Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Durvalumab

Proprietary Product Name: Imfinzi

Sponsor: AstraZeneca Pty Ltd

March 2021

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

List of abbreviations

Abbreviation	Meaning
ACM	Advisory Committee on Medicines
ADA	Anti-drug antibody
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
AJCC	American Joint Committee on Cancer
ALT	Alanine aminotransferase
ARTG	Australian Register of Therapeutic Goods
ASA	Australia specific annex
AST	Aspartate transaminase
AUC	Area under the plasma concentration time curve
AUC_{ss}	Area under the plasma concentration curve at steady state
BICR	Blinded independent central review
CI	Confidence interval
CMI	Consumer Medicines Information
$C_{min,ss}$	Trough concentration at steady state
CSR	Clinical study report
CTCAE	Common terminology criteria for adverse events
CV%	Coefficient of variation (as percentage)
D	Durvalumab
DLP	Data lock point
DoR	Duration of response
ECOG	Eastern Cooperative Oncology Group Performance Status
EORTC QLQ	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire

Abbreviation	Meaning
EP	Etoposide plus platinum based chemotherapy (carboplatin or cisplatin)
ES-SCLC	Extensive-stage small cell lung cancer
EU	European Union
HR	Hazard ratio
imAE	Immune mediated adverse event
Inv	Investigator
ITT	Intent to treat
IV	Intravenous
LS-SCLC	Limited stage small cell lung cancer
mOS	Median overall survival
MTP	Multiple testing procedure
Nab	Neutralising antibodies
NCCN	National Comprehensive Cancer Network (United States)
NR	Non responder
NSCLC	Non-small cell lung cancer
ORR	Overall response rate
OS	Overall survival
PBRER	Periodic benefit risk evaluation report
PBS	Pharmaceutical Benefits Scheme
PCI	Prophylactic cranial irradiation
PD	Pharmacodynamics
PD1	Programmed cell death protein 1
PD-L1	Programmed death-ligand 1
PFS	Progression-free survival
PI	Product Information

Abbreviation	Meaning
PK	Pharmacokinetic(s)
PNS	Paraneoplastic syndrome
PRO	Patient reported outcome
Q2W	Every 2 weeks
Q3W	Every 3 weeks
Q4W	Every 4 weeks
RECIST	Response Evaluation Criteria In Solid Tumours
RMP	Risk management plan
SAE	Serious adverse event
SCLC	Small cell lung cancer
TEAE	Treatment-emergent adverse event
TGA	Therapeutic Goods Administration
US(A)	United States (of America)
USP	United States Pharmacopeia
WHO	World Health Organization

I. Introduction to product submission

Submission details

Type of submission:	Extension of indications
Product name:	Imfinzi
Active ingredient:	Durvalumab
Decision:	Approved
Date of decision:	20 November 2020
Date of entry onto ARTG:	25 November 2020
ARTG numbers:	283215, 283216
, *Black Triangle Scheme:*[1]	Yes This product will remain in the scheme for 5 years, starting on the date the new indication was approved.
Sponsor's name and address:	AstraZeneca Pty Ltd 66 Talavera Road Macquarie park NSW 2113
Dose form:	Concentrated solution for infusion
Strength:	120 mg/2.4 mL, 500 mg/10 mL (50 mg/mL)
Container:	Vial
Pack size:	1
Approved therapeutic use:	*Small cell lung cancer (SCLC)* *Imfinzi (durvalumab) in combination with etoposide and either carboplatin or cisplatin is indicated for the first-line treatment of patients with extensive-stage small cell lung cancer (ES-SCLC).*
Route of administration:	Intravenous (IV) infusion
Dosage:	The recommended dose of Imfinzi depends on the indication. Imfinzi is administered as an intravenous infusion over 1 hour. Imfinzi is for single use in one patient only. Discard any residue. **Urothelial carcinoma**: 10 mg/kg every 2 weeks.

[1] The **Black Triangle Scheme** provides a simple means for practitioners and patients to identify certain types of new prescription medicines, including those being used in new ways and to encourage the reporting of adverse events associated with their use. The Black Triangle does not denote that there are known safety problems, just that the TGA is encouraging adverse event reporting to help us build up the full picture of a medicine's safety profile.

	Locally advanced non-small cell lung cancer (NSCLC): 10 mg/kg every 2 weeks. **Extensive stage small cell lung cancer (ES-SCLC)**: 1500 mg in combination with chemotherapy every 3 weeks (21 days) for 4 cycles, followed by 1500 mg every 4 weeks as monotherapy For further information regarding dosage, refer to the Product Information.
Pregnancy category:	D Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details. The use of any medicine during pregnancy requires careful consideration of both risks and benefits by the treating health professional. This must not be used as the sole basis of decision making in the use of medicines during pregnancy. The TGA does not provide advice on the use of medicines in pregnancy for specific cases. More information is available from obstetric drug information services in your State or Territory.

Product background

This AusPAR describes the application by AstraZeneca Pty Ltd (the sponsor) to register Imfinzi (durvalumab) 120 mg/2.4 mL, 500 mg/10 mL, concentration solution for infusion for the following extension of indications:

> *Small cell lung cancer*
>
> *Imfinzi (durvalumab) in combination with etoposide and either carboplatin or cisplatin is indicated for the first-line treatment of patients with extensive-stage small cell lung cancer.*

Small cell lung cancer (SCLC) is a neuroendocrine tumour that comprises approximately 15% of all lung cancer diagnoses. It is aggressive, characterised by rapid tumour growth, high vascularity, genomic stability, and early metastatic dissemination. It typically has a high mutational burden, which includes a bi-allelic inactivation of tumour suppressor *TP53* and retinoblastoma *RB1* genes in almost all cases. It often presents as disseminated disease.

SCLC is typically divided in to limited stage small cell lung cancer (LS-SCLC) and extensive stage small cell lung cancer (ES-SCLC). LS-SCLC is disease limited to the ipsilateral hemithorax and regional lymph nodes and can be encompassed in a safe radiotherapy field.

ES-SCLC is disease that has spread to include distant metastases, malignant pericardial or pleural effusions and/or contralateral supraclavicular and contralateral hilar lymph node involvement. It is the most common form of SCLC at diagnosis (about 70%). ES-SCLC is strongly correlated with cigarette smoking; at least 90% of patients have a heavy smoking history. As noted by the sponsor, ES-SCLC is usually initially sensitive to chemotherapy but most patients relapse within a year of therapy. The outlook for ES-SCLC is generally poor with a median overall survival (OS) of < 12 months and a 1 to 2% 5 year survival.

Etoposide and platinum based chemotherapy (EP), either carboplatin or cisplatin has been the mainstay of therapy for many years. In the submission the sponsor noted there no large Phase III studies that compare cisplatin/etoposide with carboplatin/etoposide in ES-SCLC, although several large Phase III studies using EP as the comparator in this setting have reported the medial progression-free survival (PFS) between 4 to 6 months and median OS between 7 to 11 months.[2] In addition, a randomised Phase III study reported the median PFS in first line treatment of ED-SCLC for EP as a control arm was 4.4 months and the median OS was 10.9 months.[3]

Atezolizumab was registered in July 2019 in combination with carboplatin and etoposide for the treatment of ES-SCLC, and has Pharmaceutical Benefits Scheme (PBS) listing for this indication. In the registration study the median overall survival was 12.3 months (95% confidence interval (CI) 10.8, 15.9) versus 10.3 months (95% CI 9.3, 11.3), stratified hazard ratio (HR) 0.7 (0.54, 0.91), OS 12 (51.7% versus 38.2%) and a median PFS of 5.2 months (4.4, 5.6) versus 4.3 months (4.2, 4.5), 6 months PFS 30.9% versus 22.4% and 12 months PFS 12.6% versus 5.4% for the atezolizumab plus carboplatin plus etoposide versus carboplatin plus etoposide alone, respectively.

The Australian eviQ[4] clinical guidelines for ES-SCLC include atezolizumab plus carboplatin plus etoposide (first line); topotecan (second line); etoposide plus carboplatin or cisplatin (first line); doxorubicin plus vincristine plus cyclophosphamide; irinotecan plus cisplatin as treatment options.

The American 2020 National Comprehensive Cancer Network (NCCN)[5] guidelines include atezolizumab or durvalumab +carboplatin + etoposide as the first-line preferred systemic therapy option followed by maintenance atezolizumab or durvalumab. The guidance has recently been updated (11 August 2020) to recommend four cycles of systemic therapy but notes that some patients may receive up to six cycles based on response and tolerability after four cycles.

Regulatory status

The product received initial registration on the Australian Register of Therapeutic Goods (ARTG) on 2 October 2018 for the below indications.

