27 February 2025
EMA/100461/2025
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Imfinzi

International non-proprietary name: Durvalumab

Procedure No. EMEA/H/C/004771/II/0064

Note

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

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List of abbreviations

Abbreviation or special term	Explanation
ADA	anti-drug antibody
ADR	adverse drug reaction
AE	adverse event
AEPI	adverse event of possible interest
AESI	adverse events of special interest
AJCC	American Joint Committee on Cancer
ALK	anaplastic lymphoma kinase
BICR	blinded independent central review
CD	cluster of differentiation
CI	confidence interval
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CTx	chemotherapy
D	durvalumab
DCO	data cut-off
DFS	disease-free survival
ECOG	Eastern Cooperative Oncology Group
EFS	event-free survival
EGFR	epidermal growth factor receptor
EGFRm	epidermal growth factor receptor mutation
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
ERES	exposure-response, exposure-safety
ES-SCLC	extensive stage small cell lung cancer
ESMO	European Society for Medical Oncology
EU	European Union
FA	final analysis
FDA	Food and Drug Administration
HR	hazard ratio

Abbreviation or special term	Explanation
IA	interim analysis
IA1	first interim analysis
IASLC	International Association for the Study of Lung Cancer
ICH	International Conference on Harmonisation
IDMC	independent data monitoring committee
imAE	immune-mediated adverse event
iPSP	initial paediatric study plan
ISR	incurred sample reanalysis
ITT	intent-to-treat
IxRS	interactive voice/web response system
KM	Kaplan-Meier
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
MPR	major pathological response
MTP	multiple testing procedure
nAb	neutralizing antibody
NCCN	National Comprehensive Cancer Network
NR	not reached
NSCLC	non-small cell lung cancer
OS	overall survival
pCR	pathological complete response
PD	Progressive disease
PD-1	programmed cell death protein 1
PD-L1	programmed cell death ligand-1
PIP	paediatric investigation plan
PK	pharmacokinetic(s)
PORT	post-operative radiation therapy
PRO	patient reported outcomes
PS	performance status
PT	Preferred Term
Q[x]W	every x weeks

Abbreviation or special term	Explanation
QLQ-C30	30-item Core Quality of Life Questionnaire
QLQ-CL13	13-item Lung Cancer Quality of Life Questionnaire
RECIST	Response Evaluation Criteria in Solid Tumours
SAE	serious adverse event
SAP	statistical analysis plan
TC	tumour cells
US	United States (of America)

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 November 2023 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include IMFINZI in combination with platinum-based chemotherapy as neoadjuvant treatment, followed by IMFINZI as monotherapy after surgery, for the treatment of adults with resectable (tumours ≥ 4 cm and/or node positive) NSCLC and no known EGFR mutations or ALK rearrangements for IMFINZI, based on the interim results from study D9106C00001 (AEGEAN); this is a Phase III, double-blind, placebo-controlled, multi-center international study of neoadjuvant/adjuvant durvalumab for the treatment of patients with resectable stages II and III non-small cell lung cancer. As a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 11 of the RMP has also been submitted.

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

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.

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 MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The MAH received Scientific Advice from the CHMP on 15 November 2018 (EMEA/H/SA/2752/13/2018/II). The Scientific advice pertained to clinical aspects of the dossier, see also section 2.1.3. including the patient population, endpoints (pCR and MPR cannot support a neo-adjuvant indication, EFS acceptable primary endpoint), study design (will not allow disentanglement of the relevant contribution of the neoadjuvant vs the adjuvant part) as the most critical issues.

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 Co-Rapporteur: Antonio Gomez-Outes

PRAC Rapporteur: David Olsen

Timetable	Actual dates
Submission date	27 November 2023
Start of procedure:	23 December 2023
CHMP Rapporteur Assessment Report	19 February 2024
PRAC Rapporteur Assessment Report	23 February 2024
CHMP Co-Rapporteur Assessment	2 March 2024
PRAC Outcome	7 March 2024
CHMP members comments	11 March 2024
Updated CHMP Rapporteur(s) (Joint) Assessment Report	14 March 2024
Request for supplementary information (RSI)	21 March 2024
MAH's responses submitted to the CHMP on:	12 September 2024
Rapporteur's preliminary assessment report on the MAH's responses circulated on:	25 October 2024
CHMP members comments	n/a
Updated CHMP Rapporteur Assessment Report	n/a
Request for supplementary information (RSI)	14 November 2024
MAH's responses submitted to the CHMP on:	19 December 2024
Rapporteur's preliminary assessment report on the MAH's responses circulated on:	31 January 2025
CHMP members comments	10 February 2025
Updated CHMP Rapporteur Assessment Report	20 February 2025
CHMP opinion:	27 February 2025

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Resectable (Stage IIA-IIIB[N2]) NSCLC (staged per the AJCC staging system for lung cancer 8th Edition).

State the claimed the therapeutic indication

Indication as initially claimed by the MAH:

IMFINZI in combination with platinum-based chemotherapy as neoadjuvant treatment, followed by IMFINZI as monotherapy after surgery, is indicated for the treatment of adults with resectable (tumours ≥ 4 cm and/or node positive) NSCLC and no known EGFR mutations or ALK rearrangements.

Epidemiology and risk factors, screening tools/prevention

Lung cancer is the second most common cancer (approximately 2.2 million new cases reported in 2020) and the leading cause of cancer-related death worldwide, with approximately 1.8 million deaths recorded in 2020 (Sung et al 2021). While lung cancer survival rates are improving, these remain poor and with significant geographic heterogeneity: the 5-year survival is approximately 23% in the US (SEER 2015 to 2019) and 15% in Europe (OECD/European Union 2020). Non-small cell lung cancer represents 80% to 85% of all lung cancers (Abernethy et al 2017; Cheema et al 2019).

Clinical presentation, diagnosis and stage/prognosis

Approximately 20% to 25% of NSCLC patients present with resectable lung cancer (Liang et al 2013) and this is expected to increase with the implementation of lung cancer screening in high-risk populations (Passiglia et al 2021). For early-stage NSCLC, the 5-year survival rate remains low at 56% to 65% for patients with Stage II, and 24% to 41% for patients with Stage III disease (Goldstraw et al 2016).

Management

In the adjuvant treatment setting, results from large, randomized studies of platinum-based chemotherapy have demonstrated an improvement in OS in patients with resected NSCLC. The Lung Adjuvant Cisplatin Evaluation meta-analysis of pooled data from the five largest trials of cisplatin-based chemotherapy after NSCLC complete resection indicated a 5.4% absolute benefit in 5-year survival for chemotherapy vs no chemotherapy. The benefit of adjuvant chemotherapy was different depending on stage, with higher stage correlating with an increased magnitude of benefit (HR 1.4 [95%CI: 0.95 to 2.06] for Stage IA disease; HR = 0.93 for Stage IB disease [95%CI: 0.78 to 1.10]; HR 0.83 for Stage II disease [95%CI: 0.73 to 0.95]; and HR 0.83 for Stage III disease [95%CI: 0.72 to 0.94]) (Pignon et al 2008). However, the recurrence rate remains high, ranging from 62% in patients with Stage II and 76% of patients with Stage III disease (Pignon et al 2008), which in turn is associated with poor survival rates in this patient population (Goldstraw et al 2016).

In the neoadjuvant setting, a meta-analysis including trials of neoadjuvant chemotherapy for resectable NSCLC has shown an absolute survival improvement of 5% at 5 years (NSCLC Meta-analysis Collaborative Group 2014).

Opdivo (nivolumab), Tecentriq (atezolizumab) and Keytruda (pembrolizumab), were granted extension of indications in resectable NSCLC, as neoadjuvant (EMEA/H/C/003985/II/0117, dated 26 June 2023), adjuvant treatment (EMEA/H/C/004143/II/0064 dated 07 June 2022 and EMEA/H/C/003820/II/0110 dated 19 May 2022), or a combination of both (EMEA/H/C/003820/II/0134, dated 25 March 2024).

Unmet medical need

The prevention of disease recurrence and distant metastases, and subsequent progression to an

incurable disease state, is critical to improving long-term patient outcomes (Consonni et al 2015).

2.1.2. About the product

Durvalumab, a fully human, high affinity, immunoglobulin G1 kappa monoclonal antibody, which has been engineered to reduce antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity. It is an immunomodulatory therapy that selectively blocks the interaction of PD-L1 with PD-1 and CD80 (B7.1) while leaving PD 1/PD-L2 interaction intact. Blockade of PD-L1/PD-1 and PD-L1/CD80 interactions releases inhibition of immune responses, including those that may result in tumour elimination.

Durvalumab, is authorised in Europe since September 2018 (EMEA/H/C/4771) and has been approved for a number of indications both as monotherapy and in combination with other immunotherapy agents and/or standard-of-care chemotherapies:

- As a monotherapy treatment for adult patients with unresectable Stage III, NSCLC after chemoradiation (Antonia at al 2018)
- In combination with tremelimumab and platinum-based chemotherapy for adult patients with metastatic NSCLC with no sensitizing EGFR mutation or ALK genomic tumour aberrations (Johnson et al 2023) (EMEA/H/C/004771/II/0041, decision dated 30 January 2023)
- In combination with etoposide and either carboplatin or cisplatin as first-line treatment of adult patients with ES-SCLC (Paz-Ares et al 2019), (EMEA/H/C/004771/II/0014/G, decision dated 27 August 2020).
- In combination with gemcitabine and cisplatin for adult patients with locally advanced or metastatic biliary tract cancer (Oh et al 2022) (EMEA/H/C/004771/II/0046, decision dated 16 December 2022)
- In combination with tremelimumab for adult patients with unresectable hepatocellular carcinoma (Abou-Alfa et al 2022) (EMEA/H/C/004771/II/0045, decision dated 30 January 2023)
- As monotherapy for adult patients with unresectable hepatocellular carcinoma (EMEA/H/C/004771/II/0057, decision dated 15 Nov 2023)
- In combination with carboplatin and paclitaxel for the first-line treatment of adults with primary advanced or recurrent endometrial cancer who are candidates for systemic therapy, followed by maintenance treatment
    - as monotherapy in endometrial cancer that is mismatch repair deficient (dMMR)
    - in combination with olaparib in endometrial cancer that is mismatch repair proficient (pMMR) (EMEA/H/C/004771/WS2463/0063, decision dated 26 July 2024)

The indication applied for was: IMFINZI in combination with platinum-based chemotherapy as neoadjuvant treatment, followed by IMFINZI as monotherapy after surgery, is indicated for the treatment of adults with resectable (tumours ≥ 4 cm and/or node positive) NSCLC and no known EGFR mutations or ALK rearrangements.

The final approved indication is:

IMFINZI in combination with platinum-based chemotherapy as neoadjuvant treatment, followed by IMFINZI as monotherapy as adjuvant treatment, is indicated for the treatment of adults with

resectable NSCLC at high risk of recurrence and no EGFR mutations or ALK rearrangements (for selection criteria, see section 5.1).

The recommended dose for resectable NSCLC is 500 mg in combination with platinum-based chemotherapy every 3 weeks for up to 4 cycles prior to surgery, or until disease progression that precludes definitive surgery or unacceptable toxicity, followed by 1 500 mg monotherapy every 4 weeks for up to 12 cycles after surgery.

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

The MAH did not adhere to all of the recommendations of the Scientific advice given by the CHMP in 2018, and at the presubmission meeting in May 2023. Hence, the primary endpoint of pCR was kept, the study design unchanged and still does not allow disentanglement of the contribution of the neoadjuvant part from the adjuvant part. Moreover, although the MAH was recommended to submit more mature data, immature EFS and OS data was submitted. Updated efficacy data for EFS, DFS and OS were required during the assessment procedure to allow a conclusion on the benefit-risk balance.

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity/environmental risk assessment

Durvalumab is an IgG1 monoclonal antibody, a protein being extensively degraded in the patient's body by regular proteolytic mechanisms before excretion. Durvalumab is expected to biodegrade in the environment and does not pose a significant risk to the environment. Thus, according to the "Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use" (EMEA/CHMP/SWP/4447/00 corr2), durvalumab is exempt from the submission of Environmental Risk Assessment studies as the product and excipients do not pose a significant risk to the environment.

2.2.2. Discussion on non-clinical aspects

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

Durvalumab is human monoclonal antibody of the IgG1 kappa subclass. Antibodies are considered naturally occurring proteins, which are not expected to remain either stable or biologically active in the environment for any significant period. The justification for not performing any ERA studies is accepted.

2.2.3. Conclusion on the non-clinical aspects

The updated data submitted in this application do not lead to a significant increase in environmental exposure further to the use of Durvalumab.

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

2.3. Clinical aspects

2.3.1. Introduction

The pivotal D9106C00001 study (AEGEAN) was initiated to investigate the use of durvalumab in combination with platinum-based doublet chemotherapy administered prior to surgery, followed by durvalumab monotherapy administered post-surgery (i.e., perioperative treatment) in patients with resectable Stage IIA-IIIB[N2] NSCLC (hereafter referred to as resectable NSCLC for brevity). Data from the AEGEAN study (ongoing) is reported in the current submission.

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.

In addition to the AEGEAN study, the safety and clinical pharmacology evaluation of durvalumab in the target patient population at the proposed posology is further supported by data from older studies in the durvalumab clinical development program.

Table 1 Listing of clinical studies providing clinical pharmacology and clinical safety data in the current submission

Study number (name) Study title	DCO date	Objectives of study	Study design and type of control	Route of administration and dosage regimen	
Pivotal study					
D9106C00001 (AEGEAN) A Phase III, double-blind, placebo controlled, multicenter international study of neoadjuvant/adjuvant durvalumab for the treatment of patients with resectable stages II and III NSCLC	pCR IA: 14 Jan 2022 EFS IA1: 10 Nov 2022	Efficacy, safety, tolerability, PK, immunogenicity, and health-related quality of life	Double-blind, placebo-controlled, multicenter	*Neoadjuvant phase*	• Durvalumab 1500 mg or placebo + CTx Q3W for 4 cycles followed by surgery.
				Post-surgery phase	• Durvalumab 1500 mg or placebo Q4W for 12 cycles.
Supportive studies: Durvalumab pan-tumour pool					
CD-ON-MEDI4736-1108 (Study 1108) Phase I/II study to evaluate the safety, tolerability, and PK of MEDI4736 in subjects with advanced solid tumours	16 Oct 2017	Safety, tolerability, efficacy, PK, and immunogenicity	Open-label, multiple-arm, non-randomized	*Dose-escalation*	• Durvalumab 0.1, 0.3, 1, 3, 10 mg/kg Q2W + 15 mg/kg Q3W for up to 12 months or until progression of disease
				Dose-exploration	• Durvalumab 20 mg/kg Q4W for up to 12 months
				Dose-expansion	• Durvalumab 10 mg/kg Q2W up to 12 months
D4190C00002 (Japan Study 02) A Phase I, open-label, multicenter study to evaluate the safety, tolerability, and PK of MEDI4736 in patients with advanced solid tumours	31 Mar 2018	Safety and tolerability	Open-label, non-randomized	*Dose-escalation*	• Durvalumab 1, 3, 10 mg/kg Q2W; 15 mg/kg Q3W; 20 mg/kg Q4W
				Dose-expansion	• Durvalumab 10 mg/kg Q2W • Durvalumab 20 mg/kg Q4W + Tremelimumab 1 mg/kg Q4W for 4 doses
D4191C00003 (ATLANTIC) Phase II, non-comparative, open label, multicenter, international study of MEDI4736 in patients with locally advanced or	03 Jun 2016 [a] 07 Nov 2017	Efficacy, safety, tolerability, PK, and immunogenicity	Open-label, single-arm, non-randomized	• Durvalumab 10 mg/kg Q2W for up to 12 months	

Table 1 Listing of clinical studies providing clinical pharmacology and clinical safety data in the current submission

Study number (name) Study title	DCO date	Objectives of study	Study design and type of control	Route of administration and dosage regimen
metastatic NSCLC (Stage IIIB - IV) who have received at least 2 prior systemic treatment regimens including one platinum-based chemotherapy regimen				
D4191C00001 (PACIFIC) Phase III, randomized, double blind, placebo-controlled, multicenter, international study of durvalumab as sequential therapy in patients with locally advanced, unresectable NSCLC (Stage III) who have not progressed following definitive, platinum-based concurrent chemoradiation therapy	22 Mar 2018	Efficacy, safety, tolerability, PK, immunogenicity, and health-related quality of life	Randomized, double-blind, placebo-controlled	• Durvalumab 10 mg/kg Q2W for up to 12 months

Table 1 Listing of clinical studies providing clinical pharmacology and clinical safety data in the current submission

Study number (name) Study title	DCO date	Objectives of study	Study design and type of control	Route of administration and dosage regimen	
D4191C00004 (ARCTIC) Phase III, open-label, randomized, multicenter, international study of durvalumab, given as monotherapy or in combination with tremelimumab, determined by PDL1 expression, versus SoC in patients with locally advanced or metastatic NSCLC (Stage IIIB - IV) who have received at least 2 prior systemic treatment regimens including one platinum-based chemotherapy regimen and do not have known EGFR TK activating mutations or ALK rearrangements	09 Feb 2018	Efficacy, safety, tolerability, PK, and immunogenicity	Open-label, randomized, active comparator	*Durvalumab monotherapy*	• Durvalumab IV 10 mg/kg Q2W for up to 12 months
				Tremelimumab monotherapy	• Tremelimumab IV 10 mg/kg Q4W for 24 weeks followed by IV 10 mg/kg Q12W for 24 weeks
				Combination therapy	• Durvalumab IV 20 mg/kg Q4W for 12 weeks then IV 10 mg/kg Q2W for 34 weeks + tremelimumab IV 1 mg/kg Q4W for 12 weeks (maximum of 22 doses of durvalumab + 4 doses of tremelimumab)
D419AC00001 (MYSTIC) Phase III, randomized, open-label, multicenter, global study of durvalumab monotherapy and durvalumab in combination with tremelimumab compared to SoC in patients with advanced or metastatic NSCLC	04 Oct 2018	Efficacy	Open-label, randomized, active comparator	*Durvalumab monotherapy*	• Durvalumab IV 20 mg/kg Q4W
				Combination therapy	• Durvalumab IV 20 mg/kg Q4W for 4 doses then IV 20 mg/kg Q4W (until progression of disease) + tremelimumab IV 1 mg/kg Q4W for 4 doses
D4193C00001 (HAWK) Phase II, multicenter, single-arm, global study of durvalumab monotherapy in SCCHN	31 Mar 2017 [a] 05 Oct 2018	Efficacy and health-related quality of life	Open-label, single-arm	• Durvalumab IV 10 mg/kg Q2W for 12 months or until progression of disease	

Table 1 Listing of clinical studies providing clinical pharmacology and clinical safety data in the current submission

Study number (name) Study title	DCO date	Objectives of study	Study design and type of control	Route of administration and dosage regimen	
D4193C00003 (CONDOR) Phase II, randomized, open-label, multicenter, global study of durvalumab monotherapy, tremelimumab monotherapy, and durvalumab in combination with tremelimumab in patients with recurrent or metastatic SCCHN	31 Mar 2017 [a] 27 Aug 2018	Efficacy and health-related quality of life	Open-label, randomized	*Durvalumab monotherapy*	• Durvalumab IV 10 mg/kg Q2W for up to 12 months
				Tremelimumab monotherapy	• Tremelimumab IV 10 mg/kg Q4W for 7 doses then Q12W for 2 doses for up to 12 months
				Combination therapy	• Durvalumab IV 20 mg/kg Q4W for 4 doses then IV 10 mg/kg Q2W to complete 12 months of treatment + tremelimumab IV 1 mg/kg Q4W for 4 doses
D4193C00002 (EAGLE) Phase III, randomized, open-label, multicenter, global study of durvalumab monotherapy and durvalumab in combination with tremelimumab versus SoC in patients with recurrent or metastatic SCCHN	10 Sep 2018	Efficacy	Open-label, randomized	*Durvalumab monotherapy*	• Durvalumab IV 10 mg/kg Q2W
				Combination therapy	• Durvalumab IV 20 mg/kg Q4W for 4 doses then IV 10 mg/kg Q2W for 12 months or until progression of disease + tremelimumab IV 1 mg/kg Q4W for 4 doses

Table 1 Listing of clinical studies providing clinical pharmacology and clinical safety data in the current submission

Study number (name) Study title	DCO date	Objectives of study	Study design and type of control	Route of administration and dosage regimen	
Study 22 (D4190C00022) A study of safety, tolerability, and clinical activity of durvalumab and tremelimumab administered as monotherapy, or durvalumab in combination with tremelimumab or bevacizumab in subjects with advanced uHCC	06 Nov 2020	Safety, tolerability, efficacy, PK, and immunogenicity	Open-label, multiple-arm, randomized	*Part 1*	• Tremelimumab 75 mg (1 mg/kg) Q4W × 4 doses + durvalumab 1500 mg (20 mg/kg) Q4W
				Part 2A & China Cohort	• Durvalumab monotherapy 1500 mg (20 mg/kg) Q4W or tremelimumab monotherapy 750 mg (10 mg/kg) Q4W × 7 doses followed by Q12W • Tremelimumab 75 mg (1 mg/kg) × 4 doses + durvalumab IV 1500 mg (20 mg/kg) Q4W
				Part 2B	• Tremelimumab IV 300 mg (4 mg/kg) × 1 dose + durvalumab IV 1500 mg (20 mg/kg) Q4W
				Part 3	• Durvalumab monotherapy 1500 mg (20 mg/kg) Q4W • Tremelimumab monotherapy 750 mg (10 mg/kg) Q4W × 7 doses followed by Q12W • Tremelimumab 75 mg (1 mg/kg) × 4 doses + durvalumab 1500 mg (20 mg/kg) Q4W • Tremelimumab 300 mg (4 mg/kg) × 1 dose + durvalumab 1500 mg (20 mg/kg) Q4W
				Part 4	• Durvalumab 1120 mg (15 mg/kg) + bevacizumab 15 mg/kg Q3W
DANUBE (D419BC00001) Phase III study of durvalumab	27 Jan 2020	Efficacy and safety		*Durvalumab monotherapy*	• Durvalumab 1500 mg Q4W alone

Table 1 Listing of clinical studies providing clinical pharmacology and clinical safety data in the current submission

Study number (name) Study title	DCO date	Objectives of study	Study design and type of control	Route of administration and dosage regimen	
alone and in combination with tremelimumab in patients with unresectable stage IV urothelial cancer			Randomized, open-label, controlled (SoC), multicenter	*Combination therapy*	• Durvalumab 1500 mg Q4W + tremelimumab 75 mg Q4W for 4 doses
				SoC	• SoC
KESTREL (D419LC00001) Phase III study of durvalumab alone and in combination with tremelimumab in patients with metastatic SCCHN	06 Jul 2020 [a] 19 Jan 2021	Efficacy and safety	Randomized, open-label, multicenter, global study	*Durvalumab monotherapy*	• Durvalumab 1500 mg Q4W alone
				Combination therapy	• Durvalumab 1500 mg Q4W + tremelimumab 75 mg Q4W for 4 doses
				SoC	• SoC
D419CC00002 (HIMALAYA) Randomized, open-label, multicenter phase III study of durvalumab and tremelimumab as first-line treatment in patients with advanced hepatocellular carcinoma	27 Aug 2021	Efficacy and safety	Randomized, open-label	*Durvalumab monotherapy*	• Durvalumab 1500 mg Q4W
				Combination therapy	• Durvalumab 1500 mg Q4W + tremelimumab 300 mg as a single dose
				Combination therapy	• Durvalumab 1500 mg Q4W + tremelimumab 75 mg for 4 doses
				SoC	• Sorafenib 400 mg BID

Table 1 Listing of clinical studies providing clinical pharmacology and clinical safety data in the current submission

Study number (name) Study title	DCO date	Objectives of study	Study design and type of control	Route of administration and dosage regimen	
Supportive studies: Combination studies with chemotherapy					
D419MC00004 (POSEDON) Phase III, randomized, global study to determine the efficacy of durvalumab or durvalumab and tremelimumab in combination with platinum-based chemotherapy for first-line treatment in patients with metastatic NSCLC	12 Mar 2021	Efficacy, PK, immunogenicity, safety, and tolerability	Randomized, multicenter, open-label, comparative active comparator	*Durvalumab monotherapy*	• Durvalumab 1500 mg Q3W for 4 doses + platinum based chemotherapy, then durvalumab 1500 mg Q4W until progression of disease
				Combination therapy	• Durvalumab 1500 mg Q3W for 4 doses + platinum based chemotherapy, then durvalumab 1500 mg Q4W until progression of disease + tremelimumab 75 mg Q3W for 4 doses plus 1 dose at Week 16
				SoC	• Abraxane + carboplatin, pemetrexed + cisplatin or carboplatin; or • Gemcitabine + cisplatin or carboplatin
D419QC00001 (CASPIAN) Phase III, randomized, multicenter, open-label, comparative study to determine the efficacy of durvalumab or durvalumab and tremelimumab in combination with platinum-based chemotherapy for the first line treatment in patients with extensive disease SCLC	27 Jan 2020	Efficacy, PK, immunogenicity, safety, and tolerability	Open-label, randomized, active comparator	*Durvalumab monotherapy*	• Durvalumab IV 1500 mg Q3W for 4 doses then durvalumab IV 1500 mg Q4W until progression of disease + EP for 4 cycles
				Combination therapy	• Durvalumab IV 1500 mg Q3W for 4 doses then durvalumab IV 1500 mg Q4W until progression of disease + tremelimumab IV 75 mg Q3W for 4 doses + EP for 4 cycles
				SoC	• EP for up to 6 cycles [b]

Table 1 Listing of clinical studies providing clinical pharmacology and clinical safety data in the current submission

Study number (name) Study title	DCO date	Objectives of study	Study design and type of control	Route of administration and dosage regimen	
D933AC00001 (TOPAZ-1) A Phase III, randomized, double blind, placebo-controlled, multi-regional, international study of durvalumab in combination with gemcitabine plus cisplatin versus placebo in combination with gemcitabine plus cisplatin for patients with first-line advanced biliary tract cancers	11 Aug 2021	Efficacy, safety, tolerability, PK, immunogenicity, and health-related quality of life versus SoC	Double-blind, randomized, placebo-controlled	*Durvalumab monotherapy*	• Durvalumab 1500 mg IV Q3W in combination with gemcitabine 1000 mg/m^2 and cisplatin 25 mg/m^2 (each administered on Days 1 and 8 Q3W) for up to 8 cycles followed by durvalumab 1500 mg monotherapy Q4W until clinical progression
				SoC	• Placebo in combination with gemcitabine 1000 mg/m^2 and cisplatin 25 mg/m^2 (each administered on Days 1 and 8 Q3W) for up to 8 cycles followed by placebo Q4W until clinical progression

[a] Pharmacokinetic and immunogenicity data were only available at the earlier DCO.
[b] Patients in the EP alone group were permitted an additional 2 cycles of EP (up to 6 cycles total) per the Investigator's discretion.

2.3.2. Pharmacokinetic

Analytical methods

The bioanalytical methods used for the determination of durvalumab serum concentrations and for detection of ADAs and NAbs against durvalumab in human serum in Study D9106C00001 (AEGEAN) are listed in Table 2.

Table 2 Overview of Bioanalytical Methods Used in the AEGEAN Study

Measurement	Laboratory
Durvalumab	1
	2
ADA	A
	B
nAb	I
	II

The nAb assay validated by laboratory II is formatted as a competitive ligand binding assay whereas laboratory I nAb assay is a sandwich immunoassay.

Bioanalysis at Laboratory 1: Of 2165 samples received, 768 samples were analysed in 34 accepted runs (out of 38) and within established storage stability of 1430 days.

ADA/NAb testing at laboratory A / I: 2507 samples were received and results reported from 2486 samples.

Of 110 runs performed, 105 were acceptable. 103 samples were confirmed ADA positive and were tested for NAbs. For each run a negative control (in quadruplicate) and low and high positive controls (in duplicate) were included. The acceptance criteria established by the MAH was %CV≤ 25.0% between NC replicates (excluding an outlier) and at least 50% of the PCs at each level and %CV≤ 25.0% between duplicates in at least 66.7% of all PCs.

In the ADA screening assay, 247 ng/mL ADA could be detected in presence of 100 µg/mL durvalumab with a cut point factor of 1.59. The majority of samples had concentrations of durvalumab <100 µg/mL, however, concentrations up to 613 µg/mL were detected.

Bioanalysis at B / II: Of 228 received were 111 samples quantified in 9 accepted runs (out of 11) within 567 days. Storage stability has been established to 1489 days. ISR was conducted on 14 samples and 12 (85.7%) met acceptance criteria.

Of 347 samples received, 345 samples were tested for ADAs in 14 accepted runs (out of 16) within 661 days of storage. Six samples screened positive but were not confirmed positive. No samples were tested for NAbs.

Absorption, distribution, elimination

Exposure

Study D9106C00001 (AEGEAN) PK and ADA sampling: In the neoadjuvant period, PK samples were collected pre-dose (i.e., within 60 minutes of the start of durvalumab/placebo infusion) at Cycle 2, and samples for ADA analysis were collected pre-dose at Cycles 1 and 2. After surgery (adjuvant), PK samples were collected pre-dose at Cycles 1 and 2, and ADA samples were collected pre-dose at Cycles 1, 6, and 12. The PK results are presented in Table 3.

Table 3 Summary of Durvalumab Concentrations Over Time (µg/mL) (PK Analysis Set) (AEGEAN Study)

Analysis time point/parameter	Neoadjuvant 1500 mg Q3W IV (N = 385)	Adjuvant 1500 mg Q4W IV (N = 264)
Neoadjuvant		
Week 0 - Pre-Infusion		
N	No sample	NA
Mean (SD)	No sample	NA
Median (min, max)	No sample	NA
%CV	No sample	NA
Geometric mean	No sample	NA
Geometric %CV	No sample	NA
Number of BLQ	No sample	NA
Week 3 - Pre-Infusion		
N	378	NA
Mean (SD)	92.177 (49.8033)	NA
Median (min, max)	86.667 (0.05, 488.96)	NA
%CV	54.03	NA
Geometric mean	75.5	NA
Geometric %CV	119.53	NA
Number of BLQ	3	NA
Week 4 - Pre-Infusion		
N	No sample	NA
Mean (SD)	No sample	NA
Median (min, max)	No sample	NA
%CV	No sample	NA
Geometric mean	No sample	NA
Geometric %CV	No sample	NA
Number of BLQ	No sample	NA
Week 12 - Pre-Infusion		
N	No sample	NA
Mean (SD)	No sample	NA
Median (min, max)	No sample	NA
%CV	No sample	NA

Analysis time point/parameter	Neoadjuvant 1500 mg Q3W IV (N = 385)	Adjuvant 1500 mg Q4W IV (N = 264)
Geometric mean	No sample	NA
Geometric %CV	No sample	NA
Number of BLQ	No sample	NA
Adjuvant		
Week 0 - Pre-Infusion		
N	NA	247
Mean (SD)	NA	51.202 (63.5524)
Median (min, max)	NA	39.211 (0.05, 491.83)
%CV	NA	124.12
Geometric mean	NA	26
Geometric %CV	NA	363.25
Number of BLQ	NA	9
Week 4 - Pre-Infusion		
N	NA	237
Mean (SD)	NA	115.069 (62.9743)
Median (min, max)	NA	104.212 (7.11, 613.28)
%CV	NA	54.73
Geometric mean	NA	102.3
Geometric %CV	NA	53.36
Number of BLQ	NA	0

When less than or equal to half of the results are BLQ, the BLQ results are set to the lower limit of quantification and descriptive statistics are calculated accordingly. When more than half (but not all) of the results are BLQ, the geometric mean, SD, %CV, and geometric %CV are presented as NC and the median and minimum are presented as NQ. When all results are BLQ, no descriptive statistics are calculated.

The durvalumab serum concentrations of AEGEAN were similar as those observed in durvalumab pan-tumour pool (Table 4) and the chemotherapy combination studies (POSEIDON, TOPAZ-1, and CASPIAN). The combination studies had similar dosing regimens as in AEGEAN neoadjuvant. In the combination studies, the serum durvalumab concentrations (geometric mean) at week 3 pre-infusion were 91.53 µg/mL (n = 285, geometric %CV = 100.58), 88.39 µg/mL (n = 250, geometric %CV = 56.57), and 109.5 µg/mL (n = 237, geometric %CV = 64.55) for POSEIDON, TOPAZ-1, and CASPIAN, respectively.

Table 4 Summary of Serum Durvalumab Concentrations (PK Analysis Set)

Visit, timepoint	Geometric mean, µg/mL (geometric %CV) [n]		
	AEGEAN study		Durvalumab pan-tumour pool 10 mg/kg Q2W, 20 mg/kg Q4W or 1500 mg Q4W IV (N = 3903)
	Neoadjuvant (N = 385) 1500mg Q3W IV	Adjuvant (N = 264) 1500mg Q4W IV	
Neoadjuvant			
Week 0 pre-infusion	No samples	NA	NC (NC) [3127]
Week 3 pre-infusion	75.5 (119.53) [378]	NA	No samples
Week 4 pre-infusion	No samples	NA	76.0 (85.76) [1940]

Visit, timepoint	Geometric mean, µg/mL (geometric %CV) [n]		
	AEGEAN study		Durvalumab pan-tumour pool
	Neoadjuvant (N = 385) 1500mg Q3W IV	Adjuvant (N = 264) 1500mg Q4W IV	10 mg/kg Q2W, 20 mg/kg Q4W or 1500 mg Q4W IV (N = 3903)
Week 12 pre-infusion	No samples	NA	118.1 (103.88) [1037]
Adjuvant			
Week 0 pre-infusion	NA	26.0 (363.25) [247]	NA[a]
Week 4 pre-infusion	NA	102.3 (53.36) [237]	NA[a]

[a] No supportive study in the durvalumab pan-tumour pool has an adjuvant treatment period to directly compare to AEGEAN.

When less than or equal to half of the results are BLQ, the BLQ results are set to the lower limit of quantification and descriptive statistics are calculated accordingly. When more than half (but not all) of the results are BLQ, the geometric mean, SD, %CV and geometric %CV are presented as NC and the median and minimum are presented as NQ. When all results are BLQ, no descriptive statistics are calculated.

Immunogenicity

Out of 47 ADA-positive patients, 15 patients were ADA-positive at baseline only, 25 patients were treatment-induced ADA-positive, 7 patients were ADA-positive at both baseline and post baseline, and none of them were treatment-boosted ADA-positive. Two (0.5%) patients were nAb-positive (respective titers were 1 and 256).

Table 5 Summary of ADA response to durvalumab (ADA analysis set; EFS IA1)

	Number (%) patients D + CTx (N = 377)
ADA-evaluable population[a]	375 (99.5)
ADA prevalence (any ADA-positive, baseline or post-baseline) [b]	47 (12.5)
Treatment-induced ADA-positive[b, c]	25 (6.7)
Treatment-boosted ADA-positive[b, d]	0
ADA incidence (treatment-emergent ADA-positive) [b, e]	25 (6.7)
ADA-positive at baseline and post-baseline[b]	7 (1.9)
ADA-positive at baseline only[b]	15 (4.0)
Persistent positive[b, f]	12 (3.2)
Transient positive[b, g]	20 (5.3)
nAb positive at any visit[b]	2 (0.5)

a Patients with non-missing baseline and at least 1 non-missing post-baseline pre-dose ADA results. Therefore, the ADA evaluable population (n=375) excludes two patients, who had a valid baseline value, but post-baseline values were at post dose. The denominator is the number of patients in the ADA analysis set treatment arm.
b The denominator is the number of ADA evaluable patients in treatment arm.
c Treatment-induced ADA: positive post-baseline only.
d Treatment-boosted ADA: baseline ADA titer that was boosted ≥ 4-fold following drug administration.
e Treatment-emergent ADA: either treatment-induced ADA or treatment-boosted ADA.

f Persistent Positive: at least 2 post-baseline ADA +ve results at least 16 weeks (112 days) apart, or an ADA +ve result at the last available assessment.
g Transient Positive: at least 1 post-baseline ADA +ve result, but not persistent positive.
DCO: 10 November 2022

The geometric mean serum durvalumab concentrations in patients with treatment-emergent ADAs to durvalumab were lower than those in ADA-negative patients (Table 6).

Table 6 Summary of serum concentrations (µg/mL) of durvalumab for all treatment groups in treatment-emergent ADA-positive and ADA-negative patients (PK analysis set)

Visit/ Statistic	D + CTx (N = 385)		
	Treatment emergent ADA+ [a]	ADA+ [b]	ADA-
Neoadjuvant Cycle 2 (pre-dose)			
n (n < LLOQ)	25 (0)	48 (1)	330 (2)
Geometric mean	26.84	40.65	88.20
Geometric CV (%)	389.8	240.8	44.74
Adjuvant Cycle 1 (pre-dose)			
n (n < LLOQ)	15 (0)	32 (2)	215 (7)
Geometric mean	15.55	23.17	34.65
Geometric CV (%)	268.4	160.5	151.1
Adjuvant Cycle 2 (pre-dose)			
n (n < LLOQ)	16 (0)	30 (0)	207 (0)
Geometric mean	82.77	85.16	105.1
Geometric CV (%)	49.06	43.82	54.10

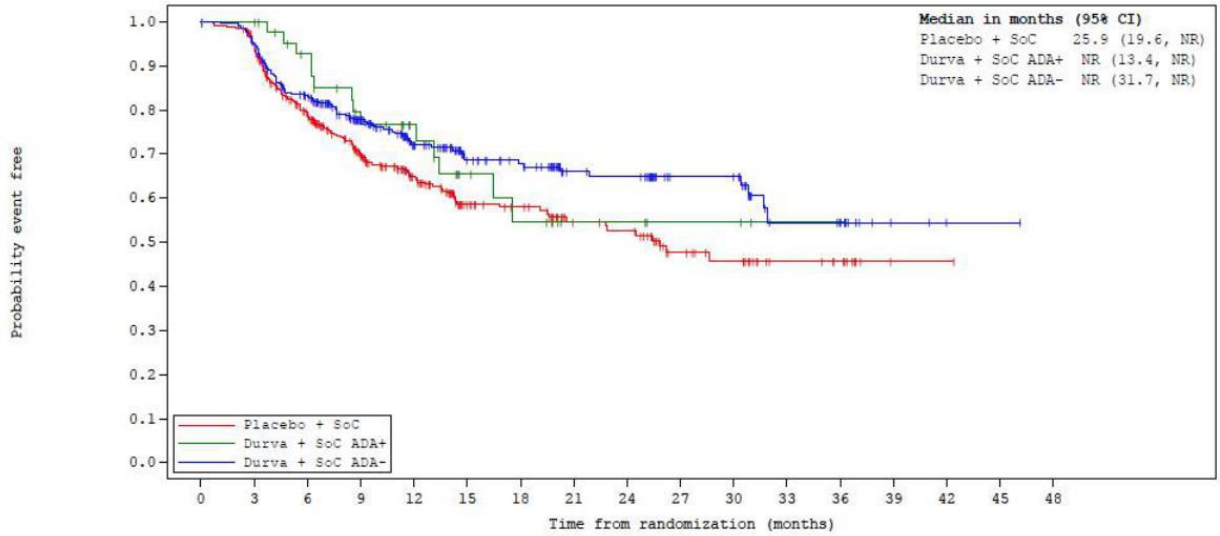
a Either treatment-induced or treatment-boosted ADA.

b ADA positive at baseline or post-baseline.

Values < LLOQ were excluded from the computation of Geometric mean and Geometric CV values.

There was no clear evidence that the presence of ADA had an impact on the efficacy of durvalumab. However, the number of durvalumab ADA-positive patients was relatively small (Figure 1).

Figure 1 Kaplan-Meier plot of EFS (using BICR per RECIST 1.1) by actual treatment received and ADA Category (ADA population, EFS IA1)



Number of patients at risk

																	Events/Randomized
Placebo + SoC	364	336	257	188	139	88	79	54	51	31	26	16	13	1	1	0	0	135/364
Durva + SoC ADA+	45	44	36	28	21	13	10	5	5	3	3	1	1	0	0	0	0	14/45
Durva + SoC ADA-	332	308	250	180	132	93	84	58	56	37	36	16	14	3	1	1	0	93/332

One month is 30.4375 days.
| indicates a censored observation.

2.3.3. Pharmacodynamics

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

2.3.4. PK/PD modelling

Pop PK analysis

A previous PopPK model was used as a starting point in this modelling analysis and data from AEGEAN added. The analysis contained 3205 subjects (385 from AEGEAN study) and a total of 12466 PK observations. PK samples below limit quantification (BLQ) of total observations were 1.64% and were excluded in the population PK analysis (M1 method). Durvalumab PK was described using a 2-compartment model with time varying CL.

The full covariate model was re-evaluated based on the current dataset and the same model structure as the previous model was considered. As a result, all significant covariates previously identified except the effect of LDH on CL were retained in the model. Subsequently, additional covariates (race, region and tumour type) were tested on CL and Vc but none of them were statistically significant. Moderate inter-individual variability was characterized on several PK parameters CL (29.69%), Vc (24.06%) and Tmax (23.42%).

The final popPK model included 9 covariate effects (albumin levels, creatinine CL, ECOG status, sex, body weight, combination therapy 1 and combination therapy 2 on clearance and body weight and sex on central volume of distribution). Parameters of the final model are shown in Table 7.

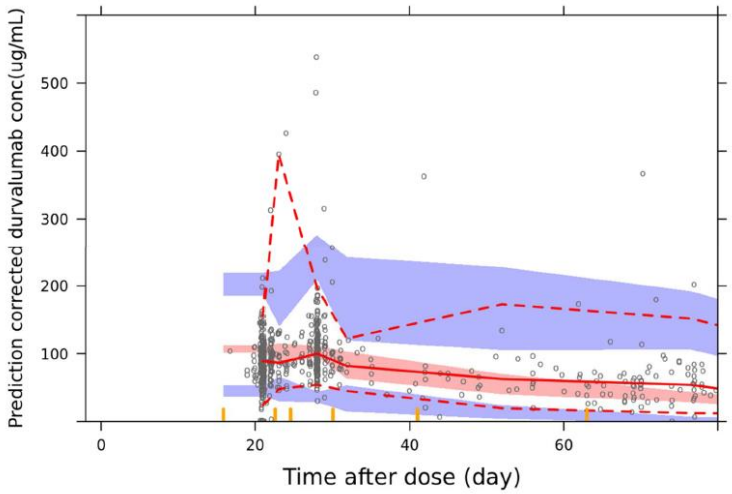
Table 7 Population PK Model Parameter Estimates

Parameter	Estimate	RSE (%)	Bootstrap median	Bootstrap 95%ci	Shrinkage (%)	Unit
Population Parameter						
CL	0.285	1.68	0.285	[0.270 ; 0.303]	-	L/day
$V_{central}$	3.42	0.962	3.42	[3.38 ; 3.48]	-	L
$V_{peripheral}$	2.30	2.09	2.30	[2.15 ; 2.44]	-	L
$Q_{intercompartmental}$	0.381	4.90	0.381	[0.297 ; 0.465]	-	L/day
T_{max} change CL	-0.412	4.91	-0.414	[-0.465 ; -0.360]	-	L/day
TC_{50} change CL	48.0	10.9	47.4	[32.8 ; 71.9]	-	day
LAM change CL	1.00	-	-	-	-	-
Covariate						
Albumin on CL	-0.526	2.88	-0.537	[-0.776 ; -0.389]	-	-
Creatinine clearance on CL	0.112	19.1	0.111	[0.0699 ; 0.153]	-	-
ECOG status on CL	-0.0604	19.1	-0.0590	[-0.0836 ; -0.0325]	-	-
Sex on CL	-0.166	7.40	-0.165	[-0.189 ; -0.139]	-	-
COMB1 on CL	-0.0701	17.9	-0.0694	[-0.0984 ; -0.0406]	-	-
COMB 2 on CL	-0.0578	29.0	-0.0561	[-0.108 ; -0.00867]	-	-
Bodyweight on CL	0.378	9.31	0.382	[0.311 ; 0.453]	-	-
Sex on Vc	-0.144	8.27	-0.143	[-0.166 ; -0.121]	-	-
Bodyweight on Vc	0.503	5.73	0.502	[0.446 ; 0.558]	-	-
Interindividual Variability						
ETA CL	0.0845	3.43	0.0832	[0.0737 ; 0.0942]	19.4	-
Cov CL-V1	0.0408	5.77	0.0407	[0.0345 ; 0.0471]	-	-
ETA Vc	0.0563	3.74	0.0563	[0.0482 ; 0.0644]	28.9	-
ETA T_{max}	0.0534	9.53	0.0537	[0.0341 ; 0.0772]	56.5	-
Residual Variability						
Proportional component	0.253	0.627	0.253	[0.245 ; 0.261]	13.5	-
Additive component	5.38	6.38	5.35	[4.16 ; 6.80]	13.5	µg/mL

CI = confidence interval; CL = Clearance; COMB1 = durvalumab+SOC; COMB2 = durvalumab+tremelimumab+SOC; Cov = Covariance; ECOG = Eastern Cooperative Oncology Group; ETA = random effect; LAM = Hill factor; LDH = Lactate Dehydrogenase; PK = Pharmacokinetics; Q = Inter-Compartmental Clearance, RSE = Relative Standard Error; SOC = Standard Of Care;TC50 = Time to 50% Change of CL Over Time; Tmax = Maximum Change of CL Over Time; V1 = Central Volume Of Distribution; V2 = Peripheral Volume Of Distribution

The final model was evaluated by means of non-parametric bootstrap analysis, GOF-plots and VPCs. A pcVPC of AEGEAN exposure is shown in Figure 2.

Figure 2 pcVPC of the Final Model vs Time after Dose – AEGEAN Study



Solid and dashed lines = the median, 5th, and 95th percentiles of the observations

Shaded red and blue areas = the 95% confidence interval of the median, 5th, and 95th percentiles predicted by the model

CI = Confidence Interval; pcVPC = Prediction-Corrected Visual Predictive Check

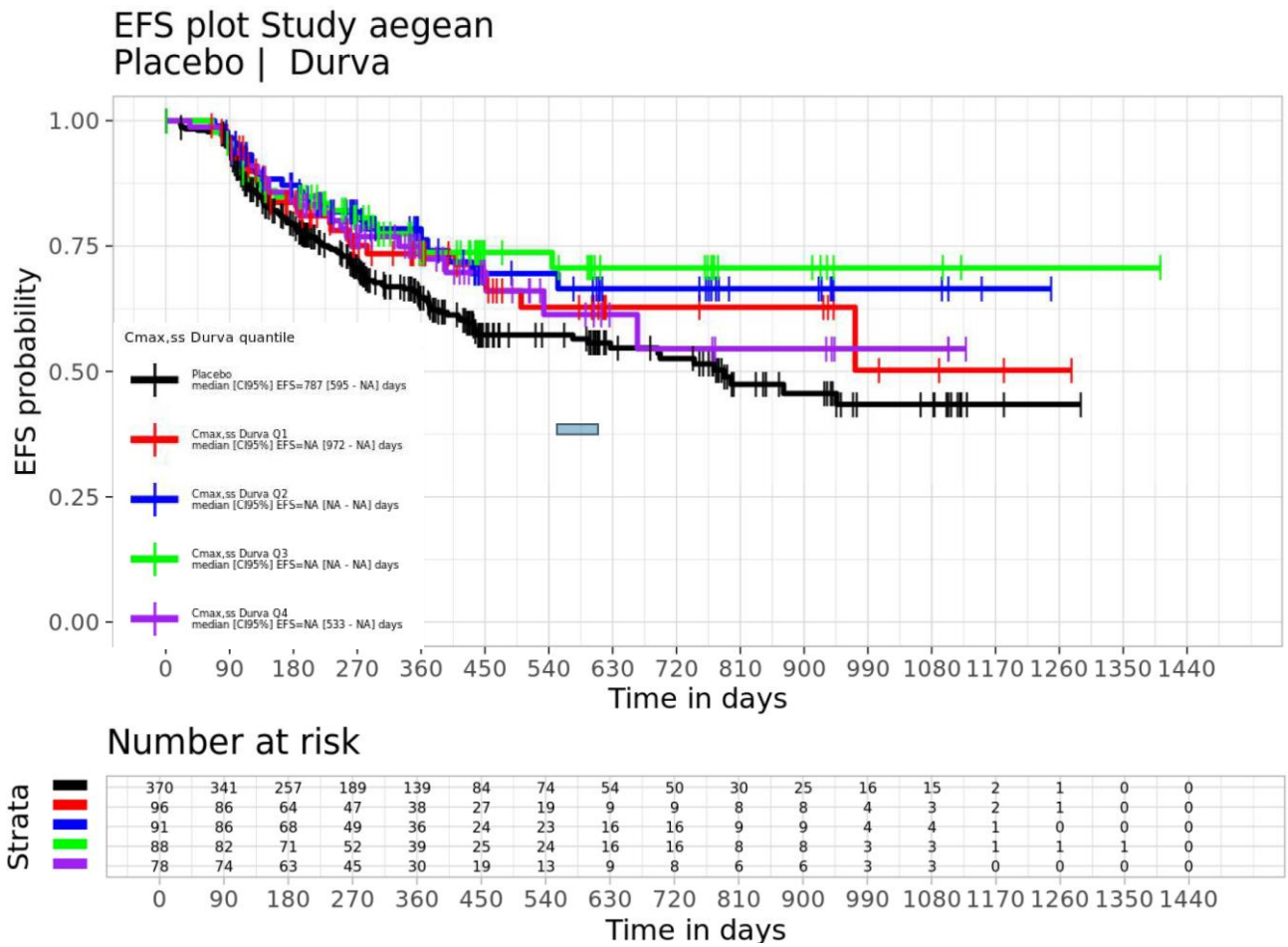
Exposure response analyses

Exposure-response analyses were performed based on data from the AEGEAN study. Exposure metrics were derived using simulated durvalumab time-course PK profiles based on individual post-hoc PK parameters following administration of 1500 mg durvalumab Q3W for 4 cycles then followed by 1500 mg Q4W for 12 cycles.

A total of 385 PK evaluable patients in durvalumab arm were analysed in the exposure response analysis, including 353 patients for the exposure efficacy analysis and 385 patients for the exposure safety analysis.

