Proposed packaging material		
Code	Imfinzi 120 mg & 500 mg – PI-01.02	
Submission	☐NDA ☐Renewal ☒Variation change detail no.: MU-121496-146080 and MU-124598-150201	
Code of previous version	N/A	
Changes	Posology Update 1500 mg Q4W for NSCLC indication, Table 2. Management of Adverse Effect (dose modification, Addition Myasthenia Gravis and Update Diabetes Melitus type 1), Pancreatitits	
Reference	☐CDS version: ☐CPIL version:	☒SmPC country/version/date: EU Q4W SmPC v8.0 ☒GRL approval: 30 January 2022
Name & Date	FTA (13 October 2022)	

IMFINZI™

DURVALUMAB

Concentrated Solution for Infusion

1 NAME OF THE MEDICINAL PRODUCT

IMFINZI 120 mg Infusion

IMFINZI 500 mg Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial of IMFINZI concentrated solution for infusion contains either 120 mg or 500 mg of durvalumab.

For the full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM

Sterile, preservative free, clear to opalescent and free from visible particles, colourless to slightly yellow, concentrated solution for infusion.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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 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).

4.2 Dose and method of administration

IMFINZI is for single use in one patient only. Discard any residue.

Posology

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
Locally Advanced NSCLC	10 mg/kg every 2 weeks or 1500 mg every 4 weeks[a]	Until disease progression, unacceptable toxicity, or a maximum of 12 months[b]
ES-SCLC	1500 mg[c] in combination with chemotherapy[d,e] every 3 weeks (21 days) for 4 cycles, followed by 1500 mg every 4 weeks as monotherapy	Until disease progression or unacceptable toxicity

[a] Patients with a body weight of 30 kg or less must receive weight-based dosing, equivalent to IMFINZI 10 mg/kg every 2 weeks or 20 mg/kg every 4 weeks as monotherapy until weight increases to greater than 30 kg.

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

[c] 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.

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

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

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

Dose escalation or reduction is not recommended. Dose withholding, or discontinuation may be required based on individual safety and tolerability.

Guidelines for management of adverse reactions are described in Table 2.

Refer to Section 4.4 Special warnings and precautions for use for further monitoring and evaluation information.

Table 2. Recommended treatment modifications and management for adverse reactions

Adverse reactions	**Severity**[a]	**IMFINZI treatment modification**	**Additional management advice**
Pneumonitis	Grade 2	Withhold dose[b]	Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
	Grade 3 or 4	Permanently discontinue	1 to 2 mg/kg/day prednisone or equivalent followed by a taper
Hepatitis	Grade 2 with ALT or AST >3-5xULN and/or total bilirubin >1.5-3xULN	Withhold dose	Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
	Grade 3 with AST or ALT ≤8xULN or total bilirubin>3-≤5xULN		
	Grade 3 with AST or ALT >8xULN or total bilirubin >5xULN	Permanently discontinue	
	Concurrent ALT or AST >3xULN and total bilirubin >2xULN with no other cause		
Colitis or diarrhoea	Grade 2 or 3	Withhold dose	Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
	Grade 4	Permanently discontinue	
Endocrinopathies: Hyperthyroidism	Grade 2-4	Withhold dose until clinically stable	Symptomatic management
Endocrinopathies: Hypothyroidism	Grade 2-4	No changes	Initiate thyroid hormone replacement as clinically indicated

Adverse reactions	**Severity**[a]	**IMFINZI treatment modification**	**Additional management advice**
Endocrinopathies: Adrenal insufficiency, Hypophysitis/hypopituitarism	Grade 2-4	Withhold dose until clinically stable	Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper and hormone replacement as clinically indicated
Immune-mediated Type 1 diabetes mellitus	Grade 2-4	No changes	Initiate treatment with insulin as clinically indicated
Nephritis	Grade 2 with serum creatinine >1.5-3x (ULN or baseline)	Withhold dose	Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
	Grade 3 with serum creatinine >3x baseline or >3-6xULN; Grade 4 with serum creatinine >6xULN	Permanently discontinue	
Rash or dermatitis (including pemphigoid)	Grade 2 for >1 week	Withhold dose	Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
	Grade 3		
	Grade 4	Permanently discontinue	
Immune-mediated myocarditis	Grade 2-4	Permanently discontinue	Initiate 2 to 4 mg/kg/day prednisone or equivalent followed by a taper[b]
Myositis/polymyositis	Grade 2 or 3	Withhold dose[c]	Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
	Grade 4	Permanently discontinue	
Infusion-related reactions	Grade 1 or 2	Interrupt or slow the rate of infusion	May consider pre-medications for prophylaxis of subsequent infusion reactions
	Grade 3 or 4	Permanently discontinue	
Infection	Grade 3 or 4	Withhold dose until clinically stable	
Myasthenia gravis	Grade 2	Withhold dose	

Adverse reactions	Severity[a]	IMFINZI treatment modification	Additional management advice
	Any Grade with signs of respiratory or autonomic insufficiency	Permanently discontinue	Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
	Grade 3 or 4		
Other immune-mediated adverse reactions	Grade 3	Withhold dose	Initiate dose of 1 mg/kg/day to 2 mg/kg/day prednisone or equivalent followed by taper
	Grade 4	Permanently discontinue	

a Common Terminology Criteria for Adverse Events, version 4.03. ALT: alanine aminotransferase; AST: aspartate aminotransferase; ULN: upper limit of normal.

b If no improvement within 2 to 3 days despite corticosteroids, promptly start additional immunosuppressive therapy. Upon resolution (Grade 0), corticosteroid taper should be initiated and continued over at least 1 month

c Permanently discontinue IMFINZI if adverse reaction does not resolve to ≤Grade 1 within 30 days or if there are signs of respiratory insufficiency.

For suspected immune-mediated adverse reactions, adequate evaluation should be performed to confirm aetiology or exclude alternate aetiologies. Based on the severity of the adverse reaction, IMFINZI should be withheld and corticosteroids administered. Consider increasing dose of corticosteroids and/or using additional systemic immunosuppressants if there is worsening or no improvement. Upon improvement to ≤ Grade 1, corticosteroid taper should be initiated and continued over at least 1 month. After withhold, IMFINZI can be resumed within 12 weeks if the adverse reactions improved to ≤ Grade 1 and the corticosteroid dose has been reduced to ≤ 10 mg prednisone or equivalent per day. IMFINZI should be permanently discontinued for recurrent Grade 3 (severe) immune-mediated adverse reactions and for any Grade 4 (life-threatening) immune-mediated adverse reactions, except for endocrinopathies that are controlled with replacement hormones.

For non-immune-mediated adverse reactions, withold IMFINZI for Grade 2 and 3 adverse reactions until ≤ Grade 1 or baseline. IMFINZI should be discontinued for Grade 4 adverse reactions (with the exception of Grade 4 laboratory abnormalities, about which the decision to discontinue should be based on accompanying clinical signs/symptoms and clinical judgment).

Special patient populations

Renal impairment

No dose adjustment is recommended for patients with mild or moderate renal impairment (see Section 5.2 Pharmacokinetic properties). Durvalumab has not been studied in subjects with severe renal impairment.

Hepatic impairment

No dose adjustment is recommended for patients with hepatic impairment. Data from patients with moderate and severe hepatic impairment are limited, however, due to minor involvement of hepatic

processes in the clearance of durvalumab, no difference in exposure is expected for these patients (see Section 5.2 Pharmacokinetic properties).

Use in paediatric patients

The safety and efficacy of durvalumab have not been established in patients younger than 18 years of age.

Use in the elderly

No dose adjustment is required for elderly patients (≥65 years of age) (see Section 5.1 Pharmacodynamic properties - Clinical trials and Section 5.2 Pharmacokinetic properties).

Method of administration

Preparation of solution

IMFINZI is supplied as single-dose vials and does not contain any preservatives. Aseptic technique must be observed.

- Visually inspect drug product for particulate matter and discolouration. IMFINZI is a clear to opalescent, colourless to slightly yellow solution. Discard the vial if the solution is cloudy, discoloured or visible particles are observed. Do not shake the vial.
- Withdraw the required volume from the vial(s) of IMFINZI and transfer into an intravenous (IV) bag containing 0.9% Sodium Chloride Injection, or 5% Dextrose Injection. Mix diluted solution by gentle inversion. The final concentration of the diluted solution should be between 1 mg/mL and 15 mg/mL. Do not freeze or shake the solution.
- Care must be taken to ensure the sterility of prepared solutions.
- Do not re-enter the vial after withdrawal of drug; only withdraw one dose per vial.
- Discard any unused portion left in the vial.
- No incompatibilities between IMFINZI and 9 g/L (0.9%) sodium chloride or 50 g/L (5%) dextrose in polyvinylchloride or polyolefin IV bags have been observed.

