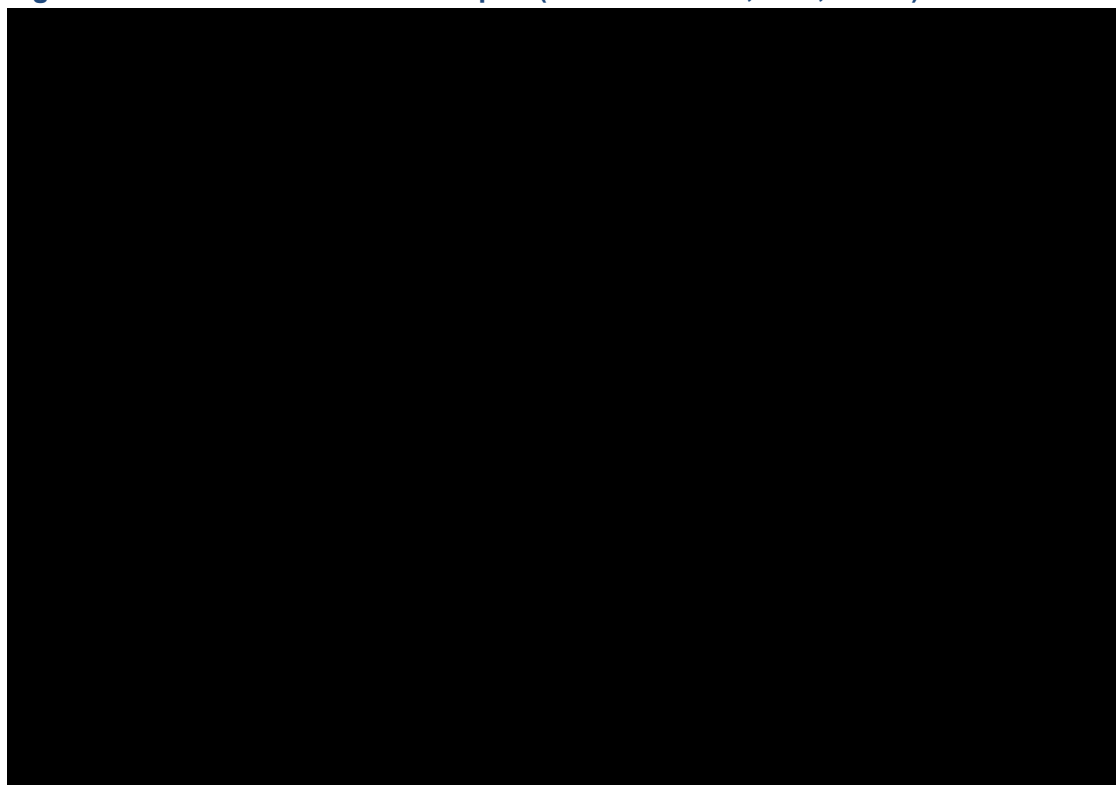
Standard parametric distributions (i.e., exponential, Weibull, log-normal, log-logistic, Gompertz, generalised gamma, gamma) were fitted separately to the perioperative D-FLOT and perioperative FLOT chemotherapy trial arms. As detailed below, the selection of parametric fits for each arm was based primarily on statistical fit, visual fit, and the observed hazard profiles, as well as prior clinical validation.

Figure 2. EFS: Log cumulative hazards, log odds and log-normal versus log time (MATTERHORN, FAS, DCO2)



Abbreviations: DCO: data cut-off; Durva: durvalumab; EFS: event-free survival; FAS: full analysis set; FLOT: fluorouracil, leucovorin, oxaliplatin and docetaxel.

Figure 3: EFS: Schoenfeld residual plot (MATTERHORN, FAS, DCO2)



Abbreviations: DCO: data cut-off; EFS: event-free survival; FAS: full analysis set

Statistical fit

An overview of the AIC scores and BIC scores for each parametric distribution is shown for perioperative D-FLOT (Table 1) and for perioperative FLOT chemotherapy (Table 2). Assessment of statistical fit indicated that for both perioperative D-FLOT and perioperative FLOT chemotherapy, the generalised gamma distribution was the best statistically fitting standard parametric curve based on AIC and the second best statistically fitting curve based on BIC. The log-normal provided the best statistical fit based on BIC and the second-best statistical fit based on AIC, for both treatment arms. Of note, the AIC and BIC scores across both arms are within five points of each other, indicating that the alternative survival distributions have similarly good fit to the data.

Table 1: EFS: goodness of fit statistics perioperative D-FLOT (MATTERHORN, FAS, DCO2)

Model	AIC	AIC rank	BIC	BIC rank
Exponential	██████	7	██████	5
Weibull	██████	5	██████	6
Log-normal	██████	2	██████	1
Log-logistic	██████	4	██████	4
Gompertz	██████	3	██████	3
Generalised gamma	██████	1	██████	2
Gamma	██████	6	██████	7

Footnotes: Bold indicates lowest AIC/BIC value

Abbreviations: AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; DCO: data cut-off; D-FLOT: Durvalumab, Fluorouracil, Leucovorin, Oxaliplatin and Docetaxel; EFS: event-free survival; FAS: full analysis set.

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Table 2: EFS: goodness of fit statistics perioperative FLOT chemotherapy (MATTERHORN, FAS, DCO2)

Model	AIC	AIC rank	BIC	BIC rank
Exponential		5		5
Weibull		6		6
Log-normal		2		1
Log-logistic		3		3
Gompertz		4		4
Generalised gamma		1		2
Gamma		7		7

Footnotes: Bold indicates lowest AIC/BIC value

Abbreviations: AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; DCO: data cut-off; EFS: event-free survival; FAS: full analysis set; FLOT: Fluorouracil: Leucovorin: Oxaliplatin and Docetaxel.

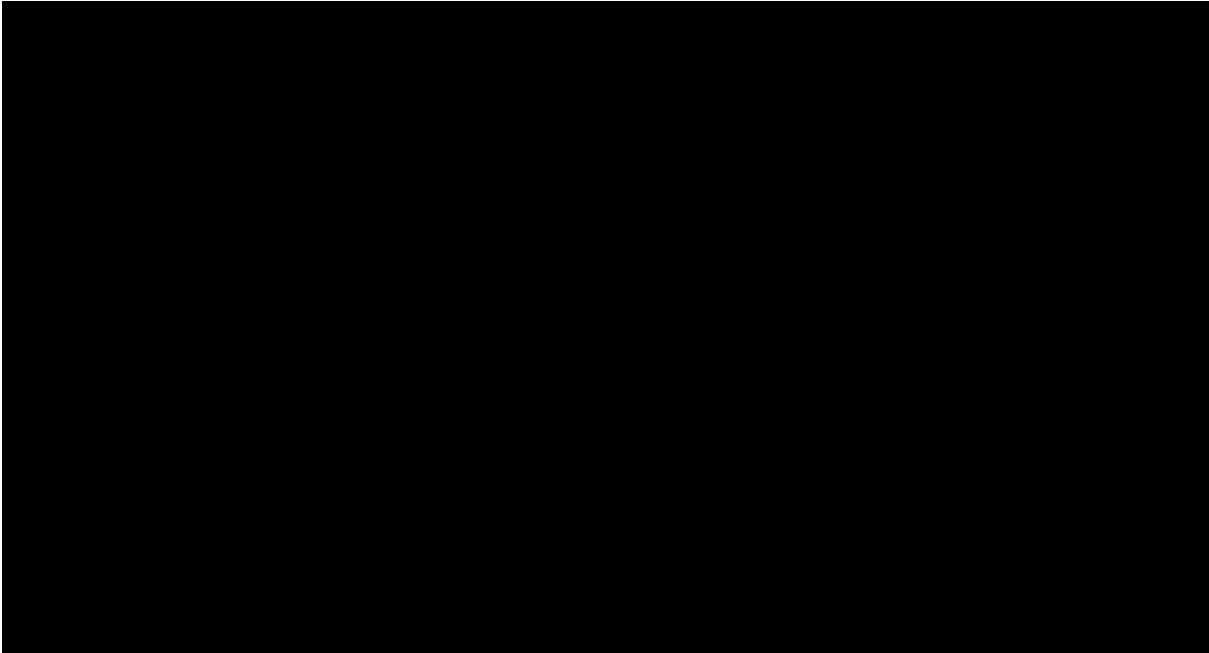
Visual fit

Figure 4 and Figure 5 show the parametric distributions highlighting the visual fit to the observed KM data and long-term predictions for perioperative D-FLOT and perioperative FLOT chemotherapy, respectively. Survival landmark estimates over a 5-year horizon for each parametric distribution are presented for perioperative D-FLOT in Table 3 and perioperative FLOT chemotherapy in Table 4.

In terms of visual fit against the perioperative D-FLOT KM curves (Figure 4), the generalised gamma and the Gompertz demonstrated the closest alignment. As shown in Table 3, all other curves notably overpredicted EFS at Year 1 and Year 2 and then tended to underestimate survival from approximately 30 months onwards. The generalised gamma in particular produced extrapolations that were most consistent to the MATTERHORN EFS data at all timepoints.

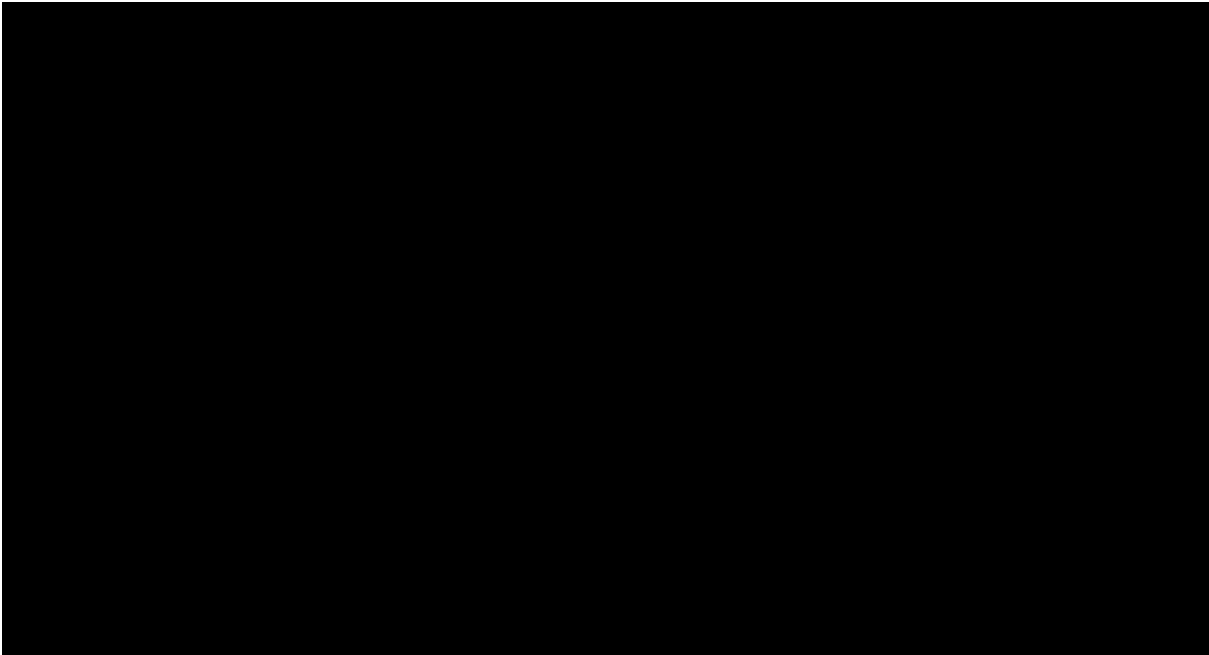
In the perioperative FLOT chemotherapy arm, the predictions using the generalised gamma distribution (as well as the log-normal and Gompertz) were again consistent with the MATTERHORN EFS data, with other distributions underestimating survival from approximately 36 months onwards.

Figure 4: EFS: observed vs. predicted for perioperative D-FLOT (MATTERHORN, FAS)



Abbreviations: EFS: event-free survival; DCO: data cut-off; FAS: full analysis set; D-FLOT: Durvalumab, Fluorouracil: Leucovorin, Oxaliplatin and Docetaxel; KM: Kaplan-Meier.

Figure 5: EFS: observed vs. predicted for perioperative FLOT chemotherapy (MATTERHORN, FAS)



Abbreviations: EFS: event-free survival; DCO: data cut-off; FAS: full analysis set; FLOT: Fluorouracil: Leucovorin: Oxaliplatin and Docetaxel; KM: Kaplan-Meier; TFR: time to first recurrence.

Table 3: EFS: predictions for perioperative D-FLOT (MATTERHORN, FAS, DCO2)

Model	1 year	2 years	3 years	5 years
MATTERHORN KM for perioperative D-FLOT		67.4%		-
Exponential				

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Weibull				
Loglogistic				
Gompertz				
Lognormal				
Generalised gamma				
Gamma				

Abbreviations: DCO: data cut-off; D-FLOT: Durvalumab, Fluorouracil, Leucovorin, Oxaliplatin and Docetaxel; EFS: event-free survival; FAS: full analysis set; KM: Kaplan-Meier.

Table 4: EFS: predictions perioperative FLOT chemotherapy (MATTERHORN, FAS, DCO2)

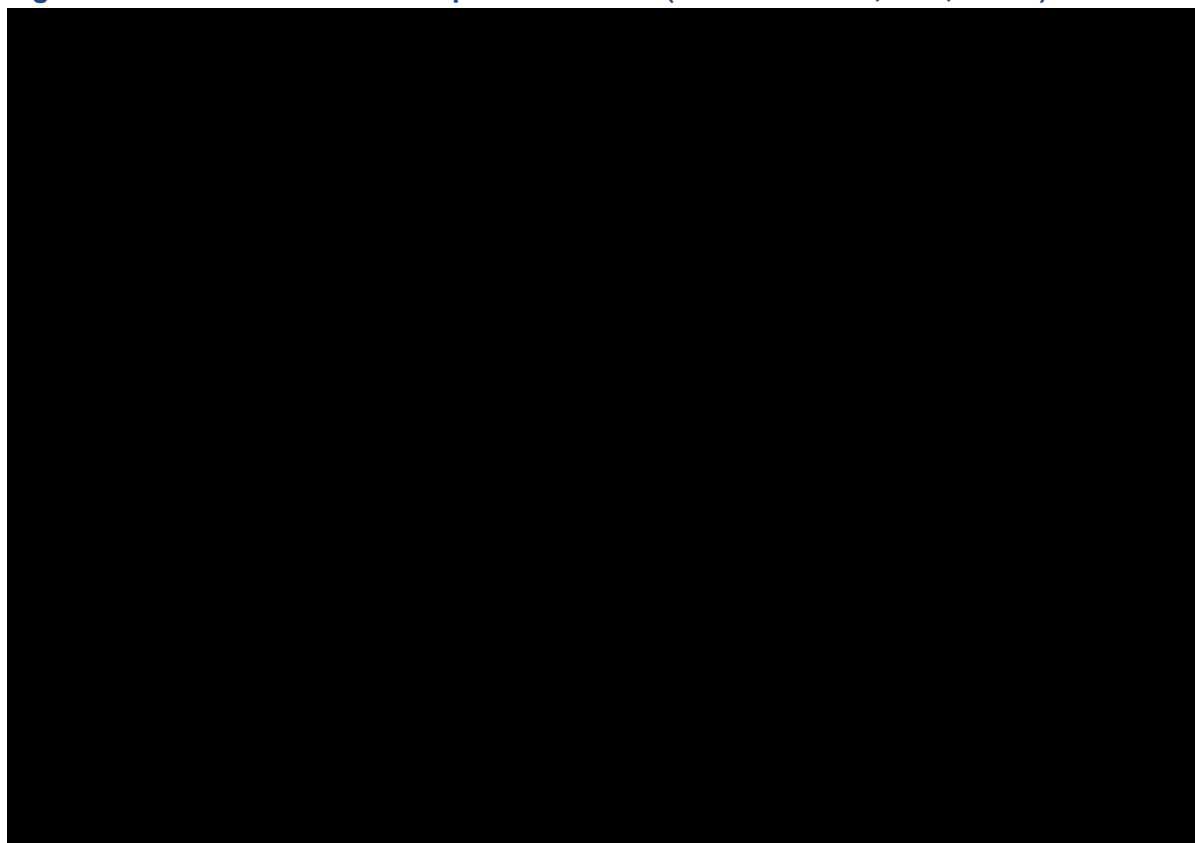
Model	1 year	2 years	3 years	5 years
MATTERHORN KM for perioperative FLOT chemotherapy		58.5%		-
Exponential				
Weibull				
Loglogistic				
Gompertz				
Lognormal				
Generalised gamma				
Gamma				

Abbreviations: EFS: event-free survival; DCO: data cut-off; FAS: full analysis set; FLOT: Fluorouracil; Leucovorin; Oxaliplatin and Docetaxel; KM: Kaplan-Meier.

