30 January 2025
EMA/57978/2025
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Imfinzi

International non-proprietary name: Durvalumab

Procedure No. EMEA/H/C/004771/II/0069

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000

Table of contents

List of abbreviations

AJCC	American Joint Committee on Cancer Staging
BICR	Blinded Independent Central Review
BOR	Best objective response
cCRT	Chemotherapy concurrent with radiotherapy
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CR	Complete response
CRT	Chemoradiation therapy
CSR	Clinical Study Report
CT	Computed tomography
D	Durvalumab
DCO	Data cut-off
DoR	Duration of response
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
eCRF	Electronic case report form
EORTC	European Organisation for Research and Treatment of Cancer
ES-SCLC	Extensive stage small-cell lung cancer
FAS	Full Analysis Set
FDA	Food and Drug Administration
FPAS	Full PD-L1 Analysis Set
GHS	Global Health Status
HR	Hazard ratio
HRQoL	Health-related quality of life
IA	Interim analysis
IC	Immune cells
IDMC	Independent Data Monitoring Committee
IF	Information fraction
IP	Investigational product
IPD	Important protocol deviations
IV	Intravenous
IVRS	Interactive Voice Response System
KM	Kaplan-Meier
LS-SCLC	Limited stage small-cell lung cancer
MRI	Magnetic resonance imaging
MTP	Multiple testing procedure
NCCN	National Comprehensive Cancer Network
NR	Not reached
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
OS	Overall survival
OS24	Proportion of patients alive at 24 months from randomization
OS36	Proportion of patients alive at 36 months from randomization
OS-IA1	First interim analysis of OS
OS-IA2	Second interim analysis of OS
PCI	Prophylactic cranial irradiation
PD-L1	Programmed cell death ligand 1

PFS	Progression-free survival
PFS2	Time from randomization to second progression or death
PFS18	Progression-free survival at 18 months following randomization
PSF24	Progression-free survival at 24 months following randomization
PFS-IA	Interim PFS analysis
PK	Pharmacokinetic
PR	Partial response
PRO	Patient-reported outcome
PS	Performance status
QLQ-C30	30-item core quality of life questionnaire
QLQ-LC-13	Quality of life questionnaire, lung cancer module
QoL	Quality of life
QxW	Every x weeks
RECIST (1.1)	Response Evaluation Criteria In Solid Tumours (Version 1.1)
RT	Radiotherapy
SAP	Statistical Analysis Plan
SCLC	Small-cell lung cancer
SCS	Summary of clinical safety
SD	Standard deviation or stable disease
SOC	System organ class
T	Tremelimumab
TC	Tumour cells
TNM	Tumour, node, metastasis
TTDM	Time to death or distant metastasis
vs	Versus
WHO	World Health Organization

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 28 June 2024 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, II and IIIB

Extension of indication to include treatment of adults with limited-stage small cell lung cancer (LS-SCLC) whose disease has not progressed following platinum-based chemoradiation therapy for IMFINZI, based on final results from study D933QC00001 (ADRIATIC); this is a phase III, randomized, double-blind, placebo-controlled, multi-centre, global study to assess the efficacy and safety of durvalumab monotherapy and durvalumab in combination with tremelimumab compared to placebo as consolidation treatment in patients with LS-SCLC whose disease had not progressed following definitive platinum-based chemoradiation therapy (ADRIATIC). As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 12,s1 of the RMP has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet and to implement editorial changes to Annex II. Furthermore, the PI is brought in line with the latest QRD template version 10.4.

The variation requested amendments to the Summary of Product Characteristics, Annex II 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 submitted a critical report addressing the possible similarity with authorised orphan medicinal products.

Scientific advice

The MAH received Scientific Advice from the CHMP on 26 July 2018 (EMEA/H/SA/3558/2/2018/II). The Scientific Advice pertained to clinical aspects of the dossier.

International collaboration

The European Medicines Agency (EMA) was an observer of the review conducted under the FDA project Orbis for this indication.

1.2. Steps taken for the assessment of the product

The Rapporteurs appointed by the CHMP were:

Rapporteur: Boje Ehmsen

Timetable	Actual dates
Submission date	28 June 2024
Start of procedure:	20 July 2024
CHMP Rapporteur Assessment Report	13 September 2024
PRAC Rapporteur Assessment Report	20 September 2024
PRAC members comments	NA
PRAC Outcome	3 October 2024
CHMP members comments	7 October 2024
Updated CHMP Rapporteur(s) (Joint) Assessment Report	10 October 2024
Request for supplementary information adopted by the CHMP on:	17 October 2024
MAH's responses submitted to the CHMP on	27 November 2024
Rapporteur's preliminary assessment report on the MAH's responses	20 December 2024
CHMP members comments	20 January 2025
Joint Rapporteur's updated assessment report on the MAH's responses circulated on:	23 January 2025
CHMP opinion	30 January 2025
The CHMP adopted a report on similarity of Imfinzi with Hetronifly on: (Appendix 1)	07 March 2025
A revised opinion was adopted by the CHMP on:	07 March 2025

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Small cell lung cancer (SCLC) is a high-grade neuroendocrine carcinoma that comprises approximately 15% of all lung cancers (Rudin et al 2021). It is characterized by exceptionally high metastatic potential with the most common sites of metastasis including the contralateral lung, brain, liver, adrenal glands, and bone.

State the claimed the therapeutic indication

IMFINZI is indicated for the treatment of patients with limited stage small-cell lung cancer (LS-SCLC) whose disease has not progressed following platinum-based chemoradiation therapy.

Epidemiology and risk factors, Biologic features

SCLC comprises approximately 15% of all lung cancers, resulting in approximately 250,000 new cases and 200,000 global deaths each year (Rudin et al 2021).

SCLC is an aggressive solid tumour characterized by rapid doubling time, high growth fraction, and early dissemination. Due to its early propensity to metastasize, SCLC also exhibits the highest concentration of circulating tumour cells among all solid tumours (Hou et al 2012). Its hallmarks include a strong association with current or former tobacco smoking and a high tumour mutation burden (Peifer et al 2012), though there remains consistently a small percentage of never smokers who are diagnosed with SCLC (approximately 2% to 8% based on recently published Phase III studies in SCLC; Rudin et al 2021, Paz-Ares et al 2019, Rudin et al 2020). SCLC is more prevalent in men, although worldwide the incidence is increasing in women. In the US, SCLC is less prevalent in African-Americans than White Americans (Rudin et al 2021). In the US during 2016 to 2020, 66% of cases of SCLC were reported in patients ≥ 65 years of age (SEER*Explorer).

Clinical presentation, stage/prognosis

SCLC can be classified according to the AJCC/International Union Against Cancer TNM staging system as well as the older US Veterans Administration diagnosis scheme for SCLC (Jett et al 2013, Kalemkerian and Gadgeel 2013, Käsmann et al 2020). Limited stage SCLC (LS-SCLC) corresponds to TNM Stages I to III and includes any tumour tissue that can be encompassed in a single radiation port. Extensive stage SCLC (ES SCLC) includes any tumour that extends beyond the boundaries of a single radiation port or distant metastatic disease (TNM Stage IV disease); this includes any malignant pleural or pericardial effusion (Micke et al 2002, Rudin et al 2021). Among patients presenting with SCLC, approximately 30% will be diagnosed with LS-SCLC and approximately 70% will be diagnosed with ES-SCLC (García-Campelo et al 2023, Byers and Rudin 2015). Concurrent inactivation of 2 key

tumour suppressors, p53 and retinoblastoma (encoded by TP53 and RB1, respectively), is found in the majority of SCLC cases (George et al 2015).

On average, median survival durations are less than 24 months for patients with LS-SCLC and approximately 12 months for patients with ES SCLC (Wang et al 2017, Rudin et al 2021).

Management

Despite excellent initial chemosensitivity, widespread chemoresistance at the time of relapse makes SCLC one of the most challenging solid tumours to treat (Fukuoka et al 1991, Roth et al 1992, Niell et al 2005, Schmittel et al 2006, Noda et al 2002, Hanna et al 2006, Rossi et al 2012, Oronsky et al 2022). The established standard of care treatment for most patients diagnosed with LS-SCLC has been definitive concurrent chemoradiotherapy (cCRT) with curative intent. Only 4% of all patients with SCLC are diagnosed with very early-stage disease (Stage I-IIA; T1-2, N0, M0) at initial presentation and are potential candidates for surgical resection followed by adjuvant platinum-based chemotherapy with or without adjuvant radiation therapy (Rudin et al 2021). Those who are medically inoperable or who decide not to pursue surgery can potentially be considered for stereotactic ablative radiotherapy or, more commonly, be treated with cCRT such as for all Stage IIB-IIIC patients (NCCN 2024, Shioyama et al 2018, Verma et al 2017a, Verma et al 2017b).

For most patients with LS-SCLC receiving cCRT, the standard systemic treatment includes 4 cycles of platinum-based chemotherapy typically administered every 21 to 28 days concurrently with radiation therapy (NCCN 2024, Dingemans et al 2021).

For radiation therapy, the most optimal dose and schedule can vary depending on geography and local practice standards. Commonly used regimens include either once daily thoracic radiation of 2 Gy with a total dose of 60 to 66 Gy delivered over a 6-week period (though higher doses up to 70 Gy are also used) or 3 Gy daily (as twice daily 1.5 Gy) with a total dose of 45 Gy that is typically administered over just 3 weeks (Faivre-Finn et al 2017, Bogart et al 2022, Bogart et al 2023, NCCN 2024). Other key considerations regarding radiation therapy include the timing of initiation of therapy. Radiation concurrent with chemotherapy is preferred over sequential chemoradiation (chemotherapy prior to radiation; Takada et al 2002, NCCN 2024, Dingemans et al 2021). Radiation should be initiated as early as possible in the treatment course, ideally with the first or second cycle of chemotherapy (Fried et al 2004, Dingemans et al 2021). Shorter time intervals from the start of any therapy to the end of radiation therapy are associated with improved survival (De Ruysscher et al 2006).

In addition, due to the predilection for SCLC to metastasize to the brain, preventative brain radiation, or prophylactic cranial irradiation (PCI), has been routinely used as a standard of care for treatment of patients with LS-SCLC. According to ESMO guidelines, PCI is recommended at the end of cCRT for patients with a confirmed tumour response and no contraindication for this procedure (Dingemans et al, 2021).

Currently, there are no approved drug therapies for patients with LS-SCLC once they have completed cCRT. The standard care for those patients is observation with surveillance.

Unmet Medical Need

Response rates for cCRT in LS-SCLC are approximately 90%, but most patients will eventually progress, with median PFS of 10 to 15 months and median OS of 25 to 30 months, both from the start of cCRT (Bogart et al 2023, Faivre-Finn et al 2017, Walls et al 2024). Among patients diagnosed with LS-SCLC who complete the entire course of cCRT with curative intent, only up to 25% will achieve long term disease control and survival (Bogart et al 2023, Faivre-Finn et al 2017, Rudin et al 2021, Walls et al 2024). These poor long-term survival outcomes underscore the significant unmet clinical need for

improved therapeutic options for patients with LS-SCLC. Moreover, there are no approved treatments for LS-SCLC after completion of cCRT.

2.1.2. About the product

Durvalumab (Imfinzi) is a fully human high affinity IgG1 kappa mAb that binds to PD L1 and selectively blocks the interaction of PD L1 with PD 1 and CD80 while leaving PD 1/PD L2 interaction intact (Stewart et al 2015). Blockade of PD L1/PD 1 and PD L1/CD80 interactions releases the inhibition of T cells and promotes an antitumour immune response, without inducing antibody dependent cell mediated cytotoxicity. Imfinzi is authorised in Europe since September 2018 (EMEA/H/C/4771) for the treatment of multiple cancers (NSCLC, HCC, BTC, ES-SCLC).

Imfinzi was granted an extension of indication for the use in combination with etoposide and either carboplatin or cisplatin for the first-line treatment of adults with extensive-stage small cell lung cancer (ES-SCLC) in August 2020 (EMEA/H/C/004771/II/0014/G). The extension of indication was supported by study D419QC00001 (CASPIAN), a Phase III randomised, multicentre, open-label, comparative study designed to determine the efficacy and safety of durvalumab, or durvalumab and tremelimumab, in combination with etoposide and platinum-based chemotherapy (EP) for the first-line treatment of patients with ES-SCLC.

The indication, as adopted by CHMP, is:

IMFINZI as monotherapy is indicated for the treatment of adults with limited-stage small cell lung cancer (LS-SCLC) whose disease has not progressed following platinum-based chemoradiation therapy.

The recommended dose is 1500 mg every 4 weeks. Treatment should be continued until disease progression, unacceptable toxicity, or a maximum of 24 months.

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

The evidence of efficacy pertinent to the proposed indication is based on the pivotal, Phase III, randomized, double-blind, 3-arm, placebo-controlled, multi centre, international Study D933QC00001 (hereafter referred to as ADRIATIC). There are no supportive studies in this indication, and therefore no pooling of efficacy data was performed.

Throughout the clinical development process, the Sponsor has followed the FDA Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (FDA 2018), the EMA Guideline on the Clinical Evaluation of Anticancer Medicinal Products (EMA 2023), and ICH scientific and regulatory guidance.

The MAH received a scientific advice from the CHMP in July 2018, addressing the proposed design of pivotal trial ADRIATIC. There was overall agreement on the design of the pivotal study, however some concerns regarding exclusions criteria, stratifications factors and primary endpoints were noticed. The CHMP disagreed with exclusion of patients with PS 2 after cCRT and recommended instead exclusion of patients with specific baseline comorbidities, as cCRT is a rigorous treatment, which can lead to temporary PS deterioration due to its toxicity. Moreover, recovery of PS can take a long time, and it is not desirable to delay treatment in this aggressive disease, especially in case of achieved SD as the best response of cCRT. However, the MAH has chosen not to modify the protocol based on this recommendation.

Inputs on using a TNM stage as stratification factor and OS as primary endpoint were incorporated. This is endorsed. The initial design for ADRIATIC included three arms. The PFS comparison of the third

arm (durvalumab + tremelimumab) versus placebo was downgraded from one of the dual primary objectives to a secondary objective in protocol amendment 3 based on external data. This issue is further discussed in the clinical efficacy section.

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

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.

Table 1 Tabular overview of clinical studies

Study number (name) Study title	DCO date	Objectives of study	Study design and type of control	Dosage regimen D Pan-tumour Pool
• **Pivotal study**				
D933QC00001 (ADRIATIC) A Phase III, randomized, double-blind, placebo-controlled, multi-center, international study of durvalumab or durvalumab and tremelimumab as consolidation treatment for patients with LS-SCLC who have not progressed following cCRT	15 Jan 2024	Efficacy, safety, tolerability, PK, immunogenicity, and health-related quality of life	Randomized, double-blind, placebo-controlled, multi-center	• Durvalumab 1500 mg IV Q4W (N = 262)
• **Supportive studies**				
CD-ON-MEDI4736-1108 (Study 1108) A 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	• Durvalumab 10 mg/kg IV Q2W and 20 mg/kg IV Q4W (N =1001)
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	• Durvalumab 10 mg/kg IV Q2W and 20 mg/kg IV Q4W (N =124)
D4191C00003 (ATLANTIC) A Phase II, non-comparative, open-label, multicenter, international study of MEDI4736 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	03 Jun 2016	Efficacy, safety, tolerability, PK, and immunogenicity	Open-label, single-arm, non-randomized	• Durvalumab 10 mg/kg IV Q2W (N = 444)
D4191C00004 (ARCTIC) A Phase III, open-label, randomized, multicenter, international study of MEDI4736, given as monotherapy or in combination with tremelimumab, determined by PD-L1 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 tyrosine kinase activating mutations or ALK rearrangements	09 Feb 2018	Efficacy, safety, tolerability, PK, and immunogenicity	Open-label, randomized, active comparator	• Durvalumab 10 mg/kg IV Q2W (N = 179)

Study number (name) Study title	DCO date	Objectives of study	Study design and type of control	Dosage regimen D Pan-tumour Pool
D4191C00001 (PACIFIC) A Phase III, randomized, double-blind, placebo-controlled, multicenter, international study of MEDI4736 as sequential therapy in patients with locally advanced, unresectable NSCLC (Stage III) who have not progressed following definitive, platinum-based cCRT	22 Mar 2018	Efficacy, safety, tolerability, PK, immunogenicity, and health-related quality of life	Randomized, double-blind, placebo-controlled	• Durvalumab 10 mg/kg IV Q2W (N = 475)
D419AC00001 (MYSTIC) A Phase III, randomized, open-label, multi-center, global study of MEDI4736 in combination with tremelimumab therapy or MEDI4736 monotherapy versus standard of care platinum-based chemotherapy in first-line treatment of patients with advanced or metastatic NSCLC	04 Oct 2018	Efficacy	Open-label, randomized, active comparator	• Durvalumab 20 mg/kg IV Q4W (N = 369)
D4193C00001 (HAWK) A Phase II, multi-center, single-arm, global study of MEDI4736 monotherapy in patients with recurrent or metastatic SCCHN	05 Oct 2018	Efficacy and health-related quality of life	Open-label, single-arm	• Durvalumab 10 mg/kg IV Q2W (N = 112)
D4193C00002 (EAGLE) A Phase III, randomized, open-label, multi-center, global study of MEDI4736 monotherapy and MEDI4736 in combination with tremelimumab versus SoC therapy in patients with recurrent or metastatic SCCHN	10 Sep 2018	Efficacy, safety	Open-label, randomized	• Durvalumab 10 mg/kg IV Q2W (N = 237)
D4193C00003 (CONDOR) A Phase II, randomized, open-label, multi-center, global study of MEDI4736 monotherapy, tremelimumab monotherapy, and MEDI4736 in combination with tremelimumab in patients with recurrent or metastatic SCCHN	27 Aug 2018	Efficacy, safety, and health-related quality of life	Open-label, randomized	• Durvalumab 10 mg/kg IV Q2W (N = 65)
D419BC00001 (DANUBE) A Phase III, randomized, open-label, controlled, multi-center, global study of first-line MEDI4736 (durvalumab) monotherapy and MEDI4736 (durvalumab) in combination with tremelimumab versus SoC in patients with unresectable Stage IV urothelial cancer	27 Jan 2020	Efficacy and safety	Randomized, open-label, controlled (SoC), multicenter	• Durvalumab 1500 mg IV Q4W (N = 345)

Study number (name) Study title	DCO date	Objectives of study	Study design and type of control	Dosage regimen D Pan-tumour Pool
D419LC00001 (KESTREL) A Phase III, randomized, open-label, multi-center, global study of MEDI4736 alone or in combination with tremelimumab versus SoC in the treatment of first-line recurrent or metastatic SCCHN patients	06 Jul 2020	Efficacy and safety	Randomized, open-label, multicenter, global	• Durvalumab 1500 mg IV Q4W (N = 202)
D4190C00022 (Study 22) 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 HCC	06 Nov 2020	Safety, tolerability, efficacy, PK, and immunogenicity	Open-label, multiple-arm, randomized	• Part 2A: • Durvalumab 20 mg/kg IV Q4W (N = 3) • Durvalumab 1500 mg IV Q4W (N = 39) • Part 3: • Durvalumab 1500 mg Q4W (N = 62)
D419CC00002 (HIMALAYA) Randomized, open-label, multicenter Phase III study of durvalumab and tremelimumab as first-line treatment in patients with advanced HCC	27 Aug 2021	Efficacy and safety	Randomized, open-label	• Durvalumab 1500 mg IV Q4W (N = 388)
D419AC00002 (PEARL) A Phase III randomized, open-label, multi-center study of durvalumab versus standard of care platinum-based chemotherapy as first line treatment in patients with PD-L1-high expression advanced NSCLC	27 Oct 2022	Efficacy, safety, PK, immunogenicity, and health-related quality of life	Randomized, open-label, multi-center	• Durvalumab 20 mg/kg IV Q4W (N = 335) (immunogenicity data only)

2.3.2. Pharmacokinetics

The new PK and immunogenicity data presented in this section are pertaining to the pivotal study D933QC00001 (hereafter referred to as ADRIATIC; DCO: 15 January 2024) and 14 supportive studies in the D Pan tumour Pool (see Table 1), in order to support the proposed indication, dosage, and duration of treatment. The D Pan tumour Pool consists of all patients from the pool of studies in which patients received at least one dose of durvalumab monotherapy given at a dose of 1500 mg Q4W or either 10 mg/kg Q2W IV or 20 mg/kg Q4W IV for any line of therapy (across tumour types), which is considered as equivalent to 1500 mg Q4W dosage.

The PK, immunogenicity, and pharmacodynamics of durvalumab have been previously characterized based on the assessment of data integrated from studies comprising the D Pan tumour Pool.

Prior population PK and exposure response relationship analyses have been conducted for the initial Marketing Authorisation Application and previous extensions of indication (e.g. PACIFIC [initial MAA, EMEA/H/C/4771], CASPIAN [II/0014/G], POSEIDON [II/0041], HIMALAYA [II/0057], and TOPAZ 1 [II/0046]). These analyses have confirmed there is no clinically meaningful covariate identified on PK, including different tumour types, and that there is no significant exposure response for both efficacy and safety endpoints at the dose levels evaluated for each study (Table 2). Therefore, durvalumab population PK and exposure response relationship analyses are not included as part of this application.

Table 2 Summary of Doses Used in Clinical Studies

Study	Durvalumab
D4191C00001 (PACIFIC)	Durvalumab IV 10 mg/kg Q2W for up to 12 months
D419QC00001 (CASPIAN)	Durvalumab IV 1500 mg Q3W × 4 doses, then durvalumab IV 1500 mg Q4W until progression of disease + etoposide + carboplatin or cisplatin for 4 cycles
D419MC00004 (POSEIDON)	Durvalumab IV 1500 mg Q3W × 4 doses + SoC, then durvalumab 1500 mg IV Q4W until progression of disease
D419CC00002 (HIMALAYA)	Durvalumab IV 1500 mg Q4W until confirmed progression of disease
D933AC00001 (TOPAZ-1)	Durvalumab IV 1500 mg 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 IV 1500 mg Q4W until progression of disease

2.3.2.1. Bioanalytical methods

Table 3 Bioanalytical Methods Used for Durvalumab in the ADRIATIC Study

Drug product	Measurement	Laboratory	Validation report	Method number
Durvalumab	Concentration	BioAgilytix	BAL-17-078-230-REP	BAL-17-078-230
		Labcorp-Shanghai	8359-995	ICSH 16-032
	ADA	PPD	RAVC2	ICDIM 166
		Labcorp-Shanghai	8387-613	ICSH 18-043
	nAb	PPD	RJRG2	ICDIM 324
		Labcorp-Shanghai	8387-615	ICSH 18-044

Table 4 Bioanalytical Methods Used for Durvalumab in the PEARL Study

Drug product	Measurement	Laboratory	Validation report	Method number
Durvalumab	ADA	BioAgilytix	BAL-15-078-147-REP	BAL-15-078-147
	nAb	AstraZeneca South San Francisco	V-IM-0085	V-IM-0085

Table 5 Summary of Durvalumab Serum Concentration Assay Parameters in the ADRIATIC Study - BioAgilytix

Method number	BAL-17-078-230
Report number	**BAL-17-078-230-REP**
LLOQ (ng/mL)	50.00
Range (ng/mL)	50.00 to 3200.00
Inter-assay %RE range	-9.0 to 2.6
Inter-assay %CV range	5.7 to 8.6
Intra-assay %RE range	-20.1 to 12.7
Intra-assay %CV range	1.2 to 8.0

Table 6 Summary of Durvalumab Serum Concentration Assay Parameters in the ADRIATIC Study – Labcorp-Shanghai

Method number	**ICSH 16-032**
Report number	**8359-995**
LLOQ (ng/mL)	50.00
Range (ng/mL)	50.00 to 3200.00
Inter-assay %RE range	-0.6 to 8.2
Inter-assay %CV range	6.6 to 11.5
Intra-assay %RE range	-14.3 to 19.5
Intra-assay %CV range	1.7 to 11.4

Table 7 Summary of Anti-Durvalumab Antibody Assay Parameters in the ADRIATIC Study – PPD

Method number	**ICDIM 166**
Screening assay cut point [a]	1.59
Screening assay false-positive rate (%)	5
Assay LOD (ng/mL) [b]	8.22
Assay detectable range (ng/mL)	8.22 to 100000
Assay drug tolerance	**Assay can detect ≥ 82.3 ng/mL positive control in the presence of ≤ 100 µg/mL of durvalumab [c]**
Inter-assay precision (%CV)	15.6 to 27.0 [d]
Intra-assay precision (%CV)	1.94 to 3.80
Confirmatory assay cut point (% inhibition) [e]	29.4
Confirmatory assay false-positive rate (%)	0.1
Validation report number	See Module 5.3.1.4 Main Validation: RAVC2 Addendum 1: RAVC4
Synopsis of amendment history	Addendum 1: Additional Stability

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

[b] Represents screening assay sensitivity.

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

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

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

Table 8 Summary of Anti-Durvalumab Antibody Assay Parameters in the ADRIATIC Study – Labcorp-Shanghai

Method number	**ICSH 18-043**
Screening assay cut point [a]	1.21
Screening assay false-positive rate (%)	5
Assay LOD (ng/mL) [b]	5.07
Assay detectable range (ng/mL)	5.07 to 500000
Assay drug tolerance	**Assay can detect ≥ 15 ng/mL positive control in the presence of ≤ 500 µg/mL of durvalumab**
Inter-assay precision (%CV)	2.3 to 9.9
Intra-assay precision (%CV)	0.8 to 2.7
Confirmatory assay cut point (% inhibition) [c]	26.5
Confirmatory assay false-positive rate (%)	1
Validation report number	See Module 5.3.1.4 Main Validation: 8387-613 Addendum 1: 8387-613 Addendum 1 Addendum 2: 8387-613 Addendum 2 Amendment 1: 8387-613 Amended Final Report 1
Synopsis of amendment history	Addendum 1: Cross-validation Addendum 2: Additional Selectivity Amendment 1: Lab and Method Information Updates

[f] Cut point was established in each validation study by statistical analysis of SN ratios of RLU responses of the individual naïve samples from patients with cancer without drug normalized relative to the pooled serum matrix blank RLU signal.

[g] Represents screening assay sensitivity.

[h] Confirmatory cut point was established for each disease state matrix by statistical analysis of the percent inhibition levels of the responses of individual naïve samples from patients with cancer tested, both with and without drug.

Note: the ADA assay validated by Labcorp-Shanghai (ICSH 18-043 Table 8) is formatted as a bridging assay similar to PPD (ICDIM 324 Table 7), but utilizes additional sample pre-treatment steps for increased drug tolerance. The Labcorp-Shanghai method begins with acid dissociation of anti-durvalumab in the samples, followed by the affinity capture step to remove excess free drug in the sample for increased drug tolerance. After second acid elution, the samples are incubated with a mixture containing biotinylated MEDI4736 and sulfo-tagged MEDI4736 to form a sulfo-tagged drug-ADA-biotinylated drug complex. The labelled drug-ADA complexes are transferred to a streptavidin plate where they are captured. A signal at or above the established cut point indicated the presence of ADA in the sample. The final sample dilution after acid sample pre-treatment, affinity capture elution, and master-mix incubation was 1:31.25.

2.3.2.2. Pivotal Study (ADRIATIC)

Study title: A Phase III, Randomized, Double blind, Placebo controlled, Multi center, International Study of Durvalumab or Durvalumab and Tremelimumab as Consolidation Treatment for Patients with Limited Stage Small Cell Lung Cancer Who Have Not Progressed Following Concurrent Chemoradiation Therapy (ADRIATIC)

Dose Rationale

Durvalumab as a monotherapy at 10 mg/kg Q2W has received a Marketing Authorisation in many global regions. The approved dosing regimen of 10 mg/kg Q2W is based on clinical and non-clinical data demonstrating appropriate clinical benefit-risk profiles.

Given the expectation of similar durvalumab PK exposure and variability, dose regimens with less frequent Q4W dosing periods and a fixed 1500 mg Q4W (equivalent to 10 mg/kg Q2W or 20 mg/kg Q4W based on a median body weight of 75 kg) dosing approach were proposed. Durvalumab PK has been well established within a range of indications at 1500 mg Q4W. This fixed dosing regimen has been approved, and is preferred by the prescribing community over the earlier approved weight-based 10 mg/kg Q2W and 20 mg/kg Q4W regimens due to convenience for the patients, ease of use, and reduced dosing errors. Durvalumab 1500 mg Q4W is currently being administered in numerous clinical studies across different tumour types.

Clinical pharmacology objectives: to assess the PK of durvalumab monotherapy, and durvalumab and tremelimumab combination therapy, and to investigate the immunogenicity of durvalumab monotherapy and durvalumab and tremelimumab combination therapy in patients with LS SCLC.

PK and ADA sampling: PK samples for durvalumab were collected post dose on Cycle 1 (within 10 minutes of the end of infusion), pre-dose (i.e. within 60 minutes prior to start of infusion) on Cycles 2, 5, and on the last scheduled Cycle, and samples for ADA analysis were collected pre-dose on Cycles 1, 5, 13, 20 and on the last scheduled Cycle. The PK and ADA data are reported from the DCO date of 15 January 2024.

PK: At the time of DCO, PK data (serum concentrations of durvalumab) were available for a total of 258 patients in the D group who were included in the PK analysis set. Durvalumab concentrations were determined using a validated bioanalytical assay with a LLOQ of 50 ng/mL. The geometric mean serum durvalumab concentration in samples collected at the end of the durvalumab infusion on Day 1, Cycle 1 (Week 0) was 306 µg/mL in patients in the D group. The geometric mean serum durvalumab concentrations at steady state ranged from 147 to 168 µg/mL, in line with the expected exposure range following 1500 mg Q4W durvalumab.

Table 9 Summary of Serum Durvalumab Concentrations Over Time (µg/mL) (PK Analysis Set) (ADRIATIC Study and D Pan-tumour Pool [Excluding ADRIATIC])

	ADRIATIC	D Pan-tumour Pool (excluding ADRIATIC)		
Visit/timepoint	1500 mg Q4W (N = 258)	1500 mg Q4W (N = 959)	20 mg/kg Q4W (N = 424)	10 mg/kg Q2W (N = 2520)
Week 0 - post-infusion				
n	222	523	376	2267
Mean	431	459	471	212

Visit/timepoint	ADRIATIC	D Pan-tumour Pool (excluding ADRIATIC)		
	1500 mg Q4W (N = 258)	1500 mg Q4W (N = 959)	20 mg/kg Q4W (N = 424)	10 mg/kg Q2W (N = 2520)
SD	328	167	213	98.2
Median	410	454	439	205
(Min, max)	(0.0500, 4720)	(0.0500, 1330)	(0.0500, 2320)	(0.0250, 1470)
CV%	76.1	36.3	45.3	46.3
Geometric mean	306	346	395	168
Geometric CV%	361	322	155	211
Number of BLQ	6	15	5	49
Week 4 - pre-infusion				
n	215	852	14	1074
Mean	89.6	81.8	102	93.7
SD	107	50.6	53.1	40.7
Median	78.5	74.5	94.7	90.4
(Min, max)	(36.7, 1560)	(0.0500, 712)	(0.0500, 177)	(0.0500, 405)
CV%	120	61.9	52.0	43.4
Geometric mean	78.4	68.3	58.7	83.0
Geometric CV%	42.7	97.1	856	70.1
Number of BLQ	0	6	1	1
Week 16 - pre-infusion				
n	119	0	0	507
Mean	160	-	-	173
SD	58.6	-	-	77.9
Median	147	-	-	162
(Min, max)	(4.22, 348)	(-, -)	(-, -)	(3.92, 595)
CV%	36.7	-	-	45.1
Geometric mean	147	-	-	155
Geometric CV%	50.9	-	-	54.2
Number of BLQ	0	0	0	0
Week 24 - pre-infusion				
n	8	202	146	398
Mean	116	166	162	188
SD	102	94.3	167	78.0
Median	106	153	133	182
(Min, max)	(23.8, 336)	(0.0500, 820)	(40.6, 1470)	(0.0500, 571)
CV%	87.6	56.8	103	41.5
Geometric mean	82.3	137	133	166
Geometric CV%	118	107	59.7	78.7
Number of BLQ	0	1	0	1

Visit/timepoint	ADRIATIC	D Pan-tumour Pool (excluding ADRIATIC)		
	1500 mg Q4W (N = 258)	1500 mg Q4W (N = 959)	20 mg/kg Q4W (N = 424)	10 mg/kg Q2W (N = 2520)
Month 3 follow-up				
n	118	216	82	625
Mean	45.0	19.3	35.7	30.0
SD	36.0	22.9	103	29.8
Median	37.7	10.7	9.68	22.4
(Min, max)	(0.0500, 230)	(0.0500, 162)	(0.0500, 662)	(0.0500, 221)
CV%	80.1	118	290	99.4
Geometric mean	29.5	6.91	6.09	14.5
Geometric CV%	187	723	1450	409
Number of BLQ	1	20	11	27

Immunogenicity: The prevalence and incidence of durvalumab-specific ADA in ADRIATIC were low (6.3% and 3.4%, respectively). Observed ADA had a low titre. These results are consistent with the low immunogenicity of durvalumab observed in previous clinical studies. Only a small proportion (1% of ADA-evaluable patients) of durvalumab-specific ADA were nAb.

ADA effect on PK: The geometric mean serum durvalumab concentrations in patients with treatment emergent ADAs to durvalumab were generally similar to those in ADA negative patients. See Table below.

Table 10 Summary of Serum Concentration of Durvalumab (µg/mL) by ADA Category in the ADRIATIC Study (PK Analysis Set)

Visit (timepoint)	D (N = 258)	
	Treatment-emergent ADA-positive to durvalumab [a] (n = 7)	ADA-negative to durvalumab [b] (n = 192)
Week 0 (end of infusion) (Cycle 1)		
n	6	171
n < LLOQ	0	5
Geometric mean [c]	393	299
Geometric CV% [c]	9.94	412
Week 4 (pre-infusion) (Cycle 2)		
n	5	166
n < LLOQ	0	0
Geometric mean [c]	59.4	79.9
Geometric CV% [c]	45.8	42.2
Week 16 (pre-infusion) (Cycle 5)		
n	1	111
n < LLOQ	0	0
Geometric mean [c]	78.9	148

Visit (timepoint)	D (N = 258)	
	Treatment-emergent ADA-positive to durvalumab [a] (n = 7)	ADA-negative to durvalumab [b] (n = 192)
Geometric CV% [c]	NC	51.2
Week 100 (pre-infusion) (Cycle 26)		
n	1	40
n < LLOQ	0	0
Geometric mean [c]	199	168
Geometric CV% [c]	NC	38.0
Month 3 follow-up		
n	3	110
n < LLOQ	0	1
Geometric mean [c]	13.0	30.2
Geometric CV% [c]	52.1	195

[a] Treatment-emergent ADA-positive is defined as either treatment-induced (post-baseline ADA-positive only) or treatment-boosted ADA (baseline positive ADA titer that was boosted to ≥ 4 fold during the study period).
[b] ADA-negative includes patients without any ADA-positive results at baseline or post-baseline against durvalumab.
[c] Calculated using log transformed data.
n = Number of patients in the ADA category.
At a time point where less than or equal to 50% of the concentration values were NQ, all NQ values were set to the LLOQ, and all descriptive statistics were calculated accordingly. At a time point where more than 50% (but not all) of the values were NQ, the geometric mean, geometric mean ± geometric SD and geometric CV% were set to NC. The maximum value was reported from the individual data, and the minimum and median were set to NQ. If all concentrations were NQ at a time point, no descriptive statistics were calculated for that time point. The geometric mean, minimum, median and maximum are reported as NQ and the geometric CV% and geometric mean ± geometric SD as NC.
LLOQ was 0.05 µg/mL.
PK analysis set - all patients who received at least one dose of study treatment per the protocol for whom any post-dose data were available and who did not violate or deviate from the protocol in ways that would significantly affect the PK analyses.

Except for the additional PEARL study, not included in the previously submitted D Pan-tumour Pool, no new data are available from all other supportive studies included in the D Pan-tumour Pool at the time of this application. Consequently, the individual study narratives submitted previously have not been repeated for brevity. A narrative of the additional study PEARL is provided below.

D419AC00002 (PEARL)

Study title: A Phase III Randomized, Open Label, Multi Centre Study of Durvalumab Versus Standard of Care Platinum Based Chemotherapy as First Line Treatment in Patients with PD L1 High Expression Advanced Non-Small Cell Lung Cancer (NSCLC)

PEARL was a randomized, open label, multi-centre, global Phase III study to determine the efficacy and safety of durvalumab versus platinum based SoC chemotherapy in the first line treatment of advanced NSCLC patients with tumours that lacked sensitizing EGFR mutation and ALK rearrangement and with PD L1 high expression.

No PK samples were collected; therefore, only immunogenicity results are reported herein.

Samples for ADA analysis were collected pre-dose on Cycles 1, 4, and 7, and 3 and 6 months after the last dose. The ADA evaluable analysis set consisted of all patients in the safety analysis set who had a non-missing baseline ADA and at least one non-missing post baseline ADA result.

Dose proportionality and time dependencies

Limited new PK data was provided from the ADRATIC study and none from the PEARL study. PK data (end of infusion and Ctrough over time) appear similar to comparable dosages from other studies, see above.

2.3.3. Pharmacodynamics

Mechanism of action

PD L1 is expressed on both tumour cells and tumour associated immune cells in the tumour microenvironment, and expression of PD L1 can be induced by inflammatory signals. Programmed cell death ligand 1 blocks T cell function and activation through interactions with its receptors PD 1 and CD80 (B7.1). Durvalumab (Imfinzi) is a fully human high affinity IgG1 kappa mAb that binds to PD L1 and selectively blocks the interaction of PD L1 with PD 1 and CD80 while leaving PD 1/PD L2 interaction intact (Stewart et al 2015). Blockade of PD L1/PD 1 and PD L1/CD80 interactions releases the inhibition of T cells and promotes an antitumour immune response, without inducing antibody dependent cell mediated cytotoxicity.

Primary and secondary pharmacology

No new pharmacodynamics data are available that have not already been submitted and assessed. Prior exposure response analyses have been conducted for the initial marketing authorisation and several extensions of indication (e.g. PACIFIC, CASPIAN, POSEIDON, HIMALAYA, and TOPAZ 1), and these indicated no significant exposure response relationship for both efficacy and safety endpoints at the flat dose of 1500 mg or equivalent doses evaluated for each study. Exposure response analyses are not included in this application for ADRIATIC.

Immunogenicity

Table 11 Overview of Durvalumab Administration, Dosing Regimen, Anti-drug Antibody Sampling Timepoints, and Immunogenicity Results in the ADRIATIC and PEARL Studies

Study number (name) DCO date	Route of administration and dosage regimen	Durvalumab ADA sampling timepoints	Durvalumab ADA results
Pivotal study			
D933QC00001 (ADRIATIC) • DCO: 15 Jan 2024	• Durvalumab 1500 mg IV Q4W in combination with placebo IV Q4W for 4 doses/cycles each, followed by durvalumab 1500 mg IV Q4W starting 4 weeks after the final dose of durvalumab in combination with placebo	Pre-dose on Cycles 1, 5, 13, and 20 and on the last scheduled Cycle	ADA prevalence was 6.3% (13/206). ADA incidence was 3.4% (7/206). 2/206 patients (1.0%) were nAb-positive.
Supportive studies a			

Study number (name) DCO date	Route of administration and dosage regimen	Durvalumab ADA sampling timepoints	Durvalumab ADA results
D419AC00002 (PEARL) • DCO: 27 Oct 2022	• Durvalumab 20 mg/kg IV Q4W	Cycles 1, 4, and 7, and 3 and 6 months after treatment discontinuation.	ADA prevalence was 3.4% (8/236). ADA incidence was 0.8% (2/236). 1/236 patient (0.4%) was nAb-positive, however, this patient was ADA-positive at baseline only.

