▼This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION

IMFINZI®
(durvalumab)

1 NAME OF THE MEDICINE

Durvalumab

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

For the full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM

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

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Urothelial carcinoma

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

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

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

Locally advanced non-small cell lung cancer (NSCLC)

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

4.2 Dose and method of administration

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

Urothelial carcinoma

The recommended dose of IMFINZI is 10 mg/kg administered as an intravenous infusion over 60 minutes every 2 weeks as long as clinical benefit is observed or until unacceptable toxicity.

Locally advanced NSCLC

The recommended dose of IMFINZI is 10 mg/kg administered as an intravenous infusion over 60 minutes every 2 weeks, for one year or until disease progression or unacceptable toxicity.

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

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

Guidelines for management of adverse reactions are described in Table 1.

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

Table 1. Recommended treatment modifications and management for adverse reactions

Adverse reactions	**Severity**[a]	**IMFINZI treatment modification**	**Additional management advice**
Pneumonitis/interstitial lung disease	Grade 2	Withhold dose[b]	Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
	Grade 3 or 4	Permanently discontinue[b]	1 to 4 mg/kg/day prednisone or equivalent followed by a taper
Hepatitis	Grade 2 with ALT or AST > 3-5 x ULN and/or total bilirubin > 1.5-3 x ULN	Withhold dose[b]	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-≤ 5 x ULN		
	Grade 3 with AST or ALT > 8 x ULN or total bilirubin > 5 x ULN	Permanently discontinue[b]	
	Concurrent ALT or AST > 3 x ULN and total bilirubin > 2 x ULN with no other cause		
Colitis or diarrhoea	Grade 2	Withhold dose[b]	Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
	Grade 3 or 4	Permanently discontinue[b]	

Adverse reactions	**Severity**[a]	**IMFINZI treatment modification**	**Additional management advice**
Endocrinopathies: Hyperthyroidism	Grade 2-4	Withhold dose until clinically stable	Symptomatic management
Endocrinopathies: Hypothyroidism	Grade 2-4	No changes	Initiate thyroid hormone replacement as clinically indicated
Endocrinopathies: Adrenal insufficiency, Hypophysitis/hypopituitarism	Grade 2-4	Withhold dose until clinically stable	Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper and hormone replacement as clinically indicated
Endocrinopathies: Type 1 diabetes mellitus	Grade 2-4	No changes	Initiate treatment with insulin as clinically indicated
Nephritis	Grade 2 with serum creatinine > 1.5-3 x (ULN or baseline)	Withhold dose[b]	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[b]	
Rash or dermatitis	Grade 2 for > 1 week	Withhold dose[b]	Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
	Grade 3		
	Grade 4	Permanently discontinue	
Myocarditis	Grade 2	Withhold dose[c]	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	
Myositis/polymyositis	Grade 2 or 3	Withhold dose[bd]	Initiate 1 to 4 mg/kg/day prednisone or equivalent followed by a taper
	Grade 4	Permanently discontinue[b]	
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	
	Grade 3 (initial)	Withhold dose[b]	

Adverse reactions	Severity[a]	IMFINZI treatment modification	Additional management advice
Other immune-mediated adverse reactions	Grade 3 (recurrent) or Grade 4	Permanently discontinue	Consider initial dose of 1 mg/kg/day to 4 mg/kg/day prednisone or equivalent followed by taper

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

[b] 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. Durvalumab can be resumed if, within 12 weeks of the last durvalumab dose, the adverse reactions have 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) adverse reactions.

[c] 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.

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

For suspected immune-mediated adverse reactions, adequate evaluation should be performed to confirm aetiology or exclude alternate aetiologies.

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 patient populations

Renal impairment

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

Hepatic impairment

No dose adjustment is recommended for patients with hepatic impairment. Data from patients with moderate and severe hepatic impairment are limited, however, due to minor involvement of hepatic processes in the clearance of durvalumab, no difference in exposure is expected for these patients (see Section 5.2 Pharmacokinetic properties).

Use in paediatric patients

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

Use in the elderly

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

Method of administration

Preparation of solution

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

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

After preparation of infusion solution

IMFINZI does not contain a preservative. Administer infusion solution immediately once prepared. If infusion solution is not administered immediately and it needs to be stored, the total time from vial puncture to the start of administration should not exceed:

- 24 hours at 2°C to 8°C
- 12 hours at room temperature.

Administration

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

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

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Refer to Section 4.2 Dose and method of administration Table 1 for recommended treatment modifications and management of adverse reactions.

Immune-mediated adverse reactions

Immune checkpoint inhibitors, including durvalumab, can cause severe and fatal immune-mediated adverse reactions, which may involve any organ system. While immune-mediated reactions usually manifest during treatment, they can also manifest after discontinuation. Early identification of such reactions and timely intervention are an important part of the safe use of durvalumab. In clinical trials, most immune-mediated adverse reactions were reversible and managed with interruptions of durvalumab, administration of corticosteroids and/or supportive care. Patients should be monitored for signs and symptoms and managed as recommended in Table 1 (see Section 4.2 Dose and method of administration).

Immune-mediated pneumonitis

Immune-mediated pneumonitis/interstitial lung disease,[1] including fatal cases, occurred in patients receiving durvalumab in clinical trials (see Section 4.8 Adverse effects).

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

Patients should be monitored for signs and symptoms of pneumonitis. Patients with suspected pneumonitis should be evaluated with radiographic imaging and managed as recommended in Table 1 (see Section 4.2 Dose and method of administration).