Urothelial carcinoma

Imfinzi (durvalumab) is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma who:

- *have disease progression during or following platinum-containing chemotherapy.*
- *have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.*

[2] Slotman et al., Use of thoracic radiotherapy for extensive stage small-cell lung cancer: a Phase III randomised controlled trial. *The Lancet*, 2015; 385(9962):36-42.
[3] Reck et al., Phase III randomized trial of ipilimumab plus etoposide and platinum versus placebo plus etoposide and platinum in extensive-stage small-cell lung cancer. *Journal of Clinical Oncology*, 2016; 34:31, 3740-3748.
[4] **eviQ** is an Australian government, freely available online resource of cancer treatment protocols developed by multidisciplinary teams of cancer specialists. With a goal to improve patient outcomes and reduce treatment variation, eviQ provides evidence-based information to support health professionals in the delivery of cancer treatments available at the time treatment decisions are being made, it is accessible via www.eviq.org.au.
[5] The National Comprehensive Cancer Network (NCCN) is a not for profit organisation in the United States comprised of over 30 cancer centres that work together to develop a comprehensive set of evidence-based diagnostic, treatment, and supportive cancer care guidelines.

This indication is approved based on objective response rate and duration of response in single arm study. An improvement in survival or disease-related symptoms has not been established.

Locally advanced non-small cell lung cancer (NSCLC)

Imfinzi (durvalumab) is indicated for the treatment of patients with locally advanced, unresectable NSCLC whose disease has not progressed following platinum-based chemoradiation therapy.

At the time the TGA considered this application, similar applications had been approved in the European Union (EU) (approved on August 2020), Singapore (approved on February 2020) and the United States (US) (approved on 30 March 2020) and applications were under consideration in Canada (submitted on October 2019, approved 21 September 2020) and Switzerland (submitted on November 2019).

Table 1: International regulatory status

Region	Submission date	Status	Approved indications
Canada	31 October 2019	Approved on 21 September 2020	*Urothelial Carcinoma* *Imfinzi (durvalumab) is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma who:* • *Have disease progression during or following platinum-containing chemotherapy* • *Have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy* *Marketing authorization with conditions was based on a promising tumour response rate and durability of response. An improvement in survival or disease-related symptoms has not been established (see Clinical Trials).* *Locally Advanced, Unresectable, Stage III Non-Small Cell Lung Cancer* *Imfinzi is indicated for the treatment of patients with locally advanced, unresectable, Stage III non-small cell lung cancer (NSCLC) whose disease has not progressed following platinum based chemoradiation therapy.* *Extensive-Stage Small Cell Lung Cancer* *Imfiinzi in combination with etoposide and either carboplatin or cisplatin is indicated for the first-line treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC).*

Region	Submission date	Status	Approved indications
EU Centralised procedure Rapporteur: Denmark Co-rapporteur: Spain	12 November 2019	Approved on 27 August 2020	*Imfinzi as monotherapy is indicated for the treatment of locally advanced, unresectable non-small cell lung cancer (NSCLC) in adults whose tumours express PD-L1 on ≥ 1% of tumour cells and whose disease has not progressed following platinum-based chemoradiation therapy (see section 5.1).* *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).*
Singapore	27 September 2019	Approved on 28 February 2020	*Locally Advanced Non-small Cell Lung Cancer (NSCLC): Imfinzi is indicated for the treatment of patients with locally advanced, unresectable NSCLC whose disease has not progressed following platinum-based chemoradiation therapy.* *Small Cell Lung Cancer (SCLC): Imfinzi in combination with etoposide and either carboplatin or cisplatin is indicated for the first-line treatment of patients with extensive-stage small cell lung cancer (ES-SCLC).*
Switzerland	26 November 2019	Approved on 6 October 2020	*Non-Small Cell Lung Cancer (NSCLC)* *Imfinzi is indicated for the treatment of patients with locally advanced, unresectable NSCLC whose disease has not progressed following definitive platinum-based chemoradiation therapy.* *Small Cell Lung Cancer (SCLC)* *Imfinzi in combination with etoposide and either carboplatin or cisplatin is indicated for the first-line treatment of patients with extensive-stage small cell lung cancer (ES-SCLC).*

Region	Submission date	Status	Approved indications
US	30 September 2019	Approved on 30 March 2020	*Imfinzi is a programmed death-ligand 1 (PD-L1) blocking antibody indicated: - for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma who:* *- have disease progression during or following platinum-containing chemotherapy. (1.1)* *- have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy. (1.1)* *This indication is approved under accelerated approval based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials. (1.1)* *- for the treatment of adult patients with unresectable, Stage III non-small cell lung cancer (NSCLC) whose disease has not progressed following concurrent platinum-based chemotherapy and radiation therapy. (1.2)* *- in combination with etoposide and either carboplatin or cisplatin, as first-line treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC). (1.3)*

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Registration timeline

The following table captures the key steps and dates for this application and which are detailed and discussed in this AusPAR.

Table 2: Timeline for Submission PM-2019-04661-1-4

Description	Date
Submission dossier accepted and first round evaluation commenced	2 December 2019
First round evaluation completed	30 April 2020

Description	Date
Sponsor provides responses on questions raised in first round evaluation	2 June 2020
Second round evaluation completed	17 July 2020
Delegate's Overall benefit-risk assessment and request for Advisory Committee advice	31 August 2020
Sponsor's pre-Advisory Committee response	15 September 2020
Advisory Committee meeting	1 and 2 October 2020
Registration decision (Outcome)	20 November 2020
Completion of administrative activities and registration on the ARTG	25 November 2020
Number of working days from submission dossier acceptance to registration decision*	221

*Statutory timeframe for standard applications is 255 working days

III. Submission overview and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations.

The TGA has adopted the EU Guideline on the evaluation of anticancer medicinal products in man;[6] and relevant appendices.

Quality

Durvalumab is a human immunoglobulin (IgG1κ) monoclonal antibody that is presented as sterile, preservative-free, clear to opalescent, colourless to slightly yellow, concentrated solutions free from visible particles. Each solution contains histidine, histidine hydrochloride monohydrate, trehalose dihydrate, polysorbate 80 and water for injection as excipients.

New quality data were included in this submission to support impurity safety levels because the flat dosing potentially exposes patients of lower body weight to higher levels of impurities in the formulation. The impurity calculations were based on what was considered a worse-case scenario for the 1500 mg dosing of 50 mg/kg, and impurities at this maximal exposure were found to be within acceptable limits.

The endotoxin limits have been updated and remain below the European Pharmacopoeia and United States Pharmacopeia (USP) limits of ≤ 5 endotoxin/kg for an aseptic product. Updated container quality data was accepted by the container safety evaluator.

The quality evaluator had no objections on quality grounds to the approval of this submission and did not recommend batch release conditions.

[6] **EMA/CHMP/205/95/Rev.4**: EU Guideline on the evaluation of anticancer medicinal products in man.

Nonclinical

No new nonclinical data were included in this submission. The nonclinical evaluator noted the exposure in the 1500 mg IV every 3 weeks (Q3W) dose regimen is approximately twice the exposure at 10 mg/kg every 2 weeks (Q2W) dose regimen. The evaluator noted previous durvalumab data that showed no target organ for toxicity for repeat dose toxicity studies in monkeys which animal: human dose ratios up to 23 based on area under the plasma concentration time curve (AUC). The major concern is the potential for embryofetal lethality in pregnancy patients. The evaluator had no objections on non-clinical ground to the extension of indications.

Clinical

The clinical dossier consisted of two safety and efficacy studies, the pivotal Phase III CASPIAN trial, and Study 1108, a Phase I/II supportive study.

Pharmacology

Pharmacokinetics

A pharmacometric model incorporating updated pharmacokinetic (PK) data from 9 supportive durvalumab monotherapy studies and the pivotal CASPIAN trial supported the selection of 1500 mg every 4 weeks (Q4W) fixed dose regimen for study in ES-SCLC as being similar in terms of AUC to 20 mg/kg Q4W. The steady state (at Day 84) geometric mean (coefficient of variation as percentage (CV%)) of the observed trough concentrations for durvalumab 1500 mg Q3W by IV administration was 241 µg/mL (49.7%), 75% higher than for durvalumab 10 mg/kg Q2W administration. No intrinsic or extrinsic factor were identified on which dose adjustment would be required.

The PK of EP in the durvalumab (D)+ EP versus EP groups was similar, suggesting no PK drug-drug interaction.

Pharmacodynamics

Programmed death-ligand 1 (PD-L1) was completely suppressed in all patients after 1, 3, or 10 mg/kg Q2W, 15 mg/kg Q3W and 20 mg/kg Q4W. In the exposure response analysis, longer OS durations observed for the fourth quartile of durvalumab PK exposure compared to the lower three quartiles, but all exposure quartiles had similar or longer median OS compared to EP alone in the CASPIAN trial. No clinically meaningful relationship between durvalumab exposure and Grade ≥ 3 Common Terminology Criteria for Adverse Events (CTCAE)[7] treatment related events or events of special interest were found. There was no apparent impact of anti-drug antibodies (ADA) on durvalumab PK or pharmacodynamics.

Dose for pivotal study

The pharmacometric analyses were the basis of the dose regimen justification for 1500 mg Q3W IV in combination with EP for four cycles followed by durvalumab 1500 mg Q4W IV monotherapy thereafter.