Table 12 Summary of ADA Response to Durvalumab in the ADRIATIC Study and D Pan tumour Pool (Safety Analysis Set)

Category	ADRIATIC D (N = 262)	D Pan-tumour Pool (N = 4642)
ADA-evaluable patients, n (%)	206 (78.6)	3511 (75.6)
ADA-positive at any visit (ADA prevalence), n (%) [a]	13 (6.3)	212 (6.0)
Median of maximum titre	2.0	4.0
(Minimum, maximum)	(1, 256)	(1, 1024)
Treatment-emergent ADA-positive (ADA incidence), n (%) [b]	7 (3.4)	93 (2.6)
Median of maximum titre	1.5	4.0
(Minimum, maximum)	(1, 256)	(1, 1024)
ADA-positive post-baseline and positive at baseline, n (%)	3 (1.5)	21 (0.6)
Median of maximum titre	4.0	8.0
(Minimum, maximum)	(1, 4)	(1, 32)
ADA-positive post-baseline only, or treatment-induced ADA, n (%)	6 (2.9)	89 (2.5)
Median of maximum titre	1.0	4.0
(Minimum, maximum)	(1, 256)	(1, 1024)
ADA-positive at baseline only, n (%)	4 (1.9)	102 (2.9)
Median of maximum titre	1.5	4.0
(Minimum, maximum)	(1, 2)	(1, 125)
Treatment-boosted ADA, n (%) [c]	1 (0.5)	4 (0.1)
Median of maximum titre	4.0	12.0
(Minimum, maximum)	(1, 4)	(1, 32)
Persistently positive, n (%) [d]	6 (2.9)	73 (2.1)

Category	ADRIATIC D (N = 262)	D Pan-tumour Pool (N = 4642)
Median of maximum titre	3.0	4.0
(Minimum, maximum)	(1, 256)	(1, 1024)
Transiently positive, n (%) [e]	3 (1.5)	37 (1.1)
Median of maximum titre	1.0	4.0
(Minimum, maximum)	(1, 1)	(1, 128)
nAb-positive at any visit, n (%)	2 (1.0)	19 (0.5)
Median of maximum titre	128.5	16.0
(Minimum, maximum)	(1, 256)	(1, 1024)

[i] ADA prevalence is the proportion of ADA-evaluable patients who were ADA-positive at any time.
[j] ADA incidence is the proportion of ADA-evaluable patients who were treatment-emergent ADA-positive.
[k] Treatment-boosted ADA is defined as baseline positive ADA titre that was boosted to ≥ 4 fold during the study period.
[l] Persistently positive is defined as having at least 2 post-baseline ADA-positive measurements with at least 16 weeks (112 days) between the first and last positive measurements, or an ADA-positive result at the last available assessment. The category includes patients meeting these criteria who are ADA-positive at baseline.
[m] Transiently positive is defined as having at least one post-baseline ADA-positive measurement and not fulfilling the conditions for persistently positive. The category includes patients meeting these criteria who are ADA-positive at baseline.

N is the number of patients in the safety analysis set in the treatment group. The denominator for calculation of percentage for all categories was the number of ADA-evaluable patients (defined as the patients in the safety analysis set who had a non-missing baseline ADA and at least one non-missing post-baseline result) in the treatment group. The denominator for ADA-evaluable patients category was N.
If a patient had more than one titre result, the maximum titre result was used, regardless of whether it was baseline or post-baseline.

2.3.4. PK/PD modelling

No new modelling or update of previous models were presented.

2.3.5. Discussion on clinical pharmacology

Bioanalysis in ADRIATIC

Analysis of serum for durvalumab for the ADRIATIC study was conducted at BioAgilytics and Labcorp Shanghai.

The PK assay was validated according to guidelines at all sites using the same critical reagents and same platform. Therefore, a cross validation between sites was not deemed necessary. This is agreed.

ADA analysis in ADRIATIC

PPD and Labcorp Shanghai were responsible for the ADA assays in the ADRIATIC study. Both strategies appear acceptable. However, the ADA assays at Labcorp Shanghai were using an acid elution step to increase drug tolerance. This is different from the PPD site, which shows a poorer drug tolerance.

No cross validation on ADA samples between the PPD and the Labcorp Shanghai site was provided. Pre-dose serum concentrations of durvalumab are frequently found to be above 100 µg/mL, where the ADA samples are collected. The lack of cross validation was justified by the MAH with the fact that the

assays are different with regard to drug tolerance. Therefore it may not be possible to show similarity. This is agreed.

The new method with better drug tolerance (Labcorp Shanghai) is a modification of the mother method (PPD), hence shares the same platform and has similar sensitivity when no durvalumab is present. The drug tolerance of the mother method is just below the mean concentration of durvalumab at time of sampling, hence some samples with lower levels of ADA may be missed using this method. However, since the pharmacokinetics and low immunogenicity of durvalumab is well-established through a number of clinical studies with both PK and ADA sampling, this can be accepted.

In the new ADRATIC study supporting the new indication in LS SCLC, PK samples were only collected at end of infusion (EOI) and at certain pre-dose time points. Hence, no new full PK profiles are available. The POPPK model was not updated with new data. Sampling for ADA analysis were performed pre-dose on Cycles 1, 5, 13, 20 and on the last scheduled Cycle. This is acceptable.

Mean serum concentrations from the ADRATIC study were compared to a pool of other studies excluding the ADRATIC study. Similarity of serum concentrations from the ADRATIC study were confirmed when compared to similar dose levels from other clinical studies (D Pan tumour pool).

The prevalence and incidence of durvalumab-specific ADA in ADRIATIC were low (6.3% and 3.4%, respectively). Observed ADA had low titres. Only 1% of durvalumab-specific ADA were nAb. A comparison of mean serum concentrations between ADA positive and ADA negative patients in the ADRATIC study could indicate that some patients were low in serum concentrations. However, few patients were positive (1, 3 or 5 at relevant pre-dose time points) and concentrations appeared reasonably similar. Moreover, no patients had durvalumab serum concentrations below quantification limit at pre-dose after the first dose. Hence, it is agreed that in general, ADA is not impacting exposure to durvalumab to a degree which may interfere with efficacy.

The new analysis provided on the PEARL study was only related to ADA, hence no PK data was available from this study. Here, samples for ADA analysis were collected pre-dose on Cycles 1, 4, and 7, and 3 and 6 months after the last dose. This is acceptable.

No new PK information was included in section 5.2 of the SmPC.

Pharmacodynamics

No new PD data or exposure-analyses have been provided in this submission. This is acceptable since durvalumab is well characterised in NSCLC and ES SCLC.

In the ADRIATIC study, the prevalence (6.3%) and incidence (3.4%) of ADA were low. Only a small proportion (1% of ADA-evaluable patients) were nAb. These results are in line with the low immunogenicity of durvalumab observed in previous clinical studies.

2.3.6. Conclusions on clinical pharmacology

Only limited new information about the PK of IV durvalumab 1500 mg Q4W monotherapy from the ADRIATIC study, and immunogenicity from ADRIATIC and PEARL studies were provided. Considering the previous knowledge of durvalumab clinical pharmacology, this is considered acceptable.

2.4. Clinical efficacy

2.4.1. Dose response study(ies)

No dose-response studies were submitted as part of this application.

2.4.2. Main study D933QC00001 (ADRIATIC)

A Phase III, Randomized, Double-blind, Placebo-controlled, Multi-center, International Study of Durvalumab or Durvalumab and Tremelimumab as Consolidation Treatment for Patients with Limited Stage Small-Cell Lung Cancer Who Have Not Progressed Following Concurrent Chemoradiation Therapy (ADRIATIC)

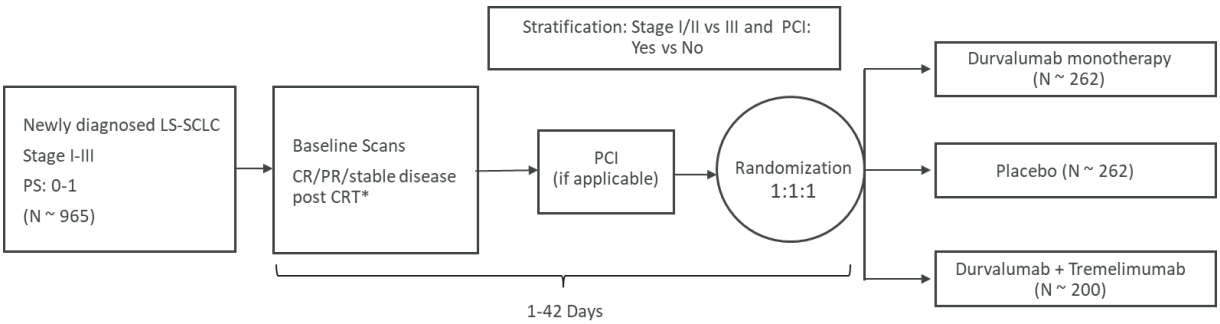
ADRIATIC is an ongoing, Phase III, randomized, double-blind, placebo-controlled, 3-arm, multi-center, international study to assess the efficacy and safety of durvalumab monotherapy (D) or durvalumab in combination with tremelimumab (D+T) compared to placebo as consolidation treatment in patients with limited stage small-cell lung cancer (LS-SCLC) whose disease had not progressed following definitive, platinum-based chemotherapy concurrent with radiotherapy (cCRT; figure 1).

Tumour assessments (computed tomography [CT] or magnetic resonance imaging [MRI]) were conducted at screening, then every 8 weeks for the first 72 weeks (relative to the date of randomization), followed by every 12 weeks until up to 96 weeks, and every 24 weeks thereafter until RECIST 1.1- defined radiological progression. After radiological progression, there was a follow-up scan no earlier than 4 weeks later, and no later than the next regularly scheduled imaging visit. Scans were evaluated according to RECIST 1.1.

Survival status was assessed at 8, 12, 16, 24, 32, 40, and 48 weeks after the last dose of study treatment, and every 8 weeks thereafter until study termination or death.

Patients received their assigned study treatment until clinical/RECIST 1.1-defined radiological progression, until intolerable toxicity, or for a maximum of 24 months, whichever occurred first.

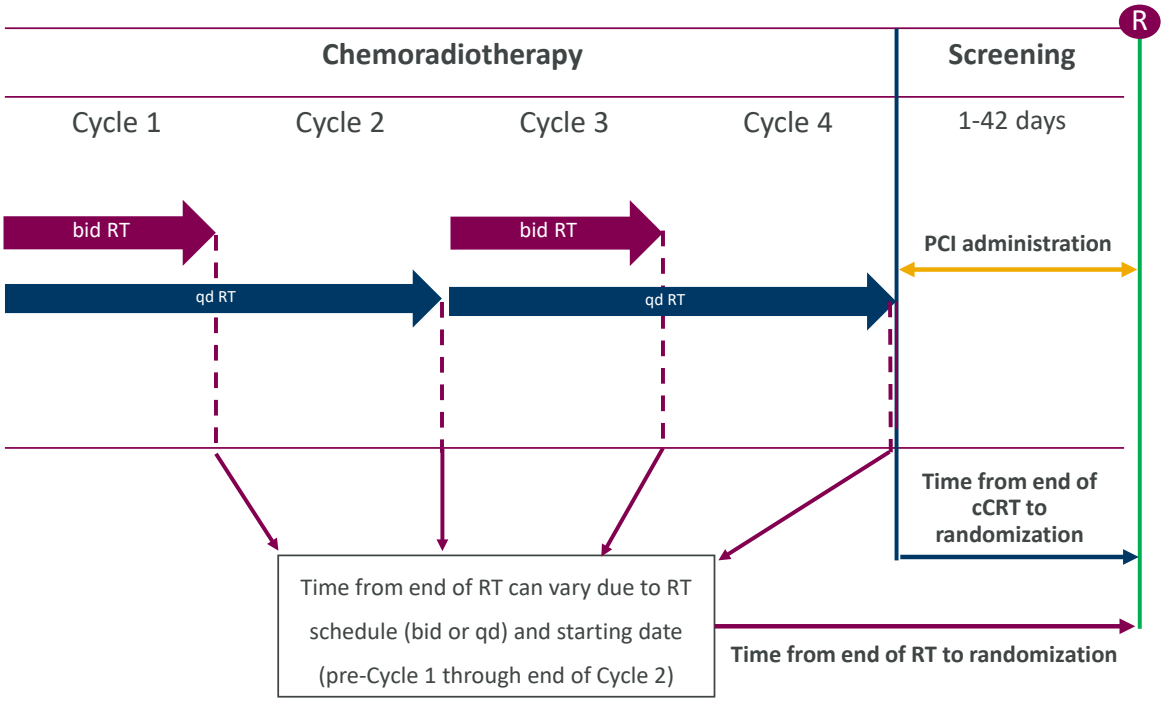
Figure 1 ADRIATIC Study Design



*Chemotherapy: 4 EP Cycles (3 permitted) and Radiotherapy: 60-66 Gy/qd/6 weeks or 45 Gy/bid/3 weeks

Baseline scans include RECIST 1.1 tumor assessment scans and brain MRI or CT scan

Figure 2 Illustration of the different time points related to standard of care treatment prior to ADRIATIC study entry



Methods

Study participants

Inclusion criteria per last version of the protocol:

1. Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

2. Provision of signed and dated, written ICF prior to any mandatory study specific procedures, sampling, and analyses.

3. Optional provision of signed and dated written genetic informed consent prior to collection of sample for genetic analysis (Not applicable for China).

4. Age ≥18 years at the time of screening. For patients aged <20 years and enrolled in Japan, a written informed consent should be obtained from the patient and his or her legally acceptable representative.

5. Histologically or cytologically documented limited-stage SCLC (Stage I-III SCLC [T any, N any, M0] according to the American Joint Committee on Cancer Staging Manual [AJCC Cancer Staging Manual, 8th Edition] or the International Association for the Study of Lung Cancer Staging Manual in Thoracic Oncology [IASLC Staging Manual in Thoracic Oncology 2016]), i.e., patients whose disease can be encompassed within a radical radiation portal. Patients who are Stage I or II must be medically inoperable as determined by investigator.

6. World Health Organization (WHO)/Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1 at enrolment and randomization.

7. Received an appropriate first line concurrent chemoradiotherapy regimen as defined below, unless after consultation with the global study medical team an alternative is acceptable:

- Received 4 cycles of platinum-based chemotherapy concurrent with RT, which must be completed within 1 to 42 days prior to randomization and the first dose of IP.
- The chemotherapy regimen must contain platinum and IV etoposide, administered as per local standard-of-care regimens.
- Received a total dose of radiation of 60 to 66 Gy over 6 weeks for standard QD radiation schedules or 45 Gy over 3 weeks for hyperfractionated BID radiation schedules. Sites are encouraged to adhere to mean organ radiation dosing as follows:
    - Mean lung dose <20 Gy and/or V20 <35%
    - Heart V50 <25%
- Radiotherapy must have commenced no later than the end of Cycle 2 of chemotherapy.
- Receipt of 3 cycles of platinum-based chemotherapy concurrent with RT will be permitted if the patient has achieved disease control and in the opinion of the Investigator, no additional benefit will be expected with additional cycle of chemotherapy.

8. Patients must have achieved CR, PR, or SD and not have progressed following definitive, platinum-based chemotherapy concurrent with radiotherapy.

9. PCI may be delivered at the discretion of investigator and local standard of care, and must be conducted after the end of cCRT and completed between 1 to 42 days to first dose of IP.

10. Tumour sample requirements:

- Mandatory availability of tumour sample, which may include a core needle biopsy, newly cut unstained slides, or fine needle aspirate (FNA) cell block samples. Tissue sample should be submitted before or within 60 days of randomization. However, patients may be enrolled into the study before the pretreatment tumour tissue sample is submitted.
- A newly acquired tumour biopsy (taken following completion of chemoradiotherapy) is optional, provided that a biopsy procedure is technically feasible, and the procedure is not associated with unacceptable clinical risk.

11. Adequate organ and marrow function independent of transfusion, infusion, or growth factor support for at least 14 days prior to screening, defined as below:

- Haemoglobin ≥9.0 g/dL
- Absolute neutrophil count ≥1.5 × 109 /L
- Platelet count ≥100 × 109/L
- Serum bilirubin ≤1.5 × the upper limit of normal (ULN). This will not apply to patients with confirmed Gilbert's syndrome (persistent or recurrent hyperbilirubinemia [predominantly unconjugated bilirubin] in the absence of evidence of haemolysis or hepatic pathology), who will be allowed in consultation with their physician.
- ALT and AST ≤2.5 × ULN
- Measured creatinine clearance (CL) >40 mL/min or calculated CL >40 mL/min as determined by Cockcroft-Gault (using actual body weight).

12. Must have a life expectancy of at least 12 weeks.

13. Body weight >30 kg.

14. Male or female.

Exclusion criteria:

1. Mixed SCLC and NSCLC histology.

2. Extensive-stage SCLC.

3. Any history of Grade ≥2 pneumonitis.

4. History of allogeneic organ transplantation.

5. 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 [granulomatosis with polyangiitis, Graves' disease, rheumatoid arthritis, hypophysitis, uveitis, etc.]). The following are 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 does not require systemic therapy
- Patients without active disease in the last 5 years may be included but only after consultation with the Study Physician
- Patients with celiac disease controlled by diet alone.

6. 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 GI conditions associated with diarrhoea, or psychiatric illness/social situations that would limit compliance with study requirements, substantially increase risk of incurring AEs or compromise the ability of the patient to give written informed consent.

7. History of another primary malignancy except for:

- Malignancy treated with curative intent and with no known active disease ≥5 years before the first dose of IP (Investigational product) 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.

8. History of leptomeningeal carcinomatosis.

9. History of active primary immunodeficiency.

10. Active infection including tuberculosis (clinical evaluation that includes clinical history, physical examination and radiographic findings, and tuberculosis testing in line with local practice), hepatitis B (known positive HBV surface antigen [HBsAg] result), hepatitis C (HCV), or human immunodeficiency virus (positive HIV ½ antibodies). Patients with a past or resolved HBV infection (defined as the presence of hepatitis B core antibody and absence of HBsAg) are eligible. Patients positive for HCV antibody are eligible only if polymerase chain reaction is negative for HCV RNA.

11. Any unresolved toxicity NCI Common Terminology Criteria for Adverse Events (CTCAE) Grade ≥2 from previous CRT with the exception of alopecia, vitiligo, and the laboratory values defined in the inclusion criteria:

- Patients with Grade ≥2 neuropathy will be evaluated on a case-by-case basis after consultation with the Study Physician.
- Patients with irreversible toxicity not reasonably expected to be exacerbated by treatment with durvalumab or tremelimumab may be included only after consultation with the Study Physician.

12. Brain metastases or spinal cord compression. All patients will have an MRI (preferred) or CT, preferably with IV contrast of the brain, prior to study entry.

13. Mean QT interval corrected for heart rate using Fridericia's formula (QTcF) ≥470 ms calculated from 3 ECGs (within 15 minutes at 5 minutes apart).

14. Known allergy or hypersensitivity to any of the study drugs or any of the study drug excipients.

15. Patients who received sequential CRT for LD-SCLC (no overlap of RT with chemotherapy).

16. Patients whose conditions have progressed while on concurrent CRT.

17. Receipt of chemotherapy that exceeds 4 cycles in total. Chemotherapy regimens other than etoposide and platinum are not permitted.

18. Prior exposure to immune-mediated therapy including, but not limited to, other anti-CTLA-4, anti-PD-1, anti-PD-L1, and anti-programmed cell death ligand 2 (anti-PD-L2) antibodies, excluding therapeutic anticancer vaccines.

19. Any concurrent chemotherapy, IP, biologic, or hormonal therapy for cancer treatment. Concurrent use of hormonal therapy for non-cancer-related conditions (e.g. hormone replacement therapy) is acceptable.

20. Receipt of live attenuated vaccine within 30 days prior to the first dose of IP. Note: Patients, if randomized, should not receive live vaccine while receiving IP and up to 30 days after the last dose of IP.

21. Major surgical procedure (as defined by the Investigator) within 42 days prior to the first dose of IP.

22. Current or prior use of immunosuppressive medication within 14 days before the first dose of durvalumab or tremelimumab. The following are 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).

23. Participation in another clinical study with an investigational product administered in the last 4 weeks.

24. Previous IP assignment in the present study.

25. Concurrent enrolment in another clinical study, unless it is an observational (non-interventional) clinical study or during the follow-up period of an interventional study.

26. Prior randomization or treatment in a previous durvalumab and/or tremelimumab clinical study regardless of treatment group assignment.

27. Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site).

28. Female patients who are pregnant or breastfeeding and male or female patients of reproductive potential who are not willing to employ effective birth control from screening to 3 months after the last dose of durvalumab monotherapy or 6 months after the last dose of durvalumab + tremelimumab combination therapy.

30. Judgment by the Investigator that the patient should not participate in the study because the patient is unlikely to comply with study procedures, restrictions, and requirements.

31. Genetics research study (optional):

Exclusion criteria for participation in the optional (DNA) genetics research component of the study include:

- Previous allogeneic bone marrow transplant
- Non-leukocyte-depleted whole blood transfusion in 120 days of genetic sample collection.

Treatments

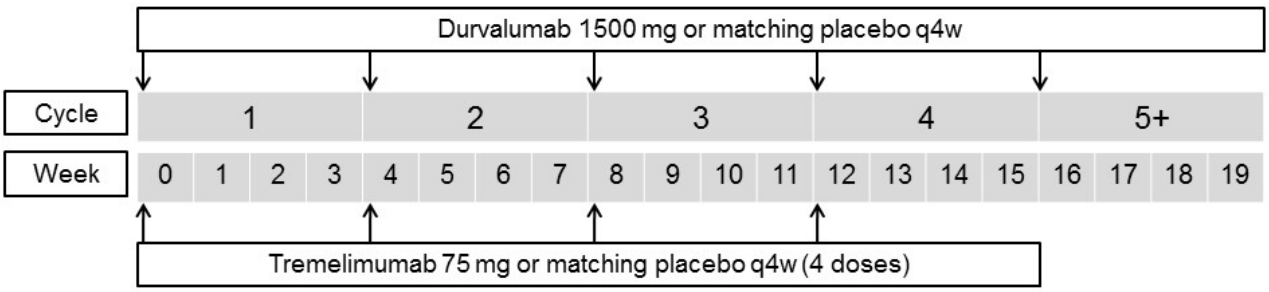
Eligible patients were randomized to 1 of the 3 treatment groups:

• Arm 1: Durvalumab monotherapy: Durvalumab (1500 mg intravenously [IV]) every 4 weeks (Q4W) in combination with tremelimumab placebo (IV) Q4W for 4 doses/cycles each, followed by durvalumab 1500 mg Q4W starting 4 weeks after the final dose of durvalumab in combination with tremelimumab placebo.

• Arm 2: Placebo: Durvalumab placebo (IV) Q4W in combination with tremelimumab placebo (IV) Q4W for 4 doses/cycles each, followed by durvalumab placebo Q4W starting 4 weeks after the final dose of the 2 placebos in combination.

• Arm 3: Durvalumab in combination with tremelimumab: Durvalumab (1500 mg IV) Q4W in combination with tremelimumab (75 mg IV) Q4W for 4 doses/cycles each, followed by durvalumab 1500 mg Q4W starting 4 weeks after the final dose of durvalumab in combination with tremelimumab.

Figure 3 Dosing schedule



After closure of randomization to the D+T group, patients newly randomized to the D or placebo groups, were to receive only one infusion of durvalumab or durvalumab placebo from Cycle 1 onwards for the duration of treatment (i.e. a maximum of 24 months). Patients no longer received the placebo infusion that was intended to mask the tremelimumab infusion since the actively enrolling

experimental group did not include tremelimumab infusion. Therefore, there was no need to maintain blinding with a second placebo infusion.

During combination treatment, tremelimumab or placebo were administered first; the durvalumab or placebo infusion started approximately 1 hour (maximum 2 hours) after the end of the tremelimumab or placebo infusion. If there were no clinically significant infusion reactions with the first cycle, and at the discretion of the Investigator, then for all other cycles, the durvalumab or placebo could be given immediately after the tremelimumab or placebo infusion had finished.

Duration of treatment: Patients received their assigned treatment until clinical/RECIST 1.1-defined radiological progression, until intolerable toxicity, or for a maximum of 24 months (26 doses/cycles), whichever occurred first.

Crossover between treatment arms was not allowed.

Dose modifications: Dose delays were permitted for immuno-oncology therapy. However, dose reduction was not permitted.

Rescue medication: As a result of imAEs that could potentially be experienced by patients on durvalumab ± tremelimumab, steroids and other immunosuppressant rescue medication were made available to this patient population. The permitted immunosuppressants were infliximab and mycophenolate.

Other interventions: PCI will not be permitted during the study. PCI must be completed within 1 to 42 days prior to randomization and the first dose of IP.

Table 13 Prohibited concomitant medications

Prohibited medication/class of drug:	**Usage**
Any investigational anticancer therapy other than those under investigation in this study	Should not be given concomitantly while the patient is on study treatment
mAbs against CTLA-4, PD-1, or PD-L1 other than those under investigation in this study	Should not be given concomitantly while the patient is on study treatment
Any concurrent chemotherapy, radiotherapy, immunotherapy, or biologic or hormonal therapy for cancer treatment other than those under investigation in this study	Should not be given concomitantly while the patient is on study treatment. (Concurrent use of hormones for non-cancer-related conditions [e.g., insulin for diabetes and hormone replacement therapy] is acceptable.
Live attenuated vaccines	Should not be given through 30 days after the last dose of IP
Immunosuppressive medications including, but not limited to, systemic corticosteroids at doses exceeding 10 mg/day of prednisone or equivalent, methotrexate, azathioprine, and tumour necrosis factor-α blockers	Should not be given concomitantly or used for premedication prior to the infusions. The following are allowed exceptions: • Use of immunosuppressive medications for the management of IP-related AEs • Use in patients with contrast allergies • In addition, use of inhaled, topical, and intranasal corticosteroids is permitted. A temporary period of steroids will be allowed if clinically indicated and considered to be essential for the management of non-immunotherapy-related events experienced by the patient (e.g.,

Prohibited medication/class of drug:	Usage
	chronic obstructive pulmonary disease, radiation, nausea, etc).
Drugs with laxative properties and herbal or natural remedies for constipation	Should be used with caution through to 90 days after the last dose of tremelimumab or placebo during the study
Sunitinib	Should not be given concomitantly or through 90 days after the last dose of tremelimumab or placebo (acute renal failure has been reported with combination therapy of tremelimumab and sunitinib)
EGFR TKIs	Should not be given concomitantly. Should be used with caution in the 90 days post last dose of durvalumab or placebo (saline or dextrose solution). Increased incidences of pneumonitis (with third generation EGFR TKIs) and increased incidence of transaminase increases (with 1st generation EGFR TKIs) has been reported when durvalumab has been given concomitantly.
Herbal and natural remedies that may have immune-modulating effects	Should not be given concomitantly unless agreed by the Sponsor

Objectives and endpoints

Table 14 Objectives and Endpoints

Objectives	Endpoints
Dual primary	
• To assess the efficacy of durvalumab monotherapy compared to placebo in terms of PFS	• PFS using BICR assessments according to RECIST 1.1
• To assess the efficacy of durvalumab monotherapy compared to placebo in terms of OS	• OS
Secondary	
• To assess the efficacy of durvalumab and tremelimumab combination compared to placebo in terms of PFS and OS [a]	• PFS using BICR assessments according to RECIST 1.1 • OS
• To further assess the efficacy of durvalumab monotherapy and durvalumab and tremelimumab combination therapy compared to placebo in terms of ORR, PFS18, PFS24, • TTDM, OS24, OS36, and PFS2 [a]	• ORR, PFS18, PFS24, and TTDM using BICR assessments according to RECIST 1.1 • OS24 and OS36 • PFS2

• To assess the efficacy of durvalumab and tremelimumab combination therapy compared to durvalumab monotherapy in terms of PFS, OS, and ORR [a]	• PFS and ORR using BICR assessments according to RECIST 1.1 • OS
• To assess disease-related symptoms and HRQoL in patients treated with durvalumab monotherapy and durvalumab and tremelimumab combination therapy compared to placebo using the EORTC QLQ-C30 v3 and QLQ-LC13 [a]	• •EORTC QLQ-C30 and QLQ-LC13: change in symptoms, functioning, and global health status/QoL
• To assess the PK of durvalumab monotherapy and durvalumab and tremelimumab combination therapy [a]	• Concentration of durvalumab and tremelimumab in serum (such as peak concentration and trough; sparse sampling)
• To investigate the immunogenicity of durvalumab monotherapy and durvalumab and tremelimumab combination therapy [a]	• Presence of ADA for durvalumab and tremelimumab (confirmatory results: positive or negative)
• To investigate the relationship between PD-L1 expression and spatial distribution within the tumour microenvironment and clinical outcomes with durvalumab monotherapy or durvalumab and tremelimumab combination therapy [a]	• PD-L1 expression in tumour and/or immune cells (cut-off ≥ 1%) relative to response/efficacy outcomes (PFS, OS, and ORR). Other PD-L1 cut-offs may also be analysed
• To assess the safety and tolerability profile of durvalumab monotherapy and durvalumab and tremelimumab combination therapy compared to placebo in patients with LS-SCLC [a]	• AEs; laboratory findings including clinical chemistry, haematology, and urinalysis; physical examinations; vital signs including blood pressure and pulse; and electrocardiograms

The dual primary objectives of this study were to assess the efficacy of durvalumab monotherapy compared to placebo in terms of PFS and OS.

PFS per RECIST 1.1, as assessed by BICR, was defined as the time from the date of randomization until the date of objective disease progression or death (by any cause in the absence of progression) regardless of whether the patient withdraws from therapy or receives another anticancer therapy prior to progression (i.e. date of event or censoring – date of randomization + 1). Patients who have not progressed or died at the time of analysis were censored at the time of the latest date of assessment from their last evaluable RECIST 1.1 assessment. However, if the patient progressed or died after 2 or more missed visits, the patient was censored at the time of the latest evaluable RECIST 1.1 assessment prior to the 2 missed visits. If the patient had no evaluable visits or did not have baseline data, they were censored at Day 1 unless they die within 2 visits of baseline, then they were treated as an event with date of death as the event date.

OS was defined as the time from the date of randomization until death due to any cause. 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.

ORR (per RECIST 1.1 using Investigator assessments) was defined as the number (%) of patients with at least 1 visit response of CR or PR. Data obtained up until progression, or the last evaluable assessment in the absence of progression, were included in the assessment of ORR. Patients who go off treatment without progression, receive a subsequent therapy, and then respond were not included as responders in the ORR.

The PFS18 and PFS24 was defined as the Kaplan-Meier estimate of PFS (per RECIST 1.1 as assessed by BICR) at 18 months and 24 months, respectively.

TTDM was defined as the time from the date of randomization until the first date of distant metastasis or death in the absence of distant metastasis. Distant metastasis was defined as any (new lesion) NL that is outside of the radiation field according to RECIST 1.1 or proven by biopsy. Patients who had not developed distant metastasis or died at the time of analysis were censored as the rules for the primary endpoint PFS.

The OS24 and OS36 were defined as the Kaplan-Meier estimate of OS at 24 months and 36 months after randomization, respectively.

PFS2 was defined as the time from the date of randomization to the earliest of the progression event subsequent to first subsequent therapy or death. The date of second progression was recorded by the Investigator in the eCRF at each assessment and defined according to local standard clinical practice and may involve any of the following: objective radiological imaging, symptomatic progression, or death. Patients alive and for whom a second disease progression had not been observed were censored at the last time known to be alive and without a second disease progression, that is, censored at the latest of the PFS or PFS2 assessment date if the patient had not had a second progression or death.

Sample size

The study planned to enrol approximately 965 patients globally in order to randomize approximately 724 patients to 1 of 3 treatment groups: durvalumab monotherapy (approximately 262 patients), placebo (approximately 262 patients), or durvalumab + tremelimumab combination therapy (approximately 200 patients) over a period of approximately 38 months. Initially, patients were randomized 1:1:1 to the 3 treatment groups.

Following implementation of CSP Version 4, once 600 patients had been randomized, a further 124 patients were subsequently randomized 1:1 to durvalumab monotherapy or placebo until a total of approximately 724 patients had been randomized.

The primary PFS analysis occurred at the earliest of:

1. When approximately 370 PFS BICR events had occurred (70.6% maturity) in the durvalumab monotherapy and placebo treatment groups
2. At OS-IA2, if OS-IA2 was statistically significant (durvalumab monotherapy vs placebo)
3. Approximately 36 months after the last patient was randomized.

If the true PFS HR was 0.65 for durvalumab monotherapy versus placebo, with 370 PFS BICR events, the study had approximately 90% power to demonstrate a statistically significant difference in PFS between durvalumab monotherapy and placebo, with an overall 2-sided significance level of 0.5%. The

true HR of 0.65 translated to a 5.4 month benefit in median PFS over 10 months on placebo if PFS was exponentially distributed. The smallest treatment difference that would be statistically significant was a HR of 0.743 (Critical value (CV)). At this time, approximately 309 PFS BICR events were also expected to have occurred in the durvalumab in combination with tremelimumab and placebo treatment groups. A recruitment period of approximately 38 months was assumed in the CSP for the primary PFS analysis.

One interim analysis of PFS was performed when approximately 308 PFS BICR events had occurred across the durvalumab monotherapy and placebo treatment groups (information fraction (IF) 83.2%, maturity 58.8%). At this time, approximately 274 PFS BICR events were also expected to have occurred in the durvalumab in combination with tremelimumab and placebo treatment groups. With 308 PFS BICR events across the durvalumab monotherapy and placebo treatment groups, the study had approximately 75% power to detect a PFS HR of 0.65 (CV=0.700) at a 0.184% significance level. The alpha level (0.5%, 2 sided) was split between the interim and primary analyses using the Lan and DeMets spending function that approximated an O'Brien Fleming approach. The actual boundary was calculated at the time of the interim analysis, based on the actual number of events available at the time of analysis, and assuming 370 PFS BICR events at the primary PFS analysis. The alpha level applied at the primary PFS analysis was adjusted (using a generalized Haybittle-Peto method to account for the actual alpha spent at the interim analysis based on the actual final total number of events, to maintain control of the overall Type I error.

The primary OS analysis occurred when approximately 348 death events had occurred (66.4% maturity) in the durvalumab monotherapy and placebo groups. At this time, approximately 276 death events were also expected to have occurred in the durvalumab in combination with tremelimumab and placebo treatment groups. If the true OS HR was 0.73 for durvalumab monotherapy versus placebo, the study had 80% power to demonstrate a statistically significant difference in OS between durvalumab monotherapy and placebo. The true HR of 0.73 translated to an approximate 8.9 month benefit in median OS over 24 months on placebo if OS was exponentially distributed. The smallest treatment difference that would be statistically significant was a HR of 0.798.

Up to three interim analyses of OS were performed: one at the time of the PFS interim analysis with approximately 242 death events anticipated across the durvalumab monotherapy and placebo groups (IF 69.5%, maturity 46.2%) and another with approximately 299 death events (IF 85.9%, maturity 57.1%). For these analyses the information fraction corresponded to the proportion of information i.e. events, available at the time of analysis. The alpha was split between the interim and primary analyses using the Lan and DeMets spending function that approximated an O'Brien Fleming approach. The actual significance boundaries were calculated at the time of each interim, based on the actual number of events available at the time of analysis, and assuming 348 death events at the primary OS analysis. In addition, an alpha of 0.01% (2-sided) was allocated for an OS assessment at the time of PFS primary analysis if OS-IA2 did not coincide with the PFS primary analysis.

The alpha level applied at the primary OS analysis was adjusted (using a generalized Haybittle-Peto method to account for the actual alpha spent at the interim analyses based on the actual final total number of events, to maintain control of the overall Type I error.

Randomisation

Patients were randomized in a 1:1:1 ratio to 1 of 3 treatment groups: durvalumab monotherapy, placebo, or durvalumab and tremelimumab combination therapy. Initially, all patients were randomized in a 1:1:1 ratio to 1 of 3 treatment groups: durvalumab monotherapy, placebo, or durvalumab and tremelimumab combination therapy. However, once 600 patients had been randomized, subsequent patients were randomized 1:1 to either durvalumab monotherapy or placebo. Randomization was

stratified by tumour, node, and metastatic classification (TNM) stage (I/II versus III) and receipt of PCI (yes versus no).

In order to ensure there were at least 5 events within each strata, if there were too few events in the Stage I/II stratification level, TNM stage could be excluded from the models leaving receipt of PCI as the sole stratification factor.

Blinding (masking)

This study was a Phase III, randomized, double-blind, placebo-controlled, multi-centre study. The IVRS/IWRS provided to the unblinded pharmacists the kit identification number to be allocated to the patient at the dispensing visit. Blinded and unblinded access and notifications were controlled using the IVRS/IWRS. Investigators remained blinded to each patient's assigned study treatment throughout the course of the study. To maintain this blind, an otherwise uninvolved 3rd party (i.e. the unblinded pharmacist) was unblinded and responsible for the reconstitution and dispensation of all study treatment and endeavoured to ensure that there were no differences in time taken to dispense following randomization. The IV bag was covered with a translucent coloured or opaque sleeve, after preparation by the unblinded pharmacist prior to dispensing to other study personnel, sleeve cover was secured (e.g. using stapling, heat-sealing), to maintain double-blind conditions.

The IVRS/IWRS was programmed with blind-breaking instructions. The Sponsor had to be notified before the blind was broken unless identification of the study treatment was required for a medical emergency in which the knowledge of the specific blinded study treatment would affect the immediate management of the patient's condition (e.g. antidote available). In this case, the Sponsor had to be notified within 24 hours after breaking the blind. The date and reason that the blind was broken had to be recorded in the source documentation and case report form (CRF) (electronic or paper), as applicable. Study unblinding did not occur until database lock and all decisions on the evaluability of the data from each individual patient had been made and documented.

Analysis sets

Table 15 Summary of outcome variables and analysis populations

Outcome variable	Populations
Efficacy Data	
PFS, OS	Full analysis set, Combination analysis set, Full PD-L1 analysis set, Combination PD-L1 analysis set
ORR*	Full analysis set, Combination analysis set, Full PD-L1 analysis set, Combination PD-L1 analysis set
PFS18, PFS24, TFST, TTDM, OS24, OS36, PFS2, BoR, DoR* and PRO endpoints*	Full analysis set, Combination analysis set
Study Population/Demography Data	
Demography characteristics (e.g. age, sex etc.)	Full analysis set, Combination analysis set
Baseline and disease characteristics	Full analysis set, Combination analysis set
Important deviations	Full analysis set, Combination analysis set

Medical/Surgical history	Full analysis set, Combination analysis set
Previous anti-cancer therapy	Full analysis set, Combination analysis set
Concomitant medications/procedures	Full analysis set, Combination analysis set
Subsequent anti-cancer therapy	Full analysis set, Combination analysis set
World Health Organization performance status	Full analysis set, Combination analysis set
PK Data	
PK data	PK analysis set
Safety Data	
Exposure	Safety analysis set, Combination safety analysis set
Adverse events	Safety analysis set, Combination safety analysis set
Laboratory measurements	Safety analysis set,
Vital Signs	Safety analysis set
Electrocardiograms	Safety analysis set
ADA	ADA analysis set, Durva ADA analysis set, Treme ADA analysis set

ADA Anti-drug antibody; DoR Duration of response; ORR Objective response rate; OS Overall survival; OS24 Proportion of patients alive at 24 months from randomization; OS36 Proportion of patients alive at 36 months from randomization; PFS Progression-free survival; PFS2 Time from randomization to second progression; PFS18 Progression-free survival at 18 months following randomization; PFS24 Progression-free survival at 24 months following randomization; PK Pharmacokinetic(s); PRO Patient-reported outcome; TFST Time to first subsequent therapy; TTDM Time to death or distant metastasis; Durva Durvalumab; Treme Tremelimumab. *Patients who are evaluable for the analysis of ORR are those with measurable disease at baseline. Patients who are evaluable for the analysis of DoR are those who responded in the ORR analysis.