Immune-mediated hepatitis

Immune-mediated hepatitis,* including a fatal case, occurred in patients receiving durvalumab in clinical trials (see Section 4.8 Adverse effects). Patients should be monitored for abnormal liver tests prior to each infusion, and as indicated based on clinical evaluation during and after discontinuation of treatment with durvalumab. Immune-mediated hepatitis should be managed as recommended in Table 1 (see Section 4.2 Dose and method of administration).

Immune-mediated colitis

Immune-mediated colitis* occurred in patients receiving durvalumab in clinical trials (see Section 4.8 Adverse effects). Patients should be monitored for signs and symptoms of colitis (including diarrhoea) and managed as recommended in Table 1 (see Section 4.2 Dose and method of administration).

Immune-mediated endocrinopathies

Hypothyroidism

Immune-mediated hypothyroidism occurred in patients receiving durvalumab in clinical trials (see Section 4.8 Adverse effects). Patients should be monitored for abnormal thyroid function tests prior to and periodically during treatment and managed as recommended in Table 1 (see Section 4.2 Dose and method of administration).

Hyperthyroidism

Immune-mediated hyperthyroidism (including thyroiditis) occurred in patients receiving durvalumab in clinical trials (see Section 4.8 Adverse effects). Patients should be monitored for abnormal thyroid function tests prior to and periodically during treatment and managed as recommended in Table 1 (see Section 4.2 Dose and method of administration).

Adrenal insufficiency

Immune-mediated adrenal insufficiency occurred in patients receiving durvalumab in clinical trials (see Section 4.8 Adverse effects). Patients should be monitored for clinical signs and symptoms of adrenal insufficiency. For symptomatic adrenal insufficiency, patients should be managed as recommended in Table 1 (see Section 4.2 Dose and method of administration).

[1] Defined as requiring use of systemic corticosteroids and with no clear alternate aetiology.

Type 1 diabetes mellitus

Immune-mediated type 1 diabetes mellitus occurred in patients receiving durvalumab in clinical trials (see Section 4.8 Adverse effects). 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 Table 1 (see Section 4.2 Dose and method of administration).

Hypophysitis/hypopituitarism

Immune-mediated hypophysitis/hypopituitarism occurred in patients receiving durvalumab in clinical trials (see Section 4.8 Adverse effects). 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 Table 1 (see Section 4.2 Dose and method of administration).

Immune-mediated nephritis

Immune-mediated nephritis[2] occurred in patients receiving durvalumab in clinical trials (see Section 4.8 Adverse effects). Patients should be monitored for abnormal renal function tests prior to and periodically during treatment with durvalumab and managed as recommended in Table 1 (see Section 4.2 Dose and method of administration).

Immune-mediated dermatological adverse reactions

Immune-mediated dermatitis[*] occurred in patients receiving durvalumab in clinical trials (see Section 4.8 Adverse effects). Bullous dermatitis and Stevens-Johnson Syndrome (SJS)/toxic epidermal necrolysis (TEN) have occurred with other products in this class. Patients should be monitored for signs and symptoms dermatitis (including rash) and managed as recommended in Table 1 (see Section 4.2 Dose and method of administration).

Other immune mediated adverse reactions

Given the mechanism of action of durvalumab, other immune-mediated adverse reactions may occur. The following clinically significant, immune-mediated adverse reactions occurred at an incidence of less than 1% each in a combined safety database of 1889 patients who received IMFINZI across clinical trials: aseptic meningitis, haemolytic anaemia, immune thrombocytopenic purpura, myocarditis, myositis, and ocular inflammatory toxicity, including uveitis and keratitis. Polymyositis with a fatal outcome (<0.1%) was reported in a patient treated with IMFINZI from an ongoing sponsored clinical study. Patients should be monitored for signs and symptoms of immune-mediated adverse reactions and managed as recommended in Table 1 (see Section 4.2 Dose and method of administration).

Infusion-related reactions

Patients should be monitored for signs and symptoms of infusion-related reactions and managed as recommended in Table 1 (see Section 4.2 Dose and method of administration). Severe infusion related reactions have been reported in patients receiving durvalumab (see Section 4.8 Adverse effects).

Efficacy in patients with PD-L1 expression <1%

Post-hoc analyses suggest efficacy may be different for patients with PD-L1 <1%. Before initiating treatment, physicians are advised to carefully evaluate the individual patient and tumour characteristics, taking into consideration the observed benefits and the side effects of durvalumab (see sections 4.8 Adverse effects and 5.1 Pharmacological properties).

[2] Defined as requiring use of systemic corticosteroids and with no clear alternate aetiology.

Use in the elderly

No overall differences in safety or efficacy were observed between patients who were ≥ 65 years of age or who were ≥ 75 years of age compared to younger patients in study 1108 (urothelial carcinoma).

No overall differences in safety were observed between patients treated with IMFINZI who were ≥ 65 years of age compared to younger patients in the PACIFIC study (NSCLC). Data from NSCLC patients 75 years of age or older are limited.

Paediatric use

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

4.5 Interactions with other medicines and other forms of interactions

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

4.6 Fertility, pregnancy and lactation

Effects on fertility

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

Use in pregnancy – Category D

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

Animal data

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

Use in lactation

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

4.7 Effects on ability to drive and use machines

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

4.8 Adverse effects (undesirable effects)

The data described below reflect exposure to IMFINZI as a single agent in patients with locally advanced or metastatic urothelial carcinoma within Study 1108 and in patients with locally advanced, unresectable NSCLC in the PACIFIC study (see 5.1 Pharmacodynamic properties – Clinical trials).

Tabulated list of adverse events

Adverse events are listed according to MedDRA system organ class. Within each system organ class, the adverse events are presented in decreasing frequency.