After preparation of infusion solution

IMFINZI does not contain a preservative.

Chemical and physical in-use stability has been demonstrated for up to 30 days at 2ºC to 8ºC and for up to 24 hours at room temperature (up to 25ºC) from the time of preparation.

From a microbiological point of view, the prepared solution for infusion should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2ºC to 8ºC or 12 hours at room temperature (up to 25ºC), unless dilution has taken place in controlled and validated aseptic conditions

Administration

Administer infusion solution intravenously over 60 minutes through an intravenous line containing a sterile, low-protein binding 0.2 or 0.22 micron in-line filter.

Do not co-administer other drugs through the same infusion line.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the tradename and the batch number of the administered product should be clearly recorded

Immune-mediated pneumonitis

Immune-mediated pneumonitis or interstitial lung disease, defined as requiring use of systemic corticosteroids and with no clear alternate etiology, occurred in patients receiving IMFINZI. (see section 4.8)

Pneumonitis and radiation pneumonitis

Radiated pneumonitis is frequently observed in patients receiving radiation therapy to the lung and the clinical presentation of pneumonitis and radiation pneumonitis is very similar. In the PACIFIC Study, in patients who had completed treatment with at least 2 cycles of concurrent chemoradiation within 1 to 42 days prior to initiation of the trial, pneumonitis or radiation pneumonitis occurred in 161 (33.9%) patients in the IMFINZI-treated group and 58 (24.8%) in the placebo group, including Grade 3 (3.4% vs 3.0%) and Grade 5 (1.1% vs 1.7%). See also Section 4.8 Adverse effects.

Patients should be monitored for signs and symptoms of pneumonitis. Suspected pneumonitis should be confirmed with radiographic imaging and other infectious and disease-related aetiologies excluded, and managed as recommended in Section 4.2

Immune-mediated hepatitis

Immune-mediated hepatitis, defined as requiring use of systemic corticosteroids and with no clear alternate etiology, occurred in patients receiving IMFINZI (see section 4.8). Patients should be monitored for abnormal liver tests prior to and periodically during treatment with IMFINZI, and as indicated based on clinical evaluation. Immune-mediated hepatitis should be managed as recommended in section 4.2.

Immune-mediated colitis

Immune-mediated colitis or diarrhoea, defined as requiring use of systemic corticosteroids and with no clear alternate etiology, occurred in patients receiving IMFINZI (see section 4.8). Patients should be monitored for signs and symptoms of colitis or diarrhoea and managed as recommended in Section 4.2

Immune-mediated endocrinopathies

Immune-mediated hypothyroidism/hyperthyroidism/thyroiditis
Immune-mediated hypothyroidism, *hyperthyroidism, or thyroiditis* occurred in patients receiving IMFINZI, and hypothyroidism may follow hyperthyroidism (see Section 4.8). Patients should be monitored for abnormal thyroid function tests prior to and periodically during treatment as indicated

based on clinical evaluation. Immune-mediated hypothyroidism, hyperthyroidism, and thyroiditis should be managed as recommended in section 4.2.

Immune-mediated adrenal insufficiency
Immune-mediated adrenal insufficiency occurred in patients receiving IMFINZI (see Section 4.8). Patients should be monitored for clinical signs and symptoms of adrenal insufficiency. For symptomatic adrenal insufficiency, patients should be managed as recommended in Section 4.2.

Immune-mediated type 1 diabetes mellitus
Immune-mediated type 1 diabetes mellitus, which can first present as diabetic ketoacidosis that can be fatal if not detected early, occurred in patients receiving IMFINZI (see section 4.8). Patients should be monitored for clinical signs and symptoms of type 1 diabetes mellitus. For symptomatic type 1 diabetes mellitus, patients should be managed as recommended in Section 4.2.

Immune-mediated hypophysitis/hypopituitarism
Immune-mediated hypophysitis/hypopituitarism occurred in patients receiving IMFINZI (see Section 4.8). Patients should be monitored for clinical signs and symptoms of hypophysitis. For symptomatic hypophysitis or hypopituitarism, patients should be managed as recommended in Section 4.2.

Immune-mediated nephritis
Immune-mediated nephritis, defined as requiring use of systemic corticosteroids and with no clear alternate etiology, occurred in patients receiving IMFINZI (see Section 4.8 Adverse effects). Patients should be monitored for abnormal renal function tests prior to and periodically during treatment with durvalumab and managed as recommended in Section 4.2

Immune-mediated rash
Immune-mediated rash or dermatitis (including pemphigoid), defined as requiring use of systemic corticosteroids and with no clear alternate etiology, occurred in patients receiving IMFINZI see Section 4.8 Adverse effects. Events of Stevens-Johnson Syndrome (SJS) or toxic epidermal necrolysis have been reported in patients treated with PD-1 inhibitors. Patients should be monitored for signs and symptoms of rash or dermatitis and managed as recommended in see Section 4.2.

Immune-mediated myocarditis

Immune-mediated myocarditis, which can be fatal, occurred in patients receiving IMFINZI (see section 4.8). Patients should be monitored for signs and symptoms of immune-mediated myocarditis and managed as recommended in section 4.2.

Other immune mediated adverse reactions
Given the mechanism of action of IMFINZI, other potential immune-mediated adverse reactions may occur. The following immune-related adverse reactions have been observed in patients treated with IMFINZI monotherapy: myasthenia gravis, myocarditis, myositis, polymyositis, meningitis, , Guillain-Barré syndrome, immune thrombocytopenia and pancreasitis (see section 4.8). Patients should be monitored for signs and symptoms and managed as recommended for other immune-mediated adverse reactions, in section 4.2

Infusion-related reactions

Patients should be monitored for signs and symptoms of infusion-related reactions. Severe infusion related reactions have been reported in patients receiving IMFINZI (see Section 4.8). Infusion-related reactions should be managed as recommended in section 4.2

Patients excluded from clinical trials

Patients with the following were excluded from clinical trials: a baseline ECOG performance score ≥ 2; active or prior documented autoimmune disease within 2 years of initiation of the study; a history of immunodeficiency; a history of severe immune-mediated adverse reactions; medical conditions that required systemic immunosuppression, except physiological dose of systemic corticosteroids (≤ 10 mg/day prednisone or equivalent); uncontrolled intercurrent illnesses; active tuberculosis or hepatitis B or C or HIV infection or patients receiving live attenuated vaccine within 30 days before or after the start of IMFINZI. In the absence of data, durvalumab should be used with caution in these populations after careful consideration of the potential benefit/risk on an individual basis. The safety of concurrent prophylactic cranial irradiation (PCI) with IMFINZI in patients with ES-SCLC is unknown.

4.5 Interactions with other medicines and other forms of interactions

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

4.6 Fertility, pregnancy and lactation

Effects on fertility

There are no data on the effects of durvalumab on fertility in humans. In repeat-dose toxicology studies of durvalumab up to 3 months duration in sexually mature cynomolgus monkeys, there were no notable effects on the male and female reproductive organs. These animals received weekly doses of durvalumab yielding 23 times the exposure (based on AUC) in humans at the recommended clinical dose.

Use in pregnancy – Category D

There are no data on the use of durvalumab in pregnant women. Based on its mechanism of action, durvalumab has the potential to impact maintenance of pregnancy and may cause foetal harm when administered to a pregnant woman. Human IgG1 is known to cross the placental barrier; therefore, durvalumab has the potential to be transmitted from the mother to the developing foetus. Durvalumab use is not recommended during pregnancy. Women of childbearing potential should use effective contraception during treatment and for at least 3 months after the last dose.

Animal data

As reported in the literature, the PD-1/PD-L1 pathway plays a central role in preserving pregnancy by maintaining maternal immune tolerance to the foetus. In mouse allogeneic pregnancy models,

disruption of PD-L1 signalling was shown to result in an increase in foetal loss. The effects of durvalumab on prenatal and postnatal development were evaluated in reproduction studies in cynomolgus monkeys. Durvalumab was administered from the confirmation of pregnancy through delivery at exposure levels approximately 6 to 20 times higher than those observed in humans at the recommended clinical dose of 10 mg/kg (based on AUC). Administration of durvalumab resulted in premature delivery, foetal loss (abortion and stillbirth) and increase in neonatal deaths compared to concurrent controls. Durvalumab was detected in infant serum on postpartum Day 1, indicating the presence of placental transfer of durvalumab. Based on its mechanism of action, foetal exposure to durvalumab may increase the risk of developing immune-mediated disorders or altering the normal immune response and immune-mediated disorders have been reported in PD-1 knockout mice.