Full analysis set

The full analysis set (FAS) included all randomized patients. The FAS was used for all efficacy analyses (including PROs).

Combination analysis set

For analyses involving the durvalumab and tremelimumab combination treatment group (i.e. durvalumab and tremelimumab combination therapy versus placebo and durvalumab monotherapy versus durvalumab and tremelimumab combination therapy), only the first 600 patients randomized (across all 3 arms) were included in the analyses, and all were included in the treatment group to which they were randomized.

Safety analysis set

The safety analysis set consisted of all patients who received at least 1 dose of study treatment. Safety data were not formally analysed but summarized using the safety analysis set according to the treatment received, that is, erroneously treated patients (i.e. those randomized to treatment A but actually given treatment B) were summarized according to the treatment they actually received.

Combination safety analysis set

The combination safety analysis set consisted of all patients from the combination analysis set who received at least 1 dose of study treatment. Data were summarized according to the treatment they actually received, applying the same approach for those receiving incorrect therapy as outlined for the safety analysis set above.

Full PD-L1 analysis set

The full PD-L1 analysis set (FPAS) consisted of all patients with evaluable PD-L1 data within the full analysis set.

Combination PD-L1 analysis set

The combination PD-L1 analysis set (CPAS) consisted of all patients with evaluable PD-L1 data within the combination analysis set.

PK analysis set

All patients who received at least 1 dose of IP per the protocol for whom any post-dose data were available and who did not violate or deviate from the protocol in ways that would significantly affect the PK analyses were included in the PK analysis set. The population was defined by the Clinical Pharmacologist (clin pharm lead) and Statistician prior to any analyses being performed.

ADA analysis sets

The anti-drug antibody (ADA) analysis set included all patients in the safety analysis set who had non-missing baseline ADA and at least 1 non-missing post-baseline ADA result of the same IP (durvalumab or tremelimumab). The durvalumab ADA analysis set consisted of all patients in the safety analysis set who had a non-missing baseline durvalumab ADA result and at least one non-missing post-baseline durvalumab ADA result. The tremelimumab ADA analysis set consisted of all patients in the safety analysis set who had a non-missing baseline tremelimumab ADA result and at least one non-missing post-baseline tremelimumab ADA result.

Statistical methods

Table 16 Efficacy Variables and Analysis Methodology

Variable	Analysis description and methodology
Dual Primary Endpoints	
PFS (D vs placebo)	The primary PFS analysis (D vs placebo) was based on RECIST 1.1 using BICR tumour assessments. The analysis was performed using a stratified log-rank test (using the TEST statement in PROC LIFETEST) adjusting for TNM stage (I/II vs III) and receipt of PCI (yes vs no) for generation of the p-value and using the Efron approach for handling ties (Efron 1977). The effect of D vs placebo treatment was estimated by the HR together with its corresponding CI (95% and [1-adjusted alpha] × 100%) from a stratified Cox proportional hazards model (Cox 1972; with ties = Efron and the stratification variables included in the strata statement) and the CI calculated using a profile likelihood approach. To ensure there were at least 5 events within each strata, if there were too few events observed in the TNM Stage I/II stratification level then TNM stage could have been excluded from the stratified models leaving receipt of PCI as the sole stratification factor. The covariates in the statistical modelling were based on the values entered into IVRS at randomization, even if it was subsequently discovered that these values were incorrect. **<u>Sensitivity Analyses</u>** The following sensitivity analyses of PFS were performed between D vs placebo. • Evaluation-time bias (interval censored analysis to assess possible bias if scans were not performed at the protocol-scheduled time points)

Variable	Analysis description and methodology
	• Attrition bias (using alternative censoring rules) • Ascertainment bias (using site Investigator assessments according to RECIST 1.1) • A sensitivity analysis for PFS examined the censoring patterns with regards to the treatment comparison of primary analysis, achieved by a KM plot of time to censoring where the censoring indicator of PFS was reversed. The effect of covariates on the HR estimate was determined using multivariable Cox proportional hazards models. **Subgroup Analyses** Subgroup analyses of PFS were conducted using unstratified Cox proportional hazards models to assess the consistency of treatment effect across expected prognostic and/or predictive factors. PFS (using BICR assessments according to RECIST 1.1) was compared between D vs placebo in the subgroups listed below: • TNM stage (Stage I/II vs III) • Receipt of PCI (yes vs no) • Time from end date of cCRT to randomization in ADRIATIC (< 14 days, ≥ 14 to < 28 days, ≥ 28 days) • Time from last dose of RT to randomization in ADRIATIC (< 28 days, ≥ 28 to < 56 days, ≥ 56 to < 84 days, ≥ 84 days) • Prior platinum chemotherapy (carboplatin vs cisplatin) • Prior RT regimen (daily vs twice daily) • Best response to CRT (CR vs PR vs stable disease) • Sex (male vs female) • Age at randomization (< 65 vs ≥ 65 years of age) • PD-L1 status (TC or IC ≥ 1%; TC and IC < 1%) • Smoking status (smoker [current/former smoker] vs non-smoker [never smoker]) • Race/ethnicity (White, Black/African-American, Asian, Other [Native Hawaiian/Pacific Islander or American Indian/Alaska Native or Others]) • Geographic region (Asia, Europe, South America/North America) • WHO/ECOG PS at baseline (0 vs 1) The consistency of treatment effect across stratification variables was determined by testing for interactions using Cox proportional hazards models.
OS (D vs placebo)	The primary analysis of OS (D vs placebo) to be analysed using stratified log-rank tests using the same methodology as described for the PFS primary endpoint. The treatment effect was estimated by the HR together with its corresponding CI (95% and [1-adjusted alpha] × 100%) from a stratified Cox proportional hazards model. **Sensitivity Analyses** A sensitivity analysis for OS examined the censoring patterns to rule out attrition bias with regards to the treatment comparison of primary analysis, achieved by a KM plot of time to censoring where the censoring indicator of OS was reversed. The effect of covariates on the HR estimate were determined using multivariable Cox proportional hazards models. **Subgroup Analyses**

Variable	Analysis description and methodology
	Subgroup analyses were generated using unstratified Cox proportional hazards models comparing OS between treatments of primary analysis in the same way as specified for PFS. The consistency of the treatment effect across stratification variables was determined by testing for interactions in Cox proportional hazards models.
Secondary Endpoints	
ORR (D vs placebo)	The ORR was based on the programmatically derived RECIST 1.1 using BICR assessments for unconfirmed (no requirement for confirmation) and confirmed (required confirmation of response no sooner than 4 weeks after the initial CR/PR was conducted) responses. Confirmed ORR was included for completeness. The analysis was performed using a Cochran-Mantel-Haenszel test, stratified using the same stratification factors as for the PFS endpoint for the comparison of D vs placebo. This analysis was performed in a subset of patients with measurable disease at baseline. **Sensitivity Analyses** A sensitivity analysis was performed, repeating the analysis of ORR using the site Investigator assessments based on RECIST 1.1, for patients with confirmed and unconfirmed responses.
DoR (D vs placebo)	DoR, using BICR assessments according to RECIST 1.1, was assessed using KM estimates and CIs for patients with unconfirmed and confirmed responses.
PFS18/ PFS24 (D vs placebo)	Landmark estimates of PFS at 18 and 24 months (i.e. PFS18 and PFS24) were assessed using KM estimates and CIs.
TTDM (D vs placebo)	The TTDM was analysed using identical methods as outlined for the analysis of PFS (i.e., a stratified log-rank test) but no subgroup analyses were performed. A sensitivity analysis of TTDM was performed using site Investigator assessments according to RECIST 1.1.
OS24/ OS36 (D vs placebo)	Landmark estimates of OS at 24 and 36 months (i.e. OS24 and OS36) were assessed using KM estimates and CIs.
PFS2 (D vs placebo)	PFS2 (using site Investigator assessments) was analysed using identical methods as outlined for the analysis of PFS (i.e. a stratified log-rank test) but no subgroup analyses were performed.
PFS, OS and ORR in PD-L1 expression groups	PFS and OS were analysed in the FPAS using the same methods as for the primary/secondary PFS and OS analyses. Analyses of ORR using BICR assessments for a confirmed response were performed in the FPAS using a stratified Cochran-Mantel-Haenszel test. The CIs for the difference in the proportion of patients with a response between treatment groups was computed using Miettinen and Nurminen's stratified confidence limits. Analyses were also performed to estimate treatment effect on PFS, OS, and ORR in PD-L1 expression subgroups (TC or IC ≥ 1%; TC and IC < 1%). These subgroup analyses were performed using the same methodologies as the analyses conducted in FPAS for PD-L1 but unstratified, meaning that treatment was the only covariate in all the models. PD-L1 was assessed using the VENTANA PD-L1 (SP263) assay, and the cut-offs were based on the prevalence observed in the CASPIAN study (Paz-Ares et al 2024).

Variable	Analysis description and methodology
PROs (D vs placebo)	Change from baseline in key symptoms (EORTC QLQ-C30 and QLQ-LC13) was examined using the mixed model repeat measurement analysis. GHS/QoL/function improvement rate (EORTC QLQ-C30 endpoints) and symptom improvement rate (EORTC QLQ-C30 and QLQ-LC13 endpoints) were analysed using a logistic regression model. Time to GHS/QoL/function deterioration (EORTC QLQ-C30 endpoints) and time to symptom deterioration (EORTC QLQ-C30 and QLQ-LC13 endpoints) were analysed using KM estimates, stratified log-rank tests and Cox proportional hazards models.

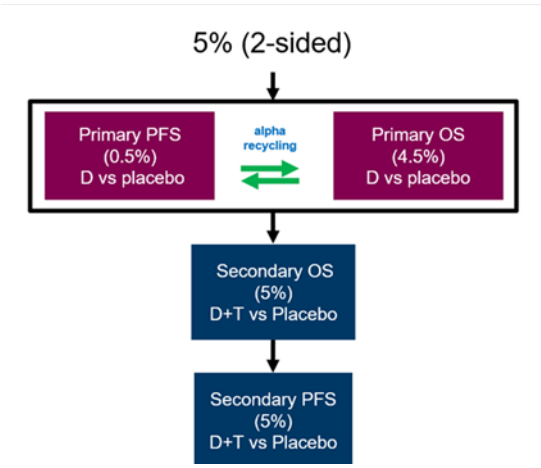
Multiplicity

The following multiple testing procedure shown in Figure 4 was used to strongly control the family-wise type I error rate (alpha) at 5% (2-sided) for testing the following primary and key secondary endpoints:

- Dual primary endpoints: PFS and OS for durvalumab monotherapy versus placebo.
- Key secondary endpoint: PFS and OS for durvalumab in combination with tremelimumab versus placebo.

The testing procedure was hierarchical in that it started with testing the 2 dual primary endpoints of PFS (per BICR) and OS as outlined in Figure 4. The overall 5% type I error (2-sided) was split among the 2 dual primary endpoints. An alpha level of 0.5% was allocated to PFS and was split between 2 potential analysis timepoints (1 interim plus 1 primary analysis). An alpha level of 4.5% was allocated to OS and was split between 4 potential analysis timepoints (2 interim analyses, 1 primary analysis, plus 1 potential additional assessment of OS at the time of primary PFS analysis if OS-IA2 timing did not coincide with the primary PFS analysis timing, as described below). An alpha of 0.01% (2-sided) was allocated to the potential additional OS analysis that was conducted at the time of PFS primary analysis if OS-IA2 timing did not coincide with the primary PFS analysis timing. The remaining 4.49% alpha level for OS was controlled at the time of planned OS-IA1, OS-IA2, and the primary analysis using the Lan-DeMets spending function that approximated an O'Brien Fleming approach.

Figure 4 MTP for Primary and Key Secondary Endpoints



If any of the PFS analyses were significant, then the allocated test mass (0.5%) could be recycled to OS, giving a total test mass of 5% for OS. In this case, the 5% was split between OS-IA1, OS-IA2, and primary OS analyses using the Lan-DeMets spending function with an alpha of 0.01% (2-sided)

allocated to the additional analysis of OS that might have occurred at the time of the PFS primary analysis if OS-IA2 timing did not coincide with the primary PFS analysis timing. If neither of the PFS analyses were significant at the 0.5% level but OS was significant at the 4.5% level, at either an interim or primary analysis, then the 4.5% could be recycled to test PFS at 5% (split between the interim and primary analyses). PFS could only be re-tested using the information available at the time of the original PFS analysis.

The alpha levels at each of the planned interim analyses were determined at the time of each analysis using the Lan-DeMets spending functions. This was derived based on the information fraction, i.e. the actual number of events available at the time of the analysis, out of the total final number of events expected for PFS and OS respectively. The alpha level applied at the primary PFS and OS analyses was adjusted (using a generalized Haybittle-Peto method) to account for the actual alpha spent at the interim analyses based on the actual final total number of events, to maintain control of the overall Type I error.

If both PFS and OS were statistically significant for the primary endpoint analyses comparing durvalumab monotherapy versus placebo, then the 5% alpha could be carried down to test durvalumab in combination with tremelimumab versus placebo. OS was tested at 5% and then, if significant, PFS was tested at 5%.

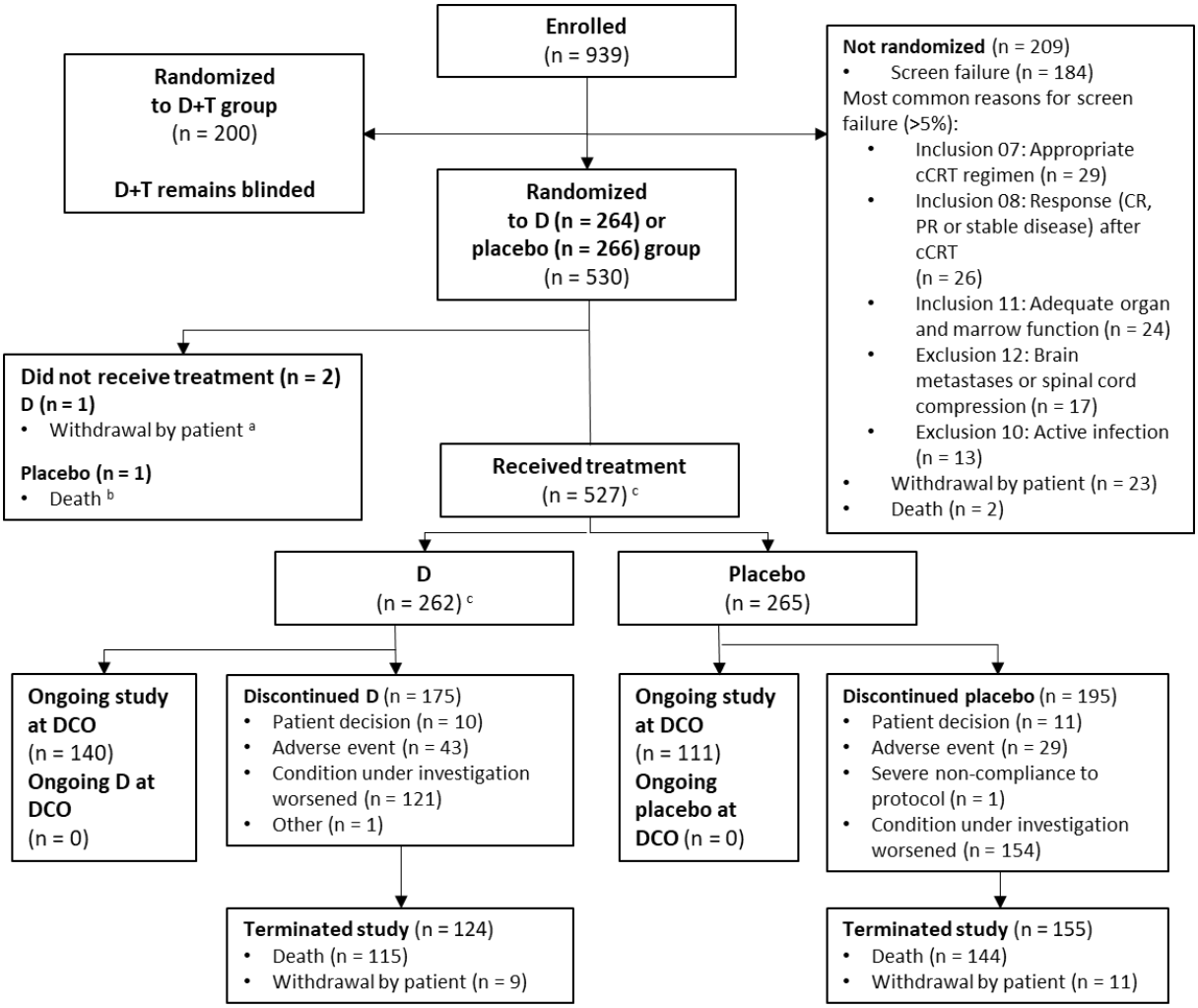
Results

Participant flow

Enrolment for the global cohort of ADRIATIC is complete with 939 patients enrolled. A total of 730 patients were randomized.

Of the 730 randomized patients, 264 were randomized to the D group, 200 to the D+T group, and 266 to the placebo group; 263 (99.6%) patients in the D group and 265 (99.6%) in the placebo group received study treatment. A total of 2 (0.4%) randomized patients did not receive any study treatment.

Figure 5 Patient Disposition at Time of Data Cut-off



a Patient missed the 3-day dosing window and subsequently withdrew.
b Patient missed the 3-day dosing window and subsequently died.
c One patient randomized to the D group received 2 cycles of tremelimumab. This patient was not included in the D or placebo SAS, the PK analysis set, or the durvalumab ADA analysis set.
D =durvalumab; DCO = data cutoff; T = tremelimumab.

Table 17 Reasons for not Randomizing Patients in the ADRIATIC Study

Patients Not Randomized	Number (%) of Patients N = 209
Death	2 (1.0)
Withdrawal by subject	23 (11.0)
Screen failure	184 (88.0)
Reasons for screen failure	
Inclusion 07: Appropriate cCRT regimen	29 (13.9)
Inclusion 08: Response (CR, PR or stable disease) after cCRT	26 (12.4)
Inclusion 11: Adequate organ and marrow function	24 (11.5)
Exclusion 12: Brain metastases or spinal cord compression	17 (8.1)
Exclusion 10: Active infection	13 (6.2)
Exclusion 29: Investigator judgement on CSP compliance	10 (4.8)
Inclusion 05: AJCC Stage I-III SCLC	9 (4.3)
Inclusion 09: PCI conducted after cCRT	8 (3.8)
Exclusion 03: History of Grade ≥ 2 pneumonitis	7 (3.3)
Exclusion 06: Uncontrolled intercurrent illness	7 (3.3)

Table 17 Reasons for not Randomizing Patients in the ADRIATIC Study

Patients Not Randomized	Number (%) of Patients N = 209
Exclusion 05: Active or prior documented autoimmune or inflammatory disorders	6 (2.9)
Inclusion 01: Capable of consent/compliance with CSP requirements	6 (2.9)
Inclusion 06: WHO/ECOG performance status	6 (2.9)
Exclusion 02: Extensive-stage SCLC	4 (1.9)
Exclusion 22: Current/prior use of immunosuppressive medication within 14 days before first dose of study treatment	4 (1.9)
Exclusion 13: Mean QTcF ≥ 470 ms	3 (1.4)
Exclusion 07: History of another primary malignancy within 5 years of first dose of study treatment	2 (1.0)
Exclusion 11: Any unresolved Grade ≥ 2 toxicity from previous CRT	2 (1.0)
Exclusion 16: Progressed while on cCRT	2 (1.0)
Exclusion 21: Major surgical procedure within 42 days prior to the first dose of study treatment	2 (1.0)
Exclusion 09: History of active primary immunodeficiency	1 (0.5)
Exclusion 17: Receipt of chemotherapy that exceeded 4 cycles in total	1 (0.5)
Exclusion 27: Involvement in the planning and/or conduct of the study	1 (0.5)
Exclusion 30: Genetics research study requirements	1 (0.5)
Inclusion 10: Tumour sample requirements	1 (0.5)
Inclusion 12: Life expectancy ≥ 12 weeks	1 (0.5)
Missing/not applicable	1 (0.5)

AJCC = American Joint Committee on Cancer; CR = complete response; CSP = clinical study protocol; ECOG = Eastern Cooperative Oncology Group; PR = partial response; QTcF = QT interval corrected for heart rate using Fridericia's formula; WHO = World Health Organization.
Descriptions of eligibility criteria provided in the table are based on the current CSP version (v5.0).
Between CSP v1.0 and v2.0, reordering and/or removal of eligibility criteria resulted in renumbering that affected Inclusion Criteria 7 and 9, and Exclusion Criteria 20 through 31. Please consult the CSR Section 9.9.1 (ADRIATIC IA CSR, Module 5.3.5.1) for details on these changes.
Patients could have had more than one reason for screen failure; patients with more than one reason for screen failure are counted once for each of those screen failure reasons.

Recruitment

The first patient was randomized into the study on 17 October 2018, and the last patient was randomized on 27 September 2021.

A total of 164 sites across 19 countries worldwide randomized at least 1 patient into the global cohort: Argentina (5 sites), Belgium (4 sites), Canada (5 sites), China (24 sites), Czech Republic (4 sites), Germany (11 sites), India (2 sites), Italy (4 sites), Japan (16 sites), Netherlands (4 sites), Poland (5 sites), Russia (10 sites), South Korea (10 sites), Spain (9 sites), Taiwan (9 sites), Turkey (9 sites), United Kingdom (1 site), USA (26 sites), and Vietnam (6 sites).

As of the data cut-off date on 15 January 2024 the median duration of OS follow-up in all patients was 30.75 months in the D group and 28.63 months in the placebo group. The median duration of PFS follow-up in all patients was 9.07 months in the D group and 7.39 months in the placebo group.

Conduct of the study

Protocol amendments

Version 5.0, 10 January 2023

The primary purpose of the current amendment is to include an interim analysis for the primary endpoint of progression free survival (PFS-IA) per BICR. ADRIATIC was initially designed to include an interim analysis for the dual PFS primary endpoints (durvalumab monotherapy vs placebo and durvalumab + tremelimumab vs placebo comparisons). This was removed during the CSP V4 amendment in November 2020 due to the anticipated proximity to PFS FA. Review of blinded event

predictions show a potential shift in study timelines which has afforded an opportunity to introduce an IA for the primary endpoint PFS analysis.

Additional clarifications on OS interim analyses and primary PFS analysis are also included in Amendment 5

Version 4.0, 13 November 2020

The primary objective of the current amendment is to revise the primary efficacy endpoint. Specifically, the analysis of OS for the comparison of durvalumab monotherapy versus placebo has been promoted, and PFS and OS will now be analysed as dual primary efficacy endpoints. In addition, emerging data indicate the need to modify previous assumptions relating to treatment effect. Thus, the total sample size has been increased from 600 to approximately 724 randomized patients, with the number of patients in each of the durvalumab monotherapy and placebo groups increased from 200 to approximately 262 patients. As recently published data also indicate that the additional efficacy benefit of combining an anti-CTLA-4-mAb with PD-1/PD-L1 inhibition over PD-1/PD-L1 inhibition alone is ambiguous, but not conclusive, thus the comparison of durvalumab plus tremelimumab versus placebo has been moved to a secondary endpoint and the number of patients will remain unchanged at approximately 200 patients. The following sections are affected:

1. OS for the comparison of durvalumab monotherapy versus placebo has been added to the primary endpoint, i.e. the study now has dual primary endpoints of PFS and OS for the comparison of durvalumab monotherapy versus placebo; the comparison of durvalumab plus tremelimumab versus placebo in terms of PFS and OS are now secondary endpoints. 2. The amendment incorporates new and updated published clinical data that support the decision to revise the study design with respect to both the primary endpoint analysis/efficacy endpoints and the treatment effect assumptions.

3. Text relating to the planned number of patients and to the sample size calculation has been updated to increase the total sample size from 600 to approximately 724 patients, with additional patients in each of the durvalumab and placebo groups (approximately 262 patients each). The number of patients in the durvalumab plus tremelimumab group is unchanged (approximately 200 patients).

4. As the number of patients in the durvalumab plus tremelimumab group is unchanged, the amendment clarifies that once 600 patients have been randomized, randomization will continue 1:1 in the durvalumab monotherapy and placebo groups.

5. Change to the study design to indicate that once 600 patients have been randomized, no further PK or ADA samples relevant to tremelimumab are required.

6. Provision for enrolment in China to continue after global enrolment is closed to allow inclusion of a total of approximately 108 patients.

7. The statistical sections have been updated to accommodate the changes described above: updated null hypotheses regarding the efficacy endpoints, sample size determination and updated timing of interim and final analyses, clarification of patients included in the analyses of the combination analysis set, definition of the combination safety analysis set, calculation or derivation of efficacy variables, updated analyses of PFS, OS, and duration of response [DoR], updated description of methods for multiplicity control reflecting the updated analyses, updated details of the interim analyses of OS and their anticipated timing.

8. The benefit-risk assessment has been updated for durvalumab and overall.

Version 3.0, 13 January 2020

1. Addition of options to continue recruitment in China, following achievement of the global recruitment target of 600 randomized patients, as required by the National Medical Products Administration and addition of China specific language into Study Objectives, Endpoints, Statistics and the collection/analysis of patient samples.

Version 2.0, 28 January 2019

1. Alignment on Small-Cell Lung Cancer disease terminology from ED/LD (Extensive Disease / Limited Disease) to ES/LS (Extensive Stage / Limited Stage) in the Clinical Study Protocol's title and content.

2. Removed TMB as biomarker exploratory objective as already included as secondary objective.

3. Clarification on objectives of exploratory objectives on samples collected.

4. Removed variables from PD-L1 exploratory objective's endpoints.

[…]

8. Inclusion criterion 3 amended to state that provision of signed and dated written genetic informed consent prior to collection of sample for genetic analysis is optional.

9. Inclusion criterion 4 amended to remove age cap of 75 years.

10. Inclusion criterion 5 amended to state that status of medically inoperable for patients who are Stage I or II is determined by investigator.

11. Inclusion criterion 7 amended to address prior chemoradiotherapy, including radiotherapy treatment (previously inclusion criterion 9) and moved PCI to inclusion criterion 9

12. Inclusion criterion 10 amended to mandatory availability of tumour samples, and detailed guidance on acceptance of samples, procedures, and order of preferences updated.

13. Exclusion criterion 3 amended to "any history of Grade ≥2 pneumonitis" – exclusion criterion now broadened to ensure patient safety.

14. Removed criterion 20 – "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" not applicable to the early disease setting in this study.

15. Exclusion criterion 29 updated for consistency with study Master ICF and most recent guidance for timelines of using effective birth control for durvalumab monotherapy and durvalumab + tremelimumab combination therapy.

16. ADA samples added to Schedule of Assessments for durvalumab at cycle 13 and 20 and for tremelimumab at cycle 7 and 10.

17. The procedure of stool samples collection for microbiome analysis added to Schedule of Assessments

18. Frequency of second progression assessment changed in Schedule of Assessments from "every 12 weeks" to "every 8 weeks".

19. Section 6.2.1 amended to state and clarify that all screening laboratory and imaging results must have been obtained after completion of chemoradiotherapy and within 42 days of randomization and the first dose of IP.

<u>Major protocol deviations</u>

At the time of DCO, 79 (14.9%) patients had at least one IPD: 46 (17.4%) patients in the D group and 33 (12.4%) patients in the placebo group (Table 18). The most frequently reported IPDs were:

- 33 patients who deviated from the key inclusion/exclusion criteria (22 [8.3%] and 11 [4.1%] patients, by respective treatment group); most of these were attributed to exceeding the maximum 42-day screening period from completion of cCRT to randomization and the first dose of study treatment specified in inclusion criterion 7
- 19 patients randomized who received their randomized study treatment at an incorrect dose or received an alternative treatment to that which they were randomized (12 [4.5%] and 7 [2.6%] patients, by respective treatment group):
    - 17 of these were attributed to administration of a tremelimumab placebo dose.
    - 1 patient randomized to placebo received only 3 cycles of combination treatment (i.e. the fourth cycle of tremelimumab placebo was not administered).
    - 1 patient randomized to the D group received 2 cycles of tremelimumab.

Two patients (one in each treatment group) were randomized but did not receive study treatment.

Table 18 Important Protocol Deviations (Full Analysis Set)

Important protocol deviation [a]	Number (%) of patients		
	D (N = 264)	Placebo (N = 266)	Total (N = 530)
Number of patients with at least 1 IPD	46 (17.4)	33 (12.4)	79 (14.9)
Baseline RECIST 1.1 scan > 42 days before randomization	3 (1.1)	0	3 (0.6)
Discrepancy in stratification factors reported between IVRS and eCRF (Stage [I/II vs III] based on TNM classification and receipt of PCI [yes vs no])	5 (1.9)	6 (2.3)	11 (2.1)
No baseline RECIST 1.1 assessment post-cCRT on or before date of randomization	2 (0.8)	1 (0.4)	3 (0.6)
Patients randomized but who did not receive study treatment	1 (0.4)	1 (0.4)	2 (0.4)
Patients randomized who received their randomized study treatment at an incorrect dose or received an alternative treatment to that which they were randomized	12 (4.5)	7 (2.6)	19 (3.6)
Patients who deviated from the following key entry criteria per CSP; these are inclusion criteria 5, 6, 7, 8, and 9 and exclusion criteria 1, 2, 3, 12, 15, 17, 18, 23, 24, and 25	22 (8.3)	11 (4.1)	33 (6.2)
Received prohibited concomitant medications. Please refer to the CSP Section 6.4 for those medications that are detailed as being 'excluded' from permitted use during the study.	5 (1.9)	11 (4.1)	16 (3.0)
Number of patients with at least 1 COVID-19-related IPD	1 (0.4)	0	1 (0.2)
Patients randomized but who did not receive study treatment	1 (0.4)	0	1 (0.2)

[a] Important deviations before the start of treatment and during treatment.

Note that the same patient may have had more than one IPD.

Baseline data

Table 19 Key Demographic and Patient Characteristics (FAS)

Characteristic		D (N = 264)	Placebo (N = 266)	Total (N = 530)
Age (years)	n	264	266	530
	Mean	61.8	61.2	61.5
	SD	8.93	9.40	9.16
	Median	62.0	62.0	62.0
	Min	28	28	28
	Max	84	79	84
Age group (years), n (%)	< 50	21 (8.0)	26 (9.8)	47 (8.9)
	≥ 50 - < 65	139 (52.7)	136 (51.1)	275 (51.9)
	≥ 65 - < 75	89 (33.7)	86 (32.3)	175 (33.0)
	≥ 75	15 (5.7)	18 (6.8)	33 (6.2)
	< 65	160 (60.6)	162 (60.9)	322 (60.8)
	≥ 65	104 (39.4)	104 (39.1)	208 (39.2)
Sex, n (%)	Male	178 (67.4)	188 (70.7)	366 (69.1)
	Female	86 (32.6)	78 (29.3)	164 (30.9)
Race, n (%)	White	130 (49.2)	137 (51.5)	267 (50.4)
	Black or African American	1 (0.4)	3 (1.1)	4 (0.8)
	Asian	131 (49.6)	121 (45.5)	252 (47.5)
	Other	2 (0.8)	5 (1.9)	7 (1.3)
Ethnic group, n (%)	Hispanic or Latino	8 (3.0)	14 (5.3)	22 (4.2)
	Not Hispanic or Latino	255 (96.6)	249 (93.6)	504 (95.1)
	Missing	1 (0.4)	3 (1.1)	4 (0.8)
Smoking history, n (%)	Never	23 (8.7)	26 (9.8)	49 (9.2)
	Smoker	241 (91.3)	240 (90.2)	481 (90.8)
	Ex-smoker	178 (67.4)	185 (69.5)	363 (68.5)
	Current smoker	63 (23.9)	55 (20.7)	118 (22.3)

Age (years) calculated relative to date of randomization.

Table 20 Key Disease Characteristics and WHO/ECOG PS at Baseline (FAS)

Characteristic	Number (%) of patients		
	D (N = 264)	Placebo (N = 266)	Total (N = 530)
WHO/ECOG PS			
(0) Normal activity	132 (50.0)	126 (47.4)	258 (48.7)
(1) Restricted activity	132 (50.0)	140 (52.6)	272 (51.3)
AJCC overall stage [a]			

I	8 (3.0)	11 (4.1)	19 (3.6)
II	25 (9.5)	23 (8.6)	48 (9.1)
III	231 (87.5)	232 (87.2)	463 (87.4)
PD-L1 status [b]			
TC AND IC < 1%	78 (29.5)	73 (27.4)	151 (28.5)
TC OR IC ≥ 1%	84 (31.8)	98 (36.8)	182 (34.3)
Missing	102 (38.6)	95 (35.7)	197 (37.2)
Extent of disease at baseline [c]			
No evidence of disease	32 (12.1)	34 (12.8)	66 (12.5)
Locally advanced (total)	232 (87.9)	232 (87.2)	464 (87.5)
Respiratory	199 (75.4)	209 (78.6)	408 (77.0)
Lymph nodes	167 (63.3)	148 (55.6)	315 (59.4)

[a] AJCC stage is derived from the TNM Stage, AJCC overall stage is at diagnosis as reported by Investigator on eCRF. AJCC 8th Edition.
[b] Testing was retrospective and not required for randomization. [c] A patient could have one or more sites of disease reported.

Table 21 Prior cCRT and PCI (FAS)

Characteristic	Number (%) of patients		
	D	Placebo	Total
	(N = 264)	(N = 266)	(N = 530)
Number of chemotherapy cycles			
2	0	1 (0.4)	1 (0.2)
3	29 (11.0)	31 (11.7)	60 (11.3)
4	234 (88.6)	234 (88.0)	468 (88.3)
6	1 (0.4)	0	1 (0.2)
Chemotherapy regimen [a]			
Cisplatin + etoposide	173 (65.5)	178 (66.9)	351 (66.2)
Carboplatin + etoposide	91 (34.5)	88 (33.1)	179 (33.8)
Radiotherapy regimen (total dose, Gy) [b]			
Once daily	195 (73.9)	187 (70.3)	382 (72.1)
< 57	8 (3.0)	2 (0.8)	10 (1.9)
≥ 60 to ≤ 66	175 (66.3)	178 (66.9)	353 (66.6)
≥ 57 to ≤ 70 (excluding ≥ 60 to ≤ 66)	12 (4.5)	7 (2.6)	19 (3.6)
> 70	0	0	0
Twice daily	69 (26.1)	79 (29.7)	148 (27.9)
< 42.75	0	0	0
45	67 (25.4)	76 (28.6)	143 (27.0)
≥ 42.75 to ≤ 47.25 (excluding 45)	1 (0.4)	0	1 (0.2)
> 47.25	1 (0.4)	3 (1.1)	4 (0.8)
Best response to cCRT			
CR	31 (11.7)	34 (12.8)	65 (12.3)
PR	191 (72.3)	200 (75.2)	391 (73.8)
Stable disease	42 (15.9)	32 (12.0)	74 (14.0)
PCI regimen			
Yes	142 (53.8)	143 (53.8)	285 (53.8)
No	122 (46.2)	123 (46.2)	245 (46.2)

[a] Chemotherapy regimen based on first cycle chemotherapy.

[b] Chest irradiation.

Table 22 Post-discontinuation disease-related anti-cancer therapy (Full analysis set)

	Number (%) of subjects		
Treatment [a]	Durva (N=264)	Placebo (N=266)	Total (N=530)
Number of subjects with post-discontinuation disease-related anti-cancer therapy	95 (36.0)	127 (47.7)	222 (41.9)
Cytotoxic Chemotherapy Single Agent	47 (17.8)	57 (21.4)	104 (19.6)
Cytotoxic Chemotherapy Platinum Doublet	54 (20.5)	56 (21.1)	110 (20.8)
Chemotherapy + Immunotherapy [c]	13 (4.9)	28 (10.5)	41 (7.7)
Chemotherapy + Targeted Therapy	6 (2.3)	7 (2.6)	13 (2.5)
Chemotherapy + Immunotherapy + Targeted Therapy [c]	1 (0.4)	4 (1.5)	5 (0.9)
Other Chemotherapy Combination	16 (6.1)	18 (6.8)	34 (6.4)
Hormonal Therapy	0	0	0
Immunotherapy Single Agent [c]	7 (2.7)	7 (2.6)	14 (2.6)
Immunotherapy + Immunotherapy [c]	2 (0.8)	1 (0.4)	3 (0.6)
Immunotherapy + Targeted Therapy [c]	1 (0.4)	3 (1.1)	4 (0.8)
Immunotherapy + Antibody Drug Conjugate Therapy	0	0	0
Radiopharmaceuticals	0	0	0
Targeted Therapy Single Agent	5 (1.9)	5 (1.9)	10 (1.9)
Targeted Therapy + Targeted Therapy	1 (0.4)	0	1 (0.2)
Targeted Therapy + Antibody-Drug Conjugate Therapy	0	0	0
Antibody-Drug Conjugate Single Agent	1 (0.4)	1 (0.4)	2 (0.4)
Investigational Agent	0	1 (0.4)	1 (0.2)
Investigational Antineoplastic Drugs	0	1 (0.4)	1 (0.2)
Other	0	0	0
Line of Treatment [b]			
Second Line	92 (34.8)	124 (46.6)	216 (40.8)
Third Line	47 (17.8)	56 (21.1)	103 (19.4)
> Third Line	22 (8.3)	22 (8.3)	44 (8.3)
Not Applicable	4 (1.5)	1 (0.4)	5 (0.9)
Therapy Class [b]			
Cytotoxic Chemotherapy	88 (33.3)	121 (45.5)	209 (39.4)
Hormonal Therapy	0	0	0
Immunotherapy [c]	23 (8.7)	39 (14.7)	62 (11.7)
Targeted Therapy	14 (5.3)	17 (6.4)	31 (5.8)
Antibody-Drug Conjugate Therapy	1 (0.4)	1 (0.4)	2 (0.4)
Experimental Therapy	1 (0.4)	2 (0.8)	3 (0.6)
Other	3 (1.1)	6 (2.3)	9 (1.7)

[a] Therapies post discontinuation of treatment.
[b] A subject can be counted in one or more of the categories. As collected on eCRF.
[c] 'Immunotherapy' includes any therapy in which at least one mechanism of action involves modulation of the immune system.

For all other categories, subjects are counted once in each category.

Table 23 Post-treatment Radiotherapy (Full analysis set)

	Number (%) of subjects		
Site	Durva (N=264)	Placebo (N=266)	Total (N=530)
Brain [a]	7 (2.7)	22 (8.3)	29 (5.5)
Chest [b]	4 (1.5)	6 (2.3)	10 (1.9)
Other	11 (4.2)	14 (5.3)	25 (4.7)

[a] Includes Brain, Brainstem, Cerebellum, Brain - Cerebral hemisphere.
[b] Includes Lung and Regional Lymph Nodes.