Urothelial carcinoma (UC) – Study 1108

The safety data described in Table 2 reflect exposure to IMFINZI in 201 patients with locally advanced or metastatic urothelial carcinoma (UC) in the UC cohort of Study 1108 (see 5.1 Pharmacodynamic properties – Clinical trials). Within the UC cohort, 192 patients had disease progression during or after one standard platinum-based regimen (2L+ post-platinum) and inform the registered indication (see 5.1 Pharmacodynamic properties – Clinical trials). Patients received IMFINZI 10 mg/kg intravenously every 2 weeks. The median duration of exposure was 2.8 months (range: 0.4 - 12.5 months). Eighty four (42%) of patients had a drug delay or interruption for an adverse event. The most common (> 2%) were liver injury (6.0%), urinary tract infection and musculoskeletal pain (4.5% each), acute kidney injury and fatigue (3.5% each) and diarrhoea/colitis (2.5%).

The most common adverse events (≥ 15%) were fatigue (47%), musculoskeletal pain and constipation (28% each), decreased appetite/hypophagia (26%), nausea (24%), anaemia (23%), urinary tract infection (20%), diarrhoea/colitis (18%), abdominal pain, acute kidney injury, rash and peripheral oedema (17% each), dyspnoea/exertional dyspnoea and cough/productive cough (16% each) and pyrexia/tumour associated fever (15%). The most common Grade 3 or 4 adverse events (≥ 3%) were anaemia (12%), liver injury (9%), hyponatraemia (8%), fatigue (7%), urinary tract infection and acute kidney injury (6% each), musculoskeletal pain (5), abdominal pain (4%) and nausea (3%).

Sixteen patients (8.0%) who were treated with IMFINZI experienced Grade 5 adverse events of cardiorespiratory arrest, intestinal obstruction, chronic hepatic failure, liver injury, cerebrovascular accident, acute kidney injury, dyspnoea/exertional dyspnoea, general physical health deterioration, sepsis, or pneumonitis. IMFINZI was discontinued for adverse events in 6.5% of patients. Serious adverse events occurred in 58% of patients. The most frequent serious adverse events (> 2%) were acute kidney injury, urinary tract infection and musculoskeletal pain (5.0% each), liver injury,

general physical health deterioration and sepsis (4.0% each), abdominal pain (3.5%), hypercalcaemia and vomiting (2.5% each).

Table 2 summarises the treatment-emergent adverse events that occurred in ≥ 10% of patients in the UC cohort of Study 1108. Table 3 summarises the Grade 3 - 4 laboratory abnormalities that occurred in ≥ 1% of patients treated with IMFINZI in the UC cohort of Study 1108 who had available baseline and post-baseline data.

Table 2. Treatment-emergent adverse events that occurred in at least 10% of the UC cohort of Study 1108

Adverse event	IMFINZI n=201	
	All grades (%)	Grade 3-4 (%)
Blood and lymphatic system disorders		
Anaemia	23	12
Endocrine disorders		
Hypothyroidism	10	0
Gastrointestinal disorders		
Constipation[a]	28	2
Nausea	24	3
Diarrhoea/colitis	18	1
Abdominal pain[b]	17	4
Vomiting	14	3
General disorders and administration site conditions		
Fatigue[c]	47	7
Peripheral oedema[d]	17	2
Pyrexia/tumour associated fever	15	1
Hepatobiliary disorders		
Liver injury	18	9
Infections		
Urinary tract infection[e]	20	6
Metabolism and nutrition disorders		
Decreased appetite/hypophagia	26	1
Hyponatraemia	10	8
Musculoskeletal and Connective Tissue Disorders		
Musculoskeletal pain[f]	28	5
Arthralgia	13	1
Psychiatric disorders		
Insomnia	10	0
Renal and urinary disorders		
Acute kidney injury[g]	17	6
Respiratory, thoracic, and mediastinal disorders		
Dyspnoea/exertional dyspnoea	16	3
Cough/productive cough	16	0
Skin and subcutaneous tissue disorders		
Rash[h]	17	1

[a] Includes faecaloma

[b] Includes abdominal pain upper, abdominal pain lower and flank pain

[c] Includes asthenia, lethargy, and malaise

[d] Includes oedema, localised oedema, oedema peripheral, lymphoedema, peripheral swelling, scrotal oedema, and scrotal swelling

[e] Includes cystitis, candiduria and urosepsis

[f] Includes back pain, musculoskeletal chest pain, musculoskeletal discomfort, myalgia, and neck pain

[g] Includes blood creatinine increased, renal failure, glomerular filtration rate decreased, azotaemia

[h] Includes dermatitis, dermatitis acneiform, dermatitis psoriasiform, psoriasis, rash maculo-papular, rash pruritic, rash papular, rash pustular, skin toxicity, eczema, erythema, erythema multiforme, rash erythematous, acne, and lichen planus

Table 3. Grade 3 or 4 laboratory abnormalities worsened from baseline occurring in ≥1% of durvalumab-treated patients with UC (n=201)

Laboratory test	Grade 3 or 4 %
Hyponatraemia	13
Lymphocyte count decreased	12
Anaemia	12
Alkaline phosphatase increased	5
Aspartate aminotransferase increased	4
Hyperglycaemia	4
Blood bilirubin increased	3
Hypercalcaemia	3
Hypermagnesaemia	3
Creatinine increased	2
Neutrophil count decreased	2
Hyperkalaemia	2
Hypokalaemia	2
Alanine aminotransferase increased	1
Hypoalbuminaemia	1
Platelet count decreased	1

Locally advanced NSCLC – PACIFIC study

The safety of IMFINZI in patients with locally advanced NSCLC who completed concurrent platinum-based chemoradiotherapy within 42 days prior to initiation of study drug was evaluated in the PACIFIC study, a multicentre, randomised, double-blind, placebo-controlled study. A total of 475 patients received IMFINZI 10 mg/kg intravenously every 2 weeks. The study excluded patients who had disease progression following chemoradiation, with active or prior autoimmune disease within 2 years of initiation of the study or with medical conditions that required systemic immunosuppression (see 5.1 Pharmacodynamic properties – Clinical trials).