Hazard profiles

The smoothed hazards for both treatment arms in the MATTERHORN trial are observed to initially increase and then decrease over time, which is in line with clinical advice to the Company regarding the clinical plausibility of cure in this setting, and thus the Company's understanding that patients who are still in the EF health state after a certain timepoint will no longer be at risk of recurrence.¹ This pattern of increasing then decreasing hazards aligns to AFT models such as the generalised gamma and log-normal. Whilst a small uptick is observed in the perioperative D-FLOT arm, this is informed by a small number at risk at maximum follow up (~ patients at risk in each arm from Month 42), and therefore the tail of the hazard should be interpreted with caution. As shown in Figure 6, the generalised gamma and log-normal distributions were able to best capture the behaviour of the observed hazards for both treatment arms.

Figure 6. EFS: Predicted hazards per distribution (MATTERHORN, FAS, DCO2)



Abbreviations: EFS: event-free survival; DCO: data cut-off; Durva: durvalumab; FAS: full analysis set; FLOT: Fluorouracil; Leucovorin; Oxaliplatin and Docetaxel; KM: Kaplan-Meier.

Clinical validation

At the time of the Company evidence submission, clinical experts were consulted by the Company on the most clinically plausible curve to extrapolate time to first recurrence (TFR), time to death (TTD) and post-recurrence survival (PRS).¹ For this alternative base case requested by the EAG, the Company conducted further clinical validation exercises with UK clinical experts.⁹ However, due to time constraints developing the *de novo* PSM at the EAG's request, the additional clinical validation exercises conducted for this alternative base case focussed specifically on OS. As TFR is defined as the time from randomisation until recurrence or progression (as per EFS) with censoring for deaths that occur before recurrence or progression, TFR and EFS are closely aligned and thus the validation exercise conducted for TFR at the time of the Company submission is expected to be applicable to EFS.

As detailed in the Company evidence submission, there was no clear consensus among clinical experts regarding the most clinically plausible curve choice for TFR, however, they stated preference for a curve with a plateau in both arms.¹

Base case selection

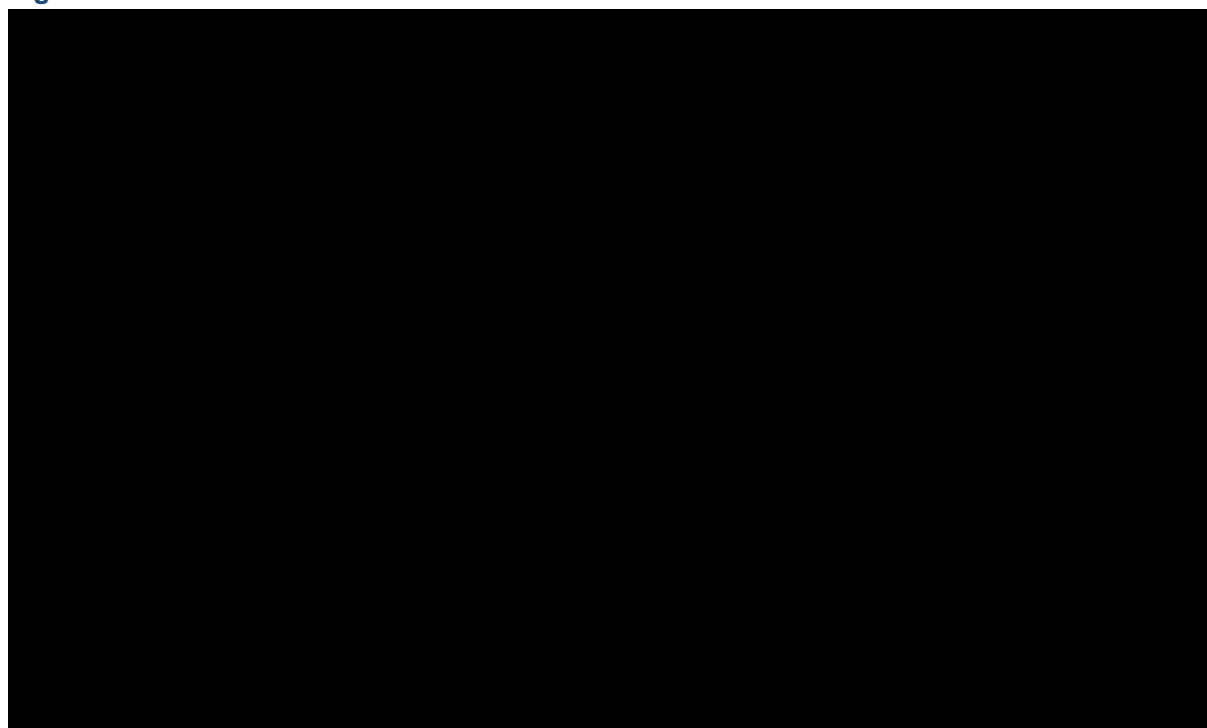
The generalised gamma distribution was selected for the extrapolation of EFS for both arms in the alternative base case analysis (see Figure 7). In the absence of clinical expert consensus on the most clinically plausible TFR (and thus, EFS) curve, selection of the generalised gamma was based primarily on the underlying hazard profile of the distribution, as well as statistical and visual fit to the data. As discussed above, the smoothed hazards for both treatment arms in the Company evidence submission template for durvalumab in combination for neoadjuvant and adjuvant treatment of resectable gastric and gastro-oesophageal junction cancer [ID6374]

MATTERHORN trial are observed to initially increase then decrease over time; the generalised gamma captures this trend over time and is reflective of the possibility of cure (whereby patients who are still in the EF health state after a certain timepoint will no longer be at risk of recurrence) in this disease setting. The generalised gamma is also one of the two best visually and statistically fitting candidate curves to the observed MATTERHORN data for both trial arms. The selection of the generalised gamma to model EFS also aligns with the Company's base case whereby the generalised gamma was used to model TFR for the transition from the EF to RD health state.

Of note, NICE TSD 14 states that *"fitting different types of parametric model to different treatment arms would require substantial justification, as different models allow very different shaped distributions"*; following assessment of statistical fit, visual fit, and hazard profiles, it was considered most appropriate to select the same extrapolation curves across both the intervention and comparator arm for EFS, as per the approach taken in the Company evidence submission.¹³

The log-normal distribution, which also provides strong statistical fit to the observed MATTERHORN data and is reflective of the observed hazard profiles for both treatment arms, was explored in a scenario analysis (Section 3.2.3). The log-normal distribution provides a more pessimistic estimate of EFS for both perioperative D-FLOT and perioperative FLOT chemotherapy.

Figure 7: Base case EFS curves



Abbreviations: EFS: event-free survival; FLOT: Fluorouracil: Leucovorin: Oxaliplatin and Docetaxel; KM: Kaplan-Meier; OS: overall survival.

Overall survival

OS data used in the model from the MATTERHORN trial are from DCO3 (September 2025; the final OS analysis).³

PH testing

Company evidence submission template for durvalumab in combination for neoadjuvant and adjuvant treatment of resectable gastric and gastro-oesophageal junction cancer [ID6374]

PH testing was undertaken using cumulative hazard plots, log-log plots and Schoenfeld statistics. As with EFS, based on the assessment of the Schoenfeld residual plot (Figure 8) the PH assumption cannot formally be rejected, with a p-value >0.05 (Schoenfeld statistics: $p=$ [REDACTED]). However, the log cumulative hazard plots, log-odds or log-normal lines are also not strictly parallel (Figure 9). The CEM therefore considers individual fits for OS from the MATTERHORN trial (i.e., parametric distributions were fitted separately to the perioperative D-FLOT and perioperative FLOT chemotherapy arms). As noted above, this is aligned with NICE guidance,⁷ which notes that separate fits require fewer assumptions than combined fits (e.g. PH during post-trial follow-up) and allow, if appropriate, for different parametric models to be applied to each treatment arm.

Standard parametric distributions (i.e., exponential, Weibull, log-normal, log-logistic, Gompertz, generalised gamma, gamma) were fitted separately to the perioperative D-FLOT and perioperative FLOT chemotherapy trial arms. As detailed below, the selection of parametric fits for each arm was based on statistical fit, visual fit, the observed hazard profiles, as well as clinical plausibility.

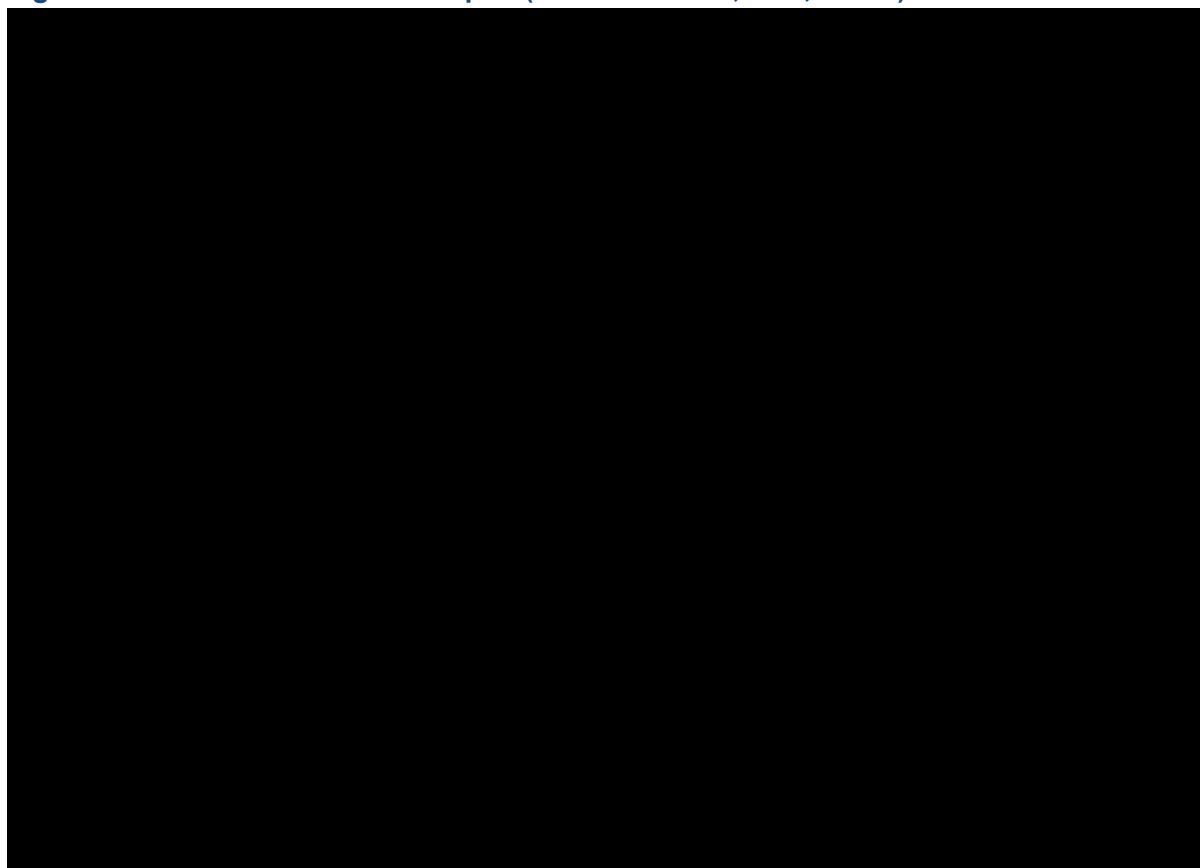
Figure 8: OS: Log cumulative hazards, log odds and log-normal versus log time (MATTERHORN, FAS, DCO3)



Abbreviations: DCO: data cut-off; Durva: durvalumab; FAS: full analysis set; FLOT: fluorouracil, leucovorin, oxaliplatin and docetaxel; OS: overall survival.

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Figure 9: OS: Schoenfeld residual plot (MATTERHORN, FAS, DCO3)



Abbreviations: DCO: data cut-off; FAS: full analysis set; OS: overall survival.

Statistical fit

An overview of the AIC scores and BIC scores for each parametric distribution is shown for perioperative D-FLOT (Table 5) and perioperative FLOT chemotherapy (Table 6). Assessment of statistical fit indicated that the log-normal distribution provided the best statistically fitting standard parametric curve across AIC/BIC for both treatment arms. The second-best fitting curve was the generalised gamma for both perioperative D-FLOT (based on AIC/BIC combined) and perioperative FLOT chemotherapy (based on AIC and BIC). Of note, the generalised gamma was within five AIC points of the log-normal for both treatment arms, indicating that both curves provide a good statistical fit to the data.

Table 5: OS: goodness of fit statistics perioperative D-FLOT (MATTERHORN, FAS, DCO3)

Model	AIC	AIC rank	BIC	BIC rank
Exponential	██████	5	██████	5
Weibull	██████	6	██████	6
Log-normal	██████	1	██████	1
Log-logistic	██████	4	██████	4
Gompertz	██████	3	██████	2
Generalised gamma	██████	2	██████	3
Gamma	██████	7	██████	7

Footnotes: Bold indicates lowest AIC/BIC value

Abbreviations: AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; D-FLOT: Durvalumab, Fluorouracil, Leucovorin, FAS: full analysis set; OS: overall survival.

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Table 6: OS: goodness of fit statistics perioperative FLOT chemotherapy (MATTERHORN, FAS, DCO3)

Model	AIC	AIC rank	BIC	BIC rank
Exponential		5		4
Weibull		7		7
Log-normal		1		1
Log-logistic		3		3
Gompertz		4		5
Generalised gamma		2		2
Gamma		6		6

Footnotes: Bold indicates lowest AIC/BIC value

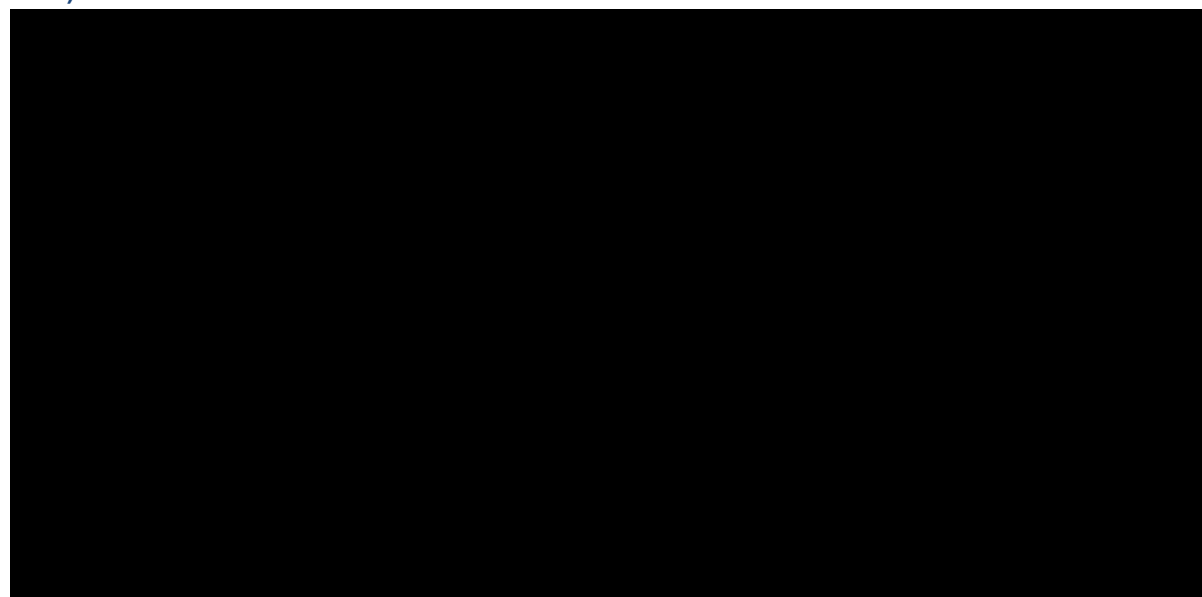
Abbreviations: AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; DCO: data cut-off; FAS: full analysis set; FLOT: Fluorouracil: Leucovorin: Oxaliplatin and Docetaxel; OS: overall survival.

