NEW ZEALAND DATA SHEET

1. PRODUCT NAME

IMFINZI® 50 mg/mL, concentrated 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

Infusion, concentrate.

Sterile, preservative free, clear to opalescent and free from visible particles, colourless to slightly yellow, concentrated solution for infusion. The solution has a pH of approximately 6.0 and an osmolality of approximately 400 mOsm/kg.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Urothelial carcinoma

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

Small Cell Lung Cancer (SCLC)

IMFINZI in combination with etoposide and either carboplatin or cisplatin is indicated for the first-line treatment of patients with extensive-stage small cell lung cancer (ES-SCLC).

Biliary Tract Cancer (BTC)

IMFINZI in combination with chemotherapy is indicated for the treatment of patients with locally advanced or metastatic biliary tract cancer (BTC).

4.2 DOSE AND METHOD OF ADMINISTRATION

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

The recommended dose of IMFINZI depends on the indication as presented in Table 1. IMFINZI is administered as an intravenous infusion over 1 hour.

Table 1. Recommended dosage of IMFINZI

Indication	Recommended IMFINZI dosage	Duration of Therapy
Urothelial Carcinoma	10 mg/kg every 2 weeks or 1500 mg every 4 weeks[a]	As long as clinical benefit is observed or until unacceptable toxicity
Locally Advanced NSCLC	10 mg/kg every 2 weeks or 1500 mg every 4 weeks[a]	For one year or until disease progression or unacceptable toxicity
ES-SCLC	1500 mg[b] in combination with chemotherapy[c,d] every 3 weeks (21 days) for 4 cycles, followed by 1500 mg every 4 weeks as monotherapy	Until disease progression or unacceptable toxicity
BTC	1500 mg[b] in combination with chemotherapy[c,e] every 3 weeks (21 days), followed by 1500 mg every 4 weeks as monotherapy	Until disease progression or until unacceptable toxicity

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

[b] Patients with a body weight of 30 kg or less must receive weight-based dosing, of IMFINZI at 20 mg/kg in combination with chemotherapy dose every 3 weeks (21 days), followed by monotherapy at 20 mg/kg every 4 weeks until weight increases to greater than 30 kg.

[c] Administer IMFINZI prior to chemotherapy when given on the same day.

[d] When IMFINZI is administered in combination with chemotherapy, refer to the Prescribing Information for etoposide and carboplatin or cisplatin for dosing information. Also see Section 5.1 for dosing information in the CASPIAN study.

[e] When IMFINZI is administered in combination with chemotherapy, refer also to the Product Information for appropriate chemotherapeutic agent for dosing information.

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

No dose reduction or escalation for IMFINZI is recommended. In general, withhold IMFINZI for severe (Grade 3) immune-mediated adverse reactions. Permanently discontinue IMFINZI for life-threatening (Grade 4) immune-mediated adverse reactions, recurrent severe (Grade 3) immune-mediated reactions that require systemic immunosuppressive treatment, or an inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks of initiating corticosteroids.

Immune-mediated adverse reactions requiring specific management are summarized in Table 2.

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

Table 2. Recommended treatment modifications and management for adverse reactions

Adverse reactions	**Severity**[a]	**IMFINZI treatment modification**	**Additional management advice**[h]
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	
Immune-mediated hepatitis	ALT or AST >3 - ≤5 x ULN or total bilirubin >1.5 - ≤3 x ULN	Withhold dose	Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
	ALT or AST > 5-≤ 10 x ULN	Withhold dose	
	ALT or AST > 10 x ULN OR total bilirubin x 3 ULN	Permanently discontinue	
	Concurrent ALT or AST > 3 x ULN and total bilirubin > 2 x ULN[d]		
Immune-mediated hepatitis with tumour involvement of the liver with abnormal baseline values[e]	ALT or AST > 2.5-≤ 5X BLV and ≤ 20 x ULN	Withhold dose	
	ALT or AST >5-7X BLV and ≤ 20X ULN OR concurrent ALT or AST 2.5-5X BLV and ≤ 20XULN AND total bilirubin > 1.5 - < 2 x ULN[d]	Withhold dose	
	AST or ALT > 7 x BLV OR > 20 ULN whichever occurs first OR bilirubin > 3ULN	Permanently discontinue	
Colitis or diarrhoea	Grade 2 or 3	Withhold dose	Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
	Grade 4	Permanently discontinue	
	Intestinal perforation of ANY grade	Permanently discontinue	Consult a surgeon immediately if an intestinal perforation is suspected

Adverse reactions	**Severity**[a]	**IMFINZI treatment modification**	**Additional management advice**[h]
Endocrinopathies: hyperthyroidism, thyroiditis	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	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	
Rash or dermatitis (including pemphigoid)	Grade 2 for > 1 week or Grade 3	Withhold dose	Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
	Grade 4	Permanently discontinue	
Myocarditis	Grade 2-4	Permanently discontinue	Initiate 2 to 4 mg/kg/day prednisone or equivalent followed by a taper[b]
Myositis/polymyositis	Grade 2 or 3	Withhold dose[c]	Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
	Grade 4	Permanently discontinue	
Infusion-related reactions	Grade 1 or 2	Interrupt or slow the rate of infusion	May consider pre-medications for prophylaxis of subsequent infusion reactions
	Grade 3 or 4	Permanently discontinue	Manage severe infusion-related reactions per institutional standard, appropriate clinical practice guidelines and/or society guidelines
Infection	Grade 3 or 4	Withhold dose until clinically stable	
Immune-mediated myasthenia gravis	Grade 2-4	Permanently discontinue	Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper

Adverse reactions	Severity[a]	IMFINZI treatment modification	Additional management advice[h]
Immune-mediated encephalitis	Grade 2-4	Permanently discontinue	Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
Other immune-mediated adverse reactions[f]	Grade 2 or 3	Withhold dose[c]	Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
	Grade 4	Permanently discontinue	

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

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

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

[d] For patients with alternative cause follow the recommendations for AST or ALT increases without concurrent bilirubin elevations.

[e] If AST and ALT are less than or equal to ULN at baseline in patients with liver involvement, withhold or permanently discontinue durvalumab based on recommendations for hepatitis with no liver involvement.

[f] Includes immune thrombocytopenia and pancreatitis.

For suspected immune-mediated adverse reactions, adequate evaluation should be performed to confirm aetiology or exclude alternate aetiologies. Upon improvement to ≤ Grade 1, corticosteroid taper should be initiated and continued over at least 1 month. Consider increasing dose of corticosteroids and/or using additional systemic immunosuppressants if there is worsening or no improvement. 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 adverse reactions as applicable.

