EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 July 2020
EMA/CHMP/210563/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Imfinzi

International non-proprietary name: durvalumab

Procedure No. EMEA/H/C/004771/II/0014/G

Note

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

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List of abbreviations

Abbreviation or special term	Explanation
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse events of special interest
AUCss	Area under the curve at steady state
BICR	Blinded independent central review
BSV	Between-subject variability
CI	Confidence interval
CL	Clearance
Cmin, ss	Minimum drug concentration at steady state
CNS	Central nervous system
COPD	Chronic obstructive pulmonary disease
CR	Complete response
CRT	Chemoradiation
CSR	Clinical study report
CT	Computer tomography
CTCAE	Common Terminology Criteria for Adverse Events
DCO	Data cut off
DLT	Dose limiting toxicity
DoR	Duration of response
DV	Dependent variable
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
EP	Etoposide and platinum-based chemotherapy
E-R	Exposure-response
ERES	Exposure-response/exposure-safety
ES-SCLC	Extensive-stage small cell lung cancer
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
GVP	Good pharmacovigilance practice
HR	Hazard ratio
HRQoL	Health-related quality of life
IASCLC	International Association for the Study of Lung Cancer
IC	Immune cell

Abbreviation or special term	Explanation
IDMC	Independent data monitoring committee
IHC	Immunohistochemistry
imAE	Immune-mediated adverse event
IPRED	individual prediction
ISS	Integrated summary of safety
ITT	Intent-to-treat
IV	Intravenous
KM	Kaplan Meier
LDH	Lactate dehydrogenase
LS-SCLC	Limited stage small cell lung cancer
mAb	Monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed model repeated measures
MRI	Magnetic resonance imaging
MTP	Multiple Testing Procedure
NCCN	National Comprehensive Cancer Network
NLR	Neutrophil-to-lymphocyte ratio
NPC	numerical predictive check
NSCLC	Non-small cell lung cancer
NTL	Non-target lesions
ORR	Objective response rate
OS	Overall survival
OS12	Overall survival rate at 12 months
OS18	Overall survival rate at 18 months
pcVPC	prediction-corrected visual predictive check
PCI	Prophylactic cranial irradiation
PD	Progressive disease
PD-1	Programmed cell death
PD-L1	Programmed cell death ligand-1
PFS	Progression-free survival
PFS2	Progression-free survival after subsequent anticancer therapy (defined as: time from randomization to second progression or death)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PRO	Patient-reported outcomes
Q2W	Every 2 weeks
Q3W	Every 3 weeks

Abbreviation or special term	Explanation
Q4W	Every 4 weeks
QD	Every day
QLQ-C30 v3	30-item Core Quality of Life Questionnaire, version 3
QLQ-LC13	13-item Lung Cancer Quality of Life Questionnaire
QoL	Quality of life
RDI	Relative dose intensity
RMP	Risk management plan
RT	Radiation therapy
SAE	Serious adverse event
SCLC	Small cell lung cancer
sIMAE	Suspected imAEs
SmPC	Summary of product characteristics
sPD-L1	Soluble PD-L1
TC	Tumor cell
TL	Target lesions
T_{max}	Time to maximum serum concentration
UC	Urothelial carcinoma
WCLC	World Congress on Lung Cancer

1. Background information on the procedure

1.1. Type II group of variations

Pursuant to Article 7.2 of Commission Regulation (EC) No 1234/2008, AstraZeneca AB submitted to the European Medicines Agency on 12 November 2019 an application for a group of variations.

The following variations were requested in the group:

Variations requested		**Type**	**Annexes affected**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I and IIIB
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of Indication to include the use of IMFINZI 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). The proposed indication is supported by study D419QC00001 (CASPIAN), an ongoing 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.
In addition, the MAH proposes to update sections 4.4 and 4.8 of the SmPC to update the safety information based on the Durvalumab Pan-Tumour Pool, a safety dataset comprising of 9 clinical studies building on the existing safety database and summarising the safety information for durvalumab monotherapy characterised across tumour types in the durvalumab clinical program to date.
The Package Leaflet is updated in accordance. The RMP version 2S1 has also been submitted.

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

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included (an) EMA Decision(s) P/0256/2019 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No

847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The Applicant received scientific advice (SA) from the CHMP regarding the design of pivotal trial CASPIAN in April 2016 (EMEA/H/SA/2752/3/2016/II).

1.2. Steps taken for the assessment of the product

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

Rapporteur: Sinan B. Sarac Co-Rapporteur: Jorge Camarero Jiménez

Timetable	Actual dates
Submission date	12 November 2019
Start of procedure:	30 November 2019
CHMP Co-Rapporteur Assessment Report	11 February 2020
CHMP Rapporteur Assessment Report	24 January 2020
PRAC Rapporteur Assessment Report	29 January 2020
PRAC Outcome	13 February 2020
CHMP members comments	17 February 2020
Updated CHMP Rapporteur(s) (Joint) Assessment Report	21 February 2020
Request for supplementary information (RSI)	27 February 2020
CHMP Rapporteur Assessment Report	28 April 2020
PRAC Rapporteur Assessment Report	28 April 2020
PRAC members comments	06 May 2020
Updated PRAC Rapporteur Assessment Report	07 May 2020
PRAC Outcome	14 May 2020
CHMP members comments	18 May 2020
Updated CHMP Rapporteur Assessment Report	20 May 2020
2nd Request for Supplementary Information	28 May 2020
CHMP Rapporteur Assessment Report	07 July 2020
CHMP members comments	13 July 2020
Updated CHMP Rapporteur Assessment Report	17 July 2020
CHMP opinion:	23 July 2020

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Claimed therapeutic indication

IMFINZI in combination with etoposide and either carboplatin or cisplatin is indicated for the first-line treatment of adults with extensive-stage small cell lung cancer (ES-SCLC).

Epidemiology

Small cell lung cancer (SCLC) comprises approximately 15% of all lung cancer diagnoses (American Cancer Society 2019). SCLC is the most aggressive lung cancer subtype characterized by rapid tumour growth, high vascularity, genomic instability, and early metastatic dissemination (Gazdar et al, Nat Rev 2017). The disease typically presents as bulky symptomatic masses, and mediastinal involvement is common. The cancer is strongly co related with cigarette smoking with almost all SCLC patients being current or former smokers (Alexandrov et al, Science 2016).

The global burden of SCLC remains substantial (GLOBOCAN 2018: Global Cancer Statistics). In the US, approximately 30,000 deaths annually are attributable to SCLC (American Cancer Society 2019). Worldwide, this number exceeds 250,000 patients per year (GLOBOCAN 2018: Global Cancer Statistics), including over 11,000 in Europe (Alvarado-Luna and Morales-Espinosa, Transl Lung Cancer Res 2016).

Biologic features

SCLC is characterised by uniform round to spindled-shaped small cells, sparse cytoplasm, high mitotic index, necrotic areas (ESMO, 2013).

Clinical presentation, diagnosis and stage/prognosis

SCLC has been traditionally classified into 2 stages according to the extent of disease: limited stage (LS) and extensive stage (ES) (Spigel and Socinski, J Thorac Oncol 2013). At their initial diagnosis, approximately 70% of patients present with ES-SCLC. Based on the TNM staging system, ES-SCLC is also defined as Stage IV disease (T any, N any, M 1a/b) or T3 4 due to multiple lung nodules that are too extensive or have tumour/nodal volume that is too large to be encompassed in a tolerable radiation plan (NCCN Guidelines for SCLC Version 2.2018). The remaining approximately 30% of patients have LS-SCLC, in which tumour involvement is confined to one hemi thorax and can be treated in a tolerable radiation field. Patients with LS-SCLC can be treated with chemotherapy and radiation with the potential for long-term survival (Stinchcombe et al. 2010). ES-SCLC has poor survival prospects: the median OS is approximately 10 months with a 1-year OS rate of approximately 40% (Socinski et al. 2009). Chemotherapy alone can palliate symptoms and prolong survival for patients with ES-SCLC; however, long-term survival is rare (Johnson et al. 2004; DeMets et al. 2010).

Management

Since the early 1980s, platinum-based chemotherapy has been the mainstay of ES-SCLC management (Aisner et al, Semin Oncol 1986; Sundstrøm et al, JCO 2002; Levy et al, JNCCN 2013). Until recently, etoposide with either carboplatin or cisplatin (EP) followed by active surveillance has largely remained the standard of care 1L treatment in the United States and Europe (NCCN Guidelines for SCLC Version 2.2018; ESMO Guidelines Working Group 2013). As 1L agents, carboplatin or cisplatin-based regimens have been demonstrated to be equally effective in terms of OS, progression free survival (PFS), and objective response rate (ORR) (Rossi et al, JCO 2012). In summary, real world evidence from the past 3 decades in the pre-immunotherapy era has demonstrated that 4 to 6 cycles of etoposide with either carboplatin or cisplatin with prophylactic cranial irradiation (PCI) as indicated has largely been the global standard-of-care 1L treatment in ES-SCLC (Alvarado-Luna and Morales-Espinosa, Transl Lung Cancer Res 2016; Calles et al, Clin Transl Oncol 2019).

Most recently, nonclinical and clinical studies have indicated that blockade of immune checkpoints (PD-1/PD-L1 and CTLA-4) can have a positive effect on antitumor immunity for SCLC. In the first line setting, recent data have suggested promising clinical benefits from the combination of a chemotherapy backbone with an immune checkpoint inhibitor. IMpower133 was a randomised, double-blind, placebo-controlled trial in patients with ES-SCLC who had not previously received treatment and demonstrated clinical benefit of atezolizumab (Tecentriq) + etoposide and carboplatin (EC) compared with placebo + EC: the median OS was 12.3 months and 10.3 months, respectively (hazard ratio [HR] for death: 0.70; 95% CI: 0.54 to 0.91; p=0.007); the median PFS was 5.2 months and 4.3 months, respectively (HR for disease progression or death: 0.77; 95% CI: 0.62 to 0.96; p=0.02) (Horn et al, NEJM 2018). Atezolizumab in combination with EC for the first line treatment of patients with ES-SCLC has been authorised in the EU (3 September 2019, EMEA/H/C/004143/II/0018).

2.1.2. About the product

Durvalumab (Imfinzi) is an anti-PD-L1 monoclonal antibody approved in the EU on 21 September 2018 as monotherapy for the treatment of locally advanced, unresectable (stage III) NSCLC in adults whose tumours express PD-L1 on ≥1% of tumour cells and whose disease has not progressed following platinum-based chemoradiation therapy.

The first study to evaluate the clinical activity of durvalumab in the SCLC disease setting was Study 1108. This was a Phase I/II, first-time-in-human, multicentre, multi-cohort, open-label, dose-escalation, and dose-expansion study in the durvalumab clinical development program. The SCLC cohort comprised 21 patients with ES SCLC who had received prior lines of treatment. Treatment with durvalumab demonstrated an ORR of 9.5% (95% CI: 1.2, 30.4), median PFS of 1.5 months (95% CI: 0.9, 1.8) and median OS of 4.8 months (95% CI: 1.3, 10.4).

It has been hypothesised that combining single agent immune checkpoint inhibitors might produce an additive improvement in tumour response (Larkin et al, NEJM 2015; Postow et al, NEJM 2015). The available data in second-line ES-SCLC and available safety data on immunotherapy indicated that a combination of two immunotherapies may be more efficacious than a monotherapy approach in ES-SCLC (Antonia et al, JCO 2016). Given the synergistic potential of durvalumab and tremelimumab (anti-CTLA-4), it was hypothesised that the combination of both these drugs with chemotherapy has the potential to further improve the response rates and response durability along with OS in patients with ES-SCLC.

The present application is based on the results from Study D419QC00001 ("CASPIAN"), which is an ongoing phase III, open-label, randomised, three-arm, multicentre trial designed to compare the

efficacy and safety of durvalumab, with or without tremelimumab, in combination with etoposide and either carboplatin or cisplatin (D+T+EP, arm 1; D+EP, arm 2) with that of etoposide and either carboplatin or cisplatin by themselves (EP alone, arm 3) as first-line treatment in patients with ES-SCLC.

The proposed indication which is considered approvable by CHMP is:

IMFINZI in combination with etoposide and either carboplatin or cisplatin is indicated for the first-line treatment of adults with extensive-stage small cell lung cancer (ES-SCLC).

The recommended dose for IMFINZI monotherapy and IMFINZI in combination with chemotherapy is presented in Table 1. IMFINZI is administered as an intravenous infusion over 1 hour.

Table 1: **Recommended Dose of IMFINZI**

Indication	**Recommended IMFINZI dose**	**Duration of Therapy**
ES-SCLC	1500 mg[b] in combination with chemotherapy[c,d] every 3 weeks (21 days) for 4 cycles, followed by 1500 mg every 4 weeks as monotherapy	Until disease progression or unacceptable toxicity

[a] It is recommended to continue treatment for clinically stable patients with initial evidence of disease progression until disease progression is confirmed.

[b] Patients with a body weight of 30 kg or less must receive weight-based dosing, equivalent to IMFINZI 20 mg/kg in combination with chemotherapy every 3 weeks (21 days) for 4 cycles, followed by 20 mg/kg every 4 weeks as monotherapy until weight increases to greater than 30 kg.

[c] Administer IMFINZI prior to chemotherapy on the same day.

[d] When IMFINZI is administered in combination with chemotherapy, refer to the Prescribing Information for etoposide and carboplatin or cisplatin for dosing information.

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

The Applicant received scientific advice (SA) from the CHMP regarding the design of pivotal trial CASPIAN in April 2016 (EMEA/H/SA/2752/3/2016/II). Overall, the recommendations from the CHMP regarding the patient population and control arm design were followed by the MAH. Certain remaining concerns, such as the role of immune checkpoint inhibitor (ICI) monotherapy as maintenance treatment and the usefulness of PD-L1 IHC as a predictive biomarker are further discussed under section 2.4.3 Discussion on clinical efficacy.

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), 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.

2.3. 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.

- Tabular overview of clinical studies

Type of study	Study identifier	Location of study report in CTD Module 5	Objective(s) of the study	Study design and type of control	Test products, dosage regimen, route of administration	No. of subjects rand/treated	Healthy subjects or diagnosis of patients	Duration of treatment	Study status[1]; type of report
Controlled Clinical Studies									
Efficacy and safety	D419QC00001 (CASPIAN) Interim CSR (Edition 1, 5 Sep 2019)	5.3.5.1	Efficacy; safety and tolerability; PK; immunogenicity; symptoms and health-related QoL	Phase 3, randomized, open-label, comparative, multicenter, global study	Arm 1: *During chemotherapy* durvalumab 1500 mg Q3W for 4 doses (Weeks 0, 3, 6, 9) plus tremelimumab 75 mg Q3W for 4 doses (Weeks 0, 3, 6, 9), and standard-of-care Q3W for 4 doses (Weeks 0, 3, 6, 9) Intravenous *Post-Chemotherapy* durvalumab Q4W Week 12 to PD tremelimumab 1 dose Week 16 Intravenous Arm 2: *During chemotherapy* durvalumab 1500 mg Q3W for 4 doses (Weeks 0, 3, 6, 9) standard-of-care Q3W for 4 doses (Weeks 0, 3, 6, 9) Intravenous *Post-Chemotherapy* durvalumab Q4W Week 12 to PD Intravenous Arm 3: standard-of-care Q3W for 4 doses (Weeks 0, 3, 6, 9) and, if clinically indicated, Q3W on Weeks 12 and 15	*Interim analysis only includes data from Arm 2 and Arm 3* 537/531 Arm 2 268/265 Arm 3 269/266	Adults with Stage IV or T3-4 SCLC too extensive or who have tumor/nodal volume too large for tolerable radiation plan	Arms 1+2: Treatment until disease progression Arm 3: Up to 6 cycles	Ongoing; Interim Edition 1

Table 2: Pharmacokinetic studies included as part of the application

Study **Primary objectives** **Design** **Data cutoff date**	**Patient type** **N (M/F)** **Age (median [range])**	**Dosing regimen**	**Key pharmacokinetic results and conclusions**
D419QC00001 (CASPIAN) Safety and efficacy Open-label, randomized DCO: 11 Mar 2019	Patients with ES-SCLC in combination with EP 537 (374/163) 63 y (28-82 y)	Durvalumab IV 1500 mg Q3W for 4 doses then durvalumab IV 1500 mg Q4W until progression of disease AND EP for 4 cycles	As expected, the PK concentrations of durvalumab were higher than in previous clinical studies because of the higher dosing regimen. 1500 mg Q3W: C_{max1}: 503 µg/mL $C_{trough,ss}$: 241 µg/mL
CD-ON-MEDI4736-1108 (Study 1108) Safety, tolerability, and efficacy Open-label, non-randomized DCO: 16 Oct 2017	Advanced melanoma, RCC, NSCLC, or CRC	Dose-escalation phase: Durvalumab IV at 0.1, 0.3, 1, 3, and 10 mg/kg Q2W and 15 mg/kg Q3W for up to 12 months or until progression of disease	Durvalumab exhibited nonlinear PK at doses <3 mg/kg and linear PK at ≥3 mg/kg. 10 mg/kg Q2W: C_{max1}: 226 to 294 µg/mL $C_{max,ss}$: 324 to 409 µg/mL $C_{trough,ss}$: 91.9 to 182 µg/mL 20 mg/kg Q4W: C_{max1}: 416 µg/mL $C_{max,ss}$: 489 µg/mL $C_{trough,ss}$: 99.6 µg/mL
	Advanced cutaneous melanoma, uveal melanoma, HCC, SCCHN, NSCLC squamous histology, NSCLC non-squamous histology, gastroesophageal cancer, TNBC, or pancreatic adenocarcinoma 21 (16/5) 64 y (35-79 y)	Dose-exploration phase: Durvalumab IV at 20 mg/kg Q4W for up to 12 months	
	Advanced cutaneous melanoma, uveal melanoma, HCC, HNSCC, NSCLC squamous histology, NSCLC non-squamous histology, gastroesophageal cancer, TNBC, pancreatic adenocarcinoma, urothelial carcinoma, GBM, ovarian cancer, soft tissue sarcoma, SCLC, MSI-high cancers, HPV-positive cancers, or nasopharyngeal carcinoma	Dose-expansion phase: Durvalumab IV at 10 mg/kg Q2W for up to 12 months	
D4191C00003 (ATLANTIC) Efficacy Open-label, non-randomized DCO: 03 Jun 2016	Locally advanced or metastatic NSCLC 444 (242/202) 62 y (23-85 y)	Durvalumab IV at 10 mg/kg Q2W for up to 12 months	Following 10 mg/kg Q2W durvalumab, the durvalumab trough concentrations were similar among the 3 cohorts in this study. 10 mg/kg Q2W: $C_{trough,ss}$: 141 to 258 µg/mL
D4191C00001 (PACIFIC) Efficacy Randomized, double-blind, placebo-controlled DCO: 22 Mar 2018	Locally advanced, unresectable NSCLC Durvalumab group: 476 (334/142) 64 y (31-84 y) Placebo group: 237 (166/71) 64 y (23-90 y)	Durvalumab IV at 10 mg/kg Q2W for up to 12 months	The PK concentrations observed were consistent with previous studies and typical of a fully human IgG1 monoclonal antibody. 10 mg/kg Q2W: C_{max1}: 191 µg/mL $C_{max,ss}$: 373 µg/mL $C_{trough,ss}$: 177 to 189 µg/mL

Study Primary objectives Design Data cutoff date	Patient type N (M/F) Age (median [range])	Dosing regimen	Key pharmacokinetic results and conclusions
D4191C00004 (ARCTIC) Efficacy versus SoC Open-label, randomized DCO: 09 Feb 2018	Locally advanced or metastatic NSCLC Sub-study A: 126 (90/36) 62.5 y (35-81 y) Sub-study B: 469 (308/161) 63 y (19-83 y)	Durvalumab IV 10 mg/kg Q2W for up to 12 months	The PK concentrations of durvalumab were consistent with previous clinical studies at the same dosing regimen. 10 mg/kg Q2W: C_{max1}: 195 to 205 µg/mL $C_{max,ss}$: 350 to 377 µg/mL $C_{trough,ss}$: 153 to 231 µg/mL
D419AC00001 (MYSTIC) Efficacy versus SoC Open-label, randomized DCO: 04 Oct 2018	Advanced or metastatic NSCLC 1118 (772/346) 65 y (28-87 y)	Durvalumab IV 20 mg/kg Q4W	Durvalumab concentrations were similar to those observed in previous studies. 20 mg/kg Q4W: C_{max1}: 453 µg/mL $C_{max,ss}$: 538 to 539 µg/mL $C_{trough,ss}$: 114 to 135 µg/mL
D4190C00002 (Japan Study 02) Safety and tolerability. Open-label, non-randomized DCO: 31 Mar 2018	Advanced solid tumors 22 (14/8) 62 y (41-72 y)	Dose-escalation phase: Durvalumab IV 1, 3, and 10 mg/kg Q2W; 15 mg/kg Q3W; 20 mg/kg Q4W	Dose proportional relationship was observed for C_{max} and AUC_{0-t} (within 1.0 to 20 mg/kg dose for C_{max} and 1.0 to 10 mg/kg Q2W dose for AUC_{0-t}) in the dose escalation phase. 10 mg/kg Q2W: C_{max1}: 118 to 155 µg/mL $C_{max,ss}$: 261 to 398 µg/mL $C_{trough,ss}$: 117 to 189 µg/mL 20 mg/kg Q4W: C_{max1}: 311 µg/mL
	Biliary tract carcinoma 42 (24/18); 64 y (37-81 y) Esophageal carcinoma 42 (36/8); 63 y (45-74 y) Squamous cell carcinoma of the head and neck 32 (28/4); 62 y (33-73 y)	Dose-expansion phase: Durvalumab IV 10 mg/kg Q2W	
D4193C00001 (HAWK) Efficacy Open-label, single-arm DCO: 31 Mar 2017	Recurrent or metastatic HNSCC with tumoral PD-L1 high expression 112 (80/32) 60 y (24-84 y)	Durvalumab IV 10 mg/kg Q2W for 12 months or until progression of disease	The observed exposure levels of durvalumab at 10 mg/kg Q2W IV were within the expected ranges based on prior knowledge. 10 mg/kg Q2W: C_{max1}: 198 µg/mL $C_{max,ss}$: 329 µg/mL $C_{trough,ss}$: 143 to 175 µg/mL
D4193C00003 (CONDOR) Efficacy Open-label, randomized DCO: 31 Mar 2017	Recurrent or metastatic HNSCC expressing low/no PD-L1 67 (54/13) 62 y (23-82 y)	Durvalumab IV 10 mg/kg Q2W	The observed exposure levels of durvalumab were within the expected ranges based on prior knowledge. 10 mg/kg Q2W: C_{max1}: 194 µg/mL $C_{max,ss}$: 320 to 399 µg/mL $C_{trough,ss}$: 156 to 274 µg/mL
D4193C00002 (EAGLE) Efficacy versus SoC Open-label, randomized DCO 10 Sep 2018	Recurrent or metastatic HNSCC 240 (202/38) 59 y (24-84 y)	Durvalumab IV 10 mg/kg Q2W	The observed exposure levels of durvalumab were within the expected ranges based on prior knowledge. 10 mg/kg Q2W: C_{max1}: 87.9 µg/mL $C_{max,ss}$: 264 µg/mL $C_{trough,ss}$: 101 to 120 µg/mL

AUC_{ss} area under the serum concentration-time curve at steady state; C_{max1} maximum serum concentration following the first dose; $C_{max,ss}$ maximum serum concentration at steady state; $C_{trough,ss}$ minimum serum concentration at steady state; DCO data cutoff; EP etoposide and carboplatin or cisplatin; ES-SCLC extensive-stage small cell lung cancer; GBM glioblastoma multiforme; HCC hepatocellular carcinoma; HNSCC head and neck squamous cell carcinoma; HPV human papillomavirus; IV intravenous; MSI microsatellite instability; MTD maximum tolerated dose; NSCLC non-small cell lung cancer; PD-L1 programmed death ligand 1; PK pharmacokinetics; Q2W every 2 weeks; Q3W every 3 weeks; Q4W every 4 weeks; Q12W every 12 weeks; SCLC small cell lung cancer; SoC standard of care; TNBC triple-negative breast cancer.

2.3.2. Pharmacokinetics

Bioanalytical methods

Durvalumab serum concentrations in the CASPIAN study were measured using the same assay as was used for the previous studies included in model development and validation.

The bioanalytical method utilised an electrochemiluminescence (ECL) assay format to measure the concentration of durvalumab in human serum. The bioanalytical method used for the determination of anti-durvalumab antibodies in human serum uses a tiered approach where clinical samples were tested in screening, confirmatory, titer, and nAb assays. The ADA screening assay is a homogeneous double-bridging ECL assay. The nAb assay is a ligand-binding sandwich immunoassay.

Method validation and sample analysis supporting the clinical studies were conducted in accordance with approved standard operating procedures and in compliance with relevant sections of 21 CFR part 58.

Pop PK analyses

A two-compartment PopPK model with both linear and nonlinear eliminations was initially developed for durvalumab and later amended to a two-compartment PopPK model with linear elimination and time-varying clearance. Residuals were described by a combined error model. The time-varying PK model structure was implemented based on the equation below:

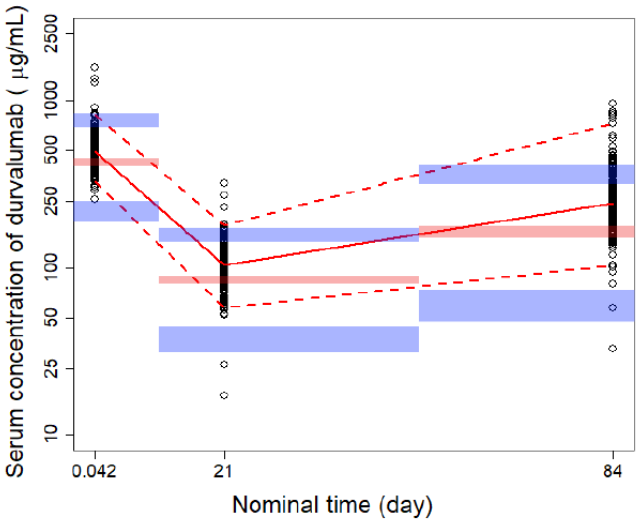
$$\mathrm{CL} = \mathrm{TVCL} \cdot e^{\frac{T_{max} \cdot t^{\gamma}}{T_{50}+t^{\gamma}}}$$

TVCL = baseline linear clearance, Tmax = logarithm maximum change in clearance, t =TAD, γ = sigmoid factor, T50= time at half-maximum change effect in clearance.

The previous PopPK analyses were based on pooled data from Phase 2 study ATLANTIC and Phase 1b/2 study 1108 after durvalumab monotherapy in patients with solid tumors (6984 samples from 1310 subjects). Dose levels of Study 1108 ranged from 0.1 to 10 mg/kg Q2W IV and from 15 mg/kg Q3W IV to 20 mg/kg Q4W IV. ATLANTIC used a dose of 10 mg/kg Q2W IV. The PopPK model was used to characterise the PK profile of durvalumab in patients with solid tumors, investigate the impact of intrinsic and extrinsic factors on PK and evaluate the need for dose adjustment in special populations.

The PopPK model was externally validated with PK data in CASPIAN (DCO: Mar 11, 2019), 647 evaluable durvalumab concentrations (validation dataset) from 259 ES-SCLC patients (validation subjects) in the durvalumab + EP group. Predicted durvalumab concentrations for validation subjects were obtained by fixing the parameters in the structural and variance model to the parameter estimates in the final model using post-hoc Bayesian forecasting with NONMEM 7. Bias (mean prediction error) and precision (root mean squared prediction error) were computed for each patient, then a t-test was used to check whether the mean prediction error across patients was significantly different from zero.

Goodness-of-fit analyses by standard sets of diagnostic plots, visual predictive checks (VPCs), and numerical predictive checks (NPCs) were performed. Based on the PopPK external validation results, the previous PopPK model underpredicted the observed durvalumab PK data from the durvalumab + EP group in CASPIAN as shown in Figure 1.

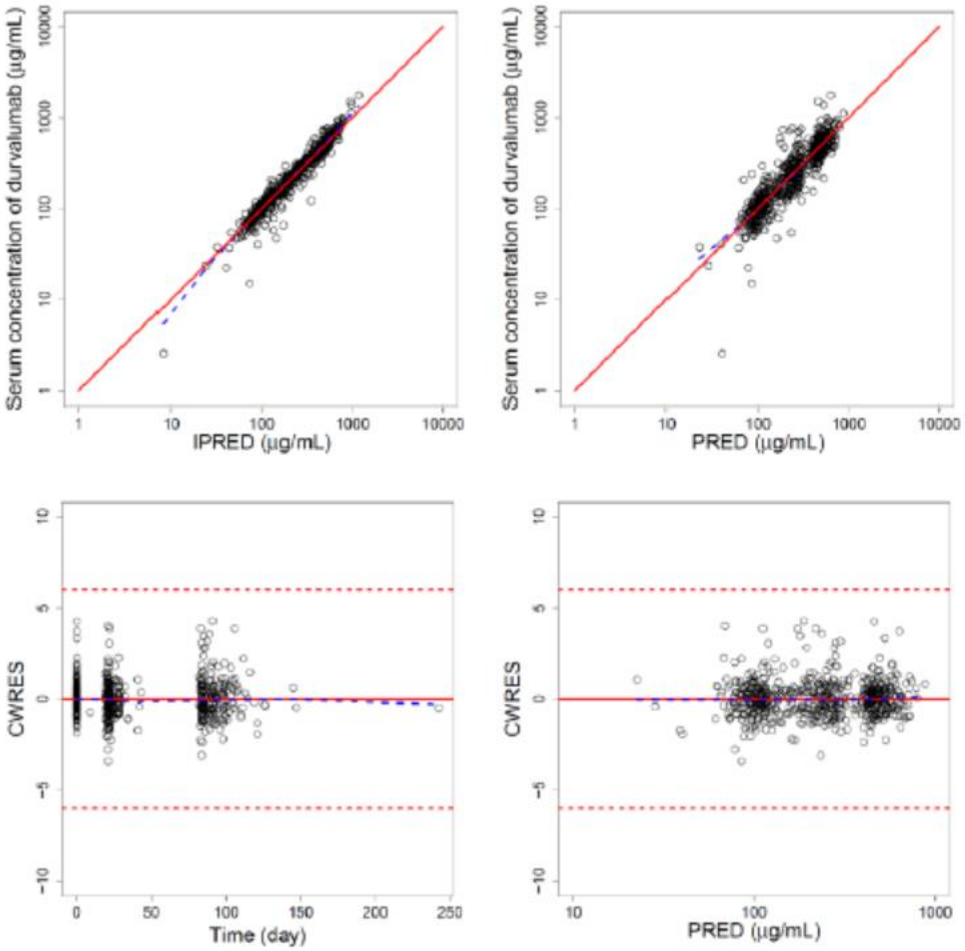


Circles are observed durvalumab serum concentrations, solid red lines represent the median observed value, and dashed red lines represent 2.5%ile and 97.5%ile of the observed values. Pink shaded areas represent the spread (5%ile and 95%ile) of the median predicted values, and purple shaded areas represent the spread (5%ile and 95%ile) of the 2.5th and 97.5th predicted percentile concentrations.

Figure 1: pcVPC of durvalumab concentration vs. nominal time for durvalumab validation subjects

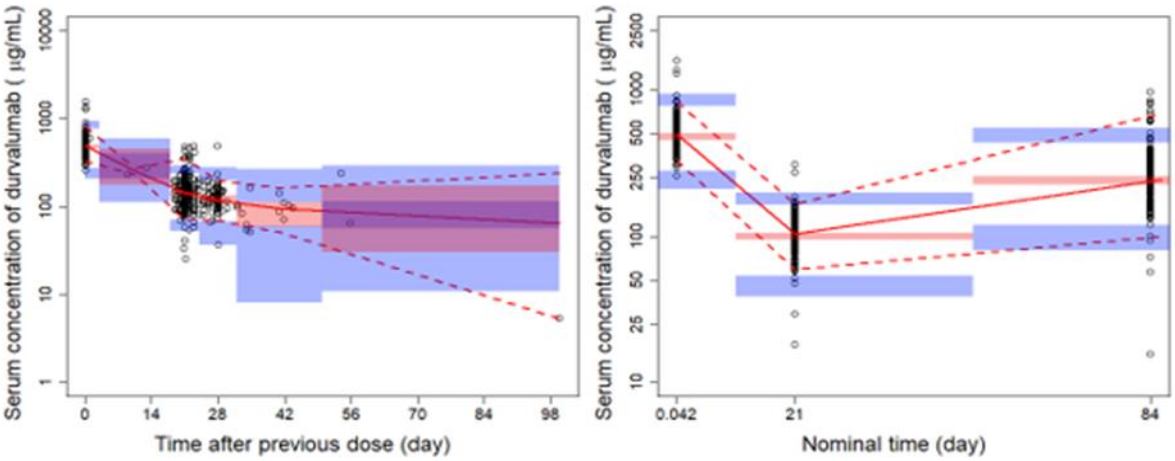
The durvalumab PopPK model was then refitted with PK data from the validation dataset only. Model structure remained, however, given the sparse PK sampling in the CASPIAN study, majority of the parameters were fixed during the refitting.

Initially, only the typical value estimates of CL, V1 and Tmax were re-estimated. Post hoc covariate analysis indicated the model did not adequately capture the body weight effect on CL since there was a significant correlation between body weight and ηCL (p=0.004). Therefore, the exponent of weight on CL was also re-estimated along with CL, V1 and Tmax. The updated PopPK model well described data from the CASPIAN study. The general goodness-of-fit plots, pcVPC (see Figure 2 and Figure 3), and NPC indicated that both the fixed and random effect components of the refitted PopPK model were reflective of the observed data.



Top: individual predicted (IPRED) serum durvalumab concentrations versus observed durvalumab concentrations (left) and population predicted (PRED) serum durvalumab concentrations versus observed serum durvalumab concentrations (right). Bottom: conditional weighted residuals (CWRES) versus time (left) and PRED (right). Points are individual data. Red solid lines represent the unit diagonal (top) or line at zero (bottom). Red dashed lines represent |CWRES| of 6. Blue dashed lines represent the loess smooth curves.

Figure 2: General goodness-of-fit plots of the updated model for durvalumab validation subjects



pcVPC, prediction-corrected visual predictive checks
Notes: Circles are observed durvalumab serum concentrations, solid red lines represent the median observed value, and dashed red lines represent the 2.5th percentile and 97.5th percentile of the observed values. Pink shaded areas represent the spread (5th percentile and 95th percentile) of the median predicted values, and purple shaded areas represent the spread (5th percentile and 95th percentile) of the 2.5th and 97.5th predicted percentile concentrations.

Figure 3: pcVPC of durvalumab concentration vs. time for validation subjects for the updated model

The mean bias for validation subjects was 0.0847% (95% CI [-0.030%, 0.200%]) which was not significantly different from zero (p value=0.147). The mean imprecision was 5.11% (95% CI [4.75%, 5.47%]).

Table 3: Summary of the re-estimated population PK parameters

Parameter	Descriptions	Estimates (RSE%)	
		Updated model	Previous model
θ_1	Clearance (CL, L/day)	0.226 (2.5%)	0.266 (2.9%)
θ_{14}	Influence of WT on CL	0.531 (20%)	0.302 (17%)
θ_2	Central volume (V_1, L)	3.13 (1.9%)	3.51 (1.0%)
θ_{18}	Log maximum magnitude change in CL (T_{max}, L/day)	-0.772 (10%)	-0.270 (39%)

CL clearance; RSE relative standard error; T_{max} log maximum magnitude of change in CL; V_1 central volume of distribution; WT weight
Source: Table 4, Population Pharmacokinetic (PopPK) Analysis of Durvalumab in Combination with Chemotherapy in the CASPIAN Study, Module 5.3.3.5

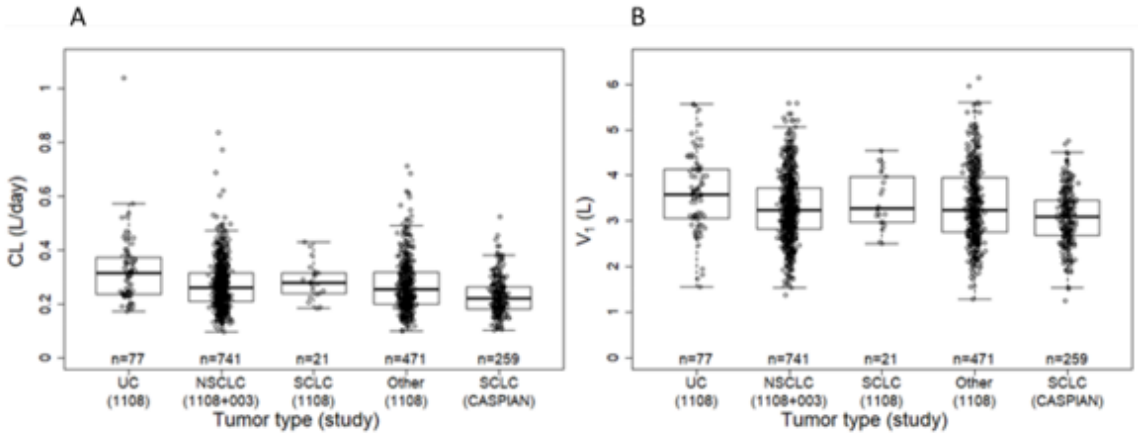
Table 4: Parameter estimates and the associated 95%CI and shrinkage from the refitted PopPK model

Parameter	Estimate (RSE%)	95% CI based on bootstrapping	BSV (CV%)	ETA shrinkage (%)
Clearance (CL, L/day)	0.226 (2.5%)	(0.214, 0.237)	27.3% (fixed*)	18.0%
Influence of WT on CL	0.531 (20%)	(0.331, 0.742)	-	-
Central volume (V_1, L)	3.13 (1.9%)	(3.01, 3.24)	22.1% (fixed*)	36.4%
Log maximum magnitude of change in CL (T_{max})	-0.772 (10%)	(-0.950, -0.610)	28.1% (fixed*)	66.3%

95% CIs were calculated based on 500 bootstrap runs
*BSV were fixed at the original monotherapy PopPK model estimates.

The model estimated typical CL was 0.226 L/day and V1 was 3.13 L which were respectively 15.0% and 10.8% lower than that estimated in previous developed PopPK model (CL=0.266 L/day and V1=3.51 L) (Table 5). The estimated Tmax decreased from -0.27 to -0.772 in the updated model, suggested a greater reduction in CL over time. The updated model also estimated a greater effect of body weight on CL, with the exponent increased from 0.302 to 0.531.

The geometric mean (%CV) of post hoc individual CLss and Vss estimates were 0.164 L/day (31.3%) and 5.48 L (13.9%), respectively, and the mean (%CV) of %change in post hoc individual CL estimates from baseline to steady state after 12 weeks dosing was -25.2% (10.5%).

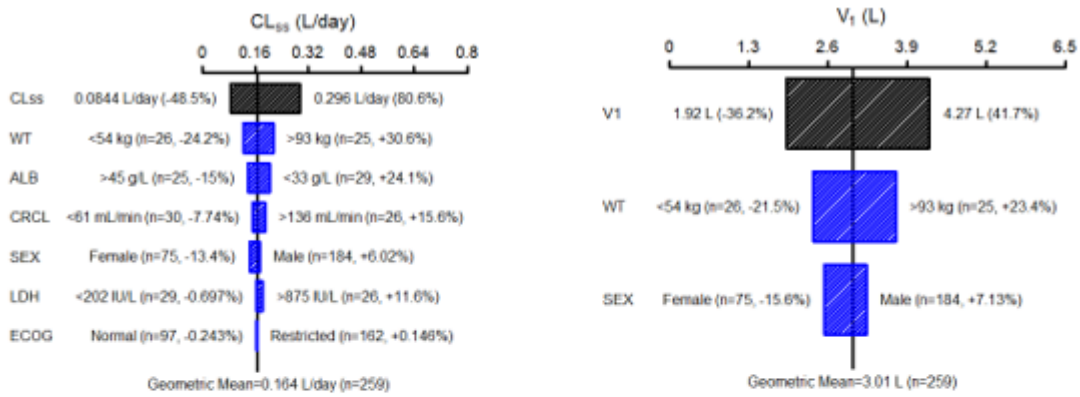


Individual post hoc PK parameters (CL [A] and V1 [B]) for studies 1108 and 003 (ATLANTIC) were obtained using the original monotherapy durvalumab PopPK model. Individual post hoc PK parameters for CASPIAN were obtained using the refitted PopPK model. The median is represented by the horizontal line in the middle of each box. The top and bottom ends of the box plot represent the 25th and 75th percentile (the lower and upper quartiles, respectively). The bars extending from the ends of the box to the outermost data represent 1.5 × (the upper or lower interquartile range).

Figure 4: Comparison of individual post hoc parameters between different cancer types in the model development dataset (including studies 1108 and 003) and CASPIAN

Impact of covariates

The effects of existing covariates (body weight, ALB, CRCL, sex, LDH and ECOG) on PK parameters were well described by the updated model. Post hoc evaluation showed that the absolute difference in geometric mean of the post hoc parameter values from the respective population geometric mean estimate at the top 10th%ile and the bottom 10th%ile of the covariate distribution or across covariate categories was up to 30.6%, 24.1%, 15.6%, 13.4%, 11.6%, and 0.243% for body weight, ALB, CRCL, sex, LDH, and ECOG on CLss, respectively, and up to 23.4% and 15.6% for body weight and sex on V1, respectively (Figure 5).



ALB albumin; CL_{ss} clearance at steady-state; CRCL creatinine clearance; ECOG Eastern Cooperative Oncology Group; LDH lactate dehydrogenase; V_1 central volume of distribution; WT body weight
Notes: The black shaded bar shows the 2.5th to 97.5th percentile of CL_{ss} or V_1 across the entire population. Each blue shaded bar represents the influence of covariates on the CL_{ss} and V_1. The label at the left end of the bar represents the covariate being evaluated. The upper and lower values for each covariate capture the top 10th percentile and the bottom 10th percentile of the covariate distribution in the population. The length of each bar describes the potential impact of the covariates on durvalumab CL_{ss} and V_1, with the percentage value in the parentheses at each end representing the percent change of CL_{ss} and V_1 from the overall geometric mean value across the entire population. The most influential covariates are at the top of the plot.

Figure 5: The effect of covariates on durvalumab CLss and V1

Additional covariates evaluated (age, BMI, baseline BIL, AST, ALT, tumour size, NLR, smoking history, and disease stage) were not significantly correlated with inter-individual variability of CL or V1. Race was found to significantly correlate with inter-individual variability on CL (Table 5). However, this may be due to a limited number of subjects in the non-White race group in the CASPIAN study (n=36/2/220/1 for Asian/Black/White/Other races).

Table 5: Impact of race on PK parameters of durvalumab

Characteristics	Race			
	Geometric mean (%CV)		%change from overall geometric mean of *post hoc* estimates in validation subjects	
	Asian	White	Asian	White
No. of subjects (%)	36 (14.1)	220 (85.9)	-	-
CL_{ss} (L/day)	0.142 (28.7)	0.168 (30.8)	-13.6%	2.17%
V_1 (L)	2.82 (15.7)	3.05 (19.3)	-6.54%	1.09%
Body weight (kg) [min, median, max]	[44, 62, 93]	[31, 74, 128]	-	-

In specific populations of interest (Asian, Japanese, subjects enrolled in different regions, and subjects with mild or moderate renal impairment), the geometric mean of individual post hoc parameters (CLss or V1) were within ±30% of those of the overall population.