The study population characteristics were: median age of 64 years (range: 23 to 90), 45% age 65 years or older, 70% male, 69% White, 27% Asian, 75% former smoker, 16% current smoker, and 51% had WHO performance status of 1. All patients received definitive radiotherapy as per protocol, of which 92% received a total radiation dose of 54 Gy to 66 Gy. The median duration of exposure to IMFINZI was 10 months (range: 0.2 to 12.6).

IMFINZI was discontinued due to adverse events in 15% of patients. The most common adverse events leading to IMFINZI discontinuation were pneumonitis or radiation pneumonitis in 6% of patients. Serious adverse events occurred in 29% of patients receiving IMFINZI. The most frequent serious adverse events reported in at least 2% of patients were pneumonitis or radiation pneumonitis (7%) and pneumonia (6%). Fatal pneumonitis or radiation pneumonitis and fatal pneumonia occurred in < 2% of patients and were similar across arms. The most common adverse events

(occurring in ≥ 20% of patients) were cough, fatigue, pneumonitis or radiation pneumonitis, upper respiratory tract infections, dyspnoea and rash.

Table 4 summarises the adverse events that occurred in at least 10% of patients treated with IMFINZI.

Table 4. Treatment-emergent adverse events occurring in at least 10% of patients in the PACIFIC Study

	IMFINZI N=475		**Placebo[a] N=234**	
Adverse reaction	All grades (%)	Grades 3-4 (%)	All grades (%)	Grades 3-4 (%)
Respiratory, thoracic and mediastinal disorders				
Cough/productive cough	40	0.6	30	0.4
Pneumonitis[b]/radiation pneumonitis	34	3.4	25	3.0
Dyspnoea[c]	25	1.5	25	2.6
Gastrointestinal disorders				
Diarrhoea	18	0.6	19	1.3
Abdominal pain[d]	10	0.4	6	0.4
Endocrine disorders				
Hypothyroidism[e]	12	0.2	1.7	0
Skin and subcutaneous tissue disorders				
Rash[f]	23	0.6	12	0
Pruritus[g]	12	0	6	0
General disorders and administration site conditions				
Fatigue[h]	34	0.8	32	1.3
Pyrexia	15	0.2	9	0
Infections				
Upper respiratory tract infections[i]	26	0.4	19	0
Pneumonia[j]	17	7	12	6

[a] The PACIFIC study was not designed to demonstrate statistically significant difference in adverse event rates for IMFINZI, as compared to placebo, for any specific adverse event listed in Table 4

[b] includes acute interstitial pneumonitis, interstitial lung disease, pneumonitis, pulmonary fibrosis

[c] includes dyspnoea and exertional dyspnoea

[d] includes abdominal pain, abdominal pain lower, abdominal pain upper, and flank pain

[e] includes autoimmune hypothyroidism and hypothyroidism

[f] includes rash erythematous, rash generalized, rash macular, rash maculopapular, rash papular, rash pruritic, rash pustular, erythema, eczema, rash and dermatitis

[g] includes pruritus generalized and pruritus

[h] includes asthenia and fatigue

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

[j] includes lung infection, pneumocystis jirovecii pneumonia, pneumonia, pneumonia adenoviral, pneumonia bacterial, pneumonia cytomegaloviral, *pneumonia haemophilus*, *pneumonia klebsiella*, pneumonia necrotising, pneumonia pneumococcal, and pneumonia streptococcal

Other adverse events occurring in less than 10% of patients treated with IMFINZI were dysphonia, dysuria, night sweats, peripheral oedema, and increased susceptibility to infections.

Table 5 lists the incidence of laboratory abnormalities worsening from baseline and occurring more frequently in IMFINZI-treated patients with locally advanced unresectable NSCLC in the PACIFIC study.

Table 5. Laboratory abnormalities worsening from baseline occurring more frequently in IMFINZI-treated patients

Laboratory abnormalities	**IMFINZI**			**Placebo**		
	N	**Any grade**	**Grade 3 or 4**	**N**	**Any grade**	**Grade 3 or 4**
Alanine aminotransferase increased	470	181 (38.5%)	11 (2.3%)	228	49 (21.5%)	1 (0.4%)
Aspartate aminotransferase increased	469	169 (36.0%)	13 (2.8%)	228	48 (21.1%)	1 (0.4%)
Creatinine increased	465	76 (16.3%)	0	226	23 (10.2%)	0
TSH elevated >ULN and above baseline	464	123 (26.5%)	NA	224	30 (13.4%)	NA
TSH decreased <LLN and below baseline	464	148 (31.9%)	NA	224	35 (15.6%)	NA

Description of selected adverse reactions

Data described below reflect exposure to IMFINZI in 1889 patients in a combined safety database which includes the PACIFIC study (475 patients with locally advanced NSCLC), Study 1108 (191 patients with urothelial carcinoma and 779 patients with various other solid tumours), and an additional open-label, single-arm trial that enrolled 444 patients with metastatic lung cancer (an indication for which durvalumab is not approved). Across all studies, IMFINZI was administered at a dose of 10 mg/kg intravenously every 2 weeks. Among the 1889 patients, 38% were exposed for 6 months or more and 18% were exposed for 12 months or more.

