29 January 2026
EMADOC-1700519818-2830778
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Imfinzi

International non-proprietary name: Durvalumab

Procedure No. EMA/VR/0000282058

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

Table of contents

List of abbreviations

Abbreviation or special term	Explanation
5-FU	5-fluorouracil
ADA	Anti-drug antibody
ADR	Adverse drug reactions
AE	Adverse event
AEPI	Adverse event of potential interest
AESI	Adverse event of special interest
AJCC	American Joint Committee on Cancer
ALK	Anaplastic lymphoma kinase
BICR	Blinded independent central review
C	Cycle
CAP	College of American Pathologists
CDx	Companion Diagnostic
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CPS	Combined positive score
CRF	Case report form
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
D	Day
DCO	Data cut-off
DCR	Disease control rate
DFS	Disease-free survival
DSS	Disease-specific survival
ECF	Epirubicin + cisplatin + fluorouracil
ECOG	Eastern Cooperative Oncology Group
EFS	Event-free survival
EGFR	Epidermal growth factor receptor
EMA	European Medicines Agency

Abbreviation or special term	Explanation
EORTC	European Organisation for Research and Treatment of Cancer
ERES	Exposure-response and exposure-safety
ESMO	European Society for Medical Oncology
EU	European Union
FA	Final Analysis
FAS	Full Analysis Set
FDA	Food and Drug Administration
FLOT	Fluorouracil (5-FU) + leucovorin + oxaliplatin + docetaxel
GC	Gastric cancer
GEJ	Gastroesophageal junction
GEJC	Gastroesophageal junction cancer
HER2	Human epidermal growth factor receptor 2
HR	Hazard ratio
HRQoL	Health-related Quality of Life
IA	Interim Analysis
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IDMC	Independent Data Monitoring Committee
IEMT	Information Exploration Management Team
imAE	Immune-mediated adverse event
IP	Investigational product
IV	Intravenous(ly)
mAb	Monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MFS	Metastasis-free survival
MMRM	Mixed model for repeated measures
mOS	Median overall survival
mPFS	Median progression-free survival
MPR	Major pathological response
MSI	Microsatellite instability
MSS	Microsatellite stable

Abbreviation or special term	Explanation
MTP	Multiple testing procedure
NA	Not applicable
nAb	Neutralizing antibody
NC	Not calculated
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NSCLC	Non-small cell lung cancer
NR	Not reported
ORR	Objective response rate
OS	Overall survival
pCR	Pathological complete response
Pbo	Placebo
PD-1	Programmed cell death-1
PD-L1	Programmed cell death-ligand-1
PFS	Progression-free survival
PIP	Paediatric Investigation Plan
PK	Pharmacokinetic(s)
PRO	Patient-reported outcome
PS	Performance status
PT	Preferred term
Q2W	Every 2 weeks
Q3W	Every 3 weeks
Q4W	Every 4 weeks
QC	Quality control
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event
SAP	Statistical analysis plan
SCC	Squamous cell carcinoma
SEER	Surveillance, Epidemiology, and End Results
SMQ	Standardised MedDRA Query
SOC	System Organ Class

Abbreviation or special term	Explanation
TAP	Tumor area positivity
TTD	Time to deterioration
uHCC	Unresectable hepatocellular carcinoma
US	United States

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, AstraZeneca AB submitted to the European Medicines Agency on 27 June 2025 an application for a variation.

The following changes were proposed:

Variation(s) requested		**Type**
C.I.6.a	C.I.6.a Addition of a new therapeutic indication or modification of an approved one	Variation type II

Extension of indication for IMFINZI to include in combination with FLOT chemotherapy as neoadjuvant and adjuvant treatment, followed by adjuvant IMFINZI monotherapy, for the treatment of adults with resectable gastric or gastro-oesophageal junction adenocarcinoma , based on interim results from study MATTERHORN, (D910GC00001); this is a randomized, double-blind, placebo-controlled, phase 3 study of neoadjuvant-adjuvant durvalumab and FLOT chemotherapy followed by adjuvant durvalumab in patients with resectable gastric and gastroesophageal junction cancer (GC/GEJC); As a consequence, sections 4.1, 4.2, 4.5, 4.8, and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 14.0 of the RMP has also been submitted.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0301/2023 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0301/2023 was completed.

The PDCO issued an opinion on compliance for the PIP P/0301/2023.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the application included a critical report addressing the possible similarity with authorised orphan medicinal products.

Information on paediatric requirements

Not applicable.

Scientific advice

The MAH received Scientific Advice from the CHMP on 28 March 2019 (EMEA/H/SA/2752/16/2019/II). The Scientific Advice pertained to clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Boje Kvorning Pires Ehmsen

Timetable	Actual dates
Submission date	27 Jun 2025
Start of procedure:	19 Jul 2025
CHMP Rapporteur's preliminary assessment report circulated on:	19 Sep 2025
Request for supplementary information and extension of timetable adopted by the CHMP on:	16 Oct 2025
MAH's responses submitted to the CHMP on:	28 Nov 2025
CHMP Rapporteur's preliminary assessment report on the MAH's responses circulated on:	6 Jan 2026
PRAC RMP advice and assessment overview adopted by PRAC	15 Jan 2026
CHMP opinion:	29 Jan 2026
The CHMP adopted a report on similarity of Imfinzi with Vyloy on date (Appendix 1)	29 Jan 2026

2. Scientific discussion

2.1. Introduction

2.1.1. Disease or condition

Resectable gastric cancer and gastro-oesophageal-junction cancer, AJCC 8th edition stages II, III and IVA, defined as tumours of stage T2 or higher with nodal involvement (N0-3) and no distant metastases (M0), or tumours of stage T0-4 with nodal involvement (N1-3) and no distant metastases (M0).

State the claimed therapeutic indication

IMFINZI in combination with FLOT chemotherapy as neoadjuvant and adjuvant treatment, followed by adjuvant IMFINZI monotherapy, is indicated for the treatment of adults with resectable gastric or gastro-oesophageal junction adenocarcinoma.

Epidemiology

Gastric cancer is one of the most commonly diagnosed malignancies worldwide and represents the fifth leading cause of cancer-related death (Bray et al 2024, Smyth et al 2020). Approximately 95% of all GCs are adenocarcinomas (Dicken et al 2005). Cancer of the GEJ develops in the anatomical region straddling the distal oesophagus and proximal stomach (Arnold et al 2020). Gastric adenocarcinoma and gastroesophageal junction adenocarcinoma, henceforth referred to as GC/GEJC, are typically grouped together and treated with the same approach due to their anatomical proximity and similar histology (Japanese Gastric Cancer Association 2023, Lordick et al 2022, NCCN Guidelines 2025a, NCCN Guidelines 2025b, Obermannová et al 2022).

Biologic features Aetiology and pathogenesis

Globally, infection with Helicobacter pylori is considered a major risk factor for the development of GC. In most countries, improved living conditions associated with economic development have

contributed to the reduction in the prevalence of H. pylori. However, other factors such as obesity, tobacco smoking, high salt intake, and heavy alcohol consumption have also been associated with an increased risk of GC (Arnold et al 2020, Morgan et al 2022, Smyth et al 2020). Risk factors for GEJC, particularly in high-income countries where incidence of the disease is rising, include gastroesophageal reflux disease, obesity, and high fat intake (Arnold et al 2020, Obermannová et al 2022).

The global incidence of GC/GEJC shows wide geographic variation. GC incidence has substantially declined over the past decades in the US and Western Europe but remains a major global health problem, particularly in Asia, where the majority of new cases (71%) are diagnosed.

Globally, the highest risk areas for GC span Eastern and Western Asia, South and Central America, and Southern and Eastern Europe (Bray et al 2024). The incidence of GEJC is highest in Eastern Asia, followed by Southern Africa, Eastern Africa, Northern Europe, and South-Central Asia (NCCN Guidelines 2025b, Obermannová et al 2022). As of 2022, approximately 40% of incident cases of GC/GEJC in the US and Europe were diagnosed as potentially resectable, locally advanced disease (clinical stages II-III per AJCC 8th edition) (Amin et al 2018, Cabasag et al 2021, Cancer Research UK 2024, United States Cancer Statistics).

Clinical presentation, diagnosis and stage/prognosis

Gastric cancer and GEJC may be asymptomatic in early stages, but common symptoms are dysphagia, asthenia, vomiting, weight loss, early satiety and iron deficiency anaemia (Lordick et al 2022). Endoscopic examination and biopsies are the gold standard for diagnosing gastric cancer.

GC and GEJC are staged according to the TNM classification of the AJCC/UICC 8th staging manual.

Although multimodal perioperative treatment strategies have improved survival outcomes in resectable GC/GEJC (Al-Batran et al 2019, Bang et al 2012, Cunningham et al 2006, Sasako et al 2011, Smalley et al 2012, Ychou et al 2011), cure rates for GC/GEJC remain at approximately 40% (Smyth et al 2020), and the majority of patients who relapse do so within 3 years of surgery (Al-Batran et al 2019, Giommoni et al 2021, Möhring et al 2023). After perioperative treatment, patients are monitored periodically without receiving any systemic anti-cancer treatment until disease symptoms appear or worsen. However, once patients' disease progresses to the advanced/metastatic stage, systemic anti-cancer therapy is not curative (Lordick et al 2022, NCCN Guidelines 2025a, NCCN Guidelines 2025b, Obermannová et al 2022). Overall, the 5-year OS rate for GC remains low (31% in the US and 25% worldwide) (NCI SEER 2023, Sexton et al 2020).

Management

Surgical resection remains the cornerstone of treatment of operable gastric cancer and may be curative in a subset of patients. For patients with stage IB or higher disease, combined modality treatment approaches, including perioperative or neoadjuvant therapies in combination with surgery are the current standard of care.

In Europe and North America, neoadjuvant and adjuvant (i.e., perioperative) FLOT chemotherapy in combination with surgical resection is the standard of care for patients with resectable Stage IB or higher GC (Lordick et al 2022, NCCN Guidelines 2025a) and resectable, locally advanced GEJC (NCCN Guidelines 2025b, Obermannová et al 2022). The FLOT regimen consists of 4 neoadjuvant and 4 adjuvant 2-week cycles of 5-FU, leucovorin, oxaliplatin, and docetaxel (Lordick et al 2022, NCCN Guidelines 2025a, NCCN Guidelines 2025b, Obermannová et al 2022). Approval of perioperative FLOT and its inclusion in treatment guidelines (NCCN evidence category 1) was based on the positive results of the phase II/III FLOT4-AIO study (NCT01216644) in patients with resectable, nonmetastatic GC or GEJC. In the phase II part of the study, results showed that FLOT

was associated with a significantly higher proportion of patients achieving pCR compared to the widely used epirubicin-cisplatin-fluorouracil or epirubicin-cisplatin-capecitabine chemotherapy regimens (ECF/ECX group) (pCR rate: 16% vs 6%, respectively; p = 0.02) (Al-Batran et al 2016).

In the Phase III part of the trial, patients in the FLOT group demonstrated a statistically significant improvement in OS compared to the ECF/ECX group (median OS: 50 months vs 35 months, respectively; HR: 0.77 [95% CI: 0.63, 0.94]; p = 0.012) (Al-Batran et al 2019). Because of its toxicity profile, perioperative FLOT is generally administered to patients with good performance status (Lordick et al 2022, NCCN Guidelines 2025a, NCCN Guidelines 2025b, Obermannová et al 2022).

For patients with resectable, locally advanced esophageal or GEJ tumors (including squamous cell carcinomas and adenocarcinomas), neoadjuvant chemoradiotherapy in combination with surgical resection represents and established treatment approach (NCCN Guidelines 2025b, Obermannová et al 2022). In this setting, adjuvant nivolumab has been approved for the treatment of patients with completely resected oesophageal or gastroesophageal tumors (R0 resection) who have residual pathologic disease after surgery (i.e., absence of pCR). This approach is based on the results of the phase III CheckMate-577 study (NCT02743494) (Kelly et al 2021, NCCN Guidelines 2025b, Obermannová et al 2022).

2.1.2. About the product

Durvalumab is a human mAb of the IgG1κ subclass that inhibits binding of PD-L1 (B7-H1) to PD-1 and CD80 (B7.1). The blockade of the PD-L1/PD-1 pathway enhances T-cell reactivity by inhibiting the immunosuppression of regulatory T cells.

Durvalumab is an established product that is currently approved for multiple indications in the EU, namely for the treatment of:

- Resectable NSCLC (tumors ≥ 4 cm and/or node positive) with no known EGFR mutations or ALK rearrangements, in combination with platinum-containing chemotherapy as neoadjuvant treatment, followed by durvalumab continued as a single agent as adjuvant treatment after surgery (EMEA/H/C/004771/II/0064).
- Unresectable Stage III following chemoradiation therapy (EMEA/H/C/004771/0000).
- Metastatic NSCLC with no sensitizing EGFR mutations or ALK genomic tumor aberrations in combination with tremelimumab and platinum-based chemotherapy (EMEA/H/C/004771/II/0041).
- Extensive-stage small cell lung cancer in combination with chemotherapy (EMEA/H/C/004771/II/0014/G).
- Limited-stage small cell lung cancer following chemoradiation therapy (EMEA/H/C/004771/II/0069).
- Locally advanced or metastatic biliary tract cancer, in combination with chemotherapy (EMEA/H/C/004771/II/0046).
- Unresectable hepatocellular carcinoma, in combination with tremelimumab (EMEA/H/C/004771/II/0045).
- Unresectable hepatocellular carcinoma, as monotherapy (EMEA/H/C/004771/II/0057)
- Primary advanced or recurrent endometrial cancer that is mismatch repair deficient in combination with chemotherapy followed by durvalumab as a single agent.
- Primary advanced or recurrent endometrial cancer that is mismatch repair proficient in combination with chemotherapy and olaparib followed by durvalumab and olaparib (EMEA/H/C/004771/WS2463).

- Resectable muscle invasive bladder cancer, in combination with gemcitabine and cisplatin as neoadjuvant treatment, followed by durvalumab continued as single agent as adjuvant treatment after radical cystectomy (EMEA/H/C/004771/II/0073).

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

The MAH sought Scientific Advice from the CHMP on the MATTERHORN study in March 2019, more specifically on the choice of EFS as the primary endpoint, the stratification factors, the FLOT control arm, and 12 months duration of adjuvant durvalumab but cautioned that the study design would not allow the optimal duration of durvalumab treatment to be assessed. CHMP advised that if an increased proportion of cured patients could not be inferred from the EFS data, the benefit-risk evaluation would require evidence of an OS benefit.

A pre-submission meeting with the Rapporteurs took place in May 2025 where it was agreed that the MATTERHORN data supported the submission of a Type II application in the proposed indication and with the proposal of submitting the OS Final Analysis during the application review. The Rapporteurs provided additional comments on various topics that should be included in the Type II application.

2.1.4. General comments on compliance with GCP

The MAH states that the MATTERHORN study was performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with ICH/GCP.

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which is considered acceptable.

2.2.1. Ecotoxicity/environmental risk assessment

Durvalumab (MEDI4736) is a human monoclonal antibody of the immunoglobulin G1 kappa (IgG1κ) subclass that inhibits the interaction of programmed cell death ligand 1 (PD-L1) with the programmed cell death-1 (PD-1) and cluster of differentiation 80 (CD80/B7.1) cell surface receptors.

Durvalumab is considered to be a non-hazardous, biodegradable product. As such, the environmental risk in terms of use and disposal is considered to be negligible and in accordance with the guideline (CHMP 2024) ERA studies are not submitted.

2.2.2. Conclusion on the non-clinical aspects

Considering the above data, durvalumab is not expected to pose a risk to the environment.

2.3. Clinical aspects

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Study name (study number)	Study title	DCO	Study objectives and dosing regimen	eCTD location
Pivotal study				
MATTERHORN (D910GC00001)	A randomized, double-blind, placebo-controlled, Phase III study of neoadjuvant-adjuvant durvalumab and FLOT chemotherapy followed by adjuvant durvalumab in patients with resectable gastric and gastroesophageal junction cancer (GC/GEJC)	20 Dec 2024	Efficacy and safety of D + FLOT vs Pbo + FLOT as well as PK and immunogenicity Treatment Arm A (D + FLOT): Durvalumab 1500 mg on Day 1 + FLOT (5-FU 2600 mg/m^2, leucovorin 200 mg/m^2, oxaliplatin 85 mg/m^2, and docetaxel 50 mg/m^2) on Days 1 and 15 Q4W for 4 cycles (2 cycles neoadjuvant + 2 cycles adjuvant) followed by durvalumab 1500 mg on Day 1 Q4W for 10 additional cycles Treatment Arm B (Pbo + FLOT): Placebo on Day 1 + FLOT on Days 1 and 15 Q4W for 4 cycles (2 cycles neoadjuvant + 2 cycles adjuvant) followed by placebo on Day 1 Q4W for 10 additional cycles	Module 5.3.5.1

Study name (study number)	Study title	DCO	Study objectives and dosing regimen	eCTD location
Key supportive studies				
HIMALAYA (D419CC00002)	Randomized, open-label, multicenter Phase III study of durvalumab and tremelimumab as first-line treatment in patients with advanced HCC	27 Aug 2021	See Appendix Table 10	Module 5.3.5.1
Study 1108 (CD-ON-MEDI4736-1108)	A Phase I/II study to evaluate the safety, tolerability, and pharmacokinetics of MEDI4736 in subjects with advanced solid tumors	16 Oct 2017	See Appendix Table 10	Module 5.3.5.2

2.4. Clinical Pharmacology

2.4.1. Bioanalytical methods

The bioanalytical methods used for the determination of durvalumab serum concentration, the detection of ADAs, and the detection of nAbs against durvalumab in human serum in the MATTERHORN study are listed in Table 1. These methods are well-established and have been used in several other clinical studies and will therefore not be assessed here. In Table 2, a summary of the method performance of the PK assay in MATTERHORN. In Table 3, a summary of the performance of the ADA assay. Finally, in Table 4, a summary the performance of the nAb assay is presented.

Table 1 Overview of Bioanalytical Methods for Durvalumab Used in the MATTERHORN Study

Measurement	Laboratory	Validation report	Method number
Durvalumab	-I	183708	X
ADA	A	RAVC2	Y
nAb	A	RJRG2	Z

Table 2 Parameter Summary of Durvalumab Serum Concentration Assay Used in the MATTERHORN Study – ICON

Method number	**X**
Report number	**183798**
LLOQ (ng/mL)	50.0
Range (ng/mL)	50.0 to 1600
Inter-assay %RE range (Quick Plex SQ 120)	-4.5% to 17.6%
Inter-assay %CV range (Quick Plex SQ 120)	5.03% to 11.8%
Intra-assay %RE range (Quick Plex SQ 120)	6.55% to 24.3%
Intra-assay %CV range (Quick Plex SQ 120)	0.718% to 1.99%
Inter-assay %RE range (Sector Imager)	-17.1% to 0.00%
Inter-assay %CV range (Sector Imager)	9.86% to 12.6%
Intra-assay %RE range (Sector Imager)	6.95% to 19.8%
Intra-assay %CV range (Sector Imager)	0.776% to 3.56%

Table 3 Parameter Summary of Anti-durvalumab Antibody Assay Used in the MATTERHORN Study – PPD

Method number	**- Y**
Screening assay cut point [a]	1.59
Screening assay false-positive rate (%)	5
Assay LOD (ng/mL) [b]	8.22
Assay detectable range (ng/mL)	8.22 to 100,000
Assay drug tolerance	Assay can detect ≥ 82.3 ng/mL positive control in the presence of ≤ 100 µg/mL of durvalumab [c]
Inter-assay precision (%CV)	15.6 to 27.0 [d]
Intra-assay precision (%CV)	1.94 to 3.80
Confirmatory assay cut point (% inhibition) [e]	29.4
Confirmatory assay falsepositive rate (%)	0.1

[a] Screening cut point was established in each validation study by statistical analysis of SN ratios of RLU responses of the individual naïve samples from patients with cancer normalized relative to the pooled serum matrix blank RLU signal.

[b] Represents screening assay sensitivity.

[c] Additional drug tolerance evaluation was performed at the AstraZeneca X laboratory. According to the report G-IM-0143, the assay can detect ≥ 100 ng/mL positive control in the presence of ≤ 161 µg/mL of durvalumab (≤ 182 µg/mL in the screening tier).

[d] The overall precision of the raw response for each positive control level (high positive control, low positive control) and re-adjusted low positive control was ≤ 23.0% and met the target criterion of ≤ 25.0%. The overall precision of the raw response for negative control was 27.0%, which was greater than the target criterion of ≤ 25.0%. High negative control response was observed in 2 runs. The runs were performed on the same day and met the final acceptance criteria of cut point factor (1.59 signal to background ratio) < low positive control signal to noise. All other runs demonstrated comparable negative control response; therefore, the overall precision of the raw response for negative control was found to be acceptable.

[e] Confirmatory cut point was established by statistical analysis of the percent inhibition levels of the responses of the individual naïve samples from patients with cancer tested both with and without drug. A 0.1% false positive rate was used for mesothelioma and other cancer indications.

Table 4 Summary of Neutralizing Antibody Against Durvalumab Assay Parameters in the MATTERHORN Study – PPD

Method number	**Z**
Assay cut point [a]	1.20
Assay false positive rate (%)	1
Assay sensitivity (ng/mL)	220.69
Assay drug tolerance	Assay can detect ≥ 2000 ng/mL of positive control in the presence of 1000 ng/mL of durvalumab in 100% serum
Inter-assay precision (%CV)	7.91 to 18.3 (based on SN)
Intra-assay precision (%CV)	2.3 to 10.3

[a]: The cut point was established by statistical analysis of SN ratios of RLU responses of the individual naïve samples from patients with cancer without drug normalized relative to the pooled serum matrix blank RLU signal.

2.4.2. Pharmacokinetics

The PK, immunogenicity, and pharmacodynamics of durvalumab have been previously well characterized based on the assessment of monotherapy data integrated from 15 studies in the

durvalumab clinical development program, hereafter referred to as the durvalumab pan-tumor pool. These data are summarized in the current durvalumab prescribing information.

The purpose of this section is to provide new PK and immunogenicity data pertaining only to the pivotal study for the current submission (Study D910GC00001, hereafter referred to as MATTERHORN) in order to support the proposed indication, dosage, and duration of treatment (see Table 1). The pivotal MATTERHORN study is supported by pooled PK and immunogenicity data for durvalumab monotherapy in the durvalumab pan-tumor pool.

The proposed dosage is durvalumab 1500 mg on Day 1 Q4W given in combination with FLOT (5-FU 2600 mg/m2, leucovorin 200 mg/m2, oxaliplatin 85 mg/m2, and docetaxel 50 mg/m2) on Days 1 and 15 of each durvalumab cycle 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 1500 mg monotherapy Q4W for 10 additional cycles (1 dose per cycle).

In the event that a patient's weight decreased to ≤ 30 kg, the protocol allowed, after consultation between the Investigator and Sponsor, receipt of a weight-based dosing regimen of 20 mg/kg of durvalumab Q4W. Weight-based dosing was allowed until the patient's weight improved to > 30 kg, at which point the patient could restart receipt of the fixed dosing of durvalumab 1500 mg Q4W. In the MATTERHORN study, the body weight of 1 patient decreased to ≤ 30 kg, and this patient therefore received durvalumab weight-based dosing. This patient was switched to the modified durvalumab regimen of 20 mg/kg in the last adjuvant treatment cycle (Cycle 14) and received 500 mg of durvalumab.

PK and ADA sampling

Serum samples for durvalumab PK were collected at pre-dose and post-infusion in Cycle 1, pre-dose in Cycle 2, pre-dose in Cycle 4, and pre-dose in Cycle 9, and at 3 months follow-up after the last dose of durvalumab. Plasma samples for docetaxel PK were collected at 30 minutes ± 10 minutes, 2 hours ± 0.5 hour, 5 hours ± 0.5 hour, and 1 day post FLOT dose in Cycle 1 regardless of the treatment arm.

Serum samples for durvalumab ADA/nAb were collected at pre-dose in Cycles 1, 2, 4, and 9 and at 3 months follow-up after the last dose of durvalumab.

Durvalumab PK

Durvalumab PK data were available for a total of 470 patients in the D + FLOT arm (Durvalumab PK Analysis Set). Durvalumab serum concentrations (Table 5) were within the expected concentration range following the 1500 mg Q4W regimen based on previously reported PK data from studies of durvalumab.

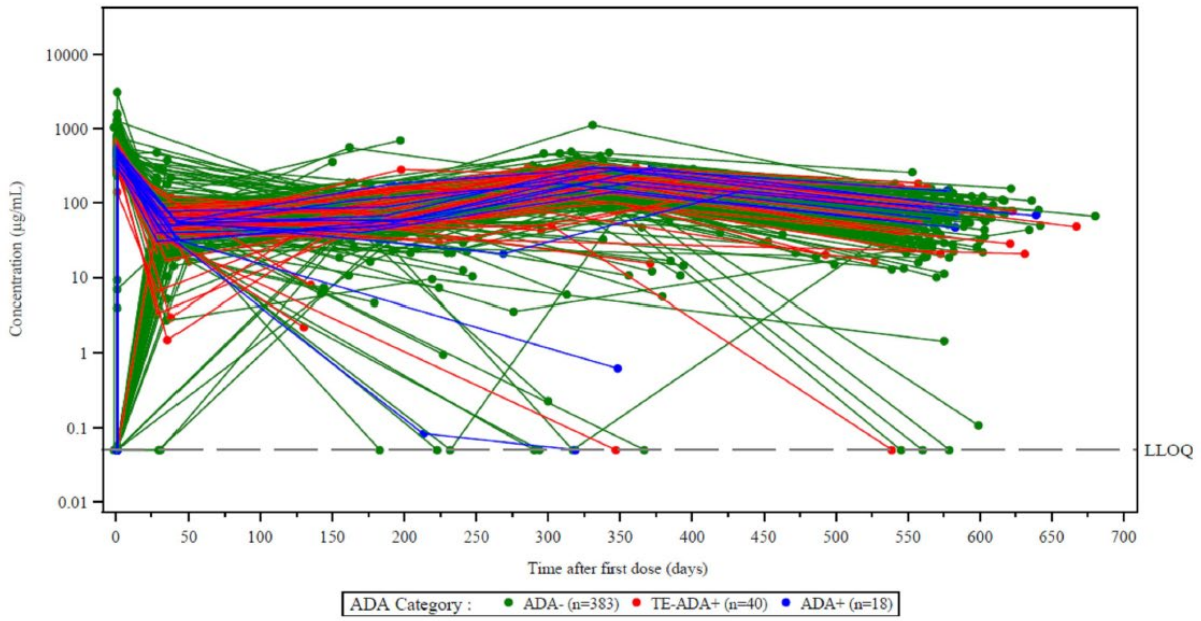
Table 5 Summary of Serum Durvalumab Concentrations (µg/mL) (Durvalumab PK Analysis Set, DCO2)

Visit, timepoint/ Summary statistic	MATTERHORN	D pan-tumor pool		
	D + FLOT 1500 mg Q4W (N = 470)	D 1500 mg Q4W (N = 1217)	D 20 mg/kg Q4W (N = 424)	D 10 mg/kg Q2W (N = 2520)
Neoadjuvant Cycle 1 (preinfusion)				
n	461	756	416	1955
n BLQ	452 [a]	729	408	1870
Geometric mean [b]	NC	NC	NC	NC
Geometric CV (%) [b]	NC	NC	NC	NC
Arithmetic mean	5.596	3.776	0.808	2.197
StDev	NC	NC	NC	NC
Median	NQ	NQ	NQ	NQ
Min	NQ	NQ	NQ	NQ
Max	641.45	557.68	188.75	454.35
Neoadjuvant Cycle 1 (postinfusion)				
n	430	758	376	2267
n BLQ	29	22	5	50
Geometric mean [b]	244.7	329.5	394.8	167.8
Geometric CV (%) [b]	1457.5	344.52	154.71	214.34
Arithmetic mean	450.66	448.30	470.92	212.25
StDev	246.023	226.408	213.292	98.334
Median	437.032	437.666	439.373	204.857
Min	0.05	0.05	0.05	0.03
Max	3072.52	4721.52	2320.59	1474.70
Neoadjuvant Cycle 2 (preinfusion)				
n	441	839	21	954
n BLQ	2	5	0	0
Geometric mean [b]	53.6	69.2	66.7	81.9
Geometric CV (%) [b]	94.55	88.26	89.10	58.93
Arithmetic mean	65.237	81.747	97.846	91.132
StDev	42.575	53.4584	143.8783	37.7272
Median	60.464	74.340	64.410	88.545
Min	0.05	0.05	17.29	0.07
Max	482.48	712.15	711.50	328.08

Visit, timepoint/ Summary statistic	MATTERHORN	D pan-tumor pool		
	D + FLOT 1500 mg Q4W (N = 470)	D 1500 mg Q4W (N = 1217)	D 20 mg/kg Q4W (N = 424)	D 10 mg/kg Q2W (N = 2520)
Month 3 Follow-up				
n	269	375	107	625
n BLQ	10	21	12	27
Geometric mean [b]	49.1	20.2	18.2	18.7
Geometric CV (%) [b]	119.89	258.17	334.51	186.73
Arithmetic mean	62.696	46.811	50.497	29.983
StDev	41.885	103.1888	105.575	29.790
Median	57.100	21.591	11.484	22.370
Min	0.05	0.05	0.05	0.05
Max	257.29	1309.39	662.50	221.37

[a] : There were 9 patients with quantifiable durvalumab concentrations at the Cycle 1, Day 1 pre-infusion timepoint (pre-dose) for MATTERHORN and 120 patients in the D pan-tumor pool combined. Despite thorough investigation by the Sponsor, the exact reasons for this discrepancy remain indeterminate.
[b] : When less than or equal to half of the results were BLQ, the BLQ results were set to the LLOQ, and descriptive statistics were calculated accordingly; when more than half (but not all) of the results were BLQ, SD, CV%, geometric mean, and geometric CV% were presented as NC, and the median and minimum were presented as NQ; when all results were BLQ, no descriptive statistics were calculated.

Figure 1 Individual durvalumab serum concentration time profile by ADA status (ADA Analysis Set; DCO2)



The plot includes data from ADA-evaluable patients. ADA+ : patients who were ADA positive at any time, but not TE-ADA positive, against durvalumab. ADA- : patients who had ADA-negative results to durvalumab at all time, baseline and post-baseline. TE-ADA+: patients who were TE-ADA positive. DCO: 20 December 2024.

2.4.3. Pharmacodynamics

No new pharmacodynamics data are available to that reported in previous submissions for durvalumab registration.

Mechanism of action

Durvalumab is a human mAb of the immunoglobulin G (IgG) 1 kappa subclass that blocks the interaction of PD-L1 (but not programmed cell death ligand-2) with PD-1 on T cells and CD80 (B7.1) on immune cells (IC). The blockade of the PD-L1/PD-1 pathway enhances T-cell reactivity by inhibiting the immunosuppression of regulatory T cells.

Primary and secondary pharmacology

Analyses of ER for efficacy and safety were not performed for this application because such analyses have been conducted for multiple pivotal studies (e.g., PACIFIC, POSEIDON, HIMALAYA, TOPAZ-1), and the corresponding results indicated no significant ER correlations for both efficacy and safety endpoints at the durvalumab dose levels evaluated for each study.

Immunogenicity

Table 6 Summary of Anti-drug Antibody Responses to Durvalumab in the MATTERHORN Study and in the Durvalumab Pan-tumor Pool (ADA Analysis Set, DCO2)

ADA category	Number (%) of patients	
	MATTERHORN	D pan-tumor pool
	D + FLOT 1500 mg Q4W (N = 475)	D 1500 mg Q4W, 20 mg/kg Q4W, and 10 mg/kg Q2W (N = 4642)
ADA-evaluable patients	441 (92.8)	3511 (75.6)
ADA positive at any visit (ADA prevalence) [a]	58 (13.2)	212 (6.0)
Median of maximum titer (minimum, maximum)	2.0 (1, 32)	4.0 (1, 1024)
Treatment-emergent ADA positive (ADA incidence) [b]	40 (9.1)	93 (2.6)
Median of maximum titer (minimum, maximum)	3.0 (1, 32)	4.0 (1, 1024)
ADA positive post-baseline and positive at baseline	1 (0.2)	21 (0.6)
Median of maximum titer (minimum, maximum)	8.0 (8, 8)	8.0 (2, 32)
ADA positive post-baseline only, or treatment-induced ADA	40 (9.1)	89 (2.5)
Median of maximum titer (minimum, maximum)	3.0 (1, 32)	4.0 (1, 1024)
ADA positive at baseline only	17 (3.9)	102 (2.9)
Median of maximum titer (minimum, maximum)	2.0 (1, 32)	4.0 (1, 125)
Treatment-boosted ADA [c]	0	4 (0.1)
Median of maximum titer (minimum, maximum)	NA (NA, NA)	12.0 (4, 32)
Persistently positive [d]	11 (2.5)	73 (2.1)
Median of maximum titer (minimum, maximum)	4.0 (1, 32)	4.0 (1, 1024)
Transiently positive ADA [e]	30 (6.8)	37 (1.1)
Median of maximum titer (minimum, maximum)	2.0 (1, 16)	4.0 (1, 128)
nAb positive at any visit	2 (0.5)	19 (0.5)
Median of maximum titer (minimum, maximum)	5.0 (2, 8)	16.0 (1, 1024)

[a] ADA prevalence is the proportion of ADA-evaluable patients who were ADA positive at any time.

[b] ADA incidence is the proportion of ADA-evaluable patients who were treatment-emergent ADA positive. These were patients who were not positive at baseline but developed ADAs post treatment, and patients who had ADA at baseline and whose ADA titer was boosted to ≥ 4-fold during the study period.

[c] Defined as baseline-positive ADA titer that was boosted to ≥ 4-fold during the study period.

[d] Defined as having at least 2 post-baseline ADA-positive measurements with at least 16 weeks (112 days) between the first and last positive measurements, or an ADA positive result at the last available assessment. The category included patients meeting these criteria who were ADA positive at baseline.

[e] Defined as having at least one post-baseline ADA-positive measurement and not fulfilling the conditions for persistently positive. The category included patients meeting these criteria who were ADA positive at baseline.

Note: The denominator for calculation of percentage for all categories was the number of ADA-evaluable patients (defined as the patients in the safety analysis set who had a non-missing baseline ADA and at least one nonmissing post-baseline results) in the treatment group. The denominator for calculation of percentage of ADA-evaluable patients category was N.

2.4.4. Discussion on clinical pharmacology

Bioanalytical methods

The PK and immunogenicity assays have previously been used in several other clinical studies. They are sufficiently validated and were previously assessed to be robust and reliable. Hence, only the assay performance in the MATTERHORN study is subject to assessment.

PK assay (ICON)

A final bioanalytical report from ICON was submitted dated 22 May 2025. 4508 primary samples and 2319 duplicate (back-up) samples were received. All samples were received in satisfactory condition. Samples were analysed in 234 runs of which 22 were rejected mainly due to failed QCs. A total of 432 samples (9.6% of all tested) were reanalyzed as incurred samples. Overall: 90.97% of all repeats were within specification.

ADA assay (PPD)

A bioanalytical report on ADA analysis was submitted, which was signed 03 Oct 2024. 3660 original samples and 2616 duplicate samples were received in good condition. Of these, 172 samples were ADA positive in tier 2. Of 162 analytical runs, only 12 runs failed. No deviations from bioanalytical plan or method were noted.

nAb assay (PPD)

A bioanalytical report on detection of neutralizing ADAs was submitted, which was signed 03 Oct 2024. 3639 samples were reported with only 7 samples positive for nAbs. The analysis was performed across eight acceptable runs (100% pass rate). No deviations or unexpected events were noted.

All in all, the performance of the PK and immunogenicity assays and the conduct of the sample analysis is considered acceptable.

Pharmacokinetics and pharmacodynamics

One already established flat dose level was used in MATTERHORN. This dose of 1500 mg per cycle was previously shown to provide similar exposure as 20 mg/kg. Sparse sampling similar to previous studies was performed in the neoadjuvant period providing the possibility to compare exposure across the D pan-tumour pool in the neoadjuvant phase cycle 1 (post infusion) and cycle 2 (pre-infusion) and at 3 months follow up. Additional samples were collected in the adjuvant period pre-dose in cycle 4 and 9. The Geometric mean and arithmetic mean serum concentrations are considered similar between MATTERHORN and the D pan-tumour pool in the neoadjuvant phase

although it is noted that the CV% (>1450) was substantial for MATTERHORN at neoadjuvant cycle 1 post infusion. The MAH clarified that this was due to outliers both below and above the expected range. No cause for these outliers could be identified.

In the adjuvant phase where durvalumab is administered alone, i.e. pre-dose in cycle 9, the concentration is higher than in cycle 2 and 4, but similar to e.g. pre-dose in cycle 5 in the adjuvant phase in the NIAGARA study, hence not a concern.

As previously concluded, ADA appeared not to influence exposure to durvalumab.

SmPC

In section 4.5 of the SmPC (Interaction with other medicinal products and other forms of interaction), the paragraph listing assessment of PK drug-drug interaction between durvalumab and concomitant treatments was replaced with a summary noting that no drug-drug interactions were identified in CASPIAN, POSEIDON, HIMALAYA, and DUO-E studies. There are no changes to the current wording in section 5.2 of the SmPC. This is considered acceptable.

2.4.5. Conclusions on clinical pharmacology

Overall, the bioanalysis and pharmacokinetics of durvalumab is well established and sufficiently described from previous clinical studies. This is also the case for the submitted MATTERHORN study.

2.5. Clinical efficacy

2.5.1. Dose response studies

Durvalumab is approved for use in multiple indications at a fixed dose of 1500 mg utilizing a Q4W dosing schedule, as described in the current prescribing information. A previous population PK model developed for durvalumab monotherapy using data from Study 1108 has indicated only a minor impact of body weight on the PK of durvalumab. PK simulation results have demonstrated that body weight-based and fixed dosing regimens yield similar median steady state PK concentrations with slightly less overall between-patient variability with fixed dosing regimen. Based on previously reported data, no dose adjustment is necessary based on intrinsic or extrinsic factors (age, renal and hepatic function, race, region, and ECOG performance status). As aligned with the standard approved dosing regimens, it is recommended that patients with a body weight of ≤ 30 kg received weight-based dosing equivalent to durvalumab 20 mg/kg in combination with chemotherapy, followed by durvalumab 20 mg/kg Q4W at any point during treatment (ie, in combination with FLOT chemotherapy in the neoadjuvant and/or adjuvant periods, or as monotherapy in the adjuvant monotherapy period), until weight increased to > 30 kg, at which point the patient could restart receipt of the fixed dosing of durvalumab 1500 mg Q4W.

At the time of MATTERHORN study design, the combination of durvalumab with different chemotherapy regimens had been shown to be tolerable and have manageable toxicity, with no new safety signals identified. On this basis the approved dose of durvalumab in combination with FLOT chemotherapy was chosen as the treatment regimen in the Matterhorn trial.

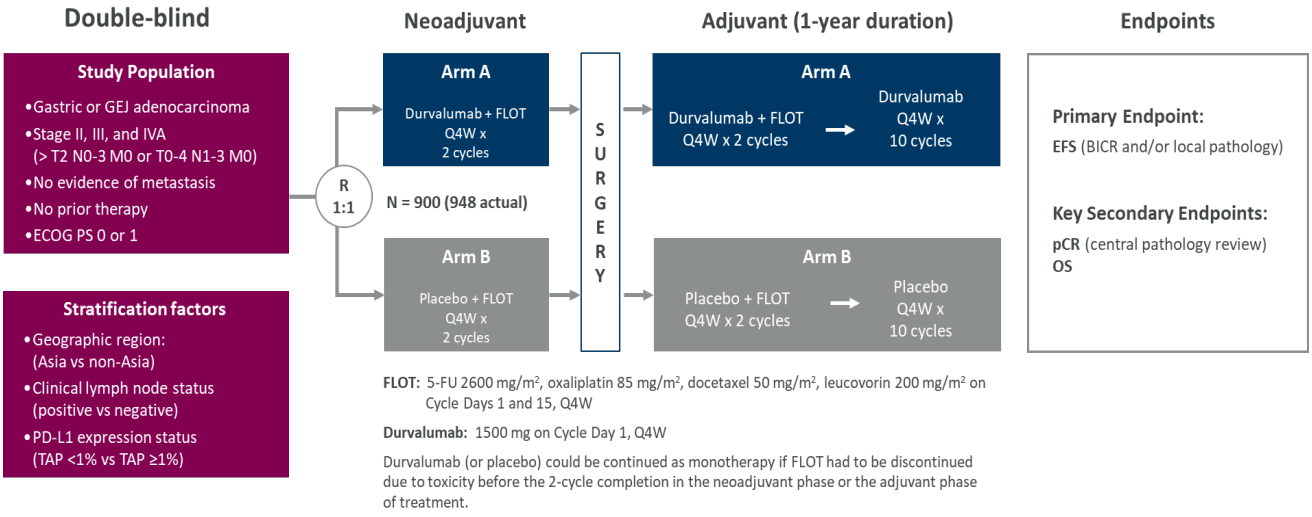
Neoadjuvant-adjuvant FLOT (5-FU 2600 mg/m^2, leucovorin 200 mg/m^2, oxaliplatin 85 mg/m^2, and docetaxel 50 mg/m^2) is the most commonly used standard treatment regimen for patients with resectable GC/GEJC, and it is administered Q2W.

2.5.2. Main study

MATTERHORN

MATTERHORN is a, randomized, double-blind, placebo-controlled, multicenter, global phase III study to assess the efficacy and safety of neoadjuvant-adjuvant durvalumab in combination with FLOT chemotherapy, followed by adjuvant durvalumab monotherapy, in patients with resectable GC/GEJC (i.e., radical-surgery eligible; Stages II to IVA per AJCC 8th edition). Globally, 948 patients were randomized in a 1:1 ratio.

Figure 2 MATTERHORN Study Design



2.5.2.1. Methods

Study participants

Main inclusion criteria:

1. Age ≥ 18 years at the time of screening. For patients aged < 20 years and enrolled in Japan, a written informed consent should be obtained from the patient and his or her legally acceptable representative.
2. Histologically documented gastric or gastroesophageal junction adenocarcinoma with resectable disease (ie, radical-surgery eligible; Stage II or higher [> T2 N0-3 M0 or T0-4 N1-3 M0] per AJCC 8th edition). GEJC includes Siewert* Type 2 and 3 tumor. Siewert* Type 1 tumor is also eligible as long as the patient is intended to be treated in the same way as for Siewert Type 2 and 3 tumors.
3. Per the judgment of the investigator, patient must be medically fit for treatment with neoadjuvant FLOT therapy prior to radical surgery.
4. At screening, complete surgical resection of the primary GC/GEJC must be deemed achievable, as assessed by a multidisciplinary evaluation, which must include a board-certified GI surgeon
5. No prior anti-cancer therapy (e.g., chemotherapy, radiation therapy, or chemoradiation therapy) for the current malignancy.
6. WHO/ECOG PS of 0 or 1.

7. Adequate organ and marrow function.
8. Must have a life expectancy of at least 24 weeks
9. Body weight > 30 kg at enrolment and randomization
10. Tumor PD-L1 expression level, confirmed by a reference laboratory using the Ventana PD-L1 (SP263) CDx Assay, must be known prior to randomization. As such, all patients must be able to undergo a new tumor biopsy during screening or to provide an available tumor sample taken < 3 months prior to enrolment. The tumor specimen submitted to establish eligibility should be of sufficient quantity to allow for PD-L1 IHC and other exploratory biomarker analyses and is preferred in formalin-fixed paraffin-embedded blocks.

Main exclusion criteria:

1. Patients with peritoneal dissemination (including tumor cells in peritoneal fluid) or distant metastasis
2. Patients with adenosquamous cell carcinoma, squamous cell carcinoma, or GI stromal tumor
3. History of allogeneic organ transplantation
4. Active or prior documented autoimmune or inflammatory disorders. The following were exceptions to this criterion: patients with vitiligo or alopecia, patients with hypothyroidism stable on hormone replacement, any chronic skin condition that does not require systemic therapy, patients without active disease in the last 5 years may be included but only after consultation with the AZ, patients with celiac disease controlled by diet alone
5. Uncontrolled intercurrent illness
6. History of another primary malignancy 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; adequately treated carcinoma in situ without evidence of disease
7. History of active primary immunodeficiency
8. Active infection including tuberculosis, hepatitis B, hepatitis C, or human immunodeficiency virus (positive HIV 1/2 antibodies). Patients with a past or resolved HBV infection are eligible. Patients positive for hepatitis C (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA
9. Mean QT interval corrected for heart rate using Fridericia's formula (QTcF) ≥ 470 ms calculated from 3 ECGs
10. Known allergy or hypersensitivity to any of the study drugs or any of the study drug excipients
11. Any concurrent chemotherapy, IP, biologic, or hormonal therapy for cancer treatment. Concurrent use of hormonal therapy for non-cancer-related conditions (e.g., hormone replacement therapy) is acceptable.
12. Major surgical procedure (as defined by the investigator) within 28 days prior to the first dose of IP. Note: Local surgery of isolated lesions for palliative intent is acceptable.