Simulation of fixed dose regimen

For fixed dose evaluation, simulations were performed using the post hoc PK parameters to predict durvalumab exposure at steady state. Steady state was defined as the last (i.e. 4th) dosing cycle of the durvalumab + EP combination treatment phase in the CASPIAN study. AUCss, Cmin,ss and Cmax,ss were predicted across body weight quartiles at the fixed dose regimen of 1500 mg Q3W IV in order to quantify the impact of body weight on exposure.

The geometric mean values of the simulated AUCss, Cmax,ss, and Cmin,ss following 1500 mg Q3W durvalumab IV infusion in the validation subjects were 9162 µg*day/mL, 690 µg/mL, and 219 µg/mL, respectively. Compared with the overall geometric mean values, the geometric mean of the simulated durvalumab exposures in the lowest quartile of body weight were 17.9%, 17.3%, and 19.6% higher, and in the highest quartile of body weight were 17.3%, 15.8%, and 20.1% lower for AUCss, Cmax,ss, and Cmin,ss, respectively (Table 6).

Table 6: Impact of body weight on simulated steady state[a] exposure of durvalumab 1500 mg IV Q3W

Characteristics		Body Weight Quartiles			
		Q1	Q2	Q3	Q4
No. of subjects (%)		65 (25.1)	66 (25.5)	64 (24.7)	64 (24.7)
AUC_{ss} (µg*day/mL)	geometric mean (%CV)	10800 (24.4)	9420 (30.1)	9140 (32.5)	7580 (35.3)
	%change[b]	17.9%	2.82%	-0.24%	-17.3%
$C_{max,ss}$ (µg/mL)	geometric mean (%CV)	809 (20.7)	716 (18.2)	670 (20.1)	581 (19.1)
	%change[b]	17.3%	3.81%	-2.86%	-15.8%
$C_{min,ss}$ (µg/mL)	geometric mean (%CV)	262 (28.3)	226 (33.4)	221 (35.2)	175 (40.5)
	%change[b]	19.6%	3.19%	0.911%	-20.1%
Body weight (kg) [min, median, max]		[31, 55, 63]	[63, 68, 72]	[72, 79, 83]	[83, 91, 128]

[a] Steady state is defined as the last (4th) dosing cycle of the durvalumab + EP combination treatment phase in the CASPIAN study

[b] %change from overall geometric mean values of simulated exposures in validation subjects

Clinical studies

Key PK results from the CASPIAN study and the supportive studies are presented in Table 2 in section 2.3.1 Introduction. CASPIAN is the pivotal study and will be the only study summarised here.

CASPIAN is a Phase III, randomized, open-label, multicentre, global study to determine the efficacy and safety of durvalumab ± tremelimumab in combination with etoposide and platinum-based chemotherapy (EP) versus EP alone as first-line treatment in patients with extensive-stage small cell lung cancer (ES-SCLC). Patients were randomized at 1:1:1 to receive durvalumab + tremelimumab + EP, durvalumab + EP or EP alone. In the durvalumab + EP arm (Arm 2), patients received 1500 mg durvalumab via IV infusion every 3 weeks (Q3W) for 4 doses during the chemotherapy combination phase, followed by 1500 mg durvalumab monotherapy every 4 weeks (Q4W) via IV infusion until progression of disease. Patients in the EP treatment group (Arm 3) received EP for up to 6 cycles.

Durvalumab PK samples were collected at Cycle 1 Day 1 post-infusion, Cycle 2 Day 1 (predose), and Cycle 5 Day 1 (predose). Samples for determination of etoposide, carboplatin, and cisplatin in serum or plasma were obtained on Day 1 of Cycle 1.

Immunogenicity assessments (ADA sampling) were performed for Cycle 1 on Day 1 (predose), Cycle 5 on Day 1 (predose), and at 3-month follow-up.

The study randomized 537 patients with SCLC to receive durvalumab + EP (268 patients) or EP chemotherapy alone (269 patients). The randomization was stratified based on planned platinum-based therapy in Cycle 1 (carboplatin or cisplatin).

As of the 11 March 2019 DCO, the interim analysis for CASPIAN only included data in the EP and durvalumab + EP treatment groups; therefore, only durvalumab PK data from durvalumab + EP treatment group and EP PK data from EP and durvalumab + EP treatment groups are presented.

Pharmacokinetics of Durvalumab

Durvalumab PK data were available for a total of 263 patients in the durvalumab + EP treatment group of CASPIAN. No formal noncompartmental analysis was conducted due to the sparse PK sampling scheme. Following administration of durvalumab 1500 mg Q3W in combination with EP, the geometric mean (n, %CV) maximum serum concentration (Cmax; end of infusion) of durvalumab at Week 0 (Cmax,w0) was 503 (n=227, 30.5%) µg/mL Durvalumab trough serum concentrations (Ctrough) at Week 3 (Ctrough,w3) and Week 12 (Ctrough,w12) were 110 (n=236, 64.4%) and 241 (n=199, 49.7%) µg/mL, respectively. Durvalumab PK concentrations were within the expected exposure range following 1500 mg Q3W in combination with EP.

Pharmacokinetics of etoposide, carboplatin, and cisplatin

The PK data for EP were available in a total of 27 patients: 13 patients in the EP treatment group and 14 patients in the durvalumab + EP treatment group. Overall, PK profiles of etoposide, carboplatin, and cisplatin were similar between EP and durvalumab + EP treatment groups, suggesting that durvalumab does not have an impact on the PK of EP when administered as a combination therapy.

2.3.3. Pharmacodynamics

Mechanism of action

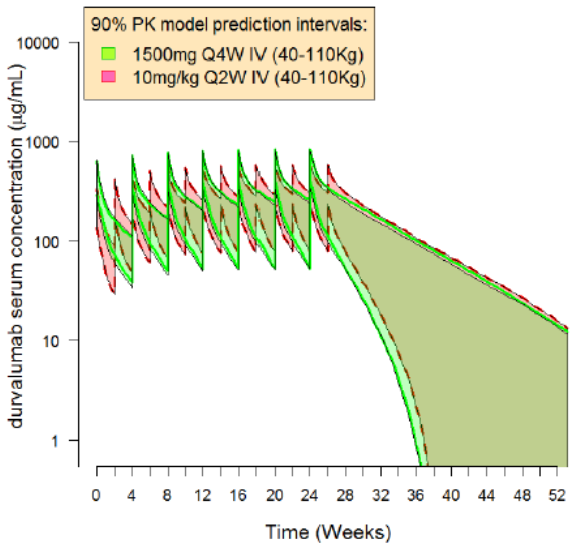
No mechanism of action studies have been submitted in this application.

Primary and secondary pharmacology

Rationale for dose selection

The approved durvalumab dose regimen in urothelial carcinoma and unresectable, Stage III NSCLC is 10 mg/kg Q2W. This regimen is aligned with the dose rationale based on nonclinical and clinical data that demonstrate a favorable benefit:risk profile in the respective patient populations.

The fixed dose of 1500 mg Q4W (equivalent to 20 mg/kg Q4W for an average body weight of 75 kg) was predicted to result in similar AUC and only modest difference in median peak and trough levels at steady state compared to 10 mg/kg Q2W based on PopPK simulations with the initial model (Figure 6).

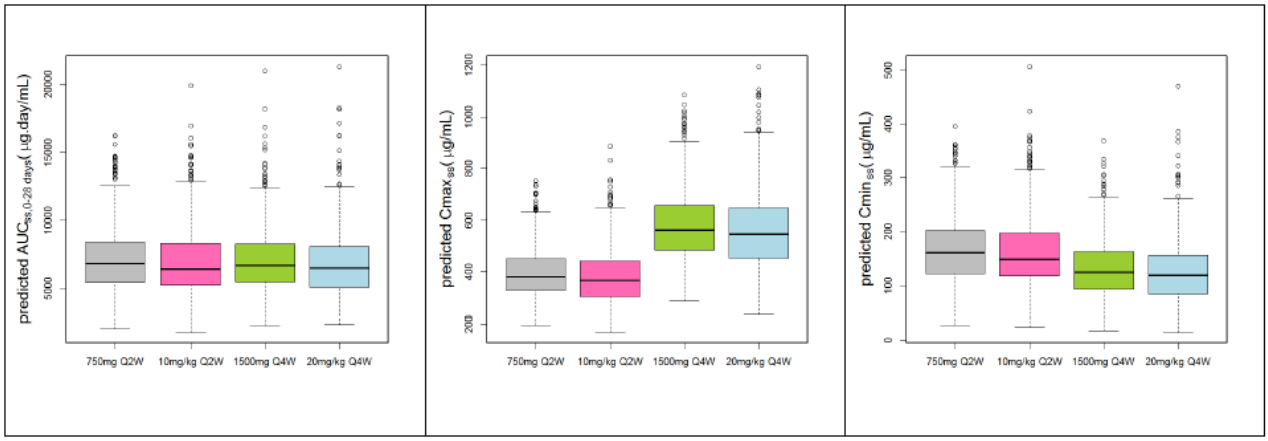


PK = pharmacokinetic; Q2W = every 2 weeks; Q4W = every 4 weeks.

The area (pink and green) represents the 90% prediction interval from the final PK model according to two different dosing schemes; they are delimited by the 5th and 95th percentiles of the simulated PK data obtained from a pool of n=1000 virtual patients.

Figure 6: Simulated PK profiles of durvalumab following 10mg/kg Q2W dosing and its fixed-dose equivalent of 1500 mg Q4W

The initial PopPK model, without time varying CL and developed on data from patients with solid tumors, identified 10 mg/kg IV Q2W as the dose of choice to maintain exposure levels above 53.3 µg/mL, with > 95% of patients expected to reach almost complete saturation of PD-L1 (99% target suppression) in Study 1108. Simulations with this model indicated that a 20 mg/kg Q4W posology and a fixed 1500 mg Q4W dose would result in comparable exposures (Figure 7). Therefore, the fixed dose of 1500 mg Q4W was selected as the dose regimen being investigated in multiple ongoing Phase 3 studies of durvalumab across cancer types.



AUC_{ss} = area under the plasma concentration-time curve at steady state; $C_{max,ss}$ = maximum concentration at steady state; $C_{min,ss}$ = trough concentration at steady state; Q2W = every 2 weeks; Q4W = every 4 weeks.

The predicted $AUC_{ss,0\text{-}28\ days}$ was used for comparison of durvalumab exposure levels predicted by the model across dosing regimens for a comparable dosing interval given the difference in dosing frequency (Q2W versus Q4W). $C_{max,ss}$ and $C_{min,ss}$ were taken as the predicted concentrations of durvalumab at Week 16 post-dose and pre-dose, respectively.

Figure 7: Boxplot of predicted AUCss, 0-28 days (left panel), Cmax,ss (middle panel), and Cmin,ss (right panel) distributions for 4 dosing regimens of durvalumab

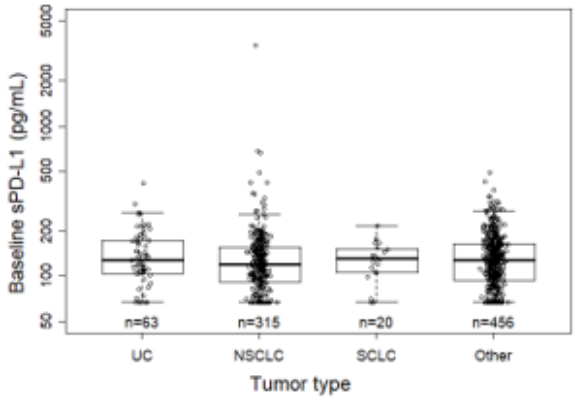
The geometric mean of end of infusion concentration levels following the first dose and trough concentration levels at Week 12 were 149% and 75% higher, respectively, when compared to those at 10 mg/kg Q2W based on pooled PK data across supportive studies (Table 7).

Table 7: Summary of serum durvalumab concentrations (PK-evaluable population)

Visit, timepoint	Geometric mean, µg/mL (geometric %CV) [n]		
	CASPIAN (N=263)	10 mg/kg Q2W pool (N=2509)	20 mg/kg Q4W pool (N=386)
Week 0, pre-infusion	NS	BLQ (NA) [88]	BLQ (NA) [6]
Week 0, post-infusion	503 (30.5) [227]	202 (46.5) [2209]	446 (38.0) [370]
Week 3, pre-infusion	110 (64.4) [236]	NS	NS
Week 12, pre-infusion	241 (49.7) [199]	137 (57.0) [235]	116 (68.0) [186]
Week 12, post-infusion	NS	273 (47.6) [132]	538 (58.9) [177]
Week 16, pre-infusion	NS	152 (55.7) [539]	NS
Week 16, post-infusion	NS	281 (38.4) [26]	NS
Week 24, pre-infusion	NS	167 (61.5) [379]	136 (59.2) [137]
Week 24, post-infusion	NS	367 (42.3) [288]	539 (47.3) [134]
3-month follow-up	NS	18.2 (186) [581]	12.8 (253) [71]

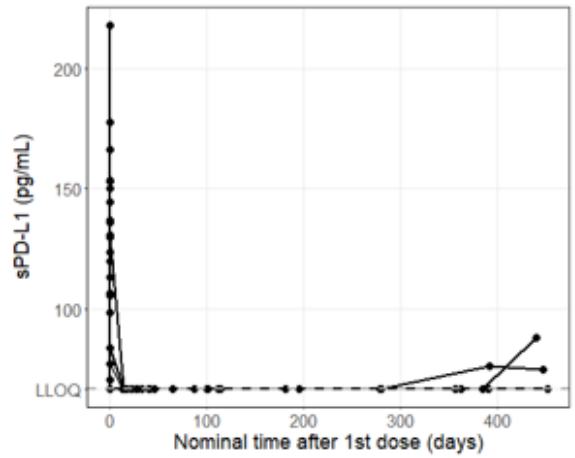
BLQ below lower limit of quantification; CV coefficient of variation; NA not applicable; NS no sample; PK pharmacokinetic; Q2W every 2 weeks; Q4W every 4 weeks.

Based on data from a previous durvalumab monotherapy trial (Study 1108), the baseline sPD-L1 levels were shown to be similar across UC, NSCLC, SCLC, and other cancer types (Figure 8). Although data on sPD-L1 suppression was not available in CASPIAN, post-baseline sPD-L1 data were available from 21 SCLC patients in Study 1108. All of these patients achieved complete sPD-L1 suppression following 10 mg/kg Q2W durvalumab treatment (Figure 9)



The median is represented by the horizontal line in the middle of each box. The top and bottom ends of the box plot represent the 25th and 75th percentile (the lower and upper quartiles, respectively). The bars extending from the ends of the box to the outermost data represent 1.5 × (the upper or lower interquartile range).

Figure 8: Distribution of baseline soluble PD-L1 levels by tumour type in study 1108



Solid black lines with dots represent the sPD-L1 profiles over time in individual patients. Dashed dark grey line represents the lower limit of quantification (LLOQ) of the sPD-L1 assay (67.1 pg/mL).

Figure 9: Individual soluble PD-L1 time profiles from SCLC patients treated with durvalumab 10 mg/kg Q2W from study 1108

Table 8: Distribution of observed serum durvalumab trough concentrations by post-baseline soluble PD-L1 level at matching time points in SCLC patients from study 1108

		Serum trough durvalumab concentration (μg/mL)			
sPD-L1	N	Mean	Median	Range (min-max)	10^{th}-90^{th} percentile
<LLOQ	34	103	85.8	41.0-264	45.6-155.8
≥LLOQ	0	-	-	-	-

LLOQ: lower limit of quantification. Trough time points are defined as one dosing interval (window: 11 to 17 days) from the previous dose.

2.3.4. PK/PD modelling

The relationship between predicted durvalumab PK exposure and the key efficacy/safety endpoints was evaluated based on data in the durvalumab + EP and EP groups from CASPIAN. The exposure-efficacy analysis was based on the full analysis population and the exposure-safety analysis was based on the safety analysis population. Patients (n=3) in the durvalumab + EP treatment group who did not receive treatment were excluded from the analysis. The total numbers of patients included in exposure-efficacy and exposure-safety analysis were 534 (EP/durvalumab + EP: 269/265), and 531 (EP/durvalumab + EP: 266/265), respectively.

The PopPK model-predicted AUCss was used as the primary exposure endpoint in the exposure-response (E-R) analysis. E-R relationships were also explored for Cmax,ss, Cmin,ss and the trough concentration after the first dose, C_{min1}.

Table 9: Baseline characteristics and exposure metrics of the ERE analysis population

Variable	EP (N=269)	Durvalumab+EP (N=265[a])
Continuous Covariates (abbreviation, unit)	**Median [min, max]**	**Median [min, max]**
Age (year)	63 [35,82]	62 [28,82]
Body weight (WT, kg)	71 [41,128]	72.2 [31,128]
Body mass index (BMI, kg/m^2)	25.1 [16.0,46.7]	25.5 [13.5,44.6]
Baseline lactate dehydrogenase (LDH, U/L)	364 [46,3461]	351 [83,6126]
Baseline albumin (ALB, g/L)[b]	39 [22.4,50.4]	40 [23.1,51.0]
AUC_{ss} (µg*day/mL)	-	9090 [3775,20743]
$C_{max,ss}$ (µg/mL)	-	686.9 [401.8,1472.6]
$C_{min,ss}$ (µg/mL)	-	221.1 [62.1,510.8]
C_{min1} (µg/mL)	-	106.2 [40.5,195.8]
Baseline Neutrophil-to-Lymphocyte Ratio (NLR)	4.01 [0.573,77.0]	3.44 [0.006,58.8]
Baseline Tumor Size per Investigator (BLTUMINV, mm)	124 [18,823]	129 [15,296]
Categorical Covariates (abbreviation, group)	**N**	**N**
Sex (Male/Female)	184/85	188/77
Race (White/Asian/Black/Other)	221/42/3/3	226/36/2/1
Smoking History (SMOKH, Never/Former/Current Smoker)	15/128/126	22/124/119
Baseline Eastern Cooperative Oncology Group performance status (ECOG, 0/>=1)	90/179	97/168
Anti-drug antibody status post-baseline (ADA, missing/0/1)	267/2/0	59/206/0
Disease Stage (DIST, III/IV)	24/245	28/237

[a] 3 subjects in the full analysis population were not included in the analysis since they did not receive treatment.
[b] 8 subjects had abnormal ALB values (<5 g/L). Those ALB values were regarded as missing values.

E-R relationship for efficacy

The E-R relationships for time-to-event variable of OS and PFS were explored by Kaplan-Meier estimates. Confounding effects of baseline prognostic factors (ECOG, ALB, LDH, NLR, baseline tumour size, smoking history and disease stage) on the E-R relationship of OS was investigated by means of a Cox proportional-hazards model developed for durvalumab + EP treated group (N=265). The final model included LDH and NLR as the only significant factors ($p<0.05$) for the OS hazard.

Table 10: Summary of model parameters from the final OS model

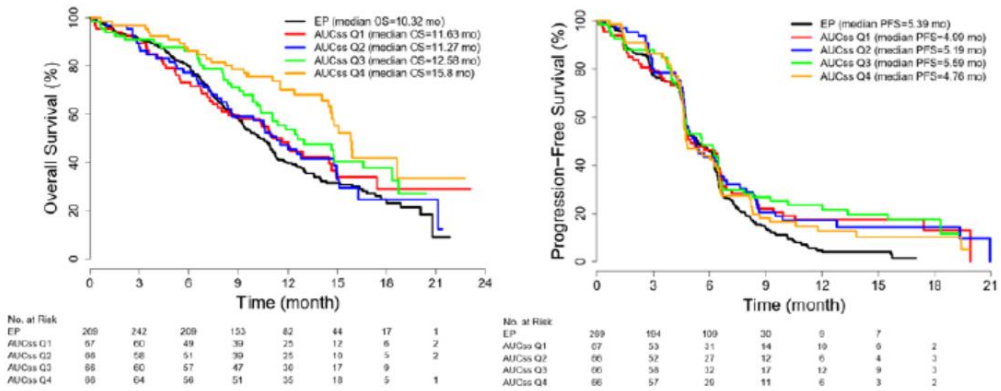
Predictor	Parameter Estimates		Wald	95% CI for β	
	β	exp(β)	p-value	Lower	Upper
Log(LDH)	0.6206	1.8601	<0.001	0.3684	0.8729
Log(NLR)	0.3295	1.3903	0.026	0.0395	0.6195

Safety endpoints were evaluated as binary outcomes (yes/no). Boxplots of exposures stratified by AE outcomes were generated. The probability of AE events was calculated and plotted across exposure quantiles in durvalumab + EP treated patients.

The effects of body weight on safety and efficacy endpoints were also evaluated. For safety endpoints, the probability of AE events was calculated by body weight quantiles in durvalumab + EP treated patients. For efficacy endpoints, Kaplan-Meier plots of OS and PFS stratified by body weight quantiles were generated. E-R analysis was performed using R 3.5.1.

Results:

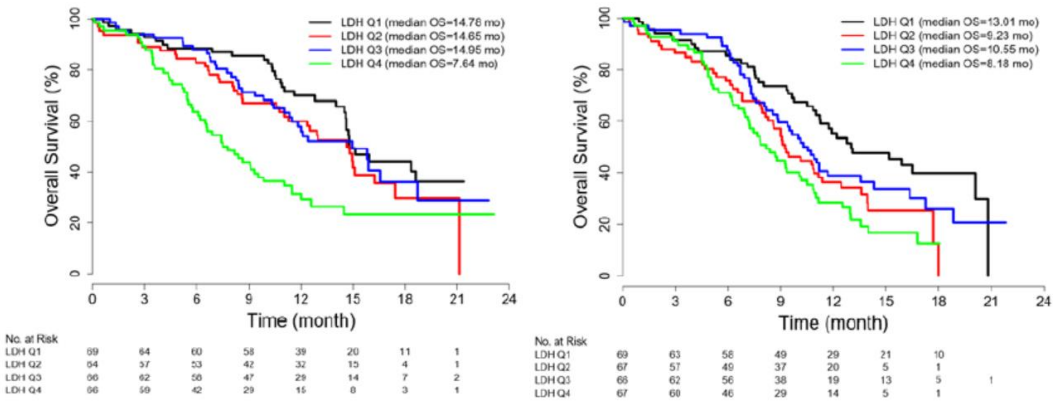
The plots of Kaplan-Meier OS curve stratified by quartiles of model-predicted AUCss, Cmax,ss, Cmin,ss, and Cmin1 for durvalumab + EP treated group (N=265) suggested that a slightly longer OS was observed in the fourth quartile of durvalumab PK exposure compared to the lower three quartiles, while all four exposure quartiles showed similar or longer median OS compared to the EP control arm (Figure 10; left panel). There was no apparent relationship between PFS and any of the durvalumab PK exposure metrics in the durvalumab + EP treated patients (Figure 10; right panel).



Kaplan–Meier OS curves (left) and PFS curves (right) stratified by AUC_{ss} quartiles in durvalumab + EP treated subjects compared to the EP arm. The median AUC_{ss} values of the quartiles were 6495 µg*day/mL, 8354 µg*day/mL, 10099 µg*day/mL, and 12737 µg*day/mL respectively.

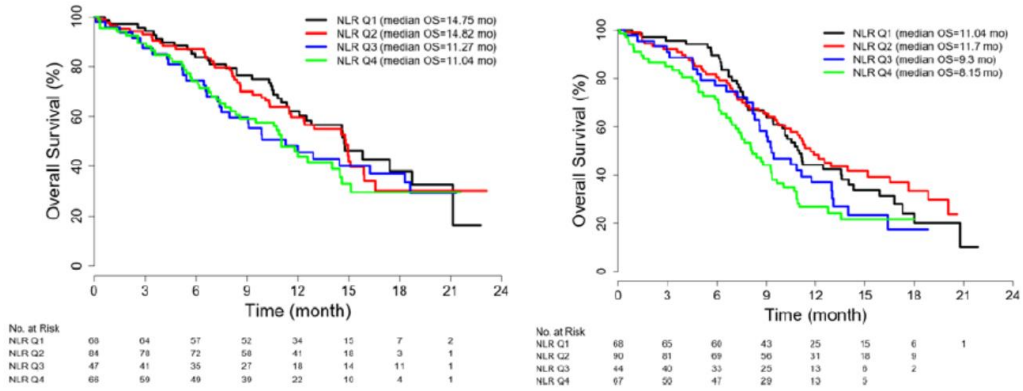
Figure 10: Kaplan-Meier OS and PFS curves stratified by AUCss quartiles

The final model included LDH and NLR as the only significant factors ($p<0.05$). Higher LDH and NLR were associated with shorter survival in both EP and durvalumab + EP groups, suggesting they are prognostic factors for OS (Figure 11 and Figure 12). Patients in the lowest AUCss or Cmin1 quartile had the highest median LDH and NLR values among all four exposure quartiles (Figure 13). Neither AUCss nor Cmin1 was significant when added on top of the final model.



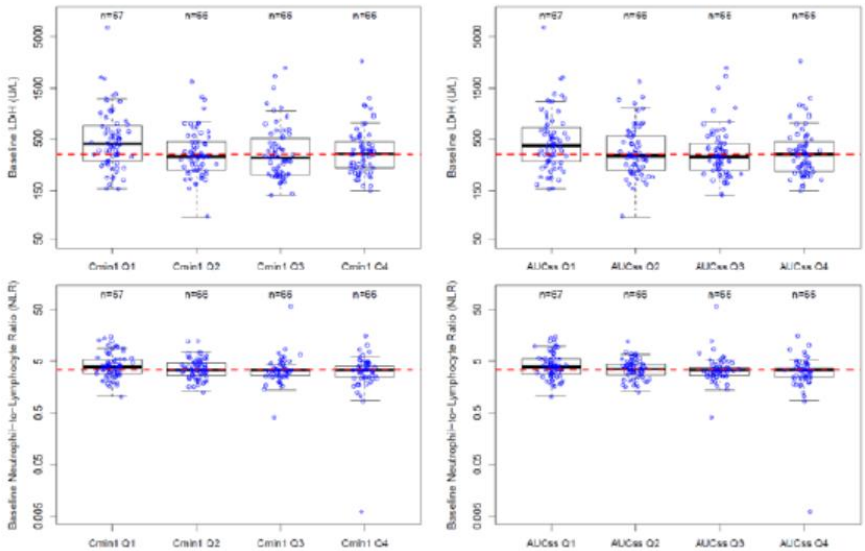
Left: Kaplan–Meier OS curves stratified by LDH quartiles in durvalumab + EP treated subjects. Missing value were imputed by the population median. The median LDH values of the quartiles were 209 U/L, 301 U/L, 411 U/L, and 719 U/L, respectively. Right: Kaplan–Meier OS curves stratified by LDH quartiles in EP treated subjects. Missing value were imputed by the population median. The median LDH values of the quartiles were 198 U/L, 305 U/L, 419U/L, and 807 U/L, respectively.

Figure 11: Kaplan-Meier OS curves stratified by LDH quartiles



Left: Kaplan–Meier OS curves stratified by NLR quartiles in durvalumab + EP treated subjects. Missing value were imputed by the population median. The median NLR values of the quartiles were 2.1, 3.4, 3.9, and 6.0, respectively. Right: Kaplan–Meier OS curves stratified by NLR quartiles in EP treated subjects. Missing value were imputed by the population median. The median NLR values of the quartiles were 2.1, 4.0, 4.5, and 7.5, respectively.

Figure 12: Kaplan-Meier OS curves stratified by NLR quartiles

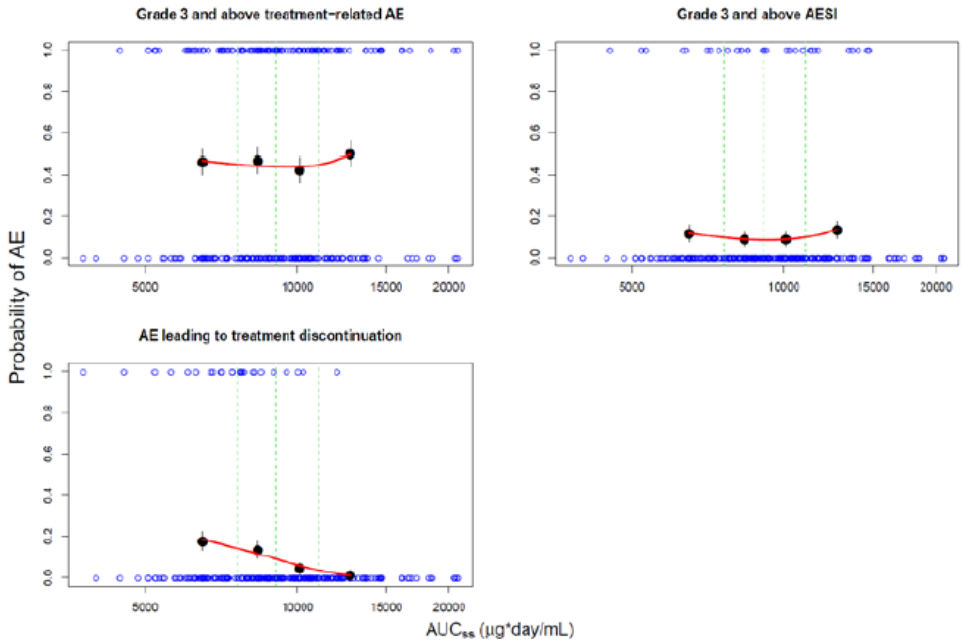


Individual subjects are represented by a blue circle. The median is represented by the horizontal line in the middle of each box. The top and bottom ends of the box plot represent the 25th and 75th percentile (the lower and upper quartiles, respectively). The bars extending from the ends of the box to the outermost data represent 1.5 × (the upper or lower interquartile range). The dashed red horizontal line represents the median value of exposures in the overall population.

Figure 13: Boxplots of LDH and NLR stratified by AUCss and Cmin1 quartiles

E-R relationship for safety

The distribution of durvalumab exposure were similar between patients who had the AE and those who didn't for Grade 3 and above treatment related AE and Grade 3 and above AESI. However, the median values of exposure appeared to be lower in patients with AE leading to treatment discontinuation among durvalumab + EP treated subjects (N=265) in the CASPIAN study (Figure 14).



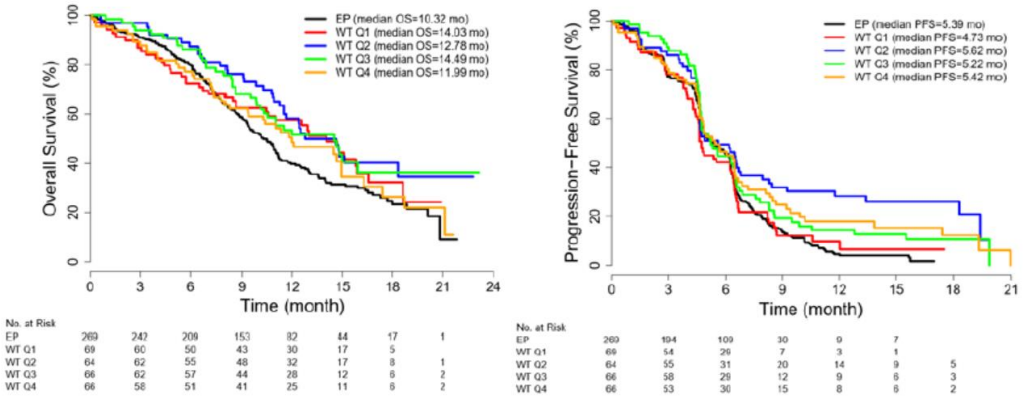
The blue open circles reflect the observed events in durvalumab + EP treated subjects. The black solid circles are the observed probability of AEs and the error bars are the standard errors (calculated as sqrt (P*(1-P)/N), where P is probability of AE and N is the number of patients in each quantile bin) for quartiles (25%, 50% and 75%, green vertical dotted lines) of exposures (plotted at the median value within each quartile). The red lines are smooth curves (loess) to show the relationship between two variables.

Figure 14: Probability of selected AEs by quartiles of AUCss (durvalumab + EP group)

There appeared to be an inverse relationship between exposure and AE leading to treatment discontinuation, which could be due to small number of AE in this category.

Body weight impact on efficacy and safety

To assess the impact of body weight on efficacy and safety endpoints following the fixed dosing regimen of durvalumab in the CASPIAN study, the Kaplan-Meier curves of OS and PFS, and probability of selected AEs were stratified by body weight for patients in the durvalumab + EP treated group. The results suggested that there was no clear trend between body weight and OS, PFS (Figure 15) or any of the safety endpoints evaluated (Table 7).



Kaplan–Meier OS and PFS curves for body weight categories in durvalumab + EP treated subjects to the EP arm. The median body weight of the quartiles were 56 kg, 68 kg, 79 kg, and 92 kg, respectively.

Figure 15: Kaplan-Meier OS and PFS curves stratified by body weight quartiles

Table 11: The percentage of patients in the durvalumab +EP group having AE by weight quartiles

AE Endpoints	% Patients in the durvalumab + EP group having AE by weight quartile % (Yes/No)			
	Q1 (N=69) [31kg-63kg]	Q2 (N=64) [63 kg-72.2kg)	Q3 (N=66) [72.2kg-83.1 kg]	Q4 (N=66) [83.1 kg-128 kg]
Grade 3 and above treatment-related AE	44.9% (31/38)	46.9% (30/34)	50.0% (33/33)	43.9% (29/37)
Grade 3 and above AESI	10.1% (7/62)	6.30% (4/60)	12.1% (8/58)	15.2% (10/56)
AE leading to treatment discontinuation	7.25% (5/64)	4.69% (3/61)	4.55% (3/63)	21.2% (14/52)

There appeared to be a numerically higher rate of AE leading to treatment discontinuation in the highest quartile of body weight.

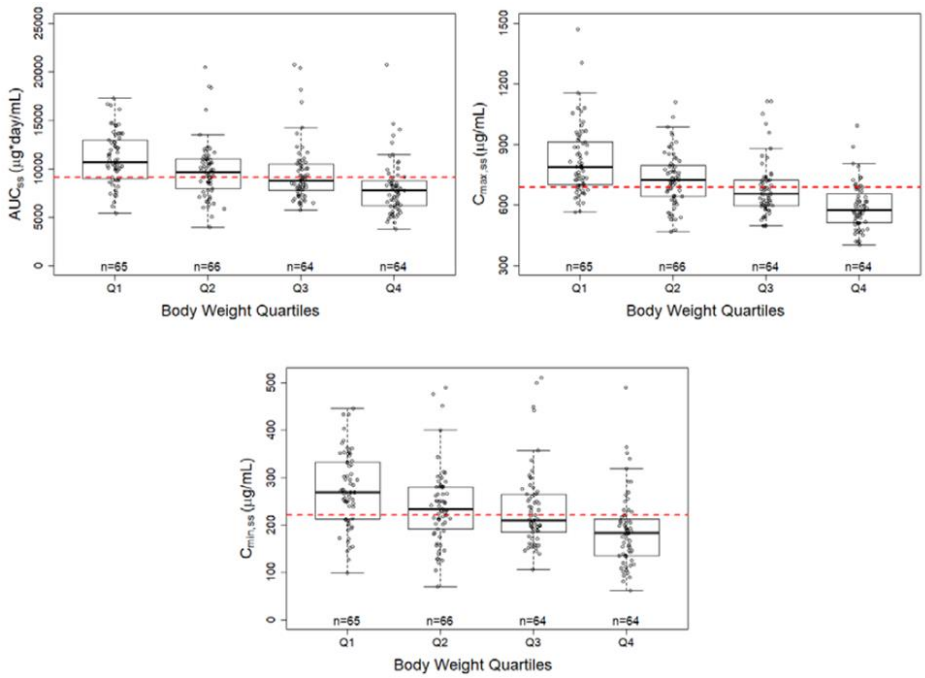


Figure 16: Simulated steady state exposures of durvalumab stratified by body weight

The results showed that there was no clinically meaningful relationship between increased durvalumab exposure and efficacy or safety risk in the durvalumab + EP treated patients in CASPIAN. Additionally, there was no apparent relationship between body weight and efficacy or safety risk in these patients.

Immunogenicity

The ADA-evaluable population was defined as patients who have a non-missing baseline ADA and at least 1 non-missing post-baseline results. ADA results were pooled across 9 supportive studies (Study 1108, ATLANTIC, PACIFIC, ARCTIC, MYSTIC, Japan Study 02, HAWK, CONDOR, and EAGLE) including subjects treated with dosing regimens of durvalumab at 10 mg/kg Q2W and 20 mg/kg Q4W (pan-tumor monotherapy pool), and compared with those in CASPIAN.

Across studies, the ADA prevalence ranged from 3.9% (5 of 127 patients) to 18.2% (4 of 22 patients), with an ADA incidence range of 0% (0 of 201 patients) to 9.1% (2 of 22 patients). The occurrence of nAb-positive subjects was <1% across the studies, with only 1 exception (ARCTIC, Sub-study B; 2.6%

[2 of 76 patients]). In the placebo-controlled PACIFIC study, immunogenicity results were similar between the placebo and active treatment groups.

Table 12: Summary of immunogenicity results for durvalumab (ADA-evaluable population)

ADA category	CASPIAN (N=201) n (%)	10 mg/kg Q2W pool (N=2044) n (%)	20 mg/kg Q4W pool (N=236) n (%)	Combined 10 mg/kg Q2W and 20 mg/kg Q4W pan-tumor pool (N=2280) n (%)
ADA prevalence[a]	11 (5.5)	120 (5.9)	19 (8.1)	139 (6.1)
Median of maximum titer	2.0	4.0	4.0	4.0
ADA incidence[b]	0 (0.0)	61 (3.0)	8 (3.4)	69 (3.0)
Median of maximum titer	NA	4.0	4.0	4.0
ADA-positive post-baseline and positive at baseline	0 (0.0)	10 (0.5)	3 (1.3)	13 (0.6)
Median of maximum titer	NA	8.0	4.0	8.0
ADA-positive post-baseline and not detected at baseline	0 (0.0)	57 (2.8)	8 (3.4)	65 (2.9)
Median of maximum titer	NA	4.0	4.0	4.0
ADA not detected post-baseline and positive at baseline	11 (5.5)	53 (2.6)	8 (3.4)	61 (2.7)
Median of maximum titer	2.0	4.0	4.0	4.0
Treatment-boosted ADA[c]	0 (0.0)	4 (0.2)	0 (0.0)	4 (0.2)
Median of maximum titer	NA	6.0	NA	6.0
Persistent positive ADA[d]	0 (0.0)	43 (2.1)	8 (3.4)	51 (2.2)
Median of maximum titer	NA	4.0	4.0	4.0
Transient positive ADA[e]	0 (0.0)	24 (1.2)	3 (1.3)	27 (1.2)
Median of maximum titer	NA	2.0	4.0	3.0
nAb positive at any visit	0 (0.0)	10 (0.5)	2 (0.8)	12 (0.5)
Median of maximum titer	NA	16.0	36.0	16.0

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

[b] ADA incidence is the proportion of ADA-evaluable patients who were treatment-emergent ADA-positive.

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

[d] 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.

[e] 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.

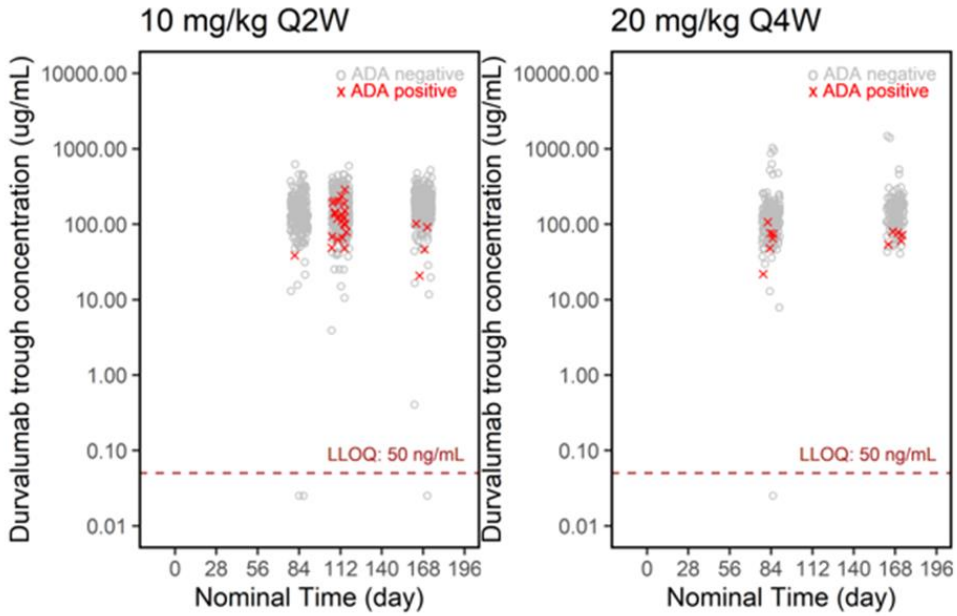
ADA anti-drug antibody; nAb neutralizing antibody; Q2W every 2 weeks; Q4W every 4 weeks.

Note: N is the number of patients in the safety analysis set in the treatment group. The denominator for calculation of percentage for all categories is the number of ADA evaluable patients (defined as the patients in the safety analysis set who have a non-missing baseline ADA and at least 1 non-missing post-baseline results) in the treatment group. The denominator for ADA evaluable patients category is N.

Note: If a patient had more than 1 titer result, the maximum titer result was used, regardless of whether it was baseline or post-baseline.

In the CASPIAN study, ADA to durvalumab could be detected as early as Week 12. A comparison of the kinetics of ADA responses in patients treated with durvalumab 1500 mg Q3W in combination with EP versus durvalumab alone could not be done due to the small number of ADA-positive patients at each post-baseline visit (n≤3 at all visits) in the pools. None of the ADA-positive patients in CASPIAN tested positive at post-baseline timepoints. Therefore, the impact of ADA on PK was not evaluated.

The impact of ADA on the PK of durvalumab has been evaluated in the previous PopPK modelling based on data from Study 1108, ATLANTIC, and PACIFIC. In the previous PopPK analysis, ADA was identified as a significant covariate and the PK-covariate relationship assessment showed that patients who were ADA positive had lower exposure levels of durvalumab with a reduction of less than 30% of PK exposure (AUCss, Cmax,ss, and Cmin,ss) compared to a typical patient.



ADA anti-drug antibody; LLOQ lower limit of quantification; Q2W once every 2 weeks; Q4W once every 4 weeks
Notes: ADA negative: patients without post-baseline ADA positive samples; ADA positive: patients with post-baseline ADA positive samples

Figure 17: Individual durvalumab trough concentrations in patients with post-baseline ADA positive samples versus others

2.3.5. Discussion on clinical pharmacology

Only sparse PK data from the D+EP arm were included in the interim report of the CASPIAN study. The dosing regimen for durvalumab has been changed from a weight-based posology in the approved indication (unresectable stage III NSCLC) to a fixed dose posology in ES-SCLC. Additionally, the regimen is switched from Q3W during the combination phase (4 initial cycles) to Q4W in the maintenance phase (as of cycle 5), until disease progression. PK sampling was sparse in the induction phase (C1D1 post-infusion, C2D1 predose and C5D1 predose) and no PK samples were collected during the maintenance phase of treatment.