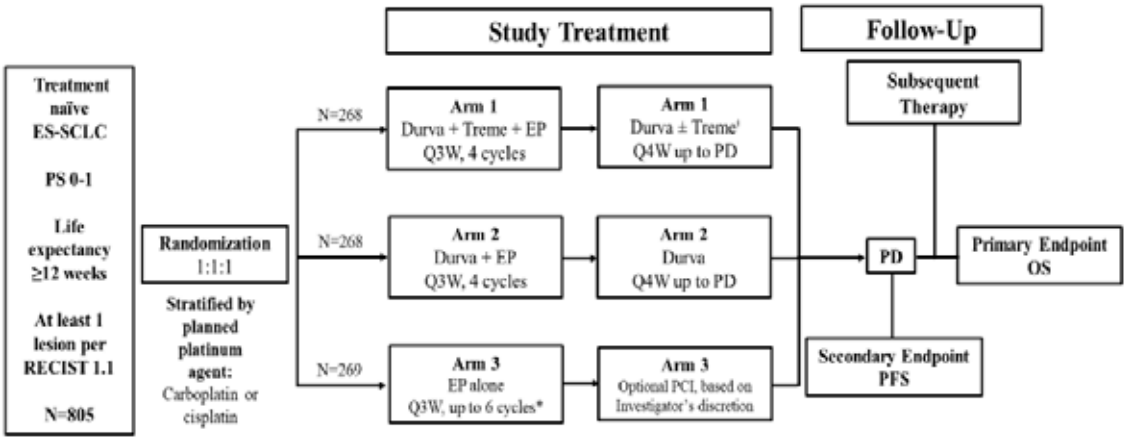
[7] **Common Terminology Criteria for Adverse Events** (**CTCAE**) is a standardised classification of side effects used in assessing drugs for cancer therapy, in particular. Specific conditions and symptoms may have values or descriptive comment for each level, but the general guideline is 1 – Mild, 2 – Moderate, 3 – Severe, 4 - Life threatening, 5 - Death.

Efficacy

The CASPIAN trial

The CASPIAN trial is an ongoing multicentre, randomised, open-label, investigator-blind, active controlled study. The study design is summarised in Figure 1 and Table 3. Arms 2 and 3 are relevant for this submission.

Figure 1: Study schema for CAPSIAN trial



ES-SCLC = extensive-stage small cell lung cancer; PS = Performance status; durva = durvalumab; treme = tremelimumab; EP = etoposide-platinum; Q3W = every 3 weeks; Q4W = every 4 weeks; PCI = prophylactic cranial radiation; PD = disease progression; OS = overall survival; PFS = progression free survival.

Table 3: The CASPIAN trial; summary of the study design

The CASPIAN trial design	
Administrative	First subject randomised: 07 April 2017 Last subject randomised: 29 May 2018 Data cut-off date for this interim OS analysis: March 2019 Clinical study report (CSR) date: 5 September 2019 A total of 209 sites across 23 countries in North and Latin America, Europe, and the Asia-Pacific. There are no patients from sites in Australia.
• 795 patients planned for the whole study, 537 randomised to D + EP (n=268), and EP only (n= 269) • Arms 2 (D + EP) and 3 (EP only) are relevant for this submission • PD-L1 testing was not performed at screening because inadequate samples/low tumour expression were expected and no association between PD-L1 and atezolizumab in ES-SCLC in Phase I study was found • Prophylactic cranial irradiation allowed (PCI) (investigator led) • Crossover not allowed, but 5.2% in the EP alone group had subsequent treatment post-progression • Arm 2 treatment continued until disease progression • Patient flow as at data cut-off date (March 2019): – Received treatment 265/268 (98.9%) D + EP group; 266/269 (98.9%) EP group	

The CASPIAN trial design		
– Survival at interim analysis: 112/265 (41.8%) D + EP group; 76/266 (28.6%) EP group – Survival on study treatment: 43/265 (16%) D + EP group; 0% EP group – Discontinued durvalumab: 222/2685(83.8%) D + EP group; 177/268 due to disease progression – Discontinued EP: 42/268 (15.8%) D + EP group; 76/269 (28.6%) EP group – Died: 149 (55.6%) D + EP group; 179 (66.5%) EP group – Withdrew from study: 7 (2.6%) D + EP group; 13 (4.8%) EP group		
Eligibility	Key inclusion criteria: • Adults with histologically or cytologically confirmed ES-SCLC suitable to receive platinum-based chemotherapy as first line treatment. • Extensive disease based on American Joint Committee on Cancer (AJCC) Stage;8(7th edition) IV SCLC (T any, N any, M1 a/b), or T3-4 due to multiple lung nodules too extensive or tumour/nodal volume too large to be encompassed in a tolerable radiation plan. • Asymptomatic or stable brain metastases, post steroid treatment with. • World Health Organization (WHO)/ Eastern Cooperative Oncology Group Performance Status (ECOG)9 Performance Status score 0 or 1.	Key exclusion criteria: • Active or prior documented autoimmune or inflammatory disorders • History of autoimmune disease, chest radiation therapy, allogeneic organ transplantation, and use of immunosuppressive medications within 14 days of study treatment. • Paraneoplastic syndrome (PNS) of autoimmune nature requiring systemic steroids or immunosuppressive agents, or symptoms suggesting worsening of PNS. • Female patients who were pregnant or breastfeeding or male or female patients of reproductive potential who were not willing to employ effective birth control

[8] **American Joint Committee on Cancer Stage**. A system to describe the amount and spread of cancer in a patient's body, using TNM. T describes the size of the tumor and any spread of cancer into nearby tissue; N describes spread of cancer to nearby lymph nodes; and M describes metastasis (spread of cancer to other parts of the body). This system was created and is updated by the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC). The AJCC staging system is used to describe most types of cancer.

[9] **ECOG Performance Status**: The Eastern Cooperative Oncology Group (ECOG) has developed criteria used by doctors and researchers to assess how a patient's disease is progressing, assess how the disease affects the daily living abilities of the patient, and determine appropriate treatment and prognosis. The following are used:
0 - Fully active, able to carry on all pre-disease performance without restriction
1- Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2 - Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours

The CASPIAN trial design		
	• Life expectancy of ≥ 12 weeks. • ≥ 1 target lesion per Response Evaluation Criteria In Solid Tumours (RECIST)10 version 1.1. • Adequate organ and marrow function; creatinine clearance (CrCl) > 60 mL (cisplatin) or > 45 mL/min (carboplatin)	
Endpoints of relevance to this submission	Primary: Overall Survival Key secondary (alpha-controlled): PFS Other secondary: Overall response rate (ORR), PFS 6 months and PFS 12 months by investigator (Inv) per RECIST version 1.1, OS 18 months, sampling for non-compartmental PK: ADA and ADA Nab, patient reported outcomes (PRO), European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ)-C30, EORTC QLQ-LC13, change in WHO/ECOG performance status, safety.	

3 - Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4 - Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5 – Dead
[10] **The Response Evaluation Criteria In Solid Tumours** (RECIST) is a voluntary international standard with unified and easily applicable criteria to define when a patient's tumour has improved ('respond'), stayed the same ('stabilise'), or worsened ('progress') during treatment. The criteria were published in February 2000 by an international collaboration including the European Organisation for Research and Treatment of Cancer (EORTC), National Cancer Institute (NCI) of the United States, and the National Cancer Institute of Canada Clinical Trials Group. Today, the majority of clinical trials evaluating cancer treatments for objective response in solid tumours use RECIST. These criteria were developed and published in February 2000, and subsequently updated in 2009.

The CASPIAN trial design	
Statistical analysis plan;[11]	**Sample size:** n = about 795 randomised 1:1:1 D plus T plus EP (Arm 1), D plus EP (Arm 2), EP only (Arm 3), assumes 3 months delay in separation of OS and PFS curves for Arm 2 versus Arm 3 **Primary endpoint:** OS**:** per protocol the final analysis was to occur when approx 425 OS events (80% maturity) had occurred. If the true HR = 0.69 at this analysis the study would have 96% power to detect a statistical significant difference with a 2-sided, alpha = 0.0357 (2-sided, overall alpha 4% for D plus EP versus EP) (Note: the actual alpha level to be used was stipulated to be based on the actual observed number of deaths at the time of the interim and the final analysis). **Interim analyses:** per protocol the interim analysis was planned when approximately 318 events (60% maturity) had occurred. If the true HR = 0.71 at the interim the study had 71% power to demonstrate a statistical significant difference with a 2-sided, alpha=0.0143 (Note: the actual alpha level to be used was stipulated to be based on the actual observed number of deaths at the time of the interim and the estimated target number of events for the final analysis) **Multiplicity:** Multiple testing procedure with alpha recycling, 5% alpha overall, 4% alpha allocated for testing of D plus EP versus EP. Lan DeMets spending function use to account for multiplicity introduced by interim analysis for superiority, alpha applied at interim and primary time points for OS testing family and PFS testing family In order: OS family (intent to treat (ITT)), then OS (Combo plus EP* versus EP), PFS family (ITT) D plus EP versus EP, then Combo plus EP* versus EP *Combo = durvalumab plus tremelimumab = Arm 1 of study not presented in support of this application
Protocol amendments and deviations	**Amendments:** version 2 added more Chinese patients; version 3 (23 Jul 2018): D plus EP versus EP comparison added as co-aim of the study; removal of Blinded Independent Central Review (BICR) from PFS assessment; updates to primary and secondary objectives; updates to multiple testing procedure (MTP); and interim analysis plan including maturity (interim analyses 1 and 2 combined into single OS interim analysis with 60% maturity, maturity for final OS increased to 80%) version 4 (29 Oct 2018): reallocated alpha in the MTP to be 4% for monotherapy (that is, D plus EP) and 1% for combination therapy (Arm 1) **Important Protocol Deviations:** 3.5% in Arms 2 and 3, similar numbers in each group

Populations and baseline characteristics

A summary of the baseline characteristics of the CASPIAN trial population is included in Table 4. The majority of patients were male (69.6%), and 93.1% of patients were either current (45.8%) or former smokers (47.3%).