13. Prior immune-mediated therapy including, but not limited to, other anti-cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), anti-PD-1, anti-PD-L1, and anti-programmed cell death-ligand 2 (anti-PD-L2) antibodies, excluding therapeutic anti-cancer vaccines.
14. Current or prior use of immunosuppressive medication within 14 days before the first dose of durvalumab. The following are exceptions to this criterion:

    (a) Intranasal, inhaled, topical steroids, or local steroid injections (e.g., intra articular injection)

    (b) Systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone or its equivalent
15. (c) Steroids as premedication for hypersensitivity reactions (e.g., CT scan premedication)

2.5.2.2. Treatments

Durvalumab or Placebo

Patients received 2 cycles of neoadjuvant therapy with 1500 mg durvalumab (or placebo) via IV infusion Q4W on Day 1 of each cycle (Figure 3). Adjuvant therapy was allowed to begin 4 to 12 weeks post-surgery.

Patients received adjuvant therapy with 1500 mg durvalumab (or placebo) Q4W for up to a maximum of 12 cycles in total (including 2 cycles of durvalumab/placebo + FLOT and 10 additional cycles of durvalumab/placebo monotherapy), with the last administration at Adjuvant Week 44, or until progression or recurrence of disease, unless there was unacceptable toxicity or withdrawal of consent, or another discontinuation criterion was met. In case of treatment delays, durvalumab/placebo treatment was not to exceed 12 months from the first dose of adjuvant therapy

FLOT Chemotherapy

Patients received 2 cycles (4 administrations Q2W) of neoadjuvant therapy with FLOT (5-FU 2600 mg/m2 Leucovorin 200 mg/m2 Oxaliplatin 85 mg/m2 Docetaxel 50 mg/m2) via IV infusion on Days 1 and 15 of each cycle (Figure 3). During the combination portion of treatment (Day 1 of each cycle), durvalumab was administered first; the FLOT infusion started approximately 1 hour (maximum 2 hours) after the end of the durvalumab infusion.

Figure 3 MATTERHORN Dosing Schedule and Study Periods

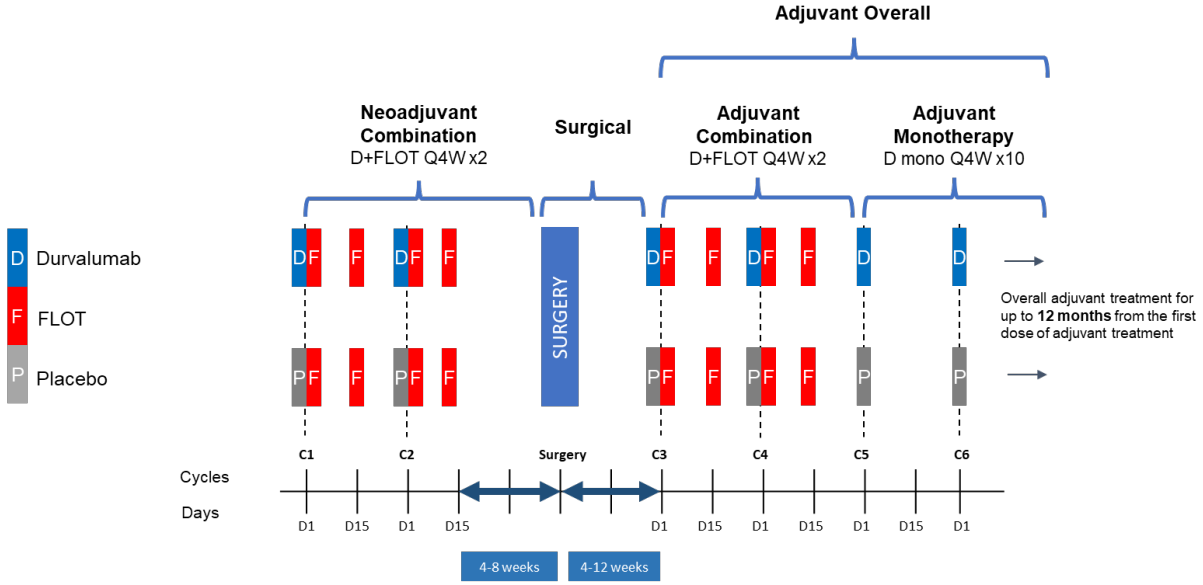


Table 7 Study treatments

Study treatment name:	Durvalumab	Placebo	FLOT chemotherapy
Dosage formulation	500-mg vial solution for infusion after dilution, containing 50 mg/mL durvalumab, 26 mM histidine/histidine-hydrochloride, 275 mM trehalose dihydrate, and 0.02% (w/v) polysorbate 80	Vial solution for infusion after dilution, containing 26 mM histidine/histidine hydrochloride, 275 mM trehalose dihydrate, and 0.02% (w/v) polysorbate 80	5-FU 2600 mg/m^2 Leucovorin 200 mg/m^2 Oxaliplatin 85 mg/m^2 Docetaxel 50 mg/m^2 vial solution for infusion after dilution, 20 mg/mL
Route of administration	IV	IV	IV
Dosing instructions	1500 mg Day 1 Q4W for 2 cycles as neoadjuvant therapy; 1500 mg Day 1 Q4W for a maximum of 12 cycles as adjuvant therapy	Day 1 Q4W for 2 cycles in the neoadjuvant period; Day 1 Q4W for a maximum of 12 cycles in the adjuvant period	Days 1 and 15 of each 4-week cycle for 2 cycles as neoadjuvant therapy; Days 1 and 15 Q4W for 2 cycles as adjuvant therapy
Packaging and labeling	Study treatment will be provided in 500-mg vials. Each 500-mg vial will be labeled in accordance with GMP Annex 13 and per country regulatory requirement.	Study treatment will be provided in vials. Each vial will be labeled in accordance with GMP Annex 13 and per country regulatory requirement.	Study treatment will be provided and labeled in accordance with regional requirements. [a]
Provider	AstraZeneca	AstraZeneca	Sourced locally by site [a]
Batch numbers	See Appendix 16.1.6 for details.	See Appendix 16.1.6 for details.	See Appendix 16.1.6 for details.

[a] Under certain circumstances when local sourcing was not feasible, FLOT chemotherapy could be supplied centrally through AstraZeneca.

Patients in either the neoadjuvant or adjuvant phase who discontinued FLOT chemotherapy due to reasons other than disease progression or recurrence could, based on investigator discretion, continue treatment with durvalumab monotherapy as described above.

PD-L1 testing

Patients provided a mandatory FFPE tumor sample at screening to determine PD-L1 expression level pre-treatment. Patients with unknown PD-L1 expression level were considered screen failures and were not eligible for randomization in the study.

PD-L1 expression level was assessed by the TAP scoring method using the VENTANA PD-L1 (SP263) CDx Assay. TAP scoring method was defined as proportion of tumor area occupied by tumor cells with membrane and immune cells with cytoplasmic/membrane PD-L1 staining at any intensity by IHC assay for stratification in which:

- TAP ≥1% PD-L1 is considered as high

- TAP <1% PD-L1 is considered low

The TAP scoring method has been shown to be reproducible with a high concordance rate between TAP score and Combined Positive Score (average positive agreement, average negative agreement, and overall percent agreement between and within readers all above 85% for both internal and combined external reader precision studies) (Liu et al 2023). The study enrolled patients regardless of their PD-L1 expression level.

Tumor assessments

Radiological efficacy was assessed according to RECIST 1.1. A "Neoadjuvant Baseline" scan was collected within 28 days prior to randomization for disease staging and for use as a RECIST 1.1 baseline for the post-neoadjuvant/pre-surgery follow-up scan. An "Adjuvant Baseline" scan was collected no sooner than 4 weeks after radical surgery and preferably within 28 days prior to the first date of adjuvant treatment. On-study adjuvant tumor assessments occurred every 12 weeks ±1 week after the date of the Adjuvant Baseline scan for 2 years and then every 24 weeks ±1 week thereafter relative to the date of the Adjuvant Baseline scan until progression/recurrence, the end of study, death, discontinuation/withdrawal from study, or Sponsor decision, whichever came first.

2.5.2.3. Objectives

Table 8 Objectives and endpoints

Objectives	Endpoint/variable
Primary	
• To compare Arm A relative to Arm B on event-free survival (EFS)	• EFS is defined as the time from randomization to the following, according to RECIST 1.1 per BICR assessment and/or locally by pathology testing: 1) Progression that precludes surgery or requires non-protocol therapy, 2) Local or distant recurrence or progression of disease, or 3) death due to any cause.
Key secondary	
• To compare Arm A relative to Arm B on overall survival (OS)	• Overall survival is length of time from randomization until the date of death due to any cause.
• To compare Arm A relative to Arm B on pathological complete response (pCR) rate	• pCR rate is defined as the proportion of patients who have no residual viable tumor in the resected specimens and as determined by pathology review.

2.5.2.4. Outcomes/endpoints

Table 9 Outcome and date of even for EFS primary analysis – Neoadjuvant period

Situation	Date of Event or Censoring	EFS Outcome
No tumour assessments at neoadjuvant baseline or post neoadjuvant baseline (unless they die or have a non-RECIST progression later, in which case they will be treated as having an event at the death or progression date)	Randomization	Censored
For subjects with no tumour assessments at neoadjuvant baseline or no post neoadjuvant baseline scans; death or non-RECIST progression	Date of death or non-RECIST progression	Event
First documented RECIST progression that precludes surgery or requires non-protocol therapy	Date of first documented RECIST progression	Event
Non-RECIST progression that requires non-protocol therapy	The date when non-RECIST progression is determined*	Event
Non-RECIST progression that precludes the surgery	Initial date of detection*	Event

Non-RECIST progression that precludes surgery assessed by pathology test only	The date of first biopsy showing progression**	Event
RECIST or non-RECIST progression which precludes surgery, or death, that occurs after the start of non-protocol therapy	Date of first evidence of (RECIST or non-RECIST*) disease progression or death	Event
Precluded from surgery for any reason other than progression, but later progressed or died	Date of first evidence of (RECIST or non-RECIST*) disease progression or death	Event
No event	Date of last evaluable RECIST assessment or local pathology test*** showing no progression (whichever is the later)	Censored

Table 10 Outcome and date of event for EFS primary analysis – Surgery period

Situation	Date of Event or Censoring	EFS Outcome
Non-RECIST progression discovered upon attempting surgery	Date of the first attempt at surgery*	Event

Non-RECIST progression (confirmed by biopsy) assessed on or after the date surgery was attempted or completed	Initial date of detection** (not the dates of confirmation biopsies)	Event
For subjects who attempted or completed the surgery but did not start adjuvant treatment, death, RECIST or non-RECIST (confirmed by biopsy) progression/recurrence after surgery	Date of death, RECIST or non-RECIST** progression/recurrence	Event
For subjects who attempted or completed the surgery but did not start adjuvant treatment, RECIST or non-RECIST (confirmed by biopsy) progression/recurrence or death that occurs after the start of non-protocol therapy	Date of first evidence of documented (RECIST or non-RECIST**) disease progression/recurrence or death	Event
No scan within the window following the date of surgery, no death, and no non-RECIST (confirmed by biopsy) progression/recurrence afterwards	Date of surgery	Censored
No scan within the window following the date of surgery, death or non-RECIST (confirmed by biopsy) progression/recurrence afterwards	Date of death or non-RECIST** progression/recurrence	Event
No event	Date of last evaluable RECIST assessment or local pathology test*** showing no progression (whichever is the later)	Censored

Table 11 Outcome and date of event for EFS primary analysis – Adjuvant period

Situation	Date of Event or Censoring	EFS Outcome
First evidence of documented RECIST recurrence of disease post-surgery in patients who had margin-negative surgery (R0) and without evidence of disease at the adjuvant baseline scans	Date of first evidence of documented RECIST recurrence of disease	Event
First evidence of documented RECIST progression of disease post-surgery in patients who had margin-negative surgery (R0) but with evidence of disease at the adjuvant baseline scans	Date of first evidence of documented RECIST progression	Event
First evidence of documented RECIST disease progression post-surgery in patients with margin positive surgery (R1/R2)	Date of first evidence of documented RECIST disease progression	Event
Non-RECIST progression (confirmed by biopsy) discovered during the adjuvant period	Initial date of detection* (not the dates of confirmation biopsies)	Event
Death due to any cause at any time	Date of death	Event
RECIST or non-RECIST (confirmed by biopsy) progression/recurrence or death that occurs after the start of non-protocol therapy	Date of First evidence of documented (RECIST or non-RECIST) disease progression/recurrence or death	Event
No event	Date of last evaluable RECIST assessment or local pathology test** showing no progression (whichever is the later)	Censored

pCR based on local assessment was derived as per the following: local assessments were performed based on local practice. The pCR ('Yes'/'No') reported in the eCRF (PATHGOM1 eCRF module, PCR eCRF field) by the investigator was be used for the analysis. Patients who are not evaluable per local pathology assessment or who did not have a surgical specimen were assigned a response of No.

2.5.2.5. Sample size

This study was planned to enrol and screen approximately 1125 patients globally in order to randomize approximately 900 patients in a 1:1 ratio to either Arm A (durvalumab + FLOT) or Arm B (placebo + FLOT).

Patient enrolment and randomization into the MATTERHORN study was completed before the IA of pCR at DCO1 (01 February 2023). A total of 1258 patients were enrolled in the study; of these, 948 patients in 20 countries worldwide were randomized 1:1: 474 patients to D + FLOT (Arm A) and 474 patients to Pbo + FLOT (Arm B), forming the FAS population. The enrolment of patients occurred over an approximately 22-month period, with the first patient enrolled on 17 November

2020, and the last patient randomized on 28 September 2022. Of note, the study was conducted during the COVID-19 pandemic.

Per protocol, with approximately 461 EFS events (~51% maturity) planned at the FA, the study had approximately 85% power to show a statistically significant difference in EFS at the 4.20% significance level (2-sided) if the assumed true treatment effect is a HR of 0.75 for the primary treatment comparison of Arm A vs Arm B; this translates to an approximate 10-month improvement in median EFS for Arm A (D + FLOT) over an assumed 30-month median EFS for Arm B (Pbo + FLOT), assuming EFS is exponentially distributed.

2.5.2.6. Randomisation

All patients were centrally assigned to randomized study treatment using an IRT/RTSM, after being confirmed to be eligible for the study. A unique randomization number was obtained via the IRT/RTSM and patients were centrally assigned to one of the two treatment arms in a 1:1 ratio.

Patients will be stratified according to geographic region (Asia vs non-Asia), clinical lymph node status (positive vs negative), and PD-L1 expression status (TAP ≥1% vs TAP <1%).

Overall, 474 patients were randomized into the D + FLOT arm and 474 into the Pbo + FLOT arm. All patients were included in the FAS.

2.5.2.7. Blinding (masking)

The study was conducted in a double-blind manner. No member of the study team at AstraZeneca, at the investigational centers, or any blinded Contract Research Organization handling data had access to the randomization scheme and treatment allocation until the time of the DCO2 analysis, after Clinical Data Lock, and the IDMC recommendation that the required statistical significance for the primary endpoint (EFS) had been reached. Exceptions were relevant persons within the Pharmaceutical Development Supply Chain at AstraZeneca or their designee, where the information was needed to package the study treatment; the drug safety departments at AstraZeneca; the pharmacists required to dispense the study treatment at the study site; and the IDMC who were provided with unblinded data for their review.

Investigators were unblinded to treatment allocation only in cases of medical emergency. Additionally, at the request of the investigator, at progression of disease, the patient could have been unblinded. The treatment codes and results were kept strictly within AstraZeneca to safeguard the integrity of the blind and hence to minimize any possible bias in data handling.

2.5.2.8. Statistical methods

Table 12 Analysis sets

Population	Description	Main analysis/outcome variable
FAS	The FAS includes all randomized patients with treatment arms assigned in accordance with the randomization, regardless of the treatment actually received. Patients who were randomized but did not subsequently receive treatment were included in the FAS. Unless otherwise specified, the FAS was used for demography summaries and all efficacy analyses, except those involving DFS endpoints.	• Demography and baseline characteristics • *Efficacy variables*: EFS, OS, pCR rate, surgery rate, R0 resection rate, MFS, DSS, MPR rate, pathological downstaging
R0 Resected Analysis Set	The R0 Resected Analysis Set includes all patients in the FAS who had a surgical resection that was defined as an R0 resection (margin-negative resection) based on local pathology assessments. This analysis set was limited to patients who had a surgical resection that was defined as an R0 resection according to local pathology assessments and did not have evidence of disease (ie, no target lesion and no non-target lesion being identified) at the post-surgery adjuvant baseline scan (before starting the adjuvant treatment) per RECIST 1.1 by the investigator. Unless otherwise specified, the R0 Resected Analysis Set was used for DFS endpoint analyses.	• *Efficacy variables*: DFS
Safety Analysis Set	The Safety Analysis Set consists of all patients who have received at least one dose of IP. Erroneously treated patients (eg, those randomized to treatment A but actually given treatment B) were accounted for in the treatment arm of the treatment they actually received. A patient who had on one or several occasions received active IP was accounted for the active IP treatment arm.	• *Safety variables*: Exposure, AEs, Laboratory measurements, Vital signs, Physical examination, and ECG

2.5.2.8.1.1. Primary endpoint

The primary endpoint, EFS according to whichever occurs first by RECIST 1.1 per BICR assessment and/or locally by pathology testing if clinically required or death, was analysed using a stratified log-rank test adjusting for the stratification variables of geographic region (Asia vs non-Asia), clinical lymph node status (positive vs negative), and PD-L1 expression status (TAP ≥1% vs TAP <1%) for the generation of the p-value (2-sided). The stratification variables in statistical modelling were based on the values entered into the IRT/RTSM at randomization, even if it is subsequently discovered that these values were incorrect.

The hazard ratio (HR) and its confidence interval (CI) were estimated from a stratified Cox proportional hazards model (with ties = Efron), adjusted for the stratification variables described above. The CI were calculated using a profile likelihood approach.

The assumption of proportionality of hazards in the Cox model was be assessed firstly by examining plots of complementary log-log (event times) versus log (time) and, if these raise concerns, by fitting a time-dependent covariate to assess the extent to which this represents random variation.

Kaplan-Meier plots of EFS were presented by treatment arm. Summaries of the numbers and percentages of patients experiencing an EFS event (including the type of event), those still in

survival follow-up, those censored including those lost to follow-up, and those who have withdrawn consent were provided along with the median EFS for each treatment arm.

2.5.2.8.1.2. Key secondary endpoints

OS was analysed using the same methodology as described for the primary EFS endpoint including a stratified log-rank test, stratified Cox proportional hazards model, and Kaplan-Meier plots.

Additional exploratory overall survival analyses could be performed after the primary analysis of overall survival using further follow-up survival data, if available. The final OS analysis was planned to be performed when approximately 51% EFS data maturity has been reached across both treatment arms or after approximately 3 years of follow-up after the last patient was randomized, whichever occurs first.

pCR Rate by Central Pathology Review: Patients achieve pCR if there was no residual viable tumor cells found at primary tumor and resected lymph nodes at the time of resection, meaning a pathological regression of -100%, based on central assessment.

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 randomization.

CIs for response rate were calculated using Clopper-Pearson exact method.

2.5.2.8.1.3. Sensitivity and subgroup analysis

Sensitivity analyses of the primary endpoint were performed to assess possible evaluation-time bias, attrition bias, and ascertainment bias (including a sensitivity analysis applying the censoring rule for two consecutive missed visits).

Ascertainment bias

The possibility of bias in the assessment and measurement of EFS per BICR was assessed using the investigator assessments according to RECIST 1.1, in place of BICR assessments. The stratified log-rank test as described for the primary analysis of EFS above was repeated using investigator assessed RECIST 1.1 data to programmatically derive EFS. The HR and CI were presented using the same stratified cox proportional hazards model as described for the primary endpoint.

Evaluation-time bias

The possibility of evaluation-time bias that could occur if scans were not performed at protocol scheduled timepoints was assessed. The mid-point between the time of the EFS event and previous evaluable RECIST assessment (using the final date of the assessment) was analyzed using a stratified log-rank test, as described for the primary analysis. Note that midpoint values resulting in non-integer values should be rounded down. For patients whose death was treated as an EFS event, the date of death was used to derive the EFS time used in the analysis.

To support this analysis, the mean of patient-level average inter-assessment times was tabulated for each treatment.

Subsequent anti-cancer/non-protocol therapy censoring

Another sensitivity analysis was performed modifying the censoring rules in case of non-protocol therapy start with no progression before (i.e., censoring at the last RECIST or non-RECIST assessment before non-protocol therapy start). This sensitivity analysis was applied to EFS primary endpoint (EFS per BICR).

The outcome and date of event for EFS with subsequent anti-cancer therapy censoring followed the same rules as for EFS primary analysis apart the non-protocol therapy with no progression before were not disregarded, but the EFS was be censored at the last RECIST or non-RECIST assessment before non-protocol therapy start.

The same stratified log-rank test and stratified cox proportional hazards model as described for the primary endpoint was used.

Censor the events occurring after missing at least two consecutive RECIST assessments

Another sensitivity analysis was performed modifying the censoring rule where events occurring after missing at least two consecutive RECIST assessments were censored at the latest RECIST assessment or local pathology test (whichever was the later), where there was no disease progression/recurrence discovered, before missing at least two consecutive RECIST assessments.

Effect of covariates on the HR estimate

As a further sensitivity analysis, Cox proportional hazards modelling was employed to assess the effect of the stratification variables on the HR estimate. A model was constructed, containing treatment and the stratification variables, to ensure that any output from the Cox modelling was likely to be consistent with the results of the stratified log-rank test.

Stratification according to eCRF

If there were any patients who were mis-stratified, a sensitivity analysis was to be carried out using the (correct) baseline data collected in the eCRF.

Events only based on RECIST 1.1 BICR assessments, local pathology tests, or deaths

Sensitivity analyses were conducted for EFS by only considering RECIST 1.1 BICR assessments, local pathology tests, or deaths to determine events. Patients who did not have an event would be censored at the date of the last evaluable RECIST 1.1 BICR assessment or local pathology test that shows no evidence of disease progression/recurrence.

Events only based on RECIST 1.1 BICR assessments or deaths

Sensitivity analysis will be conducted for EFS by only considering RECIST 1.1 BICR assessments or deaths to determine events. Patients who have not had an event would be censored at the date of the last evaluable RECIST 1.1 BICR assessment that shows no evidence of disease progression/recurrence.

Subgroup analyses:

Subgroup analyses were conducted comparing EFS (using RECIST 1.1 per BICR assessments and/or locally by pathology testing) between Arm A and Arm B in the following

Subgroups of the FAS (but not limited to):

- Sex (male vs female)
- Age at randomization (<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)

2.5.2.8.1.4. Interim Analysis and Multiplicity

The objective of IA2 was to test for early superiority of Arm A vs Arm B in relation to EFS. This analysis was performed when approximately 369 EFS events have been observed across both arms (~41% maturity).

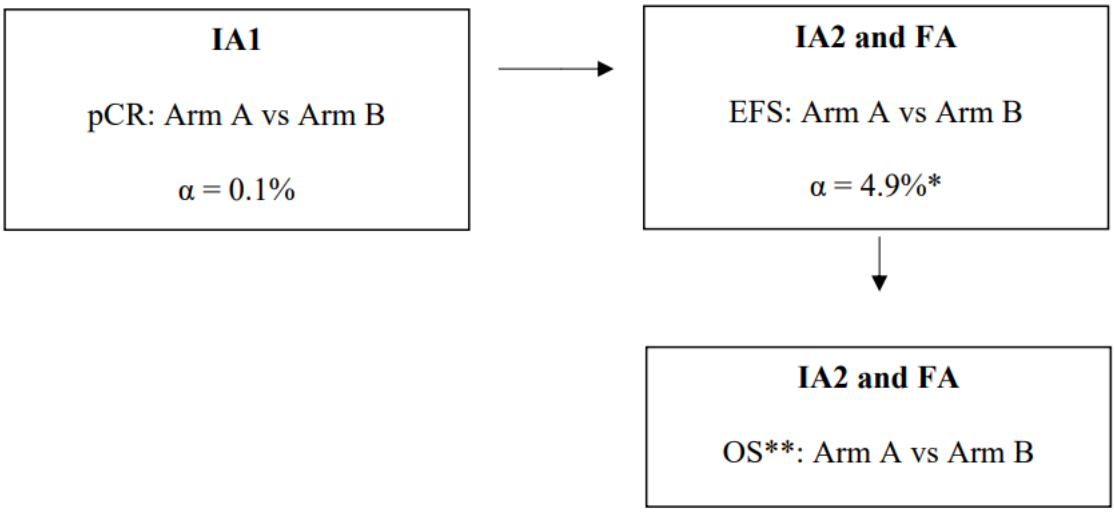
EFS at IA2 was analyzed using the same methodology as described above for the primary analysis of EFS for the FA.

Control across IA1, IA2, and FA was obtained by allocation of a nominal alpha spend of 0.1% (2-sided) for analysis of pCR at IA1 and partitioning of the remaining alpha=4.9% (2-sided) at IA2 and FA to analyse EFS, in order to maintain an overall 5% alpha (2-sided). If pCR was statistically significant at IA1, then the alpha of 0.1% for pCR was recycled to EFS, so EFS would be tested at overall alpha of 0.05. The alpha expenditure for EFS was spent between IA2 and FA using the Lan DeMets spending function that approximates an O'Brien Fleming approach, where the significance level applied depends upon the actual proportion of information (i.e., information fraction) available.

If the EFS analysis was significant at either IA2 or FA, then the associated alpha was recycled to the OS endpoint as part of the MTP at the final analysis, comparing Arm A vs Arm B.

All the other secondary efficacy and PRO endpoints will be tested, but no multiplicity adjustment will be applied as these endpoints will be considered supportive endpoints only.

Figure 4 Multiple testing procedure



EFS Event-free survival; FA Final analysis, IA1 Interim analysis 1; IA2 Interim analysis 2; OS Overall survival; pCR Pathological complete response.

Note: Arm A = neoadjuvant-adjuvant durvalumab + FLOT chemotherapy followed by adjuvant durvalumab monotherapy, and Arm B = neoadjuvant-adjuvant placebo + FLOT chemotherapy followed by adjuvant placebo monotherapy.

*Exact significance levels to be used at IA2 and FA will be determined based on the information fraction at the analysis timepoint and IA1 outcome.

**OS is only to be tested if EFS is statistically significant. At IA2, only minimal alpha of 0.01% will be allocated to OS. At FA, OS alpha allocation will be respectively 4.89% if pCR is not statistically significant at IA1 or 4.99% if pCR is statistically significant at IA1. If EFS is statistically significant at IA2 but OS is not, FA for OS will be conducted when either approximately 461 EFS events have been observed or after approximately 3 years of follow-up after last subject was randomized, whichever occurs first.

Timing of interim analyses:

DCO1 (pCR assessment): DCO1 (01 February 2023) was planned to be performed after all patients had been randomized and undergone surgical resection or been precluded from surgery, to provide a formal comparison of pCR rates by central pathology review, testing for superiority of the D + FLOT arm vs the Pbo + FLOT arm.

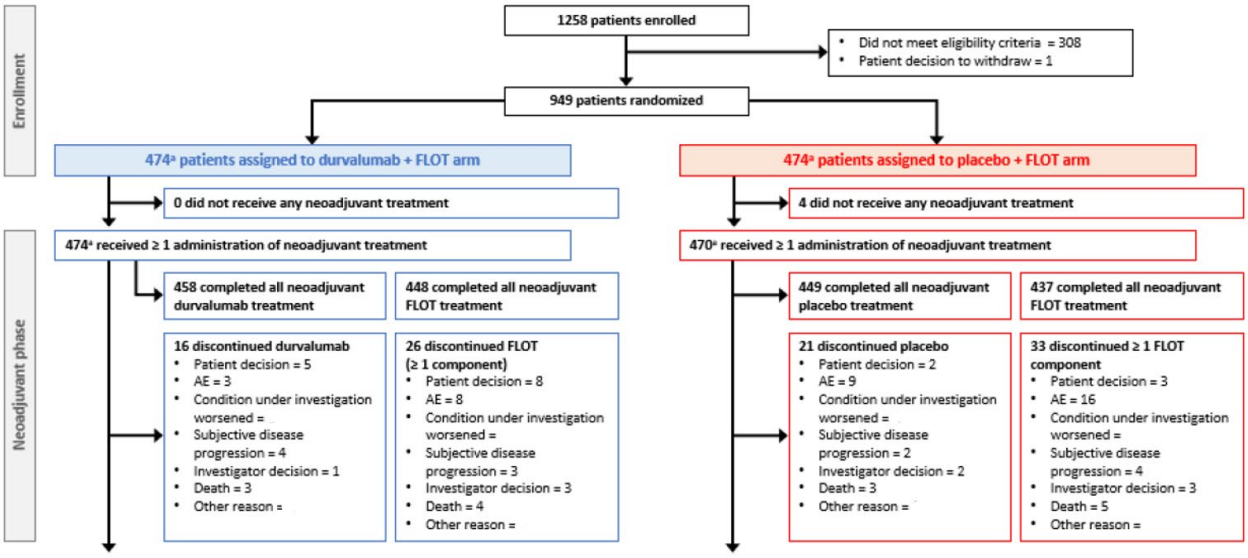
DCO2 (IA of EFS and OS): DCO2 (20 December 2024) was planned to test for early superiority of the D + FLOT arm vs the Pbo + FLOT arm in relation to EFS when approximately 41% EFS data maturity had been reached across both treatment arms.

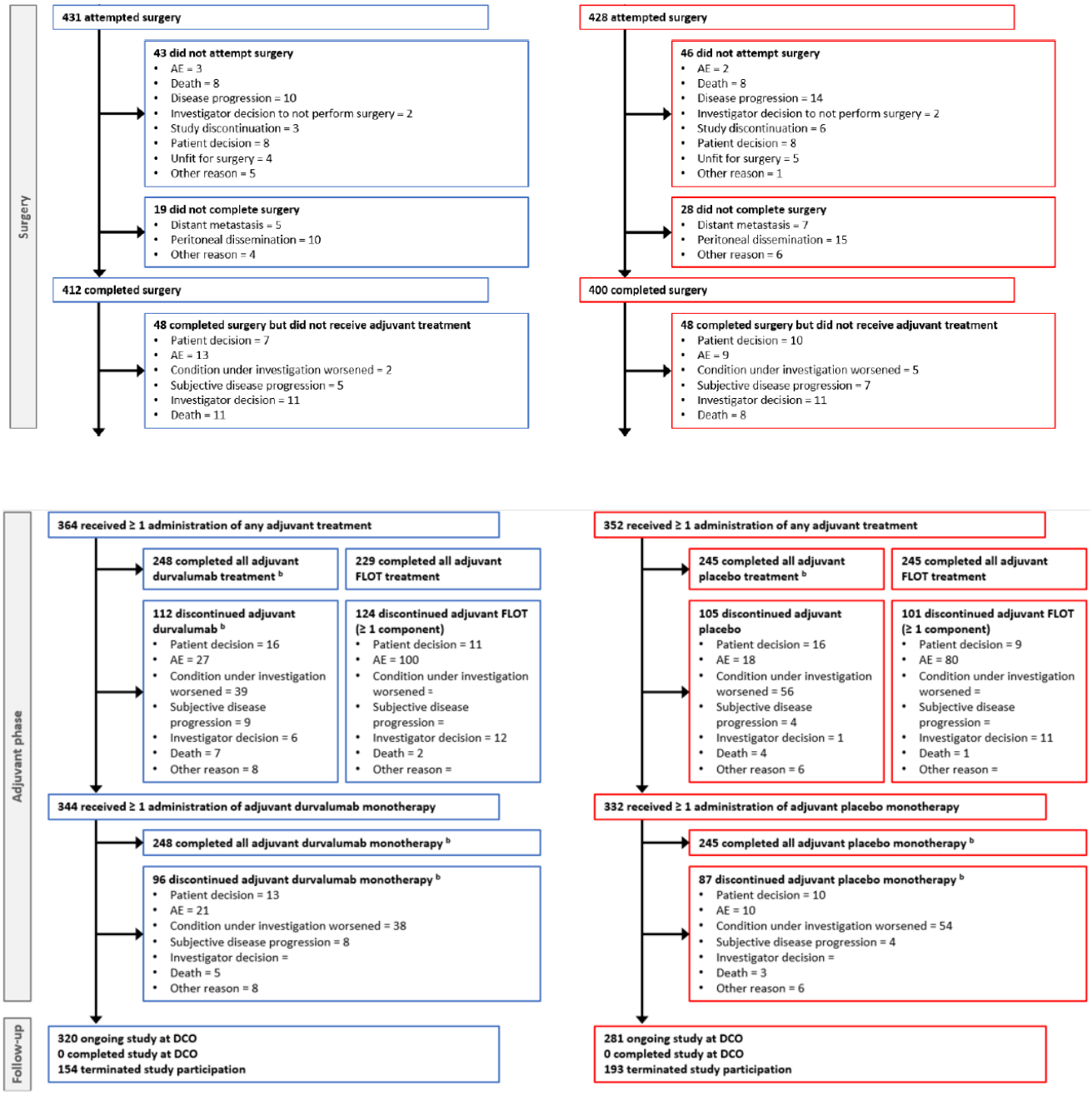
FA (final analysis of EFS and OS): DCO3 (01 September 2025). The FA of OS was planned to be performed when approximately 51% EFS data maturity will have been reached across both treatment arms and after approximately 3 years of follow-up after the last patient was randomized, whichever occurs first. OS was formally tested at the FA per the MTP.

2.5.2.9. Results

Participant flow

Figure 5 Patient Disposition (all patients)





[a] A patient was randomised twice in error under 2 different e-coded: one randomised in error receiving no study treatment and another proceeding to receive study treatment (confirmed by site). The exclusion of the first one has been performed at the level of the FAS. One patient was randomised to the Pbo+FLOT arm and included in the FAS but received both placebo and durvalumab and therefore was included in the D+FLOT arm for the purpose of the Safety Analysis Set, which includes 475 patients in the D+FLOT arm and 469 patients in the Pbo+FLOT arm.

[b] Due to language in the CSP that has since been updated, 14 patients discontinued adjuvant durvalumab/placebo monotherapy treatment prematurely, 48 weeks after the start of adjuvant therapy rather than 52 weeks; these were recorded as non-important protocol deviations.

For patients who did not receive treatment, may include patients who never received study treatment.

DCO: 20 December 2024

2.5.2.10. Recruitment

First patient enrolled: 17 November 2020

Last patient enrolled: 28 September 2022

IA of pCR at DCO1: 01 February 2023

IA of EFS and OS at DCO2: 20 December 2024

A total of 159 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).

2.5.2.11. Conduct of the study

Protocol amendments

DOCUMENT HISTORY	
Document	**Date**
Version 1.0	19 June 2020
Version 2.0	05-Dec-2023
Version 3.0	04-Mar-2024

All CSP amendments were executed based on internal decisions that considered recommendation or guidance from regulatory agencies, in response to evolving international clinical practice guidelines, or due to external emerging clinical data. All CSP amendments were made prior to the date of DCO2, and CSP Version 3.0 (dated 04 March 2024) was the last amendment version prior to the DCO2 date.

Table 13 Protocol Amendments related to changes in study conduct

Amendment number/date	Key details of amendment	Main reason(s) for amendment
Amendments made *before* the start of patient recruitment		
Not applicable		

Amendment number/date	Key details of amendment	Main reason(s) for amendment
Amendments made *after* the start of patient recruitment		
2.0 / 05 December 2023	Addition of long-term follow-up to be collected after final analysis for approximately 5 years following last patient randomized. Clarifications on when and how the formal statistical test(s) for OS would be conducted as the key secondary endpoint, prospectively specifying the criteria for claiming statistically significant treatment effect of OS.	Transition to the EU Clinical Trials Regulation and to allow for long-term follow-up to be collected after FA.
3.0 / 04 March 2024	Removal of the censoring rule for 2 consecutive missed visits from the analyses of the endpoints requiring radiologic assessment to determine events, including EFS, to minimize loss of clinically relevant events. A supportive sensitivity analysis applying the censoring rule for 2 consecutive missed visits was added. Text on analysis was clarified to note that the OS alpha to be spent at FA is only dependent on the result of pCR analysis at DCO1 (ie, 4.99% if pCR was statistically significant at DCO1 or 4.89% if pCR was not statistically significant).	To minimize loss of clinically relevant events. This is in line with health authority guidelines.

Table 14 Important Protocol Deviations (FAS)

Important protocol deviations [a]	Number (%) of patients		
	D + FLOT (N = 474)	Pbo + FLOT (N = 474)	Total (N = 948)
Patients with at least one IPD [b]	33 (7.0)	25 (5.3)	58 (6.1)
Inclusion criteria deviations			1 (0.1)
Exclusion criteria deviations	1 (0.2) [c]	6 (1.3)	7 (0.7)
Investigational product deviation	11 (2.3)	5 (1.1)	16 (1.7)
Excluded medications taken	15 (3.2)	9 (1.9)	24 (2.5)
Deviations related to study procedure	5 (1.1)	4 (0.8)	9 (0.9)
Other IPDs			1 (0.1)

[a] IPDs before the start of treatment and during treatment.
[b] The same patient may have had more than 1 IPD.
[c] One additional exclusion criteria deviation IPD that occurred prior to the DCO was identified after database lock in a patient in the D + FLOT arm, which is not included in the count appearing in the table.
DCO: 20 December 2024.

2.5.2.12. Baseline data

Table 15 Baseline Demographics (FAS)

Category Statistics	D + FLOT (N = 474)	Pbo + FLOT (N = 474)	Total (N = 948)
Age (years)			
Mean (StDev)	59.9 (11.53)	61.6 (10.14)	60.8 (10.89)
Median (min, max)	62.0	63.0	62.0 (26, 84)
Age group (years), n (%)			
< 50	86 (18.1)	57 (12.0)	143 (15.1)
≥ 50 - < 65	205 (43.2)	208 (43.9)	413 (43.6)
≥ 65 - < 75	146 (30.8)	166 (35.0)	312 (32.9)
≥ 75	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)
Race, n (%)			
Black or African American	7 (1.5)	3 (0.6)	10 (1.1)
American Indian or Alaska Native	18 (3.8)	20 (4.2)	38 (4.0)
Asian	96 (20.3)	97 (20.5)	193 (20.4)
White	321 (67.7)	322 (67.9)	643 (67.8)
Other	8 (1.7)	8 (1.7)	16 (1.7)
Not reported	24 (5.1)	24 (5.1)	48 (5.1)

Category Statistics	D + FLOT (N = 474)	Pbo + FLOT (N = 474)	Total (N = 948)
Ethnic group, n (%)			
Hispanic or Latino	89 (18.8)	101 (21.3)	190 (20.0)
Not Hispanic or Latino	385 (81.2)	373 (78.7)	758 (80.0)
Geographic region (eCRF) [a], n (%)			
Asia	90 (19.0)	90 (19.0)	180 (19.0)
Non-Asia	384 (81.0)	384 (81.0)	768 (81.0)

[a] As recorded at randomization on the eCRF or from external vendor data from samples collected on or before randomization.

DCO2: 20 December 2024.

Table 16 Disease Characteristics at Baseline (FAS)

Parameter Category	Number (%) of patients		
	D + FLOT (N = 474)	Pbo + FLOT (N = 474)	Total (N = 948)
ECOG performance status			
(0) Normal activity	337 (71.1)	366 (77.2)	703 (74.2)
(1) Restricted activity	137 (28.9)	108 (22.8)	245 (25.8)
(2) In bed ≤ 50% of the time	0	0	0
(3) In bed > 50% of the time	0	0	0
(4) 100% bedridden	0	0	0
Clinical lymph node status (eCRF) [a], n (%)			
Positive	334 (70.5)	333 (70.3)	667 (70.4)
Negative	137 (28.9)	140 (29.5)	277 (29.2)
Missing	3 (0.6)	1 (0.2)	4 (0.4)
Microsatellite instability status, n (%)			
High	25 (5.3)	24 (5.1)	49 (5.2)
Not-high	301 (63.5)	310 (65.4)	611 (64.5)
Not evaluable	69 (14.6)	52 (11.0)	121 (12.8)
Missing	79 (16.7)	88 (18.6)	167 (17.6)
PD-L1 expression level (eCRF) [a], n (%)			
TAP ≥ 1%	426 (89.9)	427 (90.1)	853 (90.0)
TAP < 1%	48 (10.1)	47 (9.9)	95 (10.0)
TAP ≥ 5%	238 (50.2)	244 (51.5)	482 (50.8)
TAP < 5%	236 (49.8)	230 (48.5)	466 (49.2)
TAP ≥ 10%	102 (21.5)	101 (21.3)	203 (21.4)
TAP < 10%	372 (78.5)	373 (78.7)	745 (78.6)
Primary tumor location			
Gastric	324 (68.4)	316 (66.7)	640 (67.5)

Parameter Category	Number (%) of patients		
	D + FLOT (N = 474)	Pbo + FLOT (N = 474)	Total (N = 948)
Gastric cardia	65 (13.7)	69 (14.6)	134 (14.1)
Fundus of the stomach	13 (2.7)	15 (3.2)	28 (3.0)
Body of stomach	162 (34.2)	164 (34.6)	326 (34.4)
Antrum pylori	84 (17.7)	68 (14.3)	152 (16.0)
Gastroesophageal junction	150 (31.6)	158 (33.3)	308 (32.5)
Siewert type 1	44 (9.3)	55 (11.6)	99 (10.4)
Siewert type 2	72 (15.2)	68 (14.3)	140 (14.8)
Siewert type 3	34 (7.2)	35 (7.4)	69 (7.3)
Histology type [b]			
Intestinal type	245 (51.7)	238 (50.2)	483 (50.9)
Diffuse type	130 (27.4)	119 (25.1)	249 (26.3)
Indeterminate type	99 (20.9)	117 (24.7)	216 (22.8)
Primary tumor stage			
T0			1 (0.1)
Tis			1 (0.1)
T1	7 (1.5)	4 (0.8)	11 (1.2)
T2	41 (8.6)	32 (6.8)	73 (7.7)
T3	307 (64.8)	321 (67.7)	628 (66.2)
T4a	101 (21.3)	103 (21.7)	204 (21.5)
T4b	16 (3.4)	14 (3.0)	30 (3.2)
AJCC staging [c]			
Stage IIA	37 (7.8)	25 (5.3)	62 (6.5)
Stage IIB	109 (23.0)	108 (22.8)	217 (22.9)
Stage III	287 (60.5)	298 (62.9)	585 (61.7)
Stage IVA	41 (8.6)	42 (8.9)	83 (8.8)
Missing			1 (0.1)

a As recorded at randomization on the eCRF or from external vendor data from samples collected on or before randomization.

b Determined by local assessment

c Stages according to AJCC 8th edition.

2.5.2.13. Numbers analysed

Table 17 Analysis sets (DCO2)

Category	Number of patients		
	D + FLOT	Pbo + FLOT	Total
Patients randomized [a]	NA	NA	949
Patients included in FAS [a,b]	474	474	948
Safety Analysis Set			
Patients included in Safety Analysis Set [a,c]	475	469	944
Patients excluded from Safety Analysis Set [c]	0	4	4
Did not receive treatment	0	4	4
R0 Resected Analysis Set			
Patients included in R0 Resected Analysis Set [d]	339	323	662
Patients excluded from R0 Resected Analysis Set [d,e,f]	135	151	286
Did not attempt/complete surgery	62	74	136
Surgery completed but did not have R0 resection	35	31	66
R0 resection and no post-surgery baseline adjuvant scan	36	44	80
R0 resection and evidence of disease at post-surgery baseline adjuvant scan	4	6	10
PK and ADA Analyses Sets			
Patients included in Durvalumab PK Analysis Set [a,g]	470	0	470
Patients excluded from Durvalumab PK Analysis Set [a,e,g]	5	469	474
Did not receive durvalumab treatment	0	469	469
Did not have any post-dose PK data available	5	2	7
Patients included in Docetaxel PK Analysis Set [a,h]	5	6	11
Patients excluded from Docetaxel PK Analysis Set [a,e,h]	470	463	933
Did not have a plasma sample collected	470	463	933
Did not have any post-dose PK data available	470	463	933
Patients included in ADA Analysis Set [a,i]	441	0	441
Patients excluded from ADA Analysis Set [a,e,i]	34	469	503
Did not receive durvalumab treatment	0	469	469
Did not have baseline ADA assessment	17	23	40
Did not have any post-dose ADA data available	19	22	41
PRO Analysis Set			
Patients included in PRO analysis set	467	459	926
Patients excluded from PRO analysis set [e]	7	15	22
Relevant language version not available	2	3	5
Patient illiterate	4	11	15
Patient cannot use device due to physical limitations	1	1	2

a A patient was randomized twice in error under 2 different e-codes: the first one randomized in error receiving no study treatment, and a second one, proceeding to receive study treatment (confirmed by site). The exclusion of the first randomisation code has been performed at the level of the FAS. One participant was randomized to the Pbo + FLOT arm and included in the FAS, but received both placebo and durvalumab and therefore was included in the D + FLOT arm for the purpose of the Safety Analysis Set, which includes 475 patients in the D + FLOT arm and 469 patients in the Pbo + FLOT arm.

b FAS: all randomized patients.
c Safety Analysis Set: all patients who received at least 1 dose of IP.
d R0 Resected Analysis Set: all patients in FAS who had a surgical resection defined as R0 resection based on local pathology assessments and no evidence of disease at the post-surgery baseline adjuvant scan.
e Patients may have been excluded for more than 1 reason.
f Categories for exclusion from the R0 Resected Analysis Set are not mutually exclusive.
g Durvalumab PK Analysis Set: all patients who receive at least 1 dose of durvalumab per the protocol and have at least 1 reportable PK concentration. Additional details are provided in Section 11.2.1.
h Docetaxel PK Analysis Set: 10 patients from selected sites who have plasma samples to determine concentration of docetaxel and who have at least 1 reportable PK concentration.
i ADA Analysis Set: all patients in the Safety Analysis Set who have a non-missing baseline durvalumab ADA result and at least 1 non-missing post-baseline durvalumab ADA result. DCO: 20 December 2024.