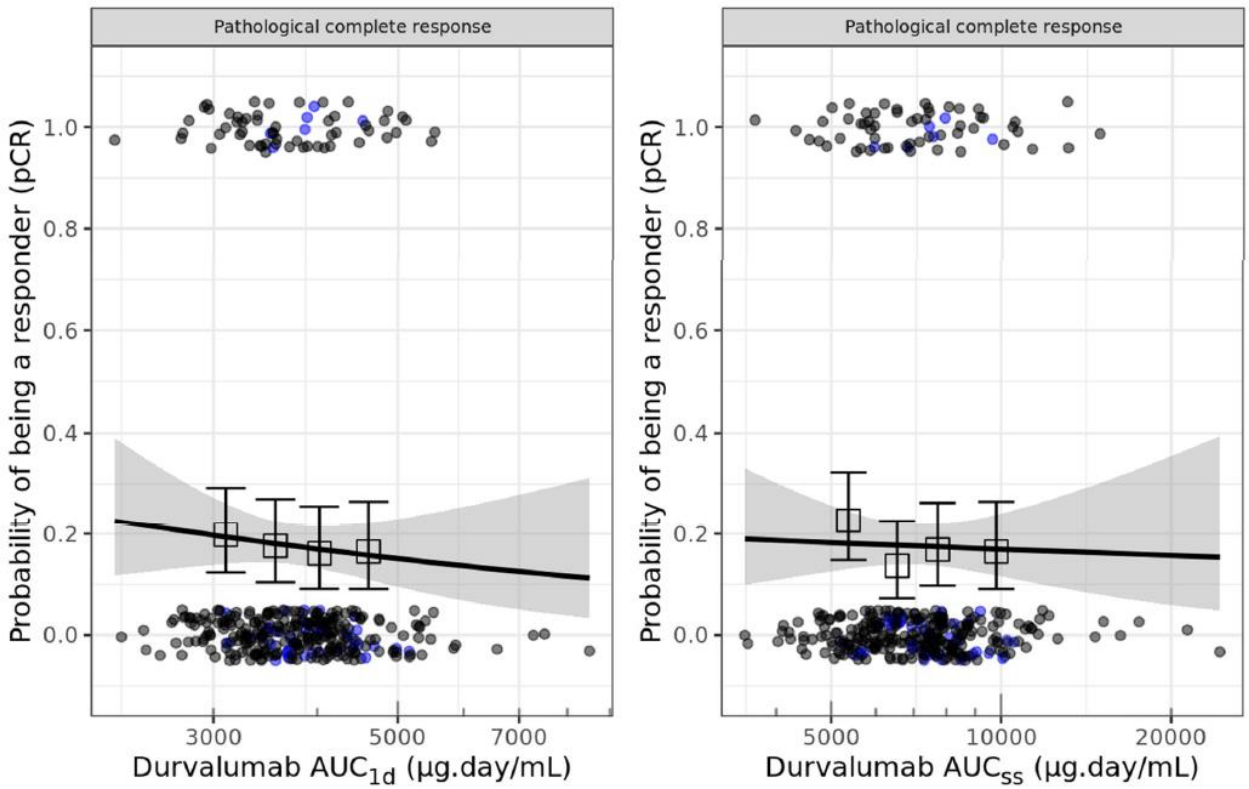
Exposure response for EFS was investigated by a Cox PH model based on durvalumab treated patients in AEGEAN study. Covariates of clinical interest, such as race, region, non-Chinese vs Chinese, disease status, baseline covariates, TEADA and exposure metrics were tested using a forward inclusion method with significant levels of $P < 0.01$. None of the investigated covariates were identified as significant. Kaplan-Meier plots of exposure quartiles at steady-state and Event Free Survival (EFS) is shown for Cmax in Figure 3.

Figure 3 EFS Kaplan-Meier Plots for Durvalumab Exposure Metrics by Quartiles at Steady-State



The pathological complete response (pCR) was analysed using a logistic regression model relating the probability of being a responder to durvalumab exposure metrics. No statistically significant relationship was identified (see Figure 4).

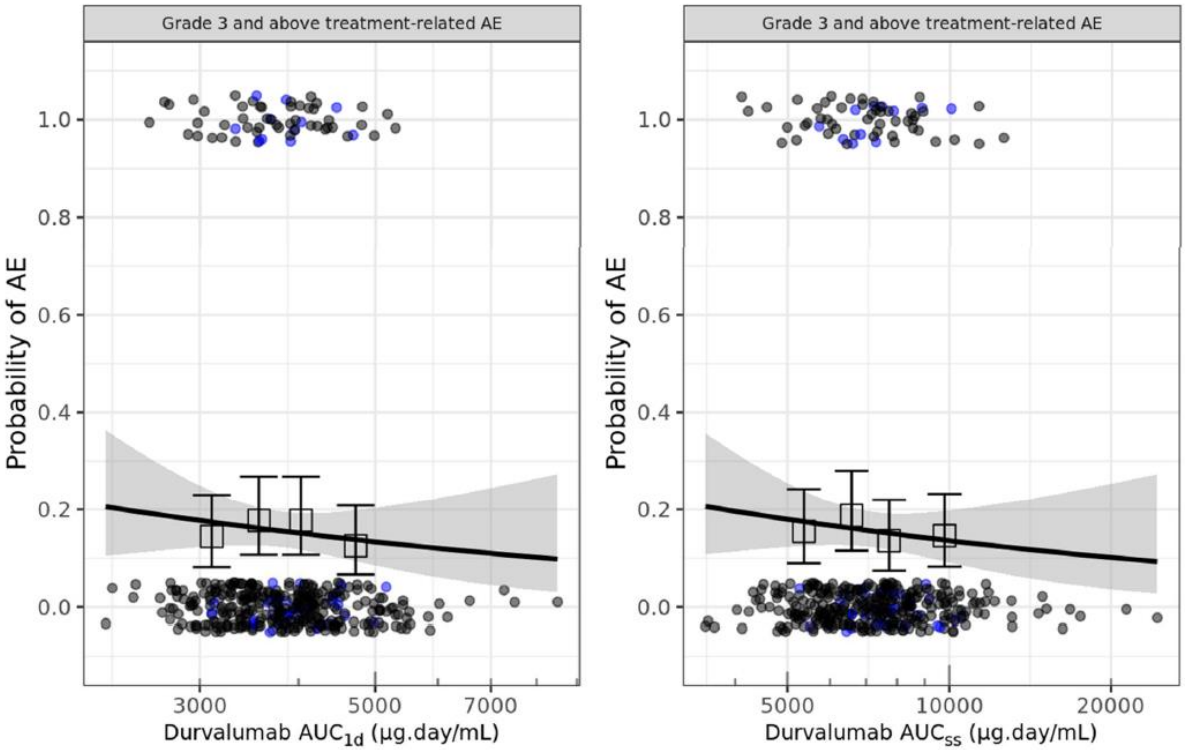
Figure 4 Relationship Between the Probability of pCR and AUCdose 1 (AUC1d) or steady-state (AUCss) for Durvalumab



Black solid circles = observed pCR in non-Chinese patient
Blue solid circles = the observed pCR in Chinese patient, open squares with error bars are the observed probability of response at each exposure quartile
Black lines = the logistic regression between two variables and the grey area represents the associated confidence interval
AUC=Area Under the Serum Concentration-Time Curve; pCR = Pathological Complete Response

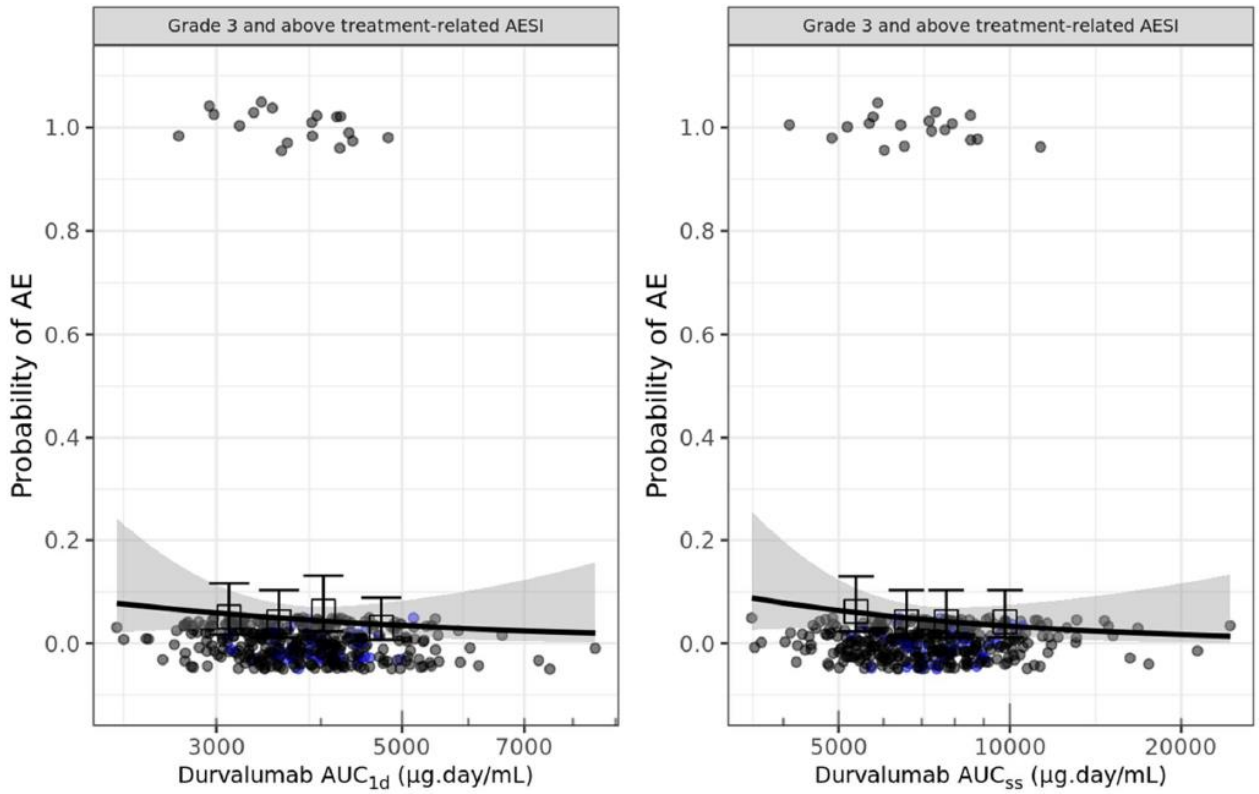
The safety endpoints of interest were Grade 3 and above treatment-related AEs, Grade 3 and above treatment-related AESIs and AEs leading to durvalumab treatment discontinuation. No statistically significant relations were identified between AUC and the safety end-points of interest from AEGEAN. See Figure 5, Figure 6, Figure 7.

Figure 5 Relationship Between the Probability of Having Grade 3 and Above Treatment-Related AEs and AUCdose 1 (AUC1d) or Steady-State (AUCss) for Durvalumab



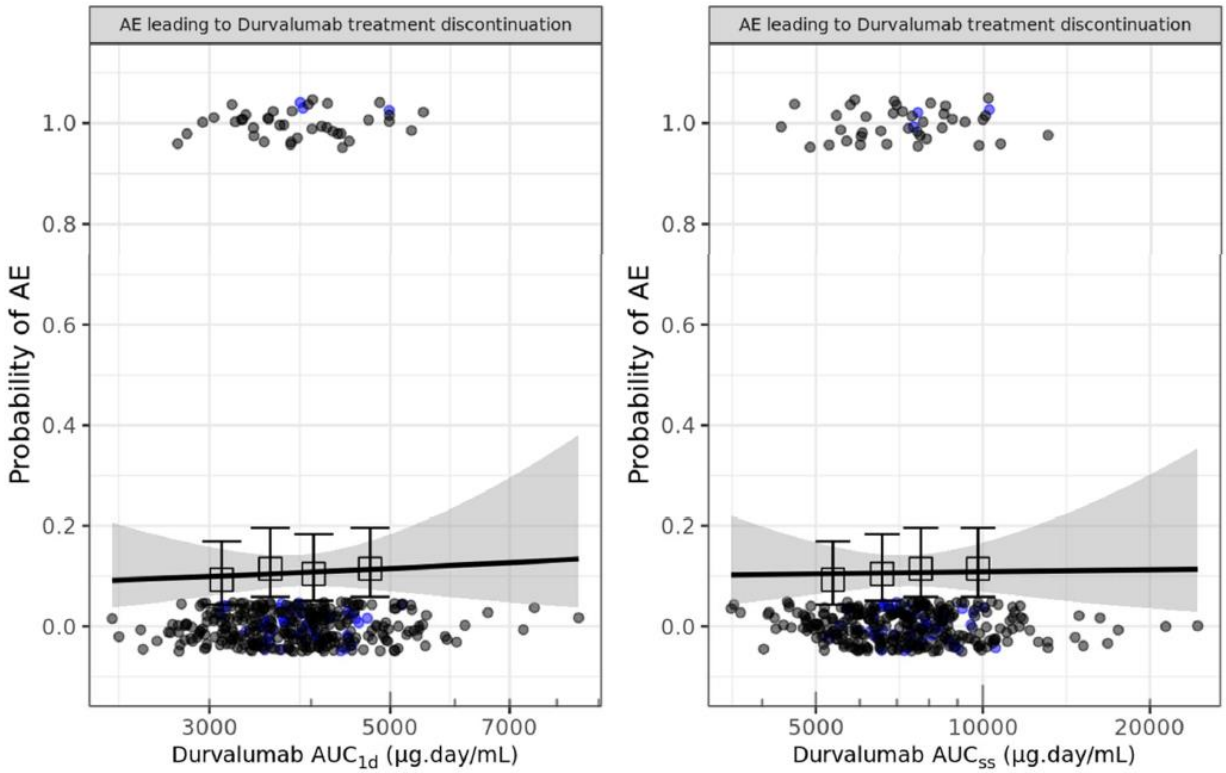
Black solid circles = the observed AE in non-Chinese patient
Blue solid circles = the observed AE in Chinese patient
open squares with error bars = the observed probability of response at each exposure quartile
Black lines = the logistic regression between two variables and the Gray area represents the associated confidence interval
AE = adverse event; AUC = Area Under the Serum Concentration-Time Curve

Figure 6 Relationship Between the Probability of Having Grade 3 and Above Treatment-Related AESIs and AUCdose 1 (AUC1d) and Steady-State (AUCss) for Durvalumab



AE = Adverse Event; AUC = Area Under the Serum Concentration-Time Curve
Black solid circles = the observed AE in non-Chinese patient
Blue solid circles = the observed AE in Chinese patient
Open squares with error bars = the observed probability of response at each exposure quartile
Black lines = the logistic regression between two variables
Grey area = the associated confidence interval

Figure 7 Relationship Between Probability of Having AEs Leading to Durvalumab Treatment Discontinuation and AUCdose 1 (AUC1d) and steady-state (AUCss) for Durvalumab



Black solid circles = the observed AE in non-Chinese patient
Blue solid circles = the observed AE in Chinese patient
Open squares with error bars = the observed probability of response at each exposure quartile
Black lines = the logistic regression between two variables
Grey area = the associated confidence interval
AE = Adverse Event; AUC = Area Under the Serum Concentration-Time Curve

2.3.5. Discussion on clinical pharmacology

Bioanalytical methods

The formulation development and analytical methods used have been described in previous submissions and will not be further discussed. Validated methods were used to determine serum concentrations and to assess immunogenicity of durvalumab in samples from the AEGEAN study.

Two bioanalytical sites and methods were used for quantification of durvalumab. Two sites and two sets of ADA/NAb methods were applied for immunogenicity testing (see Table 2). The haemolysis effect on quantification of durvalumab at the laboratory 2 was slightly out of acceptable range according to current guideline (20%), but within the planned acceptance criteria (25%) at the time of method validation (data not shown). Trough concentrations of durvalumab were generally similar in the overall population and the China subset. As a follow-up from procedure EMEA/H/C/004771/WS2463/0063, where it was concluded that haemolysis effect was not adequately evaluated for BA method ICSH 16-032, the MAH submitted the final haemolysis re-evaluation report, under ICH M10, as mentioned above, titled "Validation of a Method for the Determination of MEDI4736 in Human Serum Using Electrochemiluminescence (ECL) Final Report (Addendum No. 04) (data not shown). It is noted that in report addendum 2, 5% of haemolysis matrix was used whereas in the final report (addendum 4), 2% of haemolysis matrix was employed. The results obtained and the matrix used are still in accordance with ICH M10 Guideline. The lack of acceptable selectivity in haemolysed samples have no impact on the general conclusion on pharmacokinetics, safety or efficacy.

No cross-validations of the quantification and ADA assay applied in AEGEAN were performed. This can be accepted for the ADA testing since the ADA incidence is low and well-characterised from other studies, however, use of only one laboratory for future ADA analyses are strongly advised. Use of different analytical sites within a study, requires cross-validation of the quantification methods applied according to ICH M10. Therefore, in principle cross-validation should have been performed prior to sample analysis in AEGEAN. As the majority of samples (>95%) were analysed at laboratory 1, the issue will not be further pursued.

Bioanalysis at laboratory 1:

Incurred sample reanalysis (ISR) for AEGEAN was documented in addendum 3 to the validation report (data not shown) and passed the acceptance criteria.

ADA/NAb testing at laboratory A / I: Twenty one samples were excluded and the MAH has provided an acceptable justification for these exclusions.

It is understood that the acceptance criterion was established to be in accordance with ICHM10 Guideline. For this reason, this issue is not further pursued. However, for further procedures, the MAH should take into account for ADA and NAbs analytical methods that, according to the state of the art (Myler, Heather et al., 2022-2023), the acceptance criteria between duplicates of NC and PC controls should be CV≤20% for ADA analysis and CV≤25% for NAb analysis.

Thus, the drug tolerance of the ADA assay (laboratory A) is not sufficient and in principle more samples could be ADA positive. The issue is not further pursued in the context of this procedure, but the MAH is recommended to not use this method in the future, as more drug tolerant ADA assay have been developed for durvalumab.

Overall, the bioanalysis conducted in support of Study AEGEAN is considered acceptable.

Exposure:

In the CASPIAN study in SCLC patients, which had a comparable treatment arm, durvalumab trough serum concentrations at Week 3 were 110 µg/mL (n=236, 64.4%CV) following 1500 mg Q3W. The mean Ctrough concentrations in AEGEAN were 75.5 µg/mL (120%CV) at Week 3 (pre-surgery) 1500 mg Q3W and 102.3 µg/mL (53.4%CV) at Week 4 (post-surgery) 1500 mg Q4W. Compared to CASPIAN, the geometric mean Ctrough was lower in AEGEAN, but within the expected range. The %CV is high but largely comparable to other studies. The geometric mean Ctrough Week 3 pre-surgery was also comparable to a durvalumab pan-tumour pool mean concentration based on data from 3903 patients.

Immunogenicity

Immunogenicity was assessed in the AEGEAN study using a tiered approach with confirmation of ADA-positive samples, determination of titer and test of neutralising capacity. Of 375 patients, 47 (12.5%) had confirmed ADA positive samples pre- or post-treatment. Of these, 25 patients (6.7%) had treatment-induced or treatment-boosted ADAs. Neutralising antibodies were detected in two patients. The ADA incidence was low and within range of other studies.

No new pharmacodynamics data were submitted in this procedure.

PK modelling:

M1 method for handling BLQ-data is considered acceptable.

Structural model parameters were estimated with relatively good precision (RSE < 11%), and covariate effects with moderate good precision (RSE <30%). The non-parametric distribution of the

parameter estimates showed a good agreement with the NONMEM estimates. GOF plots showed, in general, adequate model performance in the DV vs PRED and DV vs IPRED. Prediction corrected visual predictive check (pc-VPC) were provided for the overall population and stratified by study. The pc-VPC suggest that the overall model performance of the final model is adequate. pcVPC stratified by study showed adequate model predictions for the median in the AEGEAN study.

For the efficacy analysis, the relationship of EFS to Cmax, Cmin, and AUC of durvalumab, at first cycle and at steady state was evaluated. Kaplan-Meier estimates stratified by the quartile exposure at steady-state and quartiles of body weight are overlapped, indicating no clear exposure-efficacy relationship. The graphical exploration of the durvalumab exposure metrics by pCR status showed not significant differences between responders and non-responders. Subsequently, the probability of pCR was calculated in quartiles of exposure at dose 1 and at steady state. The analysis showed no exposure pCR relationship.

For the safety analysis, the relationship between durvalumab exposure and clinical safety endpoints Grade 3 and above treatment-related AEs, Grade 3 and above treatment-related AESIs and AEs leading to durvalumab treatment discontinuation was explored based on data in the durvalumab treatment arm from the AEGEAN study. The graphical exploration of the exposure metrics for patients with an AE and patients without any AEs did not reveal any significant relationship. The results were confirmed by a logistic regression analysis, which did not identify any significant impact of the durvalumab exposure at 1500 mg dose on the incidence of Grade 3+ treatment-related AEs, Grade 3+ treatment-related AESIs or AEs leading to durvalumab treatment discontinuation.

2.3.6. Conclusions on clinical pharmacology

The clinical pharmacology properties of the combination of durvalumab with platinum-based chemotherapy in the neoadjuvant treatment, followed by durvalumab as monotherapy in the adjuvant treatment of adult patients with NSCLC have been studied based on the limited PK evidence collected in the Phase 3 trial AEGEAN. Overall, the clinical pharmacology data were acceptable.

2.4. Clinical efficacy

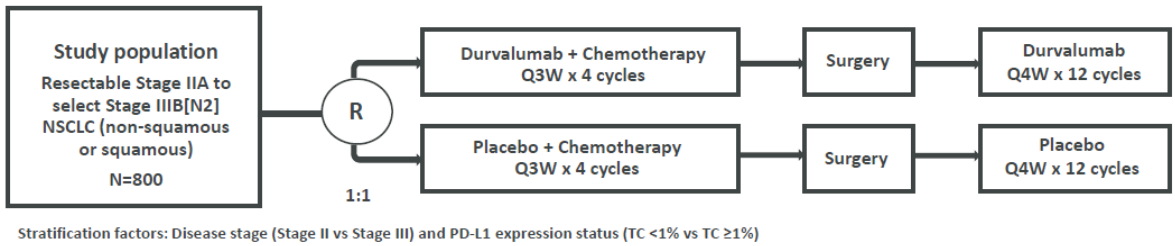
2.4.1. Dose response study(ies)

Not applicable.

2.4.2. Main study(ies)

AEGEAN – A Phase III, Double-blind, Placebo-controlled, Multi-center International Study of Neoadjuvant/Adjuvant Durvalumab for the Treatment of Patients with Resectable Stages II and III Non-small Cell Lung Cancer

Figure 8 AEGEAN Study Design



Chemotherapy options: *Squamous*: carboplatin and paclitaxel, cisplatin and gemcitabine, carboplatin and gemcitabine (permitted under certain circumstances); *Non-squamous*: carboplatin and pemetrexed, cisplatin and pemetrexed (patients were permitted to switch from cisplatin to carboplatin if unacceptable toxicity).
Note: In total 802 patients were randomized in the study.
TNM classification is based on the AJCC Cancer Staging Manual, 8th Edition.

Methods

Study participants

Main Inclusion criteria

- Age ≥ 18 years at the time of screening. For patients aged < 20 years and enrolled in Japan, a written informed consent should have been obtained from the patient and his or her legally acceptable representative.
- Newly diagnosed and previously untreated patients with histologically or cytologically documented NSCLC. Patients were to have resectable (Stage IIA to select [i.e., N2] Stage IIIB) disease (according to Version 8 of the IASLC Staging Manual in Thoracic Oncology 2016) 3 and be candidate for lobectomy, sleeve resection, or bi-lobectomy at the time of screening
    - any patient with a tumour size ≥ 4 cm
    - any patient with N1 or N2 disease (regardless of primary tumour size), including multi-station N2 disease;
    - patients with multiple tumour nodules in the same lobe or tumours that involve the main bronchus or tumours that invade visceral pleura, chest wall (including the parietal pleura and superior sulcus tumours), phrenic nerve or parietal pericardium; or tumours that are associated with atelectasis or obstructive pneumonitis that extends to the hilar region or involves part or all of the lung.
        - At screening, complete surgical resection of the primary NSCLC must have been deemed achievable, as assessed by a multidisciplinary evaluation, which was to include a thoracic surgeon who performed lung cancer surgery as a prominent part of their practice
            - T4 tumours were only eligible if they were defined as T4 based only on their size (more than 7 cm); any other reason for T4 (e.g., adherent to any of the following structures: diaphragm, mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, oesophagus, vertebral body, carina) were considered ineligible

- Nodal status should have been investigated with whole body FDG-PET, plus contrast-enhanced CT. If PET/CT scan was positive in the mediastinum, or if scan was negative but there was a T > 3 cm central tumour, or clinical N1, then it was recommended that nodal status be proven by biopsy via endobronchial ultrasound, mediastinoscopy, or thoracoscopy. See surgery eligibility below, and Section 6.1.3 of CSP Version 5.0 for more details (see Appendix 16.1.1)
- Mandatory brain MRI (preferred) with IV contrast, or brain CT with IV contrast at the time of staging.

- WHO/ECOG PS of 0 or 1 at enrolment.
- At least one lesion not previously irradiated that qualified as a RECIST 1.1 TL at baseline. Tumour assessment by CT or MRI scan must have been performed within 28 days prior to randomization.
- No prior exposure to immune-mediated therapy including, but not limited to, other anti-CTLA-4, anti-PD-1, anti-PD-L1, and anti-PD-L2 antibodies, excluding therapeutic anticancer vaccines.
- Life expectancy of at least 12 weeks.
- Confirmation of a patient's tumour PD-L1 expression was to occur prior to randomization using the VENTANA PD-L1 (SP263) Assay applied to formalin-fixed paraffin-embedded tissue sample with testing completed by the central laboratory. Samples for PD-L1 testing could include the following:
  - Newly acquired tumour tissue (preferred) or archival tissue (< 3 months old).
  - If the patient's PD-L1 expression had already been assessed using the analytically validated VENTANA PD-L1 [SP263] Assay as a part of the screening process for another AstraZeneca study, this test result could be used for the determination of eligibility.
- Provision of sufficient tumour biopsy sample for evaluation and confirmation of EGFR mutation and ALK gene rearrangement status where applicable (as well as PD-L1 expression as described above) during screening. If a local laboratory performed the ALK rearrangement status test, a well-validated, local regulatory-approved kit must have been used. Central testing was performed for EGFR mutation status. Patients with KRAS mutations in their tumours did not need to be tested for EGFR mutation/ALK gene rearrangement status, and patients with squamous cell carcinoma did not need to be tested for ALK gene rearrangement status.
- Patients were suitable for inclusion if the planned surgery to be performed was lobectomy, sleeve resection, or bi-lobectomy, as determined by the attending surgeon based on the baseline findings.

<u>Main Exclusion criteria</u>

- History of allogeneic organ transplantation.
- Active or prior documented autoimmune or inflammatory disorders (including inflammatory bowel disease [e.g., colitis or Crohn's disease], diverticulitis [with the exception of diverticulosis], systemic lupus erythematosus, Sarcoidosis syndrome, or Wegener syndrome [e.g., granulomatosis with polyangiitis, Graves' disease, rheumatoid arthritis, hypophysitis, or uveitis]). The following were exceptions to this criterion:
  - Patients with vitiligo or alopecia
  - Patients with hypothyroidism (e.g., following Hashimoto syndrome) stable on hormone replacement
  - Any chronic skin condition that did not require systemic therapy

    - Patients without active disease in the last 5 years could be included but only after consultation with the Study Physician/Medical Scientist
    - Patients with celiac disease controlled by diet alone.
- Uncontrolled intercurrent illness, including but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, uncontrolled cardiac arrhythmia, active ILD, serious chronic gastrointestinal conditions associated with diarrhoea, or psychiatric illness/social situations that would limit compliance with study requirement, substantially increase risk of incurring AEs, or compromise the ability of the patient to give written informed consent.
- History of another primary malignancy, except for the following:
    - 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.
- History of active primary immunodeficiency.
- Active infection including tuberculosis (clinical evaluation that includes clinical history, physical examination and radiographic findings, and tuberculosis testing in line with local practice), hepatitis B (known positive HBsAg result), HCV, or HIV (positive HIV 1/2 antibodies). Patients with a past or resolved HBV infection (defined as the presence of hepatitis B core antibody and absence of HBsAg) were eligible. Patients positive for HCV antibody were eligible only if polymerase chain reaction was negative for HCV RNA.
- Deemed unresectable NSCLC by multidisciplinary evaluation that must have included a thoracic surgeon who performed lung cancer surgery as a significant part of their practice.
- Patients who had pre-operative radiotherapy treatment as part of their care plan.
- Patients who had brain metastases or spinal cord compression. All patients were to have an MRI (preferred) or high-quality CT with IV contrast of the brain, prior to study entry.
- Stage IIIB N3 and Stages IIIC, IVA, and IVB NSCLC.
- Existence of more than one primary tumour such as: mixed small cell and NSCLC histology; synchronous or metachronous tumours that could represent distinct primary tumours.
- Patients whose planned surgery at enrolment includes any of the following procedures: pneumonectomy, segmentectomies, or wedge resections.
- 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) was acceptable.
- Radiotherapy treatment to more than 30% of the bone marrow or with a wide field of radiation within 4 weeks of the first dose of study drug.
- Current or prior use of immunosuppressive medication within 14 days before the first dose of durvalumab. The following were exceptions to this criterion:

- Intranasal, inhaled, topical steroids, or local steroid injections (e.g., intra articular injection)
- Systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone or its equivalent
- Steroids as premedication for hypersensitivity reactions (e.g., CT scan premedication).

Other exclusions

Female patients who were pregnant or breastfeeding, or male or female patients of reproductive potential who were not willing to employ effective birth control from screening to 90 days after the last dose of IP.

Patients with a documented test result confirming the presence of an EGFRm or ALK gene rearrangement.

Treatments

Dose and treatment regimens

Durvalumab (MEDI4736) or placebo: Patients will receive 1500 mg durvalumab or placebo via IV infusion q3w for up to a maximum of 4 cycles prior to surgery and q4w for 12 cycles following surgery, unless there is unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met.

Standard of Care: Patients will receive 1 of the following SoC regimens, based on the tumour histology and Investigator's discretion, as part of their treatment regimen prior to surgery:

1. Squamous tumour histology: Carboplatin plus paclitaxel: carboplatin AUC 6 and paclitaxel 200 mg/m2 via IV infusion on Day 1 of each 3-week cycle, for 4 cycles.*
2. Squamous tumour histology: Cisplatin plus gemcitabine: cisplatin 75 mg/m2 via IV infusion on Day 1 of each 3-week cycle, for 4 cycles, and gemcitabine 1250 mg/m2 via IV infusion on Day 1 and Day 8 of each 3-week cycle, for 4 cycles.
3. Non-squamous tumour histology: Pemetrexed plus cisplatin: pemetrexed 500 mg/m2 and cisplatin 75 mg/m2 via IV infusion on Day 1 of each 3-week cycle, for 4 cycles.*
4. Non-squamous tumour histology: Pemetrexed plus carboplatin: pemetrexed 500 mg/m2 and carboplatin AUC 5 via IV infusion on Day 1 of each 3-week cycle, for 4 cycles.*

*In the event of unfavourable tolerability, patients can switch from cisplatin to carboplatin therapy at any point during the study (assuming eligibility for the switched therapy is met).

Use of Post-operative Radiotherapy: Per protocol, a standard course of PORT was allowed within 8 weeks of resection surgery (and only after the first post-surgery RECIST 1.1 scan had been completed) for patients for whom it was indicated according to local guidance. Study treatment with durvalumab/placebo must then have been started within 3 weeks of the completion of PORT.

In case of progressive disease after the neo-adjuvant part, which precludes surgery, the patients were allowed to be treated by chemo-radiotherapy (SOC for locally advanced unresectable disease).

Frequency of tumour assessment

A RECIST 1.1 tumour assessment was performed at baseline, and upon completion of the neoadjuvant period (prior to surgery). The first post-surgical CT/MRI scan of the chest and abdomen (including the entire liver and both adrenals) was acquired 5 weeks ± 2 weeks after surgery and prior to, but as close as possible to the start of adjuvant therapy. Tumour assessments were then conducted every 12 weeks (relative to the date of surgery) until week 48, every 24 weeks (relative to the date of surgery) until week 192 (approximately 4 years), and then every 48 weeks (relative to the date of surgery) thereafter until RECIST 1.1 defined radiological PD, consent withdrawal, or death. Survival assessments were conducted at month 2, 3, and 4 following treatment discontinuation and then every 2 months until month 12 followed by every 3 months.

Objectives

Table 8 Objectives and endpoints

Objectives	Endpoints
Primary	
To compare the efficacy of durvalumab + chemotherapy administered prior to surgery followed by durvalumab post-surgery compared with placebo + chemotherapy administered prior to surgery followed by placebo post-surgery in terms of EFS	EFS
To compare the activity of durvalumab + chemotherapy administered prior to surgery compared with placebo + chemotherapy administered prior to surgery in terms of pCR	pCR (lack of any viable tumour cells after complete evaluation in the resected lung cancer specimen and all sampled regional lymph nodes)
Secondary	
To compare the efficacy of durvalumab + chemotherapy administered prior to surgery followed by durvalumab post-surgery compared with placebo + chemotherapy administered prior to surgery, followed by placebo post-surgery in terms of DFS	DFS
To compare the activity of durvalumab + chemotherapy administered prior to surgery compared with placebo + chemotherapy administered prior to surgery in terms of MPR	MPR (≤ 10% viable tumour cells in lung primary tumour after complete evaluation in the resected lung cancer specimen)
To compare the efficacy of durvalumab + chemotherapy administered prior to surgery followed by durvalumab post-surgery compared with placebo + chemotherapy administered prior to surgery followed by placebo post-surgery in terms of OS	OS
To compare the efficacy of durvalumab + chemotherapy administered prior to surgery followed by durvalumab post-surgery compared with placebo + chemotherapy administered prior to surgery followed by placebo post-surgery in patients with PD-L1 TC ≥ 1% in terms of EFS, pCR, DFS, MPR, and OS	EFS, pCR, DFS, MPR, OS
To compare disease-related symptoms and HRQoL in patients treated with durvalumab + chemotherapy administered prior to surgery followed by durvalumab post-surgery compared with placebo + chemotherapy administered prior to surgery followed by placebo post-surgery	Change from baseline in EORTC QLQ-C30 and EORTC QLQ-LC13 and time to deterioration in EORTC QLQ-C30.
To assess the PK of durvalumab	Concentration of durvalumab
To investigate the immunogenicity of durvalumab	Presence of ADAs for durvalumab
Safety	
To assess the safety and tolerability profile of durvalumab + chemotherapy administered prior to surgery followed by durvalumab post-surgery compared with placebo + chemotherapy administered prior to surgery followed by placebo post-surgery	AEs, physical examinations, vital signs (including BP, pulse, and ECGs), and laboratory findings (including clinical chemistry, haematology, and urinalysis)

Note: AEGEAN is an ongoing study. Per the MTP, DFS and OS will be formally assessed at subsequent IA/FA. EFS efficacy data will continue to be collected. Patients and investigators remain blinded to treatment assignment.

Outcomes/endpoints

Primary Endpoints:

Pathological Complete Response

Pathological complete response was defined as the absence of any residual viable tumour cells at the time of surgical resection in the primary lung lesion and lymph nodes as described by IASLC (Travis et al 2020). In the AEGEAN trial, the primary endpoint pCR was defined as the proportion of patients who have 0% residual viable tumour cells within all resected tissue (including primary lung lesion and lymph nodes) following neoadjuvant treatment as assessed by a central pathology laboratory. It is assessed following the recommended methods and definitions described by IASLC (Travis et al 2020).

Event Free Survival

EFS was defined in the AEGEAN study as time from randomization to the first of the following:

a. documented local or distant recurrence as determined by BICR using RECIST 1.1 assessments;

b. death due to any cause (event date is the date of death); or,

c. Date of determination that PD precludes surgery, or for patients who do not have surgery for a reason other than progression, the date of the RECIST 1.1 assessment documenting disease progression of lung cancer after the surgery eligibility decision date;

d. Date when PD was discovered and reported by the Investigator upon first attempt at surgery resulted in the surgery not being completed, or for patients who do not complete surgery for a reason other than progression, the date of the RECIST 1.1 assessment documenting disease progression of lung cancer after the surgery date

Sample size

The study planned to screen approximately 1333 patients in order to randomize approximately 800 eligible patients in the ITT population and approximately 740 patients in the mITT population. Patients were randomized in a 1:1 ratio to receive either durvalumab + platinum-based chemotherapy before surgery followed by durvalumab post-surgery (Arm 1) or placebo + platinum-based chemotherapy before surgery followed by placebo post-surgery (Arm 2). Patients were stratified by disease stage (Stage II versus Stage III) and by PD-L1 expression status (<1% versus ≥1%). Once global enrolment achieved 800 subjects, recruitment could continue in China only and these subjects were excluded from the global analysis. The number of subjects randomized from China was approximately 20% of the primary analysis population.

There were 3 IAs planned for this study.

There was one IA for the primary endpoint of pCR. The pCR IA occurred after all 800 patients in the ITT analysis set were randomized and analysed approximately 400 patients with no known EGFRm/ALK translocation who were randomized and had approximately 7 months follow-up to allow time for surgery to occur, where applicable, and completed the pCR assessment by central pathology, inclusive of patients who were not eligible for surgery (any patients without a central pathology assessment were considered non-pCR). It was predicted that the final analysis for the pCR endpoint when all patients (i.e., approximately 800 patients in the ITT analysis set /740 patients in the mITT analysis set) were expected to have undergone surgery and completed the pathology assessment would occur at the time of the first EFS interim analysis. In the event that the first EFS interim analysis DCO, that is, 30% maturity of EFS events in the mITT, was reached prior to all randomized patients in the ITT having completed their pathology assessment (inclusive of non-surgical patients), a separate DCO was utilized for the pCR final analysis. In the final pCR analysis, the study had more than 90% power to

detect a statistically significant difference in pCR of 12% with a 2-sided significance level of 0.4972%. This assumed that the pCR rate for the patients randomized to placebo + chemotherapy was 4%. The smallest treatment effect that would be statistically significant at the final analysis was a difference in pCR of 6.1% (10.1% in durvalumab + chemotherapy versus 4.0% in placebo + chemotherapy). The mPR was evaluated at the same timepoints as pCR.

There were two IA analyses for the primary endpoint of EFS, which were performed on the mITT, which was expected to contain approximately 740 patients without EGFRm/ALK translocation. The first EFS IA occurred when approximately 224 EFS events had occurred (approximately 30% maturity in the mITT). The second EFS IA occurred when approximately 296 EFS events had occurred (approximately 40% maturity in the mITT). The final EFS analysis will occur when approximately 371 EFS events have occurred (approximately 50% maturity in the mITT). For the final EFS analysis, if the true EFS HR is 0.67, the study will provide more than 90% power to demonstrate a statistically significant EFS effect with a 2-sided significance level of 3.8260%; this translates to a 16-month benefit (conservative estimate assuming proportional hazards; 17.6-month benefit assuming non-proportional hazards) in median EFS over an assumed 33-month median EFS on placebo + chemotherapy. The smallest treatment effect that would be statistically significant is an EFS HR of 0.805.

Randomisation

Patients were randomized in a 1:1 ratio to receive either durvalumab plus platinum-based chemotherapy before surgery followed by durvalumab post-surgery (Arm 1) or placebo plus platinum-based chemotherapy before surgery followed by placebo post-surgery (Arm 2). Patients were stratified by disease stage (Stage II versus Stage III) and by PD-L1 expression status according to the VENTANA PD-L1 [SP263] Assay (<1% versus ≥1%).

One randomization list was produced for each of the randomization strata. A blocked randomization was generated, and all centres used the same list in order to minimize any imbalance in the number of patients assigned to each treatment group. All patients were centrally assigned to randomized study treatment using an IVRS/IWRS.

Blinding (masking)

The study was conducted in a double-blind manner. The patient, the Investigator, and study center staff were blinded to the durvalumab/placebo allocation. The study center pharmacist was unblinded to the durvalumab/placebo allocation and prepared durvalumab or placebo for a patient as specified by the randomization scheme and IWRS (only the unblinded pharmacist knew the randomization/treatment allocation details). Lot numbers of durvalumab dispensed were recorded by the pharmacist and monitored by an unblinded monitor. Other study center staff and monitors were not given access to lot number information.

Analysis sets

Table 9 Summary of outcome variables and analysis populations

Outcome variable	Populations
EFS and pCR	Modified intent-to-treat analysis set

DFS	Modified Resected set and PD-L1-$TC_{\geq 1\%}$ resected set
mPR, OS, ORR, PRO (neoadjuvant period analyses)	Modified intent-to-treat analysis set
PRO (adjuvant period analyses only)	Modified Resected set
pCR, EFS, mPR, OS	PD-L1-$TC_{\geq 1\%}$ analysis set
Demography	Modified intent-to-treat analysis set (Some outputs repeated on intent-to-treat set)
Demography	Modified Resected set (some outputs repeated on the resected set)
Demography	PD-L1-$TC_{\geq 1\%}$ analysis set
Demography	PD-L1-$TC_{\geq 1\%}$ resected set
PK data	PK analysis set
Safety data	
Exposure	Safety analysis set
AEs	Safety analysis set
Laboratory measurements	Safety analysis set
Vital Signs	Safety analysis set
ADA	ADA analysis set

ADA Anti-drug antibody; AE Adverse event; DFS Disease-free survival;; EFS Event-free survival; EORTC European Organization for Research and Treatment of Cancer; EQ-5D-5L EuroQoL five dimensions, five level health state utility index; mPR Major pathological response; ORR Objective response rate; OS Overall survival; pCR Pathological complete response; PD-L1-$TC_{\geq 1\%}$ Expression of PD-L1 on tumour membrane, at any intensity, in ≥1% of tumour cells; PK Pharmacokinetic(s); PRO Patient-reported outcome;

Intent-to-treat set (ITT)

The ITT analysis set included all randomized subjects with treatment groups assigned in accordance with the randomization, regardless of the treatment actually received. This comprised all subjects randomized into the study, excluding subjects randomized in China after the global cohort Last Patient Randomized (LPR). Subjects who were randomized but did not subsequently receive treatment were included in the ITT.

Modified Intent-to-treat set (mITT)

The mITT included all subjects in the ITT, except those whose tumours had EGFRm/ALK translocation. If EGFR/ALK status was unknown for any subject in the ITT, they were included in mITT. Unless otherwise specified, the mITT was used for all efficacy analyses, including PROs. Treatment arms were compared based on randomized study treatment, regardless of the treatment actually received.

Resected set

The resected set consisted of all subjects in the ITT who had surgical resection following the neoadjuvant period, who did not have R2 margins, and whose first scan following surgery showed no evaluable disease (defined as no post-surgery R2 margins and no RECIST evidence of disease based on the investigator data i.e., no target lesions, non-target lesions, or new lesions (unless they were pathologically confirmed to be a new primary malignancy based on data reported on NLESADD page)).

Treatment arms were compared based on randomized study treatment, regardless of the treatment actually received.

Modified Resected set

The modified resected set consisted of all subjects in the resected set, excluding those whose tumours had EGFRm/ALK translocation. If EGFR/ALK status was unknown for any subject in the resected set, they were included in the modified resected set. Unless otherwise specified, this analysis set was used for DFS only. Treatment arms were compared based on randomized study treatment, regardless of the treatment actually received.

Statistical methods

Table 10 Pre-planned statistical analyses to be conducted

Endpoints Analysed	Notes
EFS[a]	HR and CI estimated from Cox proportional hazard model Stratified log-rank test
pCR[a]	Stratified Cochran-Mantel-Haenszel test
mPR[a]	Stratified Cochran-Mantel-Haenszel test
DFS[a]	HR and CI estimated from Cox proportional hazard model Stratified log-rank test
OS[a]	HR and CI estimated from Cox proportional hazard model Stratified log-rank test
ORR	Stratified Cochran-Mantel-Haenszel test
Change from baseline in symptoms (EORTC QLQ-C30)	MMRM analysis (Neoadjuvant and Adjuvant periods)
Change from baseline in symptoms (EORTC QLQ-C13)	MMRM analysis (Neoadjuvant period only)
Time to deterioration (EORTC QLQ-C30)	Stratified log-rank test (Adjuvant period only)

[a] These endpoints will be tested in a hierarchy detailed below.

Primary Endpoints

The analysis of EFS was performed in the mITT. The effect of treatment was estimated by the HR together with its corresponding 95% CI. For all analyses which were part of the MTP, p-values and adjusted confidence intervals were presented for the relevant alpha level.

EFS was analysed using a stratified log-rank test based on BICR assessment using RECIST 1.1, adjusting for disease stage (Stage II versus III) and PD-L1 expression status at baseline (<1% versus ≥1%) for generation of the p-value. The HR and CI were estimated from the stratified Cox proportional hazards model adjusted for IXRS stratification factors disease stage (Stage II versus III) and PD-L1 expression status at baseline (<1% versus ≥1%). The Cox models were fitted using PROC PHREG with the Efron method to control for ties and the CI calculated using a profile likelihood approach. The assumption of proportionality was assessed by examining plots of log(-log(survival probability)) versus log(time) and scaled Schoenfeld residuals added to the log(HR) estimate and plotted against ranked event times, together with a Grambsch-Therneau test using the rank(time) transformation.

Patients who had not experienced an EFS event were censored at the time of the latest date of assessment from their last evaluable disease assessment. If any of these events occurred after 2 or more consecutively missed postbaseline RECIST 1.1 visits, the patient was censored at the time of the

latest evaluable disease assessment prior to the 2 consecutively missed visits (note: not evaluable [NE] visit was not considered a missed visit). Given that local or distant recurrence was identified based on RECIST 1.1 visits performed after surgery, the censoring of subjects due to 2 or more consecutively missed post-baseline RECIST 1.1 visits only occurred post-surgery. The 2 missed visits were calculated from the date of surgery. Patients who had no surgery or an attempted surgery that could not be completed due to a reason other than disease progression remained in follow-up for EFS. If the patient had no evaluable disease assessments or did not have baseline data, they were censored at randomization date unless they died within 2 visits of baseline.

As a lack of proportionality was expected, due to delayed effect in IO agents, a three-component stratified max-combo test was used as a sensitivity analysis with the same stratification factors as the primary analysis. Under NPH, the HR from the primary analysis could still be meaningfully interpreted as an average HR over time unless there was extensive crossing of the survival curves. However, the variation in treatment effect was described by presenting piecewise HR calculated over distinct time periods: 0-3m, 3-6m, 6-12m, 12-24m, 24-36m etc., using a Cox regression model with time-dependent covariates, stratified by the same factors as the primary analysis. In addition, to characterize the patterns observed in any treatment effects, the proportion of subjects alive and event-free at 12 monthly intervals was summarized (using the KM plot) and presented by treatment arm along with 95% CIs using the log-log transformation.

The Restricted Mean Survival Time (RMST) was also analysed up to the minimum of the largest observed event time in each of the two arms, using the pseudo values approach (Andersen et al. 2004) to estimate the RMST for each treatment arm with 95% CIs, and the difference in means (and ratio of means) between treatment arms, with 95% CIs and p-values. The RMST difference and corresponding CI were estimated using Generalized Estimating Equations, with covariate adjustment for stratification factors. The standard error for the RMST ratio (unadjusted) was estimated from the treatment arm RMSTs using the delta method. In addition, an area-under-the-curve approach (Kaplan-Meier method) and Royston-Parmar model were also used; all RMST analyses (except RMST ratio) controlled for the stratification factors used in the primary analysis.

If lack of proportionality was found, this may have been a result of a treatment-by-covariate interaction, which was investigated. Kaplan-Meier plots of EFS were presented by treatment arm. Summaries of the number and percentage of subjects experiencing an EFS event and the type of event were provided along with median EFS and 95% CI for each treatment.

In order to assess deviation bias, a sensitivity analysis of the EFS primary endpoint may be performed if >10% of subjects in either treatment arm had deviations that may have affected the efficacy of the trial therapy. In this scenario, the primary EFS efficacy analysis may be repeated excluding the subjects with specific important deviations to assess the impact of these subjects on the primary EFS efficacy result. Disagreements between investigator and central reviews (BICR) of RECIST progression were presented for each treatment group.

An additional sensitivity analysis may have been performed for the primary treatment comparison using PD-L1 expression status at baseline (<1% versus ≥1%) and disease stage (Stage II versus Stage III) as defined by source data (instead of IXRS) as stratification factors. The EFS analysis was repeated as above, based on investigator assessment using RECIST 1.1. In addition, the EFS analysis was repeated for subjects in the PD-L1-TC≥1% analysis set including the IXRS disease stage (Stage II versus Stage III) as a stratification factor.

Subgroup analyses with treatment as the only factor may have been conducted comparing EFS in the subgroups below (but not limited to). For each subgroup, the HR (durvalumab:placebo) and 95% CI

were calculated from a Cox proportional hazards model with treatment as the only covariate. These were tabulated and also presented on a forest plot including the HR and 95% CI.

The analysis of pCR was based on assessment per central pathology review. The analysis was performed on the mITT using a Cochran-Mantel-Haenszel (CMH) test, stratified by the stratification factors from IXRS, disease stage (Stage II versus Stage III) and PD-L1 expression status (<1% versus ≥1%). The effect of treatment was estimated by the difference in proportions between treatment groups, together with their corresponding CI and p-value. The confidence intervals for the difference in proportions between groups were estimated using Miettinen and Nurminen's (MN) confidence limits.

Secondary endpoints

The analysis of MPR was based on assessment per central pathology review. The analysis was performed on the mITT using a CMH test, stratified by the stratification factors from IXRS, disease stage (Stage II versus Stage III) and PD-L1 expression status (<1% versus ≥1%). The effect of treatment was estimated by the difference in proportions between treatment groups, together with their corresponding CI and p-value from the CMH test. The confidence intervals for the difference in proportions between groups were estimated using Miettinen and Nurminen's (MN) confidence limits.

In addition, the MPR analysis was repeated for subjects in the PD-L1-TC≥1% analysis set including the IXRS disease stage (Stage II versus Stage III) as a stratification factor. A sensitivity analysis may have been performed which only included subjects with an evaluable pathology sample. The subgroup analyses were repeated for MPR, including interaction testing.

DFS was analysed using the same methodology as described for EFS in the modified resected set. DFS was analysed using the log-rank test based on BICR assessment using RECIST 1.1 stratified by disease stage (Stage II versus Stage III) and by PD-L1 expression status (<1% versus ≥1%) on the modified resected set. The assumption of NPH was tested using the same methodology as described for EFS.

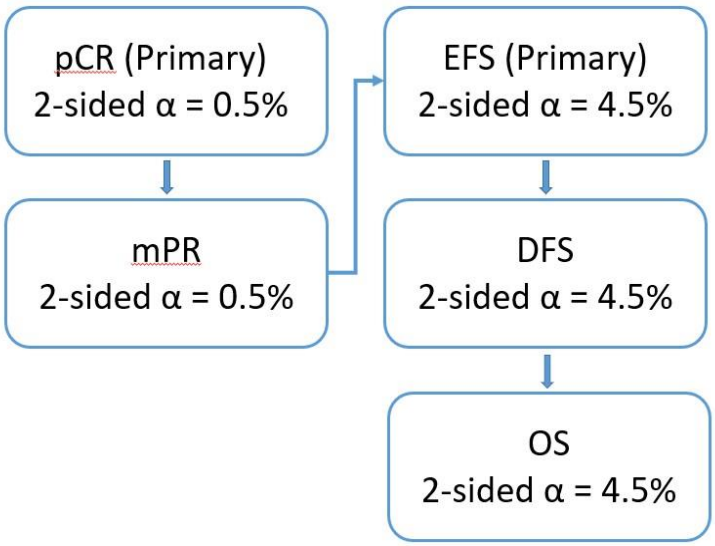
DFS was also repeated using the RECIST 1.1 investigator-based assessment. In addition, the DFS analysis was repeated for subjects in the PD-L1-TC≥1% analysis set including the IXRS disease stage (Stage II versus Stage III) as a stratification factor. The subgroup analyses were repeated for DFS.

OS was analysed on the mITT using the same methodology as described for EFS. The effect of treatment was estimated by the HR together with its corresponding 95% CI. Kaplan-Meier plots were presented by treatment arm. Summaries of the number and percentage of subjects who had died, those still in survival follow-up, those lost to follow-up, and those who had withdrawn consent were provided along with the median OS and 95% CI for each treatment. The assumption of NPH was tested using the same methodology as described for EFS. Any patient not known to have died at the time of analysis was censored based on the last recorded date on which the patient was known to be alive.