ADA sampling was performed on C1D1 predose, C5D1 predose and at 3-months follow-up in CASPIAN. The ADA prevalence in CASPIAN interim analysis and across earlier studies was low. The data indicate that immunogenicity have no clinically relevant impact on PK of durvalumab.

The initial 2-compartment Pop PK model with dual linear and nonlinear (Michaelis-Menten) elimination, was amended to include a time-varying clearance function. The amended PopPK model could not fit the

validation data from CASPIAN (D+EP arm) but underpredicted the sparse concentration data collected in ES-SCLC patients. The model was refitted with the CASPIAN data set only and the simulation-based diagnostics indicated a better fit. The reasons behind the difference in PK are unclear. The PK bridge from mg/kg to a fixed dose is based on 3 PK timepoints taken within the first 12 weeks of treatment. The CASPIAN PK data set does not contain durvalumab monotherapy data and the PK population is different. Further model validation showed the PK data was informing the model adequately.

The rationale for dose selection in arm 2 (D+EP) was based on simulations with the initial PopPK model. The fixed dose of 1500 mg Q4W was predicted to result in similar AUC at steady state as the approved 10 mg/kg Q2W durvalumab dose regimen.

A serum exposure maintained above 53.3 µg/mL was identified to result in >95% of patients reaching 99% target suppression in patients with solid tumours. Comparing PD-L1 data across cancer types in Study 1108, showed complete sPD-L1 suppression. The 1108 study included data from 21 SCLC patients presumably with worse disease status than patients enrolled in CASPIAN (treatment naïve). Therefore patients are expected to have sPD-L1 suppression throughout the treatment period of CASPIAN.

The CASPIAN study results indicated that durvalumab 1500 mg Q3W in combination with EP for 4 cycles followed by durvalumab 1500 mg Q4W monotherapy is an appropriate dose for patients with ES-SCLC.

These results of the E-R relationship for safety show no evidence of higher durvalumab exposure leading to increased rates of these AEs. Therefore, no clinically relevant E-R relationship was observed between durvalumab PK exposure and the safety endpoints of interest among durvalumab + EP treated subjects in the CASPIAN study.

Considering the significant effect from weight upon CL and V1, the conversion from weight-based to flat dose was further justified by additional simulations at body weight extremes in both genders. The shift from Q3W to Q4W after induction might result in even lower Cmin values. "Worst case" simulations suggested that 95% patients would still maintain target exposure throughout the treatment period, independent of body weight. Patients with a body weight of 30 kg or less must receive weight-based dosing, equivalent to IMFINZI 20 mg/kg in combination with chemotherapy every 3 weeks (21 days) for 4 cycles, followed by 20 mg/kg every 4 weeks as monotherapy until weight increases to greater than 30 kg.

PK drug-drug interaction between durvalumab and chemotherapy was assessed in the CASPIAN study and showed concomitant treatment with durvalumab did not impact the PK of etoposide, carboplatin or cisplatin. Additionally, based on population PK analysis, concomitant chemotherapy treatment did not meaningfully impact the PK of durvalumab (see section 4.5 of the SmPC).

2.3.6. Conclusions on clinical pharmacology

The previous amended Pop PK model underpredicted the PK data set from CASPIAN and the model was refitted to describe the PK of durvalumab in ES-SCLC patients. The rationales for the fixed dosing schedule and posology change from Q3W (induction) to Q4W (maintenance) were supported by additional simulations and considered acceptable. Further subgroup analyses of body weight extremes did not imply dose adjustment for these patients with the exception of patients with a body weight of 30 kg or less who must receive weight-based dosing.

2.4. Clinical efficacy

2.4.1. Dose response studies

No additional dose-response study was performed. In the CASPIAN study, a fixed dose of 1500 mg durvalumab and 75 mg tremelimumab were used (see discussion on clinical pharmacology).

2.4.2. Main study

CASPIAN (study D419QC00001)

CASPIAN is a phase III, open-label, randomised, three-arm, multicentre trial designed to determine the efficacy and safety of durvalumab + tremelimumab + EP (D+T+EP) or durvalumab + EP (D+EP) vs. EP alone as first-line treatment in patients with ES-SCLC. A schematic diagram of the overall study design is shown in the figure below.

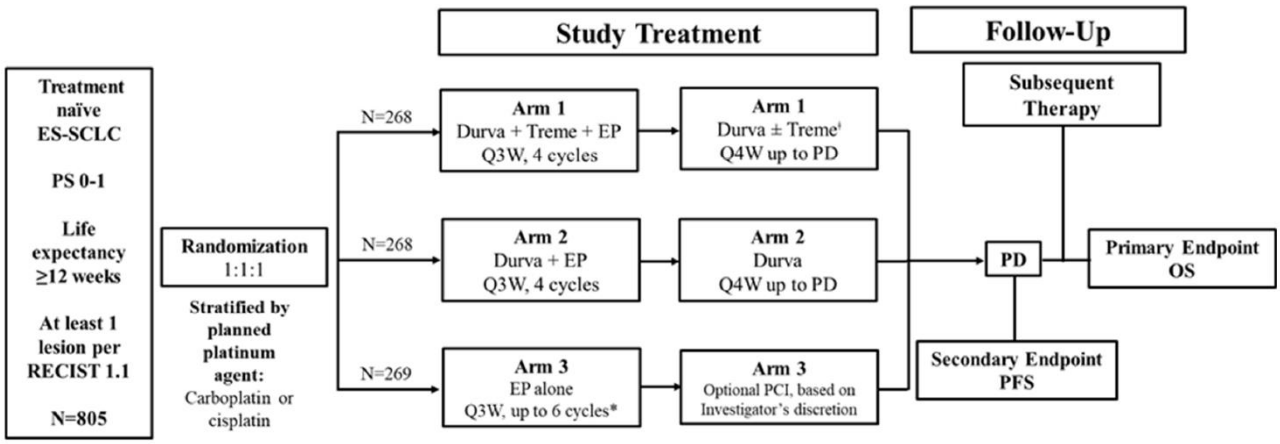


Figure 18: Flow chart of overall study design

Tumour assessments were performed at Screening as baseline with follow-ups at Week 6 ±1 week from the date of randomization, at Week 12 ±1 week and then every 8 weeks ±1 week until confirmed objective disease progression or off-study.

Methods

Study participants

Inclusion criteria:

- Male or female ≥18 years at the time of Screening (≥20 years in Japan).
- Written informed consent.
- Histologically or cytologically documented extensive disease (AJCC 7th edition stage IV SCLC [T any, N any, M1 a/b]), or T3-4 due to multiple lung nodules that are too extensive or have tumour/nodal volume that is too large to be encompassed in a tolerable radiation plan.
    - Brain metastases; must have been asymptomatic or treated and stable off steroids and anti-convulsants for at least 1 month prior to study treatment. Patients with suspected

brain metastases at screening should have had a CT/MRI of the brain prior to study entry.

- Provision of an archived tumour tissue block (or at least 15 newly cut unstained slides) where such samples exist.
- Patients must have been considered suitable to receive a platinum-based chemotherapy regimen as 1st line treatment for the ES-SCLC.
- Life expectancy ≥12 weeks at Day 1.
- WHO/ECOG Performance Status of 0 or 1 at enrolment.
- Body weight >30 kg.
- Measurable disease: at least 1 lesion, not previously irradiated, that could be accurately measured at baseline as ≥10 mm in the longest diameter (except lymph nodes which must have a short axis ≥15 mm) with computed tomography (CT) or magnetic resonance imaging (MRI) and that was suitable for accurate repeated measurements as per RECIST 1.1 guidelines.
- No prior exposure to immune-mediated therapy including, but not limited to, other anti-CTLA-4, anti-PD-1, anti-PD-L1, and anti-PD-L2 antibodies, excluding therapeutic anticancer vaccines.
- Adequate organ and bone marrow function.
- Evidence of post-menopausal status or negative urinary or serum pregnancy test for female pre-menopausal patients.

Exclusion criteria:

- Involvement in the planning and/or conduct of the study.
- Previous investigational product (IP) assignment in the present study.
- Concurrent enrolment in another clinical study, unless it was an observational (non-interventional) clinical study or during the follow up period of an interventional study.
- Participation in another clinical study with an IP during the last 4 weeks.
- Medical contraindication to etoposide platinum (carboplatin or cisplatin) based chemotherapy.
- Any history of radiotherapy to the chest prior to systemic therapy or planned consolidation chest radiation therapy. Radiation therapy outside of the chest for palliative care (i.e. bone metastasis) was allowed but must have been completed before first dose of the study medication.
- Any concurrent chemotherapy, IP, biologic, or hormonal therapy for cancer treatment.
- Concurrent use of hormonal therapy for non-cancer related conditions (e.g. hormone replacement therapy) was acceptable.
- Major surgical procedure (as defined by the investigator) within 28 days prior to the first dose of IP. Note: Local surgery of isolated lesions for palliative intent was acceptable.
- History of allogeneic organ transplantation.
- Had a paraneoplastic syndrome (PNS) of autoimmune nature, requiring systemic treatment (systemic steroids or immunosuppressive agents) or had a clinical symptomatology suggesting worsening of PNS.

- 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).
- Uncontrolled intercurrent illness, including but not limited to, ongoing or active infection, ILD, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, serious chronic gastrointestinal conditions associated with diarrhoea, or psychiatric illness/social situations that would have limited compliance with study requirement, substantially increase risk of incurring AEs or compromise the ability of the patient to give written informed consent.
- History of another primary malignancy.
- History of leptomeningeal carcinomatosis.
- History of active primary immunodeficiency.
- Active infection including tuberculosis, hepatitis B, hepatitis C, or human immunodeficiency virus (positive HIV 1/2 antibodies).
- Current or prior use of immunosuppressive medication within 14 days before the first dose of durvalumab or tremelimumab. However, systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone or its equivalent were allowed.
- Receipt of live, attenuated vaccine within 30 days prior to the first dose of IP.
- Female patients who were pregnant or breastfeeding or male or female patients of reproductive potential who were not willing to employ effective birth control.
- Known allergy or hypersensitivity to durvalumab, tremelimumab, etoposide, carboplatin, cisplatin, or any of their excipients.
- Prior randomization or treatment in a previous durvalumab and/or tremelimumab clinical study regardless of treatment arm assignment.

Treatments

Patients were to receive durvalumab, with or without tremelimumab, in combination with standard of care etoposide platinum chemotherapy (D+T+EP, arm 1 or D+EP, arm 2) or chemotherapy alone (EP alone, arm 3).

The platinum agent in the EP treatment could be either carboplatin or cisplatin, and was based on the Investigator's choice.

Duration of treatment: In the experimental arms (arms 1 and 2) the study allowed up to 4 cycles of EP (Q**3**W), which is consistent with that observed in other studies combining platinum-based chemotherapy with investigational agents, particularly immunotherapies, to minimize the toxicity burden to patients (Horn et al 2018). In the control group, at the Investigator's discretion, up to 6 cycles of EP (Q**3**W) were allowed.

After the 4 cycles of D+T+EP (arm 1) or D+EP (arm 2), durvalumab +/- tremelimumab (respectively) could be continued Q**4**W until confirmed progressive disease (PD), although treatment through progression was permitted if the patient was deriving benefit.

Treatment arms	During Chemotherapy Q3W				Post Chemotherapy Q4W		
	Cycle 1 Week 0	Cycle 2 Week 3	Cycle 3 Week 6	Cycle 4 Week 9	Week 12	Week 16	Week 20 to PD
Arm 1	EP + Durva + Treme	EP + Durva + Treme	EP + Durva + Treme	EP + Durva + Treme	Durva	Durva + Treme*	Durva
Arm 2	EP + Durva	EP + Durva	EP + Durva	EP + Durva	Durva	Durva	Durva
Arm 3	EP	EP	EP	EP**			

* In the case of dose delay(s) more than one durvalumab + tremelimumab combination dose could have been given post-chemotherapy to ensure that up to 5 combination doses were administered in Arm 1.

** In Arm 3, EP could have been given for an additional 2 cycles Q3W on Weeks 12 and 15 (ie, total 6 cycles post-randomization) if clinically indicated, at the investigators' discretion before patients entered Follow-up. PCI could also have been given at investigators discretion. This did not alter the planned scan schedule Q8W starting at Week 12 for patients in Arm 3.

Durvalumab dose was 1500 mg during chemotherapy and 1500 mg post-chemotherapy; tremelimumab dose was 75 mg.

Note: Patients whose weight fell to 30 kg or below must have received weight-based dosing – equivalent to 20 mg/kg of durvalumab and 1 mg/kg of tremelimumab until the weight improved to >30 kg, at which point the patient should have started receiving the fixed dosing of durvalumab at 1500 mg and tremelimumab at 75 mg.

Figure 19: Dosing scheme

Dosing scheme and route of administration: All medications were administered intravenously (IV).

- Durvalumab was administered at 1500 mg (flat dose) Q3W for 4 cycles in the induction phase and then at 1500 mg Q4W in the maintenance phase in both experimental arms (D+T+EP and D+EP).
- Tremelimumab was administered at 75 mg (flat dose) Q3W for 4 cycles in the induction phase and then an additional dose of 75 mg was given in week 16 in arm 1 (D+T+EP).
- EP: Etoposide was administered at 80-100 mg/m2 with either carboplatin (area under the curve 5-6) or cisplatin (75-80 mg/m2) Q3W for 4 cycles in arms 1 and 2; and for up to 6 cycles in the control arm (arm 3).

Dose modifications and interruptions: Dose reductions were not permitted for durvalumab and tremelimumab. In case of G2 AEs, durvalumab or tremelimumab were held until resolution to G≤1. In case of G≥3 AEs, durvalumab or tremelimumab were permanently discontinued.

EP-related toxicity management, dose adjustment, including dose delays and reductions were to be performed as indicated in the local prescribing information for the relevant agent. In the event of unfavourable tolerability, patients could switch between cisplatin and carboplatin therapy at any point on study (assuming eligibility for the switched therapy is met).

Crossover: Crossover was not permitted as part of this study.

Prophylactic cranial irradiation (PCI): In the EP alone active comparator arm, patients could receive PCI if clinically indicated at the Investigators' discretion. Since the risks of combining PCI with immunotherapies were unknown at the time of the study initiation, PCI was not permitted in the 2 immunotherapy arms.

Thoracic radiotherapy: Any history of radiotherapy to the chest prior to systemic therapy or planned consolidation chest radiation therapy was an exclusion criterion.

Objectives

Primary efficacy objective:

Table 13: Primary objective and endpoint

Objective	Endpoints/variables
To assess the efficacy of durvalumab + tremelimumab + EP treatment compared with EP and durvalumab + EP treatment compared with EP in terms of OS	OS

Secondary efficacy objectives:

Table 14: Secondary objective and endpoint

Objective	Endpoints/variables
To further assess the efficacy of durvalumab + tremelimumab + EP treatment compared with EP and durvalumab + EP treatment compared with EP in terms of PFS, ORR, APF6 (PFS rate at 6 months [PFS6]), APF12 (PFS rate at 12 months [PFS12]), and OS18 (OS rate at 18 months)	PFS, ORR, APF6 (PFS6) and APF12 (PFS12) using site investigator assessments according to RECIST 1.1 OS18
To assess the efficacy of durvalumab + tremelimumab + EP treatment compared with durvalumab + EP in terms of PFS and OS	PFS using site investigator assessments according to RECIST 1.1 OS
To assess the PK of durvalumab and durvalumab + tremelimumab	Concentration of durvalumab and tremelimumab in blood and non-compartmental PK parameters, such as peak concentration and trough (as data allow; sparse sampling)
To investigate the immunogenicity of durvalumab and durvalumab + tremelimumab	ADA (confirmatory results: positive or negative; titers [ADA neutralizing antibodies will also be assessed])
To assess the effect of the treatment on changes in symptoms and health-related QoL using EORTC QLQ-C30 v3 and QLQ-LC13	EORTC QLQ-C30: symptoms (fatigue, pain, nausea/vomiting, dyspnea, loss of appetite, insomnia, constipation, and diarrhea). Health-related QoL/functioning (physical function, role function, emotional function, cognitive function, social function, and global health status/QoL). EORTC QLQ-LC13: disease-related symptoms (dyspnea, cough, hemoptysis, chest pain, arm/shoulder pain, and other pain). Changes in WHO/ECOG performance status will also be assessed.

ADA anti-drug antibody; APF6 proportion of patients alive and progression free at 6 months from randomization (ie, PFS rate at 6 months/PFS6); APF12 proportion of patients alive and progression free at 12 months from randomization (ie, PFS rate at 12 months/PFS12); ECOG Eastern Cooperative Oncology Group;

Safety objectives:

Table 15: Safety objective and endpoint

Objective	Endpoints/variables
To assess the safety and tolerability profile of durvalumab and durvalumab + tremelimumab in combination with EP treatment compared with EP	AEs; physical examinations; vital signs including blood pressure and pulse rate; electrocardiograms; and laboratory findings including clinical chemistry, hematology, and urinalysis

AE adverse event; EP etoposide and platinum-based chemotherapy.

Exploratory objectives:

Table 16: Exploratory objective and endpoint

Objective	Endpoints/variables
Reported in this CSR	
To further assess the efficacy of durvalumab + tremelimumab + EP treatment compared with EP and to assess the efficacy of durvalumab + EP compared with EP in terms of PFS2	PFS2 using local standard clinical practice[a]
To characterize EP PK when in combination with durvalumab and tremelimumab	Concentration of etoposide, carboplatin or cisplatin in blood
To explore the impact of treatment and disease on health care resource use	Health care resource use will be captured, including inpatient admissions, intensive care unit admissions, and length of stay in hospital
To explore the impact of treatment and disease state on health state utility using the EQ-5D-5L	The EQ-5D-5L health state utility index will be used to derive health state utility based on patient-reported data
To assess AEs by patient self-reporting of specific CTCAE symptoms	Collection of approximately 11 symptoms via the patient-reported outcomes version of the CTCAE (PRO-CTCAE)
To assess patients' overall impression of the change in their health status since the start of study treatment	PGIC item will be collected directly from patients.
Not reported in this CSR	
To investigate the relationship between durvalumab PK exposure and clinical outcomes, efficacy, AEs, and/or safety parameters, and biomarkers, if deemed appropriate	A graphical and/or a data modelling approach will be used to analyze durvalumab PK exposure and the relationship with clinical outcomes, efficacy, AEs, and/or safety parameters, as deemed appropriate.

To investigate the relationship between a patient's expression of select genes, for example IFN-γ, within the tumor microenvironment and efficacy outcomes with durvalumab ± tremelimumab and EP	Levels of gene expression, for example, IFN-γ, within the tumor microenvironment relative to efficacy outcomes (for example, APF6/PFS6, APF12/PFS12, PFS, and OS)
To investigate the relationship between a patient's PD-L1 expression and spatial distribution within the tumor microenvironment and efficacy outcomes with durvalumab ± tremelimumab and EP	Tumoral and/or infiltrating immune cell expression of PD-L1 and spatial distribution within the tumor microenvironment relative to efficacy outcomes (for example, APF6/PFS6, APF12/PFS12, PFS, and OS)
To investigate the relationship between a patient's level of DLL3 expression on tumor cells and efficacy outcomes with durvalumab ± tremelimumab and EP	Tumoral expression of DLL3 relative to efficacy outcomes (for example, APF6/PFS6, APF12/PFS12, PFS, and OS)
To investigate the relationship between a patient's TMB and/or somatic mutations/genomic alterations and efficacy outcomes with durvalumab ± tremelimumab and EP	Levels of TMB and somatic aberrations in tumor and/or plasma relative to efficacy outcomes (for example, APF6/PFS6, APF12/PFS12, PFS, and OS)
To explore potential biomarkers in residual biological samples (eg, tumor and blood), which may influence the progression of cancer (and associated clinical characteristics) and/or prospectively identify patients likely to respond to durvalumab or durvalumab + tremelimumab treatment	Correlation of biomarkers with response to durvalumab or durvalumab + tremelimumab treatment and/or the progression of cancer
To collect and store DNA according to each country's local and ethical procedures for future exploratory research into genes/genetic variation that may influence response (ie, distribution, safety, tolerability, and efficacy) to study treatments and/or susceptibility to disease (optional)	Correlation of polymorphisms with variation in PK, pharmacodynamics, safety, or response parameters observed in patients treated with durvalumab or durvalumab + tremelimumab and/or susceptibility to disease

[a] PFS2 will be defined as the time from the date of randomization to the earliest progression event subsequent to that used for the PFS endpoint or death.

Outcomes/endpoints

Primary endpoint:

Overall survival (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 will be censored based on the last recorded date on which the patient was known to be alive.

Secondary endpoints:

Progression-free survival (PFS) per RECIST 1.1 using Investigator assessments 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 randomized therapy or receives another anticancer therapy prior to progression.

In the absence of significant clinical deterioration, the investigational site was advised to continue the patient on their randomized durvalumab + tremelimumab + EP or durvalumab + EP treatment until progression was confirmed. If progression was not confirmed, the patient was to continue their

randomized durvalumab + tremelimumab + EP or durvalumab + EP treatment and on-treatment assessments. Treatment through PD in the EP arm was at the investigator's discretion; however, a follow up scan was required for all patients in the EP arm, even if a subsequent treatment was started.

Objective response rate (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.

Proportion of patients alive and progression free at 6 and 12 months (APF6 and APF12) was defined as the Kaplan-Meier estimate of PFS (per RECIST 1.1 as assessed using site Investigator assessments) at 6 and 12 months, respectively.

Proportion of patients alive at 18 months (OS18) was defined as the Kaplan-Meier estimate of OS at 18 months.

Patient reported outcome (PRO) variables

All **PRO variables** were to be assessed using the European Organization for Research and Treatment of Cancer 30-item core quality of life questionnaire (EORTC QLQ-C30) with the Lung Cancer Module, a 13-item self-administered questionnaire from the EORTC for lung cancer (EORTC QLQ-LC13) and the EuroQoL 5-dimension, 5-level health state utility index (EQ-5D-5L) Q8W during the treatment period and Q12W until confirmed objective disease progression by RECIST v1.1. All questionnaires were scored according to published scoring guidelines or the developer's guidelines, depending on availability.

Selected exploratory endpoints:

Time from randomization to second progression (PFS2) was defined as the time from the date of randomization to the earliest of the progression event subsequent to that used for the PFS endpoint or death. The date of second progression was to be recorded by the Investigator in the eCRF and defined according to local standard clinical practice and may involve any of the following: objective radiological imaging, symptomatic progression, or death.

Time to first subsequent therapy or death (TFST) was defined as defined as the time from the date of randomization to the earlier of start date of the first subsequent anticancer therapy after discontinuation of randomized treatment, or death.

Biomarkers: Tissue samples were to be obtained from all screened patients where available. Based on availability of tissue, additional exploratory biomarkers could be evaluated. The results could be pooled with biomarker data from other durvalumab and tremelimumab studies to evaluate biological responses across indications and to compare results in monotherapy versus combination settings.

- **Tumour markers:** This study mandated the collection of archival/diagnostic tumour tissue, where available, which was to be analysed for various markers by immunohistochemistry. A primary goal was to measure PD-L1, tumour mutational burden (TMB), somatic mutations/genomic alterations and Delta-like canonical Notch ligand 3 (DLL3) expression to support exploratory objectives of investigating the following:

  1. The relationship between a patient's PD-L1 expression and spatial distribution within the tumour microenvironment and efficacy outcomes with durvalumab, tremelimumab and EP.

  2. The relationship between a patient's tumour mutational burden and/or presence of somatic mutations/genomic alterations and efficacy outcomes with durvalumab, tremelimumab and EP.

  3. The impact, if any, of the level of DLL3 expression on efficacy outcomes with durvalumab, tremelimumab and EP (once a validated assay becomes available).

Sample size

The study planned to randomize approximately 795 eligible patients 1:1:1 to D+T+EP (Arm 1), D+EP (Arm 2), or EP (Arm 3). Once global enrolment achieved 795 randomised patients, recruitment continued in China only.

If the average true OS HR is 0.69, the study will have 89% power to demonstrate a statistically significant difference at the final analysis with a 2-sided 0.93% significance level (for an overall alpha of 1%) for the comparison of D+T+EP versus EP (Arm 1 vs 3), and 96% power to demonstrate a statistically significant difference at a 2-sided 3.57% significance level (for an overall alpha of 4%) for the comparison of D+EP versus EP (Arm 2 vs 3); this translates to a 4.8-month benefit in median OS over EP (15.7 months vs 10.9 months). The smallest treatment difference that would be statistically significant is an average HR of 0.78 for D+T+EP versus EP and 0.82 for D+EP versus EP.

If the average true PFS HR is 0.71, the study will have 90% power to demonstrate a statistically significant difference at the 5% level (using a 2-sided test) for the PFS comparisons when approximately 360 PFS events have been observed in the two treatment arms to be compared.

There were to be 2 data cut-off timepoints in the study. The interim analysis of OS was to occur when approximately 318 OS events had occurred (60% maturity) in the D+T+EP and EP treatment arms and approximately 318 OS events had occurred (60% maturity) in the D+EP and EP treatment arms.

The data cut-off for the primary analysis of OS was to occur when approximately 425 OS events have occurred across the durvalumab + tremelimumab + EP and EP treatment arms (80% maturity) and approximately 425 OS events have occurred across the durvalumab + EP and EP treatment arms (80% maturity).

Randomisation

Patients were randomized in a 1:1:1 ratio in a stratified manner according to the planned platinum-based therapy for Cycle 1 (carboplatin or cisplatin) to receive treatment with D+T+EP (Arm 1), D+EP (Arm 2), or EP (Arm 3). Blocked randomization was generated, and all centers used the same list to minimize any imbalance in the number of patients assigned to each treatment arm.

Blinding (masking)

This was an open-label study; however, the AstraZeneca study team were blinded to aggregate treatment information. During the programming and preparation of statistical outputs, data were dummy blinded.

Statistical methods

CASPIAN was designed to test the hypothesis that durvalumab, with or without tremelimumab, in combination with standard of care etoposide platinum chemotherapy (D+T+EP, arm 1 or D+EP, arm 2) as 1L treatment in ES-SCLC can achieve significant clinical benefit over chemotherapy alone (EP alone, arm 3).

Pre-planned statistical and sensitivity analyses to be conducted

Endpoints analyzed	Notes
Overall survival	• Primary analysis using a stratified log-rank test adjusted for planned platinum therapy during Cycle 1, for: – durvalumab + tremelimumab + EP vs EP – durvalumab + EP vs EP • Secondary analysis (same method as primary analysis) – durvalumab + tremelimumab + EP vs durvalumab + EP • Sensitivity analysis using a Kaplan-Meier plot of time to censoring where the censoring indicator of the primary analysis is reversed – attrition bias – durvalumab + tremelimumab + EP vs EP – durvalumab + EP vs EP • Subgroup analysis using an unstratified Cox model (same comparisons as for the sensitivity analysis above) • Effect of covariates on HR estimate using a stratified Cox model (same comparisons as for the sensitivity analysis above)
Progression-free survival	• Secondary analysis using site investigator RECIST 1.1 assessments, using a stratified log-rank test adjusted for planned platinum therapy during Cycle 1 – durvalumab + tremelimumab + EP vs EP – durvalumab + EP vs EP – durvalumab + tremelimumab + EP vs durvalumab + EP • Sensitivity analysis (durvalumab ± tremelimumab + EP vs EP) using site investigator RECIST 1.1 assessments: – Interval censored analysis – evaluation time bias (log-rank test) – Analysis using alternative censoring rules – attrition bias (same method as for OS) – Subsequent anticancer therapy • Subgroup analysis (unstratified) using site investigator RECIST 1.1 assessments (same method as for OS) • Effect of covariates on HR estimate using a stratified Cox model (same method as for OS)
Objective response rate	Logistic regression for durvalumab ± tremelimumab +EP vs EP
Proportion of patients alive and progression free at 6 and 12 months	Kaplan-Meier estimates with CI using log-log transformation[a]
Proportion of patients alive at 18 months	Kaplan-Meier estimates with CI using log-log transformation[a]
Time from randomization to second progression	Stratified log-rank test for durvalumab ± tremelimumab +EP vs EP adjusting for platinum therapy planned in Cycle 1
Change from baseline in PRO symptoms	Average change from baseline using a Mixed model for repeated measures – durvalumab + tremelimumab+ EP vs EP – durvalumab + EP vs EP
Time to deterioration (EORTC QLQ-C30 and QLQ-LC13 endpoints)	Stratified log-rank test for: – durvalumab + tremelimumab+ EP vs EP – durvalumab + EP vs EP

[a] For the purposes of this analysis a month was defined as 30.4375 days.

CI confidence interval; EORTC European Organisation for Research and Treatment of Cancer; EP etoposide and platinum-based chemotherapy; HR hazard ratio; ITT intent-to-treat; OS overall survival; QLQ C30 v3 30-item Core Quality of Life Questionnaire, version 3; QLQ-LC13 13-item Lung Cancer Quality of Life Questionnaire; PRO patient-reported outcome; RECIST 1.1 Response Evaluation Criteria in Solid Tumors, version 1.1.

Analysis sets:

Full analysis set (Intention to treat - ITT): The full analysis set (FAS) included all patients randomized prior to the end of global recruitment. The full analysis set was used for demographics, patient characteristics and efficacy analyses (including PROs). Treatment groups were compared on the basis of randomized study treatment, regardless of the treatment actually received. Patients who were randomized but did not subsequently go on to receive study treatment were to be included in the analysis in the treatment group to which they were randomized.

Safety analysis set: The safety analysis set consisted of all patients recruited prior to the end of global recruitment who received at least 1 dose of study treatment. Safety data will be summarized using the safety analysis set, according to the treatment received, that is, erroneously treated patients (e.g. those randomized to treatment A but actually given treatment B) will be summarized according to the treatment they actually received.

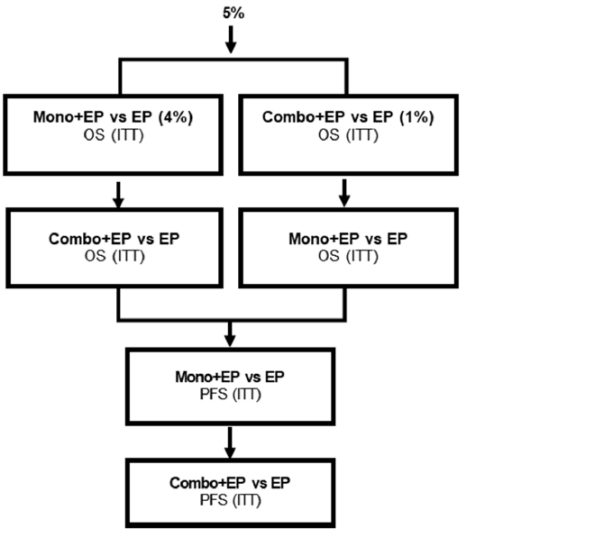
Type I error control:

In order to strongly control the type I error at 5% 2-sided, a multiple testing procedure (MTP) with gatekeeping strategy was to be used across the 2 primary endpoints of OS (Arm 1 vs. 3), OS (Arm 2 vs. 3) and the key secondary endpoint of PFS (Arm 1 vs. 3) and PFS (Arm 2 vs. 3). If the higher-level hypothesis in the MTP was rejected for superiority, the following hypothesis would then be tested as shown in Figure 20.

The overall 5% type 1 error was to be initially split between the 2 primary endpoints: an alpha level of 4% will be allocated to the analysis of OS (Arm 2 vs. 3), and an alpha level of 1% will be allocated to the analysis of OS (Arm 1 vs. 3). If the OS (Arm 2 vs. 3) analysis is significant, then 4% alpha will be recycled to the OS (Arm 1 vs. 3) endpoint; If the OS (Arm 1 vs. 3) analysis is significant, then 1% alpha will be recycled to the OS (Arm 2 vs. 3) endpoint; If both OS primary analyses are significant, then 5% alpha will be recycled to the PFS (Arm 2 vs. 3) endpoint. If PFS (Arm 2 vs. 3) is significant, then the 5% alpha will be recycled to PFS (Arm 1 vs. 3).

This testing procedure stops when the entire test mass is allocated to non-rejected hypotheses. Implementation of this pre-defined ordered testing procedure, including recycling, will strongly control type I error at 5% (2-sided), among all key hypotheses.

For the OS endpoint, there is 1 IA planned, and the alpha level will be controlled at the interim and primary analysis timepoints by using the Lan-DeMets spending function that approximates an O'Brien Fleming approach. The O'Brien Fleming boundaries for the OS interim and final analyses will be adjusted depending on the alpha used for the OS endpoint. In addition, durvalumab + tremelimumab + EP will be compared with durvalumab + EP for OS and PFS. This comparison is not included in the MTP.



Note: Alpha recycling between Mono+EP vs EP and Combo+EP vs EP OS comparisons
Mono+EP vs EP = comparison of durvalumb+EP vs EP
Combo+EP vs EP = comparison of durvalumab + tremelimumab + EP vs EP

Figure 20: Multiple testing procedures for controlling the type 1 error rate

Efficacy analyses:

OS was to be analysed using a stratified log-rank test adjusting for planned platinum therapy in cycle 1 (carboplatin or cisplatin). Any patient not known to have died at the time of analysis was to be censored based on the last recorded date on which the patient was known to be alive.

The effect of durvalumab + tremelimumab + EP versus EP treatment as well as durvalumab + EP versus EP treatment was to be estimated by the HR together with its corresponding ([1-adjusted alpha] × 100%) CI and p-value for the ITT population. The HR and CI could be estimated from the Cox proportional hazards model. Kaplan-Meier plots of OS was to be presented by treatment arm.

A secondary analysis of OS was to be performed to compare D+T+EP versus D+EP. These analyses were to be performed using the same methodology as for the primary endpoints described above.

The assumption of proportionality was to be assessed.

A sensitivity analysis for OS was to examine the censoring patterns to rule out attrition bias, which is achieved by a Kaplan-Meier plot of time to censoring, where the censoring indicator of OS is reversed.

PFS: The analysis was to be performed using a stratified log-rank test adjusting for planned platinum therapy (carboplatin or cisplatin). The effects of D+EP versus EP treatment, and of D+T+EP versus EP treatment, were to be estimated by the HR together with corresponding 95% CIs and p-values.

Patients who have not progressed or died at the time of analysis were to be censored at the time of the latest date of assessment from their last evaluable RECIST 1.1 assessment. However, if the patient progresses or dies after 2 or more missed visits, the patient was to be censored at the time of the latest evaluable RECIST 1.1 assessment. If the patient has no evaluable visits or does not have baseline data, he or she was to be censored at Day 1 unless the patient dies within 2 visits of baseline.

A secondary analysis of PFS was to be performed to compare D+T+EP versus D+EP. This analysis was to be performed using the same methodology as described above, but was not to be included in the multiple testing strategy.

The assumption of proportionality was to be assessed in the same way as for OS.

In addition, as a sensitivity analysis, patients who take subsequent therapy prior to progression or death were to be censored at their last evaluable assessment prior to taking the subsequent therapy.

ORR was to be compared between D+T+EP vs EP using logistic regression models adjusting for the same stratification factor as the primary endpoint. The results of the analysis was to be presented in terms of an odds ratio together with its associated profile likelihood 95% CI and p-value. The denominator is a subset of the ITT population who has measurable disease at Baseline. Data obtained up until progression, or the last evaluable assessment in the absence of progression, were to be included in the assessment of ORR. Patients who go off treatment without progression, receive a subsequent therapy, and then respond were not to be included as responders in the ORR.

The results of the analysis was to be presented in terms of an odds ratio together with its associated profile likelihood CI and p-value (based on twice the change in log-likelihood resulting from the addition of a treatment factor to the model).

APF6 and APF12 were to be summarized (using the Kaplan-Meier curve) and presented by treatment arm along with confidence intervals using the log-log transformation.

Table 17: SAP amendment history

Date	Brief description of change
V1.0 (09Aug2017)	NA – first version
V2.0 (04Dec2018)	Updated to reflect CSP v3, including changes to primary, secondary and exploratory objectives. Updated to reflect CSP v4, including further changes to primary and secondary objectives, updated MTP and removed BICR. Clarified subsequent anticancer therapy throughout document. Clarified 90 day safety follow-up throughout document, as 90 days following last dose, not following discontinuation. Applied consistent terminology for stratification factor "Planned platinum therapy in Cycle 1". Abbreviations added. Section 1.1 study objectives changed. Section 1.2 detail added to study design. Section 1.3 sample size details updated. Section 2.1 immunogenicity data added to Table 1. Section 2.2 changes to important deviation categories. Section 2.3 added detail about China and Japan analysis plan. Section 3.1 removed text about confirmed responses. Removed section previously numbered 3.1.4 about BICR and irRECIST. Section 3.2 removed "co-primary" terminology. Moved section previously numbered 3.2.1.1 to 3.2.2.1, clarified 2 missed visit rule, corrected example schedule change calculation, removed text on confirmed response & irRECIST. Section 3.2.1.1 removed 7 day window for survival calls. Section 3.2.2.2 added derivation of ORR using investigator assessments, removed visit window for change in tumor size. Removed section previously numbered 3.2.3.1 investigator ORR as not an exploratory endpoint (moved to earlier section). Section 3.3.1 added derivations for EORTC scales, Listed the 5 key symptoms, simplified Table 5. Section 3.3.1.1 minor clarifications. Removed sections previously numbered 3.3.1.2 & 3.3.1.3 (symptom/function improvement rate). Section 3.3.4 added detail on analysis visit window. Section 3.4 clarified 'on treatment' period, and specified FAS for listing & summary of deaths. Section 3.4.1 added OAE section, updated AESI section in line with revised CSP, and added imAE section.

Section 3.4.2 added +1 day to exposure definition, rearranged to clarify logic and add adjustment for etoposide. Added +3 days in duration of delays/interruptions, and sum only positive delays.

Section 3.4.3 RDI to be calculated only for durvalumab and tremelimumab, and not derived separately for the different treatment periods.

Section 3.4.4 Cockcroft-Gault formula added for CrCl, which can be both entered and derived. Added lymphocytes to list of parameters with bi-directional changes.

Added new Section 3.5 Biomarker variables.

Section 3.6 updated PK and immunogenicity analysis.

Section 4.1 revised in line with changes to primary objectives. Specified decimal places for efficacy outputs.

Section 4.1.1 Allow pre-dose scan to be used for RECIST in absence of a pre-randomization scan.

Added numbered section 4.1.3 for imputation rules, including clarifications on causal relationship to durvalumab, and imputation of partial death dates. Removed requirement for "overall" summary.

Section 4.2 table 6 updated in line with changed objectives. Removed formal treatment group comparison for APF6, APF12 and OS18.

Section 4.2.1 and figure 3 updated in line with changed objectives and planned interim analyses. Detail added on alpha recycling. Clarified multiple testing for ePRO endpoints, and changed from Holm to Bonferroni adjustment.

Section 4.2.2.1 clarified primary analysis as separate models for each treatment comparison, added adjusted confidence intervals (x2). Clarified and extended subgroup analysis, adding AJCC Stage and geographic region, changed 'ethnicity' to 'race'. Moved text previously in section 5.1 about "other baseline variables" into this section. Added section describing interaction test for stratification variable.

Moved section previously numbered 4.2.2.2 to 4.2.3.1, removed adjusted confidence intervals. Added K-M plots for sensitivity analyses. Added separate sensitivity analysis for subsequent anticancer therapy. Removed section on disagreements between investigator and central reviews. Removed exploratory irRECIST section.

Added new main section heading 4.2.3 for "Secondary endpoints".

Section 4.2.3.2 clarified that analysis uses a subset of the FAS.

Section 4.2.3.3 & 4.2.3.4 removed formal treatment group comparison for APF6, APF12 and OS18.

Added section 4.2.3.5 describing PK data presentation.

Added section 4.2.3.6 describing immunogenicity data presentation and moved some content from section 3.6.2.

Section 4.2.3.7 clarified, removed symptom improvement rate. Reduced MMRM analysis to the 5 key symptoms only.

Section 4.2.3.9 special data handling section added to describe issue with ePRO data at site 7716.

Date	Brief description of change
	Added new main section heading 4.2.4 for "Exploratory endpoints", including subsection for endpoints to be reported outside the main CSR. Section 4.2.4.1 removed Kaplan Meier plots. Section 4.2.5 added summary of AEs before first dose or after 90 days following last dose of study treatment. Removed some AE summaries. Defined 'most common' cutoff as 2% per treatment group. Simplified denominator for event rates. Changed summary of deaths to include all deaths not just up to 90 days after discontinuation. Added imAE section. Potential Hy's Law summaries and thyrotoxicity only include data from the 'on treatment' period. Added reference to laboratory parameters listed in current CSP. Removed box plots & scatter plots for labs and vital signs. Removed time to subsequent therapy from discontinuation of study treatment. Section 4.2.6 added pathology at diagnosis summary. Changed reference to drug dictionary. Section 4.2.7 added detail in exposure summaries, added dose interruption summaries, corrected text about identifying delays. Section 4.2.8 specified a separate summary of radiotherapy received after discontinuation of treatment. Section 5 updated with details of new planned interim analyses. Section 6 changes removed where no longer discrepant from current protocol. Added rationale for new changes. Section 7 removed various unused references. Appendix A added clarification note. Added Appendix B containing details of alpha spending procedure. Added Appendix C containing details of ePRO data to be excluded.
V3.0 (04Apr2019)	Abbreviations added. Section 2.1 removed "initially" from Safety analysis set definition. Clarified that analysis sets include patients randomized prior to the end of global recruitment. Clarified PK analysis set includes patients with post-dose *PK* data, and removed review of deviations in relation to PK. Section 3.2.2.1 corrected week 11 to week 12. Section 3.2.3.1 removed 2 missed visit rule for PFS2. Added "other" reason. Section 3.3.1 clarified that definitions for QLQ-LC13 items include side effects. Section 3.4.1 added onset time to definition of "treatment emergent". Moved OAEs to end of section. Section 3.4.3 RDI to use the last day of dosing of the respective treatment. Added new Section 3.4.7 defining concomitant medication. Section 3.6.1 updated handling of BLQ values in PK summaries. Section 3.7 clarified handling of missing discharge dates regarding DCO. Section 4.1.3 added imputation rules for end dates. Section 4.2.1 added detail on alpha spending function for PFS. Section 4.2.2.1 added description of summary of duration of follow up and prematurely censored, and demography for prematurely censored patients for OS. Specified SAS code for applying log-rank test. Section 4.2.3.1 added summary of days between RECIST assessments. Section 4.2.3.3 and 4.2.3.4 updated derivation to use 1 month = 30.4375 days. Section 4.2.3.7 clarified 75% missing data criterion. Section 4.2.8 therapy on same day as discontinuation counts as subsequent therapy. Section 5.1 added detail on alpha spending function for PFS. Section 6 added rationale for adding alpha spending adjustment for PFS. Appendix B added detail on alpha spending function for PFS, and adjusted significance levels rounded down.