2.5.2.14. Outcomes and estimation

Primary endpoint: EFS at DCO2

Table 18 Event-free Survival (FAS, DCO2)

	D + FLOT (N = 474)	Pbo + FLOT (N = 474)
Total EFS events [a], n (%)	**167 (35.2)**	**218 (46.0)**
RECIST 1.1 progression (assessed by BICR)	49 (10.3)	84 (17.7)
Disease progression in neoadjuvant period that precluded surgery	5 (1.1)	2 (0.4)
Disease progression in neoadjuvant period in patients with surgery not performed due to reasons other than progression	1 (0.2)	1 (0.2)
Disease recurrence in adjuvant period after R0 resection	41 (8.6)	71 (15.0)
Disease progression in adjuvant period after R1/R2 resection	2 (0.4)	10 (2.1)
Non-RECIST progression	51 (10.8)	59 (12.4)
Disease progression in neoadjuvant period that precluded surgery	3 (0.6)	8 (1.7)
Disease progression discovered upon attempting the surgery	18 (3.8)	28 (5.9)
Disease progression in neoadjuvant period after surgery not undertaken for reasons other than progression	1 (0.2)	1 (0.2)
Disease progression/recurrence in surgery period confirmed by local pathology testing	1 (0.2)	2 (0.4)
Disease progression/recurrence in adjuvant period confirmed by local pathology testing	28 (5.9)	20 (4.2)
Death in the absence of progression	67 (14.1)	75 (15.8)
Death in the absence of progression for non-treated patients		
Death in the absence of progression during the neoadjuvant period	21 (4.4)	19 (4.0)
Death in the absence of progression during the surgery period	22 (4.6)	21 (4.4)

	D + FLOT (N = 474)	Pbo + FLOT (N = 474)
Death in the absence of progression during the adjuvant period	24 (5.1)	33 (7.0)
Censored patients, n (%)	**307 (64.8)**	**256 (54.0)**
Event-free at time of analysis	293 (61.8)	237 (50.0)
No evaluable disease assessments at neoadjuvant baseline or post-neoadjuvant baseline	3 (0.6)	7 (1.5)
No post-surgery adjuvant baseline assessment	3 (0.6)	6 (1.3)
Withdrawn consent	8 (1.7)	6 (1.3)
Median EFS (months) [b]	**NC**	**32.82**
95% CI for median EFS [b]	40.74 - NC	27.86 - NC
EFS rate at 12 months (%) [b]	**78.18**	**74.01**
95% CI for EFS at 12 months [b]	74.11 - 81.70	69.71 - 77.80
EFS rate at 18 months (%) [b]	**73.21**	**63.62**
95% CI for EFS at 18 months [b]	68.88 - 77.04	58.98 - 67.88
EFS rate at 24 months (%) [b]	**67.44**	**58.54**
95% CI for EFS at 24 months [b]	62.90 - 71.57	53.82 - 62.96
EFS rate at 30 months (%) [b]	**64.10**	**52.48**
95% CI for EFS at 30 months [b]	59.42 - 68.40	47.61 - 57.12
EFS rate at 36 months (%) [b]	**61.99**	**47.24**
95% CI for EFS at 36 months [b]	56.95 - 66.61	41.80 - 52.49
HR [c]	**0.71**	
97.61% CI for HR [c, d]	0.56 - 0.89	
95% CI for HR [c]	**0.58 - 0.86**	
2-sided p-value [e]	**< 0.001**	
Median (range) duration of follow-up in censored patients (months)	31.64 (0.03 - 48.10)	31.44 (0.03 - 48.07)
Median (range) duration of follow-up in all patients (months)	26.79 (0.03 – 48.10)	25.82 (0.03 – 48.07)

[a] The EFS endpoint is defined in Table 1.

[b] Calculated using the KM technique.

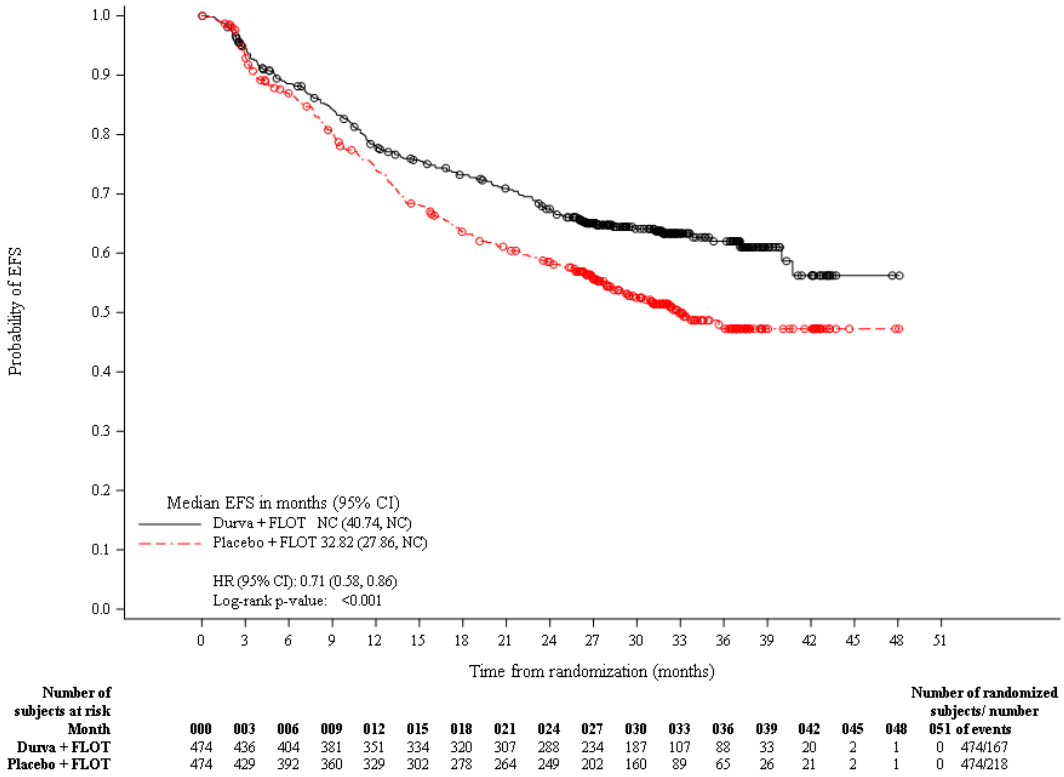
[c] Estimated from a stratified Cox proportional hazards model stratified by geographic region, clinical lymph node status, and PD-L1 expression level at randomization. An HR < 1 favors the D + FLOT arm. The corresponding CI was calculated using the profile likelihood approach.

[d] Derived based upon the exact number of EFS events using the Lan-DeMets spending function.

[e] Derived using a stratified log-rank test adjusted for geographic region, clinical lymph node status, and PD-L1 expression level at randomization. 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.

DCO2: 20 December 2024

Figure 6 Kaplan-Meier Plot of EFS (FAS, DCO2)



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

Circle indicates a censored observation.

Events were defined as the earliest of RECIST 1.1 events, non-RECIST 1.1 events, or deaths of any cause as defined in the SAP. The analysis of EFS was based on BICR assessments and/or locally by pathology testing if clinically required.

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 was calculated using a profile likelihood approach. An HR < 1 favors the D + FLOT arm.

The 2-sided p-value was calculated using a stratified log-rank test, adjusting for geographic region, clinical lymph node status, and PD-L1 expression level.

DCO2: 20 December 2024.

Key secondary endpoint: OS at DCO2

Table 19 Overall Survival (FAS, DCO2)

	D + FLOT (N = 474)	**Pbo + FLOT (N = 474)**
Death, n (%)	**145 (30.6)**	**176 (37.1)**
Censored patients, n (%)	329 (69.4)	298 (62.9)
Still in survival follow-up [a]	320 (67.5)	281 (59.3)
Terminated prior to death [b]	9 (1.9)	17 (3.6)
Voluntary discontinuation by patient	9 (1.9)	16 (3.4)
Median OS (months) [c]	**NC**	**47.21**
95% CI for median OS [c]	NC - NC	45.08 - NC
Survival rate at 12 months (%) [c]	**85.8**	**85.6**

	D + FLOT (N = 474)	Pbo + FLOT (N = 474)
95% CI for survival rate at 12 months [c]	82.31 - 88.64	82.06 - 88.48
Survival rate at 18 months (%) [c]	**81.1**	**77.1**
95% CI for survival rate at 18 months [c]	77.25 - 84.35	73.01 - 80.68
Survival rate at 24 months (%) [c]	**75.7**	**70.4**
95% CI for survival rate at 24 months [c]	71.56 - 79.33	65.97 - 74.30
Survival rate at 30 months (%) [c]	**72.0**	**64.5**
95% CI for survival rate at 30 months [c]	67.65 - 75.81	59.95 - 68.71
Survival rate at 36 months (%) [c]	**68.9**	**62.2**
95% CI for survival rate at 36 months [c]	64.31 - 73.08	57.50 - 66.60
HR, comparing durvalumab vs placebo [d]	**0.78**	
95% CI for HR [d]	**0.62 - 0.97**	
2-sided p-value [e]	**0.025**	

[a] Includes patients known to be alive at the DCO2 date.

[b] Includes patients with unknown survival status or patients who were lost to follow-up.

[c] Calculated using the KM technique.

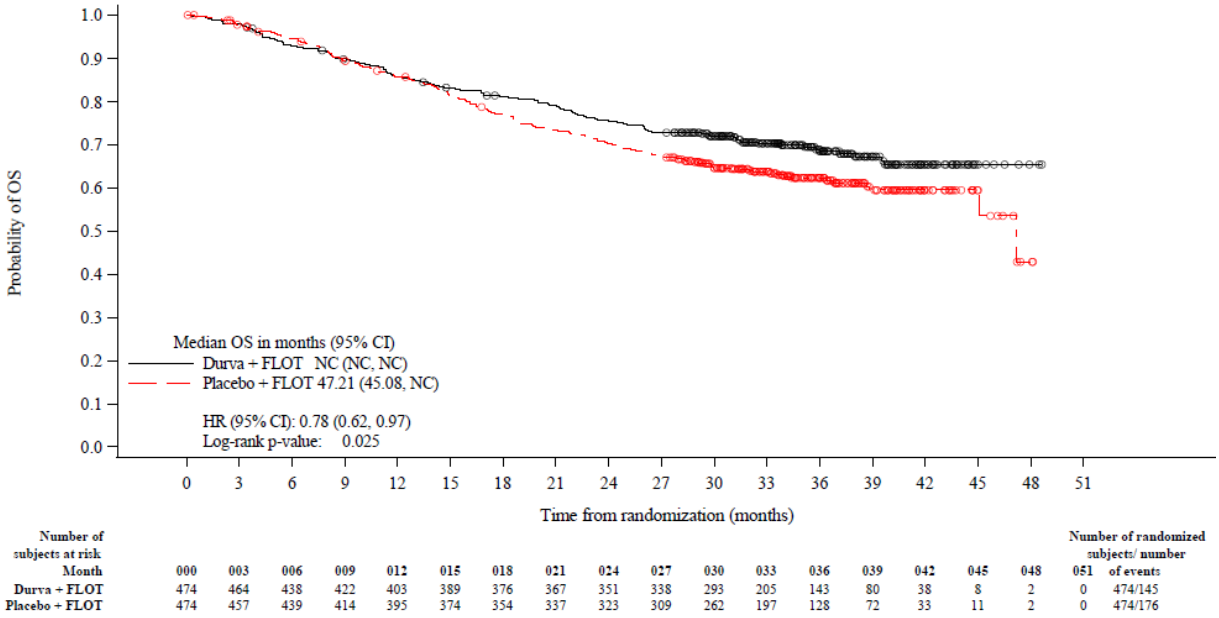
[d] The analysis was performed using a stratified Cox proportional hazards model, adjusting for geographic region, clinical lymph node status, and PD-L1 expression level. An HR < 1 favors the D + FLOT arm. The corresponding CI is calculated using the profile likelihood approach.

[e] Derived using a stratified log-rank test adjusting for geographic region, clinical lymph node status, and PD-L1 expression level at randomization.

At DCO2, a fixed alpha spend of 0.01% (2-sided) was allocated to the IA of OS, corresponding to a p-value boundary for declaring statistical significance of 0.0001.

DCO2: 20 December 2024.

Figure 7 Kaplan-Meier Plot of overall survival (FAS, DCO2)



Number of subjects at risk																	Number of randomized subjects/ number
Month	000	003	006	009	012	015	018	021	024	027	030	033	036	039	042	045	048	051	of events
Durva + FLOT	474	464	438	422	403	389	376	367	351	338	293	205	143	80	38	8	2	0	474/145
Placebo + FLOT	474	457	439	414	395	374	354	337	323	309	262	197	128	72	33	11	2	0	474/176

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 was calculated using a profile likelihood approach. An HR < 1 favors the D + FLOT arm.
The 2-sided p-value was calculated using a stratified log-rank test, adjusting for geographic region, clinical lymph node status, and PD-L1 expression level.
DCO2: 20 December 2024.

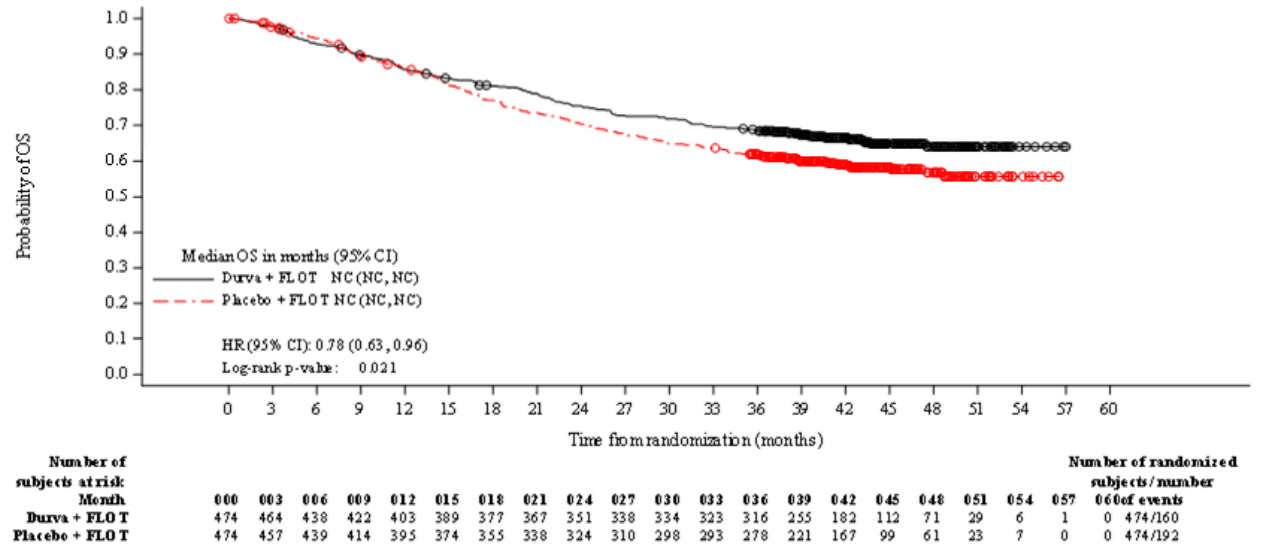
Table 20 Overall Survival (FAS, DCO3)

	D + FLOT (N = 474)	Pbo + FLOT (N = 474)
Death, n (%)	160 (33.8)	192 (40.5)
Censored patients, n (%)	314 (66.2)	282 (59.5)
Still in survival follow-up [a]	305 (64.3)	265 (55.9)
Terminated prior to death [b]	9 (1.9)	17 (3.6)
Voluntary discontinuation by patient	9 (1.9)	16 (3.4)
Other		
Median OS (months) [c]	NC	NC
95% CI for median OS [c]	NC – NC	NC – NC
Survival rate at 12 months (%) [c]	85.8	85.6
95% CI for survival rate at 12 months [c]	82.31 – 88.64	82.06 – 88.48
Survival rate at 18 months (%) [c]	81.1	77.1
95% CI for survival rate at 18 months [c]	77.26 – 84.35	73.02 – 80.68
Survival rate at 24 months (%) [c]	75.5	70.4
95% CI for survival rate at 24 months [c]	71.35 – 79.14	65.99 – 74.32
Survival rate at 30 months (%) [c]	71.8	64.7
95% CI for survival rate at 30 months [c]	67.54 – 75.69	60.19 – 68.90
Survival rate at 36 months (%) [c]	68.6	61.9
95% CI for survival rate at 36 months [c]	64.20 – 72.61	57.31 – 66.16
HR, comparing durvalumab vs placebo [d]	0.78	
95% CI for HR [d]	0.63 – 0.96	
2-sided p-value [e]	0.021	

[a] Includes patients known to be alive at the DCO date.
[b] Includes patients with unknown survival status or patients who were lost to follow-up.
[c] Calculated using the KM technique.
[d] 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 favors the D + FLOT arm. The CI is calculated using a profile likelihood approach.
[e] Calculated using a stratified log-rank test adjusted for geographic region, clinical lymph node status, and PD-L1 expression level at randomization.

At DCO3, an alpha of 4.99% (2-sided) was allocated to the FA of OS, corresponding to a p-value boundary for declaring statistical significance of 0.0499.
DCO3: 01 September 2025.

Figure 8 Kaplan-Meier Plot of Overall Survival (FAS, DCO3)



Circle symbol indicates a censored observation.
The HR and its CI are estimated from a Cox proportional hazards model, adjusted for geographic region, clinical lymph node status, and PD-L1 expression level. The CI for the HR is calculated using a profile likelihood approach. An HR < 1 favors the 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.
DCO3: 01 September 2025.

Key secondary endpoint: pCR rate by central Pathology review at DCO1

Table 21 pCR Rate assessed by central review, according to CAP-modified Ryan Tumour Regression Score (FAS, DCO1)

Group	n	Number of patients with response [a]	Response Rate (%)	95% CI [b]	Difference in response rate (%) [c]	Comparison between groups [d]		
						Odds Ratio	95% CI	2-sided p-value
D + FLOT	474	91	19.2	15.75 – 23.04	12.0	3.08	2.03 – 4.67	< 0.001
Pbo + FLOT	474	34	7.2	5.02 – 9.88				

[a] Patients achieve pCR if there is no residual viable tumor cells found at primary tumor 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 response rate – Pbo + FLOT 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 randomization.

An odds ratio > 1 favors the D + FLOT arm.
DCO: 01 February 2023.

Table 22 pCR Rate assessed by investigators (FAS; Data Captured at DCO2)

Group	n	Number of patients with response [a]	Response Rate (%)	95% CI [b]	Difference in response rate (%) [c]	Comparison between groups [d]		
						Odds Ratio	95% CI	2-sided p-value
D + FLOT	474	103	21.7	18.10 – 25.72	13.1	2.95	2.00 – 4.35	< 0.001
Pbo + FLOT	474	41	8.6	6.28 – 11.55				

[a] Patients achieve pCR if there is no residual viable tumor cells found at primary tumor and resected lymph nodes at the time of resection, meaning a pathological regression of -100%, based on investigator assessment.
[b] CIs for response rate are calculated using Clopper-Pearson exact method.
[c] Difference in response rate = D + FLOT response rate – Pbo + FLOT response rate.
[d] Not part of the multiple testing procedure. 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 randomization.

An odds ratio > 1 favors the D + FLOT arm.
DCO: 20 December 2024.

Secondary endpoint: Surgical outcomes

Table 23 Summary of patients undergoing surgery (FAS, DCO2)

	D + FLOT (N = 474)	Pbo + FLOT (N = 474)
Other [a]	4 (0.8)	6 (1.3)
Patients who completed surgery	**412 (86.9)**	**400 (84.4)**
Distal gastrectomy	38 (8.0)	38 (8.0)
Subtotal gastrectomy	79 (16.7)	72 (15.2)
Total gastrectomy	168 (35.4)	166 (35.0)
Gastroesophagectomy	127 (26.8)	124 (26.2)
Surgery rate (%)	**86.9**	**84.4**
95% CI [b]	83.55 – 89.82	80.80 – 87.54
Difference in surgery rate (%) [c]	2.5	
Comparison between arms [d]		
Odds ratio	1.23	
95% CI	0.85 – 1.77	
Type of surgical procedure and extent of resection		
Surgery laparotomy or laparoscopy [f]	412 (100)	400 (100)
Laparotomy	227 (55.1)	225 (56.3)
Laparoscopy	185 (44.9)	175 (43.8)
Type of lymphadenectomy performed [f]	412 (100)	400 (100)
D1	36 (8.7)	26 (6.5)
D2/D3	375 (91.0)	373 (93.3)
Missing	1 (0.2)	1 (0.3)
Extent of resection [f]	412 (100)	400 (100)
R0	377 (91.5)	369 (92.3)
R1	23 (5.6)	21 (5.3)
R2	11 (2.7)	10 (2.5)
Missing		
Surgical delays		
Patients with no surgical delay	383 (80.8)	377 (79.5)
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		
Logistical reasons	28 (5.9)	31 (6.5)
AE	11 (2.3)	12 (2.5)

	D + FLOT (N = 474)	Pbo + FLOT (N = 474)
Other	7 (1.5)	6 (1.3)
Duration of delay to on-study surgery		
< 2 weeks	28 (5.9)	28 (5.9)
2 to < 4 weeks	7 (1.5)	12 (2.5)
4 to < 6 weeks	5 (1.1)	4 (0.8)
≥ 6 weeks	8 (1.7)	7 (1.5)
Reason for delay for Cycle 3 Day 1 dose (initiation of adjuvant treatment) [h,i]		
AE	5 (1.1)	13 (2.7)
Logistic	2 (0.4)	4 (0.8)
Patient decision	2 (0.4)	2 (0.4)
Laboratory abnormality not reported as an AE		
Other	2 (0.4)	2 (0.4)

[a] Includes 9 patients with inoperable disease.
[b] CIs for response rate are calculated using Clopper-Pearson exact method.
[c] Difference in response rate = D + FLOT response rate – Pbo + FLOT 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 randomization.
[e] Not part of the multiple testing procedure.
[f] Patients who have completed surgery only. 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.

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 favors the D + FLOT arm.
DCO: 20 December 2024.

Secondary endpoint: Disease-free survival (DFS)

Table 24 Disease-free survival (R0 Resected Analysis Set, DCO2)

	D + FLOT (N = 339)	Pbo + FLOT (N = 323)
Total DFS events [a], n (%)	**90 (26.5)**	**119 (36.8)**
Recurrence of disease	70 (20.6)	99 (30.7)
Death in the absence of disease recurrence	17 (5.0)	19 (5.9)
Death between RECIST 1.1 adjuvant baseline scan and next RECIST 1.1 scan	3 (0.9)	1 (0.3)
Censored patients, n (%)	249 (73.5)	204 (63.2)
Disease-free at time of analysis [b]	248 (73.2)	202 (62.5)
Terminated prior to death [c]	1 (0.3)	2 (0.6)
Withdrawn consent	1 (0.3)	2 (0.6)
Median DFS (months) [d]	**NC**	**39.75**
95% CI for median DSS [d]	NC - NC	38.67 - NC
DFS rate at 12 months (%) [d]	**82.42**	**81.62**

	D + FLOT (N = 339)	Pbo + FLOT (N = 323)
95% CI for DFS rate at 12 months [d]	77.91 - 86.10	76.93 - 85.45
DFS rate at 18 months (%) [d]	**79.08**	**72.81**
95% CI for DFS rate at 18 months [d]	74.31 - 83.06	67.57 - 77.34
DFS rate at 24 months (%) [d]	**75.21**	**66.20**
95% CI for DFS rate at 24 months [d]	70.17 - 79.53	60.63 - 71.18
DFS rate at 30 months (%) [d]	**71.53**	**61.49**
95% CI for DFS rate at 30 months [d]	65.74 - 76.51	55.42 - 67.00
DFS rate at 36 months (%) [d]	**65.75**	**58.08**
95% CI for DFS rate at 36 months [d]	55.72 - 74.03	50.41 - 64.98
HR [e]	**0.70**	
95% CI for HR [e]	**0.53 - 0.93**	

[a] Events are defined as disease recurrence by RECIST 1.1 by the investigator, death due to any cause, or death between first post-surgery scan and next RECIST 1.1 scan.

[b] Includes patients known to be alive at DCO date.

[c] Includes patients with unknown survival status or patients who were lost to follow-up.

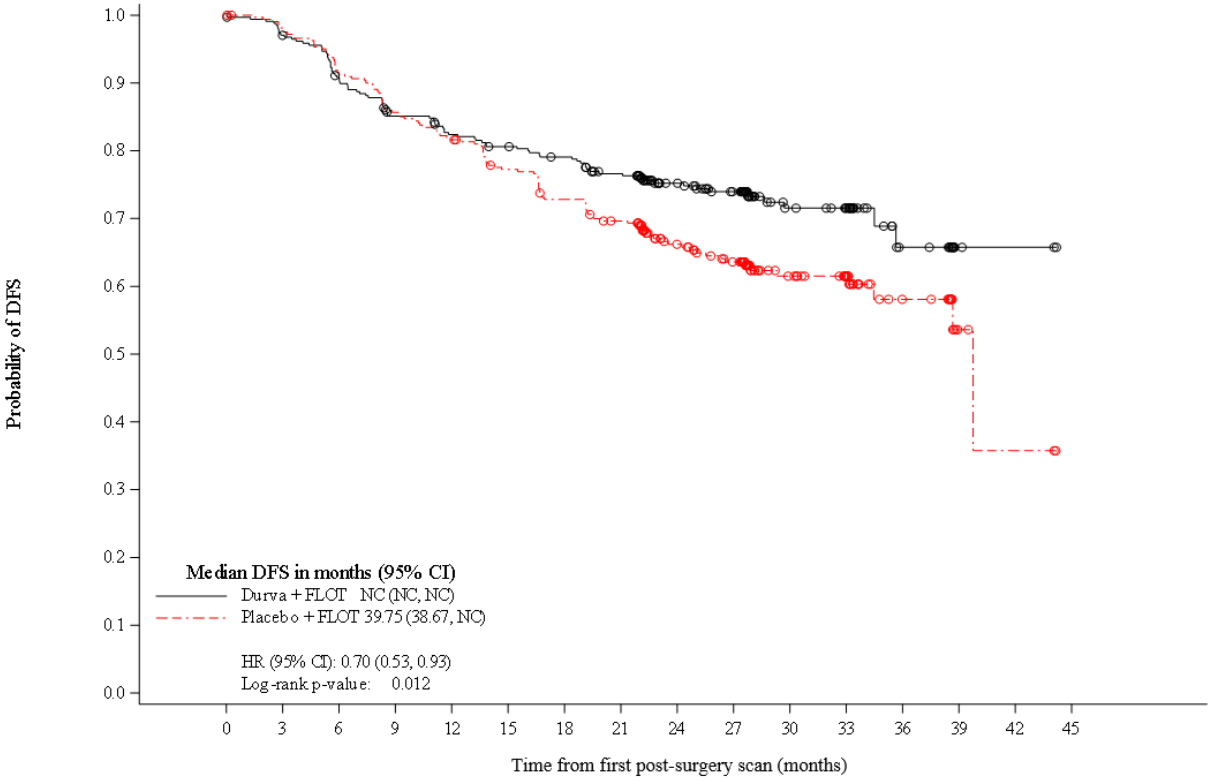
[d] Calculated using the KM technique.

[e] The analysis was performed using a stratified Cox proportional hazards, adjusting for geographic region, clinical lymph node status, and PD-L1 expression level. An HR < 1 favors the D + FLOT arm. The CI is calculated using a profile likelihood approach.

DFS is the time from date of first post-surgery scan until an event in patients who had margin-negative surgery (R0) and no evidence of disease at the adjuvant baseline scan.

DCO2: 20 December 2024.

Figure 9 Kaplan-Meier Plot of Disease-free survival (R0 Resected Analysis Set, DCO2)



Number of subjects at risk Month	000	003	006	009	012	015	018	021	024	027	030	033	036	039	042	045	Number of R0 resected subjects/ number of events
Durva + FLOT	339	327	305	283	272	265	258	244	184	168	81	74	19	3	2	0	339/90
Placebo + FLOT	323	315	293	275	262	245	230	217	157	142	72	56	23	4	2	0	323/119

DFS (defined by RECIST 1.1) is time from first post-surgery scan until the earliest of first evidence of disease recurrence or death due to any cause, in patients with R0 resection and no evidence of disease at the adjuvant baseline scan.

Circle indicates a censored observation.

Patients who are alive and disease free at time of analysis are censored at date last known alive and without DFS event. If a patient died between first post-surgery scan and next scheduled RECIST 1.1 scan, this was considered an event.

The HR and its CI 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 favors the D + FLOT arm. The p-value is not adjusted for multiplicity.

DCO2: 20 December 2024.

Secondary endpoint: Metastasis-Free Survival (MFS)

Table 25 Metastases-free survival according to investigator (FAS, DCO2)

	D + FLOT (N = 474)	Pbo + FLOT (N = 474)
Total MFS events [a], n (%)	**171 (36.1)**	**224 (47.3)**
Metastasis	93 (19.6)	130 (27.4)
Death in the absence of metastasis	78 (16.5)	94 (19.8)
Censored patients, n (%)	303 (63.9)	250 (52.7)
Metastases-free at time of analysis [b]	295 (62.2)	235 (49.6)
Withdrawn consent	8 (1.7)	14 (3.0)
Discontinued study (any other specified reason for discontinuing study)		

	D + FLOT (N = 474)	Pbo + FLOT (N = 474)
Median MFS (months) [c]	**NC**	**32.79**
95% CI for median MFS [c]	39.46 - NC	27.04 - 42.58
MFS rate at 12 months (%) [c]	**77.49**	**77.18**
95% CI for MFS rate at 12 months [c]	73.38 - 81.05	73.02 - 80.78
MFS rate at 18 months (%) [c]	**72.09**	**66.65**
95% CI for MFS rate at 18 months [c]	67.71 - 75.98	62.08 - 70.80
MFS rate at 24 months (%) [c]	**67.51**	**58.04**
95% CI for MFS rate at 24 months [c]	62.97 - 71.62	53.32 - 62.46
MFS rate at 30 months (%) [c]	**64.36**	**51.50**
95% CI for MFS rate at 30 months [c]	59.69 - 68.65	46.66 - 56.12
MFS rate at 36 months (%) [c]	**60.89**	**48.72**
95% CI for MFS rate at 36 months [c]	55.72 - 65.66	43.63 - 53.61
HR [d]	**0.72**	
95% CI for HR [d]	**0.59 - 0.88**	

[a] Events signify occurrence of a new lesion outside of local regional tumor locations identified per RECIST 1.1 assessment by the investigator.

[b] Patients who are alive and metastases-free at time of analysis are censored at the date of last evaluable RECIST assessment that is without an MFS event.

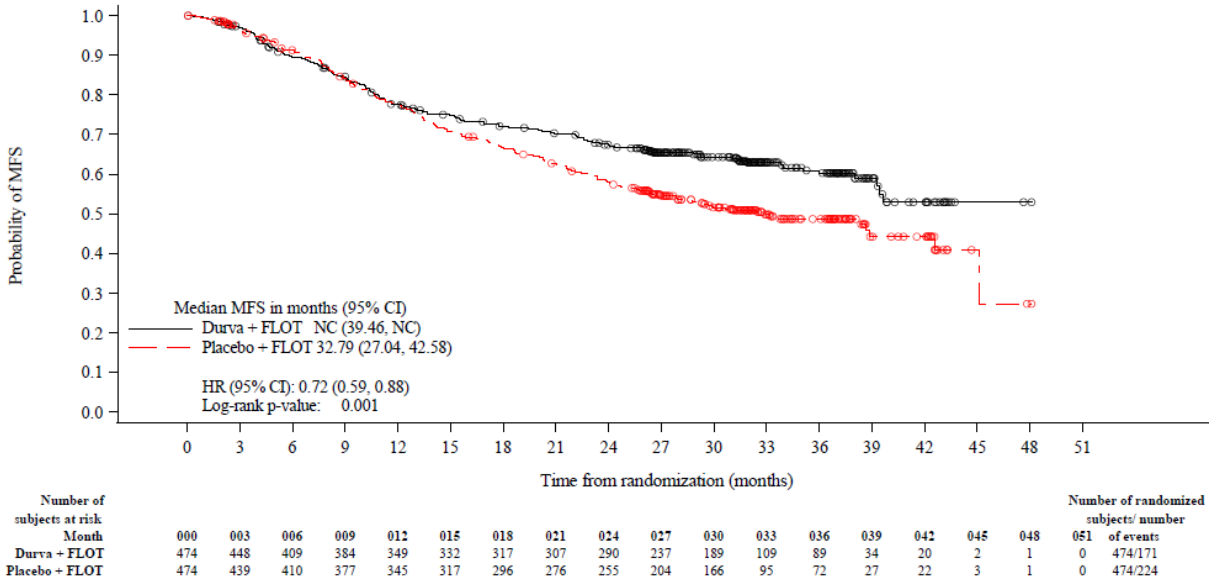
[c] Calculated using the KM technique.

[d] The analysis was performed using a stratified Cox proportional hazards model, as described for the primary analysis. An HR < 1 favors the D + FLOT arm. The CI is calculated using a profile likelihood approach.

MFS is the time from date of randomization until the earliest date of metastasis or death due to any cause.

DCO2: 20 December 2024.

Figure 10 Kaplan-Meier of metastases-free survival (FAS, DCO2)



Patients who were alive and free from metastases at the time of analysis were censored based on the last recorded date on which the patient was known to be alive without the MFS event. Evidence of metastasis is defined as the occurrence of a new lesion outside of local regional tumor locations identified per RECIST 1.1 assessment by the investigator.

A 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 favors the D + FLOT arm. The p-value is not adjusted for multiplicity.

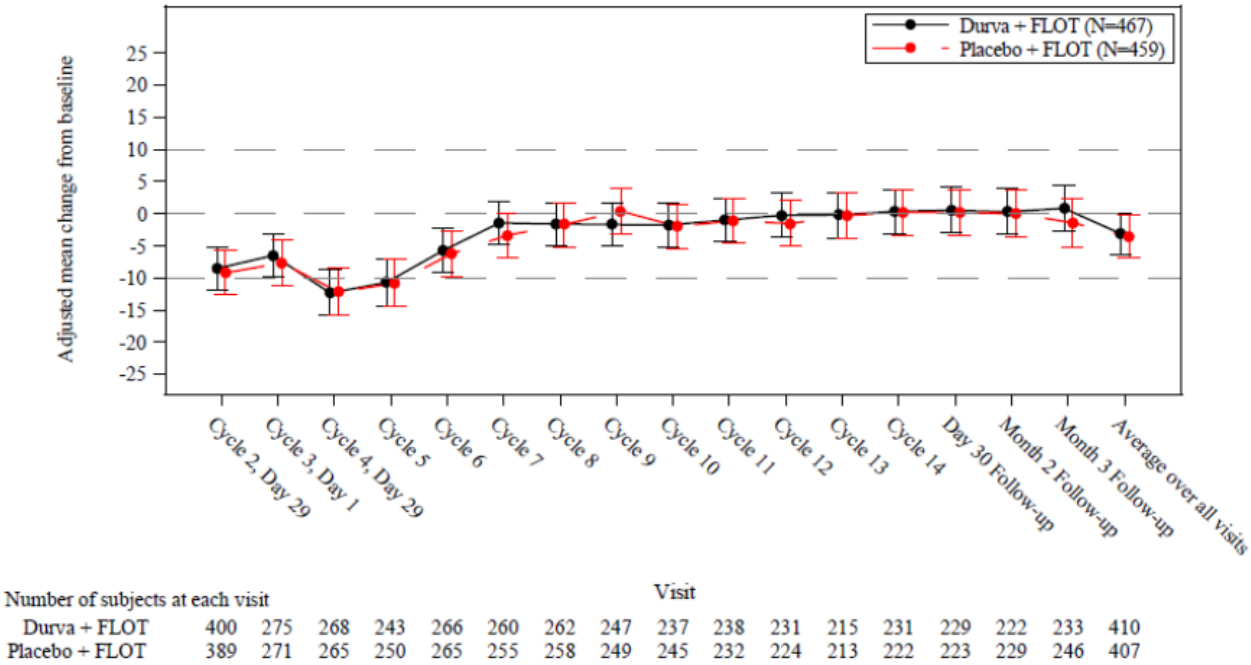
DCO2: 20 December 2024.

Patient Reported Outcomes (PROs)

PROs were assessed as secondary endpoints using the EORTC QLQ-C30 and EORTC QLQ-STO22 + IL38 questionnaires. The PRO-CTCAE questionnaire was collected as an exploratory endpoint.

The overall compliance rates for the completion of the QLQ-C30 and QLQ-STO22 + IL38 questionnaires were > 90% in both treatment arms at baseline and generally remained above 80% to the adjuvant Cycle 14.

Figure 11 Adjusted mean EORTC QLQ-C30 Global Health Status/QoL score, Change from baseline over time by MMRM analysis (PRO analysis set; DCO2)



Number of subjects at each visit																	
Durva + FLOT	400	275	268	243	266	260	262	247	237	238	231	215	231	229	222	233	410
Placebo + FLOT	389	271	265	250	265	255	258	249	245	232	224	213	222	223	229	246	407

2.5.2.15. Ancillary analyses

Sensitivity analyses

Table 26 EFS based on investigator assessment per RECIST 1.1, sensitivity analysis, ascertainment bias (FAS, DCO2)

Group	n	Number (%) of patients with event [a]	Median (95% CI) (months) [b]	Comparison between groups		
				HR [c]	95% CI [c]	2-sided p-value [d]
D + FLOT	474	177 (37.3)	NC (39.62 - NC)	0.71	0.58 - 0.86	< 0.001
Pbo + FLOT	474	232 (48.9)	31.11 (24.90 - 38.67)			

[a] Events are defined as the earliest of RECIST 1.1 events by Investigator, non-RECIST 1.1 events, or deaths of any cause as defined in the SAP.

[b] Calculated using the KM technique.

[c] Estimated from a stratified Cox proportional hazards model, adjusted for geographic region, clinical lymph node status and PD-L1 expression level at randomization. CI was calculated using a profile likelihood approach. An HR < 1 favors the D + FLOT arm.

[d] Not part of the multiple testing procedure. Analyzed using a stratified log-rank test adjusted for the same stratification factors. Analysis uses the investigator assessments according to RECIST 1.1, in place of BICR assessments.

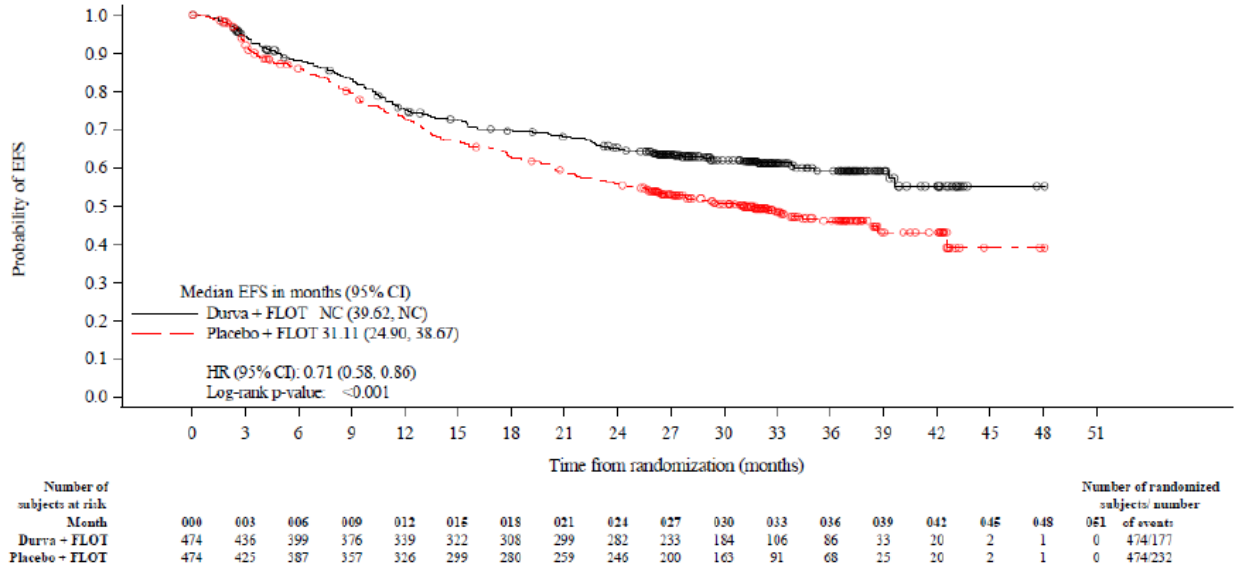
DCO: 20 December 2024.

Concordance Between BICR and Investigator Assessments of EFS Events per RECIST 1.1

In the D + FLOT and Pbo + FLOT arms, there were 165 (34.8%) and 213 (44.9%) patients, respectively, who had events declared by both BICR and investigator assessment, and 295 (62.2%) and 237 (50.0%) patients, respectively, who had non-events declared by both BICR and investigator assessment.

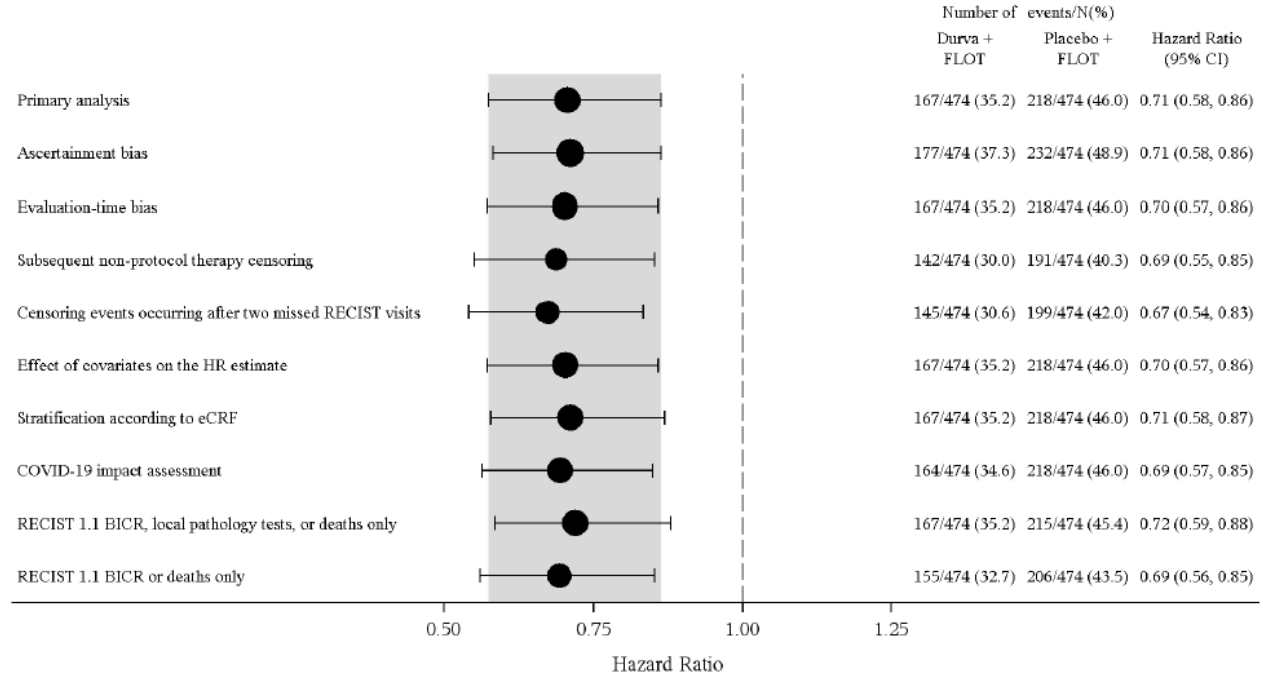
Analysis of discrepancy rates between investigator and BICR assessment of EFS events demonstrated an overall concordance of 96% (calculated as: [165 + 213 + 295 + 237]/948 × 100) on events and non-events declared by the 2 assessment methods.

Figure 12 Kaplan-Meier Plot of EFS based on investigator assessment per RECIST 1.1, Sensitivity Analysis, Ascertainment Bias (FAS, DCO2)



Circle indicates a censored observation.
Events are defined as the earliest of RECIST 1.1 events by Investigator, non-RECIST 1.1 events, or deaths of any cause as defined in the SAP.
Analysis is based on investigator 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 favors the D + FLOT arm.
Not part of the multiple testing procedure. This was calculated using a stratified log-rank test, adjusting for geographic region, clinical lymph node status, and PD-L1 expression level.
DCO: 20 December 2024.