The pre-surgery ORR was based on the BICR RECIST data, and using the latest assessment prior to surgery regardless of whether scheduled or not. The analysis was performed on the mITT population using a CMH test, stratified by the stratification factors from IXRS, disease stage (Stage II versus Stage III) and PD-L1 expression status (<1% versus ≥1%). The effect of treatment was estimated by the difference in proportions between treatment groups, together with their corresponding CI and p-value from the CMH test. The confidence intervals for the difference in proportions between groups were estimated using Miettinen and Nurminen's (MN) confidence limits. This was repeated for the site investigator assessment with the denominator defined using mITT.

Multiplicity

Figure 9 Multiple testing procedure



DFS Disease free survival; EFS Event-free survival; mPR Major pathological response; OS Overall survival; pCR Pathological complete response.

In order to control the type I error at 5% (2-sided), a multiple testing procedure (MTP) was used across the primary endpoints and the secondary endpoints included in MTP.

1. The primary endpoints: EFS and pCR in the mITT population
2. The key secondary endpoints: mPR and OS in the mITT population and DFS in the modified resected set population.

Hypotheses were tested using a multiple testing procedure with an alpha-exhaustive recycling strategy. With this approach, hypotheses were tested in a pre-defined order as outlined in Figure 2. According to alpha splitting and alpha recycling, if the higher level hypothesis in the MTP was rejected for superiority, the next lower level hypothesis was then tested. The test mass that became available after each rejected hypothesis was recycled to lower level hypotheses not yet rejected. This testing procedure stopped when the entire test mass was allocated to non-rejected hypotheses. Implementation of this pre-defined ordered testing procedure, including recycling, strongly controlled type I error at 5% (2-sided), among all the primary endpoints and the secondary endpoints included in MTP.

The testing procedure was hierarchical in that it started with testing the 2 primary endpoints EFS and pCR. The overall 2-sided 5% type I error was split between the 2 primary endpoints EFS and pCR. An alpha level of 4.5% was allocated to the EFS analysis, and an alpha level of 0.5% was allocated to the pCR analysis. As shown in Figure 2, if pCR was declared statistically significant, the 0.5% alpha was recycled to mPR. If both pCR and mPR were declared statistically significant, the 0.5% alpha was recycled to EFS, such that a total alpha level of 5% was allocated to the EFS analyses. If EFS was declared statistically significant, then the alpha level utilized for the EFS analysis (either 4.5% alpha or 5% alpha) was recycled to DFS, and if DFS was declared statistically significant, then the alpha level utilized (either 4.5% alpha or 5% alpha) was recycled again to OS.

The primary and secondary endpoints, pCR and mPR were tested at 2 timepoints, 1 interim analysis and 1 final analysis. The primary and secondary EFS, DFS and OS endpoints were tested at 3 timepoints: 2 interim analyses and 1 final analysis. It was predicted that the timing of the final analysis

for the pCR endpoint would coincide with the first EFS interim analysis and the analyses would be performed at the same time. In the event that the first EFS interim analysis DCO, that is, 30% maturity of EFS events in the mITT, was reached prior to all randomized subjects in the ITT having completed their pathology assessment (inclusive of non-surgical subjects), a separate DCO was utilized for the pCR final analysis.

The alpha level allocated to the interim or final analyses was determined by the Lan DeMets spending function that approximates O'Brien Fleming approach, where the alpha level applied at the interim depended upon the proportion of information available at the time of the analysis. A separate O'Brien Fleming spending function was used to determine the alpha level at the interim and final analyses for the next lower level of hypothesis testing under MTP based on the information proportion of that lower level of hypothesis.

If the interim results did not meet the criterion of stopping for superiority for a given hypothesis, then follow-up continued until the next planned analysis, where the hypothesis was re-tested. If the hypothesis was then rejected, subsequent testing continued hierarchically in accordance with the MTP strategy. The alpha level used at the time of each analysis was calculated based on the actual number of events, rather than the planned number of events.

For the pCR endpoint, there was 1 IA planned, and the alpha level was controlled at the interim and final analysis timepoints by using the Lan-DeMets spending function with O'Brien Fleming boundary. As the IA occurred when approximately 400 out of 740 subjects without EGFRm/ALK translocation, the 2-sided alpha was approximately 0.0078% at the interim analysis and 0.4972% at the final analysis, based on an overall alpha of 0.5% across the interim and final analyses. The actual alpha level used was based on the observed number of subjects and the final analysis alpha was derived using the Haybittle-Peto method.

If pCR and mPR were declared statistically significant, the 0.5% alpha was recycled to EFS and the EFS significance levels from this timepoint onward were recalculated using 5% overall alpha.

For the EFS endpoint, there were 2 IAs planned and the alpha was controlled at the interim and final analysis timepoints by using Lan-DeMets spending function with the O'Brien Fleming boundary. The O'Brien Fleming boundaries for the EFS interim and final analyses were adjusted to provide an overall alpha of 4.5% for the EFS endpoint. As the interim and final analyses were planned to occur with approximately 30%, 40%, and 50% maturity, respectively, which corresponded to an information fraction of approximately 60%, 80%, and 100% at each analysis, if these events were observed, the resulting alpha was calculated to be 0.6649%, 1.9243%, and 3.8260% at subsequent analyses. However, the actual alpha level used was based on the observed number of events and the target number of events for any future analyses and the final analysis alpha was derived using the Haybittle-Peto method.

The secondary endpoints included in the multiple testing procedure were DFS in the modified resected population and mPR and OS in the mITT. As for pCR and EFS, the actual alpha level of mPR, DFS and OS was based on the observed number of events/subjects however Table 11 shows an example. As for EFS and mPR, the actual alpha level of DFS and pCR was based on the observed number of events/subjects and the final analysis alpha was derived using the Haybittle-Peto method.

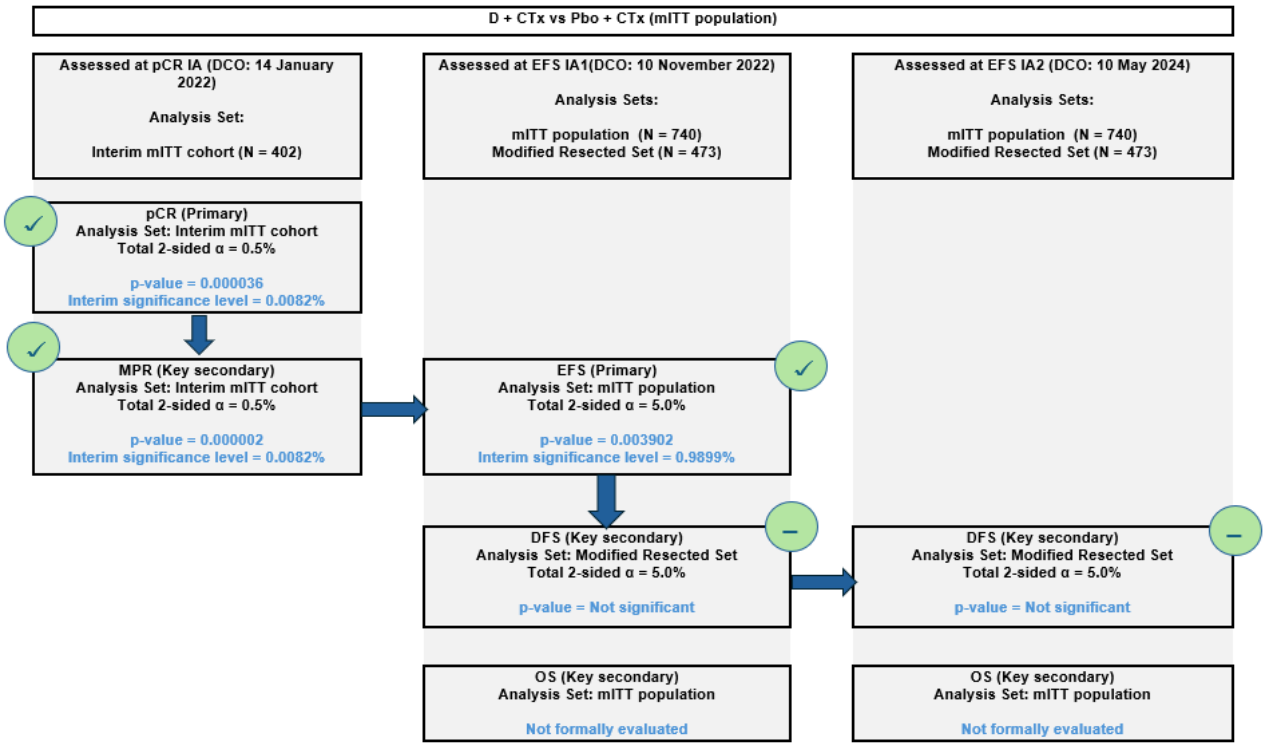
Table 11 Alpha allocation and recycling

Endpoint	Timepoint	Information fraction	Alpha (2-sided)
pCR α=0.5%	IA	54%	0.0078%
	Final	100%	0.4972%
mPR	IA	54%	0.0078%

=0.5%	Final	100%	0.4972%	
Endpoint	**Timepoint**	**Information fraction**	**Alpha (2-sided)**	
			pCR or mPR is not successful: α =4.5%	pCR and mPR are successful (recycle alpha): α =5%
EFS	IA1	60.4% (30% maturity, 224 events)	0.6649%	0.7852%
	IA2	79.8% (40% maturity, 296 events)	1.9243%	2.1814%
	Final	100% (50% maturity, 371 events)	3.8260%	4.2336%
DFS	IA1	52% (23% maturity, 144 events)	0.3109%	0.3764%
	IA2	75.8% (33% maturity, 210 events)	1.6552%	1.888%
	Final	100% (44% maturity, 277 events)	3.9521%	4.3735%
OS	IA1	56.5% (18% maturity, 131 events)	0.4800%	0.5729%
	IA2	77.2% (24% maturity, 179 events)	1.7317%	1.9710%
	Final	100% (31% maturity, 232 events)	3.9064%	4.3225%

mPR is only tested if pCR is successful. DFS is only tested if EFS is successful. OS is only tested if EFS and DFS are successful.
DFS Disease-free survival; EFS Event-free survival; IA Interim analysis; mPR Major pathological response; OS Overall survival; pCR Pathological complete response;

Figure 10 Outcome of MTP (pCR IA, EFS IA1 and EFS IA2)

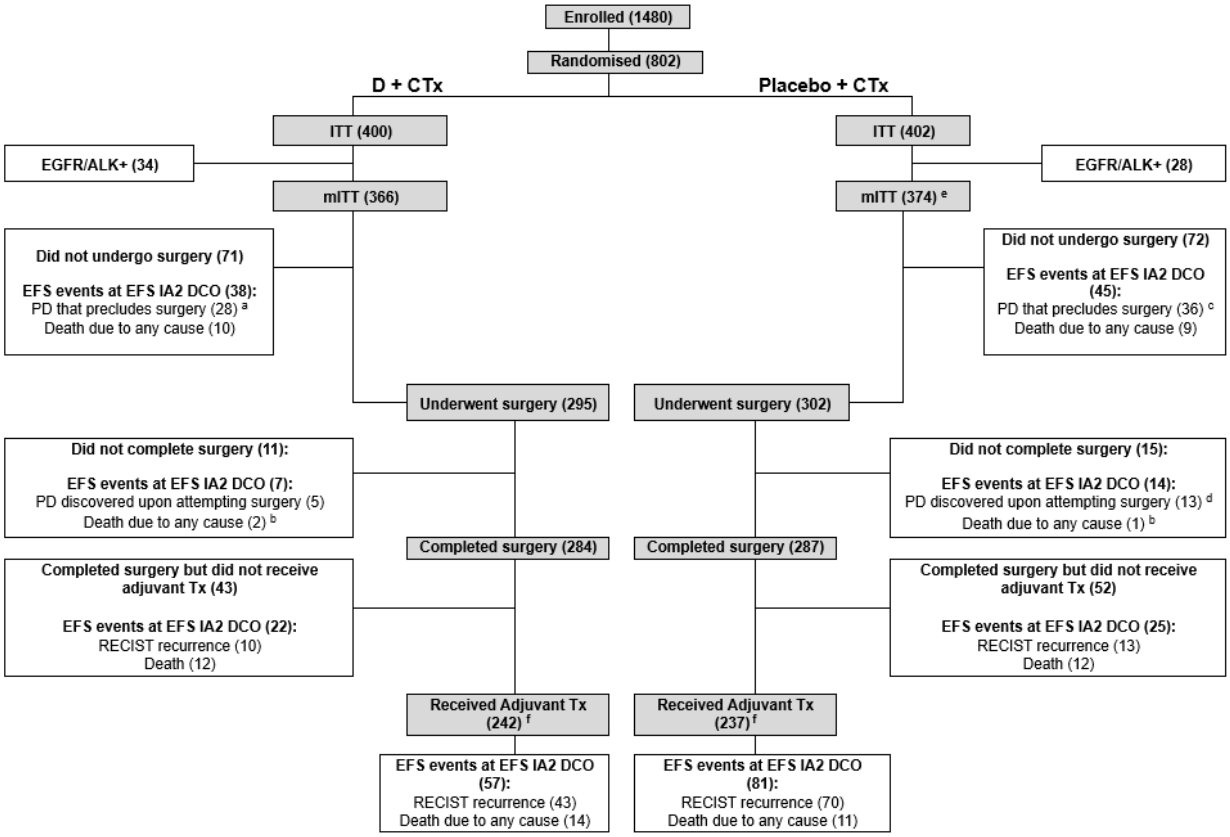


Note: Please refer to **Error! Reference source not found.** for the planned allocation of the 5% 2-sided alpha level to the 2 primary endpoints (alpha level: EFS [4.5%]; pCR [0.5%]) and that if pCR was statistically significant, the 0.5% alpha will be recycled to MPR and subsequently to EFS, if MPR is also statistically significant. Following the MTP alpha recycling strategy, since pCR and MPR were statistically significant at the pCR IA, the 0.5% alpha was recycled to EFS (providing a total 2-sided alpha level of 5%) at EFS IA1; since EFS was statistically significant at EFS IA1, the test mass (a total 2-sided alpha level of 5%) was recycled to test DFS which allows DFS to be tested at EFS IA1, IA2 and FA as appropriate. Following a statistically significant DFS the test mass can be recycled to test OS.

Results

Participant flow

Figure 11 Disposition of EFS events (mITT population, EFS IA2)



a Includes 3 events of PD after surgery not undertaken for reasons other than progression.
b These deaths occurred after surgery not completed.
c Includes 5 events of PD after surgery not undertaken for reasons other than progression.
d Includes 5 events of PD after surgery not completed for reasons other than progression.
e Includes the 3 untreated patients as they qualified for inclusion in the mITT population.
f Includes 3 patients who did not complete surgery (1 patient for D + CTx vs 2 patients for placebo + CTx).
PD; progressive disease.

At EFS IA1 (DCO: 10 November 2022), 1480 patients were enrolled (screened), 678 patients were screen failures and a total of 802 patients had been randomized.

Table 12 Overview of Patient Disposition at EFS IA1 (ITT Population)

Study period		Number (%) of patients [a]		
		D + CTx	Placebo + CTx	Total
Neoadjuvant	Received neoadjuvant treatment	400 (100)	399 (99.3)	799 (99.6)
	Completed 4 cycles of neoadjuvant doublet chemotherapy [b]	339 (84.8)	352 (88.2)	691 (86.5)
	Completed 4 cycles of neoadjuvant durvalumab/placebo [b]	348 (87.0)	356 (89.2)	704 (88.1)

Study period		Number (%) of patients [a]		
		D + CTx	Placebo + CTx	Total
Surgery	Underwent on-study surgery [c]	324 (81.0)	327 (81.3)	651 (81.2)
	Did not undergo on-study surgery [c]	76 (19.0)	75 (18.7)	151 (18.8)
	Completed on-study surgery [c]	310 (77.5)	308 (76.6)	618 (77.1)
	Did not complete on-study surgery [c]	14 (3.5)	19 (4.7)	33 (4.1)
Post-surgery	Completed on-study surgery, but did not receive adjuvant durvalumab/placebo	47 (11.8)	56 (13.9)	103 (12.8)
	Patients who had PORT	30 (7.5)	24 (6.0)	54 (6.7)
Adjuvant	Started adjuvant durvalumab /placebo [d]	264 (66.0)	255 (63.4)	519 (64.7)
	Completed adjuvant durvalumab /placebo [b]	105 (26.3)	88 (22.1)	193 (24.2)
	Ongoing adjuvant durvalumab /placebo [b]	85 (21.3)	89 (22.3)	174 (21.8)

[a] All percentages are calculated from number of patients randomized, with the exception of rows referencing footnote (b).
[b] Percentages are calculated from number of patients who received treatment.
[c] Excludes patients with surgery undertaken outside of the study.
[d] Includes 4 patients who did not complete surgery (one patient in the D + CTx arm and 3 patients in the placebo + CTx arm).
DCO: 10 November 2022.

Table 13 Patient Disposition (mITT Population; EFS IA1 and EFS IA2)

		Number (%) of patients [a]			
		EFS IA1 DCO (10 Nov 2022)		EFS IA2 DCO (10 May 2024)	
Study period	Analysis (DCO)	D + CTx (N = 366)	Pbo + CTx (N = 374)	D + CTx (N = 366)	Pbo + CTx (N = 374)
Pre-treatment	Randomized	366 (100)	374 (100)	366 (100.0)	374 (100.0)
Neoadjuvant	Received neoadjuvant treatment	366 (100)	371 (99.2)	366 (100.0)	371 (99.2)
	Completed 4 cycles of neoadjuvant treatment of both (doublet) CTx	310 (84.7)	326 (87.2)	310 (84.7)	326 (87.2)
	Completed 4 cycles of neoadjuvant durvalumab/Pbo	318 (86.9)	331 (88.5)	318 (86.9)	331 (88.5)
Surgery	Underwent on-study surgery [b]	295 (80.6)	302 (80.7)	295 (80.6)	302 (80.7)
	Did not undergo surgery on study	71 (19.4)	72 (19.3)	71 (19.4)	72 (19.3)
	Completed on-study surgery	284 (77.6)	287 (76.7)	284 (77.6)	287 (76.7)
	Did not complete on-study surgery	11 (3.0)	15 (4.0)	11 (3.0)	15 (4.0)

Post-surgery	Completed on-study surgery, but did not receive adjuvant durvalumab/Pbo	16 (13.1)	7 (15.2)	43 (11.7)	52 (13.9)
	Patients who had PORT	26 (7.1)	21 (5.6)	26 (7.1)	24 (6.4)
Adjuvant	Started adjuvant durvalumab/Pbo [c]	241 (65.8)	237 (63.4)	242 (66.1)	237 (63.4)
	Discontinued adjuvant durvalumab/Pbo	68 (18.6)	70 (18.7)	76 (20.8)	86 (23.0)
	Completed adjuvant durvalumab/Pbo	88 (24.0)	79 (21.1)	166 (45.4)	151 (40.4)
	Ongoing adjuvant durvalumab/Pbo	85 (23.2)	88 (23.5)	0	0

[a] All percentages are calculated from number of patients in the mITT population.
[b] Excludes patients with surgery done outside of study.
[c] Includes 3 patients who did not complete surgery (1 patient for D + CTx vs 2 patients for placebo + CTx).
DCO: 10 November 2022 (EFS IA1) and 10 May 2024 (EFS IA2)

Exposure

Table 14 Duration of exposure to CTx (Safety Analysis Set)

Treatment duration (weeks)		D + CTx (N = 401)	Placebo + CTx (N = 398)
Any CTx	**n**	**401**	**398**
Total [a]	Mean (sd)	12.14 (2.071)	12.03 (2.103)
	Median (Min, Max)	12.14 (2.0, 20.7)	12.14 (3.0, 22.7)
Carboplatin	**n**	**309**	**301**
Total [a]	Mean (sd)	11.68 (2.604)	11.93 (2.257)
	Median (Min, Max)	12.14 (2.0, 19.0)	12.00 (3.0, 22.7)
Actual [b]	Mean (sd)	11.17 (2.283)	11.47 (1.982)
	Median (Min, Max)	12.00 (2.0, 13.3)	12.00 (3.0, 13.4)
Cisplatin	**n**	**111**	**104**
Total [a]	Mean (sd)	11.09 (3.131)	11.42 (2.830)
	Median (Min, Max)	12.00 (3.0, 15.3)	12.07 (3.0, 17.0)
Actual [b]	Mean (sd)	10.65 (2.869)	11.00 (2.672)
	Median (Min, Max)	12.00 (3.0, 13.0)	12.00 (3.0, 13.0)
Gemcitabine	**n**	**60**	**54**
Total [c]	Mean (sd)	12.05 (2.361)	11.33 (2.833)
	Median (Min, Max)	12.14 (3.0, 19.0)	12.14 (1.0, 15.0)
Actual [d]	Mean (sd)	11.01 (1.987)	10.64 (2.750)
	Median (Min, Max)	12.00 (3.0, 13.0)	12.00 (1.0, 12.7)
Paclitaxel	**n**	**124**	**140**

Total [a]	Mean (sd)	11.52 (2.790)	11.92 (2.510)
	Median (Min, Max)	12.14 (2.0, 17.4)	12.14 (3.0, 22.7)
Actual [b]	Mean (sd)	11.11 (2.489)	11.44 (2.154)
	Median (Min, Max)	12.00 (2.0, 13.3)	12.00 (3.0, 13.0)
Pemetrexed	**n**	**221**	**206**
Total [a]	Mean (sd)	12.16 (1.921)	12.07 (1.840)
	Median (Min, Max)	12.14 (2.3, 20.7)	12.00 (3.0, 17.0)
Actual [b]	Mean (sd)	11.61 (1.554)	11.66 (1.643)
	Median (Min, Max)	12.00 (2.3, 12.9)	12.00 (3.0, 13.0)

a Total treatment duration = (min (death, DCO, last non-zero dose of CTx (cycle x, day 1) + 20) - first dose date of CTx + 1)/7, where minimum is whichever occurred first.
b Actual treatment duration = total treatment duration - total duration of dose delays, where delays = sum of (date of dose - date of previous dose - 21 days).
c Total treatment duration = (min (death, DCO, last non-zero dose of gemcitabine + W) - first dose date of gemcitabine + 1)/7, where minimum is whichever occurred first and W = 6 if the last dose was scheduled on Day 1 and W = 13 if the last dose was scheduled on Day 8.
d Actual treatment duration = total treatment duration - total duration of dose delays, where delays = sum of (date of gemcitabine dose - date of previous gemcitabine dose - X days), where X = 7 if previous dose was Day 1 of a cycle and X = 14 if previous dose was Day 8 of a cycle.
DCO: 10 November 2022

Table 15 Treatment cycles received in the neoadjuvant period (Safety analysis set - neoadjuvant period)

		Number (%) of subjects	
Treatment	Number of cycles	Durvalumab + SoC (N=401)	Placebo + SoC (N=398)
Durvalumab / placebo	n	401	398
	Mean	3.8	3.8
	Median	4.0	4.0
	Q1	4.0	4.0
	Q3	4.0	4.0
	None	1 (0.2)	0
	1	10 (2.5)	12 (3.0)
	2	8 (2.0)	12 (3.0)
	3	36 (9.0)	19 (4.8)
	4	346 (86.3)	355 (89.2)
	None	1 (0.2)	0
	>= 1 [d]	400 (99.8)	398 (100)
	>= 2 [d]	390 (97.3)	386 (97.0)
	>= 3 [d]	382 (95.3)	374 (94.0)
	4	346 (86.3)	355 (89.2)
Any SoC [a]	n	401	398
	Mean	3.8	3.8
	Median	4.0	4.0
	Q1	4.0	4.0
	Q3	4.0	4.0
	1	8 (2.0)	10 (2.5)
	2	6 (1.5)	12 (3.0)
	3	37 (9.2)	19 (4.8)
	4	350 (87.3)	357 (89.7)
	>= 1 [d]	401 (100)	398 (100)
	>= 2 [d]	393 (98.0)	388 (97.5)
	>= 3 [d]	387 (96.5)	376 (94.5)
	4	350 (87.3)	357 (89.7)

[a] Received at least one SoC component. [b] Received Cisplatin or Carboplatin. [c] Received either Cisplatin or Carboplatin in combination with a non-platinum treatment. [d] Rows are cumulative and subjects are included if they have taken at least the number of cycles. A cycle equals 21 days in the neoadjuvant period. Subjects are counted as having received a cycle of therapy as soon as the infusion has started, even if the full dose is not delivered. For SoC components, mean, median, Q1 and Q3 are calculated including subjects who have received at least one dose of that treatment. If a cycle is prolonged due to toxicity it is still counted as one cycle. Subjects who switched platinum agent of chemotherapy (26 subjects) or non-platinum agent of chemotherapy (5 subjects) are summarized in both relevant chemotherapy groups. One subject randomized to Placebo+SoC received 1 cycle of adjuvant Durva. Only their Durva cycle is reported. N = Number of subjects in treatment group. n = Number of subjects in category or analysis. Q1 = 1st Quartile. Q3 = 3rd Quartile. SoC = Standard of Care.

EFS IA2 - Data Cut-off: 2024-05-10 -

Table 16 Treatment cycles received in the adjuvant period (Safety analysis set - adjuvant period)

		Number (%) of subjects	
Treatment	Number of cycles	Durvalumab + SoC (N=266)	Placebo + SoC (N=254)
Durvalumab / placebo	n	266	254
	Mean	9.7	9.7
	Median	12.0	12.0
	Q1	8.0	8.0
	Q3	12.0	12.0
	None	0	0
	1	14 (5.3)	7 (2.8)
	2	13 (4.9)	14 (5.5)
	3	8 (3.0)	6 (2.4)
	4	8 (3.0)	13 (5.1)
	5	9 (3.4)	11 (4.3)
	6	9 (3.4)	8 (3.1)
	7	5 (1.9)	4 (1.6)
	8	8 (3.0)	9 (3.5)
	9	3 (1.1)	6 (2.4)
	10	5 (1.9)	5 (2.0)
Durvalumab / placebo	11	2 (0.8)	10 (3.9)
	12	182 (68.4)	161 (63.4)
	None	0	0
	>= 1 [a]	266 (100)	254 (100)
	>= 2 [a]	252 (94.7)	247 (97.2)
	>= 3 [a]	239 (89.8)	233 (91.7)
	>= 4 [a]	231 (86.8)	227 (89.4)
	>= 5 [a]	223 (83.8)	214 (84.3)
	>= 6 [a]	214 (80.5)	203 (79.9)
	>= 7 [a]	205 (77.1)	195 (76.8)
	>= 8 [a]	200 (75.2)	191 (75.2)
	>= 9 [a]	192 (72.2)	182 (71.7)
	>= 10 [a]	189 (71.1)	176 (69.3)
	>= 11 [a]	184 (69.2)	171 (67.3)
	12	182 (68.4)	161 (63.4)

[a] Rows are cumulative and subjects are included if they have taken at least the number of cycles.
A cycle equals 28 days in the adjuvant period.
Subjects are counted as having received a cycle of therapy as soon as the infusion has started, even if the full dose is not delivered. Mean, median, Q1 and Q3 are calculated including subjects who have received at least one dose of that treatment.
If a cycle is prolonged due to toxicity it is still counted as one cycle.
One subject randomized to Placebo+SoC received 1 cycle of adjuvant Durva. Only their Durva cycle is reported.
N = Number of subjects in treatment group. n = Number of subjects in category or analysis. Q1 = 1st Quartile.
Q3 = 3rd Quartile. SoC = Standard of Care.

EFS IA2 - Data Cut-off: 2024-05-10 -

Recruitment

A total of 183 sites (across 28 countries) randomized at least 1 patient into the global cohort: Argentina (8 sites), Austria (5 sites), Belgium (2 sites), Brazil (11 sites), Bulgaria (1 site), Canada (5 sites), Chile (2 sites), China (26 sites), Costa Rica (2 sites), France (4 sites), Germany (4 sites), Hungary (5 sites), India (10 sites), Italy (8 sites), Japan (13 sites), Mexico (7 sites), Netherlands (1 site), Peru (2 sites), Philippines (1 site), Poland (4 sites), Republic of Korea (6 sites), Romania (1 site), Russia (10 sites), Spain (8 sites), Taiwan (8 sites), Thailand (5 sites), United States (20 sites), and Vietnam (4 sites).

The first patient was enrolled on 6 December 2018 and the last patient on 18 March 2022.

The median duration of EFS follow-up at the time of the primary analysis of EFS in the mITT population was 9.1 months at DCO (10 November 2022) (EFS IA1, OS IA1).

The median duration of survival follow-up at the time of the primary analysis of EFS in the mITT population was 14.5 months at DCO (10 November 2022) (EFS IA1, OS IA1).

Conduct of the study

Table 17 Key Protocol Amendments Relevant to the Efficacy Evaluation

Amendment number/date	Key details of amendment	Main reason(s) for amendment
Amendments made *before* the start of patient randomization		
Protocol version 2.0 (Amendment 1) 04 December 2018	The pre-surgery chemotherapy treatment regimen was revised from 3 neoadjuvant cycles (with an optional fourth cycle post-surgery based on local practice and Investigator's judgment) to 4 neoadjuvant cycles for all patients.	This update was made in order to ensure compliance with major global guidelines (i.e., NCCN and ESMO). Additionally, the option to administer an optional fourth cycle of chemotherapy post-surgery was subsequently deemed to be sub-optimal in relation to study design and robust data evaluation; and therefore this was revised prior to enrolling the first patient within the study. The amendment was finalized prior to first patient being randomized, but due to a delay before it was implemented at all sites, one patient (E7401001) completed the neoadjuvant treatment as per the CSP version 1.0.
Amendments made *after* the start of patient randomization		
Protocol version 3.0 (Amendment 2) 26 November 2019	Changes to the study objectives and endpoints and their respective analysis populations were made: • EFS (previously a secondary endpoint) was added as a new primary endpoint (in addition to the existing primary endpoint of MPR). • DFS (previously a secondary endpoint) was added as a key secondary endpoint (in addition to the existing key secondary endpoint of pCR). Aligned with this update, the number of planned patients to be enrolled and randomized was increased to 1333 and 800, respectively, and the MTP was updated.	These changes were made to reflect the importance of survival endpoints in oncology to assess clinical benefit for patients. Given the prior sole primary endpoint was assessing pathological response only, EFS was changed to a primary endpoint to support potential registration. While EFS reflects the whole study period for all randomized patients, DFS reflects the period after complete surgical resection for patients in which this is achieved, and was also considered important to assess - this was therefore changed to become a key secondary endpoint. These changes were made contemporaneously with an increase in sample size to ensure the study has sufficient power for EFS as a primary endpoint, and an update to the MTP to reflect the revised endpoint hierarchy.
	The definitions of EFS and DFS were updated to the following (strikethrough text represents deletions, bold text represents additions): • EFS is defined as the time from randomization to the first of the following: a) documented disease progression~~, recurrence, or new primary invasive~~ **of lung** cancer as determined by ~~the Investigator~~ **BICR** using ~~Investigator~~ RECIST 1.1 assessments ~~(event date is the date of the RECIST 1.1 assessments)~~; b) death due to any cause (event date is the date of death); ~~c) failure of the following~~	The definitions of the endpoints of EFS and DFS were updated (including a key update to specify BICR as the assessment methodology [rather than investigator assessment] by RECIST 1.1) to reflect the change in primary (addition of EFS) and key secondary (addition of DFS) endpoints, and for consistency with the FDA-recommended definitions and prevailing clinical practice.

Amendment number/date	Key details of amendment	Main reason(s) for amendment
	~~surgical eligibility criterion: "complete surgical resection of the primary NSCLC must be deemed achievable, as assessed by a multidisciplinary evaluation, which must include a thoracic surgeon who performs lung cancer surgery as a prominent part of his/her practice" (event date is the date of this determination);~~ or ~~d~~**c**) ~~discovery~~ **PD that precludes surgery as assessed by a multidisciplinary evaluation before surgery (event date is the date of this determination), or discovered** upon attempting surgery ~~that the surgery cannot be completed~~ (event date is the date of the first attempt at surgery). • DFS is defined as the time from the date of surgery until the **first** date of disease recurrence ~~(local or distant) or new primary invasive cancer~~ **as determined by BICR** using ~~Investigator~~ RECIST 1.1 assessments **(local or distant)**, or date of death due to any cause, whichever occurs first.	
	Details of statistical analyses were updated to include stratified log-rank testing based on BICR assessment using RECIST 1.1 for EFS and DFS, and logistic regression for MPR and pCR.	The stratified log-rank test was added to test EFS and DFS for statistical significance, after their revision to primary and key secondary endpoints, respectively. The pCR and MPR analyses were simplified to use logistic regression both for testing statistical significance and adjusted treatment effect.
	Analysis populations were added for EFS (FAS) and DFS (resected patients) to perform analyses on the corresponding PD-L1 TC ≥ 1% patients i.e., PD-L1 TC ≥ 1% analysis set and PD-L1 TC ≥ 1% resected set accordingly.	The study planned to analyse the primary endpoint (formerly MPR only) on the PD-L1 TC ≥ 1% patients to understand potential benefits in PD-L1 TC ≥ 1% patients. Following the changes to primary and key secondary endpoints, the PD-L1 TC ≥ 1% analysis set and PD-L1 TC ≥ 1% resected set were added to allow analyses by PD-L1 expression for all primary and key secondary endpoints.
Protocol version 4.0 (Amendment 3) 15 April 2021	The secondary objective of pCR was changed to be a primary objective and the primary objective of MPR was changed to be a key secondary objective.	Rationale for switching to pCR (from MPR) as a primary endpoint: • The historical expected pCR rate with chemotherapy alone has been studied more extensively. • It is likely to have higher reproducibility among pathologists. • Emerging data from trials with neoadjuvant immunotherapy provide more information on its clinical relevance (Provencio et al 2020, Shu et al 2020).
	The existing secondary endpoint of OS was reclassified as a key secondary endpoint.	To reflect inclusion of OS in the MTP.
	A new exclusion criterion (#28) was added to clarify that patients whose tumours had EGFRm/ALK gene rearrangements are no longer eligible for the study In relation to this update, efficacy analysis sets were also modified to include only patients whose tumours do not contain EGFRm or ALK gene rearrangements.	New external study data suggest that such patients, who are usually treated with first line targeted therapy in the metastatic NSCLC disease setting, may have a limited response to immunotherapy (Wu et al 2020, Khan et al 2018, Wang et al 2018).

Amendment number/date	Key details of amendment	Main reason(s) for amendment
Protocol version 5.0 (Amendment 4) 10 December 2021	The definition of EFS was updated to the following (strikethrough text represents deletions, bold text represents additions): • EFS is defined as the time from randomization to the first of the following: a) ~~documented disease progression of lung cancer~~ **local or distant recurrence** as determined by BICR using RECIST 1.1 assessments; b) death due to any cause (event date is the date of death); c) PD that precludes surgery (event date is the date of this determination) or PD discovered and reported by the Investigator upon attempting surgery **that prevents completion of surgery** (event date is the date of the first attempt at surgery).	To align with the definition which is consistent with the FDA guidelines on clinical trial endpoints for the approval of cancer drugs and biologics (FDA 2018).

Table 18 Important protocol deviations (ITT population and mITT population; EFS IA1)

Important protocol deviation [a]	Number (%) patients					
	ITT population			mITT population		
	D + CTx (N = 400)	Placebo + CTx (N = 402)	Total (N = 802)	D + CTx (N = 366)	Placebo + CTx (N = 374)	Total (N = 740)
Number of patients with at least 1 important protocol deviation	17 (4.3)	19 (4.7)	36 (4.5)	16 (4.4)	19 (5.1)	35 (4.7)
Randomized but did not receive treatment	0	3 (0.7)	3 (0.4)	0	3 (0.8)	3 (0.4)
Deviated from key inclusion/exclusion criteria [b]	6 (1.5)	3 (0.7)	9 (1.1)	6 (1.6)	3 (0.8)	9 (1.2)
Baseline RECIST 1.1 assessment incorrectly completed [c]	2 (0.5)	2 (0.5)	4 (0.5)	2 (0.5)	2 (0.5)	4 (0.5)
No baseline RECIST 1.1 assessment	0	1 (0.2)	1 (0.1)	0	1 (0.3)	1 (0.1)
Received prohibited concomitant medications	7 (1.8)	8 (2.0)	15 (1.9)	7 (1.9)	8 (2.1)	15 (2.0)
Randomized but received incorrect dose or alternative treatment	2 (0.5)	2 (0.5)	4 (0.5)	1 (0.3)	2 (0.5)	3 (0.4)
Number of patients with at least 1 COVID-19 related important protocol deviation	2 (0.5)	1 (0.2)	3 (0.4)	2 (0.5)	1 (0.3)	3 (0.4)
Number of patients with at least 1 important protocol deviation, excluding COVID-19-related important protocol deviation	15 (3.8)	18 (4.5)	33 (4.1)	14 (3.8)	18 (4.8)	32 (4.3)

a Important deviations before the start of treatment and during treatment, as per SAP, are reported in this table.
b Patients randomized but subsequently discovered that they failed one of the key eligibility criteria, as per SAP.
c Scan > 42 days before start date of randomized treatment.
The same patient may have had more than 1 important protocol deviation.
DCO: 10 November 2022.

Baseline data

Table 19 Key demographic and patient characteristics (ITT population and mITT population, EFS IA1)

Characteristic	Number (%) patients					
	ITT population			mITT population		
	D + CTx (N = 400)	Placebo + CTx (N = 402)	Total (N = 802)	D + CTx (N = 366)	Placebo + CTx (N = 374)	Total (N = 740)
Age (years) [a]						
Mean (sd)	63.9 (9.20)	63.8 (8.70)	63.9 (8.95)	64.1 (9.02)	63.9 (8.59)	64.0 (8.80)
Median (min, max)	65.0 (30, 88)	65.0 (39, 85)	65.0 (30, 88)	65.0 (30, 88)	65.0 (39, 85)	65.0 (30, 88)
Age group (years), n (%)						
< 50	22 (5.5)	22 (5.5)	44 (5.5)	17 (4.6)	20 (5.3)	37 (5.0)
≥ 50 - < 65	170 (42.5)	177 (44.0)	347 (43.3)	158 (43.2)	163 (46.3)	321 (43.4)
≥ 65 - < 75	160 (40.0)	165 (41.0)	325 (40.5)	147 (40.2)	155 (41.4)	302 (40.8)
≥ 75	48 (12.0)	38 (9.5)	86 (10.7)	44 (12.0)	36 (9.6)	80 (10.8)
Sex, n (%)						
Male	262 (65.5)	291 (72.4)	553 (69.0)	252 (68.9)	278 (74.3)	530 (71.6)
Female	138 (34.5)	111 (27.6)	249 (31.0)	114 (31.1)	96 (25.7)	210 (28.4)
Race, n (%)						
White	216 (54.0)	196 (48.8)	412 (51.4)	206 (56.3)	191 (51.1)	397 (53.6)
Asian	165 (41.3)	187 (46.5)	352 (43.9)	143 (39.1)	164 (43.9)	307 (41.5)
American Indian or Alaska Native	7 (1.8)	4 (1.0)	11 (1.4)	6 (1.6)	4 (1.1)	10 (1.4)
Black or African American	5 (1.3)	3 (0.7)	8 (1.0)	4 (1.1)	3 (0.8)	7 (0.9)
Other	7 (1.8)	12 (3.0)	19 (2.4)	7 (1.9)	12 (3.2)	19 (2.6)
Ethnic group, n (%)						
Not Hispanic or Latino	332 (83.0)	344 (85.6)	676 (84.3)	303 (82.8)	318 (85.0)	621 (83.9)

Hispanic or Latino	68 (17.0)	58 (14.4)	126 (15.7)	63 (17.2)	56 (15.0)	119 (16.1)
Weight (kg)						
Mean (sd)	71.423 (16.2061)	70.273 (17.6871)	70.847 (16.9638)	72.288 (16.1826)	70.710 (17.6894)	71.491 (16.9678)
Median (min to max)	70.000 (39.00 to 152.00)	69.150 (33.40 to 182.00)	69.950 (33.40 to 182.00)	70.000 (39.00 to 152.00)	70.000 (35.00 to 182.00)	70.000 (35.00 to 182.00)
Weight group (kg)						
< 70	198 (49.5)	203 (50.5)	401 (50.0)	172 (47.0)	183 (48.9)	355 (48.0)
≥ 70 - ≤ 90	153 (38.3)	161 (40.0)	314 (39.2)	147 (40.2)	155 (41.4)	302 (40.8)
> 90	49 (12.3)	38 (9.5)	87 (10.8)	47 (12.8)	36 (9.6)	83 (11.2)
Smoking history, n (%)						
Never-smoker	72 (18.0)	74 (18.4)	146 (18.2)	51 (13.9)	56 (15.0)	107 (14.5)
Smoker	328 (82.0)	328 (81.6)	656 (81.8)	315 (86.1)	318 (85.0)	633 (85.5)
Current smoker	96 (24.0)	97 (24.1)	193 (24.1)	95 (26.0)	95 (25.4)	190 (25.7)
Habitual	86 (21.5)	93 (23.1)	179 (22.3)	85 (23.2)	91 (24.3)	176 (23.8)
Occasional	10 (2.5)	4 (1.0)	14 (1.7)	10 (2.7)	4 (1.1)	14 (1.9)
Former smoker	232 (58.0)	231 (57.5)	463 (57.7)	220 (60.1)	223 (59.6)	443 (59.9)

a Age was calculated using date of randomization.
b Note: Percentages are calculated based on the number of patients in the analysis set, N.
DCO: 10 November 2022.

Table 20 Key disease characteristics and ECOG status at baseline (ITT population and mITT population, EFS IA1)

Disease characteristic	Number (%) patients					
	ITT population			mITT population		
	D + CTx (N = 400)	Placebo + CTx (N = 402)	Total (N = 802)	D + CTx (N = 366)	Placebo + CTx (N = 374)	Total (N = 740)
ECOG performance status						
(0) Normal activity	278 (69.5)	277 (68.9)	555 (69.2)	251 (68.6)	255 (68.2)	506 (68.4)
(1) Restricted in physically strenuous activity	122 (30.5)	125 (31.1)	247 (30.8)	115 (31.4)	119 (31.8)	234 (31.6)
Disease stage at baseline [a] per source data						
IIA	19 (4.8)	28 (7.0)	47 (5.9)	18 (4.9)	24 (6.4)	42 (5.7)
IIB	100 (25.0)	92 (22.9)	192 (23.9)	86 (23.5)	86 (23.0)	172 (23.2)
III (NOS)	0	1 (0.2)	1 (0.1)	0	1 (0.3)	1 (0.1)
IIIA	186 (46.5)	178 (44.3)	364 (45.4)	173 (47.3)	165 (44.1)	338 (45.7)
IIIB	94 (23.5)	103 (25.6)	197 (24.6)	88 (24.0)	98 (26.2)	186 (25.1)
IV (NOS)	1 (0.3)	0	1 (0.1)	1 (0.3)	0	1 (0.1)
Disease stage at diagnosis [a] per IXRS						
II	118 (29.5)	119 (29.6)	237 (29.6)	102 (27.9)	108 (28.9)	210 (28.4)
III	282 (70.5)	283 (70.4)	565 (70.4)	264 (72.1)	266 (71.1)	530 (71.6)
Histology type						
Squamous	173 (43.3)	192 (47.8)	365 (45.5)	169 (46.2)	191 (51.1)	360 (48.6)
Squamous (NOS)	173 (43.3)	192 (47.8)	365 (45.5)	169 (46.2)	191 (51.1)	360 (48.6)
Non-squamous	226 (56.5)	206 (51.2)	432 (53.9)	196 (53.6)	179 (47.9)	375 (50.7)
Adenocarcinoma (NOS)	189 (47.3)	162 (40.3)	351 (43.8)	166 (45.4)	142 (38.0)	308 (41.6)
Adenocarcinoma: Acinar	18 (4.5)	15 (3.7)	33 (4.1)	15 (4.1)	13 (3.5)	28 (3.8)
Adenocarcinoma: Papillary	3 (0.8)	3 (0.7)	6 (0.7)	3 (0.8)	2 (0.5)	5 (0.7)
Adenocarcinoma: Bronchiolo-alveolar	3 (0.8)	3 (0.7)	6 (0.7)	2 (0.5)	2 (0.5)	4 (0.5)
Adenocarcinoma: Solid with mucus formation	6 (1.5)	3 (0.7)	9 (1.1)	5 (1.4)	3 (0.8)	8 (1.1)
Large cell carcinoma (NOS)	1 (0.3)	4 (1.0)	5 (0.6)	1 (0.3)	4 (1.1)	5 (0.7)
Adenosquamous carcinoma	4 (1.0)	15 (3.7)	19 (2.4)	3 (0.8)	12 (3.2)	15 (2.0)
Bronchial gland carcinoma (NOS)	2 (0.5)	1 (0.2)	3 (0.4)	1 (0.3)	1 (0.3)	2 (0.3)

Other	1 (0.3)	4 (1.0)	5 (0.6)	1 (0.3)	4 (1.1)	5 (0.7)
Squamous cell carcinoma: Spindle cell	1 (0.3)	0	1 (0.1)	1 (0.3)	0	1 (0.1)
Other	0	4 (1.0)	4 (0.5)	0	4 (1.1)	4 (0.5)
TNM Classification at baseline [b]						
T1	53 (13.3)	48 (11.9)	101 (12.6)	44 (12.0)	43 (11.5)	87 (11.8)
T2	108 (27.0)	119 (29.6)	227 (28.3)	97 (26.5)	108 (28.9)	205 (27.7)
T3	141 (35.3)	136 (33.8)	277 (34.5)	128 (35.0)	129 (34.5)	257 (34.7)
T4	98 (24.5)	99 (24.6)	197 (24.6)	97 (26.5)	94 (25.1)	191 (25.8)
N0	118 (29.5)	110 (27.4)	228 (28.4)	110 (30.1)	102 (27.3)	212 (28.6)
N1	83 (20.8)	94 (23.4)	177 (22.1)	75 (20.5)	87 (23.3)	162 (21.9)
N2	199 (49.8)	198 (49.3)	397 (49.5)	181 (49.5)	185 (49.5)	366 (49.5)
Single station	151 (37.8)	140 (34.8)	291 (36.3)	141 (38.5)	132 (35.3)	273 (36.9)
Multi-station	38 (9.5)	45 (11.2)	83 (10.3)	34 (9.3)	40 (10.7)	74 (10.0)
Missing	10 (2.5)	13 (3.2)	23 (2.9)	6 (1.6)	13 (3.5)	19 (2.6)
M0	399 (99.8)	402 (100)	801 (99.9)	365 (99.7)	374 (100)	739 (99.9)
M1	1 (0.3)	0	1 (0.1)	1 (0.3)	0	1 (0.1)
PD-L1 expression status at baseline (central laboratory data were migrated to the IXRS and source data)						
TC < 1% (per IXRS and source data)	133 (33.3)	134 (33.3)	267 (33.3)	122 (33.3)	125 (33.4)	247 (33.4)
TC ≥ 1% (per IXRS and source data)	267 (66.8)	268 (66.7)	535 (66.7)	244 (66.7)	249 (66.6)	493 (66.6)
TC 1 to 49% (per source data)	151 (37.8)	158 (39.3)	309 (38.5)	135 (36.9)	142 (38.0)	277 (37.4)
TC ≥ 50% (per source data)	116 (29.0)	110 (27.4)	226 (28.2)	109 (29.8)	107 (28.6)	216 (29.2)

a Stages according to AJCC Cancer Staging Manual, 8th Edition.
b TNM classification is based on the AJCC Cancer Staging Manual, 8th edition.
c Baseline is defined as the last observation prior to randomization if available, or otherwise, an observation after randomization but before the first dose of randomized treatment.
DCO: 10 November 2022.

There were 51 patients with EGFR mutations and 11 patients with ALK rearrangements randomised into and treated within the study; however, these patients were not included in the mITT efficacy analysis.

Table 21 Surgical details (ITT population) (ITT population and mITT population, EFS IA1)

Surgical details	ITT population		mITT population	
	D + CTx (N = 400)	Placebo + CTx (N = 402)	D + CTx (N = 366)	Placebo + CTx (N = 374)
Patients who underwent surgery, n (%)	324 (81.0)	327 (81.3)	295 (80.6)	302 (80.7)
Patients who completed surgery, n (%)	310 (77.5)	308 (76.6)	284 (77.6)	287 (76.7)
Surgical approach, n (%)				
Open procedure	159 (39.8)	162 (40.3)	145 (39.6)	153 (40.9)
Minimally invasive	159 (39.8)	156 (38.8)	145 (39.6)	142 (38.0)
Other	4 (1.0)	6 (1.5)	4 (1.1)	6 (1.6)
Missing	2 (0.5)	3 (0.7)	0	1 (0.3)
Surgery/procedure performed, n (%)				
Lobectomy	261 (65.3)	237 (59.0)	238 (65.0)	221 (59.1)
Sleeve resection	7 (1.8)	14 (3.5)	7 (1.9)	14 (3.7)
Bilobectomy	13 (3.3)	23 (5.7)	13 (3.6)	20 (5.3)
Pneumonectomy	28 (7.0)	32 (8.0)	27 (7.4)	29 (7.8)
Sleeve resection (bronchial)	2 (0.5)	2 (0.5)	2 (0.5)	2 (0.5)
Sleeve resection (arterial)	0	1 (0.2)	0	1 (0.3)
Wedge resection	1 (0.3)	2 (0.5)	1 (0.3)	2 (0.5)
Other	12 (3.0)	16 (4.0)	7 (1.9)	13 (3.5)
Days from last IP administration [a]				
n	324	327	295	302
Mean (sd)	35.8 (12.32)	35.5 (12.58)	35.7 (11.99)	36.2 (12.68)
Median	34.0	34.0	34.0	34.0
Min, Max	12, 101	7, 103	12, 91	13, 103
Duration of surgery (hours) [b]				
n	299	303	271	279
Mean (sd)	3.8 (2.18)	3.6 (2.27)	3.9 (2.24)	3.6 (2.34)
Median	3.4	3.2	3.5	3.3
Min, Max	1, 24	1, 24	1, 24	1, 24
Margins, n (%)				

R0	294 (73.5)	282 (70.1)	269 (73.5)	263 (70.3)
R1	13 (3.3)	24 (6.0)	13 (3.6)	22 (5.9)
R2	10 (2.5)	12 (3.0)	8 (2.2)	11 (2.9)
Missing	7 (1.8)	9 (2.2)	5 (1.4)	6 (1.6)
Time from surgery to first dose of adjuvant treatment (days)				
n	264	255	241	237
Mean (sd)	54.7 (20.45)	55.9 (22.04)	54.1 (20.22)	55.8 (22.02)
Median	50.5	52.0	50.0	52.0
Min, Max	22, 136	21, 141	22, 136	21, 141

a Derived using date of last dose of IP (durvalumab/placebo/CTx) and date of surgery.
b Derived from start and end time of surgery.
Percentages are calculated based on the number of patients in the analysis set, N. Excludes patients with surgery of curative
DCO: 10 November 2022.