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

Based on a population pharmacokinetic analysis, no dose adjustment is recommended for patients with mild or moderate hepatic impairment. IMFINZI has not been studied in patients with severe hepatic impairment. 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

For intravenous 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:

- 30 days at 2°C to 8°C and for up to
- 12 hours at room temperature (up to 25°C) from the time of preparation.

Administration

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

Do not co-administer other 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 2 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 2 (see Section 4.2 Dose and Method of Administration).

Immune-mediated pneumonitis and radiation pneumonitis

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

Patients should be monitored for signs and symptoms of pneumonitis. Suspected pneumonitis should be confirmed with radiographic imaging and other infectious and disease-related aetiologies excluded, and managed as recommended in Table 2 (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 Undesirable 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 2 (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 Undesirable Effects). Patients should be monitored for signs and symptoms of colitis (including diarrhoea) and managed as recommended in Table 2 (see Section 4.2 Dose and Method of Administration).

Immune-mediated endocrinopathies

Immune-mediated hypothyroidism/hyperthyroidism/thyroiditis

Immune-mediated hypothyroidism, hyperthyroidism or thyroiditis have occurred in patients receiving durvalumab in clinical trials (see Section 4.8 Undesirable Effects). Patients should be monitored for abnormal thyroid function tests prior to and periodically during treatment and managed as recommended in Table 2(see Section 4.2 Dose and Method of Administration).

Immune-mediated adrenal insufficiency

Immune-mediated adrenal insufficiency occurred in patients receiving durvalumab in clinical trials (see Section 4.8 Undesirable 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 2 (see Section 4.2 Dose and Method of Administration).

Immune-mediated type 1 diabetes mellitus

Immune-mediated type 1 diabetes mellitus, which can present with diabetic ketoacidosis, occurred in patients receiving durvalumab in clinical trials (see Section 4.8 Undesirable Effects). Patients should be monitored for clinical signs and symptoms of type 1 diabetes

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

mellitus. For symptomatic type 1 diabetes mellitus, patients should be managed as recommended in Table 2 (see Section 4.2 Dose and Method of Administration).

Immune-mediated hypophysitis/hypopituitarism

Immune-mediated hypophysitis/hypopituitarism occurred in patients receiving durvalumab in clinical trials (see Section 4.8 Undesirable Effects). Patients should be monitored for clinical signs and symptoms of hypophysitis. For symptomatic hypophysitis or hypopituitarism, patients should be managed as recommended in Table 2 (see Section 4.2 Dose and Method of Administration).

Immune-mediated nephritis

Immune-mediated nephritis, defined as requiring use of systemic corticosteroids and with no clear alternate aetiology, occurred in patients receiving durvalumab in clinical trials (see Section 4.8 Undesirable Effects). Patients should be monitored for abnormal renal function tests prior to and periodically during treatment with durvalumab and managed as recommended in Table 2 (see Section 4.2 Dose and Method of Administration).

Immune-mediated dermatological adverse reactions

Immune-mediated dermatitis (including pemphigoid), defined as requiring use of systemic corticosteroids and with no clear alternate aetiology, occurred in patients receiving durvalumab in clinical trials (see Section 4.8 Undesirable 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 2 (see Section 4.2 Dose and Method of Administration).

Immune-mediated myocarditis

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

Other immune mediated adverse reactions

Given the mechanism of action of durvalumab, other immune-mediated adverse reactions may occur. Other immune mediated adverse reactions are: aseptic meningitis, haemolytic anaemia, immune thrombocytopenia, myasthenia gravis, myositis, polymyositis, pancreatitis, encephalitis and ocular inflammatory toxicity, including uveitis and keratitis. Patients should be monitored for signs and symptoms of immune-mediated adverse reactions and managed as recommended in Table 2 (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 2 (see Section 4.2 Dose and Method of Administration). Severe infusion related reactions have been reported in patients receiving durvalumab (see Section 4.8 Undesirable 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 Undesirable Effects and 5.1 Pharmacological Properties).

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.

Of the 265 patients with ES-SCLC treated with IMFINZI in combination with chemotherapy, 101 (38%) patients were 65 years or older. There were no overall clinically meaningful differences in safety or effectiveness between patients ≥ 65 years of age and younger patients.

Of the 338 patients with BTC treated with IMFINZI in combination with chemotherapy, 158 (46.7%) patients were 65 years or older. There were no overall clinically meaningful differences in safety or effectiveness between patients ≥65 years of age and younger patients.

Paediatric use

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

4.5 INTERACTION WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION

Durvalumab is an immunoglobulin and the primary elimination pathways of durvalumab are protein catabolism via reticuloendothelial system or target mediated disposition, therefore no formal pharmacokinetic (PK) drug-drug interaction studies have been conducted since no metabolic drug-drug interactions are expected. PK drug-drug interaction between durvalumab and chemotherapy was assessed in the CASPIAN study and no clinically meaningful PK drug-drug interaction was identified.

4.6 FERTILITY, PREGNANCY AND LACTATION

Pregnancy

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.

Breast-feeding

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

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.

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 UNDESIRABLE EFFECTS

Overall summary of adverse drug reactions

The safety of IMFINZI as monotherapy is based on pooled data in 3006 patients from 9 studies across multiple tumour types.

The most frequent adverse reactions were cough (21.5%), diarrhoea (16.3%) and rash (16.0%).

Tabulated list of adverse reactions

Table 3 lists the incidence of adverse reactions in the monotherapy safety dataset. 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. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each ADR is based on the CIOMS III convention and 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 determined (cannot be estimated from available data).

Table 3. Adverse drug reactions in patients treated with IMFINZI monotherapy

System Organ Class	Adverse Drug Reaction	Frequency of any Grade		Frequency of Grade 3-4	
Respiratory, thoracic and mediastinal disorders	Cough/ Productive Cough	Very common	646 (21.5%)	Uncommon	11 (0.4%)
	Pneumonitis[a]	Common	114 (3.8%)	Uncommon	26 (0.9%)
	Dysphonia	Common	93 (3.1%)	Rare	2 (<0.1%)
	Interstitial lung disease	Uncommon	18 (0.6%)	Uncommon	4 (0.1%)
Hepatobiliary disorders	Aspartate aminotransferase increased or Alanine aminotransferase increased[a,b]	Common	244 (8.1%)	Common	69 (2.3%)
	Hepatitis[a,c]	Uncommon	25 (0.8%)	Uncommon	12 (0.4%)
Gastrointestinal disorders	Abdominal pain[d]	Very common	383 (12.7%)	Common	53 (1.8%)
	Diarrhoea	Very common	491 (16.3%)	Uncommon	19 (0.6%)