Deviations from the pre-specified statistical analysis plan:

Changes to the planned analyses are shown in Table 18. All major changes were made prior to the date of database lock (26 April 2019) and reflect changes made in protocol amendments.

Table 18: Changes to planned analyses

Key details of change (Section of this report affected)	Reason for change	Person(s)/ group(s) responsible for change
Changes made before database lock of the interim analysis (26 April 2019)		
Exploratory subgroup analysis was changed to use "race" instead of "ethnicity". (Section 11).	Considered to be a more important subgroup for exploratory subgroup analysis.	AstraZeneca
Hemoptysis and insomnia symptoms were removed from the MMRM analysis of PRO symptom scores. (Section 11.3.5.3)	The importance of hemoptysis and insomnia symptoms has reduced since protocol development.	AstraZeneca
PK analysis simplified by removing non-compartmental parameters. (Section 11.5).	Due to sparse PK sampling, non-compartmental parameters are not expected.	AstraZeneca
Added section describing interaction test for stratification variable. (Sections 11.1 and 11.2).	To clarify formal test for subgroup interactions.	AstraZeneca
Added Kaplan-Meier plots for sensitivity analyses and separate sensitivity analysis for subsequent anticancer therapy. (Sections 11.1 and 11.2).	To clarify sensitivity analyses.	AstraZeneca
ePRO section removed symptom improvement rate. (Section 11.3.5).	To simplify ePRO analysis.	AstraZeneca
Added Appendix C containing details of ePRO data from one site to be excluded from analysis. (Section 11.3.5).	Unable to verify data.	AstraZeneca
A separate Lan DeMets (O'Brien Fleming) spending function accounting for an interim and final analysis was added to PFS endpoints in the MTP. (Section 11.2).	To ensure strong control of type I error.	AstraZeneca
Changes introduced after database lock (26 April 2019)		
Added analysis of confirmed response and Duration of response. (Section 11.3.2).	To aid interpretation of the results.	AstraZeneca
Added estimate and confidence interval for the proportion alive at 12 months. (Section 11.3.4).	To aid interpretation of the OS results.	AstraZeneca
Dose reductions from all administrations were included in the summary. (Section 12.1.3).	To aid interpretation of the results.	AstraZeneca

AE adverse event; ePRO electronic patient-reported outcome (device); MMRM mixed model repeated measures; MTP multiple testing procedure; OS overall survival; PFS progression-free survival; PK pharmacokinetics; PRO patient-reported outcome.

Results

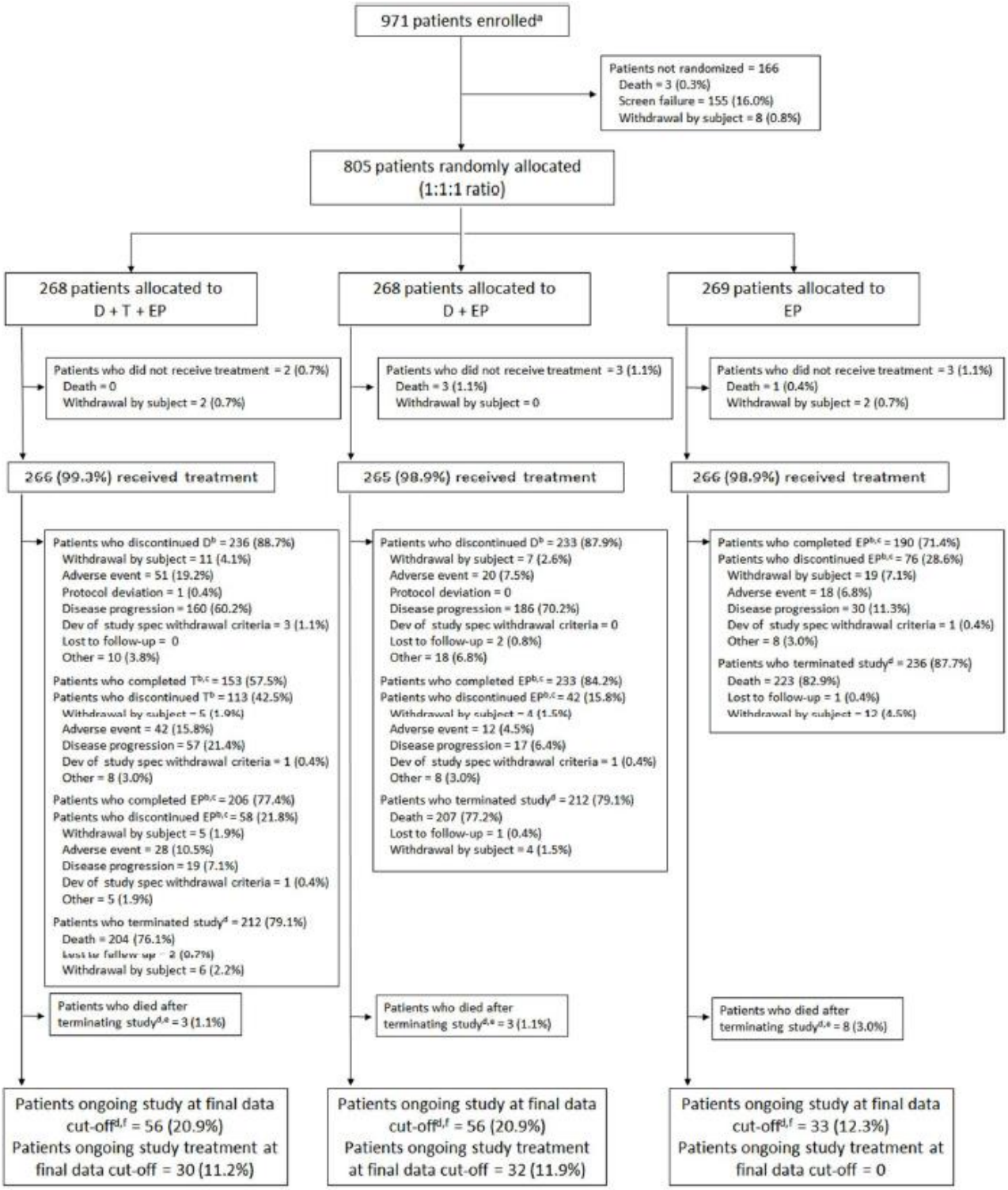
Participant flow

A total of 704 patients were enrolled into the D + EP and EP groups; of these patients, 537 patients were randomized at 209 study centres across 23 countries in North and Latin America, Europe, and Asia Pacific

Of the 537 randomized patients, 268 were randomized to the D + EP group and 269 to the EP group.

From the D+EP arm, one patient did not receive treatment because of unknown reason. This patient was verbally reported to be too sick after randomization to receive study medication.

A total of 222 (83.8%) patients in the D + EP group and 190 (71.4%) patients in the EP group completed EP treatment (1 patient for EP completion in the D + EP group is missing due the entry not being recorded on the eCRF in error).



Patient disposition is based on the global cohort.

[a] Patients giving informed consent. Any re-screened patients are counted once.

[b] Percentages are calculated from number of patients who received treatment.

[c] A patient is considered as having discontinued EP combination when all molecules are discontinued. If different reasons for discontinuation are collected, the last discontinuation reason by date is selected.

[d] Percentages are calculated from number of patients who were randomized.

[e] Obtained from public records or survival follow-up.

[f] Patients ongoing study consist of those randomized patients still receiving treatment, those randomized patients who have completed treatment and are in safety follow-up or those randomized patients who are still in survival follow-up regardless of whether they were administered treatment or not.

D durvalumab; EP etoposide and platinum-based chemotherapy.

Source: Table 14.1.1

Figure 21: Patient disposition (all patients)

Recruitment

The first patient was enrolled on 27 March 2017, and the first patient was randomized on 07 April 2017. The last patient was randomised on 29 May 2018.

Data cut-off was on 11 March 2019.

Database lock for the analyses was 26 April 2019.

Median duration of follow up in all patients was 10.58 months between both treatment groups: 11.30 months in the D+EP group and 9.86 months in the EP group.

The DCO and DBL for the final OS analysis between the D + EP and EP groups occurred on the 27 January 2020 and 03 March 2020 respectively.

The study was conducted across 209 study centres in 23 countries from North and Latin America, Europe, and Asia Pacific.

Conduct of the study

Protocol amendments:

Table 19: Protocol amendments and other significant changes to study conduct

Number (date of internal approval)	Key details of amendment (Section of this report affected)	Reason for amendment	Person(s)/ group(s) responsible for amendment[a]
Original CSP (15 December 2016)			
Amendments made after 06 April 2017 for FSI (randomized date)			
Amendment 1 Protocol version 2.0 15 January 2018	Update to the Toxicity Management Guidelines. The main changes were to the General Guidance section, addition of specific guidance for myocarditis and myositis/polymyositis, and update to specific guidance for Endocrinopathy. (Section 12.2.3).	To be consistent with updates across the clinical programme and to the Investigator's Brochure	AstraZeneca
	Updates to the descriptions of risks for durvalumab, tremelimumab, and the combination of durvalumab + tremelimumab. (Section 7.3).	To align with updates across the clinical programme.	AstraZeneca
	Updates to the Adverse Events of Special Interest. (Section 12.2.3)	To align with updates across the clinical programme.	AstraZeneca
	Addition of options to continue recruitment in mainland China, following achievement of the global recruitment target of 795 randomized patients and a further objective to evaluate consistency in efficacy and safety among SCLC patients in mainland China. (Section 8, 9.1 and 9.8.4).	Evaluation of consistency in efficacy and safety in the Chinese and Asian populations is required to facilitate the benefit-risk assessment for Chinese patients (Required by the China Food and Drug Administration)	AstraZeneca
	Inclusion of the exploratory objective: to investigate the relationship between a patient's tumor mutational burden and efficacy outcomes. (Sections 8.4, Table 5, and Table 9).	To investigate the relationship between a patient's tumor mutational burden and efficacy outcomes.	AstraZeneca
	Updates and clarification of the description of guidelines for evaluation of objective tumor response using RECIST 1.1. (Section 11.3.1, and Table 9 and Table 10).	To align with internal documentation.	AstraZeneca

	Addition of text to describe how patients can continue to receive their assigned treatment after the final data cut-off.	To align with internal documentation.	AstraZeneca
Amendment 2 Protocol version 3.0 23 July 2018	Primary objective revised to add: • The assessment of durvalumab + tremelimumab + EP treatment compared with EP in terms of OS. • The assessment the efficacy of durvalumab + EP treatment compared with EP in terms of OS. • The assessment the efficacy of durvalumab + EP treatment compared with EP in terms of PFS. Secondary objective revised to add the assessment of efficacy of durvalumab + tremelimumab + EP treatment compared with EP in terms of PFS. (Sections 7.1, 8.1, 8.2, 11.1 and 11.2)	Recent Phase III clinical data in first line ES-SCLC (IMPower133) and in first line advanced/metastatic NSCLC (KEYNOTE 021 and KEYNOTE 189) demonstrated the importance of targeting PD-L1/PD-1 plus chemotherapy, with studies in both diseases announcing positive data for PFS and OS (interim analysis for IMPower133 study).	AstraZeneca
	Removal of 'mainland China' to allow patients dosed in China Food and Drug Administration approved sites in Taiwan to be included and correction to the definition of China Cohort. (Section 9.1, 8.4, 9.8.4).	To permit non-mainland China patients to 'qualify' as China patients in the global cohort.	AstraZeneca
	Removal of the references to irRECIST. (Section 9.2, 9.7, Table 10).	irRECIST was removed as an exploratory endpoint due to technical programming challenges.	AstraZeneca

Number (date of internal approval)	Key details of amendment (Section of this report affected)	Reason for amendment	Person(s)/ group(s) responsible for amendment[a]
Amendment 3 Protocol version 4.0 29 October 2018	Primary objective revised to: • To assess the efficacy of durvalumab + tremelimumab + EP treatment compared with EP in terms of OS. • To assess the efficacy of durvalumab + EP treatment compared with EP in terms of OS. Secondary objective revised to: • To assess the efficacy of durvalumab + tremelimumab + EP treatment compared with EP in terms of PFS. • To assess the efficacy of durvalumab + EP treatment compared with EP in terms of PFS. Removal of BICR. (Sections 7.1, 7.2, 7.3, 8.1, 8.2, 9, and Table 9 and Table 10).	Based on evolving internal and external data. Co-primary endpoint of PFS was removed, but OS was retained as the primary endpoint based on IMPower133 study. IMPower133 in first-line ES-SCLC demonstrated an OS benefit with the combination of atezolizumab (PD-L1 inhibitor) + etoposide and carboplatin chemotherapy vs chemotherapy alone in ES-SCLC. As PFS was no longer a primary endpoint BICR was removed (as BICR is not required for a secondary objective).	AstraZeneca
	Update of Multiple Testing Procedure and interim analysis plan including maturity. Sections 9.8.1, 9.8.3, 9.8.4 9.8.5 and Figure 4.	To align with amendments in the CSP for the revised objectives. The original OS IA1 and OS IA2 were combined into single OS IA with 60% maturity, and the maturity for OS FA was increased to 80%.	AstraZeneca
Amendment 4 Protocol version 5.0 29 November 2018	Update of Multiple Testing Procedure. (Section 9.8.1, 9.8.3, 9.8.4 and Figure 4).	Based on evolving internal and external data, the following change was made: reallocated the alpha in the Multiple Testing Procedure to be 4% for monotherapy and 1% for combination therapy.	AstraZeneca

All protocol amendments were approved by AstraZeneca before being submitted to a regulatory authority and/or an Institutional Review Board(IRB)/Independent ethics committee (IEC).
BICR blinded-independent central review; CSP clinical study protocol; DCO data cut-off; EP etoposide and platinum-based chemotherapy; ES-SCLC extensive-stage SCLC; FA final analysis; IA interim analysis; NSCLC non-small-cell lung cancer; OS overall survival; PD-1 Programmed cell death 1; PD-L1 programmed cell death ligand 1; PFS progression-free survival; SCLC small-cell lung cancer.

Protocol deviations:

Table 20: Important protocol deviations (full analysis set)

	Number (%) of patients		
Important protocol deviation[a]	**D + EP (N=268)**	**EP (N=269)**	**Total (N=537)**
Number of patients with at least 1 important deviation	11 (4.1)	8 (3.0)	19 (3.5)
Baseline imaging was performed more than 28 days before start of study treatment	0	1 (0.4)	1 (0.2)
Baseline tumor assessments (RECIST 1.1) performed more than 42 days before the date of randomization	0	1 (0.4)	1 (0.2)
Patients randomized but who did not receive study treatment	3 (1.1)	3 (1.1)	6 (1.1)
Patients randomized who received treatment other than that to which they were randomized[b]	1 (0.4)	0	1 (0.2)
Patients who deviate from key entry criteria as per the CSP. These are inclusion criteria 3, 5, 7, 9 and exclusion criteria 7, 11, 17	6 (2.2)	3 (1.1)	9 (1.7)
Received prohibited concomitant medications (including other anti-cancer agents)[c]	1 (0.4)	1 (0.4)	2 (0.4)

[a] Important deviations before the start of treatment and during treatment.
[b] Tremelimumab was prepared in error but not administered to the patient.
[c] Includes radiotherapy and study medication.
Note that the same patient may have had more than 1 important protocol deviation.
D durvalumab; EP etoposide and platinum-based chemotherapy.

Baseline data

Table 21: Demographic and key subject characteristics (full analysis set)

	Number (%) of patients		
	D + EP (N=268)	**EP (N=269)**	**Total (N=537)**
Age[a]			
n	268	269	537
Mean (SD)	62.4 (8.12)	62.4 (8.32)	62.4 (8.22)
Median (min-max range)	62.0 (28-82)	63.0 (35-82)	63.0 (28-82)
Age group n (%)[a]			
<50 years	10 (3.7)	20 (7.4)	30 (5.6)
≥50 - <65 years	157 (58.6)	137 (50.9)	294 (54.7)
≥65 - <75 years	82 (30.6)	90 (33.5)	172 (32.0)
≥75 years	19 (7.1)	22 (8.2)	41 (7.6)
Gender n (%)			
Male	190 (70.9)	184 (68.4)	374 (69.6)
Female	78 (29.1)	85 (31.6)	163 (30.4)
Race n (%)			
White	229 (85.4)	221 (82.2)	450 (83.8)
Black or African American	2 (0.7)	3 (1.1)	5 (0.9)
Asian	36 (13.4)	42 (15.6)	78 (14.5)
Other	1 (0.4)	2 (0.7)	3 (0.6)
Missing	0	1 (0.4)	1 (0.2)
Ethnic group n (%)			
Hispanic or Latino	10 (3.7)	6 (2.2)	16 (3.0)
Not Hispanic or Latino	255 (95.1)	261 (97.0)	516 (96.1)
Missing	3 (1.1)	2 (0.7)	5 (0.9)
Body mass index group (kg/m^2) n (%)			
Underweight (<18.5)	15 (5.6)	13 (4.8)	28 (5.2)
Normal (≥18.5 to <25.0)	105 (39.2)	118 (43.9)	223 (41.5)
Overweight (≥25.0 to <30.0)	99 (36.9)	98 (36.4)	197 (36.7)
Obese (≥30.0)	47 (17.5)	40 (14.9)	87 (16.2)
Missing	2 (0.7)	0	2 (0.4)
Smoking/nicotine history n (%)			
Current	120 (44.8)	126 (46.8)	246 (45.8)
Former	126 (47.0)	128 (47.6)	254 (47.3)
Never	22 (8.2)	15 (5.6)	37 (6.9)

[a] Age at randomization.

Table 22: Stratification factors recorded at randomisation by IVRS – Full analysis set

	Number (%) of patients		
Planned platinum-based chemotherapy for Cycle 1	Durva + EP (N=268)	EP (N=269)	Total (N=537)
Cisplatin	67 (25.0)	68 (25.3)	135 (25.1)
Carboplatin	201 (75.0)	201 (74.7)	402 (74.9)

Table 23: Actual platinum-based chemotherapy received in Cycle 1 – Full analysis set

	Number (%) of patients		
Actual platinum-based chemotherapy for Cycle 1	Durva + EP (N=268)	EP (N=269)	Total (N=537)
Cisplatin	65 (24.3)	67 (24.9)	132 (24.6)
Carboplatin	199 (74.3)	199 (74.0)	398 (74.1)
None	4 (1.5)	3 (1.1)	7 (1.3)

Table 24: Disease characteristics at screening/diagnosis (full analysis set)

	Number (%) of patients		
	D + EP (N=268)	**EP (N=269)**	**Total (N=537)**
WHO/ECOG performance status			
(0) Normal activity	99 (36.9)	90 (33.5)	189 (35.2)
(1) Restricted activity	169 (63.1)	179 (66.5)	348 (64.8)
Primary tumor location[a]			
Lung	268 (100.0)	269 (100.0)	537 (100.0)
AJCC staging[a,b]			
III[c]	1 (0.4)	0	1 (0.2)
IIIA	5 (1.9)	3 (1.1)	8 (1.5)
IIIB	22 (8.2)	21 (7.8)	43 (8.0)
IV	240 (89.6)	245 (91.1)	485 (90.3)
Histology type[a]			
Small cell carcinoma (neuroendocrine)	39 (14.6)	48 (17.8)	87 (16.2)
Small cell carcinoma (combined)[d]	229 (85.4)	220 (81.8)	449 (83.6)
Other	0	1 (0.4)	1 (0.2)

[a] Primary tumor location, Histology and AJCC Staging are at diagnosis.
[b] AJCC staging: "Stage IV" combines 'Stage IV'/'Stage IVA'/'Stage IVB' from eCRF [PATHGEN] module.
[c] For the 1 Stage III patient, the TNM indicated Stage IIIb although the data were not reported this way.
[d] 'Small cell carcinoma (combined)' includes Small cell lung cancer, Small cell carcinoma (SCC), SCC oat cell/intermediate/combined oat cell categories listed in the eCRF [PATHGEN] module.
AJCC edition 7.

Table 25: Extent of disease at baseline – Full analysis set

Site of disease	Number (%) of patients		
	Durva + EP (N=268)	EP (N=269)	Total (N=537)
Total	265 (98.9)	268 (99.6)	533 (99.3)
Brain/CNS(*)	28 (10.4)	27 (10.0)	55 (10.2)
Cardiovascular	4 (1.5)	4 (1.5)	8 (1.5)
Pleural effusion	73 (27.2)	95 (35.3)	168 (31.3)
Respiratory system	190 (70.9)	197 (73.2)	387 (72.1)
Ascites	1 (0.4)	2 (0.7)	3 (0.6)
Breast	4 (1.5)	0	4 (0.7)
Gastrointestinal system	2 (0.7)	0	2 (0.4)
Genitourinary	2 (0.7)	3 (1.1)	5 (0.9)
Skin/soft tissue	8 (3.0)	14 (5.2)	22 (4.1)
Bone and locomotor	61 (22.8)	67 (24.9)	128 (23.8)
Adrenal gland	70 (26.1)	78 (29.0)	148 (27.6)
Lymph node	232 (86.6)	239 (88.8)	471 (87.7)
Pericardial effusion	14 (5.2)	25 (9.3)	39 (7.3)
Peritoneum	6 (2.2)	13 (4.8)	19 (3.5)
Neck	4 (1.5)	3 (1.1)	7 (1.3)
Pancreas	11 (4.1)	10 (3.7)	21 (3.9)
Spleen	4 (1.5)	5 (1.9)	9 (1.7)
Esophagus	0	1 (0.4)	1 (0.2)
Liver [a]	108 (40.3)	104 (38.7)	212 (39.5)
Other sites	31 (11.6)	36 (13.4)	67 (12.5)

Table 26: Primary tumour location and TNM classification at diagnosis – Full analysis set

Site	TNM class	Number (%) of patients		
		Durva + EP (N=268)	EP (N=269)	Total (N=537)
Primary tumor	TX	12 (4.5)	6 (2.2)	18 (3.4)
	T1	6 (2.2)	10 (3.7)	16 (3.0)
	T1a	4 (1.5)	5 (1.9)	9 (1.7)
	T1b	9 (3.4)	7 (2.6)	16 (3.0)
	T2	21 (7.8)	19 (7.1)	40 (7.4)
	T2a	9 (3.4)	14 (5.2)	23 (4.3)
	T2b	5 (1.9)	12 (4.5)	17 (3.2)
	T3	57 (21.3)	43 (16.0)	100 (18.6)
	T4	145 (54.1)	153 (56.9)	298 (55.5)
	Total	268 (100.0)	269 (100.0)	537 (100.0)
Regional lymph nodes	N0	19 (7.1)	18 (6.7)	37 (6.9)
	N1	11 (4.1)	12 (4.5)	23 (4.3)
	N2	112 (41.8)	103 (38.3)	215 (40.0)
	N3	122 (45.5)	135 (50.2)	257 (47.9)
	Missing	4 (1.5)	1 (0.4)	5 (0.9)
	Total	268 (100.0)	269 (100.0)	537 (100.0)
Distant metastasis	M0	28 (10.4)	26 (9.7)	54 (10.1)
	M1	85 (31.7)	80 (29.7)	165 (30.7)
	M1a	34 (12.7)	35 (13.0)	69 (12.8)
	M1b	120 (44.8)	128 (47.6)	248 (46.2)
	Missing	1 (0.4)	0	1 (0.2)
	Total	268 (100.0)	269 (100.0)	537 (100.0)

Medical history:

The most frequent (ie, ≥15% of patients in any treatment group) current medical history events by system organ class (SOC) in the D + EP and EP groups were: Cardiac disorders (32.5% and 24.5%, respectively), Gastrointestinal disorders (32.1% and 32.3%, respectively), General disorders and administration site conditions (21.6% and 19.3%, respectively), Metabolism and nutrition disorders (38.1% and 36.1%, respectively), Musculoskeletal and connective tissue disorders (25.7% and 28.6%, respectively), Nervous system disorders (15.3% and 10.8%, respectively), Psychiatric disorders (18.7% and 19.7%, respectively), Respiratory, thoracic and mediastinal disorders (54.1% and 52.8%, respectively), Vascular disorders (54.1% and 46.8%, respectively).

The most frequent (ie, ≥15% of patients in any treatment group) current medical history events by preferred term (PT) in the D + EP and EP groups were: type 2 diabetes mellitus (16.4% and 15.6%, respectively), chronic obstructive pulmonary disease (22.8% and 23.0%, respectively), cough (25.0% and 21.9%, respectively), dyspnoea (19.0% and 14.9%, respectively), hypertension (45.1% and 44.2%, respectively).

The past and current medical history reported was generally typical of the co-morbidities seen in this patient population, and similar between the treatment groups.

Surgical history was similar between the treatment groups and as expected for the patient population.

Table 27: Previous treatment modalities – All patients (full analysis set)

	Number (%) of patients		
Previous treatment modalities[a]	D + EP (N=268)	EP (N=269)	Total (N=537)
Cytotoxic Chemotherapy	3 (1.1)	3 (1.1)	6 (1.1)
Radiotherapy	8 (3.0)	10 (3.7)	18 (3.4)
Adjuvant	0	1 (0.4)	1 (0.2)
Palliative	8 (3.0)	8 (3.0)	16 (3.0)
Definitive	0	1 (0.4)	1 (0.2)

[a] Previous treatment might cover conditions other than lung cancer.

Numbers analysed

Table 28: Analysis sets

	Number of patients		
	D + EP	EP	Total
Patients randomized	268	269	537
Patients included in full analysis set[a]	268	269	537
Patients included in safety analysis set[b]	265	266	531
Patients excluded from safety analysis set	3	3	6
Did not receive treatment	3	3	6
Patients included in PK analysis set[c]	263	13	276
Patients excluded from PK analysis set	5	N/A	5
Did not receive treatment	3	N/A	3
No post-baseline assessment	2	N/A	2

[a] All randomized patients analysed on an ITT basis.
[b] All patients who received at least one dose of study treatment.
[c] All patients who received at least one dose of investigational product per the protocol for whom any PK post-dose data are available will be included in the PK analysis set. PK analysis set is not applicable for patients in EP group (except for some specific sites, see CSP Appendix 16.1.1). Reason for exclusion from the PK analysis set is therefore reported as N/A.

Outcomes and estimation

The DCO for the interim analysis was 11 March 2019. The DCO for the follow-up OS analysis between the D + EP and EP groups occurred on the 27 January 2020. The high-level results from this analysis were submitted during the procedure.

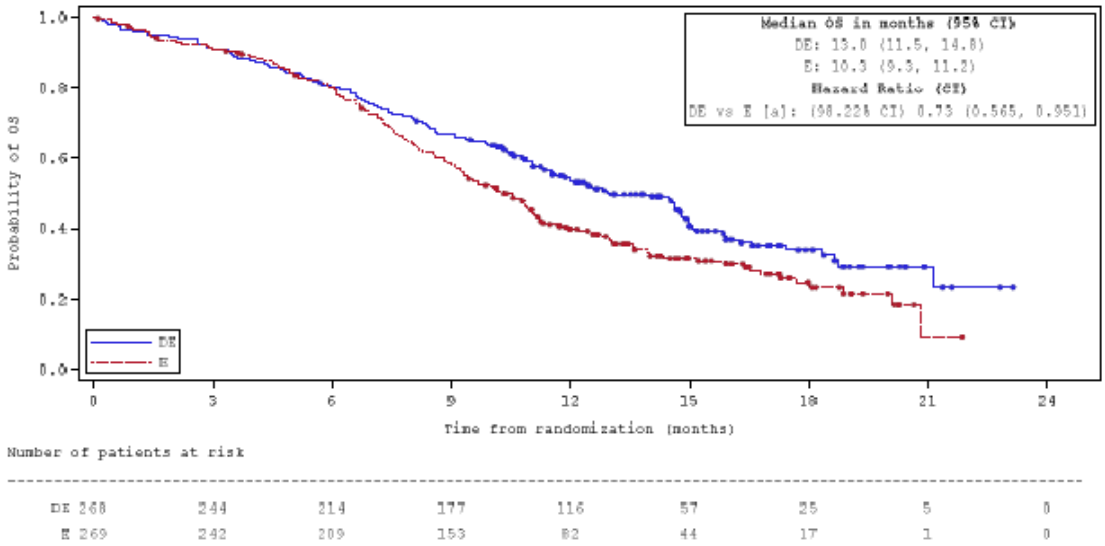
Table 29: Summary of efficacy at follow-up analysis – Full analysis set

Efficacy measure	Interim analysis DCO: 11 March 2019		Follow-up analysis DCO: 27 January 2020	
	D + EP N=268	EP N=269	D + EP N=268	EP N=269
Primary efficacy endpoint				
Overall survival (OS)				
Death, n (%)	155 (57.8)	181 (67.3)	210 (78.4)	231 (85.9)
Median survival (months) (95% CI)[a]	13.0 (11.5, 14.8)	10.3 (9.3, 11.2)	12.9 (11.3, 14.7)	10.5 (9.3, 11.2)
Hazard ratio (95% CI)[b]	0.73 (0.591, 0.909)		0.75 (0.625, 0.910)	
2-sided p-value	0.0047		0.0032	
Survival rate (%) at 12 months (95% CI)[a]	53.7 (47.4, 59.5)	39.8 (33.7, 45.8)	52.8 (46.6, 58.5)	39.3 (33.4, 45.1)
Survival rate (%) at 18 months (95% CI)[a]	33.9 (26.9, 41.0)	24.7 (18.4, 31.6)	32.0 (26.5, 37.7)	24.8 (19.7, 30.1)
Survival rate (%) at 24 months (95% CI)[a]	N/A	N/A	22.2 (17.3, 27.5)	14.4 (10.3, 19.2)
Key secondary efficacy endpoint				
Progression-free survival[c] (PFS)				
Total events, n (%)	226 (84.3)	233 (86.6)	234 (87.3)	236 (87.7)
Median (months) (95% CI)[a]	5.1 (4.7, 6.2)	5.4 (4.8, 6.2)	5.1 (4.7, 6.2)	5.4 (4.8, 6.2)
Hazard ratio (95% CI)[b]	0.78 (0.645, 0.936)		0.80 (0.665, 0.959)	
2-sided p-value[d]	0.0078		0.0157	
PFS rate (%) at 6 months (95% CI)[a]	45.4 (39.3, 51.3)	45.6 (39.3, 51.7)	45.4 (39.3, 51.3)	45.8 (39.5, 51.9)
PFS rate (%) at 12 months (95% CI)[a]	17.5 (13.1, 22.5)	4.7 (2.4, 8.0)	17.9 (13.5, 22.8)	5.3 (2.9, 8.8)
Secondary				
Objective response rate[c,e,f] (ORR)				
Number (%) of patients with a response	182 (67.9)	155 (57.6)	182 (67.9)	156 (58.0)
Odds ratio (95% CI)	1.56 (1.095, 2.218)		1.53 (1.078, 2.185)	
2-sided p-value[d]	0.0136		0.0173	

[a] Calculated using the Kaplan-Meier technique; CIs for median OS/PFS are derived based on the Brookmeyer-Crowley method and using the log-log transformation.
[b] Calculated using stratified Cox proportional hazards model, adjusting for planned platinum therapy at Cycle 1.

[c] Per Investigator's assessment and RECIST 1.1.
[d] Nominal p-value. PFS was included in the MTP hierarchy below OS. It was not able to be tested within the MTP as both the D + EP and D +T+EP arms were required to achieve statistical significance for OS prior to stepping down to PFS. ORR was not included in the MTP.
[e] Calculated *post hoc*.
[f] Confirmed ORR.
CI Confidence interval; D + EP Durvalumab in combination with etoposide and either cisplatin or carboplatin; EP Etoposide and either carboplatin; MTP Multiple testing procedure; N/A: Not available; RECIST Response Evaluation Criteria in Solid Tumors.

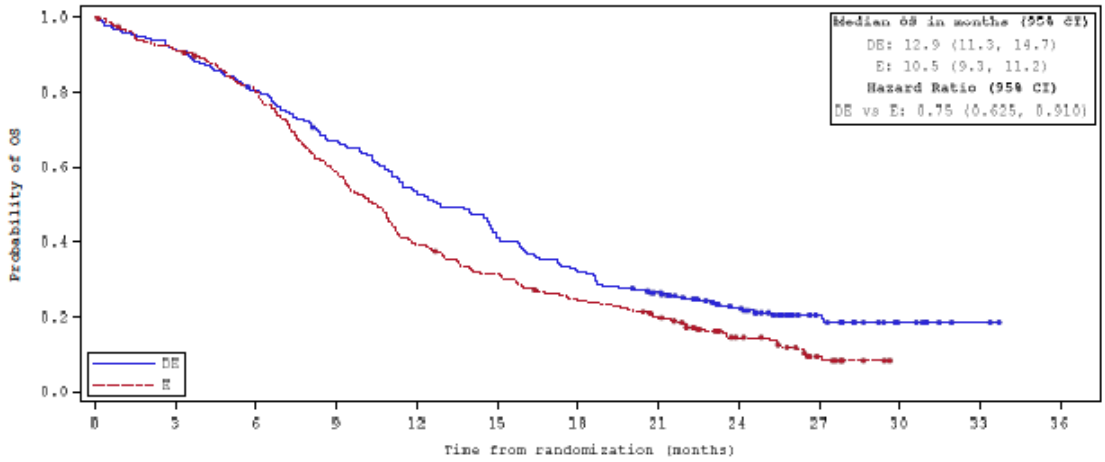
Figure 1A: Interim OS analysis (DCO: 11 March 2019)



Number of patients at risk

DE 268	244	214	177	116	57	25	5	0
E 269	242	209	153	82	44	17	1	0

Figure 1B: Follow-up OS analysis (DCO: 27 January 2020)

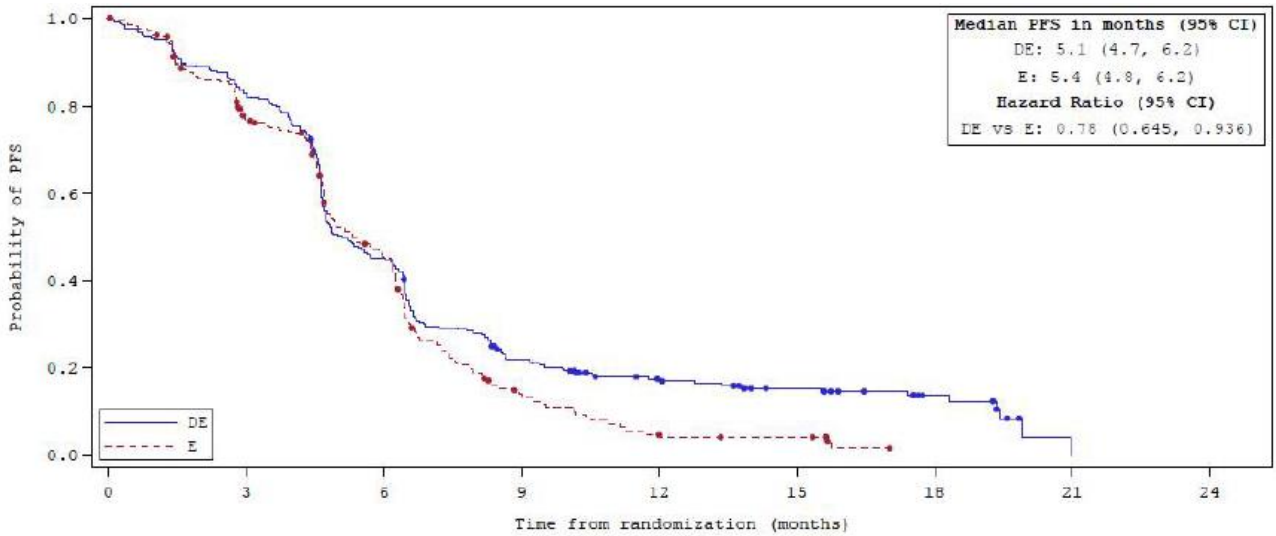


Number of patients at risk

DE 268	244	214	177	140	109	85	66	41	21	8	2	0
E 269	243	212	156	104	82	64	48	24	8	0	0	0

CI Confidence interval; DE Durvalumab in combination with etoposide and either cisplatin or carboplatin; E Etoposide and either cisplatin or carboplatin; OS Overall survival.

Figure 22: Overall survival, Kaplan-Meier plot – Full analysis set



Number of patients at risk

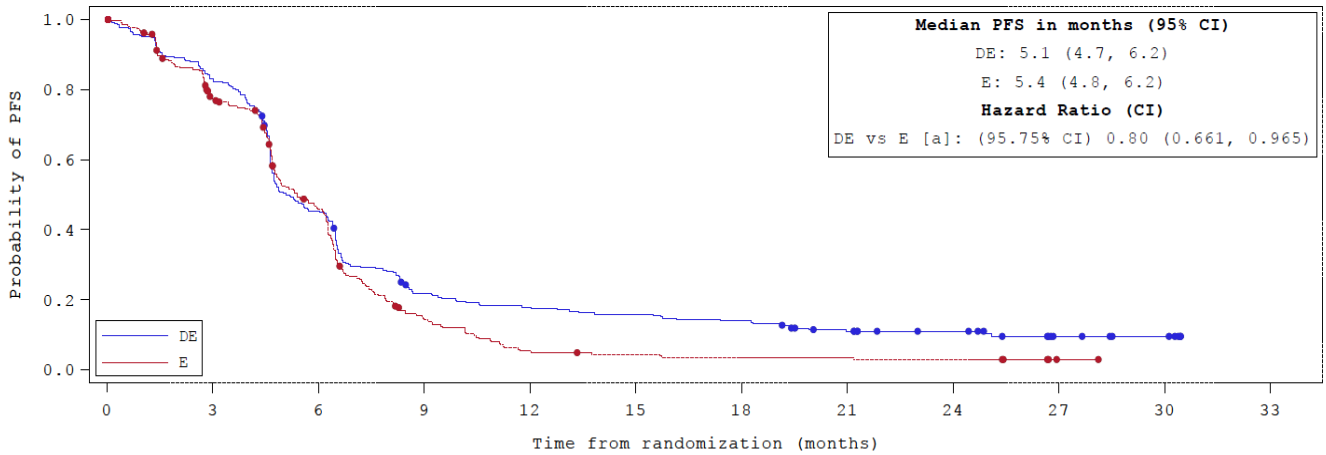
DE	268	220	119	54	34	22	10	0	0
E	269	194	109	30	9	7	0	0	0

Progression is determined by the RECIST-based assessment of the investigator.
Circle indicates a censored observation.

Secondary endpoints:

- Progression free survival:

Figure 23: Kaplan-Meier plot of progression-free survival based on site investigator assessments according to RECIST 1.1 (Full analysis set) – Interim analysis (459 events), DCO 11-MAR-2019



Number of patients at risk

DE	268	220	119	55	45	40	35	24	18	8	5	0
E	269	195	110	33	12	9	7	7	6	1	0	0

Figure 24: Kaplan-Meier plot of progression-free survival based on site investigator assessments according to RECIST 1.1 (Full analysis set) – follow-up analysis (470 events), DCO 27-Jan-2020

- ORR:

ORR was not included in the MTP and was evaluated in 2 ways: a) per protocol, without response confirmation required; and b) ad hoc sensitivity analysis requiring a confirmed response no sooner than 4 weeks after the initial CR/PR evaluation was conducted. Results in the table below reflect the DCO 11 March 2019. The data from the DCO 27 January 2020 are reflected in Table 29.

Table 30 Objective response rate (RECIST 1.1: unconfirmed and confirmed) - DCO 11-Mar-2019

	RECIST 1.1			
	Unconfirmed		Confirmed	
	D + EP N=268	EP N=269	D + EP N=268	EP N=269
Number (%) of patients with a response [a]	213 (79.5)	189 (70.3)	182 (67.9)	155 (57.6)
95% confidence interval of ORR (%) [b]	74.33, 83.99	64.59, 75.50	62.14, 73.30	51.65, 63.43
Odds ratio [c] 95% CI [c] p-value [c,d]	1.64 (1.106, 2.443) 0.0137		1.56 (1.095, 2.218) 0.0136	

[a] ORR is 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 are excluded from the analysis. Patients who went off treatment without progression, received a subsequent anticancer therapy, and then responded are not included as responders.

[b] 95% confidence interval using mid-p method.

[c] The comparisons (vs EP) were performed using a separate logistic regression model, adjusting for planned platinum therapy in Cycle 1 (carboplatin or cisplatin), with 95% CI calculated by profile likelihood.

[d] P-value, derived from logistic regression model, is based on twice the change in log-likelihood resulting from the addition of a treatment factor to the model.

An odds ratio >1 favours D + EP.
Response is determined by the RECIST-based assessment of the Investigator.
RECIST version 1.1.

Table 31 Best objective response (RECIST 1.1: unconfirmed and confirmed) - DCO 11-Mar-2019

	Number (%) of patients			
	RECIST 1.1			
	Unconfirmed		Confirmed	
	D + EP N=268	EP N=269	D + EP N=268	EP N=269
Response	213 (79.5)	189 (70.3)	182 (67.9)	155 (57.6)
CR	7 (2.6) [a]	4 (1.5) [a]	6 (2.2) [b]	2 (0.7) [b]
PR	206 (76.9) [a]	185 (68.8) [a]	176 (65.7) [b]	153 (56.9) [b]
Stable disease [c]	20 (7.5) [c]	42 (15.6) [c]	20 (7.5) [c]	42 (15.6) [c]

[a] Responses correspond to at least one visit response of CR or PR.

[b] Responses correspond to at least one visit response of CR or PR and a confirmatory scan no sooner than 4 weeks after the initial CR/PR.

[c] In practice, considering "5 weeks" as threshold to allow for the 1-week permitted time-window.

RECIST version 1.1.
Response is determined by the RECIST-based assessment of the Investigator.

Duration of response:

Table 32 Duration of response, based on investigator assessment according to RECIST 1.1 (full analysis set, patients with objective response) - DCO 11-Mar-2019

	RECIST 1.1			
	Unconfirmed		Confirmed	
	D + EP N=213	EP N=189	D + EP N=182	EP N=155
Number of responders who subsequently progressed or died	176	164	146	135
Duration of response from onset of response (months) [a,b]				
25th percentile, 75th percentile	3.3, 7.9	3.3, 6.3	3.4, 10.4	3.7, 6.8
Median (95% CI)	4.8 (3.7, 5.1)	4.8 (4.0, 5.1)	5.1 (4.9, 5.3)	5.1 (4.8, 5.3)
Percentage of patients remaining in response [b]				
At 3 months	81.6	83.5	93.4	97.3
At 6 months	33.7	29.7	39.3	34.0
At 9 months	22.2	9.9	25.8	11.1
At 12 months	19.5	5.3	22.7	6.3

At 15 months	17.1	1.8	19.9	2.1
At 18 months	10.8	NR	12.5	NR

[a] Duration of response is the time from the first CR/PR until the date of first documented progression, or death in the absence of progression. Patients who have not progressed or died are censored at their PFS censoring date.

[b] Calculated using the Kaplan-Meier technique. CI for median duration of response is derived based on Brookmeyer-Crowley method and using the log-log transformation.

Response is determined by the RECIST-based assessment of the Investigator.