Table 22 Subsequent anticancer therapy (mITT population; EFS IA1)

Anticancer therapy regimen [a]	**Number (%) patients**		
	D + CTx (N = 366)	**Placebo + CTx (N = 374)**	**Total (N = 740)**
Number of patients with post-discontinuation anticancer therapy	**55 (15.0)**	**72 (19.3)**	**127 (17.2)**
Systemic therapy	53 (14.5)	72 (19.3)	125 (16.9)
Cytotoxic chemotherapy	37 (10.1)	37 (9.9)	74 (10.0)
Single agent	10 (2.7)	8 (2.1)	18 (2.4)
Platinum doublet	26 (7.1)	24 (6.4)	50 (6.8)
Other combination	7 (1.9)	7 (1.9)	14 (1.9)
Immunotherapy	17 (4.6)	39 (10.4)	56 (7.6)
Immunotherapy only	7 (1.9)	25 (6.7)	32 (4.3)
Immunotherapy + CTx	10 (2.7)	13 (3.5)	23 (3.1)
Immunotherapy + other	1 (0.3)	1 (0.3)	2 (0.3)
Targeted therapy	3 (0.8)	6 (1.6)	9 (1.2)
Other	2 (0.5)	3 (0.8)	5 (0.7)
Radiotherapy	37 (10.1)	48 (12.8)	85 (11.5)
Concomitant chemoradiotherapy	18 (4.9)	16 (4.3)	34 (4.6)
Line of subsequent therapy			
1st subsequent therapy	47 (12.8)	67 (17.9)	114 (15.4)
2nd subsequent therapy	16 (4.4)	19 (5.1)	35 (4.7)
≥ 3rd subsequent therapy	3 (0.8)	5 (1.3)	8 (1.1)
Type of subsequent therapy			

Neoadjuvant	4 (1.1)	4 (1.1)	8 (1.1)
Adjuvant	6 (1.6)	10 (2.7)	16 (2.2)
Definitive	6 (1.6)	3 (0.8)	9 (1.2)
Maintenance	3 (0.8)	6 (1.6)	9 (1.2)
Palliative	34 (9.3)	48 (12.8)	82 (11.1)
Not applicable	5 (1.4)	4 (1.1)	9 (1.2)

a Therapies post discontinuation of study treatment. Regimen categories and line of subsequent therapy identified from medical review of preferred terms using treatment start dates.
Patients with therapies in more than one category are counted once in each of those categories. Percentages are calculated from number of patients in the modified intent-to-treat in that treatment arm.
DCO: 10 November 2022.

Table 23 Reasons for not undergoing surgery (ITT population, EFS IA1)

	Number (%) patients	
	D + CTx (N = 400)	Placebo + CTx (N = 402)
Subjects who did not undergo surgery	76 (19.0)	75 (18.7)
Disease progression	27 (6.8)	30 (7.5)
Subject decision	12 (3.0)	17 (4.2)
Inadequate lung function	6 (1.5)	7 (1.7)
Adverse event	7 (1.8)	5 (1.2)
Death	9 (2.3)	2 (0.5)
Unfit for surgery	8 (2.0)	2 (0.5)
Surgical resection with curative intent performed outside the protocol	2 (0.5)	6 (1.5)
Investigator decision	2 (0.5)	2 (0.5)
Inadequate cardiac function	1 (0.3)	1 (0.2)
Other	2 (0.5)	2 (0.5)
Missing	0	1 (0.2)

Numbers analysed

Table 24 Analysis Sets for Efficacy (EFS IA1)

	Number of patients		
	D + CTx	Placebo + CTx	Total
Patients randomized	400	402	802
Patients included in the ITT population	400	402	802
Patients included in the mITT population	366	374	740
Patients included in PD-L1 TC $\geq$ 1% analysis set	244	249	493
Patients included in PK analysis set	385	0	385
Patients included in ADA analysis set	377	364	741

Outcomes and estimation

Primary endpoint – pCR

Table 25 Pathological complete response: Primary (interim mITT cohort at pCR IA) and final analyses (mITT population at EFS IA1)

Arm	n	Number of patients with response [a]	Response Rate (%)	95% CI [b]	Comparison between arms [c]			
					Difference in proportions (%)	95% CI	Adjusted 99.9918% CI[d]	2-sided p-value
pCR IA: Interim (Primary) Analysis [d]								
D + CTx	196	35	17.86	12.76, 23.95	13.03	7.11, 19.52	0.68, 26.85	0.000036
Placebo + CTx	206	10	4.85	2.35, 8.75				
EFS IA1: Final Analysis								
D + CTx	366	63	17.21	13.49, 21.48	12.96	8.67, 17.57	NA	--
Placebo + CTx	374	16	4.28	2.46, 6.85				

a Response is defined as having 0% residual viable tumour cells within all resected tissue, without R1 or R2 margins, and without carcinoma in any examined lymph nodes at the time of resection as assessed by central pathology laboratory.
b CIs for response rate are calculated using Clopper-Pearson exact method.
c The analysis was performed using a CMH test stratified by disease stage (Stage II vs Stage III) and by PD-L1 expression status at baseline (TC < 1% vs ≥ 1%), using the stratification factors from the IXRS. A difference > 0 favours durvalumab + CTx. CIs for difference in proportions are computed using the MN stratified method.
d Adjusted for multiplicity. Based on a Lan-DeMets alpha spending function with O'Brien Fleming boundary calculated using the actual number of patients at the interim vs the final analysis, the boundary for declaring statistical significance is 0.0082% for a total 0.5% 2-sided alpha. Corresponding CIs are shown.
As the IA was statistically significant per the multiple testing procedure, pCR was not re-tested for statistical significance at the final analysis.
DCO dates: 14 January 2022 (IA at pCR IA), and 10 November 2022 (final analysis at EFS IA1).

Primary endpoint – EFS

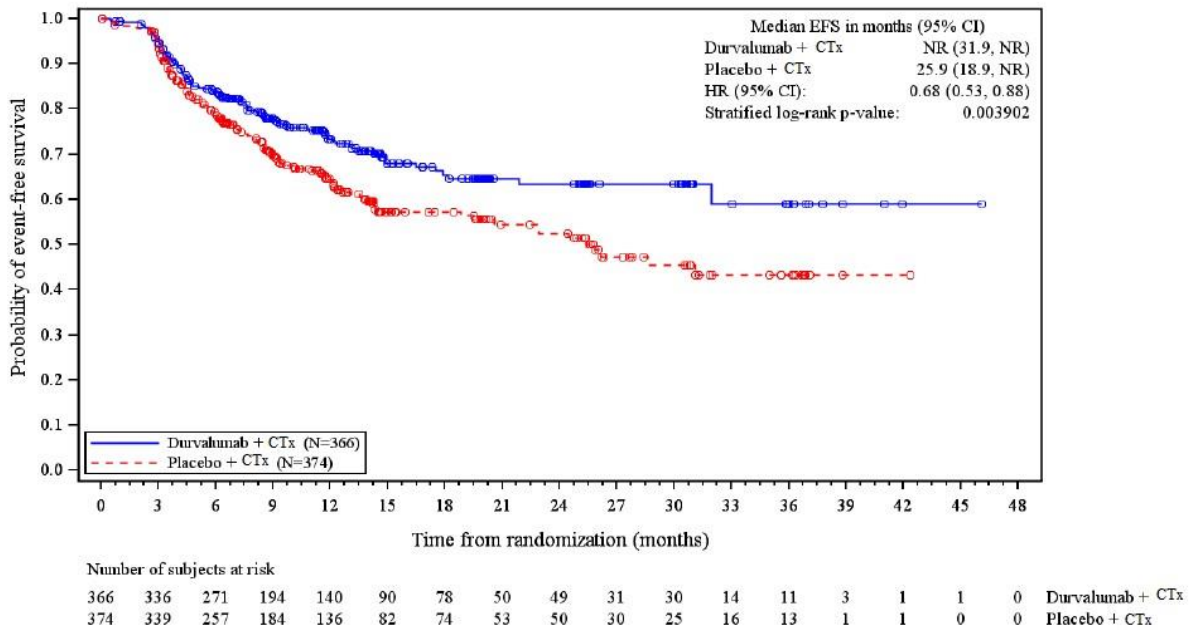
Table 26 Event-free survival (using BICR per RECIST 1.1) (mITT population, EFS IA1)

	D + CTx (N = 366)	Placebo + CTx (N = 374)
Total events, n (%) [a]	98 (26.8)	138 (36.9)
RECIST recurrence [b]	38 (10.4)	60 (16.0)
Progression that precludes surgery	26 (7.1)	35 (9.4)
PD post-surgery not undertaken for reasons other than progression	1 (0.3)	4 (1.1)
PD discovered upon attempting surgery	5 (1.4)	13 (3.5)
PD post-surgery not completed for reasons other than progression	0	5 (1.3)
Death due to any cause	29 (7.9)	30 (8.0)
Censored patients, n (%)	268 (73.2)	236 (63.1)
Censored RECIST recurrence/PD [c]	2 (0.5)	1 (0.3)
Censored death [c]	12 (3.3)	7 (1.9)
Event-free at time of analysis	239 (65.3)	214 (57.2)

No post-baseline disease assessments or no baseline data prior to neoadjuvant treatment	4 (1.1)	6 (1.6)
Withdrawn consent	11 (3.0)	8 (2.1)
Median event-free survival (months) [d]	NR	25.9
95% CI for median event-free survival [d]	31.9, NR	18.9, NR
Event-free survival rate at 12 months (%) [d]	73.4	64.5
95% CI for event-free survival rate at 12 months [d]	67.9, 78.1	58.8, 69.6
Event-free survival rate at 24 months (%) [d]	63.3	52.4
95% CI for event-free survival rate at 24 months [d]	56.1, 69.6	45.4, 59.0
HR [e]	0.68	
95% CI for HR [e]	0.53, 0.88	
99.0101% CI for HR - adjusted for multiplicity [e, g]	0.48, 0.96	
2-sided p-value [f]	0.003902	

a 2 missed visit rule applied.
b New malignancy that is not NSCLC as confirmed by pathology, is not considered an EFS event.
c Occurred after 2 or more consecutive missed visits after last assessment.
d Calculated using Kaplan-Meier technique.
e Calculated using a stratified Cox proportional hazards model adjusted for disease stage and PD-L1 expression status at baseline. A HR < 1 favours durvalumab + CTx, to be associated with longer EFS than placebo + CTx.
f Calculated using a stratified log rank test adjusting for disease stage and PD-L1 expression status at baseline.
g Based on a Lan-DeMets alpha spending function with O'Brien Fleming boundary with the observed number of events, the boundary for declaring statistical significance is 0.9899% for a 5% overall 2-sided alpha. RECIST version 1.1.
DCO: 10 November 2022.

Figure 12 Kaplan-Meier plot of EFS (using BICR per RECIST 1.1) (mITT population, EFS IA1)



A circle indicates a censored observation. 1 month = 30.4375 days.
EFS is defined as the time from randomization to the earliest progression of disease that precludes surgery or progression with surgery not completed; local or distant recurrence; or death due to any cause.
Patients who have not experienced an EFS event at the time of analysis are censored at the time of the last disease assessment. If the event occurs after two or more consecutive missed visits, the patient is censored at the last disease assessment prior to the two missed visits. A new malignancy that is not NSCLC, as confirmed by pathology, is not considered an EFS event. RECIST version 1.1.

DCO: 10 November 2022.

Updated EFS (IA2) DCO 10 May 2024

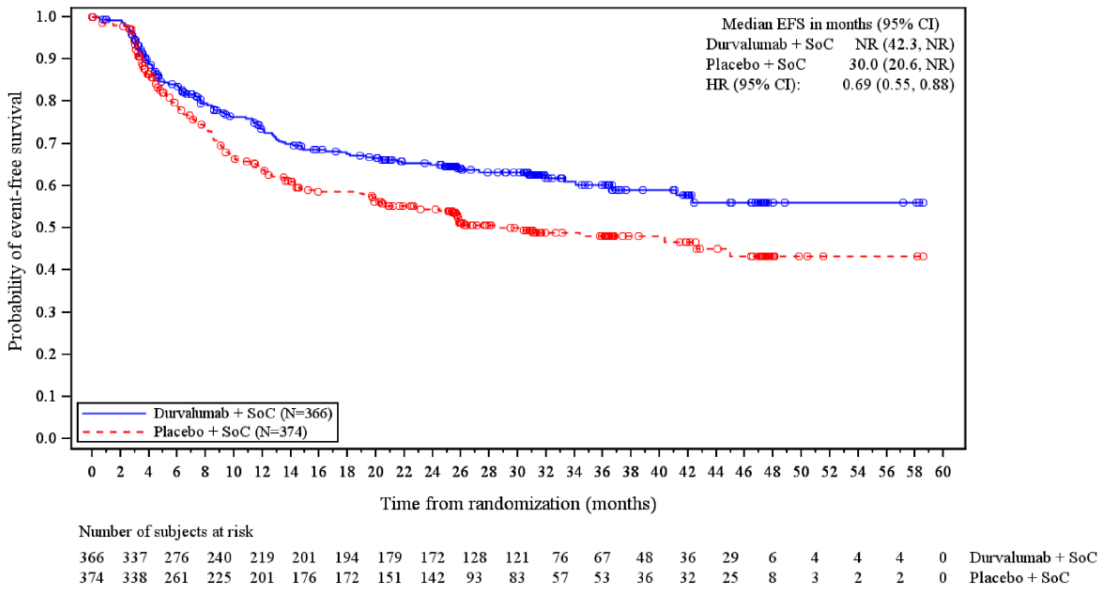
Table 27 Event-free survival (using BICR per RECIST 1.1) (mITT population; EFS IA1 and EFS IA2)

	EFS IA1 DCO (10 Nov 2022)		EFS IA2 DCO (10 May 2024)	
	D + CTx (N = 366)	Pbo + CTx (N = 374)	D + CTx (N = 366)	Pbo + CTx (N = 374)
Total events, n (%) [a]	98 (26.8)	138 (36.9)	124 (33.9)	165 (44.1)
RECIST recurrence [b]	38 (10.4)	60 (16.0)	53 (14.5)	83 (22.2)
Progression that precludes surgery	26 (7.1)	35 (9.4)	28 (7.7)	36 (9.6)
PD post-surgery not undertaken for reasons other than progression	1 (0.3)	4 (1.1)	3 (0.8)	5 (1.3)
PD discovered upon attempting surgery	5 (1.4)	13 (3.5)	5 (1.4)	13 (3.5)
PD post-surgery not completed for reasons other than progression	0	5 (1.3)	0	5 (1.3)
Death due to any cause	29 (7.9)	30 (8.0)	38 (10.4)	33 (8.8)
Censored patients, n (%)	268 (73.2)	236 (63.1)	242 (66.1)	209 (55.9)
Censored RECIST recurrence/PD [c]	2 (0.5)	1 (0.3)	2 (0.5)	1 (0.3)
Censored death [c]	12 (3.3)	7 (1.9)	25 (6.8)	25 (6.7)
Event-free at time of analysis	239 (65.3)	214 (57.2)	199 (54.4)	169 (45.2)
No post-baseline disease assessments or no baseline data prior to neoadjuvant treatment	4 (1.1)	6 (1.6)	4 (1.1)	6 (1.6)
Withdrawn consent	11 (3.0)	8 (2.1)	12 (3.3)	8 (2.1)
Median event-free survival (months) [d]	NR	25.9	NR	30.0
95% CI for median event-free survival [d]	31.9, NR	18.9, NR	42.3, NR	20.6, NR
Event-free survival rate at 12 months (%) [d]	73.4	64.5	73.3	64.1
95% CI for event-free survival rate at 12 months [d]	67.9, 78.1	58.8, 69.6	68.1, 77.7	58.7, 69.0
Event-free survival rate at 24 months (%) [d]	63.3	52.4	65.0	54.4
95% CI for event-free survival rate at 24 months [d]	56.1, 69.6	45.4, 59.0	59.4, 70.0	48.7, 59.6
Event-free survival rate at 36 months (%) [d]	NC	NC	60.1	47.9
95% CI for event-free survival rate at 36 months [d]	NC	NC	53.9, 65.8	41.8, 53.8
Median (range) duration of follow-up in censored patients (months) [e]	11.66 (0 to 46.1)	11.73 (0 to 42.4)	26.68 (0 to 58.6)	25.69 (0 to 58.5)
HR [f]	0.68		0.69	
95% CI for HR [f]	0.53, 0.88		0.55, 0.88	
99.0101% CI for HR - adjusted for multiplicity [f, g]	0.48, 0.96		--	
2-sided p-value [g, h]	0.003902		--	

[a] 2 missed visit rule applied.
[b] New malignancy that is not NSCLC as confirmed by pathology, is not considered an EFS event.
[c] Occurred after 2 or more consecutive missed visits after last assessment.
[d] Calculated using Kaplan-Meier technique.
[e] Time from randomization to date of event/censoring.

[f] Calculated using a stratified Cox proportional hazards model adjusted for disease stage and PD-L1 expression status at baseline. A HR < 1 favours durvalumab + CTx, to be associated with longer EFS than placebo + CTx.
[g] Based on a Lan-DeMets alpha spending function with O'Brien Fleming boundary with the observed number of events, the boundary for declaring statistical significance is 0.9899% for a 5% overall 2-sided alpha.
[h] Calculated using a stratified log rank test adjusting for disease stage and PD-L1 expression status at baseline.
NC, not calculable at EFS IA1.
RECIST version 1.1.
DCO: 10 November 2022 (EFS IA1) and 10 May 2024 (EFS IA2).

Figure 13 Kaplan-Meier Plot of EFS (using BICR per RECIST 1.1) (mITT population, EFS IA2 - DCO: 10 May 2024)



A circle indicates a censored observation. 1 month = 30.4375 days. See corresponding
EFS is defined as the time from randomisation to the earliest of progression of disease that precludes surgery or progression with surgery not completed; local or distant recurrence; or death due to any cause. Patients who have not experienced an EFS event at the time of analysis are censored at the time of the last disease assessment. If the event occurs after two or more consecutive missed visits, the patient is censored at the last disease assessment prior to the two missed visits. A new malignancy that is not NSCLC, as confirmed by pathology, is not considered an EFS event. RECIST version 1.1. DCO: 10 May 2024 (EFS IA2).

Secondary endpoint – disease-free survival (DFS)

The key secondary endpoint of DFS did not meet the prespecified boundary to declare statistical significance at EFS.

At EFS IA2 DCO, DFS did not meet the prespecified boundary to declare statistical significance (p-value = 0.013652 [2-sided interim significance boundary = 1.2303%], based on a total 5% 2-sided alpha for DFS across interim and final analyses). However, a descriptive summary of the key secondary efficacy endpoint of DFS at EFS IA2 is provided below.

Table 28 Disease-free survival (using BICR per RECIST 1.1) (modified resected set, EFS IA2)

	D + CTx (N = 242)	Pbo + CTx (N = 231)
Total events, n (%) [a]	60 (24.8)	81 (35.1)
Disease recurrence	44 (18.2)	69 (29.9)
Death due to any cause	16 (6.6)	12 (5.2)
Censored patients, n (%)	182 (75.2)	150 (64.9)
Censored disease recurrence [b]	1 (0.4)	0
Censored death [b]	8 (3.3)	10 (4.3)

Disease-free at time of analysis	170 (70.2)	138 (59.7)
Withdrawn consent	3 (1.2)	2 (0.9)
Median disease-free survival (months) [c]	NR	NR
95% CI for median DFS [c]	NR, NR	41.5, NR
Disease-free survival rate at 12 months (%)[c]	81.0	74.1
95% CI for DFS rate at 12 months [c]	75.2, 85.5	67.8, 79.3
Disease-free survival rate at 24 months (%)[c]	75.1	62.4
95% CI for DFS rate at 24 months [c]	68.7, 80.4	55.2, 68.8
Disease-free survival rate at 36 months (%)[c]	71.2	61.4
95% CI for DFS rate at 36 months [c]	63.8, 77.3	54.0, 68.0
Median (range) duration of follow-up in censored patients (months) [d]	27.50 (0.8 to 55.7)	22.77 (0.9 to 55.3)
Hazard ratio [e]	0.66	
95% CI for hazard ratio [e]	0.47, 0.92	
98.7697% confidence interval for hazard ratio - adjusted for multiplicity [e, f]	0.43, 1.01	
2-sided p-value [g]	0.013652	

[a] Does not include events occurring after 2 missed RECIST assessments. A new malignancy that is not NSCLC, as confirmed by pathology is not considered a DFS event.

[b] Occurred after 2 or more consecutive missed visits after last post-surgery RECIST assessment.

[c] Calculated using Kaplan-Meier technique.

[d] Time from randomization to date of event/censoring.

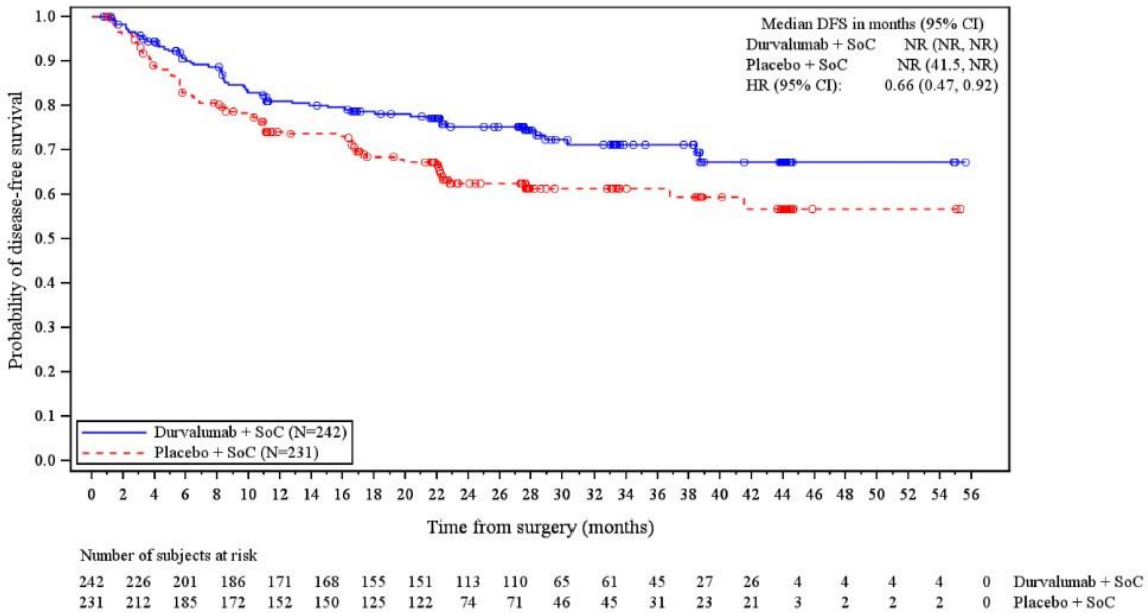
[e] Calculated using a stratified Cox proportional hazards model adjusted for disease stage and PD-L1 expression status at baseline. A hazard ratio <1 favours durvalumab + CTx, to be associated with longer DFS than placebo + CTx.

[f] Based on a Lan-DeMets alpha spending function with O'Brien-Fleming boundary with the observed number of events, the boundary for declaring statistical significance is 98.7697% for a 5% overall alpha.

[g] Calculated using a stratified log rank test adjusting for disease stage and PD-L1 expression status at baseline.

DCO: 10 May 2024.

Figure 14 Kaplan-Meier plot of DFS (using BICR per RECIST 1.1) (modified resected set)



A circle indicates a censored observation. 1 month = 30.4375 days.

DFS is defined as the time from surgery to the earliest of: disease recurrence, or death due to any cause. Subjects who have not experienced a DFS event at the time of analysis are censored at the time of the last disease assessment after surgical resection. If the event occurs after two or more consecutive missed visits, the subject is censored at the last disease assessment prior to the two missed visits. A new malignancy that is not NSCLC, as confirmed by pathology, is not considered a DFS event.

DCO: 10 May 2024.

Secondary endpoint - Major pathological response (MPR)

Table 22 **Major pathological response: Primary (interim mITT cohort at pCR IA) and final analyses (mITT population at EFS IA1])**

Arm	n	Number of patients with response [a]	Response Rate (%)	95% CI [b]	Comparison between arms [c]			
					Difference in proportions (%)	95% CI	Adjusted 99.9918% CI [d]	2-sided p-value
pCR IA: Interim (Confirmatory) Analysis [d]								
D + CTx	196	67	34.18	27.57, 41.28	20.07	11.85, 28.26	3.40, 36.42	0.000002
Placebo + CTx	206	29	14.08	9.64, 19.59				
EFS IA1: Final Analysis								
D + CTx	366	122	33.33	28.52, 38.42	21.03	15.14, 26.93	NA	--
Placebo + CTx	374	46	12.30	9.15, 16.06				

[a] Response is defined as having 10% or less residual viable tumor tissue in lung primary tumor at the time of resection as assessed by central pathology laboratory.
[b] CIs for response rate are calculated using Clopper-Pearson exact method.
[c] The analysis was performed using a CMH test stratified by disease stage (Stage II vs Stage III) and by PD-L1 expression status at baseline (TC < 1% vs ≥ 1%), using the stratification factors from the IXRS. A difference > 0 favors durvalumab + CTx. CIs for difference in proportions are computed using MN stratified method.
[d] Adjusted for multiplicity. Based on a Lan-DeMets alpha spending function with O'Brien Fleming boundary calculated using the actual number of patients at the interim vs the final analysis, the boundary for declaring statistical significance is 0.0082% for a total 0.5% 2-sided alpha. Corresponding CIs are shown.

As the IA was statistically significant per the multiple testing procedure, MPR was not re-tested for statistical significance at the final analysis.
DCO dates: 14 January 2022 (IA at pCR IA), and 10 November 2022 (final analysis, EFS IA1).
Source: Table 14.2.2.1.IA and Table 14.2.2.1.FA.

Secondary endpoint – Overall survival (descriptive analysis)

Although OS will only be formally tested following a positive DFS result, a descriptive summary of OS was provided at EFS IA1 to support the benefit-risk assessment (at 22.1% overall maturity for OS).

Table 29 IA1 Overall survival (Modified intent-to-treat)

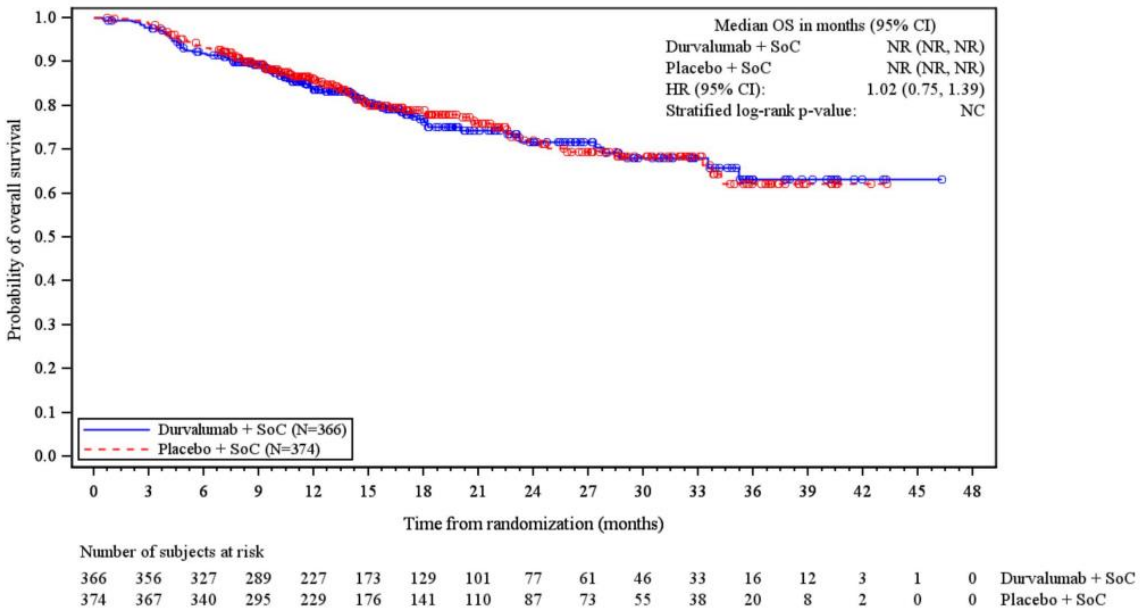
Study Code: D9106C00001 Phase III
EFS IA1 - Data Cut-off: 2022-11-10 - Unblinded Randomization
Table 14.2.5.1.IA1 Overall survival (Modified intent-to-treat)

Page 1 of 2

	Number (%) of subjects	
	Durvalumab + SoC (N=366)	Placebo + SoC (N=374)
Death, n (%)	81 (22.1)	82 (21.9)
Censored subjects, n (%)	285 (77.9)	292 (78.1)
Still in survival follow-up [a]	271 (74.0)	279 (74.6)
Terminated study prior to death [b]	14 (3.8)	13 (3.5)
Lost to follow-up	0	0
Withdrawal by subject	14 (3.8)	12 (3.2)
Other	0	1 (0.3)
Median overall survival (months) [c]	NR	NR
95% confidence interval for median overall survival [c]	NR, NR	NR, NR
Overall survival rate at 12 months (%) [c]	83.6	85.9
95% confidence interval for overall survival rate at 12 months [c]	79.2, 87.2	81.7, 89.1
Overall survival rate at 24 months (%) [c]	71.7	72.0
95% confidence interval for overall survival rate at 24 months [c]	65.2, 77.2	65.5, 77.5
Hazard ratio [d]	1.02	
95% confidence interval for hazard ratio [d]	0.75, 1.39	
2-sided p-value [e]	NC	

EFS IA1 - Data Cut-off: 2022-11-10 - Unblinded Randomization

Figure 15 Kaplan-Meier Plot of Overall Survival (mITT population; EFS IA1)



A circle indicates a censored observation. 1 month = 30.4375 days.

OS is defined as the time from date of randomization until death due to any cause. Patients who have not experienced an OS event at the time of analysis are censored at the date last known alive. Hazard ratio is calculated using a stratified Cox proportional hazards model adjusted for disease stage and PD-L1 expression status at baseline. A hazard ratio < 1 favours D + CTx, to be associated with longer OS than placebo + CTx. DCO: 10 November 2022. Source: Figure 14.2.5.2.IA1, AEGEAN CSR, Module 5.3.5.1

Updated OS analyses (IA2) DCO 10 May 2024

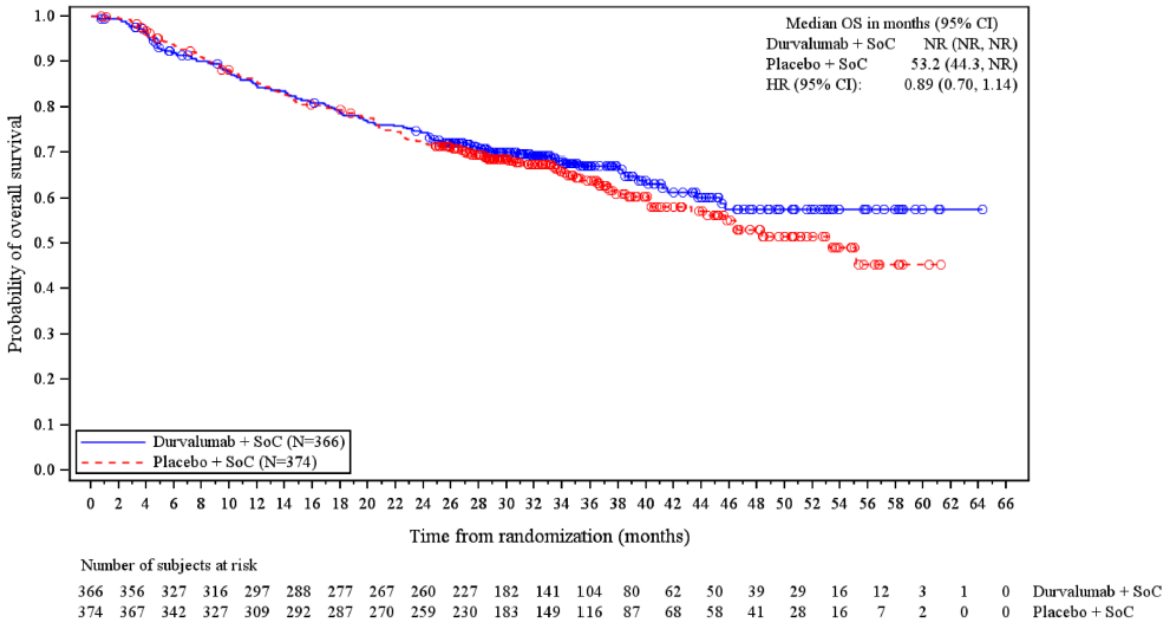
Table 30 Overall survival (mITT Population; EFS IA1 and EFS IA2)

	EFS IA1 DCO (10 Nov 2022)		EFS IA2 DCO (10 May 2024)	
	D + CTx (N = 366)	Pbo + CTx (N = 374)	D + CTx (N = 366)	Pbo + CTx (N = 374)
Death, n (%)	81 (22.1)	82 (21.9)	121 (33.1)	140 (37.4)
Censored patients, n (%)	285 (77.9)	292 (78.1)	245 (66.9)	234 (62.6)
Still in survival follow-up [a]	271 (74.0)	279 (74.6)	230 (62.8)	222 (59.4)
Terminated study prior to death [b]	14 (3.8)	13 (3.5)	15 (4.1)	12 (3.2)
Lost to follow-up	0	0	0	0
Withdrawn by patient	14 (3.8)	12 (3.2)	15 (4.1)	12 (3.2)
Other	0	1 (0.3)	0	0
Median OS (months) [c]	NR	NR	NR	53.2
95% CI for median OS [c]	NR, NR	NR, NR	NR, NR	44.3, NR
OS rate at 12 months (%) [c]	83.6	85.9	84.3	85.3
95% CI for OS rate at 12 months [c]	79.2, 87.2	81.7, 89.1	80.1, 87.7	81.2, 88.5
OS rate at 24 months (%) [c]	71.7	72.0	74.4	72.2

95% CI for OS rate at 24 months [c]	65.2, 77.2	65.5, 77.5	69.5, 78.6	67.3, 76.5
OS rate at 36 months (%) [c, d]	NC	NC	67.1	63.9
95% CI for OS rate at 36 months [c]	NC	NC	61.6, 71.9	58.4, 69.0
OS rate at 48 months (%) [c, d]	NC	NC	57.6	52.9
95% CI for OS rate at 48 months [c]	NC	NC	50.1, 64.3	45.7, 59.7
Median (range) duration of follow-up in censored patients (months) [e]	15.87 (0.8 to 46.3)	15.90 (0.7 to 43.3)	33.48 (0.8 to 64.3)	33.87 (0.7 to 61.3)
Hazard ratio [f]	1.02		0.89	
95% CI for hazard ratio [f]	0.75, 1.39		0.70, 1.14	

a Includes patients known to be alive at DCO.
b Includes patients with unknown survival status or patients who were lost to follow-up.
c Calculated using the Kaplan-Meier technique.
[d] OS rates at 36 and 48 months were not reported in the AEGEAN CSR (dated 10 July 2023).
[e] Time from randomization to date of event/censoring.
[f] Calculated using a stratified Cox proportional hazards model adjusted for disease stage and PD-L1 expression status at baseline. A HR < 1 favours D + CTx, to be associated with longer OS than placebo + CTx.
DCO: 10 November 2022 (EFS IA1) and 10 May 2024 (EFS IA2).
NC, not calculable at EFS IA1.

Figure 16 Kaplan-Meier Plot of OS (mITT population, EFS IA1 and EFS IA2) EFS IA1 (DCO: 10 November 2022) EFS IA2 (DCO: 10 May 2024)



A circle indicates a censored observation. 1 month = 30.4375 days.
OS is defined as the time from date of randomisation until death due to any cause. Patients who have not experienced an OS event at the time of analysis are censored at the date last known alive. Hazard ratio is calculated using a stratified Cox proportional hazards model adjusted for disease stage and PD-L1 expression status at baseline. A HR < 1 favours D + CTx, to be associated with longer OS than placebo + CTx. DCO: 10 November 2022 (EFS IA1) and 10 May 2024 (EFS IA2). Source: Figure 5, AEGEAN CSR Addendum 1.

Secondary endpoint – EFS in PD-L1 ≥ 1%

Study Code: D9106C00001 Phase III
EFS IA1 - Data Cut-off: 2022-11-10 - Unblinded Randomization
Table 14.2.3.3.IA1 Event-free survival based on BICR assessments (PD-L1 TC>=1% analysis set)

	Durvalumab + SoC (N=244)	Placebo + SoC (N=249)
Total events [a], n (%)	63 (25.8)	90 (36.1)
RECIST recurrence [b]	23 (9.4)	41 (16.5)
Progression that precludes surgery	15 (6.1)	22 (8.8)
PD after surgery not undertaken for reasons other than progression	0	3 (1.2)
Progressive disease discovered upon attempting surgery	2 (0.8)	9 (3.6)
PD after surgery not completed for reasons other than progression	0	4 (1.6)
Death due to any cause	23 (9.4)	18 (7.2)
Censored subjects, n (%)	181 (74.2)	159 (63.9)
Censored RECIST recurrence/PD [c]	0	0
Censored death [c]	7 (2.9)	6 (2.4)
Event-free at time of analysis	163 (66.8)	141 (56.6)
No post-baseline disease assessments or no baseline data	2 (0.8)	5 (2.0)
Lost to follow-up	0	0
Withdrawn consent	9 (3.7)	7 (2.8)
Discontinued study	0	0
Median event-free survival (months) [d]	NR	25.9
95% confidence interval for median event-free survival [d]	31.9, NR	19.5, NR
Event-free survival rate at 12 months (%) [d]	73.3	66.3
95% confidence interval for event-free survival rate at 12 months [d]	66.5, 78.9	59.3, 72.3
Event-free survival rate at 24 months (%) [d]	67.6	54.5
95% confidence interval for event-free survival rate at 24 months [d]	59.8, 74.3	46.2, 62.0
Hazard ratio [e]	0.65	
95% confidence interval for hazard ratio [e]	0.47, 0.90	
2-sided p-value [f]	0.009	

Secondary endpoint – Patient reported outcomes (PRO)

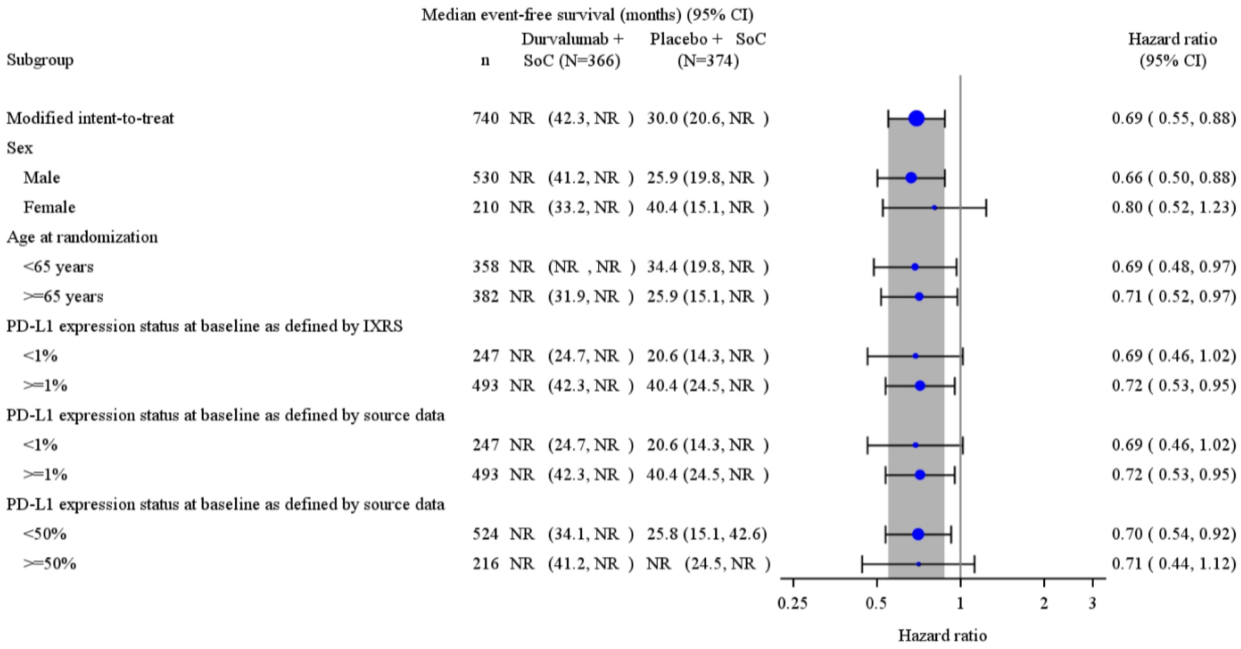
Based on patient responses to the EORTC QLQ-C30 questionnaire, the patient perception of their global health status and/or quality of life was noted in both treatment arms, with decreases in each functional domain consistently reported between treatment arms. Clinically meaningful improvements (i.e., a change from baseline score of ≥ 10 points) in the patient's overall perception of their quality of life and global health status were also reported in a notable proportion of patients, which was generally similar between treatment arms (range: 21% to 25% of patients in the D+CTx arm and 20% to 25% of patients in the placebo arm).

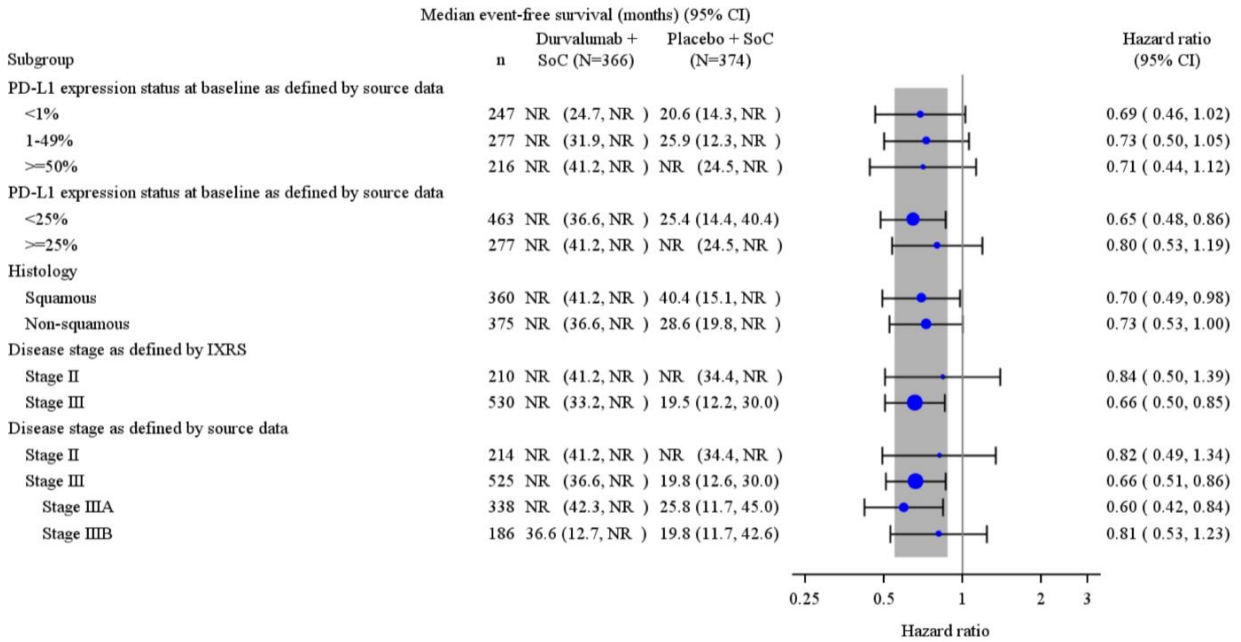
Based on patient feedback collected via EORTC QLQ-LC13 questionnaire, an improvement from baseline in coughing throughout the neoadjuvant period and pain in the chest at Week 12 was observed in both treatment arms, with no differences between arms. Conversely, an incremental worsening from baseline to Week 12 was observed for dyspnoea, pain in other parts, peripheral neuropathy, and alopecia, with no differences across arms; however, the majority of patients did not have clinically meaningful changes in assessed symptoms from baseline.

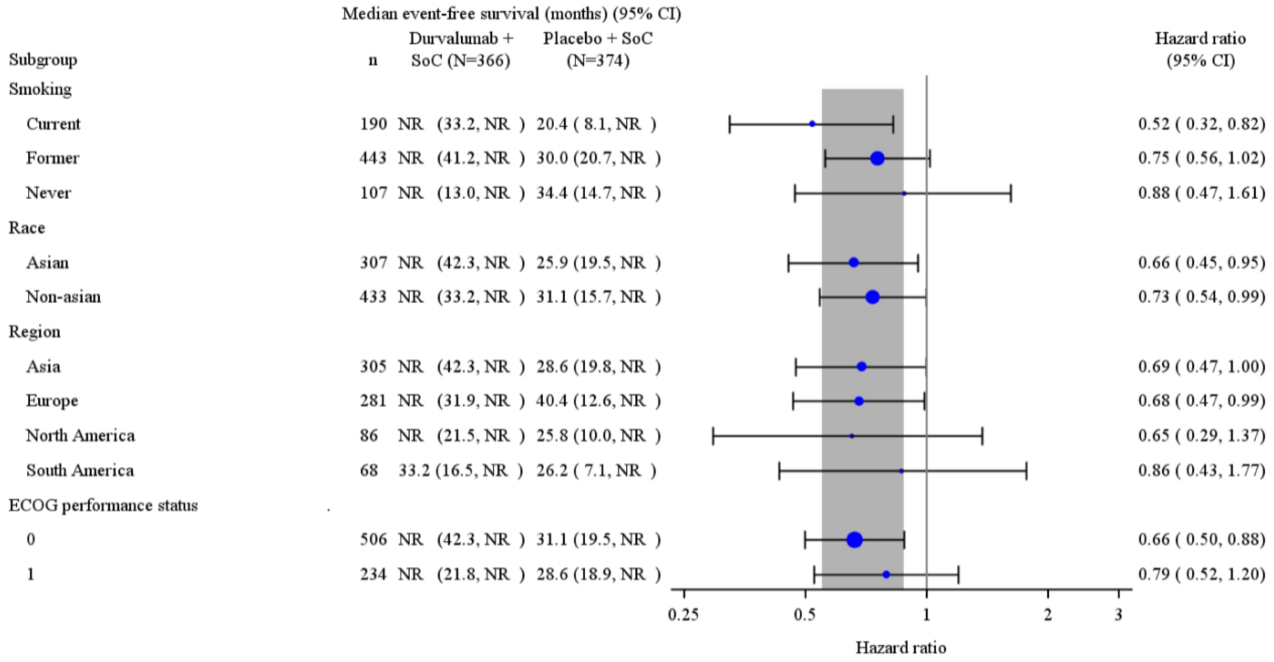
Overall, while some impact on patient perception of their health and/or quality of life was observed in both treatment arms in the neoadjuvant treatment period of the AEGEAN study, data was generally similar between treatment arms.

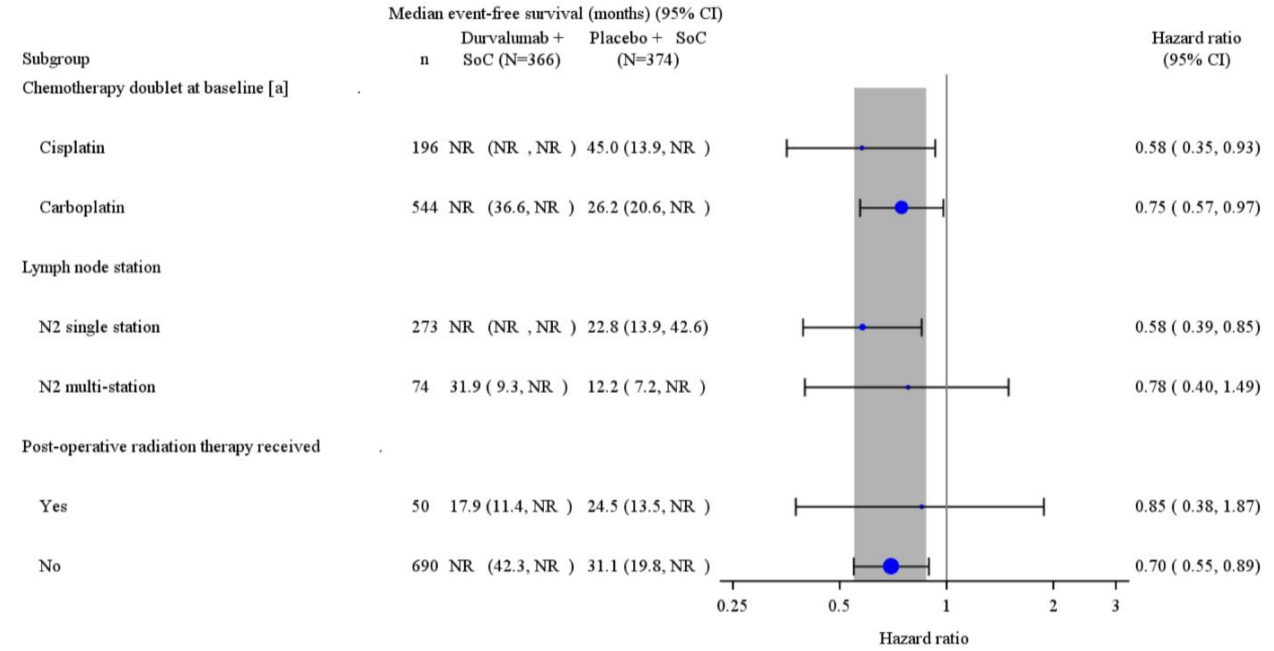
Ancillary analyses

Figure 17 EFS (using BICR per RECIST 1.1): Forest Plot by Subgroup (mITT population, EFS IA2)





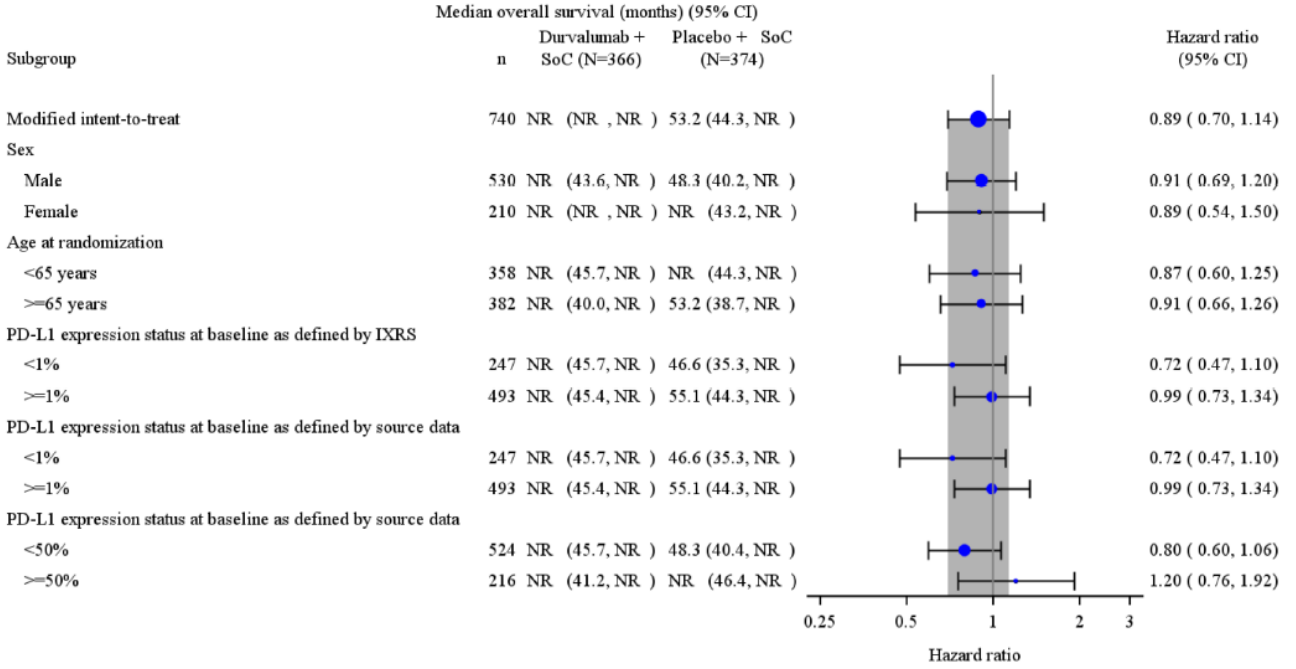




[a] Refers to the platinum base of the doublet (planned treatment).