Numbers analysed

Table 24 Analysis Sets

	Number of patients		
	D	Placebo	Total
Patients randomized	264	266	530
Patients included in FAS	264	266	530
Patients included in SAS [a]	262	265	527
Patients excluded from SAS	1	1	2
Did not receive any dose of randomized treatment	1	1	2
Patients included in FPAS	162	171	333
Patients excluded from FPAS	102	95	197
Patients included in PK analysis set [a,b]	258	173	431
Patients excluded from PK analysis set	5	93	98
Did not receive any dose of randomized treatment	1	1	2
Dose not fully received at > 1 cycles	1	0	1
No post-dose data available	3	92	95
Patients included in ADA analysis set	207	179	386
Patients included in durvalumab ADA analysis set [a]	206	175	381
Patients excluded from durvalumab ADA analysis set	57	91	148
Did not receive any dose of randomized treatment	1	1	2
No baseline and/or post-baseline durvalumab ADA sample available	56	90	146

[a] One patient randomized to the D group received 2 cycles of tremelimumab. This patient was not included in the D or placebo SAS, the PK analysis set, or the durvalumab ADA analysis set.

[b] Patients in the placebo group had samples collected (double blind) and some were analysed. Placebo patients were not included in the PK and ADA analyses

Outcomes and estimation

Primary endpoints

OS

Median OS follow-up time (ITT=FAS): 30.75 months in the D arm and 28.63 months in the placebo

In censored patients, the median duration of OS follow-up was 37.19 months in the D arm and 37.24 months in the placebo arm.

Table 25 OS, Durvalumab vs Placebo (FAS)

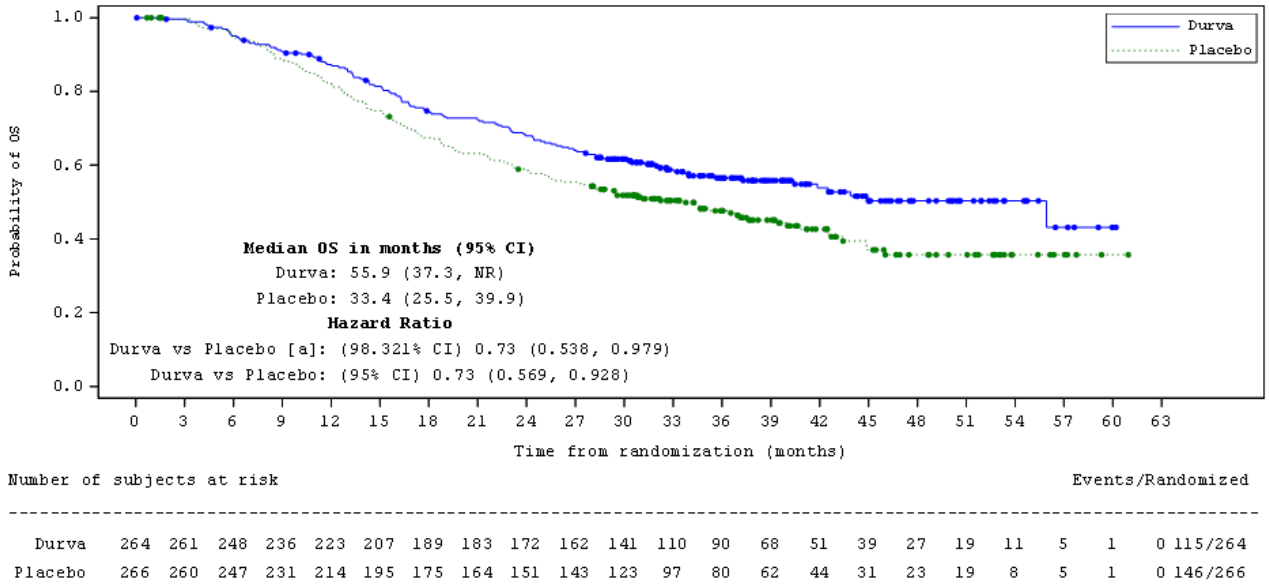
	D (N = 264)	Placebo (N = 266)
Death, n (%)	115 (43.6)	146 (54.9)
Censored patients, n (%)	149 (56.4)	120 (45.1)
Still in survival follow-up [a]	140 (53.0)	111 (41.7)
Terminated prior to death [b]	9 (3.4)	9 (3.4)
Lost to follow-up	0	0
Withdrawn consent	9 (3.4)	9 (3.4)
Other	0	0
Median OS (months) [c]	55.9	33.4
95% CI for median OS [c]	37.3, NR	25.5, 39.9
Survival rate at 24 months (OS24) [c]	68.0	58.5
95% CI for OS24 [c]	61.9, 73.3	52.3, 64.3
Survival rate at 36 months (OS36) [c]	56.5	47.6
95% CI for OS36 [c]	50.0, 62.5	41.3, 53.7
HR, D vs placebo [d, g]	0.73	
98.321% CI for HR [d, e]	0.538, 0.979	
95% CI for HR [d]	0.569, 0.928	
2-sided p-value [f]	0.01042	

a Includes patients known to be alive at the DCO.
b Includes patients with unknown survival status or patients who were lost to follow-up.
c Calculated using the KM technique. CI for median OS was derived based on Brookmeyer-Crowley method with log-log transformation. CIs for OS24 and OS36 were derived based on a log(-log(.)) transformation.
d The HR and CI were calculated using a stratified Cox proportional hazards model, adjusting for receipt of PCI (yes vs no), with treatment as only covariate and ties handled by Efron approach. CIs were calculated using the profile likelihood approach.
e Based on a Lan-DeMets alpha spending function with O'Brien Fleming type boundary with the actual number of events observed, the boundaries for declaring statistical significance were 1.679% for a 4.5% overall alpha for OS. The Lan DeMets spending function that approximates the O'Brien Fleming approach was used to derive the adjusted alpha level.
f The analysis was performed using the stratified log-rank test, adjusting for receipt of PCI (yes vs no).
g A HR < 1 favours durvalumab to be associated with a longer survival than placebo.

One month was calculated as 30.4375 days.
Stratification factor was based on the values entered into the IVRS.

DCO 15 January 2024

Figure 6 OS, Durvalumab vs Placebo, KM Plot (FAS)



Number of subjects at risk

																					Events/Randomized
Durva	264	261	248	236	223	207	189	183	172	162	141	110	90	68	51	39	27	19	11	5	1	0 115/264
Placebo	266	260	247	231	214	195	175	164	151	143	123	97	80	62	44	31	23	19	8	5	1	0 146/266

Durva = durvalumab monotherapy.

[a] Based on a Lan-DeMets alpha spending function with O'Brien Fleming type boundary with the actual number of events observed, the boundaries for declaring statistical significance were 1.679% for a 4.5% overall alpha for OS. The Lan-DeMets spending function that approximates the O'Brien Fleming approach was used to derive the adjusted alpha level.

Circle indicates a censored observation.

PFS

Median PFS follow-up time (ITT=FAS): 9.07 months in the D group and 7.39 months in the placebo group.

Table 26 PFS Using BICR Assessments According to RECIST 1.1, Durvalumab vs Placebo (FAS)

	D (N = 264)	Placebo (N = 266)
Total events [a], n (%)	139 (52.7)	169 (63.5)
RECIST progression	126 (47.7)	158 (59.4)
Target lesions [b]	31 (11.7)	31 (11.7)
Non-target lesions [b]	5 (1.9)	13 (4.9)
New lesions [b]	94 (35.6)	128 (48.1)
Death in absence of progression	13 (4.9)	11 (4.1)
Censored patients, n (%)	125 (47.3)	97 (36.5)
Censored RECIST progression [c]	0	0
Censored death [d]	18 (6.8)	18 (6.8)
Progression-free at time of analysis [e]	101 (38.3)	74 (27.8)
Lost to follow-up [f]	0	0
Withdrawn consent [f]	6 (2.3)	5 (1.9)
Discontinued study	0	0

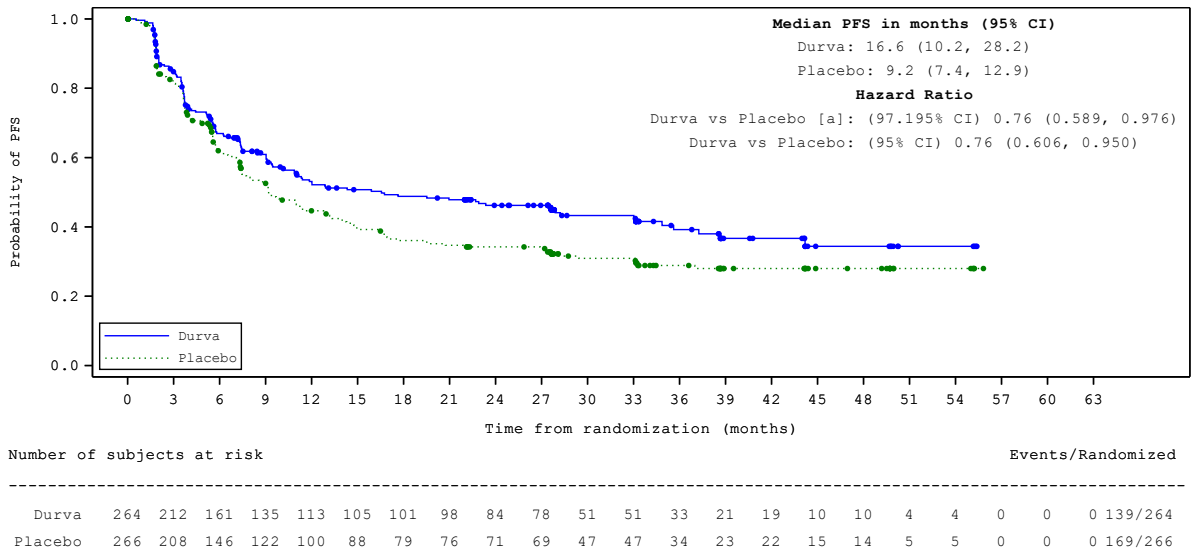
Table 26 PFS Using BICR Assessments According to RECIST 1.1, Durvalumab vs Placebo (FAS)

	D (N = 264)	Placebo (N = 266)
Median PFS (months) [g]	16.6	9.2
95% CI for median PFS [g]	10.2, 28.2	7.4, 12.9
Progression-free survival at 18 months (PFS18) [g]	48.8	36.1
95% CI for PFS18 [g]	42.2, 55.0	29.9, 42.2
Progression-free survival at 24 months (PFS24) [g]	46.2	34.2
95% CI for PFS24 [g]	39.6, 52.5	28.2, 40.3
HR, D vs placebo [h,k]	0.76	
99.816% CI for HR [h,i]	0.530, 1.084	
97.195% CI for HR [h,i]	0.589, 0.976	
95% CI for HR [h]	0.606, 0.950	
2-sided p-value [j]	0.01608	

a Patients who had not progressed or died, or who progressed or died after ≥2 missed visits were censored at the latest evaluable RECIST assessment, or Day 1 if no evaluable visits. Patients with progression within 2 visits of baseline with no evaluable visits or no baseline assessment were censored at Day 1.
b Target lesions, non-target lesions and new lesions were not mutually exclusive.
c Progression occurred after ≥2 missed visits or within 2 visits of baseline with no evaluable visits or no baseline assessment.
d Death occurred after ≥2 missed visits in the absence of progression.
e Includes patients, known to be alive, or with no baseline assessment (censored at Day 1).
f Patients censored at last evaluable RECIST assessment.
g Calculated using the KM technique. CI for median PFS based on Brookmeyer-Crowley method with log log transformation. CIs for PFS18 and PFS24 based on a log(-log(.)) transformation.
h HR and CI from a stratified Cox proportional hazards model, adjusting for TNM stage and receipt of PCI, with treatment as only covariate and ties handled by Efron approach. CIs based on the profile likelihood approach.
i Based on a Lan-DeMets alpha spending function with O'Brien Fleming type boundary with the actual number of events, the boundaries for declaring statistical significance for PFS were 0.184% for a 0.5% overall alpha and 2.805% for a 5% overall alpha.
j Based on a stratified log-rank test, adjusting for TNM stage and receipt of PCI.
k A HR < 1 favours durvalumab .
One month was calculated as 30.4375 days.
Progression was determined by the RECIST 1.1-based assessment of the BICR.
Stratification factors were based on the values entered into the IVRS.

DCO 15-Jan-2024

Figure 7 PFS, Durvalumab vs Placebo, KM Plot (FAS)



Durva = durvalumab monotherapy.

[a] Based on a Lan-DeMets alpha spending function with O'Brien Fleming type boundary with the actual number of events observed, the boundaries for declaring statistical significance were 2.805% for a 5% overall alpha for PFS. The Lan-DeMets spending function that approximates the O'Brien Fleming approach was used to derive the adjusted alpha level.

Progression was determined by the RECIST-based assessment of the BICR.

Circle indicates a censored observation.

Table 27 Treatment status at progression, based on BICR assessment according to RECIST 1.1 (Full analysis set)

	Durva (N=264)	Placebo (N=266)
Subjects who have progressed, n (%)	139	169
Prior to receiving treatment	0	0
On treatment at time of progression	110 (79.1)	128 (75.7)
Completed treatment at time of progression	6 (4.3)	7 (4.1)
Discontinued treatment prior to progression	23 (16.5)	34 (20.1)
Number of days prior to progression [a]		
n	23	34
Mean	142.4	115.3
SD	215.78	133.97
Median	79.0	63.5
Min, Max	30, 1072	30, 680
Subjects who have not progressed (censored), n (%)	125	97
Prior to receiving treatment	1 (0.8)	3 (3.1)
On treatment prior to censoring	73 (58.4)	50 (51.5)
Completed treatment prior to censoring	40 (32.0)	36 (37.1)
Discontinued treatment prior to censoring	11 (8.8)	8 (8.2)

Mean Arithmetic mean; SD Standard deviation; Min Minimum; Max Maximum.
Progression is determined by the RECIST-based assessment of the Blinded Independent Central Review (BICR).
Percentages are calculated from the number of subjects who have/have not progressed.
A window of 28 days from last dose of treatment is used to assess if subjects were still on treatment at date of progression or date of censoring.
[a] Number of days prior to progression are calculated for the subjects who have discontinued treatment.
'Prior to receiving treatment' is defined as having no treatment or having progression/censoring prior to treatment.
'Discontinued treatment' is defined as having progression/censoring date after or on treatment period and treatment is discontinued.
Subjects who have not progressed or died, or who progress or die after two or more missed visits are censored at the latest evaluable RECIST assessment, or day 1 if there are no evaluable visits. Subjects with RECIST progression within two visits of baseline who do not have any evaluable visits or do not have a baseline assessment are censored at day 1.

Table 28 Reasons for Censoring in the Primary PFS Analysis (FAS)

	Number (%) of patients	
	D (N = 264)	Placebo (N = 266)
Censored subjects	125 (47.3)	97 (36.5)
Progression-free at time of analysis [a]	101 (38.3)	74 (27.8)
No evaluable baseline and/or follow up assessments	0	1 (0.4)
Event occurred after 2 or more missed visits	18 (6.8)	18 (6.8)
Death	18 (6.8)	18 (6.8)
RECIST progression	0	0
Withdrew consent [b]	6 (2.3)	5 (1.9)

a Includes patients, known to be alive, or with no evaluable baseline RECIST assessment (censored at Day 1).

b Censored at last evaluable RECIST assessment.

Table 29 New lesions, based on BICR assessment according to RECIST 1.1 (Full analysis set)

New lesion site	Number (%) of subjects Durva (N=264)	 Placebo (N=266)
Subjects with no BICR read	17 (6.4)	20 (7.5)
Subjects with no new lesions	132 (50.0)	111 (41.7)
Subjects with new lesions	115 (43.6)	135 (50.8)
ABDOMEN [a]	1 (0.4)	6 (2.3)
ADRENAL GLAND	10 (3.8)	10 (3.8)
BONE	3 (1.1)	12 (4.5)
BRAIN/CNS	26 (9.8)	39 (14.7)
BREAST	1 (0.4)	0
CHEST [b]	5 (1.9)	7 (2.6)
DIAPHRAGM	2 (0.8)	0
DISTANT LYMPH NODE	11 (4.2)	14 (5.3)
GENITOURINARY	0	1 (0.4)
LIVER	17 (6.4)	21 (7.9)
LUNG	50 (18.9)	47 (17.7)
OTHER	0	3 (1.1)
REGIONAL LYMPH NODE	16 (6.1)	24 (9.0)
RETROPERITONEUM [d]	0	1 (0.4)

CNS Central nervous system.
New lesion is determined by the RECIST-based assessment of the Blinded Independent Central Review (BICR).
[a] Excluding liver.
[b] Excluding lung.
[c] Not otherwise specified.
[d] Excluding adrenal gland.
Note that a subject may have had more than one new lesion site.

PFS by investigator

Table 30 Progression-free survival, based on investigator assessment according to RECIST 1.1 (Full analysis set)

	Durva (N=264)	Placebo (N=266)
Total events [a], n (%)	153 (58.0)	179 (67.3)
RECIST progression	142 (53.8)	172 (64.7)
Target Lesions [b]	24 (9.1)	29 (10.9)
Non Target Lesions [b]	22 (8.3)	26 (9.8)
New Lesions [b]	121 (45.8)	145 (54.5)
Death in absence of progression	11 (4.2)	7 (2.6)
Censored subjects, n (%)	111 (42.0)	87 (32.7)
Censored RECIST progression [c]	0	0
Censored death [d]	9 (3.4)	8 (3.0)
Progression-free at time of analysis [e]	95 (36.0)	73 (27.4)
Lost to follow-up [f]	0	0
Withdrawn consent [f]	7 (2.7)	6 (2.3)
Discontinued study	0	0
Median progression-free survival (months) [g]	16.1	9.2
95% CI for median progression-free survival [g]	10.1, 23.0	7.4, 12.8
Progression-free survival at 18 months (PFS18) [g]	48.3	35.0
95% CI for PFS18 [g]	41.9, 54.4	29.1, 41.0
Progression-free survival at 24 months (PFS24) [g]	43.4	32.1
95% CI for PFS24 [g]	37.0, 49.5	26.3, 38.0
Hazard ratio, Durva versus Placebo [h] [j]	0.76	
95% CI for hazard ratio [h]	0.615, 0.948	
2-sided p-value [i]	0.0151	

Durva Durvalumab.
CI Confidence interval; One month is calculated as 30.4375 days.
Progression is determined by the RECIST-based assessment of the investigator.
[a] Subjects who have not progressed or died, or who progress or die after two or more missed visits are censored at the latest evaluable RECIST assessment, or day 1 if there are no evaluable visits. Subjects with RECIST progression within two visits of baseline who do not have any evaluable visits or do not have a baseline assessment are censored at day 1.
[b] Target Lesions, Non Target Lesions and New Lesions are not necessarily mutually exclusive categories.
[c] RECIST progression event occurred after two or more missed visits or within two visits of baseline where the subject has no evaluable visits or does not have a baseline assessment.
[d] Death occurred after two or more missed visits in the absence of RECIST progression.
[e] Includes subjects, known to be alive, or with no evaluable baseline RECIST assessment (censored at day 1).
[f] Subjects censored at last evaluable RECIST assessment.
[g] Calculated using the Kaplan-Meier technique. CI for median progression-free survival is derived based on Brookmeyer-Crowley method with log-log transformation. CI for PFS18 and PFS24 are derived based on a log(-log(.)) transformation.
[h] The hazard ratio and CI were calculated using a stratified Cox proportional hazards model, adjusting for TNM stage (Stage I/II versus III) and receipt of PCI (yes versus no), with treatment as only covariate and ties handled by Efron approach. CIs were calculated using the profile likelihood approach.
[i] The analysis was performed using the stratified log-rank test, adjusting for TNM stage (Stage I/II versus III) and receipt of PCI (yes versus no).
[j] A hazard ratio < 1 favors Durva to be associated with a longer event-free survival than Placebo.
Stratification factors are based on the values entered into the IVRS.
RECIST version 1.1.

Secondary endpoints

Table 31 Other Secondary Efficacy Results, Durvalumab vs Placebo (FAS)

Efficacy measure	Treatment group	
	D	Placebo
Objective response rate (BICR) [a]		
Unconfirmed ORR, n (%) [95% CI]	53 (30.3) [23.6, 37.7]	54 (32.0) [25.0, 39.6]
Difference in proportion, % (95% CI)	-1.2 (-11.0, 8.5)	
Confirmed ORR, n (%) [95% CI]	45 (25.7) [19.4, 32.9]	44 (26.0) [19.6, 33.3]
Difference in proportion, % (95% CI)	0.0 (-9.3, 9.1)	
Best change from baseline in target lesion size [BICR]) [b]		
Mean (SD) percentage change	-35.44 (37.023)	-35.82 (38.650)
Median (min, max) percentage change	-27.00 (-100.0, 87.7)	-24.55 (-100.0, 59.9)
Best objective response (unconfirmed)		
CR, number (%)	5 (2.9)	4 (2.4)
PR, number (%)	48 (27.4)	50 (29.6)
Stable disease, number (%)	94 (53.7)	76 (45.0)
Progressive disease, number (%)	24 (13.7)	33 (19.5)
NE, number (%)	4 (2.3)	6 (3.6)
Best objective response (confirmed)		
CR, number (%)	5 (2.9)	3 (1.8)
PR, number (%)	40 (22.9)	41 (24.3)
Stable disease, number (%)	94 (53.7)	76 (45.0)
Progressive disease, number (%)	24 (13.7)	33 (19.5)
NE, number (%)	4 (2.3)	6 (3.6)
Duration of response (BICR)		
Median (95% CI) unconfirmed DoR, months	33.0 (22.4, NR)	27.7 (9.6, NR)
Median (95% CI) confirmed DoR, months	38.8 (25.9, NR)	27.8 (9.9, NR)
TTDM by Investigator assessment (sensitivity analysis) [c]		
Median TTDM, months (95% CI)	37.3 (23.0, NR)	17.6 (12.9, NR)
HR, durvalumab vs placebo (95% CI)	0.79 (0.611, 1.028)	
Time from randomization to second progression or death		
Median PFS2, months (95% CI)	NR (NR, NR)	37.6 (25.3, NR)
HR, D vs placebo (95% CI)	0.66 (0.495, 0.880)	

a ORR was defined as the number (%) of patients with at least one visit response of CR or PR. Patients who do not have measurable disease at baseline (i.e., CR after cCRT) were excluded from the analysis. Patients who discontinued treatment without progression, received a subsequent anticancer therapy, and then responded were not included as responders. A confirmed response of CR/PR means that a response of CR/PR was recorded at 1 visit and confirmed by repeat imaging ≥ 28 days after the visit when the response was first observed with no evidence of progression between the initial and CR/PR confirmation visit.

b The best percentage change in target lesion size was defined as the maximum reduction from baseline or the minimum increase from baseline in the absence of a reduction. A negative change denotes a reduction in target lesion size.

c Date and location information for new lesions used to support TTDM analysis by BICR were incomplete.

Patient reported outcomes (PROs)

Patient-reported outcome measures were included as secondary endpoints in the study and were assessed using the **EORTC QLQ-C30** and EORTC QLQ-LC13 questionnaires.

PRO compliance at baseline for **EORTC QLQ-C30** was 81.8% in the D group and 79.7% in the placebo group and remained ≥ 73% through Week 16, > 60% through Week 36, and > 50% through Week 84 for both treatment groups. Overall compliance was moderate during the study with an overall rate of 57.5% for the D group and 59.6% for the placebo group.

Compliance at baseline for EORTC QLQ-LC13 was 82.2% in the D group and 80.8% in the placebo group and remained > 70% through Week 16, > 60% through Week 36, and > 50% through Week 84 for both treatment groups. Overall compliance rates were 61.2% for the D group and 63.3% for the placebo group.

Table 32 Adjusted Mean Change (95% CI) from Baseline (Average Over 24 Months) in Key EORTC QLQ-C30 and QLQ-LC13 Endpoints, MMRM (FAS)

Subscale	D (N = 264)	Placebo (N = 266)
QLQ-C30		
GHS/QoL [a]	-3.6 (-5.893, -1.297)	-2.5 (-4.781, -0.179)
Physical functioning [a]	-1.5 (-3.450, 0.376)	-1.3 (-3.200, 0.660)
Role functioning [a]	-2.1 (-4.596, 0.391)	-3.4 (-5.945, -0.948)
Fatigue [b]	-1.4 (-3.955, 1.164)	-0.5 (-3.064, 2.078)
Appetite loss [b]	-6.1 (-8.345, -3.869)	-8.8 (-11.092, -6.603)
QLQ-LC13		
Dyspnoea [b]	2.4 (0.278, 4.492)	2.1 (0.003, 4.230)
Cough [b]	1.2 (-1.288, 3.645)	0.9 (-1.600, 3.353)
Chest pain [b]	1.4 (-0.474, 3.198)	2.6 (0.743, 4.419)

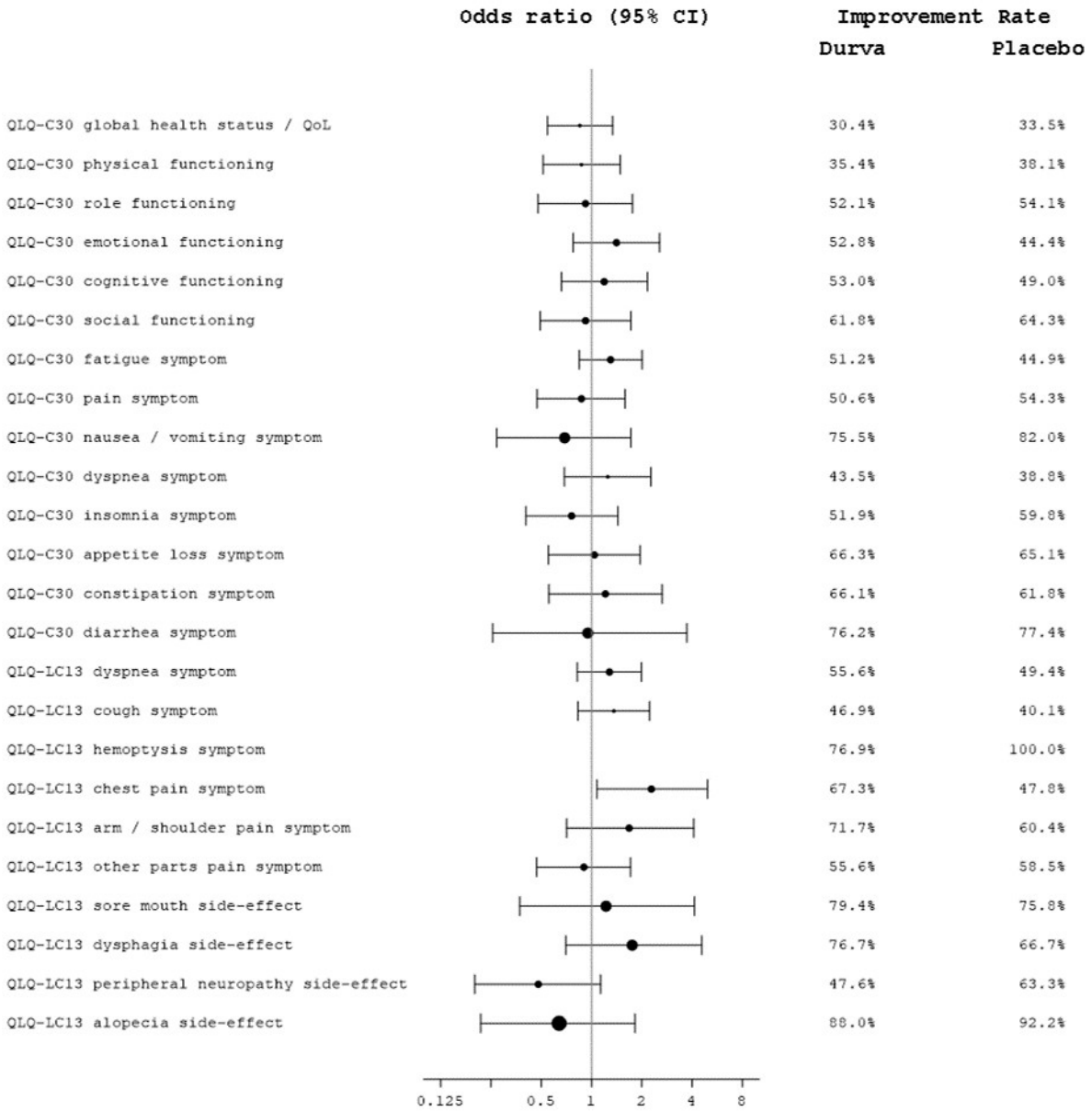
[a] Negative change from baseline indicates deterioration in GHS/QoL and functioning scales.

[b] Positive change from baseline indicates deterioration in symptom scales.

The analysis was performed, making use of all data from baseline up to progressive disease, death or 24 months, by using a MMRM model with treatment, TNM stage (Stage I/II versus III), receipt of PCI (yes vs no), visit, and the interaction between treatment and visit as fixed factors, baseline score and interaction between baseline score and visit as covariates. A toeplitz with heterogeneity covariance matrix was used to model the within-patient error and the Kenward-Roger approximation was used to estimate the degrees of freedom. Restricted maximum likelihood (REML) estimation was used. No adjustments have been made to the significance level for testing.

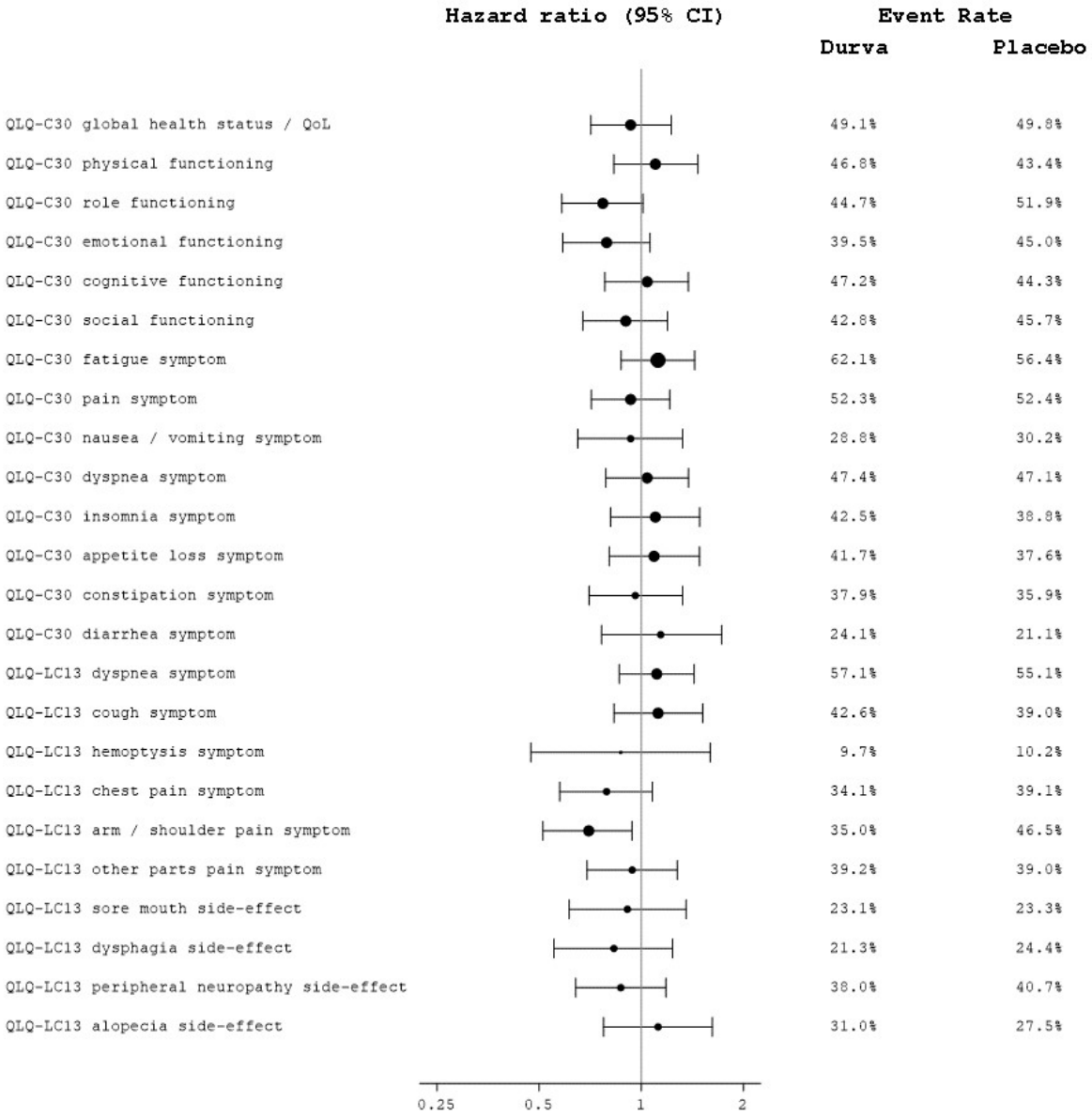
Adjusted mean represents the change from baseline (averaged over all visits, giving each visit equal weight).

Figure 8 Improvement Rate of EORTC QLQ-C30 and QLQ-LC13



Odds ratio (D vs placebo) and 95% CI for subscales/items.
Size of circle is proportional to the number of events.

Figure 9 Time to Deterioration of EORTC QLQ-C30 and QLQ-LC13



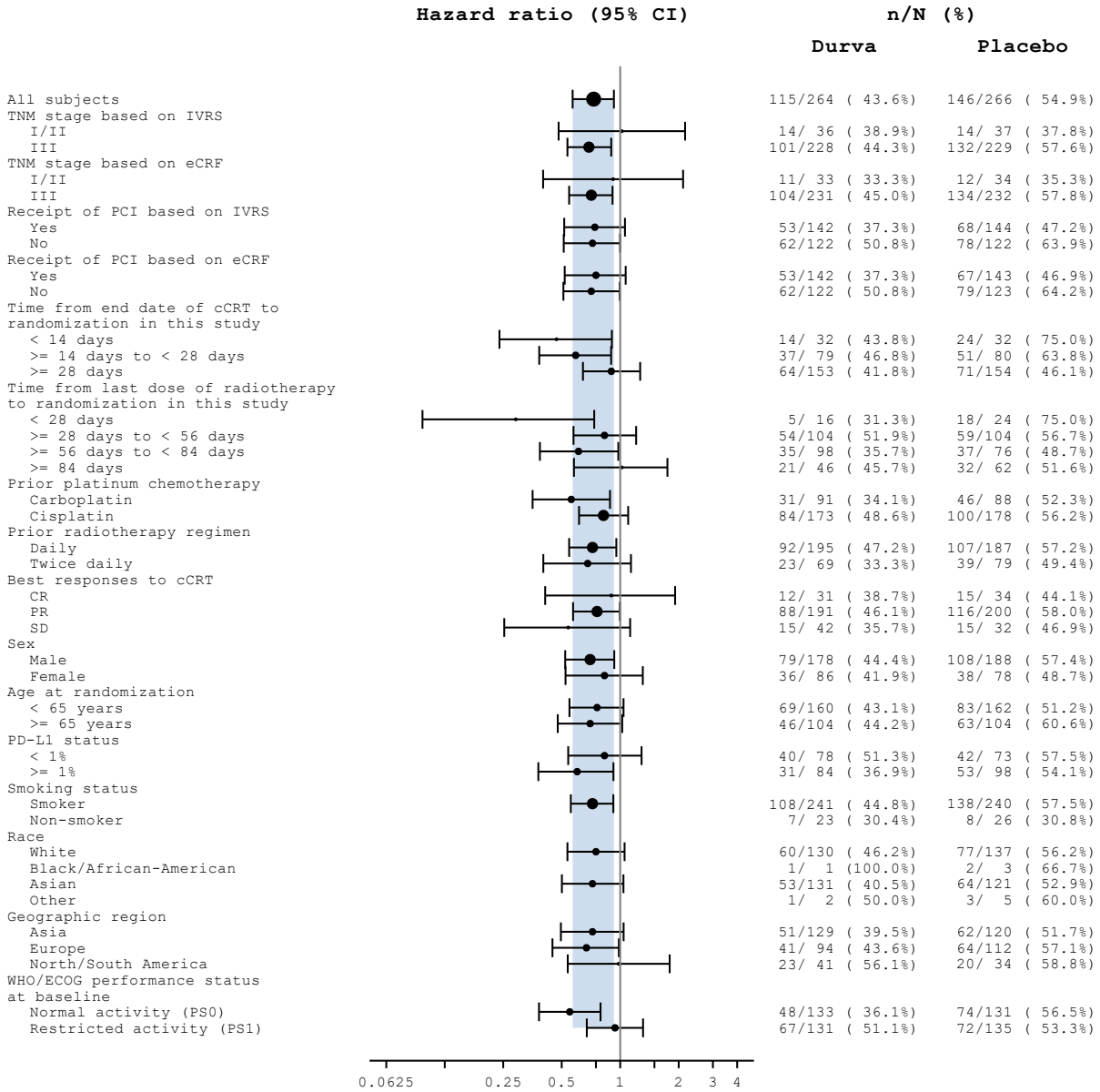
HR (D vs placebo) and 95% CI for subscales/items are displayed on a logarithmic scale.
Size of circle is proportional to the number of events.

Ancillary analyses

Subgroup analyses

OS

Figure 10 Overall Survival by Subgroup, Durvalumab vs Placebo, Forest Plot (FAS)



Durva = durvalumab monotherapy; SD = stable disease.
HR (D vs placebo) and 95% CI are displayed on a logarithmic scale.
Size of circle is proportional to the number of events.
Band represents the 95% CI for the main OS HR.