Visual fit

Figure 10 and Figure 11 show the parametric distributions highlighting the visual fit to the observed KM data and long-term predictions for perioperative D-FLOT and perioperative FLOT chemotherapy, respectively. Survival landmark estimates over a 15-year horizon for each parametric distribution are shown for perioperative D-FLOT in Table 7 and perioperative FLOT chemotherapy in Table 8.

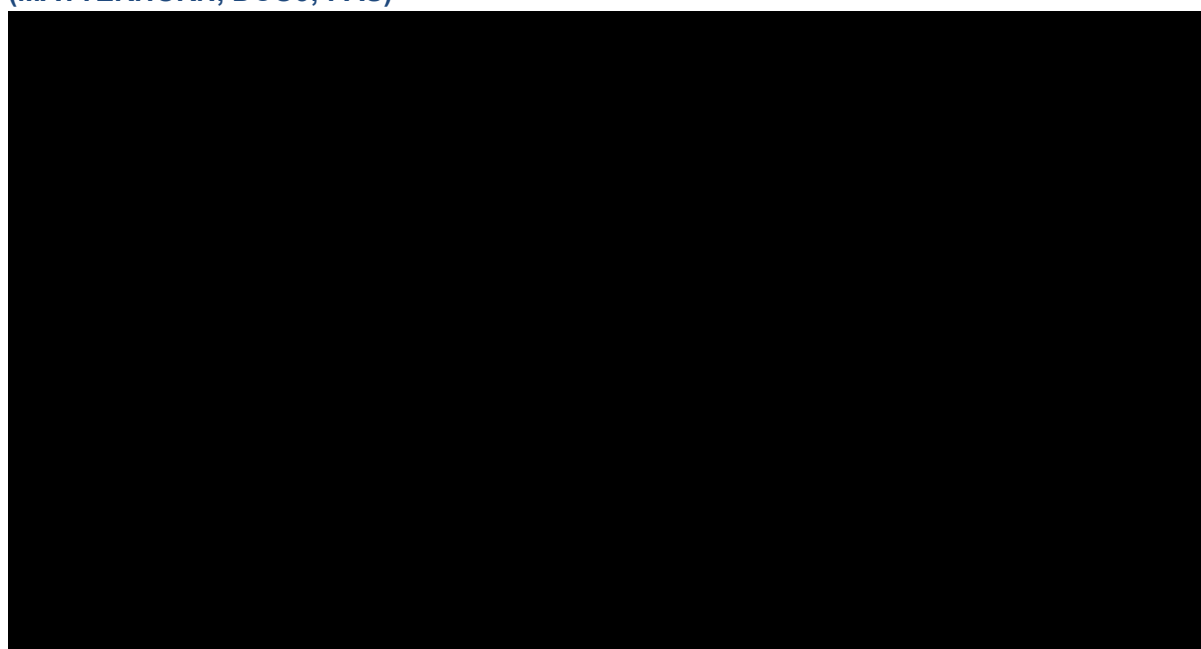
In terms of visual fit against the perioperative D-FLOT KM curves (Figure 4), all curves provided similar visual fit. However, as shown in Table 7, the generalised gamma and Gompertz distributions resulted in landmark estimates of OS that were most consistently aligned with the observed KM data. In the perioperative FLOT chemotherapy arm, the predictions using the generalised gamma distribution were again generally consistent with the MATTERHORN OS predictions.

Figure 10: OS: observed vs. predicted for perioperative D-FLOT (MATTERHORN, DCO3; FAS)



Abbreviations: DCO: data cut-off; D-FLOT: Durvalumab, Fluorouracil: Leucovorin: Oxaliplatin and Docetaxel; FAS: full analysis set; OS: overall survival.

Figure 11: OS: observed vs. predicted for perioperative FLOT chemotherapy (MATTERHORN, DCO3; FAS)



Abbreviations: DCO: data cut-off; FAS: full analysis set; FLOT: Fluorouracil: Leucovorin: Oxaliplatin and Docetaxel; KM: Kaplan-Meier; OS: overall survival.

Table 7: OS: predictions for perioperative D-FLOT (MATTERHORN, FAS, DCO3)

Model	1 year	2 years	3 years	5 years	10 years	15 years
MATTERHORN KM for perioperative D-FLOT	85.8%	75.5%	68.6%	-	-	-
Exponential	■	■	■	■	■	■
Weibull	■	■	■	■	■	■
Loglogistic	■	■	■	■	■	■
Gompertz	■	■	■	■	■	■
Lognormal	■	■	■	■	■	■
Generalised gamma	■	■	■	■	■	■
Gamma	■	■	■	■	■	■

Abbreviations: DCO: data cut-off; FAS: full analysis set; D-FLOT: Durvalumab, Fluorouracil: Leucovorin: Oxaliplatin and Docetaxel; KM: Kaplan-Meier; OS: overall survival.

Table 8: OS: predictions perioperative FLOT chemotherapy (MATTERHORN, FAS, DCO3)

Model	1 year	2 years	3 years	5 years	10 years	15 years
MATTERHORN KM for perioperative FLOT chemotherapy	85.6%	70.4%	61.9%	-	-	-
Exponential	■	■	■	■	■	■
Weibull	■	■	■	■	■	■
Loglogistic	■	■	■	■	■	■

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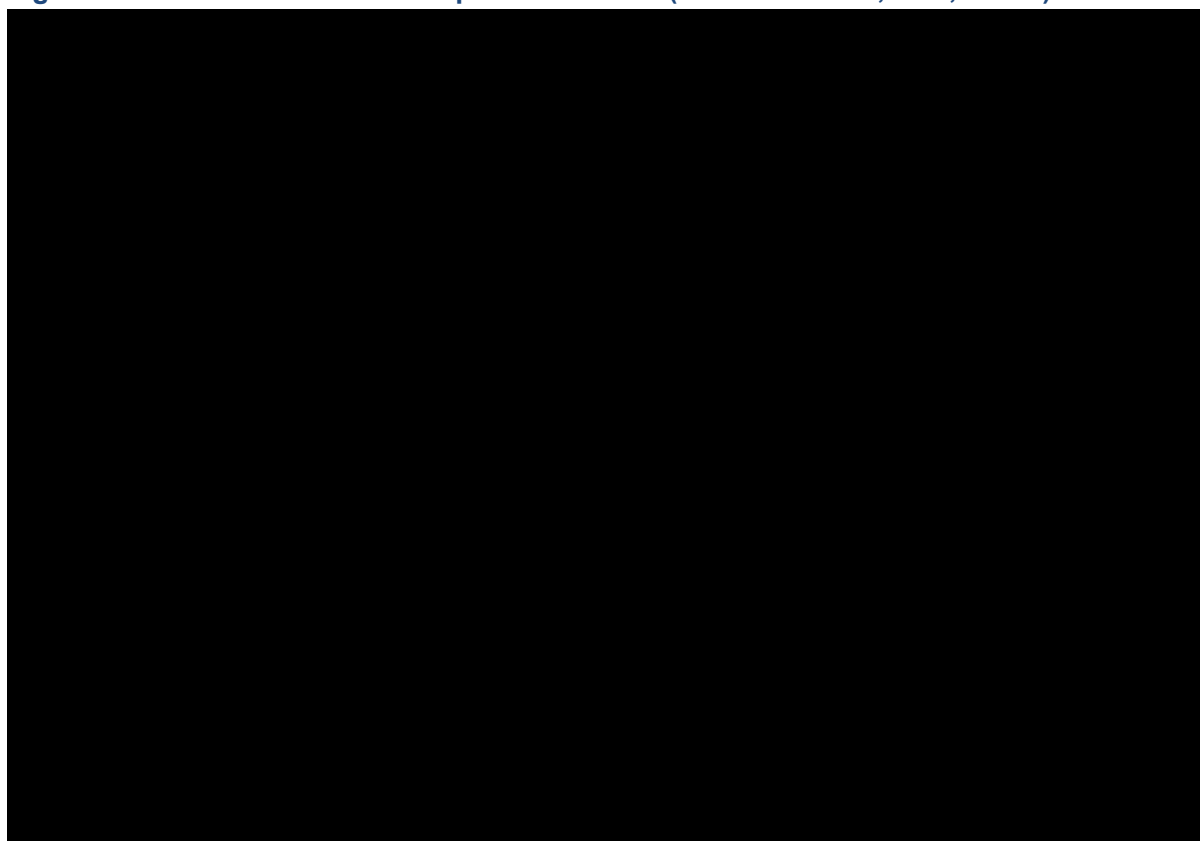
Gompertz	■	■	■	■	■	■
Lognormal	■	■	■	■	■	■
Generalised gamma	■	■	■	■	■	■
Gamma	■	■	■	■	■	■

Abbreviations: DCO: data cut-off; FAS: full analysis set; FLOT: Fluorouracil: Leucovorin: Oxaliplatin and Docetaxel; KM: Kaplan-Meier; OS: overall survival.

Hazard profiles

The smoothed hazards for both treatment arms in the MATTERHORN trial are observed to increase initially then decrease over time, which is in line with the clinical plausibility of cure in this disease setting, and thus the Company's understanding that the hazard of death among patients who remain alive and event-free after a certain timepoint will approach, and ultimately converge with that of the general population. This pattern of increasing then decreasing hazards aligns to AFT models such as the generalised gamma and log-normal; as shown in Figure 12, the generalised gamma and log-normal distribution were best able to capture the behaviour of the observed hazards for both treatment arms.

Figure 12: OS: Predicted hazards per distribution (MATTERHORN, FAS, DCO3)



Abbreviations: DCO: data cut-off; FAS: full analysis set; FLOT: Fluorouracil: Leucovorin: Oxaliplatin and Docetaxel; KM: Kaplan-Meier; OS: overall survival.

Clinical validation

Following the EAG's request for a PSM, two experts were consulted by the Company in January 2026 to gather insights on the most clinically plausible curves to model OS for perioperative D-FLOT and perioperative FLOT chemotherapy.⁹ Several curves were raised by clinical experts as Company evidence submission template for durvalumab in combination for neoadjuvant and adjuvant treatment of resectable gastric and gastro-oesophageal junction cancer [ID6374]

potentially clinically plausible, including the log-logistic and Gompertz for perioperative D-FLOT, and the Weibull, Gamma, generalised gamma and Gompertz for perioperative FLOT chemotherapy.⁹

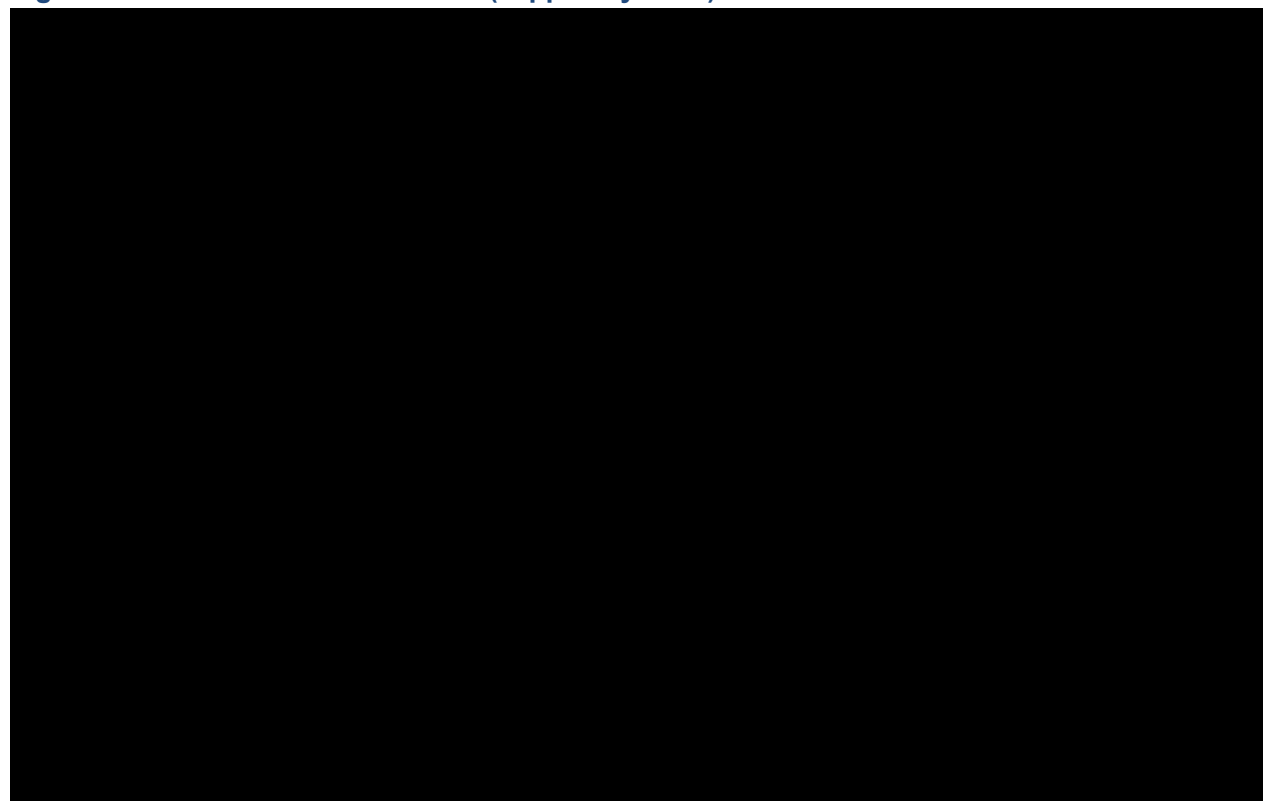
Base case selection

The generalised gamma distribution was selected for the extrapolation of OS for both arms in the alternative base case analysis requested by the EAG (Figure 13). With MATTERHORN OS data available for a maximum follow-up of approximately 4.8 years, the primary consideration in model selection for OS was the ability of candidate parametric distributions to reflect the observed hazard profile of MATTERHORN data (particularly with no cure assumed in the alternative base case), and to provide the best statistical and visual fit to the observed KM data.⁹ Based on the hazard profiles of the candidate curves, the generalised gamma and log-normal were considered for selection as the alternative base case curve for modelling OS in both treatment arms; the hazard profiles of both curves reflect the possibility of cure in this disease setting, whereby patients who are still alive and EF after a certain timepoint will have a hazard of death that approaches and ultimately converges with that of the general population. The log-normal and generalised gamma were also the two best statistically fitting curves for both treatment arms.

Based on the curve choices noted by clinical experts as part of the OS validation exercise, 15-year OS estimates for perioperative D-FLOT ranged from █% (log-logistic) to █% (Gompertz), and 15-year OS estimates for perioperative FLOT chemotherapy ranged from █% (Gamma) to █% (Gompertz).⁹ As shown in Table 7, only the generalised gamma and log-normal distributions predicted 15-year OS estimates for perioperative D-FLOT (█% and █%, respectively) that fall within the range estimated by clinical experts' plausible curves (█–█%), and notably the predicted estimates are on the conservative end of this range.⁹ As the generalised gamma was specifically mentioned by a clinical expert as a clinically plausible curve choice as part of the clinical validation meetings,⁹ the generalised gamma was selected to model OS for both treatment arms in the alternative base case analysis. The log-normal distribution was explored in a scenario analysis (Section 3.2.3).

The selection of the generalised gamma distribution in the alternative base case for both arms is in line with NICE TSD 14 which states that “*substantial justification*” would be required to fit different types of parametric models to different treatment arms.¹³ Of note, the generalised gamma (and log-normal) distributions result in 15-year OS estimates for perioperative FLOT chemotherapy (█% and █%, respectively) which are at the upper end of the range estimated by clinical experts' plausible curves (█–█%), thus leading to optimistic OS extrapolations for perioperative FLOT chemotherapy in the alternative base case analysis. This is further supported by the 5-year OS estimates for FLOT produced by the generalised gamma (█%, and the log-normal [█%]) distribution, which exceed the observed 5-year OS reported in the FLOT-4 trial (45.0%).¹⁴ Consequently, use of the generalised gamma (and the log-normal) to model OS is likely to yield conservative cost-effectiveness estimates for perioperative D-FLOT versus perioperative FLOT chemotherapy.

