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).

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 of IMFINZI is 10 mg/kg administered as an intravenous infusion over 60 minutes every 2 weeks, until disease progression or unacceptable toxicity, or a maximum of 12 months.

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 immune-mediated adverse reactions are described in Table 1 (see section 4.4).

Table 1. 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 4 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		
	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	Withhold dose	Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
	Grade 3 or 4	Permanently discontinue	
Immune-mediated hyperthyroidism	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

Adverse reactions	**Severity**[a]	**IMFINZI treatment modification**	**Corticosteroid treatment unless otherwise specified**
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	
Immune-mediated rash or dermatitis	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	Withold dose[b]	Initiate 2 to 4 mg/kg/day prednisone or equivalent followed by a taper
	Grade 3 or 4, or any Grade with positive biopsy	Permanently discontinue	
Immune-mediated myositis/polymyositis	Grade 2 or 3	Withhold dose	Initiate 1 to 4 mg/kg/day prednisone or equivalent followed by a taper
	Grade 4	Permanently discontinue[c]	
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	Withold dose until clinically stable	

Adverse reactions	Severity[a]	IMFINZI treatment modification	Corticosteroid treatment unless otherwise specified
Other immune-mediated adverse reactions	Grade 3	Withhold dose	Consider initial dose of 1 mg/kg/day to 4 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 3 to 5 days despite corticosteroids, promptly start additional immunosuppressive therapy. Upon resolution (Grade 0), corticosteroid taper should be initiated and continued over at least 1 month, after which IMFINZI can be resumed based on clinical judgment.

[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. 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 or 4 (severe or life-threatening) immune-mediated adverse reactions.

For non-immune-mediated adverse reactions, consider withholding 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 60 minutes (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.

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%) (see section 4.8).

Patients should be monitored for signs and symptoms of pneumonitis or radiation pneumonitis. Patients with suspected pneumonitis should be evaluated with radiographic imaging 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
Hypothyroidism and hyperthyroidism
Immune-mediated hypothyroidism and hyperthyroidism (including 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 and hyperthyroidism (including thyroiditis) should be managed as recommended in section 4.2.

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.

Type 1 diabetes mellitus
Immune-mediated type 1 diabetes mellitus 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.

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, 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.

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 were reported in less than 1% of patients treated with IMFINZI monotherapy in clinical trials (n = 1889): myocarditis, myositis, polymyositis. Patients should be monitored for signs and symptoms and managed as recommended in section 4.2. Events of pancreatitis have been reported in patients in the clinical study programme. 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 the PACIFIC Study: 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); 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.

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.

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 (10 mg/kg) has been evaluated in the PACIFIC Study (n = 475) in patients with locally advanced, unresectable NSCLC who had completed treatment with at least 2 cycles of concurrent chemoradiation within 1 to 42 days prior to initiation of the study. In this patient population, the most frequent adverse reactions were cough (40.2% vs 30.3% in placebo), upper respiratory tract infections (26.1% vs 11.5% in placebo) and rash (21.7% vs 12.0% in placebo). The most frequent Grade 3-4 adverse reaction was pneumonia (6.5% vs 5.6% in placebo). The overall incidence of Grade 3 or 4 adverse reactions was 12.8% in the IMFINZI arm vs 9.8% in placebo.

Tabulated list of adverse reactions
Table 2 lists the incidence of adverse reactions in patients with locally advanced, unresectable NSCLC in the PACIFIC Study, based on the frequency of that adverse reaction type regardless of investigator assessed causality. 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 2. Adverse drug reactions in patients with locally advanced unresectable NSCLC treated with IMFINZI at 10 mg/kg

	Any Grade (%)		Grade 3-4 (%)
Infections and infestations			
Upper respiratory tract infections[a]	Very common	26.1	0.4