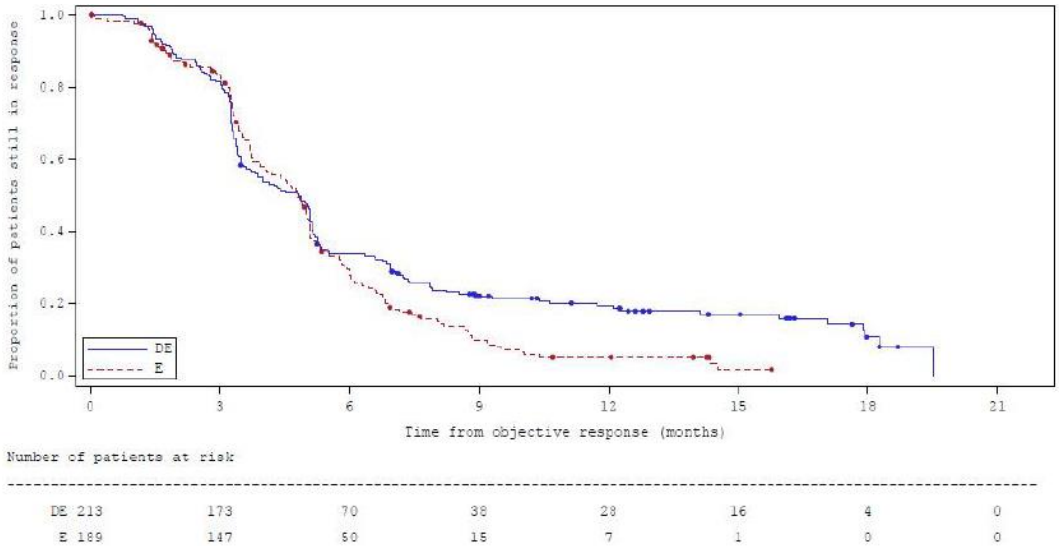


Figure 25: Duration of response based on site investigator assessment according to RECIST 1.1, Kaplan-Meier plot (full analysis set, patients with objective response) - DCO 11-Mar-2019

PROs:

Table 33: Summary of change from baseline (average over 12 months) in EORTC QLQ-C30 and EORTC QLQ-LC13 key symptoms, MMRM (full analysis set)

Symptom scale item	Statistic	D + EP (N=261)	EP (N=260)
EORTC QLQ-LC13 Cough	n	231	232
	Adjusted mean[a]	-17.1	-17.1
	Standard error	1.71	2.10
	95% CI	-20.43, -13.71	-21.21, -12.96
	Estimated difference[b]	0.0	
	99% CI for difference	-5.25, 5.29	
	2-sided p-value	0.992	
EORTC QLQ-LC13 Dyspnea	n	231	232
	Adjusted mean[a]	-8.6	-8.0
	Standard error	1.44	1.64
	95% CI	-11.40, -5.76	-11.26, -4.81
	Estimated difference[b]	-0.5	
	99% CI for difference	-4.38, 3.29	
	2-sided p-value	0.714	
EORTC QLQ-LC13 Chest pain	n	231	232
	Adjusted mean[a]	-8.1	-9.4
	Standard error	1.59	1.85
	95% CI	-11.27, -5.01	-13.04, -5.75
	Estimated difference[b]	1.3	
	99% CI for difference	-3.20, 5.71	
	2-sided p-value	0.465	
EORTC QLQ-C30 Fatigue	n	232	233
	Adjusted mean[a]	-7.4	-5.6
	Standard error	1.64	1.87
	95% CI	-10.67, -4.22	-9.24, -1.88
	Estimated difference[b]	-1.9	
	99% CI for difference	-6.28, 2.51	
	2-sided p-value	0.268	
	n	232	233

Symptom scale item	Statistic	D + EP (N=261)	EP (N=260)
EORTC QLQ-C30 Appetite loss	Adjusted mean[a]	-12.7	-8.2
	Standard error	1.65	1.94
	95% CI	-15.95, -9.47	-11.98, -4.36
	Estimated difference[b]	-4.5	
	99% CI for difference	-9.04, -0.04	
	2-sided p-value	0.009	

[a] Adjusted mean represents the change from baseline.

[b] An estimated difference < 0 favours D + EP over EP.

1 month = 30.4375 days.

Includes data up to progressive disease or 12 months (whichever is earlier), excluding visits with excessive missing data (defined as >75% missing data).

Change from baseline was analyzed separately for each treatment comparison using a MMRM model, based on restricted maximum likelihood method, with patient, treatment, age at randomization (<65 years, ≥65 years), sex (male, female), smoking status at screening (smoker, non-smoker), visit and treatment by visit interaction as fixed factors, and the appropriate baseline and baseline by visit interaction as covariates.

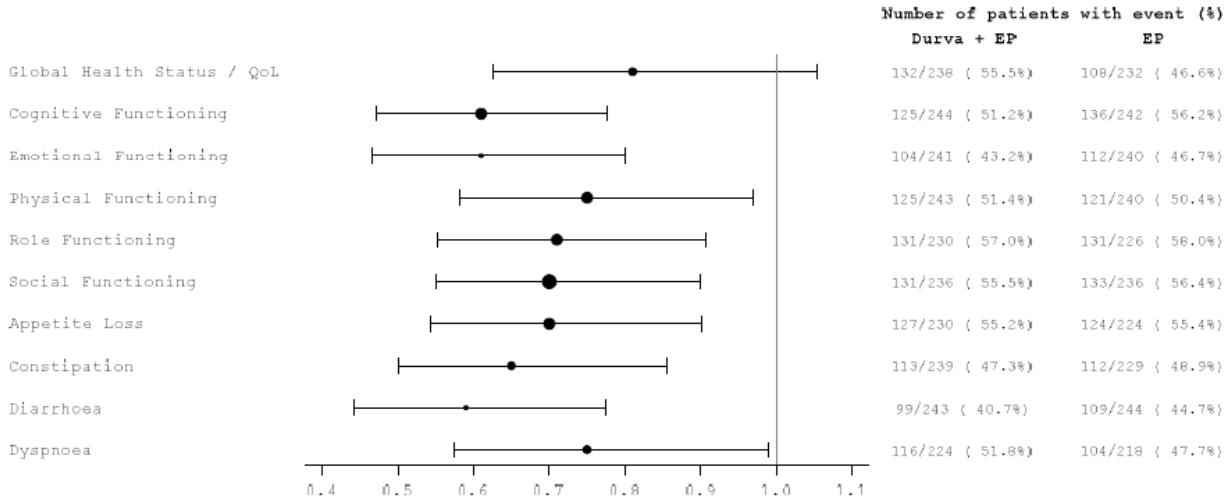
For all subscales/items, a toeplitz with heterogeneity covariance structure was used to model the within-patient error and the Kenward-Roger approximation was used to estimate the degrees of freedom.

The overall 2-sided 5% alpha is controlled across the 5 key PRO measures of cough, dyspnea and chest pain (as assessed by the EORTC QLQ-LC13) and fatigue, appetite loss (as assessed by the EORTC QLQ-C30) using the Bonferroni-adjusted procedure (1% significance level for each endpoint).

ePRO data collected at site 7716 are excluded from the analysis (see SAP Appendix C for details).

CI confidence interval; D durvalumab; EORTC European Organisation for Research and Treatment of Cancer; EP etoposide and platinum-based chemotherapy; ePRO electronic patient-reported outcome; MMRM Mixed Model Repeated Measures; PRO patient-reported outcome; QLQ-C30 30-item Core Quality of Life Questionnaire; QLQ-LC13 13-item Lung Cancer Quality of Life Questionnaire.

Source: Table 14.2.9.3



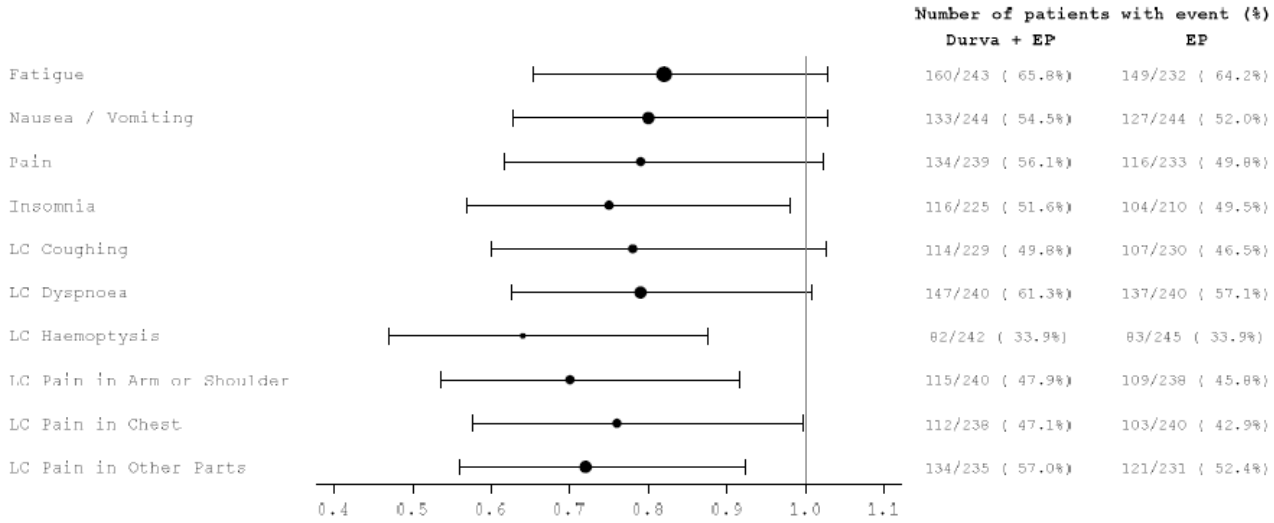


Figure 26: Forest plot of time to deterioration – EORTC QLQ-C30 and EORTC QLQ-L13 subscales/items (full analysis set)

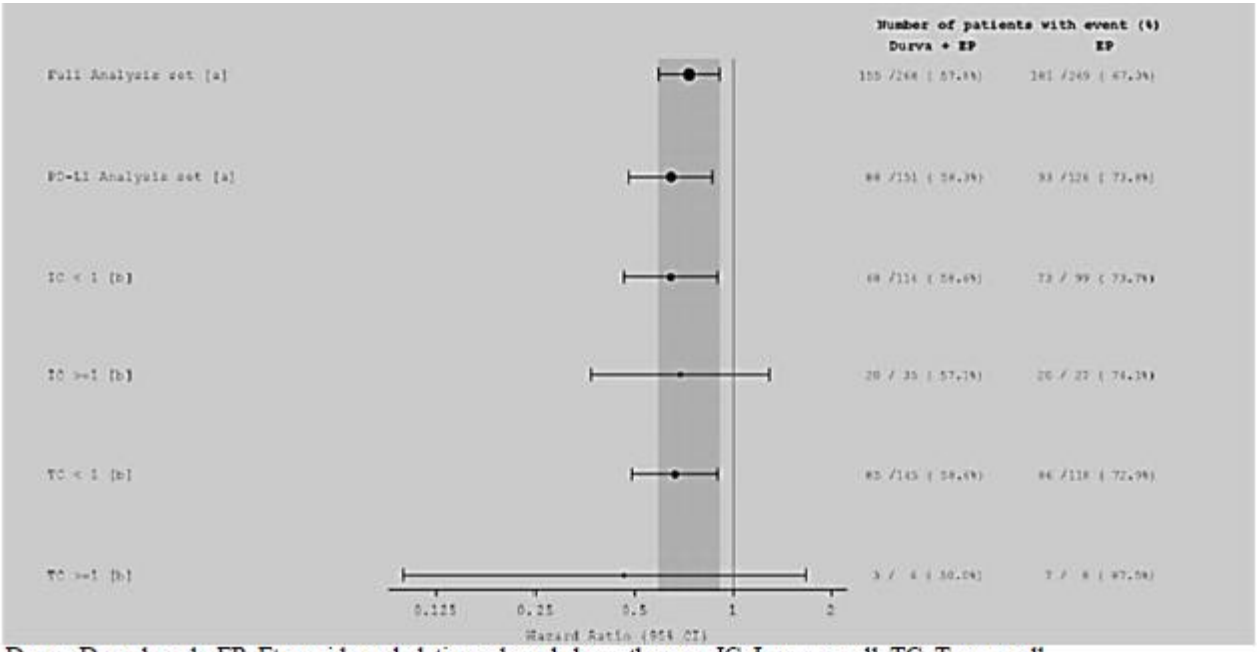
Exploratory analyses:

PD-L1 IHC status:

Table 34: Summary of PD-L1 tumour cell (TC) and immune cell (IC) scores – Full and PD-L1 analysis set

		Number (%) of Patients		
Subgroup	**Category**	**D + EP**	**EP**	**Total**
Full Analysis Set		268	269	537
PD-L1 Analysis Set [a]		151 (56.3)	126 (46.8)	277 (51.6)
Immune Cells (IC) [b]	0	89 (58.9)	72 (57.1)	161 (58.1)
	>0 to <1%	27 (17.9)	27 (21.4)	54 (19.5)
	≥1 to <25%	13 (8.6)	17 (13.5)	30 (10.8)
	≥25 to <50%	14 (9.3)	6 (4.8)	20 (7.2)
	≥50%	8 (5.3)	4 (3.2)	12 (4.3)
	IC <1%	116 (76.8)	99 (78.6)	215 (77.6)
	IC ≥1%	35 (23.2)	27 (21.4)	62 (22.4)
Tumor Cells (TC) [b]	0	124 (82.1)	98 (77.8)	222 (80.1)
	> 0 to <1%	21 (13.9)	20 (15.9)	41 (14.8)
	≥1 to <25%	5 (3.3)	5 (4.0)	10 (3.6)
	≥25 to <50%	0	1 (0.8)	1 (0.4)
	≥50%	1 (0.7)	2 (1.6)	3 (1.1)
	TC <1%	145 (96.0)	118 (93.7)	263 (94.9)
	TC ≥1%	6 (4.0)	8 (6.3)	14 (5.1)

D Durvalumab; EP Etoposide and platinum-based chemotherapy; IC Immune Cells; TC Tumor Cells.
[a] Percentages calculated from the Full Analysis Set.
[b] Percentages calculated from the PD-L1 Analysis Set.
Source: Table 14.1.1, Appendix 1.



Durva, Durvalumab; EP, Etoposide and platinum-based chemotherapy; IC: Immune cell, TC: Tumor cell
The shaded band represents the 95% confidence interval for the overall (all patients) hazard ratio.
A hazard ratio <1 favors Durva + EP to be associated with a longer overall survival than EP.
[a] Cox Proportional Hazards analysis stratified by Platinum-based chemotherapy at Cycle 1 (CARBOPLATIN or CISPLATIN).
[b] Unstratified Cox Proportional Hazards analysis.
Source: Figure 14.2.1.3; Appendix 1.

Figure 27: Forest plot of Overall survival – PD-L1 analyses sets

Table 35: Summary of Overall survival – PD-L1 analyses sets

Subgroup	Treatment	Number of Patients	Events (%)	Median (95% CI)	Hazard Ratio (95% CI) [a]	p-value [b]
Full Analysis set [c]	D + EP	268	155 (57.8)	13.0 (11.5, 14.8)	0.73 (0.591, 0.909)	0.0047
	EP	269	181 (67.3)	10.3 (9.3, 11.2)		
PD-L1 Analysis set [c]	D + EP	151	88 (58.3)	13.0 (11.3, 14.9)	0.65 (0.481, 0.865)	0.0032
	EP	126	93 (73.8)	10.2 (8.2, 11.2)		
IC <1% [d]	D + EP	116	68 (58.6)	12.1 (9.9, 14.8)	0.64 (0.461, 0.897)	0.0089
	EP	99	73 (73.7)	10.2 (8.0, 10.9)		
IC ≥1% [d]	D + EP	35	20 (57.1)	14.9 (11.3, 21.1)	0.69 (0.368, 1.289)	0.2408
	EP	27	20 (74.1)	12.5 (6.3, 15.9)		
TC <1% [d]	D + EP	145	85 (58.6)	14.5 (11.3, 14.9)	0.66 (0.491, 0.896)	0.0072
	EP	118	86 (72.9)	10.2 (8.2, 11.2)		
TC ≥1% [d]	D + EP	6	3 (50.0)	11.3 (2.9, NR)	0.46 (0.099, 1.669)	0.2528
	EP	8	7 (87.5)	8.7 (0.4, 12.5)		

D, Durvalumab; EP, Etoposide and platinum-based chemotherapy; IC, Immune cell; TC, Tumor cell.
[a] Cox Proportional Hazards analysis model
[b] Stratified Log rank test
[c] Analyses stratified by Platinum-based chemotherapy at Cycle 1 (Carboplatin or Cisplatin)
[d] Unstratified analyses
Source: Table 14.2.1, Appendix 1.

PFS2:

Table 36:Subsequent anticancer therapy or radiotherapy (full analysis set)

	Number (%) of patients		
	D + EP (N=268)	EP (N=269)	Total (N=537)
Anticancer therapy regimen[a]			
Number of patients with post-discontinuation anticancer therapy	113 (42.2)	119 (44.2)	232 (43.2)
Regimen category			
Cytotoxic chemotherapy	110 (41.0)	112 (41.6)	222 (41.3)
Single regimen	55 (20.5)	65 (24.2)	120 (22.3)
Platinum doublet	51 (19.0)	43 (16.0)	94 (17.5)
Other combination	22 (8.2)	30 (11.2)	52 (9.7)
Immunotherapy	5 (1.9)	14 (5.2)	19 (3.5)
IO Single agent	0	4 (1.5)	4 (0.7)
IO + IO combination	2 (0.7)	3 (1.1)	5 (0.9)
IO + Chemo	0	1 (0.4)	1 (0.2)
Investigational agent	3 (1.1)	6 (2.2)	9 (1.7)
Other	1 (0.4)	5 (1.9)	6 (1.1)
Line of Treatment			
Second line	113 (42.2)	119 (44.2)	232 (43.2)
Third line	33 (12.3)	39 (14.5)	72 (13.4)
>Third line	6 (2.2)	8 (3.0)	14 (2.6)
Radiotherapy[b]			
Number of patients with post-discontinuation radiotherapy	69 (25.7)	102 (37.9)	171 (31.8)
Site or region (grouped term)			
Brain	48 (17.9)	49 (18.2)	97 (18.1)
Thoracic region	16 (6.0)	43 (16.0)	59 (11.0)
Bone	12 (4.5)	10 (3.7)	22 (4.1)
Prophylactic cranial irradiation	0	21 (7.8)	21 (3.9)
Other	6 (2.2)	1 (0.4)	7 (1.3)

[a] Therapies post-discontinuation of study treatment. Regimen categories identified from medical review of preferred terms combined by regimen number. Line of treatment identified from medical review of treatment status and sequence of treatment using treatment dates.

[b] Radiotherapies post-discontinuation of study treatment.

Patients with regimens or line of treatments or therapies in more than one category are counted once in each of those categories.

After disease progression, radiotherapy was received by 1.9% of patients in the D+ EP group and 13.8% of patients in EP group.

Table 37: Subsequent radiotherapy relative to progression (full analysis set)

	Number (%) of patients	
	D + EP (N=268)	**EP (N=269)**
Number of patients who received further radiotherapy for cancer	69 (25.7)	102 (37.9)
After progression[a]	5 (1.9)	37 (13.8)
Before progression	62 (23.1)	58 (21.6)
No progression	2 (0.7)	7 (2.6)
No further radiotherapy for cancer recorded	199 (74.3)	167 (62.1)

[a] Includes therapy on the same day as progression.
Progression is determined by the RECIST-based assessment of the investigator.
Includes any radiotherapy post-discontinuation of study treatment.

Table 38: Time to second progression using local standard clinical practice (full analysis set)

	D + EP (N=268)	**EP (N=269)**
Total number of events[a], n (%)	190 (70.9)	200 (74.3)
Second progression	77 (28.7)	64 (23.8)
Objective radiological progression	69 (25.7)	58 (21.6)
Symptomatic progression	8 (3.0)	4 (1.5)
Other	0	2 (0.7)
Death in the absence of second progression	113 (42.2)	136 (50.6)
Censored subjects, n (%)	78 (29.1)	69 (25.7)
No second progression	77 (28.7)	58 (21.6)
Lost to follow-up	0	0
Withdrawn consent	1 (0.4)	11 (4.1)
Median time to second progression[b], months	9.9	8.7
95% CI for time to second progression[b]	8.4, 11.0	7.8, 9.3
HR[c,d], D + EP vs EP	0.70	
95% CI for HR[c]	0.573, 0.861	
2-sided p-value[d]	0.0007	

[a] Patients who had a first PFS event but no second event are censored at last available PFS or PFS2 assessment. Patients who died as a first PFS are then censored for PFS2 at the date of death. Patients who had a first PFS event and then died subsequently have their PFS2 event at date of death. Patients without any first PFS event are censored at their last available scan.

[b] Calculated using Kaplan-Meier technique. CI for median progression-free survival is derived based on Brookmeyer-Crowley method and using the log-log transformation.

TFST:

Table 39: Time from randomization to first subsequent anticancer therapy or death (full analysis set)

	D + EP (N=268)	EP (N=269)
Total events[a], n (%)	210 (78.4)	236 (87.7)
First subsequent therapy	117 (43.7)	126 (46.8)
Death in the absence of first subsequent therapy	93 (34.7)	110 (40.9)
Censored patients, n (%)	58 (21.6)	33 (12.3)
No first subsequent therapy	57 (21.3)	22 (8.2)
Lost to follow-up	0	0
Withdrawn consent	1 (0.4)	11 (4.1)
Discontinued study	0	0
Median time to first subsequent therapy or death (months)[b]	7.4	6.8
95% CI for median time to first subsequent therapy or death	6.7, 8.3	6.5, 7.3
HR[c,d], D + EP vs EP	0.70	
95% CI for HR[c]	0.576, 0.839	
2-sided p-value[e]	0.0001	

[a] Patients not known to have had a first subsequent anticancer therapy are censored at the last date that the patient was known not to have received a first subsequent anticancer therapy. Patients who terminated the study for reason other than death before first subsequent anticancer therapy are censored at the earliest of their last known to be alive and termination dates.

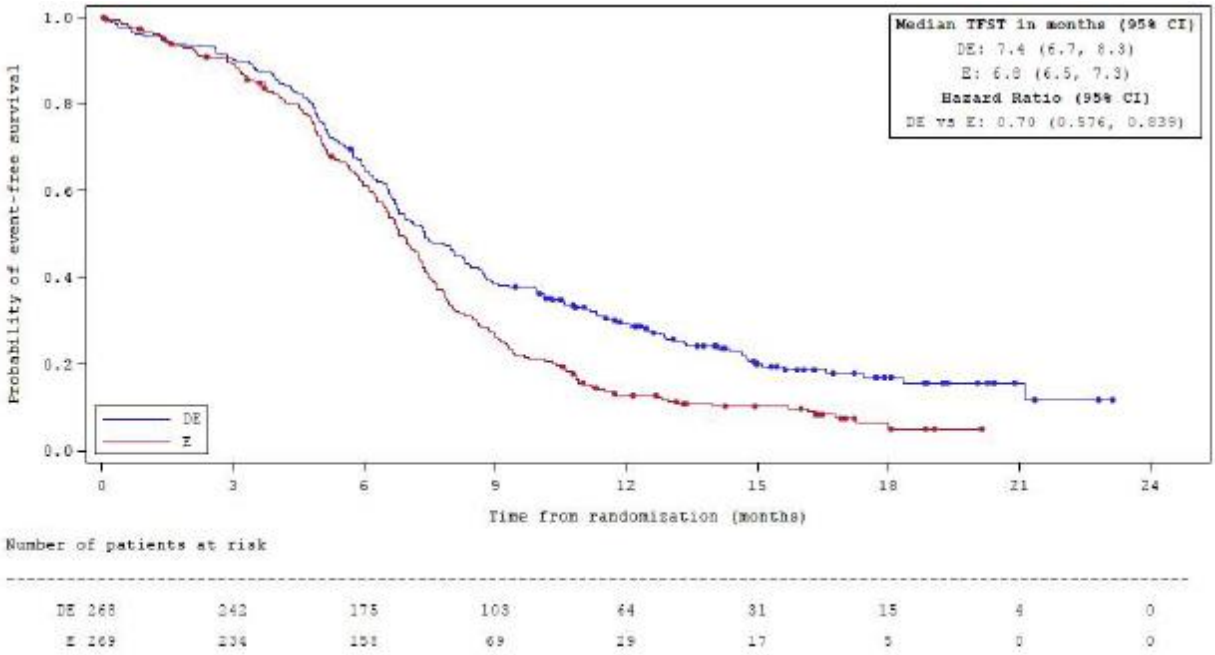
[b] Calculated using Kaplan-Meier technique. CI for median event-free survival is derived based on Brookmeyer-Crowley method and using the log-log transformation.

[c] The HR and CI were calculated using a stratified Cox proportional hazards model, adjusting for planned platinum therapy in Cycle 1 (carboplatin or cisplatin), and ties handled by Efron approach.

[d] A HR <1 favors D + EP to be associated with a longer event-free survival than EP alone.

[e] The analysis was performed using the stratified log-rank test, adjusting for planned platinum therapy in Cycle 1 (carboplatin or cisplatin), and using the rank tests of association approach.

Palliative/adjuvant radiotherapies are excluded from the subsequent anticancer therapies received.
1 month = 30.4375 days.
RECIST v1.1.
CI confidence interval; D durvalumab; EP etoposide and platinum-based chemotherapy; HR hazard ratio; N number of patients in treatment group; n number of patients in analysis.



Circle indicates a censored observation.
Palliative/adjuvant radiotherapies are excluded from the subsequent anticancer therapies received.

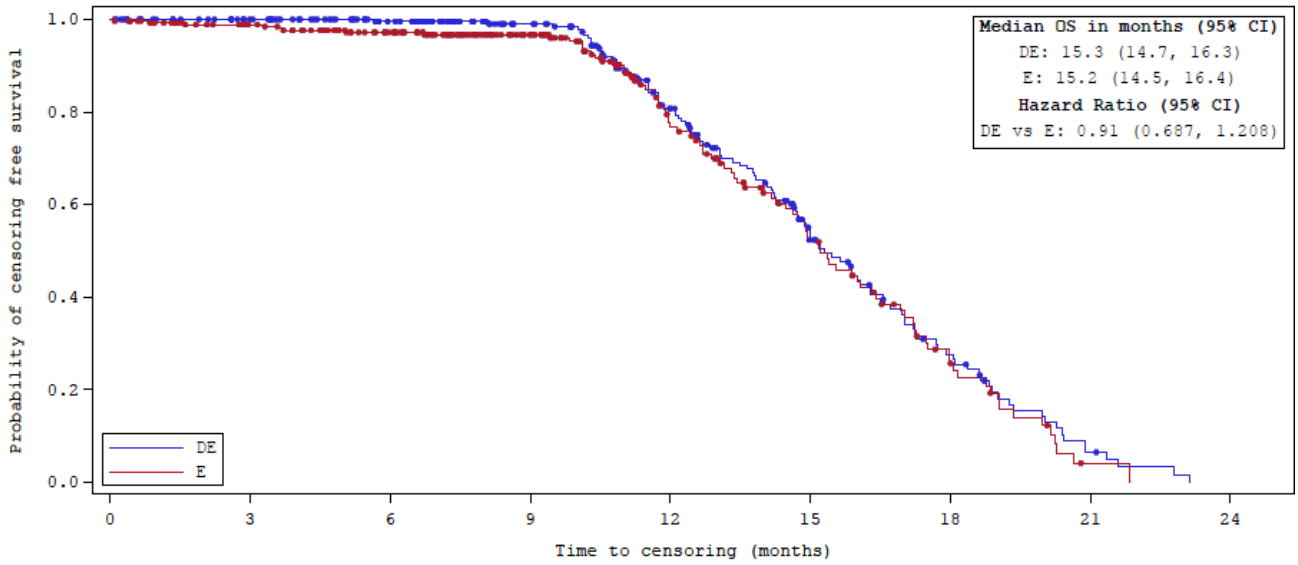
Figure 28: Time from randomization to first subsequent anticancer therapy or death, Kaplan-Meier plot

Ancillary analyses

Sensitivity analyses:

OS:

Sensitivity analysis was conducted for OS to examine the censoring patterns to identify potential attrition bias, using a Kaplan-Meier plot of time to censoring, where the censoring indicator of OS is reversed, see Figure below:



Number of patients at risk

DE 268	244	214	177	116	57	25	5	0
E 269	242	209	153	82	44	17	1	0

Figure 29: Overall survival, sensitivity analysis for attrition bias, Kaplan-Meier plot (with censoring and event flags reversed) – Full analysis set

Early censoring (>10 weeks before data cut-off) was observed for 2/268 (0.7%) patients for D + EP compared to 8/269 (3.0%) for EP. The majority of these cases (9/10) were due to withdrawal of consent.

The effect of adjusting for additional covariates was investigated, and the resulting adjusted estimate of HR was similar to the unadjusted estimate, see Table below:

Table 40: Overall survival, effect of covariates on primary and secondary analyses (Full analysis set)

				Comparison between groups [b]	
Covariates [a]	Group	N	Number (%) of patients with events	Hazard ratio	95% CI
Stratification factor	Durva + EP	268	155 (57.8)	0.73	0.591, 0.910
	EP	269	181 (67.3)		
Subgroup factors	Durva + EP	268	155 (57.8)	0.71	0.566, 0.877
	EP	269	181 (67.3)		

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Durva = Durvalumab, EP = Etoposide and platinum-based chemotherapy.
CI = Confidence interval. AJCC = American Joint Committee on Cancer. ~ Europe includes Israel.
[a] Stratification factor is the planned platinum therapy in Cycle 1 (Carboplatin, Cisplatin). Subgroup factors include the additional factors: age at randomization (< 65 years, >= 65 years), sex (male, female), performance status at baseline (0, >= 1), smoking status at screening (smoker, non-smoker), CNS metastasis at baseline (Y, N), AJCC staging at diagnosis (Stage III, Stage IV), race (asian, non-asian) and region (Asia, Europe, North and South America).
[b] The analysis was performed using Cox proportional hazards models that contains a term for treatment and the covariates. Ties were handled by the Efron approach.
A hazard ratio < 1 favors Durva + EP to be associated with a longer overall survival than EP.

To further explore robustness of the results, a sensitivity analysis using the Restrictive Mean Survival Time (RMST) approach –which may be used regardless the presence or not of proportional hazards– was done.

Table 41: Analysis of RMST

Method	RMST		RMST Ratio	RMST difference (95% CI) Unadjusted	RMST difference (95% CI) Adjusted by planned platinum
	D + EP	EP			
Area under the KM curve [a]	12.89	11.46	1.12	1.43 (0.27, 2.59) p=0.0160	1.56 (0.27, 2.85) p=0.0181
Pseudo-Value[b]	12.90	11.47	1.12	1.43 (0.26, 2.59) p=0.0161	1.43 (0.28, 2.59) p=0.0152
Royston-Parmar[c]	12.90	11.36	1.14	1.54 (0.39, 2.69) p=0.0087	1.57 (0.41, 2.74) p=0.0082

[a] CI and p-value calculated using the RMST2 function from the R 'survRM2' package

[b] Calculated using the pseudomean function from the R 'pseudo' package, with SE (for CI and p-value) estimated using Generalised Estimating Equation ('geepack' package). Difference estimated by including all data in a single model with a treatment group covariate.

[c] Calculated using the flexsurvspline function from the R 'flexsurv' package, with SE (for CI and p-value) estimated using the delta method. Model included cubic spline with 2 knots and a time-dependent covariate.

PFS:

Sensitivity analyses were conducted to assess robustness of the PFS effect to potential sources of bias in PFS measurement, including the possibility of evaluation time bias, attrition bias (by including the deaths that were censored in the primary analysis due to the death occurring after two or more missed visits in the absence of RECIST progression), and an analysis with adjustment for subsequent anticancer therapy.

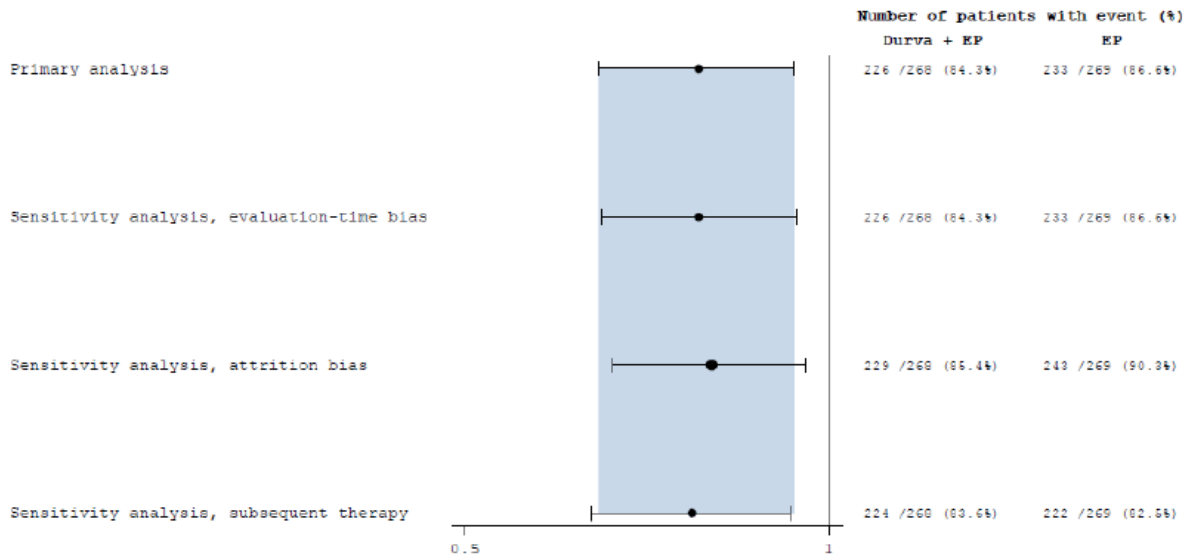
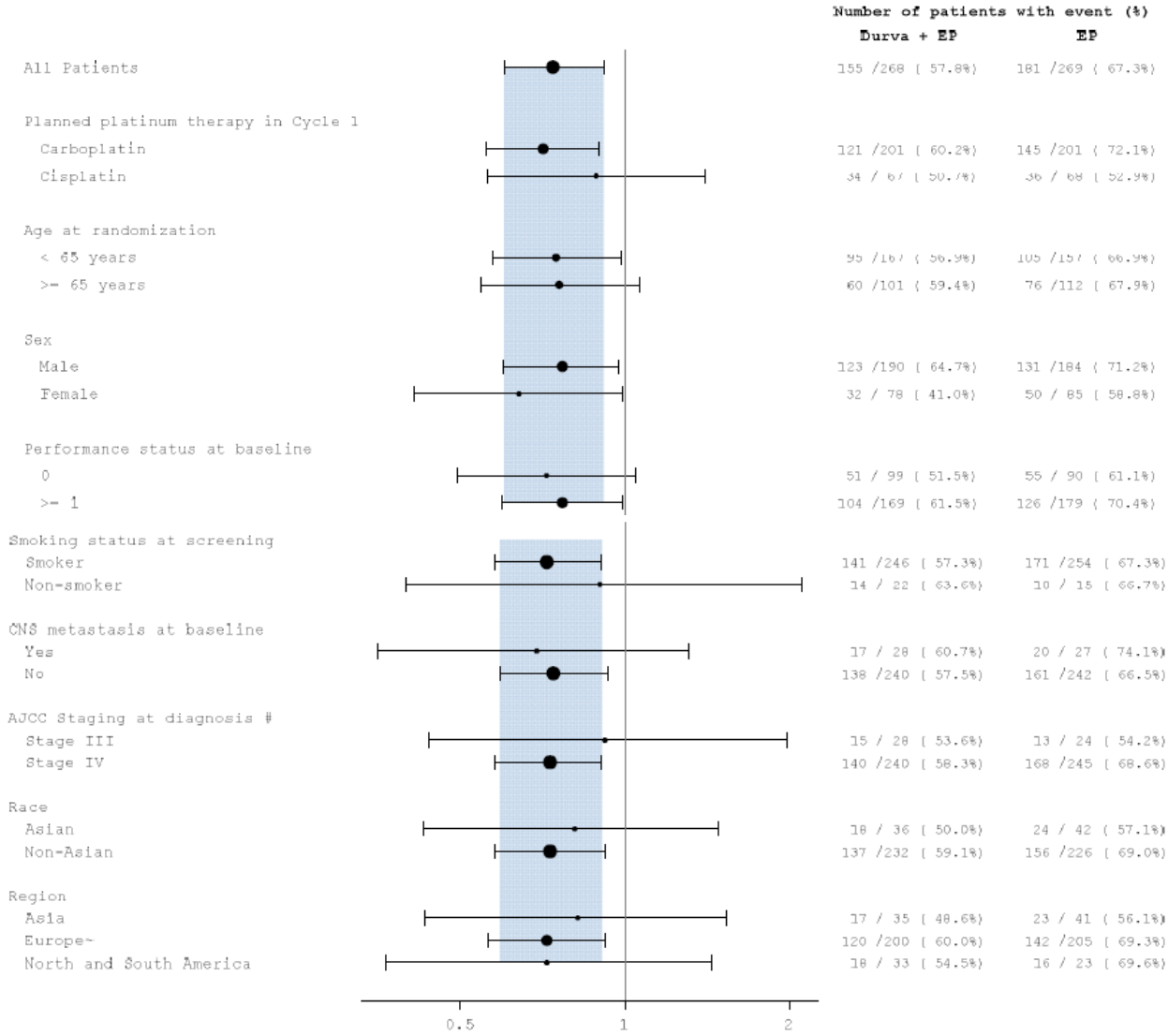


Figure 30: Forest plot of PFS (based on site investigator assessment according to RECIST 1.1) D+EP vs EP by secondary and sensitivity analyses (full analysis set)

Subgroup analyses:

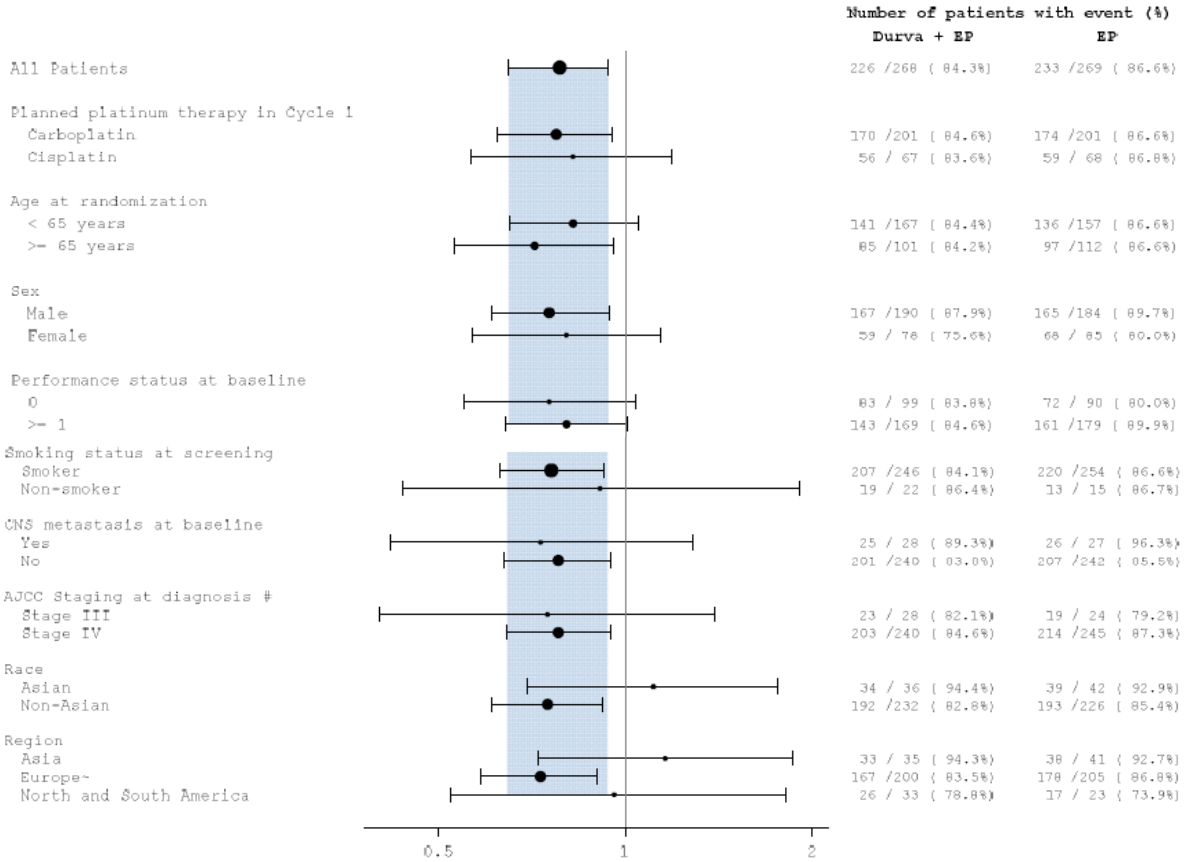
OS:



HR (Durva + EP: EP) and 95% CI.
AJCC staging = "III" (resp. "IV") includes "Stage IIIA"/"Stage IIIB" (resp. "Stage IVA"/"Stage IVB") from eCRF [PATHGEN] module. ~ Europe includes Israel.
Size of circle is proportional to the number of events across both treatment groups.
Grey band represents the 95% confidence interval for the overall (all patients) HR.
For the 'All Patients' analysis: same model as the main analysis. For the subgroup analysis: 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 favors Durva + EP to be associated with a longer OS than EP.
CNS metastasis includes brain metastasis and CNS metastasis.