Figure 13: Base case curves for OS (capped by GPM)



Abbreviations: D-FLOT: Durvalumab, Fluorouracil; Leucovorin: Oxaliplatin and Docetaxel; FLOT: Fluorouracil; Leucovorin: Oxaliplatin and Docetaxel; GPM: general population mortality; KM: Kaplan-Meier; OS: overall survival.

2.3 *Health-related quality-of-life data used in the cost-effectiveness analysis*

Health-related quality-of-life (HRQoL) data were modelled in line with the Company's base case for both the EF and RD health states. Specifically, in the EF health state, a general population-capped EF utility value of 0.840 was selected. In the RD health state, a utility value of 0.747 was selected based on the value for the RD health state accepted by NICE in the appraisal of nivolumab for patients with oesophageal cancer (OC) or GOJC (TA746), and additionally used in the NICE appraisal of nivolumab in patients with previously treated resectable advanced/recurrent OC (TA707).^{11, 15}

The Company recognise that the utility value of 0.747 for RD may not fully capture the utility decrement associated with progressed disease, given that as GOA progresses, patients experience increasingly significant reductions in HRQoL, in line with the worsening physical and emotional symptoms.¹⁶ Moreover, disease recurrence, and the fear of it, further diminish patients' HRQoL.¹⁷

This is supported by clinical advice to the EAG that the symptom burden of progressed disease is significant and could result in people experiencing lower utility than used in the Company's base case. As such, at CQs, the EAG suggested using the utility value of 0.399 from Lee *et al.* 2018, a cross-sectional survey of 326 adults.¹⁸

The Company agree with the EAG that a RD utility value of 0.399 may better reflect clinical advice to the EAG, as well as the feedback received by the Company regarding the considerable Company evidence submission template for durvalumab in combination for neoadjuvant and adjuvant treatment of resectable gastric and gastro-oesophageal junction cancer [ID6374]

symptom burden associated with disease recurrence. As such, whilst the alternative base case maintains a utility value of 0.747 in the RD health state, this should be considered a conservative estimate of the quality of life (QoL) decrement associated with progression; the true decrement is likely substantially higher.

For completeness, a scenario analysis using a RD utility value of 0.399 was conducted (Section 3.2.3). As shown, this scenario analysis reduces the ICER, further highlighting that the Company's base case and the Company's alternative base case are likely conservative.

2.4 Cost and healthcare resource use

2.4.1 Intervention and comparators' costs and resource use

In the alternative base case analysis (requested by the EAG), the intervention and comparator were costed in line with the Company's base case (see Section 3.5.1 of the Company evidence submission), with the exception of wastage costs.

In the Company's base case, vial sharing for intravenous (IV) chemotherapy drugs was assumed, and therefore associated vial wastage costs were not considered. However, in line with EAG preference, the alternative base case does not include vial sharing so associated wastage costs are applied. Of note, the impact of vial sharing for FLOT chemotherapy is equivalent between the intervention and comparator arms, and as such, the effect of vial sharing only impacts subsequent treatments. A scenario analysis whereby vial wastage is included was also explored to align with the Company's base case (see Section 3.2.3).

Additionally, treatment administration costs and surgery costs sourced from the NHS Reference costs have been updated to 2024/2025 costs, and are presented in Table 9 and Table 10, respectively.¹⁹

Table 9. Treatment administration costs

Administration type	Costs (per administration)
IV, simple chemotherapy	£256.03
IV, subsequent dose(s)	£290.30
IV, complex chemotherapy	£430.62
Oral therapies	£0

Abbreviations: IV: intravenous.

Table 10: Surgery costs

	Perioperative D-FLOT	Perioperative FLOT chemotherapy
Unit cost of surgery ^a	£18,788.28	
Proportion of patients with attempted/performed surgery	90.9%	90.3%
Cost of surgery by treatment arm ^b	£17,084	£16,965

Footnotes: ^a Unit costs of surgery (total gastrectomy) were sourced from the NHS Reference costs 2024/2025: FF01A-C Very Complex, Oesophageal, Stomach or Duodenum Procedures, 19 years and over, with CC score 0-6+ (weighted average – elective inpatients) in line with NG83;^{20, 21} ^b Costs of surgery by treatment were estimated by weighting the unit costs for surgery based on the proportion of patients receiving surgery.

Company evidence submission template for durvalumab in combination for neoadjuvant and adjuvant treatment of resectable gastric and gastro-oesophageal junction cancer [ID6374]

Abbreviations: FLOT: Fluorouracil, Leucovorin, Oxaliplatin and Docetaxel; NHS: National Health Service

2.4.2 Health-state unit costs and resource use

In line with the Company's base case, health care resource use (HCRU) inputs relating to clinical visits, hospitalisation, and imaging for each of the model health states were sourced from NICE TA746, and supplemented with clinical expert validation.^{1, 11} The approach to modelling HCRU costs in the alternative base case is also aligned to the Company's base case (see Section 3.5.2 of the Company evidence submission), however unit costs sourced from the NHS Reference costs have now been updated to the 2024/2025 costs and other costs have been inflated to 2024/2025 prices, where applicable.¹⁹ The updated costs are presented in Table 11. For completeness, the updated total HCRU costs per cycle are presented in Table 12.

Table 11: Healthcare resource unit costs

Resource item	Unit cost	Source
Oncologist	£348.71	Healthcare costing standards for England (2016); Costing year 2018/2019, inflated to 2024/2025 prices ²²
CT scan/MRI	£207.92	NHS Reference costs 2024/2025: Computerised Tomography (weighted average of direct access, outpatient and other costs; RD20A, RD21A, RD22Z, RD23Z, RD24Z, RD25Z, RD26Z, RD27Z) ¹⁹
Clinical consultation	£189.91	NHS Reference costs 2024/2025: Medical Oncology (weighted average of consultant led and nonconsultant led; WF01A, WF01B, WF01C, WF01D, WF02A, WF02B, WF02C) ¹⁹
Hospitalisation	£1,139.33	NHS Reference costs 2024/2025: Malignant GI Tract Disorders (weighted average of elective inpatients) FD11A, FD11B, FD11C, FD11D, FD11E, DF11F, F11G, FD11H, FD11J, FD11K) ¹⁹
Palliative care specialist care	£71.48	PSSRU 2024 – Specialist Nursing, Palliative/Respite Care, Adult, Non-face-to-face, inflated to 2024/2025 prices ¹⁹
Full blood count	£2.22	NHS Reference costs 2024/2025: Haematology; PATH05 822 chemical pathology service ¹⁹
Renal function test	£1.59	NHS Reference costs 2024/2025: Clinical Biochemistry; PATH04 822 chemical pathology service ¹⁹
Hepatic function test	£1.59	NHS Reference costs 2024/2025: Clinical Biochemistry; PATH04 822 chemical pathology service ¹⁹

Abbreviations: CT: computed tomography; MRI: magnetic resonance imaging; GI: Gastrointestinal; NHS: National Health Service.

Table 12: Total healthcare resource use cost per cycle

Resource item	Cost per cycle
EF	£200.89
RD	£922.02

Abbreviations: EF: event-free; RD: recurred disease

As per the Company's base case, a one-time terminal care cost was applied to all patients in the model upon transition to death, in order to capture end-of-life healthcare costs. The terminal care cost has since been inflated to 2024/2025 prices (see Table 13).

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Table 13: Terminal care cost

	Unit cost	Source
Terminal care	£10,198.35	Georghiou <i>et al.</i> (2014). ²³ As per NICE TA746. ¹¹ Costing year 2010/2011, inflated to 2024/2025 prices

Abbreviations: NICE: National Institute for health and Care Excellence; TA: technology appraisal.

2.4.3 Adverse reaction unit costs and resource use

In the alternative base case analysis (requested by the EAG), the approach to modelling adverse reaction unit cost and resource use is aligned with the Company's base case (see Section 3.5.3 of the Company evidence submission). The costs of managing adverse events (AEs) were sourced from the NHS Reference costs, as a weighted average of total treatment costs for each AE considered (see Table 14). These costs have been updated to the 2024/2025 costs.¹⁹ For completeness, the updated total one-off AE costs applied in the first cycle of the model are presented in Table 15.

Table 14: AE unit costs

Adverse event	Unit cost	Source
Neutropenia	£2,602.11	NHS Reference costs 2024/2025: Total HRGs Weighted average SA35A-E. ¹⁹ As per NICE TA997. ²⁰
Neutrophil count decreased	£2,602.11	Assumed equal to neutropenia
Diarrhoea	£539.25	NHS Reference costs 2024/2025: Non-elective short stay. FD10M. ¹⁹ Non-Malignant Gastrointestinal Tract Disorders without Interventions, with CC Score 0. As per NICE TA997. ²⁰
WBC-count decreased	£2,602.11	Assumed equal to neutropenia
Anaemia	£808.43	NHS Reference costs 2024/2025: Non-elective short stay. ¹⁹ Weighted average of SA01G-K. As per NICE TA997. ²⁰

Abbreviations: AE: adverse event; HRG: HealthCare Resource Group; NICE: National Institute of Health and Care Excellence; NHS: National Health Service; WBC: white blood cell; TA: technology appraisal.

Table 15: Total AE (one-off) costs

Treatment arm	Total cost (one-off)
Perioperative D-FLOT	£1,274.90
Perioperative FLOT chemotherapy	£1,388.49

Abbreviations: AE: adverse events; FLOT: Fluorouracil, Leucovorin, Oxaliplatin and Docetaxel.

2.5 Summary of base case analysis inputs

For completeness, a summary of inputs used in the alternative base case analysis (including those which have not changed since the Company base case) is presented in Table 16.

Table 16: Summary of variables applied in the economic model (alternative cost-effectiveness analysis)

Variable	Value	Reference to section in Company evidence submission or addendum

Company evidence submission template for durvalumab in combination for neoadjuvant and adjuvant treatment of resectable gastric and gastro-oesophageal junction cancer [ID6374]

Model settings			
Discount rate (costs and benefits)	3.5%		Section 2.1
Time horizon	█ years		
Patient baseline characteristics			
Mean age, years (SE)	██████		Section 3.2.1 of Company evidence submission
Proportion of male patients (%)	71.9		
Mean body weight, kg (SE)	██████		
Mean height, cm (SE)	██████		
Mean BSA, m² (SE)	██████		
Efficacy			
Survival curve	Perioperative D-FLOT	Perioperative FLOT chemotherapy	Section 2.2.1
EFS	Generalised gamma	Generalised gamma	
OS	Generalised gamma	Generalised gamma	
AEs			
Adverse event	Perioperative D-FLOT	Perioperative FLOT chemotherapy	Section 3.3.5 of Company evidence submission
Neutropenia	████	████	
Neutrophil count decreased	████	████	
Diarrhoea	████	████	
WBC-count decreased	████	████	
Anaemia	████	████	
Utility inputs			
EF	0.840		Section 3.4.5 of Company evidence submission
RD	0.747		
Adverse event disutility			
	Utility decrement	Duration of AE (days)	Section 3.4.4 of Company evidence submission
Neutropenia	-0.090 (0.015)	30.4	
Neutrophil Count decreased	-0.090 (0.015)	30.4	
Diarrhoea	-0.047 (0.009)	30.4	
White blood cell count decreased	-0.090 (0.015)	30.4	
Anaemia	-0.115 (0.023)	30.4	
Resource use			
Cost of surgery, perioperative D-FLOT	£17,084		Section 2.4.1 and Section 2.4.2.
Cost of surgery, perioperative FLOT chemotherapy	£16,965		
Total healthcare resource use per cycle, EF	£200.89		Section 3.5.2 of Company Submission
Total healthcare resource use per cycle, RD	£922.02		

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Terminal care cost (one-off)	£10,198.35			
	Frequency per month			
Resource item	EF	RD	Unit cost	
Oncologist	0.361	0.361	£348.71	
CT scan/MRI	0.361	0.400	£207.92	
Clinical consultation	0.000	0.665	£189.91	
Hospitalisation	0.000	0.413	£1,139.33	
Palliative care specialist care	0.000	1.561	£71.48	
Full blood count	0.000	0.961	£2.22	
Renal function test	0.000	0.704	£1.59	
Hepatic function test	0.000	0.739	£1.59	
Drug acquisition costs				Section 3.5.1 of Company evidence submission
Treatment	Cost per pack			
Durvalumab (list price; 120mg)	£592.000			
Durvalumab (list price; 500 mg)	£2,466.00			
5-FU (2.5%)	£4.082			
5-FU (5%)	£4.621			
5-FU (5%)	£6.269			
Oxaliplatin	£6.482			
	£14.269			
	£11.312			
Leucovorin	£27.633			
	£15.800			
	£60.966			
Docetaxel	£4.486			
	£9.732			
	£19.702			
Subsequent treatments				Section 3.5.1 of Company evidence submission
Regimen	Perioperative D-FLOT	Perioperative FLOT chemotherapy		
Cytotoxic chemotherapy				
Oxaliplatin	■	■		
Cisplatin	■	■		
5-FU	■	■		
Capecitabine	■	■		
Irinotecan	■	■		
Targeted therapy				
Trastuzumab	■	■		
IO monotherapy				
Nivolumab	■	■		
Pembrolizumab	■	■		
Administration costs (per admin)				

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IV, simple chemotherapy	£256.03	Section 2.4.1
IV, subsequent dose(s)	£290.30	
IV, complex chemotherapy	£430.62	
Oral therapies	£0.00	
AE costs		
Total one-off AE cost, perioperative D-FLOT	£1,274.90	Section 2.4.3
Total one-off AE cost, perioperative FLOT chemotherapy	£1,388.49	

Abbreviations: AE: adverse event; BSA: body surface area; CT: computed tomography; EF: event-free; D-FLOT: Durvalumab, Fluorouracil: Leucovorin, Oxaliplatin and Docetaxel; FLOT: Fluorouracil, Leucovorin, Oxaliplatin and Docetaxel; IV: intravenous; MRI: magnetic resonance imaging; RD: recurred disease; SE: standard error; TP: transition probability.

3. Cost-effectiveness model results

The results of the alternative base case analysis requested by the EAG are presented in the following sections.

3.1 *Base-case results*

The probabilistic cost-effectiveness results for the alternative base case analysis of perioperative D-FLOT versus perioperative FLOT chemotherapy are presented in Table 17. The deterministic base case cost-effectiveness results are presented in Table 18. All results presented throughout Section 3 include the commercial access agreement price for durvalumab (detailed in Section 3.5.2 of the Company evidence submission).

The probabilistic cost-effectiveness results for the alternative base case analysis show the total costs associated with perioperative D-FLOT are estimated to be £[REDACTED] compared with £[REDACTED] for patients treated with perioperative FLOT chemotherapy (incremental cost of £[REDACTED]). The total quality-adjusted life years (QALYs) are estimated to be higher for patients receiving perioperative D-FLOT versus perioperative FLOT chemotherapy ([REDACTED] versus [REDACTED]; incremental QALYs: [REDACTED]), resulting in an ICER for perioperative D-FLOT of £12,367 per QALY gained versus perioperative FLOT chemotherapy.

The probabilistic cost-effectiveness results for the alternative base case analysis are consistent with the deterministic results. In the deterministic alternative base case analysis, perioperative D-FLOT was associated with [REDACTED] more QALYs and increased total costs of £[REDACTED] in comparison to perioperative FLOT chemotherapy, resulting in an ICER of £12,030 per QALY gained versus perioperative FLOT chemotherapy alone. Therefore, both the probabilistic and deterministic ICERs from the alternative base case are considerably below the willingness to pay (WTP) threshold of £20,000 per QALY. The incremental net health benefit (NHB) at a WTP threshold of £30,000 per QALY is 0.90.

Taken together, the deterministic and probabilistic results from the alternative base case (as per the EAG's request) demonstrate that perioperative D-FLOT represents a cost-effective use of NHS resources in the UK. Notably, the results from the alternative base case are highly consistent with the results from the Company's base case (via a semi-Markov STM; see Section 3.3).

Table 17: Probabilistic base case results (alternative cost-effectiveness analysis)

Intervention	Total Costs	Total LYs	Total QALYs	Incremental Costs	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Perioperative D-FLOT	£■■■■	9.88	■■■■	–	–	–	–
Perioperative FLOT chemotherapy	£■■■■	7.74	■■■■	■■■■	2.14	■■■■	£12,367

Abbreviations: D-FLOT: durvalumab plus FLOT; FLOT: fluorouracil, leucovorin, oxaliplatin and docetaxel; ICER: incremental cost-effectiveness ratio; LY: life years; NHB: net health benefit; QALYs: quality-adjusted life years.