Figure 13 Forest Plot of EFS Sensitivity Analysis (FAS, DCO2)

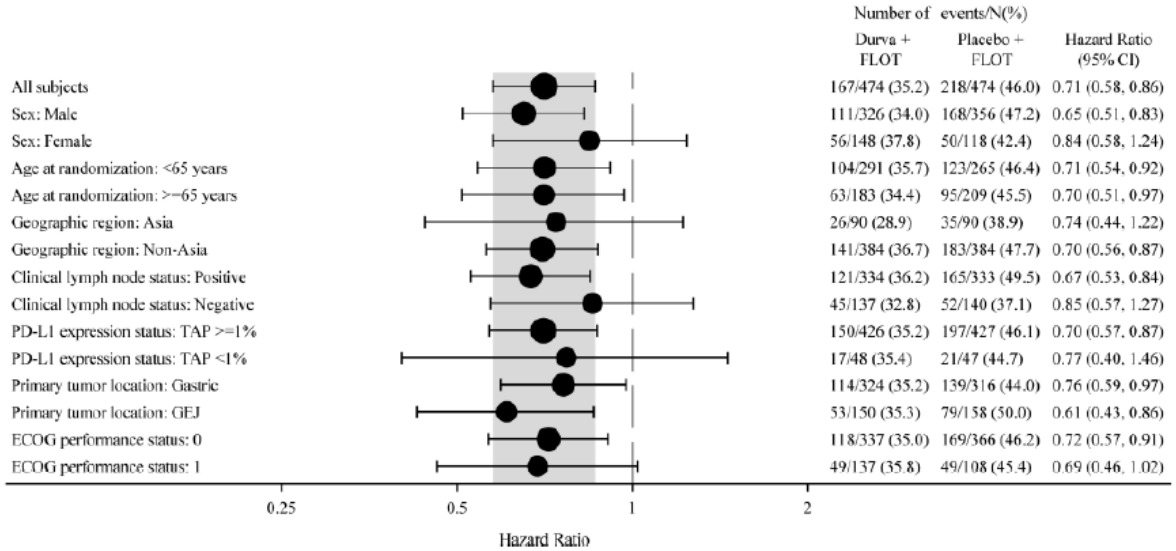


The analysis was performed using a Cox proportional hazards model with treatment as the only covariate. An HR < 1 favors the D + FLOT arm.
The CI was calculated using a profile likelihood approach. The size of the circle is proportional to the number of events. The gray band represents the 95% CI for the primary analysis HR for EFS. EFS events are defined as the earliest of the categories of events included in each sensitivity analysis or deaths of any cause, as defined in the SAP.
DCO2: 20 December 2024.

A total of 4 patients died due to COVID-19 in the D + FLOT arm compared with 1 patient in the Pbo + FLOT arm; the HR (95% CI) for OS censoring patients who died due to COVID-19 was 0.76 (0.61, 0.95).

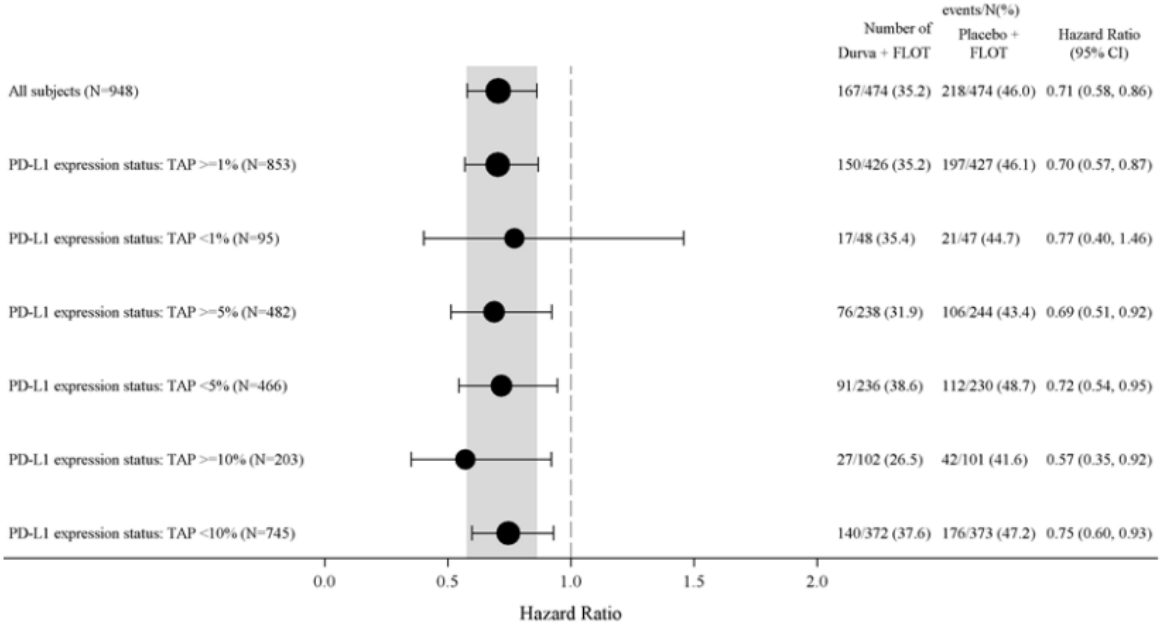
Subgroup analyses

Figure 14 Forest Plot of EFS by Subgroup (FAS, DCO2)



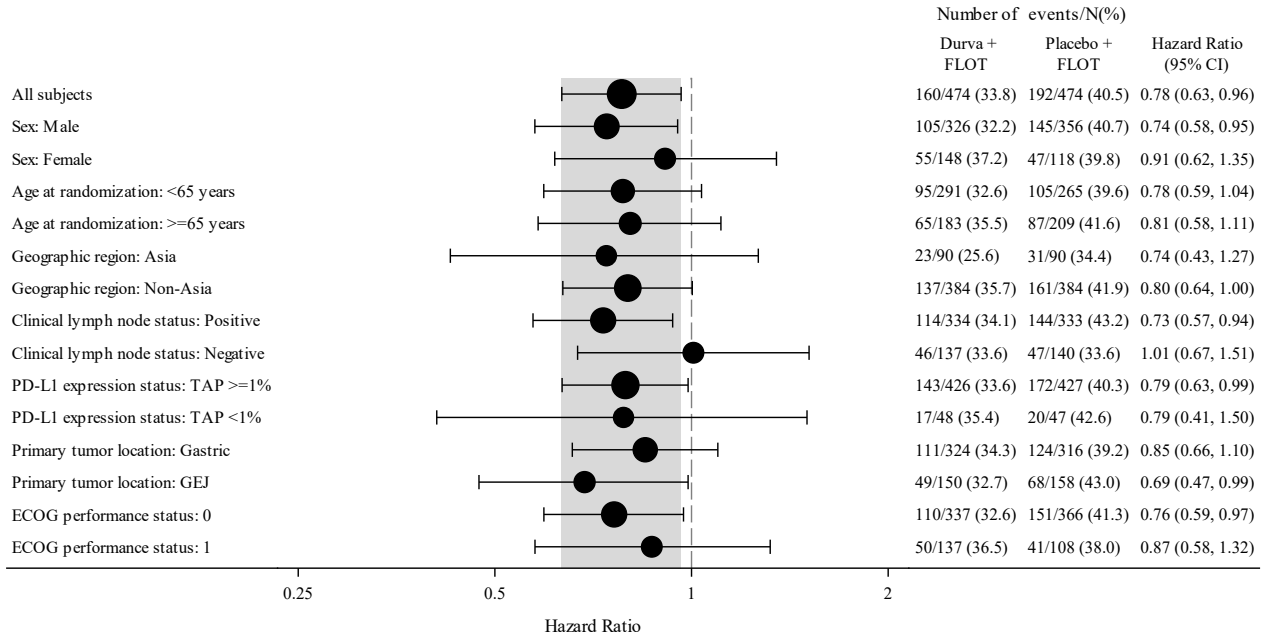
The analysis was performed using a Cox proportional hazards model with treatment as the only covariate. An HR < 1 favors the D + FLOT arm. CI was calculated using a profile likelihood approach. The size of the circle is proportion to the number of events. Gray band represents the 95% CI for the all-patients HR.
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.
Patients provided a tumor tissue sample at screening to determine PD-L1 expression level using the Ventana PD-L1 (SP263) CDx Assay and the TAP scoring method.
Analysis is based on BICR assessments and/or locally by pathology testing if clinically required.
DCO: 20 December 2024.

Figure 15 Forest Plot of EFS Subgroup Analyses by PD-L1 Expression levels (FAS; DCO2)



The analysis was performed using a Cox proportional hazards model with treatment as the only covariate. An HR < 1 favors the D + FLOT arm. CI was calculated using a profile likelihood approach. Size of circle is proportion to the number of events. Gray band represents the 95% CI for the HR in the FAS.
Events were the earliest of RECIST 1.1 events, non-RECIST 1.1 events or deaths of any cause, as defined in the SAP.
Patients provided a tumor tissue sample at screening to determine PD-L1 status using the TAP scoring method.
Analysis is based on EFS by BICR assessments and/or locally by pathology testing if clinically required.
DCO2: 20 December 2024.

Figure 16 Forest Plot of Overall Survival subgroup analyses (FAS; DCO3)

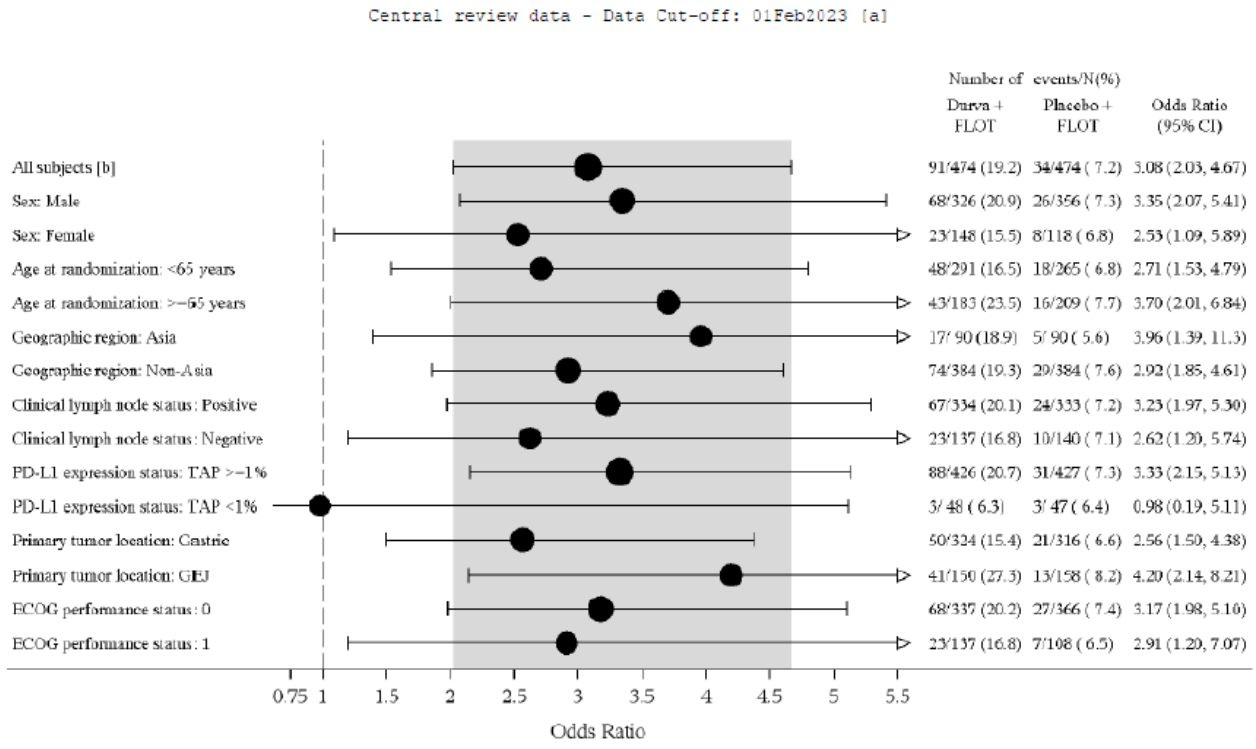


The analysis in all subjects (FAS) was performed using a stratified Cox proportional hazards model, adjusting for geographic region, clinical lymph node status, and PD-L1 expression level. The subgroup analyses were performed using a Cox proportional hazards model with treatment as the only covariate. An HR < 1 favors the D + FLOT arm. The 95% CI was calculated using a profile likelihood approach.

The size of circle is proportional to the number of events. Gray band represents the 95% CI for the all-subjects HR. Patients provide a tumor tissue sample at screening to determine PD-L1 expression level using the TAP scoring method.

DCO3: 01 September 2025.

Figure 17 Subgroup Analysis of pCR by Central Assessment (According to CAP- Modified Ryan Tumour Regression Score), Forest Plot (FAS, DCO1)



[a] Central review data locked at DCO1.

[b] Stratified by geographic region, clinical lymph node status and PD-L1 expression level at randomization. CIs for response rate are calculated using Clopper-Pearson exact method. The size of circle is proportional to the number of events. Gray band represents the 95% CI for the all-subjects odds ratio.

Patients achieve pCR if there is no residual viable tumor cells found at primary tumor and resected lymph nodes at the time of resection, meaning a pathological regression of % review, based on central assessment.

An odds ratio > 1 favors the D + FLOT arm.

DCO: 01 February 2023

EFS and OS by PD-L1 expression

Table 27 Event-free survival and its landmarks by PD-L1 expression status (FAS; DCO1)

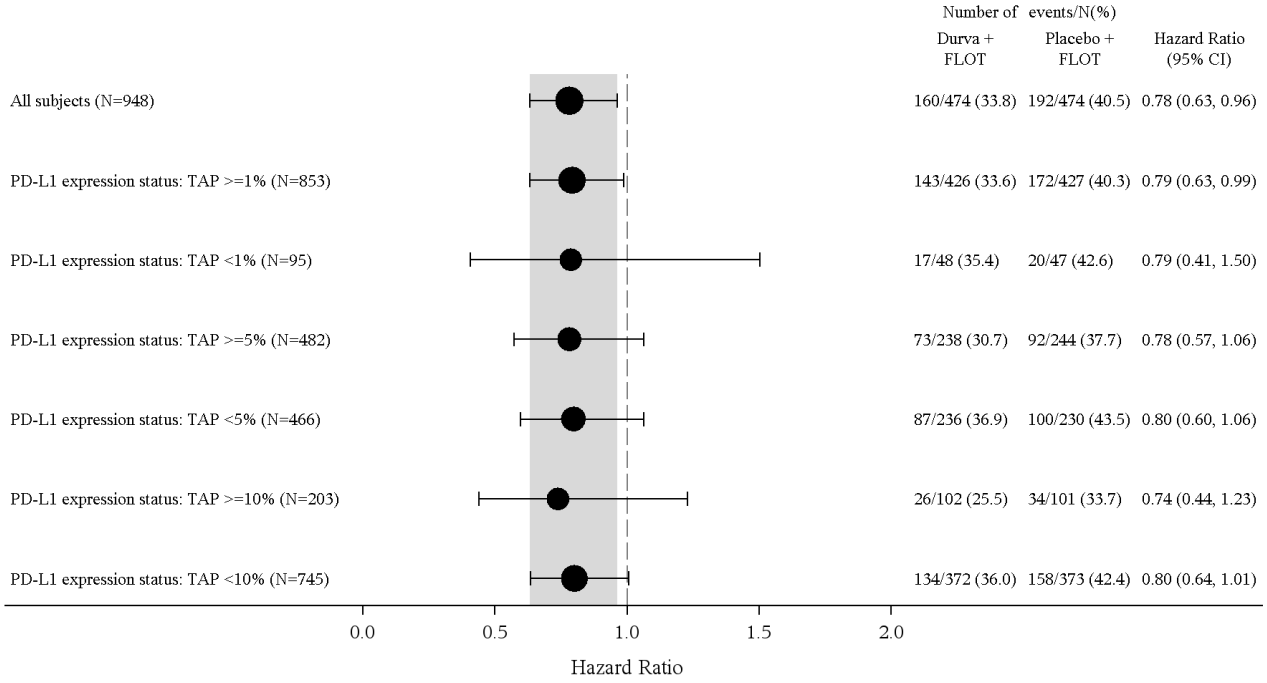
	Durva + FLOT			Placebo + FLOT			Comparison between groups	
Subgroup	N	Number of events (%)	Estimate (95% CI) [a]	N	Number of events (%)	Estimate (95% CI) [a]	Hazard ratio	95% CI
Median EFS (months) all subjects [b]	474	167 (35.2)	NC (40.74-NC)	474	218 (46.0)	32.82 (27.86-NC)	0.71	0.58-0.86
Median EFS (months) by PD-L1 expression status [b]								
TAP >=1%	426	150 (35.2)	NC (40.74-NC)	427	197 (46.1)	32.82 (27.83-NC)	0.70	0.57-0.87
TAP <1%	48	17 (35.4)	NC (19.98-NC)	47	21 (44.7)	NC (13.96-NC)	0.77	0.40-1.46
EFS rate at 12 months (%) by PD-L1 expression status [c]								
TAP >=1%	426	150 (35.2)	78.61 (74.32-82.28)	427	197 (46.1)	74.31 (69.78-78.27)	0.81	0.62-1.06
TAP <1%	48	17 (35.4)	74.40 (59.32-84.58)	47	21 (44.7)	71.18 (55.59-82.13)	0.87	0.46-1.66
EFS rate at 18 months (%) by PD-L1 expression status [c]								
TAP >=1%	426	150 (35.2)	73.60 (69.04-77.61)	427	197 (46.1)	63.75 (58.85-68.22)	0.68	0.54-0.86
TAP <1%	48	17 (35.4)	69.75 (54.27-80.87)	47	21 (44.7)	62.28 (46.52-74.60)	0.76	0.41-1.40
EFS rate at 24 months (%) by PD-L1 expression status [c]								
TAP >=1%	426	150 (35.2)	67.71 (62.91-72.03)	427	197 (46.1)	58.87 (53.88-63.50)	0.74	0.59-0.92
TAP <1%	48	17 (35.4)	65.10 (49.40-77.01)	47	21 (44.7)	55.61 (40.03-68.65)	0.73	0.41-1.31
EFS rate at 30 months (%) by PD-L1 expression status [c]								
TAP >=1%	426	150 (35.2)	64.35 (59.41-68.85)	427	197 (46.1)	52.52 (47.38-57.40)	0.68	0.55-0.85
TAP <1%	48	17 (35.4)	62.14 (46.09-74.66)	47	21 (44.7)	52.13 (36.18-65.88)	0.73	0.41-1.31
EFS rate at 36 months (%) by PD-L1 expression status [c]								
TAP >=1%	426	150 (35.2)	62.03 (56.69-66.91)	427	197 (46.1)	46.80 (41.04-52.34)	0.63	0.50-0.79
TAP <1%	48	17 (35.4)	62.14 (46.09-74.66)	47	21 (44.7)	52.13 (36.18-65.88)	0.73	0.41-1.31

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
[a] Calculated using the Kaplan-Meier technique.
[b] HR and 95% CI is calculated from a Cox proportional hazards model.
[c] HR and 95% CI is calculated using method specified by Klein et al. (2007), see SAP for further details.
Subjects provide a tumor tissue sample at screening to determine PD-L1 status using the TAP scoring method.
EFS = Event-free survival. Durva = Durvalumab. FLOT = 5-FU + Leucovorin + Oxaliplatin + Docetaxel.
N = Number of subjects in treatment group. HR = Hazard ratio. CI = Confidence Interval.
PD-L1 = Programmed cell death-ligand-1. TAP = Tumor Area Positivity Score. SAP = Statistical analysis plan.
NC = Non-calculable. RECIST version 1.1.

OS rate at 36 months (%) by PD-L1 expression status [c]								
TAP >=1%	426	130 (30.5)	69.10 (64.21-73.45)	427	159 (37.2)	62.28 (57.28-66.86)	0.78	0.62-0.98
TAP <1%	48	15 (31.3)	67.63 (51.96-79.17)	47	17 (36.2)	61.93 (46.03-74.38)	0.82	0.45-1.49

[a] Calculated using the Kaplan-Meier technique.
[b] HR and 95% CI will be calculated from a Cox proportional hazards model.
[c] HR and 95% CI will be calculated using method specified by Klein et al. (2007), see SAP for further details.
Subjects provide a tumor tissue sample at screening to determine PD-L1 status using the TAP scoring method.
OS = Overall survival. Durva = Durvalumab. FLOT = 5-FU + Leucovorin + Oxaliplatin + Docetaxel.
N = Number of subjects in treatment group. HR = Hazard ratio. CI = Confidence Interval.
PD-L1 = Programmed cell death-ligand-1. TAP = Tumor Area Positivity Score. SAP = Statistical analysis plan.
NC = Non-calculable.

Figure 18 Forest Plot of Overall Survival Subgroup Analyses by PD-L1 Expression Level (TAP 1%, 5%, and 10% cut-offs) (FAS; DCO3)



The analysis in all subjects (FAS) was performed using a stratified Cox proportional hazards model, adjusting for geographic region, clinical lymph node status, and PD-L1 expression level. The subgroup analyses were performed using a Cox proportional hazards model with treatment as the only covariate. An HR < 1 favors the D + FLOT arm. The 95% CI was calculated using a profile likelihood approach.

The size of circle is proportional to the number of events. Gray band represents the 95% CI for the all-subjects HR.

Patients provide a tumor tissue sample at screening to determine PD-L1 expression level using the TAP scoring method.

DCO3: 01 September 2025.

Immunogenicity

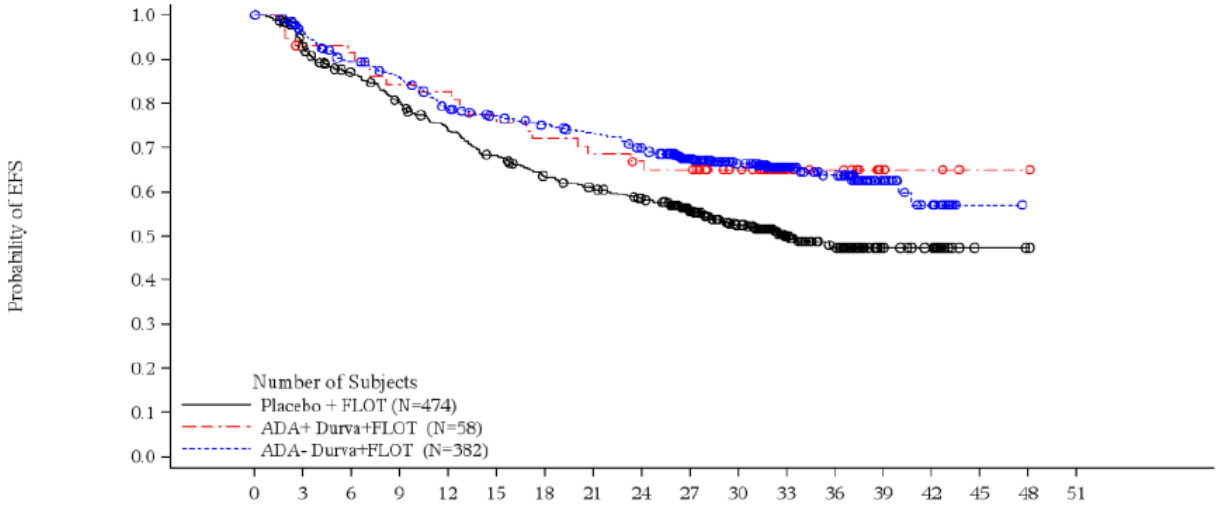
Table 28 Summary of ADA Response to durvalumab (ADA Analysis Set, DCO2)

ADA category	D + FLOT (N = 441)
ADA-evaluable patients, n (%) [a]	441 (100)
ADA positive at any point in time, baseline or post-baseline, n (%) [b]	58 (13.2)
Median of maximum titer (min, max) [c]	4.0 (2, 32)
ADA-positive post-baseline and at baseline, n (%) [b]	1 (0.2)
Median of maximum titer (min, max) [c]	8.0 (8, 8)
Treatment-induced ADA, n (%) [b,d]	40 (9.1)
Median of maximum titer (min, max) [c]	4.0 (2, 32)
ADA not detected post-baseline and positive at baseline, n (%) [b]	17 (3.9)
Median of maximum titer (min, max) [c]	3.0 (2, 32)
Treatment-boosted ADA, n (%) [b,e]	0
Median of maximum titer (min, max) [c]	NA (NA)
TE-ADA-positive, n (%) [b,f]	40 (9.1)
Median of maximum titer (min, max) [c]	4.0 (2, 32)
Persistently positive ADA n (%) [b,g]	11 (2.5)
Median of maximum titer (min, max) [c]	8.0 (2, 32)
Transiently positive ADA n (%) [b,h]	30 (6.8)
Median of maximum titer (min, max) [c]	4.0 (2, 16)
nAb positive at any time, baseline or post-baseline n (%) [b]	2 (0.5)
Median of maximum titer (min, max) [c]	5.0 (2, 8)

[a] Patients with non-missing baseline and ≥ 1 non-missing post-baseline ADA result (ADA Analysis Set).
[b] Denominator is number of ADA-evaluable patients.
[c] If a patient has > 1 titer result, the maximum result is reported, regardless if it was baseline or post-baseline.
[d] Defined as ADA-positive post-baseline but not detected at baseline.
[e] Defined as baseline positive ADA titer that was boosted to a 4-fold or higher level following first dose.
[f] Defined as either treatment-induced or treatment-boosted ADA.
[g] Defined as having ≥ 2 post-baseline ADA-positive measurements with ≥ 16 weeks between positive measurements, or ADA positive at last available assessment. May include patients who were ADA positive at baseline.
[h] Defined as having ≥ 1 post-baseline ADA-positive measurement but not fulfilling conditions for persistently positive. May include patients who were ADA positive at baseline.

DCO: 20 December 2024.

Figure 19 Kaplan-Meier Plot of EFS by randomised treatment arm and ADA status to durvalumab (ADA Analysis set; DCO2)



Number of subjects at risk Month	000	003	006	009	012	015	018	021	024	027	030	033	036	039	042	045	048	051	Number of randomized subjects/ number of events
Placebo + FLOT	474	429	392	360	329	302	278	264	249	202	160	89	65	26	21	2	1	0	474/218
ADA+ Durva+FLOT	58	53	52	48	47	44	41	39	37	36	29	15	12	4	3	1	1	0	58/20
ADA- Durva+FLOT	382	359	329	312	285	272	262	254	239	188	151	89	73	29	17	1	0	0	382/127

The plot includes data from ADA-evaluable patients.
Circle indicates a censored observation. Events are defined as the earliest of 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.
ADA+: patients in the D + FLOT arm who were ADA+ to durvalumab at any time (at baseline or post-baseline).
ADA-: patients in the D + FLOT arm who were ADA- to durvalumab, ie, without any ADA+ results (at baseline or post-baseline).
DCO: 20 December 2024.

2.5.2.16. Summary of main study(ies)

The following tables summarise the efficacy results from the main study supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit-risk assessment (see later sections).

Table 29 Summary of efficacy for study D910GC00001 (MATTERHORN)

Title: A Randomized, Double-blind, Placebo-controlled, Phase III Study of Neoadjuvant-Adjuvant Durvalumab and FLOT Chemotherapy Followed by Adjuvant Durvalumab in Patients with Resectable Gastric and Gastroesophageal Junction Cancer (GC/GEJC) (MATTERHORN)	
Study identifier	Study Code: D910GC00001 EudraCT Number: 2019-001555-40 EU CT Number: 2023-507338-26-00 NCT Number: NCT04592913
Design	This is an ongoing phase III, randomized, open-label, multi-center, parallel-group global study to assess the efficacy and safety of neoadjuvant-adjuvant durvalumab in combination with 5-FU + leucovorin + oxaliplatin + docetaxel (FLOT) chemotherapy, followed by adjuvant durvalumab monotherapy, in patients with resectable gastric cancer/gastroesophageal junction cancer (GC/GEJC).

	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		**Neoadjuvant period:** Two 4-week treatment cycles (durvalumab or placebo in combination with FLOT); Surgery period: Surgery to be performed 4 to 8 weeks after last dose of neoadjuvant therapy. **Adjuvant period**: Adjuvant therapy to begin 4 to 12 weeks post-surgery (based on the patient's recovery period), consisting of up to 12 4-week treatment cycles (durvalumab or placebo in combination with FLOT for 2 cycles, followed by durvalumab or placebo monotherapy for up to 10 cycles). Not applicable. Not applicable.
Hypothesis	Superiority		
Treatments groups	Treatment Arm A (D + FLOT):		Durvalumab 1500 mg on Day 1 + FLOT 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 1500 mg on Day 1 Q4W for 10 additional cycles (1 dose per cycle) (N=474).
	Treatment Arm B (Pbo + FLOT)		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 on Day 1 Q4W for 10 additional cycles (1 dose per cycle) (N=474).
Endpoints and definitions	Primary endpoint (Data Cut Off [DCO]2): Event-free survival	EFS	The time from randomization to the following whichever occurred first: RECIST 1.1 progression (by blinded independent central review [BICR]) that precludes surgery or requires non-protocol therapy during the neoadjuvant period; RECIST 1.1 progression/recurrence (by BICR) during the adjuvant period; non-RECIST progression that precludes surgery or requires non-protocol therapy during the neoadjuvant period, or discovered during surgery; progression/recurrence confirmed by biopsy post-surgery; or death due to any cause

	Key secondary endpoint (alpha controlled): Overall survival (DCO2)	OS	The time from the date of randomization until death due to any cause.
	Key secondary endpoint (alpha controlled): Pathological complete response rate (DCO1)	pCR rate	Proportion of patients who have no residual viable tumor in the resected specimens (primary tumor and all resected lymph nodes) as determined by central pathology review (performed according to College of American Pathologists (CAP)-modified Ryan tumor regression score).

Database lock	DCO3: 01 September 2025 (final analysis of OS). DCO2: 20 December 2024 (final analysis of EFS) DCO1: 01 February 2023 (assessment of pCR rate)		
Results and Analysis			
Analysis description	**Primary Analysis: EFS Based on BICR Assessment per RECIST 1.1 and/or Local Pathology Testing**		
Analysis population and time point description	Full analysis set (ITT population) Pre-specified Interim analysis (IA): planned for DCO2 to test for early superiority of Arm A vs Arm B in relation to EFS. This analysis was planned to be performed when approximately 41% EFS data maturity had been reached across both		
Descriptive statistics and estimate variability	Treatment group	D + FLOT	Pbo + FLOT
	Number of subjects	474	474
	Total EFS events, n (%)	167 (35.2%)	218 (46.0%)
	Median EFS [a] (95% confidence interval [CI])	NC (40.74 - NC)	32.82 (27.86 - NC)

Effect estimate per comparison	Comparison between groups	
	HR comparing durvalumab vs	0.71
	97.61% CI for HR [b]	0.56 - 0.89
	95% CI for HR [b]	0.58 - 0.86
	2-sided p-value [c]	< 0.001
Notes	[a] Calculated using the Kaplan-Meier method. [b] Estimated from a stratified Cox proportional hazards model stratified by geographic region, clinical lymph node status and PD-L1 expression status at randomization. An HR < 1 favors 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 PD-L1 expression level at randomization. Based on a Lan-DeMets alpha spending function with O'Brien Fleming boundary calculated using the actual number of EFS events at DCO2, the p-value boundary for declaring statistical significance was p < 0.0239. CI = confidence interval, D = durvalumab, EFS = event-free survival, FLOT = 5-FU + leucovorin + oxaliplatin + docetaxel, HR = hazard ratio, NC = not calculated, Pbo = placebo, PD-L1 = programmed cell death-ligand-1.	
Analysis description	**Key Secondary Analysis: Overall Survival**	
Analysis population and time point description	Full analysis set (ITT population) Final analysis (DCO3 01 September 2025).	

Descriptive statistics and estimate variability	Treatment group	D + FLOT	Pbo + FLOT
	Number of subjects	474	474
	Deaths, n (%)	160(33.8%)	192 (40.5%)
	Median OS (months) [a] 95% CI for median OS	NC (NC - NC)	NC (NC - NC)

Effect estimate per comparison	Comparison between groups	
	HR comparing durvalumab vs placebo [b]	0.78
	95% CI for HR [b]	0.50 - 1.20
	2-sided p-value [c]	0.021
Notes	[a] Calculated using the Kaplan-Meier method. [b] Estimated from a stratified Cox proportional hazards model stratified by geographic region, clinical lymph node status, and PD-L1 expression status at randomization. An HR < 1 favors 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 PD-L1 expression level at randomization. At DCO2, a fixed alpha spend of 0.01% (2-sided) was allocated to the IA of OS, corresponding to a p-value boundary for declaring statistical significance of 0.0001. CI = confidence interval, D = durvalumab, FLOT = 5-FU + leucovorin+ oxaliplatin + docetaxel, HR = hazard ratio, NC = not calculated, OS = overall survival, Pbo = placebo, PD-L1 = programmed cell death-ligand-1.	

Analysis description	**Secondary Analysis: Analysis of pCR rate** Pre-specified final pCR analysis performed at DCO1		
Analysis population and time point description	Full analysis set (ITT population) DCO1 was performed after all patients had been randomized and undergone surgical resection or been precluded from surgery. To provide a formal comparison of pCR rates by central pathology review, testing for superiority of the D + FLOT arm vs the Pbo + FLOT arm, using a fixed alpha spend of 0.1%.		
Descriptive statistics and estimate variability	Treatment group	D + FLOT	Pbo + FLOT
	Number of subjects	474	474
	Number of subjects with pCR (response) [a]	91	34
	Response rate (%)	19.2	7.2
	Response Rate 95% CI [b]	15.75 - 23.04	5.02 - 9.88
	Difference in response rate [c]	12.0	
Effect estimate per comparison	Comparison between groups [d]		
	Odds ratio comparing durvalumab vs placebo	3.08	
	95% CI	2.03 - 4.67	
	p-value	< 0.001	
Notes	[a] Patients achieve pCR if there is no residual viable tumor cells found at primary tumor and resected lymph nodes at the time of resection, meaning a pathological regression of -100%, based on central assessment. [b] 95% CIs for pCR rate were calculated using the Clopper-Pearson exact method. [c] Difference in response rate = D + FLOT response rate – Pbo + FLOT response rate. [d] Analysis performed using a stratified Cochran-Mantel-Haenszel test, stratified for geographic region, clinical lymph node status, and PD-L1 expression level at randomization. A fixed alpha of 0.1% (2 sided) was allocated to the analysis of pCR rate at DCO1, corresponding to a p-value boundary for declaring statistical significance of 0.001. CI = confidence interval, D = durvalumab, FLOT = 5-FU + leucovorin+ oxaliplatin + docetaxel, HR = hazard ratio, Pbo = placebo, pCR = pathological complete response, PD-L1 = programmed cell death-ligand-1.		

2.5.3. Discussion on clinical efficacy

Based on the results from the pivotal Matterhorn study (D910GC00001), the MAH is seeking extension of indication for the perioperative treatment of resectable GC/GEJC with the following wording:

IMFINZI in combination with FLOT chemotherapy as neoadjuvant and adjuvant treatment, followed by adjuvant IMFINZI monotherapy, is indicated for the treatment of adults with resectable gastric or gastro-oesophageal junction adenocarcinoma.

Design and conduct of clinical studies

The Matterhorn trial is a randomized, double-blind, placebo-controlled, multicenter, global phase III study. Patients with resectable GC/GEJC were randomized 1:1 to either standard of care, i.e. perioperative FLOT chemotherapy (four cycles of fluoruracil, leucoverin, oxaliplatin and docetaxel prior to and four cycles after surgery), or to durvalumab in combination with perioperative FLOT and continued with durvalumab monotherapy for 10 cycles. The primary endpoint of the trial was event free survival (EFS) assessed by BICR or confirmed by local pathology. The key secondary endpoints were overall survival (OS) and pathological complete response (pCR).

Patients were eligible if they had histologically confirmed adenocarcinoma of the stomach or gastroesophageal junction (Siewert types I, II or III), with resectable disease of AJCC 8th edition stage II or higher (defined as T2 or higher, N0-3, M0 or T0-4 N1-3 M0). Patients were required to be medically fit for treatment with neoadjuvant FLOT and to have an ECOG performance status of 0 or 1.

The selection criteria appropriately reflect the target population, i.e. patients with resectable GC/GEJC who are candidates for curative surgery and medically fit to receive perioperative FLOT chemotherapy. The population is heterogeneous, both regarding prognosis (3-year survival 70%-10% in stage IIA-IVA; Haejin Ann Surg Oncol 2017) and PD-L1 expression. However, the selection criteria encompass all patients who would be candidates for the same perioperative treatment, i.e. FLOT, which represents a standard of care option in the curative setting for GC/GEJC (ESMO Guideline - Lordick et al. 2022) in Europe.

For patients with Siewert type I and II GEJC, another standard of care option is neoadjuvant chemoradiotherapy followed by surgical resection and adjuvant nivolumab (ESMO guideline - Lordick et al. 2022).

Patients were stratified at randomization according to geographical region (Asia versus non-Asia), clinical lymph node status (positive or negative) and PD-L1 expression status (TAP <1% and TAP ≥ 1%). The stratification factors are considered acceptable, as they respectively reflect potential regional differences, known prognostic factors and a possible predictive role for response to PD-L1 inhibition.

The study design does not allow to disentangle the contribution of durvalumab to each treatment phase or a distinction of the effect contribution of a prolonged (maintenance) treatment with durvalumab monotherapy. Support for the perioperative setting if further informed from other clinical study results, such as the FLOT4-AIO, CHECKMATE-577, KEYNOTE-585 and ATTRACTION-5 (Kelly et al. 2021, Shitara et al. 2024, Kang et al. 2024). It is acknowledged that perioperative chemotherapy consisting of a neoadjuvant and an adjuvant phase for resectable GC/GEJC is supported by clinical evidence and has long represented the standard of care in Europe (Al-Batran et al. 2016, Kang et al. 2024, Lordick et al. 2022). It is also acknowledged that maintenance immunotherapy for one year has been investigated, however, these trials have similarly not allowed for the specific contribution of an adjuvant maintenance to be clearly established. In the Matterhorn study, the design does not allow separation of the effects of perioperative treatment from those of prolonged adjuvant durvalumab monotherapy, and therefore the contribution, if any, of the adjuvant maintenance phase to the observed efficacy remains uncertain.

Scientific advice

The MAH received scientific advice from EMA in March 2019. It was pointed out that the trial would not allow assessment of the contribution of a prolonged treatment with durvalumab as monotherapy. The CHMP found that the primary endpoint of EFS as defined, was acceptable. EMA

further advised that if an increased proportion of cured patients could not be inferred from the EFS data, the benefit-risk evaluation would require evidence of an OS benefit. Overall, the CHMP agreed to the trial design, population and endpoints, but criticized the study design for not being able to show the effect contribution of the durvalumab maintenance phase.

PD-L1 expression classification

Patients provided a FFPE tumour sample at screening to determine PD-L1 expression at central laboratory level pre-randomization. PD-L1 expression level was assessed by the TAP scoring method using the VENTANA PD-L1 (SP263) CDx Assay. The TAP score is defined as the proportion of tumour area occupied by tumour cells with membrane and immune cells with cytoplasmic/ membrane PD-L1 staining. The cut-off value of **TAP** at 1% was selected based on available evidence at the time of study initiation, which suggested that PD-L1 expression at a **CPS** ≥ 1 could be associated with a relative benefit from immune checkpoint inhibitors in GC/GEJC. Furthermore, available evidence showed, that when immune checkpoint inhibition was combined with chemotherapy, the median OS was similar for patients with PD-L1 CPS ≥ 1 and CPS ≥ 10 (KEYNOTE-059 study and KEYNOTE-062 study, Wainberg et al 2017, Shitara et al 2020). Studies ascertaining the concordance between the CPS method and the TAP method were not available at the time of initiation of the Matterhorn study, however the two methods were considered similar, since both methods combine the evaluation of both tumour and immune cell PD-L1 expression. Subsequently, Liu et al. (2023) showed high concordance between both methods across PD-L1 cut-offs (>85%) for gastric and oesophageal adenocarcinoma, with similar findings reported by Klempner et al. (2024). In addition, similar clinical outcomes in terms of OS, PFS, ORR, and duration of response were observed between TAP-defined and CPS-defined PD-L1-positive subgroups at analogous cut-offs in a recent study of tislelizumab in gastric and oesophageal cancer (Moehler et al 2025, Tevimbra EPAR, EMEA/H/C/005919/II/0006). Taken together, these data support the use of the TAP algorithm for the assessment of PD-L1 expression in the Matterhorn trial.

Study conduct

Protocol amendments were carried out in response to recommendations from regulatory agencies and to international clinical practice guidelines. The amendments were made prior to the date of DCO2 with version 3.0 (dated 4 March 2024) being the last amended version. Long-term follow-up for up to 5 years was allowed after final analysis and in version 3.0, the rule of censoring patients who had missed 2 consecutive visits was removed, and instead a sensitivity analysis applying this removed censoring rule, was added. The amendments inferred to the protocol are considered appropriate.

The number of important protocol deviations (IPD) is considered low: a total of 6.1% had IPD and only 1 patient in the control arm violated inclusion criteria. Six patients in the control arm versus one patient in the durvalumab arm violated exclusion criteria. Considering the nature and low amount of IPD, any impact on the overall trial results is considered unlikely.

Patient disposition and flow

No important differences in completion of neoadjuvant treatment, surgery or adjuvant treatment are observed in the two treatment arms of the Matterhorn study.

In the neoadjuvant phase the number of patients who discontinued chemotherapy (FLOT) was approximately 7% in the control arm versus approximately 5.5% in the durvalumab arm. No difference was seen in the completion rate of neoadjuvant FLOT, which was approximately 94%. Almost all patients (96%) completed all planned cycles of durvalumab during the neoadjuvant phase, with a similar proportion of patients completing placebo. The treatment arms were balanced

with regards to the proportion of patients who did not proceed to surgery (approximately 9.4%), as well as with regard to the specific reasons for not attempting surgery. A slightly higher number of patients in the control arm did not complete surgery due to peritoneal dissemination found upon surgery (10 versus 15 patients), which is not considered noteworthy.

Of the patients who completed surgery, approximately 12% in each treatment arm did not initiate adjuvant treatment. The reasons for not starting adjuvant therapy were diverse and generally balanced between treatment arms. Death prior to initiation of adjuvant therapy was reported for 11 patients in the durvalumab arm versus 8 patients in the control arm.

In the adjuvant phase, a slightly higher proportion of resected patients in the control arm (70%) than in the durvalumab arm (63%) completed all adjuvant FLOT treatment. Adjuvant durvalumab treatment was completed by 68% and 70% completed placebo. Approximately 50% of the FAS completed all eight cycles of planned chemotherapy FLOT.

The proportions of patients who discontinued FLOT in the neoadjuvant phase and did not have surgery, are aligned with the results from the FLOT arm in the FLOT4-AIO study (Al-Batram et al. 2016), in which these numbers were approximately 6% respectively. The proportion of resected patients who did not start adjuvant FLOT was higher (approximately 32%) in the FLOT4-AIO study than in the Matterhorn study. In the FLOT4-AIO study approximately 40% of included patients completed all 8 cycles of FLOT. Overall, the results of the Matterhorn study do not indicate a detriment on completion of surgery or perioperative treatment due to the addition of durvalumab.

Baseline demographics and disease characteristics

The treatment arms were well balanced with regards to sex, race, ECOG PS status and geographical region. Non-Asian patients accounted for 81% of the patient population and there were 66 European sites (out of 159 sites globally), thus ensuring broad inclusion of European patients. Age < 65 years was not equally distributed in the two treatment arms, since this group was overrepresented in the experimental arm with an approximately 11% difference (35.7% vs. 46.4%), mainly due to a larger group of subjects with age < 50 years (18% vs. 12%). This is, however, not considered likely to have impacted the overall results.

Disease characteristics were also well balanced with regards to lymph-node status, microsatellite instability (MSI) status, PD-L1 expression level, primary tumour location and histology type. Primary tumour stage was equally distributed between the treatment arms.

With respect to the PD-L1 expression, a large majority of patients in the FAS (90%) were categorized as PD-L1 positive (TAP ≥1), resulting in a relatively small PD-L1 negative subgroup for efficacy analysis (10%).

With respect to disease stage, more than half of the patients in the FAS (66.2%) had T3 tumours and stage III disease according to AJCC classification (61.7%), which is considered representative of the resectable GC/GEJC population for which the indication is sought (Plum et al. 2023 DOI: 10.1007/s00432-023-04719-w). Similar stage distribution was observed in the KEYNOTE-585 study (Shitara et al. 2024). The majority (67.5%) had the stomach as the primary tumour location, whereas the GEJC was the primary location in 32.5%, similar to what is seen in previous perioperative studies in this setting (Plum et al. 2023). Stage IV-A was present in 8.8% of patients.

The proportion with MSI high status was 5%, which is in line with the incidence seen in resectable GC populations (Pietrantonio et al. 2019 DOI: 10.1200/JCO.19.01124).

Statistical methods

The choice of EFS as the primary endpoint is supported by published meta-analyses (DOI: 10.1158/1078-0432.CCR-22-2920) demonstrating a reasonable correlation between EFS and OS in the GC/GEJC setting.

Patients who progressed during the neoadjuvant phase but remained resectable were not counted as having an event for the purpose of the EFS analysis. These patients continued in the study, underwent surgery, and only contributed an event if they later experienced disease recurrence, progression, or death.

A treatment policy strategy was used for the handling of non-protocol anticancer therapy initiated without documented disease progression. Censoring was driven almost entirely by patients who consent withdrawals were rare and balanced between arms, indicating a low risk of informative censoring.

The key secondary objectives are to compare Arm A versus Arm B in terms of OS, and pCR rate.

The FAS was used for all efficacy analyses and patients were analysed in accordance with randomisation regardless of actual treatment received. Patients randomized but not treated were included. This is endorsed as it aligns with the ITT principle

At DCO2 all study personnel was unblinded after clinical data lock. EFS was analysed at IA2 (DCO2) after clinical data lock and IDMC confirmation. The confirmatory EFS assessment was completed at DCO2, while OS was designated as the sole endpoint to be formally tested at the final (primary) analysis. As study personnel were unblinded only after DCO2, the confirmatory EFS result was not affected by unblinding, and death events for OS were ascertained objectively under the pre-specified SAP to mitigate potential bias.