Event-free survival is defined as the time from randomization to the earliest of: progression of disease that precludes surgery or progression discovered upon attempting surgery resulting in surgery not being completed; local/distant recurrence; or death. Does not include events occurring after 2 missed RECIST assessments. A new malignancy that is not NSCLC, as confirmed by pathology, is not considered an EFS event. Hazard ratio (D + CTx: placebo + CTx) and 95% CI. Grey band represents the 95% CI for the mITT population, difference in proportions. DCO: 10 May 2022.

Figure 18 OS: Forest plot by subgroup (mITT population, EFS IA2)



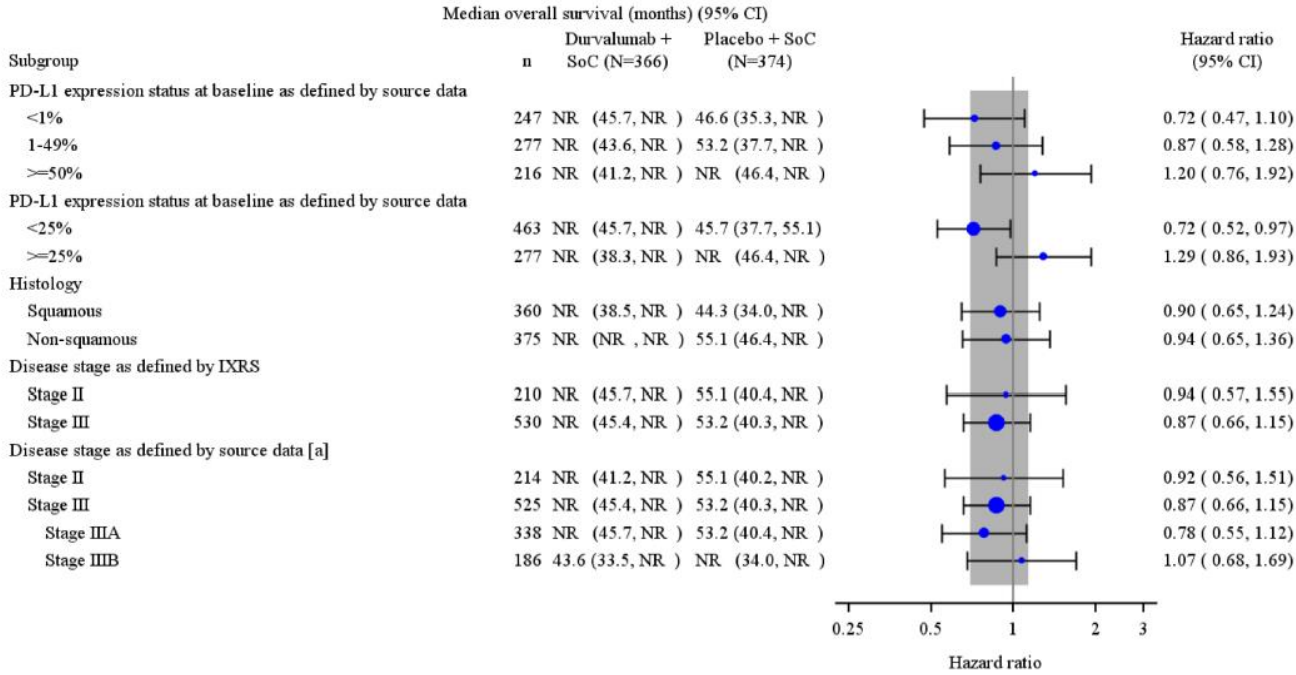
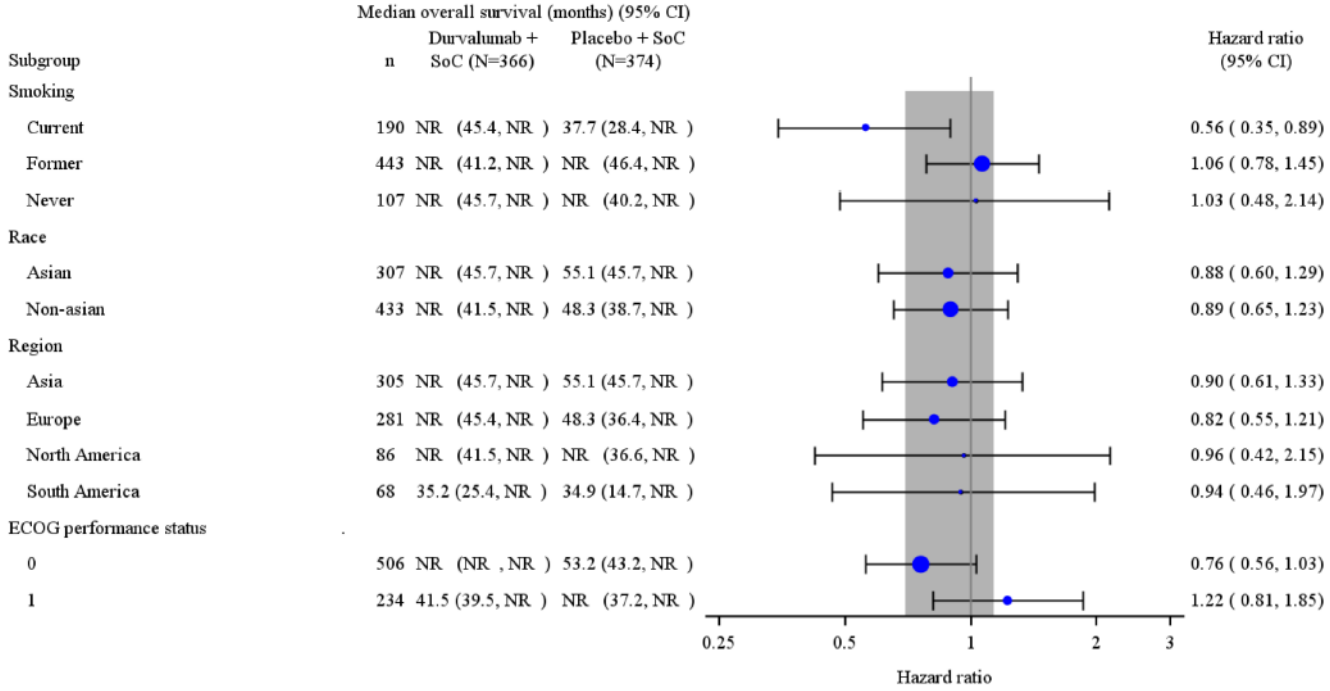


Figure 18 OS: Forest plot by subgroup (mITT population, EFS IA2)



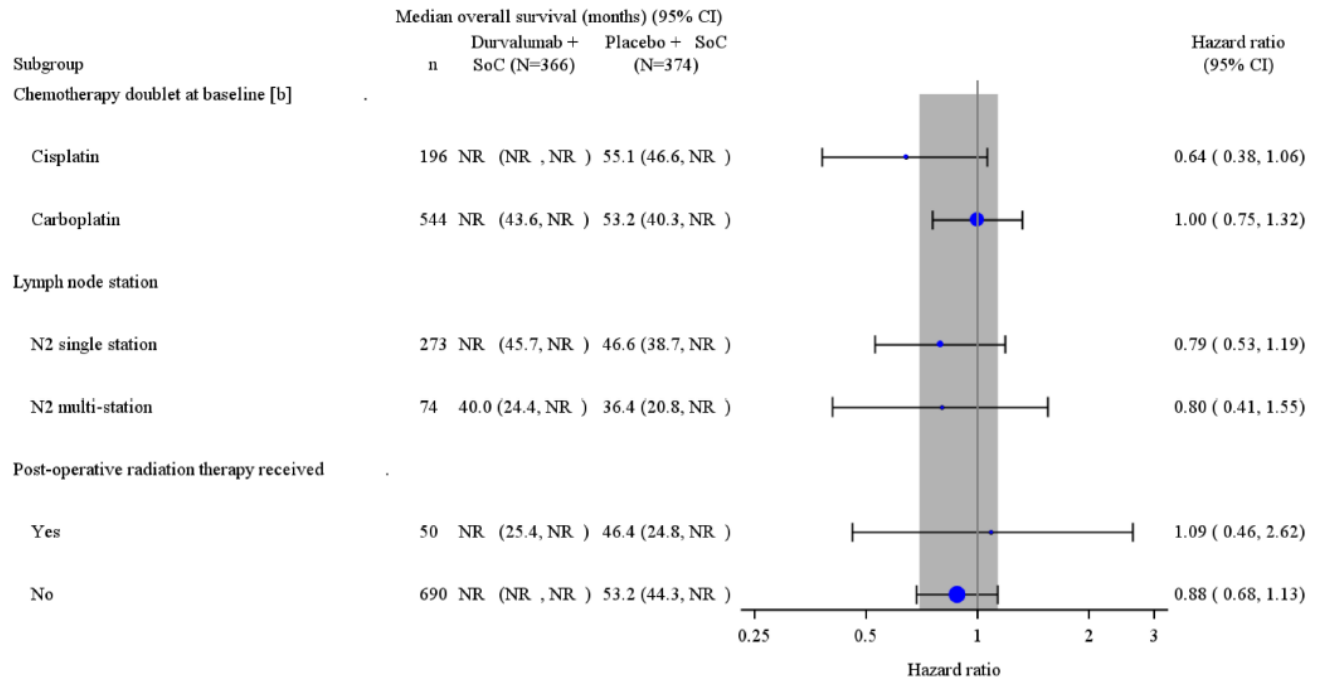
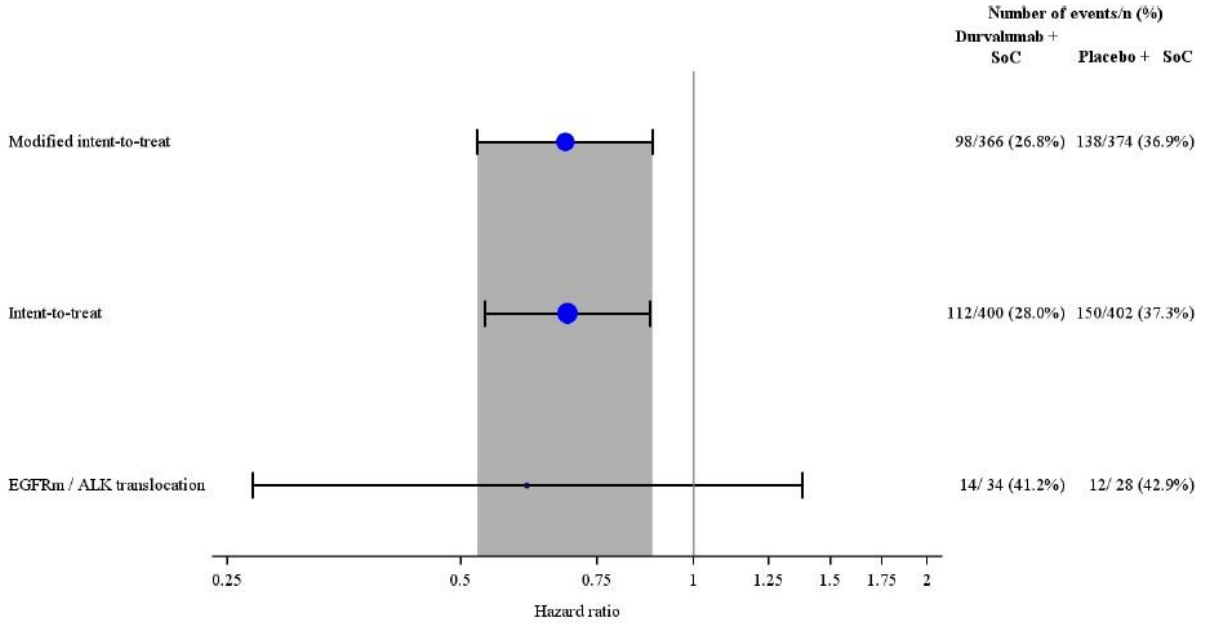
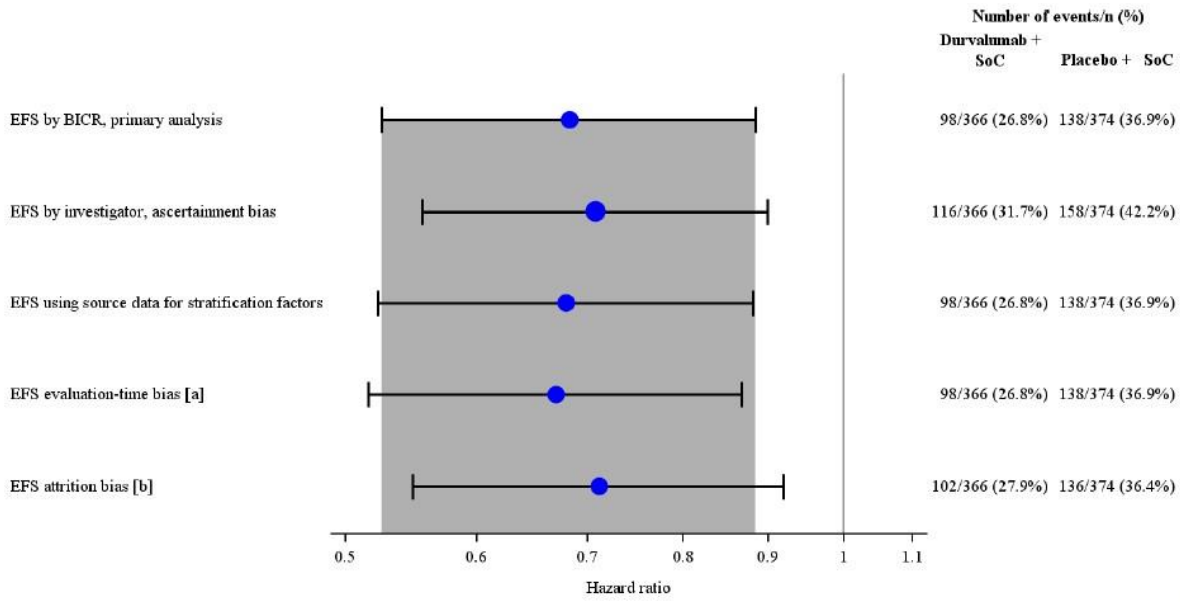


Figure 19 Event-free survival (using BICR per RECIST 1.1): Forest plot by analysis population (EFS IA1)



HR and 95% CI. A HR < 1 favours D + CTx.
Size of circle is proportional to the number of events. Grey band represents the 95% CI for the mITT population HRs.
The CIs for the ITT population and mITT population were calculated using the stratified Cox proportional hazard model. The CI for the subset of patients with EGFRm/ALK gene rearrangements was estimated without stratification .
EFS was defined as the time from randomization to the earliest of: progression of disease that precludes surgery or progression with surgery not completed; local or distant recurrence; or death due to any cause. Does not include events occurring after 2 missed RECIST assessments. A new malignancy that was not NSCLC, as confirmed by pathology, was not considered an EFS event
DCO: 10 November 2022.

Figure 20 Event-free survival (using BICR per RECIST 1.1): forest plot by primary and sensitivity analyses (mITT population; EFS IA1)



a. Event time is the midpoint between time of progression and previous evaluable disease assessments, or for those whose death was treated as an EFS event, date of death is used to derive the EFS time used in analysis.
b. Analysis uses actual event times, rather than censored times, for patients with an EFS event immediately following ≥ 2 non-evaluable disease assessments are included. patients who take subsequent therapy prior to their last evaluable RECIST assessment, progression

that precludes surgery/results in incomplete surgery or death are censored at their last evaluable assessment prior to taking subsequent therapy.

HR (durvalumab + CTx: placebo + CTx) and 95% CI. A HR < 1 favours durvalumab + CTx, to be associated with longer EFS than placebo + CTx. Size of circle is proportional to the number of events. Grey band represents the 95% CI for the primary analysis HR. RECIST version 1.1.

Summary of main study(ies)

The following tables summarise the efficacy results from the main studies 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 31 Summary of efficacy for the AEGEAN trial

Title: A Phase III, Double-blind, Placebo-controlled, Multi-center International Study of Neoadjuvant/Adjuvant Durvalumab for the Treatment of Patients with Resectable Stages II and III Non-small Cell Lung Cancer (AEGEAN)			
Study identifier	*Study Code:* D9106C00001		
Design	Phase III, randomised, multicentre, double-blind, comparative global study to determine the efficacy and safety of durvalumab in combination with platinum-based chemotherapy prior to surgery (neoadjuvant) followed by durvalumab monotherapy post-surgery (adjuvant) for treatment of patients with resectable stage II and (select) III non-small cell lung cancer.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		06 Dec 2018 (first subject in) to 10 Nov 2022 (data cut-off [DCO]; ongoing) Not applicable Not applicable
Hypothesis	Superiority		
Treatments groups	D + Chemotherapy (CTx)		Durvalumab 1500 mg in combination with chemotherapy (Q3W for 4 cycles) prior to surgery, followed by durvalumab 1500 mg monotherapy (Q4W for 12 cycles) post-surgery.
	Placebo + CTx		Placebo in combination with chemotherapy (Q3W for 4 cycles) prior to surgery, followed by placebo (Q4W for 12 cycles) post-surgery.
Endpoints and definitions	Primary endpoints	Pathological complete response (pCR)	The absence of any residual viable tumour at the time of surgical resection in the primary lung lesion and lymph nodes.
		Event-free survival (EFS)	The time from randomisation to the earliest of the following events: (a) Date of the Response Evaluation Criteria in Solid Tumours (RECIST) 1.1 assessment documenting local or distant recurrence of lung cancer using blinded independent central review (BICR) per RECIST 1.1 (after the date of surgery); (b) Date of death due to any cause; (c) Date of determination that progressive disease (PD) precludes surgery, or for patients who do not have surgery for a reason other than progression (d) Date of first attempt at surgery where PD, discovered and reported by the Investigator, resulted in the surgery not being completed, or for patients who do not complete surgery for a reason other than progression
	Secondary endpoints	Major pathological response (MPR)	10% or less residual viable tumour tissue in lung primary tumour at the time of resection.
		Disease-free survival (DFS)	The time from the date of surgery until the first of: (a) The date of disease recurrence (local or distant) (using BICR per RECIST 1.1). (b) Date of death due to any cause.

		Overall survival (OS)	The time from the date of randomisation until death due to any cause
DCO	10 Nov 2022 (first interim EFS analysis [EFS IA1]		
Results and Analysis			
Analysis description	**Primary and key secondary analyses**		
Analysis population and time point description	All randomised patients were included in the intent-to-treat (ITT) population. The primary endpoint efficacy analyses were conducted on the modified intent-to-treat (mITT) population, which includes all patients in the ITT population, excluding those whose tumours EGFRm/ALK gene rearrangements.		
	mITT population at EFS IA1 (DCO: 10 Nov 2022)		
	Treatment group	D + CTx	Placebo + CTx
	Number of subjects	366	374
	pCR (Response Rate [%])	17.21	4.28
	95% CI [a]	13.49, 21.48	2.46, 6.85
	EFS (median, months) [b]	NR	25.9
	95% CI [b]	31.9, NR	18.9, NR
	MPR (Response Rate [%])	33.33	12.30
	95% CI [a]	28.52, 38.42	9.15, 16.06
	OS (median, months) [b]	NR	NR
	95% CI [b]	NR, NR	NR, NR

	mITT population at EFS IA1 (DCO: 10 Nov 2022)		
	Primary endpoint: pCR	Comparison groups [c]	D + CTx vs. Placebo + CTx
		Difference in proportions (%)	12.96
		95% CI	8.67, 17.57
	Primary endpoint: EFS	Comparison groups	D + CTx vs. Placebo + CTx
		HR [e]	0.68
		95% CI [e]	0.53, 0.88
		99.0101% CI [e, g]	0.48, 0.96
		2-sided p-value [f]	0.003902
	Secondary endpoint: MPR	Comparison groups [c]	D + CTx vs. Placebo + CTx
		Difference in proportions (%)	21.03
		95% CI	15.14, 26.93
	Secondary endpoint: OS	Comparison groups	D + CTx vs. Placebo + CTx
		HR [h]	1.02
		95% CI [h]	0.75, 1.39
Notes	CI = confidence interval, HR = hazard ratio, NR = not reached.		

Analysis performed across trials (pooled analyses and meta-analysis)

Not applicable.

Clinical studies in special populations

Table 32 Clinical studies in special populations

	Controlled Trials
Severe Renal impairment* patients (Subjects number /total number)	0
Severe Hepatic impairment** patients (Subjects number /total number)	0
Paediatric patients <18 years (Subjects number /total number)	0
Older patients; Age 65-74 (Subjects number /total number)	D + CTx: 160/401 Placebo + CTx: 164/398
Age 75-84 (Subjects number /total number)	D + CTx: 47/401 Placebo + CTx: 36/398
Age 85+ (Subjects number /total number)	D + CTx: 2/401 Placebo + CTx: 1/398

The definitions for hepatic impairment are as follows: normal hepatic function = BIL ≤ULN and AST ≤ULN; mild hepatic impairment = BIL ≤ULN and AST >ULN or BIL >1 to 1.5 × ULN and any AST; moderate hepatic impairment = BIL >1.5 to 3 × ULN and any AST; and severe hepatic impairment = BIL >3 × ULN and any AST (where ULN of BIL is 1.9 IU/L and ULN of AST is 34 IU/L).

The definitions for renal impairment are as follows: normal renal function: CrCL ≥90 mL/min, mild renal impairment: CrCL = 60 to 89 mL/min, moderate renal impairment: CrCL = 30 to 59 mL/min, and severe renal impairment: CrCL = 15 to 29 mL/min.

Supportive study(ies)

Not applicable.

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The efficacy of durvalumab (D) for the perioperative treatment of resectable NSCLC is solely based on the pivotal AEGEAN study. This is an ongoing, phase 3, double-blind, placebo-controlled, randomised, multi-centre study, which included patients with resectable stage IIA-IIIB NSCLC of either squamous or non-squamous histology and regardless of PD-L1 status. Patients were stratified by disease stage (stage II vs stage III) and PD-L1 expression (TC<1% vs TC≥1%) according to the VENTANA PD-L1 SP263 assay.

The proposed regimen is durvalumab 1500 mg Q3W in combination with histology-based chemotherapy (4 cycles) prior to surgery, followed by durvalumab 1500 mg monotherapy Q4W for up to 12 cycles post-surgery (i.e., 16 cycles total, ≈1 year). The proposed posology is the same currently approved in other indications and the duration of treatment is aligned with other clinical trials in the same setting and therefore deemed acceptable.

Study design

The MAH received SA from the CHMP in 2018. Overall, the MAH followed the CHMP's advice, notably including EFS as primary endpoint, which is commended. In principle, the RCT design is endorsed, but the chosen trial design does not allow a separate assessment of the contribution to the efficacy of the pre-operative part versus the adjuvant post-operative part, and especially whether one or the other part could have been omitted, likely results in similar clinical outcomes without exposing patients to unnecessary toxicity. This is one of the main limitations in the design of this trial, and this had been already pointed out by the CHMP in the SA provided in 2018, recommending a more complex design (e.g. a two-stage randomization design, with a second randomization after surgery). Crossover between the study arms was not allowed, which is endorsed, since overall survival results are considered key for the B/R assessment.

According to the latest version of the protocol (version 5.0), this study had two dual primary endpoints: pathological complete response (pCR) and event-free survival (EFS), both assessed in a blinded manner (i.e., by BICR in the case of EFS, and by blinded central pathology review in the case of pCR). It is to note that pCR is not considered an ideal primary endpoint in the neoadjuvant setting, since its correlation to the clinically relevant outcomes in resectable NSCLC –such as EFS and OS– remains rather uncertain despite emerging data. Since pCR is not yet a validated surrogate endpoint in NSCLC and therefore cannot serve for regulatory decision making as standalone endpoint, it is considered supportive, since it provides information about treatment's anti-tumour activity. On the contrary, EFS is considered an adequate endpoint to measure clinical benefit in this (neo)-adjuvant setting, and its inclusion as primary endpoint follows the CHMP recommendation in the SA provided in 2018. However, it is noted that according to the Guideline on the evaluation of anticancer medicinal products in man (EMA/CHMP/205/95 Rev. 6), "*when EFS is found to be a justified primary endpoint, it is of importance that study data are analysed only when sufficiently mature, i.e. when it is foreseen that the EFS plateau is stable or when additional disease recurrence is rare*". Importantly, the scientific advice provided in 2018 already stated that a clinically relevant effect on EFS supported by an OS trend, or no apparent detriment on OS would be needed for approval purposes.

The key secondary endpoints were disease-free survival (DFS), major pathological response (MPR) and overall survival (OS). The secondary objectives and endpoints and their prioritisation are acknowledged, but not fully endorsed. The fact that testing DFS in a highly selected population (the "resected" dataset, i.e., those patients who did not have any EFS events preventing surgery, and whose surgical outcome was either R0 or R1) was prioritised over OS in the mITT –the population intended for treatment according to the proposed indication– in the hierarchical testing is considered inappropriate, as the OS analysis is considered to bring more relevant information from the clinical and regulatory perspectives. Accordingly, any results from DFS are not considered relevant to support the proposed (neo)adjuvant indication as they inherently portray selection bias. Aligned with the abovementioned views on pCR, the secondary objective/endpoint of MPR is also questioned regarding its surrogacy relation to any clinically meaningful outcome.

Regarding statistical methods, the MAH has described the assumptions considered to calculate the sample size of approximately 800 patients in the ITT and mITT population randomized 1:1. The MAH used a hierarchical MTP, starting with testing the 2 primary endpoints (i.e., pCR and EFS) and then the (key) secondary endpoints of DFS and OS. The study was considered to be positive if either of those two primary endpoints were statistically significant (i.e., the primary endpoints were dual).

Conduct of the study

Patients were recruited from 183 sites across 28 countries during approximately 4 years: 802 in the ITT population and 740 in the mITT population (366 in the durva arm and 374 in the placebo arm), which is the primary analysis population for the efficacy analyses.

The overall conduct of the study was not optimal, because the primary endpoints were amended while the study was ongoing. First, the primary endpoint was changed from MPR (major pathological response) to pCR and EFS (previously a secondary endpoint). Although such change in the primary objectives of an ongoing study is usually not appropriate, it can be agreed that pCR and/or MPR are not valid surrogates of OS in resectable NSCLC, and thus likely unsuitable for registration, which was also pointed out by the scientific advice from CHMP in 2018. Therefore, the addition of EFS as primary endpoint is considered relevant for the assessment of the benefit-risk of the applied indication. In this case, it is considered reassuring that the pivotal study is double-blinded and placebo-controlled and that EFS is assessed by BICR. Later, in April 2021, the existing secondary endpoint of OS was reclassified as a key secondary endpoint, which is approximately 3 years into the study. This change did not result in any changes in the testing hierarchy and/or sample size.

As per Protocol V4 (15-APR-2021), patients with known EGFR/ALK mutations were no longer eligible to participate in the AEGEAN trial. The exclusion of these patients is justified by external data and this is followed. However, it is important to realise that the analyses sets were modified upon this exclusion: the mITT, in which the primary analysis was to be performed (and define the targeted population as per the proposed therapeutic indication), selected patients without such mutations, acknowledging that a number of patients had already been recruited by the time this major protocol amendment took place. EFS results of the EGFR/ALK+ subgroup and the ITT are discussed below.

Regarding protocol deviations, their percentage was low (below 5%) and very similar across both treatment arms, rendering unlikely that they impacted the observed results.

The median age for the durvalumab + chemo arm (D+CTx) in the mITT was 65 years, and 85% of the included patients were more than 50 years of age, while the majority were male (68.9%) and ~39% were from Asia. 56.3% were white and ~13.9% had never smoked. There were numerically more males in the placebo arm (74.3% vs 68.9%), but this difference is not considered to have had a major impact on the study results. Overall, the baseline demographic characteristics were well-distributed between the treatment arms and considered to adequately reflect the targeted patient population.

Disease characteristics for the active D+CTx arm in the mITT show that most patients were ECOG PS 0 (68.6%) of advanced stage (stage III in 72.1%), while approximately half of the patients had tumours of squamous histology (46.2%) or non-squamous histology (53.6%). It is noted that a third of the included patients in the D+CTx arm had tumours with PD-L1 expression <1% (33.3%), while the remaining was PD-L1 ≥1%, and that there were apparently no missing data on PD-L1 status. These proportions of PD-L1 expression are in line with what is expected from patients with resectable NSCLC. The mentioned disease characteristics were fairly well distributed between the treatment arms.

The surgical details show that in the D+CTx arm of the mITT population, approximately 80% of the patients underwent surgery (80.6%), while 77.6% completed surgery. It can be hypothesised that if the surgical outcome in terms of pCR is significantly better in one of the arms, there would also be better outcomes in terms of surgical margins (higher proportions of R0 vs. the control arm). Interestingly, the surgical outcome in terms of margins (proportions of R0, R1 and R2) in AEGEAN was comparable in both arms of the treatment.

The main reason for not undergoing surgery in both treatment arms was disease progression. This can be seen as concerning, as all included patients had to have resectable disease assessed at a multi-disciplinary tumour board according to the inclusion criteria, and this could be considered a 'loss of chance of a cure' for patients who could not complete surgery after starting neoadjuvant treatment. As per study design, both arms received neo-adjuvant chemotherapy, which is not an established standard of care in this setting. It is thus impossible to determine, whether a higher proportion of patients from each arm would have undergone surgery straight after the multidisciplinary committee

decision (by sparing patients from the neoadjuvant approach). The most common reasons for not undergoing surgery were disease progression, adverse events, deaths and subject/investigator decision and the proportion of patients not undergoing surgery in AEGEAN is similar to that observed in other recent trials of neoadjuvant/perioperative immunotherapy, in which patients had a similar stage distribution to AEGEAN. Furthermore, across these recent studies, including AEGEAN, PD has consistently been identified as the most common reason for patients not proceeding to surgery. Such study design including a neoadjuvant phase in both treatment arms does not allow to balance the concerns about certain patients being unable to undergo surgery for any reason, with the potential benefit of the neoadjuvant phase in terms of surgical outcomes and long-term survival.

Efficacy data and additional analyses

At the first planned interim analysis for EFS (EFS IA1) on DCO 10-NOV-2022, the median follow-up time for EFS was approximately 9 months. Updated data from the third pre-planned interim analysis of AEGEAN (EFS IA2; DCO: 10 May 2024) were also provided during the procedure.

Pathological complete response (**pCR**), one of two primary endpoints, was formally met. At the time of EFS IA1, the difference was 12.96%, as the pCR was 17.21% in the D+CTx arm versus 4.28% in the placebo arm. This difference in pCR was in line with the primary analysis of pCR (DCO 14-JAN-2022), which had met the prespecified boundary for declaring a statistically significant improvement of pCR. However, the surrogacy of pCR after neo-adjuvant immuno-chemotherapy for any clinically relevant outcome such as EFS and OS is not considered to be established. At this time, there is limited scientific proof that improvement of pCR is predictive of long-term outcomes after the addition of immune checkpoint inhibition (such as durvalumab) and none of the pathologic response proposed endpoints (pCR, MPR) have been accepted as pivotal evidence for regulatory decision making in the neo(adjuvant) NSCLC setting in the EU (EMA/CHMP/205/95 Rev.6 and appendix 4: EMA/CHMP/703715/2012 Rev. 2).

The other primary endpoint, EFS by BICR, was also statistically significantly improved at the time of the primary analysis in the mITT [HR 0.68 (95%CI: 0.53; 0.88)], noting that median EFS was not reached (95%CI: 31.9; NR) in the D+CTx arm vs 25.9 months in the placebo arm. Given that EFS was statistically significant at EFS IA1, the provided updated analysis of EFS at EFS IA2 is descriptive (without statistical testing) and the median duration of EFS follow-up is 25.9 months at the EFS IA2 DCO with the median duration of EFS follow-up being similar for both arms. At the EFS IA2 DCO, the EFS HR was 0.69 (95%CI: 0.55, 0.88), which is consistent with EFS IA1. The median EFS was 30.0 months (95%CI: 20.6, not reached) in the placebo arm and was not reached (95%CI: 42.3; NR) in the D+CTx arm, which is clinically relevant in the targeted setting.

Several sensitivity analyses (for evaluation-time bias, attrition bias, ascertainment bias, non-proportional hazards, and for the primary treatment comparison using PD-L1 expression status at baseline (TC < 1% vs. TC ≥ 1%) and disease stage (stage II vs. stage III) as defined by source data (instead of IXRS) as stratification factors) were conducted, showing robustness in the treatment effects.

DFS was a secondary endpoint, but it did not meet the prespecified boundary to declare statistical significance at the time of EFS IA1. A descriptive analysis was submitted during the procedure, based on EFS IA2 DCO. As discussed in the study design, DFS was analysed in a highly selected population (the "resected" dataset), so conclusions from these results cannot be generalised to the overall population of the trial (ITT) nor the one intended for a (neo)adjuvant indication for added durvalumab (mITT).

Since **OS** was formally tested following a positive DFS result, only a descriptive summary of OS was provided. After approximately 22% OS events, which were equally distributed between both treatment arms, the median OS was not reached in either arm (NR), HR 1.02 (95%CI: 0.75; 1.39). Updated OS data were provided during the procedure with a median duration of OS follow-up of 33.64 months at the EFS IA2 DCO and the overall OS maturity is now 35.3%. The updated OS data showed a HR of 0.89 (95%CI: 0.70, 1.14) when comparing the D + CTx arm to the placebo arm. OS data are still considered immature and the 95% CI is overlapping 1, however no apparent detriment on OS is observed and it is reassuring that the point estimate for the OS HR is going in the right direction since the first interim analysis. The MAH has agreed to provide final OS data post-authorisation as a PAES (Annex II condition), in order to verify the impact of the intervention on overall survival and confirm the previous efficacy assumption, in the context of an approval based on EFS.

The MAH has demoted major pathological response (**MPR**) from a primary to a secondary endpoint. A statistically significant difference was shown as the MPR in D+CTx arm was 34.18% vs 14.08% in the placebo arm; with a 20.07% difference. The clinical value of MPR and whether it could be used as a surrogate for the clinically relevant time-to-event endpoints such as EFS and OS in the NSCLC setting, is unclear. As a consequence, it is not reflected in the SmPC.

PD-L1 expression remains an important predictive biomarker for immune checkpoint inhibitors across diverse NSCLC settings. As a matter of fact, in the EU, the indication for durvalumab in the locally advanced unresectable NSCLC setting after chemoradiotherapy is restricted to the PD-L1 ≥ 1% population, so EFS analyses across multiple PD-L1 cut-offs are considered a crucial subgroup analysis in the AEGEAN study. The HR for EFS by BICR in the PD-L1 ≥1% population was 0.65 (95%CI 0.47; 0.90), which is in line with the mITT analysis (HR 0.68 95%CI [0.53;0.88]), and the median EFS was not reached in the D+CTx arm vs 25.9 months in the placebo arm. A quite large subgroup of patients with tumoural PD-L1 expression<1% were included in the study (n=247), and a subgroup analysis on these patients shows the point estimate for the EFS HR for this subgroup was 0.76 (95%CI: 0.49; 1.17). This indicates that the beneficial EFS effect from added (neo)adjuvant durvalumab does not correlate with tumoural PD-L1 expression.

Subgroup analyses of EFS is discussed based on data from EFS IA2, where a larger number of events allowed more precision in the estimation of event within subgroups. Only some slight deviations are observed (e.g. Stage II patients - HR: 0.82 [95%CI: 0.49, 1.34]; Stage IIIB patients – HR: 0.81 (95%CI: 0.53, 1.23); which are likely related to the lower number of events in those subgroups (214 in Stage II and 186 in Stage IIIB). No differences seem to be observed with regards to the PD-L1 expression.

OS subgroup results showed some inconsistencies. It is noted that patients with higher PD-L1 expression levels seem to have worse outcomes than patients with lower PD-L1 expression levels; which has no biological plausibility and therefore it is considered to be a chance finding. Some other subgroups such as Stage IIIB, former smokers, and ECOG 1 also seem to have slightly worse outcomes, although no firm conclusions can be drawn due to the low number of events and wide CIs. Another observed difference was the subgroup of patients having received prior carboplatin [HR: 1.00 (95%CI: 0.75, 1.32)] vs. prior cisplatin [HR: 0.64 (95%CI: 0.38, 1.06)]. This difference cannot be explained by the lower number of patients included in the carboplatin subgroup; since the number of patients having received carboplatin was notably higher than the number of patients having received cisplatin (N=544 carboplatin; N=195 cisplatin). Although the reasons for such observation remain unclear, a possible explanation could be that the patients who received carboplatin instead of cisplatin were not fit enough as to receive cisplatin; and, therefore, the carboplatin subgroup might reflect the OS outcomes of a frailer population.

PRO data were collected as a secondary endpoint. Since the PRO endpoints were not multiplicity-protected, clinical meaningfulness of PRO data is not considered relevant to be stated in the SmPC.

Wording of the indication

Known presence of EGFR mutations or ALK rearrangements in tumoral tissue was eventually made an exclusion criterion as per protocol amendment 3 (V4), but a number of patients with these genetic aberrations were initially recruited and treated per protocol. As per statistical analyses, the ITT population included all recruited patients, but the modified ITT (mITT), in which the primary endpoints were tested, only included patients without EGFR or ALK mutations.

The revised proposed indication for Imfinzi based on this submission is:

IMFINZI in combination with platinum-based chemotherapy as neoadjuvant treatment, followed by IMFINZI as monotherapy as adjuvant treatment, is indicated for the treatment of adults with resectable NSCLC at high risk of recurrence and no EGFR mutations or ALK rearrangements (for selection criteria, see section 5.1).

As only a very small number of patients had unknown status for EGFR/ALK/KRAS mutations; i.e. 5 patients (0.7%) with unknown EGFR status; and 12 patients (1.6%) with unknown ALK rearrangement status; it is not expected that those patients could have impacted the overall trial results. The wording of the indication has therefore been revised from 'no **known** EGFR mutations or ALK rearrangements' to state 'no EGFR mutations or ALK rearrangements' .Disease with high risk of recurrence was defined in the study protocol as resectable (Stage IIA to select [i.e., N2] Stage IIIB) disease (according to Version 8 of the IASLC Staging Manual in Thoracic Oncology 2016), patients were also required to be candidate for lobectomy, sleeve resection, or bilobectomy at the time of screening. These criteria are reflected in section 5.1 of the SmPC.

2.4.4. Conclusions on the clinical efficacy

The results from the single pivotal AEGEAN study show statistically significant improvement in pCR and EFS by BIRC, which were dual primary endpoints. Although updated EFS is partly mature, the EFS benefit is considered clinically relevant. Updated OS showed a HR of 0.89 (95%CI: 0.70, 1.14), with a median follow up of 33.64 months, OS data are not considered fully mature and the 95% CI's are including 1, but the CHMP finds that there is not apparent detriment on OS observed and that it is reassuring that the point estimate for the OS HR is improved since the first interim analysis. In the context of a treatment administered in a setting where patients are eligible for treatment with curative intent, further characterisation of the treatment effect on overall survival is deemed key to the benefit risk.

The following measures are considered necessary to address issues related to efficacy:

Annex II.D Condition: PAES: In order to further characterise the long-term efficacy of IMFINZI in combination with platinum-based chemotherapy as neoadjuvant treatment, followed by IMFINZI as monotherapy as adjuvant treatment, for the treatment of adults with resectable NSCLC at high risk of recurrence, the MAH should submit the results of the final OS analysis from the study D9106C00001 (AEGEAN), a phase III, double-blind, placebo-controlled multicentre international study.

With a due date in Q2 2029

2.5. Clinical safety

Introduction

Assessment of the safety profile of durvalumab in combination with platinum-based chemotherapy as neoadjuvant treatment, followed by (adjuvant) durvalumab as monotherapy after surgery, in adults with resectable NSCLC rearrangements is based on safety data from the pivotal, phase III trial, AEGEAN (IA2, DCO: 10 May 2024).

Supportive safety data are provided in the form of pooled safety data ("D Pan-Tumour Pool") from 13 completed clinical studies on durvalumab monotherapy performed in a variety of solid tumour types.

Selected supportive safety data are also provided from three trials investigating durvalumab in combination with chemotherapy in SCLC (CASPIAN trial), biliary tract cancers (TOPAZ-1 trial), endometrial cancer (DUO-E) and NSCLC (AEGEAN) with the aim to characterize ADRs and imAEs presented in the proposed SmPC, description of the different studies can be found in Table 1.

Upon request, the MAH provided update safety data at EFS IA2 (DCO date of 10 May 2024). Unless otherwise stated safety data presented is from this DCO.

Treatment in the AEGEAN trial consisted of:

Durvalumab 1500 mg or placebo administered by IV infusion Q3W up to a maximum of 4 cycles in combination with platinum-based doublet chemotherapy prior to surgery, followed by durvalumab monotherapy 1500 mg, or placebo Q4W up to a maximum of 12 cycles, post-surgery.

Dose reduction of durvalumab due to AEs was not allowed, with dose reductions being permitted only for the chemotherapy treatments. Dose modification of durvalumab included only dose delay or interruption.

One patient randomized to the placebo/chemotherapy arm received one cycle of adjuvant durvalumab. For safety analyses, this patient is reported in the D + CTx arm with zero neoadjuvant exposure. Because of this, the number of patients in the safety analysis set differs from the number in the mITT.

The demographics according to the safety analysis set are shown in Table 33 below:

Table 33 Key Demographic and Patient Characteristics in the AEGEAN study and the D Pan-Tumour Pool (Safety Analysis Set)

Characteristic	Number (%) of patients		
	AEGEAN study		
	D + CTx (N = 401)	Placebo CTx (N = 398)	D pan-tumour Pool (N = 4045)
Age (years)			
Mean (SD)	63.9 (9.21)	63.8 (8.71)	61.9 (10.87)
Median (Min, Max)	65.0 (30, 88)	65.0 (39, 85)	63.0 (19, 96)
Age Group (years) (n%)			
< 50	22 (5.5)	22 (5.5)	482 (11.9)
≥ 50 to < 65	170 (42.4)	175 (44.0)	1768 (43.7)
≥ 60 to < 75	160 (39.9)	164 (41.2)	1356 (33.5)

Characteristic	Number (%) of patients		
	AEGEAN study		
	D + CTx (N = 401)	Placebo CTx (N = 398)	D pan-tumour Pool (N = 4045)
≥ 75	49 (12.2)	37 (9.3)	439 (10.9)
Sex, n (%)			
Male	262 (65.3)	289 (72.6)	2783 (68.8)
Female	139 (34.7)	109 (27.4)	1262 (31.2)
Race, n (%)			
White	217 (54.1)	194 (48.7)	2691 (66.5)
Black or African American	5 (1.2)	2 (0.5)	84 (2.1)
Asian	165 (41.1)	186 (46.7)	1121 (27.7)
Other	14 (3.5)	16 (4.0)	72 (1.8)
Missing	0	0	77 (1.9)
Geographic Region			
Asia	164 (40.9)	185 (46.5)	1032 (25.5)
Europe	148 (36.9)	142 (35.7)	1756 (43.4)
North America	47 (11.7)	43 (10.8)	1209 (29.9)
South America	42 (10.5)	28 (7.0)	48 (1.2)
Non-Asia Regions combined	237 (59.1)	213 (53.5)	3013 (74.5)
Baseline ECOG/WHO Performance Status (n%)			
0	279 (69.6)	273 (68.6)	1646 (40.7)
≥ 1	122 (30.4)	125 (31.4)	2394 (59.2)
Missing	0	0	5 (0.1)

AEGEAN, Study 1108 and Japan 2 collected ECOG. Arctic, Atlantic, Mystic and Pacific collected WHO. Eagle, Condor and Hawk collected both ECOG and WHO with the latest test being used for analysis.
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% bed ridden, (5) = Death.

Patient exposure

Table 34 Duration of exposure to durvalumab/placebo (safety analysis set; EFS IA1 and EFS IA2)

Exposure characteristic		EFS IA1 DCO (10 Nov 2022)		EFS IA2 DCO (10 May 2024)	
		D + CTx (N = 401)	Pbo + CTx (N = 398)	D + CTx (N = 401)	Pbo + CTx (N = 398)
Neoadjuvant period	n	401	398	401	398
Total neoadjuvant treatment duration (weeks) [a]	Mean (sd)	12.01 (2.236)	11.96 (2.214)	12.00 (2.241)	11.96 (2.214)
	Median (Min, Max)	12.14 (0.0, 19.0)	12.14 (3.0, 22.7)	12.14 (0.0, 19.0)	12.14 (3.0, 22.7)
	Total treatment years	92.3	91.3	92.3	91.3
Actual neoadjuvant treatment duration (weeks) [b]	Mean (sd)	11.46 (1.921)	11.51 (1.950)	11.46 (1.924)	11.51 (1.950)
	Median (Min, Max)	12.00 (0.0, 13.3)	12.00 (3.0, 13.0)	12.00 (0.0, 13.3)	12.00 (3.0, 13.0)
	Total treatment years	88.1	87.8	88.0	87.8
Adjuvant period	n	265	254	266	254
Total adjuvant treatment duration (weeks) [c]	Mean (sd)	33.65 (16.301)	32.43 (16.003)	40.63 (15.993)	40.00 (15.186)
	Median (Min, Max)	37.14 (4.0, 67.1)	34.43 (0.6, 58.7)	48.00 (4.0, 68.3)	48.00 (4.0, 70.6)
	Total treatment years	170.9	157.9	207.1	194.7
Actual adjuvant treatment duration (weeks) [b]	Mean (sd)	32.35 (15.847)	31.53 (15.505)	38.86 (15.209)	38.71 (14.565)
	Median (Min, Max)	36.14 (4.0, 49.1)	33.57 (0.6, 49.7)	48.00 (4.0, 52.3)	47.93 (4.0, 50.4)
	Total treatment years	164.3	153.5	198.1	188.4
Total overall	n	401	398	401	398

Total overall treatment duration (weeks) [d]	Mean (sd)	34.25 (21.274)	32.66 (20.652)	38.96 (23.822)	37.49 (23.339)
	Median (Min, Max)	32.00 (2.0, 79.3)	28.36 (3.0, 72.6)	44.86 (2.0, 81.4)	36.64 (3.0, 82.6)
	Total treatment years	263.2	249.1	299.4	286.0
Actual overall treatment duration (weeks) [e]	Mean (sd)	32.84 (20.549)	31.63 (20.117)	37.23 (22.758)	36.21 (22.528)
	Median (Min, Max)	28.71 (2.0, 61.1)	28.00 (3.0, 62.0)	40.14 (2.0, 64.4)	36.14 (3.0, 62.9)
	Total treatment years	252.4	241.2	286.1	276.2

[a] Total treatment duration = (min (last dose date where dose > 0 + 20, date of death, date of DCO) - first dose date + 1)/7, where minimum is whichever occurred first.

[b] Actual treatment duration = total treatment duration minus the total duration of dose delays for each period.

[c] Total treatment duration = (min (last dose date where dose > 0 + 27, date of death, date of DCO) - first dose date post-surgery + 1)/7, where minimum is whichever occurred first.

[d] Total treatment duration of both phases, as the addition of total neoadjuvant duration and total adjuvant duration.

[e] Actual treatment duration = total treatment duration minus the total duration of dose delays for both periods.

One patient randomized to placebo + CTx received 1 cycle of adjuvant durvalumab. This patient is reported in the D + CTx arm with zero neoadjuvant exposure.

DCO: 10 November 2022 (EFS IA1) and 10 May 2024 (EFS IA2).

See also Table 15 Treatment cycles received in the neoadjuvant period (Safety analysis set - neoadjuvant period) and Table 16 Treatment cycles received in the adjuvant period (Safety analysis set - adjuvant period)

Exposure-safety relationship analyses were not performed for AEGEAN, on the basis that prior exposure-safety relationship analyses had been conducted for multiple submissions (e.g., PACIFIC, CASPIAN, POSEIDON, HIMALAYA, and TOPAZ-1). These analyses confirmed no significant exposure-response relationship for safety endpoints at the dose levels evaluated for each study.