Table 18: Deterministic base case results (alternative cost-effectiveness analysis)

Intervention	Total Costs	Total LYs	Total QALYs	Incremental Costs	Incremental LYs	Incremental QALYs	ICER (£/QALY)	Incremental NHB at £30,000
Perioperative D-FLOT	£■■■■	9.13	■■■■	–	–	–	–	–
Perioperative FLOT chemotherapy	£■■■■	7.28	■■■■	£■■■■	1.84	■■■■	£12,030	0.90

Abbreviations: D-FLOT: durvalumab plus FLOT; FLOT: fluorouracil, leucovorin, oxaliplatin and docetaxel; ICER: incremental cost-effectiveness ratio; LY: life years; NHB: net health benefit; QALYs: quality-adjusted life years.

3.2 *Exploring uncertainty*

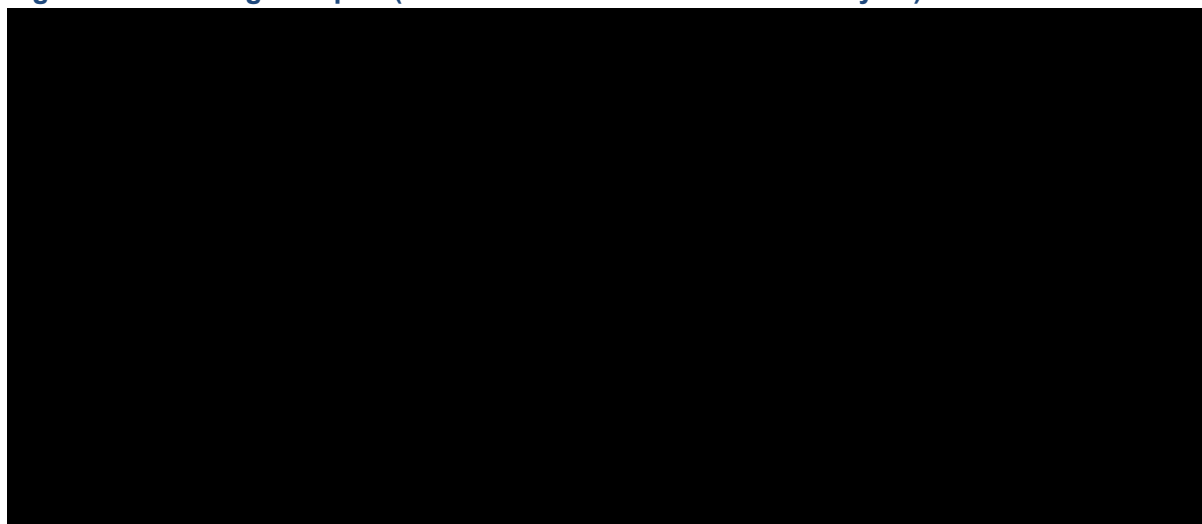
3.2.1 Probabilistic sensitivity analysis

A probabilistic sensitivity analysis (PSA) was conducted in order to assess the impact of parameter uncertainty on the results of the CEM. The PSA was run for 1,000 iterations and in each iteration model inputs for all parameters were randomly drawn from specified distributions. Where possible the 95% CIs or standard errors (SEs) associated with each parameter were used to define the distribution, otherwise it was assumed that the standard error of the parameter would be 10% of the mean value.

An ICER convergence plot for the PSA is presented in Figure 14, which demonstrated that the cumulative ICER stabilised after approximately 100 iterations. The probabilistic cost-effectiveness planes for perioperative D-FLOT versus perioperative FLOT chemotherapy alone are presented in Figure 15.

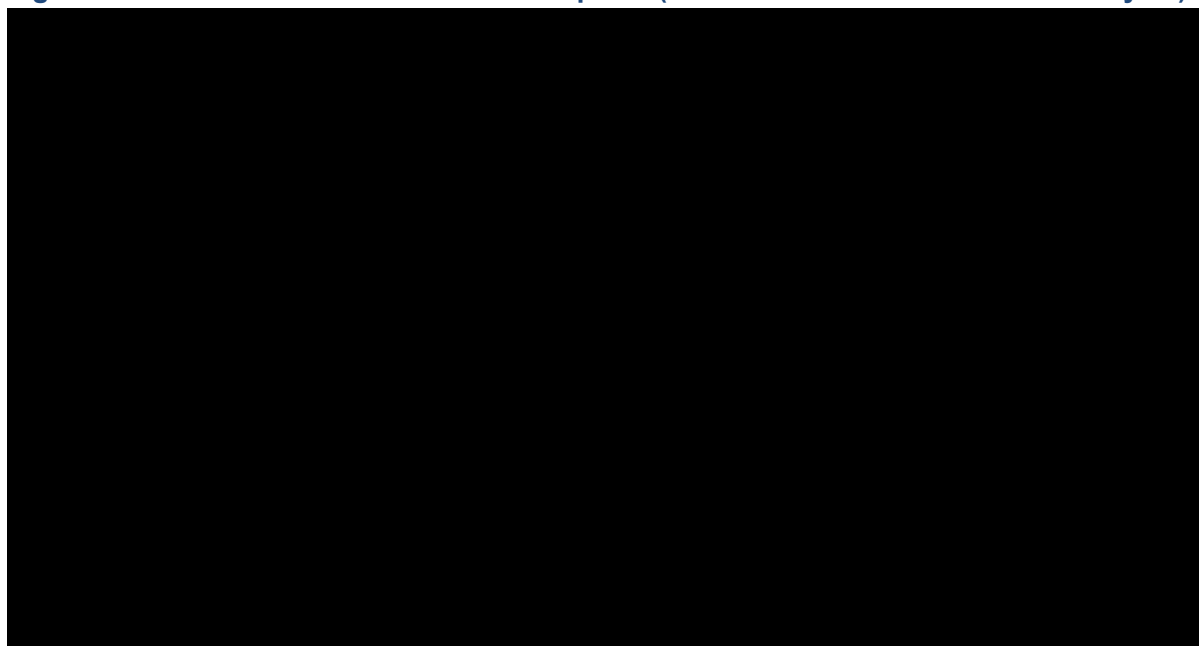
The cost-effectiveness acceptability plots are presented in Figure 16; the PSA found the probability of perioperative D-FLOT being a cost-effective use of NHS resources to be ■% and ■% at a WTP threshold of £20,000 and £30,000 per QALY gained, respectively.

Figure 14: Convergence plot (alternative cost-effectiveness analysis)



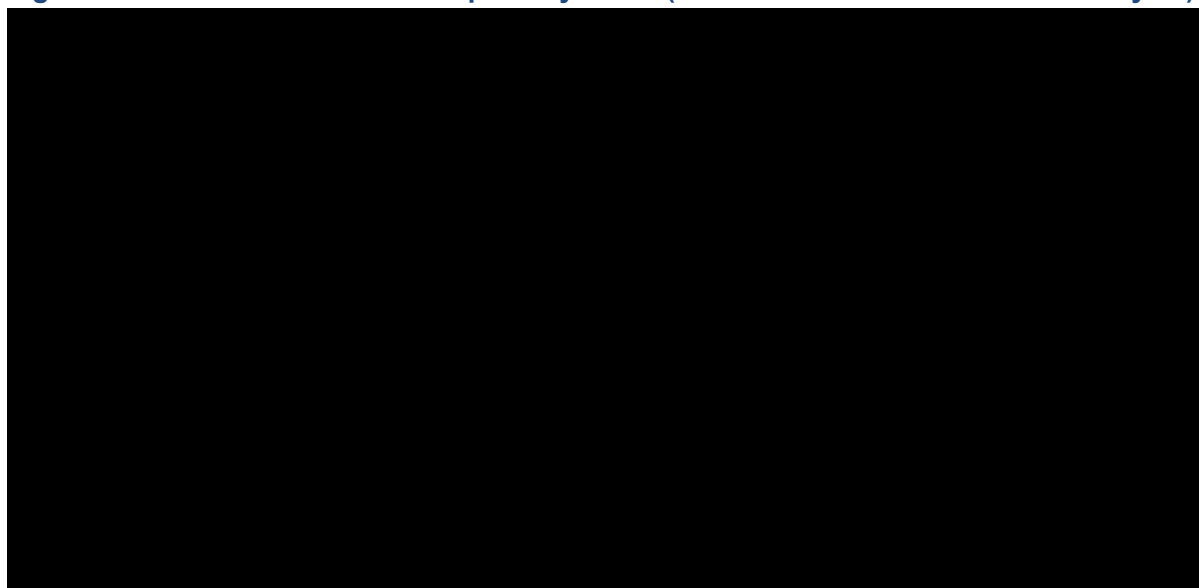
Abbreviations: ICER: incremental cost-effectiveness ratio; PSA: probabilistic sensitivity analysis.

Figure 15: Probabilistic cost-effectiveness plane (alternative cost-effectiveness analysis)



Abbreviations: FLOT: fluorouracil, leucovorin, oxaliplatin and docetaxel; QALYs: quality adjusted life years.

Figure 16: Cost-effectiveness acceptability curve (alternative cost-effectiveness analysis)



Abbreviations: FLOT: fluorouracil, leucovorin, oxaliplatin and docetaxel.

3.2.2 Deterministic sensitivity analysis

In order to assess the robustness of the alternative base case cost-effectiveness results, a deterministic sensitivity analysis (DSA) was conducted by varying the input for each parameter in the model, whilst keeping all other inputs the same. In the DSA, the base-case inputs for parameters were varied using the 95% CIs where available. In the absence of 95% CIs, upper and lower bounds were calculated assuming a SE of 10%.

A tornado diagram showing the top 10 most influential parameters on the ICER for perioperative D-FLOT versus perioperative FLOT chemotherapy is presented in Figure 17. Of note, the top three influential parameters on the ICER in this alternative cost-effectiveness analysis via a PSM

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(requested by the EAG) are the same as in the Company's cost-effectiveness analysis via a semi-Markov model.

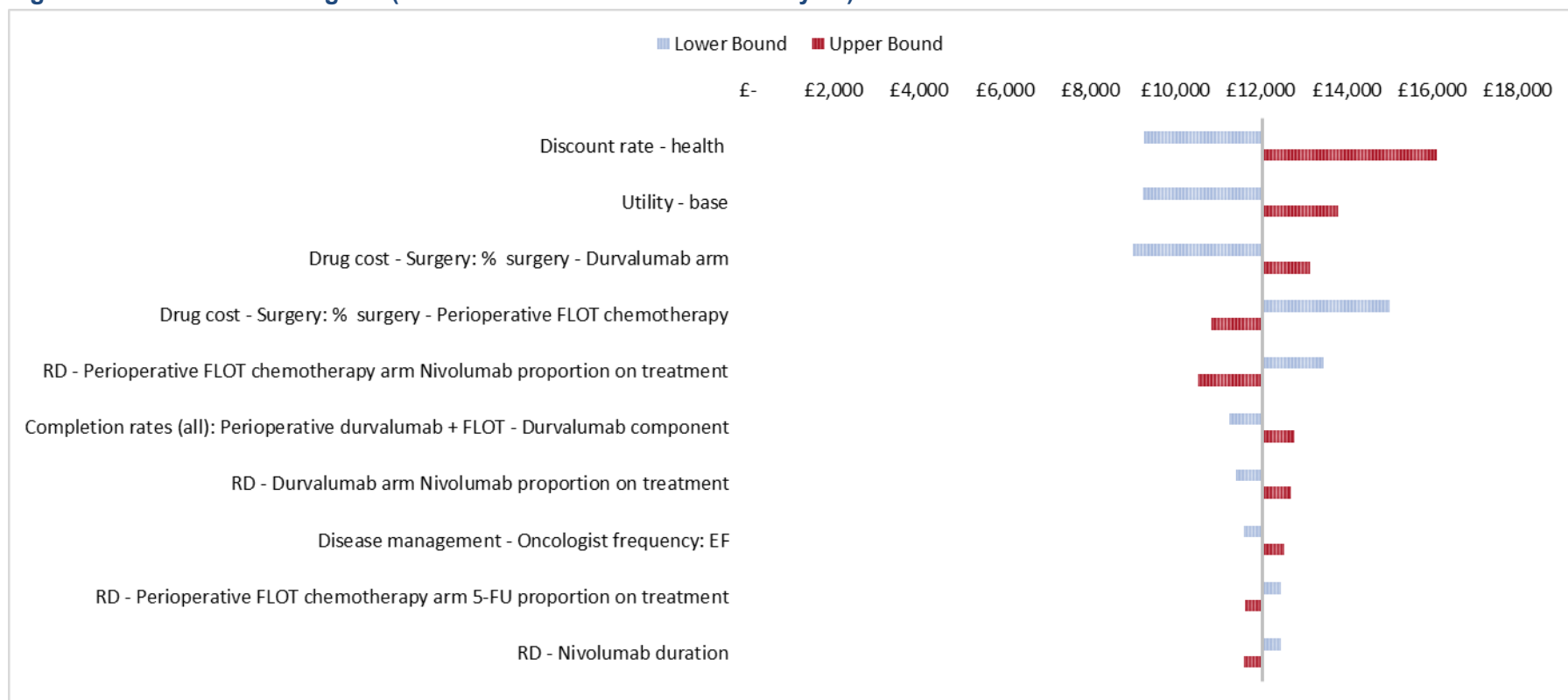
Overall, all variables tested had a minimal impact on the ICER and on the cost-effectiveness conclusions; the ICER upper bounds of all variables remained below £20,000/QALY, reflecting the robustness of the alternative base case results and the minimal uncertainty regarding perioperative D-FLOT being a cost-effective use of NHS resources in this population when compared to perioperative FLOT chemotherapy (the current SoC).

The ICER was found to be most sensitive to the discount rate for all costs and benefits. When varying the discount rate between 1.5% and 6%, the ICER varied between £9,253 and £16,109 highlighting that the greatest driver of the ICER did not preclude perioperative D-FLOT from being cost-effective compared to perioperative FLOT chemotherapy. As with the Company's base case, in the alternative base case, a discount of 3.5% was applied in line with NICE PMG36 and therefore, this should be considered to represent a minimal source of uncertainty.⁵

The variable with the second greatest impact on the ICER was the utility value for the EF health state, which when varied between [REDACTED] and [REDACTED], resulted in ICERs of £9,220/QALY and £13,803/QALY, respectively. As noted in Section 3.4.5 of the Company evidence submission, the utility value used in the Company's base case and alternative base case (0.840) was derived from the EQ-5D-5L data from the MATTERHORN trial, mapped onto the UK EQ-5D-3L value set ([REDACTED]), using the NICE preferred mapping algorithm and capped at the UK general population utility, given it was slightly higher than the age-adjusted general population.²⁴ UK clinical experts validated that the GPM-capped EF utility value was reasonable, and consistent with their understanding of QoL in patients with resectable GOA.¹ To further explore any uncertainty around the EF utility value, a scenario analysis was explored using the uncapped utility value, derived from the MATTERHORN trial (Section 3.2.3), which had a minimal impact on the ICER.

The proportion of patients receiving surgery in the D-FLOT and perioperative FLOT chemotherapy arms had the next greatest impact on the ICER. As detailed in Section 2.4.1, a one-time cost of surgical resection was included in the alternative base case for patients in the EF health state (90.9% and 90.3% in the D-FLOT and perioperative FLOT chemotherapy arms, respectively), to reflect the possibility that not all patients might receive surgery following neoadjuvant treatment. The overall impact of the proportion of patients receiving surgery was still minimal, with the ICER varying within £8,982/QALY and £13,150/QALY across the D-FLOT arm and between £10,844/QALY and £15,002/QALY in the perioperative FLOT chemotherapy arm. Moreover, because the data from MATTERHORN showed that D-FLOT did not impact the ability of patients to undergo surgery (see Section 2.6.4 of the Company evidence submission) the proportion of patients receiving surgery is not expected to differ substantially for patients receiving either treatment, so it lacks face validity to change the proportion of patients receiving surgery in one arm, without changing the other.

Figure 17: DSA tornado diagram (alternative cost-effectiveness analysis)



Abbreviations: DSA: deterministic sensitivity analyses; EF event-free; FLOT: fluorouracil, leucovorin, oxaliplatin and docetaxel; 5-FU: 5-fluorouracil; RD: recurred disease.