	Any Grade (%)		Grade 3-4 (%)
Pneumonia[b,c]	Very common	17.1	6.5
Dental and oral soft tissue infections[d]	Common	3.6	0
Oral candidiasis	Common	3.2	0
Influenza	Common	2.5	0
Endocrine disorders			
Hypothyroidism[e]	Very common	11.6	0.2
Hyperthyroidism[f]	Common	8.2	0
Adrenal insufficiency	Uncommon	0.2	0
Type 1 diabetes mellitus	Uncommon	0.2	0.2
Hypophysitis/ Hypopituitarism	Rare[g]	<0.1	<0.1
Diabetes insipidus	Rare[g]	<0.1	<0.1
Cardiac disorders			
Myocarditis	Rare[g]	<0.1	<0.1
Respiratory, thoracic and mediastinal disorders			
Cough/Productive Cough[h]	Very common	40.2	0.6
Pneumonitis[b]	Very common	12.6	1.7
Dysphonia	Common	3.8	0
Interstitial lung disease	Uncommon	0.6	0
Gastrointestinal disorders			
Diarrhoea	Very common	18.3	0.6
Abdominal pain[i]	Very common	10.1	0.4
Colitis[j]	Common	1.1	0.2
Hepatobiliary disorders			
Aspartate aminotransferase increased or Alanine aminotransferase increased[k]	Common	6.1	1.9
Hepatitis[c,l]	Uncommon	0.6	0
Skin and subcutaneous tissue disorders			
Rash[m]	Very common	21.7	0.6
Pruritus[n]	Very common	12.4	0
Dermatitis	Common	1.5	0
Night sweats	Common	2.3	0
Musculoskeletal and connective tissue disorders			
Myalgia	Common	8.0	0.2
Myositis	Uncommon	0.4	0
Polymyositis[c]	Rare[g]	<0.1	<0.1
Renal and urinary disorders			
Blood creatinine increased	Common	4.6	0.2
Dysuria	Common	2.3	0
Nephritis[o]	Uncommon	0.4	0
General disorders and administration site conditions			
Pyrexia	Very common	14.7	0.2
Peripheral oedema	Common	7.8	0
Injury, poisoning and procedural complications			
Infusion related reaction[p]	Common	1.9	0

[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 klebsiella, pneumonia necrotising, pneumonia pneumococcal and pneumonia streptococcal.

[c] fatal pneumonitis and fatal pneumonia were reported at similar rate between the IMFINZI-treated group and placebo group in the PACIFIC Study; fatal hepatitis and fatal polymyositis were reported in other clinical trials.
[d] includes gingivitis, oral infection, periodontitis, pulpitis dental, tooth abscess and tooth infection.
[e] includes autoimmune hypothyroidism and hypothyroidism.
[f] includes hyperthyroidism, autoimmune thyroiditis, thyroiditis, thyroiditis subacute and Basedow's disease.
[g] frequency is based on events not observed in the PACIFIC Study but observed in other clinical trials (n=1889).
[h] includes cough and productive cough.
[i] includes abdominal pain, abdominal pain lower, abdominal pain upper and flank pain.
[j] includes colitis, enteritis, enterocolitis, and proctitis.
[k] includes alanine aminotransferase increased, aspartate aminotransferase increased, hepatic enzyme increased and transaminases increased.
[l] includes hepatitis, autoimmune hepatitis, hepatitis toxic, hepatocellular injury, hepatitis acute, and hepatotoxicity.
[m] includes rash erythematous, rash generalised, rash macular, rash maculopapular, rash papular, rash pruritic, rash pustular, erythema, eczema and rash.
[n] includes pruritus generalised and pruritus.
[o] includes autoimmune nephritis, tubulointerstitial nephritis, nephritis, glomerulonephritis and glomerulonephritis membranous.
[p] 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 of IMFINZI. The data for the following immune-mediated adverse reactions reflect the combined safety database of 1889 patients which includes the PACIFIC Study and two additional studies (a multi-cohort, open-label clinical trial in patients with advanced solid tumours, and an open-label study in patients with locally advanced or metastatic NSCLC). Across all studies, IMFINZI was administered at a dose of 10 mg/kg every 2 weeks. The management guidelines for these adverse reactions are described in section 4.4.