System Organ Class	Adverse Drug Reaction	Frequency of any Grade		Frequency of Grade 3-4	
	Colitis[e]	Uncommon	28 (0.9%)	Uncommon	10 (0.3%)
	Pancreatitis[t]	Uncommon	6 (0.23%)	Uncommon	5 (0.17%)
Endocrine disorders	Hypothyroidism[f]	Very common	305 (10.1%)	Uncommon	5 (0.2%)
	Hyperthyroidism[g]	Common	137 (4.6%)	Rare	0
	Thyroiditis[h]	Uncommon	23 (0.8%)	Rare	2 (<0.1%)
	Adrenal insufficiency	Uncommon	18 (0.6%)	Rare	3 (<0.1%)
	Hypophysitis/ Hypopituitarism	Rare	2 (< 0.1%)	Rare	2 (< 0.1%)
	Type 1 diabetes mellitus	Rare	1 (< 0.1%)	Rare	1 (< 0.1%)
	Diabetes insipidus	Rare	1 (< 0.1%)	Rare	1 (< 0.1%)
Renal and urinary disorders	Blood creatinine increased	Common	105 (3.5%)	Rare	3 (<0.1%)
	Dysuria	Common	39 (1.3%)		0
	Nephritis[i]	Uncommon	9 (0.3%)	Rare	2 (< 0.1%)
Skin and subcutaneous tissue disorders	Rash[j]	Very common	480 (16.0%)	Uncommon	18 (0.6%)
	Pruritus[k]	Very common	325 (10.8%)	Rare	1 (< 0.1%)
	Night sweats	Common	47 (1.6%)	Rare	1 (< 0.1%)
	Dermatitis	Uncommon	22 (0.7%)	Rare	2 (< 0.1%)
	Pemphigoid[l]	Rare	3 (<0.1%)		0
Cardiac disorders	Myocarditis	Rare	1 (< 0.1%)	Rare	1 (<0.1%)
General disorders and administration site conditions	Pyrexia	Very common	414 (13.8%)	Uncommon	10 (0.3%)
	Oedema peripheral[m]	Common	291 (9.7%)	Uncommon	9 (0.3%)
Infections and infestations	Upper respiratory tract infections[n]	Very common	407 (13.5%)	Uncommon	6 (0.2%)
	Pneumonia[a,o]	Common	269 (8.9%)	Common	106 (3.5%)
	Oral candidiasis	Common	64 (2.1%)		0
	Dental and oral soft tissue infections[p]	Common	50 (1.7%)	Rare	1 (<0.1%)
	Influenza	Common	47 (1.6%)	Rare	2 (<0.1%)
Musculoskeletal and connective tissue disorders	Myalgia	Common	178 (5.9%)	Rare	2 (<0.1%)
	Myositis	Uncommon	6 (0.2%)	Rare	1 (< 0.1%)
	Polymyositis	Not determined[q]		Not determined[q]	
Nervous system disorders	Myasthenia gravis	Not determined[r]		Not determined[r]	
	Encephalitis	Not determined[u]		Not determined[u]	
Blood and lymphatic system disorders	Immune thrombocytopenia[a]	Rare	2 (<0.1%)	Rare	1 (<0.1%)
Injury, poisoning and procedural complications	Infusion related reaction[s]	Common	49 (1.6%)	Uncommon	5 (0.2%)

[a] Including fatal outcome.
[b] Includes alanine aminotransferase increased, aspartate aminotransferase increased, hepatic enzyme increased, and transaminases increased.
[c] Includes hepatitis, autoimmune hepatitis, hepatitis toxic, hepatocellular injury, hepatitis acute, hepatotoxicity and immune-mediated hepatitis.
[d] Includes abdominal pain, abdominal pain lower, abdominal pain upper, and flank pain.
[e] Includes colitis, enteritis, enterocolitis, and proctitis.
[f] Includes autoimmune hypothyroidism and hypothyroidism.
[g] Includes hyperthyroidism and Basedow's disease.

[h]Includes autoimmune thyroiditis, thyroiditis, and thyroiditis subacute.
[i] Includes autoimmune nephritis, tubulointerstitial nephritis, nephritis, glomerulonephritis and glomerulonephritis membranous.
[j] Includes rash erythematous, rash generalized, rash macular, rash maculopapular, rash papular, rash pruritic, rash pustular, erythema, eczema and rash.
[k] Includes pruritus generalized and pruritus.
[l] Includes pemphigoid, dermatitis bullous and pemphigus. Reported frequency from completed and ongoing trials is uncommon.
[m] Includes oedema peripheral and peripheral swelling.
[n] Includes laryngitis, nasopharyngitis, peritonsillar abscess, pharyngitis, rhinitis, sinusitis, tonsillitis, tracheobronchitis, and upper respiratory tract infection.
[o] Includes lung infection, pneumocystis jirovecii pneumonia, pneumonia, candida pneumonia, pneumonia legionella, pneumonia adenoviral, pneumonia bacterial, pneumonia cytomegaloviral, pneumonia haemophilus, pneumonia pneumococcal and pneumonia streptococcal.
[p] Includes gingivitis, oral infection, periodontitis, pulpitis dental, tooth abscess and tooth infection.
[q] Polymyositis (fatal) was observed in a patient treated with IMFINZI from an ongoing sponsored clinical study outside of the pooled dataset: rare in any grade, rare in Grade 3 or 4 or 5.
[r] Reported frequency from AstraZeneca-sponsored clinical studies outside of the pooled dataset is rare, with no events at Grade > 2.
[s] Includes infusion related reaction and urticaria with onset on the day of dosing or 1 day after dosing.
[t] Includes pancreatitis and pancreatitis acute
[u] Reported frequency from ongoing AstraZeneca-sponsored clinical studies outside of the pooled dataset is rare and includes two events of encephalitis, one was Grade 5 (fatal) and one was Grade 2.

Table 4 lists the incidence of laboratory abnormalities worsening from baseline in the IMFINZI monotherapy safety dataset. .

Table 4. Laboratory abnormalities worsening from baseline occurring more frequently in IMFINZI-treated patients

Laboratory abnormalities	N	Any grade	Grade 3 or 4
Alanine aminotransferase increased	2866	813 (28.4%)	69 (2.4%)
Aspartate aminotransferase increased	2858	891 (31.2%)	102 (3.6%)
Blood creatinine increased	2804	642 (22.9%)	13 (0.5%)
TSH elevated >ULN and above baseline	3006	566 (18.8%)	NA
TSH decreased <LLN and below baseline	3006	545 (18.1%)	NA

ULN = upper limit of normal; LLN = lower limit of normal

The safety of IMFINZI in combination with chemotherapy is based on data in 265 patients from the CASPIAN (SCLC) study and was consistent with IMFINZI monotherapy and known chemotherapy safety profile.