Use in lactation

There is no information regarding the presence of durvalumab in human milk, the absorption and effects on the breastfed infant, or the effects on milk production. Human IgG is excreted in human milk. In animal reproduction studies, administration of durvalumab to pregnant cynomolgus monkeys was associated with dose-related low-level excretion of durvalumab in breast milk and was associated with premature neonatal death compared to concurrent controls. Because of the potential for adverse reactions in breastfed infants from durvalumab, lactating women should be advised not to breastfeed during treatment and for at least 3 months after the last dose.

4.7 Effects on ability to drive and use machines

Based on its pharmacodynamic properties, durvalumab is unlikely to affect the ability to drive and use machines. However, if patients experience adverse reactions affecting their ability to concentrate and react, they should be advised to use caution when driving or operating machinery.

4.8 Adverse effects (undesirable effects)

Summary of the safety profile

The safety of IMFINZI as monotherapy is based on pooled data in 3006 patients across multiple tumour types. IMFINZI was administered at a dose of 10 mg/kg every 2 weeks or 20 mg/kg every 4 weeks. The most frequent (>10%) adverse reactions were cough/productive cough (21.5%), diarrhoea (16.3%), rash (16.0%), pyrexia (13.8%), upper respiratory tract infections (13.5%), abdominal pain (12.7%), pruritus (10.8%), and hypothyroidism (10.1%).

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. The most frequent (>20%) adverse reactions were neutropenia (48.7%), anaemia (38.5%), nausea (33.6%), fatigue (32.1%), alopecia (31.3%), thrombocytopenia (21.1%), and leukopenia (20.0%).

Tabulated list of adverse reactions

Table 3 lists the incidence of adverse reactions in the monotherapy safety dataset and in patients treated with IMFINZI in combination with chemotherapy in the CASPIAN study. Adverse drug

reactions are listed according to system organ class in MedDRA. Within each system organ class, the adverse drug reactions are presented in decreasing frequency. The corresponding frequency category for each ADR is defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1000); very rare (< 1/10,000); not known (cannot be estimated from available data). Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness.

Table 3. 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						
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
Immune thrombocytopenia[c]	Rare	<0.1	<0.1			
Endocrine disorders						

	IMFINZI Monotherapy			IMFINZI Combined with Chemotherapy		
	Any Grade (%)		Grade 3-4 (%)	Any Grade (%)		Grade 3-4 (%)
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]	<0.1				
Noninfective encephalitis[l]	Not known					
Meningitis[m]	Rare	<0.1	<0.1			
Guillain-Barré syndrome	Not known					
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

	IMFINZI Monotherapy			IMFINZI Combined with Chemotherapy		
	Any Grade (%)		Grade 3-4 (%)	Any Grade (%)		Grade 3-4 (%)
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[n]	Very common	12.7	1.8	Common	8.7	0.4
Colitis[o]	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[p]				Common	6.0	0.4
Pancreatitis[q]	Uncommon	0.2	0.2			
Hepatobiliary disorders						
Aspartate aminotransferase increased or Alanine aminotransferase increased[c,r]	Common	8.1	2.3	Common	8.7	1.9
Hepatitis[c,s]	Uncommon	0.8	0.4	Common	1.9	1.1
Skin and subcutaneous tissue disorders						
Rash[t]	Very common	16.0	0.6	Common	9.4	0
Pruritus[u]	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[v]	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[v]	<0.1	<0.1			
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[x]	Uncommon	0.3	<0.1			
General disorders and administration site conditions						
Pyrexia	Very common	13.8	0.3	Common	8.3	0
Peripheral oedema[y]	Common	9.7	0.3	Common	6.4	0.8
Fatigue[z]				Very common	32.1	3.4
Injury, poisoning and procedural complications						
Infusion-related reaction[aa]	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] reported frequency from ongoing AstraZeneca-sponsored clinical studies outside of the pooled dataset is rare and includes two events of encephalitis, one was Grade 5 fatal (immune-mediated encephalitis) and one was Grade 2 (autoimmune encephalitis).
[m] includes meningitis and noninfective meningitis.
[n] includes abdominal pain, abdominal pain lower, abdominal pain upper and flank pain.
[o] includes colitis, enteritis, enterocolitis, and proctitis.
[p] includes stomatitis and mucosal inflammation.
[q] includes pancreatitis and pancreatitis acute.
[r] includes alanine aminotransferase increased, aspartate aminotransferase increased, hepatic enzyme increased and transaminases increased.
[s] includes hepatitis, autoimmune hepatitis, hepatitis toxic, hepatocellular injury, hepatitis acute, hepatotoxicity and immune-mediated hepatitis.
[t] includes rash erythematous, rash generalised, rash macular, rash maculopapular, rash papular, rash pruritic, rash pustular, erythema, eczema and rash.
[u] includes pruritus generalised and pruritus.
[v] includes pemphigoid, dermatitis bullous and pemphigus. Reported frequency from completed and ongoing trials in uncommon
[w] 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.
[x] includes autoimmune nephritis, tubulointerstitial nephritis, nephritis, glomerulonephritis and glomerulonephritis membranous.
[y] includes oedema peripheral and peripheral swelling.
[z] includes fatigue and asthenia.
[aa] includes infusion-related reaction and urticaria with onset on the day of dosing or 1 day after dosing.

Description of selected adverse reactions

IMFINZI is most commonly associated with immune-mediated adverse reactions. Most of these, including severe reactions, resolved following initiation of appropriate medical therapy or withdrawal and/or treatment modifications . The data for the following immune-mediated adverse reactions reflect the combined safety database of 3006 patients which includes the PACIFIC Study and additional studies in patients with various solid tumours, in indications for which durvalumab is not approved. Across all studies, IMFINZI was administered at a dose of 10 mg/kg every 2 weeks, 20 mg/kg every 4 weeks, or 1500 mg every 3 or 4 weeks. Details for the significant adverse reactions for IMFINZI when given in combination with chemotherapy are presented if clinically relevant differences were noted in comparison to IMFINZI monotherapy. The management guidelines for these adverse reactions are described in section 4.2 and 4.4.

Immune-mediated pneumonitis

In the combined safety database with IMFINZI monotherapy, (n = 3006 multiple tumour types), immune-mediated pneumonitis occurred in 92 (3.1%) patients, including Grade 3 in 25 (0.8%) patients, Grade 4 in 2 (< 0.1%) patient, and Grade 5 in 6 (0.2%) patients. The median time to onset was 55 days (range: 2-785 days). Sixty-nine of the 92 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day), and 2 patients also received infliximab infliximab and 1 patient also received cyclosporine. IMFINZI was discontinued in 38 patients. Resolution occurred in 53 patients.

Immune-mediated pneumonitis occurred more frequently in the PACIFIC study who had completed treatment with concurrent chemoradiation within 1 to 42 days prior to initiation of the study (9.9%), than in the other patients in the combined safety database (1.8%).

In the PACIFIC Study, (n = 475 in the IMFINZI arm, and n = 234 in the placebo arm) immune-mediated pneumonitis occurred in 47 (9.9%) patients in the IMFINZI-treated group and 14 (6.0%) patients in the placebo group, including Grade 3 in 9 (1.9%) patients on IMFINZI vs. 6 (2.6%) patients on placebo and Grade 5 (fatal) in 4 (0.8%) patients on IMFINZI vs. 3 (1.3%) patients on placebo. The median time to onset in the IMFINZI-treated group was 46 days (range: 2-342 days) vs. 57 days (range: 26-253 days) in the placebo group. In the IMFINZI-treated group, all patients received systemic corticosteroids, including 30 patients who received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day), and 2 patients also received infliximab. In the placebo group, all patients received systemic corticosteroids, including 12 patients who received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day) and 1 patient also received cyclophosphamide and tacrolimus. Resolution occurred for 29 patients in the IMFINZI treated group vs. 6 in placebo.

Immune-mediated hepatitis

In the combined safety database with IMFINZI monotherapy, immune-mediated hepatitis occurred in 68 (2.3%) patients, including Grade 3 in 35 (1.2%) patient, Grade 4 in 6 (<0.2%) and Grade 5 (fatal) in 4 (< 0.1%) patient. The median time to onset was 33 days (range: 3-333 days). Forty-five of the 68 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). Three patient also received mycophenolate treatment. IMFINZI was discontinued in 9 patients. Resolution occurred in 31 patients.