Figure 31: Forest plot of overall survival by subgroup for D+EP vs EP (full analysis set)

PFS:

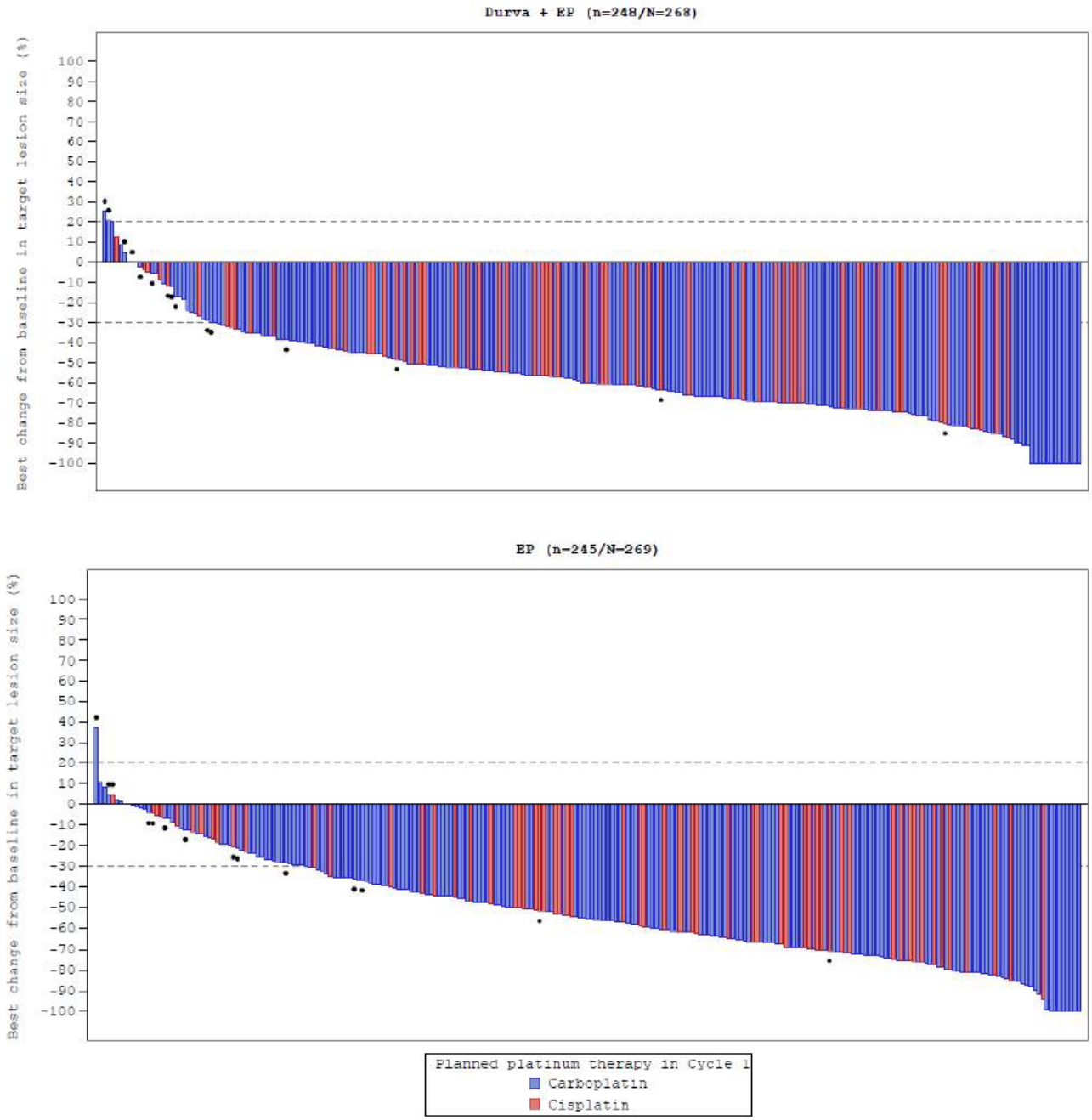


HR (D + EP: EP) and 95% CI.
AJCC staging = "III" (resp. "IV") includes "Stage IIIA"/"Stage IIIB" (resp. "Stage IVA"/"Stage IVB") from eCRF [PATHGEN] module.
Europe includes Israel.
Size of circle is proportional to the number of events across both treatment groups.
Grey band represents the 95% confidence interval for the overall (all patients) HR.
Progression is determined by the RECIST-based assessment of the investigator.
Patients 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 randomization if there are no evaluable visits. Patients with a RECIST progression within two visits of baseline who do not have any evaluable visits or do not have a baseline assessment are censored at randomization.
For the 'All Patients' analysis: same model as the main analysis. For the subgroup analysis: The HR and CIs were calculated using an unstratified Cox proportional hazards model, with treatment as only covariate and ties handled by Efron approach.

Figure 32: Forest plot of PFS based on site investigator assessments according to RECIST 1.1 by subgroup for D+EP vs EP (full analysis set)

Other ancillary analyses:

Figure 11 **Target lesion size based on site investigator assessment according to RECIST 1.1, best percentage change waterfall plot (full analysis set)**



Summary of main study

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

Table 42: Summary of Efficacy for the CASPIAN trial

Title: A phase III, randomized, multicentre, open-label, comparative study to determine the efficacy of durvalumab or durvalumab and tremelimumab in combination with platinum-based chemotherapy for the first-line treatment in patients with extensive disease small-cell lung cancer (CASPIAN)	
Study identifier	D419QC00001

Design	Phase III, open-label, randomised, three-arm		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		Not applicable, event driven Not applicable Not applicable
Hypothesis	Superiority		
Treatments groups	Arm 1 (D+T+EP)		Durvalumab + tremelimumab + cis/carboplatin + etoposide Q3Wx4 cycles (induction) then durvalumab Q6W until PD or loss of clinical benefit, additional dose of tremelimumab in W16 n=268
	Arm 2 (D+EP)		Durvalumab + cis/carboplatin + etoposide Q3Wx4 cycles (induction) then durvalumab Q6W until PD or loss of clinical benefit n=268
	Arm 3 (EP)		Cis/carboplatin + etoposide Q3Wx4-6 cycles until PD or loss of clinical benefit n=269
Endpoints and definitions	Primary endpoint	OS	Overall survival in intention-to-treat population
	Key secondary endpoint	INV-PFS	Investigator-assessed progression free survival according to RECIST 1.1 in intention-to-treat population
	Secondary[a] endpoint, post-hoc analysis	C-ORR	Objective response rate, confirmed
Clinical cut-off	Interim analysis 11 March 2019; Final analysis 27 January 2020		
Database lock	26 April 2019 and 3 March 2020, respectively		

Results and Analysis

Analysis description	**Interim analysis**			
Analysis population and time point description	Intent to treat, when at least 318 OS events (60% maturity) have occurred either in D+T+EP and EP arms or in the D+EP and EP arms.[b]			
Descriptive statistics and estimate variability	Treatment group		Arm 2 (D+EP)	Arm 3 (EP)
	Number of subjects		268	269
	Median OS, months		13.0	10.3
	95% CI		11.5, 14.8	9.3, 11.2
	Median INV-PFS, months		5.1	5.4
	95% CI		4.7, 6.2	4.8, 6.2
	C-ORR, % 95% CI		67.9 62.14, 73.30	57.6 51.65, 63.43
Effect estimate per comparison	OS	Comparison groups	Arm 2 (D+EP) vs. Arm 3 (EP)	
		Stratified Hazard Ratio	0.73	
		95% CI	0.591, 0.909	
		p-value (log-rank)	0.0047	
	INV-PFS	Comparison groups	Arm 2 (D+EP) vs. Arm 3 (EP)	
		Stratified Hazard Ratio	0.78	
		95% CI	0.645, 0.936	
		p-value (log-rank)	0.0078	
	C-ORR	Comparison groups	Arm 2 (D+EP) vs. Arm 3 (EP)	
		Odds ratio	1.56	
		95% CI	1.095, 2.218	
		p-value[c]	0.0136	
Analysis description	**Final analysis**			
Analysis population and time point description	Intent to treat, when at least 425 OS events (80% maturity) have occurred across the D+EP and EP arms.			
Descriptive statistics and estimate variability	Treatment group		Arm 2 (D+EP)	Arm 3 (EP)
	Number of subjects		268	269
	Median OS, months		12.9	10.5
	95% CI		11.3, 14.7	9.3, 11.2
	Median INV-PFS, months 95% CI		5.1 4.7, 6.2	5.4 4.8, 6.2
	C-ORR, % 95% CI		67.9 62.0, 73.5	58.0 51.8, 64.0
Effect estimate per comparison	OS	Comparison groups	Arm 2 (D+EP) vs. Arm 3 (EP)	
		Stratified Hazard Ratio	0.75	

		95% CI	0.625, 0.910
		p-value (log-rank)	0.0032
	INV-PFS	Comparison groups	Arm 2 (D+EP) vs. Arm 3 (EP)
		Stratified Hazard Ratio	0.80
		95% CI	0.665, 0.959
	C-ORR	Comparison groups	Arm 2 (D+EP) vs. Arm 3 (EP)
		Odds ratio	1.56
		95% CI	1.095, 2.218
Notes	[a]Prespecified protocol analysis of ORR did not require confirmation of response (unconfirmed response). Post-hoc analysis with confirmation of response has more clinical importance, so it was prioritised. [b]IDMC concluded that interim analysis of OS met prespecified O'Brien Fleming boundary for statistical significance between Arms 2 and 3, so those arms were unblinded, while Arm 1 remains blinded. [c]p-value, derived from logistic regression model, is based on twice the change in log-likelihood resulting from the addition of a treatment factor to the model.		

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

CASPIAN was a phase III, open-label, randomised, three-arm trial designed to determine the efficacy and safety of durvalumab + tremelimumab + EP (D+T+EP) or durvalumab + EP (D+EP) vs. EP alone as first-line treatment in patients with ES-SCLC.

The MAH has performed the first interim analysis for the D+EP group compared with the EP group, which occurred at a data cut-off of 11 March 2019. The interim analysis of OS performed by an independent committee showed statistical significance for the D+EP vs. EP comparison, which allowed for unblinding those arms to the sponsor and submitting efficacy and safety data to support the proposed new indication: durvalumab in combination with etoposide and either carboplatin or cisplatin for the first-line treatment of adults with ES-SCLC. The trial was to continue for analysis of D+T+EP at the final analysis (this arm remained blinded).

The original design of the trial had been discussed with the CHMP, although an important number of changes were implemented before and during recruitment. Allowing cisplatin as part of chemotherapy in any of the arms is considered a notable advantage. This was in fact physician's choice (carboplatin or cisplatin) and the only stratification factor prior to randomisation. It is noted that other factors such as ECOG PS or presence of brain metastases could have also been used as stratification factors.

Treatment with up to 6 cycles of chemotherapy was permitted in the control EP arm, whereas only 4 were allowed in the experimental D+EP arm. This is a matter of controversy: although most guidelines recommend 4-6 cycles of EP for the 1L treatment of ES-SCLC, evidence of efficacy benefit from 6 vs. 4 cycles is minimal and longer exposure might only lead to accumulated chemotherapy toxicity, thus probably disfavouring safety performance of the control arm.

Study design did not allow to discern the benefit from durvalumab in the induction phase (combined with chemotherapy) from that in the maintenance phase (by itself). However, some clinical evidence (numerical improvement in ORR) of the early beneficial effect from D+EP during induction, as well as efficacy in exploratory endpoints (PFS2) support the maintenance advantage.

A crucial change was implemented in the primary endpoint in V4 of the protocol: from OS and PFS to OS only, which in turn led to downgrading PFS assessment from BICR to INV. To demonstrate that integrity of the study had not been compromised, the MAH presented the timelines that relate external evidence and amendments along the protocol, along with the percentage of OS events at each of the referred milestones.

As for the change in V5 (allocating more alpha for the comparison of D+EP vs. EP than for D+T+EP vs. EP), it came from internal sources: results from the MYSTIC study showed worse performance of the tremelimumab+durvalumab arm (vs. chemotherapy) than durvalumab by itself (vs. chemotherapy). The MAH has further explained that the D+T+EP arm did not meet its primary endpoint, and presented the results disclosed at ASCO 2020, although no discussion of the contribution of tremelimumab to the D+EP regimen was provided.

Overall, statistical methods applied in the trial are endorsed.

A total of 971 patients were enrolled in the study, of whom 805 patients were finally randomised to each treatment arm in a 1:1:1 ratio. 75% of patients had been planned for carboplatin and 25% for cisplatin. Important protocol deviations occurred in a small proportion of patients and are balanced in the two reported arms. The proportion of patients with brain metastases (10.2%) is lower than that in clinical practice (15-20%, Hochstenbag et al, 2016; Lekic et al, 2011), but this is likely due to allowing only patients with asymptomatic or treated metastases for inclusion.

Efficacy data and additional analyses

At the interim OS analysis, after a median follow-up of 10.6 months at data cut-off (11-MAR-2019), 336 death events (62.6%) had occurred in arms 2 (D+EP) and 3 (EP) of the trial, satisfying the predefined O'Brien-Fleming boundary for declaring statistical significance between those arms (p-value <0.0178). The D+EP arm showed a statistical OS improvement compared to EP alone [mOS 13.0 versus 10.3 months, HR 0.73 (95% CI 0.591, 0.909), p=0.0047]. Importantly, OS results from the control arm are comparable to data from most published 1L studies of platinum + etoposide in ES-SCLC, including the control arm (carboplatin + etoposide + placebo) from study IMpower133 (Horn et al, 2018).

Data from the final OS analysis (data cut-off 27-JAN-2020, 82% of events) are overall consistent with those from the interim analysis. However, in both interim and final OS analyses, the K-M curves depict violation of the proportional hazards model, i.e. the essential assumption of the stratified Cox model. A sensitivity analysis using the RMST approach (area under the KM curve, pseudo-value and Royston-Pharma), albeit lacking the 95% Cis for the RMST ratio, supports robustness of the results.

Hierarchical testing also required a statistically significant OS improvement from D+T+EP vs. EP (arm 1 vs. 3) before proceeding to PFS. Since this did not happen, formal PFS testing was not performed. Mature data (86% of PFS events - DCO 11-MAR-2019) permitted a descriptive analysis of investigator-assessed PFS, which seems to sustain the benefit from D+EP over EP (HR 0.78; 95% CI 0.645, 0.936; nominal p=0.0078). Overall, the survival advantage from D+EP vs. EP seems to be reflected in the descriptive analysis of the key secondary endpoint – PFS.

Sensitivity analyses on both OS and PFS support the clinical advantage from D+EP over EP, as do other secondary (ORR, DoR) and exploratory endpoints (PFS2, TFST). The forest plot on OS shows the benefit from D+EP is maintained across the prespecified subgroups based on demographics, geographical region, carboplatin or cisplatin use and disease characteristics.

An exploratory analysis on PD-L1 results from available samples shows scarce IHC expression in TCs and ICs of ES-SCLC. The forest plots that depict the potential relationship of these results with OS events suggests that the benefit of D+EP vs. EP is maintained across the different subgroups of PD-L1 expression, but such limited data prevent a firm conclusion on the predictive value of this biomarker in the ES-SCLC setting.

Time to deterioration results suggest that delay of patient-reported symptoms was more pronounced in the experimental arm. However, the open-label nature of the study and reduced compliance in the questionnaires challenges definitive conclusions in PRO data.

Overall, efficacy data from the CASPIAN trial are in line with results observed in the IMpower133 study, which was conducted with atezolizumab + chemotherapy vs. chemotherapy in a similar population setting, in spite of a few differences in study design.

The complete final analysis of all three arms along with a discussion in the final CSR of CASPIAN, will be submitted by the end of 2020 (recommendation)

2.4.4. Conclusions on the clinical efficacy

The interim and final analyses of CASPIAN show a statistically significant improvement in OS for durvalumab + EP vs. EP in the first line setting of ES-SCLC. This benefit is supported by an informal analysis on mature data of the key secondary endpoint, PFS. The rest of secondary endpoints are also consistent with the primary endpoint. The role of PD-L1 expression as a predictive biomarker for checkpoint immunotherapy in SCLC remains uncertain.

2.5. Clinical safety

Introduction

The total postmarketing exposure of durvalumab since launch to 30 April 2019 is estimated to be approximately 10163 patient-years (IMFINZI Periodic Benefit-Risk Evaluation Report [PBRER], 25 June 2019). No new safety concern was identified based on the postmarketing safety reports.

The CASPIAN study was designed to determine the efficacy and safety of durvalumab (D), or durvalumab and tremelimumab (D+T), in combination with EP for the first-line treatment of patients with ES-SCLC.

The pivotal safety dataset comprises 265 patients in the D+EP group and 266 patients in the EP alone group. Data from all cycles of treatment were combined in the presentation of safety data. AEs (both in terms of MedDRA preferred terms and CTCAE grade) were listed individually by patient. The number of patients experiencing each AE was summarized by treatment group and CTCAE grade. Other safety data were assessed in terms of physical examination, clinical chemistry, haematology, vital signs, and ECGs.

D pan tumour pool: A supportive assessment of the safety and tolerability of durvalumab monotherapy (without chemotherapy) was provided in a 9-study durvalumab pan-tumour pool (**D pan tumour pool; N=3006**). This population consists of patients who have received at least 1 dose of durvalumab monotherapy given at a dose of either 10 mg/kg Q2W IV or 20 mg/kg Q4W IV for any line of therapy (across tumour types).

Each of the 9 studies included contributed with a cohort of at least 50 patients:

Table 43: Durvalumab pan-tumour pool

Study	Number of subjects by treatment regimen
D419AC00001 (MYSTIC)	20 mg/kg Q4W (n=369)
D4191C00003 (ATLANTIC)	10 mg/kg Q2W (n=444)

Study	Number of subjects by treatment regimen
D4191C00001 (PACIFIC)	10 mg/kg Q2W (n=475)
D4193C00002 (EAGLE)	10 mg/kg Q2W (n=237)
D4191C00004 (ARCTIC)	Sub-study A: 10 mg/kg Q2W (n=62) Sub-study B: 10 mg/kg Q2W (n=117)
D4193C00003 (CONDOR)	10 mg/kg Q2W (n=65)
D4193C00001 (HAWK)	10 mg/kg Q2W (n=112)
CD-ON-MEDI4736-1108 (Study 1108)[a]	10 mg/kg Q2W (n=980) 20 mg/kg Q4W (n=21)
D4190C00002 (Japan Study 2)	10 mg/kg Q2W (n=120) 20 mg/kg Q4W (n=4)

Q2W = every 2 weeks; Q4W = every 4 weeks

Study 1108 included a further 21 patients who received doses other than 10 mg/kg Q2W IV or 20 mg/kg Q4W in a dose escalation phase who are excluded from the D pan-tumor pool

Table 44: Summary of clinical studies included in the application package

Study name Status[a] DCO	Phase Study design	Patient population	Primary outcome measures	No. of randomized patients
Pivotal study				
CASPIAN Ongoing 11 Mar 2019	Phase III Randomized, open-label, comparative, multicenter	Patients with extensive-stage small cell lung cancer (ES-SCLC) who have not received prior 1L treatment	Primary efficacy: OS Secondary efficacy: PFS, PFS6/12, OS18, ORR Safety: AEs, laboratory evaluations, physical examinations, and vital signs	537 (Total)[b] 268 (D + EP) 269 (EP alone)
Supportive studies				
Study 1108 Complete 16 Oct 2017	Phase I/IIb FTIH, open-label, 3 + 3 dose-escalation, dose-expansion	Patients with advanced solid tumors, including SCLC, that are refractory to standard therapy and for which no standard therapy exists	Primary: MTD or OBD Safety: AEs, laboratory evaluations, physical examinations, and vital signs	1022 (Total) 21 (SCLC cohort)
Japan 002 Complete 31 Mar 2018	Phase I Open-label, multicenter	Patients with advanced solid tumors, that are refractory to standard therapy and for which no standard therapy exists	Primary: MTD or OBD Safety: AEs, laboratory evaluations, physical examinations, vital signs	262 (Total) 138 (D) 124 (D + T)
ATLANTIC Complete 03 Jun 2016	Phase II Non-comparative, open-label, multicenter, international	Patients with locally advanced or metastatic NSCLC (Stage IIIB – IV) who have received at least 2 prior systemic treatment regimens	Primary: ORR Safety: AEs, laboratory evaluations, physical examinations, vital signs, ECG	444 (Total)
ARCTIC Complete 09 Feb 2018	Phase III Randomized, open-label, multicenter, international	Patients with locally advanced or metastatic NSCLC (Stage IIIB-IV) who received at least 2 prior systemic treatments and do not have *EGFR* or *ALK* target mutations	Primary: PFS and OS Safety: AEs, laboratory evaluations, physical examinations, vital signs	595 (Total) 126 (Substudy A) 469 (Substudy B)

PACIFIC Ongoing 22 Mar 2018	Phase III Randomized, double-blind, placebo-controlled, multicenter, international	Patients with locally advanced, unresectable, Stage III NSCLC who have not progressed after definitive platinum-based concurrent chemoradiation	Primary efficacy: PFS and OS Safety: AEs, laboratory evaluations, physical examinations, vital signs, ECG	713 (Total) 476 (D) 237 (Placebo)
MYSTIC Complete 04 Oct 2018	Phase III Randomized, open-label, multicenter, international	Patients with Stage IV NSCLC who have not received prior chemotherapy or other systemic therapy and who do not have *EGFR* or *ALK* target mutations	Primary efficacy: PFS and OS in PD-L1 TC≥25% Safety: AEs, laboratory evaluations, physical examinations, vital signs, ECG	1118 (Total) 374 (D) 372 (D + T) 372 (SoC)
HAWK Complete 05 Oct 2018	Phase II Single-arm, multicenter, international	Patients with recurrent or metastatic HNSCC not amenable to therapy with curative intent	Primary efficacy: ORR (BICR) Safety: AEs, laboratory evaluations, physical examinations, vital signs, ECG	112 (Total)
CONDOR Complete 27 Aug 2018	Phase II Randomized, open-label, multicenter, international	Patients with recurrent or metastatic HNSCC not amenable to therapy with curative intent	Primary efficacy: ORR (BICR) Safety: AEs, laboratory evaluations, physical examinations, vital signs, ECG	267 (Total) 67 (D) 67 (T) 133 (D + T)
EAGLE Complete 10 Sep 2018	Phase III Randomized, open-label, multicenter, international	Patients with recurrent or metastatic HNSCC not amenable to therapy with curative intent	Primary efficacy: OS, PFS Safety: AEs, laboratory evaluations, physical examinations, vital signs, ECG	736 (total) 240 (D) 247 (D + T) 249 (SoC)

Definitions, adverse events of special interest (AESIs) and immune-mediated adverse events (imAEs):

AESIs: In the durvalumab clinical program, AESIs are AEs that include, but are not limited to, events with a potential inflammatory or immune mediated mechanism as a result of the mechanism of action of durvalumab that may require more frequent monitoring and/or interventions such as corticosteroids, immunosuppressants, and/or endocrine therapy. Endocrine therapies include standard endocrine supplementation, as well as treatment of symptoms resulting from endocrine disorders (e.g. therapies for hyperthyroidism include beta blockers, calcium channel blockers, methimazole, propylthiouracil, and sodium perchlorate).

The categories for AESIs include the following: pneumonitis, hepatic events, diarrhoea/colitis, intestinal perforations, hypothyroid events, hyperthyroid events, thyroiditis, adrenal insufficiency, hypophysitis, type I diabetes mellitus, renal events, dermatitis/rash, myocarditis, myositis, infusion/hypersensitivity reactions, myasthenia gravis, Guillain-Barre syndrome, pancreatic events, other rare/miscellaneous events.

imAEs: In the durvalumab clinical program, a suspected imAE is an AESI that required the use of systemic steroids (regardless of dose) or other immunosuppressants, and/or endocrine therapy for specific endocrine events. A confirmed imAE is a suspected imAE that, after medical review, is deemed consistent with an immune mediated mechanism of action, and where there is no clear alternate aetiology. Serologic, immunologic, and histologic (biopsy) data, as appropriate, will be used to support characterization of an imAE.

Steps to manually adjudicate the imAEs: The process for adjudicating imAEs starting from the study level AE reporting dataset through to confirmed imAE includes the steps depicted in Figure 33.

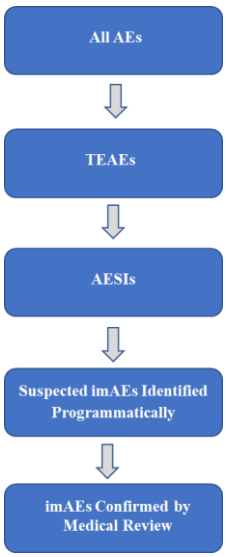


Figure 33: The process for adjudicating imAEs

- From all AEs reported in a study, treatment emergent adverse events (TEAE) were defined. This definition varied slightly between studies and was dependent upon the AE reporting period for the study.
-
- The suspected imAEs were identified as AESI treated with systemic steroids, other immunosuppressants, and/or endocrine therapy, except Pneumonitis AESI for which all are suspected imAE. Endocrine therapies included standard endocrine supplementation, as well as treatment of symptoms resulting from endocrine disorders (for example, therapies for hyperthyroidism include beta blockers [e.g., propranolol], calcium channel blockers [eg, verapamil, diltiazem], methimazole, propylthiouracil, and sodium perchlorate).
- All suspected imAEs underwent medical review.
- Confirmed imAEs were those suspected imAEs that after medical review did not have a clear alternate aetiology and were consistent with immune-mediated mechanism of action.

Patient exposure

Table 45: Duration of exposure – durvalumab (safety analysis set)

Treatment duration	D + EP (N = 265)
	D (n = 265)
Number of infusions	
Mean (SD)	8.8 (5.19)
Median (Min, Max)	7.0 (1, 25)
Total exposure duration (weeks)[a]	
Mean (SD)	32.95 (21.059)
Median (Min, Max)	28.00 (0.3, 94.3)
Total treatment years	167.348
Actual exposure duration (weeks)[b]	
Mean (SD)	31.76 (20.245)
Median (Min, Max)	26.29 (0.3, 93.4)
Total treatment years	161.292
Number of cycles received[c]	
Mean (SD)	8.8 (5.18)
Median (Min, Max)	7.0 (1, 25)
Relative dose intensity	
n	265
Mean (SD)	95.42 (8.308)
Median (Min, Max)	100.00 (45.5, 108.7)
Q1	91.30
Q3	100.00
Total cumulative dose	
n	265
Mean (SD)	13166.38 (7787.236)
Median (Min, Max)	10500 (1500, 37500)
Q1	9000
Q3	16500
Total study drug	3489091.7

[a] Total exposure duration (weeks) = [(last dose date + xx days where dose >0 mg or death or DCO date, whichever occurs first) - first dose date + 1] / 7, where xx=20/27 for chemotherapy/post-chemotherapy cycles respectively.

[b] Actual exposure duration is total treatment duration excluding total duration of any dose

In the D pan-tumour pool (N=3006), mean total exposure duration in weeks was 25.6 (SD 24.3); median was 16.0 weeks (Min 0, Max 152) and total treatment-years was 1474.2.'

Table 46: Duration of exposure – chemotherapy (safety analysis set)

Treatment duration	D + EP (N=265)			EP (N=266)		
	Etop (n = 265)	Carbo (n = 208)	Cispl (n = 65)	Etop (n = 266)	Carbo (n = 208)	Cispl (n = 67)
Number of infusions						
Mean (SD)	11.2 (2.63)	3.6 (0.88)	3.7 (1.45)	14.6 (4.68)	4.9 (1.52)	4.3 (1.94)
Median (Min, Max)	12.0 (2, 24)	4.0 (1, 6)	4.0 (1, 12)	18.0 (1, 18)	6.0 (1, 6)	4.0 (1, 7)
Total exposure duration (weeks)[a]						
Mean (SD)	11.77 (3.031)	11.83 (3.238)	11.13 (3.720)	16.33 (5.764)	16.56 (5.698)	14.35 (7.067)
Median (Min, Max)	11.86 (0.3, 20.7)	12.14 (0.6, 21.0)	12.14 (0.3, 17.9)	18.71 (0.4, 26.6)	19.00 (0.4, 26.9)	14.00 (1.7, 25.9)
Total treatment years	59.797	47.146	13.867	83.244	66.004	18.423
Number of cycles received[b]						
Mean (SD)	3.7 (0.81)	3.6 (0.88)	3.5 (1.00)	4.9 (1.54)	4.9 (1.52)	4.3 (1.93)
Median (Min, Max)	4.0 (1, 6)	4.0 (1, 6)	4.0 (1, 5)	6.0 (1, 6)	6.0 (1, 6)	4.0 (1, 6)
Number of cycles received[b,c]						
≥1	265 (100.0)	208 (100.0)	65 (100.0)	266 (100.0)	208 (100.0)	67 (100.0)
≥2	249 (94.0)	193 (92.8)	59 (90.8)	249 (93.6)	196 (94.2)	56 (83.6)
≥3	242 (91.3)	185 (88.9)	54 (83.1)	238 (89.5)	187 (89.9)	52 (77.6)
≥4	230 (86.8)	169 (81.3)	51 (78.5)	225 (84.6)	174 (83.7)	46 (68.7)
≥5	3 (1.1)	2 (1.0)	1 (1.5)	167 (62.8)	130 (62.5)	33 (49.3)
≥6	1 (0.4)	1 (0.5)	0	151 (56.8)	115 (55.3)	32 (47.8)
Relative Dose Intensity (RDI)[d]						
Mean	119.37	103.04	98.30	114.49	100.32	93.16
SD	23.753	13.255	25.016	15.851	13.402	24.814
Median	125.00	100.00	106.50	125.00	100.00	100.00
Min	62.5	45.0	25.0	33.3	52.0	17.8
Q1	105.60	100.00	100.00	104.20	100.00	88.90
Q3	125.00	117.50	106.70	125.00	100.00	106.70
Max	270.8	150.0	205.9	131.3	120.0	189.3
Total Cumulative Dose						
n	265	208	65	266	208	67
Mean	1077.62	18.90	279.24	1380.83	25.20	321.13
SD	316.783	4.973	90.338	467.776	8.495	142.028
Median	1200.00	20.00	308.00	1500.00	30.00	320.00
Min	160.0	5.0	75.0	80.0	5.0	75.0
Q1	960.00	18.00	283.20	1200.00	20.00	220.00
Q3	1200.00	20.00	320.00	1800.00	30.00	450.00
Max	2600.0	30.0	617.6	1890.0	36.0	480.00
Total study drug	285569.9	3930.3	18150.5	367300.6	5241.6	21515.8

[a] Total exposure duration (weeks) = [(last dose date + xx days where dose >0 mg or death or DCO date, whichever occurs first) - first dose date + 1] / 7, where xx=20/27 for chemotherapy/post-chemotherapy cycles respectively. For etoposide, xx = 18/25 days respectively if last dose is administered on day 3, with appropriate adjustment if dosing is stopped on day 1 or 2 of the cycle.

[b] A cycle corresponds to a period of 21 days during EP administration, and 28 days after cycle 4, at least one dose of any treatment (etoposide/carboplatin/cisplatin) must be administered for a cycle to be considered to have taken place.

[c] Rows are cumulative and patients are included if they have taken treatment up to and including that number of cycles. Percentages are based on n (=number of patients who received at least one dose of the molecule).

[d] Cisplatin was administered by splitting the dose over multiple days within a cycle.

Carbo carboplatin; cispl cisplatin;D durvalumab; DCO data cut-off; EP etoposide and platinum-based chemotherapy; Etop etoposide; Max maximum; Min minimum; SD standard deviation.

Source: Tables 14.3.1.2, Module 5.3.5.1, and Tables i0218ex200 and i0218ex201, Appendix 1

Out of a total of 531 patients treated, 17 patients who initially received cisplatin were switched to carboplatin therapy, and no patients initially treated with carboplatin switched to cisplatin. Of the 17 patients whose treatment was switched, 8 were in the D + EP group and 9 were in the EP alone group.

Dose modifications:

Dose interruptions: In the D + EP group, a total of 3 patients required a durvalumab dose interruption (all 3 were due to an AE). A total of 2 patients required an etoposide dose interruption (both due to an AE), no patients required a carboplatin dose interruption, and 1 patient required a cisplatin dose interruption (due to an AE). In the EP group, 9 patients required an etoposide dose interruption (7 due to an AE and 2 due to other reasons), 3 patients required a carboplatin dose interruption (all due to AEs), and no patients required a cisplatin dose interruption.

Dose delays: In the D + EP group, 149 (56.2%) patients had dose delays to durvalumab, the majority of whom had only 1 delay (78 [29.4%]); the most common reason for a dose delay was AEs (109 [41.1%]). A total of 113 (42.6%) patients had dose delays to etoposide, the majority of whom had 1 delay (72 [27.2%]); the most common reason was due to an AE (84 [31.7%]). A total of 89 (42.8%) carboplatin-treated patients had dose delays to carboplatin, the majority of whom had 1 delay (54 [26.0%]); the most common reason was due to an AE (70 [33.7%]). A total of 23 (35.4%) cisplatin-treated patients had dose delays to cisplatin, the majority of whom had 1 delay (16 [24.6%]); the

most common reason was due to an AE (14 [21.5%]). In the EP group, 144 (54.1%) patients had dose delays to etoposide, the majority of whom had 1 delay (76 [28.6%]); the most common reason was due to an AE (105 [39.5%]). A total of 118 (56.7%) carboplatin-treated patients had dose delays to carboplatin, the majority of whom had 1 delay (61 [29.3%]); the most common reason was due to an AE (88 [42.3%]). A total of 29 (43.3%) cisplatin-treated patients had dose delays to cisplatin, the majority of whom had 1 delay (19 [28.4%]); the most common reason was due to an AE (20 [29.9%]).

Dose reductions: In the D + EP group, a total of 30 (11.3%) patients required an etoposide dose reduction, the majority of whom had only 1 reduction (26 [9.8%]); the most common reason due to an AE (27 [10.2%]). A total of 22 (10.6%) patients required a carboplatin dose reduction, the majority of whom had 1 reduction (20 [9.6%]); the most common reason due to an AE (21 [10.1%]). A total of 5 (7.7%) patients required a cisplatin dose reduction, the majority of whom had 1 reduction (4 [6.2%]); the most common reason due to an AE (5 [7.7%]). In the EP group, 42 (15.8%) patients required an etoposide dose reduction, the majority of whom had only 1 reduction (39 [14.7%]); the most common reason due to AEs (38 [14.3%]). A total of 22 (10.6%) patients required a carboplatin dose reduction, all of whom had 1 reduction; the most common reason due to an AE (19 [9.1%]). A total of 12 (17.9%) patients required a cisplatin dose reduction, the majority of whom had 1 reduction (11 [16.4%]); the most common reason due to an AE (12 [17.9%]).

Dose intensity: The median relative dose intensity of D was 100% in the D + EP group. The median relative dose intensity for EP was not calculated due to the permissive ranges for these medications.

Adverse events

Table 47: Overview of adverse events (safety analysis set)

	Number (%) of patients[a]		
	CASPIAN		**D pan-tumor pool[b]**
AE Category	**D + EP (N=265)**	**EP (N=266)**	**(N=3006)**
Any AE	260 (98.1)	258 (97.0)	2867 (95.4)
Any AE of CTCAE grade 3 or 4	163 (61.5)	166 (62.4)	1290 (42.9)
Any AE with outcome of death	13 (4.9)	15 (5.6)	164 (5.5)
Any SAE	82 (30.9)	96 (36.1)	1068 (35.5)
Any AE leading to discontinuation of study treatment[c]	25 (9.4)	25 (9.4)	282 (9.4)
Any AE leading to dose delay or interruption of any study treatment[d]	124 (46.8)	124 (46.6)	871 (29.0)

Table 48: Adverse events in any category (safety analysis set)

AE category	Number (%) of patients[a]	
	D + EP (N=265)	EP (N=266)
Any AE	260 (98.1)	258 (97.0)
Any AE causally related to treatment[b]	237 (89.4)	240 (90.2)
Any AEs of CTCAE Grade 3 or 4	163 (61.5)	166 (62.4)
Any AEs of CTCAE Grade 3 or 4, causally related to treatment[b]	121 (45.7)	138 (51.9)
Any AEs with outcome of death	13 (4.9)	15 (5.6)
Any AEs with outcome of death, causally related to treatment[b]	5 (1.9)	2 (0.8)
Any SAEs (including events with outcome of death)	82 (30.9)	96 (36.1)
Any SAEs (including events with outcome of death), causally related to treatment[b]	35 (13.2)	50 (18.8)
Any AEs leading to discontinuation of study treatment[c]	25 (9.4)	25 (9.4)
Any AEs leading to discontinuation of study treatment, causally related to treatment[b,c]	15 (5.7)	13 (4.9)
Any AEs leading to dose delay/interruption[d]	111 (41.9)	100 (37.6)

[a] Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories.
[b] Causally related to any of the study treatments, as assessed by the investigator. Missing responses are counted as related.
[c] AEs on the AE CRF page with Action taken = "Drug permanently discontinued" for at least one treatment.
[d] AEs on the AE CRF page with Action taken = "Drug interrupted" for either molecule.
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 study treatment or up to the date of initiation of the first subsequent anticancer therapy (whichever occurs first).
Percentages are based on the total numbers of patients in the treatment group (N).
CTCAE version 4.03. MedDRA version 21.1.
AE adverse event; CRF electronic case report form; CTCAE Common Terminology Criteria for Adverse Events; D durvalumab; EP etoposide and platinum-based chemotherapy; SAE serious adverse event.

Table 49: Most common adverse events (frequency ≥15% in either treatment group in CASPIAN) (safety analysis set)

Preferred Term	CASPIAN				D pan-tumor pool[a] (N=3006)	
	D + EP (N=265)		EP (N=266)			
	n (%)[b]	m/100 PY[c]	n (%)[b]	m/100 PY[c]	n (%)[b]	m/100 PY[c]
Patients with any AE	260 (98.1)	155.0	258 (97.0)	304.9	2867 (95.4)	194.5
Neutropenia	111 (41.9)	66.2	124 (46.6)	146.5	25 (0.8)	1.7
Anaemia	102 (38.5)	60.8	125 (47.0)	147.7	396 (13.2)	26.9
Nausea	89 (33.6)	53.1	89 (33.5)	105.2	542 (18.0)	36.8
Alopecia	83 (31.3)	49.5	91 (34.2)	107.5	27 (0.9)	1.8
Constipation	44 (16.6)	26.2	51 (19.2)	60.3	506 (16.8)	34.3
Decreased appetite	48 (18.1)	28.6	46 (17.3)	54.4	614 (20.4)	41.7
Thrombocytopenia	41 (15.5)	24.4	53 (19.9)	62.6	45 (1.5)	3.1
Fatigue	48 (18.1)	28.6	45 (16.9)	53.2	800 (26.6)	54.3
Vomiting	39 (14.7)	23.2	44 (16.5)	52.0	357 (11.9)	24.2
Asthenia	40 (15.1)	23.8	40 (15.0)	47.3	349 (11.6)	23.7
Leukopenia	40 (15.1)	23.8	32 (12.0)	37.8	14 (0.5)	0.9

AE adverse event; CTCAE Common Terminology Criteria for Adverse Events (version 4.03); D durvalumab; EP etoposide and platinum-based chemotherapy; PT preferred term; PY patient years.

[a] Includes Study 1108, Japan Study 2, ATLANTIC, ARCTIC, PACIFIC, MYSTIC, HAWK, CONDOR, and EAGLE. Does not include disease progression AEs reported in Study 1108

[b] Number (%) of patients with AEs. Patients with multiple AEs are counted once for each system organ class and preferred term.

[c] Event rate per 100 patient years (number of patients with AEs divided by the total duration of treatment across all patients in given group, multiplied by 100).

Table 50. Adverse events by any reported CTCAE grade in CASPIAN (safety analysis set)

	Number (%) of patients[a]		
	CASPIAN		
Any reported CTCAE grade	D + EP (N=265)	EP (N=266)	D pan-tumor pool[b] (N=3006)
Total	260 (98.1)	258 (97.0)	2867 (95.4)
Grade 1	229 (86.4)	215 (80.8)	2589 (86.1)
Grade 2	215 (81.1)	226 (85.0)	2268 (75.4)
Grade 3	158 (59.6)	154 (57.9)	1238 (41.2)
Grade 4	47 (17.7)	56 (21.1)	190 (6.3)
Grade 5	13 (4.9)	15 (5.6)	163 (5.4)
Grade 3 or 4	163 (61.5)	166 (62.4)	1290 (42.9)
Grade 3 or higher	169 (63.8)	172 (64.7)	1336 (44.4)

AE adverse event; CTCAE Common Terminology Criteria for Adverse Events (version 4.03); D durvalumab; EP etoposide and platinum-based chemotherapy; PT preferred term; SOC system organ class.

[a]Number (%) of patients with any AE, sorted by international order for SOC and alphabetically for PT and then grade. Patients with multiple events in the same SOC/CTCAE grade are counted only once in that SOC/CTCAE grade. Patients with events in more than one PT/CTCAE grade are counted once in each of those PTs/CTCAE grades. Patients with multiple events in the same PT/CTCAE grade are counted only once in that PT/CTCAE grade.

[b]Includes Study 1108, Japan Study 2, ATLANTIC, ARCTIC, PACIFIC, MYSTIC, HAWK, CONDOR, and EAGLE.

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

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

Table 51: Most common (frequency ≥2% in either treatment group in CASPIAN) AEs of any CTCAE Grade 3 or 4 (safety analysis set)

	Number (%) of patients[a]		
	CASPIAN		
Preferred Term	D + EP (N=265)	EP (N=266)	D pan-tumor pool[b] (N=3006)
Patients with any AE of CTCAE Grade 3 or 4	163 (61.5)	166 (62.4)	1290 (42.9)
Neutropenia	64 (24.2)	88 (33.1)	7 (0.2)
Anaemia	24 (9.1)	48 (18.0)	138 (4.6)
Leukopenia	17 (6.4)	14 (5.3)	3 (<0.1)
Neutrophil count decreased	17 (6.4)	17 (6.4)	4 (0.1)
Thrombocytopenia	15 (5.7)	25 (9.4)	12 (0.4)
Febrile neutropenia	14 (5.3)	17 (6.4)	1 (<0.1)
Hyponatraemia	10 (3.8)	7 (2.6)	101 (3.4)
Lipase increased	9 (3.4)	4 (1.5)	20 (0.7)
Hypertension	8 (3.0)	1 (0.4)	41 (1.4)
Amylase increased	6 (2.3)	1 (0.4)	15 (0.5)
Pneumonia	5 (1.9)	9 (3.4)	77 (2.6)
Platelet count decreased	4 (1.5)	6 (2.3)	3 (<0.1)
White blood cell count decreased	4 (1.5)	6 (2.3)	2 (<0.1)

AE adverse event; CTCAE Common Terminology Criteria for Adverse Events (version 4.03); D durvalumab; EP etoposide and platinum-based chemotherapy; PT preferred term.

[a]Number (%) of patients with AEs of CTCAE grade 3 or 4, sorted by decreasing frequency of PT in the CASPIAN D + EP group. Patients with multiple events in the same PT are counted only once in that PT. Patients with events in more than one PT are counted once in each of those PTs.

[b]Includes Study 1108, Japan Study 2, ATLANTIC, ARCTIC, PACIFIC, MYSTIC, HAWK, CONDOR, and EAGLE.

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

Table 52: **Adverse events by category reported during the first 4 EP cycles of EP chemotherapy by category Safety analysis set**

AE Category / Preferred Term	Number (%) of patients[a]			
	CASPIAN			
	D + EP (N=265)		EP (N=266)	
	EP Cycles 1-4	All EP cycles	EP Cycles 1-4	All EP cycles
Any AE	259 (97.7)	260 (98.1)	252 (94.7)	258 (97.0)
Any AE of CTCAE grade 3 or 4	163 (61.5)	163 (61.5)	154 (57.9)	166 (62.4)
Any AE with outcome of death	13 (4.9)	13 (4.9)	10 (3.8)	15 (5.6)
Any SAE	82 (30.9)	82 (30.9)	80 (30.1)	96 (36.1)
Any AE leading to discontinuation of study treatment[b]	25 (9.4)	25 (9.4)	21 (7.9)	25 (9.4)
Any AE leading to dose delay or interruption of any study treatment[c]	111 (41.9)	124 (46.8)	90 (33.8)	124 (46.6)

AE adverse event; CTCAE Common Terminology Criteria for Adverse Events (version 4.03); D durvalumab; EP etoposide and platinum-based chemotherapy; SAE serious adverse event.

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

[c]AEs on the AE CRF form with Action taken = "Drug interrupted" for either molecule.

