Durvalumab in combination for neoadjuvant and adjuvant treatment of resectable gastric and gastro-oesophageal junction adenocarcinoma

For Zoom – contains redacted information

Technology appraisal committee B (streamlined) [31 March 2026] **PART 1**

Chair: Charles Crawley

Lead team: Tony Wootton, Soon Song, Daniel Gallacher

External assessment group: Liverpool Reviews & Implementation Group (LRiG)

Technical team: Janet Boadu, Mary Hughes, Emily Crowe

Company: AstraZeneca

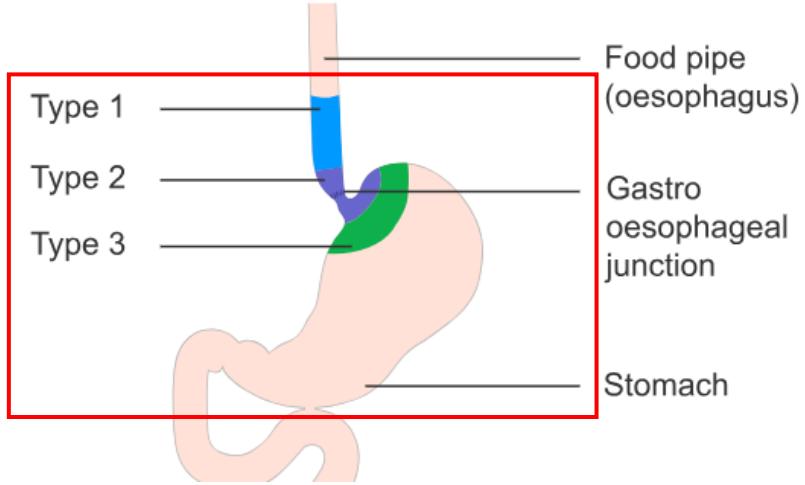
Durvalumab in combination for neoadjuvant and adjuvant treatment of resectable gastric and gastro-oesophageal junction adenocarcinoma

- ✓ **Background and key issues**
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ❑ Summary

NICE National Institute for Health and Care Excellence

Background on gastric and gastro-oesophageal junction adenocarcinoma

Often diagnosed at an advanced stage



Adapted from Cancer Research UK

Causes

- Gastric (stomach) cancer (GC): malignant tumour from cells in the stomach; gastro-oesophageal junction (GOJ) cancer: centre of tumour < 5cm above or below where oesophagus meets stomach
- Risk factors include diet, alcohol consumption, smoking, *H.pylori* infection and obesity

Epidemiology

- GC is more common in men; approx. half of all new cases diagnosed in people aged 75 years and over

Diagnosis and classification

- Gastric and GOJ cancer are often diagnosed at an advanced stage

Symptoms and prognosis

- Initial symptoms are vague and similar to other stomach conditions; advanced stages may include lack of appetite, weight loss, fluid in abdomen and blood in stool
- 5-year survival for people with gastric cancer was 21.6% between 2013 and 2017

Patient perspectives

Current NHS treatments for resectable gastric cancer are intense and can cause serious side effects

Submissions from [two patient experts]

- 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
- 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
- Some groups, like older or frail patients, may benefit less, and equality issues must be considered

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

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

*See appendix for patient organisation submission
Abbreviations: D-FLOT, durvalumab in combination with 5-fluorouracil, leucovorin, oxaliplatin and docetaxel

Clinical perspectives (1/2)

Submissions from clinical experts [Christie Hospital and Imperial College London]

Christie Hospital

- FLOT became standard of care in 2018, but still is unmet need as recurrence is common and long-term prognosis poor (50% survival at 5 years)
- MATTERHORN is well designed study representative of the UK population
- EFS and 3-year survival both significant and would be impactful for people
- People benefited from D-FLOT regardless of PD-L1 TAP testing
- Durvalumab did not negatively impact on QoL for people
- Maintenance durvalumab for 12 months will alter the curative pathway – requiring more oncology support
- Clinicians will have to be aware of the immune related toxicities; serious toxicity occurs in less than 5% of people

Lethal cancer where currently 50% of people with early disease undergoing curative treatment are still dying…it is undoubtedly an unmet need

Abbreviations: D-FLOT, durvalumab in combination with 5-fluorouracil, leucovorin, oxaliplatin and docetaxel; DCO, data cut-off; EFS, event-free survival; FLOT, 5-fluorouracil, leucovorin, oxaliplatin, docetaxel; PD-L1, programmed death ligand-1; QoL, quality of life; TAP, tumour area positivity

Clinical perspectives (2/2)

Submissions from clinical experts [Christie Hospital and Imperial College London]

Imperial College London

- Primary aim of treatment for resectable gastric and gastro-oesophageal junction adenocarcinoma is to achieve cure, typically through surgery combined with perioperative systemic therapy
- Evidence from MATTERHORN indicates adding durvalumab to perioperative FLOT chemotherapy improves overall and event-free survival, the effect of HRQOL is not clear
- 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
- 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

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

Abbreviations: FLOT, 5-fluorouracil, leucovorin, oxaliplatin, docetaxel; PD-L1, programmed death ligand-1; HRQoL, health related quality of life;

Equality considerations

From Company and Patient organisation [Stomach Cancer UK], patient expert

Age:

- Older patients are often under-represented in perioperative trials. Frailty may limit eligibility, but age alone should not restrict access where performance status is adequate

Health inequalities:

- Variety of genetic and environmental factors increase likelihood of developing GOA; many environmental factors more prevalent in people from lower socioeconomic backgrounds
- People from deprived backgrounds may present later with more advanced disease and may have poorer nutritional status and more comorbidities, affecting fitness for perioperative FLOT before adding durvalumab