Immune-mediated pneumonitis

In the urothelial carcinoma cohort of Study 1108 (n=201), 2 cases of immune-mediated pneumonitis occurred (one Grade 1 and one Grade 5 event).

In the combined safety database with IMFINZI monotherapy, 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 urothelial carcinoma cohort of Study 1108, immune-mediated hepatitis occurred in 5 (2.5%) patients, including Grade 3 in 4 (2.0%) patients, and Grade 5 in 1 (0.5%) patient. In the PACIFIC Study, immune-mediated hepatitis occurred in 3 (0.6%) patients. There were no Grade 3 or higher cases.

In the combined safety database with IMFINZI monotherapy, immune-mediated hepatitis occurred in 19 (1%) patients, including Grade 3 in 11 (0.6%) patients and Grade 5 in 1 (< 0.1%) patient. The median time to onset was 70.0 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 12 patients.

Immune-mediated colitis

In the urothelial carcinoma cohort of Study 1108, immune-mediated colitis or diarrhoea occurred in 4 (2.0%) patients (diarrhoea in 4 patients (2.0%, Grade 1 or 2) and colitis in 1 patient (0.5%, Grade 2). In the PACIFIC Study, immune-mediated colitis or diarrhoea occurred in 5 (1.1%) patients, including Grade 3 in 2 (0.4%) patients.

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 urothelial carcinoma cohort of Study 1108, immune-mediated hypothyroidism occurred in 13 (6.5%) patients, there were no Grade 3 or 4 cases. In the PACIFIC Study, immune-mediated hypothyroidism occurred in 44 (9.3%) patients in the IMFINZI-treated group and 3 (1.3%) patients in the placebo group, including Grade 3 in 1 (0.2%) patient on IMFINZI vs. 0 patients on placebo. The median time to onset in the IMFINZI-treated group was 106.5 days (range: 13-377 days) vs. 98 days (range: 0-99 days) in the placebo group. In the IMFINZI-treated group, 41 patients received hormone replacement therapy. In the placebo group, all 3 patients received hormone replacement therapy.

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, 2 patients received high-dose corticosteroids (at least 40 mg prednisone or equivalent per day) for hypothyroidism followed by hormone replacement. No patients discontinued IMFINZI due to hypothyroidism.

Hyperthyroidism

In the urothelial carcinoma cohort of Study 1108, immune-mediated hyperthyroidism occurred in 3 (1.5%) patients (Grade 1 or 2). In the PACIFIC Study, immune-mediated hyperthyroidism occurred in 13 (2.7%) patients. There were no Grade 3-4 cases.

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). No patients discontinued IMFINZI due to hyperthyroidism. Resolution occurred in 23 patients. Eight patients experienced hypothyroidism following hyperthyroidism.

Adrenal insufficiency

In the urothelial carcinoma cohort of Study 1108, immune-mediated adrenal insufficiency occurred in 1 (0.5%) patient (Grade 1). In the PACIFIC Study, immune-mediated adrenal insufficiency occurred in 1 (0.2%) patients. There were no Grade 3-4 cases.

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). No patients discontinued IMFINZI due to adrenal insufficiency. Resolution occurred in 1 patient.

Type 1 diabetes mellitus

In the PACIFIC study, immune-mediated type 1 diabetes mellitus occurred in 1 (0.2%) 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 did not discontinue IMFINZI.

Immune-mediated nephritis

In the urothelial carcinoma cohort of Study 1108, immune-mediated nephritis occurred in 1 (0.5%) patient (Grade 1). In the PACIFIC Study, immune-mediated nephritis occurred in 1 (0.2%) patient. There were no Grade 3-4 cases.

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 urothelial carcinoma cohort of Study 1108, immune-mediated rash or dermatitis occurred in 3 (1.5%) patients, including Grade 3 in 1 (0.5%) patient. In the PACIFIC Study, immune-mediated rash or dermatitis occurred in 9 (1.9%) patients in the IMFINZI-treated group and 1 (0.4%) patient in the placebo group, including Grade 3 in 2 (0.4%) patients on IMFINZI vs. 0 patients on placebo.

The median time to onset in the IMFINZI-treated group was 36 days (range: 5-110 days) vs. 110 days in the one placebo patient. In the IMFINZI-treated group, all 9 patients received systemic corticosteroids, including 5 patients who received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). In the placebo group, the 1 patient received systemic corticosteroids.

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

Infusion related reactions occurred in 2 (1%) of patients with urothelial carcinoma in Study 1108, and in 9 (1.9%) patients in the PACIFIC Study. 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. There were no Grade 4 or 5 events.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at http://www.tga.gov.au/reporting-problems.

4.9 Overdose

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

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

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

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

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

Clinical trials

Urothelial carcinoma (UC)

Single-arm phase 2 study in patients with unresectable or metastatic UC after prior chemotherapy (Study 1108)

The efficacy of IMFINZI was evaluated in a phase 1/2 multi-cohort, open-label clinical trial (Study 1108).

The UC cohort of Study 1108 enrolled 201 patients with inoperable locally advanced or metastatic urothelial carcinoma (UC). Of these patients, 192 had disease progression on or after a platinum-based therapy (the 2L post-platinum cohort), including those whose disease had progressed within 12 months of receiving therapy in a neo-adjuvant or adjuvant setting. The trial excluded patients with a history of immunodeficiency; medical conditions that required systemic immunosuppression (not to exceed 10 mg per day of prednisone or equivalent); history of severe autoimmune disease; untreated CNS metastases; HIV; active tuberculosis, or hepatitis B or C infection.