Immune-mediated colitis

In the combined safety database with IMFINZI monotherapy, immune-mediated colitis or diarrhoea occurred in 58 (1.9%) patients, including Grade 3 in 9 (0.3%) patients and Grade 4 in 2 (<0.1%) patient. The median time to onset was 70 days (range: 1-394 days). Thirty-eight of the 58 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). One patient also received infliximab treatment and 1 patient also received mycophenolate. IMFINZI was discontinued in 9 patients. Resolution occurred in 43 patients.

Immune-mediated endocrinopathies

Immune-mediated hypothyroidism

In the combined safety database with IMFINZI monotherapy, immune-mediated hypothyroidism occurred in 245 (8.2%) patients, including Grade 3 in 4 (0.1%) patients. The median time to onset was 85 days (range: 1-562 days). Of the 245 patients, 240 patients received hormone replacement therapy and 6 patients received high-dose corticosteroids (at least 40 mg prednisone or equivalent per day) for immune-mediated hypothyroidism followed by hormone replacement. No patients discontinued IMFINZI due to immune-mediated hypothyroidism.

Immune-mediated hyperthyroidism

In the combined safety database with IMFINZI monotherapy, immune-mediated hyperthyroidism occurred in 50 (1.7%) patients, there were no Grade 3 or 4 cases. The median time to onset was 43

days (range: 1-196 days). Forty-six of the 50 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 immune-mediated hyperthyroidism. Resolution occurred in 39 patients. Twenty patients experienced hypothyroidism following hyperthyroidism.

Immune-mediated thyroiditis

In the combined safety database with IMFINZI monotherapy, immune-mediated thyroiditis occurred in 12 (0.4%) patients, including Grade 3 in 2 (<0.1%) patients. The median time to onset was 49 days (range: 14-106 days). Of the 12 patients, 10 patients received hormone replacement therapy and 1 patient received high-dose corticosteroids (at least 40 mg prednisone or equivalent per day) followed by hormone replacement. One patient discontinued IMFINZI due to immune-mediated thyroiditis. Three patients experienced hypothyroidism following thyroiditis.

Immune-mediated adrenal insufficiency

In the combined safety database with IMFINZI monotherapy, immune-mediated adrenal insufficiency occurred in 14 (0.5%) patients, including Grade 3 in 3 (<0.1%) patients. The median time to onset was 146 days (range: 20-547 days). All 14 patients received systemic corticosteroids; 4 of the 14 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). No patients discontinued IMFINZI due to immune-mediated adrenal insufficiency. Resolution occurred in 3 patients.

Immune-mediated type 1 diabetes mellitus

In one study with 475 locally advance, unresectable NSCLC patients, immune-mediated type 1 diabetes mellitus occurred in 1 (<0.1%) patient, (Grade 3). The time to onset was 43 days. This patient recovered with sequelae, required long-term insulin therapy and IMFINZI was permanently discontinued due to immune-mediated type 1 diabetes mellitus.

Immune-mediated hypophysitis/hypopituitarism

In the combined safety database with IMFINZI monotherapy, immune-mediated hypophysitis/ hypopituitarism occurred in 2 (<0.1%) patients, both Grade 3. The time to onset for the events was 44 days and 50 days. Both patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day) and one patient discontinued IMFINZI due to immune-mediated hypophysitis/hypopituitarism.

Immune-mediated nephritis

In the combined safety database with IMFINZI monotherapy, immune-mediated nephritis occurred in 14 (0.5%) patients, including Grade 3 in 2 (< 0.1%) patients. The median time to onset was 71 days (range: 4-393 days). Nine 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 8 patients.

Immune-mediated rash

In the combined safety database with IMFINZI monotherapy, immune-mediated rash or dermatitis occurred in 50 (1.7%) patients, including Grade 3 in 12 (0.4%) patients. The median time to onset

was 43 days (range: 4-333 days). Twenty-three of the 50 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). IMFINZI was discontinued in 3 patients. Resolution occurred in 32 patients.

Infusion-related reactions

In the combined safety database with IMFINZI monotherapy, infusion-related reactions occurred in 49 (1.6%) patients, including Grade 3 in 5 (0.2%) patients. There were no Grade 4 or 5 events.

Laboratory abnormalities

In patients treated with durvalumab monotherapy, the proportion of patients who experienced a shift from baseline to a Grade 3 or 4 laboratory abnormality was as follows: 2.4% for alanine aminotransferase increased, 3.6% for aspartate aminotransferase increased, 0.5% for blood creatinine increased, 5.7% for amylase increased and 5.6% for lipase increased. The proportion of patients who experienced a TSH shift from baseline that was ≤ ULN to any grade > ULN was 18.8% and a TSH shift from baseline that was ≥ LLN to any grade < LLN was 18.1%.

In patients treated with durvalumab in combination with chemotherapy, the proportion of patients who experienced a shift from baseline to a Grade 3 or 4 laboratory abnormality was as follows: 4.9% for alanine aminotransferase increased, 4.6% for aspartate aminotransferase increased, 3.4% for blood creatinine increased, 4.8% for amylase increased and 8.1% for lipase increased. The proportion of patients who experienced a TSH shift from baseline that was ≤ ULN to any grade > ULN was 17.7% and a TSH shift from baseline that was ≥ LLN to any grade < LLN was 31.3%.

Immunogenicity

Immunogenicity of IMFINZI as monotherapy is based on pooled data in 2280 patients who were treated with IMFINZI 10 mg/kg every 2 weeks, or 20 mg/kg every 4 weeks as a single-agent and evaluable for the presence of anti-drug antibodies (ADA). Sixty nine patients (3.0%) tested positive for treatment emergent ADA. Neutralising antibodies (nAb) against durvalumab were detected in 0.5% (12/2280) of patients. The presence of ADA did not have a clinically relevant effect on safety. There are insufficient number of patients to determine ADA impact on efficacy. Based on population PK analysis, slightly lower exposure are expected in ADA-positive patients however, the reduction of PK exposure is less than 30% compared to a typical patient and is not considered clinically relevant.

In the CASPIAN study, of 201 patients who were treated with IMFINZI 1500 mg every 3 weeks in combination with chemotherapy and evaluable for the presence of ADAs, 0 (0%) patients tested positive for treatment-emergent ADAs. The impact of treatment-emergent ADA on PK, clinical safety and efficacy of durvalumab was not evaluable as no patient samples tested positive for treatment-emergent durvalumab ADA.

Elderly

No overall differences in safety were reported between elderly (≥ 65 years) and younger patients. Data from NSCLC and ES-SCLC patients 75 years of age or older are limited.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at e-meso.pom.go.id.

4.9 Overdose

There is no specific treatment in the event of durvalumab overdose, and symptoms of overdose are not established. In the event of an overdose, physicians should follow general supportive measures and should treat symptomatically.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

Expression of programmed cell death ligand-1 (PD-L1) protein is an adaptive immune response that helps tumours evade detection and elimination by the immune system. PD-L1 expression can be induced by inflammatory signals (e.g., IFN-gamma) and can be expressed on both tumour cells and tumour-associated immune cells in tumour microenvironment. PD-L1 blocks T-cell function and activation through interaction with PD-1 and CD80 (B7.1). By binding to its receptors, PD-L1 reduces cytotoxic T-cell activity, proliferation, and cytokine production.

Durvalumab is a fully human, high affinity, immunoglobulin G1 kappa (IgG1κ) monoclonal antibody that blocks the interaction of PD-L1 with PD-1 and CD80 (B7.1). Durvalumab does not induce antibody dependent cell-mediated cytotoxicity (ADCC). Blockade of PD-L1/PD-1 and PD-L1/CD80 interactions enhances antitumour immune responses. These antitumour responses may result in tumour elimination.

In preclinical studies, PD-L1 blockade by durvalumab led to increased T-cell activation and decreased tumour size in xenograft mouse models of human melanoma and/or pancreatic cancer cells as well as mouse syngeneic colorectal cancer.

Clinical trials

Durvalumab doses of 10 mg/kg every 2 weeks or 1500 mg every 4 weeks were evaluated in NSCLC and ES-SCLC clinical studies. Based on the modelling and simulation of exposure, exposure-safety relationships and exposure-efficacy data comparisons, there are no anticipated clinically significant differences in efficacy and safety between durvalumab doses of 10 mg/kg every 2 weeks or 1500 mg every 4 weeks.