3.2.3 Scenario analysis

Scenario analyses were conducted to explore the impact of structural assumptions and alternative inputs on the results of the PSM. The majority of scenario analyses were conducted to align to the Company evidence submission, with a few additional scenario analyses, as detailed throughout Section 2 above. A complete list of the scenario analyses explored along with the rationale for their selection is provided in Table 19.

Table 19: Summary of scenario analyses (alternative cost-effectiveness analysis)

Model element	Alternative base case	Scenario analysis	Justification
EFS	Generalised gamma	1: Log-normal	The generalised gamma was selected in the alternative base case based primarily on statistical fit, visual fit and observed hazards. The generalised gamma also aligns with the Company's base case whereby the generalised gamma was selected to model TFR. The use of the log-normal distribution for EFS was explored in a scenario, given the log-normal provides strong statistical fit for both treatment arms, and reflects the observed hazard profile of the MATTERHORN EFS data.
OS	Generalised gamma	2: Log-normal	The generalised gamma was selected in the alternative base case based primarily on statistical fit and observed hazards, as well as clinical plausibility.⁹ The use of the log-normal distribution for OS was explored in a scenario, given the log-normal reflects the best statistically fitting curve choice for both treatment arms and reflects the observed hazard profile of the MATTERHORN OS data.
Cure assumption	No cure assumption	3a: Cure at 5 years; SMR of 1.0	In the alternative base case, no cure was assumed to align with the EAG preference on cure. To align to the Company's base case, this scenario analysis includes a cure assumption at five years, after which patients who are still in the EF health state are no longer at risk of recurrence, are no longer followed up regularly, and have a risk of death that is equal to that of

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Model element	Alternative base case	Scenario analysis	Justification
			the general population. This is in line with clinical expert feedback to the Company.¹ Clinical experts consulted by the Company as part of the Company evidence submission validated that the SMR of 1.1 accepted by NICE in the appraisal of nivolumab for early oesophageal or GOJC (TA746) is conservative, with the true SMR likely to be lower than 1.1 in UK clinical practice.^{1, 11} Therefore this scenario analysis explores the impact of a cure assumption at five years, with no SMR applied (i.e., an SMR of 1.0).
		3b: Cure at 5 years; SMR of 1.1	In the alternative base case, no cure was assumed to align with the EAG preference on cure. Whilst scenario 3a applies cure without an SMR as per expert feedback, a conservative scenario has been performed with an SMR of 1.1, to explore the impact of the SMR value on the ICER.¹
Utility values	UK general population utility cap applied (EF utility value: 0.840)	4a: UK general population utility cap excluded (EF utility value: [REDACTED])	The utility value for the EF health state derived from MATTERHORN ([REDACTED]) was higher than the gender- and age-adjusted utility value for the UK general population (0.840).²⁴ As such, the EF utility value was capped to the UK general population utility in the alternative base case. This scenario explored the impact of not capping the EF utility to the UK general population and using the utility value derived directly from the MATTERHORN trial.²
	RD utility value: 0.747, based on TA746 ¹¹	4b: RD utility value: [REDACTED], based on the data from MATTERHORN	Low numbers of EQ-5D-5L observations were recorded after progression or recurrence in the MATTERHORN trial (N=[REDACTED]).² Consequently, in the alternative base case, utility values for the RD health state were instead sourced from TA746.¹¹ For completeness, a scenario analysis using an RD utility value derived from MATTERHORN (with the decrement associated with recurrent disease based on the MMRM [REDACTED] removed from the general population-capped EF state utility value [0.840–[REDACTED]]), was explored.²

Model element	Alternative base case	Scenario analysis	Justification
		4c: RD utility value: 0.399, based on Lee <i>et al.</i> 2018 ¹⁸	Based on clinical advice to the EAG and the Company, the alternative base case is RD utility value is highly conservative and therefore a scenario analysis using an RD utility value of 0.399 from Lee <i>et al.</i> 2018 (a cross-sectional survey of 326 adults) was explored. ^{1, 18}
	Age-adjusted utility decrements included	4d: Age-adjusted utility decrements excluded	In the alternative base case analysis, age-adjusted utility decrements were applied in line with the NICE reference case (PMG36). ⁵ The impact of excluding age-adjusted utility decrements has been explored in a scenario analysis.
Subsequent treatments	The distribution of subsequent therapies informed by the MATTERHORN trial ^a and supplemented by UK clinical expert validation. ¹	5: All subsequent treatments included, regardless of whether they were received before/after progression	This scenario analysis explores the impact of including all subsequent treatments, regardless of whether they were received before/after progression. Of note, the alternative base case approach of including subsequent treatments for patients who had experienced progression and recurrence was aligned with validation from UK clinical experts collected as part of the Company evidence submission. ¹
Vial sharing	Excluded	6: Included	In the alternative base case analysis, vial sharing was not included, as per the EAG's preferred assumptions. This scenario explores the impact of excluding costs of vial wastage on the ICER.
Time horizon	■ years	7: 30 years	This scenario was conducted to explore the impact of using a shorter model time horizon.
Discounting costs/effects	3.5%	8: 1.5%	A discount of costs/effect of 3.5% is in line with NICE PMG36. ⁵ This scenario explores the impact of reducing this discount on the ICER.

^a Distribution of subsequent therapies informed from the MATTERHORN trial for patients who had experienced progression/recurrence (i.e., non-death event) as an EFS event.
Abbreviations: EAG: Evidence Assessment Group; EF: event-free; EFS: event-free survival; EQ-5D-5L: EuroQol 5-Dimension 5-Level; GOJC: Gastric Oncology Joint Committee; ICER: incremental cost-effectiveness ratio; MMRM: mixed model for repeated measures; OS: overall survival; RD: recurred disease; SMR: standardised mortality ratio; TFR: time to first recurrence; UK: United Kingdom.

A summary of the deterministic results of these scenario analyses is presented in Table 20, inclusive of the commercial access agreement for D-FLOT. In these analyses the conclusions of the alternative base case analysis were unchanged, with the ICER for the comparison of perioperative D-FLOT and perioperative FLOT chemotherapy being cost-effective (ICER range: £9,611–£13,396 per QALY) across the full range of scenario analyses conducted, demonstrating the minimal uncertainty and robustness associated with the alternative base case results. All scenarios demonstrated positive incremental QALYs (range: ■) in favour of perioperative D-FLOT.

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Table 20: Summary of scenario analysis results – deterministic (alternative cost-effectiveness analysis)

Scenario		Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Alternative base case		████	██	£12,030
1	EFS – log-normal	████	██	£13,396
2	OS – log-normal	████	██	£12,394
3a	Cure applied with SMR of 1	████	██	£11,222
3b	Cure applied with SMR of 1.1	████	██	£11,474
4a	No UK population cap applied	████	██	£12,135
4b	Alternative RD utility value based on MATTERHORN	████	██	£12,177
4c	RD utility value set to 0.399	████	██	£10,666
4d	Do not apply age-adjusted utility	████	██	£11,264
5	Subsequent therapy distributions based on all patients with treatment in MATTERHORN	████	██	£12,757
6	Vial sharing applied	████	██	£11,770
7	Time horizon – 30 years	████	██	£12,125
8	Discounting costs/effects – 1.5%	████	██	£9,611

Abbreviations: EFS: event-free survival; ICER: incremental cost-effectiveness ratio; OS: overall survival; QALY: quality-adjusted life year; RD: recurred disease; SMR: standardized mortality ratio; UK: United Kingdom.

3.3 Interpretation and conclusions of the economic evidence

As detailed in Section 1, the Company's base case employed a semi-Markov STM to determine the cost-effectiveness of perioperative D-FLOT versus perioperative FLOT chemotherapy in resectable GOA. Whilst the Company maintains that the semi-Markov STM structure is appropriate for this decision problem, the Company developed a *de novo* PSM in response to a request from the EAG for a PSM that permits the direct extrapolation of OS data from MATTERHORN.

The alternative cost-effectiveness analysis via a PSM demonstrates that perioperative D-FLOT represents a cost-effective use of NHS resources, with a deterministic ICER of £12,030 and a probabilistic ICER of £12,367. Of note, the Company's base case demonstrated highly comparable results (deterministic ICER of £12,416 and a probabilistic ICER of £12,508; see Section 3.10 of the Company evidence submission). Whilst the Company's base case (via a STM) and this alternative analysis (via a PSM) are not directly comparable due to slight differences in base case assumptions, the concordant findings across both models strongly support the cost-effectiveness of perioperative D-FLOT in resectable GOA, with consistent ICERs considerably below the £20,000 WTP threshold.

Additionally, as the EAG considered that the Company's base case did not predict the OS for perioperative D-FLOT or perioperative FLOT chemotherapy that was demonstrated in the MATTERHORN trial at three years, for clarity Table 21 below presents the 2-, 3- and 5-year OS modelled in the Company's base case (via a STM) and in the alternative base case (via PSM), alongside OS from the MATTERHORN trial (at both DCOs). For completeness, OS data for patients who received perioperative FLOT in the FLOT4 trial is also presented to externally validate the modelled OS.¹⁴

As shown in Table 21, the PSM predicts OS at 2- and 3-years that is highly aligned with MATTERHORN OS data at the final OS analysis (DCO3), thereby addressing the EAG's concerns regarding the semi-Markov STM modelling approach. For perioperative D-FLOT, at Year 2 and Year 3, the alternative base case (via a PSM) predicts OS within █% of the MATTERHORN data. For perioperative FLOT chemotherapy, at Year 2, the modelled predicted OS and MATTERHORN DCO3 are aligned with a █% difference in estimates; at Year 3, the difference is █%. Of note, the model-predicted OS estimates are overpredicted to a greater extent versus the MATTERHORN data in the perioperative FLOT chemotherapy arm compared with the perioperative D-FLOT arm at both Year 2 and Year 3, indicating that the alternative base case may in fact represent a conservative estimate of the cost-effectiveness of perioperative D-FLOT versus perioperative FLOT chemotherapy.

Table 21: Comparison of OS modelled by the semi-Markov STM and the PSM versus MATTERHORN trial OS

	2-year	3-year	5-year
Perioperative D-FLOT			
MATTERHORN DCO2, % (95% CI)	75.7 █	█	NR
MATTERHORN DCO3, % (95% CI)	75.5 █	68.6 █	NR
Semi-Markov STM Model, %	█	█	█

Company evidence submission template for durvalumab in combination for neoadjuvant and adjuvant treatment of resectable gastric and gastro-oesophageal junction cancer [ID6374]

PSM Model, %	████	████	████
Perioperative FLOT chemotherapy			
MATTERHORN DCO2, % (95% CI)	70.4 (████)	████	NR
MATTERHORN DCO3, % (95% CI)	70.4 (████)	61.9 (████)	NR
FLOT4, % (95% CI)	68 (63, 73)	57 (52, 62)	45.0 (38, 51)
Semi-Markov STM Model, %	████	████	████
PSM Model, %	████	████	████

Abbreviations: CI: confidence interval; DCO: data cut-off; D-FLOT: Durvalumab, Fluorouracil, Leucovorin, Oxaliplatin and Docetaxel; FLOT: fluorouracil, leucovorin, oxaliplatin and docetaxel; OS: overall survival; PSM: partitioned survival model; STM: state transition model.

Sources: AstraZeneca Data on File (MATTERHORN Clinical Study Report DCO2),² AstraZeneca Data on File (MATTERHORN Clinical Study Report DCO3),³ Janjigian et al. 2025,²⁵ Tabernero, *et al.* Presented at ESMO 2025,⁴ Al-Batran et al. 2019.¹⁴

3.4 Conclusion

The Company maintains that the semi-Markov STM approach used in the Company base case remains appropriate for this decision problem. However, in response to a request from the EAG, the Company has developed a *de novo* PSM informed by OS and EFS data from the MATTERHORN trial. Results of the Company's base case semi-Markov STM and the EAG-requested PSM are highly consistent. Together, the Company's base case and the alternative cost-effectiveness analysis via a PSM requested by the EAG provide comprehensive and consistent evidence for the cost-effectiveness of perioperative D-FLOT versus the current SoC for patients with resectable GOA, regardless of the modelling approach used.

Patients with resectable GOA have a critical unmet need for novel regimens that enhance the efficacy of FLOT, improve long-term disease control and ultimately increase survival rates and the likelihood of cure.²⁶ As shown by the results of the MATTERHORN trial, perioperative D-FLOT will prevent or delay disease progression and recurrence, without compromising patient HRQoL or their ability to undergo surgery, making it a highly impactful and efficacious treatment regimen. If recommended, perioperative D-FLOT will address the significant unmet needs within the resectable GOA disease setting.

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Appendix A: MATTERHORN OS at DCO3

Since the difference in OS between the D-FLOT arm and control arm of the MATTERHORN trial was not statistically significant at DCO2 (see Section 2.6.2 of the Company Evidence Submission), in line with the study protocol an additional OS analysis was performed at approximately 3 years of follow up after the last patient was randomised in the trial.²⁷ DCO3 occurred approximately 8 months after DCO2 (DCO3: 1st September 2025) and at the time of DCO3, the OS data had an overall maturity of 37.1%.^{3, 4} Median duration of follow-up was 43.0 months in the D-FLOT arm and 42.9 months in the control arm.

At DCO3, median OS was not reached in either treatment arm (Table 22).⁴ After approximately 13 months post-randomisation, there was a clear and sustained separation in the KM curves of OS in favour of the D-FLOT arm (Figure 18) which remained consistent over the duration of follow up with numerical improvements in OS rates in the D-FLOT arm compared to the control arm at 18 months (81.1% vs. 77.1%), 24 months (75.7% vs. 70.4%) and 36 months (68.6% vs. 61.9%).⁴

At the final OS analysis (DCO3), D-FLOT demonstrated a statistically significant OS benefit versus the control arm (HR: 0.78; 95% CI: 0.63, 0.96; 2-sided p=0.021).⁴

Table 22. Summary of OS (FAS, DCO3)

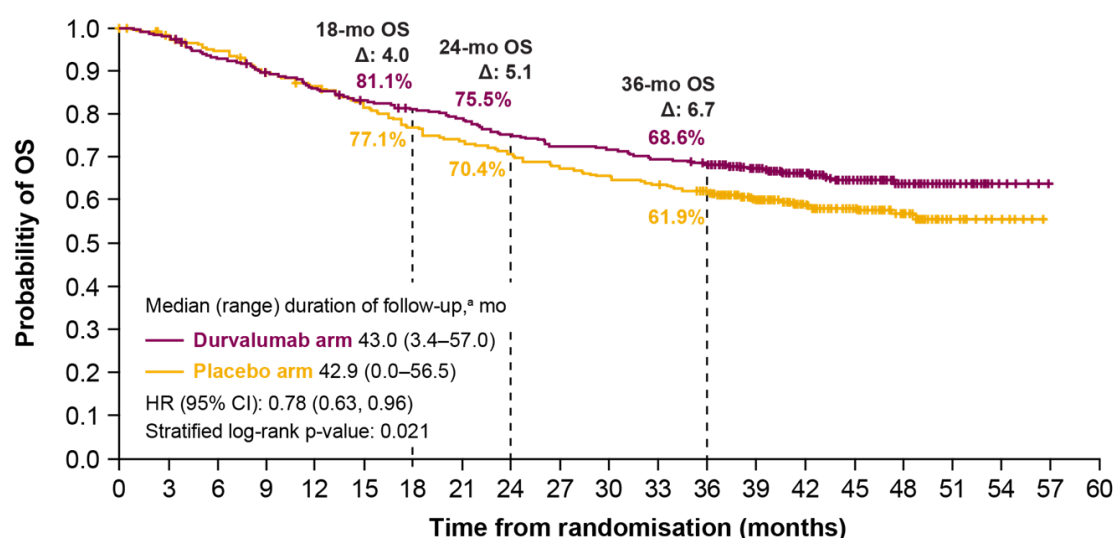
	D-FLOT arm (n=474)	Control arm (n=474)
Total number of deaths, n (%)	██████	██████
HR ^a	0.78	
95% CI	0.63, 0.96	
2-sided p-value ^b	0.021	
Median OS, ^c months (95% CI)	NC (NC, NC)	NC (NC, NC)
Landmark OS,^c % (95% CI)		
12 months	85.8 (82.3, 88.6)	85.6 (82.1, 88.5)
18 months	81.1 (77.3, 84.4)	77.1 (73.0, 80.7)
24 months	75.5 ██████	70.4 (66.0, 74.3)
30 months	████████	████████
36 months	68.6 ██████	61.9 ██████

Footnotes: The threshold to declare statistical significance at DCO3 was p<0.0499, with a fixed alpha spend of 4.99% (2-sided) allocated for the final analysis of OS. ^a 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 D-FLOT arm. The CI is calculated using a profile likelihood approach. ^b Derived using a stratified log-rank test adjusted for geographic region, clinical lymph node status, and PD-L1 expression status at randomisation. ^c Calculated using the KM technique.