EFS and OS were analysed using a stratified log-rank test and a stratified Cox PH model.

Visual inspection of the Kaplan–Meier curves suggest a durable, non-crossing separation between treatment arms, with no indication of a material violation of the proportional hazards assumption.

Sensitivity analyses were performed for EFS, including but not limited to, analyses addressing potential ascertainment bias by using investigator assessment in place of BIRC assessment. Additional sensitivity analyses addressed potential evaluation time bias, censoring of patients who initiated non-protocol anticancer therapy without documented disease progression and censoring of events after 2 missed RECIST assessments. These sensitivity analyses are deemed relevant to establish robustness of the primary analysis.

Subgroup analyses included sex (male vs. female), age at randomization (<65 vs. ≥65 years of age) and the stratification factors from the randomisation.

Efficacy data and additional analyses

Endpoint Results

The Matterhorn trial met its primary endpoint, EFS assessed by BICR. At the DCO date of the primary EFS analysis **IA2** (DCO2: 20 December 2024), a total of 385 EFS events had occurred across the 2 treatment arms in the FAS population, corresponding to 40.6% maturity, i.e. approximately 83% information fraction (385/461), with 167 events (35.2%) in the D + FLOT arm and 218 events (46%) in the placebo + FLOT arm.

Median EFS was not reached in the experimental arm and was 32.5 months in the placebo arm. The absolute improvement in EFS at the time of DCO was 10.8%, with a HR of 0.71 (95% CI: 0.58, 0.86; 2-sided p-value < 0.001). At DCO the median follow-up was 26.79 (0.03-48.10) months in

the durvalumab arm and 25.82 (0.02-48.07) in the placebo arm and ~57% of the FAS had 2 years of follow-up.

The **final OS** analysis was conducted at DCO3 (01 September 2025, data maturity of 37.1% [352/948]) and showed a statistically significant improvement in OS with the addition of durvalumab, with a HR of 0.78 (95% CI: 0.63, 0.96; 2-sided p-value = 0.021). At the DCO3 date, 160 patients (33.8%) had died from any cause in the D + FLOT arm vs 192 patients (40.5%) in the Pbo + FLOT arm.

Median OS was not reached in either arm (95% CI: NC, NC), while the median OS for the placebo arm was 47.21 months. Because of immaturity of OS data, less than 11 subjects were at risk at the time of empirical median OS. For this reason, the median OS estimate is considered to be of limited quality. After approximately 13 months post-randomization, there is a separation in the KM curves of OS in favour of the D + FLOT arm.

The pCR rate by central pathology review was a key secondary endpoint at DCO1 (1 February 2023). The pCR rate per central pathology review was 19.2% (95% CI: 15.75 to 23.04) in the D + FLOT arm and 7.2% (95% CI: 5.02 to 9.88) in the Pbo + FLOT arm, which corresponds to a difference in pCR rate of 12.0% (odds ratio: 3.08 [95% CI: 2.03, 4.67]; p < 0.001).

The effect of neoadjuvant durvalumab on the pCR rate was observed across all subgroups, with the exception of the PD-L1 negative subgroup where HR was 0.98 (95% CI: 0.19-5.11). Of note, the FLOT4-AIO study showed a pCR rate of 16% in the FLOT arm vs 6% in the control arm (Al-Batran et al 2016), however there were differences in the criteria for pCR evaluation in the FLOT4-AIO study (used the Becker criteria) and the Matterhorn study (used CAP-modified Ryan criteria), as well as regional differences and baseline differences which plausibly explain the different results in pCR in the FLOT only arm.

No difference in surgical outcomes was observed between the two treatment arms. Secondary efficacy endpoints including DFS and MFS favoured the durvalumab arm. There were no clinically meaningful differences between the treatment arms with regards to patient reported outcomes (PROs).

Subgroup analyses

Overall, across most analysed subgroups, the EFS and OS results were consistent with those observed in the FAS, however with some variability between subgroups.

<u>Lymph node status</u>

A clinically positive lymph node status was present in 70.5% of patients and in this subgroup the EFS analysis showed a HR of 0.67 (95% CI 0.53-0.87). For the complementary and smaller subgroup, i.e. the prognostically better lymph node negative group (140 patients in each arm), the EFS analysis showed a HR of 0.85 (95% CI 0.57 -1.27), indicating a smaller absolute magnitude of benefit. Efficacy in the lymph node negative subgroup is supported by a statistically significant pCR result in the FAS (DCO1). No OS effect is observed in the lymph node negative subgroup with the addition of durvalumab (HR = 1.01 [95% CI: 0.67, 1.51]).

The subgroup analysis according to clinical lymph node status was pre-planned and predefined. Clinical lymph node status was also a stratification factor. Given the substantial size of the subgroup and the well-established prognostic differences associated with lymph node status, the results are considered informative.

The analyses indicate that the absolute magnitude of benefit associated with the addition of durvalumab is smaller in patients with lymph node-negative disease compared with those with

lymph node positive disease. This information is considered relevant for prescribers and is therefore reflected in section 5.1 of the SmPC.

PD-L1 expression

It is biologically plausible that the treatment effect of durvalumab would increase with increasing PD-L1 expression, and this would be consistent with the pCR analysis. In this analysis, no clear effect was observed in the PD-L1 negative subgroup (HR 0.98; 95% CI: 0.19-5.11), while a more pronounced effect was observed in the PD-L1 positive subgroup (HR 0.70; CI: 0.57-0.87).

Furthermore, evidence from clinical trials in the metastatic GC/GEJC setting has suggested an association between increasing level of PD-L1 expression and greater benefit from immunotherapy (the CheckMate 649 trial and KEYNOTE-590 trial).

The MAH investigated the impact of different PD-L1 expression cut-offs on EFS. Across the different cut-offs (TAP ≥ 5% and TAP ≥10%), HR were consistently in a similar range with 95% CI below 1. A greater treatment effect was observed in the PD-L1 >10% subgroup (HR of 0.57; 95% CI 0.35 – 0.92).

The OS subgroup analyses according to PD-L1 expression showed HR point estimates between 0.78 and 0.80 across the pre-specified TAP ≥1% subgroups and the exploratory TAP subgroups defined by cut-offs of 5% and 10%. These results indicate a generally consistent OS treatment effect of durvalumab across the PD-L1 expression levels evaluated.

Overall, the data in the Matterhorn trial do not allow for firm conclusions regarding PD-L1 expression as a predictive marker of treatment effect of durvalumab in the perioperative setting, which may be in part due to the small size of the PD-L1-negative subgroup. Therefore, restriction of the indication based on PD-L1 expression is not justified, and an all-comer population can be supported.

2.5.4. Conclusions on the clinical efficacy

In the Matterhorn trial a statistically significant benefit in EFS was shown at IA2 with the addition of durvalumab to perioperative FLOT in patients with resectable GC/GEJC. OS, a key secondary endpoint, also reached statistical significance at the final analysis (data maturity 37.1%), with a HR of 0.78 (95% CI: 0.63, 0.96) in favour of durvalumab. The findings are consistent with the results observed for the exploratory endpoints of DFS and MFS. The observed improvement in EFS was generally consistent across most pre-defined subgroups. The trial design does not allow to disentangle the contribution of durvalumab to each treatment phase and the study does not assess the optimised duration of adjuvant therapy.

2.6. Clinical safety

2.6.1. Introduction

The pivotal safety dataset consists of 944 patients, who were randomized and received at least 1 dose of study treatment: 475 patients in the D + FLOT arm and 469 patients in the Pbo + FLOT arm. The safety DCO was 20 December 2024.

It should be noted that 1 patient randomized to the placebo + FLOT arm received a single dose of durvalumab and, as a result, is included in the D + FLOT arm for the safety analyses. Furthermore, 4 patients in the Full Analysis Set, who were randomized to the placebo + FLOT arm did not receive any study treatment despite being randomized and, as a result, are not included in the safety dataset.

2.6.2. Patient exposure

For the dosing schedule and study periods in the MATTERHORN study, see Figure 3.

Table 30 Summary of study treatment exposure (Safety Analysis Set)

Parameter		MATTERHORN				D pantumor pool
		Overall study [a]		Adjuvant monotherapy period		
		D + FLOT (N = 475)	Pbo + FLOT (N = 469)	D + FLOT (N = 345)	Pbo + FLOT (N = 331)	D (N = 4642)
Total number of infusions	N	475	469	345	331	4642
	Mean (SD)	9.64 (5.243)	9.52 (5.321)	8.65 (2.727)	8.75 (2.590)	11.17 (11.139)
	Median (min, max)	14.0 (1.0, 14.0)	14.0 (1.0, 14.0)	10.0 (1.0, 12.0)	10.0 (1.0, 12.0)	6.0 (1.0, 76.0)
Total treatment duration (weeks) [b]	N	475	469	345	331	4642
	Mean (SD)	40.72 (22.048)	40.10 (22.468)	35.59 (11.236)	36.03 (10.644)	32.79 (39.096)
	Median (min, max)	56.0	56.0	40.0	40.0	18.0 (0.4, 300.0)
	Patient-years exposure [c]	370.7	360.4	235.3	228.5	2917.5

[a] The overall study includes the neoadjuvant, surgery, and adjuvant overall periods. The adjuvant monotherapy period is contained within the adjuvant overall period of the study and is shown here for the purpose of safety analysis. No study treatment was administered during the surgery period.

[b] Total treatment duration = (last dose date + X days or death date or DCO whichever occurs earlier - first dose date + 1)/7. X is defined as the planned frequency in dosing (in days) - 1. For Q4W, X = 27. For Q2W, X = 13.

[c] Patient-years exposure = total treatment duration × 7/365.25 where treatment duration = (last dose date + X days or death date or DCO whichever occurs earlier- first dose date + 1)/7. X is defined as the planned frequency in dosing (in days) - 1. For Q4W, X = 27. For Q2W, X = 13.

Table 31 Duration of exposure to durvalumab/placebo (Safety Analysis Set, DCO2)

Exposure characteristic		D + FLOT (N = 475)	Pbo + FLOT (N = 469)	Total (N = 944)
Overall study	**n**	**475**	**469**	**944**
Total overall treatment duration (months) [a]	Mean (StDev)	9.36 (5.071)	9.22 (5.167)	9.29 (5.117)
	Median (min, max)	12.88 ( )	12.88 ( )	12.88 (0.3, 17.7)
	Total treatment years	370.7	360.4	731.0
Actual overall treatment duration (months) [a]	Mean (StDev)	8.87 (4.843)	8.77 (4.908)	8.82 (4.873)
	Median (min, max)	12.68 ( )	12.48 ( )	12.65 (0.3, 13.4)
	Total treatment years	351.2	342.9	694.1
Neoadjuvant period	**n**	**475**	**469**	**944**
Total neoadjuvant treatment duration (months) [b]	Mean (StDev)	1.91 (0.265)	1.89 (0.306)	1.90 (0.286)
	Median (min, max)	1.84 ( )	1.84 ( )	1.84 (0.3, 3.0)
	Total treatment years	75.5	73.7	149.3
Actual neoadjuvant treatment duration (months) [c]	Mean (StDev)	1.81 (0.191)	1.79 (0.228)	1.80 (0.210)
	Median (min, max)	1.84 ( )	1.84 ( )	1.84 (0.3, 2.0)
	Total treatment years	71.6	69.9	141.5

Exposure characteristic		D + FLOT (N = 475)	Pbo + FLOT (N = 469)	Total (N = 944)
Adjuvant overall period	**n**	**361**	**349**	**710**
Total adjuvant treatment duration (months) [b]	Mean (StDev)	9.81 (3.167)	9.86 (3.146)	9.83 (3.155)
	Median (min, max)	11.20 ( )	11.20 ( )	11.20 (0.4, 15.7)
	Total treatment years	295.1	286.6	581.8
Actual adjuvant treatment duration (months) [c]	Mean (StDev)	9.30 (3.067)	9.38 (2.999)	9.34 (3.032)
	Median (min, max)	11.04 ( )	11.04 ( )	11.04 (0.4, 11.5)
	Total treatment years	279.7	272.9	552.6
Adjuvant monotherapy period	**n**	**345**	**331**	**676**
Total adjuvant monotherapy treatment duration (months) [b]	Mean (StDev)	8.19 (2.584)	8.29 (2.448)	8.23 (2.517)
	Median (min, max)	9.20 ( )	9.20 ( )	9.20 (0.7, 13.3)
	Total treatment years	235.3	228.5	463.9
Actual adjuvant monotherapy treatment duration (months) [c]	Mean (StDev)	7.95 (2.521)	8.05 (2.388)	8.00 (2.456)
	Median (min, max)	9.20 ( )	9.20 ( )	9.20 (0.7, 11.2)
	Total treatment years	228.6	222.1	450.7

[a] Total/actual overall exposure was calculated as the sum of the neoadjuvant and adjuvant total/actual exposure.
[b] Total (intended) durvalumab/placebo exposure = (min (last durvalumab/placebo dose date in period where dose > 0 mg + 27), date of death or DCO) – first durvalumab/placebo date in period + 1)/30.4375.
[c] Actual durvalumab/placebo exposure = intended exposure – total duration of dose delays. A dose delay is defined as any length of time (days) where a patient has not taken any of the planned dose. The duration of dose delays are calculated as the sum of (date of dose – date of previous dose – 28 days). If a patient permanently discontinues durvalumab/placebo during a dose delay, then the date of last administration of study treatment recorded is used for exposure calculations.
DCO: 20 December 2024.

Table 32 Duration of exposure to any FLOT (Safety Analysis Set, DCO2)

Exposure characteristic		**D + FLOT (N = 475)**	**Pbo + FLOT (N = 469)**	**Total (N = 944)**
Overall study	**n**	**475**	**469**	**944**
Total overall treatment duration (months) [a]	Mean (StDev)	3.36 (1.023)	3.34 (1.076)	3.35 (1.049)
	Median (min, max)	3.71 ( )	3.71 ( )	3.71 (0.3, 6.0)
	Total treatment years	132.9	130.5	263.4
Actual overall treatment duration (months) [a]	Mean (StDev)	3.08 (0.896)	3.07 (0.935)	3.07 (0.915)
	Median (min, max)	3.68 ( )	3.68 ( )	3.68 (0.3, 4.0)
	Total treatment years	121.8	120.1	241.9
Neoadjuvant period	**n**	**475**	**469**	**944**
Total neoadjuvant treatment duration (months) [b]	Mean (StDev)	1.94 (0.307)	1.92 (0.355)	1.93 (0.332)
	Median (min, max)	1.87 ( )	1.87 ( )	1.87 (0.3, 3.2)
	Total treatment years	76.9	75.0	151.9
Actual neoadjuvant treatment duration (months) [c]	Mean (StDev)	1.80 (0.219)	1.79 (0.268)	1.80 (0.245)
	Median (min, max)	1.84 ( )	1.84 ( )	1.84 (0.3, 2.1)
	Total treatment years	71.4	69.9	141.3
Adjuvant overall period	**n**	**354**	**345**	**699**
Total adjuvant treatment duration (months) [b]	Mean (StDev)	1.90 (0.473)	1.93 (0.441)	1.91 (0.458)
	Median (min, max)	1.87 ( )	1.87 ( )	1.87 (0.4, 3.7)
	Total treatment years	56.0	55.4	111.4

Exposure characteristic		D + FLOT (N = 475)	Pbo + FLOT (N = 469)	Total (N = 944)
Actual adjuvant treatment duration (months) [c]	Mean (StDev)	1.71 (0.353)	1.74 (0.320)	1.73 (0.338)
	Median (min, max)	1.84 ( )	1.84 ( )	1.84 (0.4, 2.1)
	Total treatment years	50.4	50.2	100.6

[a] Total/actual overall exposure was calculated as the sum of the neoadjuvant and adjuvant total/actual exposure.

[b] Total (intended) FLOT exposure = (min(last FLOT dose date in period where dose > 0 mg + 13, date of death or DCO) - first FLOT date in period + 1)/30.4375.

[c] Actual exposure = intended exposure - total duration of dose delays. A dose delay is defined as any length of time (days) where a patient has not taken any of the planned dose. The duration of dose delays are calculated as the sum of (date of dose - date of previous dose - 14 days). If a patient permanently discontinued the treatment during a dose delay, then the date of last administration of study treatment recorded was used for exposure calculations.

DCO: 20 December 2024.

Table 33 Treatment cycles received of durvalumab or placebo and any FLOT administration (Safety Analysis Set; DCO2)

	D + FLOT (N = 475)		Pbo + FLOT (N = 469)	
	Durvalumab	Any FLOT	Placebo	Any FLOT
Neoadjuvant treatment cycles / FLOT administrations				
Number of patients	475	475	469	469
Mean	2.0	3.9	2.0	3.9
Median	2.0	4.0	2.0	4.0
Q1	2.0	4.0	2.0	4.0
Q3	2.0	4.0	2.0	4.0
Cumulative neoadjuvant cycles / FLOT administrations received, n (%)				
None	0	0	0	0
≥ 1 cycle	475 (100)	475 (100)	469 (100)	469 (100)
Cycle 1 Day 1	NA	475 (100)	NA	469 (100)
Cycle 1 Day 15	NA	469 (98.7)	NA	459 (97.9)
2 cycles	461 (97.1)	462 (97.3)	451 (96.2)	452 (96.4)
Cycle 2 Day 1	NA	462 (97.3)	NA	452 (96.4)
Cycle 2 Day 15	NA	456 (96.0)	NA	446 (95.1)
Adjuvant treatment cycles / FLOT administrations				
Number of patients [a, b]	361	354	349	345
Mean [a]	10.1	3.7	10.2	3.8
Median [a]	12.0	4.0	12.0	4.0

	D + FLOT (N = 475)		Pbo + FLOT (N = 469)	
	Durvalumab	Any FLOT	Placebo	Any FLOT
Q1 [a]	9.0	4.0	10.0	4.0
Q3 [a]	12.0	4.0	12.0	4.0
Cumulative adjuvant cycles / FLOT administrations received, n (%)				
None	114 (24.0)	121 (25.5)	120 (25.6)	124 (26.4)
≥ 1 cycle	361 (76.0)	354 (74.5)	349 (74.4)	345 (73.6)
Cycle 3 Day 1	NA	354 (74.5)	NA	345 (73.6)
Cycle 3 Day 15	NA	341 (71.8)	NA	333 (71.0)
≥ 2 cycles	348 (73.3)	318 (66.9)	336 (71.6)	319 (68.0)
Cycle 4 Day 1	NA	318 (66.9)	NA	319 (68.0)
Cycle 4 Day 15	NA	292 (61.5)	NA	302 (64.4)
≥ 3 cycles	343 (72.2)	NA	331 (70.6)	NA
≥ 4 cycles	331 (69.7)	NA	322 (68.7)	NA
≥ 5 cycles	321 (67.6)	NA	310 (66.1)	NA
≥ 6 cycles	310 (65.3)	NA	304 (64.8)	NA
≥ 7 cycles	297 (62.5)	NA	294 (62.7)	NA
≥ 8 cycles	284 (59.8)	NA	282 (60.1)	NA
≥ 9 cycles	276 (58.1)	NA	271 (57.8)	NA
≥ 10 cycles	269 (56.6)	NA	262 (55.9)	NA
≥ 11 cycles	263 (55.4)	NA	256 (54.6)	NA
12 cycles	246 (51.8)	NA	240 (51.2)	NA

[a] Includes patients who received at least 1 adjuvant treatment cycle.
[b] Due to language in the CSP that has since been updated, 14 patients discontinued adjuvant durvalumab/placebo monotherapy treatment prematurely, 48 weeks after the start of adjuvant therapy rather than 52 weeks; these were recorded as non-important protocol deviations. Eight (2.3%) patients were in the D + FLOT arm, and 6 (1.8%) patients were in the Pbo + FLOT arm (Table 14.1.1).

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.
DCO2: 20 December 2024.

2.6.3. Adverse events

Safety data are presented for the following periods and pools:

The overall study of MATTERHORN includes TEAEs from the first dose of study treatment until the earliest of: last dose of study treatment + 90 days, date of withdrawal of consent, date of first dose of subsequent anti-cancer therapy (excluding palliative radiotherapy), date of death, or date of DCO.

- The adjuvant monotherapy period of MATTERHORN includes TEAEs from the first dose of adjuvant durvalumab/placebo monotherapy after the last dose of FLOT in adjuvant period had been administered (or the start of adjuvant durvalumab/placebo in patients who did not receive adjuvant FLOT), until the earliest of: date of last dose of adjuvant treatment + 90 days, date of first dose of subsequent anti-cancer therapy (excluding palliative radiotherapy), date of death, or date of DCO.

- The D pan-tumor pool includes TEAEs observed until 90 days following the last dose of study treatment or until the initiation of the first subsequent anti-cancer therapy (excluding palliative radiotherapy), following the last dose of study treatment, whichever occurred first.

Table 34 Demographic and baseline characteristics (Safety Analysis Set)

Parameter	Number (%) of patients		
	MATTERHORN		D pan-tumor pool
	D + FLOT (N = 475)	Pbo + FLOT (N = 469)	D (N = 4642)
Age (years)			
Mean (SD)	59.9 (11.52)	61.5 (10.12)	61.9 (10.69)
Median (min, max)	62.0	63.0	63.0 (19, 96)
Age group (years), n (%)			
< 50	86 (18.1)	57 (12.2)	537 (11.6)
≥ 50 to < 65	205 (43.2)	207 (44.1)	2089 (45.0)
≥ 65 to < 75	147 (30.9)	163 (34.8)	1542 (33.2)
≥ 75	37 (7.8)	42 (9.0)	474 (10.2)
< 65	291 (61.3)	264 (56.3)	2626 (56.6)
≥ 65	184 (38.7)	205 (43.7)	2016 (43.4)
Sex, n (%)			
Male	327 (68.8)	351 (74.8)	3229 (69.6)
Female	148 (31.2)	118 (25.2)	1413 (30.4)
Race, n (%)			
White	322 (67.8)	319 (68.0)	2892 (62.3)
Black/African American	7 (1.5)	3 (0.6)	85 (1.8)
Asian	96 (20.2)	95 (20.3)	1514 (32.6)
Other	26 (5.5)	28 (6.0)	74 (1.6)
Missing	24 (5.1)	24 (5.1)	77 (1.7)
Geographic region, n (%)			
Asia	90 (18.9)	88 (18.8)	1422 (30.6)
Europe	257 (54.1)	248 (52.9)	1924 (41.4)
North America	42 (8.8)	39 (8.3)	1246 (26.8)
South America	86 (18.1)	94 (20.0)	50 (1.1)
Non-Asia Regions	385 (81.1)	381 (81.2)	3220 (69.4)
ECOG/WHO PS, n (%) [a,b]			
0	338 (71.2)	362 (77.2)	1845 (39.7)
≥ 1	137 (28.8)	107 (22.8)	2792 (60.1)
Missing	0	0	5 (0.1)

[a] MATTERHORN, Study 1108, Japan Study 02, DANUBE, Study 22, HIMALAYA, ADRIATIC, and PEARL collected ECOG PS. ARCTIC, ATLANTIC, MYSTIC and PACIFIC collected WHO PS. EAGLE, CONDOR, HAWK, and KESTREL collected both ECOG PS and WHO PS, with the latest test being used for analysis.

[b] ECOG/ WHO PS (0) = normal activity, (1) = restricted activity, (2) = in bed ≤ 50% of the time, (3) = in bed > 50% of the time, (4) = 100% bedridden, (5) = death.

Table 35 Overview of adverse events by Category (Safety analysis set)

Parameter	Number (%) of patients [a]								
	MATTERHORN								D pantumor pool
	Overall study [b]		Neoadjuvant period		Adjuvant overall period		Adjuvant monotherapy period		
	D + FLOT (N = 475)	Pbo + FLOT (N = 469)	D + FLOT (N = 475)	Pbo + FLOT (N = 469)	D + FLOT (N = 365)	Pbo + FLOT (N = 351)	D + FLOT (N = 345)	Pbo + FLOT (N = 331)	D (N = 4642)
Any AE	471 (99.2)	463 (98.7)	458 (96.4)	447 (95.3)	353 (96.7)	338 (96.3)	274 (79.4)	260 (78.5)	4381 (94.4)
Any AE possibly related to any study treatment [c]	453 (95.4)	444 (94.7)	435 (91.6)	427 (91.0)	332 (91.0)	303 (86.3)	172 (49.9)	120 (36.3)	2711 (58.4)
Any AE possibly related to durvalumab/placebo [c]	282 (59.4)	244 (52.0)	173 (36.4)	165 (35.2)	196 (53.7)	145 (41.3)	137 (39.7)	83 (25.1)	2711 (58.4)
Any AE possibly related to any FLOT (at least 1 drug) [c]	450 (94.7)	438 (93.4)	430 (90.5)	423 (90.2)	317 (86.8)	289 (82.3)	77 (22.3)	56 (16.9)	N/A
Any AE of maximum CTCAE Grade 3 or 4 [d]	340 (71.6)	334 (71.2)	223 (46.9)	226 (48.2)	195 (53.4)	207 (59.0)	73 (21.2)	68 (20.5)	1782 (38.4)
Any AE of maximum CTCAE Grade 3 or 4, possibly related to any study treatment [c,d]	283 (59.6)	277 (59.1)	193 (40.6)	200 (42.6)	158 (43.3)	162 (46.2)	31 (9.0)	30 (9.1)	540 (11.6)
Any AE of maximum CTCAE Grade 3 or 4, possibly related to durvalumab/placebo [c,d]	67 (14.1)	58 (12.4)	30 (6.3)	25 (5.3)	31 (8.5)	38 (10.8)	19 (5.5)	19 (5.7)	540 (11.6)
Any AE of maximum CTCAE Grade 3 or 4, possibly related to any FLOT (at least 1 drug) [c,d]	272 (57.3)	268 (57.1)	189 (39.8)	199 (42.4)	145 (39.7)	148 (42.2)	13 (3.8)	15 (4.5)	N/A
Any TEAE with outcome of death [f]	23 (4.8)	20 (4.3)	9 (1.9)	8 (1.7)	7 (1.9)	8 (2.3)	5 (1.4)	7 (2.1)	267 (5.8)
Any TEAE with outcome of death, possibly related to any study treatment [c]	6 (1.3)	2 (0.4)	4 (0.8)	1 (0.2)	2 (0.5)	1 (0.3)			33 (0.7)
Any TEAE with outcome of death, possibly related to durvalumab/placebo [c]	3 (0.6)	1 (0.2)			2 (0.5)	1 (0.3)			33 (0.7)
Any TEAE with outcome of death, possibly related to any FLOT (at least 1 drug) [c]	3 (0.6)	2 (0.4)	3 (0.6)	1 (0.2)			0	0	N/A
Any SAE (including events with outcome of death) [e]	229 (48.2)	207 (44.1)	99 (20.8)	86 (18.3)	105 (28.8)	91 (25.9)	50 (14.5)	48 (14.5)	1657 (35.7)
Any SAE (including events with outcome of death), possibly related to any study treatment [c,e]	108 (22.7)	79 (16.8)	53 (11.2)	48 (10.2)	52 (14.2)	34 (9.7)	13 (3.8)	6 (1.8)	370 (8.0)

Parameter	Number (%) of patients [a]								
	MATTERHORN								D pantumor pool
	Overall study [b]		Neoadjuvant period		Adjuvant overall period		Adjuvant monotherapy period		
	D + FLOT (N = 475)	Pbo + FLOT (N = 469)	D + FLOT (N = 475)	Pbo + FLOT (N = 469)	D + FLOT (N = 365)	Pbo + FLOT (N = 351)	D + FLOT (N = 345)	Pbo + FLOT (N = 331)	D (N = 4642)
Any SAE (including events with outcome of death), possibly related to durvalumab/placebo [c,e]	40 (8.4)	25 (5.3)	11 (2.3)	9 (1.9)	21 (5.8)	16 (4.6)	11 (3.2)	6 (1.8)	370 (8.0)
Any SAE (including events with outcome of death), possibly related to any FLOT (at least 1 drug) [c,e]	81 (17.1)	72 (15.4)	48 (10.1)	46 (9.8)	34 (9.3)	29 (8.3)	2 (0.6)	2 (0.6)	N/A
Any AE leading to discontinuation of any study treatment	142 (29.9)	107 (22.8)	36 (7.6)	38 (8.1)	97 (26.6)	64 (18.2)	20 (5.8)	10 (3.0)	489 (10.5)
Any AE leading to discontinuation of durvalumab/placebo	48 (10.1)	30 (6.4)	12 (2.5)	10 (2.1)	26 (7.1)	16 (4.6)	20 (5.8)	9 (2.7)	489 (10.5)
Any AE leading to discontinuation of any FLOT (at least 1 drug)	121 (25.5)	95 (20.3)	31 (6.5)	36 (7.7)	78 (21.4)	53 (15.1)			N/A
Any AE leading to discontinuation of both durvalumab/placebo and any FLOT (at least 1 drug)	21 (4.4)	14 (3.0)	7 (1.5)	7 (1.5)	5 (1.4)	3 (0.9)	0	0	N/A
Any AE leading to discontinuation of any study treatment, possibly related to any study treatment [c]	122 (25.7)	90 (19.2)	31 (6.5)	34 (7.2)	90 (24.7)	54 (15.4)	16 (4.6)	9 (2.7)	234 (5.0)
Any AE leading to discontinuation of durvalumab/placebo, possibly related to durvalumab/placebo [c]	29 (6.1)	19 (4.1)	5 (1.1)	5 (1.1)	20 (5.5)	13 (3.7)	14 (4.1)	8 (2.4)	234 (5.0)
Any AE leading to discontinuation of any FLOT (at least 1 drug), possibly related to any FLOT [c]	96 (20.2)	77 (16.4)	24 (5.1)	32 (6.8)	73 (20.0)	42 (12.0)			N/A
Any AE leading to discontinuation of both durvalumab/placebo and any FLOT (at least 1 drug), possibly related to both durvalumab/placebo and any FLOT [c]	3 (0.6)	3 (0.6)					0	0	N/A
Any AE leading to durvalumab/placebo dose delay or interruption [g]	268 (56.4)	241 (51.4)	137 (28.8)	126 (26.9)	182 (49.9)	159 (45.3)	76 (22.0)	64 (19.3)	1286 (27.7)
Any AE leading to any FLOT dose delay	252 (53.1)	239 (51.0)	182 (38.3)	157 (33.5)	128 (35.1)	130 (37.0)	0	0	N/A
Any AE leading to any FLOT dose interruption [h]	272 (57.3)	250 (53.3)	189 (39.8)	167 (35.6)	148 (40.5)	134 (38.2)	0	0	N/A
Any AE leading to any FLOT dose reduction	199 (41.9)	185 (39.4)	123 (25.9)	118 (25.2)	97 (26.6)	91 (25.9)	0	0	N/A

Parameter	Number (%) of patients [a]								
	MATTERHORN								D pantumor pool
	Overall study [b]		Neoadjuvant period		Adjuvant overall period		Adjuvant monotherapy period		
	D + FLOT (N = 475)	Pbo + FLOT (N = 469)	D + FLOT (N = 475)	Pbo + FLOT (N = 469)	D + FLOT (N = 365)	Pbo + FLOT (N = 351)	D + FLOT (N = 345)	Pbo + FLOT (N = 331)	D (N = 4642)
Any AE leading to surgery not being performed	3 (0.6)	2 (0.4)	3 (0.6)	2 (0.4)	0	0	0	0	N/A
Any AE leading to a delay in surgery	11 (2.3)	12 (2.6)	11 (2.3)	12 (2.6)	0	0	0	0	N/A

[c] Patients with multiple events in the same category are counted only once in that category. Patients with events in more than 1 category are counted once in each of those categories.

[d] The overall study includes the neoadjuvant, surgery, and adjuvant overall periods. The adjuvant monotherapy period is contained within the adjuvant overall period of the study and is shown here for the purpose of safety analysis.

[e] As assessed by the investigator. Missing responses are counted as related.

[f] Maximum CTCAE grade per patient/treatment period/event is considered.

[g] Seriousness, as assessed by the investigator. An AE with missing seriousness is considered serious.

[h] AEs with outcome of death were reported in patients in the overall study.

[i] Includes AEs on the AE case report form with action taken indicating dose delay or dose interruption, and AEs meeting study level dose delay definitions, where applicable.

[j] Dose interruption includes dose delay.

Includes AEs with an onset date on or after the date of first dose or pre-treatment AEs that increase in severity on or after the date of the first dose up to and including 90 days following the date of the last dose of study medication or up to and including the date of initiation of the first subsequent therapy, whichever occurs first.

N/A = not applicable; this is used for AE categories that are specific to the MATTERHORN study and are therefore not reported for any of the studies included in the D pan-tumor pool (AEs possibly related to any FLOT; AEs leading to discontinuation of any FLOT; AEs leading to discontinuation of both durvalumab/placebo and any FLOT; AEs leading to discontinuation of any FLOT, possibly related to any FLOT; AEs leading to discontinuation of both durvalumab/placebo and any FLOT, possibly related to both durvalumab/placebo and any FLOT; and AEs leading to FLOT dose delay, dose interruption, or dose reduction).

AEs and their associated characteristics (e.g., changes in grade, outcome, and causality) were allocated to the treatment period in which they first occurred.

Disease progression AEs reported in Study 1108 are not included.

Table 36 Summary of Adverse Events by SOC and PT (≥ 5% of Patients in Either Treatment Arm in the Overall MATTERHORN Study) (Safety Analysis Set; DCO2)

SOC PT	Number (%) of Patients [a]				
	MATTERHORN				D Pan-tumor Pool
	Overall Study [b]		Adjuvant Monotherapy Period		
	D + FLOT (N = 475)	Pbo + FLOT (N = 469)	D + FLOT (N = 345)	Pbo + FLOT (N = 331)	D (N = 4642)
Patients with any AE	471 (99.2)	463 (98.7)	274 (79.4)	260 (78.5)	4381 (94.4)
Gastrointestinal disorders	**409 (86.1)**	**391 (83.4)**	**137 (39.7)**	**117 (35.3)**	**2420 (52.1)**

SOC PT	Number (%) of Patients [a]				
	MATTERHORN				D Pan-tumor Pool
	Overall Study [b]		Adjuvant Monotherapy Period		
	D + FLOT (N = 475)	Pbo + FLOT (N = 469)	D + FLOT (N = 345)	Pbo + FLOT (N = 331)	D (N = 4642)
Diarrhoea	296 (62.3)	270 (57.6)	44 (12.8)	38 (11.5)	701 (15.1)
Nausea	241 (50.7)	237 (50.5)	18 (5.2)	18 (5.4)	739 (15.9)
Vomiting	124 (26.1)	120 (25.6)	14 (4.1)	9 (2.7)	452 (9.7)
Abdominal pain	82 (17.3)	96 (20.5)	17 (4.9)	21 (6.3)	327 (7.0)
Constipation	77 (16.2)	81 (17.3)	13 (3.8)	12 (3.6)	710 (15.3)
Stomatitis	60 (12.6)	44 (9.4)	5 (1.4)	5 (1.5)	127 (2.7)
Dysphagia	47 (9.9)	36 (7.7)	15 (4.3)	16 (4.8)	163 (3.5)
Gastrooesophageal reflux disease	35 (7.4)	41 (8.7)	20 (5.8)	17 (5.1)	109 (2.3)
Dyspepsia	33 (6.9)	27 (5.8)	9 (2.6)	10 (3.0)	133 (2.9)
Abdominal pain upper	26 (5.5)	27 (5.8)	9 (2.6)	9 (2.7)	171 (3.7)
Dry mouth	25 (5.3)	14 (3.0)	8 (2.3)	2 (0.6)	145 (3.1)
General disorders and administration site conditions	**307 (64.6)**	**302 (64.4)**	**60 (17.4)**	**52 (15.7)**	**2412 (52.0)**
Fatigue	137 (28.8)	146 (31.1)	19 (5.5)	19 (5.7)	1052 (22.7)
Asthenia	95 (20.0)	71 (15.1)	14 (4.1)	10 (3.0)	529 (11.4)
Pyrexia	95 (20.0)	71 (15.1)	12 (3.5)	7 (2.1)	578 (12.5)
Oedema peripheral	32 (6.7)	30 (6.4)	7 (2.0)	7 (2.1)	365 (7.9)
Mucosal inflammation	27 (5.7)	23 (4.9)	1 (0.3)	1 (0.3)	67 (1.4)
Malaise	24 (5.1)	26 (5.5)	4 (1.2)	3 (0.9)	86 (1.9)
Nervous system disorders	**280 (58.9)**	**262 (55.9)**	**42 (12.2)**	**30 (9.1)**	**1191 (25.7)**
Peripheral sensory neuropathy	96 (20.2)	88 (18.8)	4 (1.2)	3 (0.9)	43 (0.9)
Dysgeusia	78 (16.4)	61 (13.0)	2 (0.6)	1 (0.3)	77 (1.7)

SOC PT	Number (%) of Patients [a]				
	MATTERHORN				D Pan-tumor Pool
	Overall Study [b]		Adjuvant Monotherapy Period		
	D + FLOT (N = 475)	Pbo + FLOT (N = 469)	D + FLOT (N = 345)	Pbo + FLOT (N = 331)	D (N = 4642)
Neuropathy peripheral	73 (15.4)	70 (14.9)	2 (0.6)	5 (1.5)	82 (1.8)
Paraesthesia	38 (8.0)	32 (6.8)	4 (1.2)	2 (0.6)	99 (2.1)
Dizziness	31 (6.5)	27 (5.8)	11 (3.2)	4 (1.2)	283 (6.1)
Headache	29 (6.1)	25 (5.3)	3 (0.9)	5 (1.5)	353 (7.6)
Polyneuropathy	26 (5.5)	23 (4.9)			5 (0.1)
Skin and subcutaneous tissue disorders	**257 (54.1)**	**239 (51.0)**	**94 (27.2)**	**31 (9.4)**	**1444 (31.1)**
Alopecia	145 (30.5)	149 (31.8)	7 (2.0)	1 (0.3)	42 (0.9)
Rash	65 (13.7)	34 (7.2)	25 (7.2)	8 (2.4)	452 (9.7)
Pruritus	51 (10.7)	25 (5.3)	34 (9.9)	11 (3.3)	513 (11.1)
Dry skin	36 (7.6)	22 (4.7)	15 (4.3)	1 (0.3)	175 (3.8)
Palmar-plantar erythrodysaesthesia syndrome	24 (5.1)	22 (4.7)			8 (0.2)
Investigations	**246 (51.8)**	**255 (54.4)**	**59 (17.1)**	**50 (15.1)**	**1504 (32.4)**
Neutrophil count decreased	119 (25.1)	138 (29.4)	12 (3.5)	12 (3.6)	39 (0.8)
Weight decreased	70 (14.7)	88 (18.8)	13 (3.8)	11 (3.3)	350 (7.5)
White blood cell count decreased	46 (9.7)	62 (13.2)	9 (2.6)	5 (1.5)	54 (1.2)
Platelet count decreased	34 (7.2)	27 (5.8)	4 (1.2)	3 (0.9)	62 (1.3)
Alanine aminotransferase increased	33 (6.9)	25 (5.3)	9 (2.6)	8 (2.4)	298 (6.4)
Aspartate aminotransferase increased	26 (5.5)	22 (4.7)	8 (2.3)	8 (2.4)	315 (6.8)

SOC PT	Number (%) of Patients [a]				
	MATTERHORN				D Pan-tumor Pool
	Overall Study [b]		Adjuvant Monotherapy Period		
	D + FLOT (N = 475)	Pbo + FLOT (N = 469)	D + FLOT (N = 345)	Pbo + FLOT (N = 331)	D (N = 4642)
Blood and lymphatic system disorders	**239 (50.3)**	**254 (54.2)**	**49 (14.2)**	**63 (19.0)**	**820 (17.7)**
Neutropenia	153 (32.2)	155 (33.0)	19 (5.5)	28 (8.5)	40 (0.9)
Anaemia	119 (25.1)	147 (31.3)	28 (8.1)	33 (10.0)	629 (13.6)
Thrombocytopenia	31 (6.5)	25 (5.3)	1 (0.3)	2 (0.6)	83 (1.8)
Leukopenia	27 (5.7)	30 (6.4)	2 (0.6)	3 (0.9)	25 (0.5)
Infections and infestations	**239 (50.3)**	**221 (47.1)**	**104 (30.1)**	**96 (29.0)**	**1769 (38.1)**
COVID-19	85 (17.9)	74 (15.8)	34 (9.9)	32 (9.7)	26 (0.6)
Pneumonia	34 (7.2)	32 (6.8)	9 (2.6)	11 (3.3)	383 (8.3)
Urinary tract infection	28 (5.9)	20 (4.3)	9 (2.6)	7 (2.1)	294 (6.3)
Metabolism and nutrition disorders	**220 (46.3)**	**233 (49.7)**	**55 (15.9)**	**47 (14.2)**	**1727 (37.2)**
Decreased appetite	145 (30.5)	141 (30.1)	24 (7.0)	19 (5.7)	880 (19.0)
Hypokalaemia	39 (8.2)	53 (11.3)	5 (1.4)	6 (1.8)	207 (4.5)
Hypoalbuminaemia	31 (6.5)	39 (8.3)			181 (3.9)
Respiratory, thoracic and mediastinal disorders	**155 (32.6)**	**160 (34.1)**	**42 (12.2)**	**34 (10.3)**	**1956 (42.1)**
Cough	42 (8.8)	41 (8.7)	13 (3.8)	9 (2.7)	712 (15.3)
Epistaxis	38 (8.0)	51 (10.9)			48 (1.0)
Dyspnoea	26 (5.5)	23 (4.9)	6 (1.7)	2 (0.6)	638 (13.7)
Pleural effusion	14 (2.9)	29 (6.2)	1 (0.3)	5 (1.5)	144 (3.1)
Musculoskeletal and connective tissue disorders	**120 (25.3)**	**99 (21.1)**	**58 (16.8)**	**40 (12.1)**	**1640 (35.3)**
Arthralgia	41 (8.6)	31 (6.6)	27 (7.8)	16 (4.8)	574 (12.4)

SOC PT	Number (%) of Patients [a]				
	MATTERHORN				D Pan-tumor Pool
	Overall Study [b]		Adjuvant Monotherapy Period		
	D + FLOT (N = 475)	Pbo + FLOT (N = 469)	D + FLOT (N = 345)	Pbo + FLOT (N = 331)	D (N = 4642)
Back pain	24 (5.1)	29 (6.2)	10 (2.9)	9 (2.7)	475 (10.2)
Injury, poisoning and procedural complications	**114 (24.0)**	**108 (23.0)**	**13 (3.8)**	**20 (6.0)**	**604 (13.0)**
Procedural pain	34 (7.2)	31 (6.6)			35 (0.8)
Infusion related reaction	33 (6.9)	17 (3.6)			59 (1.3)
Endocrine disorders	**67 (14.1)**	**21 (4.5)**	**28 (8.1)**	**6 (1.8)**	**683 (14.7)**
Hypothyroidism	37 (7.8)	8 (1.7)	14 (4.1)	3 (0.9)	472 (10.2)
Psychiatric disorders	**66 (13.9)**	**62 (13.2)**	**11 (3.2)**	**7 (2.1)**	**705 (15.2)**
Insomnia	34 (7.2)	38 (8.1)	1 (0.3)	5 (1.5)	340 (7.3)

Table 37 Overview of Adverse Events Possibly Related to Durvalumab/Placebo by Preferred Term (> 5% of Patients in Either Treatment Arm in the Overall MATTERHORN Study) (Safety Analysis Set)

Parameter	Number (%) of patients [a]				
	MATTERHORN				D pantumor pool
	Overall study [b]		Adjuvant monotherapy period		
	D + FLOT (N = 475)	Pbo + FLOT (N = 469)	D + FLOT (N = 345)	Pbo + FLOT (N = 331)	D (N = 4642)
Patients with any AE possibly related to durvalumab/placebo [c]	282 (59.4)	244 (52.0)	137 (39.7)	83 (25.1)	2711 (58.4)
Diarrhoea	80 (16.8)	71 (15.1)	17 (4.9)	13 (3.9)	317 (6.8)
Nausea	40 (8.4)	39 (8.3)	3 (0.9)	4 (1.2)	268 (5.8)
Fatigue	38 (8.0)	8 (8.1)	7 (2.0)	5 (1.5)	520 (11.2)
Rash	37 (7.8)	18 (3.8)	12 (3.5)	5 (1.5)	315 (6.8)
Pruritus	32 (6.7)	12 (2.6)	25 (7.2)	7 (2.1)	320 (6.9)
Hypothyroidism	31 (6.5)	6 (1.3)	13 (3.8)	3 (0.9)	397 (8.6)
Asthenia	23 (4.8)	26 (5.5)	4 (1.2)	4 (1.2)	227 (4.9)
Neutropenia	21 (4.4)	26 (5.5)	5 (1.4)	7 (2.1)	23 0.5)

[a] Number (%) of patients with possibly related AEs, sorted in decreasing frequency of PT (according to the MATTERHORN D + FLOT column). Patients with multiple possibly related events are counted once for each PT.

[b] The overall study includes the neoadjuvant, surgery, and adjuvant overall periods. The adjuvant monotherapy period is contained within the adjuvant overall period of the study and is shown here for the purpose of safety analysis.

[c] Possibly related to treatment, as assessed by the investigator. Missing responses are counted as related.

Includes AEs with an onset date on or after the date of first dose or pre-treatment AEs that increase in severity on or after the date of the first dose up to and including 90 days following the date of the last dose of study medication or up to and including the date of initiation of the first subsequent therapy, whichever occurs first. Adverse events related to surgery are not included.

Disease progression AEs reported in Study 1108 are not included.