All patients received IMFINZI 10 mg/kg via intravenous infusion every 2 weeks for up to 12 months or until unacceptable toxicity or confirmed disease progression. Tumour assessments were performed at Weeks 6, 12 and 16, then every 8 weeks for the first year and every 12 weeks thereafter. The primary efficacy endpoint was Objective Response Rate (ORR) according to RECIST v1.1 as assessed by Blinded Independent Central Review (BICR). Additional efficacy endpoints included Duration of Response (DoR) and Overall Survival (OS).

In the 2L post-platinum cohort, the median age was 67 years (range: 34 to 88), 71% were male, 70% were Caucasian, 67% had visceral metastasis (including 36% with liver metastasis), 12% had lymph-node-only metastasis, 32% had an ECOG performance status of 0, the remainder had an ECOG performance status of 1 and 44% of patients had a baseline creatinine clearance of <60 mL/min. Sixty-nine percent of patients received prior cisplatin, 29% had prior carboplatin and 36% received 2 or more prior lines of systemic therapy.

Tumour specimens were evaluated for PD-L1 expression on tumour cells (TC) and immune cells (IC) using the Ventana PD-L1 (SP263) Assay. All testing was performed prospectively at a central laboratory. Of the 192 2L+ post-platinum UC patients, 99 were classified as PD-L1 high (TC ≥ 25% or IC ≥ 25%), 80 as PD-L1 low/negative (TC < 25% and IC < 25%) and samples for 13 patients were inadequate for evaluation.

Table 6 summarises the efficacy results for the 2L+ post-platinum UC patients. The median duration of follow-up was 16.9 months (range: 0.4-37.7). In 36 patients who had received only neoadjuvant or adjuvant therapy prior to study entry, 27.8% responded.

Among the total 33 responding patients, 88% patients had ongoing responses of 6 months or longer and 64% had ongoing responses of 12 months or longer.

Table 6 Efficacy Results for Study 1108[a]

Parameter	2L+ Post-platinum UC		
	Total	**PD-L1 High (≥25%)**	**PD-L1 Low/Neg (<25%)**
	N=192	**N=99**	**N=80**
ORR, n (%) (95% CI)	33 (17.2) (12.1, 23.3)	27 (27.3) (18.8, 37.1)	4 (5.0) (1.4, 12.3)
CR, n (%)	11 (5.7)	8 (8.1)	2 (2.5)
PR, n (%)	22 (11.5)	19 (19.2)	2 (2.5)
Median DoR (95% CI)	NR (12.3, NE)	NR (8.2, NE)	12.25 (1.4, NE)
Median OS months (95% CI)	10.5 (6.6, 15.7)	19.8 (9.3, NE)	4.8 (3.1, 8.1)
OS at 12 months, % (95% CI)	46.1 (38.2, 53.5)	57.3 (46.1, 66.9)	28.0 (17.5, 39.6)
OS at 24 months, % (95% CI)	32.0 (22.9, 41.4)	43.9 (30.1, 57.0)	14.2 (6.0, 25.8)

[a]Median duration of follow up 16.9 months. All treated UC patients who had received prior platinum-based therapy, including those patients who progressed within 12 months of receiving therapy in a neo-adjuvant/adjuvant setting.

CR = Complete Response;; NE = Not Estimable; NR = Not Reached; CI = Confidence Interval

Exploratory PD-L1 subgroup analysis

An exploratory post-hoc analysis was conducted of the study 1108 results in UC patients by tumour cell (TC) and tumour-infiltrating immune cell (IC) PD-L1 expression with 'low' and 'high' defined at various cut-off levels (although the test was only validated at a cut-off of TC/IC 25% for this tumour type). The analysis showed a consistent trend of correlation between ORR and PD-L1 expression (high versus low) at all cut-offs, more so for IC than for TC. There were no responses seen in patients who had both TC<1% and IC<1%.

Non-small cell lung cancer (NSCLC)

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

The efficacy of IMFINZI was evaluated in the PACIFIC study, a randomised, double-blind, placebo-controlled, multicentre study in 713 patients with histologically or cytologically confirmed locally advanced, unresectable NSCLC. Patients had completed at least 2 cycles of definitive platinum-based chemotherapy with radiation therapy within 1 to 42 days prior to initiation of the study and had an ECOG performance status of 0 or 1. Ninety-two percent of patients had received a total dose of 54 to 66 Gy of radiation. The study excluded patients who had progressed following chemoradiation therapy, patients with prior exposure to any anti-PD-1 or anti-PD-L1 antibody, patients with active or prior documented autoimmune disease within 2 years of initiation of the study; a history of immunodeficiency; a history of severe immune-mediated adverse reactions; medical conditions that required systemic immunosuppression(except physiological dose of systemic corticosteroids); active tuberculosis or hepatitis B or C or HIV infection or patients receiving live attenuated vaccine within 30 days before or after the start of IMFINZI. Patients were randomised 2:1 to receive 10 mg/kg IMFINZI (n=476) or 10 mg/kg placebo (n=237) via intravenous infusion every 2 weeks for up to 12 months or until unacceptable toxicity or confirmed disease progression. Randomisation was stratified by gender, age (<65 years vs. ≥ 65 years) and

smoking status (smoker vs. non- smoker). Patients with disease control at 12 months were given the option to be re-treated upon disease progression. Tumour assessments were conducted every 8 weeks for the first 12 months and then every 12 weeks thereafter.

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

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

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

The study demonstrated a statistically significant improvement in PFS and OS in the IMFINZI-treated group compared with the placebo group (see Table 7 and Figures 2 and 3).