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

Adverse drug reactions

As part of this group of variations, the applicant has updated the Durvalumab Pan-Tumor pool with the safety and tolerability information from an additional 1117 patients to include a total of 3006 patients. This population consists of all patients from the Monotherapy Pool studies who have received at least 1 dose of durvalumab monotherapy given at a dose of either 10mg/kg Q2W IV or 20mg/kg Q4W IV for any line of therapy (across tumour types).

Table 53: Monotherapy Pool

Study	Pan-tumour durvalumab pool
MYSTIC	20mg/kg Q4W (n=369)
ATLANTIC	10 mg/kg Q2W IV (n = 444)
Study 1108	10 mg/kg Q2W (n=980) 20mg/kg Q4W (n=21)
ARCTIC	Sub-study A: 10mg/kg Q2W (n=62) Sub-study B: 10mg/kg Q2W (n=117)
PACIFIC	10 mg/kg Q2W (n=475)
HAWK	10mg/kg Q2W (n=112)
CONDOR	10mg/kg Q2W (n=67)
EAGLE	10mg/kg Q2W (n=240)
Japan Study 2	10mg/kg Q2W (n=120) 20mg/kg Q4W (n=4)

Based on biological plausibility consistent with the mechanism of action of durvalumab, temporal association and re-challenge responses, known risks associated with the anti-PD-1/PD-L1 drug class, and context of background rates in target populations, the ADRs with durvalumab monotherapy have been determined.

The safety of IMFINZI given in combination with chemotherapy is based on data in 265 patients with SCLC. IMFINZI was administered at a dose of 1500 mg every 3 weeks in combination with chemotherapy followed by monotherapy every 4 weeks.

A comparative analysis between durvalumab (monotherapy and/or in combination with tremelimumab) treatment plus EP and EP in CASPIAN was performed using a Bayesian framework to identify AEs/laboratory events with an increased frequency in these treatment groups compared with EP, defined as AEs/laboratory events that have a 95% posterior probability that the risk ratio is greater than 1. Those events not already on the known ADR list were medically reviewed further for alternative causes (medical history, concomitant medications, comorbidities or other risk factors), biological plausibility, rechallenge response in order to determine whether an AE is an additional ADR.

Table 54: Adverse drug reactions in patients treated with IMFINZI monotherapy and IMFINZI in combination with chemotherapy

	IMFINZI Monotherapy			**IMFINZI Combined with Chemotherapy**		
	Any Grade (%)		**Grade 3-4 (%)**	**Any Grade (%)**		**Grade 3-4 (%)**
Infections and infestations						
Upper respiratory tract infections[a]	Very common	13.5	0.2	Common	9.1	0.4
Pneumonia[b,c]	Common	8.9	3.5	Common	5.7	1.9
Oral candidiasis	Common	2.1	0	Uncommon	0.8	0
Dental and oral soft tissue infections[d]	Common	1.7	<0.1	Common	1.1	0
Influenza	Common	1.6	<0.1	Uncommon	0.4	0
Blood and lymphatic system disorders						

	IMFINZI Monotherapy			IMFINZI Combined with Chemotherapy		
	Any Grade (%)		Grade 3-4 (%)	Any Grade (%)		Grade 3-4 (%)
Neutropenia[e]				Very common	48.7	29.1
Anaemia				Very common	38.5	9.1
Thrombocytopenia[f]				Very common	21.1	6.8
Leukopenia[g]				Very common	20.0	7.9
Febrile neutropenia				Common	6.4	5.3
Pancytopenia				Common	3.0	1.5
Endocrine disorders						
Hypothyroidism[h]	Very common	10.1	0.2	Common	9.4	0
Hyperthyroidism[i]	Common	4.6	0	Common	9.8	0
Thyroiditis[j]	Uncommon	0.8	<0.1	Common	1.5	0
Adrenal insufficiency	Uncommon	0.6	<0.1	Common	1.1	0
Type 1 diabetes mellitus	Rare	<0.1	<0.1	Uncommon	0.8	0.8
Hypophysitis/ Hypopituitarism	Rare	<0.1	<0.1			
Diabetes insipidus	Rare	<0.1	<0.1			
Metabolism and nutrition disorders						
Decreased appetite				Very common	18.1	0.8
Nervous System Disorders						
Myasthenia gravis	Rare[k]					
Cardiac disorders						
Myocarditis	Rare	<0.1	<0.1			
Respiratory, thoracic and mediastinal disorders						
Cough/Productive Cough	Very common	21.5	0.4	Very common	14.7	0.8
Pneumonitis[b]	Common	3.8	0.9	Common	2.6	0.8
Dysphonia	Common	3.1	<0.1	Uncommon	0.8	0
Interstitial lung disease	Uncommon	0.6	0.1	Uncommon	0.8	0
Gastrointestinal disorders						
Diarrhoea	Very common	16.3	0.6	Common	9.8	1.1
Abdominal pain[l]	Very common	12.7	1.8	Common	8.7	0.4
Colitis[m]	Uncommon	0.9	0.3	Uncommon	0.8	0
Nausea				Very common	33.6	0.4
Constipation				Very common	16.6	0.8
Vomiting				Very common	14.7	0
Stomatitis[n]				Common	6.0	0.4
Hepatobiliary disorders						
Aspartate aminotransferase increased or Alanine aminotransferase increased[o]	Common	8.1	2.3	Common	8.7	1.9
Hepatitis[c,p]	Uncommon	0.8	0.4	Common	1.9	1.1
Skin and subcutaneous tissue disorders						
Rash[q]	Very common	16.0	0.6	Common	9.4	0
Pruritus[r]	Very common	10.8	<0.1	Common	7.5	0
Night sweats	Common	1.6	<0.1	Uncommon	0.4	0

	IMFINZI Monotherapy			IMFINZI Combined with Chemotherapy		
	Any Grade (%)		Grade 3-4 (%)	Any Grade (%)		Grade 3-4 (%)
Dermatitis	Uncommon	0.7	<0.1	Common	1.5	0
Alopecia				Very common	31.3	1.1
Pemphigoid[s]	Rare	<0.1	0			
Musculoskeletal and connective tissue disorders						
Myalgia	Common	5.9	<0.1	Common	3.4	0
Myositis	Uncommon	0.2	<0.1			
Polymyositis	Rare[t]					
Renal and urinary disorders						
Blood creatinine increased	Common	3.5	<0.1	Common	1.9	0
Dysuria	Common	1.3	0	Common	1.9	0
Nephritis[u]	Uncommon	0.3	<0.1			
General disorders and administration site conditions						
Pyrexia	Very common	13.8	0.3	Common	8.3	0
Peripheral oedema[v]	Common	9.7	0.3	Common	6.4	0.8
Fatigue[w]				Very common	32.1	3.4
Injury, poisoning and procedural complications						
Infusion-related reaction[x]	Common	1.6	0.2	Common	1.9	0.4

[a] includes laryngitis, nasopharyngitis, peritonsillar abscess, pharyngitis, rhinitis, sinusitis, tonsillitis, tracheobronchitis and upper respiratory tract infection.

[b] includes lung infection, pneumocystis jirovecii pneumonia, pneumonia, pneumonia adenoviral, pneumonia bacterial, pneumonia cytomegaloviral, pneumonia haemophilus, pneumonia pneumococcal, pneumonia streptococcal, candida pneumonia and pneumonia legionella.

[c] including fatal outcome.

[d] includes gingivitis, oral infection, periodontitis, pulpitis dental, tooth abscess and tooth infection.

[e] includes neutropenia and neutrophil count decreased.

[f] includes thrombocytopenia and platelet count decreased.

[g] includes leukopenia and white blood cell count decreased.

[h] includes autoimmune hypothyroidism, hypothyroidism.

[i] includes hyperthyroidism and Basedow's disease.

[j] includes autoimmune thyroiditis, thyroiditis, and thyroiditis subacute.

[k] reported frequency from AstraZeneca-sponsored clinical studies outside of the pooled dataset is rare, with no events at Grade > 2.

[l] includes abdominal pain, abdominal pain lower, abdominal pain upper and flank pain.

[m] includes colitis, enteritis, enterocolitis, and proctitis.

[n] includes stomatitis and mucosal inflammation.

[o] includes alanine aminotransferase increased, aspartate aminotransferase increased, hepatic enzyme increased and transaminases increased.

[p] includes hepatitis, autoimmune hepatitis, hepatitis toxic, hepatocellular injury, hepatitis acute, hepatotoxicity and immune-mediated hepatitis.

[q] includes rash erythematous, rash generalised, rash macular, rash maculopapular, rash papular, rash pruritic, rash pustular, erythema, eczema and rash.

[r] includes pruritus generalised and pruritus.

[s] includes pemphigoid, dermatitis bullous and pemphigus. Reported frequency from completed and ongoing trials is uncommon.

[t] polymyositis (fatal) was observed in a patient treated with IMFINZI from an ongoing sponsored clinical study outside of the pooled dataset: rare in any grade, rare in Grade 3 or 4 or 5.

[u] includes autoimmune nephritis, tubulointerstitial nephritis, nephritis, glomerulonephritis and glomerulonephritis membranous.

[v] includes oedema peripheral and peripheral swelling.

[w] includes fatigue and asthenia.

[x] includes infusion-related reaction and urticaria with onset on the day of dosing or 1 day after dosing.

Serious adverse event/deaths/other significant events

SAEs:

Table 55: Most common SAEs (frequency ≥2 patients in any treatment group by PT) (safety analysis set)

	CASPIAN		
	D + EP (N=265)	EP (N=266)	D pan-tumor pool[a] (N=3006)
Preferred Term	**n (%)[b]**	**n (%)[b]**	**n (%)[b]**
Patients with any SAE	82 (30.9)	96 (36.1)	1068 (35.5)
Febrile neutropenia	12 (4.5)	12 (4.5)	0
Anaemia	5 (1.9)	12 (4.5)	19 (0.6)
Pneumonia	6 (2.3)	9 (3.4)	104 (3.5)
Thrombocytopenia	1 (0.4)	9 (3.4)	3 (<0.1)
Neutropenia	2 (0.8)	7 (2.6)	1 (<0.1)
Pancytopenia	4 (1.5)	3 (1.1)	1 (<0.1)
Hyponatraemia	2 (0.8)	4 (1.5)	14 (0.5)
Pneumonitis	3 (1.1)	3 (1.1)	38 (1.3)
Diarrhoea	1 (0.4)	4 (1.5)	13 (0.4)
Acute kidney injury	2 (0.8)	2 (0.8)	20 (0.7)
Chronic obstructive pulmonary disease	3 (1.1)	1 (0.4)	15 (0.5)
Pleural effusion	2 (0.8)	2 (0.8)	37 (1.2)
Cerebrovascular accident	0	3 (1.1)	4 (0.3)
General physical health deterioration	2 (0.8)	1 (0.4)	27 (0.9)
Hypokalaemia	0	3 (1.1)	2 (<0.1)
Respiratory tract infection	2 (0.8)	1 (0.4)	7 (0.2)
Sepsis	2 (0.8)	1 (0.4)	39 (1.3)
Sudden death	2 (0.8)	1 (0.4)	2 (<0.1)
Syncope	1 (0.4)	2 (0.8)	11 (0.4)
Transient ischaemic attack	2 (0.8)	1 (0.4)	2 (<0.1)
Upper respiratory tract infection	2 (0.8)	1 (0.4)	5 (0.2)
Vomiting	0	3 (1.1)	21 (0.7)
Acute myocardial infarction	0	2 (0.8)	2 (<0.1)
Atrial fibrillation	2 (0.8)	0	18 (0.6)
Constipation	2 (0.8)	0	13 (0.4)
Death	0	2 (0.8)	8 (0.3)
Deep vein thrombosis	2 (0.8)	0	2 (<0.1)
Dyspnoea	0	2 (0.8)	72 (2.4)
Lung infection	0	2 (0.8)	22 (0.7)
Nausea	0	2 (0.8)	11 (0.4)
Pyrexia	0	2 (0.8)	35 (1.2)
Septic shock	2 (0.8)	0	8 (0.3)
Type 1 diabetes mellitus	2 (0.8)	0	1 (<0.1)

AE adverse event; CTCAE Common Terminology Criteria for Adverse Events (version 4.03); D durvalumab; EP etoposide and platinum-based chemotherapy; PT preferred term; SAE serious adverse event.
[a]Includes Study 1108, Japan Study 2, ATLANTIC, ARCTIC, PACIFIC, MYSTIC, HAWK, CONDOR, and EAGLE.
[b]Number (%) of patients with an SAE.
MedDRA version 21.1.
Patients with multiple AEs with outcome of death are counted once for each PT. Patients with events in more than one PT are counted once in each of those PT.

Deaths:

Table 56: All deaths – full analysis set (CASPIAN)

Category	Number (%) of patients Durva + EP (N=268)	 EP (N=269)
Total number of deaths	155 (57.8)	181 (67.3)
Death related to disease under investigation only [a]	135 (50.4)	153 (56.9)
Death related to disease under investigation [a] and an AE with outcome of death	6 (2.2)	5 (1.9)
AE onset prior to subsequent therapy [b]	6 (2.2)	5 (1.9)
AE with outcome of death only	5 (1.9)	7 (2.6)
AE onset prior to subsequent therapy [b]	5 (1.9)	7 (2.6)
Death after end of safety follow-up period and not due to disease under investigation [d]	0	3 (1.1)
Unknown reason for death [e]	9 (3.4)	12 (4.5)
Other deaths [f]	0	1 (0.4)

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Durva = Durvalumab, EP = Etoposide and platinum-based chemotherapy.
[a] Death related to disease under investigation is determined by the investigator.
[b] Includes adverse events 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 study treatment or up to the date of initiation of the first subsequent anticancer therapy (whichever occurs first).
[c] AE start date <= 90 days following the last dose of study treatment and AE start date > the date of initiation of the first subsequent anticancer therapy (whichever occurs first).
[d] Death not due to disease progression or a treatment-emergent adverse event.
[e] Such patients may have an SAE recorded as unknown death.
[f] Patients who died and are not captured in the earlier categories - includes randomized patients who died before receiving study treatment.
Main categories are mutually exclusive, patients are only reported in one category.
Percentages are based on the total numbers of patients in the treatment group (N).

Data cut-off: 11MAR2019

Table 57. Adverse events with outcome of death, by system organ class and preferred term (safety analysis set)

MedDRA system organ class Preferred term	Number (%) of patients[a] CASPIAN D + EP (N=265)	 EP (N=266)	 D pan-tumor pool[b,c] (N=3006)
Patients with AE with outcome of death	13 (4.9)	15 (5.6)	164 (5.5)
Infections and infestations	**2 (0.8)**	**1 (0.4)**	**33 (1.1)**
Pneumonia	0	1 (0.4)	10 (0.3)
Sepsis	1 (0.4)	0	10 (0.3)
Septic shock	1 (0.4)	0	4 (0.1)
Blood and lymphatic system disorders	**1 (0.4)**	**3 (1.1)**	**2 (<0.1)**
Haematotoxicity	0	1 (0.4)	0
Pancytopenia	1 (0.4)	1 (0.4)	0
Thrombocytopenia	0	1 (0.4)	0
Metabolism and nutrition disorders	**1 (0.4)**	**0**	**2 (<0.1)**
Dehydration	1 (0.4)	0	1 (<0.1)
Nervous system disorders	**0**	**1 (0.4)**	**4 (0.1)**
Cerebrovascular accident	0	1 (0.4)	2 (<0.1)
Cardiac disorders	**1 (0.4)**	**3 (1.1)**	**16 (0.5)**
Cardiac arrest	1 (0.4)	1 (0.4)	4 (0.1)
Cardiac failure acute	0	1 (0.4)	0
Cardiopulmonary failure	0	1 (0.4)	2 (<0.1)
Vascular disorders	**0**	**1 (0.4)**	**5 (0.2)**
Haemorrhage	0	1 (0.4)	1 (<0.1)
Respiratory, thoracic and mediastinal disorders	**5 (1.9)**	**3 (1.1)**	**50 (1.7)**
Acute respiratory failure	1 (0.4)	1 (0.4)	6 (0.2)
Aspiration	1 (0.4)	0	0
Hypoxia	1 (0.4)	0	0
Pneumonitis	0	2 (0.8)	6 (0.2)
Pulmonary artery thrombosis	1 (0.4)	0	0
Pulmonary embolism	1 (0.4)	0	6 (0.2)
Hepatobiliary disorders	**1 (0.4)**	**0**	**6 (0.2)**
Hepatotoxicity	1 (0.4)	0	0
General disorders and administration site conditions	**2 (0.8)**	**4 (1.5)**	**31 (1.0)**
Death	0	2 (0.8)	8 (0.3)
Sudden cardiac death	0	1 (0.4)	2 (<0.1)
Sudden death	2 (0.8)	1 (0.4)	2 (<0.1)

AE adverse event; D durvalumab; EP etoposide and platinum-based chemotherapy; PT preferred term; SOC system organ class.
[a]Number (%) of subjects with AE with outcome of death, sorted by international order for and alphabetical order for PT. Patients with multiple AEs with outcome of death are counted once for each PT. Patients with events in more than one PT are counted once in each of those PT.
[b]Includes Study 1108, Japan Study 2, ATLANTIC, ARCTIC, PACIFIC, MYSTIC, HAWK, CONDOR, and EAGLE.
[c]Only PTs that correspond to PTs in CASPIAN are included in the table for the D pan-tumor pool
Patients with multiple AEs with outcome of death are counted once for each SOC/PT.
Includes AEs with an onset date on or after the date of first dose or pre-treatment AEs that increase in severity on or after the date of first dose and up to and including the earlier of 90 days following the date of last dose of study treatment or up to the date of initiation of the first subsequent therapy (whichever occurs first).

AESIs/imAEs:

Table 58. Immune-mediated adverse events in any category – Safety Analysis Set

AE Category	Number (%) of patients[a]		
	CASPIAN		D pan-tumor pool (N=3006)
	D + EP (N=265)	EP (N=266)	
Any AE	53 (20.0)	9 (3.4)	463 (15.4)
Any AE causally related to treatment[c]	48 (18.1)	2 (0.8)	393 (13.1)
Any AE of CTCAE Grade 3 or 4[b]	11 (4.2)	0 (0.0)	83 (2.8)
Any AE of CTCAE Grade 3 or 4, causally related to treatment[c, d]	10 (3.8)	0 (0.0)	76 (2.5)
Any SAE (including AEs with outcome of death)[e]	5 (1.9)	1 (0.4)	81 (2.7)
Any SAE, causally related to treatment[c, e]	5 (1.9)	0 (0.0)	78 (2.6)
Any AE with outcome of death	1 (0.4)	1 (0.4)	9 (0.3)
Any AE with outcome of death, causally related to treatment[c]	1 (0.4)	0 (0.0)	9 (0.3)
Received systemic corticosteroids	24 (9.1)	5 (1.9)	249 (8.3)
Received high dose corticosteroids	17 (6.4)	2 (0.8)	157 (5.2)
Received endocrine therapy	37 (14.0)	3 (1.1)	258 (8.6)
Received other immunosuppressants[f]	0 (0.0)	0 (0.0)	7 (0.2)
Any AE leading to discontinuation of study treatment	3 (1.1)	0 (0.0)	69 (2.3)
Event outcome resolved	27 (10.2)	5 (1.9)	202 (6.7)
Event outcome not resolved	26 (9.8)	4 (1.5)	261 (8.7)

[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] All CTCAE grades per patient, not just the maximum, are considered when identifying whether there is a grade 3 or 4.
[c] As assessed by the investigator. Missing responses are counted as related.
[d] Maximum CTCAE grade per patient is considered.

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

Pneumonitis:

Table 59: Pneumonitis adverse events of special interest and immune mediated adverse events (safety analysis set)

				Treatment Related[a]		Received Intervention						Event Outcome,n	
Treatment/ AESI Category	Any AE	Any SAE [b]	CTCAE Grade 3-4	Any CTCAE Grade	CTCAE Grade 3-4	Systemic Cortico Steroid	High Dose Steroid	Other Immuno Suppre-ssants	Requires Endocrine Therapy	Leading to dis-contin-uation of study drug	Resulted in Death	Not Resolved	Resolved
Durva + EP													
Pneumonitis													
AESI	9(3.4)	4(1.5)	2(0.8)	7(2.6)	1(0.4)	7(2.6)	6(2.3)	0(0.0)	0(0.0)	1(0.4)	0(0.0)	3(1.1)	6(2.3)
simAE	9(3.4)	4(1.5)	2(0.8)	7(2.6)	1(0.4)	7(2.6)	6(2.3)	0(0.0)	0(0.0)	1(0.4)	0(0.0)	3(1.1)	6(2.3)
imAE	7(2.6)	2(0.8)	1(0.4)	6(2.3)	1(0.4)	6(2.3)	5(1.9)	0(0.0)	0(0.0)	1(0.4)	0(0.0)	2(0.8)	5(1.9)
EP													
Pneumonitis													
AESI	5(1.9)	3(1.1)	1(0.4)	0(0.0)	0(0.0)	2(0.8)	2(0.8)	0(0.0)	0(0.0)	0(0.0)	2(0.8)	1(0.4)	2(0.8)
simAE	5(1.9)	3(1.1)	1(0.4)	0(0.0)	0(0.0)	2(0.8)	2(0.8)	0(0.0)	0(0.0)	0(0.0)	2(0.8)	1(0.4)	2(0.8)
imAE	2(0.8)	1(0.4)	0(0.0)	0(0.0)	0(0.0)	1(0.4)	1(0.4)	0(0.0)	0(0.0)	0(0.0)	1(0.4)	0(0.0)	1(0.4)
Durvalumab Pan-Tumor Pool													
Pneumonitis													
AESI	136(4.5)	47(1.6)	32(1.1)	100(3.3)	25(0.8)	94(3.1)	70(2.3)	3(<0.1)	3(<0.1)	41(1.4)	6(0.2)	58(1.9)	72(2.4)
simAE	132(4.4)	46(1.5)	30(1.0)	98(3.3)	24(0.8)	93(3.1)	69(2.3)	3(<0.1)	3(<0.1)	41(1.4)	6(0.2)	56(1.9)	70(2.3)
imAE	107(3.6)	40(1.3)	25(0.8)	84(2.8)	21(0.7)	85(2.8)	64(2.1)	3(<0.1)	3(<0.1)	38(1.3)	6(0.2)	43(1.4)	58(1.9)

The median time to onset was 57 days (range: 2-785 days).

Hepatic events:

Table 60: Hepatic events adverse events of special interest and immune mediated adverse events (safety analysis set)

				Treatment Related[a]		Received Intervention						Event Outcome,n	
Treatment/ AESI Category	Any AE	Any SAE [b]	CTCAE Grade 3-4	Any CTCAE Grade	CTCAE Grade 3-4	Systemic Cortico Steroid	High Dose Steroid	Other Immuno Suppre-ssants	Requires Endocrine Therapy	Leading to dis-contin-uation of study drug	Resulted in Death	Not Resolved	Resolved
Durva + EP													
Hepatic Events													
AESI	36(13.6)	1(0.4)	10(3.8)	22(8.3)	5(1.9)	8(3.0)	6(2.3)	0(0.0)	0(0.0)	2(0.8)	1(0.4)	8(3.0)	27(10.2)
simAE	8(3.0)	1(0.4)	6(2.3)	6(2.3)	5(1.9)	8(3.0)	6(2.3)	0(0.0)	0(0.0)	2(0.8)	1(0.4)	2(0.8)	5(1.9)
imAE	7(2.6)	1(0.4)	5(1.9)	6(2.3)	5(1.9)	7(2.6)	6(2.3)	0(0.0)	0(0.0)	1(0.4)	1(0.4)	1(0.4)	5(1.9)
EP													
Hepatic Events													
AESI	21(7.9)	1(0.4)	5(1.9)	12(4.5)	4(1.5)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	3(1.1)	18(6.8)
simAE	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
imAE	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Durvalumab Pan-Tumor Pool													
Hepatic Events													
AESI	321(10.7)	40(1.3)	107(3.6)	141(4.7)	41(1.4)	68(2.3)	45(1.5)	3(<0.1)	16(0.5)	18(0.6)	6(0.2)	140(4.7)	175(5.8)
simAE	68(2.3)	19(0.6)	43(1.4)	38(1.3)	23(0.8)	68(2.3)	45(1.5)	3(<0.1)	7(0.2)	9(0.3)	4(0.1)	34(1.1)	30(1.0)
imAE	36(1.2)	10(0.3)	21(0.7)	31(1.0)	20(0.7)	36(1.2)	25(0.8)	2(<0.1)	2(<0.1)	7(0.2)	2(<0.1)	12(0.4)	22(0.7)

The median time to onset of the events of hepatitis was 67 days (range: 7-333 days).

Diarrhoea/colitis:

Table 61: Diarrhoea/colitis adverse events of special interest and immune mediated adverse events (safety analysis set)

			Treatment Related[a]		Received Intervention						Event Outcome,n	
Treatment/ AESI Category	Any AE	Any SAE [b]	CTCAE Grade 3-4	Any CTCAE Grade	CTCAE Grade 3-4	Systemic Cortico Steroid	High Dose Steroid	Other Immuno Suppre-ssants	Requires Endocrine Therapy	Leading to dis-contin-uation of study drug	Resul ted in Death	Not Resol ved	Resol ved
Durva + EP Diarrhoea/Colitis													
AESI	27(10.2)	1(0.4)	3(1.1)	17(6.4)	2(0.8)	4(1.5)	2(0.8)	0(0.0)	0(0.0)	1(0.4)	0(0.0)	3(1.1)	24(9.1)
simAE	4(1.5)	0(0.0)	1(0.4)	4(1.5)	1(0.4)	4(1.5)	2(0.8)	0(0.0)	0(0.0)	1(0.4)	0(0.0)	0(0.0)	4(1.5)
imAE	4(1.5)	0(0.0)	1(0.4)	4(1.5)	1(0.4)	4(1.5)	2(0.8)	0(0.0)	0(0.0)	1(0.4)	0(0.0)	0(0.0)	4(1.5)
EP Diarrhoea/Colitis													
AESI	31(11.7)	4(1.5)	3(1.1)	15(5.6)	2(0.8)	1(0.4)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	5(1.9)	26(9.8)
simAE	1(0.4)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(0.4)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(0.4)
imAE	1(0.4)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(0.4)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(0.4)
Durvalumab Pan-Tumor Pool Diarrhoea/Colitis													
AESI	523(17.4)	25(0.8)	27(0.9)	248(8.3)	18(0.6)	58(1.9)	38(1.3)	2(<0.1)	11(0.4)	9(0.3)	0(0.0)	88(2.9)	435(14.5)
simAE	57(1.9)	12(0.4)	11(0.4)	38(1.3)	10(0.3)	57(1.9)	37(1.2)	2(<0.1)	4(0.1)	9(0.3)	0(0.0)	15(0.5)	42(1.4)
imAE	52(1.7)	12(0.4)	11(0.4)	38(1.3)	10(0.3)	52(1.7)	34(1.1)	2(<0.1)	3(<0.1)	9(0.3)	0(0.0)	13(0.4)	39(1.3)

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The median time to onset was 73 days (range: 1-394 days).

Endocrinopathies:

Table 62: Adrenal insufficiency adverse events of special interest and immune mediated adverse events (safety analysis set)

			Treatment Related[a]		Received Intervention						Event Outcome,n	
Treatment/ AESI Category	Any AE	Any SAE [b]	CTCAE Grade 3-4	Any CTCAE Grade	CTCAE Grade 3-4	Systemic Cortico Steroid	High Dose Steroid	Other Immuno Suppre-ssants	Requires Endocrine Therapy	Leading to dis-contin-uation of study drug	Resul ted in Death	Not Resol ved	Resol ved
Durva + EP Adrenal Insufficiency													
AESI	3(1.1)	0(0.0)	0(0.0)	2(0.8)	0(0.0)	1(0.4)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	2(0.8)	1(0.4)
simAE	1(0.4)	0(0.0)	0(0.0)	1(0.4)	0(0.0)	1(0.4)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(0.4)	0(0.0)
imAE	1(0.4)	0(0.0)	0(0.0)	1(0.4)	0(0.0)	1(0.4)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(0.4)	0(0.0)
EP Adrenal Insufficiency													
AESI	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
simAE	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
imAE	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Durvalumab Pan-Tumor Pool Adrenal Insufficiency													
AESI	19(0.6)	5(0.2)	4(0.1)	10(0.3)	3(<0.1)	14(0.5)	4(0.1)	0(0.0)	4(0.1)	0(0.0)	0(0.0)	14(0.5)	5(0.2)
simAE	14(0.5)	4(0.1)	3(<0.1)	9(0.3)	3(<0.1)	14(0.5)	4(0.1)	0(0.0)	4(0.1)	0(0.0)	0(0.0)	11(0.4)	3(<0.1)
imAE	12(0.4)	4(0.1)	3(<0.1)	9(0.3)	3(<0.1)	12(0.4)	4(0.1)	0(0.0)	3(<0.1)	0(0.0)	0(0.0)	9(0.3)	3(<0.1)

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The median time to onset was 145.5 days (range: 20-547 days). Resolution occurred in 3 patients.

Table 63: Type I diabetes mellitus adverse events of special interest and immune mediated adverse events (safety analysis set)

				Treatment Related[a]		Received Intervention						Event Outcome,n	
Treatment/ AESI Category	Any AE	Any SAE [b]	CTCAE Grade 3-4	Any CTCAE Grade	CTCAE Grade 3-4	Systemic Cortico Steroid	High Dose Steroid	Other Immuno Suppre- ssants	Requires Endocrine Therapy	Leading to dis- contin- uation of study drug	Resul ted in Death	Not Resol ved	Resol ved
Durva + EP													
Type 1 Diabetes Mellitus													
AESI	13(4.9)	4(1.5)	5(1.9)	4(1.5)	3(1.1)	0(0.0)	0(0.0)	0(0.0)	7(2.6)	1(0.4)	0(0.0)	10(3.8)	3(1.1)
simAE	7(2.6)	4(1.5)	5(1.9)	3(1.1)	3(1.1)	0(0.0)	0(0.0)	0(0.0)	7(2.6)	1(0.4)	0(0.0)	6(2.3)	1(0.4)
imAE	3(1.1)	2(0.8)	3(1.1)	2(0.8)	2(0.8)	0(0.0)	0(0.0)	0(0.0)	3(1.1)	0(0.0)	0(0.0)	3(1.1)	0(0.0)
EP													
Type 1 Diabetes Mellitus													
AESI	9(3.4)	0(0.0)	1(0.4)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	5(1.9)	0(0.0)	0(0.0)	3(1.1)	6(2.3)
simAE	5(1.9)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	5(1.9)	0(0.0)	0(0.0)	1(0.4)	4(1.5)
imAE	2(0.8)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	2(0.8)	0(0.0)	0(0.0)	0(0.0)	2(0.8)
Durvalumab Pan-Tumor Pool													
Type 1 Diabetes Mellitus													
AESI	97(3.2)	6(0.2)	27(0.9)	19(0.6)	5(0.2)	6(0.2)	3(<0.1)	0(0.0)	30(1.0)	1(<0.1)	0(0.0)	49(1.6)	48(1.6)
simAE	1(<0.1)	1(<0.1)	1(<0.1)	1(<0.1)	1(<0.1)	0(0.0)	0(0.0)	0(0.0)	1(<0.1)	1(<0.1)	0(0.0)	0(0.0)	1(<0.1)
imAE	1(<0.1)	1(<0.1)	1(<0.1)	1(<0.1)	1(<0.1)	0(0.0)	0(0.0)	0(0.0)	1(<0.1)	1(<0.1)	0(0.0)	0(0.0)	1(<0.1)

The time to onset was 43 days.

Table 64: Hyperthyroid adverse events of special interest and immune mediated adverse events (safety analysis set)

				Treatment Related[a]		Received Intervention						Event Outcome,n	
Treatment/ AESI Category	Any AE	Any SAE [b]	CTCAE Grade 3-4	Any CTCAE Grade	CTCAE Grade 3-4	Systemic Cortico Steroid	High Dose Steroid	Other Immuno Suppre- ssants	Requires Endocrine Therapy	Leading to dis- contin- uation of study drug	Resul ted in Death	Not Resol ved	Resol ved
Durva + EP													
Hyperthyroid Events													
AESI	27(10.2)	0(0.0)	0(0.0)	22(8.3)	0(0.0)	1(0.4)	1(0.4)	0(0.0)	14(5.3)	0(0.0)	0(0.0)	8(3.0)	19(7.2)
simAE	14(5.3)	0(0.0)	0(0.0)	13(4.9)	0(0.0)	1(0.4)	1(0.4)	0(0.0)	14(5.3)	0(0.0)	0(0.0)	4(1.5)	10(3.8)
imAE	14(5.3)	0(0.0)	0(0.0)	13(4.9)	0(0.0)	1(0.4)	1(0.4)	0(0.0)	14(5.3)	0(0.0)	0(0.0)	4(1.5)	10(3.8)
EP													
Hyperthyroid Events													
AESI	1(0.4)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(0.4)
simAE	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
imAE	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Durvalumab Pan-Tumor Pool													
Hyperthyroid Events													
AESI	167(5.6)	2(<0.1)	0(0.0)	132(4.4)	0(0.0)	11(0.4)	4(0.1)	0(0.0)	47(1.6)	1(<0.1)	0(0.0)	37(1.2)	130(4.3)
simAE	49(1.6)	2(<0.1)	0(0.0)	40(1.3)	0(0.0)	11(0.4)	4(0.1)	0(0.0)	45(1.5)	1(<0.1)	0(0.0)	10(0.3)	39(1.3)
imAE	43(1.4)	2(<0.1)	0(0.0)	39(1.3)	0(0.0)	11(0.4)	4(0.1)	0(0.0)	39(1.3)	1(<0.1)	0(0.0)	8(0.3)	35(1.2)

The median time to onset was 43 days (range: 1-196 days). Thirty-nine (39) of the 43 patients received medical therapy (thiamazole, carbimazole, propylthiouracil, perchlorate, calcium channel blocker, or beta-blocker), 11 patients received systemic corticosteroids and 4 of the 11 patients received high-dose systemic corticosteroid treatment (at least 40 mg prednisone or equivalent per day). One patient discontinued IMFINZI due to hyperthyroidism. Resolution occurred in 35 patients. Eighteen (18) patients experienced hypothyroidism following hyperthyroidism.

Table 65: Thyroiditis adverse events of special interest and immune mediated adverse events (safety analysis set)

				Treatment Related[a]		Received Intervention						Event Outcome,n	
Treatment/ AESI Category	Any AE	Any SAE [b]	CTCAE Grade 3-4	Any CTCAE Grade	CTCAE Grade 3-4	Systemic Cortico Steroid	High Dose Steroid	Other Immuno Suppre-ssants	Requires Endocrine Therapy	Leading to dis-contin-uation of study drug	Resul ted in Death	Not Resol ved	Resol ved
Durva + EP													
Thyroiditis													
AESI	4(1.5)	0(0.0)	0(0.0)	4(1.5)	0(0.0)	1(0.4)	1(0.4)	0(0.0)	4(1.5)	0(0.0)	0(0.0)	3(1.1)	1(0.4)
simAE	4(1.5)	0(0.0)	0(0.0)	4(1.5)	0(0.0)	1(0.4)	1(0.4)	0(0.0)	4(1.5)	0(0.0)	0(0.0)	3(1.1)	1(0.4)
imAE	4(1.5)	0(0.0)	0(0.0)	4(1.5)	0(0.0)	1(0.4)	1(0.4)	0(0.0)	4(1.5)	0(0.0)	0(0.0)	3(1.1)	1(0.4)
EP													
Thyroiditis													
AESI	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
simAE	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
imAE	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Durvalumab Pan-Tumor Pool													
Thyroiditis													
AESI	23(0.8)	1(<0.1)	2(<0.1)	20(0.7)	2(<0.1)	4(0.1)	1(<0.1)	0(0.0)	10(0.3)	1(<0.1)	0(0.0)	15(0.5)	8(0.3)
simAE	12(0.4)	1(<0.1)	2(<0.1)	11(0.4)	2(<0.1)	4(0.1)	1(<0.1)	0(0.0)	10(0.3)	1(<0.1)	0(0.0)	7(0.2)	5(0.2)
imAE	11(0.4)	1(<0.1)	2(<0.1)	10(0.3)	2(<0.1)	4(0.1)	1(<0.1)	0(0.0)	9(0.3)	1(<0.1)	0(0.0)	6(0.2)	5(0.2)

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The median time to onset was 41 days (range: 14-106 days).Two patients experienced hypothyroidism following thyroiditis.

Table 66: Hypothyroid adverse events of special interest and immune mediated adverse events (safety analysis set)

				Treatment Related[a]		Received Intervention						Event Outcome,n	
Treatment/ AESI Category	Any AE	Any SAE [b]	CTCAE Grade 3-4	Any CTCAE Grade	CTCAE Grade 3-4	Systemic Cortico Steroid	High Dose Steroid	Other Immuno Suppre-ssants	Requires Endocrine Therapy	Leading to dis-contin-uation of study drug	Resul ted in Death	Not Resol ved	Resol ved
Durva + EP													
Hypothyroid Events													
AESI	26(9.8)	0(0.0)	0(0.0)	24(9.1)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	24(9.1)	0(0.0)	0(0.0)	18(6.8)	8(3.0)
simAE	24(9.1)	0(0.0)	0(0.0)	22(8.3)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	24(9.1)	0(0.0)	0(0.0)	17(6.4)	7(2.6)
imAE	20(7.5)	0(0.0)	0(0.0)	18(6.8)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	20(7.5)	0(0.0)	0(0.0)	13(4.9)	7(2.6)
EP													
Hypothyroid Events													
AESI	4(1.5)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	2(0.8)	0(0.0)	0(0.0)	4(1.5)	0(0.0)
simAE	2(0.8)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	2(0.8)	0(0.0)	0(0.0)	2(0.8)	0(0.0)
imAE	1(0.4)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(0.4)	0(0.0)	0(0.0)	1(0.4)	0(0.0)
Durvalumab Pan-Tumor Pool													
Hypothyroid Events													
AESI	353(11.7)	5(0.2)	5(0.2)	287(9.5)	5(0.2)	17(0.6)	6(0.2)	0(0.0)	242(8.1)	0(0.0)	0(0.0)	259(8.6)	94(3.1)
simAE	247(8.2)	5(0.2)	4(0.1)	205(6.8)	4(0.1)	17(0.6)	6(0.2)	0(0.0)	242(8.1)	0(0.0)	0(0.0)	196(6.5)	51(1.7)
imAE	222(7.4)	4(0.1)	4(0.1)	188(6.3)	4(0.1)	16(0.5)	5(0.2)	0(0.0)	218(7.3)	0(0.0)	0(0.0)	175(5.8)	47(1.6)

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The median time to onset was 85 days (range: 1-562 days).

Hypophysitis: There were 2 (<0.1%) patients with hypophysitis in the D pan-tumour pool. The time to onset for the events was 44 days and 50 days. In both patients the event was considered an AESI, simAE and imAE. The events were CTCAE Grade 3 in severity and required high-dose steroids. Neither of the patients required endocrine therapy, but the event remained not resolved in both. There were no cases of hypophysitis in the CASPIAN study.

Renal events: There were no immune-mediated renal events in the study.

Nephritis:

In the combined safety database with IMFINZI monotherapy, immune-mediated nephritis occurred in 9 (0.3%) patients, including Grade 3 in 2 (< 0.1%) patients. The median time to onset was 87 days (range: 29-393 days). Six (0.2%) patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day) and 1 patient also received mycophenolate. IMFINZI was discontinued in 5 patients. Resolution occurred in 6 patients.

Dermatitis/rash:

Table 67: Dermatitis/rash adverse events of special interest and immune mediated adverse events (safety analysis set)

				Treatment Related[a]		Received Intervention						Event Outcome,n	
Treatment/ AESI Category	Any AE	Any SAE [b]	CTCAE Grade 3-4	Any CTCAE Grade	CTCAE Grade 3-4	Systemic Cortico Steroid	High Dose Steroid	Other Immuno Suppre- ssants	Requires Endocrine Therapy	Leading to dis- contin- uation of study drug	Resul ted in Death	Not Resol ved	Resol ved
Durva + EP Dermatitis/Rash													
AESI	48(18.1)	0(0.0)	0(0.0)	33(12.5)	0(0.0)	6(2.3)	3(1.1)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	8(3.0)	40(15.1)
simAE	6(2.3)	0(0.0)	0(0.0)	3(1.1)	0(0.0)	6(2.3)	3(1.1)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	6(2.3)
imAE	5(1.9)	0(0.0)	0(0.0)	3(1.1)	0(0.0)	5(1.9)	3(1.1)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	5(1.9)
EP Dermatitis/Rash													
AESI	25(9.4)	0(0.0)	0(0.0)	12(4.5)	0(0.0)	3(1.1)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	7(2.6)	18(6.8)
simAE	3(1.1)	0(0.0)	0(0.0)	2(0.8)	0(0.0)	3(1.1)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	2(0.8)	1(0.4)
imAE	2(0.8)	0(0.0)	0(0.0)	2(0.8)	0(0.0)	2(0.8)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(0.4)	1(0.4)
Durvalumab Pan-Tumor Pool Dermatitis/Rash													
AESI	726(24.2)	4(0.1)	24(0.8)	476(15.8)	21(0.7)	52(1.7)	24(0.8)	0(0.0)	21(0.7)	4(0.1)	0(0.0)	269(8.9)	457(15.2)
simAE	52(1.7)	1(<0.1)	12(0.4)	37(1.2)	12(0.4)	52(1.7)	24(0.8)	0(0.0)	4(0.1)	3(<0.1)	0(0.0)	20(0.7)	32(1.1)
imAE	45(1.5)	1(<0.1)	12(0.4)	36(1.2)	12(0.4)	45(1.5)	20(0.7)	0(0.0)	3(<0.1)	3(<0.1)	0(0.0)	14(0.5)	31(1.0)

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The median time to onset was 41 days (range: 4-333 days).

Pancreatic events:

Table 68: Pancreatic adverse events of special interest and immune mediated adverse events (safety analysis set)

				Treatment Related[a]		Received Intervention						Event Outcome,n	
Treatment/ AESI Category	Any AE	Any SAE [b]	CTCAE Grade 3-4	Any CTCAE Grade	CTCAE Grade 3-4	Systemic Cortico Steroid	High Dose Steroid	Other Immuno Suppre- ssants	Requires Endocrine Therapy	Leading to dis- contin- uation of study drug	Resul ted in Death	Not Resol ved	Resol ved
Durva + EP Pancreatic Events													
AESI	17(6.4)	0(0.0)	11(4.2)	10(3.8)	8(3.0)	1(0.4)	1(0.4)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	5(1.9)	12(4.5)
simAE	1(0.4)	0(0.0)	1(0.4)	1(0.4)	1(0.4)	1(0.4)	1(0.4)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(0.4)
imAE	1(0.4)	0(0.0)	1(0.4)	1(0.4)	1(0.4)	1(0.4)	1(0.4)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(0.4)
EP Pancreatic Events													
AESI	9(3.4)	0(0.0)	6(2.3)	3(1.1)	2(0.8)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	3(1.1)	6(2.3)
simAE	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
imAE	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Durvalumab Pan-Tumor Pool Pancreatic Events													
AESI	63(2.1)	5(0.2)	37(1.2)	39(1.3)	20(0.7)	5(0.2)	2(<0.1)	0(0.0)	0(0.0)	4(0.1)	0(0.0)	24(0.8)	39(1.3)
simAE	5(0.2)	1(<0.1)	2(<0.1)	3(<0.1)	1(<0.1)	5(0.2)	2(<0.1)	0(0.0)	0(0.0)	1(<0.1)	0(0.0)	2(<0.1)	3(<0.1)
imAE	4(0.1)	0(0.0)	1(<0.1)	3(<0.1)	1(<0.1)	4(0.1)	2(<0.1)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	2(<0.1)	2(<0.1)

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Myocarditis: 6 patients in the D pan-tumour pool had myocarditis as an AESI, out of which only 1 was assigned as simAE/imAE. No patients in the CASPIAN trial were reported with this AE.

