ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

IMFINZI 50 mg/mL concentrate for solution for infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of concentrate for solution for infusion contains 50 mg of durvalumab.
One vial of 2.4 mL of concentrate contains 120 mg of durvalumab.
One vial of 10 mL of concentrate contains 500 mg of durvalumab.

Durvalumab is produced in mammalian (Chinese hamster ovary) cells by recombinant DNA technology.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion (sterile concentrate).

Clear to opalescent, colourless to slightly yellow solution, free from visible particles. The solution has a pH of approximately 6.0 and an osmolality of approximately 400 mOsm/kg.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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).

4.2 Posology and method of administration

Treatment must be initiated and supervised by a physician experienced in the treatment of cancer.

PD-L1 testing for patients with locally advanced NSCLC
Patients with locally advanced NSCLC should be evaluated for treatment based on the tumour expression of PD-L1 confirmed by a validated test (section 5.1).

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.

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

Guidelines for management of immune-mediated adverse reactions are described in Table 2 (see section 4.4).

Table 2. Recommended treatment modifications for IMFINZI and management recommendations

Adverse reactions	Severity[a]	IMFINZI treatment modification	Corticosteroid treatment unless otherwise specified
Immune-mediated pneumonitis/interstitial lung disease	Grade 2	Withhold dose	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
Immune-mediated hepatitis	Grade 2 with ALT or AST > 3-5 x ULN and/or total bilirubin > 1.5-3 x ULN	Withhold dose	Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
	Grade 3 with AST or ALT > 5-≤ 8 x ULN or total bilirubin > 3-≤ 5x ULN		

Adverse reactions	Severity[a]	IMFINZI treatment modification	Corticosteroid treatment unless otherwise specified
	Grade 3 with AST or ALT > 8 x ULN or total bilirubin > 5 x ULN	Permanently discontinue	
	Concurrent ALT or AST > 3 x ULN and total bilirubin > 2 x ULN with no other cause		
Immune-mediated 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	
Immune-mediated hyperthyroidism, thyroiditis	Grade 2-4	Withhold dose until clinically stable	Symptomatic treatment, see section 4.8
Immune-mediated hypothyroidism	Grade 2-4	No changes	Initiate thyroid hormone replacement as clinically indicated
Immune-mediated adrenal insufficiency or 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
Immune-mediated nephritis	Grade 2 with serum creatinine > 1.5-3 x (ULN or baseline)	Withhold dose	Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
	Grade 3 with serum creatinine > 3 x baseline or > 3-6 x ULN; Grade 4 with serum creatinine > 6 x ULN	Permanently discontinue	

Adverse reactions	Severity[a]	IMFINZI treatment modification	Corticosteroid treatment unless otherwise specified
Immune-mediated 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]
Immune-mediated 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	Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
	Any Grade with signs of respiratory or autonomic insufficiency	Permanently discontinue	
	Grade 3 or 4		
Other immune-mediated adverse reactions	Grade 3	Withhold dose	Initiate 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 etiology or exclude alternate etiologies. 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, withhold 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 populations
Paediatric population
The safety and efficacy of IMFINZI in children and adolescents aged below 18 years of age have not been established. No data are available.

Elderly
No dose adjustment is required for elderly patients (≥ 65 years of age) (see section 5.1). Data on patients aged 75 years of age or older are limited.

Renal impairment
No dose adjustment of IMFINZI is recommended in patients with mild or moderate renal impairment. Data from patients with severe renal impairment are too limited to draw conclusions on this population (see section 5.2).

Hepatic impairment
Data from patients with moderate and severe hepatic impairment are limited. Due to minor involvement of hepatic processes in the clearance of durvalumab no dose adjustment of IMFINZI is recommended for patients with hepatic impairment as no difference in exposure is expected (see section 5.2).

Method of administration
IMFINZI is for intravenous use. It is to be administered as an intravenous infusion solution over 1 hour (see section 6.6).

For instructions on dilution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance(s) 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
Radiation 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%).

Patients should be monitored for signs and symptoms of pneumonitis or radiation 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 and thyroiditis
Immune-mediated hypothyroidism, hyperthyroidism and 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 and 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 or hypopituitarism occurred in patients receiving IMFINZI (see section 4.8). Patients should be monitored for clinical signs and symptoms of hypophysitis or hypopituitarism. 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). Patients should be monitored for abnormal renal function tests prior to and periodically during treatment with IMFINZI 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). Events of Stevens-Johnson Syndrome 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 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, myositis, polymyositis, meningitis, encephalitis, Guillain-Barré syndrome, immune thrombocytopenia, cystitis noninfective and pancreatitis (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 Interaction with other medicinal products and other forms of interaction

The use of systemic corticosteroids or immunosuppressants before starting durvalumab, except physiological dose of systemic corticosteroids (≤ 10 mg/day prednisone or equivalent), is not recommended because of their potential interference with the pharmacodynamic activity and efficacy of durvalumab. However, systemic corticosteroids or other immunosuppressants can be used after starting durvalumab to treat immune-related adverse reactions (see section 4.4).

No formal pharmacokinetic (PK) drug-drug interaction studies have been conducted with durvalumab. Since the primary elimination pathways of durvalumab are protein catabolism via reticuloendothelial system or target-mediated disposition, no metabolic drug-drug interactions are expected. 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

Women of childbearing potential
Women of childbearing potential should use effective contraception during treatment with durvalumab and for at least 3 months after the last dose of durvalumab.

Pregnancy

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 in a mouse allogeneic pregnancy model, disruption of PD-L1 signaling was shown to result in an increase in foetal loss. Animal studies with durvalumab are not indicative of reproductive toxicity (see section 5.3). Human IgG1 is known to cross the placental barrier and placental transfer of durvalumab was confirmed in animal studies. Durvalumab may cause foetal harm when administered to a pregnant woman and is not recommended during pregnancy and in women of childbearing potential not using effective contraception during treatment and for at least 3 months after the last dose.

Breast-feeding
It is unknown whether durvalumab is secreted in human breast milk. Available toxicological data in cynomolgus monkeys have shown low levels of durvalumab in breast milk on Day 28 after birth (see section 5.3). In humans, antibodies may be transferred to breast milk, but the potential for absorption and harm to the newborn is unknown. However, a potential risk to the breast-fed child cannot be excluded. A decision must be made whether to discontinue breast feeding or to discontinue or abstain from durvalumab therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Fertility
There are no data on the potential effects of durvalumab on fertility in humans or animals.

4.7 Effects on ability to drive and use machines

Durvalumab has no or negligible influence on the ability to drive and use machines.