Table 7. Efficacy Results for the PACIFIC Study[a]

	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%, 61.8%)
p-value	0.005	
PFS		
Number of events (%)	214 (45.0%)	157 (66.2%)
Median PFS (months) (95% CI)	16.8 (13.0, 18.1)	5.6 (4.6, 7.8)
HR (95% CI)	0.52 (0.42, 0.65)	

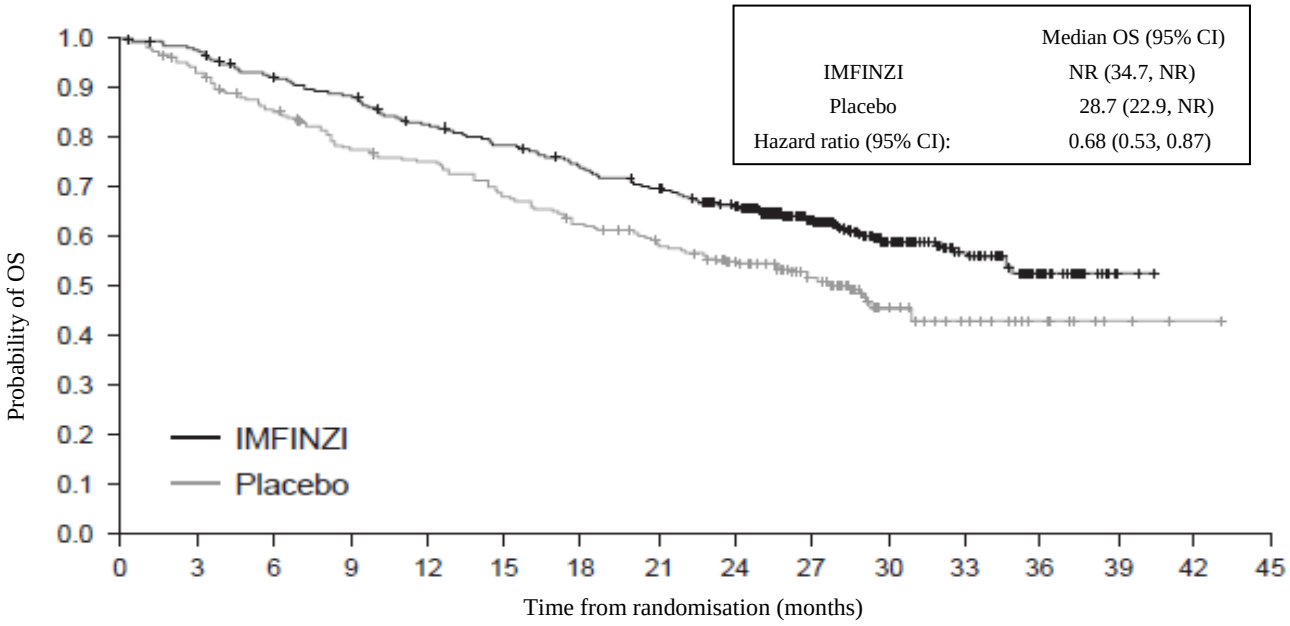
	IMFINZI (n= 476)	**Placebo (n= 237)**
p-value	p < 0.0001	
PFS at 12 months (%) (95% CI)	55.9% (51.0%, 60.4%)	35.3% (29.0%, 41.7%)
PFS at 18 months (%) (95% CI)	44.2% (37.7%, 50.5%)	27.0% (19.9%, 34.5%)
PFS2		
Median PFS2[b] (months) (95% CI)	28.3 (25.1, 34.7)	17.1 (14.5, 20.7)
HR (95% CI)	0.58 (0.46, 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

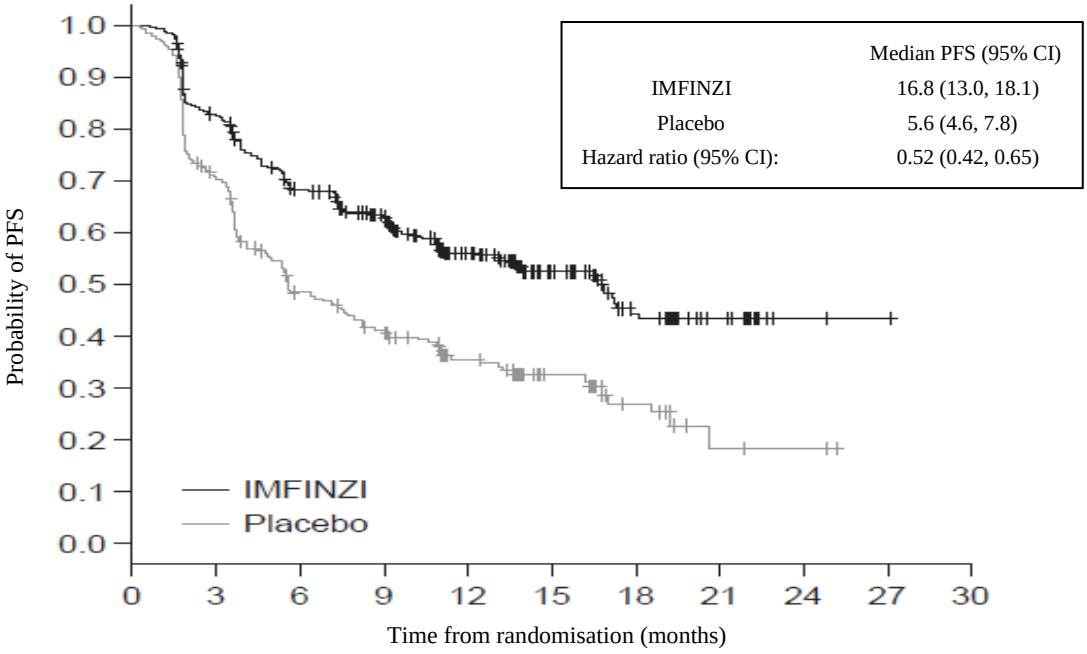
Figure 2. Kaplan-Meier curve of OS (PACIFIC study)