[11] The table shows the details of the amended SAP. Both the original and the amended SAP were taken into consideration by the Delegate in reaching the decision. Original SAP details submitted by sponsor are listed below:
Multiplicity: Multiple testing procedure with alpha recycling, 5% 2-sided alpha overall, 4% alpha allocated for OS testing of D plus EP versus EP. Lan DeMets spending function use to account for multiplicity introduced by interim analysis for superiority, alpha applied at interim and final time points for OS testing family and PFS testing family: 4% 2-sided alpha for OS (D plus EP* versus EP), and 1% 2-sided alpha for OS (Combo plus EP versus EP), then (if both OS tests were statistically significant (Combo plus EP versus EP), then (if both OS tests were statistically significant) PFS (D plus EP versus EP), then (if preceding tests were statistically significant) PFS (Combo plus EP* versus EP).

Table 4: The CASPIAN trial; summary of baseline demographics

Characteristic	Category	D plus EP (n = 268)	EP (n = 269)
Age	Median (range)	62 (22 to 82)	63 (35 to52)
Age group	< 65 years ≥ 65 to < 75 years ≥ 75 years	167 (62.3%) 82 (30.6%) 19 (7.1%)	157(58.1%) 90 (33.5%) 22 (8.2%)
Sex	Male	190 (70.9%)	184 (68.4%)
Race	White Black Asian Unknown/Other	229 (85.4%) 2 (0.1%) 36 (13.4%) 1 (0.4%)	221 (82.2%) 3 (1.1%) 42 (15.6%) 3 (1.1%)
ECOG PS	0 1	99 (36.9%) 169 (63.1%)	90 (33.5%) 179 (66.5%)
Smoking	Current Former Never	120 (44.8%) 126 (47.0%) 22 (8.2%)	126 (46.8%) 128 47.6%) 15(5.6%)
Stage (AJCC staging)[8]	III IIIA IIIB IV	1 (0.4%) 5 (1.9%) 22 (8.2%) 240 (89.6%)	0 (%) 3 (1.1%) 21 (7.8%) 245 (91.1%)
Histology	SCLC (neuroendocrine) SCLC (combined) Other	39 (14.6%) 229 (85.4%) 0 (0%)	48 (17.8%) 220(81.8%) 1 (0.4%)

For the characteristics of age group to histology, the number of patients is given followed by percentage. D = durvalumab; EP = etoposide-platinum; ECOG PS = Eastern Cooperative Oncology Group Performance Score; AJCC = American Joint Committee on Cancer; SCLC = small cell lung cancer.

Across the study 39.5% of patients had liver metastases and 10.2% of patients had brain/central nervous system metastases. Prior anticancer therapy was minimal (1.1% cytotoxic; 3.4% radiotherapy).

The median number of cycles received for each of etoposide, carboplatin and cisplatin were 4/4/4 for the D + EP group and 6/6/4 for the EP only group (see Table 5).

Table 5: The CASPIAN trial; number of cycles of etoposide and platinum therapy (carboplatin or cisplatin) in each treatment arm

	Durvalumab plus etoposide-platinum (n = 265)			Etoposide-platinum (n = 266)		
Cycles received	Etoposide	Carboplatin	Cisplatin	Etoposide	Carboplatin	Cisplatin
Number of cycles received						
≥ 1	265 (100%)	208 (100%)	65 (100%)	266 (100%)	208 (100%)	67 (100%)
≥ 2	249 (94%)	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%)

Prophylactic cranial irradiation (PCI) was received by 7.8% of the EP group.

Results

At the time of primary analysis 336 events (62.6% maturity for overall OS) had occurred, with approximately 58% and 67% of events (deaths) in the D plus EP and EP along groups, respectively, and a median duration of follow up follow-up for all patients was 11.3 months in the D plus EP group and 9.86 months in the EP group.

Primary efficacy outcome: The primary efficacy outcome was OS. Results are summarised in Table 6 and Figure 1, below. Results for OS in Table 6 are presented for the March 2019 cut–off from the clinical study report with supplementary data from the January 2020 cut-off provided at second round of TGA evaluation.

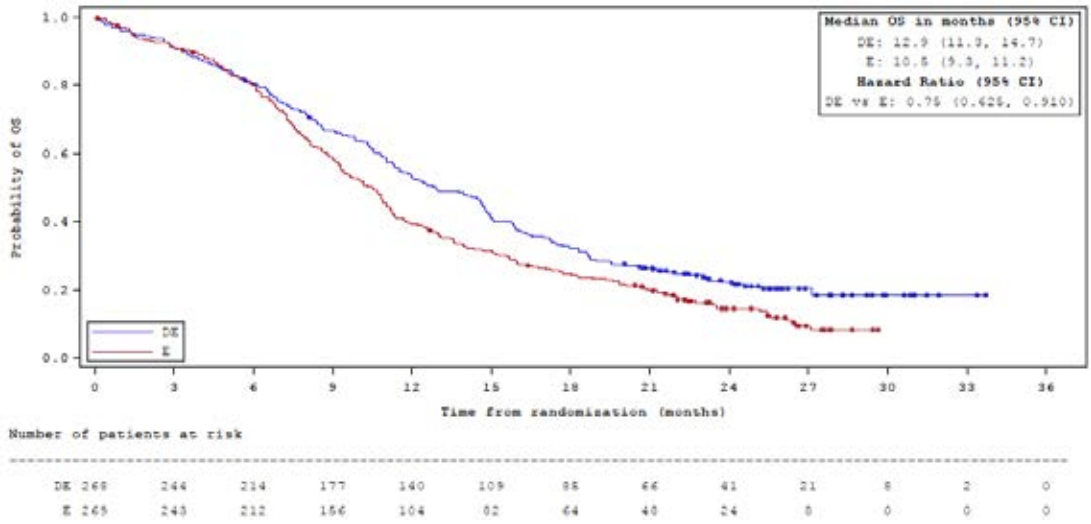
Table 6: The CASPIAN trial; primary efficacy outcome (overall survival)

	D plus EP (n = 268) 03/ 2019	EP (n = 269) 03/2019	D plus EP (n = 268) 01/ 2020	EP (n = 269) 01/2020
HR, D plus EP versus. EP	0.73		0.75	
95% CI for HR	(0.59, 0.91)		(0.63, 0.91)	
2-sided p-value	0.0047		0.0032	
Events, death, n (%)	155 (57.8)	181 (67.3)	210 (78.4)	231(85.9)
Censored subjects, n (%)	113 (42.2)	88 (32.7)	58 (21.6)	38 (14.1)
Still in survival follow-up n (%)	112 (41.8)	77 (28.6)	56 (20.9)	31 (11.5)
Median OS (months)	13.0	10.3	12.9	10.5
95% CI for median OS	(11.5, 14.8)	(9.3, 11.2)	(11.3, 14.7)	(9.3, 11.2)
Survival rate at 12 months (%)	53.7	39.8	52.8	39.3
95% CI for survival rate at 12 months (%)	(47.4, 59.5)	(33.7, 45.8)	(46.6, 58.5)	(33.4, 45.1)
Survival rate at 18 months (%)	33.9	24.7	32.0	24.8
95% CI for survival rate at 18 months (%)	(26.9, 41.0)	(18.4, 31.6)	(26.5, 37.7)	(19.7, 30.1)

Median duration of follow up: D + EP 11.3 months, EP 9.9 months, data cut 11 March 2019, and January 2020). D = durvalumab, EP = etoposide and platinum-based chemotherapy, CI = confidence interval, HR = hazard ratio, OS = overall survival

The survival rate at 24 months in the January 2020 data set was 22.2% (95% CI: 17.3, 27.5) versus 14.4% (95% CI: 10.3, 19.2).

Figure 2: The CASPIAN trial; primary efficacy outcome (Kaplan-Meier curve for overall survival)



Intent to treat population, full set analysis, data cut off: 27 January 2020

D = durvalumab, e = Etoposide and platinum-based chemotherapy, OS = overall survival, CI = confidence interval.

Circle indicate a censored observation. CI = confidence interval. 1 month = 30.4375 days.

A sensitivity analysis for OS adjusting for predefined baseline covariates (platinum agent, age, sex, World Health Organization (WHO) performance status, smoking status, brain/CNS metastases, disease stage at diagnosis, race, and region) provided an adjusted HR estimate for D plus EP versus EP of 0.71 (95% CI: 0.566, 0.877). Subgroup analyses were considered exploratory by the evaluator.

Key secondary outcome: PFS was based on investigator assessment.