Table 33 Overall survival, subgroup analyses (Full analysis set)

Overall survival, subgroup analyses (Full analysis set)

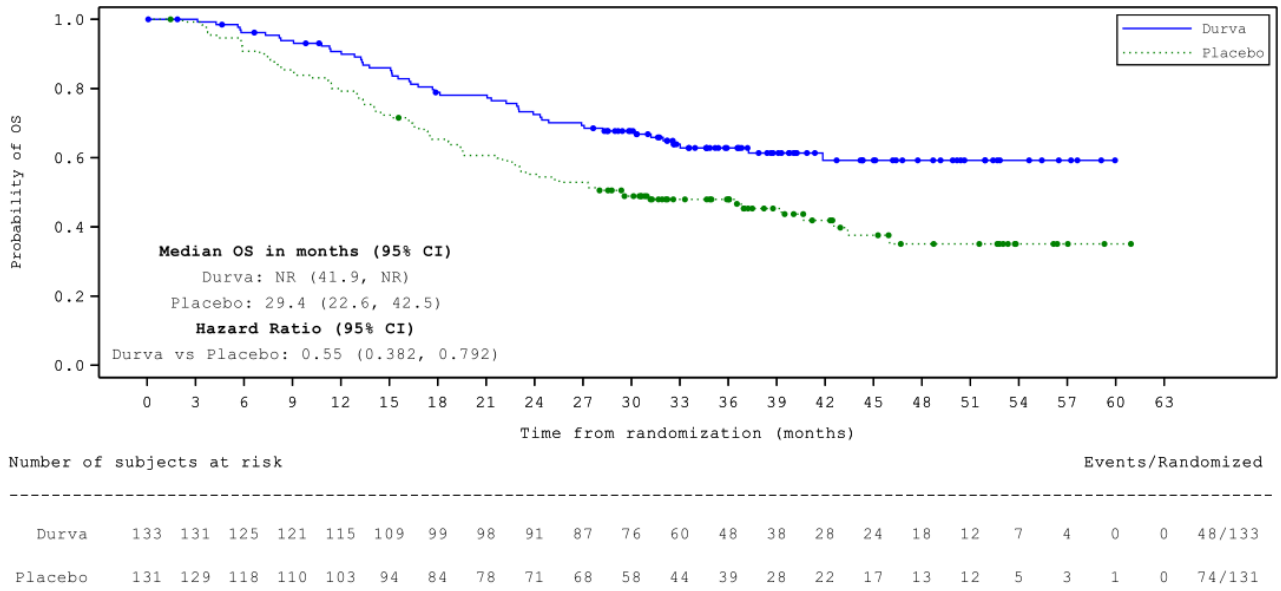
				Comparison between groups [a]	
Subgroup	Group	N	Number (%) of subjects with events	Hazard ratio	95% CI
All subjects					
	Durva	264	115 (43.6)	0.73	0.569, 0.928
	Placebo	266	146 (54.9)		
TNM stage based on IVRS					
I/II	Durva	36	14 (38.9)	1.02	0.482, 2.158
	Placebo	37	14 (37.8)		
III	Durva	228	101 (44.3)	0.69	0.535, 0.899
	Placebo	229	132 (57.6)		
TNM stage based on eCRF					
I/II	Durva	33	11 (33.3)	0.92	0.401, 2.107
	Placebo	34	12 (35.3)		
III	Durva	231	104 (45.0)	0.71	0.546, 0.913
	Placebo	232	134 (57.8)		
Receipt of PCI based on IVRS					
Yes	Durva	142	53 (37.3)	0.74	0.515, 1.058
	Placebo	144	68 (47.2)		
No	Durva	122	62 (50.8)	0.72	0.512, 0.999
	Placebo	122	78 (63.9)		
Receipt of PCI based on eCRF					
Yes	Durva	142	53 (37.3)	0.75	0.518, 1.067
	Placebo	143	67 (46.9)		
No	Durva	122	62 (50.8)	0.71	0.510, 0.994
	Placebo	123	79 (64.2)		
Time from end date of cCRT to randomization in this study [b]					
< 14 days	Durva	32	14 (43.8)	0.47	0.239, 0.906
	Placebo	32	24 (75.0)		
>= 14 days to < 28 days	Durva	79	37 (46.8)	0.59	0.383, 0.898
	Placebo	80	51 (63.8)		
>= 28 days	Durva	153	64 (41.8)	0.90	0.643, 1.267
	Placebo	154	71 (46.1)		
Time from last dose of radiotherapy to randomization in this study					
< 28 days	Durva	16	5 (31.3)	0.29	0.096, 0.735
	Placebo	24	18 (75.0)		
>= 28 days to < 56 days	Durva	104	54 (51.9)	0.83	0.575, 1.208
	Placebo	104	59 (56.7)		
>= 56 days to < 84 days	Durva	98	35 (35.7)	0.61	0.386, 0.978
	Placebo	76	37 (48.7)		
>= 84 days	Durva	46	21 (45.7)	1.02	0.578, 1.750
	Placebo	62	32 (51.6)		
Prior platinum chemotherapy [c]					
Carboplatin	Durva	91	31 (34.1)	0.56	0.354, 0.886
	Placebo	88	46 (52.3)		
Cisplatin	Durva	173	84 (48.6)	0.82	0.614, 1.099
	Placebo	178	100 (56.2)		
Prior radiotherapy regimen					
Daily	Durva	195	92 (47.2)	0.72	0.546, 0.955
	Placebo	187	107 (57.2)		
Twice daily	Durva	69	23 (33.3)	0.68	0.402, 1.136
	Placebo	79	39 (49.4)		

Best responses to cCRT					
CR	Durva	31	12 (38.7)	0.90	0.411, 1.917
	Placebo	34	15 (44.1)		
PR	Durva	191	88 (46.1)	0.76	0.572, 0.996
	Placebo	200	116 (58.0)		
SD	Durva	42	15 (35.7)	0.54	0.253, 1.125
	Placebo	32	15 (46.9)		
Sex					
Male	Durva	178	79 (44.4)	0.70	0.521, 0.932
	Placebo	188	108 (57.4)		
Female	Durva	86	36 (41.9)	0.83	0.523, 1.307
	Placebo	78	38 (48.7)		
Age at randomization					
< 65 years	Durva	160	69 (43.1)	0.76	0.548, 1.040
	Placebo	162	83 (51.2)		
>= 65 years	Durva	104	46 (44.2)	0.70	0.477, 1.024
	Placebo	104	63 (60.6)		
PD-L1 status					
< 1%	Durva	78	40 (51.3)	0.83	0.540, 1.288
	Placebo	73	42 (57.5)		
>= 1%	Durva	84	31 (36.9)	0.60	0.379, 0.923
	Placebo	98	53 (54.1)		
Smoking status					
Smoker [d]	Durva	241	108 (44.8)	0.72	0.557, 0.922
	Placebo	240	138 (57.5)		
Non-smoker	Durva	23	7 (30.4)		
	Placebo	26	8 (30.8)		
Race					
White	Durva	130	60 (46.2)	0.75	0.535, 1.053
	Placebo	137	77 (56.2)		
Black/African-American	Durva	1	1 (100.0)		
	Placebo	3	2 (66.7)		
Asian	Durva	131	53 (40.5)	0.72	0.501, 1.039
	Placebo	121	64 (52.9)		
Other	Durva	2	1 (50.0)		
	Placebo	5	3 (60.0)		
Geographic region					
Asia	Durva	129	51 (39.5)	0.72	0.495, 1.041
	Placebo	120	62 (51.7)		
Europe	Durva	94	41 (43.6)	0.67	0.448, 0.984
	Placebo	112	64 (57.1)		
North/South America [e]	Durva	41	23 (56.1)	0.98	0.537, 1.797
	Placebo	34	20 (58.8)		
WHO/ECOG performance status at baseline					
Normal activity (PS0)	Durva	133	48 (36.1)	0.55	0.382, 0.792
	Placebo	131	74 (56.5)		
Restricted activity (PS1)	Durva	131	67 (51.1)	0.94	0.673, 1.311
	Placebo	135	72 (53.3)		

Durva Durvalumab.
cCRT Concurrent chemoradiation therapy; CI Confidence interval; CR Complete response; ECOG Eastern Cooperative Oncology Group; eCRF Case report form (electronic); IVRS Interactive voice response system; N Number of subjects in treatment group; PCI Prophylactic cranial irradiation; PD-L1 Programmed cell death ligand; PR Partial response; PS Performance status; SD Stable disease; TNM Tumor, node and metastatic classification; WHO World Health Organization.
[a] For all subjects the analysis is the main stratified OS analysis, while for subgroups the hazard ratio and CI were calculated using an unstratified Cox proportional hazards model, with treatment as only covariate and ties handled by Efron approach.
[b] End date of cCRT is the latest of last date of last cycle of platinum chemotherapy (last date + cycle length) or last dose of radiotherapy.
[c] Subjects are grouped according to the platinum agent they received for Cycle 1.
[d] Smoker: Current or former smoker.
[e] Argentina is grouped with North America.
A hazard ratio < 1 favors Durva to be associated with a longer survival than Placebo.
Stratification factors are based on the values entered into the IVRS and recorded on the eCRF. Other subgroup factors are based on values recorded on the eCRF.
If too few events are available (i.e. less than 20 events across both treatment groups in a subgroup) for a meaningful analysis of a particular subgroup, then comparison results for that specific subgroup will not be presented.

Data cut-off: 15JAN2024

Figure 11 Overall survival, Kaplan-Meier plot - Durva versus Placebo, subjects with WHO/ECOG PS0 at baseline (Full analysis set)

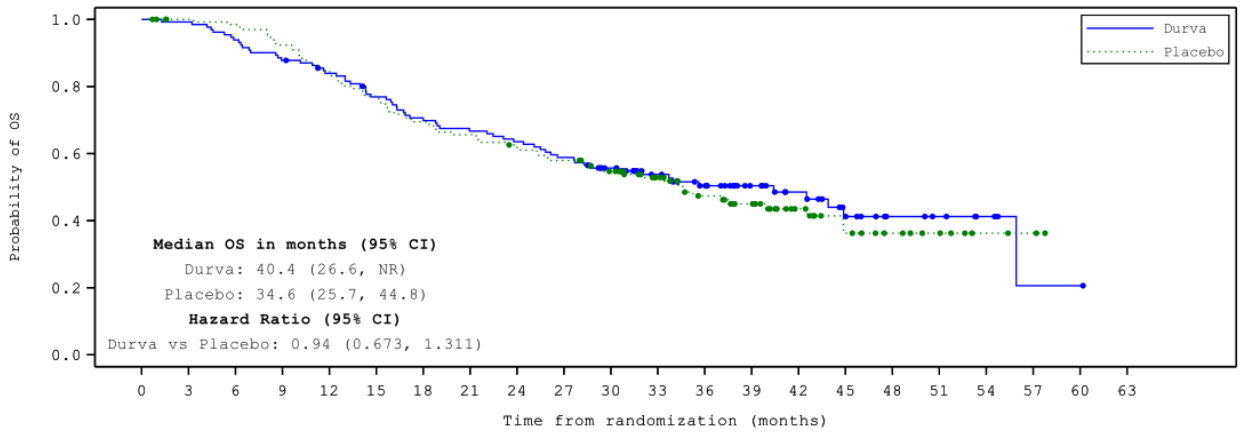


Number of subjects at risk

																						Events/Randomized
Durva	133	131	125	121	115	109	99	98	91	87	76	60	48	38	28	24	18	12	7	4	0	48/133
Placebo	131	129	118	110	103	94	84	78	71	68	58	44	39	28	22	17	13	12	5	3	1	0	74/131

CI Confidence interval; ECOG Eastern Cooperative Oncology Group; NR Not reached; OS Overall Survival; PS Performance status; WHO World Health
Organization; One month is calculated as 30.4375 days.
PS0 indicates Performance status = "Normal activity".
Circle indicates a censored observation.

Figure 12 Overall survival, Kaplan-Meier plot - Durva versus Placebo, subjects with WHO/ECOG PS1 at baseline (Full analysis set)



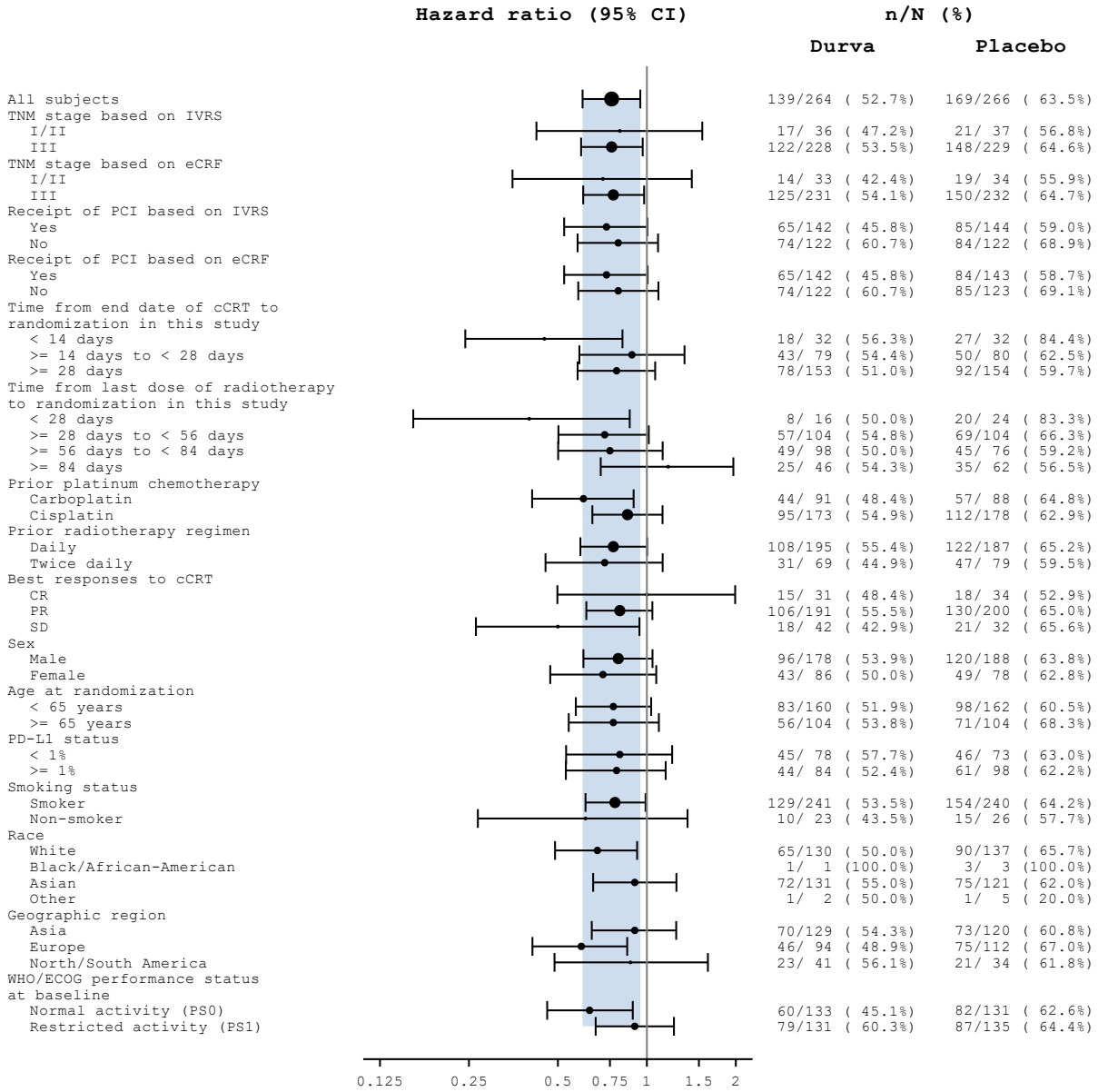
Number of subjects at risk

																						Events/Randomized
Durva	131	130	123	115	108	98	90	85	81	75	65	50	42	30	23	15	9	7	4	1	1	0	67/131
Placebo	135	131	129	121	111	101	91	86	80	75	65	53	41	34	22	14	10	7	3	2	0	0	72/135

CI Confidence interval; ECOG Eastern Cooperative Oncology Group; NR Not reached; OS Overall Survival; PS Performance status; WHO World Health
Organization; One month is calculated as 30.4375 days.
PS1 indicates Performance status = "Restricted activity".
Circle indicates a censored observation.

PFS

Figure 13 PFS by Subgroup, Durvalumab vs Placebo, Forest Plot (FAS)



Durva = durvalumab monotherapy; SD = stable disease.
HR (D vs placebo) and 95% CI are displayed on a logarithmic scale.
Size of circle is proportional to the number of events.
Band represents the 95% CI for the main PFS HR.

Table 34 Progression-free survival, based on BICR assessment according to RECIST 1.1, subgroup analyses (Full analysis set) - Data cut-off: 15 Jan 2024

				Comparison between groups [b]	
Subgroup	Group	N	Number (%) of subjects with events [a]	Hazard ratio	95% CI
TNM stage based on IVRS					
I/II	Durva	36	17 (47.2)	0.81	0.423, 1.540
	Placebo	37	21 (56.8)		
III	Durva	228	122 (53.5)	0.76	0.599, 0.968
	Placebo	229	148 (64.6)		
TNM stage based on eCRF					
I/II	Durva	33	14 (42.4)	0.71	0.351, 1.419
	Placebo	34	19 (55.9)		
III	Durva	231	125 (54.1)	0.77	0.609, 0.979
	Placebo	232	150 (64.7)		
Receipt of PCI based on IVRS					
Yes	Durva	142	65 (45.8)	0.73	0.525, 1.004
	Placebo	144	85 (59.0)		
No	Durva	122	74 (60.7)	0.80	0.583, 1.091
	Placebo	122	84 (68.9)		
Receipt of PCI based on eCRF					
Yes	Durva	142	65 (45.8)	0.73	0.525, 1.006
	Placebo	143	84 (58.7)		
No	Durva	122	74 (60.7)	0.80	0.586, 1.094
	Placebo	123	85 (69.1)		
Time from end date of cCRT to randomization in this study [c]					
< 14 days	Durva	32	18 (56.3)	0.45	0.243, 0.827
	Placebo	32	27 (84.4)		
>= 14 days to < 28 days	Durva	79	43 (54.4)	0.89	0.591, 1.341
	Placebo	80	50 (62.5)		
>= 28 days	Durva	153	78 (51.0)	0.79	0.583, 1.067
	Placebo	154	92 (59.7)		
Time from last dose of radiotherapy to randomization in this study					
< 28 days	Durva	16	8 (50.0)	0.40	0.162, 0.875
	Placebo	24	20 (83.3)		
>= 28 days to < 56 days	Durva	104	57 (54.8)	0.72	0.502, 1.015
	Placebo	104	69 (66.3)		
>= 56 days to < 84 days	Durva	98	49 (50.0)	0.75	0.501, 1.131
	Placebo	76	45 (59.2)		
>= 84 days	Durva	46	25 (54.3)	1.18	0.698, 1.962
	Placebo	62	35 (56.5)		
Prior platinum chemotherapy [d]					
Carboplatin	Durva	91	44 (48.4)	0.61	0.409, 0.902
	Placebo	88	57 (64.8)		
Cisplatin	Durva	173	95 (54.9)	0.86	0.654, 1.130
	Placebo	178	112 (62.9)		
Prior radiotherapy regimen					
Daily	Durva	195	108 (55.4)	0.77	0.596, 1.002
	Placebo	187	122 (65.2)		
Twice daily	Durva	69	31 (44.9)	0.72	0.454, 1.131
	Placebo	79	47 (59.5)		
Best responses to cCRT					
CR	Durva	31	15 (48.4)	1.00	0.498, 1.990
	Placebo	34	18 (52.9)		
PR	Durva	191	106 (55.5)	0.81	0.624, 1.044
	Placebo	200	130 (65.0)		
SD	Durva	42	18 (42.9)	0.50	0.264, 0.944
	Placebo	32	21 (65.6)		

Sex					
Male	Durva	178	96 (53.9)	0.80	0.610, 1.045
	Placebo	188	120 (63.8)		
Female	Durva	86	43 (50.0)	0.71	0.471, 1.076
	Placebo	78	49 (62.8)		
Age at randomization					
< 65 years	Durva	160	83 (51.9)	0.77	0.575, 1.034
	Placebo	162	98 (60.5)		
>= 65 years	Durva	104	56 (53.8)	0.77	0.544, 1.098
	Placebo	104	71 (68.3)		
PD-L1 status					
< 1%	Durva	78	45 (57.7)	0.81	0.533, 1.218
	Placebo	73	46 (63.0)		
>= 1%	Durva	84	44 (52.4)	0.79	0.532, 1.158
	Placebo	98	61 (62.2)		
Smoking status					
Smoker [e]	Durva	241	129 (53.5)	0.78	0.620, 0.990
	Placebo	240	154 (64.2)		
Non-smoker	Durva	23	10 (43.5)	0.62	0.268, 1.373
	Placebo	26	15 (57.7)		
Race					
White	Durva	130	65 (50.0)	0.68	0.489, 0.927
	Placebo	137	90 (65.7)		
Black/African-American	Durva	1	1 (100.0)		
	Placebo	3	3 (100.0)		
Asian	Durva	131	72 (55.0)	0.91	0.658, 1.259
	Placebo	121	75 (62.0)		
Other	Durva	2	1 (50.0)		
	Placebo	5	1 (20.0)		
Geographic region					
Asia	Durva	129	70 (54.3)	0.91	0.651, 1.257
	Placebo	120	73 (60.8)		
Europe	Durva	94	46 (48.9)	0.60	0.410, 0.859
	Placebo	112	75 (67.0)		
North/South America [f]	Durva	41	23 (56.1)	0.88	0.487, 1.609
	Placebo	34	21 (61.8)		
WHO/ECOG performance status at baseline					
Normal activity (PS0)	Durva	133	60 (45.1)	0.64	0.460, 0.896
	Placebo	131	82 (62.6)		
Restricted activity (PS1)	Durva	131	79 (60.3)	0.91	0.671, 1.235
	Placebo	135	87 (64.4)		

Durva Durvalumab.
cCRT Concurrent chemoradiation therapy; CI Confidence interval; CR Complete response; ECOG Eastern Cooperative Oncology Group; eCRF Case report form (electronic); IVRS Interactive voice response system; N Number of subjects in treatment group; PCI Prophylactic cranial irradiation; PD-L1 Programmed cell death ligand; PR Partial response; PS Performance status; SD Stable disease; TNM Tumor, node and metastatic classification; WHO World Health Organization.
Progression is determined by the RECIST-based assessment of the Blinded Independent Central Review (BICR).
[a] Subjects who have not progressed or died, or who progress or die after two or more missed visits are censored at the latest evaluable RECIST assessment, or day 1 if there are no evaluable visits. Subjects with RECIST progression within two visits of baseline who do not have any evaluable visits or do not have a baseline assessment are censored at day 1.
[b] For all subjects the analysis is the main stratified PFS analysis, while for subgroups the hazard ratio and CI were calculated using an unstratified Cox proportional hazards model, with treatment as only covariate and ties handled by Efron approach.
[c] End date of cCRT is the latest of last date of last cycle of platinum chemotherapy (last date + cycle length) or last dose of radiotherapy.
[d] Subjects are grouped according to the platinum agent they received for Cycle 1.
[e] Smoker: Current or former smoker.
[f] Argentina is grouped with North America.
A hazard ratio < 1 favors Durva to be associated with a longer event-free survival than Placebo.
Stratification factors are based on the values entered into the IVRS and recorded on the eCRF. Other subgroup factors are based on values recorded on the eCRF.
If too few events are available (i.e. less than 20 events across both treatment groups in a subgroup) for a meaningful analysis of a particular subgroup, then comparison results for that specific subgroup will not be presented.
RECIST version 1.1.

Table 35 OS and PFS Using BICR Assessments According to RECIST 1.1 (Asian vs Non-Asian) (FAS)

	Overall FAS		Asian		Non-Asian	
	D (N = 264)	Placebo (N = 266)	D (N = 131)	Placebo (N = 121)	D (N = 133)	Placebo (N = 145)
OS						
Death, n (%)	115 (43.6)	146 (54.9)	53 (40.5)	64 (52.9)	62 (46.6)	82 (56.6)
Median OS, months	55.9	33.4	55.9	36.5	40.4	27.3
95% CI for median OS	37.3, NR	25.5, 39.9	41.9, NR	28.1, 44.9	30.4, NR	22.6, 40.7
OS HR, D vs placebo (95% CI) [a]	0.73 (0.569, 0.928)		0.72 (0.501, 1.039)		0.75 (0.536, 1.038)	
PFS						
Total PFS events, n (%) [b]	139 (52.7)	169 (63.5)	72 (55.0)	75 (62.0)	67 (50.4)	94 (64.8)
Median PFS, months	16.6	9.2	12.9	14.2	22.7	7.4
95% CI for median PFS	10.2, 28.2	7.4, 12.9	8.5, 33.1	9.1, 19.6	10.9, 35.6	5.6, 11.0
PFS HR, D vs placebo (95% CI) [a]	0.76 (0.606, 0.950)		0.91 (0.658, 1.259)		0.66 (0.482, 0.904)	

a The HR and CI were calculated using an unstratified Cox proportional hazards model, with treatment as only covariate and ties handled by Efron approach. A HR< 1 favours durvalumab to be associated with a longer event-free survival than placebo.

b Patients who had not progressed or died, or who progressed or died after 2 or more missed visits were censored at the latest evaluable RECIST assessment, or Day 1 if there were no evaluable visits. Patients with RECIST progression within 2 visits of baseline who did not have any evaluable visits or did not have a baseline assessment were censored at Day 1.

NR = not reached.

Table 36 OS and PFS Using BICR Assessments According to RECIST 1.1 (by Time From End of RT to Randomization) (FAS)

	Overall FAS		**< 28 days**		**≥ 28 days to < 56 days**		**≥ 56 days to < 84 days**		**≥ 84 days**	
	D (N = 264)	**Placebo (N = 266)**	**D (N = 16)**	**Placebo (N = 24)**	**D (N = 104)**	**Placebo (N = 104)**	**D (N = 98)**	**Placebo (N = 76)**	**D (N = 46)**	**Placebo (N = 62)**
OS										
Death, n (%)	115 (43.6)	146 (54.9)	5 (31.3)	18 (75.0)	54 (51.9)	59 (56.7)	35 (35.7)	37 (48.7)	21 (45.7)	32 (51.6)
Median OS, months	55.9	33.4	NR	14.4	34.0	27.3	NR	36.8	NR	42.5
95% CI for median OS	37.3, NR	25.5, 39.9	13.2, NR	8.1, 24.2	25.5, NR	19.9, 44.8	42.5, NR	23.2, NR	23.8, NR	29.4, NR
OS HR, D vs placebo (95% CI) [a]	0.73 (0.569, 0.928)		0.29 (0.096, 0.735)		0.83 (0.575, 1.208)		0.61 (0.386, 0.978)		1.02 (0.578, 1.750)	
PFS										
Total PFS events, n (%) [b]	139 (52.7)	169 (63.5)	8 (50.0)	20 (83.3)	57 (54.8)	69 (66.3)	49 (50.0)	45 (59.2)	25 (54.3)	35 (56.5)
Median PFS, months	16.6	9.2	9.4	4.7	10.9	7.3	27.5	13.3	12.9	17.0
95% CI for median PFS	10.2, 28.2	7.4, 12.9	3.5, NR	2.8, 8.1	7.5, 35.6	5.6, 9.2	11.3, 38.7	7.4, 19.4	7.5, 44.2	9.2, 37.0
PFS HR, D vs placebo (95% CI) [a]	0.76 (0.606, 0.950)		0.40 (0.162, 0.875)		0.72 (0.502, 1.015)		0.75 (0.501, 1.131)		1.18 (0.698, 1.962)	

a. The HR and CI were calculated using an unstratified Cox proportional hazards model, with treatment as only covariate and ties handled by Efron approach. An HR< 1 favours durvalumab to be associated with a longer event-free survival than placebo.

b. Patients who had not progressed or died, or who progressed or died after 2 or more missed visits were censored at the latest evaluable RECIST assessment, or Day 1 if there were no evaluable visits. Patients with RECIST progression within 2 visits of baseline who did not have any evaluable visits or did not have a baseline assessment were censored at Day 1.

NR = not reached.

PD-L1 status

PD-L1 status was known for a subset of patients (FPAS). Patients had missing PD-L1 status due to sample availability, as testing was retrospective and not required for randomization, and some available samples did not meet the sample quality requirements of the VENTANA PD L1 (SP263) assay. Patients were considered to have a high PD-L1 status if the proportion of tumour and/or immune cells in the tissue sample was ≥ 1% (TC or IC ≥ 1%).

Table 37 Summary of OS - PD-L1 Subgroups

Subgroup	Treatment	N	Number of events (%)	Median PFS (95% CI)	HR (95% CI) [a]
FAS [b]	D	264	115 (43.6)	55.9 (37.3, NR)	0.73 (0.569, 0.928)
	Placebo	266	146 (54.9)	33.4 (25.5, 39.9)	
FPAS [b]	D	162	71 (43.8)	55.9 (34.0, NR)	0.73 (0.535, 0.992)
	Placebo	171	95 (55.6)	32.2 (24.2, 39.9)	
PD-L1 TC and IC categories (FPAS) [c]					
TC and IC < 1%	D	78	40 (51.3)	34.0 (26.2, NR)	0.83 (0.540, 1.288)
	Placebo	73	42 (57.5)	31.1 (21.6, 42.5)	
TC or IC ≥ 1%	D	84	31 (36.9)	NR (41.9, NR)	0.60 (0.379, 0.923)
	Placebo	98	53 (54.1)	33.4 (23.5, NR)	
TC and IC < 5%	D	79	41 (51.9)	34.0 (25.8, NR)	0.84 (0.546, 1.288)
	Placebo	74	43 (58.1)	31.1 (21.6, 37.6)	
TC or IC ≥ 5%	D	83	30 (36.1)	NR (41.9, NR)	0.59 (0.370, 0.914)
	Placebo	97	52 (53.6)	33.4 (24.1, NR)	
TC and IC < 10%	D	80	42 (52.5)	32.6 (25.8, NR)	0.86 (0.559, 1.312)
	Placebo	74	43 (58.1)	31.1 (21.6, 37.6)	
TC or IC ≥ 10%	D	82	29 (35.4)	NR (41.9, NR)	0.57 (0.358, 0.892)
	Placebo	97	52 (53.6)	33.4 (24.1, NR)	
TC and IC < 25%	D	119	54 (45.4)	42.5 (30.4, NR)	0.68 (0.474, 0.974)
	Placebo	115	67 (58.3)	29.4 (21.7, 37.6)	
TC or IC ≥ 25%	D	43	17 (39.5)	NR (30.2, NR)	0.75 (0.403, 1.359)
	Placebo	56	28 (50.0)	34.6 (25.7, NR)	
TC and IC < 50%	D	143	63 (44.1)	42.5 (32.6, NR)	0.65 (0.467, 0.900)
	Placebo	140	83 (59.3)	29.4 (22.6, 36.8)	
TC or IC ≥ 50%	D	19	8 (42.1)	NR (15.2, NR)	1.10 (0.430, 2.656)
	Placebo	31	12 (38.7)	NR (27.3, NR)	

a. Cox Proportional Hazards analysis model.
b. Analyses stratified by receipt of PCI (yes versus no). Stratification factors are based on the values entered into the IVRS.
c. Unstratified analyses.

FPAS = full PD-L1 analysis set; IVRS = Interactive Voice Response System; NR = not reached.

Table 38 Summary of PFS, Based on BICR Assessment According to RECIST 1.1 - PD-L1 Subgroups

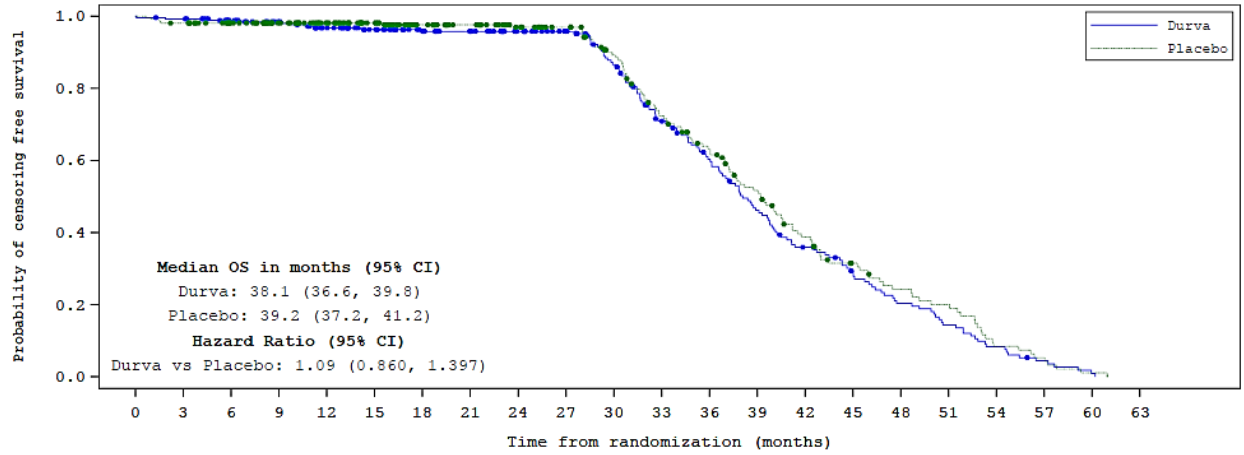
Subgroup	Treatment	N	Number of events (%)	Median PFS (95% CI)	HR (95% CI) [a]
FAS [b]	D	264	139 (52.7)	16.6 (10.2, 28.2)	0.76 (0.606, 0.950)
	Placebo	266	169 (63.5)	9.2 (7.4, 12.9)	
FPAS [b]	D	162	89 (54.9)	16.8 (9.5, 33.1)	0.80 (0.599, 1.055)
	Placebo	171	107 (62.6)	11.0 (7.7, 14.6)	
PD-L1 TC and IC categories (FPAS) [c]					
TC and IC < 1%	D	78	45 (57.7)	12.0 (9.0, 34.9)	0.81 (0.533, 1.218)
	Placebo	73	46 (63.0)	9.2 (5.6, 16.9)	
TC or IC ≥ 1%	D	84	44 (52.4)	27.9 (9.4, 38.7)	0.79 (0.532, 1.158)
	Placebo	98	61 (62.2)	11.3 (7.5, 16.6)	
TC and IC < 5%	D	79	45 (57.0)	12.0 (9.0, 34.9)	0.79 (0.524, 1.192)
	Placebo	74	47 (63.5)	9.2 (6.0, 15.0)	
TC or IC ≥ 5%	D	83	44 (53.0)	27.9 (9.0, 38.7)	0.80 (0.540, 1.179)
	Placebo	97	60 (61.9)	12.9 (7.4, 17.0)	
TC and IC < 10%	D	80	46 (57.5)	12.0 (9.0, 27.5)	0.80 (0.532, 1.204)
	Placebo	74	47 (63.5)	9.2 (6.0, 15.0)	
TC or IC ≥ 10%	D	82	43 (52.4)	27.9 (9.4, 38.7)	0.79 (0.530, 1.165)
	Placebo	97	60 (61.9)	12.9 (7.4, 17.0)	
TC and IC < 25%	D	119	65 (54.6)	12.0 (9.4, 35.6)	0.76 (0.539, 1.058)
	Placebo	115	71 (61.7)	9.9 (6.4, 16.4)	
TC or IC ≥ 25%	D	43	24 (55.8)	27.6 (4.4, 37.3)	0.93 (0.548, 1.553)
	Placebo	56	36 (64.3)	11.2 (7.4, 27.4)	
TC and IC < 50%	D	143	77 (53.8)	16.6 (9.5, 34.9)	0.76 (0.560, 1.036)
	Placebo	140	87 (62.1)	11.5 (7.3, 15.0)	
TC or IC ≥ 50%	D	19	12 (63.2)	27.6 (3.7, NR)	1.12 (0.530, 2.274)
	Placebo	31	20 (64.5)	11.2 (7.4, 33.1)	

a Cox Proportional Hazards analysis model.
b Analyses stratified by TNM stage (Stage I/II versus III) and receipt of PCI (yes versus no). Stratification factors are based on the values entered into the IVRS.
c Unstratified analyses.
FPAS = full PD-L1 analysis set; IVRS = Interactive Voice Response System; NR = not reached.

Sensitivity analyses

OS

Figure 14 Overall survival, time to censoring, Kaplan-Meier plot (with censoring indicators reversed) - Durva versus Placebo (Full analysis set)



Number of subjects at risk — Events/Randomized

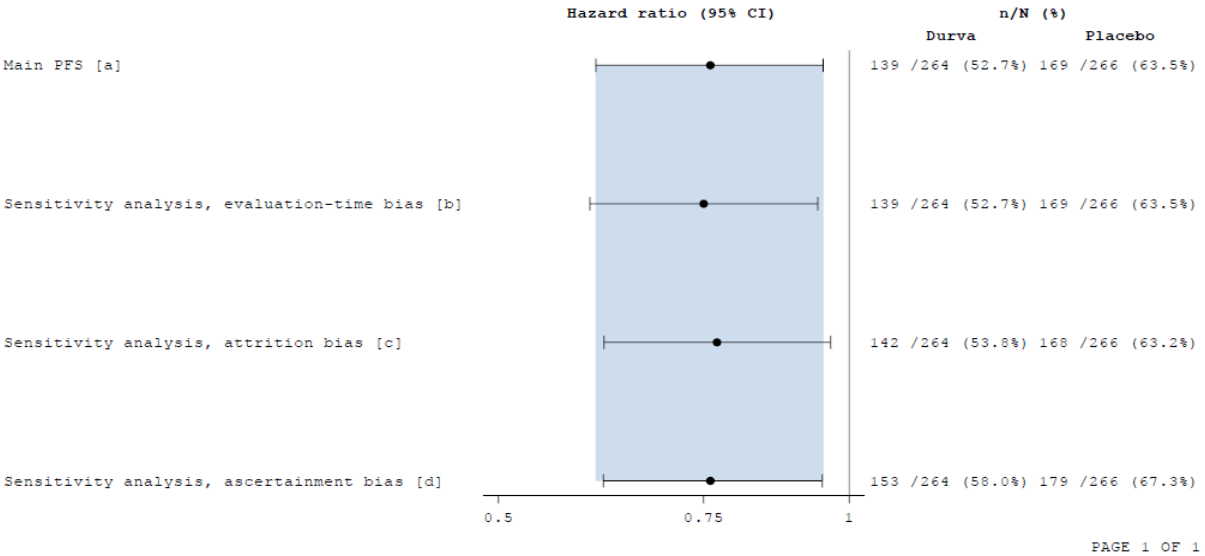
Durva	264	261	248	236	223	207	189	183	172	162	141	110	90	68	51	39	27	19	11	5	1	0	149/264
Placebo	266	260	247	231	214	195	175	164	151	143	123	97	80	62	44	31	23	19	8	5	1	0	120/266

PAGE 1 OF 1

Durva Durvalumab.
CI Confidence interval; OS Overall Survival; One month is calculated as 30.4375 days.
Circle indicates an event observation.

PFS

Figure 15 Progression-free survival, main and sensitivity analyses, forest plot, by analysis method - Durva versus Placebo (Full analysis set)



PAGE 1 OF 1

Forest plot for analyses in Table [a] 14.2.1.1.A, [b] 14.2.1.3.A, [c] 14.2.1.4.1.A, [d] 14.2.1.2.A.
Durva Durvalumab.
CI Confidence interval.
Hazard ratio (Durva versus Placebo) and 95% CI are displayed on a logarithmic scale.
Size of circle is proportional to the number of events.
Grey band represents the 95% CI for the main PFS hazard ratio.

Data cut-off: 15JAN2024

Table 39 Progression-free survival, sensitivity analysis for evaluation-time bias based on BICR assessment according to RECIST 1.1 (Full analysis set)

	Durva (N=264)	Placebo (N=266)
Total events [a], n (%)	139 (52.7)	169 (63.5)
RECIST progression	126 (47.7)	158 (59.4)
Death in absence of progression	13 (4.9)	11 (4.1)
Censored subjects, n (%)	125 (47.3)	97 (36.5)
Censored RECIST progression [b]	0	0
Censored death [c]	18 (6.8)	18 (6.8)
Progression-free at time of analysis	101 (38.3)	74 (27.8)
Lost to follow-up	0	0
Withdrawn consent	6 (2.3)	5 (1.9)
Discontinued study	0	0
Median progression-free survival (months) [d]	15.7	8.3
95% CI for median progression-free survival [d]	10.1, 30.3	6.5, 12.2
Hazard ratio, Durva versus Placebo [e] [g]	0.75	
95% CI for hazard ratio [e]	0.599, 0.940	
2-sided p-value [f]	0.0126	

The midpoint between the time of progression and the previous evaluable RECIST assessment (using the final date of the assessment) are analyzed using a stratified log-rank test, as described for the primary analysis of PFS. Midpoint values resulting in non-integer values are rounded down. For subjects whose death was treated as PFS event, the date of death will be used to derive the PFS time used in the analysis.
Durva Durvalumab.
CI Confidence interval; One month is calculated as 30.4375 days.
Progression is determined by the RECIST-based assessment of the Blinded Independent Central Review (BICR).
[a] Subjects who have not progressed or died, or who progress or die after two or more missed visits are censored at the latest evaluable RECIST assessment, or day 1 if there are no evaluable visits. Subjects with RECIST progression within two visits of baseline who do not have any evaluable visits or do not have a baseline assessment are censored at day 1.
[b] RECIST progression event occurred after two or more missed visits or within two visits of baseline where the subject has no evaluable visits or does not have a baseline assessment.
[c] Death occurred after two or more missed visits in the absence of RECIST progression.
[d] Calculated using the Kaplan-Meier technique. CI for median progression-free survival is derived based on Brookmeyer-Crowley method with log-log transformation.
[e] The hazard ratio and CI were calculated using a stratified Cox proportional hazards model, adjusting for TNM stage (Stage I/II versus III) and receipt of PCI (yes versus no), with treatment as only covariate and ties handled by Efron approach. CIs were calculated using the profile likelihood approach.
[f] The analysis was performed using the stratified log-rank test, adjusting for TNM stage (Stage I/II versus III) and receipt of PCI (yes versus no).
[g] A hazard ratio < 1 favors Durva to be associated with a longer event-free survival than Placebo.
Stratification factors are based on the values entered into the IVRS.
RECIST version 1.1.