Immune-mediated pneumonitis

In the combined safety database with IMFINZI monotherapy, (n = 1889 multiple tumour types), immune-mediated pneumonitis occurred in 79 (4.2%) patients, including Grade 3 in 12 (0.6%) patients, Grade 4 in 1 (< 0.1%) patient, and Grade 5 in 5 (0.3%) patients. The median time to onset was 53 days (range: 1-341 days). Forty-five of the 79 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day), and 2 patients also received infliximab. IMFINZI was discontinued in 26 patients. Resolution occurred in 42 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 (10.7%), than in the other patients in the combined safety database (2.0%).

In the PACIFIC Study, (n = 475 in the IMFINZI arm, and n = 234 in the placebo arm) immune-mediated pneumonitis occurred in 51 (10.7%) patients in the IMFINZI-treated group and 16 (6.8%) patients in the placebo group, including Grade 3 in 8 (1.7%) 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 53 days (range: 1-341 days) vs. 55.5 days (range: 0-231 days) in the placebo group. In the IMFINZI-treated group, 44 of the 51 patients received systemic corticosteroids, including 28 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, 11 of the 16 patients received systemic corticosteroids, including 9 patients who received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). Resolution occurred for 27 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 19 (1.0%) patients, including Grade 3 in 11 (0.6%) patients and Grade 5 (fatal) in 1 (< 0.1%) patient.

The median time to onset was 70 days (range: 15-312 days). Thirteen of the 19 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). One patient also received mycophenolate treatment. IMFINZI was discontinued in 4 patients. Resolution occurred in 13 patients.

Immune-mediated colitis
In the combined safety database with IMFINZI monotherapy, immune-mediated colitis or diarrhoea occurred in 31 (1.6%) patients, including Grade 3 in 6 (0.3%) patients and Grade 4 in 1 (<0.1%) patient. The median time to onset was 74 days (range: 1-365 days). Sixteen of the 31 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). One patient also received infliximab treatment. IMFINZI was discontinued in 8 patients. Resolution occurred in 23 patients.

Immune-mediated endocrinopathies
Hypothyroidism
In the combined safety database with IMFINZI monotherapy, immune-mediated hypothyroidism occurred in 137 (7.3%) patients, including Grade 3 in 1 (< 0.1%) patient. The median time to onset was 85 days (range: 9-378 days). Of the 137 patients, 134 patients received hormone replacement therapy and two patients received high-dose corticosteroids (at least 40 mg prednisone or equivalent per day) for hypothyroidism followed by hormone replacement. IMFINZI was not discontinued in any patient due to hypothyroidism.

Hyperthyroidism
In the combined safety database with IMFINZI monotherapy, immune-mediated hyperthyroidism occurred in 34 (1.8%) patients, there were no Grade 3 or 4 cases. The median time to onset was 41 days (range: 14-195 days). Twenty-six of the 34 patients received medical therapy (thiamazole, carbimazole, propylthiouracil or beta-blocker), 12 patients received thyroxine when hyperthyroidism transitioned to hypothyroidism, 12 patients received systemic corticosteroids and 3 of the 12 patients received high-dose systemic corticosteroid treatment (at least 40 mg prednisone or equivalent per day). IMFINZI was not discontinued in any patient due to hyperthyroidism. Eight patients experienced hypothyroidism following hyperthyroidism.

Adrenal insufficiency
In the combined safety database with IMFINZI monotherapy, immune-mediated adrenal insufficiency occurred in 7 (0.4%) patients, including Grade 3 in 1 (<0.1%) patient. The median time to onset was 141 days (range: 70-265 days). All 7 patients received systemic corticosteroids; 2 of the 7 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). IMFINZI was not discontinued in any patient due to adrenal insufficiency. Resolution occurred in 1 patient.

Type 1 diabetes mellitus
In the combined safety database with IMFINZI monotherapy, immune-mediated type 1 diabetes mellitus occurred in 1 (< 0.1%) patient (Grade 3). IMFINZI was discontinued due to type 1 diabetes mellitus. The time to onset was 42 days. This 1 patient received insulin.

Hypophysitis/Hypopituitarism
In the combined safety database with IMFINZI monotherapy, immune-mediated hypopituitarism occurred in 1 (< 0.1%) patient (Grade 3). This 1 patient received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day) and IMFINZI was not discontinued.