The safety of IMFINZI in combination with chemotherapy is based on data in 338 patients from the TOPAZ-1 (BTC) study and was consistent with Imfinzi monotherapy and known chemotherapy safety profiles.

Description of selected adverse reactions

The data below reflect information for significant adverse reactions for IMFINZI as monotherapy in the pooled safety dataset across tumour types (n=3006).

The management guidelines for these adverse reactions are described in sections 4.2 and 4.4.

Immune-mediated pneumonitis

In patients receiving IMFINZI monotherapy, immune-mediated pneumonitis occurred in 92 (3.1%) patients, including Grade 3 in 25 (0.8%) patients, Grade 4 in 2 (< 0.1%) patients, and Grade 5 in 6 (0.2%) patients. The median time to onset was 55 days (range: 2-785 days). Sixty-nine of the 92 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day), 2 patients also received infliximab and 1 patient also received cyclosporine. IMFINZI was discontinued in 38 patients. Resolution occurred in 53 patients. Immune-mediated pneumonitis occurred more frequently in patients in the PACIFIC Study who had completed treatment with concurrent chemoradiation within 1 to 42 days prior to initiation of the study (9.9%), compared to the other patients in the combined safety database (1.8%).

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

Immune-mediated hepatitis

In patients receiving IMFINZI monotherapy, immune-mediated hepatitis occurred in 67 (2.2%) patients, including Grade 3 in 35 (1.2%) patients, Grade 4 in 6 (0.2%) and Grade 5 in 4 (0.1%) patients. The median time to onset was 36 days (range: 3-333 days). Forty-four of the 67 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). Three patients also received mycophenolate treatment. IMFINZI was discontinued in 9 patients. Resolution occurred in 29 patients.

Immune-mediated colitis

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

Immune-mediated endocrinopathies

Immune-mediated hypothyroidism

In patients receiving IMFINZI monotherapy, immune-mediated hypothyroidism occurred in 245 (8.2%) patients, including Grade 3 in 4 (0.1%) patients. The median time to onset was 85 days (range: 1-562 days). Of the 245 patients, 240 patients received hormone replacement therapy, 6 patients received high-dose corticosteroids (at least 40 mg prednisone or equivalent per day) for immune-mediated hypothyroidism followed by hormone replacement. No patients discontinued IMFINZI due to immune-mediated hypothyroidism. Immune-mediated hypothyroidism was preceded by immune-mediated hyperthyroidism in 20 patients or immune-mediated thyroiditis in 3 patients.

Immune-mediated hyperthyroidism

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

(range: 1-253 days). Forty-six of the 50 patients received medical therapy (thiamazole, carbimazole, propylthiouracil, perchlorate, calcium channel blocker,or beta-blocker), 11 patients received systemic corticosteroids and 4 of the 11 patients received high-dose systemic corticosteroid treatment (at least 40 mg prednisone or equivalent per day). One patient discontinued IMFINZI due to immune-mediated hyperthyroidism. Resolution occurred in 39 patients.

Immune-mediated thyroiditis

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

Immune-mediated adrenal insufficiency

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

Immune-mediated type 1 diabetes mellitus

In patients receiving IMFINZI monotherapy, Grade 3 immune-mediated type 1 diabetes mellitus occurred in 1 (<0.1%) patient. The time to onset was 43 days. This patient required long-term insulin therapy and IMFINZI was permanently discontinued due to immune-mediated type 1 diabetes mellitus.

Immune-mediated hypophysitis/Hypopituitarism

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

Immune-mediated nephritis

In patients receiving IMFINZI monotherapy, immune-mediated nephritis occurred in 14 (0.5%) patients, including Grade 3 in 2 (<0.1%) patients. The median time to onset was 71 days (range: 4-393 days). Nine patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day) and 1 patient also received mycophenolate. IMFINZI was discontinued in 5 patients. Resolution occurred in 8 patients.

Immune-mediated rash

In patients receiving IMFINZI monotherapy, immune-mediated rash or dermatitis (including pemphigoid) occurred in 50 (1.7%) patients, including Grade 3 in 12 (0.4%) patients. The median time to onset was 43 days (range: 4-333 days). Twenty-four of the 50 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). IMFINZI was discontinued in 3 patients. Resolution occurred in 31 patients.

Infusion-related reactions

In patients receiving IMFINZI monotherapy, infusion related reactions occurred in 49 (1.6%) patients, including Grade 3 in 5 (0.2%) patients. There were no Grade 4 or 5 events.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions via https://nzphvc.otago.ac.nz/reporting/.

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 advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764 766).

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 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 Efficacy and Safety

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

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 5 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 5 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)

Table 5 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**
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.

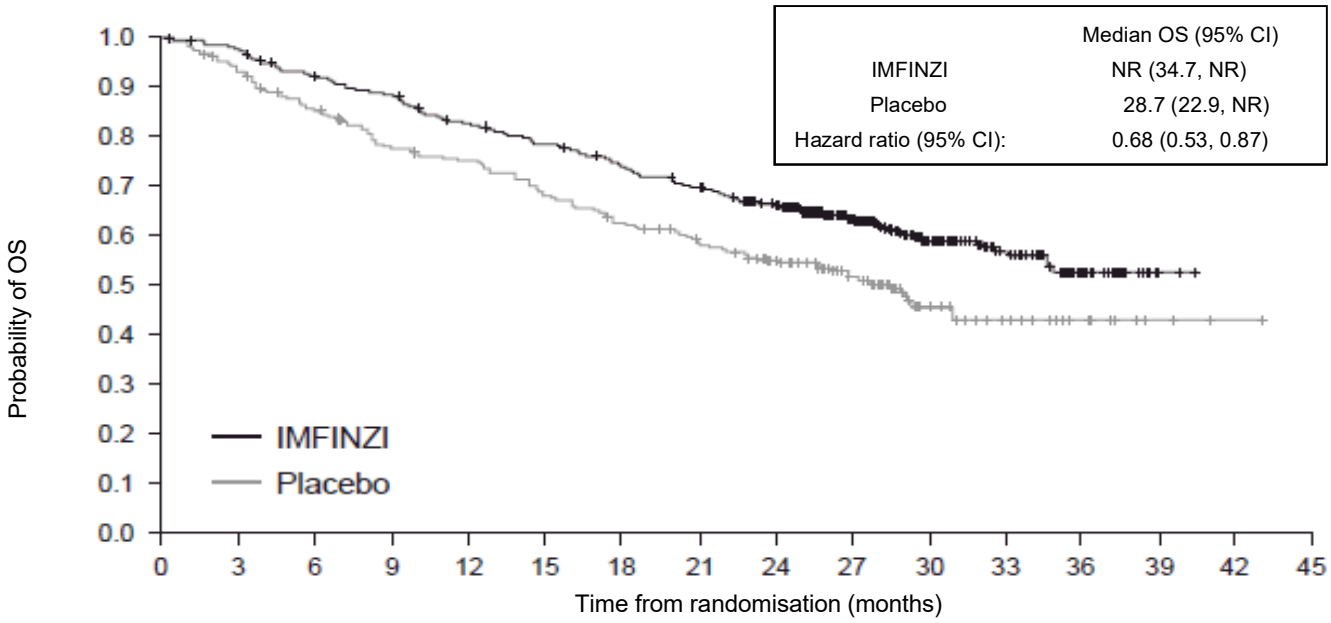
The study demonstrated a statistically significant improvement in PFS and OS in the IMFINZI - treated group compared with the placebo group (see Table 6 and Figures 1 and 2).