Number of patients at risk

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

Figure 3. Kaplan-Meier curve of PFS (PACIFIC study)



Number of patients at risk

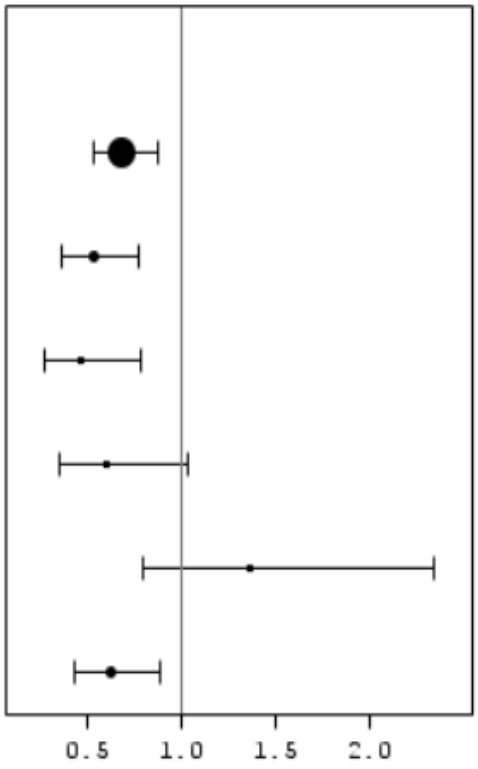
Month	0	3	6	9	12	15	18	21	24	27	30
IMFINZI	476	377	301	264	159	86	44	21	4	1	0
Placebo	237	163	106	87	52	28	15	4	3	0	0

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

Post-hoc subgroup analysis by PD-L1 expression

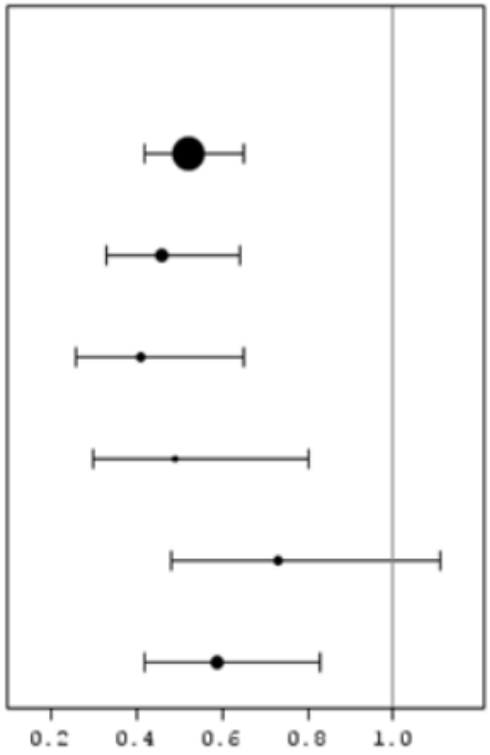
Additional subgroup analyses were conducted to evaluate the efficacy by tumour PD-L1 expression (≥ 25%, 1-24%, ≥ 1%, < 1%) and for patients whose PD-L1 status could not be established (PD-L1 unknown). PFS and OS results are summarised in Figures 4 and 5. Overall the safety profile of durvalumab in PD-L1 TC ≥1% subgroup was consistent with the intent to treat population, as was the PD-L1 TC <1% subgroup.

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



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

Figure 5. Forest plot of PFS by PD-L1 expression (PACIFIC study)



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

Patient reported outcomes

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

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

5.2 Pharmacokinetic properties

The pharmacokinetics of IMFINZI was studied in 1902 patients with solid tumours with doses ranging from 0.1 to 20 mg/kg administered once every two, three or four weeks.

Distribution

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

Excretion

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

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, mild renal impairment (creatinine clearance (CRCL) 60 to 89 mL/min), moderate renal impairment (creatinine clearance (CRCL) 30 to 59 mL/min), mild hepatic impairment (bilirubin ≤ ULN and AST > ULN or bilirubin >1.0 to 1.5 × ULN and any AST) and ECOG/WHO status had no clinically significant effect on the pharmacokinetics of durvalumab.

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

Immunogenicity

As with all therapeutic proteins, there is a potential for 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) patients tested positive for treatment-emergent ADAs. Neutralising antibodies against durvalumab were detected in 0.5% (8/1570) patients. The presence of ADAs did not have a clinically relevant effect on pharmacokinetics or safety.

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

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

5.3 Preclinical safety data

Genotoxicity

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

Carcinogenicity

The carcinogenic potential of durvalumab has not been evaluated.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

IMFINZI concentrated solution for infusion contains the following excipients: histidine, histidine hydrochloride monohydrate, trehalose dihydrate, polysorbate 80 and water for injection.

6.2 Incompatibilities

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

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special precautions for storage

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

6.5 Nature and contents of container

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

2.4 mL of concentrated solution for infusion in a 10 mL Type 1 glass vial with an elastomeric stopper and a grey flip-off aluminium seal containing 120 mg durvalumab. Pack size of 1 vial.

6.6 Special precautions for disposal

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 Physicochemical properties

Durvalumab is a human immunoglobulin (IgG1κ) monoclonal antibody.

CAS number: 1428935-60-7

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription only medicine (Schedule 4).

8 SPONSOR

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9 DATE OF FIRST APPROVAL

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10 DATE OF REVISION

15 October 2019

Summary table of changes

Section changed	Summary of new information
4.2	Extension of allowable time at room temperature after preparation of infusion solution.

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