Table 7: The CASPIAN trial; secondary outcome (progression-free survival analysis)

	D + EP N = 268	EP N = 269
HR, D plus EP versus EP	0.78	
95% CI for HR	0.645, 0.936	
Total number of events	226 (84.3%)	233 (86.6%)
Median PFS months (95% CI)	5.1 (4.7, 6.2)	5.4 (4.8, 6.2)
PFS at 6 months	45.4% (39.3, 51.3)	45.6% (39.3, 51.7)
PFS at 12 months	17.5% (13.1, 22.5)	4.7% (2.4, 8.0)

D = durvalumab, EP = etoposide and platinum-based chemotherapy, CI = confidence interval, HR = hazard ratio, PFS = progression free survival.

Time to subsequent treatment or death: Median time to first subsequent therapy or death: 7.4 months D plus EP group; 6.8 months EP group; HR: 0.70 (95% CI: 0.58, 0.84). Median time from progression to first next anticancer therapy: 41.0 days D plus EP group; 19.0 days EP group.

Other secondary outcome, overall response rate and duration of response:

ORR (Inv): D plus EP group 79.5%; EP group 70.3% in the alone group, OR 1.64; (95% CI: 1.11, 2.44; p =0.0137).

Median duration of response (DoR) was 4.8 months in both groups. At 12 months the proportion of patients remaining in response was 22.7% in the D plus EP group versus 6.3% in the EP group, and at 15 months it was 19.9% D plus EP group versus 2.1% in the EP group. At the data cut of January 2020 16% of the D plus EP group were still on durvalumab.

Post-discontinuation anti-cancer treatment was administered to 43.2% of patients, and was similar in both treatment groups: 41.3% received chemotherapy and 3.5% received an immunotherapy. Post-discontinuation radiotherapy was received by 25.7% in the D plus EP group and 37.9% of the EP group. After disease progression, radiotherapy was received by 1.9% patients in the D plus EP group and 13.8% of the EP group.

Study 1108 (supportive study)

This Phase I/II, open-label, first-in-human, dose escalation/exploration, dose expansion study of durvalumab monotherapy in 1,022 patients with solid tumours provided results from a 21 patient SCLC cohort. In the dose-escalation and-exploration phases, patients received IV doses of 0.1 to 10 mg/kg durvalumab Q2W and 15 mg/kg Q3W; and 20 mg/kg Q4W. In the dose-expansion phase the dose was 10 mg/kg durvalumab IV Q2W for up to 12 months. The efficacy endpoint in the dose-expansion phase was ORR (RECIST;[10] version 1.1 by blinded independent central review (BICR)): 9.5% (95% CI: 1.2, 30.4). The median time to response was 3.4 months (range: 1.3 to 5.5 months), but the median DoR was not reached (non-responder (NR); 95% CI: 14.6, NR). Median PFS (Inv) was 1.5 months (95% CI: 0.9, 1.8) with a 12-month PFS of 14.3% (95% CI: 3.6, 32.1). Median OS was 4.8 months (95% CI: 1.3, 10.4) with a 12-month OS of 27.6% (95% CI: 10.2, 48.4).

Safety

Safety data from the D plus EP and EP arms of the CASPIAN trial was supplemented by an integrated safety set from a pan-tumour durvalumab monotherapy pool that included nine safety data studies.

Exposure

The CASPIAN trial data inform the safety of the D plus EP combination form 265 patients, with a median range of exposure duration of 28 weeks (range 0.3 to 94.3 weeks), and a median of 7 infusions (range 1 to 25) and with 20% of patients exposed to more than 12 treatment infusions. The durvalumab monotherapy pool included data from 3006 subjects who received at least one dose of durvalumab given at 10 mg/kg Q2W or 20 mg/kg Q4W IV for any line of therapy. These patients had a median exposure of 16 weeks (range 0 to 152). The median duration of EP exposure was 11.9 weeks, 12.1 weeks, and 12.1 weeks, for the etoposide, carboplatin and cisplatin components, respectively in the D plus EP group and 18.7 weeks, 19.0 weeks, and 14.0 weeks, for the etoposide, carboplatin and cisplatin components, respectively in the EP group.

The periodic benefit risk evaluation report (PBRER) dated 15 June 2020 states 9,641 patients have received durvalumab in AstraZeneca or Medimmune (sponsor or sponsor subsidiary) sponsored interventional studies in multiple tumours, stages of disease, and lines of therapy, including 4,296 patients who received durvalumab monotherapy, 2,910 who received durvalumab in combination with an investigational and/or approved product, and 2,435 in combination with tremelimumab. An expanded access program for durvalumab in combination with platinum and etoposide for the first-line treatment of ES-SCLC has enrolled 156 patients.

Overview of adverse events

Table 8: The CASPIAN trial; selected summary of safety parameters

	CASPIAN trial, (n = 531)		D pan-tumour (Monotherapy pool), (n = 3,006)
	D plus EP, (n = 265) **Median number of EP cycles = 4**	**EP, (n = 266)** **Median number of EP cycles = 6**	
Treatment-emergent adverse events (TEAEs)			
Any AE	260 (98.1)	258 (97.0)	2,867 (95.4)
Most common AEs > 15% in either arm of CASPIAN trial			
neutropenia	*41.9%*	*46.6%*	*0.8%*
anaemia	*38.5%*	*47%*	*13.2%*
nausea	*33.6%*	*33.5%*	*18.0%*
alopecia	*31.3%*	*34.2%*	*0.9%*
constipation	*16.6%*	*19.2%*	*16.8%*
decreased appetite	*18.1%*	*17.3%*	*20.4%*
thrombocytopenia	*15.5%*	*19.9%*	*1.5%*
fatigue	*18.1%*	*16.9%*	*26.6%*
vomiting	*14.7%*	*16.5%*	*11.9%*
asthenia	*15.1%*	*15.0%*	*11.6%*
leukopenia	*15.1%*	*12.0%*	*0.5%*
Any CTCAE;[7] Grade 3 or 4	163 (61.5%)	166 (62.4%)	1,290 (42.9)
Most common ≥ Grade 3 AEs (≥ 10% in any arm):			
neutropenia	*29.1%*	*39.1%*	*0.2%*
anaemia	*9.1%*	*18.1%*	*4.6%*
thrombocytopenia	*6.8%*	*11.7%*	0.4%
Study treatment discontinuation due to AE	25 (9.4%)	25 (9.4%)	282 (9.4)
Study treatment dose delay or interruption due to AE	124 (46.8%)	124 (46.6%)	871 (29.0)
Any ADR[a,b]	89.4%	90.2%	
Any CTCAE Grade 3 or 4 ADR	45.7%	51.9%	
Serious adverse events (SAE)			
Any SAE	82 (30.9%)	96 (36.1%)	1,068 (35.5%)
Most common SAEs (≥ 2%):			
febrile neutropenia	*4.5%*	*4.5%*	

	CASPIAN trial, (n = 531)		D pan-tumour (Monotherapy pool), (n = 3,006)
	D plus EP, (n = 265) **Median number of EP cycles = 4**	**EP, (n = 266)** **Median number of EP cycles = 6**	
Anaemia	*1.9%*	*4.5%*	
Pneumonia	*2.3%*	*3.4%*	
Thrombocytopenia	*0.4%*	*3.4%*	
Neutropenia	*0.8%*	*2.6%*	
Deaths			
Death in absence of progression	*12.7%*	*14.5%*	
Fatal AEs	*4.9%*	*5.6%*	*5.5%*
Fatal ADRs	*1.9%*	*0.8%*	

AE = adverse event, ADR = Adverse drug reaction, TEAE = treatment-emergent adverse event, TRAE = treatment-related adverse event

a Neutropenia, anaemia, thrombocytopenia, leukopenia, alopecia, nausea, vomiting, constipation, fatigue, decreased appetite all very common in D plus EP and EP groups; febrile neutropenia, pancytopenia, stomatitis, pneumonitis, hypothyroidism, abdominal pain, aspartate transaminase (AST) or alanine aminotransferase (ALT) increased, blood creatinine increased, dysuria, rash, pruritus, pyrexia, peripheral oedema, upper respiratory tract infection, pneumonia, dental and oral soft tissue infections, myalgia, infusion-related reaction common in both groups

b Cough very common in D plus EP group, common in EP group.

The evaluator did not describe a clinical pattern for the fatal adverse events (AE) and adverse drug reactions (ADR). Common serious adverse events (SAE and frequencies are listed in Table 8. Discontinuation due to AEs were not reported for more than 2% of any System Organ Class.

Adverse events of special interest and otherwise of note

Events reported for D plus EP, EP, and pooled monotherapy, respectively, occurred in 19.6%/2.6%/17.7%, with Grade 3 or 4 events in 4.5%/0.4%/3.9%, of which 2.3% in the D plus EP arm of the CASPIAN trial were fatal. Additional treatment required included corticosteroids for 9.4%/1.9/10.3, and high dose steroids 6.8/0.8/6.1. Endocrine therapies were required in 14.7/0.8/10.0%, and the majority of the endocrinopathies were thyroid disorders but mostly CTCAE;[7] Grade 1 or 2. Resolution of the events had occurred in 40-44% of the cases involving durvalumab at the time of reporting.