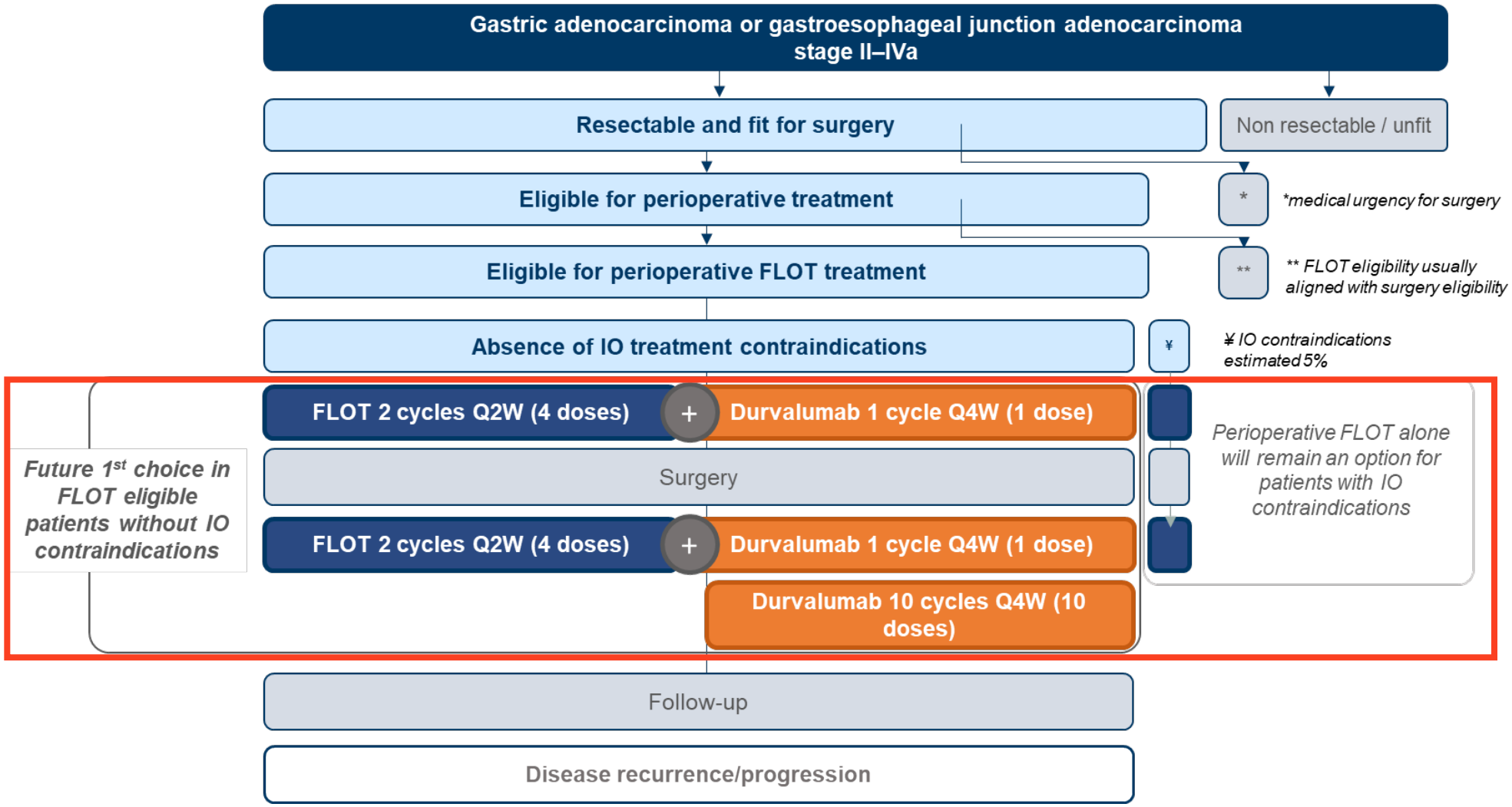
Implementation:

- Across ethnic and national groups, access to clear information and interpretation services should support informed consent for complex perioperative chemo- and immunotherapy pathways
- Access to centres offering durvalumab plus FLOT should not depend on geography; rural patients should not face disproportionate travel burdens

Are there any equality issues relevant to the potential recommendations?

Abbreviations: FLOT 5-fluorouracil, leucovorin, oxaliplatin, docetaxel; GOA, gastro-oesophageal adenocarcinoma

Company's Anticipated Treatment pathway



EAG:

- Clinical advice to the EAG agreed company's description of SoC in NHS practice is accurate

Abbreviations: FLOT, FLOT: 5-fluorouracil, leucovorin, oxaliplatin, and docetaxel; GOA, gastro-oesophageal adenocarcinoma; IO, immuno-oncology; Q2, biweekly; Q4W: monthly.

Technology (IMFINZI, AstraZeneca)

Marketing authorisation (pending)	• Anticipated via MHRA September 2026. Anticipated license wording: durvalumab in combination with FLOT chemotherapy as neoadjuvant and adjuvant treatment, followed by adjuvant durvalumab monotherapy, for the treatment of adults with resectable gastric or gastro-oesophageal junction adenocarcinoma
Mechanism of action	• Durvalumab 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 • Durvalumab binds to and inhibits PD-L1, enabling the immune system to find and attack cancer cells
Administration	• Intravenous infusion over 1 hour • Licensed dose is 1,500mg every 4 weeks for 2 cycles in neoadjuvant phase; followed by 12 cycles in adjuvant phase
Price	• List prices for 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 • Average costs for a course of treatment (2 cycles neoadjuvant phase, followed by 12 cycles adjuvant phase): 500mg/10mL formulation: £103,572 per course • There is a confidential patient access scheme

Abbreviations: MHRA, Medicines and Healthcare products Regulatory Agency (UK)

Key issues

Issue	ICER impact
Relevance of Nivolumab as a comparator	Unknown 
PD-L1 status in the MATTERHORN trial and NHS clinical practice	Unknown 
Cost-effectiveness model structure	Small 

Abbreviations: ICER, incremental cost-effectiveness ratio; PD-L1, Programmed Death-Ligand 1

Key issues: Relevance of Nivolumab as a comparator

Background

- Nivolumab is included as a comparator in NICE final scope, after surgery for people with GOJ adenocarcinoma who have residual disease after previous neoadjuvant chemoradiotherapy (CRT)
- Nivolumab is recommended for adjuvant treatment of completely resected OC GOJC in adults with residual disease after previous neoadjuvant CRT (TA746)

Company

- Nivolumab is not relevant comparator; clinical advice to the company was that:
  - CRT is considered an option only for people ineligible for surgery and neoadjuvant FLOT
  - Rare people with GOA who have neoadjuvant CRT can tolerate surgery (and be eligible for nivolumab)
  - Nivolumab primarily used in OC/GOJC patients with squamous cell carcinoma rather than GOA
  - CRT and nivolumab anticipated to be removed as treatment options from ESMO guidelines update

EAG comments

- Agrees that nivolumab is not a relevant comparator for the reasons provided by the company

Other considerations (clinical experts)

- Agree nivolumab is not an appropriate comparator
- For adenocarcinomas, CRT only offered when FLOT is not an option

NICE

Is nivolumab a relevant comparator?

Abbreviations: CRT, chemoradiotherapy; D-FLOT, durvalumab in combination with 5-fluorouracil, leucovorin, oxaliplatin and docetaxel; FLOT, 5-fluorouracil, leucovorin, oxaliplatin and docetaxel; GOA, gastro-oesophageal adenocarcinoma; GOC, gastric oesophageal cancer; GOJ, gastro-oesophageal junction; OC, oesophageal cancer; SoC, standard of care

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Key clinical trial- MATTERHORN

Clinical trial designs and outcomes

EAG:

- Clinical advice to the EAG is that the EFS and OS results are clinically meaningful