Abbreviations: CI: confidence interval; DCO: data cut-off; FAS: full analysis set; HR: hazard ratio; IA: interim analysis; KM: Kaplan-Meier; NC: not calculated; NR: not reached; OS: overall survival; RECIST: Response Evaluation Criteria in Solid Tumours.

Source: AstraZeneca Data on File (MATTERHORN Clinical Study Report; DCO3);³ Tabernero, *et al.* Presented at ESMO 2025.⁴

Figure 18. KM curves for OS (FAS, DCO3)



Footnotes: Cross 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 favours the D-FLOT 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. ^a In censored participants.

Abbreviations: CI: confidence interval; DCO: data cut-off; FAS: full analysis set; HR: hazard ratio; KM: Kaplan-Meier; OS: overall survival; PD-L1: programmed death-ligand 1.

Source: Tabernero, *et al.* Presented at ESMO 2025.⁴

Single Technology Appraisal

Durvalumab in combination for neoadjuvant and adjuvant treatment of resectable gastric and gastro-oesophageal junction adenocarcinoma [ID6374]

EAG report – factual accuracy check and confidential information check

“Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release.” (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Monday 2 February 2026** using the below comments table.

All factual errors will be highlighted in a report and presented to the appraisal committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and information that is submitted as **confidential** should be highlighted in turquoise and all information submitted as **depersonalised data** in pink.

Issue 1 Description of pCR data from MATTERHORN

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 3.3.1 Page 35 Description EAG report states: "At DCO1, the pCR rate was 12.0% higher in the D-FLOT arm than in the FLOT arm (Table 6). The company reported that this treatment effect is clinically meaningful (CS, p61)."	Please can the text be amended to include that this treatment effect is clinically meaningful and statistically significant.	The improved pCR rate for the D-FLOT versus the FLOT arm was statistically significant and clinically meaningful. The statistically significant nature of the treatment effect should be mentioned to accurately portray the Company's presentation of these data in the Company submission.	The EAG has amended the text as proposed. The EAG comment has also been amended so the EAG now highlights the relevance of the outcome to the decision problem.

Issue 2 Statements related to median duration of follow-up in the MATTERHORN trial

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Sections 2.1 and 3.2.2 Pages 16 and 27 Description The EAG report states that median follow-up for DCO3 is not available. For example: Page 16: "Median follow-up not reported for DCO3".	Please can this sentence be removed and/or replaced with the median duration of follow-up at DCO3 (D-FLOT arm: 43.0 months; FLOT arm: 42.9 months) wherever relevant in the EAG report.	The median duration of follow-up at DCO3 is reported in Tabernero et al. (2025) which was provided in the reference pack alongside the submission.	Thank you for highlighting that this data is available. The EAG has amended the text on page 26 and page 27 "At DCO3, the median duration of follow-up was 43.0 months in the D-FLOT arm and 42.9 months in the FLOT arm."

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 27: “median follow-up not reported for DCO3”.			
Section 3.3.1 Page 35 Description EAG report states “the EAG has been unable to source the median follow-up for OS [...] at either DCO2 or DCO3”.	Please can this text be removed and/or replaced with the median duration of follow-up at DCO2 and DCO3.	For DCO2, the overall median duration of follow-up for the trial is reported in Janjigian et al. (2025) as 31.5 months. For DCO3, as above, the median duration of follow-up at DCO3 is reported in Tabernero et al. (2025) which was provided in the reference pack alongside the submission.	The EAG has amended the statement that the EAG was unable to source median follow-up for OS at DCO3. However, it remains factually accurate that the EAG was unable to source median follow-up for OS at DCO2. The median duration of follow-up reported in Janjigian et al. (2025) is not specific to OS.

Issue 3 Statement referring to subgroup analyses for OS

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 3.3.2 Page 40 Description EAG report states “subgroup results were not presented for OS”.	Please can this statement be amended to clarify that the EAG report is referring to subgroup analyses using alternative PD-L1 cut-off values (TAP ≥5% or TAP <5% and TAP ≥10% or TAP <10%) rather than any subgroup analyses for OS.	The sentence currently incorrectly implies that no subgroup analyses were presented for OS. Pre-specified OS subgroup analyses were presented in Section 2.8.2, Figure 15, of the CS (DCO2) and in the Tabernero et al. (2025) publication provided in the reference pack (for DCO3).	The EAG has amended the text to state: “Furthermore, results from subgroup analyses that used alternative cut off values for PD-L1 TAP score were not presented for OS.”

Issue 4 Reference to CheckMate-577 and KEYNOTE-585 trials

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 3.2.3 Page 28 Description EAG report discusses the proportion of patients with PD-L1 expression $\geq 1\%$ in MATTERHORN trial compared with trials that are not relevant for the decision problem such as CheckMate-577 and KEYNOTE-585.	Please can this sentence be removed: <i>However, clinical advice to the EAG suggested that it was unlikely that approximately 90% of patients would have PD-L1 expression level $\geq 1\%$, as in the MATTERHORN trial. The EAG highlights the proportions of patients with PD-L1 expression levels $\geq 1\%$ in other trials of immunotherapies for patients with GOA were 16.2% in the CheckMate 577 trial²² (nivolumab) and 74.6% in the KEYNOTE-585 trial²³ (pembrolizumab)</i>	The EAG agrees with the company that nivolumab is not a relevant comparator for this appraisal, as it is used in a different population, including patients with oesophageal cancer and squamous cell carcinoma (Issue 1). To avoid reader confusion and maintain focus on the defined decision problem, we recommend removing any references to this clinical trial. Regarding PD-L1, the clinical advisor's assertion that 90% of patients would have PD-L1 expression $\geq 1\%$ is uncertain and not supported by robust evidence. The trials cited (CheckMate 577 and KEYNOTE-585) are not pertinent to the decision problem, include different patient populations, and employed different PD-L1 assays. Furthermore, PD-L1 testing is not routinely performed in early gastro-oesophageal cancers, and there is insufficient real-world evidence to justify extrapolating PD-L1 expression rates across populations. Consequently, it is not possible to reliably estimate the	The EAG does not believe text relating to clinical advice received should be deleted; this uncertainty relates to Key Issue 2 (PD-L1 status in the MATTERHORN trial and NHS clinical practice) The EAG agree with the company's reasoning for deleting text that refers to the CheckMate-577 and KEYNOTE-585 trials. This text has been deleted.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		proportion of patients with PD-L1 $\geq 1\%$ in the target population for this appraisal.	
Section 3.2.4 Page 29 Description EAG comment includes trials that are not relevant for the decision problem such as KEYNOTE-585.	Please can this sentence be removed: <i>The EAG highlights that the definition of EFS used in the MATTERHORN trial (see Error! Reference source not found.) is similar to that used in the trial of another perioperative immunotherapy (pembrolizumab in KEYNOTE-585</i>	Trial cited is a negative study and not relevant for the decision problem. Suggest removing to avoid reader confusion.	Text deleted for clarity.
Section 3.5 Page 44 Description EAG mentions a comparator they agree is not relevant for the decision problem.	Please can this sentence be removed: <i>If nivolumab was considered a relevant comparator, then an indirect comparison would have been necessary. Evidence for nivolumab is available from the CheckMate-577 trial (see Section Error! Reference source not found.).</i>	The EAG concurs with the company that nivolumab is not a relevant comparator for this appraisal, as it is used in a different population, including patients with oesophageal cancer and squamous cell carcinoma (Issue 1). To avoid reader confusion and maintain focus on the defined decision problem, we recommend removing any references to this clinical trial.	Text deleted for clarity.
Section 3.6 Page 45 Description	Please can this sentence be amended from: <i>Additional information about the FLOT4 and CheckMate-577 trials,</i>	The EAG concurs with the company that nivolumab is not a relevant comparator for this appraisal, as it is used in a different population, including patients with oesophageal	All text relating to the CheckMate-577 trial has been deleted

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
EAG mentions a comparator they agree is not relevant for the decision problem.	<i>and how they compare with the MATTERHORN trial, is presented in Sections Error! Reference source not found. and Error! Reference source not found.</i> To: <i>Additional information about the FLOT4 trial, and how it compares with the MATTERHORN trial, is presented in Sections Error! Reference source not found. and Error! Reference source not found.</i>	cancer and squamous cell carcinoma (Issue 1). To avoid reader confusion and maintain focus on the defined decision problem, we recommend removing any references to this clinical trial.	
Section 3.6.2 Pages 47 and 48 Description EAG report provides detailed discussion of the CheckMate-577 trial and a comparison between this trial and the MATTERHORN trial.	Please can this section be removed.	As outlined by the EAG, nivolumab as adjuvant treatment for OC/GOJC is not considered a comparator in this appraisal (Issue 1). As nivolumab is not a comparator to D-FLOT, it is not relevant to the decision problem to provide a detailed comparison of the MATTERHORN trial and the CheckMate-577 trial. For consistency with the EAG's view on nivolumab as not a relevant comparator, detailed discussion of CheckMate-577 should be removed.	The EAG has removed this section.

Issue 5 Description of AI-assisted SLR methodology

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 3.1 Page 24 and 25 Description The EAG reports description of the methodology used for the quality assessment stage of the AI-assisted SLR methodology is incorrect. Page 24: “The company’s quality assessment procedures, including the tool used and the level of human and AI involvement, were unclear”. Page 25: “for the updated SLR, data were extracted by one reviewer and an AI platform operating in a second reviewer role, with human oversight”.	Please can the sentence stating that the quality assessment procedures are unclear be removed. Please can the sentence on the methodology of the quality assessment stage of the SLR be updated to: for the updated SLR, data were extracted by two human reviewers. Consensus was reached between the two human reviewers and this was compared to data extracted by two AI reviewers to test and validate the use of AI for data extraction.	The methodology used for the AI-assisted SLR was clearly outlined in Appendix B. Full details on the methodology of the quality assessment step is provided in Appendix B.1.2 and Appendix B.1.4. It is incorrect to state that the quality assessment procedures were unclear. In addition, the EAG’s description of the methodology for the data extraction stage of the AI-assisted SLR update is incorrect. For the data extraction, data extraction was conducted by two human reviewers and two rounds of AI data extraction was also conducted (using ChatGPT Pro [model v5.0]), as presented in Appendix B.1.4, Figure 4. Data extracted by the two human reviewers were compared and consensus was reached. The data extracted by the AI reviewers were compared to the human extracted consensus data to validate the AI-based data extraction. Based on this validation exercise, the AI reviewer	The EAG recognises that the single applicable RCT (MATTERHORN) was correctly identified and integrated into the CS. We therefore minimised the description of our critique of the SLRs as any issues identified in the use of AI in the updated SLR were unlikely to affect Appraisal Committee decision making. With regard to the statement in EAG report page 24 (Section 3.1), the CS refers to the original Risk of Bias tool or “ROB 1” (Higgins 2011) in the prompt scripts used to instruct the AI (CS, Appendix B1.2, Table 8, first, second and third prompt), but the quality assessment presented in CS Section 2.5 references CRD/University of York (2008) <i>Systematic Reviews: CRD’s guidance for undertaking reviews in health care</i> and Table 9 presented quality assessment fields from the

		qualified as a 'second reviewer', based on the rubric in Motzfeldt Jensen et al. 2025.¹³	CRD RCT checklist applied to the MATTERHORN study. There is an apparent mismatch between the 'quality assessment' tool described in the methods (including the tool used to instruct the AI) and the quality assessment tool reported in the CS. The EAG is therefore unclear as to whether reference to "ROB1" in the CS is a presentational error, if the AI was actually instructed to report quality assessment based on the CRD RCT checklist (but this has not been reported) and the combination of human and AI used given other descriptions of the method are unclear. With regard to the statement in EAG report page 25 (EAG report, Section 3.1, Table 2), the EAG has amended the text to read "by two human reviewers. Consensus was reached between the two human reviewers and this was compared to data extracted by two AI reviewers."

Issue 6 Description of intervention and comparator dosing schedules

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 3.2.2 Page 26 Description The EAG report states “Durvalumab (IV administration): 1500mg on Day 1 Q4W for 2 cycles as neoadjuvant therapy; 1500mg on Day 1 Q4W for a maximum of 10 cycles of adjuvant therapy” and “Placebo (IV administration): on Day 1 Q4W for 2 cycles in the neoadjuvant period; on Day 1 Q4W for a maximum of 10 cycles in the adjuvant period”.	Please can this be amended to: “Durvalumab (IV administration): 1500mg on Day 1 Q4W for 2 cycles as neoadjuvant therapy; 1500mg on Day 1 Q4W for a maximum of 12 cycles in combination with FLOT followed by 10 cycles as monotherapy” “Placebo (IV administration): on Day 1 Q4W for 2 cycles in the neoadjuvant period; on Day 1 Q4W for a maximum of 12 cycles in combination with FLOT followed by 10 cycles as monotherapy”.	The description of the durvalumab and placebo administration schedules is currently incorrect. In the MATTERHORN trial and in line with the expected marketing authorisation, durvalumab was administered for two cycles as neoadjuvant therapy and for up to 12 cycles as adjuvant therapy. In the adjuvant period, durvalumab was administered in combination with FLOT for two cycles and as monotherapy for up to a further 10 cycles. The same dosing schedule was used for the placebo component in the FLOT arm.	The EAG has amended the text as proposed.

Issue 7 Difference in modelled and MATTERHORN trial D-FLOT and FLOT OS

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 4.2.2 Page 56 Description The EAG report states “As shown in	Please can this be amended to: “As shown in Table 15, whilst at two years the difference between modelled survival and that seen in	The original statement only mentions the relative difference between D-FLOT and FLOT but does not clarify whether this is relative difference or absolute	The EAG has amended the text as proposed (Section 4.2.2)

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Table 15, whilst at two years the difference between modelled survival and that seen in the MATTERHORN trial favours FLOT, by three years this has changed such that the difference in OS between patients treated with D-FLOT and FLOT is modelled to be 19.4% higher than seen in the MATTERHORN trial.”	the MATTERHORN trial favours FLOT, by three years this has changed such that the absolute differences in OS between modelled and observed are -2.3% for D-FLOT and -3.6% for FLOT, leading to a 19.4% relative modelled difference between patients treated with D-FLOT and FLOT compared with the MATTERHORN trial.”	difference. The corresponding absolute difference at three years is only 1.3% in favour of FLOT, which should be stated to ensure accurate interpretation. Without highlighting that [REDACTED] is relative difference and stating that the absolute difference is 1.3%, this sentence is misleading and may lead to incorrect interpretation.	
The EAG report states: “That the OS gain for D-FLOT at three years is already modelled to be [REDACTED] higher than FLOT is therefore concerning. As the modelled and MATTERHORN trial OS difference between D-FLOT and FLOT grew substantially between years two and three in the model (from [REDACTED]) the extrapolations beyond three years may be even more biased towards D-FLOT than the difference at three years suggests.”	Please can this be amended to: “That the OS gain for D-FLOT at three years is already modelled to be [REDACTED] higher relative to FLOT is therefore concerning (absolute difference: 1.3%). As the modelled and MATTERHORN trial OS relative difference between D-FLOT and FLOT grew substantially between years two and three in the model (from [REDACTED]) the extrapolations beyond three years may be even more biased towards D-FLOT than the difference at three years suggests.”	As above.	The EAG has amended the text as proposed (Section 4.2.2)

Typographical errors

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 13 EAG report states “ <i>MATTERHORN trial subgroup results for EFS and OS for PD-L1 expression levels $\geq 1\%$ and $< 1\%$ were presented in the CS</i> ”.	Please can this be amended to: <i>MATTERHORN trial subgroup results for EFS and OS for PD-L1 expression levels $\geq 1\%$ TAP and $< 1\%$ TAP were presented in the CS.</i>	The method of measurement of PD-L1 should be included for clarity. In the MATTERHORN trial, PD-L1 expression was measured using tumour area positivity (TAP).	The EAG has amended the text as proposed (Issue 2 table, column 2).
Page 19 EAG report states: “ <i>The company considered that FLOT was the only relevant comparator to durvalumab with FLOT</i> ”.	Please can this be amended to: <i>The company considered that perioperative FLOT was the only relevant comparator to durvalumab with FLOT.</i>	For clarity, it should be specified that perioperative FLOT is the only comparator.	The EAG has amended the text as proposed (Table 1, column 4).
Page 22 EAG report states “ <i>Conditions that increase risk of GOA are also associated with underlying inequalities and men are almost twice as likely to develop GOC as 320(CS, Section 1.3.1).</i> ”	Please can this be amended as follows: <i>Conditions that increase risk of GOA are also associated with underlying inequalities and men are almost twice as likely to develop GOC as women (CS, Section 1.3.1).</i>	Typographical error.	The EAG has amended the text as proposed (Section 2.4).
Page 40 EAG report states that the EFS HR for the TAP $\geq 1\%$ subgroup is 0.70 (0.57 to 0.98).	Please can this be amended to: 0.70 (0.57 to 0.87).	Incorrect reporting of trial results. The correct results are reported in Section 2.8.1, Table 14, of the CS.	The EAG has amended the text as proposed (Table 8, column 4)
Page 43 EAG report states “ <i>Immune-mediated AEs were more common</i>	Please can the repetitive discussion of the immune-mediated AEs be removed.	Typographical error. Repeated sentences on the immune-mediated AEs are not necessary.	The EAG has amended the text as proposed, removing the repeated text. The EAG

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
<i>in the D-FLOT arm (23.2%) in comparison to the FLOT arm (7.2%)". This is repeated on page 44 of the EAG report.</i>			has moved the following sentence "These were described (CS, p79) as mostly low grade and manageable and/or reversible with appropriate medical management per standard management guidelines" to appear earlier in Section 3.3.4 (after the initial mention of the immune-mediated AEs.)
Page 69 The EAG report states: "However, the [REDACTED] difference in OS at three years observed in the MATTERHORN trial for patients treated with D-FLOT over FLOT has been extrapolated in the company model into a [REDACTED] (undiscounted) life year gain with >95% of this gain coming via model projections after three years. "	Please amend as the model predicts a [REDACTED] life year again.	The model results presented are incorrect.	The EAG has amended the text as proposed (section 5.5).