Table 6. 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)	
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

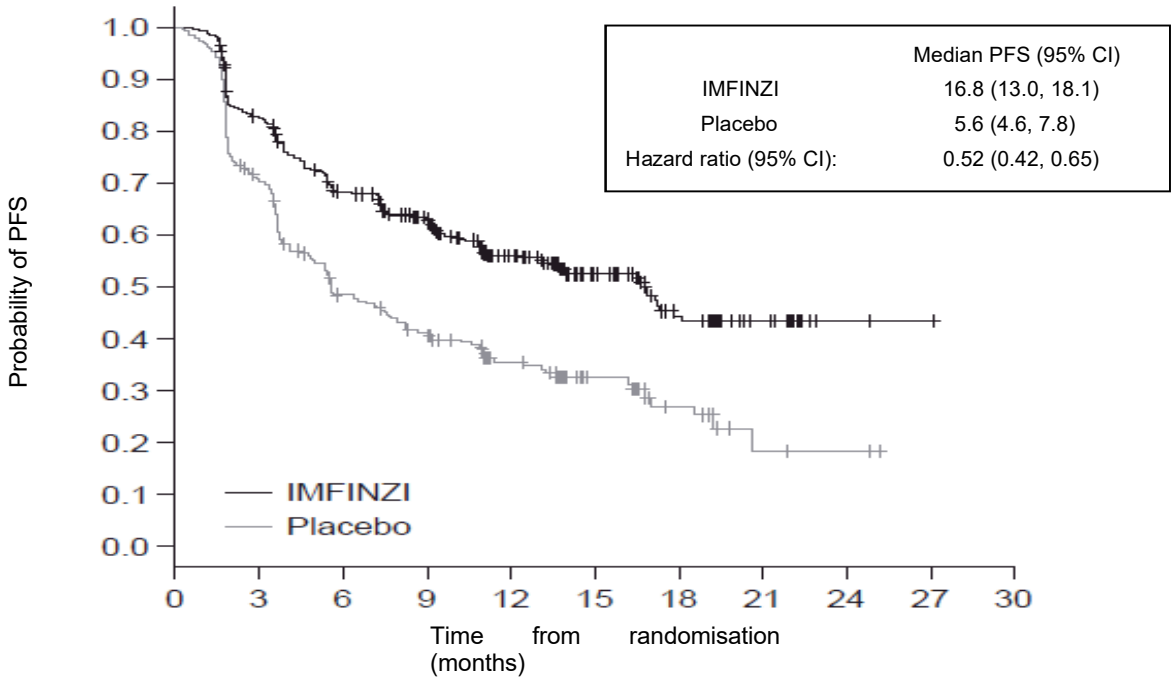
Figure 1. Kaplan-Meier curve of OS (PACIFIC study)



Number of patients at risk

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

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



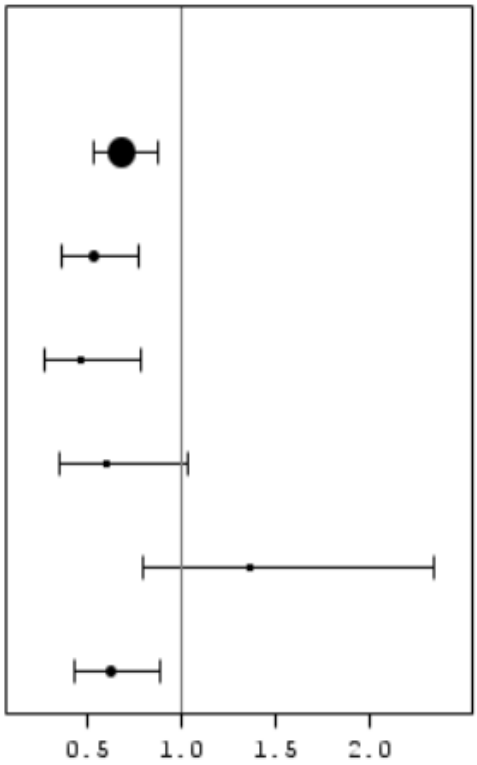
Number of patients at risk

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

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

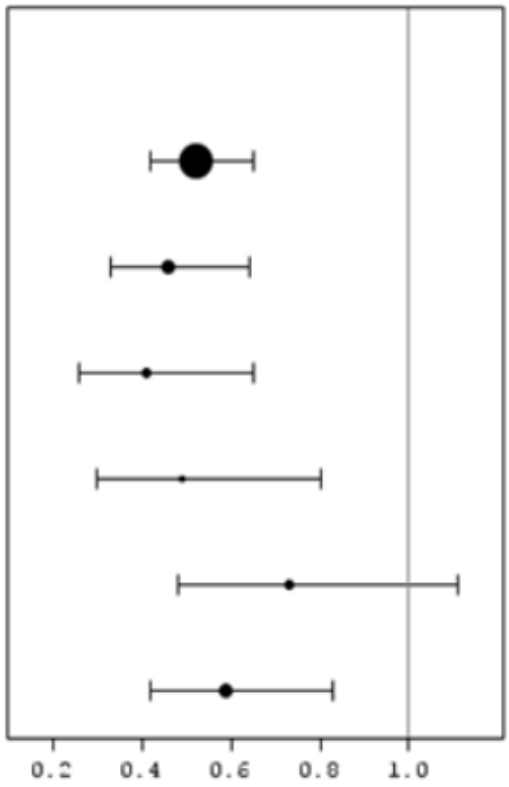
Post-hoc subgroup analysis by PD-L1 expression
Additional subgroup analyses were conducted to evaluate the efficacy by tumour PD-L1 expression (≥ 25%, 1-24%, ≥ 1%, < 1%) and for patients whose PD-L1 status could not be established (PD-L1 unknown). PFS and OS results are summarised in Figures 4 and 5. 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 3. Forest plot of OS by PD-L1 expression (PACIFIC study)



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

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



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

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

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

SCLC – CASPIAN Study
CASPIAN was a study designed to evaluate the efficacy of IMFINZI with or without tremelimumab in combination with etoposide and either carboplatin or cisplatin. CASPIAN was a randomized, open-label, multicenter study in 805 treatment naïve ES-SCLC patients with WHO/ECOG Performance status of 0 or 1, suitable to receive a platinum-based chemotherapy regimen as first-line treatment for SCLC, with life expectancy ≥12 weeks, , at least one target lesion by RECIST 1.1 and adequate organ and bone marrow function. Patients with asymptomatic or treated brain metastases were eligible. The study excluded patients with a history of chest radiation therapy; a history of active primary immunodeficiency; autoimmune disorders including paraneoplastic syndrome (PNS); active or prior documented autoimmune or inflammatory disorders; use of systemic immunosuppressants within 14 days before the first dose of the treatment except physiological dose of systemic corticosteroids; active tuberculosis or hepatitis B or C or HIV infection; or patients receiving live attenuated vaccine within 30 days before or after the start of IMFINZI.