4.8 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						
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	Not known[l]					
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[c]	Common	3.8	0.9	Common	2.6	0.8
Dysphonia	Common	3.1	<0.1	Uncommon	0.8	0

	IMFINZI Monotherapy			IMFINZI Combined with Chemotherapy		
	Any Grade (%)		Grade 3-4 (%)	Any Grade (%)		Grade 3-4 (%)
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
Dermatitis	Uncommon	0.7	<0.1	Common	1.5	0
Alopecia				Very common	31.3	1.1
Pemphigoid[v]	Rare	<0.1	0			
Psoriasis	Uncommon	0.8	<0.1	Uncommon	0.4	0
Musculoskeletal and connective tissue disorders						
Myalgia	Common	5.9	<0.1	Common	3.4	0
Myositis	Uncommon	0.2	<0.1			
Polymyositis	Rare[w]	<0.1	<0.1			
Arthralgia	Very common	10.3	0.3	Common	2.6	0.4
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			
Cystitis noninfective	Rare	<0.1	0			
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 is 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 associated with immune-mediated adverse reactions. Most of these, including severe reactions, resolved following initiation of appropriate medical therapy 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%) patients 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), 2 patients also received 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 patients 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%) patients, Grade 4 in 6 (0.2%) patients and Grade 5 (fatal) in 4 (0.1%) patients. 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 patients 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%) patients. 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. 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). 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 the combined safety database with IMFINZI monotherapy, Grade 3 immune-mediated type 1 diabetes mellitus occurred in 1 (<0.1%) patient. 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 (including pemphigoid) 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 authorisation 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 via the national reporting system listed in Appendix V.

4.9 Overdose

There is no information on overdose with durvalumab. In case of overdose, patients should be closely monitored for signs or symptoms of adverse reactions, and appropriate symptomatic treatment instituted immediately.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: PD-1/PDL-1 (Programmed cell death protein 1/death ligand 1) inhibitors.
ATC code: L01FF03

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 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, immunoglobulin G1 kappa (IgG1κ) monoclonal antibody that selectively blocks the interaction of PD-L1 with PD-1 and CD80 (B7.1). Durvalumab does not induce antibody dependent cell-mediated cytotoxicity (ADCC). Selective blockade of PD-L1/PD-1 and PD-L1/CD80 interactions enhances antitumour immune responses and increases T-cell activation.

Clinical efficacy and safety

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 modeling 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.

NSCLC – PACIFIC Study

The efficacy of IMFINZI was evaluated in the PACIFIC Study, a randomised, double-blind, placebo-controlled, multicentre study in 713 patients with 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 a 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%), age ≥ 75 years (8%), White (69%), Asian (27%), other (4%), current smoker (16%), past-smoker (75%), never smoker (9%), ECOG Performance Status 0 (49%), ECOG Performance Status 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 v1.1.

The study demonstrated a statistically significant improvement in PFS in the IMFINZI-treated group compared with the placebo group [hazard ratio (HR) = 0.52 (95% CI: 0.42, 0.65), p < 0.0001]. The study demonstrated a statistically significant improvement in OS in the IMFINZI-treated group compared with the placebo group [HR = 0.68 (95% CI: 0.53, 0.87), p = 0.00251].

In the 5 year follow-up analysis, with a median follow-up of 34.2 months, IMFINZI continued to demonstrate improved OS and PFS compared to placebo. The OS and PFS results from the primary analysis and the follow-up analysis are summarized in Table 4.

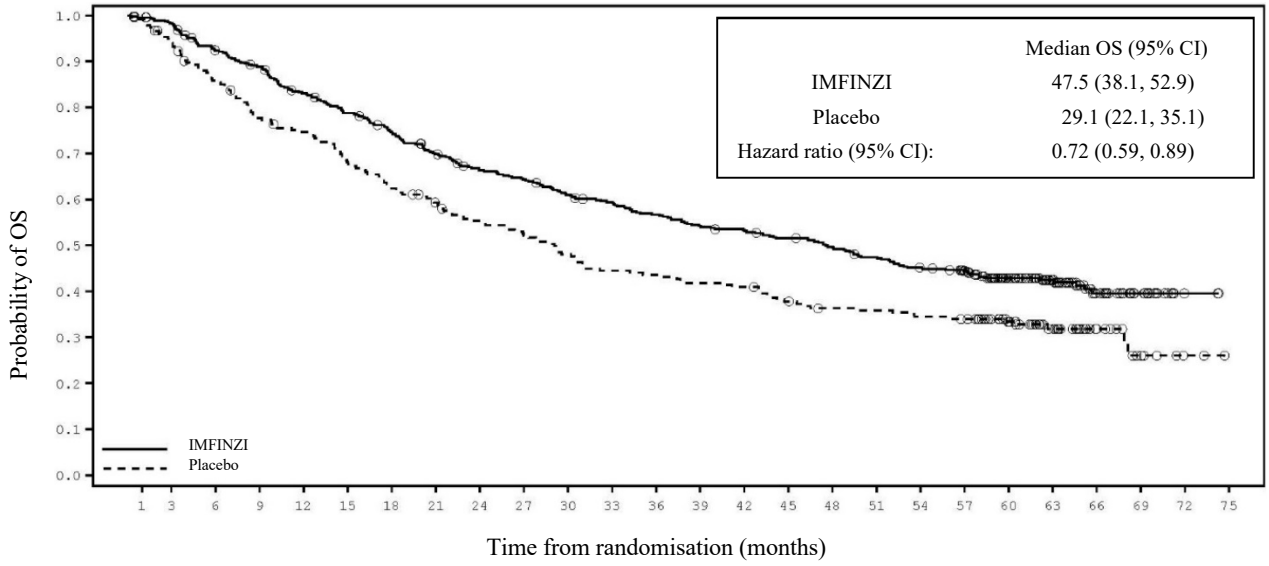
Table 4. Efficacy results for the PACIFIC Study

	Primary Analysis[a]		**5 Year Follow-up Analysis[b]**	
	IMFINZI (n = 476)	**Placebo (n = 237)**	**IMFINZI (n = 476)**	**Placebo (n = 237)**
OS				
Number of deaths (%)	183 (38.4%)	116 (48.9%)	264 (55.5%)	155 (65.4%)
Median (months) (95% CI)	NR (34.7, NR)	28.7 (22.9, NR)	47.5 (38.1, 52.9)	29.1 (22.1, 35.1)
HR (95% CI)	0.68 (0.53, 0.87)		0.72 (0.59, 0.89)	
2- sided p-value	0.00251			
OS at 24 months (%) (95% CI)	66.3% (61.7%, 70.4%)	55.6% (48.9%, 61.3%)	66.3% (61.8%, 70.4%)	55.3% (48.6%, 61.4%)
p-value	0.005			
OS at 48 months (%) (95% CI)			49.7% (45.0%, 54.2%)	36.3% (30.1%, 42.6%)
OS at 60 months (%) (95% CI)			42.9% (38.2%, 47.4%)	33.4% (27.3%, 39.6%)
PFS				
Number of events (%)	214 (45.0%)	157 (66.2%)	268 (56.3%)	175 (73.8%)
Median PFS (months) (95% CI)	16.8 (13.0, 18.1)	5.6 (4.6, 7.8)	16.9 (13.0, 23.9)	5.6 (4.8, 7.7)
HR (95% CI)	0.52 (0.42, 0.65)		0.55 (0.45, 0.68)	
p-value	$p < 0.0001$			
PFS at 12 months (%) (95% CI)	55.9% (51.0%, 60.4%)	35.3% (29.0%, 41.7%)	55.7% (51.0%, 60.2%)	34.5% (28.3%, 40.8%)
PFS at 18 months (%) (95% CI)	44.2% (37.7%, 50.5%)	27.0% (19.9%, 34.5%)	49.1% (44.2%, 53.8%)	27.5% (21.6%, 33.6%)
PFS at 48 months (%) (95% CI)			35.0% (29.9%, 40.1%)	19.9% (14.4%, 26.1%)
PFS at 60 months (%) (95% CI)			33.1% (28.0%, 38.2%)	19.0% (13.6%, 25.2%)
PFS2[c]				
Median PFS2 (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] Primary analysis of PFS at data cut-off 13 February 2017. Primary analysis of OS and PFS2 at data cut-off 22 March 2018.
[b] Follow-up OS and PFS analysis at data cut-off 11 January 2021.
[c] 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

Kaplan-Meier curves for OS and PFS from the 5 year follow-up analysis are presented in Figures 1 and 2.