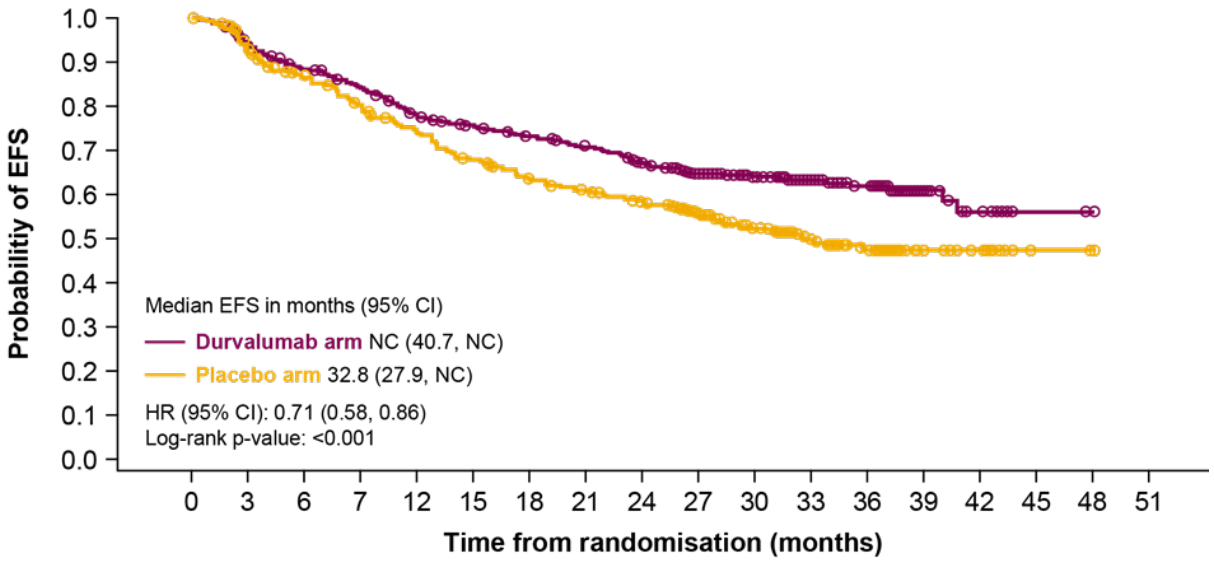
	MATTERHORN trial
Design	Phase 3, randomised, multi-centre, double-blind, placebo-controlled
Population	Adults with resectable GOA (Stage II to IVA), not received anti-cancer therapy, ECOG score of 0 or 1, and adequate organ and marrow function
Intervention (N=474)	**Durvalumab:** 1,500 mg Day 1 of each 4-week cycle for 2 cycles as neoadjuvant therapy; 1,500 mg Day 1 every 4 weeks for max of 12 cycles as adjuvant therapy **FLOT chemotherapy:** Days 1 & 15 of each 4-week cycle for 2 cycles as neoadjuvant therapy; days 1 & 15 of each 4-week cycle for 2 cycles as adjuvant therapy
Comparator(s) (N=474)	**Placebo:** Day 1 every 4 weeks for 2 cycles in the neoadjuvant period; Day 1 every four weeks for a maximum of 12 cycles in the adjuvant period **FLOT chemotherapy:** Days 1 & 15 of each 4-week cycle for 2 cycles as neoadjuvant therapy; Days 1 & 15 every 4 weeks for 2 cycles as adjuvant therapy
Primary outcome	EFS (events defined using BICR for RESIST v1.1)
Key secondary outcomes	OS, pCR (see appendix)
Locations	Multicentre across 20 countries (incl. UK = 8 sites)
Used in model?	Yes

Abbreviations: BICR: blinded independent central review; EFS, event-free survival; GOA, gastro-oesophageal adenocarcinoma; OS, overall survival; pCR, pathological complete response; Q4W: Every 4 weeks; RECIST: Response Evaluation Criteria in Solid Tumours

MATTERHORN clinical trial results – EFS at DCO2 (December 2024 DCO)

D-FLOT improves EFS compared to placebo + FLOT; 29% reduction in risk of EFS event

KM curves for EFS (using BICR for RECIST v1.1) (FAS, December 2024 DCO2)



EFS	D-FLOT (n=474)	Control (n=474)
Events* n (%)	167 (35.2)	218 (46.0)
Median EFS months (95% CI)	NR (40.7, NC)	32.8 (27.9, NC)
HR (95% CI)	0.71 (0.58 to 0.86)	
2-sided p-value	<0.001	
Median duration of follow-up in censored patients, months (range)	31.6 (0.0, 48.1)	31.4 (0.0, 48.1)

*EFS events (using BICR for RECIST v1.1)

Abbreviations: BICR: blinded independent central review; CI: confidence interval; DCO: data cut-off; D-FLOT, durvalumab in combination with 5-fluorouracil, leucovorin, oxaliplatin and docetaxel; DCO, data cut-off; FLOT, 5-fluorouracil, leucovorin, oxaliplatin, docetaxel EFS: event-free survival; FAS: full analysis set; HR: hazard ratio; KM: Kaplan-Meier; NC: not calculated; NR: not reached; RECIST: Response Evaluation Criteria in Solid Tumours

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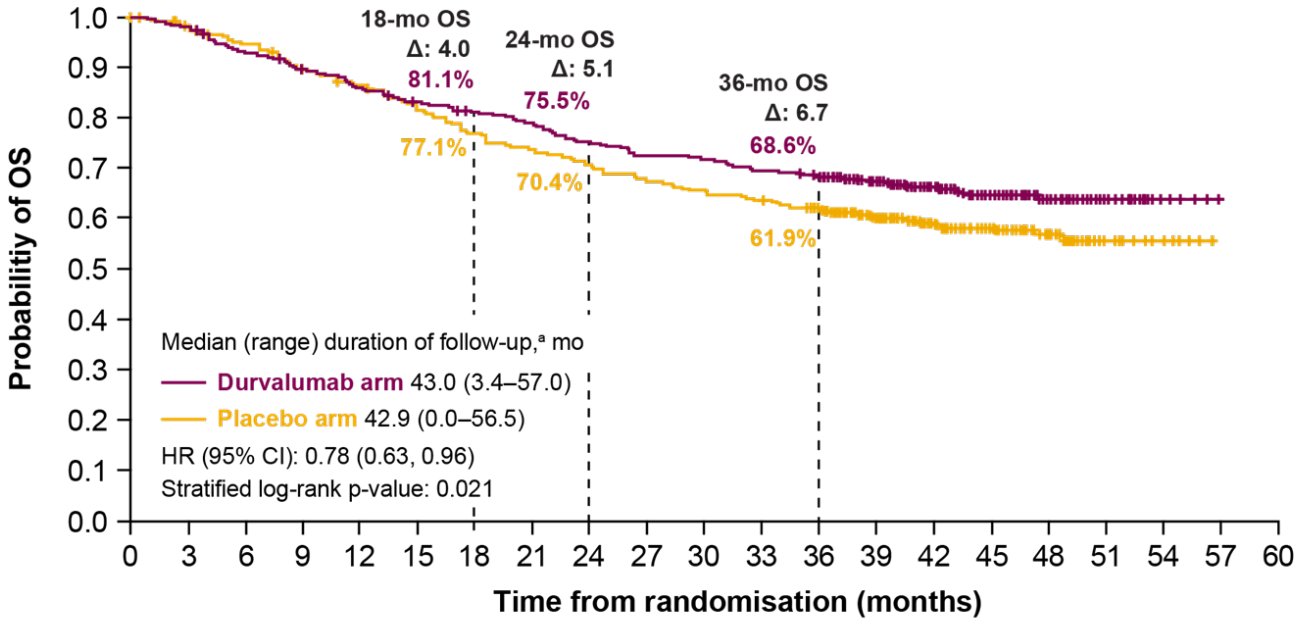
MATTERHORN clinical trial results – OS at DCO3 (September 2025 DCO)

D-FLOT demonstrated a statistically significant OS benefit vs control arm

KM curves for OS (FAS, September 2025 DCO3)