Non-small cell lung cancer (NSCLC)

Randomised, placebo-controlled phase 3 study in patients with locally advanced, unresectable NSCLC after chemoradiation (PACIFIC study)

The efficacy of IMFINZI was evaluated in the PACIFIC study, a randomised, double-blind, placebo-controlled, multicentre study in 713 patients with histologically or cytologically confirmed locally advanced, unresectable NSCLC. Patients had completed at least 2 cycles of definitive platinum-based chemotherapy with radiation therapy within 1 to 42 days prior to initiation of the

study and had an ECOG performance status of 0 or 1. Ninety-two percent of patients had received a total dose of 54 to 66 Gy of radiation. The study excluded patients who had progressed following chemoradiation therapy, patients with prior exposure to any anti-PD-1 or anti-PD-L1 antibody, patients with active or prior documented autoimmune disease within 2 years of initiation of the study; a history of immunodeficiency; a history of severe immune-mediated adverse reactions; medical conditions that required systemic immunosuppression(except physiological dose of systemic corticosteroids); active tuberculosis or hepatitis B or C or HIV infection or patients receiving live attenuated vaccine within 30 days before or after the start of IMFINZI. Patients were randomised 2:1 to receive 10 mg/kg IMFINZI (n=476) or 10 mg/kg placebo (n=237) via intravenous infusion every 2 weeks for up to 12 months or until unacceptable toxicity or confirmed disease progression. Randomisation was stratified by gender, age (<65 years vs. ≥ 65 years) and smoking status (smoker vs. non- smoker). Patients with disease control at 12 months were given the option to be re-treated upon disease progression. Tumour assessments were conducted every 8 weeks for the first 12 months and then every 12 weeks thereafter.

Patients were enrolled regardless of their tumour PD-L1 expression level. Where available, archival tumour tissue specimens taken prior to chemoradiation therapy were retrospectively tested for PD-L1 expression on tumour cells (TC) using the VENTANA PD-L1 (SP263) IHC assay. Of the 713 patients randomised, 63% of patients provided a tissue sample of sufficient quality and quantity to determine PD-L1 expression and 37% were unknown.

The demographics and baseline disease characteristics were well balanced between study arms. Baseline demographics of the overall study population were as follows: male (70%), age ≥ 65 years (45%), white (69%), Asian (27%), other (4%), current smoker (16%), past-smoker (75%), and never smoker (9%), WHO/ECOG PS 0 (49%), WHO/ECOG PS 1 (51%). Disease characteristics were as follows: Stage IIIA (53%), Stage IIIB (45%), histological sub-groups of squamous (46%), non-squamous (54%). Of 451 patients with PD L1 expression available, 67% were TC ≥ 1% [PD-L1 TC 1-24% (32%), PD L1 TC ≥ 25% (35%)] and 33% were TC < 1%.

The two primary endpoints of the study were progression-free survival (PFS) and overall survival (OS) of IMFINZI vs. placebo. Secondary efficacy endpoints included PFS at 12 months (PFS 12) and 18 months (PFS 18) from randomisation and Time from Randomisation to Second Progression (PFS2). PFS was assessed by Blinded Independent Central Review (BICR) according to RECIST 1.1.

The study demonstrated a statistically significant improvement in PFS and OS in the IMFINZI-treated group compared with the placebo group (see Table 4 and Figures 1 and 2).

Table 4. Efficacy Results for the PACIFIC Study[a]

	IMFINZI (n = 476)	**Placebo (n = 237)**
OS		
Number of deaths (%)	183 (38.4%)	116 (48.9%)

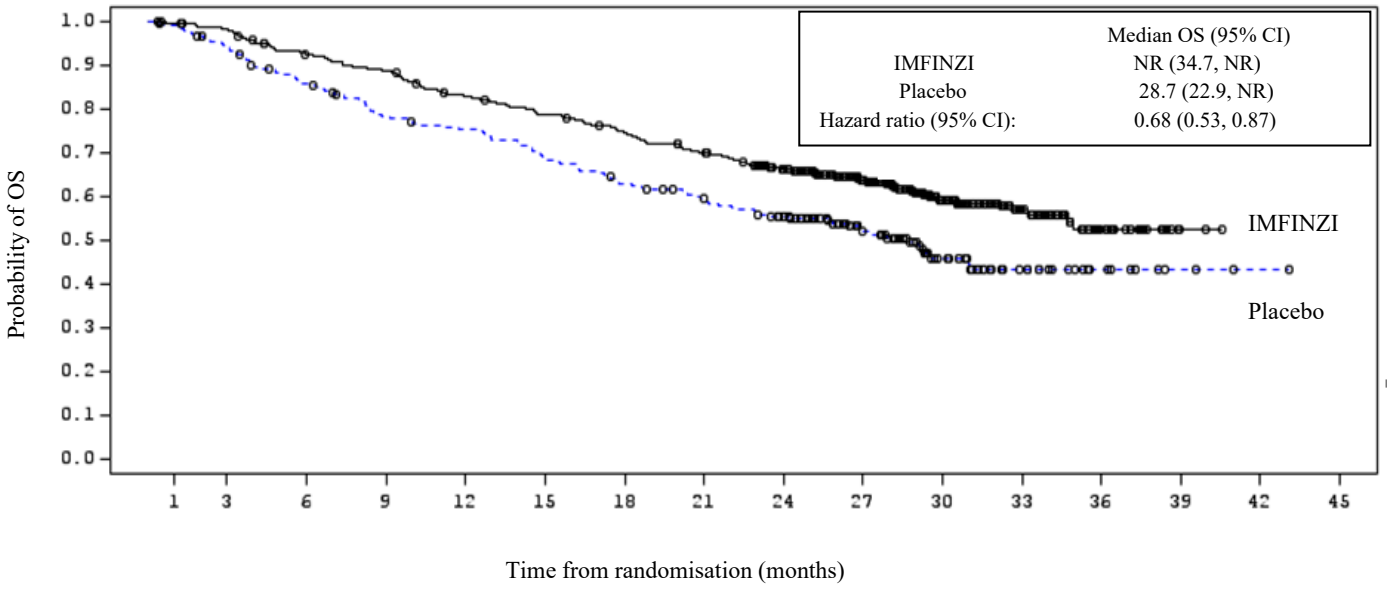
	IMFINZI (n = 476)	Placebo (n = 237)
Median (months) (95% CI)	NR (34.7, NR)	28.7 (22.9, NR)
HR (95% CI)	0.68 (0.53, 0.87)	
2- sided p-value	0.00251	
OS at 24 months (%) (95% CI)	66.3% (61.7%, 70.4%)	55.6% (48.9%, 61.8%)
p-value	0.005	
PFS		
Number of events (%)	214 (45.0%)	157 (66.2%)
Median PFS (months) (95% CI)	16.8 (13.0, 18.1)	5.6 (4.6, 7.8)
HR (95% CI)	0.52 (0.42, 0.65)	
p-value	$p < 0.0001$	
PFS at 12 months (%) (95% CI)	55.9% (51.0%, 60.4%)	35.3% (29.0%, 41.7%)
PFS at 18 months (%) (95% CI)	44.2% (37.7%, 50.5%)	27.0% (19.9%, 34.5%)
PFS2[b]		
Median PFS2[b] (months) (95% CI)	28.3 (25.1, 34.7)	17.1 (14.5, 20.7)
HR (95% CI)	0.58 (0.46, 0.73)	
p-value	$p < 0.0001$	

[a] The analysis of OS and PFS2 was performed approximately 13 months after the primary analysis of PFS.

[b] PFS2 is defined as the time from the date of randomisation until the date of second progression (defined by local standard clinical practice) or death.