Myasthenia gravis and Guillain-Barré syndrome: No cases reported in CASPIAN or D pan-tumour pool

Myositis: 12 patients in the D pan-tumour pool had myositis as an AESI, none assigned as simAE/imAE.

Infusion-related reactions:

Table 69: AESI of infusion-related reaction (safety analysis set)

	Number (%) of patients[a]					
		CTCAE Grade				
Group term Preferred term	Any AE	1	2	3	4	5
D + EP (N=265)						
Infusion-related reaction (grouped term)	5 (1.9)	2 (0.8)	2 (0.8)	1 (0.4)	0	0
Infusion-related reaction	4 (1.5)	2 (0.8)	2 (0.8)	0	0	0
Urticaria	1 (0.4)	0	0	1 (0.4)	0	0
EP (N=266)						
Infusion-related reaction (grouped term)	3 (1.1)	2 (0.8)	3 (1.1)	0	0	0
Infusion-related reaction	3 (1.1)	2 (0.8)	3 (1.1)	0	0	0
Urticaria	0	0	0	0	0	0

[a] Number (%) of patients with any AESI, sorted by category, sub-category, preferred term and then Grade

Hypersensitivity/anaphylactic reactions (grouped term): reported in 3 patients in the D+EP group:

- Patient 1: Drug hypersensitivity reported as allergic reaction to enoxaparin (Grade 1; not related; recovered).
- Patient 2: Drug hypersensitivity reported as allergic reaction to Voltaren gel (Grade 3; not related; recovered).
- Patient 3: Drug eruption reported as drug eruption (Grade 1; not related; recovered).

AESIs of hypersensitivity/anaphylactic reactions (grouped term) were reported in 2 patients in the EP group for:

- Patient 4: Drug hypersensitivity reported as allergic reaction to Augmentin (Grade 2; not related; recovered).
- Patient 5: Drug eruption reported as drug eruption (Grade 2; not related; recovered).

Infections:

Table 70. Overview of infection AEs (safety analysis set)

AE Category	Number (%) of patients[a]		
	CASPIAN		D pan-tumor pool[b] (N=3006)
	D + EP (N=265)	EP (N=266)	
Any infection AE	89 (33.6)	82 (30.8)	1203 (40.0)
Any infection AE of CTCAE Grade 3 or 4	16 (6.0)	15 (5.6)	237 (7.9)
Any infection AE with outcome = death	2 (0.8)	1 (0.4)	33 (1.1)
Any infection SAE (including events with outcome = death)	24 (9.1)	18 (6.8)	278 (9.2)
Any infection AE leading to discontinuation of study treatment[c]	3 (1.1)	2 (0.8)	40 (1.3)
Any infection AE leading to dose delay/interruption[d]	14 (5.3)	9 (3.4)	197 (6.6)

Laboratory findings

Table 71. Clinically important changes from baseline in haematology parameters (SAS)

Parameter	n/N (%) of patients								
	CASPIAN						D pan-tumour pool[a] (N=3006)		
	D + EP (N=265)			EP (N=266)					
	≥1 CTCAE Grade changes	≥2 CTCAE grade changes	CTCAE grade changes to 3 or 4	≥1 CTCAE Grade changes	≥2 CTCAE grade changes	CTCAE grade changes to 3 or 4	≥1 CTCAE Grade changes	≥2 CTCAE grade changes	CTCAE grade changes to 3 or 4
Hemoglobin (g/L)	214/263 (81.4)	74/263 (28.1)	35/263 (13.3)	216/262 (82.4)	98/262 (37.4)	57/262 (21.8)	1042/2875 (36.2)	132/2875 (4.6)	131/2875 (4.6)
Leukocytes (10^9/L)	196/263 (74.5)	11/263 (42.2)	55/263 (20.9)	192/262 (73.3)	122/262 (46.6)	58/262 (22.1)	441/2878 (15.3)	50/2878 (1.7)	13/2878 (0.5)
Platelets (10^9/L)	139/263 (52.9)	54/263 (20.5)	32/263 (12.2)	146/262 (55.7)	59/262 (22.5)	38/262 (14.5)	362/2873 (12.6)	36/2873 (1.3)	23/2873 (0.8)
Neutrophils (10^9/L)	180/261 (69.0)	155/261 (59.4)	108/ 261 (41.4)	181/261 (69.3)	161/261 (61.7)	124/261 (47.5)	174/2866 (6.1)	85/2866 (3.0)	29/2866 (1.0)
Lymphocytes (10^9/L)	130/258 (50.4)	72/ 258 (27.9)	35/258 (13.6)	114/ 257 (44.4)	72/257 (28.0)	32/257 (12.5)	1284/2863 (44.8)	556/2863 (19.4)	413/2863 (14.4)

Table 72. Clinically important changes from baseline in clinical chemistry parameters (SAS)

Parameter	n/N (%) of patients								
	CASPIAN						D pan-tumor pool[a] (N=3006)		
	D + EP (N=265)			EP (N=266)					
	≥1 CTCAE Grade changes	≥2 CTCAE grade changes	CTCAE grade changes to 3 or 4	≥1 CTCAE Grade changes	≥2 CTCAE grade changes	CTCAE grade changes to 3 or 4	≥1 CTCAE Grade changes	≥2 CTCAE grade changes	CTCAE grade changes to 3 or 4
Alanine aminotransferase (U/L)	98/263 (37.3)	21/263 (8.0)	13/263 (4.9)	94/260 (36.2)	12/260 (4.6)	7/260 (2.7)	813/2866 (28.4)	129/2866 (4.5)	69/2866 (2.4)
Aspartate aminotransferase (U/L)	90/263 (34.2)	17/263 (6.5)	12/263 (4.6)	76/260 (29.2)	5/260 (1.9)	3/260 (1.2)	891/2858 (31.2)	137/2858 (4.8)	102/2858 (3.6)
Alkaline phosphatase (U/L)	98/263 (37.3)	11/263 (4.2)	13/263 (4.9)	90/258 (34.9)	7/258 (2.7)	9/258 (3.5)	812/2850 (28.5)	131/2850 (4.6)	101/2850 (3.5)
Albumin (g/L)	30/262 (11.5)	15/262 (5.7)	2/262 (0.8)	25/253 (9.9)	10/253 (4.0)	3/253 (1.2)	877/2837 (30.9)	325/2837 (11.5)	49/2837 (1.7)
Bilirubin (µmol/L)	40/262 (15.3)	14/262 (5.3)	5/262 (1.9)	43/257 (16.7)	6/257 (2.3)	2/257 (0.8)	267/2859 (9.3)	105/2859 (3.7)	55/2859 (1.9)
Corrected calcium (mmol/L)									
High	13/260 (5.0)	8/260 (3.1)	9/260 (3.5)	10/253 (4.0)	3/253 (1.2)	5/253 (2.0)	313/2821 (11.1)	111/2821 (3.9)	76/2821 (2.7)
Low	136/260 (52.3)	11/260 (4.2)	9/260 (3.5)	139/253 (54.9)	12/253 (4.7)	6/253 (2.4)	746/2821 (26.4)	39/2821 (1.4)	12/2821 (0.4)
Sodium (mmol/L)									
High	45/263 (17.1)	1/263 (0.4)	0	36/261 (13.8)	2/261 (0.8)	0	180/2870 (6.3)	12/2870 (0.4)	5/2870 (0.2)
Low	121/263 (46.0)	30/263 (11.4)	30/263 (11.4)	103/261 (39.5)	34/261 (13.0)	34/261 (13.0)	1095/2870 (38.2)	240/2870 (8.4)	244/2870 (8.5)

Potassium (mmol/L)									
High	113/263 (43.0)	17/263 (6.5)	4/263 (1.5)	112/261 (42.9)	20/261 (7.7)	8/261 (3.1)	659/2864 (23.0)	147/2864 (5.1)	36/2864 (1.3)
Low	40/263 (15.2)	16/263 (6.1)	16/263 (6.1)	39/261 (14.9)	9/261 (3.4)	10/261 (3.8)	367/2864 (12.8)	59/2864 (2.1)	61/2864 (2.1)
Magnesium (mmol/L)									
High	0	0	0	1/16 (6.3)	1/16 (6.3)	1/16 (6.3)	148/2699 (5.5)	29/2699 (1.1)	29/2699 (1.1)
Low	9/18 (50.0)	4/18 (22.2)	2/18 (11.1)	7/16 (43.8)	3/16 (18.8)	1/16 (6.3)	345/2699 (12.8)	12/2699 (0.4)	11/2699 (0.4)
Glucose (mmol/L)									
High	107/259 (41.3)	37/259 (14.3)	14/259 (5.4)	99/258 (38.4)	34/258 (13.2)	14/258 (5.4)	1248/2843 (43.9)	370/2843 (13.0)	143/2843 (5.0)
Low	7/259 (2.7)	5/259 (1.9)	2/259 (0.8)	12/258 (4.7)	6/258 (2.3)	1/258 (0.4)	145/2843 (5.1)	44/2843 (1.5)	13/2843 (0.5)
Creatinine (µmol/L)	223/263 (84.8)	57/263 (21.7)	9/263 (3.4)	218/261 (83.5)	41/261 (15.7)	3/261 (1.1)	642/2804 (22.9)	69/2804 (2.5)	13/2804 (0.5)
Lipase (U/L)	47/235 (20.0)	28/235 (11.9)	19/235 (8.1)	31/227 (13.7)	17/227 (7.5)	7/227 (3.1)	38/302 (12.6)	19/302 (6.3)	17/302 (5.6)
Amylase (U/L)	65/248 (26.2)	20/248 (8.1)	12/248 (4.8)	48/238 (20.2)	13/238 (5.5)	12/238 (5.0)	71/300 (23.7)	23/300 (7.7)	17/300 (5.7)

Table 73. Abnormal on-treatment thyroid tests (safety analysis set)

	Number (%) of patients		
	CASPIAN		
Thyroid Tests	**D + EP (N=265)**	**EP (N=266)**	**D pan-tumor pool[a] (N=3006)**
Elevated TSH >ULN	82 (30.9)	48 (18.0)	901 (30.0)
with TSH ≤ULN at baseline	47	20	566
with at least one T3 free/T4 free <LLN[b]	26 (55.3)	4 (20.0)	338 (59.7)
with all T3 free/T4 free ≥LLN[b]	18 (38.3)	11 (55.0)	199 (35.2)
with all T3 free/T4 free missing[b]	3 (6.4)	5 (25.0)	29 (5.1)
Low TSH <LLN	99 (37.4)	55 (20.7)	693 (23.1)
with TSH ≥LLN at baseline	83	44	545
with at least one T3 free/T4 free >ULN[b]	39 (47.0)	9 (20.5)	247 (45.3)
with all T3 free/T4 free ≤ULN[b]	33 (39.8)	29 (65.9)	265 (48.6)
with all T3 free/T4 free missing[b]	11 (13.3)	6 (13.6)	33 (6.1)

Hy's law: There were no confirmed Hy's Law cases in either group in CASPIAN. In the D + EP group, 4 of the 7 patients that met the potential Hy's Law criteria had a corresponding AE/SAE of hepatic nature. In the EP group, the 1 patient that met the potential Hy's Law criteria and had a corresponding AE of hepatic nature.

Safety in special populations

AE profile according to age:

Table 74: Adverse events in any category – patient level by age group

	Number of patients [a]											
	Caspian											
	Durvalumab + EP (N=265)				EP (N=266)				Durvalumab pan-tumor pool (N=3006)			
	< 50 (n=10)	>=50 - <65 (n=154)	>=65 - <75 (n=82)	>=75 (n=19)	< 50 (n=20)	>=50 - <65 (n=136)	>=65 - <75 (n=89)	>=75 (n=21)	< 50 (n=377)	>=50 - <65 (n=1351)	>=65 - <75 (n=992)	>=75 (n=286)
Any AE	9 (90.0)	151 (98.1)	82 (100.0)	18 (94.7)	19 (95.0)	132 (97.1)	86 (96.6)	21 (100.0)	362 (96.0)	1278 (94.6)	952 (96.0)	275 (96.2)
Any AE of maximum CTCAE grade 3 or grade 4 [b]	5 (50.0)	85 (55.2)	55 (67.1)	11 (57.9)	11 (55.0)	77 (56.6)	55 (61.8)	14 (66.7)	144 (38.2)	530 (39.2)	374 (37.7)	125 (43.7)
Any AE with outcome = death	0	9 (5.8)	2 (2.4)	2 (10.5)	0	6 (4.4)	7 (7.9)	2 (9.5)	17 (4.5)	65 (4.8)	64 (6.5)	18 (6.3)
Any SAE (including events with outcome = death) [c]	2 (20.0)	42 (27.3)	28 (34.1)	10 (52.6)	4 (20.0)	45 (33.1)	37 (41.6)	10 (47.6)	131 (34.7)	446 (33.0)	357 (36.0)	134 (46.9)
Any AE leading to discontinuation of any study treatment	0	16 (10.4)	6 (7.3)	3 (15.8)	1 (5.0)	8 (5.9)	12 (13.5)	4 (19.0)	27 (7.2)	121 (9.0)	106 (10.7)	28 (9.8)
Any AE leading to discontinuation of durvalumab	0	12 (7.8)	3 (3.7)	3 (15.8)	0	0	0	0	27 (7.2)	121 (9.0)	106 (10.7)	28 (9.8)
Any AE leading to dose modification of any study treatment [d]	4 (40.0)	64 (41.6)	46 (56.1)	10 (52.6)	10 (50.0)	66 (48.5)	41 (46.1)	7 (33.3)	82 (21.8)	375 (27.8)	320 (32.3)	94 (32.9)

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AE profile according to gender:

Table 75: Adverse events in any category – patient level by sex

	Number of patients [a]					
	Caspian					
	Durvalumab + EP (N=265)		EP (N=266)		Durvalumab pan-tumor pool (N=3006)	
	Male (n=188)	Female (n=77)	Male (n=181)	Female (n=85)	Male (n=1948)	Female (n=1058)
Any AE	184 (97.9)	76 (98.7)	175 (96.7)	83 (97.6)	1851 (95.0)	1016 (96.0)
Any AE of maximum CTCAE grade 3 or grade 4 [b]	108 (57.4)	48 (62.3)	109 (60.2)	48 (56.5)	762 (39.1)	411 (38.8)
Any AE with outcome = death	11 (5.9)	2 (2.6)	10 (5.5)	5 (5.9)	112 (5.7)	52 (4.9)
Any SAE (including events with outcome = death) [c]	53 (28.2)	29 (37.7)	59 (32.6)	37 (43.5)	682 (35.0)	386 (36.5)
Any AE leading to discontinuation of any study treatment	20 (10.6)	5 (6.5)	16 (8.8)	9 (10.6)	194 (10.0)	88 (8.3)
Any AE leading to discontinuation of durvalumab	14 (7.4)	4 (5.2)	0	0	194 (10.0)	88 (8.3)
Any AE leading to dose modification of any study treatment [d]	95 (50.5)	29 (37.7)	91 (50.3)	33 (38.8)	550 (28.2)	321 (30.3)

AE profile according to geographic region:

Table 76: Adverse events in any category – patient level by geographic region

	Number of patients [a]											
	Caspian											
	Durvalumab + EP (N=265)				EP (N=266)				Durvalumab pan-tumor pool (N=3006)			
	Asia (n=35)	Europe (n=198)	North America (n=24)	South America (n=8)	Asia (n=39)	Europe (n=205)	North America (n=17)	South America (n=5)	Asia (n=657)	Europe (n=1263)	North America (n=1072)	South America (n=14)
Any AE	34 (97.1)	194 (98.0)	24 (100.0)	8 (100.0)	39 (100.0)	197 (96.1)	17 (100.0)	5 (100.0)	613 (93.3)	1190 (94.2)	1052 (98.1)	12 (85.7)
Any AE of maximum CTCAE grade 3 or grade 4 [b]	22 (62.9)	112 (56.6)	17 (70.8)	5 (62.5)	30 (76.9)	112 (54.6)	11 (64.7)	4 (80.0)	206 (31.4)	454 (35.9)	509 (47.5)	4 (28.6)
Any AE with outcome = death	1 (2.9)	10 (5.1)	2 (8.3)	0	0	13 (6.3)	2 (11.8)	0	21 (3.2)	75 (5.9)	66 (6.2)	2 (14.3)
Any SAE (including events with outcome = death) [c]	15 (42.9)	52 (26.3)	12 (50.0)	3 (37.5)	19 (48.7)	66 (32.2)	8 (47.1)	3 (60.0)	183 (27.9)	423 (33.5)	457 (42.6)	5 (35.7)
Any AE leading to discontinuation of any study treatment	2 (5.7)	21 (10.6)	2 (8.3)	0	3 (7.7)	21 (10.2)	1 (5.9)	0	62 (9.4)	129 (10.2)	88 (8.2)	3 (21.4)
Any AE leading to discontinuation of durvalumab	2 (5.7)	14 (7.1)	2 (8.3)	0	0	0	0	0	62 (9.4)	129 (10.2)	88 (8.2)	3 (21.4)
Any AE leading to dose modification of any study treatment [d]	17 (48.6)	95 (48.0)	6 (25.0)	6 (75.0)	18 (46.2)	97 (47.3)	6 (35.3)	3 (60.0)	189 (28.8)	338 (26.8)	342 (31.9)	2 (14.3)

AE profile according to smoking status:

Table 77: Adverse events in any category – patient level by smoking history

	Number of patients [a]					
	Caspian				Durvalumab pan-tumor pool (N=3006)	
	Durvalumab + EP (N=265)		EP (N=266)			
	Smoker (n=243)	Never Smoker (n=22)	Smoker (n=251)	Never Smoker (n=15)	Smoker (n=2227)	Never Smoker (n=768)
Any AE	240 (98.8)	20 (90.9)	243 (96.8)	15 (100.0)	2131 (95.7)	726 (94.5)
Any AE of maximum CTCAE grade 3 or grade 4 [b]	148 (60.9)	8 (36.4)	151 (60.2)	6 (40.0)	872 (39.2)	299 (38.9)
Any AE with outcome = death	11 (4.5)	2 (9.1)	13 (5.2)	2 (13.3)	127 (5.7)	36 (4.7)
Any SAE (including events with outcome = death) [c]	77 (31.7)	5 (22.7)	91 (36.3)	5 (33.3)	793 (35.6)	271 (35.3)
Any AE leading to discontinuation of any study treatment	24 (9.9)	1 (4.5)	23 (9.2)	2 (13.3)	234 (10.5)	45 (5.9)
Any AE leading to discontinuation of durvalumab	17 (7.0)	1 (4.5)	0	0	234 (10.5)	45 (5.9)
Any AE leading to dose modification of any study treatment [d]	114 (46.9)	10 (45.5)	118 (47.0)	6 (40.0)	660 (29.6)	210 (27.3)

AE profile according to PD-L1 IHC status:

Table 78: Adverse events by category – PD-L1 IC <1% and PD-L1 TC ≥ analyses sets

	Number (%) of Patients [a]					
	PD-L1 Analysis Set				Safety Analysis Set	
	IC <1%		IC ≥1%			
Adverse event (AE) category	D + EP (N=116)	EP (N=97)	D + EP (N=35)	EP (N=27)	D + EP (N=265)	EP (N=266)
Any AE	115 (99.1)	93 (95.9)	34 (97.1)	26 (96.3)	260 (98.1)	258 (97.0)
Any AE causally related to treatment [b]	105 (90.5)	89 (91.8)	32 (91.4)	25 (92.6)	237 (89.4)	240 (90.2)
Any AE of CTCAE grade 3 or 4	74 (63.8)	51 (52.6)	20 (57.1)	17 (63.0)	163 (61.5)	166 (62.4)
Any AE of CTCAE grade 3 or 4, causally related to treatment [b]	53 (45.7)	43 (44.3)	16 (45.7)	16 (59.3)	121 (45.7)	138 (51.9)
Any AE with outcome = death	6 (5.2)	8 (8.2)	1 (2.9)	1 (3.7)	13 (4.9)	15 (5.6)
Any AE with outcome = death, causally related to treatment [b]	0	1 (1.0)	0	0	5 (1.9)	2 (0.8)
Any SAE (including events with outcome = death)	38 (32.8)	32 (33.0)	10 (28.6)	6 (22.2)	82 (30.9)	96 (36.1)
Any SAE (including events with outcome = death), causally related to treatment [b]	12 (10.3)	15 (15.5)	3 (8.6)	4 (14.8)	35 (13.2)	50 (18.8)
Any AE causing discontinuation of study treatment [c]	9 (7.8)	16 (16.5)	4 (11.4)	2 (7.4)	25 (9.4)	25 (9.4)
Any AE causing discontinuation of study treatment, causally related to treatment [b] [c]	3 (2.6)	9 (9.3)	2 (5.7)	1 (3.7)	15 (5.7)	13 (4.9)
Any AE leading to dose delay/interruption [d]	47 (40.5)	31 (32.0)	11 (31.4)	8 (29.6)	111 (41.9)	100 (37.6)

CTCAE = Common Terminology Criteria for Adverse Events (version 4.03). MedDRA version 21.1 D Durvalumab, EP Etoposide and platinum-based chemotherapy.
[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] Causally related to any of the study treatments, as assessed by the investigator. Missing responses are counted as related.
[c] AEs on the AE CRF form with Action taken = 'Drug permanently discontinued' for at least one treatment.
[d] AEs on the AE CRF form with Action taken = 'Drug interrupted' for either molecule.
Percentages are based on the total numbers of patients in the treatment group (N).
Source: Table 14.3.1, Appendix 1; and Table 14.3.2.1, CASPIAN Interim CSR, Module 5.3.5.1.

Table 79: Adverse events by category – PD-L1 TC <1% and PD-L1 TC ≥ analyses sets

	Number (%) of Patients [a]					
	PD-L1 Analysis Set				Safety Analysis Set	
	TC <1%		TC ≥1%			
Adverse event (AE) category	D + EP (N=145)	EP (N=116)	D + EP (N=6)	EP (N=8)	D + EP (N=265)	EP (N=266)
Any AE	143 (98.6)	111 (95.7)	6 (100.0)	8 (100.0)	260 (98.1)	258 (97.0)
Any AE causally related to treatment [b]	131 (90.3)	107 (92.2)	6 (100.0)	7 (87.5)	237 (89.4)	240 (90.2)
Any AE of CTCAE grade 3 or 4	90 (62.1)	63 (54.3)	4 (66.7)	5 (62.5)	163 (61.5)	166 (62.4)
Any AE of CTCAE grade 3 or 4, causally related to treatment [b]	67 (46.2)	55 (47.4)	2 (33.3)	4 (50.0)	121 (45.7)	138 (51.9)
Any AE with outcome = death	7 (4.8)	9 (7.8)	0	0	13 (4.9)	15 (5.6)
Any AE with outcome = death, causally related to treatment [b]	0	1 (0.9)	0	0	5 (1.9)	2 (0.8)
Any SAE (including events with outcome = death)	46 (31.7)	36 (31.0)	2 (33.3)	2 (25.0)	82 (30.9)	96 (36.1)
Any SAE (including events with outcome = death), causally related to treatment [b]	15 (10.3)	18 (15.5)	0	1 (12.5)	35 (13.2)	50 (18.8)
Any AE causing discontinuation of study treatment [c]	11 (7.6)	18 (15.5)	2 (33.3)	0	25 (9.4)	25 (9.4)
Any AE causing discontinuation of study treatment, causally related to treatment [b] [c]	4 (2.8)	10 (8.6)	1 (16.7)	0	15 (5.7)	13 (4.9)
Any AE leading to dose delay/interruption [d]	57 (39.3)	37 (31.9)	1 (16.7)	2 (25.0)	111 (41.9)	100 (37.6)

CTCAE = Common Terminology Criteria for Adverse Events (version 4.03). MedDRA version 21.1 D Durvalumab, EP Etoposide and platinum-based chemotherapy.
[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] Causally related to any of the study treatments, as assessed by the investigator. Missing responses are counted as related.
[c] AEs on the AE CRF form with Action taken = 'Drug permanently discontinued' for at least one treatment.
[d] AEs on the AE CRF form with Action taken = 'Drug interrupted' for either molecule.
Percentages are based on the total numbers of patients in the treatment group (N).
Source: Table 14.3.2, Appendix 1.

Safety related to drug-drug interactions and other interactions

Durvalumab is a monoclonal antibody, therefore, no formal PK drug-drug-interaction studies have been conducted. Pharmacokinetic drug-drug interaction between durvalumab and EP was assessed in CASPIAN and no clinically meaningful PK drug-drug interaction was identified.

Discontinuation due to adverse events

Table 80. Most common (frequency ≥2 patients in either CASPIAN treatment group) adverse events leading to discontinuation by PT (safety analysis set)

	CASPIAN		
	D + EP (N=265)	**EP (N=266)**	**D pan-tumor pool[a] (N=3006)**
Preferred Term	**n (%)[b]**	**n (%)[b]**	**n (%)[b]**
Patients with an AE leading to discontinuation	25 (9.4)	25 (9.4)	282 (9.4)
Acute kidney injury	3 (1.1)	4 (1.5)	2 (<0.1)
Thrombocytopenia	0	3 (1.1)	1 (<0.1)
Neutropenia	1 (0.4)	2 (0.8)	0
Sudden death	2 (0.8)	1 (0.4)	2 (<0.1)
Deafness	0	2 (0.8)	0

Post marketing experience

At the time of data cut-off (DCO) for the most recent Development Safety Update Report (12 July 2019), an estimated 8817 patients have received durvalumab in AstraZeneca (the Sponsor) or MedImmune sponsored interventional studies in multiple tumour types, stages of disease, and lines of therapy. Of these, 4067 patients received durvalumab monotherapy, 2423 patients received durvalumab in combination with tremelimumab, and 2327 patients received durvalumab in combination with an investigational and or an approved product. An estimated 8343 patients have been randomized to the various treatment/comparator arms in sponsor-blinded studies. In addition, 2482 patients have participated in the durvalumab Early Access Programme (EAP; Study D4194C00002 for patients with locally advanced, unresectable NSCLC whose disease has not progressed following platinum-based chemoradiation therapy). One hundred twenty-one patients have been enrolled in the durvalumab urothelial carcinoma (UC) EAP (Named Patient Supply) in Australia; this access program closed on 15 January 2019. The total post-marketing exposure of durvalumab since launch to 30 April 2019 is estimated to be approximately 10163 patient-years (IMFINZI Periodic Benefit-Risk Evaluation Report [PBRER], 25 June 2019). No new safety concern was identified based on the post-marketing safety reports.

2.5.1. Discussion on clinical safety

The known safety profile of durvalumab as monotherapy was based on the PACIFIC study, which recruited patients with locally advanced, unresectable NSCLC after chemoradiation. In that target population, the most frequent ADRs associated to this immune checkpoint inhibitor were cough, upper

respiratory tract infections, rash, diarrhoea, pneumonia, pyrexia, pneumonitis, pruritus, hypothyroidism and abdominal pain. Other less common immune-mediated AEs have been further characterised with supportive safety data from a pool of 3006 patients treated with durvalumab monotherapy across 9 studies from diverse cancers and stages. This pooled safety dataset allows for characterization of the safety profile of durvalumab in a larger patient population that includes patients across various tumour types and stages of disease, thus providing a reference to more fully evaluate the durvalumab safety profile.

Nevertheless, the safety outcome of durvalumab in the CASPIAN study might differ for many reasons. Treatment-naïve advanced SCLC is a completely different clinical setting with shorter survival, which also implies much lesser exposure: 7 cycles as median vs. 20 in the PACIFIC study. Moreover, durvalumab was combined with chemotherapy and administered at a fixed dosing regimen which significantly differs from the one already authorized, i.e., 10 mg/kg every 2 weeks.

The safety profile of durvalumab in combination with EP (D+EP) in the proposed indication is based on data from 531 patients included in the CASPIAN trial who received at least one dose of the study treatment (265 patients in the D+EP arm and 266 in the EP alone arm).

The overview of AEs suggests the SOC comparator (etoposide + cis/carboplatin) is slightly more toxic, particularly regarding haematological AEs, but this may be due to the protocol allowing for longer chemotherapy exposure (6 vs. 4 cycles) in this arm. A *post hoc* analysis comparing AEs reported during the first four cycles of treatment did not reveal major differences between treatment arms apart from a higher incidence of anaemia and neutropenia (Grade 3-4 and SAEs) in the EP arm. According to the MAH the cause of these differences may be multifactorial (advanced disease condition, existing co-morbidities and unknown causes).

High-grade (G3/4), SAEs and AEs leading to discontinuation of treatment occurred in similar proportions in both arms, although their pattern differed slightly: AEs of haematological nature predominated in the EP arm, whereas imAEs and thoracic disorders prevailed in the D+EP arm.

A similar number of patients died from AEs in both reported arms from CASPIAN. Most of those G5 AEs were associated to haematological toxicity, infections and/or respiratory/thoracic disorders, but deaths from pneumonia were more frequent in the D+EP arm. Only 1 patient in the D+EP arm experimented death related to an imAE of hepatotoxicity. The deaths from two patients from the EP arm had been classified as due to 'pneumonitis', but a revision of the narratives did not find solid evidence for this diagnosis.

Accounting for the mechanism of action of durvalumab and the open label nature of the trial, the proportion of patients with imAEs was significantly higher in the D+EP arm than in the EP arm. Nevertheless, most of the difference is attributable to low grade manageable thyroid disorders and rash, with very few patients from the D+EP arm experimenting more severe events. Furthermore, as compared to the early days of immunotherapy, most oncologists nowadays have experience dealing with imAEs, allowing for early detection and manageability.

The incidence and severity of pneumonitis associated to durvalumab in CASPIAN was inferior to that seen in the PACIFIC study. A potential explanation for this difference is the fact that all the patients in the latter trial had received high-dose thoracic irradiation –a known risk factor for pneumonitis– as part of their previous treatment. Suspected pneumonitis should be confirmed with radiographic imaging and other infectious and disease-related aetiologies excluded, and managed as recommended in section 4.2 of the SmPC.

The safety profile of durvalumab did not vary significantly across subgroups of gender, race, geographic region, smoking status and ECOG. Nevertheless, patients aged ≥ 75 years presented a

higher incidence of SAEs (around 50% in both arms and in the D pan-tumour pool), G5 AEs and AEs leading to permanent discontinuation even though data are limited in this patient population.

Overall, incidence of AEs, SAEs, deaths and discontinuations due to AEs in the D+EP group was comparable with the monotherapy pool (D pan-tumour pool). In contrast, G3/4 AEs were more frequent in the D+EP group, driven by the higher incidence of haematological AEs related to chemotherapy.

Since the risks of combining prophylactic cranial irradiation (PCI) with immunotherapies were unknown at the time of the study initiation, PCI was not permitted in the 2 immunotherapy arms. Therefore, the safety of concurrent PCI with durvalumab in patients with ES-SCLC is unknown.

2.5.2. Conclusions on clinical safety

In safety terms, adding durvalumab to SOC etoposide + carbo/cisplatin in the target population results in predictable toxicity corresponding to the known safety profile of the individual components. Higher proportion and severity of AEs typical from chemotherapy in the control arm are attributed to considerably longer exposure.

Overall, no new safety concerns arise from the results of CASPIAN, although it is recommended that practicing Oncologists be particularly aware of higher incidence of imAEs associated to durvalumab, in most cases manageable with adequate treatment.

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 with this application.

All safety concerns have been removed as no additional risk minimization measures or pharmacovigilance activities were considered necessary to manage the safety profile of durvalumab. This is endorsed. The RMP has been revised throughout to reflect this were appropriate. All issues considered resolved.

The revised RMP sufficiently reflect the known risk profile of durvalumab. All safety concerns have been removed and sections II – VI are now considered acceptable.

The PRAC considered that the risk management plan version 2 is acceptable. The CHMP endorsed this advice without changes.

Safety concerns

Table 70: Summary of safety concerns

Summary of safety concerns	
Important identified risks	None

Important potential risks	None
Missing Information	None

Pharmacovigilance plan

There are no safety concerns, so only routine pharmacovigilance activities are required.

No additional pharmacovigilance activities are proposed.

Risk minimisation measures

Not applicable as there are no safety concerns.

2.7. Update of the Product information

As a consequence of this group of variation including a new indication, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2 and 6.6 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

Changes were also made to the PI to bring it in line with the current QRD template, 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:

Overall, the wording in the PL is similar to the text previously tested during the MAA. The changes are considered 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 MAH is seeking an extension of indication for durvalumab (IMFINZI) in combination with etoposide and either carboplatin or cisplatin in the first-line treatment of adults with extensive-stage small cell lung cancer (ES-SCLC).

SCLC is a highly aggressive, lethal and widely metastatic lung cancer that comprises 15% of global lung cancer incidence (Gazdar et al, Nat Rev 2017). Nearly all patients with SCLC have a history of tobacco use and about 70% of them present with extensive-stage (ES) at diagnosis, which limits median overall survival to 10-12 months.

3.1.2. Available therapies and unmet medical need

Platinum-based chemotherapy, often combined with etoposide, has been the mainstay of ES-SCLC management since the 1980s (Levy et al, J Natl Compr Can Netw 2013). Although ES-SCLC initially

responds to cytotoxic therapy, it almost always rapidly relapses with resistance to further therapies. The median time to progression is 4 to 6 months (Slotman et al 2015). In the past few years, however, nonclinical and clinical studies have shown promising benefit from adding an immune checkpoint inhibitor to the standard chemotherapy backbone. The IMpower133 study was a placebo-controlled trial that evaluated the benefit of adding atezolizumab to carboplatin + etoposide, with improved survival in the experimental arm [mOS 12.3 vs 10.3 months, HR 0.70 (95% CI 0.54, 0.91), p=0.007)] (Horn et al, NEJM 2018). This is the only anti-PD-L1 inhibitor approved in combination with chemotherapy in the 1L setting of ES-SCLC to date.

3.1.3. Main clinical studies

Study D419QC00001 ("CASPIAN") is an ongoing phase III, open-label, randomised, three-arm, multicentre trial designed to compare the efficacy and safety of durvalumab, with or without tremelimumab, in combination with etoposide and either carboplatin or cisplatin (D+T+EP, arm 1; D+EP, arm 2) with that of etoposide and either carboplatin or cisplatin by themselves (EP alone, arm 3) as first-line treatment in patients with extensive-stage small-cell lung cancer (ES-SCLC). Randomisation was 1:1:1 with planned platinum-based therapy: carboplatin or cisplatin as stratification factor. The two experimental arms received chemotherapy for 4 cycles and then remained in maintenance with durvalumab, whereas up to 6 cycles of chemotherapy and no maintenance treatment were permitted in the control arm.

The primary efficacy endpoint is OS compared between the D+EP and EP alone groups, and separately, between the D+T+EP and EP groups. The overall 5% Type 1 error was split between the two comparisons. The key secondary efficacy endpoint is INV-assessed PFS according to RECIST 1.1 criteria.

The MAH has submitted efficacy and safety results from 537 patients allocated to arms 2 (n=268) and 3 (n=269) of the CASPIAN study to support the extension of the licensed indication of durvalumab to the first line treatment of ES-SCLC.

3.2. Favourable effects

- At data cut-off there was 63% maturity of OS data from arms 2 and 3. The study met its primary endpoint with a statistically significant improvement in OS from D+EP over EP alone [median OS 13.0 vs. 10.3 months, HR 0.73 (95% CI 0.59, 0.91), p=0.0047] at the pre-planned interim analysis. The K-M curves remain separated after month 6. Data from final OS analysis (82% of events) are overall consistent with those from the interim analysis (63% events).
- Investigator-assessed PFS with mature data (86% of events) supports the OS benefit: HR 0.78 (95% CI 0.65, 0.94), nominal p=0.0078. Though mPFS is comparable between arms (5.1 months for D+EP and 5.4 months for EP alone), K-M curves do not separate until after the 6th month. PFS2 shows a clear difference favouring the D+EP arm.
- The efficacy benefit from D+EP vs. EP is seen across ancillary analyses of OS and PFS (sensitivity, subgroup), other secondary endpoints (ORR, DoR) and exploratory endpoints (PFS2, TFST).

3.3. Uncertainties and limitations about favourable effects

- An exploratory analysis on available PD-L1 results (52% of the ITT) shows scarce IHC expression in TCs and ICs. Although the forest plots that depict the potential relationship of these results with OS events suggests that the benefit of D+EP vs. EP is maintained across the different subgroups of PD-

L1 expression, the role of PD-L1 expression as a predictive biomarker for checkpoint immunotherapy in SCLC remains uncertain.

- PFS could not be formally tested at the interim analysis within the MTP as both the D+EP and D+T+EP groups were required to achieve statistical significance for OS prior to stepping down to PFS. Thus, the PFS analysis for D+EP vs EP can only be considered as descriptive.
- Treatment effect from durvalumab during induction and maintenance phases cannot be differentiated.

3.4. Unfavourable effects

- The proportion of patients with any AEs, G3/4, G5 AEs and AEs leading to discontinuation of treatment were comparable between the D+EP and EP arms, but their pattern differed slightly: haematological toxicity predominated in the EP arm, whereas imAEs and thoracic disorders prevailed in the D+EP arm.
- A *post hoc* analysis comparing AEs reported during the first four cycles of treatment did not reveal major differences between treatment arms apart from a higher incidence of anaemia and neutropenia (Grade 3-4 and SAEs) in the EP arm.
- Numerically higher rates of SAEs were reported in the EP arm (36%) as compared to the D+EP arm (31%). Most hospital admissions in both arms were related to AEs of haematological nature and infections.
- The proportion of patients with imAEs was significantly higher in the D+EP arm (20%) as compared to the EP (3.4%) arm, with most of this difference being attributable to low grade thyroid disorders and rash. The most common imAEs in the experimental arm were hypothyroidism, hyperthyroidism, pneumonitis, hepatic events and dermatitis/rash.
- Clinical laboratory profiles of patients in both arms mainly reflected haematological toxicity from the chemotherapy backbone and thyroid autoimmunity in the D+EP arm. Shifts in liver biochemistry parameters were numerically higher in the D+EP arm.
- Patients ≥75 years presented higher incidence of SAEs, G5 AEs and AEs leading to permanent discontinuation in both arms of the study. Of note, the incidence of SAEs in this age subgroup was around 50% in both arms, as was in the pan-tumour pool (286 out of 3006 patients ≥ 75 years).

3.5. Uncertainties and limitations about unfavourable effects

Although adjudication of causality from the investigator was respected, it seems that more patients than those reported presented SAEs and G5 AEs attributable to pneumonia in the D+EP arm.

3.6. Effects Table

Table 81: Effects Table for durvalumab + EP vs. EP alone in the first line treatment of adult patients with extensive-stage small cell lung cancer, data cut-off 27-JAN-2020

Effect	Unit	D+EP (experimental)	EP (control)	Uncertainties / Strength of evidence
Favourable Effects				
*OS ITT (n=537)	Months	12.9	10.5	Stratified HR 0.75 (0.625, 0.910) p=0.0032
§INV-assessed PFS ITT	Months	5.1	5.4	§Stratified HR 0.78 (0.65, 0.94)

Effect	Unit	D+EP (experimental)	EP (control)	Uncertainties / Strength of evidence
(n=537)				§p=0.0136
§Confirmed ORR ITT (n=537)	%	67.9	57.6	§Odds ratio 1.56, p=0.0136
¤**Unfavourable Effects**				
AEs	%	98.1	97.0	
G3/4 AEs	%	61.5	62.4	
Serious AEs	%	30.9	36.1	
AESIs	%	52.1	39.1	
imAEs	%	19.6	2.6	
G5 AEs	% (n)	4.9 (13)	5.6 (15)	
AEs leading to treatment discontinuation	%	9.4	9.4	

* Primary endpoint, final analysis
§ Interim analysis, not formally tested
¤ Safety population n=531

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Considering the descriptive nature of the analysis of the key secondary endpoint –INV-PFS–, updated OS data seem to confirm the long-term advantage from adding durvalumab to SOC EP.

Efficacy results from the CASPIAN trial are in line with what is expected from adding a PD-L1 checkpoint inhibitor to standard chemotherapy in a highly aggressive cancer such as SCLC. Albeit short-term benefit seems limited, overall survival is improved in the ITT population. Regarding duration of treatment, it is debatable whether allowing up to 6 cycles of chemotherapy contributed to improve efficacy outcomes in the control arm, while it undeniably added considerable haematological toxicity.

As with most trials of immune-targeted monoclonal antibodies, there seems to be a group of patients who benefit most. The clinical behaviour of the disease might serve as a guide, but certain biological indicators could aid to identify those subjects. An exploratory *ad hoc* analysis on PD-L1 IHC results from available samples in the trial does not show a clear relationship to efficacy in terms of OS.

The open-label nature of the trial increases the likelihood of investigator bias. The protocol and primary analysis plan were modified during the conduct of the study, but the MAH has provided some reassurance regarding the timelines of the amendments and the external nature of the data that prompted them.

Most of the safety issues in the study were related to the backbone combination of platinum + etoposide, but the potential emergence of imAEs related to durvalumab requires constant vigilance and experience from the clinician.

3.7.2. Balance of benefits and risks

A modest, though clinically relevant survival improvement was seen in the durvalumab + EP arm vs. the control arm in the final analysis of the CASPIAN trial. This advantage is supported across other endpoints, sensitivity analyses and population subgroups.

Valid pharmacological arguments that endorse posology changes have been provided.

3.7.3. Additional considerations on the benefit-risk balance

Although the role of PD-L1 IHC expression as a predictive biomarker for checkpoint immunotherapy in ES-SCLC remains uncertain, the overall outcome of the CASPIAN trial, consistent with results from the IMpower133 study conducted with atezolizumab, highlights the importance of PD-L1 checkpoint inhibition as an addition to chemotherapy with etoposide and a platinum agent in the first line setting of ES-SCLC.

3.8. Conclusions

The overall B/R of Imfinzi (durvalumab) is positive.

4. Recommendations

Outcome

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

Variations accepted		**Type**	**Annexes affected**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I and IIIB
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of Indication to include the use of IMFINZI 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). As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC were updated.
The proposed indication is supported by study D419QC00001 (CASPIAN), an ongoing 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.
In addition, the MAH proposes to revise sections 4.4 and 4.8 of the SmPC to update the safety information based on the Durvalumab Pan-Tumour Pool, a safety dataset comprising of 9 clinical studies building on the existing safety database and summarising the safety information for durvalumab monotherapy characterised across tumour types in the durvalumab clinical program to date.
The Package Leaflet is updated in accordance. The RMP version 2 has also been agreed. The MAH also took the opportunity of this group of variations to update the PI in line with QRD template v10.1.

The group of variations leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

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