Specific events of note in the CASPIAN trial were:

- Any grade immune mediated AEs (imAEs) for D plus EP versus EP: pneumonitis (2.6% versus 0.8%), hepatic events (2.6% versus 0.0%), diarrhoea/colitis (1.5% versus 0.4%), hypothyroid (9.1% versus 0.8%), hyperthyroid (5.3% versus 0%) events, thyroiditis (1.5% versus 0.0%), type 1 diabetes mellitus (1.5% versus 0.0%), dermatitis (1.5% versus 0.8%)
- CTCAE;[7] Grade 3 or 4 imAEs for D plus EP versus EP: pneumonitis (0.8% versus 0.4%), hepatic events (1.9% versus 0.0%), diarrhoea/colitis (0.4% versus 0.0%), type 1 diabetes mellitus (1.5% versus 0.0%)

Infusion reactions (group term) were reported in less than 2% of patients in the D plus EP and EP alone groups; the majority were CTCAE;[7] Grade 1 or 2, with 1 patient in the D plus EP group experiencing a CTCAE;[7] Grade 3 event. None of the adverse events of special interest (AESI) of infusion related reactions led to discontinuation of study treatment and all events were resolved by the date of data cut-off.

Pemphigoid occurred in 1.7% patients and was Grade 3 in 0.4% patients. This is a newly described imAE for durvalumab. There were no events of myasthenia gravis or Guillain-Barre syndrome, 0.8% in the D plus EP group had arthritis.

The median time to onset for immune mediated events reported for D plus EP varied with the affected organ and ranged from 28 days for immune mediated diarrhoea /colitis to 191 days for pneumonitis.

Clinical chemistry: in clinical chemistry parameters, shifts to CTCAE;[7] Grade 3 or 4 occurred in more patients in the D plus EP group than the EP group for alanine aminotransferase (ALT; 4.9% and 2.7%), aspartate aminotransferase (AST; 4.6% and 1.2%), potassium low (6.1% and 3.8%), magnesium low (11.1% and 6.3%), creatinine (3.4% and 1.1%), and lipase (8.1% and 3.1%).

Renal: as reported in the study, patients developed severe renal impairment during the study. While on study treatment, 3.2%, 0.8% and 0.8% of patients in the D plus EP group had shifts from normal at Baseline to moderate renal impairment, severe renal impairment and kidney failure, respectively. Corresponding proportions in the EP alone group were 2.8%, 0% and 0% of patients, respectively. Transient changes to renal function were also noted during the study.

Hepatotoxicity: events of liver function test elevations were tabulated for D plus EP and EP. Total case numbers were greater in the D plus EP versus EP only arms for AST elevation, ALT elevation, elevations of both and elevation of bilirubin. Potential Hy's Law[12] cases were reported for 2.6%/0.4% but these were not confirmed. A similar proportion of potential Hy's Law cases appeared in the pooled monotherapy data (1.9%).

Immunogenicity: of the 201 patients with ADA evaluable results, 11 were ADA positive, all were positive at Baseline only, and none had neutralising antibodies. Among those patients there were no infusion reactions and no clear signal indicating a relationship to ADA. The incidence of hypersensitivity/anaphylactic reactions was low, reported in 3 patients in the D plus EP group and 2 patients in the EP alone group.

Risk management plan

The risk management plan (RMP) evaluator has reviewed the Imfinzi core RMP(version 7.0 dated 2 April 2020; data lock point (DLP) 26 April 2019) with Australian specific annex (ASA) version 8.0 (Succession 2) dated 18 May 2020. It is noted that an EU RMP is available for Imfinzi. The sponsor noted that it is a requirement to provide the EU RMP to the TGA when an EU RMP is available.

The evaluator's main concern was the sponsor's proposal to discontinue the provision of a Patient Alert Card for health professionals to provide to patients. The sponsor has suggested that the information in the patient alert card is available in the Consumer Medicines Information (CMI), that the safety of durvalumab is now well established, and a

[12] **Hy's Law**: Evidence of hepatocellular injury with a rise in alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) > 3 x the upper limit of normal (ULN) and total bilirubin > 2 x ULN, and no other reason to explain rise in aminotransferases and total bilirubin. Hy's law is a rule of thumb that a patient is at high risk of a fatal drug-induced liver injury if given a medication that causes hepatocellular injury with jaundice.

patient alert card is not warranted. Aside from this issue, the core RMP and ASA were acceptable to the RMP evaluator.

The summary of safety concerns and their associated risk monitoring and mitigation strategies are summarised in Table 9.[13]

Table 9: Summary of safety concerns and their associated risk monitoring and mitigation strategies

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	Immune-mediated pneumonitis	ü¶	–	ü	ü†
	Immune-mediated hepatitis	ü¶	–	ü	ü†
	Immune-mediated colitis or diarrhoea	ü¶	–	ü	ü†
	Immune-mediated hypothyroidism	ü¶	–	ü	ü†
	Immune-mediated hyperthyroidism	ü¶	–	ü	ü†
	Immune-mediated thyroiditis	ü¶	–	ü	ü†
	Immune-mediated adrenal insufficiency	ü¶	–	ü	ü†
	Immune-mediated hypophysitis or hypopituitarism	ü¶	–	ü	ü†
	Immune-mediated type 1 diabetes mellitus	ü¶	–	ü	ü†
	Immune-mediated nephritis	ü¶	–	ü	ü†
	Immune-mediated rash or dermatitis including pemphigoid	ü¶	–	ü	ü†

[13] *Routine risk minimisation* activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.
Routine pharmacovigilance practices involve the following activities:

- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labelling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
	Immune-mediated myocarditis	ü¶	–	ü	ü†
	Immune-mediated myositis/polymyositis	ü¶	–	ü	ü†
	Immune-mediated myasthenia gravis	ü¶	–	ü	–
	Infusion-related reaction	ü		ü	ü†
Important potential risks	Immune-mediated pancreatitis	ü¶	–	ü	–
	Other rare potential immune-mediated adverse reactions (including immune-related neuropathies) (ASA only)) (Guillain-Barre) and (ocular inflammatory toxicity (ASA only))	ü	–	ü	–
	Delayed onset of durvalumab effect and comparative early survival detriment, applicable to the second line urothelial carcinoma post platinum indication only (ASA only)	ü‖	–	ü	–

‖ Phase 3 study (D419BC00001, DANUBE)

Adverse event follow-up form for adverse reactions immune-mediated adverse reaction (imAR)

† HCP educational materials

Risk-benefit analysis

Delegate's considerations

In this submission the sponsor seeks an extension of the indications of durvalumab to include use in combination with etoposide and either carboplatin or cisplatin in patients with ES-SCLC.

The submission is supported by the CASPIAN trial, an open-label, multicentre, multinational, parallel group study of three regimens, two of which are relevant to the submission (Arms 2 and 3 of the CASPIAN trial. The study compared durvalumab and etoposide plus a platinum therapy (mostly carboplatin) with etoposide and platinum as first-line treatment in ES-SCLC. Patients needed to be fit enough to receive the etoposide and platinum chemotherapy backbone regimen. ECOG performance status was 0 or 1, but patients with asymptomatic or brain metastases were eligible. The participants, with

mean age 63, mostly male, mostly white and mostly former or current smokers, are reasonably representative of the current Australian population of ES-SCLC patients.

The chemotherapy backbone treatments in the two arms were not identical: the durvalumab arm received 4 cycles and the comparator arm 6 cycles, based on tolerability, and a little over half the EP group received all 6 cycles. This aspect of design adds complexity to the clinical interpretation of the results, and the generalisability to the Australian context. Although guidelines generally recommend 4 to 6 cycles of EP therapy, there is some variability.

Because of the different EP regimens in Arms 2 and 3 of the trial the comparison does not lend itself to an assessment of the contribution of durvalumab to the efficacy and/or toxicity over and above EP in the D plus EP regimen, and does add some uncertainty about the relative contributions of each of the components to the outcome. One could consider D plus 4 cycles of EP versus 6 cycles of EP as in the same way one might compare Drug A with Drug B in another study, rather than considering durvalumab as an add-on therapy to EP. This is acceptable but whether patients in the D plus EP or EP arms would have benefited or been disadvantaged by their allocated number of cycles of EP is unknown. The approach of using 4 cycles of EP with an immunomodulator for ES-SCLC was accepted for atezolizumab to support its indication in first-line ES-SCLC. The alignment of endpoints with the IMpower133 study in atezolizumab;[14] at protocol amendment 3 is also noted.

The open-label nature of the study adds complexity in the interpretation of the outcomes. The potential for bias adds some uncertainty to the investigator reported outcomes because of the open-label nature of the study. The key secondary endpoint of PFS was investigator assessed, although sensitivity analyses that adjusted for some forms of bias were consistent with the main analysis. D plus EP and EP alone showed similar PFS at the time-point of the initial interim analysis. While the proportional hazard of a PFS event is less in the D plus EP group (HR 0.78 (95% CI 0.65, 0.94)), the median PFS and PFS at 6 months are similar between the groups. At the 12 month time point the small number of patients remaining in the EP group limit the utility of the comparison. The ORR is also an investigator assessed outcome, and favours D plus EP in both complete and partial response, and is consistent with the direction of the OS data. The median duration of response is similar in both groups but the proportion of patients remaining in the response (low numbers of patients contributing notwithstanding) is greater at 12 and 15 months.