NR: Not Reached

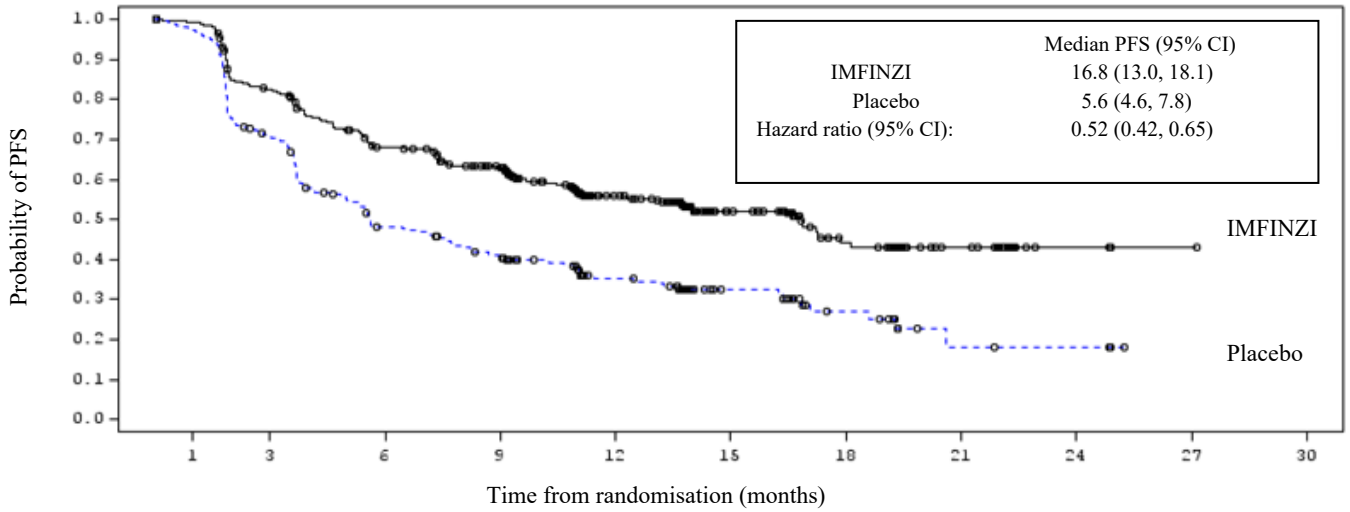
Figure 1. Kaplan-Meier curve of OS (PACIFIC study)



Number of patients at risk

Month	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45
IMFINZI	476	464	431	415	385	364	343	319	274	210	115	57	23	2	0	0
Placebo	237	220	198	178	170	155	141	130	117	78	42	21	9	3	1	0

Figure 2. Kaplan-Meier curve of PFS (PACIFIC study)



Number of patients at risk

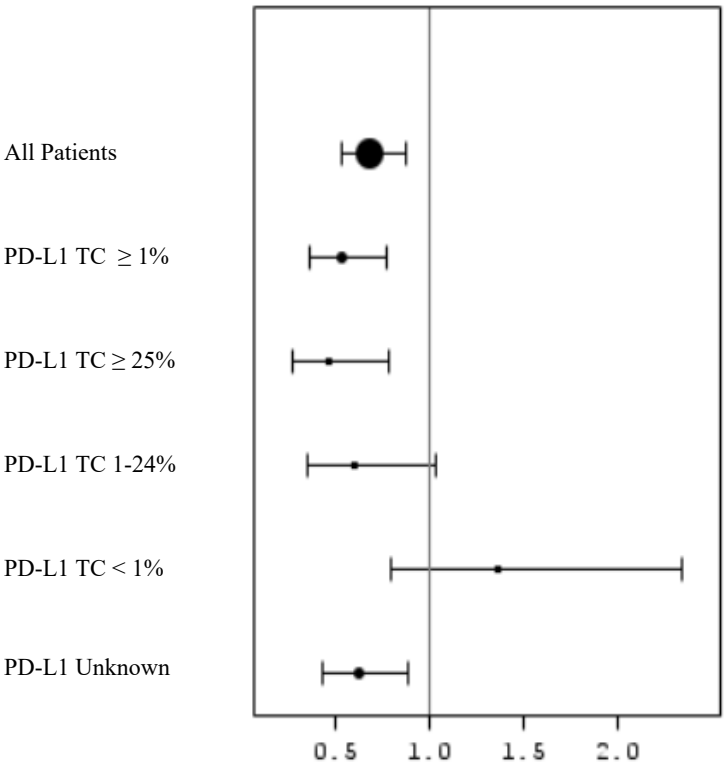
Month	0	3	6	9	12	15	18	21	24	27	30
IMFINZI	476	377	301	264	159	86	44	21	4	1	0
Placebo	237	163	106	87	52	28	15	4	3	0	0

The improvements in PFS and OS in favour of patients receiving IMFINZI compared to those receiving placebo were consistently observed in all predefined subgroups analysed, including ethnicity, age, gender, smoking history, EGFR mutation status and histology. ALK mutation status was not analysed in this study.

Post-hoc subgroup analysis by PD-L1 expression

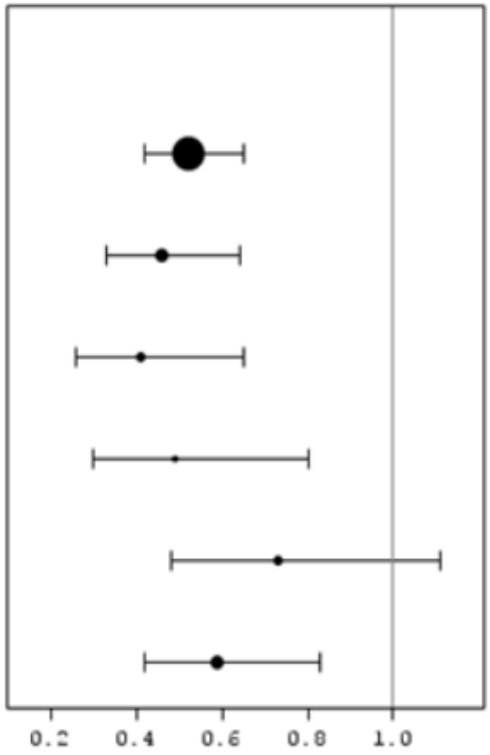
Additional subgroup analyses were conducted to evaluate the efficacy by tumour PD-L1 expression (≥ 25%, 1-24%, ≥ 1%, < 1%) and for patients whose PD-L1 status could not be established (PD-L1 unknown). PFS and OS results are summarised in Figures 3 and 4. Overall the safety profile of durvalumab in PD-L1 TC ≥1% subgroup was consistent with the intent to treat population, as was the PD-L1 TC <1% subgroup.

Figure 3. Forest plot of OS by PD-L1 expression (PACIFIC study)



	Events/N (%)		
	IMFINZI	**Placebo**	**HR (95% CI)**
All Patients	183/476 (38.4%)	116/237 (48.9%)	0.68 (0.53, 0.87)
PD-L1 TC ≥ 1%	70/212 (33.0%)	45/91 (49.5%)	0.53 (0.36, 0.77)
PD-L1 TC ≥ 25%	37/115 (32.2%)	23/44 (52.3%)	0.46 (0.27, 0.78)
PD-L1 TC 1-24%	33/97 (34.0%)	22/47 (46.8%)	0.60 (0.35, 1.03)
PD-L1 TC < 1%	41/90 (45.6%)	19/58 (32.8%)	1.36 (0.79, 2.34)
PD-L1 Unknown	72/174 (41.4%)	52/88 (59.1%)	0.62 (0.43, 0.89)

Figure 4. Forest plot of PFS by PD-L1 expression (PACIFIC study)



	Events/N (%) IMFINZI	Placebo	HR (95% CI)
All Patients	214/476 (45.0%)	157/237 (66.2%)	0.52 (0.42, 0.65)
PD-L1 TC ≥ 1%	84/212 (39.6%)	59/91 (64.8%)	0.46 (0.33, 0.64)
PD-L1 TC ≥ 25%	48/115 (41.7%)	31/44 (70.5%)	0.41 (0.26, 0.65)
PD-L1 TC 1-24%	36/97 (37.1%)	28/47 (59.6%)	0.49 (0.30, 0.80)
PD-L1 TC < 1%	49/90 (54.4%)	40/58 (69.0%)	0.73 (0.48, 1.11)
PD-L1 Unknown	81/174 (46.6%)	58/88 (65.9%)	0.59 (0.42, 0.83)

Patient reported outcomes

Patient-reported symptoms, function and health-related quality of life (HRQoL) were collected using the EORTC QLQ-C30 and its lung cancer module (EORTC QLQ-LC13). The LC13 and C30 were assessed at baseline and every 4 weeks for the first 8 weeks, then every 8 weeks until completion of the treatment period or discontinuation of study drug due to toxicity or disease progression. Compliance was similar between the IMFINZI and placebo treatment groups (83% vs 85.1% overall of evaluable forms completed).

At baseline, no differences in patient reported symptoms, function or HRQoL were observed between IMFINZI and placebo groups. Throughout the duration of the study to week 48, there was no clinically meaningful difference between IMFINZI and placebo groups in symptoms, functioning and HRQoL (as assessed by a difference of greater than or equal to 10 points).