Adverse events

Table 35 Overview of AEs by Category in the AEGEAN Study and the D Pan-Tumour Pool (Safety Analysis Set)

AE category	Number (%) of patients [a]				
	AEGEAN Study				D pan-tumour pool (N = 4045)
	Neoadjuvant period		Overall period [b]		
	D + CTx (N = 401)	Placebo + CTx (N = 398)	D + CTx (N = 401)	Placebo + CTx (N = 398)	
Any AE	**365 (91.0)**	**357 (89.7)**	**387 (96.5)**	**379 (95.2)**	**3825 (94.6)**
Any AE possibly related to any study treatment [c]	330 (82.3)	313 (78.6)	250 (87.3)	325 (81.7)	2340 (57.8)
Any AE possibly related to durvalumab/placebo [c]	159 (39.7)	143 (35.9)	224 (55.9)	180 (45.2)	2332 (57.7)
Any AE possibly related to CTx (at least one component) [c]	318 (79.3)	309 (77.6)	319 (79.6)	313 (78.6)	NA
Any AE possibly related to surgery [c]	NA	NA	138 (34.4)	144 (36.2)	NA
Any AE possibly related to PORT [c]	NA	NA	13 (3.2)	4 (1.0)	NA
Any AE of maximum CTCAE Grade 3 or 4 [d]	**131 (32.7)**	**145 (36.4)**	**175 (43.6)**	**172 (43.2)**	**1600 (39.6)**
Any AE of maximum CTCAE Grade 3 or 4, possibly related to any study treatment [c d]	118 (29.4)	130 (32.7)	134 (33.4)	133 (33.4)	465 (11.5)
Any AE of maximum CTCAE Grade 3 or 4, possibly related to durvalumab/placebo [c d]	37 (9.2)	38 (9.5)	59 (14.7)	47 (11.8)	459 (11.3)
Any AE of maximum CTCAE Grade 3 or 4, possibly related to CTx (at least one component) [c d]	112 (27.9)	126 (31.7)	113 (28.2)	127 (31.9)	NA
Any AE of maximum CTCAE Grade 3 or 4, possibly related to surgery [c d]	NA	NA	27 (6.7)	29 (7.3)	NA
Any AE of maximum CTCAE Grade 3 or 4, possibly related to PORT [c d]	NA	NA	4 (1.0)	0	NA
Any AE with outcome of death	**8 (2.0)**	**4 (1.0)**	**23 (5.7)**	**15 (3.8)**	**231 (5.7)**
Any AE with outcome of death, possibly related to any study treatment [c]	3 (0.7)	1 (0.3)	7 (1.7)	2 (0.5)	27 (0.7)
Any AE with outcome of death, possibly related to durvalumab/placebo [c]	2 (0.5)	0	6 (1.5)	0	27 (0.7)

AE category	Number (%) of patients [a]				
	AEGEAN Study				D pan-tumour pool (N = 4045)
	Neoadjuvant period		Overall period [b]		
	D + CTx (N = 401)	Placebo + CTx (N = 398)	D + CTx (N = 401)	Placebo + CTx (N = 398)	
Any AE with outcome of death, possibly related to CTx (at least one component) [c]	2 (0.5)	1 (0.3)	2 (0.5)	2 (0.5)	NA
Any AE with outcome of death, possibly related to surgery [c]	NA	NA	6 (1.5)	4 (1.0)	NA
Any AE with outcome of death, possibly related to PORT [c]	NA	NA	0	0	NA
Any SAE (including events with outcome of death) [e]	**83 (20.7)**	**66 (16.6)**	**157 (39.2)**	**126 (31.7)**	**1447 (35.8)**
Any SAE (including events with outcome of death), possibly related to any study treatment [c e]	53 (13.2)	43 (10.8)	76 (19.0)	50 (12.6)	288 (7.1)
Any SAE (including events with outcome of death), possibly related to durvalumab/placebo [c e]	19 (4.7)	20 (5.0)	42 (10.5)	26 (6.5)	287 (7.1)
Any SAE (including events with outcome of death), possibly related to CTx (at least one component) [c e]	44 (11.0)	37 (9.3)	46 (11.5)	40 (10.1)	NA
Any SAE with outcome of death, possibly related to surgery [c e]	NA	NA	34 (8.5)	34 (8.5)	NA
Any SAE with outcome of death, possibly related to PORT [c e]	NA	NA	5 (1.2)	1 (0.3)	NA
Any AE leading to discontinuation of any study treatment	**54 (13.5)**	**30 (7.5)**	**78 (19.5)**	**39 (9.8)**	**397 (9.8)**
Any AE leading to discontinuation of durvalumab/placebo	26 (6.5)	15 (3.8)	51 (12.7)	25 (6.3)	397 (9.8)
Any AE possibly related to any study treatment leading to discontinuation of any study treatment [c]	47 (11.7)	27 (6.8)	64 (16.0)	31 (7.8)	183 (4.5)
Any AE possibly related to durvalumab/placebo leading to discontinuation of durvalumab/placebo [c]	16 (4.0)	6 (1.5)	34 (8.5)	12 (3.0)	182 (4.5)
Any AE leading to discontinuation of 2 CTxs	26 (6.5)	17 (4.3)	26 (6.5)	17 (4.3)	NA
Any AE leading to discontinuation of CTx (at least one component), possibly related to CTx (at least one component) [c]	34 (8.5)	27 (6.8)	34 (8.5)	27 (6.8)	NA
Any AE leading to dose modification of any study treatment [f]	**148 (36.9)**	**126 (31.7)**	**196 (48.9)**	**152 (38.2)**	**1129 (27.9)**
Any AE leading to dose delay or interruption of any study treatment [g]	116 (28.9)	100 (25.1)	173 (43.1)	134 (33.7)	1120 (27.7)
Any AE leading to dose delay or interruption of durvalumab/placebo [g]	110 (27.4)	87 (21.9)	168 (41.9)	123 (30.9)	1120 (27.7)

AE category	Number (%) of patients [a]				
	AEGEAN Study				D pan-tumour pool (N = 4045)
	Neoadjuvant period		Overall period [b]		
	D + CTx (N = 401)	Placebo + CTx (N = 398)	D + CTx (N = 401)	Placebo + CTx (N = 398)	
Any AE leading to dose interruption or reduction of CTx (at least one component)	143 (35.7)	122 (30.7)	143 (35.7)	122 (30.7)	NA
Any AE leading to surgery not done [h]	**7 (1.7)**	**4 (1.0) [h]**	**7 (1.7)**	**4 (1.0) [h]**	**NA**
Any AE leading to a delay in surgery (more than 40 days after the last dose of study treatment in neoadjuvant period) [i]	**15 (3.7) [i]**	**16 (4.0)**	**15 (3.7) [i]**	**16 (4.0)**	**NA**
Any AE leading to a delay in adjuvant treatment	**NA**	**NA**	**8 (2.0)**	**6 (1.5)**	**NA**
Any AE leading to adjuvant treatment not given	**NA**	**NA**	**28 (7.0)**	**20 (5.0)**	**NA**
Any AESIs or AEPIs	**191 (47.6)**	**152 (38.2)**	**268 (66.8)**	**209 (52.5)**	**2381 (58.9)**
Any AESIs or AEPIs possibly related to any study treatment [c]	107 (26.7)	77 (19.3)	183 (45.6)	108 (27.1)	**1536 (38.0)**
Any AESIs or AEPIs leading to a delay in surgery (more than 40 days after the last dose of study treatment in neoadjuvant period)	7 (1.7)	2 (0.5)	7 (1.7)	2 (0.5)	NA
Any AESIs or AEPIs leading to discontinuation of any study treatment	16 (4.0)	5 (1.3)	30 (7.5)	10 (2.5)	142 (3.5)
Any imAE [j]	**33 (8.2)**	**19 (4.8)**	**102 (25.4)**	**41 (10.3)**	**705 (17.4)**
Infusion related reaction [k]	**NC**	**NC**	**8 (2.0)**	**5 (1.3)**	**65 (1.6)**

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 Overall period refers to the neoadjuvant period, post-surgery, and adjuvant period, i.e., D + CTx followed by surgery and durvalumab monotherapy, and placebo + CTx followed by surgery and placebo.

c As assessed by the investigator. Missing responses are counted as related. Study treatment includes durvalumab, CTx, placebo, in this context surgery is not included as a study treatment.

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 reduction, dose delay or dose interruption, and AEs meeting study level dose delay definitions, where applicable.

g 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.

h Taken from the SURG form. Note that one additional patient in the placebo + CTx arm had an AE leading to surgery not done (5 patients in total) without an AE number (identifying the PT) specified on the SURG form.

i Taken from the SURG form (including AE and unresolved toxicity). Note that one additional patient in the D + CTx arm had an AE (unresolved toxicity) leading to a delay in surgery, without an AE number (identifying the PT) specified on the SURG form (16 patients in total) and one additional patient in the placebo + CTx arm had an AE leading to a delay in surgery, without an AE number (identifying the PT) specified on the SURG form (17 patients in total)

j AEs adjudicated as imAEs (see the Durvalumab and Tremelimumab Global imAE Characterization Charter).

k Incidence as an ADR (not calculated for the neoadjuvant period).

Neoadjuvant period includes AEs between date of first dose and the day before surgery, or for patients without surgery up to the earliest of ≤ 90 days after date of last dose of neoadjuvant treatment, first dose of subsequent anti-cancer therapy. Includes AEs with an onset date during this period and AEs with an onset date prior to dosing which worsen during this period.
Overall period and Durvalumab Pan-Tumour 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 surgery) or up to and including the date of initiation of the first subsequent therapy (whichever occurs first).
Disease progression AEs reported in Study 1108 are not included in this summary.
All studies use CTCAE version 4.03 except for AEGEAN which uses CTCAE version 5.0.
MedDRA version 26.1.

Table 36 Summary of AEs and Event Rates in the AEGEAN Study and the D Pan-Tumour Pool (Frequency ≥ 5% in Either AEGEAN Treatment Arm [Overall Period]; Safety Analysis Set)

	Number (%) of patients [a]									
	AEGEAN Study								D pan-tumour pool (N = 4045, Dur = 2240.4)	
	Neoadjuvant period				Overall period [b]					
	D + CTx (N = 401, Dur = 92.3)		Placebo + CTx (N = 398, Dur = 91.3)		D + CTx (N = 401, Dur = 299.4)		Placebo + CTx (N = 398, Dur = 286)			
MedDRA Preferred Term	Number (%) of patients [a]	Event rate (per 100 patient years) [c]	Number (%) of patients [a]	Event rate (per 100 patient years) [c]	Number (%) of patients [a]	Event rate (per 100 patient years) [c]	Number (%) of patients [a]	Event rate (per 100 patient years) [c]	Number (%) of patients [a]	Event rate (per 100 patient years) [c]
Patients with any AE	***365 (91.0)***	***395.4***	***357 (89.7)***	***391.0***	***387 (96.5)***	***129.3***	***379 (95.2)***	***132.5***	***3825 (94.6)***	***170.7***
Anaemia	120 (29.9)	130.0	112 (28.1)	122.7	140 (34.9)	46.8	128 (32.2)	44.8	521 (12.9)	23.3
Constipation	84 (20.9)	91.0	74 (18.6)	81.1	104 (25.9)	34.7	90 (22.6)	31.5	651 (16.1)	29.1
Nausea	93 (23.2)	100.8	106 (26.6)	116.1	103 (25.7)	34.4	119 (29.9)	41.6	678 (16.8)	30.3
Decreased appetite	55 (13.7)	59.6	58 (14.6)	63.5	74 (18.5)	24.7	73 (18.3)	25.5	769 (19.0)	34.3
Alopecia	69 (17.2)	74.8	62 (15.6)	67.9	69 (17.2)	23.0	64 (16.1)	22.4	36 (0.9)	1.6
Neutropenia	67 (16.7)	72.6	72 (18.1)	78.9	68 (17.0)	22.7	72 (18.1)	25.2	32 (0.8)	1.4
Neutrophil count decreased	65 (16.2)	70.4	59 (14.8)	64.6	66 (16.5)	22.0	59 (14.8)	20.6	24 (0.6)	1.1
Rash	40 (10.0)	43.3	29 (7.3)	31.8	63 (15.7)	21.0	33 (8.3)	11.5	394 (9.7)	17.6
Fatigue	50 (12.5)	54.2	42 (10.6)	46.0	56 (14.0)	18.7	47 (11.8)	16.4	998 (24.7)	44.5

MedDRA Preferred Term	Number (%) of patients [a]									
	AEGEAN Study								D pan-tumour pool (N = 4045, Dur = 2240.4)	
	Neoadjuvant period				Overall period [b]					
	D + CTx (N = 401, Dur = 92.3)		Placebo + CTx (N = 398, Dur = 91.3)		D + CTx (N = 401, Dur = 299.4)		Placebo + CTx (N = 398, Dur = 286)			
	Number (%) of patients [a]	Event rate (per 100 patient years) [c]	Number (%) of patients [a]	Event rate (per 100 patient years) [c]	Number (%) of patients [a]	Event rate (per 100 patient years) [c]	Number (%) of patients [a]	Event rate (per 100 patient years) [c]	Number (%) of patients [a]	Event rate (per 100 patient years) [c]
COVID-19	15 (3.7)	16.3	11 (2.8)	12.0	54 (13.5)	18.0	45 (11.3)	15.7	1 (< 0.1)	< 0.1
Diarrhoea	40 (10.0)	43.3	35 (8.8)	38.3	53 (13.2)	17.7	51 (12.8)	17.8	649 (16.0)	29.0
Pruritus	31 (7.7)	33.6	16 (4.0)	17.5	51 (12.7)	17.0	26 (6.5)	9.1	462 (11.4)	20.6
Asthenia	42 (10.5)	45.5	42 (10.6)	46.0	50 (12.5)	16.7	58 (14.6)	20.3	466 (11.5)	20.8
Hypothyroidism	9 (2.2)	9.8	6 (1.5)	6.6	47 (11.7)	15.7	12 (3.0)	4.2	379 (9.4)	16.9
Procedural pain	2 (0.5)	2.2	4 (1.0)	4.4	46 (11.5)	15.4	49 (12.3)	17.1	34 (0.8)	1.5
Vomiting	36 (9.0)	39.0	34 (8.5)	37.2	45 (11.2)	15.0	44 (11.1)	15.4	422 (10.4)	18.8
Arthralgia	18 (4.5)	19.5	29 (7.3)	31.8	44 (11.0)	14.7	51 (12.8)	17.8	540 (13.3)	24.1
Insomnia	29 (7.2)	31.4	35 (8.8)	38.3	43 (10.7)	14.4	48 (12.1)	16.8	300 (7.4)	13.4
Leukopenia	35 (8.7)	37.9	33 (8.3)	36.1	37 (9.2)	12.4	33 (8.3)	11.5	22 (0.5)	1.0
Pneumonia	17 (4.2)	18.4	11 (2.8)	12.0	37 (9.2)	12.4	35 (8.8)	12.2	307 (7.6)	13.7
Cough	15 (3.7)	16.3	15 (3.8)	16.4	36 (9.0)	12.0	46 (11.6)	16.1	643 (15.9)	28.7
Alanine aminotransferase increased	30 (7.5)	32.5	18 (4.5)	19.7	34 (8.5)	11.4	27 (6.8)	9.4	256 (6.3)	11.4
Dyspnoea	13 (3.2)	14.1	9 (2.3)	9.9	34 (8.5)	11.4	26 (6.5)	9.1	596 (14.7)	26.6
Platelet count decreased	29 (7.2)	31.4	34 (8.5)	37.2	31 (7.7)	10.4	35 (8.8)	12.2	41 (1.0)	1.8
White blood cell count decreased	27 (6.7)	29.3	34 (8.5)	37.2	27 (6.7)	9.0	34 (8.5)	11.9	23 (0.6)	1.0
Pyrexia	19 (4.7)	20.6	20 (5.0)	21.9	26 (6.5)	8.7	36 (9.0)	12.6	520 (12.9)	23.2

MedDRA Preferred Term	Number (%) of patients [a]									
	AEGEAN Study								D pan-tumour pool (N = 4045, Dur = 2240.4)	
	Neoadjuvant period				Overall period [b]					
	D + CTx (N = 401, Dur = 92.3)		Placebo + CTx (N = 398, Dur = 91.3)		D + CTx (N = 401, Dur = 299.4)		Placebo + CTx (N = 398, Dur = 286)			
	Number (%) of patients [a]	Event rate (per 100 patient years) [c]	Number (%) of patients [a]	Event rate (per 100 patient years) [c]	Number (%) of patients [a]	Event rate (per 100 patient years) [c]	Number (%) of patients [a]	Event rate (per 100 patient years) [c]	Number (%) of patients [a]	Event rate (per 100 patient years) [c]
Thrombocytopenia	26 (6.5)	28.2	30 (7.5)	32.9	26 (6.5)	8.7	30 (7.5)	10.5	69 (1.7)	3.1
Myalgia	19 (4.7)	20.6	21 (5.3)	23.0	25 (6.2)	8.4	30 (7.5)	10.5	196 (4.8)	8.7
Headache	16 (4.0)	17.3	13 (3.3)	14.2	24 (6.0)	8.0	25 (6.3)	8.7	323 (8.0)	14.4
Hypertension	13 (3.2)	14.1	13 (3.3)	14.2	24 (6.0)	8.0	17 (4.3)	5.9	170 (4.2)	7.6
Dyspepsia	17 (4.2)	18.4	8 (2.0)	8.8	24 (6.0)	8.0	14 (3.5)	4.9	122 (3.0)	5.4
Dizziness	13 (3.2)	14.1	18 (4.5)	19.7	22 (5.5)	7.3	22 (5.5)	7.7	236 (5.8)	10.5
Aspartate aminotransferase increased	14 (3.5)	15.2	9 (2.3)	9.9	22 (5.5)	7.3	13 (3.3)	4.5	278 (6.9)	12.4
Hiccups	20 (5.0)	21.7	17 (4.3)	18.6	21 (5.2)	7.0	17 (4.3)	5.9	30 (0.7)	1.3
Neuropathy peripheral	16 (4.0)	17.3	23 (5.8)	25.2	19 (4.7)	6.3	26 (6.5)	9.1	78 (1.9)	3.5
Back pain	6 (1.5)	6.5	8 (2.0)	8.8	14 (3.5)	4.7	20 (5.0)	7.0	441 (10.9)	19.7
Hypoaesthesia	11 (2.7)	11.9	23 (5.8)	25.2	13 (3.2)	4.3	27 (6.8)	9.4	44 (1.1)	2.0
Hypokalaemia	6 (1.5)	6.5	13 (3.3)	14.2	13 (3.2)	4.3	23 (5.8)	8.0	174 (4.3)	7.8

[a] Number (%) of patients with AEs, sorted in decreasing frequency of MedDRA PT using the AEGEAN overall D + CTx column. Patients with multiple AEs are counted once for each PT.

[b] Overall period refers to the neoadjuvant period, post-surgery, and adjuvant period, i.e., D + CTx followed by surgery and durvalumab monotherapy, and placebo + CTx followed by surgery and placebo.

[c] Number of patients with AEs divided by total number of years at risk for AEs summed across all patients within a group, multiplied by 100.

Neoadjuvant period includes AEs between date of first dose and the day before surgery, or for patients without surgery up to the earliest of ≤ 90 days after date of last dose of neoadjuvant treatment, first dose of subsequent anti-cancer therapy. Includes AEs with an onset date during this period and AEs with an onset date prior to dosing which worsen during this period.

Overall period and Durvalumab Pan-Tumour 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 surgery) or up to and including the date of initiation of the first subsequent therapy (whichever occurs first).

Disease progression AEs reported in Study 1108 are not included in this summary.

Percentages are based on the total number of patients in the treatment group (N).

MedDRA Preferred Term	Number (%) of patients [a]									
	AEGEAN Study								D pan-tumour pool (N = 4045, Dur = 2240.4)	
	Neoadjuvant period				Overall period [b]					
	D + CTx (N = 401, Dur = 92.3)		Placebo + CTx (N = 398, Dur = 91.3)		D + CTx (N = 401, Dur = 299.4)		Placebo + CTx (N = 398, Dur = 286)			
	Number (%) of patients [a]	Event rate (per 100 patient years) [c]	Number (%) of patients [a]	Event rate (per 100 patient years) [c]	Number (%) of patients [a]	Event rate (per 100 patient years) [c]	Number (%) of patients [a]	Event rate (per 100 patient years) [c]	Number (%) of patients [a]	Event rate (per 100 patient years) [c]

Dur = Total number of years at risk for AEs summed across all patients within a group. Where total number of years at risk for AEs = (last dose date + X days or death date or DCO whichever occurs earlier – first dose date + 1)/365.25. X is defined as the planned frequency in dosing (in days) – 1.
For Q2W, X = 13. For Q3W, X = 20. For Q4W, X = 27.
MedDRA version 26.1

Treatment-related adverse events

Table 37 Summary of AEs Possibly Related to Any Study Treatment by PT in the AEGEAN Study and the D Pan-Tumour Pool (Frequency ≥ 5% in Either AEGEAN Treatment Arm [Overall Period]) (Safety Analysis Set)

MedDRA PT	Number (%) of patients [a]				
	AEGEAN Study				D pan-tumour pool (N = 4045)
	Neoadjuvant period		Overall period [b]		
	D + CTx (N = 401)	Placebo + CTx (N = 398)	D + CTx (N = 401)	Placebo + CTx (N = 398)	
Patients with any AE possibly related to study treatment [c]	***330 (82.3)***	***313 (78.6)***	***350 (87.3)***	***325 (81.7)***	***2340 (57.8)***
Anaemia	102 (25.4)	94 (23.6)	106 (26.4)	97 (24.4)	87 (2.2)
Nausea	83 (20.7)	99 (24.9)	87 (21.7)	99 (24.9)	247 (6.1)
Decreased appetite	48 (12.0)	47 (11.8)	50 (12.5)	48 (12.1)	235 (5.8)
Alopecia	66 (16.5)	59 (14.8)	66 (16.5)	61 (15.3)	12 (0.3)
Neutrophil count decreased	64 (16.0)	58 (14.6)	64 (16.0)	58 (14.6)	10 (0.2)
Neutropenia	60 (15.0)	64 (16.1)	61 (15.2)	64 (16.1)	19 (0.5)
Constipation	42 (10.5)	49 (12.3)	46 (11.5)	51 (12.8)	67 (1.7)
Fatigue	45 (11.2)	35 (8.8)	46 (11.5)	37 (9.3)	489 (12.1)
Hypothyroidism	8 (2.0)	3 (0.8)	45 (11.2)	6 (1.5)	310 (7.7)
Rash	25 (6.2)	25 (6.3)	41 (10.2)	26 (6.5)	267 (6.6)
Diarrhoea	30 (7.5)	18 (4.5)	36 (9.0)	22 (5.5)	297 (7.3)
Asthenia	33 (8.2)	37 (9.3)	35 (8.7)	39 (9.8)	194 (4.8)
Leukopenia	33 (8.2)	32 (8.0)	35 (8.7)	32 (8.0)	12 (0.3)
Pruritus	22 (5.5)	7 (1.8)	35 (8.7)	8 (2.0)	283 (7.0)
Vomiting	30 (7.5)	30 (7.5)	32 (8.0)	30 (7.5)	100 (2.5)
Platelet count decreased	28 (7.0)	31 (7.8)	30 (7.5)	32 (8.0)	16 (0.4)
Alanine aminotransferase increased	26 (6.5)	16 (4.0)	30 (7.5)	22 (5.5)	116 (2.9)
White blood cell count decreased	27 (6.7)	33 (8.3)	27 (6.7)	33 (8.3)	9 (0.2)
Arthralgia	13 (3.2)	16 (4.0)	27 (6.7)	22 (5.5)	146 (3.6)
Thrombocytopenia	25 (6.2)	29 (7.3)	25 (6.2)	29 (7.3)	29 (0.7)
Hypoaesthesia	10 (2.5)	20 (5.0)	10 (2.5)	20 (5.0)	8 (0.2)

[a] Number (%) of patients with AEs, sorted in decreasing frequency of PT using the AEGEAN overall D + CTx column. Patients with multiple AEs are counted once for each PT.

[b] Overall period refers to the neoadjuvant period, post-surgery, and adjuvant period, i.e., D + CTx followed by surgery and durvalumab monotherapy, and placebo + CTx followed by surgery and placebo.

[c] Possibly related to any study drug, as assessed by the investigator. Missing responses are counted as possibly related. Study treatment refers to durvalumab/placebo or CTx and does not include surgery.

Percentages are based on the total number of patients in the treatment group (N).

Neoadjuvant period includes AEs between date of first dose and the day before surgery, or for patients without surgery up to the earliest of ≤ 90 days after date of last dose of neoadjuvant treatment, first dose of subsequent anti-cancer therapy. Includes AEs with an onset date during this period and AEs with an onset date prior to dosing which worsen during this period.

Overall period and Durvalumab Pan-Tumour Pool includes AEs with an onset date on or after the date of first dose or pretreatment 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 surgery) or up to and including the date of initiation of the first subsequent therapy (whichever occurs first).

Disease progression AEs reported in Study 1108 are not included in this summary.

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Maximum CTCAE Grade 3 or 4 adverse events

Table 38 Overview of AEs of Maximum CTCAE Grade 3 or 4 in the AEGEAN Study and the D Pan-Tumour Pool (Frequency ≥ 1% in Either AEGEAN Treatment Arm [Overall Period]) by PT (Safety Analysis Set)

MedDRA SOC / Preferred term	Number (%) of patients [a]				
	AEGEAN study				D pan-tumour pool (N = 4045)
	Neoadjuvant period		Overall period [b]		
	D + CTx (N = 401)	Placebo + CTx (N = 398)	D + CTx (N = 401)	Placebo + CTx (N = 398)	
Patients with any AE of maximum CTCAE Grade 3 or 4	***131 (32.7)***	***145 (36.4)***	***175 (43.6)***	***172 (43.2)***	***1600 (39.6)***
Neutrophil count decreased	42 (10.5)	45 (11.3)	42 (10.5)	45 (11.3)	6 (0.1)
Neutropenia	36 (9.0)	39 (9.8)	36 (9.0)	39 (9.8)	9 (0.2)
Anaemia	22 (5.5)	24 (6.0)	26 (6.5)	26 (6.5)	180 (4.4)
Pneumonia	7 (1.7)	5 (1.3)	12 (3.0)	10 (2.5)	122 (3.0)
Leukopenia	8 (2.0)	13 (3.3)	9 (2.2)	13 (3.3)	4 (< 0.1)
Platelet count decreased	8 (2.0)	14 (3.5)	9 (2.2)	14 (3.5)	8 (0.2)
White blood cell count decreased	8 (2.0)	12 (3.0)	8 (2.0)	12 (3.0)	2 (< 0.1)
Myelosuppression	7 (1.7)	3 (0.8)	7 (1.7)	3 (0.8)	0
Pulmonary embolism	2 (0.5)	2 (0.5)	7 (1.7)	4 (1.0)	31 (0.8)
Hypokalaemia	4 (1.0)	2 (0.5)	6 (1.5)	3 (0.8)	45 (1.1)
Thrombocytopenia	6 (1.5)	9 (2.3)	6 (1.5)	9 (2.3)	17 (0.4)
Acute kidney injury	2 (0.5)	0	4 (1.0)	1 (0.3)	32 (0.8)
Amylase increased	0	1 (0.3)	4 (1.0)	1 (0.3)	26 (0.6)
Drug-induced liver injury	2 (0.5)	1 (0.3)	4 (1.0)	1 (0.3)	4 (< 0.1)
Hypertension	1 (0.2)	4 (1.0)	4 (1.0)	6 (1.5)	54 (1.3)
Lipase increased	3 (0.7)	1 (0.3)	4 (1.0)	1 (0.3)	52 (1.3)
Pneumonitis	1 (0.2)	1 (0.3)	4 (1.0)	1 (0.3)	28 (0.7)
Vomiting	4 (1.0)	4 (1.0)	4 (1.0)	5 (1.3)	33 (0.8)
Febrile neutropenia	3 (0.7)	5 (1.3)	3 (0.7)	5 (1.3)	1 (< 0.1)
Pneumothorax	0	2 (0.5)	3 (0.7)	8 (2.0)	12 (0.3)
Interstitial lung disease	0	0	1 (0.2)	4 (1.0)	5 (0.1)
Asthenia	0	4 (1.0)	0	5 (1.3)	53 (1.3)

[a] Number (%) of patients with AEs of maximum CTCAE Grade 3 or 4 sorted in decreasing frequency of PT (AEGEAN Overall D + CTx column).

[b] Overall period refers to the neoadjuvant period, post-surgery, and adjuvant period, i.e., D + CTx followed by surgery and durvalumab monotherapy, and placebo + CTx followed by surgery and placebo.

Maximum CTCAE Grade per patient/event is considered. Patients with multiple AEs of CTCAE Grade 3 or 4 are counted once for each PT.

Percentages are based on the total number of patients in the treatment group (N).
Neoadjuvant period includes AEs between date of first dose and the day before surgery, or for patients without surgery up to the earliest of ≤ 90 days after date of last dose of neoadjuvant treatment, first dose of subsequent anti-cancer therapy. Includes AEs with an onset date during this period and AEs with an onset date prior to dosing which worsen during this period.
Overall period and Durvalumab Pan-Tumour 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 surgery) or up to and including the date of initiation of the first subsequent therapy (whichever occurs first).
Disease progression AEs reported in Study 1108 are not included in this summary.
MedDRA version 26.1, CTCAE version 4.03 except for AEGEAN which uses CTCAE version 5.0.

Adverse drug reactions

ADR safety signals were reviewed by the MAH, based on biological plausibility consistent with the mechanism of action of durvalumab, temporal association and re challenge responses, known risks associated with the anti PD 1/PD L1 drug class, totality of the data, and context of background rates in target populations. Those events not already on the known ADR list were medically reviewed further for alternative causes (medical history, concomitant medications, comorbidities or other risk factors), biological plausibility, and rechallenge response, which were considered to determine whether an AE is an additional ADR.

The most common AEs were considered consistent with the mechanism of action of chemotherapy including (but not limited to) haematological and gastrointestinal toxicities included in the current SmPC (for IMFINZI in combination with chemotherapy column) including leukopenia, neutropenia, febrile neutropenia, thrombocytopenia, pancytopenia, decreased appetite, constipation, nausea and vomiting. Upon evaluation of AEGEAN study data, safety variables were reviewed to ensure the safety profile of durvalumab observed in the AEGEAN study were consistent with previous findings in terms of the nature and frequency of the existing ADRs.

Adverse Drug Reaction categories in AEGEAN, the D pan-tumour pool, and the D + CTx and CTx pools are presented in Table 39 and Table 40 presents the ADR terms and CIOMS categories.

In addition, the MAH proposed revisions to align the adverse reactions by decreased frequency within each System Organ Class in the column "IMFINZI in combination with chemotherapy of Table 3 of section 4.8 of the SmPC; as a result of the updated safety pool, several ADRs frequencies were updated as follows:

Pancytopenia: from common to uncommon.

Immune thrombocytopenia: from uncommon to rare.

Thyroiditis: from common to uncommon.

Dysphonia: from uncommon to common

Colitis : from uncommon to common

Peripheral oedema: from very common to common

Of note, hypophysitis/hypopituitarism and nephritis with uncommon frequency, and noninfective encephalitis and myocarditis with rare frequency, were added to the "in combination with chemotherapy" column, as these ADR occurred for the first time in the D + CTx pool in the context of AEGEAN study.

Table 39 Adverse Drug Reactions by ADR Category (AEGEAN Study, D Pan Tumour Pool, and D + CTx and CTx Pools) (Safety Analysis Set)

ADR category	Number (%) of patients				
	AEGEAN Study - Overall period [a]		D pan-tumour pool (N = 4045)	D + CTx Pool (N = 1239) [b]	CTx Pool (N = 1242) [b]
	D +CTx (N = 401)	Placebo+ CTx (N = 398)			
Patients with any ADR	370 (92.3)	354 (88.9)	2959 (73.2)	1172 (94.6)	1166 (93.9)
ADRs of maximum CTCAE Grade 3 or 4 [c]	127 (31.7)	133 (33.4)	497 (12.3)	573 (46.2)	593 (47.7)
ADRs of any CTCAE Grade 3 or 4 [d]	133 (33.2)	136 (34.2)	506 (12.5)	580 (46.8)	599 (48.2)
Serious ADRs [e]	72 (18.0)	44 (11.1)	437 (10.8)	207 (16.7)	190 (15.3)
ADRs with an outcome of death	10 (2.5)	4 (1.0)	28 (0.7)	13 (1.0)	11 (0.9)
ADRs leading to discontinuation of durvalumab / placebo treatment	32 (8.0)	13 (3.3)	146 (3.6)	62 (5.0)	31 (2.5)
ADRs leading to dose delay or interruption of durvalumab / placebo [f]	122 (30.4)	81 (20.4)	527 (13.0)	382 (30.8)	244 (19.6)

[a] Overall period refers to the neoadjuvant period, post-surgery, and adjuvant period, i.e., D + CTx followed by surgery and durvalumab monotherapy and placebo + CTx followed by surgery and placebo.

[b] D + CTx and CTx pools include AEGEAN, TOPAZ-1, CASPIAN data, and DUO-E.

[c] Maximum CTCAE grade per patient is considered.

[d] All CTCAE graders per patient, not just the maximum are considered when identifying whether there is a Grade 3 or 4.

[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.

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 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 surgery) or up to and including the date of initiation of the first subsequent therapy (whichever occurs first).

Maximum CTCAE grade per patient is considered.

Disease progression AEs reported in Study 1108 are not included in this summary.

Percentages are based on the total number of patients in the treatment group (N).

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Table 40 Adverse Drug Reactions by ADR Term and CIOMS Category (AEGEAN Study, D Pan Tumour Pool, and D + CTx and CTx Pools) (Safety Analysis Set)

ADR system organ class/ ADR term	AEGEAN Study - Overall period [a]				D pan-tumour pool (N = 4045)		D + CTx pool (N = 1239) [d]		CTx pool (N = 1242) [d]	
	D +CTx (N = 401)		Placebo+ CTx (N = 398)							
	Number (%) of patients [b]	CIOMS III category [c]	Number (%) of patients [b]	CIOMS III category [c]	Number (%) of patients [b]	CIOMS III category [c]	Number (%) of patients [b]	CIOMS III category [c]	Number (%) of patients [b]	CIOMS III category [c]
Patients with any ADR	***370 (92.3)***	**-**	***354 (88.9)***	**-**	***2959 (73.2)***	**-**	***1172 (94.6)***	**-**	***1166 (93.9)***	**-**
Blood and lymphatic system disorders										
Immune thrombocytopenia	0	NR	0	NR	3 (< 0.1)	Rare	1 (< 0.1)	Rare	0	NR
Anaemia	140 (34.9)	Very common	128 (32.2)	Very common	NA	NA	516 (41.6)	Very common	535 (43.1)	Very common
Neutropenia	128 (31.9)	Very common	127 (31.9)	Very common	NA	NA	524 (42.3)	Very common	565 (45.5)	Very common
Leukopenia	60 (15.0)	Very common	61 (15.3)	Very common	NA	NA	204 (16.5)	Very common	216 (17.4)	Very common
Thrombocytopenia	55 (13.7)	Very common	60 (15.1)	Very common	NA	NA	290 (23.4)	Very common	297 (23.9)	Very common
Febrile neutropenia	4 (1.0)	Uncommon	6 (1.5)	Common	NA	NA	32 (2.6)	Common	39 (3.1)	Common
Pancytopenia	1 (0.2)	Uncommon	2 (0.5)	Uncommon	NA	NA	11 (0.9)	Uncommon	7 (0.6)	Uncommon
Cardiac disorders										
Myocarditis	1 (0.2)	Uncommon	0	NR	5 (0.1)	Uncommon	1 (< 0.1)	Rare	0	NR
Endocrine disorders										
Hypothyroidism	50 (12.5)	Very common	16 (4.0)	Common	439 (10.9)	Very common	143 (11.5)	Very common	42 (3.4)	Common
Hyperthyroidism	19 (4.7)	Common	11 (2.8)	Common	199 (4.9)	Common	74 (6.0)	Common	20 (1.6)	Common
Thyroiditis	3 (0.7)	Uncommon	2 (0.5)	Uncommon	30 (0.7)	Uncommon	12 (1.0)	Uncommon	2 (0.2)	Uncommon
Adrenal insufficiency	4 (1.0)	Uncommon	0	NR	24 (0.6)	Uncommon	12 (1.0)	Uncommon	1 (< 0.1)	Rare
Hypopituitarism/Hypophysitis	2 (0.5)	Uncommon	0	NR	3 (< 0.1)	Rare	2 (0.2)	Uncommon	0	NR
Type I diabetes mellitus	1 (0.2)	Uncommon	0	NR	3 (< 0.1)	Rare	5 (0.4)	Uncommon	0	NR
Diabetes insipidus	0	NR	0	NR	1 (< 0.1)	Rare	0	NR	0	NR
Eye disorders										
Uveitis	0	NR	1 (0.3)	Uncommon	1 (< 0.1)	Rare	2 (0.2)	Uncommon	1 (< 0.1)	Rare

ADR system organ class/ ADR term	AEGEAN Study - Overall period [a]				D pan-tumour pool (N = 4045)		D + CTx pool (N = 1239) [d]		CTx pool (N = 1242) [d]	
	D +CTx (N = 401)		Placebo+ CTx (N = 398)							
	Number (%) of patients [b]	CIOMS III category [c]	Number (%) of patients [b]	CIOMS III category [c]	Number (%) of patients [b]	CIOMS III category [c]	Number (%) of patients [b]	CIOMS III category [c]	Number (%) of patients [b]	CIOMS III category [c]
Gastrointestinal disorders										
Nausea	103 (25.7)	Very common	119 (29.9)	Very common	NA	NA	426 (34.4)	Very common	432 (34.8)	Very common
Diarrhoea	53 (13.2)	Very common	51 (12.8)	Very common	649 (16.0)	Very common	213 (17.2)	Very common	200 (16.1)	Very common
Abdominal pain	18 (4.5)	Common	31 (7.8)	Common	522 (12.9)	Very common	188 (15.2)	Very common	184 (14.8)	Very common
Colitis	5 (1.2)	Common	4 (1.0)	Common	37 (0.9)	Uncommon	13 (1.0)	Common	8 (0.6)	Uncommon
Pancreatitis	3 (0.7)	Uncommon	1 (0.3)	Uncommon	8 (0.2)	Uncommon	8 (0.6)	Uncommon	3 (0.2)	Uncommon
Constipation	104 (25.9)	Very common	90 (22.6)	Very common	NA	NA	321 (25.9)	Very common	321 (25.8)	Very common
Vomiting	45 (11.2)	Very common	44 (11.1)	Very common	NA	NA	196 (15.8)	Very common	195 (15.7)	Very common
Stomatitis	25 (6.2)	Common	25 (6.3)	Common	NA	NA	86 (6.9)	Common	82 (6.6)	Common
General disorders and administration site conditions										
Pyrexia	26 (6.5)	Common	36 (9.0)	Common	520 (12.9)	Very common	137 (11.1)	Very common	130 (10.5)	Very common
Oedema peripheral	15 (3.7)	Common	14 (3.5)	Common	380 (9.4)	Common	99 (8.0)	Common	71 (5.7)	Common
Fatigue	103 (25.7)	Very common	101 (25.4)	Very common	NA	NA	428 (34.5)	Very common	426 (34.3)	Very common
Hepatobiliary disorders										
AST or ALT increased	47 (11.7)	Very common	33 (8.3)	Common	369 (9.1)	Common	135 (10.9)	Very common	113 (9.1)	Common
Hepatitis	6 (1.5)	Common	1 (0.3)	Uncommon	45 (1.1)	Common	23 (1.9)	Common	6 (0.5)	Uncommon
Infections and infestations										
Upper respiratory tract infections	25 (6.2)	Common	28 (7.0)	Common	489 (12.1)	Very common	94 (7.6)	Common	88 (7.1)	Common
Pneumonia	38 (9.5)	Common	37 (9.3)	Common	319 (7.9)	Common	70 (5.6)	Common	72 (5.8)	Common
Oral candidiasis	3 (0.7)	Uncommon	5 (1.3)	Common	76 (1.9)	Common	10 (0.8)	Uncommon	10 (0.8)	Uncommon
Influenza	5 (1.2)	Common	5 (1.3)	Common	57 (1.4)	Common	10 (0.8)	Uncommon	7 (0.6)	Uncommon

ADR system organ class/ ADR term	AEGEAN Study - Overall period [a]				D pan-tumour pool (N = 4045)		D + CTx pool (N = 1239) [d]		CTx pool (N = 1242) [d]	
	D +CTx (N = 401)		Placebo+ CTx (N = 398)							
	Number (%) of patients [b]	CIOMS III category [c]	Number (%) of patients [b]	CIOMS III category [c]	Number (%) of patients [b]	CIOMS III category [c]	Number (%) of patients [b]	CIOMS III category [c]	Number (%) of patients [b]	CIOMS III category [c]
Dental and oral soft tissue infections	3 (0.7)	Uncommon	5 (1.3)	Common	56 (1.4)	Common	19 (1.5)	Common	17 (1.4)	Common
Injury, poisoning and procedural complications										
Infusion related reaction	8 (2.0)	Common	5 (1.3)	Common	65 (1.6)	Common	37 (3.0)	Common	37 (3.0)	Common
Metabolism and nutrition disorders										
Decreased appetite	74 (18.5)	Very common	73 (18.3)	Very common	NA	NA	252 (20.3)	Very common	245 (19.7)	Very common
Musculoskeletal and connective tissue disorders										
Arthralgia	44 (11.0)	Very common	51 (12.8)	Very common	540 (13.3)	Very common	149 (12.0)	Very common	137 (11.0)	Very common
Myalgia	25 (6.2)	Common	30 (7.5)	Common	196 (4.8)	Common	81 (6.5)	Common	101 (8.1)	Common
Myositis	0	NR	1 (0.3)	Uncommon	10 (0.2)	Uncommon	6 (0.5)	Uncommon	1 (< 0.1)	Rare
Immune-mediated arthritis	1 (0.2)	Uncommon	1 (0.3)	Uncommon	3 (< 0.1)	Rare	4 (0.3)	Uncommon	1 (< 0.1)	Rare
Polymyositis	0	NR	0	NR	0	NR	0	NR	1 (< 0.1)	Rare
Nervous system disorders										
Myasthenia Gravis	1 (0.2)	Uncommon	0	NR	3 (< 0.1)	Rare	3 (0.2)	Uncommon	0	NR
Meningitis	0	NR	0	NR	1 (< 0.1)	Rare	0	NR	0	NR
Noninfective encephalitis	1 (0.2)	Uncommon	1 (0.3)	Uncommon	0	NR	1 (< 0.1)	Rare	1 (< 0.1)	Rare
Neuropathy peripheral	46 (11.5)	Very common	54 (13.6)	Very common	NA	NA	223 (18.0)	Very common	249 (20.0)	Very common
Renal and urinary disorders										
Blood creatinine increased	14 (3.5)	Common	16 (4.0)	Common	145 (3.6)	Common	39 (3.1)	Common	69 (5.6)	Common
Dysuria	7 (1.7)	Common	3 (0.8)	Uncommon	60 (1.5)	Common	26 (2.1)	Common	27 (2.2)	Common
Nephritis	2 (0.5)	Uncommon	0	NR	12 (0.3)	Uncommon	2 (0.2)	Uncommon	4 (0.3)	Uncommon
Cystitis noninfective	0	NR	0	NR	4 (< 0.1)	Rare	2 (0.2)	Uncommon	2 (0.2)	Uncommon
Respiratory, thoracic and mediastinal disorders										

ADR system organ class/ ADR term	AEGEAN Study - Overall period [a]				D pan-tumour pool (N = 4045)		D + CTx pool (N = 1239) [d]		CTx pool (N = 1242) [d]	
	D +CTx (N = 401)		Placebo+ CTx (N = 398)							
	Number (%) of patients [b]	CIOMS III category [c]	Number (%) of patients [b]	CIOMS III category [c]	Number (%) of patients [b]	CIOMS III category [c]	Number (%) of patients [b]	CIOMS III category [c]	Number (%) of patients [b]	CIOMS III category [c]
Cough/Productive cough	47 (11.7)	Very common	53 (13.3)	Very common	754 (18.6)	Very common	151 (12.2)	Very common	128 (10.3)	Very common
Pneumonitis	21 (5.2)	Common	6 (1.5)	Common	137 (3.4)	Common	34 (2.7)	Common	17 (1.4)	Common
Dysphonia	13 (3.2)	Common	4 (1.0)	Common	103 (2.5)	Common	20 (1.6)	Common	11 (0.9)	Uncommon
Interstitial lung disease	3 (0.7)	Uncommon	6 (1.5)	Common	21 (0.5)	Uncommon	7 (0.6)	Uncommon	7 (0.6)	Uncommon
Skin and subcutaneous tissue disorders										
Rash	83 (20.7)	Very common	52 (13.1)	Very common	619 (15.3)	Very common	238 (19.2)	Very common	158 (12.7)	Very common
Pruritus	51 (12.7)	Very common	26 (6.5)	Common	462 (11.4)	Very common	150 (12.1)	Very common	94 (7.6)	Common
Night sweats	0	NR	1 (0.3)	Uncommon	60 (1.5)	Common	4 (0.3)	Uncommon	3 (0.2)	Uncommon
Psoriasis	1 (0.2)	Uncommon	1 (0.3)	Uncommon	30 (0.7)	Uncommon	4 (0.3)	Uncommon	4 (0.3)	Uncommon
Dermatitis	7 (1.7)	Common	4 (1.0)	Common	28 (0.7)	Uncommon	25 (2.0)	Common	6 (0.5)	Uncommon
Pemphigoid	1 (0.2)	Uncommon	0	NR	6 (0.1)	Uncommon	3 (0.2)	Uncommon	1 (< 0.1)	Rare
Alopecia	69 (17.2)	Very common	64 (16.1)	Very common	NA	NA	299 (24.1)	Very common	288 (23.2)	Very common

[a] Overall period refers to the neoadjuvant period, post-surgery, and adjuvant period, i.e., D + CTx followed by surgery and durvalumab monotherapy and placebo + CTx followed by surgery and placebo.

[b] Number (%) of patients with AEs, sorted in alphabetical order by ADR SOC. Within in each ADR SOC, ADR PTs are ordered in descending frequency in the D pan-tumour in pool, followed by descending in frequency in the D + CTx group.

[c] CIOMS III convention and is defined as: (1) very common (≥ 1/10); (2) common (≥ 1/100 to < 1/10); (3) uncommon (≥ 1/1,000 to < 1/100); (4) rare (≥ 1/10,000 to < 1/1,000); (5) very rare (< 1/10,000); and (6) NR (no result - cannot be estimated from available data).

[d] D + CTx and CTx pools include AEGEAN, TOPAZ-1, CASPIAN, and DUO-E data

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 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 surgery if later) or up to and including the date of initiation of the first subsequent therapy (whichever occurs first).

ADR terms are grouped PTs.

Percentages are based on the total number of patients in the treatment group (N).

Disease progression AEs reported in Study 1108 are not included in this summary.

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

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Some ADRs are specific to chemotherapy, and thus not applicable to the D pan-tumour pool.

Serious adverse event/deaths/other significant events

Table 41 Overview of SAEs in the AEGEAN Study and the D Pan-Tumour Pool (Frequency ≥ 1% in Either AEGEAN Treatment Arm [Overall Period]; Safety Analysis Set)

	AEGEAN Study								D pan-tumour pool (N = 4045, Dur = 2240.4)	
	Neoadjuvant period				Overall period [a]					
	D + CTx (N = 401, Dur = 92.3)		Placebo + CTx (N = 398, Dur = 91.3)		D + CTx (N = 401, Dur = 299.4)		Placebo + CTx (N = 398, Dur = 286)			
MedDRA Preferred term	Number (%) of patients [b]	Event rate (per 100 patient years) [c]	Number (%) of patients [b]	Event rate (per 100 patient years)[b]	Number (%) of patients [b]	Event rate (per 100 patient years) [b]	Number (%) of patients [b]	Event rate (per 100 patient years) [c]	Number (%) of patients [b]	Event rate (per 100 patient years) [c]
Patients with any SAE	***83 (20.7)***	***89.9***	***66 (16.6)***	***72.3***	***157 (39.2)***	***52.4***	***126 (31.7)***	***44.1***	***1447 (35.8)***	***64.6***
Pneumonia	10 (2.5)	10.8	8 (2.0)	8.8	23 (5.7)	7.7	18 (4.5)	6.3	152 (3.8)	6.8
Anaemia	6 (1.5)	6.5	5 (1.3)	5.5	7 (1.7)	2.3	5 (1.3)	1.7	27 (0.7)	1.2
COVID-19	1 (0.2)	1.1	2 (0.5)	2.2	7 (1.7)	2.3	5 (1.3)	1.7	0	NA
Pneumonitis	1 (0.2)	1.1	1 (0.3)	1.1	7 (1.7)	2.3	1 (0.3)	0.3	44 (1.1)	2.0
Myelosuppression	6 (1.5)	6.5	2 (0.5)	2.2	6 (1.5)	2.0	2 (0.5)	0.7	0	NA
Vomiting	5 (1.2)	5.4	2 (0.5)	2.2	5 (1.2)	1.7	2 (0.5)	0.7	24 (0.6)	1.1
Drug-induced liver injury	3 (0.7)	3.3	1 (0.3)	1.1	5 (1.2)	1.7	1 (0.3)	0.3	4 (< 0.1)	0.2
Pneumothorax	0	NA	2 (0.5)	2.2	4 (1.0)	1.3	9 (2.3)	3.1	15 (0.4)	0.7
COVID-19 pneumonia	3 (0.7)	3.3	1 (0.3)	1.1	4 (1.0)	1.3	3 (0.8)	1.0	0	NA
Neutropenia	4 (1.0)	4.3	2 (0.5)	2.2	4 (1.0)	1.3	2 (0.5)	0.7	2 (< 0.1)	0.1
Acute kidney injury	3 (0.7)	3.3	0	NA	4 (1.0)	1.3	1 (0.3)	0.3	30 (0.7)	1.3
Platelet count decreased	3 (0.7)	3.3	0	NA	4 (1.0)	1.3	0	NA	2 (< 0.1)	0.1
Pulmonary embolism	1 (0.2)	1.1	1 (0.3)	1.1	3 (0.7)	1.0	4 (1.0)	1.4	31 (0.8)	1.4
Cardiac failure	0	NA	1 (0.3)	1.1	0	NA	4 (1.0)	1.4	7 (0.2)	0.3

[a] Overall period refers to the neoadjuvant period, post-surgery, and adjuvant period, i.e., D + CTx followed by surgery and durvalumab monotherapy, and placebo + CTx followed by surgery and placebo.
[b] Number (%) of patients with AEs, sorted by descending frequency of PT in the D + CTx arm.
[c] Number of patients with AEs divided by total number of years at risk for AEs summed across all patients within a group, multiplied by 100.
Patients with multiple AEs are counted once for each SOC / PT.
Neoadjuvant period includes AEs between date of first dose and the day before surgery, or for patients without surgery up to the earliest of ≤ 90 days after date of last dose of neoadjuvant treatment, first dose of subsequent anti-cancer therapy. Includes AEs with an onset date during this period and AEs with an onset date prior to dosing which worsen during this period.
Overall period and Durvalumab Pan-Tumour 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 surgery) or up to and including the date of initiation of the first subsequent therapy (whichever occurs first).
Disease progression AEs reported in Study 1108 are not included in this summary.
Percentages are based on the total numbers of patients in the treatment group (N).
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Dur = Total number of years at risk for AEs summed across all patients within a group. Where total number of years at risk for AEs = (last dose date + X days or death date or DCO whichever occurs earlier - first dose date + 1)/365.25. X is defined as the planned frequency in dosing (in days) - 1. For Q2W, X = 13. For Q3W, X = 20. For Q4W, X = 27.