The primary endpoint of overall survival is robust and in terms of percentage of patients with events, and proportional hazards for the event, OS was favourable for the D plus EP combination. The proportion of survivors was numerically greater in the D plus EP group at 12 months and 18 months. The median OS gain from D plus EP over EP was 2.7 months or 2.4 months, depending on the data cut date and this would appear modest. Whether this benefit is clinically meaningful is uncertain and the Advisory Committee on Medicines (ACM) is requested to comment. It is recognised that patients with ES-SCLC present with advanced disease and the outlook is generally poor.

The safety of the D plus EP was compared to EP and to a pooled safety set comprising data from the use of durvalumab as monotherapy. The limitations of the comparative safety information include the differences in exposure to EP in both proportion and duration of exposure between the two groups. The difference in exposure to chemotherapy is a likely contributor to the greater frequency of haematological adverse events of greater severity in the EP group.

[14] Horn, L et al. First-Line Atezolizumab plus Chemotherapy in Extensive-Stage Small-Cell Lung Cancer, N Eng J Med, 2018; 379; 2220-2229.

The safety profile of durvalumab was consistent with its established profile and with other members of the PD1/PD-L1 class, and in many instances the adverse effects are manageable. As expected immune mediated adverse events were more common in the D plus EP arm, driven by thyroid endocrinopathies, and many events were Grade 1 to 2. Nevertheless, there was a greater use of corticosteroids (9.4% versus 1.9%) and endocrine therapies (14.7% versus 0.8%) in the D plus EP versus EP arms. Immune mediated events are clinically relevant and an important factor in the benefit risk considerations of durvalumab for this indication for the population and for the clinician deciding therapy to recommend to the individual patient.

Immunogenicity was low, no neutralising antibodies were detected and there was no apparent pattern of adverse events in the small proportion of patients with baseline durvalumab antidrug-antibodies. This is considered a benefit for durvalumab.

Regarding the dosing, an acceptable justification, support from the non-clinical evaluation, the pharmacometrics and direct evidence from the CASPIAN trial support the fixed-dosing regimen of 1500 mg Q3W for this indication in patients with a body weight of > 30 kg. The quality evaluator considered the potential for increased exposure to impurities and proposal acceptable from a quality perspective.

An outstanding matter for the RMP evaluator is the matter of the Patient Alert Card that includes a listed safety profile of durvalumab. The sponsor proposes routine risk minimisation activities for durvalumab without the provision of a Patient Alert Card. As the sponsor makes the Patient Alert Card available to health professionals who may or may not choose to provide the card to the patient its effectiveness as a risk minimisation measure is difficult to ascertain. Similar information is available in the CMI, and is also likely to be available through patient information provided through treatment centres. These patients are seen as a minimum monthly for their treatment after the induction phase. As there are a variety of approaches to a Patient Alert Card between and within product classes, the function and portability of the cards, uncertainty about access and therefore the effectiveness, the view of the ACM is sought.

The main concerns regarding the CASPIAN trial are the open-label study design and the uncertainty about progression-free survival. The reduced risk in the D plus EP group from the proportional hazards model is noted but in terms of time gained for the patients for this measure of efficacy the evidence is less clear in early to medium term treatment. Survival but with disease progression in patients who would otherwise die early of rapidly progressive disease may be an explanation, as many the delayed onset of effect typically seen with programmed cell death protein 1 (PD-1)/PD-L1 inhibitors. The ORR and its components albeit investigator assessed, are in the direction of the median overall survival (mOS) results. The mOS results themselves are modest but for a disease generally diagnosed late, potentially clinically meaningful. The ACM is requested to comment. A broader range of toxicities can result from the D plus EP combination than EP alone. Many were less severe than seen with a longer course of EP, but the greater use of corticosteroids and endocrine therapies indicates the requirement for active management of these conditions. Although rare, not all toxicities from the D plus EP combination or EP alone are reversible or self-limiting. As noted above the low level of immunogenicity for durvalumab is considered beneficial. At this time, but subject to advice and comment from the ACM, the considerations weigh in favour of the D plus EP combination for the requested indication and dosing regimen.

Proposed conditions of registration

If the submission is approved, the Delegate proposed to impose the following conditions of registration, provided below. The sponsor is invited to provide comment:

- The Imfinzi core RMP version 7.0 (date 2 April 2020; DLP 26 April 2019) with ASA version 8.0 (Succession 2) (date 18 May 2020), included with submission

PM-2019-04661-1-4, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

- Provide the TGA with the final clinical study report for the CASPIAN trial.

Questions for the sponsor

The sponsor provided the following response to questions from the Delegate.

1. ***Please provide the rationale for including dosing for patients of less than 30 kg weight in the Imfinzi PI for ES-SCLC when a) the safety and efficacy in paediatric patients has not been established and b) there are no data from patients of ≤ 30 kg weight in the dossier for this submission.***

The sponsor notes that the ES-SCLC indication proposed is not for paediatric patients. Additionally, the sponsor acknowledges that there were no patients of ≤ 30 kg weight enrolled in the CASPIAN trial. However, the sponsor wishes to provide providers with information regarding weight-based dosing for patients of ≤ 30 kg weight, as the 1500 mg fixed dose would not be appropriate for these patients. The rationale for weight-based dosing in patients ≤ 30 kg weight is provided below.

The fixed dose of 1500 mg was not recommended for patients with body weight of 30 kg or less to avoid over-exposure in patients with extremely low body weight and comply with the USP recommended endotoxin limit of 5.0 endotoxin unit/kg body weight/hour. Based on the US Food and Drug Administration agreed durvalumab endotoxin specification of less than or equal to 0.090 endotoxin unit/mg protein, a body weight cut-off of 30 kg was chosen to ensure that the USP criteria was met in the worst-case scenario (1500 mg durvalumab dose/30 kg patient × 0.09 endotoxin unit/mg × 1hr = 4.5 endotoxin unit/kg per hour). This lower body weight cut-off of 30 kg was implemented for all the durvalumab studies utilising 1500 mg fixed dose including CASPIAN trial.

For patients with body weight of 30 kg or below, the recommended dosage is a body weight based dosing regimen of 20 mg/kg durvalumab Q3W IV for 4 doses in combination with EP, followed by 20 mg/kg Q4W IV durvalumab monotherapy thereafter. The dose of 20 mg/kg is recommended as it is equivalent to 1500 mg in an average 75 kg patient and predicted to have similar exposure as 1500 mg durvalumab. This regimen of 20 mg/kg Q4W durvalumab as a monotherapy had been used across multiple studies including a Phase I trial across different tumour types (Study 1108 in sponsor submitted dossier) and a Phase III trial in NSCLC (MYSTIC trial) and showed complete target suppression (measured by soluble PD-L1) and manageable safety profiles.

Given that all patients in the CASPIAN trial had a body weight of over 30 kg, no clinical data are available regarding safety and efficacy in patients weighing 30 kg or below. Hence, PK simulations were used to compare the predicted exposure in patients weighing 30 kg or below (dosage: 20 mg/kg) versus those over 30 kg (dosage: 1500 mg) to evaluate the impact of low body weight on efficacy and safety outcomes.

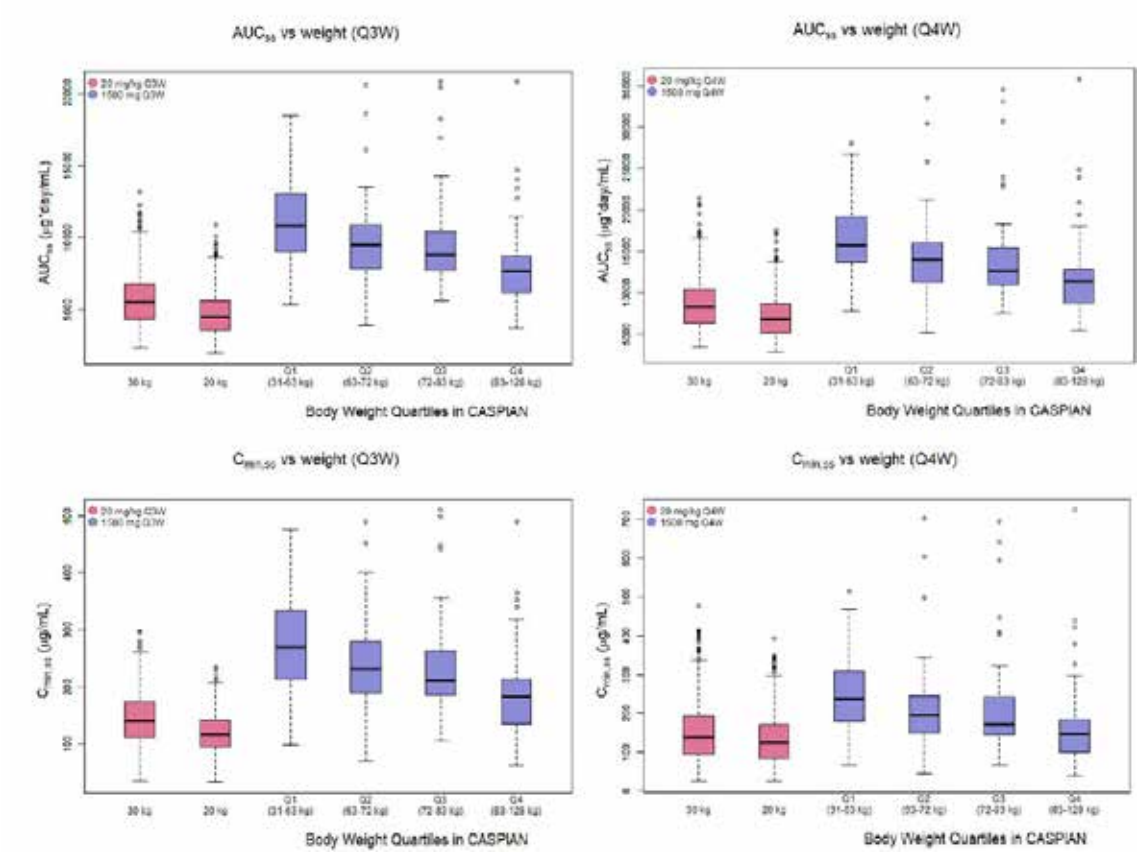
Using the durvalumab population PK (PopPK) model that incorporated the data from the CASPIAN trial, simulations were performed to predict durvalumab exposure (AUC_{ss}, $C_{min,ss}$) for 20 mg/kg Q3W or Q4W for body weight of 30 or 20 kg, which was compared to the simulated exposure (based on post hoc PK parameters) across the body weight quartiles in CASPIAN trial at the fixed dose of 1500 mg Q3W or Q4W, respectively (see Figure 2, below). The results showed that the predicted AUC_{ss} and $C_{min,ss}$ for 30 kg or 20 kg body weight are generally lower compared with those in CASPIAN trial across the body weight quartiles. Therefore, there is no expected safety concern for dosing patients with body weight of 30 kg or below at 20 mg/kg.