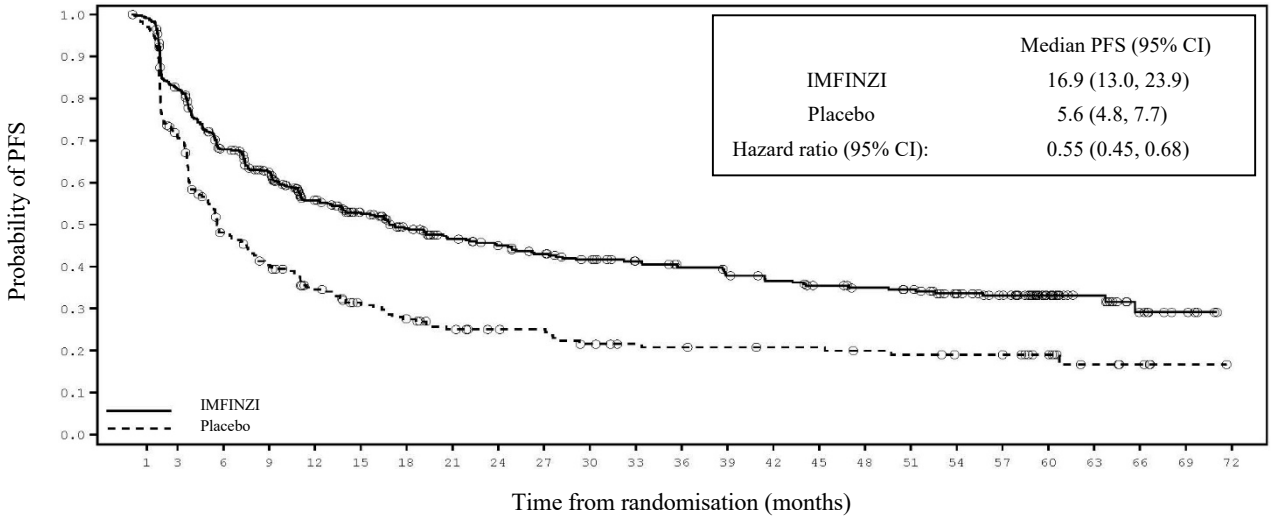
Figure 1. Kaplan-Meier curve of OS



Number of patients at risk

Month	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54	57	60	63	66	69	72	75
IMFINZI	476	464	431	414	385	364	343	319	298	289	273	264	252	241	236	227	218	207	196	183	134	91	40	18	2	0
Placebo	237	220	199	179	171	156	143	133	123	116	107	99	97	93	91	83	78	77	74	72	56	33	16	7	2	0

Figure 2. Kaplan-Meier curve of PFS



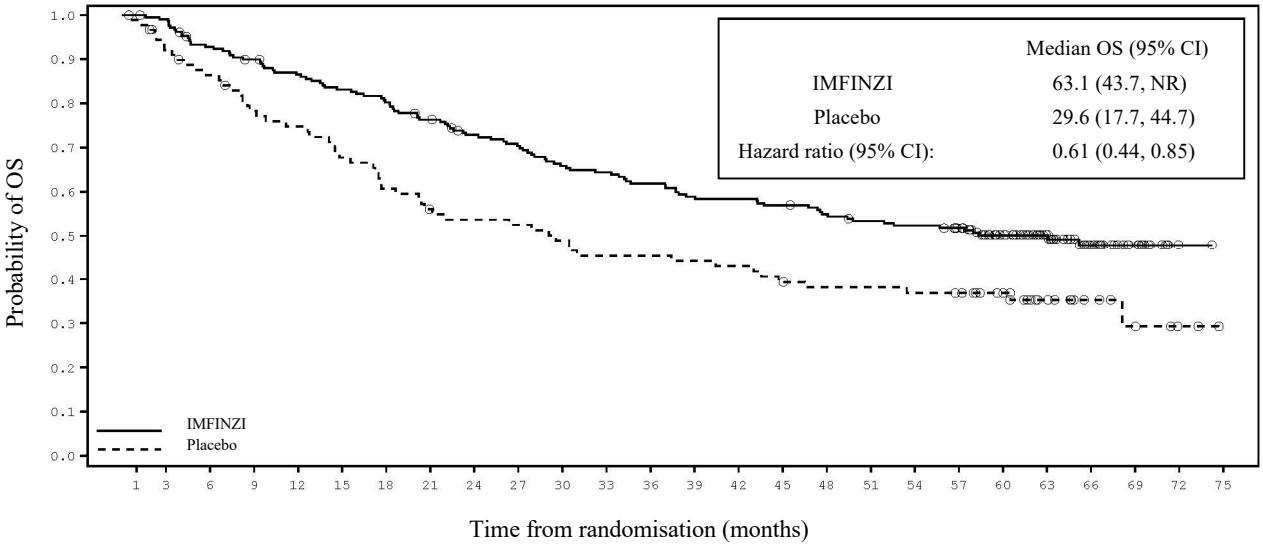
Number of patients at risk

Month	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54	57	60	63	66	69	72
IMFINZI	476	377	301	267	215	190	165	147	137	128	119	110	103	97	92	85	81	78	67	57	34	22	11	5	0
Placebo	237	164	105	87	68	56	48	41	37	36	30	27	26	25	24	24	22	21	19	19	14	6	4	1	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.

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 cannot be established (PD-L1 unknown). PFS and OS results from the 5 year follow-up analysis are summarised in Figures 3, 4, 5 and 6.