OS	D-FLOT (n=474)	Control (n=474)
Total number of deaths, n (%)	[redacted]	[redacted]
Median OS months (95% CI)	NC (NC, NC)	NC (NC, NC)
HR (95% CI)	0.78 (0.63 to 0.96)	
2-sided p-value	0.021	

See appendix for DCO2 results

EAG:

- OS HR and 95% CI almost identical to 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

Abbreviations: CI: confidence interval; DCO: data cut-off; FAS: full analysis set; HR: hazard ratio; KM: Kaplan-Meier; NC: not calculated; NR: not reached; OS: overall survival

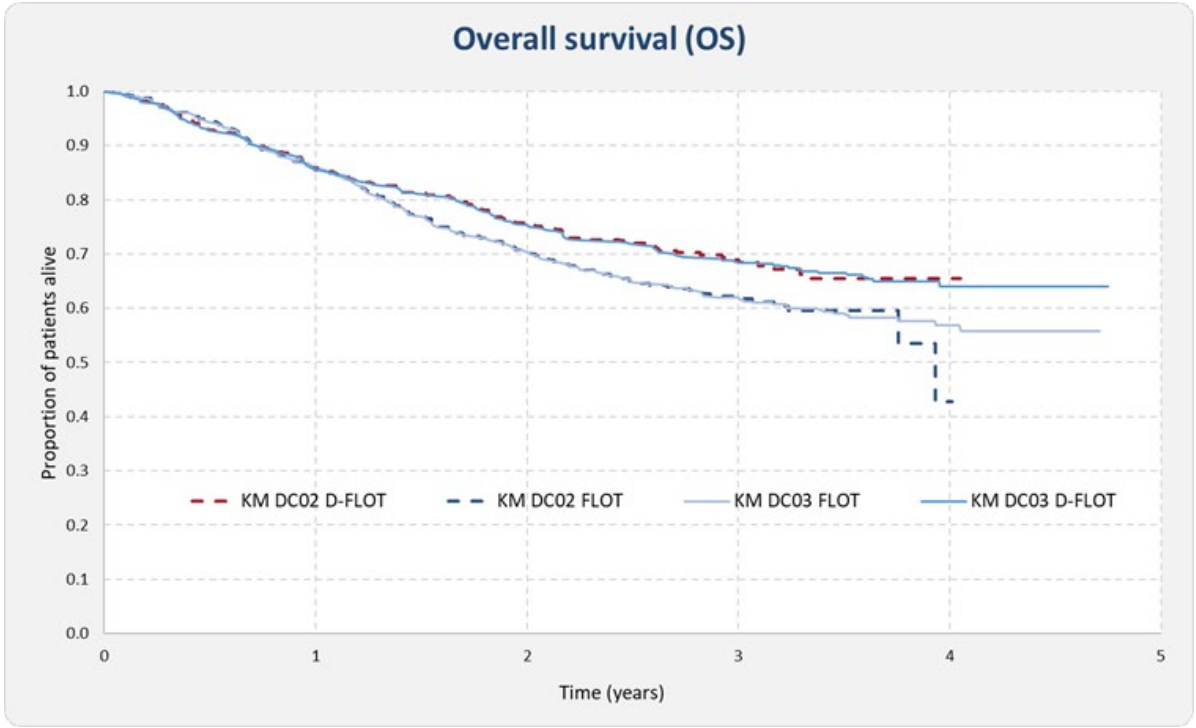
OS DCO3 versus DCO2

Company

- In semi-Markov model, MATTERHORN (DCO2) used as primary source of clinical data to inform model transition probabilities
- In new PSM, EFS data sourced from DCO2; OS data sourced from September 2025 (DCO3) reflecting availability of updated OS data since submission of company's base case
- Company noted OS data from DCO2 highly consistent with DCO3, due to stable HR across data cuts; KM curves from both data cuts also similar; demonstrated by overlaid KM curves

EAG comments

- Notes event rates were relatively low for EFS (DCO2) and OS (DCO2 and DCO3)
- Does not consider further data should be collected as timing of trial analyses based on an appropriate sample size and power calculation
- Notes low event rate means that it was not possible for the company to calculate median EFS time or median OS time for D-FLOT arm at DCO2, or median OS time for either arm at DCO3



Abbreviations: DCO, data cut-off; D-FLOT, durvalumab in combination with 5-fluorouracil, leucovorin, oxaliplatin and docetaxel; EFS, event-free survival; FAS, full analysis set; FLOT, 5-fluorouracil, leucovorin, oxaliplatin and docetaxel; HR, hazard ratio; KM, Kaplan-Meier; OS, overall survival

Key issues: PD-L1 status in MATTERHORN (1/2)

Background

- NICE final scope: if evidence allows, results by level of PD-L1 expression will be considered

Company

- Provided subgroup analyses for clinical effectiveness (EFS and OS) of D-FLOT by PD-L1 status
- Results from MATTERHORN show consistent treatment benefit regardless of PD-L1 expression level
- Clinical expert advice: PD-L1 expression not routinely tested in resectable GOA + doesn't determine treatment decisions; D-FLOT would be offered to everyone in clinical practice, regardless of characteristics
- As PD-L1 expression will not inform treatment or cost-effectiveness decisions, economic subgroup analyses by PD-L1 expression were not explored

Outcome, DCO, subgroup	D-FLOT # events / # total (%)	FLOT # events / # total (%)	HR (95% CI) D-FLOT vs FLOT
EFS, DCO2, TAP ≥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 ≥1%	[redacted]	[redacted]	[redacted]
OS, DCO2, TAP <1%	[redacted]	[redacted]	[redacted]
OS, DCO3, TAP ≥1%	NR	NR	0.79 (0.63 to 0.99)
OS, DCO3, TAP <1%	NR	NR	0.79 (0.41 to 1.50)

Abbreviations: #, number; CI, confidence interval; D-FLOT, durvalumab in combination with 5-fluorouracil, leucovorin, oxaliplatin and docetaxel; DCO, data cut-off; EFS, event-free survival; FLOT, 5-fluorouracil, leucovorin, oxaliplatin, docetaxel; GOA, gastro-oesophageal adenocarcinoma; HR, hazard ratio; NR, not reported; OS, overall survival; PD-L1, programmed death ligand-1; TAP, tumour area positivity

Key issues: PD-L1 status in MATTERHORN (2/2)

EAG comments

- PD-L1 subgroup results consistent overall in MATTERHORN population, but trial not powered to detect subgroup differences; insufficient evidence to determine if PD-L1 status affects treatment effect
- If PD-L1 affects treatment effectiveness, variation could affect results for overall trial population and therefore generalisability to NHS practice (90% of trial population had PD-LI expression ≥1% [see appendix])
- At clarification, EAG requested an estimate of the % of people with GOA in UK with PD-L1 expression level TAP ≥1% and TAP <1%; company unable to provide any relevant data
- Although MATTERHORN not powered to assess subgroups by PD-L1 expression level, point estimates favoured D-FLOT vs FLOT regardless of PD-L1 status
- Data on PD-L1 status for people receiving perioperative treatment for GOA in UK would improve clarity on generalisability of overall trial results

Other considerations (clinical expert)

- Patients benefited from D-FLOT regardless of PD L1 TAP testing
- PD-L1 TAP testing is not required as 90% of patients in the trial were positive for this test
- 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

- Did MATTERHORN recruit fewer people with PD-L1 <1% than would be expected in clinical practice?
- Would PD-L1 status be expected to have an impact on the clinical effectiveness of durvalumab?