Immune-mediated events

Table 38 Overview of Immune-mediated Adverse Events by Category (Safety Analysis Set)

Parameter	Number (%) of patients [a]				
	MATTERHORN				D pantumor pool
	Overall study [b]		Adjuvant monotherapy period		
	D + FLOT (N = 475)	Pbo + FLOT (N = 469)	D + FLOT (N = 345)	Pbo + FLOT (N = 331)	D (N = 4642)
Any imAE	110 (23.2)	34 (7.2)	46 (13.3)	12 (3.6)	853 (18.4)
Any imAE possibly related to any study treatment [c]	99 (20.8)	31 (6.6)	41 (11.9)	10 (3.0)	720 (15.5)
Any imAE possibly related to durvalumab/placebo [c]	90 (18.9)	24 (5.1)	40 (11.6)	10 (3.0)	720 (15.5)
Any imAE possibly related to any FLOT (at least 1 drug)	90 (18.9)	24 (5.1)			N/A
Any imAE of maximum CTCAE Grade 3 or 4 [d]	34 (7.2)	17 (3.6)	11 (3.2)	5 (1.5)	203 (4.4)
Any imAE of maximum CTCAE Grade 3 or 4, possibly related to any study treatment [c,d]	32 (6.7)	16 (3.4)	11 (3.2)	4 (1.2)	N/A
Any imAE of maximum CTCAE Grade 3 or 4, possibly related to durvalumab/placebo [c,d]	28 (5.9)	13 (2.8)	10 (2.9)	4 (1.2)	174 (3.7)
Any imAE of maximum CTCAE Grade 3 or 4, possibly related to any FLOT (at least 1 drug) [c,d]	8 (1.7)	6 (1.3)			N/A
Any serious imAE	23 (4.8)	13 (2.8)	6 (1.7)	3 (0.9)	201 (4.3)
Any serious imAE possibly related to any study treatment [c]	21 (4.4)	12 (2.6)	6 (1.7)	2 (0.6)	N/A
Any serious imAE possibly related to durvalumab/placebo [c]	20 (4.2)	11 (2.3)	6 (1.7)	2 (0.6)	181 (3.9)
Any serious imAE possibly related to any FLOT (at least 1 drug) [c]	2 (0.4)	4 (0.9)	0	0	N/A
Any treatment-emergent imAE with an outcome of death [e]					15 (0.3)
Any treatment-emergent imAE with an outcome of death, possibly related to any study treatment [c]					N/A
Any treatment-emergent imAE with an outcome of death, possibly related to durvalumab/placebo [c]					13 (0.3)
Any treatment-emergent imAE with an outcome of death, possibly related to any FLOT (at least 1 drug) [c]	0	0	0	0	N/A
Any imAE leading to discontinuation of any study treatment	24 (5.1)	14 (3.0)	10 (2.9)	6 (1.8)	141 (3.0)
Any imAE leading to discontinuation of durvalumab/placebo	21 (4.4)	13 (2.8)	10 (2.9)	6 (1.8)	141 (3.0)
Any imAE leading to discontinuation of any FLOT (at least 1 drug)	9 (1.9)	4 (0.9)	0	0	N/A

Parameter	Number (%) of patients [a]				
	MATTERHORN				D pantumor pool
	Overall study [b]		Adjuvant monotherapy period		
	D + FLOT (N = 475)	Pbo + FLOT (N = 469)	D + FLOT (N = 345)	Pbo + FLOT (N = 331)	D (N = 4642)
Received systemic corticosteroids	67 (14.1)	29 (6.2)	27 (7.8)	10 (3.0)	495 (10.7)
Received high-dose steroids (≥ 40 mg prednisone equivalent steroids)	47 (9.9)	25 (5.3)	17 (4.9)	8 (2.4)	334 (7.2)
Received other immunosuppressants	3 (0.6)	2 (0.4)	1 (0.3)	1 (0.3)	21 (0.5)
Received endocrine therapy	51 (10.7)	7 (1.5)	21 (6.1)	3 (0.9)	443 (9.5)
Any imAE with an outcome of resolving [f]	17 (3.6)	1 (0.2)			104 (2.2)
Any imAE with an outcome of resolved with sequelae [f]			0	0	17 (0.4)
Any imAE with an outcome of resolved [f]	53 (11.2)	24 (5.1)	23 (6.7)	6 (1.8)	293 (6.3)
Any imAE with an outcome of not resolved [f, g]	36 (7.6)	9 (1.9)	13 (3.8)	6 (1.8)	421 (9.1)
Any imAE with an outcome of death [f]					18 (0.4)

[a] Patients with multiple events in the same category are counted only once in that category. Patients with events in more than 1 category are counted once in each of those categories. The overall study includes the neoadjuvant, surgery, and adjuvant overall periods. The adjuvant monotherapy period is contained within the adjuvant overall period of the study and is shown here for the purpose of safety analysis.

[b] Possibly related is defined as reasonable possibility that the AE was caused by treatment, as assessed by investigator. Missing responses are counted as possibly related

[c] Grade 3: severe; Grade 4: life-threatening.

[d] Outcome of event with the worst outcome is considered. Outcomes from worst to best are death, not resolved, resolving, resolved with sequelae, and resolved.

[e] If a patient has multiple events within a specific AE type then the outcome of the event with the worst outcome is counted regardless of treatment-emergent period. Outcomes from worst to best are death, not resolved, resolving, resolved with sequelae, and resolved.

[f] Reasons of not recovered/not resolved and unknown map to an outcome of not resolved.

Includes AEs with an onset date on or after the date of first dose or pre-treatment AEs that increase in severity on or after the date of the first dose up to and including 90 days following the date of the last dose of study medication or up to and including the date of initiation of the first subsequent therapy, whichever occurs first.

N/A = not applicable; this is used for AE categories that are specific to the MATTERHORN study and are therefore not reported for any of the studies included in the D pan-tumor pool (imAEs possibly related to any FLOT; imAEs of maximum CTCAE Grade 3 or 4, possibly related to any study treatment; imAEs of maximum CTCAE Grade 3 or 4, possibly related to any FLOT; serious imAEs related to any study treatment, serious imAEs possibly related to any FLOT; imAEs with an outcome of death, possibly related to any study treatment; imAEs with an outcome of death, possibly related to any FLOT; and imAEs leading to discontinuation of any FLOT).

Adverse drug reactions

Table 39 Adverse Drug Reactions in any category – Patient Level (Safety Analysis Set)

ADR category	Number (%) of patients [a]				
	MATTERHORN		D pan-tumor pool	D + CTx pool [c] (N = 2244)	CTx pool [c] (N = 2237)
	Overall study [b]				
	D + FLOT (N = 475)	Pbo + FLOT (N = 469)	D (N = 4642)		
Patients with any ADR	461 (97.1)	448 (95.5)	3366 (72.5)	2149 (95.8)	2119 (94.7)
Any ADR of maximum CTCAE Grade 3 or 4 [d]	296 (62.3)	287 (61.2)	559 (12.0)	1090 (48.6)	1107 (49.5)
Any serious ADR [e]	111 (23.4)	92 (19.6)	520 (11.2)	387 (17.2)	342 (15.3)
Any ADR with an outcome of death	7 (1.5)	4 (0.9)	39 (0.8)	21 (0.9)	17 (0.8)
Any ADR with an outcome of death during the treatment-emergent period	6 (1.3)	4 (0.9)	33 (0.7)	19 (0.8)	16 (0.7)
Any ADR leading to discontinuation of any treatment	97 (20.4)	68 (14.5)	184 (4.0)	245 (10.9)	158 (7.1)
Any ADR leading to discontinuation of durvalumab/placebo	29 (6.1)	20 (4.3)	184 (4.0)	139 (6.2)	51 (2.3)
Any ADR leading to dose delay or interruption of durvalumab/placebo [f]	214 (45.1)	201 (42.9)	607 (13.1)	727 (32.4)	444 (19.8)

[a] Number (%) of patients with ADRs.

[b] The overall study includes the neoadjuvant, surgery, and adjuvant overall periods. The adjuvant monotherapy period is contained within the adjuvant overall period of the study. For treatment period definitions, refer to Section 9.8.1.4, MATTERHORN CSR, Module 5.3.5.1.

[c] D + CTx and CTx pools include data from 6 studies: MATTERHORN, CASPIAN, TOPAZ-1, DUO-E, NIAGARA, and AEGEAN.

[d] Maximum CTCAE grade per patient/treatment period/event is considered.

[e] Seriousness as assessed by the investigator. An AE with missing seriousness is considered serious.

[f] Includes AEs on the AE CRF with action taken indicating dose delay or dose interruption, and AEs meeting study level dose delay definitions, where applicable.

Table 40 ADRs in patients by ADR SOC, ADR term and CIOMS III Category (Safety Analysis set)

	MATTERHORN				D pan-tumor pool		D + CTx pool [b]		CTx pool [b]	
	Overall study [a]									
	D + FLOT (N = 475)		Pbo + FLOT (N = 469)		D (N = 4642)		(N = 2244)		(N = 2237)	
ADR SOC/ ADR term	n (%) [c]	CIOMS III cat. [d]	n (%) [c]	CIOMS III cat. [d]	n (%) [c]	CIOMS III cat. [d]	n (%) [c]	CIOMS III cat. [d]	n (%) [c]	CIOMS III cat. [d]
Patients with any ADR	461 (97.1)	–	448 (95.5)	–	3366 (72.5)	–	2149 (95.8)	–	2119 (94.7)	–
Blood and lymphatic system disorders										
Neutropenia	263 (55.4)	Very common	283 (60.3)	Very common	NA	–	1001 (44.6)	Very common	1085 (48.5)	Very common
Anaemia	119 (25.1)	Very common	147 (31.3)	Very common	NA	–	840 (37.4)	Very common	895 (40.0)	Very common
Leukopenia	72 (15.2)	Very common	92 (19.6)	Very common	NA	–	334 (14.9)	Very common	379 (16.9)	Very common
Thrombocytopenia	61 (12.8)	Very common	52 (11.1)	Very common	NA	–	442 (19.7)	Very common	440 (19.7)	Very common
Febrile neutropenia	17 (3.6)	Common	17 (3.6)	Common	NA	–	60 (2.7)	Common	67 (3.0)	Common
Immune thrombocytopenia [e]	0	NR	0	NR	3 (0.1) [f]	Rare	1 (< 0.1)	Rare	0	NR
Pancytopenia	0	NR	0	NR	NA	–	14 (0.6)	Uncommon	9 (0.4)	Uncommon
Cardiac disorders										
Acute myocardial infarction [g]	5 (1.1)	Common	3 (0.6)	Uncommon	NA	–	5 (0.2)	Uncommon	3 (0.1)	Uncommon
Myocarditis [e]	1 (0.2)	Uncommon	1 (0.2)	Uncommon	8 (0.2)	Uncommon	3 (0.1)	Uncommon	1 (< 0.1)	Rare
Endocrine disorders										
Hypothyroidism [e]	39 (8.2)	Common	9 (1.9)	Common	540 (11.6)	Very common	249 (11.1)	Very common	63 (2.8)	Common
Hyperthyroidism [e]	22 (4.6)	Common	9 (1.9)	Common	261 (5.6)	Common	129 (5.7)	Common	41 (1.8)	Common
Adrenal insufficiency [e]	7 (1.5)	Common	1 (0.2)	Uncommon	28 (0.6)	Uncommon	20 (0.9)	Uncommon	2 (0.1) [f]	Rare
Thyroiditis [e]	5 (1.1)	Common	2 (0.4)	Uncommon	38 (0.8)	Uncommon	18 (0.8)	Uncommon	4 (0.2)	Uncommon
Hypopituitarism/hypophysitis [e]					6 (0.1)	Uncommon	9 (0.4)	Uncommon	0	NR
Type 1 diabetes mellitus [e]					4 (0.1) [f]	Rare	8 (0.4)	Uncommon	0	NR
Diabetes insipidus [e]	0	NR	0	NR	1 (<0.1)	Rare	0	NR	0	NR
Eye Disorders										
Uveitis [e]					1 (<0.1)	Rare	2 (0.1) [f]	Rare	2 (0.1) [f]	Rare
Gastrointestinal disorders										
Diarrhoea [e]	296 (62.3)	Very common	270 (57.6)	Very common	701 (15.1)	Very common	618 (27.5)	Very common	544 (24.3)	Very common
Nausea	241 (50.7)	Very common	237 (50.5)	Very common	NA	–	951 (42.4)	Very common	924 (41.3)	Very common
Vomiting	124 (26.1)	Very common	120 (25.6)	Very common	NA	–	422 (18.8)	Very common	412 (8.0)	Very common
Abdominal pain [e]	108 (22.7)	Very common	117 (24.9)	Very common	549 (11.8)	Very common	402 (17.9)	Very common	370 (16.5)	Very common
Stomatitis	84 (17.7)	Very common	66 (14.1)	Very common	NA	–	205 (9.1)	Common	178 (8.0)	Common
Constipation	77 (16.2)	Very common	81 (17.3)	Very common	NA	–	600 (26.7)	Very common	603 (27.0)	Very common
Colitis [e]	16 (3.4)	Common	9 (1.9)	Common	39 (0.8)	Uncommon	37 (1.6)	Common	18 (0.8)	Uncommon
Pancreatitis [e]	7 (1.5)	Common	2 (0.4)	Uncommon	11 (0.2)	Uncommon	17 (0.8)	Uncommon	6 (0.3)	Uncommon
Pancreatic exocrine insufficiency	3 (0.6)	Uncommon	5 (1.1)	Common	1 (<0.1)	Rare	4 (0.2)	Uncommon	5 (0.2)	Uncommon

General disorders and administration site conditions										
Fatigue	224 (47.2)	Very common	213 (45.4)	Very common	NA	–	925 (41.2)	Very common	896 (40.1)	Very common
Pyrexia [e]	95 (20.0)	Very common	71 (15.1)	Very common	578 (12.5)	Very common	341 (15.2)	Very common	288 (12.9)	Very Common
Oedema peripheral [e]	35 (7.4)	Common	32 (6.8)	Common	399 (8.6)	Common	182 (8.1)	Common	155 (6.9)	Common
Hepatobiliary disorders										
Aspartate aminotransferase increased/alanine aminotransferase increased [e]	44 (9.3)	Common	38 (8.1)	Common	422 (9.1)	Common	235 (10.5)	Very common	199 (8.9)	Common
Hepatitis [e]	13 (2.7)	Common	9 (1.9)	Common	51 (1.1)	Common	40 (1.8)	Common	19 (0.8)	Uncommon
Infections and infestations										
Pneumonia [e]	35 (7.4)	Common	33 (7.0)	Common	399 (8.6)	Common	126 (5.6)	Common	118 (5.3)	Common
Upper respiratory tract infections [e]	31 (6.5)	Common	30 (6.4)	Common	550 (11.8)	Very common	153 (6.8)	Common	145 (6.5)	Common
Influenza [e]	8 (1.7)	Common	3 (0.6)	Uncommon	65 (1.4)	Common	20 (0.9)	Uncommon	14 (0.6)	Uncommon
Dental and oral soft tissue infections [e]	4 (0.8)	Uncommon	5 (1.1)	Common	62 (1.3)	Common	29 (1.3)	Common	25 (1.1)	Common
Oral candidiasis [e]	4 (0.8)	Uncommon	4 (0.9)	Uncommon	82 (1.8)	Common	16 (0.7)	Uncommon	16 (0.7)	Uncommon
Injury, poisoning and procedural complications										
Infusion related reaction [e]	34 (7.2)	Common	18 (3.8)	Common	70 (1.5)	Common	78 (3.5)	Common	57 (2.5)	Common
Metabolism and nutrition disorders										
Decreased appetite	145 (30.5)	Very common	141 (30.1)	Very common	NA	–	538 (24.0)	Very common	516 (23.1)	Very common

Musculoskeletal and connective tissue disorders										
Arthralgia [e]	41 (8.6)	Common	31 (6.6)	Common	574 (12.4)	Very common	245 (10.9)	Very common	203 (9.1)	Common
Myalgia [e]	19 (4.0)	Common	13 (2.8)	Common	212 (4.6)	Common	131 (5.8)	Common	129 (5.8)	Common
Immune-mediated arthritis [e]	1 (0.2)	Uncommon	1 (0.2)	Uncommon	4 (0.1) [f]	Rare	6 (0.3)	Uncommon	2 (0.1) [f]	Rare
Myositis [e]					10 (0.2)	Uncommon	12 (0.5)	Uncommon	1 (< 0.1)	Rare
Polymyalgia rheumatica [e]	0	NR	0	NR	3 (0.1) [f]	Rare	1 (< 0.1)	Rare	0	NR
Polymyositis [e]	0	NR	0	NR	0	NR	0	NR	1 (< 0.1)	Rare
Nervous system disorders										
Neuropathy peripheral	195 (41.1)	Very common	176 (37.5)	Very common	NA	–	484 (21.6)	Very common	484 (21.6)	Very common
Guillain-Barré syndrome [e]					0	NR	1 (< 0.1)	Rare	0	NR
Encephalitis [e]	0	NR	0	NR	3 (0.1) [f]	Rare	1 (< 0.1)	Rare	1 (< 0.1)	Rare
Meningitis [e]	0	NR	0	NR	1 (<0.1)	Rare	0	NR	0	NR
Myasthenia gravis [e]	0	NR	0	NR	3 (0.1) [f]	Rare	4 (0.2)	Uncommon	0	NR
Renal and urinary disorders										
Dysuria [e]	8 (1.7)	Common	4 (0.9)	Uncommon	62 (1.3)	Common	62 (2.8)	Common	50 (2.2)	Common
Blood creatinine increased [e]	5 (1.1)	Common	7 (1.5)	Common	158 (3.4)	Common	142 (6.3)	Common	152 (6.8)	Common
Nephritis [e]					13 (0.3)	Uncommon	12 (0.5)	Uncommon	6 (0.3)	Uncommon
Cystitis noninfective [e]	0	NR	0	NR	4 (0.1) [f]	Rare	5 (0.2)	Uncommon	3 (0.1)	Uncommon

Respiratory, thoracic and mediastinal disorders										
Cough/Productive cough [e]	47 (9.9)	Common	46 (9.8)	Common	838 (18.1)	Very common	242 (10.8)	Very common	207 (9.3)	Common
Pulmonary embolism [g]	20 (4.2)	Common	9 (1.9)	Common	NA	–	20 (0.9)	Uncommon	9 (0.4)	Uncommon
Pneumonitis [e]	15 (3.2)	Common	5 (1.1)	Common	183 (3.9)	Common	59 (2.6)	Common	25 (1.1)	Common
Dysphonia [e]	13 (2.7)	Common	6 (1.3)	Common	108 (2.3)	Common	41 (1.8)	Common	25 (1.1)	Common
Interstitial lung disease [e]	3 (0.6)	Uncommon	3 (0.6)	Uncommon	33 (0.7)	Uncommon	11 (0.5)	Uncommon	10 (0.4)	Uncommon
Skin and subcutaneous tissue disorders										
Alopecia	145 (30.5)	Very common	149 (31.8)	Very common	NA	–	493 (22.0)	Very common	494 (22.1)	Very common
Rash [e]	95 (20.0)	Very common	56 (11.9)	Very common	695 (15.0)	Very common	443 (19.7)	Very common	265 (11.8)	Very common
Pruritus [e]	51 (10.7)	Very common	25 (5.3)	Common	513 (11.1)	Very common	281 (12.5)	Very common	158 (7.1)	Common
Dermatitis [e]	9 (1.9)	Common	8 (1.7)	Common	37 (0.8)	Uncommon	38 (1.7)	Common	17 (0.8)	Uncommon
Night sweats [e]	2 (0.4)	Uncommon	3 (0.6)	Uncommon	60 (1.3)	Common	8 (0.4)	Uncommon	9 (0.4)	Uncommon
Psoriasis [e]	2 (0.4)	Uncommon	1 (0.2)	Uncommon	30 (0.6)	Uncommon	8 (0.4)	Uncommon	5 (0.2)	Uncommon
Pemphigoid [e]					6 (0.1)	Uncommon	5 (0.2)	Uncommon	2 (0.1) [f]	Rare
Vascular disorders										
Deep vein thrombosis [g]	2 (0.4)	Uncommon	7 (1.5)	Common	NA	–	2 (0.1)	Rare	7 (0.3)	Uncommon

[a] The overall study includes the neoadjuvant, surgery, and adjuvant overall periods. The adjuvant monotherapy period is contained within the adjuvant overall period of the study. For treatment period definitions, refer to Section 9.8.1.4, MATTERHORN CSR, Module 5.3.5.1.

[b] D + CTx and CTx pools include data from 6 studies: MATTERHORN, CASPIAN, TOPAZ-1, DUO-E, NIAGARA, and AEGEAN.

[c] Number (%) of patients with ADRs, sorted in alphabetical order by ADR SOC and by decreasing frequency of ADR PT (according to the MATTERHORN D + FLOT column).

[d] CIOMS III convention and is defined as: (1) very common (≥ 1/10); (2) common (≥ 1/100 to < 1/10); (3) uncommon (≥ 1/1000 to < 1/100); (4) rare (≥ 1/10000 to < 1/1000); (5) very rare (< 1/10000); and (6) NR (not reported - cannot be estimated from available data)

[e] Known ADR for both durvalumab and FLOT chemotherapy.

[f] Percentage has been rounded up (CIOMS category is based on actual percentage).

[g] Adverse reaction only applies to FLOT-related ADRs in the MATTERHORN study.

A patient can have one or more PTs reported under a given SOC.

Includes AEs with an onset date on or after the date of first dose or pre-treatment AEs that increased in severity on or after the date of the first dose up to and including 90 days following the date of the last dose of study medication or up to and including the date of initiation of the first subsequent therapy, whichever occurred first.

ADR terms are grouped PTs.

Disease progression AEs reported in Study 1108 are not included.

Urticaria events in the infusion related reaction ADR term includes Urticaria starting on the same day or 1 day after the latest dose.

MedDRA Version 27.1.

2.6.4. Serious adverse event/deaths/other significant events

Serious adverse events

Table 41 Overview of SAEs by SOC and PT (> 1% of Patients in Either Treatment Arm in the Overall MATTERHORN Study) (Safety Analysis Set; DCO2)

SOC PT	Number (%) of Patients [a]				
	MATTERHORN				D Pantumor Pool
	Overall Study [b]		Adjuvant Monotherapy Period		
	D + FLOT (N = 475)	Pbo + FLOT (N = 469)	D + FLOT (N = 345)	Pbo + FLOT (N = 331)	D (N = 4642)
Patients with any SAE	229 (48.2)	207 (44.1)	50 (14.5)	48 (14.5)	1657 (35.7)
Gastrointestinal disorders	**81 (17.1)**	**72 (15.4)**	**15 (4.3)**	**17 (5.1)**	**267 (5.8)**
Vomiting	10 (2.1)	10 (2.1)	0	0	26 (0.6)
Diarrhoea	9 (1.9)	12 (2.6)			24 (0.5)
Ileus	7 (1.5)	2 (0.4)	4 (1.2)	1 (0.3)	9 (0.2)
Dysphagia	6 (1.3)	4 (0.9)	1 (0.3)	3 (0.9)	16 (0.3)
Nausea	6 (1.3)	2 (0.4)			12 (0.3)
Abdominal pain	5 (1.1)	2 (0.4)			37 (0.8)
Colitis	5 (1.1)	3 (0.6)			10 (0.2)
Intestinal obstruction	2 (0.4)	5 (1.1)	1 (0.3)	4 (1.2)	8 (0.2)
Infections and infestations	**70 (14.7)**	**63 (13.4)**	**10 (2.9)**	**9 (2.7)**	**450 (9.7)**
Pneumonia	14 (2.9)	16 (3.4)	3 (0.9)	2 (0.6)	190 (4.1)
COVID-19	9 (1.9)	5 (1.1)			1 (<0.1)
Septic shock	8 (1.7)	2 (0.4)			11 (0.2)
Device related infection	6 (1.3)	1 (0.2)			9 (0.2)
Sepsis	5 (1.1)	6 (1.3)			57 (1.2)
Pneumonia aspiration	3 (0.6)	9 (1.9)			13 (0.3)
Blood and lymphatic system disorders	**26 (5.5)**	**25 (5.3)**	**1 (0.3)**	**1 (0.3)**	**55 (1.2)**
Febrile neutropenia	10 (2.1)	15 (3.2)	0	0	0
Neutropenia	10 (2.1)	4 (0.9)	0	0	2 (<0.1)
Anaemia	5 (1.1)	3 (0.6)			34 (0.7)
Injury, poisoning and procedural complications	**26 (5.5)**	**26 (5.5)**	**4 (1.2)**	**6 (1.8)**	**100 (2.2)**
Gastrointestinal anastomotic leak	7 (1.5)	3 (0.6)	0	0	0
Failure to anastomose	1 (0.2)	5 (1.1)	0	0	0
Metabolism and nutrition disorders	**22 (4.6)**	**10 (2.1)**	**7 (2.0)**	**2 (0.6)**	**135 (2.9)**
Decreased appetite	4 (0.8)	5 (1.1)	1 (0.3)	1 (0.3)	13 (0.3)
General disorders and administration site conditions	**19 (4.0)**	**15 (3.2)**	**1 (0.3)**	**2 (0.6)**	**197 (4.2)**
Pyrexia	9 (1.9)	8 (1.7)	0	0	54 (1.2)

SOC PT	Number (%) of Patients [a]				
	MATTERHORN				D Pantumor Pool
	Overall Study [b]		Adjuvant Monotherapy Period		
	D + FLOT (N = 475)	Pbo + FLOT (N = 469)	D + FLOT (N = 345)	Pbo + FLOT (N = 331)	D (N = 4642)
Respiratory, thoracic and mediastinal disorders	**16 (3.4)**	**18 (3.8)**	**3 (0.9)**	**3 (0.9)**	**383 (8.3)**
Pulmonary embolism	8 (1.7)	4 (0.9)			38 (0.8)
Investigations	**3 (0.6)**	**5 (1.1)**	**0**	**0**	**53 (1.1)**
Neutrophil count decreased	2 (0.4)	5 (1.1)	0	0	0

[a] Number (%) of patients with SAEs, sorted in decreasing frequency of system organ class and preferred term (MATTERHORN Overall Durvalumab + FLOT column). Patients with multiple AEs are counted once for each system organ class / preferred term.

[b] The overall study includes the neoadjuvant, surgery, and adjuvant overall periods. The adjuvant monotherapy period is contained within the adjuvant overall period of the study and is shown here for the purpose of safety analysis.

Disease progression AEs reported in Study 1108 are not included.

Deaths

Table 42 All deaths (safety analysis set)

Category	Number (%) of patients				
	MATTERHORN				Durvalumab Pan-Tumor Pool
	Overall		Adjuvant Monotherapy		
	Durvalumab + FLOT (N=475)	Placebo + FLOT (N=469)	Durvalumab + FLOT (N=345)	Placebo + FLOT (N=331)	(N=4642)
Total number of deaths	145 (30.5)	174 (37.1)	67 (19.4)	85 (25.7)	3113 (67.1)
Death related to disease under investigation only [a]	98 (20.6)	133 (28.4)	55 (15.9)	72 (21.8)	2723 (58.7)
AE with outcome of death only [b]	12 (2.5)	17 (3.6)	2 (0.6)	5 (1.5)	143 (3.1)
AE outcome of death only and onset date > 90 days following last dose or > date of subsequent anti-cancer therapy (whichever occurs first)	5 (1.1)	4 (0.9)			13 (0.3)
Death related to disease under investigation and with AE with outcome of death [a] [b]	11 (2.3)	3 (0.6)	3 (0.9)	2 (0.6)	124 (2.7)
Death related to disease under investigation and AE with outcome of death > 90 days after last dose or > date of subsequent anti-cancer therapy (whichever occurs first)	1 (0.2)	2 (0.4)	0	0	7 (0.2)
Subjects with unknown reason for death	8 (1.7)	5 (1.1)	2 (0.6)	2 (0.6)	52 (1.1)
Other deaths [c]	10 (2.1)	10 (2.1)	5 (1.4)	3 (0.9)	51 (1.1)

Table 43 Treatment-emergent Adverse Events With Outcome of Death by SOC and PT (≥ 1 Patient in Either Treatment Arm, MATTERHORN Overall Study) (Safety Analysis Set)

SOC PT	Number (%) of Patients [a]				
	MATTERHORN				D Pantumor Pool
	Overall Study		Adjuvant Monotherapy Period		
	D + FLOT (N = 475)	Pbo + FLOT (N = 469)	D + FLOT (N = 345)	Pbo + FLOT (N = 331)	D (N = 4642)
Patients with any TEAE with an outcome of death	24 (5.1)	20 (4.3)	5 (1.4)	7 (2.1)	267 (5.8)
Infections and infestations	**12 (2.5)**	**8 (1.7)**	**2 (0.6)**	**3 (0.9)**	**50 (1.1)**
Septic shock	6 (1.3)	2 (0.4)			6 (0.1)
Abdominal sepsis			0	0	0
COVID-19					0
COVID-19 pneumonia					0
Pneumonia	1 (0.2)	1 (0.2)	0	0	18 (0.4)

SOC PT	Number (%) of Patients [a]				
	MATTERHORN				D Pantumor Pool
	Overall Study		Adjuvant Monotherapy Period		
	D + FLOT (N = 475)	Pbo + FLOT (N = 469)	D + FLOT (N = 345)	Pbo + FLOT (N = 331)	D (N = 4642)
Pneumonia aspiration	1 (0.2)	2 (0.4)			2 (<0.1)
Post procedural pneumonia			0	0	0
Sepsis					13 (0.3)
Respiratory, thoracic and mediastinal disorders	**4 (0.8)**	**3 (0.6)**			**59 (1.3)**
Pulmonary embolism	2 (0.4)	1 (0.2)	0	0	8 (0.2)
Diffuse alveolar damage			0	0	0
Pneumonitis			0	0	7 (0.2)
Acute respiratory distress syndrome					0
Respiratory distress			0	0	3 (0.1)
Cardiac disorders	**3 (0.6)**	**2 (0.4)**			**31 (0.7)**
Acute coronary syndrome			0	0	0
Cardiopulmonary failure			0	0	2 (<0.1)
Myocardial ischaemia			0	0	0
Cardiac arrest					7 (0.2)
Myocardial infarction			0	0	7 (0.2)
Gastrointestinal disorders	**3 (0.6)**	**3 (0.6)**	**3 (0.9)**	**1 (0.3)**	**17 (0.4)**
Gastrointestinal perforation	1 (0.2)	1 (0.2)			0
Intestinal perforation					0
Volvulus of small bowel					0
Intestinal ischaemia			0	0	0
Pneumoperitoneum					0
Metabolism and nutrition disorders			**0**	**0**	**4 (0.1)**
Diabetic ketoacidosis			0	0	0
Malnutrition			0	0	0
Blood and lymphatic system disorders			**0**	**0**	**5 (0.1)**
Febrile neutropenia			0	0	0
Injury, poisoning and procedural complications			**0**	**0**	**3 (0.1)**
Craniocerebral injury			0	0	0
Nervous system disorders					**12 (0.3)**
Ischemic stroke					2 (<0.1)
Vascular disorders			**0**	**0**	**10 (0.2)**
Aortic rupture			0	0	0
Shock haemorrhagic			0	0	1 (<0.1)

SOC PT	Number (%) of Patients [a]				
	MATTERHORN				D Pantumor Pool
	Overall Study		Adjuvant Monotherapy Period		
	D + FLOT (N = 475)	Pbo + FLOT (N = 469)	D + FLOT (N = 345)	Pbo + FLOT (N = 331)	D (N = 4642)

[a] Number (%) of patients with AEs with outcome of death during treatment-emergent period, sorted in decreasing frequency of system organ class and preferred term (MATTERHORN Overall D + FLOT column). Patients with multiple AEs are counted once for each system organ class / preferred term.

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). MedDRA version 27.1.

2.6.5. Laboratory findings

Table 44 Clinically Important Changes in Hematology Parameters (Safety Analysis Set)

Parameter	n/N (%) of patients					
	MATTERHORN				D pan-tumor pool	
	Overall study [a]					
	D + FLOT (N = 475)		Pbo + FLOT (N = 469)		D (N = 4642)	
	≥ 2 CTCAE grade changes	CTCAE grade changes to 3 or 4	≥ 2 CTCAE grade changes	CTCAE grade changes to 3 or 4	≥ 2 CTCAE grade changes	CTCAE grade changes to 3 or 4
Hemoglobin	71/472 (15.0)	35/472 (7.4)	77/466 (16.5)	39/466 (8.4)	252/4443 (5.7)	217/4443 (4.9)
Low	69/472 (14.6)	34/472 (7.2)	77/466 (16.5)	39/466 (8.4)	244/4443 (5.5)	211/4443 (4.7)
High					8/4443 (0.2)	6/4443 (0.1)
Leukocytes	192/472 (40.7)	66/472 (14.0)	192/466 (41.2)	77/466 (16.5)	89/4443 (2.0)	27/4443 (0.6)
Low	192/472 (40.7)	66/472 (14.0)	192/499 (41.2)	77/466 (16.5)	85/4443 (1.9)	23/4443 (0.5)
High	0	0	0	0	4/4443 (0.1)	4/4443 (0.1)
Lymphocytes	163/472 (34.5)	59/472 (12.5)	159/465 (34.2)	62/465 (13.3)	822/4350 (18.9)	551/4350 (12.7)
Low	134/472 (28.4)	59/472 (12.5)	123/465 (26.5)	61/465 (13.1)	769/4350 (17.7)	544/4350 (12.5)
High	39/472 (8.3)		45/465 (9.7)		64/4350 (1.5)	8/4350 (0.2)
Neutrophils	295/472 (62.5)	194/472 (41.1)	301/466 (64.6)	207/466 (44.4)	130/4338 (3.0)	36/4338 (0.8)
Platelets	22/472 (4.7)	5/472 (1.1)	17/466 (3.6)	9/466 (1.9)	82/4440 (1.8)	54/4440 (1.2)

[g] The overall study includes the neoadjuvant, surgery, and adjuvant overall periods. The adjuvant monotherapy period is contained within the adjuvant overall period of the study.

Derived from laboratory assessments between the start of treatment and up to and including 90 days following the date of last dose of study medication or until the initiation of the first subsequent therapy (whichever occurred first). In Study 1108, it was derived from laboratory assessments between the start of treatment and up to and including 97 days following the date of last dose of study medication or until the initiation of the first subsequent therapy excluding palliative radiotherapy (whichever occurred first).

Patient's worst (highest CTCAE grade) changes from baseline are used.

Percentages have been calculated using the number of patients with a baseline value and a post-baseline value.

All studies use CTCAE Version 5.0.

Table 45 Clinically Important Changes in Clinical Chemistry Parameters (Safety Analysis Set)

	n/N (%) of patients					
	MATTERHORN				D pan-tumor pool	
	Overall study [a]					
	D + FLOT (N = 475)		Pbo + FLOT (N = 469)		D (N = 4642)	
Parameter	≥ 2 CTCAE grade changes	CTCAE grade changes to 3 or 4	≥ 2 CTCAE grade changes	CTCAE grade changes to 3 or 4	≥ 2 CTCAE grade changes	CTCAE grade changes to 3 or 4
Alanine aminotransferase	92/471 (19.5)	34/471 (7.2)	61/468 (13.0)	29/468 (6.2)	191/4434 (4.3)	83/4434 (1.9)
Albumin	80/471 (17.0)	7/471 (1.5)	95/467 (20.3)	1/467 (0.2)	535/4386 (12.2)	61/4386 (1.4)
Alkaline phosphatase	35/471 (7.4)	15/471 (3.2)	22/467 (4.7)	7/467 (1.5)	132/4412 (3.0)	32/4412 (0.7)
Amylase	57/444 (12.8)	28/444 (6.3)	41/445 (9.2)	20/445 (4.5)	125/1994 (6.3)	90/1994 (4.5)
Aspartate aminotransferase	69/469 (14.7)	26/469 (5.5)	55/468 (11.8)	30/468 (6.4)	163/4423 (3.7)	84/4423 (1.9)
Corrected calcium	12/471 (2.5)	6/471 (1.3)	22/467 (4.7)	14/467 (3.0)	211/4258 (5.0)	122/4258 (2.9)
Low	9/471 (1.9)	4/471 (0.8)	19/467 (4.1)	12/467 (2.6)	65/4258 (1.5)	26/4258 (0.6)
High	4/471 (0.8)	2/471 (0.4)	3/467 (0.6)	2/467 (0.4)	148/4258 (3.5)	96/4258 (2.3)
Creatinine	59/472 (12.5)	9/472 (1.9)	33/468 (7.1)	6/468 (1.3)	385/4370 (8.8)	49/4370 (1.1)
Gamma-glutamyl transferase	117/462 (25.3)	47/462 (10.2)	90/456 (19.7)	28/456 (6.1)	199/3215 (6.2)	69/3215 (2.1)
Glucose [b]	28/470 (6.0)	6/470 (1.3)	31/467 (6.6)	10/467 (2.1)	63/4201 (1.5)	21/4201 (0.5)
Lipase	125/448 (27.9)	71/448 (15.8)	115/443 (26.0)	67/443 (15.1)	183/1869 (9.8)	145/1869 (7.8)
Magnesium	11/456 (2.4)	6/456 (1.3)	12/453 (2.6)	7/453 (1.5)	102/3820 (2.7)	89/3820 (2.3)
Low	6/456 (1.3)	-	6/453 (1.3)		39/3820 (1.0)	20/3820 (0.5)
High	6/456 (1.3)	6/456 (1.3)	6/453 (1.3)	6/453 (1.3)	73/3820 (1.9)	73/3820 (1.9)
Potassium	54/472 (11.4)	41/472 (8.7)	54/468 (11.5)	45/468 (9.6)	338/4426 (7.6)	183/4426 (4.1)

Parameter	n/N (%) of patients					
	MATTERHORN				D pan-tumor pool	
	Overall study [a]					
	D + FLOT (N = 475)		Pbo + FLOT (N = 469)		D (N = 4642)	
	≥ 2 CTCAE grade changes	CTCAE grade changes to 3 or 4	≥ 2 CTCAE grade changes	CTCAE grade changes to 3 or 4	≥ 2 CTCAE grade changes	CTCAE grade changes to 3 or 4
Low	38/472 (8.1)	39/472 (8.3)	39/468 (8.3)	39/468 (8.3)	96/4426 (2.2)	98/4426 (2.2)
High	17/472 (3.6)	3/472 (0.6)	15/468 (3.2)	6/468 (1.3)	247/4426 (5.6)	87/4426 (2.0)
Sodium	25/472 (5.3)	21/472 (4.4)	27/468 (5.8)	23/468 (4.9)	378/4435 (8.5)	373/4435 (8.4)
Low	21/472 (4.4)	21/472 (4.4)	22/468 (4.7)	22/468 (4.7)	358/4435 (8.1)	366/4435 (8.3)
High	4/472 (0.8)	-	5/468 (1.1)		20/4435 (0.5)	7/4435 (0.2)
Total bilirubin	22/472 (4.7)	10/472 (2.1)	19/466 (4.1)	5/466 (1.1)	202/4427 (4.6)	79/4427 (1.8)

[a] The overall study includes the neoadjuvant, surgery, and adjuvant overall periods. The adjuvant monotherapy period is contained within the adjuvant overall period of the study.

[b] For MATTERHORN, random glucose is presented; for ADRIATIC and the D pan-tumor pool, random and fasting glucose are collected but only fasting glucose is presented; other studies in the D pan-tumor pool contain a mix of random, fasting, and non-fasting glucose.

Derived from laboratory assessments between the start of treatment and up to and including 90 days following the date of last dose of study medication or until the initiation of the first subsequent therapy (whichever occurred first). In Study 1108, it was derived from laboratory assessments between the start of treatment and up to and including 37 days following the date of last dose of study medication or until the initiation of the first subsequent therapy excluding palliative radiotherapy (whichever occurred first).

Patient's worst (highest CTCAE grade; highest grade in the direction of high corrected calcium) changes from baseline are used.

Percentages have been calculated using the number of patients with a baseline value and a post-baseline value. All studies use CTCAE Version 5.0.

Table 46 Abnormal Thyroid Function Tests (Safety Analysis Set)

Thyroid function tests	Number (%) of patients		
	MATTERHORN		D pan-tumor pool
	Overall study [a]		
	D + FLOT (N = 475)	Pbo + FLOT (N =469)	D (N = 4642)
On-treatment elevated TSH > ULN	122 (25.7)	68 (14.5)	1457 (31.4)
On-treatment elevated TSH > ULN with TSH ≤ ULN at baseline *	95 (20.0)	51 (10.9)	929 (20.0)
with at least 1 T3 free/T4 free < LLN [b]	42 (44.2)	16 (31.4)	560 (60.3)
with all other T3 free/T4 free ≥ LLN [b]	43 (45.3)	23 (45.1)	303 (32.6)
with all T3 free/T4 free missing [b]	10 (10.5)	12 (23.5)	66 (7.1)
On-treatment low TSH < LLN	142 (29.9)	95 (20.3)	1041 (22.4)
On-treatment low TSH < LLN with baseline TSH ≥ LLN *	120 (25.3)	68 (14.5)	847 (18.2)
with at least 1 T3 free/T4 free > ULN [b]	32 (26.7)	10 (14.7)	373 (44.0)

Thyroid function tests	Number (%) of patients		
	MATTERHORN		D pan-tumor pool
	Overall study [a]		
	D + FLOT (N = 475)	Pbo + FLOT (N =469)	D (N = 4642)
with all other T3 free/T4 free ≤ ULN [b]	71 (59.2)	46 (67.6)	409 (48.3)
with all T3 free/T4 free missing [b]	17 (14.2)	12 (17.6)	65 (7.7)
Number of patients with at least 1 baseline and post-baseline TSH result *	459 (96.6)	453 (96.6)	4246 (91.5)
On-treatment elevated TSH > ULN and above baseline [b]	118 (25.7)	63 (13.9)	1291 (30.4)
On-treatment decreased TSH < LLN and below baseline [b]	142 (30.9)	91 (20.1)	972 (22.9)

[a] The overall study includes the neoadjuvant, surgery, and adjuvant overall periods. The adjuvant monotherapy period is contained within the adjuvant overall period of the study.

[b] Percentage is based on number of patients in the main category above denoted with a *.

Baseline is defined as the last result obtained prior to the start of study treatment.

Derived from laboratory assessments between the start of treatment and up to and including X days following the date of last dose of study medication or until the initiation of the first subsequent therapy (whichever occurs first). X = 90 (+ 7 for Study 1108 to allow for visit window) for MATTERHORN and studies in the D pan-tumor pool that do not recognize a 30-day washout period; X = 30 for studies in D pan-tumor pool that recognize a 30-day washout period.

Table 47 Reversibility of Creatinine Clearance (Safety Analysis Set)

Category	MATTERHORN				D pan-tumor pool	
	Overall study [a]					
	D + FLOT (N = 475)		Pbo + FLOT (N =469)		D (N = 4642)	
	Evaluable patients	N (%)	Evaluable patients	N (%)	Evaluable patients	N (%)
Patients shifting into a worse renal impairment category from baseline [b]	419	195 (46.5)	409	160 (39.1)	4128	1359 (32.9)
Patients whose shift from baseline was reversible and transient [c]	165	140 (84.8)	135	114 (84.4)	1039	886 (85.3)

[a] The overall study includes the neoadjuvant, surgery, and adjuvant overall periods. The adjuvant monotherapy period is contained within the adjuvant overall period of the study.

[b] Evaluable patients defined as patients with a baseline CrCl value and an on-treatment CrCl value, used as denominator.

[c] Evaluable patients defined as patients with a subsequent CrCl value after worsening from baseline, used as denominator. Reversible and transient is defined as a subsequent CrCl value that is higher than the worst CrCl value and in a better impairment category.

Baseline is defined as the last result obtained prior to the start of study treatment.

Derived from laboratory assessments between the start of treatment and up to and including X days following the date of last dose of study medication or until the initiation of the first subsequent therapy (whichever occurs first). X = 37 for Study 1108; X = 90 for MATTERHORN and studies in the D pan-tumor pool.