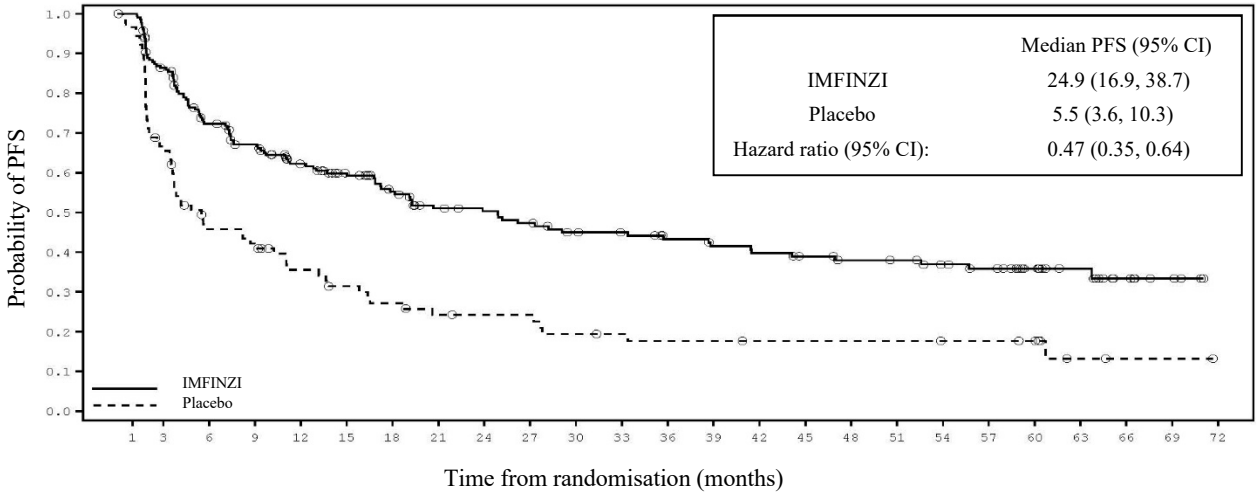
Figure 3. Kaplan-Meier curve of OS for PD-L1 TC ≥ 1%



Number of patients at risk

Month	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54	57	60	63	66	69	72	75
IMFINZI	212	208	193	186	178	171	165	156	146	141	132	129	124	118	117	114	109	105	103	98	74	52	29	14	1	0
Placebo	91	81	75	67	64	58	52	47	45	44	41	38	38	37	36	33	31	31	30	29	24	14	8	5	2	0

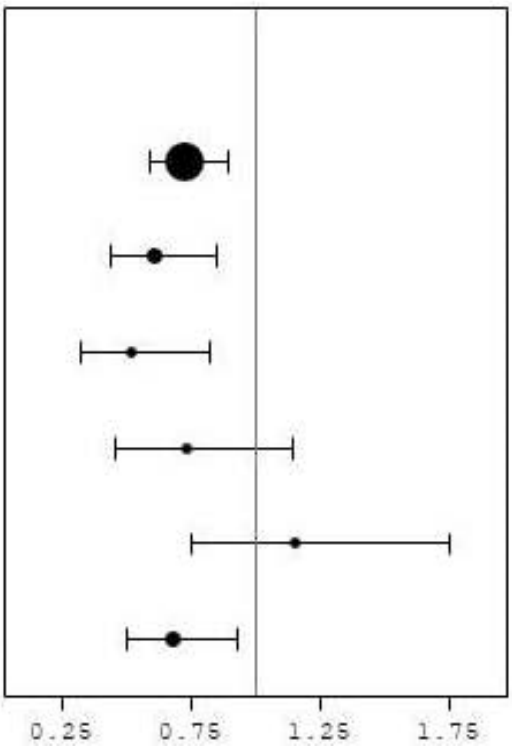
Figure 4. Kaplan-Meier curve of PFS for PD-L1 TC ≥ 1%



Number of patients at risk

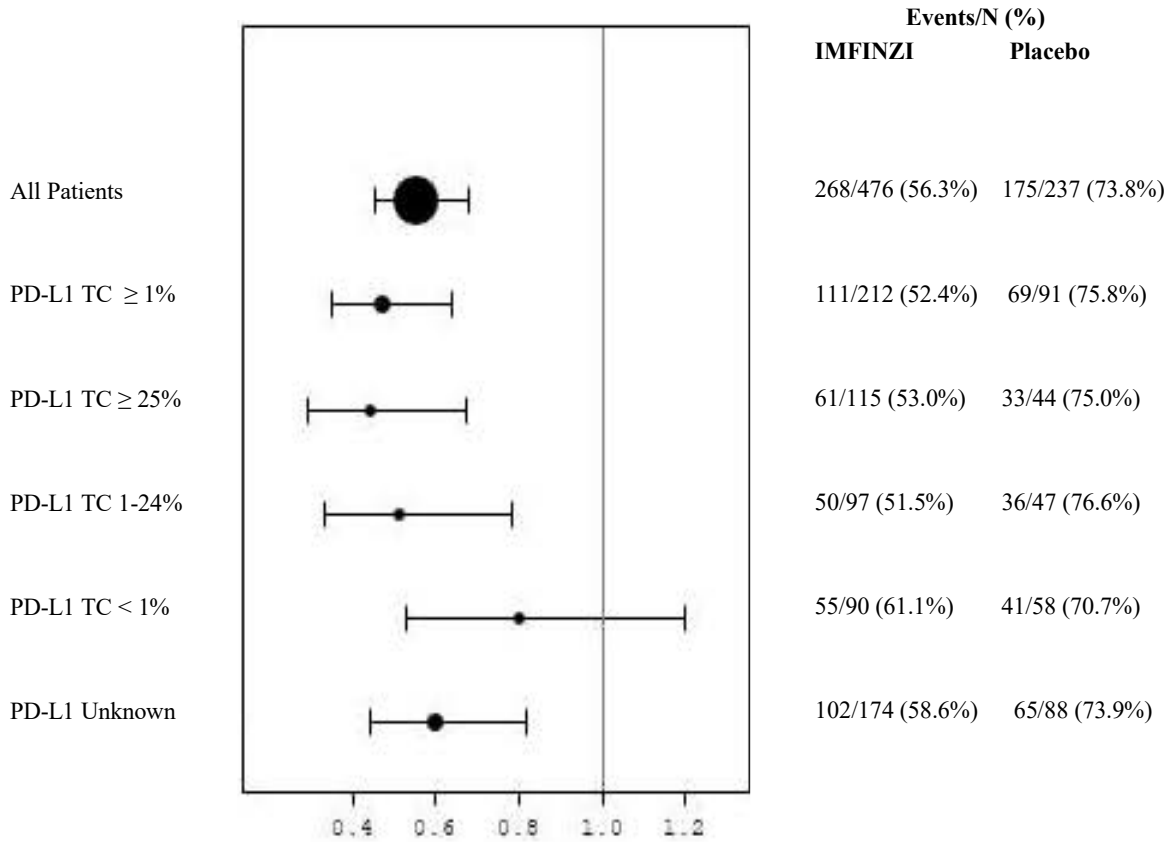
Month	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54	57	60	63	66	69	72
IMFINZI	212	175	142	127	107	95	82	70	67	63	57	55	50	47	45	42	39	38	34	31	22	15	8	4	0
Placebo	91	59	38	34	26	22	19	16	15	15	12	11	10	10	9	9	9	9	8	8	7	2	1	1	0

Figure 5. Forest plot of OS by PD-L1 expression



	Events/N (%) IMFINZI	Placebo
All Patients	264/476 (55.5%)	155/237 (65.4%)
PD-L1 TC ≥ 1%	103/212 (48.6%)	56/91 (61.5%)
PD-L1 TC ≥ 25%	51/115 (44.3%)	27/44 (61.4%)
PD-L1 TC 1-24%	52/97 (53.6%)	29/47 (61.7%)
PD-L1 TC < 1%	59/90 (65.6%)	35/58 (60.3%)
PD-L1 Unknown	102/174 (58.6%)	64/88 (72.7%)

Figure 6. Forest plot of PFS by PD-L1 expression



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.