Abbreviations: D-FLOT, durvalumab in combination with 5-fluorouracil, leucovorin, oxaliplatin and docetaxel; FLOT, 5-fluorouracil, leucovorin, oxaliplatin, docetaxel; GOA, gastro-oesophageal adenocarcinoma; PD-L1, programmed death ligand-1; TAP, tumour area positivity

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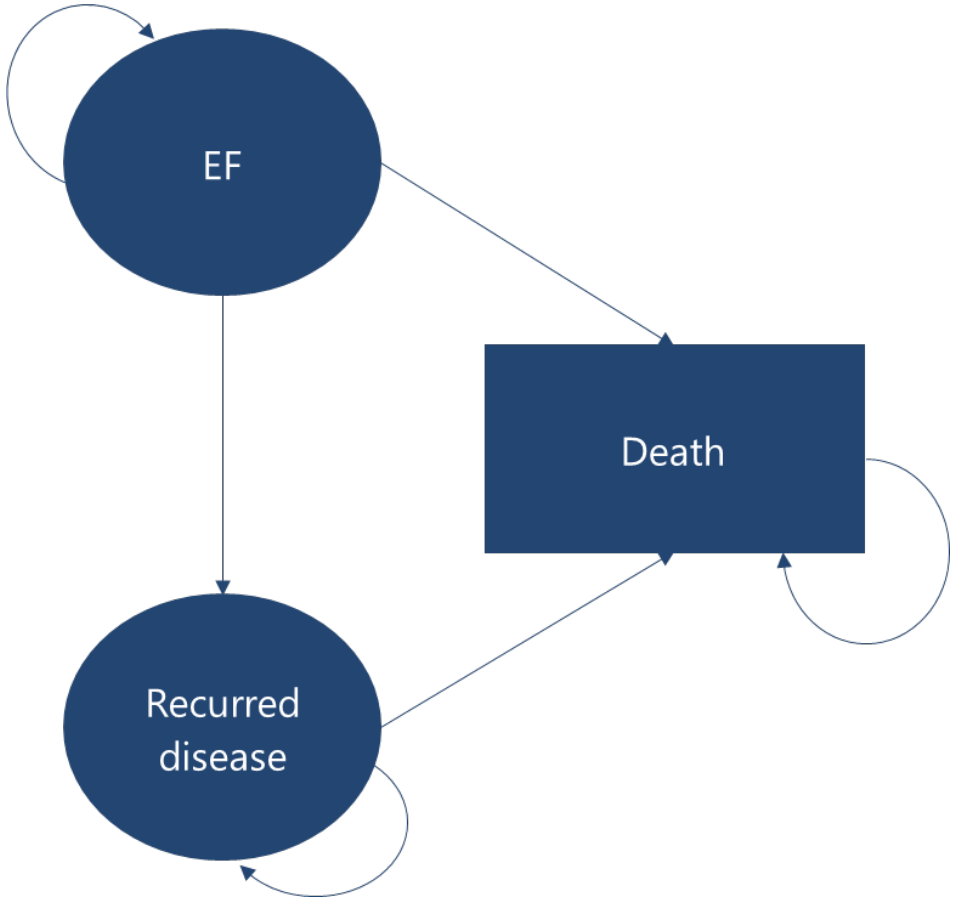
Company's updated model overview

Company produced new PSM model in line with the EAG's request



Model structure:

- 3 mutually excusive health states: event-free, recurred disease, death
- Company's original model was a semi-Markov model
- EAG requested a partitioned survival model

Cycle length: 4 weeks (with half cycle correction)

Time horizon: Lifetime

Abbreviations: EF, event-free; PSM, partitioned survival model

Key issues: Cost-effectiveness model structure

Background

- Company developed a semi-Markov model; EAG noted in this approach OS modelled as surrogate outcome and modelled OS does not reflect trial OS at 3 years
- EAG highlighted the company's semi-Markov model resulted in biased estimates of OS for D-FLOT and FLOT that could not be rectified by changing parameter values
- EAG requested company produce a PSM, which would potentially remove or reduce OS bias

Company

- Company produced new PSM model in line with the EAG's request
- Results from the alternative base case are highly consistent with the company's original base case (semi-Markov model)

EAG comments

- Satisfied with company's approach to curve selection for OS and EFS for D-FLOT and FLOT but considers generalised gamma and log-normal equally as plausible (see appendix); EAG produced additional results for different OS and EFS distributions for D-FLOT and FLOT
- Satisfied that other parameter changes in the model have been correctly implemented

Is the company's updated model suitable for decision making?

Abbreviations: D-FLOT, durvalumab in combination with 5-fluorouracil, leucovorin, oxaliplatin, docetaxel; EF, event-free; EFS, event-free survival; FLOT, 5-fluorouracil, leucovorin, oxaliplatin, docetaxel; OS, overall survival; PSM, partitioned survival model

Summary of company assumptions

Assumption	Company PSM
Patient characteristics	**Baseline characteristics** - MATTERHORN trial FAS (December 2024 DCO)
Health-related quality of life (HRQoL)	**EF health state:** EQ-5D-5L values from MATTERHORN mapped to EQ5D-3L-derived UK utility values (Hernández Alava *et al*. 2020) **RD health state:** Aligned with the RD utility for TA746; (nivolumab for the adjuvant treatment of patients with OC or GOJC [TA746])
Efficacy	**EFS:** sourced from MATTERHORN (DCO2 (December 2024; final EFS analysis) - generalised gamma distribution selected for both arms **OS:** sourced from MATTERHORN (DCO3 (September 2025; final OS analysis) - generalised gamma distribution selected for both arms
Resource use and costs	**Health care resource use inputs:** sourced from TA746; validated by clinical expert **Healthcare resource unit costs, treatment administration costs, surgery costs:** NHS reference costs (2024-2025) **Terminal care cost:** Georghiou *et al.* (2014) (as per TA746), 2024/2025 prices
AE disutilities	**AE disutilities:** based on any cause Grade 3/4 AEs experienced by ≥5% of patients in either treatment arm in MATTERHORN SAS (December 2024 DCO)
Severity Modifier	QALY weighting of 1.0

Abbreviations: AE, adverse event; DCO, data cut-off; EF, event-free; EFS, event-free survival; EQ5D, EuroQol 5-Dimension; FAS, full analysis set; GOJC, gastro-oesophageal junction cancer; OC, oesophageal cancer; OS, overall survival; QALY, Quality-Adjusted Life Year; RD, recurred disease; SAS, statistical analysis system; TA, technical appraisal.