Immune-mediated nephritis
In the combined safety database with IMFINZI monotherapy, immune-mediated nephritis occurred in 3 (0.2%) patients, including Grade 3 in 1 (< 0.1%) patient. The median time to onset was 95 days (range: 28-239 days). Two (0.1%) patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). IMFINZI was discontinued in all 3 patients. Resolution occurred in 2 patients.

Immune-mediated rash
In the combined safety database with IMFINZI monotherapy, immune-mediated rash or dermatitis occurred in 30 (1.6%) patients, including Grade 3 in 7 (0.4%) patients. The median time to onset was 74 days (range: 1-365 days). Eleven of the 30 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). IMFINZI was discontinued in 2 patients. Resolution occurred in 18 patients.

Infusion related reactions
In the combined safety database with IMFINZI monotherapy, infusion related reactions occurred in 35 (1.9%) patients, including Grade 3 in 5 (0.3%) patients.

Laboratory abnormalities
In patients treated with durvalumab in the PACIFIC Study, the proportion of patients who experienced a laboratory abnormality worsening from baseline was as follows: 38.5% (all Grades), 2.3% (Grades 3-4) for alanine aminotransferase increased, 36.0% (all Grades), 2.8% (Grade 3-4) for aspartate aminotransferase increased, 16.3% (all Grades) for creatinine increased, 26.5% (all Grades) for TSH elevated > ULN and above baseline, 31.9% (all Grades) for TSH decreased < LLN and below baseline.

Immunogenicity
Of the 1570 patients who were treated with IMFINZI 10 mg/kg every 2 weeks and evaluable for the presence of anti-drug antibodies (ADAs), 2.9% (45/1570) of patients tested positive for treatment-emergent ADAs. Neutralising antibodies (nAbs) against durvalumab were detected in 0.5% (8/1570) of patients. The presence of ADAs 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.

Elderly
No overall differences in safety were reported between elderly (≥ 65 years) and younger patients. Data from NSCLC 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: Antineoplastic agents, monoclonal antibodies. ATC code: L01XC28

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

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]. See Table 3 and Figures 1 and 2.

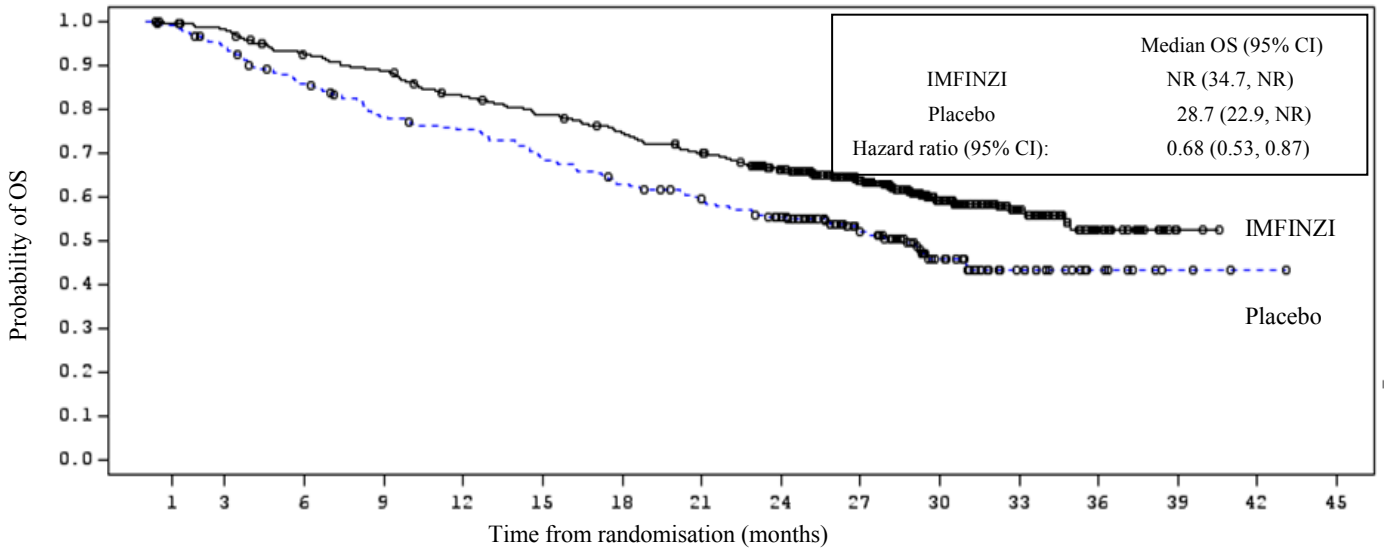
Table 3. Efficacy results for the PACIFIC Study[a]