2.6.6. Safety in special populations

Intrinsic Factors

Effect of Sex

Table 48 Overview of adverse events by category – Patient level by sex (Safety analysis set; DCO2)

Parameter	Sex Group	Number (%) of Patients [a]				
		MATTERHORN				D Pan-tumor Pool
		Overall Study		Adjuvant Monotherapy Period		
		D + FLOT (N1 = 327) (N2 = 148)	Pbo + FLOT (N1 = 351) (N2 = 118)	D + FLOT (N1 = 238) (N2 = 107)	Pbo + FLOT (N1 = 255) (N2 = 76)	D (N1 = 3229) (N2 = 1413)
Any AE	Male	324 (99.1)	346 (98.6)	193 (81.1)	200 (78.4)	3033 (93.9)
	Female	147 (99.3)	117 (99.2)	81 (75.7)	60 (78.9)	1348 (95.4)
Any AE possibly related to any study treatment [b]	Male	310 (94.8)	331 (94.3)	119 (50.0)	87 (34.1)	1879 (58.2)
	Female	143 (96.6)	113 (95.8)	53 (49.5)	33 (43.4)	832 (58.9)
Any AE possibly related to durvalumab/placebo [b]	Male	191 (58.4)	184 (52.4)	94 (39.5)	61 (23.9)	1879 (58.2)
	Female	91 (61.5)	60 (50.8)	43 (40.2)	22 (28.9)	832 (58.9)
Any AE of CTCAE Grade 3 or Grade 4 [c]	Male	243 (74.3)	256 (72.9)	51 (21.4)	55 (21.6)	1368 (42.4)
	Female	114 (77.0)	92 (78.0)	24 (22.4)	18 (23.7)	589 (41.7)
Any AE possibly related to any study treatment of CTCAE Grade 3 or Grade 4 [b, c]	Male	192 (58.7)	203 (57.8)	18 (7.6)	20 (7.8)	392 (12.1)
	Female	95 (64.2)	76 (64.4)	13 (12.1)	10 (13.2)	161 (11.4)
Any AE possibly related to Durvalumab/Placebo of CTCAE Grade 3 or Grade 4 [b, c]	Male	43 (13.1)	41 (11.7)	10 (4.2)	13 (5.1)	392 (12.1)
	Female	25 (16.9)	17 (14.4)	9 (8.4)	6 (7.9)	161 (11.4)
Any AE of maximum CTCAE Grade 3 or Grade 4 [d]	Male	231 (70.6)	245 (69.8)	49 (20.6)	51 (20.0)	1242 (38.5)
	Female	109 (73.6)	89 (75.4)	24 (22.4)	17 (22.4)	540 (38.2)
Any AE possibly related to any study treatment of maximum CTCAE Grade 3 or Grade 4 [b, d]	Male	188 (57.5)	201 (57.3)	18 (7.6)	20 (7.8)	380 (11.8)
	Female	95 (64.2)	76 (64.4)	13 (12.1)	10 (13.2)	160 (11.3)
Any AE possibly related to Durvalumab/Placebo of maximum CTCAE Grade 3 or Grade 4 [b, d]	Male	42 (12.8)	41 (11.7)	10 (4.2)	13 (5.1)	380 (11.8)
	Female	25 (16.9)	17 (14.4)	9 (8.4)	6 (7.9)	160 (11.3)
Any AE with outcome = death	Male	19 (5.8)	18 (5.1)	6 (2.5)	6 (2.4)	199 (6.2)
	Female	8 (5.4)	4 (3.4)			76 (5.4)
Any AE with outcome = death, possibly related to any study treatment [b]	Male	6 (1.8)	3 (0.9)			32 (1.0)
	Female			0	0	5 (0.4)
Any AE with outcome = death, possibly related to Durvalumab/Placebo [b]	Male	2 (0.6)	1 (0.3)			32 (1.0)
	Female			0	0	5 (0.4)
Any AE with outcome = death during treatment-emergent period	Male	16 (4.9)	16 (4.6)	5 (2.1)	6 (2.4)	193 (6.0)
	Female	7 (4.7)	4 (3.4)			74 (5.2)
Any AE with outcome = death during treatment-emergent period, possibly related to any study treatment [b]	Male	5 (1.5)	2 (0.6)			28 (0.9)
	Female			0	0	5 (0.4)
Any AE with outcome = death during treatment-emergent period, possibly related to Durvalumab/Placebo [b]	Male	2 (0.6)	1 (0.3)			28 (0.9)
	Female			0	0	5 (0.4)
Any SAE (including events with outcome = death) [e]	Male	160 (48.9)	162 (46.2)	33 (13.9)	40 (15.7)	1152 (35.7)
	Female	69 (46.6)	45 (38.1)	17 (15.9)	8 (10.5)	505 (35.7)
Any SAE (including events with outcome = death), possibly related to any study treatment [b, e]	Male	73 (22.3)	59 (16.8)	6 (2.5)	4 (1.6)	281 (8.7)
	Female	35 (23.6)	20 (16.9)	7 (6.5)	2 (2.6)	89 (6.3)
Any SAE (including events with outcome = death), possibly related to Durvalumab/Placebo [b, e]	Male	25 (7.6)	20 (5.7)	5 (2.1)	4 (1.6)	281 (8.7)
	Female	15 (10.1)	5 (4.2)	6 (5.6)	2 (2.6)	89 (6.3)
Any AE leading to discontinuation of any study treatment	Male	93 (28.4)	81 (23.1)	13 (5.5)	9 (3.5)	349 (10.8)
	Female	49 (33.1)	26 (22.0)	7 (6.5)	1 (1.3)	140 (9.9)
Any AE leading to discontinuation of Durvalumab/Placebo	Male	31 (9.5)	22 (6.3)	13 (5.5)	8 (3.1)	349 (10.8)
	Female	17 (11.5)	8 (6.8)	7 (6.5)	1 (1.3)	140 (9.9)
Any AE possibly related to any study treatment leading to discontinuation of any study treatment [b]	Male	77 (23.5)	68 (19.4)	9 (3.8)	8 (3.1)	163 (5.0)
	Female	45 (30.4)	22 (18.6)	7 (6.5)	1 (1.3)	71 (5.0)

Any AE possibly related to Durvalumab/Placebo leading to discontinuation of Durvalumab/Placebo [b]	Male	17 (5.2)	14 (4.0)	8 (3.4)	7 (2.7)	163 (5.0)
	Female	12 (8.1)	5 (4.2)	6 (5.6)	1 (1.3)	71 (5.0)
Any AE leading to dose modification of any study treatment [f]	Male	244 (74.6)	243 (69.2)	59 (24.8)	49 (19.2)	894 (27.7)
	Female	119 (80.4)	90 (76.3)	17 (15.9)	15 (19.7)	401 (28.4)
Any AE leading to dose delay or interruption of any study treatment [g]	Male	221 (67.6)	216 (61.5)	59 (24.8)	49 (19.2)	889 (27.5)
	Female	103 (69.6)	77 (65.3)	17 (15.9)	15 (19.7)	397 (28.1)
Any AE leading to dose delay or interruption of Durvalumab/Placebo [g]	Male	181 (55.4)	180 (51.3)	59 (24.8)	49 (19.2)	889 (27.5)
	Female	87 (58.8)	61 (51.7)	17 (15.9)	15 (19.7)	397 (28.1)
Any adjudicated imAE [h]	Male	71 (21.7)	27 (7.7)	28 (11.8)	9 (3.5)	583 (18.1)
	Female	39 (26.4)	7 (5.9)	18 (16.8)	3 (3.9)	270 (19.1)

[a] Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories.
[b] As assessed by the investigator. Missing responses are counted as related.
[c] All CTCAE grades per patient/treatment period, not just the maximum, are considered when identifying whether there is a Grade 3 or 4.
[d] Maximum CTCAE grade per patient/treatment period/event is considered.
[e] Seriousness, as assessed by the investigator. An AE with missing seriousness is considered serious.
[f] Includes AEs on the AE CRF form with action taken indicating dose reduction, dose delay or dose interruption, and AEs meeting study level dose delay definitions, where applicable.
[g] Includes AEs on the AE CRF form with action taken indicating dose delay or dose interruption, and AEs meeting study level dose delay definitions, where applicable.
[h] Excludes AESI group of infusion or hypersensitivity reactions.

N1 = Total number of male patients, N2 = Total number of female patients; Percentages are calculated from N1 and N2 for male and female, respectively.
Adjuvant monotherapy period includes AEs which start or first worsen between date of first dose of adjuvant monotherapy treatment up to and including 90 days following the date of last dose of study medication or up to and including the date of initiation of the first subsequent therapy (whichever occurs first).
Overall period and Durvalumab Pan-Tumor Pool includes adverse events with an onset date on or after the date of first dose or pre-treatment AEs that increase in severity on or after the date of first dose up to and including 90 days following the date of last dose of study medication or up to and including the date of initiation of the first subsequent therapy (whichever occurs first).
Disease progression adverse events reported in Study 1108 are not included in this summary.
All studies use CTCAE version 4.03 except for MATTERHORN which uses version 5.0. For MATTERHORN, CTCAE grades are reported during treatment-emergent period. For D Pan-Tumor pool, CTCAE grades are reported during the full duration of the AE.

Effect of Age

Table 49 Overview of adverse events by category – Patient Level by age (Safety analysis set; DCO2)

Parameter	Age Group (Years)	Number (%) of Patients [a]				
		MATTERHORN				D Pan-tumor Pool
		Overall Study		Adjuvant Monotherapy Period		
		D + FLOT (N1 = 86) (N2 = 205) (N3 = 147) (N4 = 37)	Pbo + FLOT (N1 = 57) (N2 = 207) (N3 = 163) (N4 = 42)	D + FLOT (N1 = 71) (N2 = 149) (N3 = 104) (N4 = 21)	Pbo + FLOT (N1 = 43) (N2 = 146) (N3 = 121) (N4 = 21)	D (N1 = 537) (N2 = 2089) (N3 = 1542) (N4 = 474)
Any AE	<50	84 (97.7)	56 (98.2)	53 (74.6)	31 (72.1)	504 (93.9)
	≥50 - <65	205 (100)	205 (99.0)	118 (79.2)	117 (80.1)	1957 (93.7)
	≥65 - <75	145 (98.6)	162 (99.4)	87 (83.7)	96 (79.3)	1466 (95.1)
	≥75	37 (100)	40 (95.2)	16 (76.2)	16 (76.2)	454 (95.8)
Any AE possibly related to any study treatment [b]	<50	80 (93.0)	54 (94.7)	31 (43.7)	19 (44.2)	282 (52.5)
	≥50 - <65	200 (97.6)	196 (94.7)	77 (51.7)	51 (34.9)	1239 (59.3)
	≥65 - <75	200 (97.6)	196 (94.7)	77 (51.7)	51 (34.9)	1239 (59.3)
	≥75	33 (89.2)	38 (90.5)	10 (47.6)	12 (57.1)	271 (57.2)
Any AE possibly related to durvalumab/placebo [b]	<50	58 (67.4)	31 (54.4)	25 (35.2)	11 (25.6)	282 (52.5)
	≥50 - <65	113 (55.1)	106 (51.2)	61 (40.9)	37 (25.3)	1239 (59.3)
	≥65 - <75	88 (59.9)	86 (52.8)	42 (40.4)	25 (20.7)	919 (59.6)
	≥75	23 (62.2)	21 (50.0)	9 (42.9)	10 (47.6)	271 (57.2)
Any AE of CTCAE Grade 3 or Grade 4 [c]	<50	62 (72.1)	32 (56.1)	10 (14.1)	5 (11.6)	215 (40.0)
	≥50 - <65	147 (71.7)	161 (77.8)	33 (22.1)	39 (26.7)	852 (40.8)
	≥65 - <75	118 (80.3)	124 (76.1)	24 (23.1)	26 (21.5)	659 (42.7)
	≥75	30 (81.1)	31 (73.8)	8 (38.1)	3 (14.3)	231 (48.7)
Any AE possibly related to any study treatment of CTCAE Grade 3 or Grade 4 [b, c]	<50	51 (59.3)	31 (54.4)	7 (9.9)	4 (9.3)	44 (8.2)
	≥50 - <65	121 (59.0)	121 (58.5)	12 (8.1)	18 (12.3)	252 (12.1)
	≥65 - <75	91 (61.9)	106 (65.0)	10 (9.6)	7 (5.8)	193 (12.5)
	≥75	24 (64.9)	21 (50.0)	2 (9.5)	1 (4.8)	64 (13.5)
Any AE possibly related to Durvalumab/Placebo of CTCAE Grade 3 or Grade 4 [b, c]	<50	19 (22.1)	7 (12.3)	7 (9.9)	2 (4.7)	44 (8.2)
	≥50 - <65	22 (10.7)	28 (13.5)	4 (2.7)	12 (8.2)	252 (12.1)
	≥65 - <75	21 (14.3)	17 (10.4)	7 (6.7)	4 (3.3)	193 (12.5)
	≥75	6 (16.2)	6 (14.3)	1 (4.8)	1 (4.8)	64 (13.5)
Any AE of maximum CTCAE Grade 3 or Grade 4 [d]	<50	62 (72.1)	31 (54.4)	10 (14.1)	5 (11.6)	197 (36.7)
	≥50 - <65	141 (68.8)	155 (74.9)	33 (22.1)	36 (24.7)	789 (37.8)
	≥65 - <75	109 (74.1)	119 (73.0)	22 (21.2)	24 (19.8)	587 (38.1)
	≥75	28 (75.7)	29 (69.0)	8 (38.1)	3 (14.3)	209 (44.1)
Any AE possibly related to any study treatment of maximum CTCAE Grade 3 or Grade 4 [b, d]	<50	51 (59.3)	30 (52.6)	7 (9.9)	4 (9.3)	43 (8.0)
	≥50 - <65	119 (58.0)	121 (58.5)	12 (8.1)	18 (12.3)	245 (11.7)
	≥65 - <75	91 (61.9)	105 (64.4)	10 (9.6)	7 (5.8)	191 (12.4)
	≥75	22 (59.5)	21 (50.0)	2 (9.5)	1 (4.8)	61 (12.9)
Any AE possibly related to Durvalumab/Placebo of maximum CTCAE Grade 3 or Grade 4 [b, d]	<50	19 (22.1)	7 (12.3)	7 (9.9)	2 (4.7)	43 (8.0)
	≥50 - <65	22 (10.7)	28 (13.5)	4 (2.7)	12 (8.2)	245 (11.7)
	≥65 - <75	21 (14.3)	17 (10.4)	7 (6.7)	4 (3.3)	191 (12.4)
	≥75	5 (13.5)	6 (14.3)	1 (4.8)	1 (4.8)	61 (12.9)
Any AE with outcome = death	<50	2 (2.3)	1 (1.8)	0	0	24 (4.5)
	≥50 - <65	8 (3.9)	6 (2.9)	3 (2.0)	4 (2.7)	109 (5.2)
	≥65 - <75	12 (8.2)	10 (6.1)	2 (1.9)	3 (2.5)	110 (7.1)
	≥75	5 (13.5)	5 (11.9)			32 (6.8)
Any AE with outcome = death, possibly related to any study treatment [b]	<50			0	0	2 (0.4)
	≥50 - <65					14 (0.7)
	≥65 - <75	1 (0.7)	2 (1.2)	0	0	15 (1.0)
	≥75					6 (1.3)
Any AE with outcome = death, possibly related to Durvalumab/Placebo [b]	<50			0	0	2 (0.4)
	≥50 - <65					14 (0.7)
	≥65 - <75	0	0	0	0	15 (1.0)
	≥75			0	0	6 (1.3)

Any AE with outcome = death during treatment-emergent period	<50	2 (2.3)	1 (1.8)	0	0	23 (4.3)
	≥50 - <65	8 (3.9)	6 (2.9)	3 (2.0)	4 (2.7)	107 (5.1)
	≥65 - <75	9 (6.1)	9 (5.5)	2 (1.9)	3 (2.5)	106 (6.9)
	≥75	4 (10.8)	4 (9.5)	0	0	31 (6.5)
Any AE with outcome = death during treatment-emergent period, possibly related to any study treatment [b]	<50			0	0	1 (0.2)
	≥50 - <65					13 (0.6)
	≥65 - <75	1 (0.7)	1 (0.6)	0	0	14 (0.9)
	≥75			0	0	5 (1.1)
Any AE with outcome = death during treatment-emergent period, possibly related to Durvalumab/Placebo [b]	<50			0	0	1 (0.2)
	≥50 - <65					13 (0.6)
	≥65 - <75	0	0	0	0	14 (0.9)
	≥75			0	0	5 (1.1)
Any SAE (including events with outcome = death) [e]	<50	34 (39.5)	18 (31.6)	4 (5.6)	2 (4.7)	179 (33.3)
	≥50 - <65	92 (44.9)	92 (44.4)	22 (14.8)	25 (17.1)	704 (33.7)
	≥65 - <75	77 (52.4)	71 (43.6)	16 (15.4)	19 (15.7)	557 (36.1)
	≥75	26 (70.3)	26 (61.9)	8 (38.1)	2 (9.5)	217 (45.8)
Any SAE (including events with outcome = death), possibly related to any study treatment [b, e]	<50	17 (19.8)	12 (21.1)	2 (2.8)	1 (2.3)	34 (6.3)
	≥50 - <65	38 (18.5)	29 (14.0)	4 (2.7)	3 (2.1)	166 (7.9)
	≥65 - <75	39 (26.5)	28 (17.2)	5 (4.8)	1 (0.8)	121 (7.8)
	≥75	14 (37.8)	10 (23.8)	2 (9.5)	1 (4.8)	49 (10.3)
Any SAE (including events with outcome = death), possibly related to Durvalumab/Placebo [b, e]	<50	8 (9.3)	3 (5.3)	2 (2.8)	1 (2.3)	34 (6.3)
	≥50 - <65	12 (5.9)	12 (5.8)	3 (2.0)	3 (2.1)	166 (7.9)
	≥65 - <75	14 (9.5)	6 (3.7)	5 (4.8)	1 (0.8)	121 (7.8)
	≥75	6 (16.2)	4 (9.5)	1 (4.8)	1 (4.8)	49 (10.3)
Any AE leading to discontinuation of any study treatment	<50	30 (34.9)	16 (28.1)	4 (5.6)	2 (4.7)	36 (6.7)
	≥50 - <65	54 (26.3)	40 (19.3)	4 (2.7)	4 (2.7)	196 (9.4)
	≥65 - <75	45 (30.6)	36 (22.1)	9 (8.7)	3 (2.5)	192 (12.5)
	≥75	13 (35.1)	15 (35.7)	3 (14.3)	1 (4.8)	65 (13.7)
Any AE leading to discontinuation of Durvalumab/Placebo	<50	9 (10.5)	2 (3.5)	4 (5.6)	2 (4.7)	36 (6.7)
	≥50 - <65	9 (4.4)	12 (5.8)	4 (2.7)	4 (2.7)	196 (9.4)
	≥65 - <75	22 (15.0)	8 (4.9)	9 (8.7)	2 (1.7)	192 (12.5)
	≥75	8 (21.6)	8 (19.0)	3 (14.3)	1 (4.8)	65 (13.7)
Any AE possibly related to any study treatment leading to discontinuation of any study treatment [b]	<50	28 (32.6)	14 (24.6)	4 (5.6)	2 (4.7)	12 (2.2)
	≥50 - <65	49 (23.9)	34 (16.4)	3 (2.0)	3 (2.1)	94 (4.5)
	≥65 - <75	35 (23.8)	33 (20.2)	6 (5.8)	3 (2.5)	88 (5.7)
	≥75	10 (27.0)	9 (21.4)	3 (14.3)	1 (4.8)	40 (8.4)
Any AE possibly related to Durvalumab/Placebo leading to discontinuation of Durvalumab/Placebo [b]	<50	8 (9.3)	2 (3.5)	3 (4.2)	2 (4.7)	12 (2.2)
	≥50 - <65	6 (2.9)	10 (4.8)	3 (2.0)	3 (2.1)	94 (4.5)
	≥65 - <75	10 (6.8)	4 (2.5)	6 (5.8)	2 (1.7)	88 (5.7)
	≥75	5 (13.5)	3 (7.1)	2 (9.5)	1 (4.8)	40 (8.4)
Any AE leading to dose modification of any study treatment [f]	<50	65 (75.6)	35 (61.4)	17 (23.9)	10 (23.3)	115 (21.4)
	≥50 - <65	161 (78.5)	148 (71.5)	34 (22.8)	29 (19.9)	568 (27.2)
	≥65 - <75	109 (74.1)	123 (75.5)	20 (19.2)	22 (18.2)	467 (30.3)
	≥75	28 (75.7)	27 (64.3)	5 (23.8)	3 (14.3)	145 (30.6)
Any AE leading to dose delay or interruption of any study treatment [g]	<50	59 (68.6)	33 (57.9)	17 (23.9)	10 (23.3)	112 (20.9)
	≥50 - <65	149 (72.7)	129 (62.3)	34 (22.8)	29 (19.9)	565 (27.0)
	≥65 - <75	90 (61.2)	108 (66.3)	20 (19.2)	22 (18.2)	465 (30.2)
	≥75	26 (70.3)	23 (54.8)	5 (23.8)	3 (14.3)	144 (30.4)

Any AE leading to dose delay or interruption of Durvalumab/Placebo [g]	<50	47 (54.7)	27 (47.4)	17 (23.9)	10 (23.3)	112 (20.9)
	≥50 - <65	121 (59.0)	104 (50.2)	34 (22.8)	29 (19.9)	565 (27.0)
	≥65 - <75	75 (51.0)	91 (55.8)	20 (19.2)	22 (18.2)	465 (30.2)
	≥75	25 (67.6)	19 (45.2)	5 (23.8)	3 (14.3)	144 (30.4)
Any adjudicated imAE [h]	<50	26 (30.2)	4 (7.0)	11 (15.5)	3 (7.0)	76 (14.2)
	≥50 - <65	49 (23.9)	15 (7.2)	21 (14.1)	3 (2.1)	377 (18.0)
	≥65 - <75	27 (18.4)	8 (4.9)	11 (10.6)	5 (4.1)	302 (19.6)
	≥75	8 (21.6)	7 (16.7)	3 (14.3)	1 (4.8)	98 (20.7)

[a] Patients with multiple events in the same category are counted only once in that category. Patients with events in more than 1 category are counted once in each of those categories.
[b] As assessed by the investigator. Missing responses are counted as related.
[c] All CTCAE grades per patient/treatment period, not just the maximum, are considered when identifying whether there is a Grade 3 or 4.
[d] Maximum CTCAE grade per patient/treatment period/event is considered.
[e] Seriousness, as assessed by the investigator. An AE with missing seriousness is considered serious.
[f] Includes AEs on the AE case report form with action taken indicating dose delay or dose interruption, and AEs meeting study level dose delay definitions, where applicable.
[g] Includes AEs on the AE CRF form with action taken indicating dose delay or dose interruption, and AEs meeting study level dose delay definitions, where applicable.
[h] Excludes AESI group of infusion or hypersensitivity reactions.

N1 = Total number of <50 years patients, N2 = Total number of ≥50 to <65 years patients, N3 = Total number of ≥65 to <75 years patients, N4 = Total number of ≥75 years patients. Adjuvant monotherapy period includes AEs which start or first worsen between date of first dose of adjuvant monotherapy treatment up to and including 90 days following the date of last dose of study medication or up to and including the date of initiation of the first subsequent therapy (whichever occurs first). Overall period and Durvalumab pan-tumor pool includes AEs with an onset date on or after the date of first dose or pre-treatment AEs that increase in severity on or after the date of first dose up to and including 90 days following the date of last dose of study medication or up to and including the date of initiation of the first subsequent therapy (whichever occurs first). Disease progression adverse events reported in Study 1108 are not included in this summary.

Effect of Race

Table 50 Overview of adverse events by category – Patient level by race (Safety analysis set; DCO2)

		Number (%) of Patients [a]				
		MATTERHORN				D Pan-tumor Pool
		Overall Study		Adjuvant Monotherapy Period		
Parameter	Race Group	D + FLOT (N1 = 322) (N2 = 7) (N3 = 96) (N4 = 26) (N5 = 24)	Pbo + FLOT (N1 = 319) (N2 = 3) (N3 = 95) (N4 = 28) (N5 = 24)	D + FLOT (N1 = 230) (N2 = 6) (N3 = 70) (N4 = 18) (N5 = 21)	Pbo + FLOT (N1 = 217) (N2 = 3) (N3 = 77) (N4 = 19) (N5 = 15)	D (N1 = 2892) (N2 = 85) (N3 = 1514) (N4 = 74) (N5 = 77)
Any AE	White	319 (99.1)	313 (98.1)	192 (83.5)	173 (79.7)	2747 (95.0)
	Black or African American	7 (100)	3 (100)	5 (83.3)	3 (100)	84 (98.8)
	Asian	95 (99.0)	95 (100)	52 (74.3)	59 (76.6)	1401 (92.5
	Other	26 (100)	28 (100)	10 (55.6)	12 (63.2)	72 (97.3)
	Missing	24 (100)	24 (100)	15 (71.4)	13 (86.7)	77 (100)
Any AE possibly related to any study treatment [b]	White	306 (95.0)	296 (92.8)	119 (51.7)	80 (36.9)	1700 (58.8)
	Black or African American	6 (85.7)	3 (100)			59 (69.4)
	Asian	95 (99.0)	95 (100)	34 (48.6)	22 (28.6)	856 (56.5)
	Other	23 (88.5)	27 (96.4)	5 (27.8)	8 (42.1)	48 (64.9)
	Missing	23 (95.8)	23 (95.8)	11 (52.4)	10 (66.7)	48 (62.3)
Any AE possibly related to durvalumab/placebo [b]	White	195 (60.6)	175 (54.9)	97 (42.2)	56 (25.8)	1700 (58.8)
	Black or African American	4 (57.1)	2 (66.7)			59 (69.4)
	Asian	53 (55.2)	39 (41.1)	24 (34.3)	13 (16.9)	856 (56.5)
	Other	13 (50.0)	13 (46.4)	3 (16.7)	8 (42.1)	48 (64.9)
	Missing	17 (70.8)	15 (62.5)	10 (47.6)	6 (40.0)	48 (62.3)

Any AE of CTCAE Grade 3 or Grade 4 [c]	White	233 (72.4)	231 (72.4)	51 (22.2)	50 (23.0)	1271 (43.9)
	Black or African American	7 (100)	3 (100)			47 (55.3)
	Asian	84 (87.5)	81 (85.3)	14 (20.0)	15 (19.5)	555 (36.7)
	Other	14 (53.8)	18 (64.3)	4 (22.2)	6 (31.6)	40 (54.1)
	Missing	19 (79.2)	15 (62.5)	5 (23.8)	2 (13.3)	44 (57.1)
Any AE possibly related to any study treatment of CTCAE Grade 3 or Grade 4 [b,c]	White	177 (55.0)	176 (55.2)	20 (8.7)	19 (8.8)	331 (11.4)
	Black or African American	6 (85.7)	2 (66.7)			9 (10.6)
	Asian	80 (83.3)	76 (80.0)	5 (7.1)	9 (11.7)	199 (13.1)
	Other	8 (30.8)	14 (50.0)	2 (11.1)	2 (10.5)	10 (13.5)
	Missing	16 (66.7)	11 (45.8)			4 (5.2)
Any AE possibly related to Durvalumab/Placebo of CTCAE Grade 3 or Grade 4 [b,c]	White	45 (14.0)	45 (14.1)	12 (5.2)	12 (5.5)	331 (11.4)
	Black or African American					9 (10.6)
	Asian	15 (15.6)	7 (7.4)	2 (2.9)	5 (6.5)	199 (13.1)
	Other	2 (7.7)	2 (7.1)	2 (11.1)	2 (10.5)	10 (13.5)
	Missing	5 (20.8)	4 (16.7)			4 (5.2)
Any AE of maximum CTCAE Grade 3 or Grade 4 [d]	White	218 (67.7)	223 (69.9)	49 (21.3)	48 (22.1)	1164 (40.2)
	Black or African American	7 (100)	3 (100)			42 (49.4)
	Asian	82 (85.4)	80 (84.2)	14 (20.0)	15 (19.5)	514 (33.9)
	Other	14 (53.8)	15 (53.6)	4 (22.2)	3 (15.8)	37 (50.0)
	Missing	19 (79.2)	13 (54.2)	5 (23.8)	2 (13.3)	25 (32.5)
Any AE possibly related to any study treatment of maximum CTCAE Grade 3 or Grade 4 [b,d]	White	173 (53.7)	175 (54.9)	20 (8.7)	19 (8.8)	327 (11.3)
	Black or African American	6 (85.7)	2 (66.7)			8 (9.4)
	Asian	80 (83.3)	75 (78.9)	5 (7.1)	9 (11.7)	191 (12.6)
	Other	8 (30.8)	14 (50.0)	2 (11.1)	2 (10.5)	10 (13.5)
	Missing	16 (66.7)	11 (45.8)			4 (5.2)
Any AE possibly related to Durvalumab/Placebo of maximum CTCAE Grade 3 or Grade 4 [b,d]	White	44 (13.7)	45 (14.1)	12 (5.2)	12 (5.5)	327 (11.3)
	Black or African American					8 (9.4)
	Asian	15 (15.6)	7 (7.4)	2 (2.9)	5 (6.5)	191 (12.6)
	Other	2 (7.7)	2 (7.1)	2 (11.1)	2 (10.5)	10 (13.5)
	Missing	5 (20.8)	4 (16.7)			4 (5.2)
Any AE with outcome = death	White	24 (7.5)	15 (4.7)	6 (2.6)	4 (1.8)	179 (6.2)
	Black or African American	0	0	0	0	6 (7.1)
	Asian	2 (2.1)	1 (1.1)	0	0	66 (4.4)
	Other	1 (3.8)	4 (14.3)			4 (5.4)
	Missing			0	0	20 (26.0)
Any AE with outcome = death, possibly related to any study treatment [b]	White	7 (2.2)	2 (0.6)			17 (0.6)
	Black or African American	0	0	0	0	1 (1.2)
	Asian			0	0	19 (1.3)
	Other	0	0	0	0	0
Any AE with outcome = death, possibly related to Durvalumab/Placebo [b]	White					17 (0.6)
	Black or African American	0	0	0	0	1 (1.2)
	Asian			0	0	19 (1.3)
	Other	0	0	0	0	0
Any AE with outcome = death during treatment-emergent period	White	20 (6.2)	13 (4.1)	5 (2.2)	4 (1.8)	176 (6.1)
	Black or African American	0	0	0	0	6 (7.1)
	Asian	2 (2.1)	1 (1.1)	0	0	61 (4.0)
	Other	1 (3.8)	4 (14.3)			4 (5.4)
	Missing			0	0	20 (26.0)
Any AE with outcome = death during treatment-emergent period, possibly related to any study treatment [b]	White	6 (1.9)	1 (0.3)			16 (0.6)
	Black or African American	0	0	0	0	1 (1.2)
	Asian			0	0	16 (1.1)
	Other	0	0	0	0	0
Any AE with outcome = death during treatment-emergent period, possibly related to Durvalumab/Placebo [b]	White					16 (0.6)
	Black or African American	0	0	0	0	1 (1.2)
	Asian			0	0	16 (1.1)
	Other	0	0	0	0	0

Any SAE (including events with outcome = death) [e]	White	161 (50.0)	144 (45.1)	35 (15.2)	32 (14.7)	1051 (36.3)
	Black or African American	1 (14.3)	3 (100)	0	0	41 (48.2)
	Asian	46 (47.9)	39 (41.1)	13 (18.6)	10 (13.0)	486 (32.1)
	Other	7 (26.9)	10 (35.7)			35 (47.3)
	Missing	14 (58.3)	11 (45.8)	2 (9.5)	2 (13.3)	44 (57.1)
Any SAE (including events with outcome = death), possibly related to any study treatment [b,e]	White	68 (21.1))	47 (14.7)	9 (3.9)	3 (1.4)	185 (6.4)
	Black or African American	0	0	0	0	5 (5.9)
	Asian	31 (32.3)	26 (27.4)	3 (4.3)	3 (3.9)	171 (11.3)
	Other			0	0	6 (8.1)
	Missing	9 (37.5)	4 (16.7)			3 (3.9)
Any SAE (including events with outcome = death), possibly related to Durvalumab/Placebo [b] [e]	White	28 (8.7)	18 (5.6)	7 (3.0)	3 (1.4)	185 (6.4)
	Black or African American	0	0	0	0	5 (5.9)
	Asian	9 (9.4)	6 (6.3)	3 (4.3)	3 (3.9)	171 (11.3)
	Other	0	0	0	0	6 (8.1)
	Missing	3 (12.5)	1 (4.2)			3 (3.9)
Any AE leading to discontinuation of any study treatment	White	103 (32.0)	73 (22.9)	16 (7.0)	4 (1.8)	320 (11.1)
	Black or African American					5 (5.9)
	Asian	21 (21.9)	23 (24.2)	2 (2.9)	5 (6.5)	144 (9.5)
	Other	3 (11.5)	2 (7.1)			5 (6.8)
	Missing	13 (54.2)	9 (37.5)			15 (19.5)
Any AE leading to discontinuation of Durvalumab/Placebo	White	39 (12.1)	20 (6.3)	16 (7.0)	4 (1.8)	320 (11.1)
	Black or African American					5 (5.9)
	Asian	6 (6.3)	7 (7.4)	2 (2.9)	4 (5.2)	144 (9.5)
	Other					5 (6.8)
	Missing	2 (8.3)	2 (8.3)			15 (19.5)
Any AE possibly related to any study treatment leading to discontinuation of any study treatment [b]	White	88 (27.3)	60 (18.8)	13 (5.7)	3 (1.4)	142 (4.9)
	Black or African American					2 (2.4)
	Asian	18 (18.8)	21 (22.1)	1 (1.4)	5 (6.5)	87 (5.7)
	Other	3 (11.5)	2 (7.1)			2 (2.7)
	Missing	11 (45.8)	7 (29.2)			1 (1.3)
Any AE possibly related to Durvalumab/Placebo leading to discontinuation of Durvalumab/Placebo [b]	White	23 (7.1)	13 (4.1)	11 (4.8)	3 (1.4)	142 (4.9)
	Black or African American					2 (2.4)
	Asian	4 (4.2)	5 (5.3)	1 (1.4)	4 (5.2)	87 (5.7)
	Other					2 (2.7)
	Missing					1 (1.3)
Any AE leading to dose modification of any study treatment [f]	White	242 (75.2)	217 (68.0)	47 (20.4)	40 (18.4)	826 (28.6)
	Black or African American	5 (71.4)	3 (100)	3 (50.0)	3 (100)	27 (31.8)
	Asian	81 (84.4)	86 (90.5)	20 (28.6)	15 (19.5)	389 (25.7)
	Other	18 (69.2)	15 (53.6)	4 (22.2)	6 (31.6)	28 (37.8)
	Missing	17 (70.8)	12 (50.0)			25 (32.5)
Any AE leading to dose delay or interruption of any study treatment [g]	White	221 (68.6)	198 (62.1)	47 (20.4)	40 (18.4)	817 (28.3)
	Black or African American	5 (71.4)	3 (100)	3 (50.0)	3 (100)	27 (31.8)
	Asian	68 (70.8)	69 (72.6)	20 (28.6)	15 (19.5)	389 (25.7)
	Other	14 (53.8)	12 (42.9)	4 (22.2)	6 (31.6)	28 (37.8)
	Missing	16 (66.7)	11 (45.8)			25 (32.5)
Any AE leading to dose delay or interruption of Durvalumab/Placebo [g]	White	181 (56.2)	170 (53.3)	47 (20.4)	40 (18.4)	817 (28.3)
	Black or African American	5 (71.4)	3 (100)	3 (50.0)	3 (100)	27 (31.8)
	Asian	58 (60.4)	49 (51.6)	20 (28.6)	15 (19.5)	389 (25.7)
	Other	13 (50.0)	11 (39.3)	4 (22.2)	6 (31.6)	28 (37.8)
	Missing	11 (45.8)	8 (33.3)			25 (32.5)
Any adjudicated imAE [h]	White	76 (23.6)	25 (7.8)	35 (15.2)	8 (3.7)	538 (18.6)
	Black or African American	2 (28.6)	1 (33.3)			10 (11.8)
	Asian	20 (20.8)	4 (4.2)	6 (8.6)	2 (2.6)	273 (18.0)
	Other	3 (11.5)	2 (7.1)	1 (5.6)	1 (5.3)	16 (21.6)
	Missing	9 (37.5)	2 (8.3)	3 (14.3)	1 (6.7)	16 (20.8)

[a] Patients with multiple events in the same category are counted only once in that category. Patients with events in more than 1 category are counted once in each of those categories.
[b] As assessed by the investigator. Missing responses are counted as related.
[c] All CTCAE grades per patient/treatment period, not just the maximum, are considered when identifying whether there is a Grade 3 or 4.
[d] Maximum CTCAE grade per patient/treatment period/event is considered.
[e] Seriousness, as assessed by the investigator. An AE with missing seriousness is considered serious.
[f] Includes AEs on the AE case report form with action taken indicating dose delay or dose interruption, and AEs meeting study level dose delay definitions, where applicable.
[g] Includes AEs on the AE CRF form with action taken indicating dose delay or dose interruption, and AEs meeting study level dose delay definitions, where applicable.
[h] Excludes AESI group of infusion or hypersensitivity reactions.

N1 = Total number of White patients, N2 = Total number of Black or African American patients, N3 = Total number of Asian patients, N4 = Total number of Other patients, N5 = Total number of Missing patients; Percentages are calculated from N1, N2, N3, N4, and N5 for White, Black or African American, Asian, Other, and Missing, respectively.
Adjuvant monotherapy period includes AEs which start or first worsen between date of first dose of adjuvant monotherapy treatment up to and including 90 days following the date of last dose of study medication or up to and including the date of initiation of the first subsequent therapy (whichever occurs first).
Overall period and Durvalumab pan-tumor pool includes adverse events with an onset date on or after the date of first dose or pre-treatment AEs that increase in severity on or after the date of first dose up to and including 90 days following the date of last dose of study medication or up to and including the date of initiation of the first subsequent therapy (whichever occurs first).
Disease progression adverse events reported in Study 1108 are not included in this summary.
DCO2: 20 December 2024.

Effect of Baseline ECOG/WHO PS

Table 51 Overview of adverse events by category – patient level by baseline ECOG/WHO PS (safety analysis set; DCO2)

Parameter	Baseline ECOG/ WHO	Number (%) of Patients [a]				
		MATTERHORN				D Pan-tumor Pool
		Overall Study		Adjuvant Monotherapy Period		
		D + FLOT (N1 = 338) (N2 = 137) (N3 = 0)	Pbo + FLOT (N1 = 362) (N2 = 107) (N3 = 0)	D + FLOT (N1 = 250) (N2 = 95) (N3 = 0)	Pbo + FLOT (N1 = 263) (N2 = 68) (N3 = 0)	D (N1 = 1845) (N2 = 2792) (N3 = 5)
Any AE	0	336 (99.4)	360 (99.4)	200 (80.0)	209 (79.5)	1736 (94.1)
	≥ 1	135 (98.5)	103 (96.3)	74 (77.9)	51 (75.0)	2640 (94.6)
Any AE possibly related to any study treatment [b]	0	320 (94.7)	346 (95.6)	121 (48.4)	92 (35.0)	1141 (61.8)
	≥ 1	133 (97.1)	98 (91.6)	51 (53.7)	28 (41.2)	1566 (56.1)
Any AE possibly related to durvalumab/placebo [b]	0	198 (58.6)	182 (50.3)	94 (37.6)	62 (23.6)	1141 (61.8)
	≥ 1	84 (61.3)	62 (57.9)	43 (45.3)	21 (30.9)	1566 (56.1)
Any AE of CTCAE Grade 3 or Grade 4 [c]	0	253 (74.9)	274 (75.7)	56 (22.4)	62 (23.6)	637 (34.5)
	≥ 1	104 (75.9)	74 (69.2)	19 (20.0)	11 (16.2)	1318 (47.2)
Any AE possibly related to any study treatment of CTCAE Grade 3 or Grade 4 [b, c]	0	205 (60.7)	223 (61.6)	26 (10.4)	26 (9.9)	192 (10.4)
	≥ 1	82 (59.9)	56 (52.3)	5 (5.3)	4 (5.9)	360 (12.9)
Any AE possibly related to Durvalumab/Placebo of CTCAE Grade 3 or Grade 4 [b, c]	0	46 (13.6)	43 (11.9)	14 (5.6)	17 (6.5)	192 (10.4)
	≥ 1	22 (16.1)	15 (14.0)	5 (5.3)	2 (2.9)	360 (12.9)
Any AE of maximum CTCAE Grade 3 or Grade 4 [d]	0	239 (70.7)	263 (72.7)	54 (21.6)	57 (21.7)	591 (32.0)
	≥ 1	101 (73.7)	71 (66.4)	19 (20.0)	11 (16.2)	1191 (42.7)
Any AE possibly related to any study treatment of maximum CTCAE Grade 3 or Grade 4 [b, d]	0	201 (59.5)	222 (61.3)	26 (10.4)	26 (9.9)	191 (10.4)
	≥ 1	82 (59.9)	55 (51.4)	5 (5.3)	4 (5.9)	348 (12.5)
Any AE possibly related to Durvalumab/Placebo of maximum CTCAE Grade 3 or Grade 4 [b, d]	0	45 (13.3)	43 (11.9)	14 (5.6)	17 (6.5)	191 (10.4)
	≥ 1	22 (16.1)	15 (14.0)	5 (5.3)	2 (2.9)	348 (12.5)
Any AE with outcome = death	0	23 (6.8)	17 (4.7)	6 (2.4)	7 (2.7)	80 (4.3)
	≥ 1	4 (2.9)	5 (4.7)	0	0	193 (6.9)
Any AE with outcome = death, possibly related to any study treatment [b]	0	6 (1.8)	2 (0.6)			10 (0.5)
	≥ 1	1 (0.7)	1 (0.9)	0	0	27 (1.0)
Any AE with outcome = death, possibly related to Durvalumab/Placebo [b]	0	3 (0.9)	1 (0.3)			10 (0.5)
	≥ 1	0	0	0	0	27 (1.0)
Any AE with outcome = death during treatment-emergent period	0	19 (5.6)	15 (4.1)	5 (2.0)	7 (2.7)	78 (4.2)
	≥ 1	4 (2.9)	5 (4.7)	0	0	187 (6.7)
Any AE with outcome = death during treatment-emergent period, possibly related to any study treatment [b]	0	5 (1.5)	1 (0.3)			9 (0.5)
	≥ 1	1 (0.7)	1 (0.9)	0	0	24 (0.9)
Any AE with outcome = death during treatment-emergent period, possibly related to Durvalumab/Placebo [b]	0	3 (0.9)	1 (0.3)			9 (0.5)
	≥ 1	0	0	0	0	24 (0.9)
Any SAE (including events with outcome = death) [e]	0	155 (45.9)	158 (43.6)	37 (14.8)	42 (16.0)	560 (30.4)
	≥ 1	74 (54.0)	49 (45.8)	13 (13.7)	6 (8.8)	1095 (39.2)
Any SAE (including events with outcome = death), possibly related to any study treatment [b, e]	0	67 (19.8)	58 (16.0)	9 (3.6)	6 (2.3)	144 (7.8)
	≥ 1	41 (29.9)	21 (19.6)			226 (8.1)
Any SAE (including events with outcome = death), possibly related to Durvalumab/Placebo [b, e]	0	23 (6.8)	18 (5.0)	7 (2.8)	6 (2.3)	144 (7.8)
	≥ 1	17 (12.4)	7 (6.5)			226 (8.1)
Any AE leading to discontinuation of any study treatment	0	96 (28.4)	80 (22.1)	13 (5.2)	9 (3.4)	159 (8.6)
	≥ 1	46 (33.6)	27 (25.2)	7 (7.4)	1 (1.5)	330 (11.8)
Any AE leading to discontinuation of Durvalumab/Placebo	0	31 (9.2)	21 (5.8)	13 (5.2)	8 (3.0)	159 (8.6)
	≥ 1	17 (12.4)	9 (8.4)	7 (7.4)	1 (1.5)	330 (11.8)
Any AE possibly related to any study treatment leading to discontinuation of any study treatment [b]	0	80 (23.7)	68 (18.8)	11 (4.4)	8 (3.0)	89 (4.8)
	≥ 1	42 (30.7)	22 (20.6)	5 (5.3)	1 (1.5)	145 (5.2)

Any AE possibly related to Durvalumab/Placebo leading to discontinuation of Durvalumab/Placebo [b]	0	18 (5.3)	14 (3.9)	9 (3.6)	7 (2.7)	89 (4.8)
	≥ 1	11 (8.0)	5 (4.7)	5 (5.3)	1 (1.5)	145 (5.2)
Any AE leading to dose modification of any study treatment [f]	0	258 (76.3)	260 (71.8)	56 (22.4)	51 (19.4)	529 (28.7)
	≥ 1	105 (76.6)	73 (68.2)	20 (21.1)	13 (19.1)	766 (27.4)
Any AE leading to dose delay or interruption of any study treatment [g]	0	234 (69.2)	229 (63.3)	56 (22.4)	51 (19.4)	528 (28.6)
	≥ 1	90 (65.7)	64 (59.8)	20 (21.1)	13 (19.1)	758 (27.1)
Any AE leading to dose delay or interruption of Durvalumab/Placebo [g]	0	194 (57.4)	192 (53.0)	56 (22.4)	51 (19.4)	528 (28.6)
	≥ 1	74 (54.0)	49 (45.8)	20 (21.1)	13 (19.1)	758 (27.1)
Any adjudicated imAE [h]	0	81 (24.0)	25 (6.9)	34 (13.6)	9 (3.4)	363 (19.7)
	≥ 1	29 (21.2)	9 (8.4)	12 (12.6)	3 (4.4)	489 (17.5)

[a] Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories.
[b] As assessed by the investigator. Missing responses are counted as related.
[c] All CTCAE grades per patient/treatment period, not just the maximum, are considered when identifying whether there is a Grade 3 or 4.
[d] Maximum CTCAE grade per patient/treatment period/event is considered.
[e] Seriousness, as assessed by the investigator. An AE with missing seriousness is considered serious.
[f] Includes AEs on the AE CRF form with action taken indicating dose reduction, dose delay or dose interruption, and AEs meeting study level dose delay definitions, where applicable.
[g] Includes AEs on the AE CRF form with action taken indicating dose delay or dose interruption, and AEs meeting study level dose delay definitions, where applicable.
[h] Excludes AESI group of infusion or hypersensitivity reactions.
N1 = Total number of baseline ECOG/WHO=0, N2 = Total number of baseline ECOG/WHO >=1, N3 = Total number of missing baseline ECOG/WHO; Percentages are calculated from N1, N2, and N3 for baseline ECOG/WHO=0, baseline ECOG/WHO >=1, and missing baseline ECOG/WHO, respectively.
Adjuvant monotherapy period includes AEs which start or first worsen between date of first dose of adjuvant monotherapy treatment up to and including 90 days following the date of last dose of study medication or up to and including the date of initiation of the first subsequent therapy (whichever occurs first). Overall period and Durvalumab Pan-Tumor Pool includes adverse events with an onset date on or after the date of first dose or pre-treatment AEs that increase in severity on or after the date of first dose up to and including 90 days following the date of last dose of study medication or up to and including the date of initiation of the first subsequent therapy (whichever occurs first). Disease progression adverse events reported in Study 1108 are not included in this summary.
All studies use CTCAE version 4.03 except for MATTERHORN which uses version 5.0. For MATTERHORN, CTCAE grades are reported during treatment-emergent period. For D Pan-Tumor pool, CTCAE grades are reported during the full duration of the AE.