SCLC – CASPIAN Study

CASPIAN was a study designed to evaluate the efficacy of IMFINZI with or without tremelimumab in combination with etoposide and either carboplatin or cisplatin. CASPIAN was a randomized, open-label, multicenter study in 805 treatment naïve ES-SCLC patients with WHO/ECOG Performance status of 0 or 1, suitable to receive a platinum-based chemotherapy regimen as first-line treatment for SCLC, with life expectancy ≥12 weeks, at least one target lesion by RECIST 1.1 and adequate organ and bone marrow function. Patients with asymptomatic or treated brain metastases were eligible. The study excluded patients with a history of chest radiation therapy; a history of active primary immunodeficiency; autoimmune disorders including paraneoplastic syndrome (PNS); active or prior documented autoimmune or inflammatory disorders; use of systemic immunosuppressants within 14 days before the first dose of the treatment except

physiological dose of systemic corticosteroids; active tuberculosis or hepatitis B or C or HIV infection; or patients receiving live attenuated vaccine within 30 days before or after the start of IMFINZI.

Randomisation was stratified by the planned platinum-based therapy in cycle 1 (carboplatin or cisplatin).

Patients were randomised 1:1:1 to receive:

- Arm 1: IMFINZI 1500 mg + tremelimumab 75 mg + etoposide and either carboplatin or cisplatin
- Arm 2: IMFINZI 1500 mg + etoposide and either carboplatin or cisplatin
- Arm 3: Either carboplatin (AUC 5 or 6 mg/mL/min) or cisplatin (75-80 mg/m2) on Day 1 and etoposide (80-100 mg/m2) intravenously on Days 1, 2, and 3 of each 21-day cycle for between 4 – 6 cycles.

For patients randomised to Arm 1 and 2, etoposide and either carboplatin or cisplatin was limited to 4 cycles on an every 3 week schedule subsequent to randomisation. IMFINZI monotherapy continued until disease progression or unacceptable toxicity. Administration of IMFINZI monotherapy was permitted beyond disease progression if the patient was clinically stable and deriving clinical benefit as determined by the investigator.

Patients randomised to Arm 3, were permitted to receive a total of up to 6 cycles of etoposide and either carboplatin or cisplatin. After completion of chemotherapy, prophylactic cranial irradiation (PCI) was permitted only in Arm 3 per investigator discretion.

Tumour assessments were conducted at Week 6 and Week 12 from the date of randomisation, and then every 8 weeks until confirmed objective disease progression. Survival assessments were conducted every 2 months following treatment discontinuation.

The primary endpoints of the study were Overall Survival (OS) of IMFINZI + chemotherapy (Arm 2) vs. chemotherapy alone (Arm 3) and IMFINZI + tremelimumab + chemotherapy (Arm 1) vs. chemotherapy alone (Arm 3). The key secondary endpoint was progression-free survival (PFS). Other secondary endpoints were Objective Response Rate (ORR), OS and PFS landmarks and Patient-Reported Outcomes (PRO). PFS and ORR were assessed using Investigator assessments according to RECIST v1.1.

The demographics and baseline disease characteristics were well balanced between the two study arms (268 patients in Arm 2 and 269 patients in Arm 3). Baseline demographics of the overall study population were as follows: male (69.6%), age ≥ 65 years (39.6%), median age 63 years (range: 28 to 82 years), white (83.8%), Asian (14.5%), black or African American (0.9%), other (0.6 %), non-Hispanic or Latino (96.1%), current or past-smoker (93.1%), never smoker (6.9%), WHO/ECOG PS 0 (35.2%), WHO/ECOG PS 1 (64.8%), Stage IV 90.3%, 24.6% of the patients received cisplatin and 74.1% of the patients received carboplatin. In Arm 3, 56.8% of the patients received 6 cycles of etoposide + platinum and 7.8% of the patients received PCI.

At a planned interim (primary) analysis the study demonstrated a statistically significant improvement in OS with IMFINZI + etoposide + platinum (Arm 2) vs. etoposide + plantinum alone (Arm 3) [HR=0.73 (95% CI: 0.591, 0.909), p=0.0047]. IMFINZI + etoposide + plantinum demonstrated an improvement in PFS vs. etoposide + plantinum alone [HR=0.78 (95% CI: 0.645, 0.936). See Table 7 and Figures 4 and 5.

In the planned follow-up analysis (median: 25.1 months), IMFINZI + etoposide + platinum (Arm 2) vs. etoposide + platinum (Arm 3) continued to demonstrate improved OS. The OS, PFS, ORR and DoR results from the planned follow-up analysis are summarized in Table 5; Kaplan-Meier curves for OS and PFS are presented in Figures 5 and 6.

Table 5. Efficacy Results for the CASPIAN Study
Follow-up OS, PFS, ORR and DoR analysis at data cut-off 27 January 2020.

	Arm 2: IMFINZI + etoposide and either carboplatin or cisplatin (n=268)	**Arm 3: etoposide and either carboplatin or cisplatin (n=269)**
OS		
Number of deaths (%)	155 (57.8)	181 (67.3)
Median OS (months) (95% CI)	13.0 (11.5, 14.8)	10.3 (9.3, 11.2)
HR (95% CI)[d]	0.73 (0.591, 0.909)	
p-value[c]	0.0047	
OS at 12 months (%) (95% CI)	53.7 (47.4, 59.5)	39.8 (33.7, 45.8)
OS at 18 months (%) (95% CI)	33.9 (26.9, 41.0)	24.7 (18.4, 31.6)
PFS		
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)
HR (95% CI)[d]	0.78 (0.645, 0.936)	
p-value[b]	0.0078	
PFS at 6 months (%) (95% CI)	45.4 (39.3, 51.3)	45.6 (39.3, 51.7)
PFS at 12 months (%) (95% CI)	17.5 (13.1, 22.5)	4.7 (2.4, 8.0)
ORR n (%)[a]	182 (67.9)	155 (57.6)
Complete Response n (%)	6 (2.2)	2 (0.7)
Partial Response n (%)	176 (65.7)	153 (56.9)
Odds ratio (95% CI)[e]	1.56 (1.095, 2.218)	
p-value[b]	0.0136	

Median DoR (months) (95% CI)[a]	5.1 (4.9, 5.3)	5.1 (4.8, 5.3)
DoR at 12 months (%)[a]	22.7	6.3

[a] Confirmed Objective Response.

[b] Nominal p-value. PFS was included in the Multiple Testing Procedure (MTP) hierarchy at the second level. It was not able to be tested within the MTP as both Arm 1 and Arm 2 were required to achieve statistical significance prior to stepping down to PFS. ORR was not included in the MTP.

[c] Based on a Lan-DeMets alpha spending function with O'Brien Fleming type boundary with the actual number of events observed, the boundaries for declaring statistical significance are 0.0178 for a 4% overall alpha (Lan◦and◦DeMets 1983).

[d] 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.

[e] The analysis was performed using a logistic regression model adjusting for planned platinum therapy in Cycle 1 (carboplatin or cisplatin) with 95% CI calculated by profile likelihood.