Table 40 Progression-free survival, sensitivity analysis for attrition bias based on BICR assessment according to RECIST 1.1 (Full analysis set)

	Durva (N=264)	Placebo (N=266)
Total events [a], n (%)	142 (53.8)	168 (63.2)
RECIST progression	125 (47.3)	156 (58.6)
Death in absence of progression	17 (6.4)	12 (4.5)
Censored subjects, n (%)	122 (46.2)	98 (36.8)
Censored RECIST progression or death	15 (5.7)	19 (7.1)
Progression-free at time of analysis	101 (38.3)	74 (27.8)
Lost to follow-up	0	0
Withdrawn consent	6 (2.3)	5 (1.9)
Discontinued study	0	0
Median progression-free survival (months) [b]	16.8	9.2
95% CI for median progression-free survival [b]	10.9, 31.2	7.4, 13.2
Hazard ratio, Durva versus Placebo [c] [e]	0.77	
95% CI for hazard ratio [c]	0.616, 0.964	
2-sided p-value [d]	0.0226	

The analysis was performed by repeating the primary PFS analysis except that the actual PFS event times, rather than the censored times, of subjects who progressed or died in the absence of progression immediately following two or more non-evaluable tumor assessments are included. In addition, subjects who took subsequent anti-cancer therapy prior to progression or death are censored at their last evaluable assessment prior to taking the subsequent anti-cancer therapy.
Durva Durvalumab.
CI Confidence interval; One month is calculated as 30.4375 days.
Progression is determined by the RECIST-based assessment of the Blinded Independent Central Review (BICR).
[a] Subjects who have not progressed or died are censored at the latest evaluable RECIST assessment, or day 1 if there are no evaluable visits. Subjects who have no evaluable visits or do not have baseline data will be censored at study day 1.
[b] Calculated using the Kaplan-Meier technique. CI for median progression-free survival is derived based on Brookmeyer-Crowley method with log-log transformation.
[c] The hazard ratio and CI were calculated using a stratified Cox proportional hazards model, adjusting for TNM stage (Stage I/II versus III) and receipt of PCI (yes versus no), with treatment as only covariate and ties handled by Efron approach. CIs were calculated using the profile likelihood approach.
[d] The analysis was performed using the stratified log-rank test, adjusting for TNM stage (Stage I/II versus III) and receipt of PCI (yes versus no).
[e] A hazard ratio < 1 favors Durva to be associated with a longer event-free survival than Placebo.
Stratification factors are based on the values entered into the IVRS.
RECIST version 1.1.

Summary of main study

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

Table 41 Summary of efficacy for trial ADRIATIC

Title: A Phase III, Randomized, Double-blind, Placebo-controlled, Multi-centre, International Study of Durvalumab or Durvalumab and Tremelimumab as Consolidation Treatment for Patients with Limited Stage Small-Cell Lung Cancer Who Have Not Progressed Following Concurrent Chemoradiation Therapy (ADRIATIC)		
Study identifier	Study Code: D933QC00001 EudraCT Number: 2018-000867-10 EU CT number: 2023-509602-29-00 NCT Number: NCT03703297	
Design	This is an ongoing, Phase III, randomised, double-blind, placebo-controlled, 3-arm, multi-centre, international study to assess the efficacy and safety of durvalumab monotherapy (D) or durvalumab in combination with tremelimumab (D+T) compared to placebo as consolidation treatment in patients with limited stage small-cell lung cancer (LS-SCLC) whose disease had not progressed following definitive, platinum-based chemotherapy concurrent with radiotherapy (cCRT).	
	Duration of main phase:	27 September 2018 (first patient enrolled) to 15 January 2024 (data cut-off [DCO]; ongoing)
	Duration of Run-in phase:	Not applicable
	Duration of Extension phase:	Not applicable
Hypothesis	Superiority	
Treatments groups	D	Durvalumab (1500 mg intravenously [IV]) every 4 weeks (Q4W) in combination with tremelimumab placebo (IV) Q4W for 4 doses/ cycles each, followed by durvalumab 1500 mg Q4W starting 4 weeks after the final dose of durvalumab in combination with tremelimumab placebo; N = 264
	Placebo	Durvalumab placebo (IV) Q4W in combination with tremelimumab placebo (IV) Q4W for 4 doses/cycles each, followed by durvalumab placebo Q4W starting 4 weeks after the final dose of the 2 placebos in combination; N = 266

	D+T		Durvalumab (1500 mg IV) Q4W in combination with tremelimumab (75 mg IV) Q4W for 4 doses/cycles each, followed by durvalumab 1500 mg Q4W starting 4 weeks after the final dose of durvalumab in combination with tremelimumab; N = 200 The analysis of OS for the D+T vs placebo comparison did not meet the prespecified boundary for declaring statistical significance. Therefore, D+T remains blinded until the next planned analysis and data for the D+T group are not presented in this summary.
Endpoints and definitions	Dual primary endpoints	OS for D vs. placebo	Time from the date of randomisation until death due to any cause.
		PFS for D vs. placebo	Time from the date of randomisation until the date of objective disease progression or death (by any cause in the absence of progression) regardless of whether the patient withdrew from randomised therapy or received another anti-cancer therapy prior to progression, using BICR assessments according to RECIST 1.1.
	Secondary endpoint	Objective response rate (ORR)	Number (%) of patients with at least 1 visit response of complete response (CR) or partial response (PR) (no requirement for confirmation of response). Patients who did not have measurable disease at baseline (i.e., CR after cCRT) were excluded from the analysis. Assessed using BICR assessments according to RECIST 1.1.
	Secondary endpoint	Time from randomisation to second progression or death (PFS2)	Time from the date of randomisation to the earliest of the progression event subsequent to the first subsequent anticancer therapy (excluding radiotherapy) or death
Database lock	12 February 2024		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	The efficacy analyses were conducted on the intent-to-treat (ITT) population (defined as the FAS) as of the DCO of 15 January 2024. The FAS includes all randomised patients. Treatment groups were compared on the basis of randomised study treatment, regardless of the treatment actually received.		
Descriptive statistics and estimate variability	Treatment group	**D**	**Placebo**
	Number of subjects	264	266

	OS (median, months) 95% CI [a]	 55.9 37.3, NR	 33.4 25.5, 39.9
	PFS (median, months) 95% CI [a]	 16.6 10.2, 28.2	 9.2 7.4, 12.9
Effect estimate per comparison	Dual Primary endpoint **OS**	Comparison groups	**D vs Placebo**
		HR [b]	0.73
		95% CI [b]	0.569, 0.928
		2-sided p-value [c]	0.01042 [d]
	Dual Primary endpoint **PFS**	Comparison groups	**D vs Placebo**
		HR [e]	0.76
		95% CI [e]	0.606, 0.950
		2-sided p-value [f]	0.01608 [g]
Notes	a Calculated using the Kaplan-Meier technique. CI for median OS and PFS was derived based on Brookmeyer-Crowley method with log-log transformation. b The HR and CI were calculated using a stratified Cox proportional hazards model, adjusting for receipt of PCI (yes vs no), with treatment as the only covariate and ties handled by Efron approach. CIs were calculated using the profile likelihood approach. c The analysis was performed using the stratified log-rank test, adjusting for receipt of PCI (yes vs no). d The boundary for declaring statistical significance was 1.679% for a 4.5% overall alpha. e The HR and CI were calculated using a stratified Cox proportional hazards model, adjusting for TNM stage (Stage I/II vs III) and receipt of PCI (yes vs no), with treatment as the only covariate and ties handled by Efron approach. CIs were calculated using the profile likelihood approach. f The analysis was performed using the stratified log-rank test, adjusting for TNM stage (Stage I/II vs III) and receipt of PCI (yes vs no). g The boundary for declaring statistical significance was 2.805% for a 5% overall alpha.		
Analysis description	**Secondary analysis**		
Descriptive statistics and estimate variability	Treatment group	**D**	**Placebo**
	Number of patients	264	266
	ORR (number [%] of patients with a response) [a] 95% CI [a]	53 (30.3) 23.6, 37.7	54 (32.0) 25.0, 39.6
	PFS2 (median, months) [b] 95% CI [b]	NR NR, NR	37.6 25.3, NR
Effect estimate per comparison [d]		Comparison groups	**D vs Placebo**
	ORR	Difference in proportion (%) [e]	-1.2

		95% CI [e]	-11.0, 8.5
		Comparison groups	**D vs Placebo**
	PFS2	HR [f]	0.66
		95% CI [f]	0.495, 0.880
Notes	a	Patients who did not have measurable disease at baseline (i.e., CR after cCRT) were excluded from the analysis. Patients who discontinued treatment without progression, received a subsequent anti-cancer therapy, and then responded were not included as responders.	
	b	Calculated using the Kaplan-Meier technique. CI for median was derived based on Brookmeyer-Crowley method with log-log transformation.	
	c	Calculated using the Kaplan-Meier technique. CI derived based on a log(-log(.)) transformation.	
	d	No effect estimates were performed for DoR, OS24, OS36, PFS18, or PFS24.	
	e	The analysis was performed using a Cochran-Mantel-Haenszel test stratified by TNM stage (Stage I/II vs III) and receipt of PCI (yes vs no). CIs were calculated using Miettinen and Nurminen's method.	
	f	The HR and CI were calculated using a stratified Cox proportional hazards model, adjusting for TNM stage (Stage I/II vs III) and receipt of PCI (yes vs no), with treatment as the only covariate and ties handled by Efron approach. CIs were calculated using the profile likelihood approach.	

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

Not applicable.

Clinical studies in special populations

Table 42 Clinical studies in special populations

	Controlled Trials	Non-controlled trials
Severe renal impairment* patients (Subjects number /total number)	Durvalumab = 0/262	NA
Moderate or severe hepatic impairment** patients (Subjects number /total number)	Durvalumab = 0/262	NA
Paediatric patients <18 years (Subjects number /total number)	Durvalumab = 0/262 Placebo = 0 /265	NA
Older patients; Age 65-74 (Subjects number /total number)	Durvalumab = 88/262 Placebo = 86 /265	NA
Age 75-84 (Subjects number /total number)	Durvalumab = 15/262 Placebo = 18 /265	NA
Age 85+ (Subjects number /total number)	Durvalumab = 0/262 Placebo = 0 /265	NA

*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.
**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).

Supportive study(ies)

Not applicable.

2.4.3. Discussion on clinical efficacy

Durvalumab (Imfinzi) is an anti-PD-L1 antibody already approved as monotherapy or in combination for different cancers, mostly in the advanced setting. Based on results from the pivotal trial ADRIATIC (study D933QC00001), the MAH is seeking the following extension of indication:

IMFINZI is indicated for the treatment of patients with limited stage small-cell lung cancer (LS-SCLC) whose disease has not progressed following platinum-based chemoradiation therapy.

Design and conduct of clinical studies

The evidence of efficacy pertinent to the proposed indication is solely based on the ADRIATIC study: an ongoing, Phase III, randomized, double-blind, placebo-controlled, 3-arm, multi-centre study which aimed to assess the efficacy and safety of durvalumab monotherapy(D) or durvalumab in combination with tremelimumab (D+T) compared to placebo as consolidation treatment in patients with limited stage small-cell lung cancer (LS-SCLC) whose disease had not progressed following definitive, platinum-based chemotherapy concurrent with radiotherapy.

The design of the study was discussed in a scientific advice, which was generally followed, except for not allowing inclusion of patients with PS2 after cCRT.

Approximately 724 patients were randomised in a 1:1:1 ratio to three treatment groups: Durvalumab monotherapy, placebo, or Durvalumab with Tremelimumab. After 600 patients were randomized, the remaining patients were assigned in a 1:1 ratio to either Durvalumab monotherapy or placebo.

Randomization was stratified by TNM stage (I/II vs. III) and receipt of PCI.

The in- and exclusion criteria from the ADRIATIC study are considered adequate and reflect the target population with LS-SCLC for consolidation treatment with durvalumab. Inclusion of patients with SD after cCRT could be considered of concern, as those patients have a higher risk of recurrence/disease progression and might require an earlier intervention (such as consolidation chemotherapy) than those with a good response to cCRT. Delaying treatment for this group (i.e. by offering them placebo) could result in inferior outcomes, i.e. loss of chance. Durvalumab was administered at one of its approved fixed doses of 1500mg every 4 weeks, for a maximum of 24 months in the absence of progression/unacceptable toxicity. This is endorsed and sufficiently reflected in sections 4.2 and 5.1 of the SmPC.

The provided justification for the duration of treatment is acceptable, since based on the literature a high probability of relapse within 2 years of diagnosis is expected and an anticipated PFS of 10-15 months following cCRT. The choice of placebo as the comparator arm for D and D+T arms is well justified and endorsed, as the standard approach for patients is this clinical setting is surveillance only.

The overall methodology on cross over, dose delays, prohibited medications and other procedures is endorsed.

Statistical methods: ADRIATIC has dual primary objectives which were to assess the efficacy of durvalumab monotherapy compared to placebo in terms of PFS per RECIST 1.1 as assessed by BICR, and OS. The choice of primary endpoints is relevant for this setting and supported. The use of BICR mitigates intrinsic bias and is supported. No crossover between treatment arms was allowed, strengthening the objectiveness of the primary endpoints.

In both treatment arms, 18 deaths were initially censored, which could have potentially inflated the PFS estimate. However, a sensitivity analysis for attrition bias was conducted, in which these censored deaths were reclassified as events using the actual time of death, addressing this issue.

The PFS and OS analysis was conducted using a stratified log-rank test, adjusting for TNM stage and receipt of PCI. Hazard ratios were estimated with a stratified Cox proportional hazards model, and confidence intervals were provided. Multiple sensitivity analyses were performed to address potential biases, including evaluation-time, attrition, and ascertainment biases. Three additional sensitivity analyses (RMST, censoring subsequent anticancer therapy, and RPSFTM) to support the robustness of the primary results for OS and PFS.

The removal of TNM stratification for OS was due to fewer than 5 events in one stratum and used PCI only for stratification. The multiplicity was designed using a hierarchical testing procedure with alpha recycling to control the family-wise error rate at 5% for the dual primary and key secondary endpoints. The initial alpha level for PFS was set at a very stringent 0.5%, which likely contributed to its initial failure to reach significance. Following this, the alpha was recycled from the significant OS result, allowing PFS to be re-tested under less stringent conditions, ultimately leading to its significance. Although this approach is consistent with EMA guidelines, it raises considerations about the robustness of the PFS finding, given the initial non-significance under the more conservative alpha allocation. However, the key secondary endpoint of PFS comparing the combo group and placebo was not tested because the key secondary endpoint of OS for the combo group did not meet the significance threshold. Consequently, the demonstration of the key secondary endpoints failed, and all other secondary endpoints and subgroup analyses were not alpha-adjusted, rendering them exploratory rather than confirmatory.

Results: 730 patients were randomised in the recruitment period: 264 were randomized to the D group, 200 to the D+T group, and 266 to the placebo group. As expected, the majority of patients not randomized were due to screening failures (88%), whereas the rest were due to subject withdrawing IC or death. The most common reasons for screening failure in ADRIATIC were for receiving inappropriate cCRT regimen, lack of response to chemoradiation, insufficient organ or bone marrow function and brain metastasis or spinal cord compressions. A very low number of patients (1 patient in each arm) did not receive the allocated treatment.

The original protocol of ADRIATIC study was amended 4 times. The most relevant amendment (Amendment 3, November 2020) was implemented during while enrolment was ongoing and more than 3 years before the first IA. The D+T arm was closed for enrolment as per the initial statistical plan (after 200 patients were randomized to D+T). OS for D vs Placebo arm had been added to the primary endpoint, so the study had dual primary endpoints (OS and PFS by BICR for D vs Placebo). The justification for this amendment was based on external data (CASPIAN, STIMULI, CHECKMATE-451 and CHECKMATE-032 studies) indicating that efficacy gains by the addition of CTLA-4A inhibition might be limited. Especially, a planned IA of CASPIAN study demonstrated statistically significant improvement in OS for D+EP vs EP alone (HR: 0.73, 95% CI: 0.59, 0.91; p = 0.0047) in ES-SCLC. The combination of D+T+EP compared to EP alone did not meet the efficacy boundary for statistical significance for OS at this IA and remained blinded until the final analysis (Paz-Ares et al 2019). The rationale for refocusing the primary objective of ADRIATIC study on durvalumab versus placebo comparison only is acceptable, since the results of all the above-mentioned studies were published before the implementation of protocol changes. To maintain the power of the study due to adjustment in statistical assumptions (new target HR for OS and PFS), the sample size was increased by 124 patients (to be allocated to the Durvalumab and Placebo arms only). The MAH claimed that the study integrity and double blinding were maintained. In addition, the study team did not have access to aggregate summaries with treatment group allocation before the first IA review. The provided justification is considered acceptable.

Major protocol deviations were nearly balanced between arms: ~17% in the D arm vs. ~12% in the Placebo arm. This small difference is driven by inclusion and exclusion criteria violations (22 patients in

the D arm vs. 11 in the Placebo arm) and drug administration (12 patients in the D arm vs. 7 in the Placebo arm).

Importantly, study conduct deviations (e.g. missing baseline assessments) were infrequent in both arms. Overall, it is considered unlikely that study integrity was affected by major protocol deviations.

The demographic and clinical characteristics of the patients at baseline were generally balanced in both arms of ADRIATIC and are considered representative of the overall patient population with LS-SCLC in Europe. The median age was 62 years (range: 28 to 84), 70% of the patients were men and most were white (50%) or Asian (48%). A slightly higher number of patients had ECOG PS 1 in the Placebo arm compared to D arm (140 pts vs. 132 in the D arm), albeit it is anticipated that the results of ADRIATIC study should not have been influenced by this minor imbalance. A majority of patient (88%) had stage III disease, followed by stage II (9%) and stage I disease (3%). Initially it was planned to cap inclusion of stage III patients to 85% of study population, however this requirement was removed with the amendment 3, as the MAH expected to enrol sufficient number of patients with stage I/II. Overall, the distribution of stages is representative of the population with LS-SCLC. The majority of patients in both groups received 4 cycles of chemotherapy with cisplatin and etoposide. Most patients in ADRIATIC received once daily radiotherapy, now perceived as inferior to the twice daily regimen, this category was balanced between both arms, and thus not expected to have favoured either. PCI regimen has been used in ~54% across treatment arms. Noticeably, this is somehow lower than excepted, in light that nearly 86% of patients achieved good response to cCRT (CR+PR) and PCI is recommended in this setting, unless contraindicated or in stage I (NCCN and ESMO guidelines, Dingemans et al 2021). Nevertheless, since ADRIATIC was a global study and the use of PCI was based on local guidelines, this acceptable.

Efficacy data and additional analyses

At the data cut-off on 15 January 2024, and with a median follow-up of ~31 months and OS maturity of 43.6% in the D arm (115 events), treatment with Durvalumab resulted in 23 months of median survival benefit compared to placebo in LS- SCLC (HR 0.73, 95% CI 0.569, 0.928; p=0.01). The KM curves separate about 6 months from the randomization and remain separated. The pattern of late separation in survival KM curves has been known for checkpoint inhibitors and does not raise any concerns. To note, mOS of the placebo arm is longer than historically described. In the CONVERT study, the mOS was around 25 months for patients who received once daily cCRT and the mOS was 30 months for twice daily schedule (Faivre-Finn et all, 2017). The use of immunotherapy after progression (16% of patients in the placebo arm) might have contributed to the observed longer mOS in ADRIATIC and this is overall acceptable. The practice of censoring at the last date known to be alive if death is not confirmed is acknowledged. In conclusion the OS benefit of D, in addition to being statistically significant, is of a high clinical value: currently there are no approved therapies in this setting with a high unmet medical need for consolidation therapy for patients with LS-SCLC with a response to cCRT.

Regarding PFS, 139 and 169 PFS events occurred in the D and Placebo arm, respectively. Median follow-up of PFS was 9 and 7.4 months. As per blinded evaluation of images, D was superior to placebo to prevent progression or death in patients with LS-SCLC. With 52.7% of PFS events in the D arm and 63.5% in the Placebo arm, the HR for PFS was 0.76 (95% CI 0.606, 0.95; p=0.016), noting mPFS of 16.6 months in the D arm vs. 9.2 months in the Placebo arm. The K-M curves separate as of the fourth month from randomisation and remain separated. More patients were censored in D arm (125/264 in D arm vs. 97/266) compared to placebo; the most common reason being lack of documented progression (101/125 patients in the D arm vs. 74/97 in the placebo arm). Other causes of censoring were balanced between arms. Overall, PFS censoring was in line with EMA guidelines and it is reassuring that it was fairly balanced between groups.

Interestingly, the mPFS of placebo arm is nearly 5 months shorter than expected based on the historical data from phase III studies CONVERT and RTOG 0538 (Faivre-Finn et all, 2017; Bogart et al, 2023). The reason behind this phenomenon is unclear, given that the two treatment groups' demographics, baseline disease and treatments (use of cCRT, PCI) were generally well balanced. This issue will not be pursued further, as mPFS reflects the prognosis of patients enrolled in the pivotal study. Slightly more patients in the Placebo arm compared to the D arm (135 vs 115, respectively) developed new lesions. Overall, the patterns of the disease's spread are as expected in SCLC, especially in light of the fact that PCI was used for about half of study population and patients with SD after cCRT were included. The rates of progression as assessed by the Investigator but not central review (14.4% vs 11.7%) and progression as assessed by BICR but not the Investigator (8.3% vs 6.4%) were similar (data not shown). Results of PFS by investigator were overall corresponding to those reported by BICR.

Similar rates of objective ORR by BICR were observed across the two arms of ADRIATIC. The best achieved response was a stable disease for most patients, CR rates were similar between groups. The duration of response in responders was ~ 10 months longer in the D arm compared to placebo, supporting the observed OS benefit from this arm vs. placebo. Time to second progression or death (PFS2) was not reached in the D arm compared to 37.6 months in the placebo arm, respectively.

PRO data was collected using the EORTC QLQ-C30 questionnaire and the EORTC QLQ-LC13 questionnaire. No clinically meaningful differences in the key PRO endpoints were observed between treatment arms.

Overall, subgroup analyses for OS and PFS were generally consistent with the primary analysis, except for the subgroups of "patients with ≥ 84 days from last dose of radiotherapy to randomization in this study", "patients with WHO PS 1 at baseline" and "Asian race" (PFS only). KM curves for OS for patients with baseline PS 1 are overlapping until the timepoint of 33 months while early separation of curves (around 3 months) is observed for the subgroup with baseline PS 0. Interestingly, mOS is 5.2 months shorter for the placebo arm in the subgroup of PS 0, which is rather unexpected. It is agreed that PS is a dynamic variable, which may change during the treatment course. In addition, the higher PS (PS 1) at baseline in ADRIATIC can also be an indicator of unresolved toxicity from the chemoradiation, therefore the observed results for PFS and OS based on baseline PS are not fully reliable and might be a "chance" finding, also in light of lack of strategies to control for type I error. A comparison of mPFS in Asian and non-Asian subgroups reveals that the placebo arm performs poorly in the non-Asian subgroup (nearly 7 months shorter) resulting in greater benefit of durvalumab in the non-Asian population. As mentioned earlier, it is not fully understood why the underperformance of placebo is observed in ADRIATIC. This might reflect the prognosis of patients enrolled in the pivotal study and cannot be solved. The observed benefit in terms of mOS regardless of race outweighs the uncertainties about the results of PFS.

In patients with primary stage I/II, the reported OS was: HR: 1.02; (95% CI: 0.482, 2.158), the apparent absence of effect on OS in this population could be explained by the need for longer follow-up to detect a survival benefit, since these patients are expected to have a good prognosis. This is agreed, as based on the literature, the mean survival for inoperable stage I and II is ~ 20 months (Doerr et al, 2022). The number of events in this subgroup was low and the CI is wide and, therefore, no conclusions can be drawn. Since the sample size is small, the distribution of stages I and II is representative of the overall patient population with LS-SCLC and there is a high unmedical need for the improvement of outcomes for patients with inoperable stage I/II, the justification and this uncertainty are accepted.

No clear benefit with durvalumab was observed for either OS (HR: 1.02; 95% CI:0.578, 1.750) or PFS (HR: 1.18; 95% CI: 0.698, 1.962) in patients with ≥ 84 days from last dose of radiotherapy, given as

a part of cCRT, to randomization in the pivotal study. From an ad hoc analysis of baseline characteristics of this subgroup in comparison to ITT (data not shown), some differences between these two groups were noted: a greater proportion of patients in the subgroup had received cisplatin (87.0% vs 66.2% in ITT, respectively), twice daily RT (72.2% vs 27.9%), and PCI (72.2% vs 53.8%). The median durations from last RT dose and from last cCRT to randomization were 100.0 days and 36.0 days, respectively, in this subgroup, which were longer than those for the ITT population (58.0 days and 30.0 days, respectively). The MAH justified that the lack of observed OS and PFS benefit is attributed to the longer recovery time from the initial treatment's toxicities leading to *"missing the potentially optimal timing for durvalumab consolidation following cCRT"*. This is partially agreed on as the subgroup had received the most intensive treatment regimen and a longer recovery time from toxicities of both cCRT and PCI would be expected, albeit this subgroup represents the clinical practice for the most fit patients with LS-SCLC and the lack of OS and PFS benefit raised initial concerns. Upon request from the CHMP, the MAH provided supplementary discussion about the observed findings, claiming that there was a high degree of uncertainty in the HR estimates, expressed by the wide CIs and related to the small size of subgroup and imbalanced number of patients in the treatment arms. In addition, mPFS and mOS of placebo arm was longer compared to ITT, which would lead to a relative underperformance of the durvalumab arm in this subgroup. The CHMP endorsed this argumentation, however there was some remaining uncertainty about the effect of the durvalumab maintenance in the most fit patients receiving the ESMO guidelines preferred standard of treatment (bid cCRT+PCI), which cannot be accurately estimated from the results of the ADRIATIC study. In conclusion, the results in subgroup analyses were in general consistent with the primary analysis and the observed uncertainties in some subgroups are accepted due to the small sample size and the lack of multiplicity control.

Testing of PD-L1 status was not required for randomization and was available for ~63% of the study population. A validated assay (SP263) was used to assess the PD-L1 positivity both on tumour and immune cells. Among the patients with an evaluable tissue sample, 55% (182/333) had a high PD-L1 status (TC or IC ≥ 1%). This is considered acceptable and in line with the literature described incidence of PD-L1 positivity in SCLC (Acheampong et al, 2020).

The OS and PFS benefits of consolidation treatment with durvalumab are observed regardless of PD-L1 status in the prespecified threshold. Nevertheless, the magnitude of effect differs between patients with tumours having high and low PD-L1 expression (mOS benefit NR for high PD-L1 vs. 3 months in the low, respectively). This lower magnitude of effect is still of a high clinical importance in this disease setting. The additional analyses for OS and PFS for the cut-offs of 5, 10, 25, 50% confirmed that PFS and OS benefit is observed regardless of PD-L1 expression. Similarly the trend toward longer PFS and OS is observed with higher PD-L1 expression, however 3 months of PFS and OS benefit observed for patients with PD-L1 <1% is considered to be clinically relevant. Furthermore, the small sample size of subgroups and the exploratory nature of analyses prevent from making any conclusions.

In conclusion, the results in subgroup analyses were in general consistent with the primary analysis and the observed uncertainties in some subgroups are accepted due to small sample size and lack of multiplicity control.

The RMST analysis (data not shown), which does not rely on the proportional hazards assumption, showed consistent and statistically significant improvements in OS (+3.31 months; p=0.0150) and PFS (+3.55 months; p=0.0098). Sensitivity analyses censoring subsequent therapy confirmed the consistency for PFS (HR=0.76) but showed reduced precision for OS (HR=0.86; 95% CI: 0.571, 1.299) due to censoring bias and decreased data maturity. The RPSFTM analysis demonstrated consistent HR estimates across methods, further confirming that subsequent therapy had minimal impact on the primary results.

Sensitivity analyses incorporating both TNM and PCI, as well as PCI alone, confirmed the consistent and statistically significant results for both OS and PFS.

Overall results of sensitivity analyses are reassuring.

Wording of the indication:

Overall, the proposed wording of the indication reflects the study population of ADRIATIC. One amendment was proposed by the CHMP and accepted by the MAH. The final indication states:

*Imfinzi **as monotherapy** is indicated for the treatment of adults with limited-stage small cell lung cancer (LS-SCLC) whose disease has not progressed following platinum-based chemoradiation therapy.*

2.4.4. Conclusions on the clinical efficacy

The primary analysis of the study ADRIATIC showed statistically significant and clinically relevant improvements in survival and PFS from consolidation treatment with durvalumab in patients with LS SCLC who responded to cCRT.

2.5. Clinical safety

Introduction

Durvalumab is a human IgG1 kappa mAb that binds to PD-L1 and blocks the interaction of PD-L1 with PD-1 and CD80 (B7.1). The most important risks associated with the anti-PD-1/PD-L1 drug class are considered to be immune-mediated.

The pivotal safety dataset is based on the PFS-IA/OS-IA1 analysis (DCO 15 January 2024) from ADRIATIC, an ongoing, Phase III, randomized, double-blind, placebo-controlled, 3-arm, multi-centre, international study.

For a more thorough description of the pivotal study (ADRIATIC) see the Clinical Efficacy section.

D Pan-tumour Pool: Comprises safety data from 4642 patients in 15 (14 completed and ADRIATIC ongoing) individual studies which included durvalumab monotherapy treatment groups. This population consists of all patients from the pool of studies in which patients received at least one dose of durvalumab monotherapy given at a dose of 1500 mg Q4W or equivalent dose of either 10 mg/kg Q2W IV or 20 mg/kg Q4W IV for any line of therapy (across tumour types), which is considered as equivalent to the 1500 mg Q4W dosage.

The safety data from the ADRIATIC study are presented alongside the D Pan-tumour Pool data allowing for a comparative assessment using the largest safety pool available for durvalumab monotherapy.

The list of studies contributing to the safety pool is described in Table 1 Tabular overview of clinical studies.

Patient exposure

Table 43 Summary of Study Treatment Exposure in ADRIATIC and the D Pan-tumour Pool (Safety Analysis Set)

Parameter	ADRIATIC		Pan-tumour Pool
	D (N = 262)	Placebo (N = 265)	D (N = 4642)
Total treatment duration (weeks) [a]			
Mean (SD)	54.48 (40.087)	48.99 (38.256)	32.79 (39.096)
Median (min, max)	40.00 (4.0, 108.0)	35.86 (4.0, 108.1)	18.00 (0.4, 300.0)
Patient-years exposure	273.6	248.8	2917.5
Total treatment duration (weeks) [a]; n (%)			
≥ 16	201 (76.7)	197 (74.3)	2596 (55.9)
≥ 24	173 (66.0)	165 (62.3)	2034 (43.8)
≥ 52	114 (43.5)	107 (40.4)	1017 (21.9)
≥ 76	102 (38.9)	80 (30.2)	427 (9.2)
≥ 104	46 (17.6)	41 (15.5)	286 (6.2)

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

Patient Year exposure = Total treatment duration (years) summed across all patients within a group. Where treatment duration (years) = (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 Q4W, X = 27.

Baseline data

Table 44 Demographic and Baseline Characteristics in ADRIATIC and the D Pan-tumour Pool (Safety Analysis Set)

Parameter	Number of Patients (%)		
	ADRIATIC		Pan-tumour Pool
	D (N = 262)	Placebo (N = 265)	D (N = 4642)
Age (years)			
n	262	265	4642
Mean	61.8	61.2	61.9
SD	8.93	9.41	10.69
Median	62.0	62.0	63.0
Min	28	28	19
Max	84	79	96
Age group (years), n (%)			
< 50	21 (8.0)	26 (9.8)	537 (11.6)
≥ 50 to < 65	138 (52.7)	135 (50.9)	2089 (45.0)
≥ 65 to < 75	88 (33.6)	86 (32.5)	1542 (33.2)
≥ 75	15 (5.7)	18 (6.8)	474 (10.2)

Parameter	Number of Patients (%)		
	ADRIATIC		Pan-tumour Pool
	D (N = 262)	Placebo (N = 265)	D (N = 4642)
Sex, n (%)			
Male	178 (67.9)	187 (70.6)	3229 (69.6)
Female	84 (32.1)	78 (29.4)	1413 (30.4)
Race, n (%)			
White	128 (48.9)	137 (51.7)	2892 (62.3)
Black/African American	1 (0.4)	3 (1.1)	85 (1.8)
Asian	131 (50.0)	121 (45.7)	1514 (32.6)
Other	2 (0.8)	4 (1.5)	74 (1.6)
Missing	0	0	77 (1.7)
Geographic region, n (%)			
Asia	129 (49.2)	120 (45.3)	1422 (30.6)
Europe	94 (35.9)	112 (42.3)	1924 (41.4)
North America	37 (14.1)	30 (11.3)	1246 (26.8)
South America	2 (0.8)	3 (1.1)	50 (1.1)
Non-Asia Regions	133 (50.8)	145 (54.7)	3220 (69.4)
Baseline ECOG/WHO PS, n (%) [a]			
0	131 (50.0)	131 (49.4)	1845 (39.7)
≥ 1	131 (50.0)	134 (50.6)	2792 (60.1)
Missing	0	0	5 (0.1)

a. ADRIATIC, 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.

Adverse events

Table 45 Overview of AEs by Category in ADRIATIC and the D Pan-tumour Pool (Safety Analysis Set)

AE category	Number (%) of patients [a]		
	ADRIATIC		Pan-tumour Pool
	D (N = 262)	Placebo (N = 265)	D (N = 4642)
Any AE	247 (94.3)	234 (88.3)	4381 (94.4)
Any AE causally related to any study treatment [b]	176 (67.2)	129 (48.7)	2711 (58.4)
Any AE causally related to durvalumab/placebo [b]	176 (67.2)	129 (48.7)	2711 (58.4)
Any AE of maximum CTCAE Grade 3 or 4 [c]	64 (24.4)	64 (24.2)	1782 (38.4)

AE category	Number (%) of patients [a]		
	ADRIATIC		Pan-tumour Pool
	D (N = 262)	Placebo (N = 265)	D (N = 4642)
Any AE of maximum CTCAE Grade 3 or 4, causally related to any study treatment [b, c]	23 (8.8)	16 (6.0)	540 (11.6)
Any AE of maximum CTCAE Grade 3 or 4, causally related to durvalumab/placebo [b, c]	23 (8.8)	16 (6.0)	540 (11.6)
Any AE with outcome of death	7 (2.7)	5 (1.9)	275 (5.9)
Any AE with outcome of death, causally related to any study treatment [b]	2 (0.8)	0	37 (0.8)
Any AE with outcome of death, causally related to durvalumab/placebo [b]	2 (0.8)	0	37 (0.8)
Any SAE (including events with outcome of death) [d]	78 (29.8)	64 (24.2)	1657 (35.7)
Any SAE (including events with outcome of death), causally related to any study treatment [b, d]	32 (12.2)	17 (6.4)	370 (8.0)
Any SAE (including events with outcome of death), causally related to durvalumab/placebo [b, d]	32 (12.2)	17 (6.4)	370 (8.0)
Any AE leading to discontinuation of any study treatment	43 (16.4)	28 (10.6)	489 (10.5)
Any AE leading to discontinuation of durvalumab/placebo	43 (16.4)	28 (10.6)	489 (10.5)
Any AE leading to discontinuation of any study treatment, causally related to any study treatment [b]	30 (11.5)	15 (5.7)	234 (5.0)
Any AE leading to discontinuation of durvalumab, causally related to durvalumab/placebo [b]	30 (11.5)	15 (5.7)	234 (5.0)
Any AE leading to dose modification of any study treatment [e]	91 (34.7)	76 (28.7)	1295 (27.9)
Any AE leading to dose delay or interruption of any study treatment [f]	91 (34.7)	76 (28.7)	1286 (27.7)
Any AE leading to dose delay or interruption of durvalumab/placebo [f]	91 (34.7)	76 (28.7)	1286 (27.7)

a. Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories.
b. As assessed by the Investigator. Missing responses are counted as related.
c. Maximum CTCAE Grade of 3 or 4 is derived for each patient/treatment period/event and excludes patients who experienced Grade 3 or 4 events with a Grade 5 event.
d. Seriousness, as assessed by the Investigator. An AE with missing seriousness is considered serious.
e. Includes AEs on the AE CRF form with action taken indicating dose reduction, dose delay or dose interruption, and AEs meeting study-level dose delay definitions, where applicable.
f. Includes AEs on the AE CRF form with action taken indicating dose delay or dose interruption, and AEs meeting study-level dose delay definitions, where applicable.

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

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

MedDRA version 26.1, CTCAE version 4.03.

Common adverse events

The most commonly reported AEs in the D group were radiation pneumonitis (22.9%), decreased appetite (16.8%), hypothyroidism (16.0%) and cough (15.3%). The most commonly reported AEs in

the placebo group were radiation pneumonitis (23.4%), headache (13.2%), and fatigue and decreased appetite (12.8% each).

The common AEs (≥ 5% in either group) that were reported at a higher frequency (≥ 5 percentage points) in the D group compared to the placebo group were: hypothyroidism (16.0% vs 3.8%, respectively), pruritus (13.0% vs 7.2%), and hyperthyroidism (10.3% vs 1.5%), all of which are known ADRs for durvalumab.

The only AE reported in ≥ 20% of patients by PT in both treatment groups was radiation pneumonitis (22.9% in the D group; 23.4% in the placebo group) consistent with expectations in patients with LS-SCLC who had received prior cCRT.