Deaths

Table 42 Adverse Events and Event Rate with Outcome of Death in the AEGEAN Study and Corresponding Incidence and Rate in the D Pan-Tumour Pool by System Organ Class and Preferred Term (Safety Analysis Set)

	AEGEAN Study								D pan-tumour pool (N = 4045, Dur = 2240.4)	
	Neoadjuvant period				Overall period [a]					
	D + CTx (N = 401, Dur = 92.3)		Placebo + CTx (N = 398, Dur = 91.3)		D + CTx (N = 401, Dur = 299.4)		Placebo + CTx (N = 398, Dur = 286)			
MedDRA SOC/Preferred term	Number (%) of patients [b]	Event Rate (per 100 patient years) [c]	Number (%) of patients [b]	Event Rate (per 100 patient years) [c]	Number (%) of patients [b]	Event Rate (per 100 patient years) [c]	Number (%) of patients [b]	Event Rate (per 100 patient years) [c]	Number (%) of patients [b]	Event Rate (per 100 patient years) [c]
Patients with any AE with an outcome of death	***8 (2.0)***	***8.7***	***4 (1.0)***	***4.4***	***23 (5.7)***	***7.7***	***15 (3.8)***	***5.2***	***231 (5.7)***	***10.3***
Infections and infestations	**4 (1.0)**	**4.3**	**1 (0.3)**	**1.1**	**13 (3.2)**	**4.3**	**7 (1.8)**	**2.4**	**46 (1.1)**	**2.1**
Pneumonia	0	NA	1 (0.3)	1.1	3 (0.7)	1.0	4 (1.0)	1.4	15 (0.4)	0.7
COVID-19 pneumonia	2 (0.5)	2.2	0	NA	3 (0.7)	1.0	1 (0.3)	0.3	0	NA
COVID-19	0	NA	0	NA	2 (0.5)	0.7	0	NA	0	NA

MedDRA SOC/Preferred term	AEGEAN Study								D pan-tumour pool (N = 4045, Dur = 2240.4)	
	Neoadjuvant period				Overall period [a]					
	D + CTx (N = 401, Dur = 92.3)		Placebo + CTx (N = 398, Dur = 91.3)		D + CTx (N = 401, Dur = 299.4)		Placebo + CTx (N = 398, Dur = 286)			
	Number (%) of patients [b]	Event Rate (per 100 patient years) [c]	Number (%) of patients [b]	Event Rate (per 100 patient years) [c]	Number (%) of patients [b]	Event Rate (per 100 patient years) [c]	Number (%) of patients [b]	Event Rate (per 100 patient years) [c]	Number (%) of patients [b]	Event Rate (per 100 patient years) [c]
Sepsis	2 (0.5)	2.2	0	NA	2 (0.5)	0.7	0	NA	13 (0.3)	0.6
Septic shock	0	NA	0	NA	2 (0.5)	0.7	0	NA	6 (0.1)	0.3
Pneumonia aspiration	0	NA	0	NA	1 (0.2)	0.3	0	NA	2 (< 0.1)	0.1
Pneumonia streptococcal	0	NA	0	NA	1 (0.2)	0.3	0	NA	0	NA
Infection	0	NA	0	NA	0	NA	1 (0.3)	0.3	0	NA
Infectious pleural effusion	0	NA	0	NA	0	NA	1 (0.3)	0.3	0	NA
Respiratory, thoracic and mediastinal disorders	**1 (0.2)**	**1.1**	**0**	**NA**	**6 (1.5)**	**2.0**	**2 (0.5)**	**0.7**	**51 (1.3)**	**2.3**
Interstitial lung disease	0	NA	0	NA	2 (0.5)	0.7	0	NA	0	NA
Bronchopleural fistula	0	NA	0	NA	1 (0.2)	0.3	0	NA	0	NA
Haemoptysis	1 (0.2)	1.1	0	NA	1 (0.2)	0.3	0	NA	2 (< 0.1)	0.1
Immune-mediated lung disease	0	NA	0	NA	1 (0.2)	0.3	0	NA	0	NA
Pneumonitis	0	NA	0	NA	1 (0.2)	0.3	0	NA	7 (0.2)	0.3
Acute respiratory failure	0	NA	0	NA	0	NA	1 (0.3)	0.3	7 (0.2)	0.3
Pulmonary haemorrhage	0	NA	0	NA	0	NA	1 (0.3)	0.3	1 (< 0.1)	< 0.1

MedDRA SOC/Preferred term	AEGEAN Study								D pan-tumour pool (N = 4045, Dur = 2240.4)	
	Neoadjuvant period				Overall period [a]					
	D + CTx (N = 401, Dur = 92.3)		Placebo + CTx (N = 398, Dur = 91.3)		D + CTx (N = 401, Dur = 299.4)		Placebo + CTx (N = 398, Dur = 286)			
	Number (%) of patients [b]	Event Rate (per 100 patient years) [c]	Number (%) of patients [b]	Event Rate (per 100 patient years) [c]	Number (%) of patients [b]	Event Rate (per 100 patient years) [c]	Number (%) of patients [b]	Event Rate (per 100 patient years) [c]	Number (%) of patients [b]	Event Rate (per 100 patient years) [c]
Cardiac disorders	**1 (0.2)**	**1.1**	**2 (0.5)**	**2.2**	**1 (0.2)**	**0.3**	**3 (0.8)**	**1.0**	**28 (0.7)**	**1.2**
Myocarditis	1 (0.2)	1.1	0	NA	1 (0.2)	0.3	0	NA	0	NA
Cardiac failure	0	NA	0	NA	0	NA	1 (0.3)	0.3	2 (< 0.1)	0.1
Cardiac failure acute	0	NA	1 (0.3)	1.1	0	NA	1 (0.3)	0.3	1 (< 0.1)	< 0.1
Myocardial ischaemia	0	NA	1 (0.3)	1.1	0	NA	1 (0.3)	0.3	0	NA
General disorders and administration site conditions	**1 (0.2)**	**1.1**	**0**	**NA**	**1 (0.2)**	**0.3**	**1 (0.3)**	**0.3**	**45 (1.1)**	**2.0**
Death	1 (0.2)	1.1	0	NA	1 (0.2)	0.3	0	NA	21 (0.5)	0.9
Multiple organ dysfunction syndrome	0	NA	0	NA	0	NA	1 (0.3)	0.3	0	NA
Metabolism and nutrition disorders	**1 (0.2)**	**1.1**	**0**	**NA**	**1 (0.2)**	**0.3**	**1 (0.3)**	**0.3**	**3 (< 0.1)**	**0.1**
Decreased appetite	1 (0.2)	1.1	0	NA	1 (0.2)	0.3	1 (0.3)	0.3	0	NA
Injury, poisoning and procedural complications	**0**	**NA**	**0**	**NA**	**1 (0.2)**	**0.3**	**0**	**NA**	**3 (< 0.1)**	**0.1**
Post procedural pulmonary embolism	0	NA	0	NA	1 (0.2)	0.3	0	NA	0	NA
Vascular disorders	**0**	**NA**	**0**	**NA**	**1 (0.2)**	**0.3**	**0**	**NA**	**10 (0.2)**	**0.4**
Aortic aneurysm rupture	0	NA	0	NA	1 (0.2)	0.3	0	NA	0	NA

MedDRA SOC/Preferred term	AEGEAN Study								D pan-tumour pool (N = 4045, Dur = 2240.4)	
	Neoadjuvant period				Overall period [a]					
	D + CTx (N = 401, Dur = 92.3)		Placebo + CTx (N = 398, Dur = 91.3)		D + CTx (N = 401, Dur = 299.4)		Placebo + CTx (N = 398, Dur = 286)			
	Number (%) of patients [b]	Event Rate (per 100 patient years) [c]	Number (%) of patients [b]	Event Rate (per 100 patient years) [c]	Number (%) of patients [b]	Event Rate (per 100 patient years) [c]	Number (%) of patients [b]	Event Rate (per 100 patient years) [c]	Number (%) of patients [b]	Event Rate (per 100 patient years) [c]
Gastrointestinal disorders	**0**	**NA**	**0**	**NA**	**0**	**NA**	**1 (0.3)**	**0.3**	**15 (0.4)**	**0.7**
Duodenal ulcer perforation	0	NA	0	NA	0	NA	1 (0.3)	0.3	0	NA
Nervous system disorders	**0**	**NA**	**1 (0.3)**	**1.1**	**0**	**NA**	**1 (0.3)**	**0.3**	**7 (0.2)**	**0.3**
Subarachnoid haemorrhage	0	NA	1 (0.3)	1.1	0	NA	1 (0.3)	0.3	0	NA

[a] Overall period refers to the neoadjuvant period, post-surgery, and adjuvant period, i.e., D + CTx followed by surgery and durvalumab monotherapy, and placebo + CTx followed by surgery and placebo.

[b] Number (%) of patients with AEs, sorted by descending frequency by SOC and PT in the D + CTx arm.

[c] Number of patients with AEs divided by the total number of years at risk for AEs across all patients in given group, multiplied by 100.

[d] Primary cause of death was 'death'; secondary cause of death was not specified.

Patients with multiple AEs are counted once for each SOC / PT.

Neoadjuvant period includes AEs between date of first dose and the day before surgery, or for patients without surgery up to the earliest of ≤ 90 days after date of last dose of neoadjuvant treatment, first dose of subsequent anti-cancer therapy. Includes AEs with an onset date during this period and AEs with an onset date prior to dosing which worsen during this period.

Overall period and Durvalumab Pan-Tumour 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 surgery) or up to and including the date of initiation of the first subsequent therapy (whichever occurs first).

Disease progression AEs reported in Study 1108 are not included in this summary.

Percentages are based on the total numbers of patients in the treatment group (N).

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Dur = Total number of years at risk for AEs summed across all patients within a group. Where total number of years at risk for AEs = (last dose date + X days or death date or DCO whichever occurs earlier - first dose date + 1)/365.25. X is defined as the planned frequency in dosing (in days) - 1. For Q2W, X = 13. For Q3W, X = 20. For Q4W, X = 27.

Table 43 Summary of All Deaths (ITT Population; EFS IA1 and EFS IA2)

Category	Number (%) patients			
	EFS IA1 DCO (10 Nov 2022)		EFS IA2 DCO (10 May 2024)	
	D + CTx (N = 400)	Pbo + CTx (N = 402)	D + CTx (N = 400)	Pbo + CTx (N = 402)
Total number of deaths	83 (20.8)	86 (21.4)	**128 (32.0)**	**150 (37.3)**
Death related to disease under investigation only [a]	50 (12.5)	66 (16.4)	83 (20.8)	121 (30.1)
TEAE with outcome of death only [b]	19 (4.8)	12 (3.0)	19 (4.8)	12 (3.0)
Death related to disease under investigation and with TEAE with an outcome of death [a,b]	4 (1.0)	3 (0.7)	4 (1.0)	3 (0.7)
AE with outcome of death only (AE start date falling after safety follow-up period) [c]	3 (0.8)	1 (0.2)	3 (0.8)	1 (0.2)
Death related to disease under investigation (AE start date falling after safety follow-up period) [c]	0	1 (0.2)	0	1 (0.2)
Patients with unknown reason for death	2 (0.5)	0	7 (1.8)	3 (0.7)
Other deaths [d]	5 (1.3)	3 (0.7)	12 (3.0)	9 (2.2)
Total number of perioperative deaths [e]	4 (1.0)	8 (2.0)	4 (1.0)	8 (2.0)

[a] Death related to disease under investigation is determined by the investigator as recorded on the DEATH form.

[b] Includes AEs with an onset date on or after the date of first dose or pre-treatment AEs that increased in severity and resulted in an outcome of death on or after the date of first dose up to and including the earliest of: maximum date of (last dose or surgery) + 90 days, date of first dose of subsequent anti-cancer therapy.

[c] Includes AEs with outcome of death on or after the earliest of: maximum date of (last dose or surgery) + 90 days, or date of first dose of subsequent anti-cancer therapy.

[d] Patients who died and are not captured in the earlier categories. [e] Includes deaths within 30 days of surgery.

Rows within the "Total number of deaths" section are mutually exclusive; patients are only reported in one category.

DCO: 10 November 2022 (EFS IA1) and 10 May 2024 (EFS IA2).

Immune-mediated adverse events

Table 44 Immune-Mediated Adverse Events in Any Category in the AEGEAN Study and the D Pan-Tumour Pool (Safety Analysis Set)

AE Category	Number (%) of patients [a]				
	AEGEAN Study				D pan-tumour pool (N = 4045)
	Neoadjuvant period		Overall period [b]		
	D + CTx (N = 401)	Placebo + CTx (N = 398)	D + CTx (N = 401)	Placebo + CTx (N = 398)	
Any imAE	33 (8.2)	19 (4.8)	102 (25.4)	41 (10.3)	704 (17.4)
Any imAE of CTCAE Grade 3 or 4	6 (1.5)	5 (1.3)	18 (4.5)	10 (2.5)	175 (4.3)
Any serious imAE (including events with outcome of death) [c]	6 (1.5)	6 (1.5)	21 (5.2)	10 (2.5)	154 (3.8)
Any imAE with outcome of death	1 (0.2)	0	5 (1.2)	0	14 (0.3)
Any imAE possibly related to study treatment [d]	31 (7.7)	17 (4.3)	98 (24.4)	32 (8.0)	579 (14.3)
Any imAE possibly related to study treatment of CTCAE Grade 3 or 4 [d]	6 (1.5)	5 (1.3)	18 (4.5)	10 (2.5)	147 (3.6)
Any serious imAE possibly related to study treatment [c d]	6 (1.5)	6 (1.5)	21 (5.2)	10 (2.5)	137 (3.4)
Any imAE possibly related to study treatment with outcome of death [c, d]	1 (0.2)	0	5 (1.2)	0	12 (0.3)
Received systemic corticosteroids	25 (6.2)	15 (3.8)	62 (15.5)	25 (6.3)	417 (10.3)
Received high dose steroids [e]	17 (4.2)	12 (3.0)	46 (11.5)	18 (4.5)	273 (6.7)
Received endocrine therapy	9 (2.2)	6 (1.5)	47 (11.7)	18 (4.5)	359 (8.9)
Received other immunosuppressants	2 (0.5)	0	5 (1.2)	1 (0.3)	15 (0.4)
Any imAE leading to discontinuation of study treatment	8 (2.0)	1 (0.3)	19 (4.7)	4 (1.0)	111 (2.7)

[a] Patients with multiple events in the same category were counted only once in that category. Patients with events in more than one category were counted once in each of those categories.

[b] Overall period refers to the neoadjuvant period, post-surgery, and adjuvant period, i.e., D + CTx followed by surgery and durvalumab monotherapy, and placebo + CTx followed by surgery and placebo.

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

[d] As assessed by the investigator, and programmatically derived from individual causality assessments for combination studies. Missing responses are counted as possibly related.

[e] A dose of ≥ 40 mg prednisone or equivalent per day (oral) was considered to be a high dose.

Neoadjuvant period includes AEs between date of first dose and the day before surgery, or for patients without surgery up to the earliest of ≤ 90 days after date of last dose of neoadjuvant treatment, first dose of subsequent anti-cancer therapy. Includes AEs with an onset date during this period and AEs with an onset date prior to dosing which worsen during this period.

Overall period and Durvalumab Pan-Tumour 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 surgery) or up to and including the date of initiation of the first subsequent therapy (whichever occurs first).
MedDRA Version 26.1, AESI/AEPI list version 19.1, CTCAE version 4.03 except for AEGEAN which uses CTCAE version 5.0.

Table 45 Immune-mediated AEs by event type (safety analysis set – overall period, EFS IA2)

Events type/Treatment arm [a]	Number (%) patients													
				Treatment related [c]		Received intervention				Led to discontinuation of study drug [e]	Event outcome		
	Any AE	Any SAE [b]	Any CTCAE Grade 3 or 4	Any CTCAE Grade	Any CTCAE Grade 3 or 4	Systemic cortico-steroid	High dose steroids [d]	Other immuno-suppressants	Requires endocrine therapy		Resulted in death	Not resolved	Resolved
Pneumonitis (grouped term)													
D + CTx	18 (4.5)	11 (2.7)	6 (1.5)	18 (4.5)	6 (1.5)	18 (4.5)	18 (4.5)	2 (0.5)	0	5 (1.2)	4 (1.0)	3 (0.7)	11 (2.7)
P + CTx	7 (1.8)	3 (0.8)	4 (1.0)	6 (1.5)	4 (1.0)	7 (1.8)	6 (1.5)	0	0	2 (0.5)	0	5 (1.3)	2 (0.5)
D Pan-Tumour Pool	105 (2.6)	51 (1.3)	29 (0.7)	89 (2.2)	25 (0.6)	105 (2.6)	78 (1.9)	3 (< 0.1)	0	41 (1.0)	7 (0.2)	36 (0.9)	62 (1.5)
Hepatic events (grouped term)													
D + CTx	13 (3.2)	6 (1.5)	8 (2.0)	13 (3.2)	8 (2.0)	13 (3.2)	11 (2.7)	0	0	5 (1.2)	0	1 (0.2)	12 (3.0)
P + CTx	4 (1.0)	1 (0.3)	1 (0.3)	4 (1.0)	1 (0.3)	4 (1.0)	2 (0.5)	0	0	0	0	1 (0.3)	3 (0.8)
D Pan-Tumour Pool	112 (2.8)	39 (1.0)	75 (1.9)	82 (2.0)	55 (1.4)	112 (2.8)	86 (2.1)	7 (0.2)	0	26 (0.6)	6 (0.1)	56 (1.4)	50 (1.2)
Diarrhoea/colitis (grouped term)													
D + CTx	3 (0.7)	1 (0.2)	0	3 (0.7)	0	3 (0.7)	3 (0.7)	1 (0.2)	0	2 (0.5)	0	1 (0.2)	2 (0.5)
P + CTx	5 (1.3)	4 (1.0)	3 (0.8)	5 (1.3)	3 (0.8)	5 (1.3)	4 (1.0)	0	0	1 (0.3)	0	1 (0.3)	4 (1.0)
D Pan-Tumour Pool	76 (1.9)	20 (0.5)	15 (0.4)	51 (1.3)	15 (0.4)	76 (1.9)	52 (1.3)	3 (< 0.1)	0	12 (0.3)	0	22 (0.5)	54 (1.3)
Intestinal perforation (grouped term)													
D + CTx	0	0	0	0	0	0	0	0	0	0	0	0	0
P + CTx	0	0	0	0	0	0	0	0	0	0	0	0	0
D Pan-Tumour Pool	0	0	0	0	0	0	0	0	0	0	0	0	0

Events type/Treatment arm [a]	Number (%) patients													
				Treatment related [c]		Received intervention				Led to discontinuation of study drug [e]	Event outcome		
	Any AE	Any SAE [b]	Any CTCAE Grade 3 or 4	Any CTCAE Grade	Any CTCAE Grade 3 or 4	Systemic cortico-steroid	High dose steroids [d]	Other immuno-suppressants	Requires endocrine therapy		Resulted in death	Not resolved	Resolved
Hypothyroid events (grouped term)													
D + CTx	42 (10.5)	0	0	40 (10.0)	0	0	0	0	42 (10.5)	0	0	30 (7.5)	12 (3.0)
P + CTx	10 (2.5)	0	0	6 (1.5)	0	0	0	0	10 (2.5)	0	0	5 (1.3)	5 (1.3)
D Pan-Tumour Pool	309 (7.6)	5 (0.1)	4 (< 0.1)	260 (6.4)	4 (< 0.1)	17 (0.4)	6 (0.1)	0	304 (7.5)	0	0	248 (6.1)	61 (1.5)
Hyperthyroid events (grouped term)													
D + CTx	7 (1.7)	0	0	6 (1.5)	0	1 (0.2)	0	0	7 (1.7)	0	0	0	7 (1.7)
P + CTx	6 (1.5)	0	0	3 (0.8)	0	1 (0.3)	1 (0.3)	0	6 (1.5)	0	0	3 (0.8)	3 (0.8)
D Pan-Tumour Pool	62 (1.5)	2 (< 0.1)	0	53 (1.3)	0	11 (0.3)	4 (< 0.1)	0	58 (1.4)	1 (< 0.1)	0	15 (0.4)	47 (1.2)
Thyroiditis (grouped term)													
D + CTx	1 (0.2)	0	0	1 (0.2)	0	0	0	0	1 (0.2)	0	0	1 (0.2)	0
P + CTx	2 (0.5)	0	0	1 (0.3)	0	0	0	0	2 (0.5)	0	0	2 (0.5)	0
D Pan-Tumour Pool	16 (0.4)	1 (< 0.1)	2 (< 0.1)	15 (0.4)	2 (< 0.1)	5 (0.1)	3 (< 0.1)	0	13 (0.3)	1 (< 0.1)	0	11 (0.3)	5 (0.1)
Adrenal insufficiency (grouped term)													
D + CTx	3 (0.7)	1 (0.2)	0	1 (0.2)	0	2 (0.5)	0	0	1 (0.2)	0	0	1 (0.2)	2 (0.5)
P + CTx	0	0	0	0	0	0	0	0	0	0	0	0	0
D Pan-Tumour Pool	20 (0.5)	7 (0.2)	6 (0.1)	13 (0.3)	5 (0.1)	20 (0.5)	7 (0.2)	0	7 (0.2)	0	0	15 (0.4)	5 (0.1)

Events type/Treatment arm [a]	Number (%) patients													
				Treatment related [c]		Received intervention				Led to discontinuation of study drug [e]	Event outcome		
	Any AE	Any SAE [b]	Any CTCAE Grade 3 or 4	Any CTCAE Grade	Any CTCAE Grade 3 or 4	Systemic cortico-steroid	High dose steroids [d]	Other immuno-suppressants	Requires endocrine therapy		Resulted in death	Not resolved	Resolved
Hypophysitis (grouped term)													
D + CTx	1 (0.2)	0	0	1 (0.2)	0	1 (0.2)	0	0	0	0	0	0	1 (0.2)
P + CTx	0	0	0	0	0	0	0	0	0	0	0	0	0
D Pan-Tumour Pool	4 (< 0.1)	4 (< 0.1)	3 (< 0.1)	4 (< 0.1)	3 (< 0.1)	4 (< 0.1)	2 (< 0.1)	0	1 (< 0.1)	2 (< 0.1)	0	3 (< 0.1)	1 (< 0.1)
Type I diabetes mellitus (grouped term)													
D + CTx	0	0	0	0	0	0	0	0	0	0	0	0	0
P + CTx	0	0	0	0	0	0	0	0	0	0	0	0	0
D Pan-Tumour Pool	4 (< 0.1)	3 (< 0.1)	3 (< 0.1)	4 (< 0.1)	3 (< 0.1)	0	0	0	4 (< 0.1)	1 (< 0.1)	0	2 (< 0.1)	2 (< 0.1)
Renal events (grouped term)													
D + CTx	2 (0.5)	0	0	2 (0.5)	0	2 (0.5)	1 (0.2)	0	0	1 (0.2)	0	1 (0.2)	1 (0.2)
P + CTx	0	0	0	0	0	0	0	0	0	0	0	0	0
D Pan-Tumour Pool	17 (0.4)	5 (0.1)	5 (0.1)	11 (0.3)	5 (0.1)	17 (0.4)	12 (0.3)	1 (< 0.1)	0	7 (0.2)	0	9 (0.2)	8 (0.2)
Dermatitis/rash events (grouped term)													
D + CTx	22 (5.5)	0	2 (0.5)	20 (5.0)	2 (0.5)	22 (5.5)	9 (2.2)	0	0	3 (0.7)	0	3 (0.7)	19 (4.7)
P + CTx	7 (1.8)	0	1 (0.3)	7 (1.8)	1 (0.3)	7 (1.8)	4 (1.0)	0	0	0	0	1 (0.3)	6 (1.5)
D Pan-Tumour Pool	65 (1.6)	5 (0.1)	17 (0.4)	52 (1.3)	17 (0.4)	65 (1.6)	34 (0.8)	0	0	5 (0.1)	0	24 (0.6)	41 (1.0)

Events type/Treatment arm [a]	Number (%) patients												
				Treatment related [c]		Received intervention				Led to discontinuation of study drug [e]	Event outcome		
	Any AE	Any SAE [b]	Any CTCAE Grade 3 or 4	Any CTCAE Grade	Any CTCAE Grade 3 or 4	Systemic cortico-steroid	High dose steroids [d]	Other immuno-suppressants	Requires endocrine therapy		Resulted in death	Not resolved	Resolved
Myocarditis events (grouped term)													
D + CTx	1 (0.2)	1 (0.2)	0	1 (0.2)	0	1 (0.2)	1 (0.2)	0	0	1 (0.2)	1 (0.2)	0	0
P + CTx	0	0	0	0	0	0	0	0	0	0	0	0	0
D Pan-Tumour Pool	5 (0.1)	4 (< 0.1)	4 (< 0.1)	3 (< 0.1)	3 (< 0.1)	5 (0.1)	5 (0.1)	2 (< 0.1)	0	3 (< 0.1)	0	4 (< 0.1)	1 (< 0.1)
Myositis events (grouped term)													
D + CTx	0	0	0	0	0	0	0	0	0	0	0	0	0
P + CTx	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.3)	0	0	1 (0.3)	0	0	1 (0.3)
D Pan-Tumour Pool	4 (< 0.1)	3 (< 0.1)	3 (< 0.1)	4 (< 0.1)	3 (< 0.1)	4 (< 0.1)	4 (< 0.1)	0	0	2 (< 0.1)	0	2 (< 0.1)	2 (< 0.1)
Pancreatic events (grouped term)													
D + CTx	2 (0.5)	0	1 (0.2)	2 (0.5)	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)	0	0	0	0	2 (0.5)
P + CTx	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.3)	0	0	0	0	1 (0.3)	0
D Pan-Tumour Pool	9 (0.2)	2 (< 0.1)	4 (< 0.1)	7 (0.2)	3 (< 0.1)	9 (0.2)	5 (0.1)	0	0	1 (< 0.1)	0	3 (< 0.1)	6 (0.1)
Myasthenia gravis (grouped term)													
D + CTx	1 (0.2)	0	0	1 (0.2)	0	1 (0.2)	0	0	0	1 (0.2)	0	0	1 (0.2)
P + CTx	0	0	0	0	0	0	0	0	0	0	0	0	0
D Pan-Tumour Pool	2 (< 0.1)	2 (< 0.1)	1 (< 0.1)	2 (< 0.1)	1 (< 0.1)	2 (< 0.1)	2 (< 0.1)	0	0	1 (< 0.1)	0	2 (< 0.1)	0

Events type/Treatment arm [a]	Number (%) patients												
				Treatment related [c]		Received intervention				Led to discontinuation of study drug [e]	Event outcome		
	Any AE	Any SAE [b]	Any CTCAE Grade 3 or 4	Any CTCAE Grade	Any CTCAE Grade 3 or 4	Systemic cortico-steroid	High dose steroids [d]	Other immuno-suppressants	Requires endocrine therapy		Resulted in death	Not resolved	Resolved
Guillain-Barré syndrome events (grouped term)													
D + CTx	0	0	0	0	0	0	0	0	0	0	0	0	0
P + CTx	0	0	0	0	0	0	0	0	0	0	0	0	0
D Pan-Tumour Pool	1 (< 0.1)	1 (< 0.1)	1 (< 0.1)	1 (< 0.1)	1 (< 0.1)	1 (< 0.1)	1 (< 0.1)	0	0	1 (< 0.1)	0	1 (< 0.1)	0
Other rare/miscellaneous AEs													
D + CTx	4 (1.0)	1 (0.2)	2 (0.5)	4 (1.0)	2 (0.5)	4 (1.0)	4 (1.0)	1 (0.2)	0	1 (0.2)	0	1 (0.2)	3 (0.7)
P + CTx	3 (0.8)	1 (0.3)	0	3 (0.8)	0	3 (0.8)	1 (0.3)	1 (0.3)	0	0	0	2 (0.5)	1 (0.3)
D Pan-Tumour Pool	54 (1.3)	9 (0.2)	11 (0.3)	30 (0.7)	10 (0.2)	54 (1.3)	18 (0.4)	0	0	7 (0.2)	1 (< 0.1)	34 (0.8)	19 (0.5)

[a] N = 401 for D + CTx arm; N = 398 for placebo + CTx arm; N = 4045 for D pan-tumour pool.

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

[c] Possibly related to any of the study treatments, as assessed by the investigator. Missing responses are counted as related.

[d] A dose of ≥ 40 mg prednisone or equivalent per day (oral) was considered to be a high dose.

[e] AEs on the AE eCRF page with Action taken = "Drug permanently discontinued" for at least one treatment.

Note: Additional events since EFS IA1 are not necessarily new adjuvant events as there were updates to the neoadjuvant and post-surgery periods at EFS IA2 from EFS IA1.

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 surgery) or up to and including the date of initiation of the first subsequent therapy (whichever occurs first).

Reasons of NOT RECOVERED/NOT RESOLVED, RECOVERING/RESOLVING, and UNKNOWN map to an outcome of Not Resolved. Of these, imAEs were recovering/resolving for 20 (5.0%) patients in the D + CTx arm and 3 (0.8%) patients in the placebo + CTx arm .

Reasons of RECOVERED/RESOLVED, RECOVERED/RESOLVED WITH SEQUELAE map to an outcome of Resolved.

MedDRA Version 26.1. CTCAE version 4.03 except for AEGEAN which uses CTCAE version 5.0.

AEGEAN DCO: 10 May 2024.

The D pan-tumour pool includes the following studies: ATLANTIC, Study 1108, ARCTIC, PACIFIC, Japan Study 2, CONDOR, EAGLE, MYSTIC, HAWK, DANUBE, KESTREL, Study 22, and HIMALAYA.

Table 46 Summary of AEs and/or AESIs of pneumonitis, interstitial lung disease and immune-mediated lung disease (safety analysis set – overall period, EFS IA2, DCO: 10 May 2024)

MedDRA PT/ Treatment arm	Number (%) patients [a]						
	Investigator reported AEs						
	Any AE	Any SAE	Maximum CTCAE Grade 3 or 4 [b]	Any AE possibly related to study treatment [c]	Leading to discontinuation of any study treatment [d]	Resulted in death	imAE [e]
Any AESI of pneumonitis [Grouped term] (includes pneumonitis, interstitial lung disease or immune-mediated lung disease)							
D + CTx (N = 401)	24 (6.0)	12 (3.0)	6 (1.5)	24 (6.0)	9 (2.2)	4 (1.0)	18 (4.5)
P + CTx (N = 398)	12 (3.0)	4 (1.0)	5 (1.3)	10 (2.5)	4 (1.0)	0	7 (1.8)
Pneumonitis							
D + CTx (N = 401)	18 (4.5)	7 (1.7)	4 (1.0)	18 (4.5)	7 (1.7)	1 (0.2)	12 (3.0)
P + CTx (N = 398)	6 (1.5)	1 (0.3)	1 (0.3)	4 (1.0)	2 (0.5)	0	3 (0.8)
Interstitial lung disease							
D + CTx (N = 401)	3 (0.7)	3 (0.7)	1 (0.2)	3 (0.7)	1 (0.2)	2 (0.5)	3 (0.7)
P + CTx (N = 398)	6 (1.5)	3 (0.8)	4 (1.0)	6 (1.5)	2 (0.5)	0	4 (1.0)
Immune-mediated lung disease							
D + CTx (N = 401)	3 (0.7)	2 (0.5)	1 (0.2)	3 (0.7)	1 (0.2)	1 (0.2)	3 (0.7)
P + CTx (N = 398)	0	0	0	0	0	0	0

a Patients with multiple events in the same PT are counted only once in that PT.
b Excludes any patients with an AE of Grade 5 within the PT.
c Possibly related to any study drug, as assessed by the investigator. Study treatment refers to durvalumab/placebo or CTx and does not include surgery.
d Action taken: drug permanently discontinued. Any study treatment includes durvalumab, placebo and chemotherapy.
e AEs adjudicated as imAEs (see the Durvalumab and Tremelimumab Global ImAE Characterization Charter in Appendix 16.1.9).
Includes AEs between date of first dose and the earliest of: maximum date of (last dose or surgery) + 90 days, date of first dose of subsequent anti-cancer therapy. Includes AEs with an onset date during this period and AEs with an onset date prior to dosing which worsen during this period.
Note: Additional events since EFS IA1 are not necessarily new adjuvant events as there were updates to the neoadjuvant and post-surgery periods at EFS IA2 from EFS IA1.

MedDRA version 26.1 at EFS IA2.
DCO: 10 May 2024.

Table 47 IA1Subjects with at least one treatment-emergent adverse event in any category by durvalumab ADA category

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	Durvalumab + SOC (N=377)			
AE category	TE-ADA+ [a]	nAb+	ADA+ [b]	ADA-
Any AE leading to dose interruption or reduction of study treatment [c]	10 (40.0)	1 (50.0)	16 (34.0)	164 (50.0)
Any AESIs or AEPIs	19 (76.0)	2 (100)	31 (66.0)	212 (64.6)
Any AESIs or AEPIs possibly related to durvalumab/placebo	12 (48.0)	2 (100)	21 (44.7)	149 (45.4)
Immune mediated AEs [d]	12 (48.0)	1 (50.0)	18 (38.3)	126 (38.4)
Infusion reaction AEs [d]	3 (12.0)	1 (50.0)	3 (6.4)	9 (2.7)

Data Cut-off: 2022-11-10

Pneumonitis and radiation pneumonitis in the subset of patients who received post-operative radiotherapy

Table 48 Pneumonitis or Radiation Pneumonitis events by grouped term and preferred term and maximum CTCAE grade (Safety analysis set)

		Number (%) of patients [a]			
		AEGEAN		AEGEAN+TOPAZ-1+CASPIAN+DUO-E	
Grouped term/ Preffered Term	Maximum reported CTCAE grade	Durvalumab + CTx (N=30)	Placebo + CTx (N=27)	Durvalumab + Chemo (N=868)	Chemo (N=871)
Pneumonitis or radiation pneumonitis	Total	10 (33.3)	3 (11.1)	27 (3.1)	17 (2.0)
	Grade 3	2 (6.7)	0	7 (0.8)	3 (0.3)
	Grade 4	0	0	0	0
	Grade 5	0	0	1 (0.1)	2 (0.2)
	Grade 3 or 4	2 (6.7)	0	7 (0.8)	3 (0.3)

Laboratory findings

Table 49 Clinically Important Changes in Haematology Parameters (Safety Analysis Set [Overall Period a]) – DCO 2022-11-10 EFS IA1

	Number (%) of patients								
	AEGEAN study						D pan-tumour pool [a] (N = 4045)		
	D + CTx (N = 401)			Placebo + CTx (N = 398)					
Chemistry parameter	≥ 1 CTCAE Grade changes	≥ 2 CTCAE Grade changes	CTCAE Grade changes to 3 or 4	≥ 1 CTCAE Grade changes	≥ 2 CTCAE Grade changes	CTCAE Grade changes to 3 or 4	≥ 1 CTCAE Grade changes	≥ 2 CTCAE Grade changes	CTCAE Grade changes to 3 or 4
Haemoglobin	314/399 (78.7)	98/399 (24.6)	40/399 (10.0)	298/398 (74.9)	89/398 (22.4)	35/398 (8.8)	1489/3868 (38.5)	209/3868 (5.4)	193/3868 (5.0)
Low	313/399 (78.4)	97/399 (24.3)	39/399 (9.8)	297/398 (74.6)	88/398 (22.1)	34/398 (8.5)	1489/3868 (38.5)	209/3868 (5.4)	193/3868 (5.0)
High	3/399 (0.8)	1/399 (0.3)	1/399 (0.3)	3/398 (0.8)	2/398 (0.5)	2/398 (0.5)	NA	NA	NA
Leukocytes	251/399 (62.9)	103/399 (25.8)	46/399 (11.5)	254/398 (63.8)	115/398 (28.9)	43/398 (10.8)	640/3868 (16.5)	75/3868 (1.9)	22/3868 (0.6)
Lymphocytes	183/399 (45.9)	126/399 (31.6)	42/399 (10.5)	164/398 (41.2)	98/398 (24.6)	35/398 (8.8)	1706/3828 (44.6)	748/3828 (19.5)	507/3828 (13.2)
Low	163/399 (40.9)	105/399 (26.3)	42/399 (10.5)	148/398 (37.2)	81/398 (20.4)	35/398 (8.8)	1700/3828 (44.4)	738/3828 (19.3)	506/3828 (13.2)

Chemistry parameter	Number (%) of patients								
	AEGEAN study						D pan-tumour pool [a] (N = 4045)		
	D + CTx (N = 401)			Placebo + CTx (N = 398)					
	≥ 1 CTCAE Grade changes	≥ 2 CTCAE Grade changes	CTCAE Grade changes to 3 or 4	≥ 1 CTCAE Grade changes	≥ 2 CTCAE Grade changes	CTCAE Grade changes to 3 or 4	≥ 1 CTCAE Grade changes	≥ 2 CTCAE Grade changes	CTCAE Grade changes to 3 or 4
High	27/399 (6.8)	27/399 (6.8)	0/399	24/398 (6.0)	24/398 (6.0)	0/398	11/3828 (0.3)	11/3828 (0.3)	1/3828 (< 0.1)
Neutrophils	208/399 (52.1)	159/399 (39.8)	97/399 (24.3)	221/398 (55.5)	180/398 (45.2)	109/398 (27.4)	269/3833 (7.0)	119/3833 (3.1)	37/3833 (1.0)
Platelets	184/398 (46.2)	46/398 (11.6)	27/398 (6.8)	174/398 (43.7)	45/398 (11.3)	30/398 (7.5)	558/3865 (14.4)	64/3865 (1.7)	44/3865 (1.1)

[a] Overall period refers to the neoadjuvant period, post-surgery and adjuvant period, i.e., D + CTx followed by surgery and durvalumab monotherapy, and placebo + CTx followed by surgery and placebo.

Percentages are based on the total number of patients in the treatment group (N).
Overall period and D pan-tumour pool is derived from laboratory assessments from the start of treatment up to and including 90 days following the date of last dose of study medication (or surgery if later) or up to and including the date of initiation of the first subsequent therapy (whichever occurs first).
Patient's worst (highest CTCAE grade) changes from baseline are used.

All studies use CTCAE version 4.03 except for AEGEAN which uses CTCAE version 5.0. Version 4.03 of the CTCAE grading criteria only assessed haemoglobin in the low direction, in CTCAE version 5.0 haemoglobin is a bi-directional lab parameter.

Table 50 Clinically Important Changes in Clinical Chemistry Parameters (Safety Analysis Set [Overall Period a]) – DCO 2022-11-10 EFS IA1

Chemistry parameter	Number (%) of patients								
	AEGEAN study						D pan-tumour pool [a] (N = 4045)		
	D + CTx (N = 401)			Placebo + CTx (N = 398)					
	≥ 1 CTCAE Grade changes	≥ 2 CTCAE Grade changes	CTCAE Grade changes to 3 or 4	≥ 1 CTCAE Grade changes	≥ 2 CTCAE Grade changes	CTCAE Grade changes to 3 or 4	≥ 1 CTCAE Grade changes	≥ 2 CTCAE Grade changes	CTCAE Grade changes to 3 or 4
Alanine aminotransferase	196/398 (49.2)	44/398 (11.1)	23/398 (5.8)	167/396 (42.2)	17/396 (4.3)	8/396 (2.0)	1219/3860 (31.6)	224/3860 (5.8)	145/3860 (3.8)
Albumin	45/396 (11.4)	24/396 (6.1)	4/396 (1.0)	39/396 (9.8)	20/396 (5.1)	1/396 (0.3)	1144/3821 (29.9)	475/3821 (12.4)	60/3821 (1.6)
Alkaline phosphatase	75/397 (18.9)	8/397 (2.0)	2/397 (0.5)	60/396 (15.2)	4/396 (1.0)	1/396 (0.3)	1166/3840 (30.4)	192/3840 (5.0)	168/3840 (4.4)
Amylase	96/384 (25.0)	30/384 (7.8)	18/384 (4.7)	91/386 (23.6)	21/386 (5.4)	14/386 (3.6)	292/1225 (23.8)	83/1225 (6.8)	66/1225 (5.4)
Aspartate aminotransferase	186/398 (46.7)	26/398 (6.5)	14/398 (3.5)	148/396 (37.4)	15/396 (3.8)	7/396 (1.8)	1324/3850 (34.4)	259/3850 (6.7)	235/3850 (6.1)
Corrected calcium	204/394 (51.8)	22/394 (5.6)	15/394 (3.8)	207/396 (52.3)	29/396 (7.3)	20/396 (5.1)	1370/3696 (37.1)	196/3696 (5.3)	111/3696 (3.0)
Low	201/394 (51.0)	20/394 (5.1)	13/394 (3.3)	204/396 (51.5)	26/396 (6.6)	18/396 (4.5)	1033/3696 (27.9)	54/3696 (1.5)	20/3696 (0.5)

Chemistry parameter	Number (%) of patients								
	AEGEAN study						D pan-tumour pool [a] (N = 4045)		
	D + CTx (N = 401)			Placebo + CTx (N = 398)					
	≥ 1 CTCAE Grade changes	≥ 2 CTCAE Grade changes	CTCAE Grade changes to 3 or 4	≥ 1 CTCAE Grade changes	≥ 2 CTCAE Grade changes	CTCAE Grade changes to 3 or 4	≥ 1 CTCAE Grade changes	≥ 2 CTCAE Grade changes	CTCAE Grade changes to 3 or 4
High	8/394 (2.0)	4/394 (1.0)	4/394 (1.0)	9/396 (2.3)	5/396 (1.3)	3/396 (0.8)	376/3696 (10.2)	144/3696 (3.9)	91/3696 (2.5)
Creatinine	126/398 (31.7)	81/398 (20.4)	9/398 (2.3)	105/396 (26.5)	60/396 (15.2)	13/396 (3.3)	1139/3796 (30.0)	154/3796 (4.1)	33/3796 (0.9)
Gamma glutamyl transferase	138/383 (36.0)	29/383 (7.6)	18/383 (4.7)	133/378 (35.2)	23/378 (6.1)	8/378 (2.1)	648/1765 (36.7)	187/1765 (10.6)	170/1765 (9.6)
Glucose [b]	15/202 (7.4)	2/202 (1.0)	1/202 (0.5)	13/212 (6.1)	5/212 (2.4)	3/212 (1.4)	1694/3826 (44.3)	546/3826 (14.3)	227/3826 (5.9)
Low	15/202 (7.4)	2/202 (1.0)	1/202 (0.5)	13/212 (6.1)	5/212 (2.4)	3/212 (1.4)	185/3826 (4.8)	57/3826 (1.5)	19/3826 (0.5)
High	0/202	0/202	0/202	0/212	0/212	0/212	1592/3826 (41.6)	500/3826 (13.1)	209/3826 (5.5)
Lipase	79/349 (22.6)	34/349 (9.7)	17/349 (4.9)	79/333 (23.7)	33/333 (9.9)	23/333 (6.9)	286/1225 (23.3)	130/1225 (10.6)	103/1225 (8.4)
Magnesium	106/389 (27.2)	35/389 (9.0)	22/389 (5.7)	96/386 (24.9)	32/386 (8.3)	24/386 (6.2)	569/3297 (17.3)	58/3297 (1.8)	54/3297 (1.6)
Low	85/389 (21.9)	24/389 (6.2)	11/389 (2.8)	76/386 (19.7)	22/386 (5.7)	14/386 (3.6)	401/3297 (12.2)	18/3297 (0.5)	14/3297 (0.4)
High	27/389 (6.9)	11/389 (2.8)	11/389 (2.8)	27/386 (7.0)	16/386 (4.1)	16/386 (4.1)	188/3297 (5.7)	41/3297 (1.2)	41/3297 (1.2)
Potassium	180/398 (45.2)	37/398 (9.3)	20/398 (5.0)	182/395 (46.1)	40/395 (10.1)	28/395 (7.1)	1363/3853 (35.4)	295/3853 (7.7)	157/3853 (4.1)
Low	63/398 (15.8)	14/398 (3.5)	14/398 (3.5)	79/395 (20.0)	20/395 (5.1)	20/395 (5.1)	468/3853 (12.1)	77/3853 (2.0)	79/3853 (2.1)
High	133/398 (33.4)	26/398 (6.5)	6/398 (1.5)	115/395 (29.1)	20/395 (5.1)	8/395 (2.0)	949/3853 (24.6)	222/3853 (5.8)	80/3853 (2.1)
Sodium	167/398 (42.0)	26/398 (6.5)	22/398 (5.5)	155/396 (39.1)	26/396 (6.6)	24/396 (6.1)	1671/3861 (43.3)	328/3861 (8.5)	325/3861 (8.4)
Low	138/398 (34.7)	21/398 (5.3)	21/398 (5.3)	131/396 (33.1)	23/396 (5.8)	23/396 (5.8)	1469/3861 (38.0)	313/3861 (8.1)	319/3861 (8.3)
High	43/398 (10.8)	5/398 (1.3)	1/398 (0.3)	30/396 (7.6)	3/396 (0.8)	1/396 (0.3)	249/3861 (6.4)	15/3861 (0.4)	6/3861 (0.2)
Total bilirubin	46/397 (11.6)	12/397 (3.0)	5/397 (1.3)	32/395 (8.1)	7/395 (1.8)	2/395 (0.5)	505/3853 (13.1)	202/3853 (5.2)	103/3853 (2.7)

[a] Overall period refers to the neoadjuvant period, post-surgery and adjuvant period, i.e., D + CTx followed by surgery and durvalumab monotherapy, and placebo + CTx followed by surgery and placebo.

[b] AEGEAN study collects data for random, fasting and non-fasting glucose and this table presents fasting glucose only for AEGEAN columns. Pooled column contains a mix of random, fasting and non-fasting glucose.

Percentages are based on the total number of patients in the treatment group (N).
Overall period and D pan-tumour pool is derived from laboratory assessments from the start of treatment up to and including 90 days following the date of last dose of study medication (or surgery if later) or up to and including the date of initiation of the first subsequent therapy (whichever occurs first).
Patient's worst (highest CTCAE grade; highest CTC grade in the direction of high corrected calcium) changes from baseline are used.
All studies use CTCAE version 4.03 except for AEGEAN which uses CTCAE version 5.0.

Table 51 Abnormal Thyroid Tests (Safety Analysis Set [Overall Period a]) – DCO 2022-11-10 EFS IA1

Thyroid Function Tests	Number (%) of patients [b]		
	AEGEAN study		D pan-tumour pool [a] (N = 4045)
	D + CTx (N = 401)	Placebo + CTx (N = 398)	
On-treatment elevated TSH > ULN	122 (30.4)	94 (23.6)	1269 (31.4)
On-treatment elevated TSH > ULN with TSH ≤ ULN at baseline *	85	58	780
with at least one T3 free/T4 free < LLN	57 (67.1)	20 (34.5)	456 (58.5)
with all other T3 free/T4 free ≥ LLN	27 (31.8)	33 (56.9)	270 (34.6)
with all T3 free/T4 free missing	1 (1.2)	5 (8.6)	54 (6.9)
On-treatment low TSH < LLN	105 (26.2)	80 (20.1)	880 (21.8)
On-treatment low TSH < LLN with baseline TSH ≥ LLN *	85	54	709
with at least one T3 free/T4 free > ULN	44 (51.8)	17 (31.5)	310 (43.7)
with all other T3 free/T4 free ≤ ULN	37 (43.5)	35 (64.8)	348 (49.1)
with all T3 free/T4 free missing	4 (4.7)	2 (3.7)	51 (7.2)
Number of patients with at least one baseline and post-baseline TSH result *	395	393	3679
On-treatment elevated TSH > ULN	115 (29.1)	79 (20.1)	1108 (30.1)
On-treatment elevated TSH > ULN with baseline TSH ≤ ULN	97 (24.6)	75 (19.1)	816 (22.2)

[a] Overall period refers to the neoadjuvant period, post-surgery and adjuvant period, i.e., D + CTx followed by surgery and durvalumab monotherapy, and placebo + CTx followed by surgery and placebo.

[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.
Percentages are based on the total number of patients in the treatment group (N).
Overall period and D pan-tumour pool is derived from laboratory assessments from the start of treatment up to and including 90 days following the date of last dose of study medication (or surgery if later) or up to and including the date of initiation of the first subsequent therapy (whichever occurs first).
T3 = Triiodothyronine, T4 = Thyroxine.

Table 52 PHL cases assessed as confirmed Hy's law cases (EFS IA1)

Study day met PHL biochemical pattern criteria[a]	Baseline ALT/Peak ALT (Study Day)	Peak TBL (Study Day)	Relevant AEs around time of the event (Study Days, Maximum CTCAE Grade)	Action taken with study drug	Steroids?	Outcome
Day 142 (drug-induced liver injury first episode) Day 342 (drug-induced liver injury second episode)	5/416 U/L (Day 140; reference range: 0-34.99 U/L) Second PHL ALT peak 1947 U/L (Day 342)	42.75 µmol/L (Day 143; ref range: 0-16.929 µmol/L) Second PHL 331.74 µmol/L (Day 345)	SAE of hepatic failure (Days 135-265, Grade 4) SAE of drug-induced liver injury (Days 142-148, Grade 4) SAE of hepatic failure (Days 331-453, during follow-up, Grade 4) SAE of drug-induced liver injury (Days 342-365, during follow-up, Grade 4)	N/A (patient had completed the maximum 4 cycles of neoadjuvant therapy) – adjuvant treatment was not administered because of the first event of hepatic failure	Multiple courses of IV and oral steroids from Day 142	Drug-induced liver injury and hepatic failure (first episodes) resolved at Day 148 and Day 265, respectively Drug-induced liver injury and hepatic failure (second episodes) resolved at Day 365 and Day 453, respectively
Day 49	20/153 U/L (Day 42; ref range: 5-45 U/L)	184.851 µmol/L (Day 70; ref range: 0-17.1 µmol/L)	SAE of immune-mediated hepatitis (Days 42-135, Grade 3) SAE of drug-induced liver injury (Days 49-70, Grade 3)	Permanent discontinuation on Day 70 due to drug-induced liver injury and immune-mediated hepatitis	Oral steroids started on Day 42 at 10 mg for immune-mediated hepatitis (increased to 50 mg on Day 63)	Immune-mediated hepatitis resolved at Day 135 Drug-induced liver injury resolved at Day 70
Day 84	17/1147 U/L (Day 84; ref range 0-50 U/L)	71.82 µmol/L (Day 88; ref range 0-20.52 µmol/L)	SAE of hepatitis (Days 80-105, Grade 4)	N/A (patient had completed the maximum 4 cycles of neoadjuvant	IV steroids (20 mg on Day 81 increased to 40 mg on Day 83)	Hepatitis resolved at Day 105

Study day met PHL biochemical pattern criteria[a]	Baseline ALT/Peak ALT (Study Day)	Peak TBL (Study Day)	Relevant AEs around time of the event (Study Days, Maximum CTCAE Grade)	Action taken with study drug	Steroids?	Outcome
			SAE of drug-induced liver injury (Days 84-90, Grade 3) AE of hyponatraemia (Days 80-84; Grade 4) AE of Klebsiella bacteraemia (Days 91-97; Grade 2) AE of ALP increased (Days 106-119; Grade 1)	therapy) – adjuvant treatment was not administered because of the events	then oral steroids administered from Day 95	Drug-induced liver injury resolved at Day 90

[a] For PHL and Hy's law the elevation in transaminases must have preceded or have been coincident with the elevation in TBL (i.e., on the same day).

Safety in special populations

Age

Table 53 Adverse Events in any Category in the AEGEAN Study and the D Pan-Tumour Pool – Patient Level by Age Group (Safety Analysis Set)

AE category	Number (%) of patients [a]				
	AEGEAN study				D pan-tumour pool
	Neoadjuvant period		Overall period [b]		
	D + CTx (N1 = 22) (N2 = 170) (N3 = 160) (N4 = 49)	Placebo + CTx (N1 = 22) (N2 = 175) (N3 = 164) (N4 = 37)	D + CTx (N1 = 22) (N2 = 170) (N3 = 160) (N4 = 49)	Placebo + CTx (N1= 22) (N2 = 175) (N3 = 164) (N4 = 37)	(N1 = 482) (N2 = 1768) (N3 = 1356) (N4 = 439)
Any AE possibly related to any study treatment [c]					
< 50 years	18 (81.8)	16 (72.7)	18 (81.8)	17 (77.3)	255 (52.9)
≥ 50 to < 65 years	142 (83.5)	138 (78.9)	150 (88.2)	142 (81.1)	1033 (58.4)
≥ 65 to < 75 years	128 (80.0)	128 (78.0)	138 (86.3)	133 (81.1)	804 (59.3)
≥ 75 years	42 (85.7)	31 (83.8)	44 (89.8)	33 (89.2)	248 (56.5)
Any AE possibly related to durvalumab/placebo [c]					
< 50 years	8 (36.4)	9 (40.9)	9 (40.9)	10 (45.5)	253 (52.5)
≥ 50 to < 65 years	63 (37.1)	58 (33.1)	93 (54.7)	72 (41.1)	1030 (58.3)
≥ 65 to < 75 years	69 (43.1)	65 (39.6)	96 (60.0)	82 (50.0)	801 (59.1)
≥ 75 years	19 (38.8)	11 (29.7)	26 (53.1)	16 (43.2)	248 (56.5)
Any AE possibly related to any study treatment of maximum CTCAE Grade 3 or Grade 4 [c d]					
< 50 years	4 (18.2)	4 (18.2)	5 (22.7)	4 (18.2)	40 (8.3)
≥ 50 to < 65 years	47 (27.6)	51 (29.1)	55 (32.4)	51 (29.1)	204 (11.5)
≥ 65 to < 75 years	48 (30.0)	63 (38.4)	54 (33.8)	66 (40.2)	165 (12.2)
≥ 75 years	19 (38.8)	12 (32.4)	20 (40.8)	12 (32.4)	56 (12.8)
Any AE possibly related to durvalumab/placebo of maximum CTCAE Grade 3 or Grade 4 [c d]					
< 50 years	1 (4.5)	1 (4.5)	2 (9.1)	1 (4.5)	39 (8.1)
≥ 50 to < 65 years	16 (9.4)	12 (6.9)	27 (15.9)	13 (7.4)	199 (11.3)
≥ 65 to < 75 years	17 (10.6)	24 (14.6)	24 (15.0)	31 (18.9)	165 (12.2)
≥ 75 years	3 (6.1)	1 (2.7)	6 (12.2)	2 (5.4)	56 (12.8)
Any AE with outcome of death					
< 50 years	0	0	0	0	23 (4.8)
≥ 50 to < 65 years	5 (2.9)	1 (0.6)	9 (5.3)	4 (2.3)	89 (5.0)
≥ 65 to < 75 years	1 (0.6)	3 (1.8)	10 (6.3)	9 (5.5)	90 (6.6)
≥ 75 years	2 (4.1)	0	4 (8.2)	2 (5.4)	29 (6.6)
Any SAE (including events with outcome of death) [e]					
< 50 years	1 (4.5)	2 (9.1)	2 (9.1)	4 (18.2)	165 (34.2)
≥ 50 to < 65 years	36 (21.2)	27 (15.4)	63 (37.1)	51 (29.1)	596 (33.7)
≥ 65 to < 75 years	34 (21.3)	32 (19.5)	71 (44.4)	61 (37.2)	482 (35.5)
≥ 75 years	12 (24.5)	5 (13.5)	21 (42.9)	10 (27.0)	204 (46.5)
Any AE leading to discontinuation of durvalumab/placebo					
< 50 years	0	0	0	0	35 (7.3)
≥ 50 to < 65 years	11 (6.5)	2 (1.1)	17 (10.0)	4 (2.3)	153 (8.7)

AE category	Number (%) of patients [a]				
	AEGEAN study				D pan-tumour pool (N1 = 482) (N2 = 1768) (N3 = 1356) (N4 = 439)
	Neoadjuvant period		Overall period [b]		
	D + CTx (N1 = 22) (N2 = 170) (N3 = 160) (N4 = 49)	Placebo + CTx (N1 = 22) (N2 = 175) (N3 = 164) (N4 = 37)	D + CTx (N1 = 22) (N2 = 170) (N3 = 160) (N4 = 49)	Placebo + CTx (N1= 22) (N2 = 175) (N3 = 164) (N4 = 37)	
≥ 65 to < 75 years	10 (6.3)	13 (7.9)	26 (16.3)	18 (11.0)	156 (11.5)
≥ 75 years	5 (10.2)	0	8 (16.3)	3 (8.1)	53 (12.1)

[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] Overall period refers to the neoadjuvant period, post-surgery, and adjuvant period, i.e., D + CTx followed by surgery and durvalumab monotherapy, and placebo + CTx followed by surgery and placebo.