Figure 5. Kaplan-Meier curve of OS

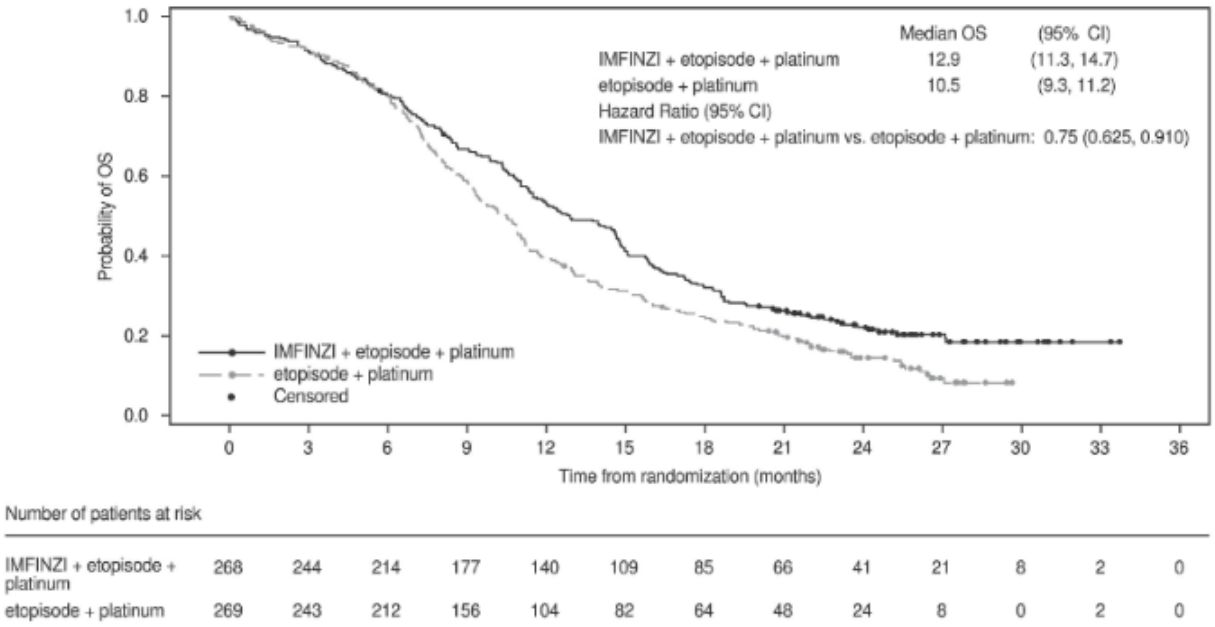
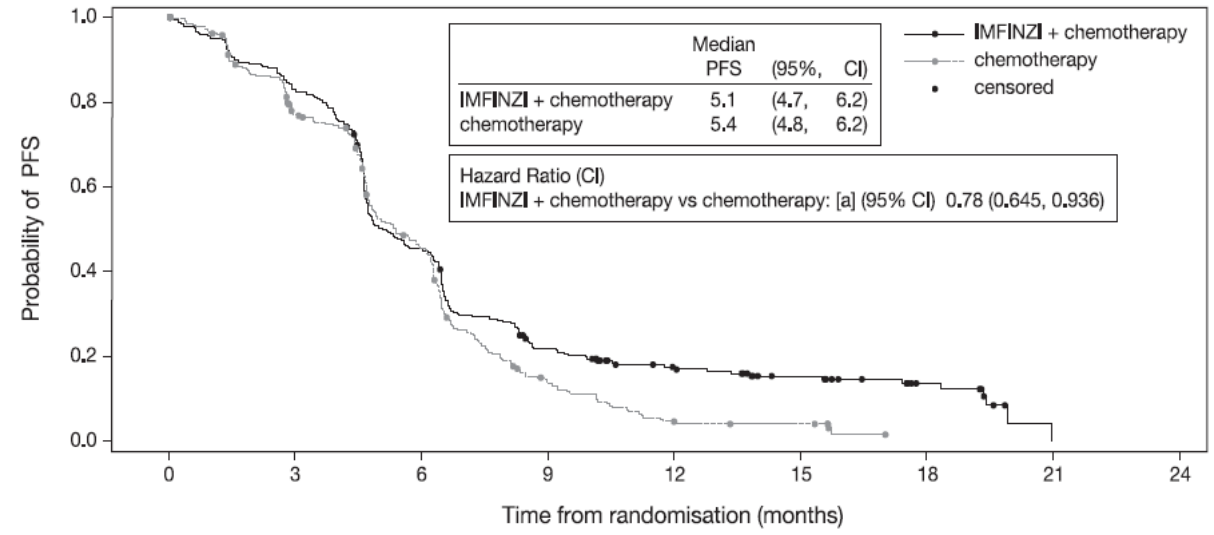


Figure 6. Kaplan-Meier curve of PFS



Number of patients at risk	0	3	6	9	12	15	18	21	24
IMFINZI + chemotherapy	268	220	119	54	34	22	10	0	0
chemotherapy	269	194	109	30	9	7	0	0	0

Subgroup analysis
The improvements in OS in favor of patients receiving IMFINZI + chemotherapy compared to those receiving chemotherapy alone, were consistently observed across the prespecified subgroups based on demographics, geographical region, carboplatin or cisplatin use and disease characteristics.

5.2 Pharmacokinetic properties

The pharmacokinetics (PK) of durvalumab was assessed for both IMFINZI monotherapy and in combination with chemotherapy.
The pharmacokinetics of IMFINZI was studied in 2903 patients with solid tumours with doses ranging from 0.1 to 20 mg/kg administered once every two, three or four weeks as monotherapy.

Distribution

PK exposure increased more than dose-proportionally (non-linear PK) at doses <3 mg/kg and dose proportionally (linear PK) at doses ≥ 3 mg/kg. Steady state was achieved at approximately 16 weeks. Based on population PK analysis that included 1878 patients who received durvalumab monotherapy in the dose range of ≥ 10 mg/kg Q2W, the steady state volume of distribution (Vss) was 5.64 L.

Excretion

Durvalumab clearance (CL) decreased over time resulting in a geometric mean steady state clearance (CLss) of 8.16 mL/h at Day 365; the decrease in CLss was not considered clinically relevant. The terminal half-life (t1/2), based on baseline CL, was approximately 18 days. There was

no clinically meaningful difference between the PK of durvalumab as a single agent and in combination with chemotherapy.

Special Populations

Age (19–96 years), body weight (31-149 kg), gender, positive anti-drug antibody (ADA) status, albumin levels, LDH levels, creatinine levels, soluble PD-L1, tumour type, race, mild renal impairment (creatinine clearance (CRCL) 60 to 89 mL/min), moderate renal impairment (creatinine clearance (CRCL) 30 to 59 mL/min), mild hepatic impairment (bilirubin ≤ ULN and AST > ULN or bilirubin >1.0 to 1.5 × ULN and any AST) and ECOG/WHO status had no clinically significant effect on the pharmacokinetics of durvalumab.

The effect of severe renal impairment (CRCL 15 to 29 mL/min) or moderate (bilirubin >1.5 to 3 x ULN and any AST) or severe (bilirubin >3.0 x ULN and any AST) hepatic impairment on the pharmacokinetics of durvalumab is unknown; however, as IgG monoclonal antibodies are not primarily cleared via hepatic pathways, a change in hepatic function is not expected to influence durvalumab exposure.

Laboratory abnormalities

In patients treated with durvalumab monotherapy, the proportion of patients who experienced a shift from baseline to a Grade 3 or 4 laboratory abnormality was as follows: 2.4% for alanine aminotransferase increased, 3.6% for aspartate aminotransferase increased, 0.5% for blood creatinine increased, 5.7% for amylase increased and 5.6% for lipase increased. The proportion of patients who experienced a TSH shift from baseline that was ≤ ULN to any grade > ULN was 18.8% and a TSH shift from baseline that was ≥ LLN to any grade < LLN was 18.1%.

In patients treated with durvalumab in combination with chemotherapy, the proportion of patients who experienced a shift from baseline to a Grade 3 or 4 laboratory abnormality was as follows: 4.9% for alanine aminotransferase increased, 4.6% for aspartate aminotransferase increased, 3.4% for blood creatinine increased, 4.8% for amylase increased and 8.1% for lipase increased. The proportion of patients who experienced a TSH shift from baseline that was ≤ ULN to any grade > ULN was 17.7% and a TSH shift from baseline that was ≥ LLN to any grade < LLN was 31.3%.

Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. Of the 2280 patients who were treated with IMFINZI 10 mg/kg every 2 weeks and evaluable for the presence of anti-drug antibodies (ADA). Sixty nine patients (3.0%) tested positive for treatment emergent ADA. Neutralising antibodies against durvalumab were detected in 0.5% (12/2280) patients. The presence of ADAs did not have a clinically relevant effect on pharmacokinetics or safety.

In the CASPIAN study, of the 201 patients who were treated with IMFINZI 1500 mg every 3 weeks in combination with chemotherapy and evaluable for the presence of ADAs, 0 (0%) patients tested positive for treatment-emergent ADAs. The impact of treatment-emergent ADA on pharmacokinetics and clinical safety of durvalumab was not evaluable as no patient samples tested positive for treatment-emergent durvalumab ADA.

Immunogenicity assay results are highly dependent on several factors, including assay sensitivity and specificity, assay methodology, sample handling, timing of sample collection, concomitant medications and underlying disease.

For these reasons, comparison of incidence of antibodies to IMFINZI with the incidence of antibodies to other products may be misleading.

5.3 Preclinical safety data

Genotoxicity

The genotoxic potential of durvalumab has not been evaluated. As a large protein molecule, durvalumab is not expected to interact directly with DNA or other chromosomal material.

Carcinogenicity

The carcinogenic potential of durvalumab has not been evaluated.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Histidine,
Histidine hydrochloride monohydrate,
Trehalose dihydrate,
Polysorbate 80,
Water for injection.

6.2 Incompatibilities

Incompatibilities were either not assessed or not identified as part of registration of this medicine.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store unopened vials under refrigeration at 2°C to 8°C in the original carton to protect from light. Do not freeze. Do not shake.

6.5 PACK SIZE

120 mg: Box, 1 vial @ 2.4 ml, Reg No: DKI2051303949A1
500 mg: Box, 1 vial @ 10 ml, Reg No: DKI2051303949A1

HARUS DENGAN RESEP DOKTER

Manufactured by
Catalent Indiana LLC
Bloomington, Indiana, USA

Released by

AstraZeneca AB, Gärtunavägen, Södertälje Sweden

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