	IMFINZI (n = 476)	**Placebo (n = 237)**

	IMFINZI (n = 476)	Placebo (n = 237)
OS		
Number of deaths (%)	183 (38.4%)	116 (48.9%)
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%, 61.3%)
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		
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 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

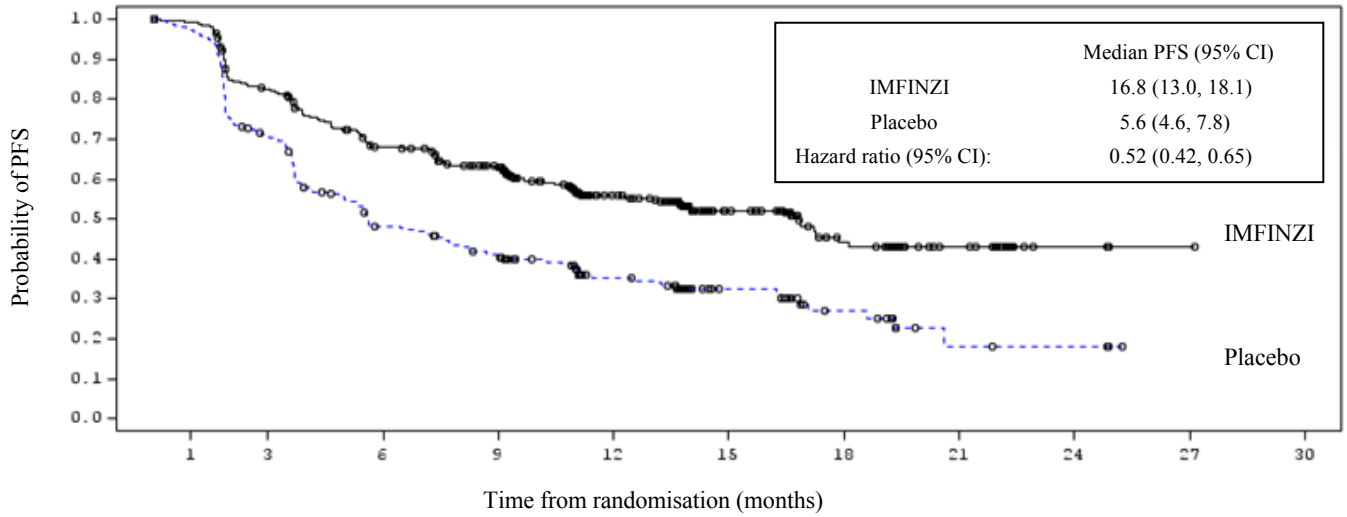
Figure 1. Kaplan-Meier curve of OS



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