[c] As assessed by the investigator. Missing responses are counted as possibly related. Study treatment includes durvalumab, CTx, placebo, in this context surgery is not included as a study treatment.

[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.

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. Percentages are calculated from N1, N2, N3, and N4 for < 50 years, ≥ 50 to < 65 years, ≥ 65 to < 75 years and ≥ 75 years, respectively.

Neoadjuvant period includes AEs between date of first dose and the day before surgery, or for patients without surgery up to the earliest of ≤ 90 days after date of last dose of neoadjuvant treatment, first dose of subsequent anti-cancer therapy. Includes AEs with an onset date during this period and AEs with an onset date prior to dosing which worsen during this period.

Overall period and Durvalumab Pan-Tumour 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 surgery) or up to and including the date of initiation of the first subsequent therapy (whichever occurs first).

Disease progression AEs reported in Study 1108 are not included in this summary.

All studies use CTCAE version 4.03 except for AEGEAN which uses CTCAE version 5.0.

MedDRA version 26.1.

Sex

Table 54 Adverse Events in any Category in the AEGEAN Study and the D Pan-Tumour Pool – Patient Level by Sex (Safety Analysis Set)

AE category	Number (%) of patients [a]				
	AEGEAN study				D pan-tumour pool (N1 = 2783) (N2 = 1262)
	Neoadjuvant period		Overall period [b]		
	D + CTx (N1 = 262) (N2 = 139)	Placebo + CTx (N1 = 289) (N2 = 109)	D + CTx (N1 = 262) (N2 = 139)	Placebo + CTx (N1 = 289) (N2 = 109)	
Any AE possibly related to any study treatment [c]					
Male	218 (83.2)	227 (78.5)	228 (87.0)	237 (82.0)	1605 (57.7)
Female	112 (80.6)	86 (78.9)	122 (87.8)	88 (80.7)	735 (58.2)
Any AE possibly related to durvalumab/placebo [c]					
Male	102 (38.9)	100 (34.6)	135 (51.5)	131 (45.3)	1597 (57.4)
Female	57 (41.0)	43 (39.4)	89 (64.0)	49 (45.0)	735 (58.2)
Any AE possibly related to any study treatment of maximum CTCAE Grade 3 or Grade 4 [c]					

AE category	Number (%) of patients [a]				
	AEGEAN study				D pan-tumour pool (N1 = 2783) (N2 = 1262)
	Neoadjuvant period		Overall period [b]		
	D + CTx (N1 = 262) (N2 = 139)	Placebo + CTx (N1 = 289) (N2 = 109)	D + CTx (N1 = 262) (N2 = 139)	Placebo + CTx (N1 = 289) (N2 = 109)	
Male	82 (31.3)	102 (35.3)	95 (36.3)	104 (36.0)	324 (11.6)
Female	36 (25.9)	28 (25.7)	39 (28.1)	29 (26.6)	141 (11.2)
Any AE possibly related to durvalumab/placebo of maximum CTCAE Grade 3 or Grade 4 [c d]					
Male	30 (11.5)	27 (9.3)	44 (16.8)	35 (12.1)	319 (11.5)
Female	7 (5.0)	11 (10.1)	15 (10.8)	12 (11.0)	140 (11.1)
Any AE with outcome of death					
Male	6 (2.3)	2 (0.7)	17 (6.5)	10 (3.5)	167 (6.0)
Female	2 (1.4)	2 (1.8)	6 (4.3)	5 (4.6)	64 (5.1)
Any SAE (including events with outcome of death) [e]					
Male	62 (23.7)	52 (18.0)	115 (43.9)	98 (33.9)	989 (35.5)
Female	21 (15.1)	14 (12.8)	42 (30.2)	28 (25.7)	458 (36.3)
Any AE leading to discontinuation of durvalumab/placebo					
Male	16 (6.1)	13 (4.5)	31 (11.8)	21 (7.3)	289 (10.4)
Female	10 (7.2)	2 (1.8)	20 (14.4)	4 (3.7)	108 (8.6)

[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] Overall period refers to the neoadjuvant period, post-surgery, and adjuvant period, i.e., D + CTx followed by surgery and durvalumab monotherapy, and placebo + CTx followed by surgery and placebo.

[c] As assessed by the investigator. Missing responses are counted as possibly related. Study treatment includes durvalumab, CTx, placebo, in this context surgery is not included as a study treatment.

[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.

N1 = Total number of male patients, N2 = Total number of female patients. Percentages are calculated from N1 and N2 for male and female respectively.

Neoadjuvant period includes AEs between date of first dose and the day before surgery, or for patients without surgery up to the earliest of ≤ 90 days after date of last dose of neoadjuvant treatment, first dose of subsequent anti-cancer therapy. Includes AEs with an onset date during this period and AEs with an onset date prior to dosing which worsen during this period.

Overall period and Durvalumab Pan-Tumour 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 surgery) or up to and including the date of initiation of the first subsequent therapy (whichever occurs first).

Disease progression AEs reported in Study 1108 are not included in this summary.

All studies use CTCAE version 4.03 except for AEGEAN which uses CTCAE version 5.0.

MedDRA version 26.1.

Race

For the overall period of AEGEAN, there were no clinically meaningful differences in the AEs reported in durvalumab-treated patients by race.

Although data should be interpreted with caution given the small sample size for Black patients or African American patients (N = 7 patients), in the D + CTx and placebo + CTx arms, there was a higher incidence of AEs possibly related to any study treatment in Black patients or African American patients (100% for both treatment arms, with all events in the D + CTx arm possibly related to durvalumab/placebo), compared to White patients (84.8% vs 80.9%, respectively), Asian patients

(88.5% vs 80.1%), and Black or African American patients in the D pan-tumour pool (69.0%). However, there was no specific clustering of PTs in Black or African American patients. In Asian patients, the incidence of AEs possibly related to durvalumab/placebo was higher in the D + CTx arm (54.5%) compared to the placebo + CTx arm (40.3%), but consistent with the D pan-tumour pool (54.7%).

ECOG PS

For the overall period of AEGEAN, there were no clinically meaningful differences in the AEs reported in patients according to baseline ECOG/WHO PS. There was a slightly lower frequency of AEs possibly related to any study treatment in patients with an ECOG of ≥ 1 (D + CTx: 83.6% vs placebo + CTx: 77.6%) compared to 0 (88.2% vs 82.1%, respectively), a trend also observed in the D pan-tumour pool (54.9% vs 62.1%). No notable differences in the nature and incidence of other AEs were observed according to baseline ECOG/WHO PS status.

Extrinsic factors

The safety profile of durvalumab was assessed in relation to the following extrinsic factors: Geographic region (Asia, Europe, North America, South America, and Non-Asia Regions) There were no clinically meaningful differences in the safety profile of durvalumab-treated patients in AEGEAN or the D pan-tumour pool with respect to geographic region.

Safety related to drug-drug interactions and other interactions

Durvalumab is an immunoglobulin, therefore, no formal pharmacokinetic 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.

Discontinuation due to adverse events

Table 55 Overview of AEs Leading to Discontinuation of any Study Treatment in the AEGEAN Study and the D Pan-Tumour Pool (Reported for ≥ 2 Patients in Either AEGEAN Treatment Arm [Overall Period]; Safety Analysis Set)

	AEGEAN Study								D pan-tumour pool (N = 4045, Dur = 2240.4)	
	Neoadjuvant period				Overall period [a]					
	D + CTx (N = 401, Dur = 92.3)		Placebo + CTx (N = 398, Dur = 91.3)		D + CTx (N = 401, Dur = 299.4)		Placebo + CTx (N = 398, Dur = 286)			
MedDRA System organ class / Preferred term	Number (%) of patients [b]	Event rate (per 100 patient years) [c]	Number (%) of patients [b]	Event rate (per 100 patient years) [c]	Number (%) of patients [b]	Event rate (per 100 patient years) [c]	Number (%) of patients [b]	Event rate (per 100 patient years) [c]	Number (%) of patients [b]	Event rate (per 100 patient years) [c]
Patients with any AE leading to discontinuation of any study treatment	***54 (13.5)***	***58.5***	***30 (7.5)***	***32.9***	***78 (19.5)***	***26.1***	***39 (9.8)***	***13.6***	***397 (9.8)***	***17.7***

MedDRA System organ class / Preferred term	AEGEAN Study								D pan-tumour pool (N = 4045, Dur = 2240.4)	
	Neoadjuvant period				Overall period [a]					
	D + CTx (N = 401, Dur = 92.3)		Placebo + CTx (N = 398, Dur = 91.3)		D + CTx (N = 401, Dur = 299.4)		Placebo + CTx (N = 398, Dur = 286)			
	Number (%) of patients [b]	Event rate (per 100 patient years) [c]	Number (%) of patients [b]	Event rate (per 100 patient years) [c]	Number (%) of patients [b]	Event rate (per 100 patient years) [c]	Number (%) of patients [b]	Event rate (per 100 patient years) [c]	Number (%) of patients [b]	Event rate (per 100 patient years) [c]
Anaemia	6 (1.5)	6.5	0	NA	6 (1.5)	2.0	0	NA	6 (0.1)	0.3
Pneumonitis	2 (0.5)	2.2	1 (0.3)	1.1	7 (1.7)	2.3	2 (0.5)	0.7	36 (0.9)	1.6
Neutropenia	3 (0.7)	3.3	2 (0.5)	2.2	3 (0.7)	1.0	2 (0.5)	0.7	1 (< 0.1)	< 0.1
Myelosuppression	3 (0.7)	3.3	1 (0.3)	1.1	3 (0.7)	1.0	1 (0.3)	0.3	0	NA
Peripheral sensory neuropathy	3 (0.7)	3.3	0	NA	3 (0.7)	1.0	0	NA	0	NA
Rash	1 (0.2)	1.1	0	NA	3 (0.7)	1.0	0	NA	3 (< 0.1)	0.1
Blood creatinine increased	2 (0.5)	2.2	2 (0.5)	2.2	2 (0.5)	0.7	3 (0.8)	1.0	3 (< 0.1)	0.1
Acute kidney injury	2 (0.5)	2.2	1 (0.3)	1.1	2 (0.5)	0.7	1 (0.3)	0.3	5 (0.1)	0.2
Asthenia	2 (0.5)	2.2	1 (0.3)	1.1	2 (0.5)	0.7	1 (0.3)	0.3	4 (< 0.1)	0.2
Renal impairment	2 (0.5)	2.2	1 (0.3)	1.1	2 (0.5)	0.7	1 (0.3)	0.3	0	NA
Diarrhoea	1 (0.2)	1.1	0	NA	2 (0.5)	0.7	0	NA	8 (0.2)	0.4
Hypersensitivity	2 (0.5)	2.2	0	NA	2 (0.5)	0.7	0	NA	0	NA
Immune-mediated hepatitis	1 (0.2)	1.1	0	NA	2 (0.5)	0.7	0	NA	0	NA
Nausea	2 (0.5)	2.2	0	NA	2 (0.5)	0.7	0	NA	1 (< 0.1)	< 0.1
Vomiting	2 (0.5)	2.2	0	NA	2 (0.5)	0.7	0	NA	1 (< 0.1)	< 0.1
Interstitial lung disease	0	NA	0	NA	1 (0.2)	0.3	2 (0.5)	0.7	8 (0.2)	0.4
Tinnitus	1 (0.2)	1.1	2 (0.5)	2.2	1 (0.2)	0.3	2 (0.5)	0.7	0	NA
Fatigue	0	NA	1 (0.3)	1.1	0	NA	2 (0.5)	0.7	6 (0.1)	0.3
Infusion related reaction	0	NA	2 (0.5)	2.2	0	NA	2 (0.5)	0.7	1 (< 0.1)	< 0.1
Muscular weakness	0	NA	1 (0.3)	1.1	0	NA	2 (0.5)	0.7	0	NA
Neutrophil count decreased	0	NA	2 (0.5)	2.2	0	NA	2 (0.5)	0.7	1 (< 0.1)	< 0.1
Tuberculosis	0	NA	0	NA	0	NA	2 (0.5)	0.7	1 (< 0.1)	< 0.1

[a] Overall period refers to the neoadjuvant period, post-surgery, and adjuvant period, i.e., D + CTx followed by surgery and durvalumab monotherapy, and placebo + CTx followed by surgery and placebo.

[b] Number (%) of patients with AEs, sorted by descending frequency of PT in the D + CTx arm.

[c] Number of patients with AEs divided by total number of years at risk for AEs summed across all patients within a group, multiplied by 100.

Patients with multiple AEs are counted once for each PT.

Neoadjuvant period includes AEs between date of first dose and the day before surgery, or for patients without surgery up to the earliest of ≤ 90 days after date of last dose of neoadjuvant treatment, first dose of subsequent anti-cancer therapy. Includes AEs with an onset date during this period and AEs with an onset date prior to dosing which worsen during this period.
Overall period and Durvalumab Pan-Tumour 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 surgery) or up to and including the date of initiation of the first subsequent therapy (whichever occurs first).
Disease progression AEs reported in Study 1108 are not included in this summary.
Percentages are based on the total numbers of patients in the treatment group (N).
MedDRA version 26.1
Dur = Total number of years at risk for AEs summed across all patients within a group. Where total number of years at risk for AEs = (last dose date + X days or death date or DCO whichever occurs earlier - first dose date + 1) / 365.25. X is defined as the planned frequency in dosing (in days) - 1. For Q2W, X = 13. For Q3W, X = 20. For Q4W, X = 27.

Surgery

Adverse Events Leading to Surgery Not Being Done: The proportion of patients with AEs that led to on-study surgery not being done was similar across treatment arms: 7 patients (1.7%) in the D + CTx arm and 4 patients (1.0%) in the placebo + CTx arm (Table 35), and one additional patient in the placebo + CTx arm also had an AE leading to on-study surgery not being done that was not included in the tabulations or listings, because the PT was not specified. Of the AEs reported in the D + CTx arm, pneumonitis, colitis, and pruritus are known durvalumab ADRs, and were also imAEs. None of the AEs by PT leading to on-study surgery not being done were reported for more than one patient in either treatment arm.

Surgical Delays: In AEGEAN, of the patients who underwent on-study surgery, 17.8% of patients in the

D + CTx arm and 20.6% in the placebo + CTx arm had a delay to on-study surgery, most commonly due to logistical reasons (9.5% vs 11.3% of patients, respectively). Delays were most frequently of < 4 weeks duration.

The proportion of patients with AEs that led to a delay to on-study surgery was similar across both treatment arms: 15 patients (3.7%) in the D + CTx arm vs 16 patients (4.0%) in the placebo + CTx arm (Table 35), and one additional patient in each arm also had an AE that delayed on-study surgery that was not included in the tabulations or listings, because the PT was not specified. None of the AEs by PT leading to a delay in on-study surgery were reported for more than one patient in the D + CTx arm, and PTs reported for more than one patient in the placebo + CTx arm were COVID-19 (0.2% vs 1.0% in the D + CTx arm), anaemia (0.2% vs 0.8%), and pneumonia (0% vs 0.5%).

Adverse Events Possibly Related to Surgery: The proportion of patients who underwent on-study surgery with an AE possibly related to surgery as assessed by the investigator was similar in the D + CTx and placebo + CTx arms (42.5% vs 44.4%, respectively; using the number of patients in the safety analysis set who underwent surgery [N = 325 and N = 326] as the denominator), and most of these AEs occurred in the post-surgery period. For the overall period, the most frequently reported PT (reported for > 5% of patients in either treatment arm) was procedural pain (12.0% and 11.7% respectively). The proportion of deaths assessed by the investigator as possibly related to surgery was 1.5% in the D + CTx arm and 1.0% in the placebo + CTx arm (Table 35), corresponding to 1.8% vs 1.2% of patients who underwent surgery.

Surgical Complications: The proportion of patients who underwent on-study surgery who had a surgical complication (assessed using via the Clavien-Dindo score) was similar in each treatment arm for the ITT population: 195/324 (60.2%) patients in the D + CTx arm vs 193/327 (59.0%) patients in the placebo + CTx arm. Most surgical complications were maximum Clavien-Dindo classification Grade 1 or 2.

Post marketing experience

As of 30 April 2023, the cumulative world-wide post-approval patient exposure since launch is estimated to be 118467 patient-years. No new safety concerns have been identified based on post-marketing safety reports.

2.5.1. Discussion on clinical safety

The safety assessment is based on safety data from all 799 treated subjects who received at least one dose of study treatment, either durvalumab + CTx (N= 401) or placebo + CTx (N=398) in the ongoing study D9106C00001 (AEGEAN). These data are from the second planned interim analysis for EFS (DCO date of 10 May 2024). Supportive safety data from 13 clinical trials conducted in several solid tumour settings (and across different dosing regimens), provide a pooled estimate of the risk associated with durvalumab monotherapy. This, while not directly comparable with data from the randomised pivotal AEGEAN trial, can serve to "contextualize" the potential added risk of combining durvalumab with chemotherapy and surgery. Unless otherwise specified, the assessment will be focused on the study AEGEAN.

Patient exposure

The median total duration of exposure for the overall period (neoadjuvant + adjuvant period) was longer in the durvalumab + CTx arm (40.1 weeks) compared to the placebo plus CTx arm (36.1 weeks). The median number of cycles received during the adjuvant phase was 12 for both arms, with 68.4% and 63.4% of patients receiving 12 cycles, respectively. In the neoadjuvant period, the median total duration of exposure was the same in both arms (12.14 weeks) with a median of 4 cycles received in both treatment arms. It is important to note that (only) 66% and 64% of patients started adjuvant treatment in the durvalumab and placebo arm, respectively.

Adverse events

Almost all patients in the durva+CTx arm experienced at least one AE (96.5%), similar to the rates of AEs experienced by patients in the placebo+CTx arm (95.2%).

In the overall period, **the most frequently reported AEs** in both arms (durva + CTx vs CTx) and with a similar incidence were anaemia (34.9% vs 32.2%), nausea (25.7% vs 29.9%), constipation (25.9% vs 22.6%), decreased appetite (18.5% vs 18.3%), alopecia (17.2% vs 16.1%), neutropenia (17.0% vs 18.1%) and neutropenia/neutrophil count decreased (16.5% vs 14.8%). The similar frequencies in the two arms suggest that chemotherapy is likely the major contributing factor to the most commonly observed AEs. This is supported by the observation of similar frequencies of the same AE categories during the neoadjuvant period, again with no meaningful differences between the treatment arms, and by the fact that these AE categories were all (with the exception of decreased appetite) found at greater frequencies in the durva+CTx-treated patients in AEGEAN than in the pooled durva monotherapy cohort.

AEs reported more frequently in the durva + chemo arm than in the placebo + chemo included the SOCs of skin and subcutaneous tissue disorders (46.4% vs 37.9%,), infections and infestations (46.4% vs 42.2%), investigations (38.4% vs 34.2%) and endocrine disorders (15.2% vs 6.5%). By PT, pruritus (12.7% vs 6.5%), rash (15.7% vs 8.3%), hypothyroidism (11.7% vs 3.0% patients) and hyperthyroidism (4.2% vs 2.0%), ALT (8.5% vs 6.8%) and AST (5.5% vs 3.3%) were more frequently reported in the durva + chemo arm. These AEs are already identified ADRs for durvalumab and they are included in the SmPC.

Treatment-related AEs were more commonly reported in the durva-CTx arm (87.3%) compared with the placebo-CTx arm (81.7%). As for the overall AE profile, the most commonly described treatment-related AEs were well balanced between the experimental and control arm suggesting that chemotherapy is also a major contributor to these. The increased frequency of treatment-related AEs in the durva+CTx arm compared to the placebo+CTx arm is mainly due to rash (10.2% vs. 6.5%), hypothyroidism (11.2% vs. 1.5%), pruritus (8.7% vs. 2.0%) and ALT increased (7.5% vs. 5.5%). These are AEs known to be associated with durvalumab and the observed levels are considered acceptable at this time. Regarding the incidence of patients who had AEs possibly related to chemotherapy, there were no meaningful differences between treatment arms (79.3% vs 77.6%); hence it seems that durvalumab does not worsen the toxicities of chemotherapy.

Regarding Grade 3-4 AEs, nearly half of patients had an AE of CTCAE Grade 3 or higher in the overall period, in a similar proportion across arms, (43.6% in the durvalumab + CTx vs 43.2% in the CTx arm). The most frequent AEs by PT were also balanced: neutrophil count decreased (10.5% vs 11.3%), neutropenia (9.0% vs 9.8%) and anaemia (6.5% vs 6.5%). In the neoadjuvant period, the proportion of patients with any AE of maximum CTCAE Grade 3 or 4 was 32.7% vs 36.4%. The nature of Grade 3 or 4 AEs with onset or worsening in the neoadjuvant period were comparable with those reported for the overall period, and incidences were similar across arms.

Serious adverse events: In the overall period, the incidence of patients with SAEs was higher in the durva + chemo arm (39.2%) than in the placebo + chemo arm (31.7%), with the most frequently reported SAEs in both treatment arms being pneumonia (5.7% vs 4.5%, respectively), anaemia (1.7% vs 1.3%), and COVID-19 (1.7% vs 1.3%). Of these, the incidence of drug-related SAEs, was also higher in the durva + chemo arm (19%) than in the placebo + chemo arm (12.6%). From these SAEs considered as possibly related to any study treatment, in the durva + chemo arm 10.5% of patients reported SAEs possibly related to durvalumab, while they were considered as possibly related to chemotherapy in a 11.5% of the patients. In the placebo + chemo arm, causality was assessed as possibly related to placebo for 6.5% of patients and possibly related to chemo for 10.1% of patients. The SAEs most frequently reported and assessed as related to durvalumab/placebo (>1% patients) were pneumonitis (1.7% vs 0.3%) and drug-induced liver injury (1.2% vs 0%).

Deaths: A similar proportion of deaths was reported in durvalumab + chemotherapy arm (32.0%) in comparison to the placebo + chemotherapy arm (37.3%). The majority of deaths were attributed, by the investigator, to the disease, 83 (20.8%) vs 121(30.1%), respectively. The other deaths were reported as due to TEAEs [19 (4.8%) vs 12 (3.0%)], related to disease under investigation and with TEAE [4 (1.0%) vs 3 (0.7%)], AE with outcome of death only (AE start date falling after safety follow-up period) [3 (0.8) vs 1 (0.2%)], death related to disease under investigation (AE start date falling after safety follow-up period) [0 vs 1 (0.2%)], patients with unknown reason for death [7 (1.8)% vs 3 (0.7)] and other deaths [12 (3.0%) vs 9 (2.2%)].

At EFS IA1 DCO, for the overall period, a higher proportion of patients reported an **AEs with an outcome of death** in the durvalumab + chemotherapy arm, 23 (5.7%) vs 15 patients (3.8%) in the placebo + chemotherapy arm, from which 7 deaths (1.7%) vs 2 (0.5%) were possibly related to any study treatment. None of these patients received post operative radiotherapy (PORT). The primary causes for these 7 deaths, considered as causally related to any study treatment, in durva + chemo arm, were: decreased appetite (1), myocarditis (1), and respiratory, thoracic and mediastinal disorders [5 deaths: 1 haemoptysis, 1 immune-mediated lung disease, 2 interstitial lung disease, 1 pneumonitis]. Indeed, some of these AEs are known ADRs of durvalumab. The two deaths causally related to the study drugs in the placebo arm were due to infection (1) and pneumonia (1). While the proportion of deaths due to AEs was higher in the durvalumab arm it was in line with the observed in the durvalumab monotherapy pool (5.7%).

The proportion of patients who died from other causes than their baseline disease (NSCLC) was higher in the D + CTx arm than in the placebo + CTx arm, this observation was consistent across EFS IA1 and EFS IA2 DCO.

Adverse events of special interest: The incidence of **AESIs** (AEs that have a likely inflammatory or immune-mediated pathophysiological basis resulting from the mechanism of action of durvalumab and requiring more frequent monitoring and/or interventions) was 45.6% of patients in the durvalumab arm and 32.7% in the placebo arm. Most of them were considered related to study treatment (37.4% vs 21.1%). Most of these events were Grade 1 or Grade 2 with only 18 (4.5%) and 11 (2.8%) of Grade 3 or 4 in the durvalumab and placebo arms, respectively. The AESIs in durvalumab + chemo arm was resolved in 29.9%, however 14.7% were not resolved. Not resolved imAEs were mostly driven by hypothyroidism (7.5%) in addition to pneumonitis (0.7%) and dermatitis/rash (0.7%), which are known immuno-related ADR of durvalumab and these events are often managed with continued hormone therapy, steroids and other immunosuppressant. These AEs are already reported in the SmPC.

Adjudicated imAEs were reported in the durvalumab arm with a higher incidence (25.4%) compared to the placebo arm (10.3%), mainly driven by hypothyroid events (10.5% vs 2.5%) and dermatitis/rash events (5.5% vs 1.8%), and was consistent with the known safety profile of durvalumab. The majority of imAEs were mild or moderate (Grade 1 or 2) in severity. However, 6 of 18 patients with immune-mediated pneumonitis had AEs CTCAE Grade ≥ 3 in the durvalumab + chemotherapy arm (4 of 7 patients in the placebo arm), which included 4 (1.0%) patients with an AE with outcome of death (none in the placebo arm).

In comparison to the pooled durvalumab safety dataset, the incidence of imAEs in the durvalumab + chemotherapy arm of study AEGAN was higher than the observed in the durvalumab monotherapy pool (25.4% vs 17.4%), although this discrepancy may be explained by the longer median durvalumab exposure in the AEGAN study compared to the pool (40.1 weeks vs 16.14 weeks, respectively).

Regarding **immunogenicity**, there was a higher proportion of patients with infusion reactions among ADA-positive patients (3 [6.4%] patients) compared to ADA-negative patients (9 [2.7%] patients), although numbers are too low to draw conclusions.

Among the small subset of patients who received **post-operative radiotherapy**, (n=30 and 27 for the active and placebo arm, respectively), the frequency of pneumonitis and radiation pneumonitis was three times higher in the durvalumab arm than in the control arm, despite interpretation possibly hampered by the small number of patients, an increase of pneumonitis or radiation pneumonitis frequency was also observed in the PACIFIC trial, the findings from AEGEAN study were added to the Pneumonitis and radiation pneumonitis subsection of section 4.4 of the SmPC.

Laboratory findings: Shifts to CTCAE Grade 3 or 4 haematology, clinical chemistry, hepatic function, thyroid function, and renal function parameters were similar across the durva + chemo and placebo + chemo arms. Haematology and clinical chemistry values were of a maximum CTCAE Grade 0 (normal), 1, or 2 for the majority of patients in both treatment arms in the neoadjuvant period and overall period.

Shifts to CTCAE Grade 3 or 4 clinical chemistry parameters that were reported at a higher frequency in durva + chemo arm compared to the placebo + chemo arm (i.e., > 2% difference across arms) were ALT (5.8% vs 2.0%) and GGT (4.7% vs 2.1%). For total bilirubin, the proportion of patients with shifts to CTCAE Grade 3 or 4 was 1.3% in the durva + chemo arm vs 0.5% in the placebo + chemo arm.

Overall, liver biochemistry test abnormalities observed on-treatment were higher for patients in the durva + chemo arm (16.1%) vs the placebo + chemo arm (9.1%). Liver biochemistry test

abnormalities in both treatment arms were typically in the range of ≥ 3 × to ≤ 5 × ULN or > 5 × to ≤ 8 × ULN for ALT or AST (i.e., mild to moderate).

As expected, considering the already known safety profile of durvalumab, thyroid function alterations were most frequently reported in the durva +chemo arm than in the placebo + chemo arm: 21.4 % patients reported TSH increases (> ULN) from baseline (≤ ULN) in the durva +chemo arm, vs. 14.7% patients in the placebo + chemo arm. Decreases (< lower limit of normal [LLN]) from baseline (≥ LLN) were reported in 85 (21.4 %) subjects in the durva +chemo arm and 54 (13.7 %) subjects in the chemo arm.

Safety in special populations: The MAH presented data by sex, age, race and baseline ECOG/WHO PS. Adverse events possibly related to durvalumab/placebo were more frequently reported in the durva + chemo arm in females compared to males (64% vs 51.1%, respectively), bearing in mind that the majority of patients enrolled were male (65.3% in the durva + chemo arm and 72.6% in the placebo + chemo arm). However, the incidence of maximum CTCAE Grade 3 or 4 AEs assessed as possibly related to durvalumab/placebo was higher in males in the durva + chemo arm compared to females (16.8% vs 10.8%, respectively). Moreover, the incidence of SAEs was also higher in males in the D + CTx arm compared to females (43.9% v 30.2%, respectively).

Some differences in the AEs reported in durvalumab-treated patients by age were observed. The proportion of patients ≥ 75 years with any AE possibly related to any study treatment of maximum CTCAE Grade 3 or 4 was higher than those ≥ 65 to < 75 years in the durva + chemo arm (40.8% vs 32.5%, respectively), and this trend was reversed in the placebo + chemo arm (27.0% vs 40.2%). In relation to the AE leading to discontinuation of durvalumab/placebo, in the durva + chemo the proportion of patients was higher with increasing age (0%, 10%, 16.3% and 16.3% in patients aged < 50 years, ≥ 50 to < 65 years, ≥ 65 to < 75 years, and ≥ 75 years, respectively). The increase in frequency of serious ADR in the durvalumab + CTx arm of Aegean between patients aged 75 years and above, and the totality of the study arm regardless of age (26.5% versus 18.0%, respectively), was more marked than in the durvalumab + chemo safety pool (19.4% versus 16.7%), this finding was reflected in section 4.4 of the SmPC.

Regarding race, there was a higher incidence of AEs possibly related to any study treatment in Black patients or African American patients (100% for both treatment arms, with all events in the durva + chemo arm possibly related to durvalumab/placebo), compared to White race and Asian race, but the sample size is very small (7 patients) and there was no specific clustering of PTs in Black or African American patients. In Asian patients, the incidence of AEs possibly related to durvalumab/placebo was higher in the durva + chemo arm (54.5%) compared to the placebo + chemo arm (40.3%).

With respect to ECOG status, there was a slightly lower frequency of AEs possibly related to any study treatment in patients with an ECOG of ≥ 1 (durva + chemo: 83.6% vs placebo + chemo: 77.6%) compared to 0 (88.2% vs 82.1%, respectively).

Discontinuations/dose modifications: Discontinuations of any study drug due to AEs were more common in the durvalumab + chemotherapy arm compared to placebo + chemotherapy arm (19.5% vs 9.8%) in the overall period, with the majority occurring in the neoadjuvant period (13.5% vs 7.5%, respectively), and mainly due to anaemia (1.5% vs 0), pneumonitis (1.7% vs 0.3%), neutropenia (0.7% vs 0.5%), myelosuppression (0.7% vs 0.3%), peripheral sensory neuropathy and rash (each 0.7% vs 0%) and blood creatinine increased (0.5% vs 0.8%). Of note, these "chemotherapy toxicities" are slightly higher in the durvalumab + chemotherapy arm than in the placebo + chemotherapy arm. AEs leading to discontinuation of durvalumab/placebo were reported with a higher frequency in the durva + chemo arm (12%) vs the placebo + chemo arm (6%). AEs leading to discontinuation of any

chemo compound were reported for 12.2% vs 7.8% of patients. AEs leading to discontinuation of both (doublet) chemotherapy agents were reported for 6.5% vs 4.3% of patients.

In the neoadjuvant period, the most frequent AEs (≥ 3 patients in either arm) leading to discontinuation of any study treatment were similar to those of the overall period: anaemia (1.5% vs 0%), neutropenia (0.7% vs 0.5%), myelosuppression (0.7% vs 0.3%), and peripheral sensory neuropathy (0.7% vs 0%). Hence, the combination of durva+CTx is associated with a greater risk of impacting the ability to receive planned treatment.

Risks relating to surgery (AEs leading to surgery not being done, surgical delays, AEs possibly related to surgery and surgical complications): Overall, the frequency and nature of AEs leading to on-study surgery not being done was similar across treatment arms: 7 patients (1.7%) in the D + CTx arm and 4 patients (1.0%) in the placebo + CTx arm, and indicated that the addition of durvalumab to chemotherapy did not impact a patient's ability to undergo on-study surgery. The proportion of patients with any delay to on-study surgery was 17.8% in the durva + chemo arm vs 20.6% in the placebo + chemo arm, mainly due to logistical reasons (9.5% vs 11.3%). Surgical delay due to an AE was reported for 11 (3.4%) vs 13 (4.0%) patients, and due to unresolved toxicity (i.e., unresolved AE from neoadjuvant period) for 5 (1.5%) vs 4 (1.2%) patients in the durva and placebo arm, respectively. The remaining categories of risks relating to surgery were similar between the experimental and control arms. The high rate of patients not receiving surgery is a major concern and is also commented in the clinical efficacy section. The risk of not undergoing surgery does not seem to be related to a safety issue.

Section 4.8 of the SmPC

The results of the AEGAN study have been pooled with results of the TOPAZ-1, CASPIAN, and DUO-E studies, in which durvalumab was given in combination with chemotherapy. This is supported. No new ADRs have been identified.

2.5.2. Conclusions on clinical safety

Overall, the safety profile of durvalumab + chemotherapy as neoadjuvant treatment, and then as monotherapy post-surgery as adjuvant treatment, seems to be consistent with the known safety profile of durvalumab and no new safety signals have been identified. However, the addition of durvalumab to chemotherapy translated into a higher toxicity as compared to chemotherapy alone, with a higher rate of SAEs, AEs leading to discontinuations and deaths due to AEs. Of note, the addition of durvalumab in the neoadjuvant phase did not impact the disposition of patients undergoing surgery.

2.5.3. 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.

2.6. Risk management plan

The MAH submitted an updated RMP version 11.2 with this application.

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

The PRAC considered that the risk management plan version 11.2 is acceptable.

Safety concerns

There are no safety concerns.

Pharmacovigilance plan

Not applicable.

Risk minimisation measures

Not applicable as there are no safety concerns.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8, and 5.1 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

2.7.1. 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:

This Type II variation includes an extension of indication for durvalumab (IMFINZI) in combination with platinum-based chemotherapy as neoadjuvant treatment, followed by IMFINZI as monotherapy after surgery, for the treatment of adults with resectable NSCLC and no known EGFR mutations or ALK rearrangements, and concerns the same route of administration (intravenous use) and age group (adults). The Type II variation affects the Package Leaflet (PL) for IMFINZI 50 mg/mL concentrate for solution for infusion in Section 1 (What IMFINZI is and what it is used for) and Section 4 (Possible side effects). Overall, the wording in the PL is similar to the text previously tested during the IMFINZI MAA. IMFINZI is administered as an IV infusion by a medical professional and as such AstraZeneca considers that the changes are not significant enough to warrant an additional user consultation for this new indication.

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

The approved indication is:

IMFINZI in combination with platinum-based chemotherapy as neoadjuvant treatment, followed by IMFINZI as monotherapy as adjuvant treatment, is indicated for the treatment of adults with resectable NSCLC at high risk of recurrence and no EGFR mutations or ALK rearrangements (for selection criteria, see section 5.1).

3.1.1. Disease or condition

Resectable (Stage IIA-IIIB[N2]) NSCLC (staged per the AJCC staging system for lung cancer 8th Edition).

Approximately 20% to 25% of NSCLC patients present with resectable lung cancer (Liang et al 2013) and this is expected to increase with the implementation of lung cancer screening in high-risk populations (Passiglia et al 2021). For early-stage NSCLC, the 5-year survival rate remains low at 56% to 65% for patients with Stage II, and 24% to 41% for patients with Stage III disease (Goldstraw et al 2016). Despite complete surgical resection, patients with resectable NSCLC are at substantial risk for recurrence and death.

3.1.2. Available therapies and unmet medical need

The standard approach for patients with stage II/III resectable NSCLC is potentially curative surgery followed by adjuvant chemotherapy. In terms of overall survival, the benefit of adjuvant chemotherapy depends on stage, with higher stage correlating with an increased magnitude of benefit (HR 1.4 [95%CI: 0.95 to 2.06] for Stage IA disease; HR 0.93 for Stage IB disease [95%CI: 0.78 to 1.10]; HR 0.83 for Stage II disease [95%CI: 0.73 to 0.95]; and HR 0.83 for Stage III disease [95%CI: 0.72 to 0.94]) (Pignon et al 2008). However, the recurrence rate remains high, ranging from 62% in patients with Stage II and 76% of patients with Stage III disease (Pignon et al 2008), which in turn is associated with poor survival rates in this patient population (Goldstraw et al 2016). The prevention of disease recurrence and distant metastases, and subsequent progression to an incurable disease state, is therefore critical to improving long-term patient outcomes (Consonni et al 2015). Neoadjuvant treatment may be an option in patients with potentially resectable disease, particularly those with single-station mediastinal nodal involvement, or superior sulcus tumours or chest wall invasion in the setting of N1 nodal involvement. In the neoadjuvant setting, a meta-analysis including trials of neoadjuvant chemotherapy for resectable NSCLC has shown an absolute survival improvement of 5% at 5 years (NSCLC Meta-analysis Collaborative Group 2014).

Recently, the addition of anti-PD-1/PD-L1 inhibitors across the neoadjuvant and adjuvant phases of treatment to resectable NSCLC has shown EFS and DFS benefits, respectively, conducting to approval in Europe of added Opdivo (neoadjuvant setting, tumours PD-L1≥1%), Tecentriq (adjuvant setting, PD-L1≥50%), and Keytruda (adjuvant setting, PD-L1 unrestricted, and combination of neoadjuvant and adjuvant).

3.1.3. Main clinical studies

The single pivotal study for the extension of indication for durvalumab is AEGEAN, an ongoing, phase 3, randomised, double-blind, placebo-controlled, multi-centre study comparing durvalumab Q3W or placebo + platinum-based chemotherapy (according to histology) for 4 cycles followed by surgery, and then durvalumab monotherapy Q4W or placebo for up to 12 cycles (16 cycles in total). Randomisation was stratified by disease stage (II vs. III) and by PD-L1 expression according to the Ventana SP263 assay (TC <1% vs. TC ≥1%). The ITT population was constituted by 802 patients, recruited between 2018 and 2022.

The dual primary endpoints were pathological complete response (pCR) by blinded pathology review and event-free survival (EFS) by BICR, while the key secondary endpoint was OS. These analyses were performed in the modified ITT population (mITT, n=740), which excluded patients with EGFR or ALK mutations. Other secondary endpoints included major pathological response (MPR) and disease-free survival (DFS), the last tested only in the "resected" subpopulation from the mITT.

3.2. Favourable effects

The first interim analysis for EFS (EFS IA1) and pCR was prespecified according to the number of EFS events, which limited overall follow-up: At DCO 10-NOV-2022, median EFS follow-up was ~9 months. The MAH provided updated data from the third preplanned interim analysis of AEGEAN with a median follow-up for EFS of 25.9 months (EFS IA2; DCO: 10 May 2024).

- Primary endpoint: Pathological complete response (pCR) in the mITT at the time of the EFS IA1 was 17.21% in the D+CTx arm versus 4.28% in the placebo + CTx arm, the difference was 12.96%. This difference in pCR was in line with the primary analysis of pCR (DCO 14-JAN-2022), which met the prespecified boundary for declaring a statistically significant improvement in pCR for the D+CTx arm as compared with the placebo + CTx arm, with a 2-sided p-value of 0.000036 (2-sided significance boundary: 0.0082).
- Primary endpoint: EFS by BIRC was statistically significantly improved in the mITT. The median EFS was not reached (95% CI: 31.9; NR) in the D+CTx arm vs 25.9 months in the placebo arm with an HR of 0.68 (95% CI: 0.53; 0.88). Maturity: 26.8% and 36.9% of the patients in the D+CTx and placebo+CTx arms of the mITT had respectively an event. The KM curves show a separation in favour of the D+CTx arm after approximately 5 months of therapy. Updated descriptive analysis at EFS IA2 showed an EFS HR of 0.69 (95%CI: 0.55, 0.88), consistent with EFS IA1. The updated median EFS was 30.0 months (95%CI: 20.6, not reached) in the placebo arm vs not reached (95%CI: 42.3; NR) in the D+CTx arm.
- Secondary endpoint OS: Since OS will only be formally tested following a positive DFS result, only a descriptive summary of OS was provided. At EFS IA2, the median duration of OS follow-up was 33.64 months and the overall OS maturity was 35.3%, the HR was 0.89 (95%CI: 0.70, 1.14) when comparing the D + CTx arm to the placebo arm.

3.3. Uncertainties and limitations about favourable effects

- The design of pivotal clinical AEGEAN does not allow to disentangle the contribution of durvalumab to each treatment phase, and whether neoadjuvant and/or adjuvant durvalumab are both needed. Therefore, AEGEAN results can only be discussed in the context of an indication for durvalumab as neoadjuvant and adjuvant treatment for NSCLC, referred together as a perioperative regimen.
- Despite a maturity of OS data sufficient to rule out a detrimental effect, long term outcomes in terms of OS are deemed key to the benefit risk in the context of patients who are receiving treatment with a curative intent. Thus, in order to further characterise the efficacy of durvalumab in the approved indication, results from the final OS analysis will be submitted by Q2 2029 (see Annex II condition, PAES).

3.4. Unfavourable effects

Almost all patients in the durva + CTx arm experienced at least one AE (96.5%), similar to the rates of AEs experienced by patients in the placebo+CTx arm. The most commonly reported AEs in the durva + CTx arm (for the overall period) included: Anaemia (34.9%), nausea (25.7%), constipation (25.9%), decreased appetite (18.5%), alopecia (17.2%), neutropenia (17.0%) and neutrophil count decreased (16.5%).

Serious adverse events: The frequency of SAEs reported during the overall period in the durva-arm was about 6 percentage points higher than in the placebo-arm, both for any SAEs (39.2% vs. 31.7%) and for SAEs assessed to be possibly related to any study treatment (19.0% vs. 12.6%).

Deaths: The risk of having any AE with an outcome of death was higher in the durva + CTx arm (5.7%) than in the placebo+CTx arm (3.8%). For AEs with an outcome of death assessed by the investigator as possibly related to durvalumab/placebo, there were 6 events in the durva + CTx arm versus 0 in the placebo+CTx arm. Five of these 6 fatal AEs potentially related to durvalumab were imAEs.

Adverse events of special interest primarily include immune-mediated AEs (imAEs). The risk of experiencing an imAE during the overall trial period was 23.7% for patients on the durva + CTx arm compared to 9.3% for those on the placebo+CTx arm.

A trend towards increasing toxicity with increasing **age** was noted in the durva + CTx arm. Particularly for risk of death from AE, risk of any SAE and risk of AE leading to discontinuation.

Discontinuations/dose modifications: The rate of discontinuation due to any AE was greater in the durva + CTx arm compared to placebo+CTx arm (19.5% vs. 9.8%). The risk of any AE leading to dose modification of any study treatment was also greater in the durva + CTx arm compared to the placebo+CTx arm (47.4% vs. 36.7%).

Risks relating to surgery (AEs leading to surgery not being done, surgical delays, AEs possibly related to surgery and surgical complications) did not seem to differ greatly between the durva + CTx arm and the placebo+CTx arm.

3.5. Uncertainties and limitations about unfavourable effects

None

3.6. Effects Table

Table 56 Effects Table for durvalumab in combination with chemotherapy in the perioperative setting of NSCLC, patients without EGFR/ALK mutations (data cut-off: 10 May 2024)

Effect	Short description	Unit	Treatment D+CTx	Control Placebo + CTx	Uncertainties / Strength of evidence Ref
Favourable Effects (mITT)			**N=366**	**N=347**	
pCR	Pathological complete response	%	17.21	4.28	pCR IA: DCO 10 November 2022
EFS by BICR	Event-free survival	Months (95%CI)	NR (42.3; NR)	30.0 (20.6; NR)	EFS IA2 DCO: 10 May 2024 median EFS follow-up 25.9 months
		HR (95%CI)	0.69 (0.55, 0.88)		
OS	Overall survival	Months (95%CI)	NR (NR; NR)	53.2 (44.3; NR)	35.3% of events median OS follow-up 33.64 months
		HR (95%CI)	0.89 (0.70, 1.14)		
Unfavourable Effects (safety set)			**N = 401**	**N = 398**	
Grade 3-4	High grade AE	%	43.6	43.2	
Grade 5	AEs leading to death	%	5.7	3.8	
SAEs	Serious AEs	%	39.2	31.7	
AEs disc.	AEs leading to discontinuation	%	19.5	9.8	
ImAEs Leading to death	Immune-related AEs leading to death	Cases	6	0	

Abbreviations: BICR: Blinded independent review. NR: Not reached. mITT: modified ITT, patients with EGFRm/ALK was excluded.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The MAH submitted the results from pivotal study AEGEAN to support the extension of indication for durvalumab in the (neo-)adjuvant treatment of resectable NSCLC, which evaluated a perioperative treatment regimen of neoadjuvant platinum-based chemotherapy + durvalumab or placebo, surgery, and then adjuvant durvalumab or placebo for 16 cycles in total. The design of the trial proposed hierarchical testing in which EFS and pCR were to be tested first, followed by DFS, OS and MPR.

AEGEAN met its primary endpoints of pCR and EFS at the prespecified number of events for each test, but pathological endpoints (pCR and MPR) have not been demonstrated to reflect long term benefits in resectable NSCLC, and thus they have not yet been considered pivotal in regulatory decisions for products intended in the neoadjuvant setting. pCR provides information about treatment's anti-tumour activity and therefore it is considered as supportive, but it is not yet a fully validated surrogate endpoint in NSCLC, and therefore, benefits in pCR cannot be considered as predictive of effects in other clinical endpoints such as EFS or OS.

EFS also met the prespecified boundary for declaring statistically significance at the first interim analysis (IA1). Updated EFS results from the second interim analysis of EFS (IA2) indicate clinically

relevant benefit observed after a considerable median follow-up time (25.9 months). OS data are considered immature with a HR of 0.89 (95%CI: 0.70, 1.14) and a 95% CI overlapping 1, but no apparent detriment on OS is observed and it is reassuring that the point estimate for the OS HR has improved since the first interim analysis. In order to address this uncertainty, the MAH committed to provide final OS data post-authorisation as an Annex II condition.

The study design including a neoadjuvant phase in both treatment arms does not allow to balance the concerns about certain patients being unable to undergo surgery for any reason, with the potential benefit of the neoadjuvant phase in terms of surgical outcomes and long-term survival.

Safety data show an increased risk of treatment-related deaths in the active arm, which is of concern. Although many adverse events are related to the chemotherapy-backbone, added durvalumab seems to worsen the safety profile, in terms of a higher rate of SAEs, AEs leading to discontinuation, and deaths due to AEs. However, considering the clinically relevant EFS benefit and the absence of an apparent detrimental effect on OS, the benefit-risk of the new indication is considered positive. The final OS data will be provided as a post-authorisation measure (Annex II).

3.7.2. Balance of benefits and risks

Adding durvalumab to chemotherapy in the neoadjuvant setting followed by durvalumab in the adjuvant setting in adult patients with resectable NSCLC and no EGFR mutations or ALK rearrangements, resulted in a beneficial effect on EFS and pCR with no apparent detriment on OS. The safety profile of adding durvalumab to chemotherapy translated into higher toxicity, however considering the beneficial effects, the benefit-risk is considered positive.

3.7.3. Additional considerations on the benefit-risk balance

N/A

3.8. Conclusions

The overall B/R of Imfinzi is positive.

In accordance with the Commission Delegated Regulation (EU) No 357/2014, criteria 2(a), the following measures are considered necessary to address issues related to efficacy:

Annex II.D Condition: PAES: In order to further characterise the long-term efficacy of IMFINZI in combination with platinum-based chemotherapy as neoadjuvant treatment, followed by IMFINZI as monotherapy as adjuvant treatment, for the treatment of adults with resectable NSCLC at high risk of recurrence, the MAH should submit the results of the final OS analysis from the study AEGEAN (D9106C00001), a phase III, double-blind, placebo-controlled, multi-centre international study, with a due date in Q2 2029.

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 change:

Variation accepted		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II and IIIB

Extension of indication to include the treatment in combination with platinum-based chemotherapy as neoadjuvant treatment, followed by monotherapy as adjuvant treatment, is indicated for the treatment of adults with resectable NSCLC at high risk of recurrence and no EGFR mutations or ALK rearrangements for IMFINZI, based on the interim results from study D9106C00001 (AEGEAN); this is a Phase III, double-blind, placebo-controlled, multi-center international study of neoadjuvant/adjuvant durvalumab for the treatment of patients with resectable stages II and III non-small cell lung cancer. As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 11.2 of the RMP has also been approved.

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.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Obligation to conduct post-authorisation measures

In accordance with the Commission Delegated Regulation (EU) No 357/2014, criteria 2(a), the MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
In order to further characterise the efficacy of IMFINZI in combination with platinum-based chemotherapy as neoadjuvant treatment, followed by IMFINZI as monotherapy as adjuvant treatment, for the treatment of adults with resectable NSCLC at high risk of recurrence, the MAH should submit the results of the final OS analysis from the pivotal AEGEAN study (D9106C00001).	**Final OS analysis:** Q2 2029

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'Product Name-H-C-Product Number-II-0064'

Attachments

1. SmPC, Annex II, Package Leaflet (changes highlighted) as adopted by the CHMP on 27 February 2025.