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, every 4 weeks for the first 8 weeks, followed by every 8 weeks until completion of the treatment period or discontinuation of IMFINZI 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 and 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, multicentre study in 805 treatment naïve ES-SCLC patients with WHO/ECOG Performance status of 0 or 1, body weight >30 kg, 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 (carboplatin or cisplatin) therapy in cycle 1.

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/m^2) on Day 1 and etoposide (80-100 mg/m^2) 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 every 4 weeks 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 etoposide + platinum, PCI was permitted only in Arm 3 per investigator discretion.

Tumour assessments were conducted at Week 6 and Week 12 from the date of randomization, 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 + etoposide + platinum (Arm 2) vs. etoposide + platinum alone (Arm 3) and IMFINZI + tremelimumab + etoposide + platinum (Arm 1) vs. etoposide + platinum 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 + platinum alone (Arm 3) [HR=0.73 (95% CI: 0.591, 0.909), p=0.0047]. Although not formally tested for significance, IMFINZI + etoposide + platinum demonstrated an improvement in PFS vs. etoposide + platinum alone [HR=0.78 (95% CI: 0.645, 0.936)].

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 7 and 8.

Table 5. Efficacy Results for the CASPIAN Study[a]

	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 (%)	210 (78.4)	231 (85.9)
Median OS (months) (95% CI)	12.9 (11.3, 14.7)	10.5 (9.3, 11.2)
HR (95% CI)[b]	0.75 (0.625, 0.910)	
p-value[c]	0.0032	
OS at 18 months (%) (95% CI)	32.0 (26.5, 37.7)	24.8 (19.7, 30.1)
PFS		
Number of events (%)	234 (87.3)	236 (87.7)
Median PFS (months) (95% CI)	5.1 (4.7, 6.2)	5.4 (4.8, 6.2)
HR (95% CI)[b]	0.80 (0.665, 0.959)	
PFS at 6 months (%) (95% CI)	45.4 (39.3, 51.3)	45.8 (39.5, 51.9)
PFS at 12 months (%) (95% CI)	17.9 (13.5, 22.8)	5.3 (2.9, 8.8)
ORR n (%) (95% CI)[d]	182 (67.9) (62.0, 73.5)	156 (58.0) (51.8, 64.0)
Complete Response n (%)	7 (2.6)	2 (0.7)
Partial Response n (%)	175 (65.3)	154 (57.2)
Median DoR (months) (95% CI)[d,e]	5.1 (4.9, 5.3)	5.1 (4.8, 5.3)

[a] Follow-up OS, PFS, ORR and DoR analysis at data cut-off 27 January 2020.

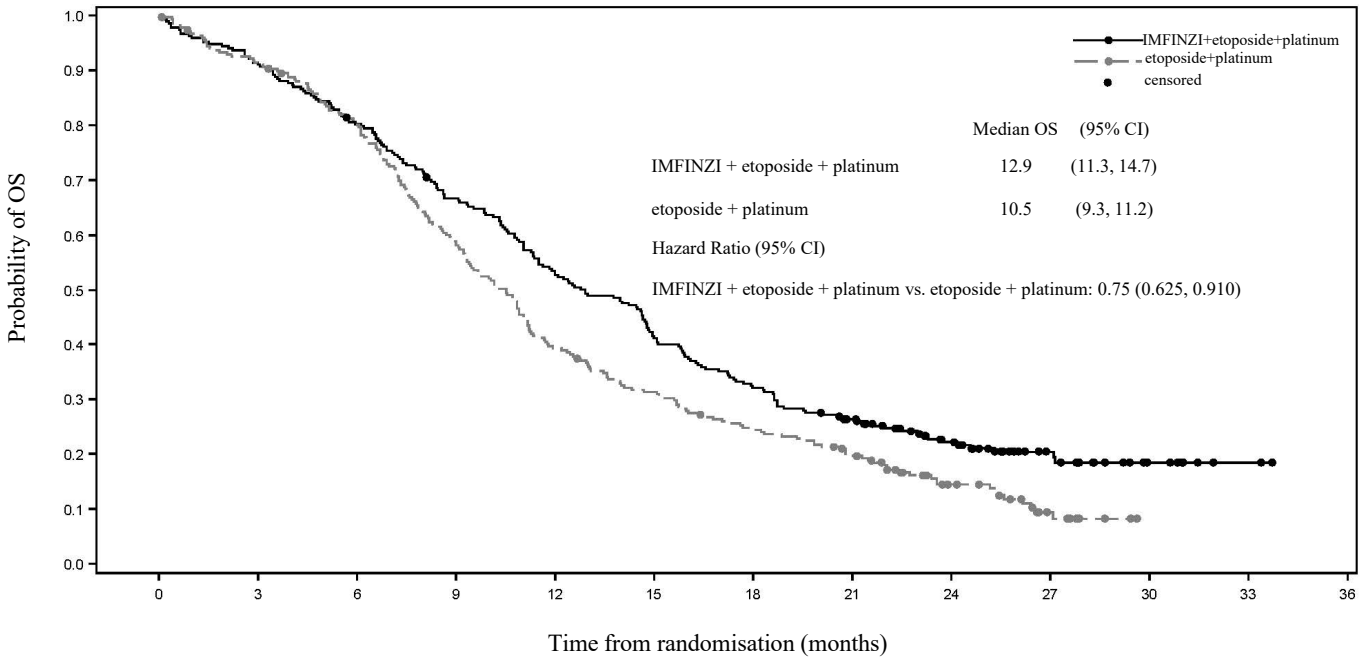
[b] The analysis was performed using the stratified log-rank test, adjusting for planned platinum therapy in Cycle 1 (carboplatin or cisplatin), and using the rank tests of association approach.

[c] At the interim analysis (data cut-off 11 March 2019) the OS p-value was 0.0047, which met the boundary for declaring statistical significance of 0.0178 for a 4% overall 2-sided alpha, based on a Lan-DeMets alpha spending function with O'Brien Fleming type boundary with the actual number of events observed.

[d] Confirmed Objective Response.