Extrinsic Factors

Table 52 Overview of adverse events by category – patient level by geographic region (safety analysis set; DCO2)

		Number (%) of Patients [a]				
		MATTERHORN				D Pan-tumor Pool
		Overall Study		Adjuvant Monotherapy Period		
Parameter	Geographic Region Group	D + FLOT (N1 = 90) (N2 = 257) (N3 = 42) (N4 = 86) (N5 = 385)	Pbo + FLOT (N1 = 88) (N2 = 248) (N3 = 39) (N4 = 94) (N5 = 381)	D + FLOT (N1 = 66) (N2 = 197) (N3 = 27) (N4 = 55) (N5 = 279)	Pbo + FLOT (N1 = 72) (N2 = 173) (N3 = 21) (N4 = 65) (N5 = 259)	D (N1 = 1422) (N2 = 1924) (N3 = 1246) (N4 = 50) (N5 = 3220)
Any AE	Asia	89 (98.9)	88 (100)	49 (74.2)	55 (76.4)	1312 (92.3)
	Europe	254 (98.8)	243 (98.0)	160 (81.2)	138 (79.8)	1800 (93.6)
	North America	42 (100)	39 (100)	26 (96.3)	17 (81.0)	1223 (98.2)
	South America	86 (100)	93 (98.9)	39 (70.9)	50 (76.9)	46 (92.0)
	Non-Asia Regions combined	382 (99.2)	375 (98.4)	225 (80.6)	205 (79.2)	3069 (95.3)
Any AE possibly related to any study treatment [b]	Asia	89 (98.9)	88 (100)	33 (50.0)	19 (26.4)	804 (56.5)
	Europe	245 (95.3)	228 (91.9)	96 (48.7)	65 (37.6)	1086 (56.4)
	North America	40 (95.2)	39 (100)	13 (48.1)	6 (28.6)	786 (63.1)
	South America	79 (91.9)	89 (94.7)	30 (54.5)	30 (46.2)	35 (70.0)
	Non-Asia Regions combined	364 (94.5)	356 (93.4)	139 (49.8)	101 (39.0)	1907 (59.2)
Any AE possibly related to durvalumab/placebo [b]	Asia	49 (54.4)	36 (40.9)	23 (34.8)	11 (15.3)	804 (56.5)
	Europe	148 (57.6)	127 (51.2)	76 (38.6)	40 (23.1)	1086 (56.4)
	North America	35 (83.3)	32 (82.1)	11 (40.7)	5 (23.8)	786 (63.1)
	South America	50 (58.1)	49 (52.1)	27 (49.1)	27 (41.5)	35 (70.0)
	Non-Asia Regions combined	233 (60.5)	208 (54.6)	114 (40.9)	72 (27.8)	1907 (59.2)

Any AE of CTCAE Grade 3 or Grade 4 [c]	Asia	79 (87.8)	77 (87.5)	14 (21.2)	15 (20.8)	514 (36.1)
	Europe	181 (70.4)	176 (71.0)	42 (21.3)	37 (21.4)	768 (39.9)
	North America	32 (76.2)	23 (59.0)	8 (29.6)	4 (19.0)	653 (52.4)
	South America	65 (75.6)	72 (76.6)	11 (20.0)	17 (26.2)	22 (44.0)
	Non-Asia Regions combined	278 (72.2)	271 (71.1)	61 (21.9)	58 (22.4)	1443 (44.8)
Any AE possibly related to any study treatment of CTCAE Grade 3 or Grade 4 [b, c]	Asia	75 (83.3)	72 (81.8)	5 (7.6)	9 (12.5)	195 (13.7)
	Europe	140 (54.5)	127 (51.2)	17 (8.6)	13 (7.5)	205 (10.7)
	North America	19 (45.2)	18 (46.2)			143 (11.5)
	South America	53 (61.6)	62 (66.0)	7 (12.7)	8 (12.3)	10 (20.0)
	Non-Asia Regions combined	212 (55.1)	207 (54.3)	26 (9.3)	21 (8.1)	358 (11.1)
Any AE possibly related to Durvalumab/Placebo of CTCAE Grade 3 or Grade 4 [b, c]	Asia	14 (15.6)	7 (8.0)	2 (3.0)	5 (6.9)	195 (13.7)
	Europe	32 (12.5)	37 (14.9)	10 (5.1)	6 (3.5)	205 (10.7)
	North America	9 (21.4)	1 (2.6)			143 (11.5)
	South America	13 (15.1)	13 (13.8)	6 (10.9)	8 (12.3)	10 (20.0)
	Non-Asia Regions combined	54 (14.0)	51 (13.4)	17 (6.1)	14 (5.4)	358 (11.1)
Any AE of maximum CTCAE Grade 3 or Grade 4 [d]	Asia	77 (85.6)	76 (86.4)	14 (21.2)	15 (20.8)	475 (33.4)
	Europe	170 (66.1)	170 (68.5)	40 (20.3)	37 (21.4)	695 (36.1)
	North America	31 (73.8)	21 (53.8)	8 (29.6)	3 (14.3)	592 (47.5)
	South America	62 (72.1)	67 (71.3)	11 (20.0)	13 (20.0)	20 (40.0)
	Non-Asia Regions combined	263 (68.3)	258 (67.7)	59 (21.1)	53 (20.5)	1307 (40.6)
Any AE possibly related to any study treatment of maximum CTCAE Grade 3 or Grade 4 [b, d]	Asia	75 (83.3)	71 (80.7)	5 (7.6)	9 (12.5)	187 (13.2)
	Europe	138 (53.7)	126 (50.8)	17 (8.6)	13 (7.5)	204 (10.6)
	North America	18 (42.9)	18 (46.2)			139 (11.2)
	South America	52 (60.5)	62 (66.0)	7 (12.7)	8 (12.3)	10 (20.0)
	Non-Asia Regions combined	208 (54.0)	206 (54.1)	26 (9.3)	21 (8.1)	353 (11.0)
Any AE possibly related to Durvalumab/Placebo of maximum CTCAE Grade 3 or Grade 4 [b, d]	Asia	14 (15.6)	7 (8.0)	2 (3.0)	5 (6.9)	187 (13.2)
	Europe	32 (12.5)	37 (14.9)	10 (5.1)	6 (3.5)	204 (10.6)
	North America	8 (19.0)	1 (2.6)			139 (11.2)
	South America	13 (15.1)	13 (13.8)	6 (10.9)	8 (12.3)	10 (20.0)
	Non-Asia Regions combined	53 (13.8)	51 (13.4)	17 (6.1)	14 (5.4)	353 (11.0)

Any AE with outcome = death	Asia	2 (2.2)	1 (1.1)	0	0	65 (4.6)
	Europe	16 (6.2)	11 (4.4)	4 (2.0)	2 (1.2)	126 (6.5)
	North America	1 (2.4)	2 (5.1)			77 (6.2)
	South America	8 (9.3)	8 (8.5)	2 (3.6)	4 (6.2)	7 (14.0)
	Non-Asia Regions combined	25 (6.5)	21 (5.5)	6 (2.2)	7 (2.7)	210 (6.5)
Any AE with outcome = death, possibly related to any study treatment [b]	Asia			0	0	19 (1.3)
	Europe	3 (1.2)	1 (0.4)	0	0	10 (0.5)
	North America			0	0	7 (0.6)
	South America	3 (3.5)	1 (1.1)			1 (2.0)
	Non-Asia Regions combined	7 (1.8)	2 (0.5)			18 (0.6)
Any AE with outcome = death, possibly related to Durvalumab/Placebo [b]	Asia			0	0	19 (1.3)
	Europe	0	0	0	0	10 (0.5)
	North America			0	0	7 (0.6)
	South America					1 (2.0)
	Non-Asia Regions combined					18 (0.6)
Any AE with outcome = death during treatment-emergent period	Asia	2 (2.2)	1 (1.1)	0	0	60 (4.2)
	Europe	15 (5.8)	10 (4.0)	4 (2.0)	2 (1.2)	124 (6.4)
	North America	1 (2.4)	2 (5.1)			76 (6.1)
	South America	5 (5.8)	7 (7.4)	1 (1.8)	4 (6.2)	7 (14.0)

	Non-Asia Regions combined	21 (5.5)	19 (5.0)	5 (1.8)	7 (2.7)	207 (6.4)
Any AE with outcome = death during treatment-emergent period, possibly related to any study treatment [b]	Asia			0	0	16 (1.1)
	Europe	3 (1.2)	1 (0.4)	0	0	10 (0.5)
	North America			0	0	6 (0.5)
	South America					1 (2.0)
	Non-Asia Regions combined	6 (1.6)	1 (0.3)			17 (0.5)
Any AE with outcome = death during treatment-emergent period, possibly related to Durvalumab/Placebo [b]	Asia			0	0	16 (1.1)
	Europe	0	0	0	0	10 (0.5)
	North America			0	0	6 (0.5)
	South America					1 (2.0)
	Non-Asia Regions combined					17 (0.5)
Any SAE (including events with outcome = death) [e]	Asia	44 (48.9)	36 (40.9)	13 (19.7)	10 (13.9)	460 (32.3)
	Europe	126 (49.0)	118 (47.6)	28 (14.2)	25 (14.5)	648 (33.7)
	North America	22 (52.4)	16 (41.0)	3 (11.1)	4 (19.0)	531 (42.6)
	South America	37 (43.0)	37 (39.4)	6 (10.9)	9 (13.8)	18 (36.0)
	Non-Asia Regions combined	185 (48.1)	171 (44.9)	37 (13.3)	38 (14.7)	1197 (37.2)
Any SAE (including events with outcome = death), possibly related to any study treatment [b, e]	Asia	30 (33.3)	23 (26.1)	3 (4.5)	3 (4.2)	170 (12.0)
	Europe	57 (22.2)	40 (16.1)	6 (3.0)	2 (1.2)	125 (6.5)
	North America	7 (16.7)	6 (15.4)	0	0	69 (5.5)
	South America	14 (16.3)	10 (10.6)	4 (7.3)	1 (1.5)	6 (12.0)
	Non-Asia Regions combined	78 (20.3)	56 (14.7)	10 (3.6)	3 (1.2)	200 (6.2)
Any SAE (including events with outcome = death), possibly related to Durvalumab/Placebo [b, e]	Asia	9 (10.0)	6 (6.8)	3 (4.5)	3 (4.2)	170 (12.0)
	Europe	18 (7.0)	16 (6.5)	5 (2.5)	2 (1.2)	125 (6.5)
	North America			0	0	69 (5.5)
	South America	8 (9.3)	3 (3.2)	3 (5.5)	1 (1.5)	6 (12.0)
	Non-Asia Regions combined	31 (8.1)	19 (5.0)	8 (2.9)	3 (1.2)	200 (6.2)
Any AE leading to discontinuation of any study treatment	Asia	19 (21.1)	20 (22.7)	2 (3.0)	5 (6.9)	141 (9.9)
	Europe	90 (35.0)	73 (29.4)	13 (6.6)	3 (1.7)	218 (11.3)
	North America	12 (28.6)	8 (20.5)	2 (7.4)	1 (4.8)	123 (9.9)
	South America	21 (24.4)	6 (6.4)	3 (5.5)	1 (1.5)	7 (14.0)
	Non-Asia Regions combined	123 (31.9)	87 (22.8)	18 (6.5)	5 (1.9)	348 (10.8)
Any AE leading to discontinuation of Durvalumab/Placebo	Asia	6 (6.7)	7 (8.0)	2 (3.0)	4 (5.6)	141 (9.9)
	Europe	25 (9.7)	18 (7.3)	13 (6.6)	3 (1.7)	218 (11.3)
	North America	6 (14.3)	3 (7.7)	2 (7.4)	1 (4.8)	123 (9.9)
	South America	11 (12.8)	2 (2.1)	3 (5.5)	1 (1.5)	7 (14.0)
	Non-Asia Regions combined	42 (10.9)	23 (6.0)	18 (6.5)	5 (1.9)	348 (10.8)
Any AE possibly related to any study treatment leading to discontinuation of any study treatment [b]	Asia	16 (17.8)	18 (20.5)	1 (1.5)	5 (6.9)	86 (6.0)
	Europe	76 (29.6)	61 (24.6)	10 (5.1)	3 (1.7)	85 (4.4)
	North America	11 (26.2)	6 (15.4)			60 (4.8)
	South America	19 (22.1)	5 (5.3)	3 (5.5)	1 (1.5)	3 (6.0)
	Non-Asia Regions combined	106 (27.5)	72 (18.9)	15 (5.4)	4 (1.5)	148 (4.6)
Any AE possibly related to Durvalumab/Placebo leading to discontinuation of Durvalumab/Placebo [b]	Asia	4 (4.4)	5 (5.7)	1 (1.5)	4 (5.6)	86 (6.0)
	Europe	12 (4.7)	12 (4.8)	9 (4.6)	3 (1.7)	85 (4.4)
	North America					60 (4.8)
	South America	8 (9.3)	2 (2.1)	2 (3.6)	1 (1.5)	3 (6.0)
	Non-Asia Regions combined	25 (6.5)	14 (3.7)	13 (4.7)	4 (1.5)	148 (4.6)
Any AE leading to dose modification of any study treatment [f]	Asia	76 (84.4)	80 (90.9)	20 (30.3)	14 (19.4)	367 (25.8)
	Europe	188 (73.2)	154 (62.1)	43 (21.8)	26 (15.0)	516 (26.8)
	North America	34 (81.0)	26 (66.7)	6 (22.2)	4 (19.0)	398 (31.9)
	South America	65 (75.6)	73 (77.7)	7 (12.7)	20 (30.8)	14 (28.0)
	Non-Asia Regions combined	287 (74.5)	253 (66.4)	56 (20.1)	50 (19.3)	928 (28.8)
Any AE leading to dose delay or interruption of any study treatment [g]	Asia	64 (71.1)	64 (72.7)	20 (30.3)	14 (19.4)	367 (25.8)
	Europe	168 (65.4)	141 (56.9)	43 (21.8)	26 (15.0)	509 (26.5)
	North America	32 (76.2)	21 (53.8)	6 (22.2)	4 (19.0)	396 (31.8)
	South America	60 (69.8)	67 (71.3)	7 (12.7)	20 (30.8)	14 (28.0)
	Non-Asia Regions combined	260 (67.5)	229 (60.1)	56 (20.1)	50 (19.3)	919 (28.5)

Any AE leading to dose delay or interruption of Durvalumab/Placebo [g]	Asia	55 (61.1)	44 (50.0)	20 (30.3)	14 (19.4)	367 (25.8)
	Europe	138 (53.7)	115 (46.4)	43 (21.8)	26 (15.0)	509 (26.5)
	North America	25 (59.5)	19 (48.7)	6 (22.2)	4 (19.0)	396 (31.8)
	South America	50 (58.1)	63 (67.0)	7 (12.7)	20 (30.8)	14 (28.0)
	Non-Asia Regions combined	213 (55.3)	197 (51.7)	56 (20.1)	50 (19.3)	919 (28.5)
Any adjudicated imAE [h]	Asia	20 (22.2)	4 (4.5)	6 (9.1)	2 (7.8)	262 (18.4)
	Europe	65 (25.3)	19 (7.7)	30 (15.2)	7 (4.0)	349 (18.1)
	North America	6 (14.3)	2 (5.1)	1 (3.7)	1 (4.8)	231 (18.5)
	South America	19 (22.1)	9 (9.6)	9 (16.4)	2 (3.1)	11 (22.0)
	Non-Asia Regions combined	90 (23.4)	30 (7.9)	40 (14.3)	10 (3.9)	591 (18.4)

[a] Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories.
[b] As assessed by the investigator. Missing responses are counted as related.
[c] All CTCAE grades per patient/treatment period, not just the maximum, are considered when identifying whether there is a Grade 3 or 4.
[d] Maximum CTCAE grade per patient/treatment period/event is considered.
[e] Seriousness, as assessed by the investigator. An AE with missing seriousness is considered serious.
[f] Includes AEs on the AE CRF form with action taken indicating dose reduction, dose delay or dose interruption, and AEs meeting study level dose delay definitions, where applicable.
[g] Includes AEs on the AE CRF form with action taken indicating dose delay or dose interruption, and AEs meeting study level dose delay definitions, where applicable.
[h] Excludes AESI group of infusion or hypersensitivity reactions.

N1 = Total number of Asia patients, N2 = Total number of Europe patients. N3 = Total number of North America patients, N4 = Total number of South America patients, N5 = Total number of Non-Asia Regions combined patients; Percentages are calculated from N1, N2, N3, N4, and N5 for Asia, Europe, North America, South America, and Non-Asia Regions combined, respectively.

Adjuvant monotherapy period includes AEs which start or first worsen between date of first dose of adjuvant monotherapy treatment up to and including 90 days following the date of last dose of study medication or up to and including the date of initiation of the first subsequent therapy (whichever occurs first). Overall period and Durvalumab Pan-Tumor Pool includes adverse events with an onset date on or after the date of first dose or pre-treatment AEs that increase in severity on or after the date of first dose up to and including 90 days following the date of last dose of study medication or up to and including the date of initiation of the first subsequent therapy (whichever occurs first).
Disease progression adverse events reported in Study 1108 are not included in this summary.
All studies use CTCAE version 4.03 except for MATTERHORN which uses version 5.0. For MATTERHORN, CTCAE grades are reported during treatment-emergent period. For D Pan-Tumor pool, CTCAE grades are reported during the full duration of the AE.
DCO2: 20 December 2024.

2.6.7. Safety related to drug-drug interactions and other interactions

Durvalumab is an immunoglobulin, therefore, no formal PK drug-drug interaction studies have been conducted. Pharmacokinetic drug-drug interaction of durvalumab with other therapeutics is not anticipated given that durvalumab is not primarily cleared via hepatic or renal pathways.

2.6.8. Discontinuation due to adverse events

Table 53 Overview of Adverse Events Leading to Discontinuation of Durvalumab/Placebo (>1 Patient in Either Treatment Arm in the Overall MATTERHORN Study) (Safety Analysis Set)

Parameter	Number (%) of patients [a]				
	MATTERHORN				D pantumor pool
	Overall study [b]		Adjuvant monotherapy period		
	D + FLOT (N = 475)	Pbo + FLOT (N = 469)	D + FLOT (N = 345)	Pbo + FLOT (N = 331)	D (N = 4642)
Patients with any AE leading to discontinuation of durvalumab/placebo	48 (10.1)	30 (6.4)	20 (5.8)	9 (2.7)	489 (10.5)
Pneumonitis	4 (0.8)	2 (0.4)	3 (0.9)	1 (0.3)	48 (1.0)
Immune-mediated hepatitis	3 (0.6)	1 (0.2)			2 (<0.1)
Diabetic ketoacidosis			0	0	0
Colitis	2 (0.4)	2 (0.4)			5 (0.1)
Immune-mediated nephritis					0
Rash					3 (0.1)
Hepatitis	1 (0.2)	2 (0.4)	1 (0.3)	1 (0.3)	6 (0.1)
Pneumonia	1 (0.2)	2 (0.4)	0	0	28 (0.6)
Diarrhoea					9 (0.2)

[a] Number (%) of patients with AEs, sorted in decreasing frequency of PT (according to the MATTERHORN D + FLOT column). Patients with multiple events are counted once for each PT.

[b] The overall study includes the neoadjuvant, surgery, and adjuvant overall periods. The adjuvant monotherapy period is contained within the adjuvant overall period of the study and is shown here for the purpose of safety analysis.

Disease progression AEs reported in Study 1108 are not included.

2.6.9. Adverse Events Leading to Dose Modifications

Dose reduction of durvalumab due to AEs was not allowed, with dose reductions being permitted only for FLOT components. Dose modification of durvalumab included only dose delay or infusion interruption. The most frequently reported AEs leading to dose modification overall (neutropenia and neutrophil count decreased) reflect the known safety profile of FLOT chemotherapy.

MATTERHORN:

Overall Study

The proportion of patients with AEs leading to durvalumab/placebo dose delay or interruption was 56.4% in the D + FLOT arm and 51.4% in the Pbo + FLOT arm.

The most frequently reported AEs (> 5% of patients in either arm) leading to dose delay of durvalumab or placebo were neutropenia (15.2% vs 15.6%), neutrophil count decreased (10.5% vs 14.3%), and COVID-19 (5.7% vs 5.8%).

Neoadjuvant Period

In the neoadjuvant period, the proportion of patients with AEs leading to durvalumab/placebo dose delay or interruption was 28.8% in the D + FLOT arm and 26.9% in the Pbo + FLOT arm.

The most frequently reported AEs (> 5% of patients in either arm) leading to dose delay of durvalumab or placebo were neutrophil count decreased (7.2% vs 8.3%) and neutropenia (6.9% vs 8.1%)

Adjuvant Overall Period

In the adjuvant overall period, the proportion of patients with AEs leading to durvalumab/placebo dose delay or interruption was 49.9% in the D + FLOT arm and 45.3% in the Pbo + FLOT arm.

The most frequently reported AEs (> 5% of patients in either arm) leading to dose delay of durvalumab or placebo were neutropenia (13.2% vs 12.8%), neutrophil count decreased (6.3% vs 10.3%), and COVID-19 (6.0% vs 5.7%).

Adjuvant Monotherapy Period

In the adjuvant monotherapy period, the proportion of patients with AEs leading to durvalumab/placebo dose delay or interruption was 22.0% in the D + FLOT arm and 19.3% in the Pbo + FLOT arm.

The most frequently reported AE (> 4% of patients in either arm) leading to dose delay of durvalumab or placebo was COVID-19 (4.6% vs 3.9%).

Comparison to the D Pan-tumor Pool:

Adverse events leading to dose delay or interruption of durvalumab were higher in the overall study D + FLOT arm vs the D pan-tumor pool (56.4% vs 27.7%). A lower proportion of AEs leading to dose delay or interruption of durvalumab was reported for the adjuvant monotherapy period of MATTERHORN vs the D pan-tumor pool (22.0% vs 27.7%).

2.6.10. Post marketing experience

As of 31 October 2024, the cumulative world-wide post-approval patient exposure since launch is estimated to be 213030 patient-years.

2.6.11. Discussion on clinical safety

The primary safety population consists of 944 patients, who were randomized in the pivotal MATTERHORN study, and received at least 1 dose of study treatment: 475 patients in the D+FLOT arm and 469 patients in the Pbo+FLOT arm. The pooled safety population of durvalumab in combination with chemotherapy has been updated accordingly in section 4.8 of the SmPC to reflect the additional 475 patients exposed to durvalumab in combination with chemotherapy, to a total of 2244 patients.

As of the DCO2 (20 December 2024), the median duration of **exposure of durvalumab or placebo** (Pbo) was 12.68 months in the D + FLOT arm vs 12.48 months in the Pbo+FLOT arm. Exposure to durvalumab and Pbo was similar between arms in both the neoadjuvant and adjuvant periods. The median actual duration of **exposure to any FLOT chemotherapy** was in each arm and was similar across arms in both the neoadjuvant and adjuvant periods. Completion of neoadjuvant FLOT chemotherapy was similar between arms, and thus not affected by the addition of durvalumab. In the adjuvant period, slightly more patients in the placebo arm completed the full FLOT regimen (64.4%) than in the durvalumab arm (61.5%), indicating that the addition of durvalumab may have had a slight detrimental effect on the ability to tolerate individual components of the adjuvant FLOT cycles. A similar number of patients in both arms did not receive any neoadjuvant FLOT, which is expected in this clinical setting.

The size of the primary safety population and the overall exposure is considered sufficient for an assessment of the overall safety profile of added durvalumab to the perioperative FLOT chemotherapy regimen. More males were included in the study, and a large majority of patients were of excellent performance status at baseline.

Overall, the majority of patients reported at least 1 **adverse event** (99.2 vs 98.7%). The most frequently reported AEs in both treatment arms (> 10%) were nausea, neutropenia, alopecia, decreased appetite, fatigue, vomiting, anemia, neutrophil count decreased, peripheral sensory neuropathy, diarrhoea and abdominal pain.

At the PT level, AEs that were reported more frequently for D+FLOT vs Pbo+FLOT were pyrexia (20.0% vs 15.1%), rash (13.7% vs 7.2%), and pruritus (10.7% vs 5.3%). Asthenia was also reported more often for D+FLOT vs Pbo+FLOT (20.0% vs 15.1%).

When comparing to the D pan-tumor pool, it is clear that a higher incidence of haematological toxicity (e.g., neutropenia, anaemia, and neutrophil count decreased) and gastrointestinal events (e.g., diarrhoea, nausea, decreased appetite, and vomiting) was commonly observed in the Matterhorn study, which is consistent with the known safety profile of FLOT chemotherapy.

Overall **AEs related to any study treatment** were similar between the treatment arms (95.4% vs 94.7%) and commonly observed were diarrhoea, nausea, neutropenia, and alopecia. More hypothyroidism was observed in the D containing arm (6.5% vs 1.3%), which is expected as this is a well-known ADR of durvalumab. Overall, ADRs to FLOT chemotherapy (any component) were considered balanced between the treatment arms as expected, and the rates of immune-mediated events were higher in the D+FLOT arm (23.2% vs 7.2% during the overall study period). 14.1% of patients in the D+FLOT arm received systemic corticosteroids compared to 6.2% in the placebo+FLOT arm. The types and frequencies of immune-related events were similar to those observed in prior durvalumab studies.

The identified adverse drug reactions for D+FLOT are consistent with the known ADR profiles of the FLOT regimen and durvalumab, respectively. FLOT ADRs were primarily haematological, gastrointestinal, and cardiac, and the rates of these did not differ between the D+FLOT and Pbo+FLOT arms, except for colitis and pancreatitis, which are known ADRs to durvalumab.

As a consequence of updating the pooled safety population of durvalumab in combination with chemotherapy, some ADRs frequencies have been updated in section 4.8 of the SmPC: uveitis (from uncommon to common) and pancreatic exocrine insufficiency (from rare to uncommon). Also, new ADRs have been added to the ADR table: pulmonary embolism with frequency uncommon and Guillain-Barré syndrome with frequency rare. With respect to pulmonary embolism, a footnote was added below the ADR table stating that the ADR is causally related to oxaliplatin in the MATTERHORN study, which is acceptable.

Following the request from the CHMP, deep vein thrombosis and acute myocardial infarction were also added as an ADR table in section 4.8 of the SmPC with frequency rare and uncommon respectively. The request was based on the fact that these ADRs were observed in the FLOT+D regimen, and should therefore be reported accordingly in the SmPC.

Serious adverse events were frequent in both arms of Matterhorn (48% vs. 44%), but no clear pattern could be discerned at the PT level.

There were 145 deaths in the D+FLOT arm and 174 in the P+FLOT arm, indicating no OS detriment from the addition of D to the perioperative FLOT regimen. There were 5.1% vs 4.3% TEAEs with outcome of death in the D+FLOT and P+FLOT arms, respectively, and in the D+FLOT arm these events were related to infections, thromboembolic events, or myocardial ischaemia, which is

consistent with the known safety profile of FLOT. However, few durvalumab-related AEs also led to death: pneumonitis, diabetic ketoacidosis, and immune-mediated intestinal perforation (one death each).

Changes in haematology parameters were more frequent in the D+FLOT arm than in the D pan-tumor pool, owing to the haematological toxicities associated with FLOT. However, the addition of durvalumab to FLOT did not appear to increase the risk of haematological toxicity. 7.2% of patients in the D+FLOT arm experienced ALT increases to grade 3 or 4, compared to 6.2% in the P+FLOT arm and 1.9% in the D pan-tumor pool. Thus, the added risk of ALT increases from durvalumab is comparable to the risk of ALT increases from durvalumab monotherapy alone. Occurrence of abnormal thyroid function tests were generally comparable between the D+FLOT arm and the D pan-tumor pool, indicating that the effect of durvalumab on risk of abnormal thyroid function was not different in the D+FLOT regimen compared to other durvalumab regimens.

No new safety concerns were identified for any special populations (sex, age, race, geographic region, ECOG PS).

Durvalumab was discontinued due to AEs in 10.1% of patients in the D+FLOT arm, which is comparable to the D pan-tumor pool. Reasons for discontinuation were known immune-related ADRs such as pneumonitis, hepatitis and diabetic ketoacidosis. Dose reductions of durvalumab were not allowed. 56.4% of patients in the D+FLOT arm experienced an AE leading to delay or interruption of durvalumab. This is more than twice as many patients as in the D pan-tumor pool. The primary reasons for durvalumab delay or interruption were neutropenia and COVID-19, indicating that the main reasons for the increased occurrence of durvalumab delays and interruptions were the haematological toxicities from the FLOT regimen and the COVID-19 pandemic. More patients (21.4% vs 15.1%) in the D+FLOT arm experienced an AE leading to "discontinuation of any FLOT (at least 1 drug)" in the adjuvant period.

2.6.12. Conclusions on clinical safety

The addition of durvalumab to neoadjuvant and adjuvant FLOT chemotherapy was associated with increased rates of immune-mediated adverse events and serious adverse events compared with FLOT alone. Furthermore, a slightly higher proportion of patients in the durvalumab + FLOT arm also experienced AEs leading to discontinuation of adjuvant FLOT. Three fatal known ADRs considered related to durvalumab were reported (ketoacidosis, intestinal perforation and pneumonitis).

Overall, the safety profile observed in the MATTERHORN was consistent with the known safety profiles of durvalumab and FLOT chemotherapy.

2.6.13. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.7. Risk management plan

The MAH submitted an updated RMP version 14.1 with this application. The main proposed RMP changes were the following:

Addition of the proposed new indication with corresponding dosage information, updated epidemiology data relevant to the new indication added, clinical trial exposure data in support of

the new indication added, and new data on exposure of special populations deriving from MATTERHORN.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 14.1 is acceptable.

2.8. Update of the Product information

As a consequence of this variation, sections 4.1, 4.2, 4.5, 4.8, and 5.1 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

2.8.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

A readability test was performed for the original dossier and found acceptable. This Type II variation includes an extension of indication for durvalumab used in combination with FLOT chemotherapy as neoadjuvant and adjuvant treatment, followed by adjuvant durvalumab as monotherapy, for the treatment of adults with resectable gastric or gastro-oesophageal junction adenocarcinoma.

The variation affects the Package Leaflet Section 1 and 3 and overall, the wording in the PL is similar to the text previously tested during the IMFINZI MAA. Therefore, it is justified to consider the PL User Testing report provided for the MAA is relevant for this application.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The approved indication is the following: *IMFINZI in combination with FLOT chemotherapy as neoadjuvant and adjuvant treatment, followed by adjuvant IMFINZI monotherapy, is indicated for the treatment of adults with resectable gastric or gastro-oesophageal junction adenocarcinoma.*

The target population investigated comprised patients with resectable gastric and gastro-oesophageal junction cancer (GC/GEJC), AJCC 8th edition stages II to IVa, who were eligible for perioperative chemotherapy with FLOT.

Gastric cancer is one of the most commonly diagnosed malignancies worldwide and represents the fifth leading cause of cancer-related death (Bray et al 2024, Smyth et al 2020). Approximately 95% of all GCs are adenocarcinomas (Dicken et al 2005). As of 2022, approximately 40% of incident cases of GC/GEJC in Europe and the US were diagnosed as potentially resectable, locally advanced disease (clinical stages II-III per AJCC 8th edition) (Amin et al 2018, Cabasag et al 2021, Cancer Research UK 2024, United States Cancer Statistics).

3.1.2. Available therapies and unmet medical need

Five-year overall survival rates for patients with resectable GC/GEJC remain limited, and in the order of 40% (Smyth et al 2020). Approximately 70-80% of disease recurrences occur within the first 3 years following surgery (Al-Batran et al 2019, Giommoni et al 2021, Möhring et al 2023).

Prognosis within this population is heterogeneous, and is strongly dependent on disease stage, with reported 3-year survival rates ranging from 70% in early stages to around 10% in more advanced resectable disease; Haejin Ann Surg Oncol 2017).

In Europe, the current standard of care is perioperative chemotherapy with FLOT. This is based on the results of the randomised phase II/III FLOT4-AIO study (Al-Batran et al 2016), in which treatment with FLOT demonstrated an improvement in OS compared with ECF/ECX group (median OS: 50 months vs 35 months, respectively).

In patients with resectable, locally advanced oesophageal or GEJ tumors (including both squamous cell carcinomas and adenocarcinomas), neoadjuvant chemoradiotherapy followed by surgical resection also represents an established treatment option. In patients with residual pathological disease, adjuvant immunotherapy with nivolumab has been shown to provide clinical benefit and is part of the current treatment practice (NCCN Guidelines 2025b, Obermannová et al 2022).

3.1.3. Main clinical studies

The single pivotal study for this extension of indication for durvalumab is the Matterhorn Study, an ongoing phase III, randomised, double-blinded, placebo-controlled, multi-center, global study to evaluate the efficacy and safety of durvalumab in combination with neoadjuvant and adjuvant FLOT in resectable GC/GEJC, followed by 10 cycles of durvalumab monotherapy (D + FLOT arm), compared with placebo and perioperative FLOT (Pbo + FLOT arm). The primary endpoint was EFS (BICR and/or local pathology) and the key secondary endpoints were pCR (central pathology review) and OS.

3.2. Favourable effects

- **EFS by BICR** (EFS maturity 40.6%, primary analysis): At **IA2** (DCO2: 20 December 2024), the D + FLOT arm showed superiority with 35.2% EFS events versus 46.0% in the Pbo + FLOT arm (HR 0.71, 95% CI: 0.58, 0.86, 2-sided p-value < 0.001), with a median EFS not reached in the durvalumab arm and 32.8 months in the placebo arm, at a median follow-up of approximately 26 months.
- **OS** (OS maturity 37.1%, final analysis): At **DCO3** (01 September 2025), the analysis reached statistical significance with a HR of 0.78 (95% CI: 0.63, 0.96; 2-sided p-value = 0.021). At the time of the analysis, a total of 160 patients (33.8%) had died in the D + FLOT arm compared with 192 patients (40.5%) in the Pbo + FLOT arm. Median OS was not reached in either arm (95% CI: NR, NR).
- **Pathological complete response (pCR):** At **DCO1** (1 February 2023), the pCR rate was superior in the D + FLOT arm (19.2%) compared to the Pbo + FLOT arm (7.2%), (odds ratio: 3.08 [95% CI: 2.03, 4.67]; p < 0.001).
- The addition of neoadjuvant durvalumab did not prevent patients from undergoing surgery, which is considered critical in this curative setting. The proportion of R0 resections was balanced in the treatment arms (~92%), as were the R1 and R2 resections. Patients with any surgical delay were balanced as well (~10%).

3.3. Uncertainties and limitations about favourable effects

- The study design does not allow to disentangle the contribution of durvalumab to each treatment phase. It remains unclear whether both the neoadjuvant and adjuvant parts are necessary, and the study does not assess the optimised duration of adjuvant therapy.

Therefore, the study results can only be interpreted within the context of a comprehensive peri-operative approach, including both neoadjuvant and adjuvant treatment for resectable gastric or gastro-oesophageal junction adenocarcinoma.

- The PD-L1 negative subgroup (TAP < 1%) comprised a small proportion of the full analysis set (approximately 10%). As a result, the assessment of the magnitude of the treatment benefit of durvalumab in this subgroup is limited. However, this does not support a restriction of the indication based on PD-L1 status.

3.4. Unfavourable effects

The primary **safety population** consists of 475 patients in the D+FLOT arm and 469 patients in the Pbo+FLOT arm. As of the DCO2 (20 December 2024), the median duration of **exposure of durvalumab or placebo** (Pbo) was 12.68 months in the D + FLOT arm vs 12.48 months in the Pbo+FLOT arm. The most frequently reported adverse events (> 10%) were nausea, neutropenia, alopecia, decreased appetite, fatigue, vomiting, anemia, neutrophil count decreased, peripheral sensory neuropathy, diarrhea and abdominal pain. At the PT level, AEs that were reported more frequently for D+FLOT vs Pbo+FLOT were pyrexia (20.0% vs 15.1%), rash (13.7% vs 7.2%), and pruritus (10.7% vs 5.3%). Asthenia was also reported more often for D+FLOT vs Pbo+FLOT (20.0% vs 15.1%). Overall **AEs related to any study treatment** were similar between the treatment arms (95.4% vs 94.7%) and commonly observed were diarrhea, nausea, neutropenia, and alopecia. More hypothyroidism was observed in the D containing arm (6.5% vs 1.3%) and the rates of immune-mediated events were higher in the D+FLOT arm (23.2% vs 7.2% during the overall study period). 14.1% of patients in the D+FLOT arm received systemic corticosteroids compared to 6.2% in the placebo + FLOT arm.

The identified adverse drug reactions for D+FLOT are consistent **with the known ADR profiles of the FLOT regimen and durvalumab, respectively. FLOT ADRs were primarily haematological and gastrointestinal, and the rates of these did not differ between the D+FLOT and Pbo+FLOT arms, except for colitis and pancreatitis, which are known ADRs to durvalumab.**

Serious adverse events **were frequent in both arms of Matterhorn (48% vs. 44%), but no clear pattern could be discerned at the PT level. There were 5.1% vs 4.3%** TEAEs with outcome of death **in the D+FLOT and P+FLOT arms, respectively, and in the D+FLOT arm these events were related to infections or thromboembolic events, which is consistent with the known safety profile of FLOT. However, few durvalumab-related AEs also led to death: pneumonitis, diabetic ketoacidosis, and immune-mediated intestinal perforation (one death each).**

Durvalumab was discontinued due to AEs in 10.1% of patients in the D+FLOT arm, which is comparable to the D pan-tumor pool. Reasons for discontinuation were known immune-related ADRs such as pneumonitis, hepatitis and diabetic ketoacidosis.

3.5. Uncertainties and limitations about unfavourable effects

N/A.

3.6. Effects Table

Table 54: Effects Table for durvalumab in combination with FLOT chemotherapy as neoadjuvant and adjuvant treatment, followed by adjuvant durvalumab monotherapy, for the treatment of adults with resectable GC/GEJC (DCO for EFS analysis 20 December 2024, DCO for OS analysis 01 September 2025).

Effect	Short description	Unit	Treatment Durvalumab + FLOT N = 474	Control Placebo + FLOT N = 474	Uncertainties / Strength of evidence	References
Favourable Effects						
EFS (per BICR or central pathology review)	Event free survival	% of patients with events having occurred	35.2% Median follow-up 26.79 months	46.0% Median follow-up 25.82 months	Maturity 40.6% HR of 0.71 (95% CI: 0.58, 0.86; 2-sided p-value < 0.001)	
OS	Overall survival	Median months	Not reached (95% CI: NC, NC)	Not reached (95% CI: NC, NC)	Maturity 37.1% HR 0.78 (95% CI: 0.63, 0.96; 2-sided p-value = 0.021)	
Unfavourable Effects						
Grade 3-4	High grade AEs	%	71.6	71.2	Sufficient median follow-up (~12 months)	CSR
SAE	Serious AEs	%	48	44		
Death due to AE	AEs leading to death	%	5.4	4.3		
AE leading to disc.	AEs leading to discontinuations	%	10.1	2.7		
ImAEs	Immune-related AEs	%	23.2	7.2		

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The addition of durvalumab to perioperative FLOT followed by 10 cycles of durvalumab as monotherapy in patients with resectable GC/GEJC, led to a statistically significant and clinically meaningful improvement in EFS of 10.8 % at DCO (EFS maturity 40.6%) compared to the current standard of care. Importantly, the final analysis showed a statistically significant improvement in OS in the FAS (HR 0.78, 95% CI: 0.63, 0.96). These results are considered clinically relevant in a context of unmet medical need.

The data in the Matterhorn trial do not allow for firm conclusions regarding PD-L1 expression as a predictive marker of treatment effect of durvalumab in the perioperative setting, which may be in part due to the small size of the PD-L1-negative subgroup.

The clinically relevant improvement of both EFS and OS of the addition of durvalumab to the perioperative FLOT chemotherapy regimen outweighs the slightly higher toxicity of the combination.

3.7.2. Balance of benefits and risks

Overall, the Matterhorn study relevantly addresses an unmet medical need in the population investigated, showing a clinically meaningful benefit on EFS and OS. The study design does not allow the contribution of prolonged adjuvant treatment with durvalumab as monotherapy to be determined. Therefore, the study results can only be interpreted in the context of the overall peri-operative treatment strategy, including both perioperative and adjuvant maintenance treatment with durvalumab in patients with resectable GC/GEJC.

The addition of durvalumab to perioperative FLOT chemotherapy was associated with higher rates of immune-mediated adverse events and serious adverse events compared with FLOT alone. Furthermore, a slightly higher proportion of patients in the durvalumab + FLOT arm experienced AEs leading to discontinuation of adjuvant FLOT. Three fatal known ADRs considered durvalumab-related were reported (ketoacidosis, intestinal perforation and pneumonitis). Overall, the safety profile of durvalumab in combination with FLOT chemotherapy was consistent with the known safety profiles of durvalumab and FLOT chemotherapy.

3.8. Conclusions

The overall benefit-risk balance of durvalumab in combination with FLOT chemotherapy as neoadjuvant and adjuvant treatment, followed by adjuvant durvalumab monotherapy for resectable gastric or gastro-oesophageal junction adenocarcinoma, is considered positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following changes:

Variation accepted		Type	Annexes affected
C.I.6.a	C.I.6.a Addition of a new therapeutic indication or modification of an approved one	Type II	I, IIIB

Extension of indication for IMFINZI to include in combination with FLOT chemotherapy as neoadjuvant and adjuvant treatment, followed by adjuvant IMFINZI monotherapy, for the treatment of adults with resectable gastric or gastro-oesophageal junction adenocarcinoma , based on interim results from study MATTERHORN, (D910GC00001); this is a randomized, double-blind, placebo-controlled, phase 3 study of neoadjuvant-adjuvant durvalumab and FLOT chemotherapy followed by adjuvant durvalumab in patients with resectable gastric and gastroesophageal junction cancer (GC/GEJC); As a consequence, sections 4.1, 4.2, 4.5, 4.8, and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 14.1 of the RMP has also been submitted.

The requested variation(s) proposed amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I and IIIB and to the Risk Management Plan are recommended.

Similarity with authorised orphan medicinal products

The CHMP is by consensus of the opinion that Imfinzi is not similar to Vyloy within the meaning of Article 3 of Commission Regulation (EC) No. 847/200.

Reminders to the MAH

1. In accordance with Article 13(3) of Regulation (EC) No 726/2004 the Agency makes available a European Public Assessment Report (EPAR) on the medicinal product assessed by the Committee for Medicinal Products for Human Use. The EPAR is first published after the granting of the initial marketing authorisation (MA) and is continuously updated during the lifecycle of the medicinal product. In particular, following a major change to the MA, the Agency further publishes the assessment report of the CHMP and the reasons for its opinion in favour of granting the change to the authorisation, after deletion of any information of a commercially confidential nature.

   Should you consider that the CHMP assessment report contains commercially confidential information, **please provide the EMA Procedure Assistant your proposal for deletion of commercially confidential information** (CCI) in "track changes" and with detailed justification by 16th February 2026.

   The principles to be applied for the deletion of CCI are published on the EMA website at https://www.ema.europa.eu/en/documents/other/heads-medicines-agencies/european-medicines-agency-guidance-document-identification-commercially-confidential-information_en.pdf

   In addition, should you consider that the CHMP assessment report contains personal data, please provide the EMA Procedure Assistant your proposal for deletion of these data in "track changes" and with detailed justification by 16th of February 2026. We would like to remind you that, according to Article 4(1) of Regulation (EU) 2016/679 (General Data Protection Regulation, "GDPR") 'personal data' means any information, relating to an identified or identifiable natural person (the 'data subject'). An identifiable natural person is one who can be identified, directly or indirectly, in particular by reference to an identifier such as a name, an identification number, location data, an online identifier or to one or more factors specific to the physical, physiological, genetic, mental, economic, cultural or social identity of that natural person.

   It is important to clarify that pseudonymised data are also considered personal data. According to Article 4(5) of GDPR pseudonymisation means that personal data is processed in a manner that the personal data can no longer be attributed to a specific data subject without the use of additional information (e.g. key-coded data).

   Accordingly, the name and the patient identification number are two examples of personal data which may relate to an identified or identifiable natural person. The definitions also encompass for instance: office e-mail address or phone number of a company, data concerning health, e.g. information in medical records, clinical reports or case narratives which relates to an identifiable individual."

2. The MAH is reminded to submit an eCTD closing sequence with the final documents provided by Eudralink during the procedure (including final PI translations, if applicable) within 15 days after the Commission Decision, if there will be one within 2 months from adoption of the CHMP Opinion, or prior to the next regulatory activity, whichever is first. If the Commission Decision will be adopted within 12 months from CHMP Opinion, the closing sequence should be submitted within 30 days after the Opinion. For additional guidance see chapter 4.1 of the Harmonised Technical Guidance for eCTD Submissions in the EU.

3. If a revised RMP is being approved as part of this procedure, **please send to the EMA Procedure Assistant** one redacted PDF document containing the RMP body, Annex 4 and

Annex 6, as applicable, together with a redacted RMP file that can show the content that is proposed for redaction, and the signed RMP Publication Declaration, **by 16th February 2026.**