Company alternative base case: cPAS prices included – deterministic*

Comparison between perioperative D-FLOT versus perioperative FLOT	ICER (£/QALY) versus perioperative FLOT
Company base case: generalised gamma distribution for OS and EFS extrapolation for D-FLOT and FLOT)	**Under £20,000**

EAG comments (see appendix for further detail)

- Considers generalised gamma and log-normal equally as plausible; therefore, following OS and EFS distribution combinations should all be considered equally informative for decision making

EAG additional results: OS and EFS distributions for D-FLOT and FLOT	ICER (£/QALY) versus perioperative FLOT
D-FLOT: OS and EFS generalised gamma FLOT: OS and EFS log-normal	**Under £20,000**
D-FLOT: OS and EFS log-normal FLOT: OS and EFS generalised gamma	**Under £30,000**
D-FLOT: OS and EFS log-normal FLOT: OS and EFS log-normal	**Under £20,000**

*without severity modifier applied. Abbreviations: D-FLOT, durvalumab in combination with 5-fluorouracil, leucovorin, oxaliplatin and docetaxel; EFS, event-free survival; FLOT, 5-fluorouracil, leucovorin, oxaliplatin, docetaxel; ICER, incremental cost-effectiveness ratio; OS, overall survival; QALY, quality-adjusted life year

Company alternative base case: cPAS prices included- probabilistic*

Comparison between perioperative D-FLOT versus perioperative FLOT	ICER (£/QALY) versus perioperative FLOT
Company base case: generalised gamma distribution for OS and EFS extrapolation for D-FLOT and FLOT)	**Under £20,000**

EAG comments (see appendix for further detail)

- Considers generalised gamma and log-normal equally as plausible; therefore, following OS and EFS distribution combinations should all be considered equally informative for decision making

EAG additional results: OS and EFS distributions for D-FLOT and FLOT	ICER (£/QALY) versus perioperative FLOT
D-FLOT: OS and EFS generalised gamma FLOT: OS and EFS log-normal	**Under £20,000**
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Other (non-key issues) identified by EAG

The EAG noted the following areas of uncertainty, but were not key issues. Scenarios exploring these uncertainties reduce and/or have small impact on ICER

- **Progressed disease utility value (0.747):** Clinical advice to EAG is that this value does not represent the HRQoL experienced by patients. EAG considers a lower progressed disease utility value may be warranted. Company scenario reducing utility value to 0.399 decreases the ICER
- **Vial sharing:** Company's first model included vial sharing of IV chemotherapy. Clinical advice to EAG was vial sharing is not consistently practiced in NHS; EAG considered it should not be included in the base case. Company excluded vial sharing in its PSM; scenario exploring the impact of including vial sharing decreases the ICER
- **Subsequent treatments:** Modelled subsequent treatments based on treatments received and duration by people in MATTERHORN. Ramucirumab used in trial but not clinical practice so was replaced by irinotecan. EAG's clinical adviser noted replacing costs of ramucirumab with irinotecan was appropriate reflection of NHS practice. EAG states this assumes all other outcomes (EFS, OS) would not change with this replacement
- **Cure assumption:** Company's original model included cure assumption at 5 years; EAG considered this uncertain. In PSM this assumption was implemented as a scenario by company; decreases the ICER

Abbreviations: EFS, event-free survival; HRQoL, health-related quality of life; ICER, incremental cost-effectiveness ratio; IV, intravenous; OS, overall survival; PSM, partitioned survival model

Company deterministic scenario analysis

No.	Scenario (applied to company alternative base case)	Incremental costs (£) versus perioperative FLOT	Incremental QALYs versus perioperative FLOT	ICER (£/QALY) versus perioperative FLOT
Alternative base case (company base case using PSM)		[redacted]	[redacted]	**£12,030**
1	EFS – log-normal	[redacted]	[redacted]	£13,396
2	OS – log-normal	[redacted]	[redacted]	£12,394
3a	Cure applied with SMR of 1	[redacted]	[redacted]	£11,222
3b	Cure applied with SMR of 1.1	[redacted]	[redacted]	£11,474
4a	No UK population cap applied	[redacted]	[redacted]	£12,135
4b	Alternative RD utility value based on MATTERHORN	[redacted]	[redacted]	£12,177
4c	RD utility value set to 0.399	[redacted]	[redacted]	£10,666
4d	Do not apply age-adjusted utility	[redacted]	[redacted]	£11,264
5	Subsequent therapy distributions based on all patients with treatment in MATTERHORN	[redacted]	[redacted]	£12,757
6	Vial sharing applied	[redacted]	[redacted]	£11,770
7	Time horizon – 30 years	[redacted]	[redacted]	£12,125
8	Discounting costs/effects – 1.5%	[redacted]	[redacted]	£9,611

Abbreviations: D-FLOT, durvalumab in combination with 5-fluorouracil, leucovorin, oxaliplatin and docetaxel; EFS, event-free survival; FLOT, 5-fluorouracil, leucovorin, oxaliplatin, docetaxel; ICER: incremental cost-effectiveness ratio; OS: overall survival; QALY: quality-adjusted life year; RD: recurred disease; SMR: standardized mortality ratio

Durvalumab in combination for neoadjuvant and adjuvant treatment of resectable gastric and gastro-oesophageal junction adenocarcinoma

- Background and key issues
- Clinical effectiveness
- Modelling and cost effectiveness
- **Summary**

NICE National Institute for Health and Care Excellence

Key issues

Key issue	ICER impact	Slide
Relevance of Nivolumab as a comparator	Unknown 	11
PD-L1 status in the MATTERHORN trial and NHS clinical practice	Unknown 	17
Cost-effectiveness model structure	Small 	21

Abbreviations: ICER, incremental cost-effectiveness ratio; PD-L1, Programmed Death-Ligand 1

Committee decision making

Key issue	Questions for committee	Impact on ICER
Relevance of Nivolumab as a comparator	• Is nivolumab a relevant comparator?	Unknown
PD-L1 status in MATTERHORN trial and NHS clinical practice	• Did MATTERHORN recruit fewer people with PD-L1 <1% than would be expected in clinical practice? • Would PD-L1 status be expected to have an impact on the clinical effectiveness of durvalumab?	Unknown
Cost-effectiveness model structure	• Is the company's updated cost effectiveness (PSM) model appropriate for decision making?	Small
Other considerations	• Are there any equality issues or uncaptured benefits to consider?	Unknown
Threshold	• What is the committee preferred ICER threshold - and why?	