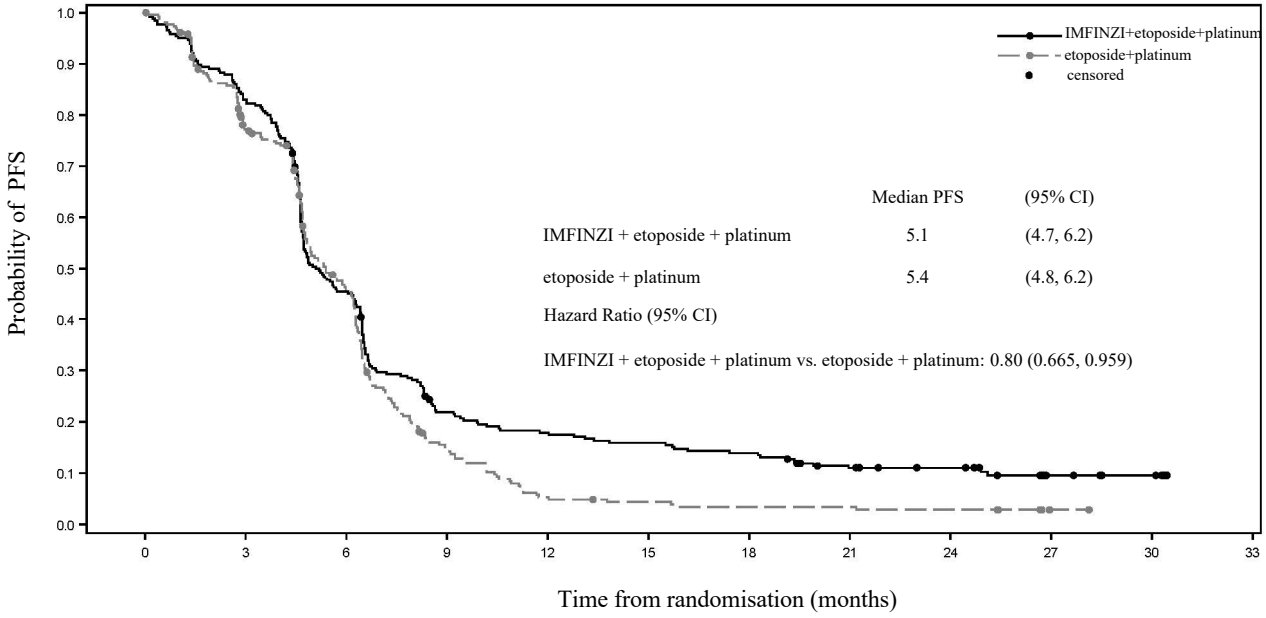
[e] Post-hoc analysis.

Figure 7. Kaplan-Meier curve of OS



Number of patients at risk	0	3	6	9	12	15	18	21	24	27	30	33	36
IMFINZI + etoposide + platinum	268	244	214	177	140	109	85	66	41	21	8	2	0
etoposide + platinum	269	243	212	156	104	82	64	48	24	8	0	0	0

Figure 8. Kaplan-Meier curve of PFS



Number of patients at risk	0	3	6	9	12	15	18	21	24	27	30	33
IMFINZI + etoposide + platinum	268	220	119	55	45	40	35	24	18	8	5	0
etoposide + platinum	269	195	110	33	12	9	7	7	6	1	0	0

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

Paediatric population
The European Medicines Agency has deferred the obligation to submit the results of studies with durvalumab in all subsets of the paediatric population in the treatment of malignant neoplasms (except central nervous system tumours, haematopoietic and lymphoid tissue neoplasms) (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

The pharmacokinetics (PK) of durvalumab was assessed for both IMFINZI monotherapy and in combination with chemotherapy.

The PK of durvalumab was studied in 2903 patients with solid tumours with doses ranging from 0.1 to 20 mg/kg administered intravenously once every two, three or four weeks as monotherapy. 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 every 2 weeks, the geometric mean steady state volume of distribution (V_{ss}) was 5.64 L. Durvalumab clearance (CL) decreased over time resulting in a geometric mean steady state clearance (CL_{ss}) of 8.16 mL/h at Day 365; the decrease in CL_{ss} was not considered clinically relevant. The terminal half-life ($t_{1/2}$), 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. The primary elimination pathways of durvalumab are protein catabolism via reticuloendothelial system or target mediated disposition.

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 or ECOG status had no clinically significant effect on the PK of durvalumab.

Patients with renal impairment
Mild (creatinine clearance (CrCL) 60 to 89 mL/min) and moderate renal impairment (creatinine clearance (CrCL) 30 to 59 mL/min) had no clinically significant effect on the PK of durvalumab.The effect of severe renal impairment (CrCL 15 to 29 mL/min) on the PK of durvalumab is unknown.

Patients with hepatic impairment
Mild hepatic impairment (bilirubin ≤ ULN and AST > ULN or bilirubin > 1.0 to 1.5 × ULN and any AST) had no clinically significant effect on the PK of durvalumab. The effect of moderate hepatic impairment (bilirubin > 1.5 to 3 x ULN and any AST) or severe hepatic impairment (bilirubin > 3.0 x ULN and any AST) 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.

5.3 Preclinical safety data

Carcinogenicity and mutagenicity
The carcinogenic and genotoxic potential of durvalumab has not been evaluated.

Reproductive toxicology
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, and in mouse allogeneic pregnancy models disruption of PD-L1 signalling was shown to result in an increase in foetal loss. In animal reproduction studies, administration of durvalumab to pregnant cynomolgus monkeys from the confirmation of pregnancy through delivery, at exposure levels approximately 18 times higher than those observed at the clinical dose of 10 mg/kg of durvalumab (based on AUC), was associated with placental transfer but not with maternal toxicity or effects on embryofoetal development, pregnancy outcome or postnatal development. Negligible levels of durvalumab was found in milk of cynomolgous monkey on Day 28 after birth.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Histidine
Histidine hydrochloride monohydrate
Trehalose dihydrate
Polysorbate 80
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

Unopened vial
3 years.

Diluted solution

Chemical and physical in-use stability has been demonstrated for up to 30 days at 2°C to 8°C and for up to 24 hours at room temperature (up to 25°C) 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 2°C to 8°C or 12 hours at room temperature (up to 25°C), unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).

Do not freeze.

Store in the original package in order to protect from light.

For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

2.4 mL of concentrate in a Type 1 glass vial with an elastomeric stopper and a gray flip-off aluminium seal containing 120 mg durvalumab. Pack size of 1 vial.

10 mL of concentrate in a Type 1 glass vial with an elastomeric stopper and a white flip-off aluminium seal containing 500 mg durvalumab. Pack size of 1 vial.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Preparation of solution
IMFINZI is supplied as a single-dose vial and does not contain any preservatives, aseptic technique must be observed.

- Visually inspect the medicinal product for particulate matter and discolouration. IMFINZI is 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 sodium chloride 9 mg/mL (0.9%) solution for injection, or glucose 50 mg/mL (5%) solution for 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.

- Discard any unused portion left in the vial.

Administration
- Administer the infusion solution intravenously over 1 hour through an intravenous line containing a sterile, low-protein binding 0.2 or 0.22 micron in-line filter.

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

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

AstraZeneca AB
SE-151 85 Södertälje
Sweden

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1322/002 120 mg vial
EU/1/18/1322/001 500 mg vial

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21 September 2018

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

AstraZeneca Pharmaceuticals LP
Frederick Manufacturing Center (FMC)
633 Research Court
Frederick,
Maryland
21703
United States

Name and address of the manufacturers responsible for batch release

AstraZeneca AB
Gärtunavägen
SE-151 85 Södertälje
Sweden

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

IMFINZI 50 mg/ml concentrate for solution for infusion
durvalumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One ml of concentrate contains 50 mg of durvalumab.
One vial of 2.4 ml of concentrate contains 120 mg of durvalumab.
One vial of 10 ml of concentrate contains 500 mg of durvalumab.