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

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

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

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

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

The primary endpoints of the study were Overall Survival (OS) of IMFINZI + chemotherapy (Arm 2) vs. chemotherapy alone (Arm 3) and IMFINZI + tremelimumab + chemotherapy (Arm 1) vs.

chemotherapy alone (Arm 3). The key secondary endpoint was progression-free survival (PFS). Other secondary endpoints were Objective Response Rate (ORR), OS and PFS landmarks and Patient Reported Outcomes (PRO). PFS and ORR were assessed using Investigator assessments according to RECIST v1.1.

At a planned interim analysis, IMFINZI + chemotherapy (Arm 2) vs chemotherapy (Arm 3) met the efficacy boundary of the primary endpoint of OS. The results are summarised below.

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

The study demonstrated a statistically significant and clinically meaningful improvement in OS with IMFINZI + chemotherapy (Arm 2) vs. chemotherapy alone (Arm 3) [HR=0.73 (95% CI: 0.591, 0.909), p=0.0047]. IMFINZI + chemotherapy demonstrated an improvement in PFS vs. chemotherapy alone [HR=0.78 (95% CI: 0.645, 0.936) nominal p-value=0.0078]. See Table 7 and Figures 4 and 5.

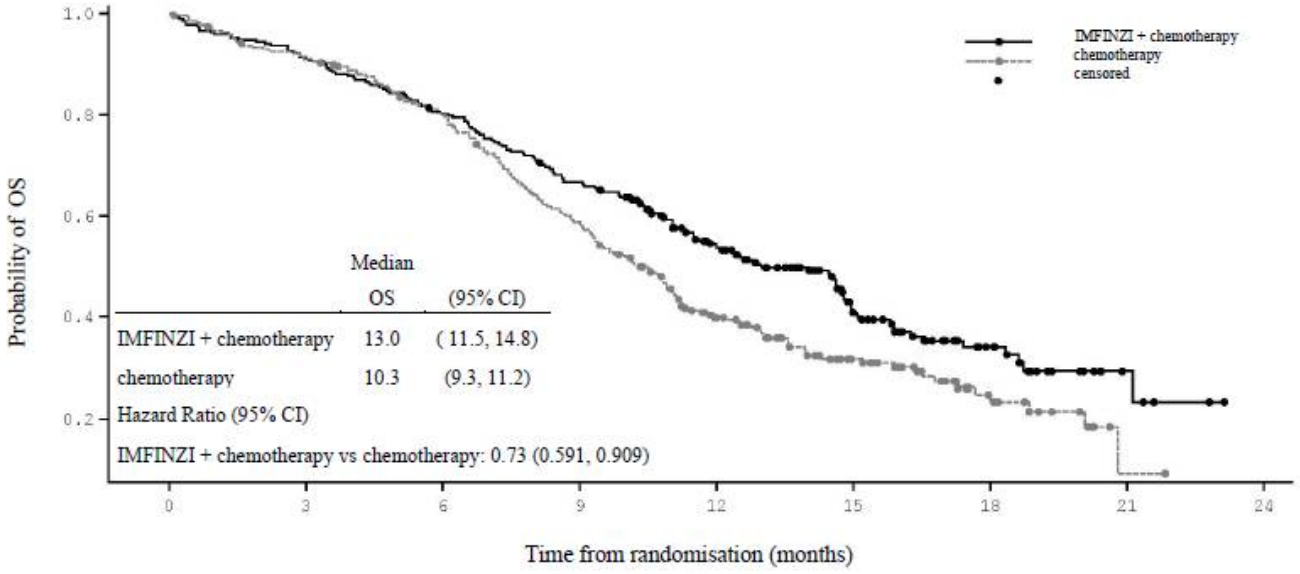
Table 7. Efficacy Results for the CASPIAN Study

	Arm 2: IMFINZI + etoposide and either carboplatin or cisplatin (n=268)	**Arm 3: etoposide and either carboplatin or cisplatin (n=269)**
OS		
Number of deaths (%)	155 (57.8)	181 (67.3)
Median OS (months) (95% CI)	13.0 (11.5, 14.8)	10.3 (9.3, 11.2)
HR (95% CI)[d]	0.73 (0.591, 0.909)	
p-value[c]	0.0047	
OS at 12 months (%) (95% CI)	53.7 (47.4, 59.5)	39.8 (33.7, 45.8)
OS at 18 months (%) (95% CI)	33.9 (26.9, 41.0)	24.7 (18.4, 31.6)
PFS		
Number of events (%)	226 (84.3)	233 (86.6)
Median PFS (months) (95% CI)	5.1 (4.7, 6.2)	5.4 (4.8, 6.2)
HR (95% CI)[d]	0.78 (0.645, 0.936)	
p-value[b]	0.0078	
PFS at 6 months (%) (95% CI)	45.4 (39.3, 51.3)	45.6 (39.3, 51.7)
PFS at 12 months (%) (95% CI)	17.5 (13.1, 22.5)	4.7 (2.4, 8.0)
ORR n (%)[a]	182 (67.9)	155 (57.6)
Complete Response n (%)	6 (2.2)	2 (0.7)
Partial Response n (%)	176 (65.7)	153 (56.9)
Odds ratio (95% CI)[e]	1.56 (1.095, 2.218)	
p-value[b]	0.0136	
Median DoR (months) (95% CI)[a]	5.1 (4.9, 5.3)	5.1 (4.8, 5.3)
DoR at 12 months (%)[a]	22.7	6.3

[a] Confirmed Objective Response.