In CASPIAN trial, no clinically meaningful relationship between exposure and efficacy (OS and PFS) was observed, and the efficacy results were similar across body weight quartiles.

The median predicted exposure for patients weighing 30 kg and 20 kg following 20 mg/kg Q3W or Q4W dosing were only modestly lower (up to 28% and 41% for AUC_{ss}, and 24% and 36% for $C_{min,ss}$ for 30 kg and 20 kg, respectively) compared to those from CASPIAN trial at the highest body weight quartile, with partially overlapping individual exposure ranges (see Figure 2, below).

Furthermore, following 20 mg/kg Q3W or Q4W dosing, 96 to 98% and 97 to 99% of patients weighing 30 and 20 kg, respectively, would maintain $C_{min,ss}$ above 50 µg/mL, the target durvalumab trough concentration for complete target suppression based on nonclinical and clinical data. Given these findings, the modest decrease of exposure in 30 kg and 20 kg patients is not expected to result in any clinically meaningful impact on efficacy outcomes.

Figure 3: Durvalumab exposure (AUC_{ss}, $C_{min,ss}$) simulations for 20 mg/kg Q3W or 20 mg/kg Q4W dosage and administration



AUC_{ss} area under the concentration-time curve over one dosing interval at steady state; $C_{min,ss}$ trough concentration at steady state. Steady state is defined as week 12 (end of the 4th dosing cycle) for Q3W regimens and week 52 for Q4W regimens. 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 circles represent outliers outside of the 1.5 × (the upper or lower interquartile range).

Taken together, based on the predicted exposure, clinical results and exposure-response relationships in CASPIAN trial, the dose of 20 mg/kg durvalumab IV Q3W for 4 doses in combination with EP followed by 20 mg/kg IV Q4W durvalumab monotherapy is considered an appropriate dose regimen as first line treatment for patients with ES SCLC with body weight less or equal to 30 kg.

2. Please point to the sections/analyses in the dossier that support the new statement in Section 4.4 of the Imfinzi PI that relates to the elderly.

The statement is supported by the summary of clinical safety and the summary of clinical efficacy submitted by sponsor.

Advisory committee considerations[15]

The Advisory Committee on Medicines (ACM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following.

Specific advice to the delegate

The ACM advised the following in response to the Delegate's specific request for advice:

1. ***The backbone chemotherapy differed between the two arms of the main study supporting the requested indication, the CASPIAN trial. Four cycles of etoposide and platinum therapy (carboplatin or cisplatin, EP) were used in the durvalumab plus etoposide platinum (D plus EP) arm of the CASPIAN trial whereas the EP arm could have up to 6 cycles. Please comment on the generalisability of the chemotherapy component of treatment in this study to the Australian context.***

The ACM noted that 4 cycles of carboplatin/etoposide is standard of care in Australia as per the eVIQ and CA Clinical Guidelines.[4] The committee stated that dose variation seen in study are consistent with different studies and represents standards in multiple countries.

The OS of standard arm is consistent with other published literature, especially from the IMpower 133 trial that was conducted using another PD-L1 inhibitor, atezolizumab.

2. ***Please comment on the clinical meaningfulness of the data that are presented in support of the requested indication.***

The ACM agreed that the survival improved with no major toxicity issues and that there was prolonged duration of disease control however noted that the durability of efficacy outcomes are yet to be fully established.

The ACM advised that the evidence supporting durvalumab is sufficient, and noted that this is consistent with the level of evidence for another product Tecentriq (atezolizumab), which has previously been approved for the same indication.

3. ***The RMP evaluator favoured the availability of a Patient Alert Card. The sponsor has provided a rationale for discontinuing this post-marketing measure. Noting the setting in which durvalumab is prescribed can the committee comment on the utility of the sponsor's patient alert card? Is the sponsor's stated justification for omitting a patient alert card in this setting acceptable?***

The ACM noted that the sponsor has suggested that the information in the Patient Alert Card is available in the CMI, that the safety of durvalumab is now well established, and a Patient Alert Card is not warranted. However, the committee indicated the need for the Patient Alert Card as it is clear and contains individual treatment specifics, directs health professionals to clinical decision tools and does not depend on access to other record systems. The committee further highlighted that the differences in treatment approach for

[15] The ACM provides independent medical and scientific advice to the Minister for Health and the Therapeutic Goods Administration (TGA) on issues relating to the safety, quality and efficacy of medicines supplied in Australia including issues relating to pre-market and post-market functions for medicines.
The Committee is established under Regulation 35 of the Therapeutic Goods Regulations 1990. Members are appointed by the Minister. The ACM was established in January 2017 replacing Advisory Committee on Prescription Medicines (ACPM) which was formed in January 2010. ACM encompass pre and post-market advice for medicines, following the consolidation of the previous functions of the Advisory Committee on Prescription Medicines (ACPM), the Advisory Committee on the Safety of Medicines (ACSOM) and the Advisory Committee on Non-Prescription Medicines (ACNM). Membership comprises of professionals with specific scientific, medical or clinical expertise, as well as appropriate consumer health issues relating to medicines.

adverse effects of immunotherapy versus chemotherapy is not yet optimally socialised in the clinical community, and the need remains for treatment advice that is presented on the alert card.

The ACM noted that the patient may not receive a CMI, the CMI is not patient specific and does not assist with clinical decision making. It was further noted that the patient is less likely to carry a CMI than alert card.

The ACM went on to discuss the possibility of supporting the expansion of this tool.

Conclusion

The ACM considered this product to have an overall positive benefit-risk profile for the indication:

> *Durvalumab in combination with etoposide and either carboplatin or cisplatin (D + EP) is indicated for the first line treatment of patients with Extensive-Stage Small Cell Lung Cancer (ES-SCLC)*

Outcome

Based on a review of quality, safety and efficacy, the TGA approved the registration of Imfinzi (durvalumab) 50 mg/mL, concentrated solution for infusion, vial, indicated for the following extension of indications:

> ***Small cell lung cancer (SCLC)***
>
> *Imfinzi (durvalumab) in combination with etoposide and either carboplatin or cisplatin is indicated for the first-line treatment of patients with extensive-stage small cell lung cancer (ESSCLC)*

As such, the full indications at this time were:

> ***Urothelial carcinoma***
>
> *Imfinzi (durvalumab) is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma who:*
>
> - *have disease progression during or following platinum-containing chemotherapy.*
> - *have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.*
>
> *This indication is approved based on objective response rate and duration of response in a single arm study. An improvement in survival or disease-related symptoms has not been established.*
>
> ***Locally advanced non-small cell lung cancer (NSCLC)***
>
> *Imfinzi (durvalumab) is indicated for the treatment of patients with locally advanced, unresectable NSCLC whose disease has not progressed following platinum-based chemoradiation therapy.*
>
> ***Small cell lung cancer (SCLC)***
>
> *Imfinzi (durvalumab) in combination with etoposide and either carboplatin or cisplatin is indicated for the first-line treatment of patients with extensive-stage small cell lung cancer (ESSCLC).*

Specific conditions of registration applying to these goods

- The Imfinzi core RMP version 7.0 (date 2 April 2020; DLP 26 April 2019) with ASA version 8.0 (Succession 2) (date 18 May 2020), included with submission PM-2019-04661-1-4, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.
- Sponsor to provide the TGA with the final clinical study report for the CASPIAN trial.

Attachment 1. Product Information

The PI for Imfinzi approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at < >.

Therapeutic Goods Administration

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