3. LIST OF EXCIPIENTS

Excipients: histidine, histidine hydrochloride monohydrate, trehalose dihydrate, polysorbate 80, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion

120 mg/2.4 ml
500 mg/10 ml
1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intravenous use.
Read the package leaflet before use.
For single use only.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

AstraZeneca AB
SE-151 85 Södertälje
Sweden

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1322/002 120 mg vial
EU/1/18/1322/001 500 mg vial

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

IMFINZI 50 mg/ml sterile concentrate
durvalumab
IV

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

120 mg/2.4 ml
500 mg/10 ml

6. OTHER

AstraZeneca AB

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

IMFINZI 50 mg/mL concentrate for solution for infusion
durvalumab

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What IMFINZI is and what it is used for

IMFINZI is used to treat a type of lung cancer called non-small cell lung cancer (NSCLC) in adults. It is used when your NSCLC:
- has spread within your lung and cannot be removed by surgery, and
- has responded or stabilised after initial treatment with chemotherapy and radiotherapy.

IMFINZI is used to treat a type of lung cancer called extensive-stage small cell lung cancer (ES-SCLC) in adults. It is used when your SCLC:
- has spread within your lungs (or to other parts of the body) and
- has not previously been treated.

IMFINZI contains the active substance durvalumab which is a monoclonal antibody, a type of protein designed to recognise a specific target substance in the body. IMFINZI works by helping your immune system fight your cancer.

If you have any questions about how IMFINZI works or why this medicine has been prescribed for you, ask your doctor or pharmacist.

IMFINZI will be given in combination with chemotherapy for SCLC. It is important that you also read the package leaflets for the specific chemotherapy you may be receiving. If you have any questions about these medicines, ask your doctor.

2. What you need to know before you are given IMFINZI

You should not be given IMFINZI
- if you are allergic to durvalumab or any of the other ingredients of this medicine (listed in section 6 “Contents of the pack and other information”). Talk to your doctor if you are not sure.

Warnings and precautions
Talk to your doctor before you are given IMFINZI if:

- you have an autoimmune disease (an illness where the body's immune system attacks its own cells);
- you have had an organ transplant;
- you have lung problems or breathing problems;
- you have liver problems.

If any of the above apply to you (or you are not sure), talk to your doctor before you are given IMFINZI.

When you are given IMFINZI, you can have some serious side effects.

If you have any of the following, call or see your doctor straight away. Your doctor may give you other medicines that prevent more severe complications and to help reduce your symptoms. Your doctor may delay the next dose of IMFINZI or stop your treatment with IMFINZI, if you have:

- **inflammation of the lungs**: symptoms may include new or worsening cough, shortness of breath or chest pain;
- **inflammation of the liver**: symptoms may include nausea or vomiting, feeling less hungry, pain on the right side of your stomach, yellowing of skin or whites of eyes, drowsiness, dark urine or bleeding or bruising more easily than normal;
- **inflammation of the intestines**: symptoms may include diarrhoea or more bowel movements than usual, or stools that are black, tarry or sticky with blood or mucus, severe stomach pain or tenderness;
- **inflammation of glands** (especially the thyroid, adrenal, pituitary and pancreas): symptoms may include fast heart rate, extreme tiredness, weight gain or weight loss, dizziness or fainting, hair loss, feeling cold, constipation, headaches that will not go away or unusual headaches, abdominal pain, nausea and vomiting;
- **type 1 diabetes**: symptoms may include high blood sugar, feeling more hungry or thirsty than usual, passing urine more often than usual, fast and deep breathing, confusion, or a sweet smell to your breath, a sweet or metallic taste in your mouth or a different odour to your urine or sweat;
- **inflammation of the kidneys**: symptoms may include decrease in the amount of urine you pass;
- **inflammation of the skin**: symptoms may include rash, itching, skin blistering or ulcers in the mouth or on other moist surfaces;
- **inflammation of the heart muscle**: symptoms may include chest pain, shortness of breath, or irregular heartbeat;
- **inflammation or problems of the muscles**: symptoms may include muscle pain, or weakness or rapid fatigue of the muscles;
- **infusion-related reactions**: symptoms may include chills or shaking, itching or rash, flushing, shortness of breath or wheezing, dizziness or fever;
- **inflammation of the brain** (encephalitis) **or inflammation of the membrane around the spinal cord and brain** (meningitis): symptoms may include seizures, neck stiffness, headache, fever, chills, vomiting, eye sensitivity to light, confusion and sleepiness;
- **inflammation of the nerves:** symptoms may include pain, weakness, and paralysis in the extremities (Guillain-Barré syndrome);
- **low number of platelets:** symptoms may include bleeding (nose or gum bleeding) and/or bruising.

If you have any of the symptoms listed above, call or see your doctor straight away.

Children and adolescents
IMFINZI should not be used in children and adolescents below 18 years of age.

Other medicines and IMFINZI
Tell your doctor if you are taking, have recently taken or might take any other medicines. This includes herbal medicines and medicines obtained without a prescription.

Pregnancy
- Tell your doctor if you are pregnant, think you may be pregnant or are planning to have a baby.
- If you are a woman who could become pregnant you must use effective birth control while you are being treated with IMFINZI and for at least 3 months after your last dose.

Breast-feeding
- Tell your doctor if you are breast-feeding.
- Ask your doctor if you can breast-feed during or after treatment with IMFINZI.
- It is not known if IMFINZI passes into human breast milk.

Driving and using machines
IMFINZI is not likely to affect you being able to drive and use machines.

However, if you have side effects that affect your ability to concentrate and react, you should be careful when driving or operating machines.

3. How you are given IMFINZI

IMFINZI will be given to you in a hospital or clinic under the supervision of an experienced doctor.
- The recommended dose of IMFINZI is 10 mg per kg of your body weight every 2 weeks or 1500 mg every 3 or 4 weeks.
- Your doctor will give you IMFINZI through an infusion (drip) into your vein for about 1 hour.
- Your doctor will decide how many treatments you need.

If you miss an appointment to get IMFINZI
- Call your doctor straight away to reschedule your appointment.
- It is very important that you do not miss a dose of this medicine.

If you have any further questions about your treatment, ask your doctor.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

When you get IMFINZI, you can have some serious side effects (see section 2).