Table 46 AEs and Event Rate Occurring in at Least 5% of Patients in Any Treatment Group in ADRIATIC by SOC and PT and Corresponding Frequency and Rate in the D Pan-tumour Pool (Safety Analysis Set)

	ADRIATIC				Pan-tumour Pool	
	D (N = 262)		Placebo (N = 265)		D (N = 4642)	
SOC/MedDRA PT	Number (%) of patients [a]	Event rate (per 100 pt years) [b]	Number (%) of patients [a]	Event rate (per 100 pt years) [b]	Number (%) of patients [a]	Event rate (per 100 pt years) [b]
Patients with any AE	247 (94.3)	90.3	234 (88.3)	94.1	4381 (94.4)	150.2
Infections and infestations	99 (37.8)	36.2	87 (32.8)	35.0	1770 (38.1)	60.7
COVID-19	18 (6.9)	6.6	17 (6.4)	6.8	27 (0.6)	0.9
Pneumonia	29 (11.1)	10.6	20 (7.5)	8.0	383 (8.3)	13.1
Upper respiratory tract infection	8 (3.1)	2.9	14 (5.3)	5.6	247 (5.3)	8.5
Blood and lymphatic system disorders	30 (11.5)	11.0	24 (9.1)	9.6	819 (17.6)	28.1
Anaemia	23 (8.8)	8.4	16 (6.0)	6.4	629 (13.6)	21.6
Endocrine disorders	65 (24.8)	23.8	15 (5.7)	6.0	683 (14.7)	23.4
Hyperthyroidism	27 (10.3)	9.9	4 (1.5)	1.6	215 (4.6)	7.4
Hypothyroidism	42 (16.0)	15.4	10 (3.8)	4.0	472 (10.2)	16.2
Metabolism and nutrition disorders	88 (33.6)	32.2	66 (24.9)	26.5	1727 (37.2)	59.2
Decreased appetite	44 (16.8)	16.1	34 (12.8)	13.7	880 (19.0)	30.2
Psychiatric disorders	31 (11.8)	11.3	27 (10.2)	10.9	705 (15.2)	24.2
Insomnia	16 (6.1)	5.8	13 (4.9)	5.2	340 (7.3)	11.7
Nervous system disorders	77 (29.4)	28.1	76 (28.7)	30.5	1190 (25.6)	40.8
Dizziness	32 (12.2)	11.7	20 (7.5)	8.0	283 (6.1)	9.7
Headache	24 (9.2)	8.8	35 (13.2)	14.1	353 (7.6)	12.1
Respiratory, thoracic and mediastinal disorders	122 (46.6)	44.6	87 (32.8)	35.0	1956 (42.1)	67.0

Table 46 AEs and Event Rate Occurring in at Least 5% of Patients in Any Treatment Group in ADRIATIC by SOC and PT and Corresponding Frequency and Rate in the D Pan-tumour Pool (Safety Analysis Set)

	ADRIATIC				Pan-tumour Pool	
	D (N = 262)		Placebo (N = 265)		D (N = 4642)	
SOC/MedDRA PT	Number (%) of patients [a]	Event rate (per 100 pt years) [b]	Number (%) of patients [a]	Event rate (per 100 pt years) [b]	Number (%) of patients [a]	Event rate (per 100 pt years) [b]
Cough	40 (15.3)	14.6	32 (12.1)	12.9	712 (15.3)	24.4
Dyspnoea	25 (9.5)	9.1	18 (6.8)	7.2	638 (13.7)	21.9
Pneumonitis	28 (10.7)	10.2	16 (6.0)	6.4	172 (3.7)	5.9
Gastrointestinal disorders	111 (42.4)	40.6	101 (38.1)	40.6	2421 (52.2)	83.0
Constipation	27 (10.3)	9.9	26 (9.8)	10.5	710 (15.3)	24.3
Diarrhoea	29 (11.1)	10.6	22 (8.3)	8.8	702 (15.1)	24.1
Nausea	33 (12.6)	12.1	29 (10.9)	11.7	739 (15.9)	25.3
Vomiting	12 (4.6)	4.4	18 (6.8)	7.2	453 (9.8)	15.5
Skin and subcutaneous tissue disorders	81 (30.9)	29.6	60 (22.6)	24.1	1444 (31.1)	49.5
Pruritus	34 (13.0)	12.4	19 (7.2)	7.6	513 (11.1)	17.6
Rash	28 (10.7)	10.2	16 (6.0)	6.4	452 (9.7)	15.5
Musculoskeletal and connective tissue disorders	73 (27.9)	26.7	87 (32.8)	35.0	1640 (35.3)	56.2
Arthralgia	18 (6.9)	6.6	29 (10.9)	11.7	574 (12.4)	19.7
Back pain	17 (6.5)	6.2	20 (7.5)	8.0	474 (10.2)	16.2
General disorders and administration site conditions	89 (34.0)	32.5	84 (31.7)	33.8	2413 (52.0)	82.7
Asthenia	26 (9.9)	9.5	20 (7.5)	8.0	529 (11.4)	18.1
Fatigue	32 (12.2)	11.7	34 (12.8)	13.7	1052 (22.7)	36.1
Investigations	73 (27.9)	26.7	56 (21.1)	22.5	1504 (32.4)	51.6

Table 46 AEs and Event Rate Occurring in at Least 5% of Patients in Any Treatment Group in ADRIATIC by SOC and PT and Corresponding Frequency and Rate in the D Pan-tumour Pool (Safety Analysis Set)

	ADRIATIC				Pan-tumour Pool	
	D (N = 262)		Placebo (N = 265)		D (N = 4642)	
SOC/MedDRA PT	Number (%) of patients [a]	Event rate (per 100 pt years) [b]	Number (%) of patients [a]	Event rate (per 100 pt years) [b]	Number (%) of patients [a]	Event rate (per 100 pt years) [b]
Alanine aminotransferase increased	15 (5.7)	5.5	13 (4.9)	5.2	299 (6.4)	10.2
Weight decreased	19 (7.3)	6.9	11 (4.2)	4.4	350 (7.5)	12.0
White blood cell count decreased	18 (6.9)	6.6	11 (4.2)	4.4	54 (1.2)	1.9
Injury, poisoning and procedural complications	78 (29.8)	28.5	80 (30.2)	32.2	602 (13.0)	20.6
Radiation pneumonitis	60 (22.9)	21.9	62 (23.4)	24.9	163 (3.5)	5.6

a. Number (%) of patients with AEs, sorted by international order for SOC and alphabetically for PT.
b. Number of patients with AEs divided by the 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.
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 treatment or up to and including the date of initiation of the first subsequent therapy (whichever occurs first).
pt = patient.
MedDRA version 26.1.

Grade 3-4 adverse events

Table 47 AEs of Maximum CTCAE Grade 3 or 4 by PT in ADRIATIC and the D Pan-tumour Pool (Sorted by Frequency) (≥ 1% of Patients in Any Treatment Group in ADRIATIC) (Safety Analysis Set)

	Number (%) of patients [a]		
	ADRIATIC		Pan-tumour Pool
MedDRA PT	D (N = 262)	Placebo (N = 265)	D (N = 4642)
Patients with any AE of maximum CTCAE Grade 3 or 4	64 (24.4)	6 (24.2)	1782 (38.4)
Pneumonia	7 (2.7)	9 (3.4)	152 (3.3)
Diarrhoea	5 (1.9)	0	39 (0.8)
Lipase increased	5 (1.9)	4 (1.5)	60 (1.3)
Pulmonary embolism	5 (1.9)	3 (1.1)	39 (0.8)
Amylase increased	3 (1.1)	0	40 (0.9)
Anaemia	3 (1.1)	3 (1.1)	201 (4.3)
Hyperglycaemia	3 (1.1)	0	42 (0.9)
Hypertension	3 (1.1)	0	66 (1.4)
Pneumonitis	3 (1.1)	2 (0.8)	33 (0.7)
Radiation pneumonitis	3 (1.1)	5 (1.9)	11 (0.2)
Chronic obstructive pulmonary disease	1 (0.4)	4 (1.5)	12 (0.3)
Fatigue	1 (0.4)	4 (1.5)	95 (2.0)

a. Number (%) of patients with AEs, sorted in decreasing frequency of PT (ADRIATIC D column). Patients with multiple AEs are counted once for each PT.

Maximum CTCAE grade per patient/event is considered.

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

MedDRA version 26.1

Adverse Drug Reactions

No new safety findings were noted that impact the characterization of these events. Based on the analysis and review, no new ADRs were identified specific to durvalumab.

Table 48 ADRs by ADR SOC and ADR term (ADRIATIC and the D Pan-tumour Pool) (Safety Analysis Set)

	ADRIATIC				Pan-tumour Pool	
	D (N = 262)		Placebo (N = 265)		D (N = 4642)	
ADR SOC/ADR term	Number (%) of patients [a]	CIOMS III category [b]	Number (%) of patients [a]	CIOMS III category [b]	Number (%) of patients [a]	CIOMS III category [b]
Patients with any ADR	192 (73.3)		157 (59.2)		3366 (72.5)	
Blood and lymphatic system disorders						
Immune thrombocytopenia	0	NR	1 (0.4)	Uncommon	3 (0.1)	Uncommon
Cardiac disorders						
Myocarditis	1 (0.4)	Uncommon	0	NR	8 (0.2)	Uncommon
Endocrine disorders						
Adrenal insufficiency	3 (1.1)	Common	0	NR	28 (0.6)	Uncommon
Diabetes insipidus	0	NR	0	NR	1 (< 0.1)	Rare
Hyperthyroidism	31 (11.8)	Very common	4 (1.5)	Common	261 (5.6)	Common
Hypopituitarism/Hypophysitis	2 (0.8)	Uncommon	0	NR	6 (0.1)	Uncommon
Hypothyroidism	42 (16.0)	Very common	12 (4.5)	Common	540 (11.6)	Very common
Thyroiditis	3 (1.1)	Common	0	NR	38 (0.8)	Uncommon
Type 1 diabetes mellitus	1 (0.4)	Uncommon	0	NR	4 (0.1)	Uncommon
Eye disorders						
Uveitis	0	NR	0	NR	1 (< 0.1)	Rare
Gastrointestinal disorders						
Abdominal pain	12 (4.6)	Common	19 (7.2)	Common	549 (11.8)	Very common
Colitis	0	NR	3 (1.1)	Common	39 (0.8)	Uncommon
Diarrhoea	29 (11.1)	Very common	22 (8.3)	Common	702 (15.1)	Very common
Pancreatitis	1 (0.4)	Uncommon	1 (0.4)	Uncommon	11 (0.2)	Uncommon

Table 48 ADRs by ADR SOC and ADR term (ADRIATIC and the D Pan-tumour Pool) (Safety Analysis Set)

	ADRIATIC				Pan-tumour Pool	
	D (N = 262)		Placebo (N = 265)		D (N = 4642)	
ADR SOC/ADR term	Number (%) of patients [a]	CIOMS III category [b]	Number (%) of patients [a]	CIOMS III category [b]	Number (%) of patients [a]	CIOMS III category [b]
General disorders and administration site conditions						
Oedema peripheral	8 (3.1)	Common	5 (1.9)	Common	399 (8.6)	Common
Pyrexia	11 (4.2)	Common	13 (4.9)	Common	578 (12.5)	Very common
Hepatobiliary disorders						
Aspartate aminotransferase increased/ Alanine aminotransferase increased	17 (6.5)	Common	14 (5.3)	Common	422 (9.1)	Common
Hepatitis	4 (1.5)	Common	3 (1.1)	Common	51 (1.1)	Common
Infections and infestations						
Dental and oral soft tissue infections	3 (1.1)	Common	4 (1.5)	Common	62 (1.3)	Common
Influenza	3 (1.1)	Common	1 (0.4)	Uncommon	65 (1.4)	Common
Oral candidiasis	4 (1.5)	Common	2 (0.8)	Uncommon	82 (1.8)	Common
Pneumonia	32 (12.2)	Very common	23 (8.7)	Common	399 (8.6)	Common
Upper respiratory tract infections	19 (7.3)	Common	21 (7.9)	Common	550 (11.8)	Very common
Injury, poisoning and procedural complications						
Infusion related reaction	4 (1.5)	Common	0	NR	70 (1.5)	Common
Musculoskeletal and connective tissue disorders						
Arthralgia	18 (6.9)	Common	29 (10.9)	Very common	574 (12.4)	Very common
Immune-mediated arthritis	0	NR	0	NR	3 (0.1)	Uncommon

Table 48 ADRs by ADR SOC and ADR term (ADRIATIC and the D Pan-tumour Pool) (Safety Analysis Set)

	ADRIATIC				Pan-tumour Pool	
	D (N = 262)		Placebo (N = 265)		D (N = 4642)	
ADR SOC/ADR term	Number (%) of patients [a]	CIOMS III category [b]	Number (%) of patients [a]	CIOMS III category [b]	Number (%) of patients [a]	CIOMS III category [b]
Myalgia	11 (4.2)	Common	10 (3.8)	Common	212 (4.6)	Common
Myositis	0	NR	0	NR	10 (0.2)	Uncommon
Nervous system disorders						
Encephalitis	1 (0.4)	Uncommon	0	NR	3 (0.1)	Uncommon
Meningitis	0	NR	0	NR	1 (< 0.1)	Rare
Myasthenia gravis	0	NR	0	NR	3 (0.1)	Uncommon
Renal and urinary disorders						
Blood creatinine increased	10 (3.8)	Common	5 (1.9)	Common	158 (3.4)	Common
Cystitis noninfective	0	NR	0	NR	4 (0.1)	Uncommon
Dysuria	1 (0.4)	Uncommon	2 (0.8)	Uncommon	62 (1.3)	Common
Nephritis	1 (0.4)	Uncommon	0	NR	13 (0.3)	Uncommon
Respiratory, thoracic and mediastinal disorders						
Cough/Productive cough	45 (17.2)	Very common	37 (14.0)	Very common	838 (18.1)	Very common
Dysphonia	0	NR	4 (1.5)	Common	108 (2.3)	Common
Interstitial lung disease	7 (2.7)	Common	1 (0.4)	Uncommon	33 (0.7)	Uncommon
Pneumonitis	36 (13.7)	Very common	16 (6.0)	Common	183 (3.9)	Common
Skin and subcutaneous tissue disorders						
Dermatitis	5 (1.9)	Common	6 (2.3)	Common	37 (0.8)	Uncommon
Night sweats	0	NR	1 (0.4)	Uncommon	60 (1.3)	Common

Table 48 ADRs by ADR SOC and ADR term (ADRIATIC and the D Pan-tumour Pool) (Safety Analysis Set)

	ADRIATIC				Pan-tumour Pool	
	D (N = 262)		Placebo (N = 265)		D (N = 4642)	
ADR SOC/ADR term	Number (%) of patients [a]	CIOMS III category [b]	Number (%) of patients [a]	CIOMS III category [b]	Number (%) of patients [a]	CIOMS III category [b]
Pemphigoid	0	NR	0	NR	6 (0.1)	Uncommon
Pruritus	34 (13.0)	Very common	19 (7.2)	Common	513 (11.1)	Very common
Psoriasis	0	NR	2 (0.8)	Uncommon	30 (0.6)	Uncommon
Rash	37 (14.1)	Very common	22 (8.3)	Common	695 (15.0)	Very common

a. Number (%) of patients with ADRs, sorted in alphabetical order by ADR SOC and ADR PT.

b. 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).

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

ADR terms are grouped PTs.

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

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 1 day after latest dose.

MedDRA version 26.1.

Serious adverse event/deaths/other significant events

Deaths

Table 49 AEs and Event Rate with Outcome of Death in ADRIATIC and Corresponding Frequency and Event Rate in the D Pan-tumour Pool by SOC and PT (Safety Analysis Set)

MedDRA SOC/PT	ADRIATIC				Pan-tumour Pool	
	D (N = 262)		Placebo (N = 265)		D (N = 4642)	
	Number (%) of patients [a]	Event rate (per 100 pt years) [b]	Number (%) of patients [a]	Event rate (per 100 pt years) [b]	Number (%) of patients [a]	Event rate (per 100 pt years) [b]
Patients with any AE with an outcome of death	7 (2.7)	2.6	5 (1.9)	2.0	275 (5.9)	9.4
Infections and infestations	4 (1.5)	1.5	4 (1.5)	1.6	54 (1.2)	1.9
COVID-19	0	NA	1 (0.4)	0.4	0	NA
Pneumonia	2 (0.8)	0.7	2 (0.8)	0.8	19 (0.4)	0.7
Pneumonia bacterial	2 (0.8)	0.7	0	NA	4 (0.1)	0.1
Sepsis	0	NA	1 (0.4)	0.4	14 (0.3)	0.5
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	NA	1 (0.4)	0.4	2 (< 0.1)	<0.1
Squamous cell carcinoma of the hypopharynx	0	NA	1 (0.4)	0.4	0	NA
Nervous system disorders	1 (0.4)	0.4	0	NA	12 (0.3)	0.4
Encephalopathy	1 (0.4)	0.4	0	NA	1 (< 0.1)	< 0.1
Cardiac disorders	1 (0.4)	0.4	0	NA	31 (0.7)	1.1
Cardiac failure	1 (0.4)	0.4	0	NA	3 (0.1)	0.1
Respiratory, thoracic and mediastinal disorders	1 (0.4)	0.4	0	NA	62 (1.3)	2.1
Pneumonitis	1 (0.4)	0.4	0	NA	10 (0.2)	0.3

a. Number (%) of patients with AEs, sorted by international order for SOC and alphabetically for PT.

b. Number of patients with AEs divided by the 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.

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 treatment 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.

pt = patient.

MedDRA version 26.1.

Table 50 Adverse events with outcome of death - key subject information (Safety analysis set)

			Durva						
Sex/Age [a] (years)	Event term as reported by the investigator	Adverse event (MedDRA preferred term)	Time from first dose to AE (days)	Time from last dose to AE (days) [b]	Treatment period [c]	Time from first dose to death (days)	Time from last dose to death (days)	Received treatment for AE	Reasonable possibility AE caused by IP [d]
M/66	LUNG INFECTION RIGHT LOWER LOBE	Pneumonia	125	41	On-trt	129	45	Yes	No/No
F/67	HEART FAILURE	Cardiac failure	546	29	On-trt	548	31	Yes	No/No
M/71	BACTERIAL PNEUMONIA	Pneumonia bacterial	156		On-trt	189	116	Yes	No/No
F/50	BACTERIAL PNEUMONIA	Pneumonia bacterial	517	77	On-trt	552	112	Yes	No/No
F/71	PNEUMONITIS	Pneumonitis	1		On-trt	39	39	Yes	Yes/Yes
M/67	PNEUMONIA	Pneumonia	94	9	On-trt	95	10	Yes	No/No
M/77	ENCEPHALOPATHY	Encephalopathy	114		On-trt	176	66	Yes	Yes/No
M/67	MALIGNANT NEOPLASM (SQUAMOUS CARCINOMA) IN HYPOPHARYNX	Squamous cell carcinoma of the hypopharynx	342	5	On-trt	650	313	Yes	No/No
M/56	PNEUMONIA	Pneumonia	377	30	On-trt	380	33	Yes	No/No
M/79	PNEUMONIA	Pneumonia	513	71	On-trt	514	72	Yes	No/No
M/76	SEPSIS	Sepsis	111	55	On-trt	112	56	Yes	No/No
M/61	COVID-19 CONFIRMED	COVID-19	378	15	On-trt	389	26	Yes	No/No

Durva Durvalumab; Treme Tremelimumab.
AE Adverse event; F Female; IP Investigational product; M Male.
[a] Age at randomization.
[b] Calculated for AEs starting after the discontinuation of all treatment.
[c] Pre-trt defined as assessment date before first dose. On-trt defined as assessment date on or between first dose and last dose + 90 days. Follow-up defined as assessment date after last dose + 90 days.
[d] Possibly related to treatment (presented in the following order Durva/Placebo and Treme/Placebo), as assessed by the investigator. Includes AEs with an onset date or pre-treatment AEs that increase in severity on or after the date of first dose and up to and including 90 days following the date of last dose of treatment or up to the date of initiation of the first subsequent systemic anti-cancer therapy (whichever occurs first).
MedDRA version 26.1.

Serious adverse events

Table 51 Overview of SAEs in ADRIATIC and the D Pan-tumour Pool (Frequency > 1% in any ADRIATIC Treatment Group) (Safety Analysis Set)

	ADRIATIC				Pan-tumour Pool	
	D (N = 262)		Placebo (N = 265)		D (N = 4642)	
MedDRA PT	Number (%) of patients [a]	Event rate (per 100 pt years) [b]	Number (%) of patients [a]	Event rate (per 100 pt years) [b]	Number (%) of patients [a]	Event rate (per 100 pt years) [b]
Patients with any SAE	78 (29.8)	28.5	64 (24.2)	25.7	1657 (35.7)	56.8
Radiation pneumonitis	13 (5.0)	4.8	7 (2.6)	2.8	31 (0.7)	1.1
Pneumonia	12 (4.6)	4.4	10 (3.8)	4.0	190 (4.1)	6.5
Pneumonitis	8 (3.1)	2.9	6 (2.3)	2.4	58 (1.2)	2.0
Interstitial lung disease	6 (2.3)	2.2	0	NA	18 (0.4)	0.6

MedDRA PT	ADRIATIC				Pan-tumour Pool	
	D (N = 262)		Placebo (N = 265)		D (N = 4642)	
	Number (%) of patients [a]	Event rate (per 100 pt years) [b]	Number (%) of patients [a]	Event rate (per 100 pt years) [b]	Number (%) of patients [a]	Event rate (per 100 pt years) [b]
Immune-mediated lung disease	4 (1.5)	1.5	0	NA	6 (0.1)	0.2
Pneumonia bacterial	3 (1.1)	1.1	0	NA	5 (0.1)	0.2
Chronic obstructive pulmonary disease	1 (0.4)	0.4	4 (1.5)	1.6	17 (0.4)	0.6
Asthenia	0	NA	3 (1.1)	1.2	14 (0.3)	0.5

a. Number (%) of patients with AEs, sorted by decreasing frequency in D group in ADRIATIC.
b. Number of patients with AEs divided by the 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.
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 treatment 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.
pt = patient.
MedDRA version 26.1.

Adverse events of special interest

Immune-mediated Adverse Events

This section summarizes imAE rates for the pivotal safety dataset (SAS in ADRIATIC) as well as supportive data from the D Pan-tumour Pool. The D Pan-tumour Pool, as larger patient population that includes patients across various tumour types and stages of disease, allowed for the identification of rare events (e.g. hypophysitis and myocarditis) that are consistent with the established safety profile of durvalumab.

Table 52 ImAEs in Any Category in ADRIATIC and the D Pan-tumour Pool (Safety Analysis Set)

imAE Category	Number (%) of patients		
	ADRIATIC		Pan-tumour Pool
	D (N = 262)	Placebo (N = 265)	D (N = 4642)
Any AE	84 (32.1)	27 (10.2)	853 (18.4)
Any AE causally related to any study treatment [a]	79 (30.2)	24 (9.1)	720 (15.5)
Any AE causally related to durvalumab/placebo [a]	79 (30.2)	24 (9.1)	720 (15.5)
Any AE of maximum CTCAE Grade 3 or 4 [b]	14 (5.3)	4 (1.5)	204 (4.4)
Any AE of maximum CTCAE Grade 3 or 4, causally related to any study treatment [a,b]	14 (5.3)	4 (1.5)	175 (3.8)
Any AE of maximum CTCAE Grade 3 or 4, causally related to durvalumab/placebo [a,b]	14 (5.3)	4 (1.5)	175 (3.8)
Any SAE	24 (9.2)	8 (3.0)	202 (4.4)
Any SAE, causally related to any study treatment [a]	23 (8.8)	8 (3.0)	182 (3.9)
Any SAE, causally related to durvalumab/placebo [a]	23 (8.8)	8 (3.0)	182 (3.9)
Any SAE with outcome of death [c]	1 (0.4)	0	18 (0.4)
Any SAE with outcome of death, causally related to any study treatment [a,c]	1 (0.4)	0	16 (0.3)
Any SAE with outcome of death, causally related to durvalumab/placebo [a,c]	1 (0.4)	0	16 (0.3)
Any AE leading to discontinuation of any study treatment	19 (7.3)	7 (2.6)	142 (3.1)
Any AE leading to discontinuation of durvalumab/placebo	19 (7.3)	7 (2.6)	142 (3.1)
Received therapy			
Received systemic corticosteroids	50 (19.1)	18 (6.8)	496 (10.7)
Received ≥ 40 mg prednisone equivalent steroids	36 (13.7)	15 (5.7)	335 (7.2)
Received other immunosuppressants	3 (1.1)	1 (0.4)	21 (0.5)
Received endocrine therapy	41 (15.6)	9 (3.4)	442 (9.5)
AE outcome [c,d]			
AE resolved	30 (11.5)	13 (4.9)	312 (6.7)

imAE Category	Number (%) of patients		
	ADRIATIC		Pan-tumour Pool
	D (N = 262)	Placebo (N = 265)	D (N = 4642)
AE not resolved	54 (20.6)	14 (5.3)	541 (11.7)

a. Causally related is defined as reasonable possibility that the AE was caused by treatment, as assessed by Investigator. Missing responses are counted as causally related.

b. Grade 3: severe, Grade 4: life-threatening.

c. If a subject has multiple events within a specific AE type, then the outcome of the event with the worst outcome is counted. Outcomes from worst to best are death, not resolved, resolved.

d. Reasons of not recovered/not resolved, recovering/resolving, unknown map to an outcome of not resolved. Reasons of recovered/resolved, recovered/resolved with sequelae map to an outcome of resolved.

The table includes AEs with an onset date or that worsen on or after the date of first dose and up to and including 90 days following the date of last dose of treatment or up to the day prior to start of subsequent cancer therapy, whichever comes first.

Subjects with multiple occurrences in the same category are counted once per category regardless of the number of occurrences.

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

AESI or AEPI Version 19.0; MedDRA Version 26.1; CTCAE version 4.03.

n = Number of subjects per category; N = Number of subjects per treatment group.

Excerpt from the summary table including imAEs that occurred in ≥ 2 persons in the ADRIATIC trial:

Table 53 ImAEs by Event Type in ADRIATIC and the D Pan-tumour Pool (Safety Analysis Set)

Event type/ treatment [a]	Number (%) of patients [b]												
	Any AE	Any SAE	Maximum CTCAE Grade 3 or 4 [d]	Maximum CTCAE Grade 3 [d]	Maximum CTCAE Grade 4 [d]	Received intervention				AEs leading to discontinuation of any treatment	Event outcome [c]		
						Systemic corticosteroids	≥ 40 mg prednisone equivalent steroid	Other immuno-suppressants	Endocrine therapy		Resulted in death	Not resolved [e]	Resolved [e]
Pneumonitis (grouped term)													
D	31 (11.8)	17 (6.5)	5 (1.9)	5 (1.9)	0	31 (11.8)	25 (9.5)	1 (0.4)	0	13 (5.0)	1 (0.4)	12 (4.6)	18 (6.9)

Event type/ treatment [a]	Number (%) of patients [b]												
	Any AE	Any SAE	Maximum CTCAE Grade 3 or 4 [d]	Maximum CTCAE Grade 3 [d]	Maximum CTCAE Grade 4 [d]	Received intervention				AEs leading to discontinuation of any treatment	Event outcome [c]		
						Systemic corticosteroids	≥ 40 mg prednisone equivalent steroid	Other immuno-suppressants	Endocrine therapy		Resulted in death	Not resolved [e]	Resolved [e]
Placebo	8 (3.0)	5 (1.9)	2 (0.8)	1 (0.4)	1 (0.4)	8 (3.0)	7 (2.6)	0	0	3 (1.1)	0	5 (1.9)	3 (1.1)
D Pan-tumour Pool	147 (3.2)	79 (1.7)	39 (0.8)	37 (0.8)	2 (< 0.1)	147 (3.2)	114 (2.5)	4 (0.1)	0	60 (1.3)	10 (0.2)	52 (1.1)	85 (1.8)
Hepatic events (grouped term)													
D	3 (1.1)	1 (0.4)	1 (0.4)	1 (0.4)	0	3 (1.1)	3 (1.1)	1 (0.4)	0	1 (0.4)	0	1 (0.4)	2 (0.8)
Placebo	3 (1.1)	1 (0.4)	1 (0.4)	0	1 (0.4)	3 (1.1)	3 (1.1)	0	0	1 (0.4)	0	0	3(1.1)
D Pan-tumour Pool	120 (2.6)	44 (0.9)	79 (1.7)	70 (1.5)	9 (0.2)	120 (2.6)	94 (2.0)	9 (0.2)	0	30 (0.6)	6 (0.1)	58 (1.2)	56 (1.2)
Diarrhoea/colitis (grouped term)													
D	2 (0.8)	1 (0.4)	2 (0.8)	2 (0.8)	0	2 (0.8)	2 (0.8)	1 (0.4)	0	2 (0.8)	0	2 (0.8)	0
Placebo	5 (1.9)	1 (0.4)	0	0	0	5 (1.9)	4 (1.5)	1 (0.4)	0	2 (0.8)	0	1 (0.4)	4 (1.5)
D Pan-tumour Pool	79 (1.7)	22 (0.5)	17 (0.4)	15 (0.3)	2 (< 0.1)	79 (1.7)	55 (1.2)	5 (0.1)	0	15 (0.3)	1 (< 0.1)	24 (0.5)	54 (1.2)
Hypothyroid events (grouped term)													
D	36 (13.7)	0	0	0	0	0	0	0	36 (13.7)	1 (0.4)	0	30 (11.5)	6 (2.3)
Placebo	9 (3.4)	0	0	0	0	0	0	0	9 (3.4)	0	0	6 (2.3)	3 (1.1)

Event type/ treatment [a]	Number (%) of patients [b]												
	Any AE	Any SAE	Maximum CTCAE Grade 3 or 4 [d]	Maximum CTCAE Grade 3 [d]	Maximum CTCAE Grade 4 [d]	Received intervention				AEs leading to discontinuation of any treatment	Event outcome [c]		
						Systemic corticosteroids	≥ 40 mg prednisone equivalent steroid	Other immuno-suppressants	Endocrine therapy		Resulted in death	Not resolved [e]	Resolved [e]
D Pan-tumour Pool	384 (8.3)	7 (0.2)	7 (0.2)	7 (0.2)	0	19 (0.4)	7 (0.2)	0	379 (8.2)	1 (< 0.1)	0	305 (6.6)	79 (1.7)
Adrenal insufficiency (grouped term)													
D	3 (1.1)	1 (0.4)	1 (0.4)	1 (0.4)	0	3 (1.1)	0	0	0	0	0	2 (0.8)	1 (0.4)
Placebo	0	0	0	0	0	0	0	0	0	0	0	0	0
D Pan-tumour Pool	24 (0.5)	9 (0.2)	8 (0.2)	8 (0.2)	0	24 (0.5)	8 (0.2)	0	7 (0.2)	1 (< 0.1)	0	18 (0.4)	6 (0.1)
Type I diabetes mellitus (grouped term)													
D	1 (0.4)	1 (0.4)	1 (0.4)	1 (0.4)	0	0	0	0	1 (0.4)	0	0	1 (0.4)	0
Placebo	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)	1 (< 0.1)	0	0	0	5 (0.1)	1 (< 0.1)	0	3 (0.1)	2 (< 0.1)
Hypophysitis (grouped term)													
D	1 (0.4)	1 (0.4)	1 (0.4)	1 (0.4)	0	1 (0.4)	0	0	0	0	0	1 (0.4)	0
Placebo	0	0	0	0	0	0	0	0	0	0	0	0	0
D Pan-tumour Pool	6 (0.1)	6 (0.1)	5 (0.1)	5 (0.1)	0	6 (0.1)	3 (0.1)	0	1 (< 0.1)	3 (0.1)	0	5 (0.1)	1 (< 0.1)

Event type/ treatment [a]	Number (%) of patients [b]												
	Any AE	Any SAE	Maximum CTCAE Grade 3 or 4 [d]	Maximum CTCAE Grade 3 [d]	Maximum CTCAE Grade 4 [d]	Received intervention				AEs leading to discontinuation of any treatment	Event outcome [c]		
						Systemic corticosteroids	≥ 40 mg prednisone equivalent steroid	Other immuno-suppressants	Endocrine therapy		Resulted in death	Not resolved [e]	Resolved [e]
Hyperthyroid events (grouped term)													
D	5 (1.9)	0	0	0	0	1 (0.4)	1 (0.4)	0	5 (1.9)	0	0	0	5 (1.9)
Placebo	1 (0.4)	0	0	0	0	0	0	0	1 (0.4)	0	0	0	1 (0.4)
D Pan-tumour Pool	76 (1.6)	3 (0.1)	0	0	0	15 (0.3)	8 (0.2)	0	71 (1.5)	1 (< 0.1)	0	14 (0.3)	62 (1.3)
Thyroiditis (grouped term)													
D	2 (0.8)	0	0	0	0	0	0	0	2 (0.8)	0	0	1 (0.4)	1 (0.4)
Placebo	0	0	0	0	0	0	0	0	0	0	0	0	0
D Pan-tumour Pool	21 (0.5)	1 (< 0.1)	2 (< 0.1)	2 (< 0.1)	0	6 (0.1)	3 (0.1)	0	18 (0.4)	1 (< 0.1)	0	13 (0.3)	8 (0.2)
Renal events (grouped term)													
D	0	0	0	0	0	0	0	0	0	0	0	0	0
Placebo	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)	4 (0.1)	1 (< 0.1)	17 (0.4)	12 (0.3)	1 (< 0.1)	0	7 (0.2)	0	9 (0.2)	8 (0.2)

Event type/ treatment [a]	Number (%) of patients [b]												
	Any AE	Any SAE	Maximum CTCAE Grade 3 or 4 [d]	Maximum CTCAE Grade 3 [d]	Maximum CTCAE Grade 4 [d]	Received intervention				AEs leading to discontinuation of any treatment	Event outcome [c]		
						Systemic corticosteroids	≥ 40 mg prednisone equivalent steroid	Other immuno-suppressants	Endocrine therapy		Resulted in death	Not resolved [e]	Resolved [e]
Dermatitis/Rash (grouped term)													
D	5 (1.9)	0	1 (0.4)	1 (0.4)	0	5 (1.9)	1 (0.4)	0	0	0	0	3 (1.1)	2 (0.8)
Placebo	0	0	0	0	0	0	0	0	0	0	0	0	0
D Pan-tumour Pool	74 (1.6)	6 (0.1)	20 (0.4)	20 (0.4)	0	74 (1.6)	37 (0.8)	0	0	5 (0.1)	0	28 (0.6)	46 (1.0)
Pancreatic events (grouped term)													
D	2 (0.8)	0	2 (0.8)	1 (0.4)	1 (0.4)	2 (0.8)	1 (0.4)	0	0	0	0	0	2 (0.8)
Placebo	0	0	0	0	0	0	0	0	0	0	0	0	0
D Pan-tumour Pool	11 (0.2)	2 (< 0.1)	6 (0.1)	4 (0.1)	2 (< 0.1)	11 (0.2)	6 (0.1)	0	0	1 (< 0.1)	0	3 (0.1)	8 (0.2)

a. N = 262 for D group; N = 265 for placebo group; N = 4642 for D Pan-tumour Pool.
b. Subjects with multiple occurrences in the same category are counted once per category regardless of the number of occurrences.
c. If a subject has multiple events within a specific group, then the outcome of the event with the worst outcome is counted. Outcomes from worst to best are death, not resolved, resolved.
d. Grade 3: severe, Grade 4: life-threatening.
e. Not resolved includes outcomes of: not recovered/not resolved; recovering/resolving; unknown. Resolved includes outcomes of: recovered/resolved, recovered/resolved with sequelae.

The table includes AEs with an onset date or that worsen on or after the date of first dose up to and including 90 days following the date of last dose of treatment or up to the day prior to start of subsequent cancer therapy, whichever comes first.
Disease progression AEs reported in Study 1108 are not included in this summary.
MedDRA Version 26.1, AESI list version 19.0, CTCAE version 4.03.

Infusion/Hypersensitivity Reactions

Infusion/hypersensitivity reaction (grouped term) AESIs were reported in 4 (1.5%) patients in the D group and 2 (0.8%) patients in the placebo group. All infusion/hypersensitivity reaction (grouped term) AESIs were CTCAE Grade 1 or 2 and did not lead to discontinuation of study treatment.

In the D Pan-tumour Pool, 102 (2.2%) patients had AESIs of infusion/hypersensitivity reaction (grouped term). Maximum CTCAE Grade 3 or 4 events were reported in 12 (0.3%) patients, including 6 (0.1%) Grade 3 Infusion related reactions and no CTCAE Grade 5 events were reported.

Pneumonitis or Radiation Pneumonitis Adverse Events

Pneumonitis or radiation pneumonitis was reported in 100 (38.2%) patients in the D group and 80 (30.2%) in the placebo group (see Table 46). Maximum CTCAE Grade 3 or 4 pneumonitis or radiation pneumonitis was reported in 3.1% of patients in the D group and 2.6% in the placebo group. In the D group, 1 patient (0.4%) had a fatal pneumonitis or radiation pneumonitis event (PT: pneumonitis) and no patients in the placebo group had a fatal pneumonitis or radiation pneumonitis event.

Laboratory findings

Haematology:

In ADRIATIC, shifts in haematology parameters to CTCAE Grade 3 or 4 were reported in similar proportions of patients in the D and placebo groups. The frequency of shifts in haematology parameters to CTCAE Grade 3 or 4 was comparable between the D group in ADRIATIC and the D Pan-tumour Pool (Table 54).

Table 54 Clinically important changes in haematology parameters in ADRIATIC and the D Pan-tumour Pool (Safety Analysis Set)

	n/N (%) of Patients					
	ADRIATIC				Pan-tumour Pool	
	D (N = 262)		Placebo (N = 265)		D (N = 4642)	
Parameter	≥ 2 CTCAE Grade Changes	CTCAE Grade Changes to 3 or 4	≥ 2 CTCAE Grade Changes	CTCAE Grade Changes to 3 or 4	≥ 2 CTCAE Grade Changes	CTCAE Grade Changes to 3 or 4
Haemoglobin	5/257 (1.9)	3/257 (1.2)	1/262 (0.4)	2/262 (0.8)	242/4443 (5.4)	211/4443 (4.7)
Leukocytes	2/257 (0.8)	1/257 (0.4)	9/262 (3.4)	3/262 (1.1)	85/4443 (1.9)	23/4443 (0.5)
Lymphocytes	27/257 (10.5)	27/257 (10.5)	31/262 (11.8)	25/262 (9.5)	775/4085 (19.0)	534/4085 (13.1)
Low	25/257 (9.7)	27/257 (10.5)	30/262 (11.5)	25/262 (9.5)	763/4085 (18.7)	533/4085 (13.0)
High	2/257 (0.8)	0/257	2/262 (0.8)	0/262	13/4085 (0.3)	1/4085 (< 0.1)
Neutrophils	8/252 (3.2)	1/252 (0.4)	10/251 (4.0)	2/251 (0.8)	138/4401 (3.1)	39/4401 (0.9)
Platelets	4/257 (1.6)	2/257 (0.8)	4/262 (1.5)	2/262 (0.8)	75/4440 (1.7)	51/4440 (1.1)

a. ADRIATIC study collects data for random, fasting and non-fasting glucose and this table presents fasting glucose only for ADRIATIC 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) with a non-missing CTCAE grade change.

Derived from laboratory assessments between the start of treatment and up to and including 90 days following the date of last dose of study treatment or until the initiation of the first subsequent therapy (whichever occurred first).

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

All studies use CTCAE version 4.03.

Clinical chemistry:

In ADRIATIC, shifts in clinical chemistry parameters to CTCAE Grade 3 or 4 were reported in similar proportions of patients in the D and placebo groups. The frequency of shifts in clinical chemistry parameters to CTCAE Grade 3 or 4 was comparable between the D group in ADRIATIC and the D Pan-tumour Pool (Table 55).