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Durvalumab in combination for neoadjuvant and adjuvant treatment of resectable gastric and gastro-oesophageal junction adenocarcinoma [ID6374] Response to company addendum

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1 INTRODUCTION

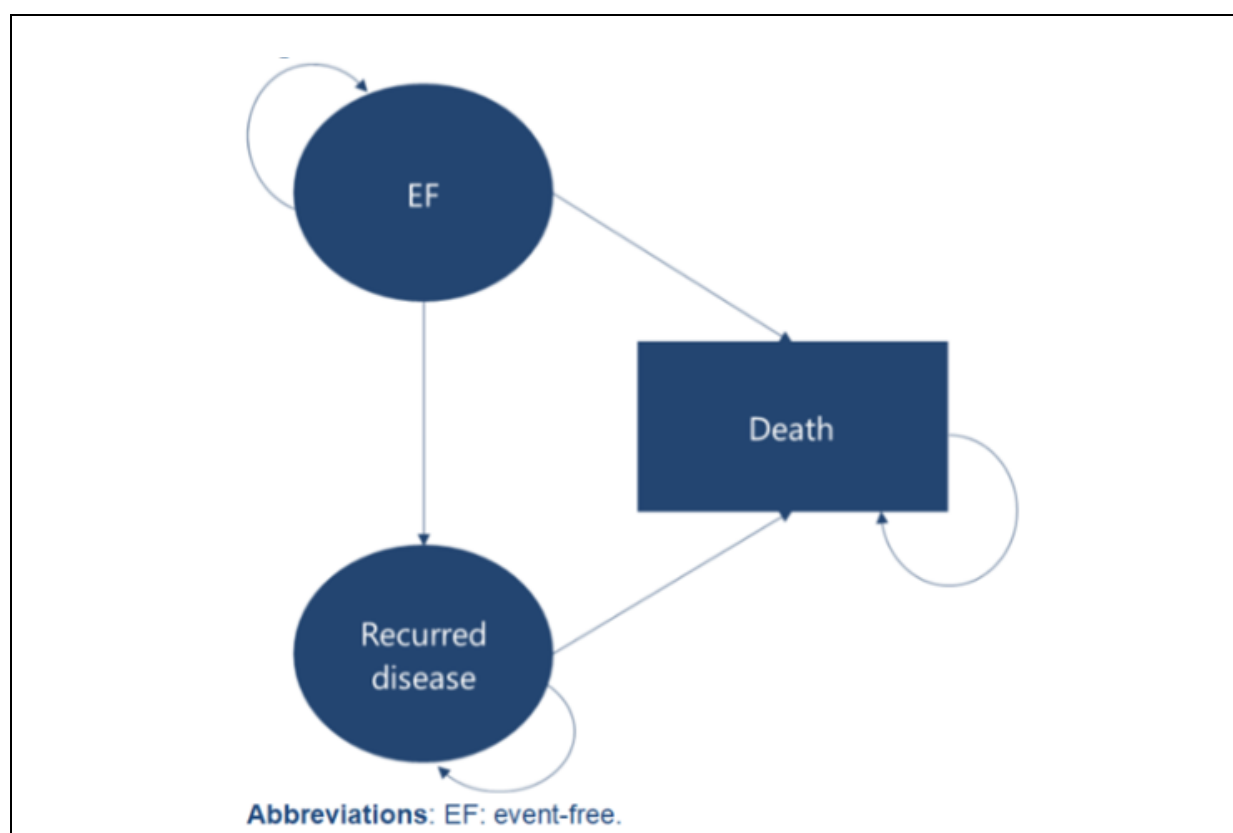
In the EAG report for durvalumab in combination for neoadjuvant and adjuvant treatment of resectable gastric and gastro-oesophageal junction adenocarcinoma, the EAG highlighted that the structure of the company economic model resulted in biased estimates of overall survival (OS) for D-FLOT and FLOT that could not be rectified by changing parameter values. The EAG requested that the company produce a partitioned survival model (PSM), which would potentially remove or reduce the OS bias.

In response to this request, the company produced an addendum with a new cost-effectiveness model with a PSM structure. This addendum to the EAG report provides the EAG critique of this new model and cost-effectiveness results.

2 PARTITIONED SURVIVAL MODEL

2.1 Model structure and parameterisation

The company developed a *de novo* PSM with the same three health states as the semi-Markov model in the original submission (Figure 1). However, state occupancy is now derived from event-free survival (EFS) and OS extrapolations estimated from MATTERHORN trial data. The model cycle length is 4 weeks and includes a half-cycle correction. The time horizon is ■■■ years (lifetime). The economic model perspective is the NHS and personal social services (PSS).



Source: Company addendum, Figure 1

Figure 1 Company PSM model structure

The proportion of patients in the event-free state was defined as the proportion alive and event-free from EFS, the proportion in the relapsed/diseased state as the proportion alive from OS minus the proportion of event-free patients, and the proportion dead as one minus OS.

The company selected distributions for OS and EFS for patients treated with D-FLOT and FLOT through assessment of AIC and BIC statistics, closeness of estimates from distributions of OS and EFS to MATTERHORN trial OS and EFS KM data and clinical opinion on plausibility of long-term OS and EFS beyond the MATTERHORN trial time horizon. Using these criteria,

the company considered that the generalised gamma distribution was the most appropriate model for extrapolating EFS and OS across both treatment arms, with the log-normal distribution for both OS and EFS explored as a scenario analysis. No other distributions were considered as plausible candidates.

The majority of parameters in the model remained unchanged in the PSM from the company model originally submitted, with the following exceptions:

- the cure assumption at 5 years was removed and instead explored as a scenario analysis (Company Addendum page 7 and 8)
- the vial sharing assumption was removed (Company Addendum Section 2.4.1)
- administration, surgery, health state costs and adverse event costs were updated to reflect 2024/2025 NHS Reference Costs (Company Addendum Sections 2.4.1 to 2.4.3).

2.2 **EAG critique**

The EAG is satisfied with the company's approach to curve selection for OS and EFS for both D-FLOT and FLOT but considers that the generalised gamma and log-normal are equally as plausible given the methods for curve selection employed by the company. As such, results using the generalised gamma and log-normal distributions should be given equal weight in decision making. The EAG notes that if different distributions are used for OS and EFS (such as generalised gamma for EFS and log-normal for OS) then in some cases the curves cross resulting in kinks in one of the curves representing a sudden discrete step in a hazard function which is unlikely to be clinically plausible. As such, the EAG considers that using the same distribution for OS and EFS provides more realistic survival projections. However, the EAG considers that there is no reason that the same distribution should necessarily be used for D-FLOT and FLOT. Therefore, the following OS and EFS distribution combinations should all be considered equally informative for decision making:

- D-FLOT: OS and EFS generalised gamma. FLOT: OS and EFS generalised gamma
- D-FLOT: OS and EFS log-normal. FLOT: OS and EFS log-normal
- D-FLOT: OS and EFS generalised gamma. FLOT: OS and EFS log-normal
- D-FLOT: OS and EFS log-normal. FLOT: OS and EFS generalised gamma.

The EAG is satisfied with the other parameter changes in the model and considers that these have been correctly implemented.

Whilst not making a change to utility values, the company stated in the addendum that:

“at CQs, the EAG suggested using the utility value of 0.399 from Lee et al. 2018, a cross-sectional survey of 326 adults” (Company Addendum page 23).

As a point of clarity, the EAG does consider that a lower progressed disease utility value than in the company base case may be warranted but did not suggest that any specific value should be used.

2.3 Results

Company deterministic and probabilistic base case results and full deterministic and probabilistic sensitivity analyses and scenario analyses are provided in Section 3 of the Company Addendum. Company deterministic base case results and results using the OS and EFS distribution combinations for D-FLOT and FLOT summarised in Section 2.2 are shown in Table 1 to Table 4. The results use the proposed PAS price for durvalumab and list prices (eMIT 2024 or BNF) for all other drugs.

A confidential appendix has been produced by the EAG using confidential prices for the following treatments:

- nivolumab
- pembrolizumab
- trastuzumab.

For all other treatments in the confidential appendix, eMIT 2025 prices were used.

Table 1 Company's deterministic base-case cost-effectiveness results without severity weighting (generalised gamma distribution for OS and EFS extrapolation for D-FLOT and FLOT)

	Total costs	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Perioperative FLOT chemotherapy	██████	████	=	=	=
Perioperative D-FLOT	██████	████	██████	██████	£12,030

The company considers a disease severity modifier of 1.0 was appropriate.

D-FLOT=durvalumab plus FLOT; FLOT=fluorouracil, leucovorin, oxaliplatin and docetaxel; ICER=incremental cost-effectiveness ratio; QALYs=quality-adjusted life years.

Table 2 Deterministic base-case cost-effectiveness results without severity weighting (log-normal distribution for OS and EFS extrapolation for D-FLOT and FLOT)

	Total costs	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Perioperative FLOT chemotherapy	██████	████	=	=	=
Perioperative D-FLOT	██████	████	██████	████	£13,268

The company considers a disease severity modifier of 1.0 was appropriate.

D-FLOT=durvalumab plus FLOT; FLOT=fluorouracil, leucovorin, oxaliplatin and docetaxel; ICER=incremental cost-effectiveness ratio; QALYs=quality-adjusted life years.

Table 3 Deterministic base-case cost-effectiveness results without severity weighting (generalised gamma distribution for OS and EFS extrapolation for D-FLOT and log-normal for FLOT)

	Total costs	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Perioperative FLOT chemotherapy	██████	████	=	=	=
Perioperative D-FLOT	██████	████	██████	████	£7,259

The company considers a disease severity modifier of 1.0 was appropriate.

D-FLOT=durvalumab plus FLOT; FLOT=fluorouracil, leucovorin, oxaliplatin and docetaxel; ICER=incremental cost-effectiveness ratio; QALYs=quality-adjusted life years.

Table 4 Deterministic base-case cost-effectiveness results without severity weighting (log-normal distribution for OS and EFS extrapolation for D-FLOT and generalised gamma for FLOT)

	Total costs	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Perioperative FLOT chemotherapy	██████	████	=	=	=
Perioperative D-FLOT	██████	████	██████	████	£21,510

The company considers a disease severity modifier of 1.0 was appropriate.

D-FLOT=durvalumab plus FLOT; FLOT=fluorouracil, leucovorin, oxaliplatin and docetaxel; ICER=incremental cost-effectiveness ratio; QALYs=quality-adjusted life years.

Single Technology Appraisal

Durvalumab in combination for neoadjuvant and adjuvant treatment of resectable gastric and gastro-oesophageal junction cancer [ID6374]

Clarification with Clinical Experts

Clinical Expert Name:

Prof Was Mansoor

Date:

14/04/2026

Following the lead team meeting held on 31st March 2026, the Chair would like clarification on the following:

Query 1

Whether the MATTERHORN population is representative of UK clinical practice. The concern is that the study appears to have recruited a disproportionately large proportion of patients with PD-L1 expression. If PD-L1 were a prognostic factor or a treatment-effect modifier, then over-representation of PD-L1-positive patients could affect the generalisability of the study results to the broader UK population. If the high proportion of PD-L1-positive patients is due to the study using a different assay or a different PD-L1 threshold, then is it correct to assume this would not matter, given clinicians are not routinely testing for PD-L1 and therefore would not know this?

Response

1. Regarding whether the Matterhorn population is representative of the UK population with regards to the the sub groups included in the trial, then i would say they are representative. This is based on the fact that most patients were male (72%), 60% of these patients were under the age of 65 and the patients were predominantly non Asian

(80%). Regarding the disease characteristics, in all previous large UK based peri-operative trials similar in design to this (MAGIC, ST03, Neo Aegis) 65-70% of the patients were node +ve. In Matterhorn, 67% of the patients are node positive and so are representative. The distribution of the primary cancer and histology are also representative of what we see in the UK based trials and in practice. Regarding the specific question about the TAP PD-L1 positive rates, this is a more difficult question to answer. PD-L1 expression has not been shown to be prognostic but is obviously a treatment effect modifier. In limited early disease stage (stage 1-3) studies, the CPS PD-L1 score has been demonstrated to be 40-50%. There is good concordance between TAP score and CPS PD-L1 score and therefore, based on this it could be said that this trial did demonstrate a much higher PD-L1 expression than we would expect. The counter argument to this is that the concordance studies have only been done in the metastatic state where PD-L1 over expression is different and TAP PD-L1 testing has never been done in previously peri-operative studies. In the Rationale 305 study (non resectable gastric/ GOJ adenocarcinoma study), prevalence of TAP score $\geq 1\%$ was between 75-85%. This is quite close correlation with the Matterhorn trial. However the Rationale 305 population was on 22-23% non Asian. If we assume a strong correlation between CPS PD-L1 and TAP, then the Checkmate 859 trial (predominantly a non Asian study) demonstrated a CPS PD-L1 score in its population of 78% - again showing some consistency that the PD-L1 expression when set at 1% is high regardless of which assay is used. Based on all of the above and accepting there is a lack of direct evidence for this stage of cancer, it is believable that the TAP PD-L1 score is as stated in the Matterhorn trial (if the same assay methodology as the trial is used). It is right to assume that clinicians are not testing for PD-L1 (using any assay) in the peri-operative setting.

Query 2

Whether the TAP assay and the 1% threshold are well-established and validated for determining PD-L1 expression levels. The Chair is also questioning why there can be such a large discrepancy between studies (for example, whether this is disease-area-related); in one oesophageal cancer study around 16% of patients were PD-L1 positive, whereas in the MATTERHORN trial, around 90% of the population had PD-L1 expression $\geq 1\%$.

Response

Regarding your second question ie whether TAP assay and the 1% threshold are well established and validated to determine PD-L1 expression levels, the retrospective analysis of the RATIONALE 305 trial looked at this assay with a $\geq 1\%$ cut off and demonstrated statistically significant improvement in OS vs placebo. In the UK, TAP testing for UGI cancers is not established because the RATIONALE series of trials were not approved by NICE, however in other tumour management and globally this assay is established.

With regards to why there is a discrepancy in expression between trials and primary sites, there is heterogeneity within this cancer gp generally which part explains the variation in expression. However, almost certainly there will also be variation in reporting between trials. There have been improvements in how we do the assay and understand the assay which account for these differences. Furthermore, biomarker expression as we move from the proximal oesophagus down to the distal stomach and expression may also differ according to stage of cancer and histological sub type.