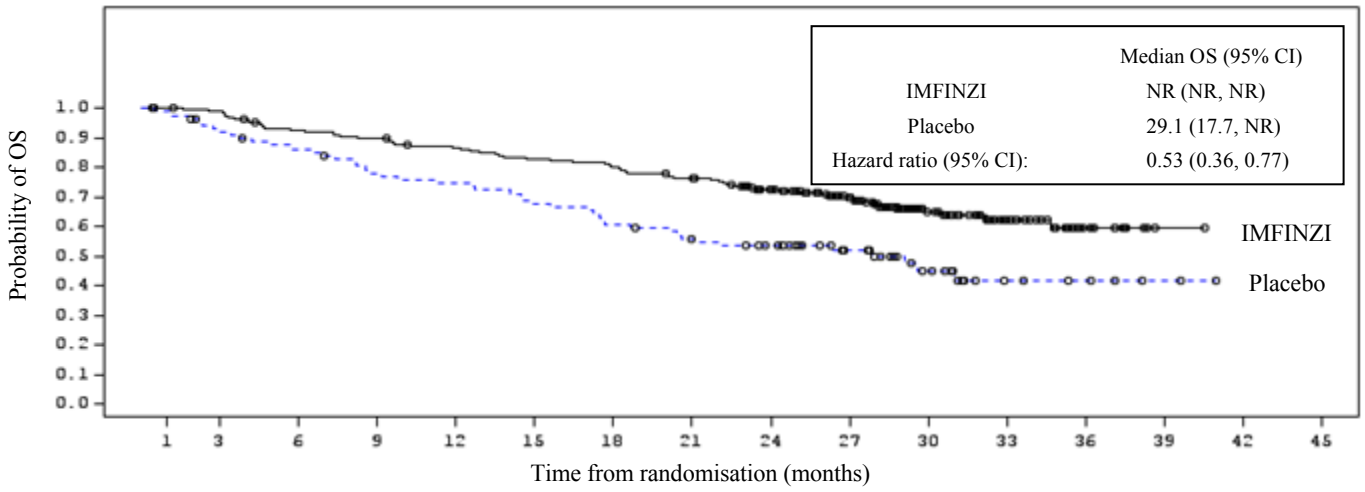
Number of patients at risk

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.

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 are summarised in Figures 3, 4, 5 and 6.

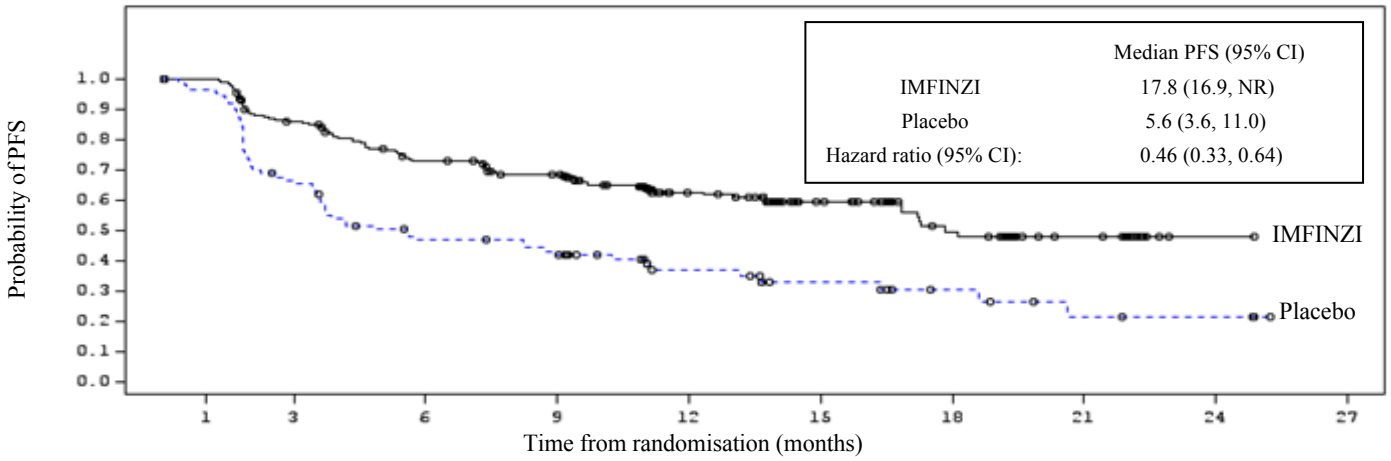
Figure 3. Kaplan-Meier curve of OS for PD-L1 TC ≥ 1%



Number of patients at risk

Month	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45
IMFINZI	212	208	193	187	178	171	165	156	134	105	62	34	12	1	0	0
Placebo	91	81	75	67	64	58	52	46	41	29	17	7	5	2	0	0