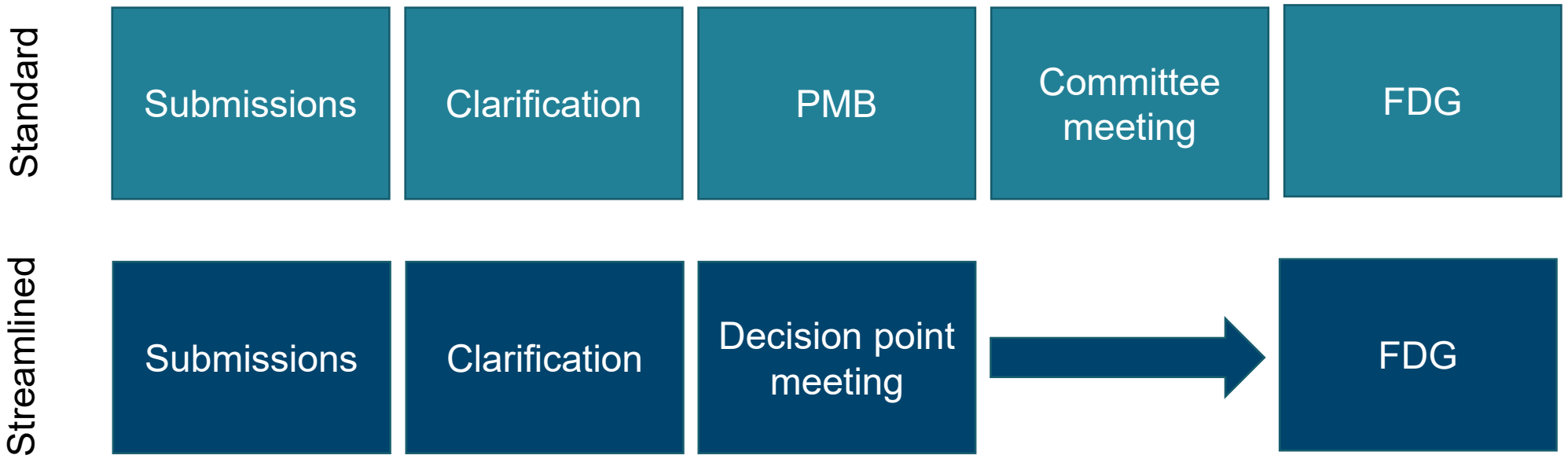
Abbreviations: ICER, incremental cost-effectiveness ratio; PD-L1, Programmed Death-Ligand 1; PSM, partitioned survival model.

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

Supplementary appendix

NICE National Institute for Health and Care Excellence

Process: streamlined approach



- Chair/lead team to confirm if they agree with the proposed streamlined process
  - If yes – NICE team to update committee and publish FDG
  - If no – NICE team to schedule full committee meeting
- If more time is needed for scrutinising the evidence before a decision, this is possible

NICE

Abbreviations: FDG, final draft guidance; PMB, pre-meeting briefing

Decision problem: Comparators (1/3)

	Final scope issued by NICE	Decision problem addressed in the company submission and rationale if different from the final NICE scope	EAG comment
Comparator(s)	Established clinical management without durvalumab, including but not limited to: • chemotherapy (FLOT), before and after surgery • people with GOJ adenocarcinoma: nivolumab, after surgery in adults with residual disease after previous neoadjuvant chemoradiotherapy	FLOT chemotherapy, before and after surgery Company considered nivolumab not a relevant comparator; no evidence presented TA746 Recommends nivolumab for adjuvant treatment of completely resected OC GOJC in adults with residual disease after previous neoadjuvant CRT; clinical advice to the company was: • CRT considered a treatment option only for those not eligible for surgery and neoadjuvant FLOT • very rare people with GOA who receive neoadjuvant CRT can tolerate surgery (and potentially be eligible for nivolumab) • nivolumab primarily used in OC/GOJC patients with SCC rather than GOA • CRT and nivolumab anticipated to be removed as treatment options from ESMO guidelines update	Agrees nivolumab is not an appropriate comparator; appropriate comparator is perioperative FLOT chemotherapy

Abbreviations: Abbreviations: CRT, chemoradiotherapy; ESMO, European Society for Medical Oncology; FLOT, 5-fluorouracil, leucovorin, oxaliplatin and docetaxel; GOA, gastro-oesophageal adenocarcinoma; GOJC, gastro-oesophageal junction cancer; OC, oesophageal cancer; SCC, squamous cell carcinoma.

Decision problem: Subgroups (2/3)

	Final scope issued by NICE	Decision problem addressed in the company submission and rationale if different from the final NICE scope	EAG comment
Final scope issued by NICE	If evidence allows, results by level of PD-L1 expression will be considered	Subgroup analyses for EFS and OS, including by PD-L1 expression level (TAP ≥1% vs TAP <1%) were provided MATTERHORN trial subgroup analyses results indicate a consistent treatment benefit regardless of PD-L1 expression level Clinical advice to company suggests PD-L1 expression is not routinely tested in all people with resectable GOA and does not determine their treatment decisions 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. Notes MATTERHORN subgroup analyses results by PD-L1 expression status were limited by the small proportion of people (10.0%) in the PD-L1 expression level <1% subgroup

Abbreviations: Abbreviations: EFS, event-free survival; GOA, gastro-oesophageal adenocarcinoma; OS, overall survival; PD-L1, programmed death-ligand 1; TAP, tumour area positivity

Decision problem: Population, intervention, outcomes (3/3)

	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	Aligned with final scope	
Intervention	D-FLOT before surgery (neoadjuvant) and after surgery (adjuvant), then adjuvant durvalumab monotherapy	Aligned with final scope	
Outcomes	Outcome measures to be considered include: • OS, EFS, response rate, AEs of treatment, HRQoL	Outcomes included: • OS, EFS, pCR, surgical outcomes, DFS, DSS, MFS, pathological downstaging, AEs, HRQoL	Aligned with final scope

Abbreviations: AE, adverse event; CS, company submission; D-FLOT, durvalumab with chemotherapy; DFS, disease-free survival; DSS, disease-specific survival; EAG, Evidence Assessment Group; EFS, event-free survival; HRQoL, health-related quality of life; MFS, metastasis-free survival; OS, overall survival; pCR, pathological complete response

Patient perspectives

Back to key patient expert statement

People with resectable stomach cancer and their caregivers report considerable anxiety and dread around the possibility of recurrence

Submissions from [Stomach Cancer UK]

- Resectable gastric and GOJ cancer carries a high risk of recurrence despite intensive chemotherapy and radical surgery. Patients have significant fear of relapse
- Many patients are willing to endure high toxicity with hope of a cure.
- Patients and caregivers placed particular weight on improving pathological complete response…as something tangible and emotionally significant. In a disease where recurrence is common even a moderate reduction in recurrence is highly significant to patients: MATTERHORN demonstrated a meaningful improvement in pCR and EFS with D-FLOT
- Gastric cancer has historically seen slower therapeutic innovation than other tumours. D-FLOT is first immunotherapy-based curative treatment [for this population] Patients [want] meaningful advancement in the curative-intent setting

"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."

"Better survival and the same amount of side effects as chemo. It's a no-brainer, isn't it?!"