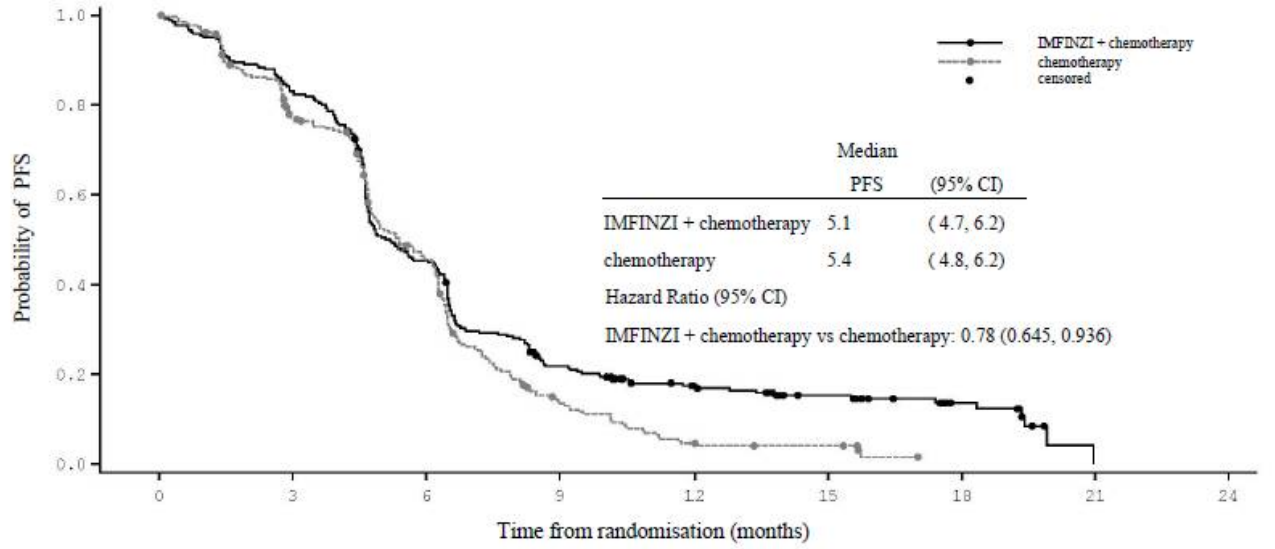
[b] Nominal p-value. PFS was included in the Multiple Testing Procedure (MTP) hierarchy at the second level. It was not able to be tested within the MTP as both Arm 1 and Arm 2 were required to achieve statistical significance prior to stepping down to PFS. ORR was not included in the MTP.
[c] Based on a Lan-DeMets alpha spending function with O'Brien Fleming type boundary with the actual number of events observed, the boundaries for declaring statistical significance are 0.0178 for a 4% overall alpha (Lan◦and◦DeMets 1983).
[d] The analysis was performed using the stratified log-rank test, adjusting for planned platinum therapy in Cycle 1 (carboplatin or cisplatin), and using the rank tests of association approach.
[e] The analysis was performed using a logistic regression model adjusting for planned platinum therapy in Cycle 1 (carboplatin or cisplatin) with 95% CI calculated by profile likelihood.

Figure 5. Kaplan-Meier curve of OS



Number of patients at risk	0	3	6	9	12	15	18	21	24
IMFINZI + chemotherapy	268	244	214	177	116	57	25	5	0
chemotherapy	269	242	209	153	82	44	17	1	0

Figure 6. Kaplan-Meier curve of PFS



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

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

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). Both questionnaires were administered up to second disease progression (PFS2) or death (whichever came first). At baseline, patient reported symptoms, functioning or HRQoL scores were comparable between the study arms. Compliance was 60% or higher over 84 weeks in IMFINZI + chemotherapy and 20 weeks in the chemotherapy only arm.

Delay in time to deterioration of symptoms, functioning, and global health status/QoL:

IMFINZI + chemotherapy demonstrated improvement by delaying time to deterioration in a broad range of patient-reported symptoms, function, and global health status/QoL compared to chemotherapy alone (see Tables 8 and 9).

Table 8: Delay in median time to deterioration in global health status/QoL and function (EORTC QLQ-C30)[a]

	Time to deterioration (months) Arm 2 (N=261) vs. Arm 3 (N=260)
Global health status/QoL	8.4 vs. 7.2 0.81 (0.63, 1.05); p=0.1166
Physical	8.5 vs. 6.5 0.75 (0.58, 0.97); p=0.0276
Cognitive	8.4 vs. 6.0 0.61 (0.47, 0.78); p=<0.00001
Role	7.4 vs. 5.9 0.71 (0.55, 0.90); p=0.0059
Emotional	12.9 vs. 7.3 0.61 (0.46, 0.80); p=0.0003
Social	7.6 vs. 6.2 0.70 (0.55, 0.90); p=0.0048

[a] p-values for time to deterioration based on stratified log-rank test and were not adjusted for multiplicity

Table 9: Delay in median time to deterioration in symptoms (EORTC QLQ-C30 and QLQ-LC13)[a]

Symptom scale	**Delay in time to deterioration (months) Arm 2 (N=261) vs. Arm 3 (N=260)**
Coughing	9.3 vs. 7.7 0.78 (0.60, 1.03); p=0.0747
Dyspnoea (QLQ-C30)	9.0 vs. 7.4 0.75 (0.57, 0.99); p=0.0406
Dyspnoea (QLQ-LC13)	6.5 vs. 5.5 0.79 (0.63, 1.01); p=0.0578
Pain	7.8 vs. 6.7 0.79 (0.62, 1.02); p=0.0718
Chest pain	10.6 vs. 7.8 0.76 (0.58, 1.00); p=0.0464
Arm or shoulder pain	9.9 vs. 7.5 0.70 (0.54, 0.92); p=0.0088

Symptom scale	Delay in time to deterioration (months) Arm 2 (N=261) vs. Arm 3 (N=260)
Pain in other parts of body	7.8 vs. 6.4 0.72 (0.56, 0.92); p=0.0096
Fatigue	5.5 vs. 4.3 0.82 (0.65, 1.03); p=0.0835
Insomnia	8.6 vs. 7.3 0.75 (0.57, 0.98); p=0.0349
Appetite loss	8.3 vs. 6.6 0.70 (0.54, 0.90); p=0.0054
Constipation	11.1 vs. 7.3 0.65 (0.50, 0.86); p=0.0018
Diarrhoea	14.6 vs. 7.7 0.59 (0.44, 0.77); p=0.0002
Nausea/vomiting	8.4 vs. 6.6 0.80 (0.63, 1.03); p=0.0809
Haemoptysis	18.3 vs. 10.5 0.64 (0.47, 0.88); p=0.0049

[a] p-values for time to deterioration based on stratified log-rank test and were not adjusted for multiplicity

Change from baseline in lung cancer symptoms over 12 months (mixed model for repeated measures):

IMFINZI + chemotherapy improved appetite loss by demonstrating a statistically significant difference in mean change from baseline versus chemotherapy alone during the overall time period from randomisation until 12 months (Estimated mean difference -4.5; 99% CI -9.04, -0.04; p=0.009). Both treatment arms demonstrated numerical symptom reduction in cough, chest pain, dyspnoea and fatigue over the same time period.