Table 55 Clinically Important Changes in Clinical Chemistry Parameters in ADRIATIC and the D Pan-tumour Pool (Safety Analysis Set)

	n/N (%) of Patients					
	ADRIATIC				Pan-tumour Pool	
	D (N = 262)		Placebo (N = 265)		D (N = 4642)	
Parameter	≥ 2 CTCAE Grade Changes	CTCAE Grade Changes to 3 or 4	≥ 2 CTCAE Grade Changes	CTCAE Grade Changes to 3 or 4	≥ 2 CTCAE Grade Changes	CTCAE Grade Changes to 3 or 4
Alanine aminotransferase	15/258 (5.8)	6/258 (2.3)	10/261 (3.8)	6/261 (2.3)	254/4434 (5.7)	166/4434 (3.7)
Albumin	9/254 (3.5)	0/254	6/256 (2.3)	2/256 (0.8)	535/4386 (12.2)	61/4386 (1.4)
Alkaline phosphatase	6/257 (2.3)	3/257 (1.2)	1/261 (0.4)	1/261 (0.4)	211/4412 (4.8)	179/4412 (4.1)
Amylase	15/251 (6.0)	7/251 (2.8)	7/248 (2.8)	6/248 (2.4)	116/1780 (6.5)	86/1780 (4.8)
Aspartate aminotransferase	11/258 (4.3)	6/258 (2.3)	6/261 (2.3)	4/261 (1.5)	285/4423 (6.4)	254/4423 (5.7)
Corrected calcium	1/253 (0.4)	0/253	3/256 (1.2)	2/256 (0.8)	214/4258 (5.0)	123/4258 (2.9)
Low	1/253 (0.4)	0/253	3/256 (1.2)	2/256 (0.8)	67/4258 (1.6)	29/4258 (0.7)
High	0/253	0/253	0/256	0/256	151/4258 (3.5)	96/4258 (2.3)
Creatinine	13/258 (5.0)	0/258	11/261 (4.2)	2/261 (0.8)	183/4370 (4.2)	38/4370 (0.9)
Gamma glutamyl transferase	21/227 (9.3)	15/227 (6.6)	12/239 (5.0)	7/239 (2.9)	239/2294 (10.4)	209/2294 (9.1)
Glucose [a]	4/63 (6.3)	2/63 (3.2)	3/65 (4.6)	1/65 (1.5)	613/4392 (14.0)	264/4392 (6.0)
Low	0/63	0/63	0/65	0/65	70/4392 (1.6)	23/4392 (0.5)
High	4/63 (6.3)	2/63 (3.2)	3/65 (4.6)	1/65 (1.5)	562/4392 (12.8)	244/4392 (5.6)
Lipase	20/240 (8.3)	16/240 (6.7)	28/223 (12.6)	20/223 (9.0)	171/1662 (10.3)	137/1662 (8.2)

Parameter	n/N (%) of Patients					
	ADRIATIC				Pan-tumour Pool	
	D (N = 262)		Placebo (N = 265)		D (N = 4642)	
	≥ 2 CTCAE Grade Changes	CTCAE Grade Changes to 3 or 4	≥ 2 CTCAE Grade Changes	CTCAE Grade Changes to 3 or 4	≥ 2 CTCAE Grade Changes	CTCAE Grade Changes to 3 or 4
Magnesium	8/223 (3.6)	4/223 (1.8)	3/238 (1.3)	3/238 (1.3)	97/3820 (2.5)	84/3820 (2.2)
Low	4/223 (1.8)	0/223	0/238	0/238	36/3820 (0.9)	17/3820 (0.4)
High	4/223 (1.8)	4/223 (1.8)	3/238 (1.3)	3/238 (1.3)	72/3820 (1.9)	71/3820 (1.9)
Potassium	10/258 (3.9)	5/258 (1.9)	8/261 (3.1)	6/261 (2.3)	338/4426 (7.6)	183/4426 (4.1)
Low	2/258 (0.8)	2/258 (0.8)	4/261 (1.5)	4/261 (1.5)	97/4426 (2.2)	100/4426 (2.3)
High	9/258 (3.5)	3/258 (1.2)	4/261 (1.5)	2/261 (0.8)	248/4426 (5.6)	88/4426 (2.0)
Sodium	14/258 (5.4)	14/258 (5.4)	17/260 (6.5)	17/260 (6.5)	377/4435 (8.5)	371/4435 (8.4)
Low	14/258 (5.4)	14/258 (5.4)	16/260 (6.2)	16/260 (6.2)	358/4435 (8.1)	364/4435 (8.2)
High	0/258	0/258	1/260 (0.4)	1/260 (0.4)	27/4435 (0.6)	15/4435 (0.3)
Total bilirubin	7/258 (2.7)	0/258	6/261 (2.3)	0/261	219/4427 (4.9)	109/4427 (2.5)

Percentages are based on the total number of patients in the treatment group (N) with a non-missing CTCAE grade change.
Derived from laboratory assessments between the start of treatment and up to and including 90 days following the date of last dose of study treatment or until the initiation of the first subsequent therapy (whichever occurred first).
Patient's worst (highest CTCAE grade; highest Common Toxicity Criteria grade in the direction of high corrected calcium) changes from baseline are used.
All studies use CTCAE version 4.03.

Thyroid function

In ADRIATIC, elevated TSH values greater than the ULN and low TSH values less than the LLN were observed in greater proportions of patients in the D group compared to the placebo group. Hyperthyroidism and hypothyroidism are known risks of durvalumab. There were no unexpected findings in TSH results during the study.

The frequency of elevated and low TSH values was comparable between the D group in ADRIATIC and the D Pan-tumour Pool.

The proportion of patients in the D Pan-tumour Pool who experienced a TSH shift from baseline that was ≤ ULN to any grade > ULN was 20% and a TSH shift from baseline that was ≥ LLN to any grade < LLN was 18.2%.

Safety in special populations

Sex:

Assessment of the durvalumab monotherapy safety profile by sex did not raise any new safety concerns. Owing to the smaller proportion of female patients relative to male patients, differences between groups should be interpreted with caution.

Age:

The frequency of AEs with an outcome of death in the D group increased with increasing age (0%, 0.7%, 5.7%, and 6.7% in patients aged < 50, ≥ 50 to < 65, ≥ 65 to < 75, and ≥ 75 years, respectively), a trend also observed in the placebo group (0%, 1.5%, 1.2%, and 11.1%, respectively) and in the D Pan tumour Pool (4.5%, 5.2%, 7.1%, and 6.8%, respectively).

The frequency of AEs leading to discontinuation of any study treatment in the D group increased with increasing age (4.8%, 12.3%, 20.5%, and 46.7% in patients aged < 50, ≥ 50 to < 65, ≥ 65 to < 75, and ≥ 75 years, respectively), a trend not observed in the placebo group (11.5%, 8.1%, 14.0%, and 11.1%, respectively) but was also observed in the D Pan tumour Pool (6.7%, 9.4%, 12.5%, and 13.7%, respectively).

Table 56 Adverse events in any category - patient level by age group (Safety analysis set)

		Number (%) of patients[a]		
		ADRIATIC		
		Durvalumab (N1=21) (N2=138) (N3=88) (N4=15)	Placebo (N1=26) (N2=135) (N3=86) (N4=18)	D Pan-Tumor Pool (N1=537) (N2=2089) (N3=1542) (N4=474)
AE category	Age group			
Any AE of maximum CTCAE grade 3 or grade 4 [c]	<50	4 (19.0)	5 (19.2)	197 (36.7)
	>=50 - <65	33 (23.9)	29 (21.5)	789 (37.8)
	>=65 - <75	24 (27.3)	22 (25.6)	587 (38.1)
	>=75	3 (20.0)	8 (44.4)	209 (44.1)
Any AE with outcome = death	<50	0	0	24 (4.5)
	>=50 - <65	1 (0.7)	2 (1.5)	109 (5.2)
	>=65 - <75	5 (5.7)	1 (1.2)	110 (7.1)
	>=75	1 (6.7)	2 (11.1)	32 (6.8)
Any SAE (including events with outcome = death) [d]	<50	5 (23.8)	4 (15.4)	179 (33.3)
	>=50 - <65	38 (27.5)	29 (21.5)	704 (33.7)
	>=65 - <75	31 (35.2)	21 (24.4)	557 (36.1)
	>=75	4 (26.7)	10 (55.6)	217 (45.8)
Any SAE (including events with outcome = death), causally related to any study treatment [b] [d]	<50	2 (9.5)	2 (7.7)	34 (6.3)
	>=50 - <65	18 (13.0)	8 (5.9)	166 (7.9)
	>=65 - <75	10 (11.4)	6 (7.0)	121 (7.8)
	>=75	2 (13.3)	1 (5.6)	49 (10.3)
Any AE leading to discontinuation of any study treatment	<50	1 (4.8)	3 (11.5)	36 (6.7)
	>=50 - <65	17 (12.3)	11 (8.1)	196 (9.4)
	>=65 - <75	18 (20.5)	12 (14.0)	192 (12.5)
	>=75	7 (46.7)	2 (11.1)	65 (13.7)

AE = Adverse Event. SAE = Serious Adverse Event.
N1 = Total number of patients for Age group <50 within the treatment group, N2 = Total number of patients for Age group >=50 - <65 within the treatment group, N3 = Total number of patients for Age group >=65 - <75 within the treatment group, N4 = Total number of patients for Age group >=75 within the treatment group. Percentages are calculated from N1, N2, N3, and N4 for <50 years, >=50 - <65 years, >=65 - <75 years and >=75 years, respectively.
[b] As assessed by the investigator. Missing responses are counted as related.
[c] Maximum CTCAE grade of 3 or 4 is derived for each patient/treatment period/event and excludes patients who experienced grade 3 or 4 events with a grade 5 event.
[d] Seriousness, as assessed by the investigator. An AE with missing seriousness is considered serious.
Includes adverse events with an onset date on or after the date of first dose or pre-treatment AEs that increase in severity on or after the date of first dose up to and including 90 days following the date of last dose of study medication or up to and including the date of initiation of the first subsequent therapy (whichever occurs first).
Disease progression adverse events reported in Study 1108 are not included in this summary.
CTCAE = Common Terminology Criteria for Adverse Events. All studies use version 4.03.

Race:

Table 57 Adverse events in any category - patient level by race (Safety analysis set)

		Number (%) of patients[a]		
		ADRIATIC		
		Durvalumab (N1=128) (N2=1) (N3=131) (N4=2) (N5=0)	Placebo (N1=137) (N2=3) (N3=121) (N4=4) (N5=0)	D Pan-Tumor Pool (N1=2892) (N2=85) (N3=1514) (N4=74) (N5=77)
AE category	Race group			
Any AE	White	123 (96.1)	120 (87.6)	2747 (95.0)
	Black or African American	1 (100)	2 (66.7)	84 (98.8)
	Asian	121 (92.4)	108 (89.3)	1401 (92.5)
	Other	2 (100)	4 (100)	72 (97.3)
	Missing	0	0	77 (100)
Any AE of maximum CTCAE grade 3 or grade 4 [c]	White	35 (27.3)	41 (29.9)	1164 (40.2)
	Black or African American	1 (100)	0	42 (49.4)
	Asian	28 (21.4)	22 (18.2)	514 (33.9)
	Other	0	1 (25.0)	37 (50.0)
	Missing	0	0	25 (32.5)
Any SAE (including events with outcome = death) [d]	White	38 (29.7)	34 (24.8)	1051 (36.3)
	Black or African American	0	0	41 (48.2)
	Asian	40 (30.5)	30 (24.8)	486 (32.1)
	Other	0	0	35 (47.3)
	Missing	0	0	44 (57.1)

AE = Adverse Event. SAE = Serious Adverse Event.

N1 = Total number of White patients within the treatment group, N2 = Total number of Black or African American patients within the treatment group, N3 = Total number of Asian patients within the treatment group, N4 = Total number of Other patients within the treatment group, N5 = Total number of Missing patients within the treatment group. Percentages are calculated from N1, N2, N3, N4 and N5 for White, Black or African American, Asian, Other and Missing respectively.

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

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

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

CTCAE = Common Terminology Criteria for Adverse Events. All studies use version 4.03.

ECOG/WHO PS:

In general, the frequencies of AEs of any grade, CTCAE Grade 3 or 4 AEs, SAEs, AEs leading to discontinuation of any study treatment, and AEs leading to dose modification of any study treatment in the D group in ADRIATIC were numerically higher in patients with a baseline ECOG/WHO PS of ≥ 1 compared to those with an ECOG/WHO PS of 0.

Geographical region:

In general, the frequencies of AEs of any grade and SAEs in the D group in ADRIATIC were similar across geographical regions (see Table 58). Differences in the frequencies of the AEs most commonly reported may be a result of the intrinsic factors of sex, age, and race, and are discussed above.

Table 58 Adverse events in any category - patient level by geographic region (Safety analysis set)

		Number (%) of patients[a]		
		ADRIATIC		
		Durvalumab (N1=129) (N2=94) (N3=37) (N4=2) (N5=133)	Placebo (N1=120) (N2=112) (N3=30) (N4=3) (N5=145)	D Pan-Tumor Pool (N1=1422) (N2=1924) (N3=1246) (N4=50) (N5=3220)
AE category	Geographic Region group			
Any AE	Asia	119 (92.2)	107 (89.2)	1312 (92.3)
	Europe	90 (95.7)	95 (84.8)	1800 (93.6)
	North America	36 (97.3)	29 (96.7)	1223 (98.2)
	South America	2 (100)	3 (100)	46 (92.0)
	Non-Asia Regions	128 (96.2)	127 (87.6)	3069 (95.3)
Any AE of maximum CTCAE grade 3 or grade 4 [c]	Asia	27 (20.9)	22 (18.3)	475 (33.4)
	Europe	22 (23.4)	28 (25.0)	695 (36.1)
	North America	15 (40.5)	13 (43.3)	592 (47.5)
	South America	0	1 (33.3)	20 (40.0)
	Non-Asia Regions	37 (27.8)	42 (29.0)	1307 (40.6)
Any AE with outcome = death	Asia	0	3 (2.5)	65 (4.6)
	Europe	6 (6.4)	1 (0.9)	126 (6.5)
	North America	1 (2.7)	1 (3.3)	77 (6.2)
	South America	0	0	7 (14.0)
	Non-Asia Regions	7 (5.3)	2 (1.4)	210 (6.5)

Any SAE (including events with outcome = death) [d]	Asia	40 (31.0)	29 (24.2)	460 (32.3)
	Europe	27 (28.7)	24 (21.4)	648 (33.7)
	North America	11 (29.7)	11 (36.7)	531 (42.6)
	South America	0	0	18 (36.0)
	Non-Asia Regions	38 (28.6)	35 (24.1)	1197 (37.2)
Any AE leading to discontinuation of any study treatment	Asia	13 (10.1)	14 (11.7)	141 (9.9)
	Europe	14 (14.9)	9 (8.0)	218 (11.3)
	North America	16 (43.2)	5 (16.7)	123 (9.9)
	South America	0	0	7 (14.0)
	Non-Asia Regions	30 (22.6)	14 (9.7)	348 (10.8)
Any AE leading to dose modification of any study treatment [e]	Asia	46 (35.7)	39 (32.5)	367 (25.8)
	Europe	35 (37.2)	24 (21.4)	516 (26.8)
	North America	10 (27.0)	11 (36.7)	398 (31.9)
	South America	0	2 (66.7)	14 (28.0)
	Non-Asia Regions	45 (33.8)	37 (25.5)	928 (28.8)
Any AE leading to dose delay or interruption of any study treatment [f]	Asia	46 (35.7)	39 (32.5)	367 (25.8)
	Europe	35 (37.2)	24 (21.4)	509 (26.5)
	North America	10 (27.0)	11 (36.7)	396 (31.8)
	South America	0	2 (66.7)	14 (28.0)
	Non-Asia Regions	45 (33.8)	37 (25.5)	919 (28.5)

AE = Adverse Event. SAE = Serious Adverse Event.
N1 = Total number of Asia patients within the treatment group, N2 = Total number of Europe patients within the treatment group, N3 = Total number of North America patients within the treatment group, N4 = Total number of South America patients within the treatment group, N5 = Total number of Non-Asia Regions patients within the treatment group. Percentages are calculated from N1, N2, N3, N4 and N5 for Asia, Europe, North America, South America and Non-Asia Regions respectively.
[c] Maximum CTCAE grade of 3 or 4 is derived for each patient/treatment period/event and excludes patients who experienced grade 3 or 4 events with a grade 5 event.
[d] Seriousness, as assessed by the investigator. An AE with missing seriousness is considered serious.
[e] Includes AEs on the AE CRF form with action taken indicating dose reduction, dose delay or dose interruption, and AEs meeting study level dose delay definitions, where applicable.
[f] Includes AEs on the AE CRF form with action taken indicating dose delay or dose interruption, and AEs meeting study level dose delay definitions, where applicable.
Includes adverse events with an onset date on or after the date of first dose or pre-treatment AEs that increase in severity on or after the date of first dose up to and including 90 days following the date of last dose of study medication or up to and including the date of initiation of the first subsequent therapy (whichever occurs first).
Disease progression adverse events reported in Study 1108 are not included in this summary.
CTCAE = Common Terminology Criteria for Adverse Events. All studies use version 4.03.

The frequencies of CTCAE Grade 3 or 4 AEs and AEs leading to discontinuation of any study treatment were higher in North American patients compared to other geographical regions in the D group in ADRIATIC and are summarized below. These differences may be due to the higher proportions of female patients (North America [59.5%] vs Asia [17.8%] and Europe [41.5%]) and older patients (≥ 65 to < 75 years: North America [40.5%] vs Asia [34.1%] and Europe [30.9%]) in the North America region. An increased frequency of AEs leading to discontinuation of any study treatment was observed in female patients and older patients and increased frequency of CTCAE Grade 3 or 4 AEs was observed in female patients (see above):

- The frequency of CTCAE Grade 3 or 4 AEs in the D group was higher in North American patients (40.5%) compared to Asian patients (20.9%) and European patients (23.4%), a trend also observed in the placebo group (43.3%, 18.3%, and 25.0%) and in the D Pan tumour Pool (47.5%, 33.4%, and 36.1%).
- The frequency of AEs leading to discontinuation of any study treatment in the D group was higher in North American patients (43.2%) compared to Asian patients (10.1%) and European patients (14.9%), a trend also observed in the placebo group (16.7%, 11.7%, and 8.0%) but not observed in the D Pan-tumour Pool (9.9%, 9.9%, and 11.3%).

Safety related to drug-drug interactions and other interactions

Durvalumab is an immunoglobulin; therefore, no formal pharmacokinetic drug-drug interaction studies have been conducted.

Discontinuation due to adverse events

AEs leading to discontinuation of any study treatment were reported in a higher proportion of patients in the D group compared to the placebo group and were higher in the D group in ADRIATIC compared to the D Pan-tumour Pool.

Table 59 Overview of AEs Leading to Discontinuation of any Study Treatment in ADRIATIC and the D Pan-tumour Pool (Reported in ≥ 2 Patients in any ADRIATIC Treatment Group) (Safety Analysis Set)

	ADRIATIC				Pan-tumour Pool	
	D (N = 262)		Placebo (N = 265)		D (N = 4642)	
MedDRA PT	Number (%) of patients [a]	Event rate (per 100 pt years) [b]	Number (%) of patients [a]	Event rate (per 100 pt years) [b]	Number (%) of patients [a]	Event rate (per 100 pt years) [b]
Patients with any AE leading to discontinuation of any study treatment	43 (16.4)	15.7	28 (10.6)	11.3	489 (10.5)	16.8
Radiation pneumonitis	10 (3.8)	3.7	5 (1.9)	2.0	16 (0.3)	0.5
Pneumonitis	8 (3.1)	2.9	3 (1.1)	1.2	48 (1.0)	1.6
Immune-mediated lung disease	4 (1.5)	1.5	0	NA	5 (0.1)	0.2
Pneumonia	3 (1.1)	1.1	2 (0.8)	0.8	28 (0.6)	1.0
Diarrhoea	2 (0.8)	0.7	0	NA	10 (0.2)	0.3

a. Number (%) of patients with AEs, sorted by decreasing frequency in D group in ADRIATIC.
b. Number of patients with AEs divided by the 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.
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 treatment 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.
pt = patient.
MedDRA version 26.1.

Post marketing experience

As of 30 April 2023, durvalumab has been approved for the treatment of Stage III NSCLC in 86 countries, and in combination with chemotherapy as treatment of extensive stage small cell lung cancer in 84 countries. Additionally, durvalumab is approved in 10 countries for the treatment of urothelial carcinoma and in Japan for the treatment of HCC. Durvalumab is also approved in combination with tremelimumab and platinum-based chemotherapy for treatment of patients with metastatic NSCLC in 33 countries; in combination with tremelimumab for the treatment of unresectable hepatocellular carcinoma in 33 countries, in combination with chemotherapy for the treatment of biliary tract cancer in 46 countries, and is provisionally approved in combination with chemotherapy for the treatment of malignant pleural mesothelioma in Australia.

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 results from ADRIATIC are presented and compared with to the durvalumab monotherapy pool (all tumours).

In comparison to the currently reported durvalumab monotherapy safety pool in the SmPC (N=4045), the new proposed pool (N=4642) also contains the safety datasets from both PEARL (n=335) and ADRIATIC (n=262). Although PEARL was not individually assessed, it is considered appropriate that its safety results are included in the new database.

Exposure was markedly shorter in the D Pan-Tumour Pool compared to ADRIATIC: 18 weeks compared to 40 weeks in the durvalumab arm and 35 weeks in the placebo arm. This is most likely due to the rather early clinical setting and study design of ADRIATIC (which allowed for durvalumab for up to 2 years) and the fact that the pool included many trials in the advanced setting, and whose prognosis limited duration of treatment.

In the D Pan-Tumour pool, 286 patients (of which 46 are from ADRIATIC) had received durvalumab for more than two years, which is considered satisfactory in terms of evaluating long-term safety.

Demographics and baseline characteristics were comparable between the two arms in ADRIATIC. They were overall also comparable to the D Pan-tumour Pool with some exceptions: There were more patients with ECOG 1, from North America and White in the pool, compared to ADRIATIC.

The main safety issues with durvalumab are related to the MoA (mAb that binds to PD-L1 blocking T-cell function and activation through interactions with its receptors PD-1 and CD80) leading to various immune-related adverse events.

There were more AEs and TRAEs in the durvalumab arm compared to the placebo arm in the ADRIATIC trial, which was expected, and the frequencies in the durvalumab arm were generally comparable to those from the Pan-tumour monotherapy pool.

The most frequent were hypothyroidism (16.0% vs. 3.8%), pruritus (13.0% vs. 7.2%), and pneumonitis (10.7% vs. 6.0%) (In Table 46, the reported frequency from pneumonitis corresponds to its definition as a preferred term, not a grouped term). When pooling patients for which the preferred term was “interstitial lung disease” (ILD), and considering adjudication by immune causality, the frequency of immune-mediated pneumonitis in patients treated with durvalumab in ADRIATIC is 11.8%. For the Pan-tumour pool the corresponding frequency for Pneumonitis/ILD is lower: 6.8%. However, the median exposure in the pool is less than half of the exposure in Adriatic and more pneumonitis is expected in patients having received thoracic radiation (as opposed to many patients in the Pan-tumour pool, who had other malignancies), as was seen in the PACIFIC trial. Radiation pneumonitis is listed separately.

The frequency for hypothyroidism PT in the durvalumab arm of ADRIATIC and the Pan-tumour pool were 16% (n=42) and 10.2% (N=472), respectively. For the immunologically based grouped term of hypothyroid events (Table 53), the corresponding frequencies are 13.7% (N=36) and 8.3% (N=384).

The only AE reported in ≥ 20% of patients by PT in both treatment groups was radiation pneumonitis (22.9% in the D group; 23.4% in the placebo group; Table 46) consistent with expectations in patients with LS-SCLC who had received prior cCRT.

There was also a higher frequency of COVID-19 (6.9% vs 0.6%), which can be ascribed to the higher number of patients in ADRIATIC being treated during the pandemic as opposed to in the Pan-tumour pool.

Serious AEs were reported in 29.8% of patients in the D group and 24.2% of patients in the placebo group (Table 51). The most frequently reported SAEs in the D and placebo groups were radiation pneumonitis (5.0% and 2.6%, respectively), pneumonia (4.6% and 3.8%), and pneumonitis (3.1% and 2.3%).

As expected, based on the mechanism of action, there were more **imAEs** (immune-mediated AEs) in the durvalumab arm compared to the placebo arm in ADRIATIC (Table 52). The most frequent immunological events were hypothyroid and pneumonitis events with one fatal outcome for the latter imAE. The overall frequency of imAEs were lower in the Pan-tumour pool; here the median exposure was less than half that of the ADRIATIC study, which may in part explain the difference.

In ADRIATIC **pneumonitis** imAE were reported in 31 (11.8%) patients in the durvalumab arm and 8 (3.0%) patients in the placebo group (Table 53), and high-dose corticosteroid treatment was administered in 25 patients and 7 patients, respectively. One fatal event was reported in the D group. The median time to onset for the imAEs of pneumonitis was 55.0 days (range: 1 to 375 days) in the D group and 65.5 days (range: 24 to 124 days) in the placebo group. Resolution occurred for 18 patients in the IMFINZI treated group vs. 3 in placebo.

The frequency of the imAE pneumonitis was lower in the Pan-tumour pool compared to the durvalumab arm in ADRIATIC (3,2% vs 11.8%). One likely explanation is the added risk of pneumonitis in patients having received prior irradiation against the lungs. In the Pan-tumour pool the median time to onset was 56.0 days (range: 1-1308 days), and the median time to resolution was 51.0 days (range: 3-589 days).

In ADRIATIC **hypothyroid** event imAEs were reported in 36 (13.7%) patients in the D group and 9 (3.4%) patients in the placebo group. All hypothyroid event imAEs were CTCAE Grade 1 or 2 in both groups. All affected patients received hormone replacement therapy. The frequency was lower in the Pan-tumour pool (8.3%, n=384), and 379/384 patients received hormone replacement therapy. The median time to onset was 90.5 days (range 1-951 days), and the median time to resolution was 60.0 days (range: 6-418 days), which occurred in 79/384 patients.

Other immune-related AEs occurred with a frequency of < 2% in the durvalumab arm in ADRIATIC, and are well-known from previously assessed monotherapy studies – see SmPC.

Haematology changes from baseline were generally consistent with the reported AE profiles, and data are comparable to haematology data in the D Pan-tumour Pool.

Liver transaminase elevations were comparable between the durvalumab arm in ADRIATIC and the Pan-tumour pool and of the same magnitude as previously known (Common).

In ADRIATIC, elevated **TSH** values and low TSH values were observed in greater proportions of patients in the D group compared to the placebo group and was comparable to the D Pan-tumour Pool. Hyperthyroidism and hypothyroidism are known risks of durvalumab.

Regarding safety in special population: there were some differences between AE frequencies in males and females in ADRIATIC, but given the low number of patients (178 males, 84 females) and the fact, that there were no differences in the Pan-tumour pool, no definite conclusion may be drawn.

On the effect per **age**: In the SmPC under Elderly in section 4.8 the following is stated*: No overall differences in safety were reported between elderly (≥ 65 years) and younger patients.* Although the various adverse events frequencies increased with age in the durvalumab arm and the durvalumab Pan tumour pool, this also occurred to some extent in the placebo arm, and there was no specific trend observed by individual PTs. It is thus acceptable that no specific information regarding elderly is added to the SmPC.

Regarding **race**: In ADRIATIC the patients were almost exclusively White or Asian. Generally, the frequencies were similar both in ADRIATIC and the Pan-tumour pool. The frequency of AEs Grade 3-4 in the D group was higher in White patients (27.3%) compared to Asian patients (21.4%), which was also observed in the placebo group (29.9% vs 18.2%) and in the D Pan-tumour Pool (40.2% vs 33.9%).

In general, the various AE frequencies were numerically higher in patients with **ECOG/WHO PS** ≥1 compared to 0 in the ADRIATIC trial. This was also the case in the Pan-tumour pool although generally with a smaller difference.

Differences in **geographical region**s in ADRIATIC may be due to sex, age, and race, and should therefore be interpreted with caution.

The frequency of AEs leading to discontinuation of any study treatment was higher in the D group in ADRIATIC (16.4%) compared to the D Pan-tumour Pool (10.5%). The AEs were predominantly lung-related: pneumonitis, radiation pneumonitis, immune-mediated lung disease, and pneumonia, which is expected given the disease in ADRIATIC compared to the Pan-tumour pool as well as prior treatment (cCRT).

The frequency of AEs leading to dose modification of durvalumab was higher for the D group in ADRIATIC compared to the D Pan-tumour pool (34.7% vs 27.9%, respectively, Table 45). The most frequent AEs leading to dose modification were lung-related, as for discontinuation.

The key risks associated with durvalumab consolidation treatment in LS-SCLC patients following platinum-based chemoradiation therapy are immunological, mainly pneumonitis and hypothyroid events, and related to prior radiation in the form of radiation pneumonitis. No new safety concerns have been identified.

2.5.2. Conclusions on clinical safety

In ADRIATIC, no new safety concerns were observed, but, as expected in this clinical setting, and considering previous chemoradiation, there was a higher frequency of lung-related adverse events in these patients, as compared to the Pan-tumour monotherapy safety pool.

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 (version 12 succession 1) 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 12.1 is acceptable.

The CHMP endorsed the Risk Management Plan version 12.1 with the following content:

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. Particularly, section 4.1 of the SmPC has been updated to include the new indication of IMFINZI as monotherapy for the treatment of adults with limited-stage small cell lung cancer (LS-SCLC), section 4.2 has been updated to include the recommended dose in this indication, including a maximum duration of treatment of 24 months, section 4.4 has been updated to add the description of the safety findings from study ADRIATIC with regards to Pneumonitis and radiation pneumonitis, section 4.8 has been updated with specific summary of safety profile of durvalumab as monotherapy in LS-SCLC, and ADR frequencies were revised throughout the section based on updated safety pool for durvalumab pan tumour, and 5.1 has been updated based on final results from study D933QC00001 (ADRIATIC); this was a phase III, randomized, double-blind, placebo-controlled, multi-centre study of durvalumab monotherapy and durvalumab in combination with tremelimumab as consolidation treatment in patients with LS-SCLC.

Changes were also made to the PI to bring it in line with the current QRD template (v10.4), which were reviewed and accepted by the CHMP.

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 affects the Package Leaflet 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 and the changes are not significant enough to warrant an additional user consultation for this new indication.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The claimed new therapeutic indication of durvalumab is:

IMFINZI as monotherapy is indicated for the treatment of patients with limited stage small-cell lung cancer (LS-SCLC) whose disease has not progressed following platinum-based chemoradiation therapy.

SCLC is a high-grade neuroendocrine carcinoma that comprises approximately 15% of all lung cancers, resulting in approximately 250,000 new cases and 200,000 global deaths each year[1]. SCLC is an aggressive solid tumour characterized by rapid doubling time, high growth fraction, and early dissemination. It is characterized by exceptionally high metastatic potential with the most common sites of metastasis including the contralateral lung, brain, liver, adrenal glands, and bone. Among patients presenting with SCLC, approximately 30% will be diagnosed with LS-SCLC and approximately 70% will be diagnosed with ES-SCLC[2][3]. Among patients diagnosed with LS-SCLC who complete the entire course of cCRT with curative intent, only up to 25% will achieve long term disease control and survival[1][4][5][6].

In this clinical scenario, the main aimof treatment with Imfinzi is to improve survival.

3.1.2. Available therapies and unmet medical need

Established guidelines recommend use of 4 cycles of platinum-based chemotherapy typically concurrently with radiation therapy[7][8] in the LS-SCLC setting. Only 4% of all patients with SCLC are diagnosed with very early-stage disease (Stage I-IIA; T1-2, N0, M0) at initial presentation and are potential candidates for surgical resection followed by adjuvant platinum-based chemotherapy with or without adjuvant radiation therapy[1]. In addition, due to the predilection for SCLC to metastasize to the brain, PCI has been routinely used as a standard of care for treatment of patients with LS-SCLC. According to ESMO guidelines PCI is recommended at the end of cCRT for patients with a confirmed tumour response and no contraindication for this procedure[8].

Response rates for cCRT in LS-SCLC are approximately 90%, but most patients will eventually progress, with median PFS of 10 to 15 months and median OS of 25 to 30 months, both from the start of cCRT[4][5][6]. The poor long-term survival outcomes underscore the unmet clinical need for improved therapeutic options for patients with LS-SCLC. Currently, there are no approved drug therapies for patients with LS-SCLC once they have completed cCRT. The standard care for those patients is observation with surveillance.

3.1.3. Main clinical studies

ADRIATIC is an ongoing, Phase III, randomized 1:1:1, double-blind, placebo-controlled, 3-arm, multi-centre, international study to assess the efficacy and safety of durvalumab monotherapy (D) or durvalumab in combination with tremelimumab (D+T) compared to placebo as consolidation treatment in patients with limited stage small-cell lung cancer (LS-SCLC) whose disease had not progressed following definitive, platinum-based chemotherapy concurrent with radiotherapy (cCRT). After 600 patients had been randomized, the D+T group was closed to further randomization and subsequent patients were randomized 1:1 to either the D or placebo group. It was planned that a further 124 patients would subsequently be randomized 1:1 to either the D or placebo group.

Randomisation was stratified based on TNM stage (I/II vs III), and receipt of PCI (yes vs no). Crossover was not allowed. The primary objectives were the comparison of OS and PFS assessed by

[1] Rudin et al 2021
[2] García-Campelo et al 2023
[3] Byers and Rudin 2015
[4] Bogart et al 2023
[5] Faivre-Finn et al 2017
[6] Walls et al 2024
[7] NCCN 2024
[8] Dingemans et al ,2021

blinded independent review, between the durvalumab monotherapy arm, and the control arm in the ITT population. Key secondary endpoints were ORR and PFS2.

As from October 2018, 730 patients were randomly assigned to receive D (n= 264) group, D+T (n=200) or placebo (n=266). The results of D vs. placebo arms form the basis for this submission; D+T arm remains blinded. As of the data cut-off date on 15 January 2024, the median duration of survival follow-up in all patients was 30.75 months in the D group and 28.63 months in the placebo group.

3.2. Favourable effects

- **OS:** Durvalumab showed improved overall survival compared to placebo in the targeted population. With 43.6% of OS events in the D arm and 54.9% in the placebo arm, the HR for OS was 0.73 (95% CI 0.569, 0.928; p = 0.01042), noting a benefit of nearly two years of mOS with durvalumab compared to placebo (mOS of 55.9 months in the D arm vs. 33.4 months in the placebo arm).
- **BICR-PFS:** As per blinded evaluation of images, Durvalumab was superior to placebo in preventing progression or death in patients with LS-SCLC. With 52.7% of PFS events in the D arm and 63.5% in the Placebo arm, the HR for PFS was 0.76 (95% CI 0.606,0.950; p= 0.01608), noting mPFS of 16.6 months in the D arm vs. 9.2 months in the placebo arm.

3.3. Uncertainties and limitations about favourable effects

- None

3.4. Unfavourable effects

- Well-known immune-related adverse events were seen. In particular there was a high frequency of pneumonitis and hypothyroidism (GT).
- There were AE leading to death (7 out of 262 in the durvalumab arm and 5/265 in the placebo arm). Of the 7 deaths in the durvalumab arm 2 were considered related and were due to pneumonitis and encephalopathy.
- There was a higher frequency of pneumonitis in ADRIATIC compared to the Pan-tumour safety pool (10.7% vs 3.7%)

3.5. Uncertainties and limitations about unfavourable effects

- Whether the difference in frequency of pneumonitis between ADRIATIC and the Pan-tumour safety pool is related to prior radiation, the location of the disease (lung), and/or longer exposure (or all) is uncertain. The subsection dedicated to Pneumonitis and radiation pneumonitis in section 4.4 of the SmPC has been updated to describe the specific safety findings from the ADRIATIC Study.

3.6. Effects Table

Table 60 Effects Table for Imfinzi for LS-SCLC (data cut-off: 15 January 2024)

Effect	Short description	Unit	Treatment Durvalumab N=264	Control Placebo N=266	Uncertainties / Strength of evidence	References
Favourable Effects						
BICR-PFS	Median Progression free survival by blinded independent central review	Months	16.6 95%CI: 10.2, 28.2	9.2 95%CI: 7.4,12.9	Median duration of PFS follow-up 9.07 mo (D arm) 7.39 mo (placebo arm). Number of events : 52.7% (D arm) 63.5% (Placebo arm)	CSR
	Hazard ratio (95%CI)	NA	0.76 (0.606, 0.950)			
OS	Median Overall survival	Months	55.9 95%CI: 37.3, NR	33.4 95%CI: 25.5, 39.9	Median duration of OS follow-up: 30.75 mo (D arm) 28.63 mo (placebo arm) Number of events: 43.6% (D arm) 54.9% (placebo arm)	
	Hazard ratio (95%CI)	NA	0.73 (0.569, 0.928)			
Unfavourable Effects					**Pan-tumour pool N=4642 / Uncertainties**	
SAE	Including events with an outcome of death	N (%)	78 (29.8)	64 (24.2)	1657 (35.7)	
Death due to AE		N (%)	7 (2.7)[1]	5 (1.9)	275 (5.9)/ Many patients with several prior treatments in pool	
Discontinuation due to AE		N (%)	43 (16.4)	28 (10.6)	489 (10.5)	Table 59
Resp., thoracic and mediast. disorders	SOC – all SOC - SAE	N (%)	122 (46.6) 10 (7.6)	87 (32.8) 6 (4.6)	1956 (42.1) 98 (5.3)	Table 46
imPneumonitis (grouped term - GT)	All grades AE SAE Received steroids; >40 mg prednisolone	N (%)	31 (11.8) 17 (6.5) 25 (9.5)	8 (3.0) 5 (1.9) 7 (2.6)	147 (3.2) 79 (1.7) 114 (2.5)	Table 53
imHypothyroid events (GT)	All grades AE[2] SAE	N (%)	36 (13.7) 0	9 (3.4) 0	384 (8.3) 7 (0.2)	

Notes:

[1]Two deaths considered related; pneumonitis and encephalopathy.

[2]In ADRIATIC all hypothyroid patients received endocrine therapy, which did 379/384 in the Pan-tumour pool.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Poor long-term survival outcomes underscore the unmet clinical need for improved therapeutic options in patients with LS-SCLC. Currently, there are no approved drug therapies for patients with LS-SCLC once they have completed cCRT. The standard care for those patients is observation with surveillance.

After sufficient follow-up, the overall outcomes of durvalumab consolidation therapy observed in ADRIATIC are promising: a median benefit of nearly two years of mOS with durvalumab compared to placebo. In addition, durvalumab was superior to placebo in preventing progression or death in patients with LS-SCLC, noting nearly doubled mPFS in the durvalumab vs. the placebo arm. Those results are of a clinical value and durvalumab addresses the high unmet medical need by clinically and statistically significantly improving both PFS and OS.

In ADRIATIC, no new safety concerns were observed, but as expected in this clinical setting, and considering previous chemoradiation, there was a higher frequency of lung-related adverse events in these patients.

3.7.2. Balance of benefits and risks

A benefit of nearly two years in median overall survival in the durvalumab arm compared to the placebo arm was observed. This is of a high clinical value: currently there are no approved therapies in this setting with a high unmet medical need for consolidation therapy for patients with LS-SCLC with a response to cCRT. The toxicities from durvalumab are well-known and manageable, even with an increased risk of pneumonitis, and are considerably outweighed by the expected survival gains.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable.

3.8. Conclusions

The overall B/R of Imfinzi is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following 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 treatment of adults with limited-stage small cell lung cancer (LS-SCLC) whose disease has not progressed following platinum-based chemoradiation therapy for IMFINZI, based on results from study D933QC00001 (ADRIATIC); this is a phase III, randomized, double-blind, placebo-controlled, multi-centre, global study to assess the efficacy and safety of durvalumab monotherapy and durvalumab in combination with tremelimumab compared to placebo as consolidation treatment in patients with LS-SCLC whose disease had not progressed following definitive platinum-based chemoradiation therapy. 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 12.1 of the RMP has also been approved. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet and to implement editorial changes to Annex II. Furthermore, the PI is brought in line with the latest QRD template version 10.4.

The variation leads to amendments to the Summary of Product Characteristics, Annex II and Package Leaflet and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annexes I, II and IIIB and to the Risk Management Plan are recommended.

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Imfinzi is not similar to Hetronifly within the meaning of Article 3 of Commission Regulation (EC) No. 847/200. See appendix 1.

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 'Imfinzi-H-C-004771-II-0069'

Attachments

1. SmPC, Annex II, Package Leaflet (changes highlighted) as adopted by the CHMP on 30 January 2025.