Abbreviations: D-FLOT, durvalumab in combination with 5-fluorouracil, leucovorin, oxaliplatin and docetaxel; EFS, event-free survival; EFS, event-free survival; GOJ, gastro-oesophageal junction; pCR, pathological complete response

MATTERHORN trial key baseline characteristics

Back to key issue

Characteristic- final analysis set- data cut-off 2	Durvalumab (N=474)	Control (N=474)
Age, Median (range)	62 (26–84)	63 (28–83)
Sex, n (%) - Male	326 (68.8%)	356 (75.1%)
Sex, n (%) - Female	148 (31.2%)	118 (24.9%)
Region, n (%)		
Asia	90 (19.0%)	90 (19.0%)
Rest of the world	384 (81.0%)	384 (81.0%)
Race or ethnic group, n (%)[b]		
White	321 (67.7%)	322 (67.9%)
Asian	96 (20.3%)	97 (20.5%)
American Indian or Alaska Native	18 (3.8%)	20 (4.2%)
Black or African American	7 (1.5%)	3 (0.6%)
Other	8 (1.7%)	8 (1.7%)
Not reported	24 (5.1%)	24 (5.1%)
ECOG performance status, n (%) - 0	337 (71.1%)	366 (77.2%)
ECOG performance status, n (%) - 1	137 (28.9%)	108 (22.8%)
Primary tumour location, n (%) - Gastric	324 (68.4%)	316 (66.7%)
Primary tumour location, n (%) - GOJ	150 (31.6%)	158 (33.3%)
PD-L1 expression, (TAP, n (%)) <1%	48 (10.1%)	47 (9.9%)
PD-L1 expression, (TAP, n (%)) ≥1%	426 (89.9%)	427 (90.1%)

MATTERHORN clinical trial results – pCR rate at DC1 (February 2023 DCO)

Perioperative D-FLOT prior to surgery resulted in a statistically significant and clinically meaningful improvement in pCR rate vs control

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

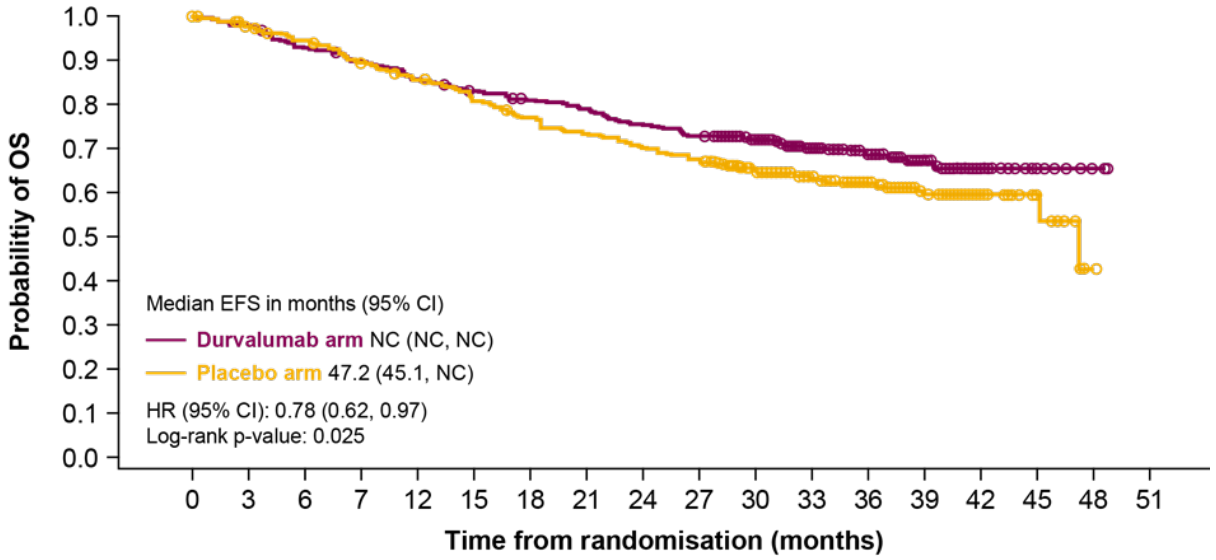
Back to key clinical trial - MATTERHORN

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

MATTERHORN clinical trial results – OS at DCO2 (December 2024 DCO)

OS results favoured D-FLOT, but not statistically significant

KM curves for OS (FAS, December 2024 DCO2)



OS	D-FLOT (n=474)	Control (n=474)
Total number of deaths, n (%)	145 (30.6)	176 (37.1)
Median OS months (95% CI)	NR (NC, NC)	47.2 (45.1, NC)
HR (95% CI)	0.78 (0.62 to 0.97)	
2-sided p-value	<0.025	

[MATTERHORN clinical trial results DCO3]

Abbreviations: CI: confidence interval; DCO: data cut-off; FAS: full analysis set; HR: hazard ratio; KM: Kaplan-Meier; NC: not calculated; NR: not reached; OS: overall survival

Adverse events (1/2)

Company

- Reported incidences of AEs of any cause and possibly related to treatment at DCO2 of MATTERHORN trial
- Proportion of people with immune-mediated AEs higher in D-FLOT vs control arm (23.2% vs. 7.2%) (as expected); mostly low grade, manageable and/or reversible with appropriate medical management
- Overall, D-FLOT as neoadjuvant and adjuvant treatment followed by adjuvant durvalumab monotherapy demonstrated a tolerable and manageable safety profile, consistent with safety profile of individual agents and resectable GOA
- Most frequently reported AEs aligned with known toxicities of FLOT, and similar across treatment arms
- Combination of durvalumab and FLOT did not result in an increased frequency or severity of known chemotherapy-related toxicities or known durvalumab-related toxicities
- No new safety concerns identified for durvalumab when given in combination with FLOT chemotherapy
- Nature and severity of AEs reported for D-FLOT arm during the adjuvant monotherapy period were consistent with the established safety profile of durvalumab monotherapy

Other considerations (clinical expert)

- Clinicians should be aware of rare immune toxicities that can arise due to durvalumab administration; significant toxicities occur in less than 5% of people
- Noted in terms of MATTERHORN trial, all adverse events were as expected

Abbreviations: AE, adverse event; DCO2, data cut-off 2; D-FLOT, durvalumab in combination with 5-fluorouracil, leucovorin, oxaliplatin and docetaxel; FLOT, 5-fluorouracil, leucovorin, oxaliplatin, and docetaxel; GOA, gastric or oesophageal adenocarcinoma

Adverse events (2/2)

EAG comments

- Note immune-mediated AEs more common in D-FLOT arm than FLOT arm
- Considers sufficient detail on AEs has been provided in company submission
- EAG agrees with company what AE associated with the FLOT components of D-FLOT and FLOT regimes make the most significant contribution to AEs reported overall.
- Overall, agrees with company that no new safety concerns were identified in MATTERHORN, and nature and severity of AEs reported for D-FLOT arm during adjuvant monotherapy period were consistent with the established safety profile of durvalumab monotherapy

Abbreviations: AE, adverse event; D-FLOT, durvalumab in combination with 5-fluorouracil, leucovorin, oxaliplatin and docetaxel; FLOT, 5-fluorouracil, leucovorin, oxaliplatin, and docetaxel

EAG comments on curve selection

EAG comments

- Considers generalised gamma and log-normal equally plausible given company's methods for curve selection for OS and EFS for D-FLOT and FLOT
- Results using generalised gamma and log-normal distributions should be given equal weight
- Notes using different OS and EFS distributions can cause curves to cross, resulting in clinically implausible kinks in the hazard function
- Considers same distribution for OS and EFS provides more realistic survival projections, but no reason same distribution should be used for D-FLOT and FLOT
- Following OS and EFS distribution combinations should all be considered equally informative; EAG produced results for OS and EFS distributions for D-FLOT and FLOT:

    - 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

Back to key issue; back to company base case results

Abbreviations: D-FLOT, durvalumab in combination with 5-fluorouracil, leucovorin, oxaliplatin and docetaxel; EFS, event-free survival; FLOT, 5-fluorouracil, leucovorin, oxaliplatin, docetaxel; OS, overall survival.