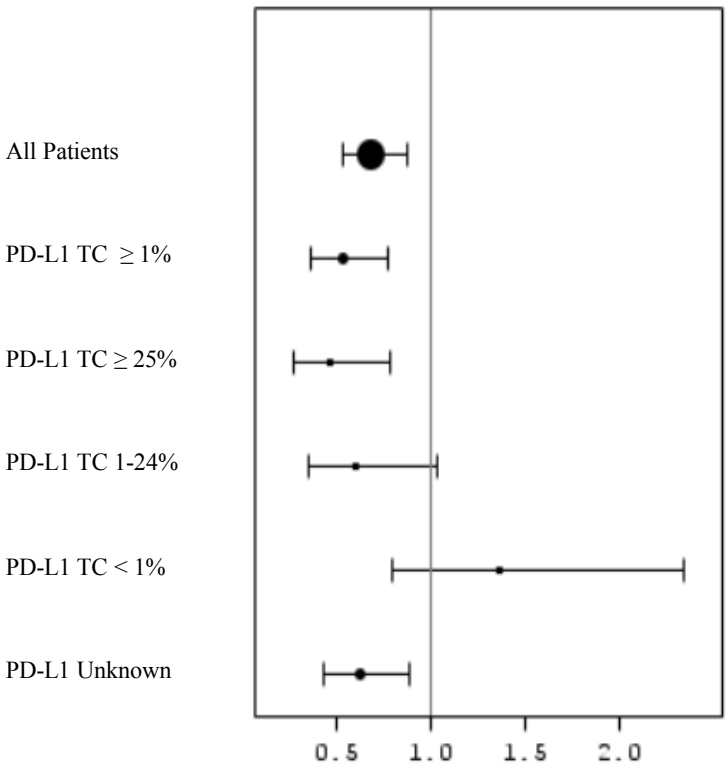
Figure 4. Kaplan-Meier curve of PFS for PD-L1 TC ≥ 1%



Number of patients at risk

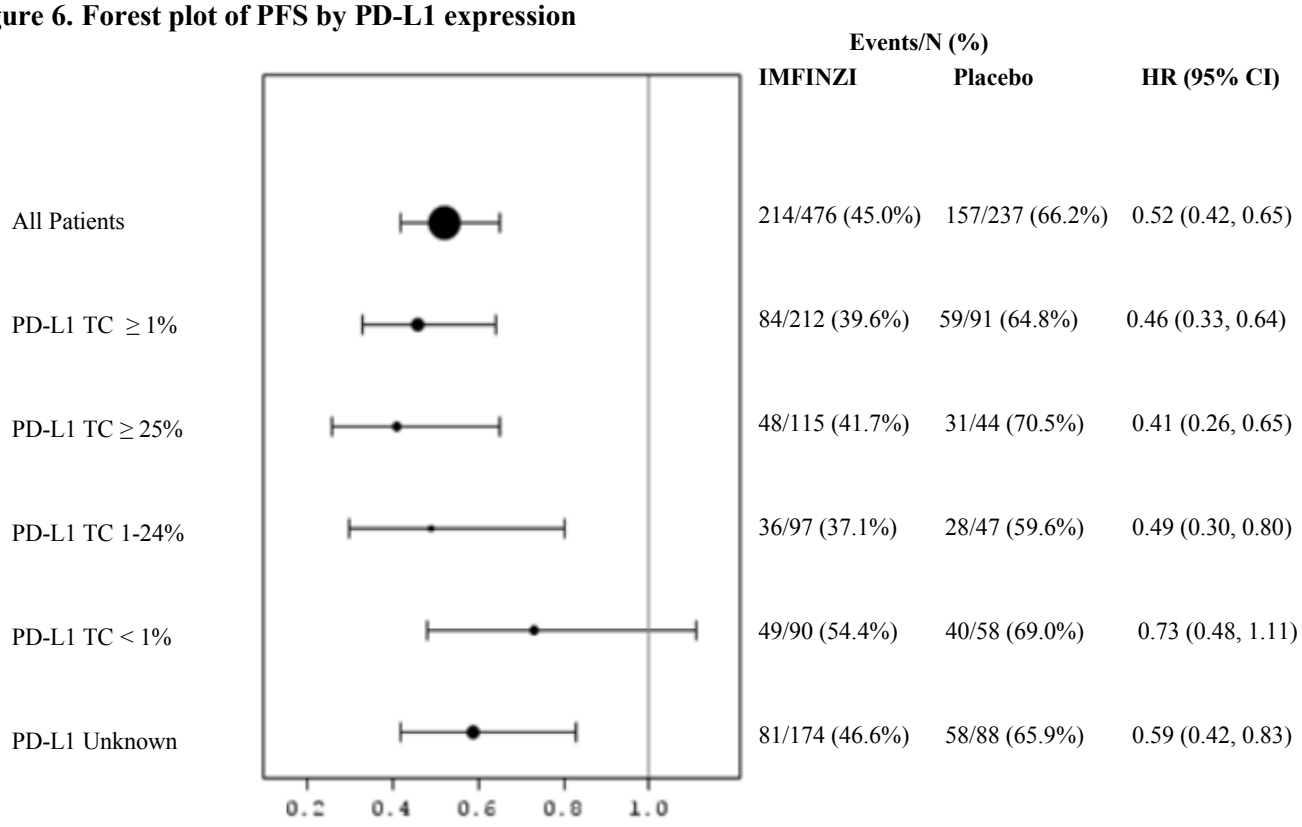
Month	0	3	6	9	12	15	18	21	24	27
IMFINZI	212	174	143	127	82	52	30	14	1	0
Placebo	91	59	39	34	20	13	8	4	3	0