Talk to your doctor straight away if you get any of the following side effects, that have been reported in clinical trials with patients receiving IMFINZI alone and includes the serious side effects listed in section 2:

Very common (may affect more than 1 in 10 people)
- infections of the upper respiratory tract
- underactive thyroid gland that can cause tiredness or weight gain
- cough
- diarrhoea
- stomach pain
- skin rash or itchiness
- fever
- joint pain (arthralgia)

Common (may affect up to 1 in 10 people)
- serious lung infections (pneumonia)
- fungal infection in the mouth
- tooth and mouth soft tissue infections
- flu-like illness
- overactive thyroid gland that can cause fast heart rate or weight loss
- inflammation of the lungs (pneumonitis)
- hoarse voice (dysphonia)
- abnormal liver tests (aspartate aminotransferase increased; alanine aminotransferase increased)
- night sweats
- muscle pain (myalgia)
- abnormal kidney function tests (blood creatinine increased)
- painful urination
- swelling of the legs (oedema peripheral)
- reaction to the infusion of the medicine that can cause fever or flushing

Uncommon (may affect up to 1 in 100 people)
- inflammation of thyroid gland
- decreased secretion of hormones produced by the adrenal glands that can cause tiredness
- scarring of lung tissue
- inflammation of the liver that can cause nausea or feeling less hungry
- blistering of the skin
- inflammation of the gut or intestine (colitis)
- inflammation of the muscle
- inflammation of the kidneys (nephritis) that can decrease the amount of your urine
- inflammation of the pancreas
- red, itchy, dry, scaly patches of thickened skin (psoriasis)

Rare (may affect up to 1 in 1000 people)
- a condition leading to high blood sugar levels (type 1 diabetes mellitus)
- underactive function of pituitary gland (hypopituitarism including diabetes insipidus) that can cause tiredness, an increase in the amount of your urine
- inflammation of the heart
- a condition in which the muscles become weak and there is a rapid fatigue of the muscles (myasthenia gravis)
- inflammation of the membrane around the spinal cord and brain (meningitis)
- low number of platelets caused by an immune reaction (immune thrombocytopenia)
- Inflammation of the bladder. Signs and symptoms may include frequent and/or painful urination, urge to pass urine, blood in urine, pain or pressure in lower abdomen.

The following side effects have been reported in clinical trials in patients taking IMFINZI in combination with chemotherapy:

Very common (may affect more than 1 in 10 people)
- low number of white blood cells
- low number of red blood cells
- low number of platelets
- nausea; vomiting; constipation
- hair loss
- feeling less hungry
- feeling tired or weak
- cough

Common (may affect up to 1 in 10 people)

- diarrhoea
- fever
- low number of white blood cells with signs of fever
- skin rash or itchiness
- underactive thyroid gland; overactive thyroid gland; inflammation of thyroid gland
- serious lung infections (pneumonia)
- tooth and mouth soft tissue infections
- abnormal liver tests (aspartate aminotransferase increased; alanine aminotransferase increased)
- swelling of legs (oedema peripheral)
- stomach pain
- inflammation of the mouth or lips
- muscle pain (myalgia)
- inflammation of the lungs (pneumonitis)
- infection of the upper respiratory tract
- low number of red blood cells, white blood cells, and platelets (Pancytopenia)
- decreased secretion of hormones produced by the adrenal glands that can cause tiredness
- inflammation of the liver that can cause nausea or feeling less hungry
- abnormal kidney function tests (blood creatinine increased)
- painful urination
- reaction to the infusion of the medicine that can cause fever or flushing
- joint pain (arthralgia)

Uncommon (may affect up to 1 in 100 people)
- fungal infection in the mouth
- flu-like illness
- type 1 diabetes mellitus
- hoarse voice (dysphonia)
- scarring of lung tissue
- inflammation of the gut or intestine (colitis)
- night sweats
- red, itchy, dry, scaly patches of thickened skin (psoriasis)

Talk to your doctor straight away if you get any of the side effects listed above.

Reporting of side effects
If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store IMFINZI

IMFINZI will be given to you in a hospital or clinic and the healthcare professional will be responsible for its storage. The storage details are as follows:
Keep this medicine out of the sight and reach of children.
Do not use this medicine after the expiry date which is stated on the carton and vial label after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C to 8°C).
Do not freeze.
Store in the original package in order to protect from light.
Do not use if this medicine is cloudy, discoloured or contains visible particles.

Do not store any unused portion of the infusion solution for re-use. Any unused medicine or waste material should be disposed of in accordance with local requirements.

6. Contents of the pack and other information

What IMFINZI contains
The active substance is durvalumab.

Each mL of concentrate for solution for infusion contains 50 mg of durvalumab.

Each vial contains either 500 mg of durvalumab in 10 mL of concentrate or 120 mg of durvalumab in 2.4 mL of concentrate.

The other ingredients are: histidine, histidine hydrochloride monohydrate, trehalose dihydrate, polysorbate 80, water for injections.

What IMFINZI looks like and contents of the pack
IMFINZI concentrate for solution for infusion is a sterile, preservative-free, clear to opalescent, colourless to slightly yellow solution, free from visible particles.

It is available in packs containing either 1 glass vial of 2.4 mL of concentrate or 1 glass vial of 10 mL of concentrate.

Marketing Authorisation Holder
AstraZeneca AB
SE-151 85 Södertälje
Sweden

Manufacturer
AstraZeneca AB
Gärtunavägen
SE-151 85 Södertälje
Sweden

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu

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The following information is intended for healthcare professionals only:

Preparation and administration of the infusion

- Parenteral medicinal products should be inspected visually for particulate matter and discolouration prior to administration. The concentrate is a clear to opalescent, colourless to slightly yellow solution, free from visible particles. Discard the vial if the solution is cloudy, discoloured or visible particles are observed.
- Do not shake the vial.
- Withdraw the required volume of concentrate from the vial(s) and transfer into an intravenous bag containing sodium chloride 9 mg/mL (0.9%) solution for injection, or glucose 50 mg/mL (5%) solution for injection, to prepare a diluted solution with a final concentration ranging from 1 to 15 mg/mL. Mix diluted solution by gentle inversion.
- The medicinal product, once diluted, should be used immediately. The diluted solution must not be frozen. 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.
- If refrigerated, intravenous bags must be allowed to come to room temperature prior to use. Administer the infusion solution intravenously over 1 hour using a sterile, low-protein binding 0.2 or 0.22 micron in-line filter.
- Do not co-administer other medicinal products through the same infusion line.
- IMFINZI is single-dose. Discard any unused portion left in the vial.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

ANNEX IV

SCIENTIFIC CONCLUSIONS AND GROUNDS FOR THE VARIATION TO THE TERMS OF THE MARKETING AUTHORISATION(S)

Scientific conclusions

Taking into account the PRAC Assessment Report on the PSUR(s) for durvalumab, the scientific conclusions of CHMP are as follows:

In response to a PRAC request in context of procedure EMEA/H/C/PSUSA/00010723/201904, the MAH performed a review of psoriasis and suitable related terms. The cumulative review presented in the present PSUR, including a case overview (70 cases) and review of 14 cases that met selection criteria. Data from clinical studies and disproportionality analysis are included. In view of available data on psoriasis, the PRAC considers a causal relationship between durvalumab and psoriasis is at least a reasonable possibility. The PRAC Rapporteur concluded that the product information of products containing durvalumab should be amended accordingly.

Therefore the event of psoriasis should be added to the list of adverse drug reactions (ADRs) in section 4.8 of the SmPC with a frequency uncommon. The Package leaflet is updated accordingly.

The CHMP agrees with the scientific conclusions made by the PRAC.

Grounds for the variation to the terms of the marketing authorisation(s)

On the basis of the scientific conclusions for durvalumab the CHMP is of the opinion that the benefit-risk balance of the medicinal product(s) containing durvalumab is unchanged subject to the proposed changes to the product information

The CHMP recommends that the terms of the marketing authorisation(s) should be varied.