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



	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 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).

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 PK of durvalumab was studied in 1902 patients with solid tumours with doses ranging from 0.1 to 20 mg/kg administered intravenously once every two, three or four weeks. 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 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. The primary elimination pathways of durvalumab are protein catabolism via reticuloendothelial system or target mediated disposition.

Special populations
Age (19–96 years), body weight (34-149 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
If not used immediately, chemical and physical in-use stability of IMFINZI has been demonstrated for no more than 24 hours at 2°C to 8°C or 4 hours at room temperature up to 25°C from the time of vial puncture to the start of administration.

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 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 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

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

MedImmune UK Ltd
6 Renaissance Way
Liverpool,
L24 9JW
United Kingdom

MedImmune Pharma B.V.
Lagelandseweg 78
6545CG Nijmegen,
Netherlands

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**

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

The marketing authorisation holder shall submit the first periodic safety update report 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 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 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.

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;
- **type 1 diabetes**: symptoms may include high blood sugar, feeling more hungry or thirsty than usual, passing urine more often than usual;
- **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 of the muscles**: symptoms may include muscle pain or weakness;
- **Infusion-related reactions**: symptoms may include chills or shaking, itching or rash, flushing, shortness of breath or wheezing dizziness, or fever.

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.
- Your doctor will give you IMFINZI through an infusion (drip) into your vein for about 60 minutes, every 2 weeks.
- Your doctor will decide how many treatments you need.

The recommended dose is 10 mg of durvalumab per kilogram of your body weight.

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 durvalumab, 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
- serious lung infections (pneumonia)
- underactive thyroid gland that can cause tiredness or weight gain
- cough
- inflammation of the lungs (pneumonitis)
- diarrhoea
- stomach pain
- skin rash or itchiness
- fever

Common (may affect up to 1 in 10 people)
- tooth and mouth soft tissue infections
- flu
- overactive thyroid gland that can cause fast heart rate or weight loss
- hoarse voice (dysphonia)
- inflammation of the gut or intestine (colitis)
- 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)
- decreased secretion of hormones produced by the adrenal glands that can cause tiredness
- a condition leading to high blood sugar levels (type 1 diabetes mellitus)
- inflammation of the liver that can cause nausea or feeling less hungry
- inflammation of the muscle

- inflammation of the kidneys (nephritis) that can decrease the amount of your urine

Rare (may affect up to 1 in 1000 people)
- 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

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.

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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. If not used immediately, the total time from vial puncture to start of the administration should not exceed 24 hours at 2 ºC to 8 ºC or 4 hours at room temperature (up to 25 ºC). If refrigerated, intravenous bags must be allowed to come to room temperature prior to use. Administer the infusion solution intravenously over 60 minutes 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.