Patient-reported outcome results should be interpreted in the context of the open-label study design.

BTC – TOPAZ-1 Study

TOPAZ-1 was a study designed to evaluate the efficacy of Imfinzi in combination with gemcitabine and cisplatin. TOPAZ-1 was a randomised, double-blind, placebo-controlled, multicentre study in 685 patients with histologically confirmed locally advanced or metastatic BTC and ECOG performance status of 0 or 1. Patients who developed recurrent disease more than 6 months after surgery and/or completion of adjuvant therapy were included. Patients must have had at least one target lesion by RECIST v1.1 and adequate organ and bone marrow function.

The study excluded patients with ampullary carcinoma, active or prior documented autoimmune or inflammatory disorders, HIV infection or active infections, including tuberculosis or hepatitis C or patients with current or prior use of immunosuppressive medication within 14 days before the first dose of Imfinzi.

Randomisation was stratified by disease status and primary tumour location.

Patients were randomised 1:1 to receive:

- Arm 1: Imfinzi 1500 mg administered intravenously on Day 1+ gemcitabine 1000 mg/m^2 and cisplatin 25 mg/m^2 (each administered on Days 1 and 8) every 3 weeks (21 days) for up to 8 cycles, followed by Imfinzi 1500 mg every 4 weeks as long as clinical benefit is observed or until unacceptable toxicity, or
- Arm 2: Placebo administered intravenously on Day 1+ gemcitabine 1000 mg/m^2 and cisplatin 25 mg/m^2 (each administered on Days 1 and 8) every 3 weeks (21 days) for

up to 8 cycles, followed by placebo every 4 weeks as long as clinical benefit is observed or until unacceptable toxicity.

Tumour assessments were conducted every 6 weeks for the first 24 weeks after the date of randomisation, and then every 8 weeks until confirmed objective disease progression.

The primary endpoint of the study was OS and the key secondary endpoint was PFS. Other secondary endpoints were ORR, DoR and PRO. PFS, ORR and DoR were Investigator assessed according to RECIST v1.1.

The demographics and baseline disease characteristics were well balanced between the two study arms (341 patients in Arm 1 and 344 patients in Arm 2). Baseline demographics of the overall study population were as follows: male (50.4%), age <65 years (53.3%), white (37.2%), Asian (56.4%), black or African American (2.0%), other (4.2%), non-Hispanic or Latino (93.1%), ECOG PS 0 (49.1%), vs. PS 1 (50.9%), primary tumour location intrahepatic cholangiocarcinoma (55.9%), extrahepatic cholangiocarcinoma (19.1%) and gallbladder cancer (25.0%), disease status recurrent (19.1%) vs. initially unresectable (80.7%), metastatic (86.0%) vs. locally advanced (13.9%).

The study demonstrated a statistically significant and clinically meaningful improvement in OS and PFS at a pre-planned interim analysis based on a Lan-DeMets alpha spending function with O'Brien Fleming type boundary and the actual number of events observed (Lan◦and◦DeMets 1983). The results in OS were [HR=0.80, (95% CI: 0.66, 0.97), p=0.021] and in PFS [HR=0.75, (95% CI: 0.63, 0.89), p=0.001]. The maturity for OS was 61.9% and the maturity for PFS was 83.6%. The boundary for declaring statistical significance for OS was 0.03 for an 4.9% overall alpha. Results from this analysis for PFS, ORR and DoR are presented in Table 10. PFS is also presented in Figure 7.

Table 10. Efficacy Results for the TOPAZ-1 Study

	IMFINZI **+ gemcitabine and cisplatin (n=341)**	**Placebo + gemcitabine and cisplatin (n=344)**
OS (DCO: 25 Feb 2022)		
Number of deaths (%)	248 (72.7)	279 (81.1)
Median OS (months) (95% CI)[a]	12.9 (11.6, 14.1)	11.3 (10.1, 12.5)
HR (95% CI)[b]	0.76 (0.64, 0.91)	
OS at 12 months (%) (95% CI)[a]	54.3 (48.8, 59.4)	47.1 (41.7, 52.3)
OS at 18 months (%) (95% CI)[a]	34.8 (29.6, 40.0)	24.1 (19.6, 28.9)
OS at 24 months (%) (95% CI)[a]	23.6 (18.7, 28.9)	11.5 (7.6, 16.2)
PFS (DCO: 11 Aug 2021)		
Number of events (%)	276 (80.9)	297 (86.3)
Median PFS (months) (95% CI)[a]	7.2 (6.7, 7.4)	5.7 (5.6, 6.7)
HR (95% CI)[b]	0.75 (0.63, 0.89)	
p-value[b,c]	0.001	
PFS at 9 months (%) (95% CI)[a]	34.8 (29.6, 40.0)	24.6 (20.0, 29.5)
PFS at 12 months (%) (95% CI)[a]	16.0 (12.0, 20.6)	6.6 (4.1, 9.9)
ORR (DCO: 11 Aug 2021) **n (%)[d]**	91 (26.7)	64 (18.7)

Complete Response n (%)	7 (2.1)	2 (0.6)
Partial Response n (%)	84 (24.6)	62 (18.1)
Odds ratio (95 % CI)[e]	1.60 (1.11, 2.31)	
p-value[e]	0.011	
DoR (DCO: 11 Aug 2021)		
Median DoR (months) (95% CI)[a]	6.4 (5.9, 8.1)	6.2 (4.4, 7.3)
DoR at 9 months (%)[a]	32.6	25.3
DoR at 12 months (%)[a]	26.1	15.0

[a] Calculated using the Kaplan-Meier technique. CI for median derived based on Brookmeyer-Crowley method.
[b] The analysis for HR was performed using a stratified Cox proportional hazards model and 2-sided p-value is based on a stratified log-rank test, both are adjusted for disease status and primary tumor location.
[c] p-value based on the results from the pre-planned interim analysis. Based on a Lan-DeMets alpha spending function with Pocock type boundary and the actual number of events observed, the boundary for declaring statistical significance was 0.0481 for an 4.9% overall alpha (Lan◦and◦DeMets 1983).
[d] Confirmed objective response by Investigator per RECIST 1.1.
[e] The analysis was performed using a stratified CMH test with factors for disease status and tumor location. Nominal 2-sided p-value.

Figure 7: Kaplan-Meier curve of OS (DCO: 25 Feb 2022)

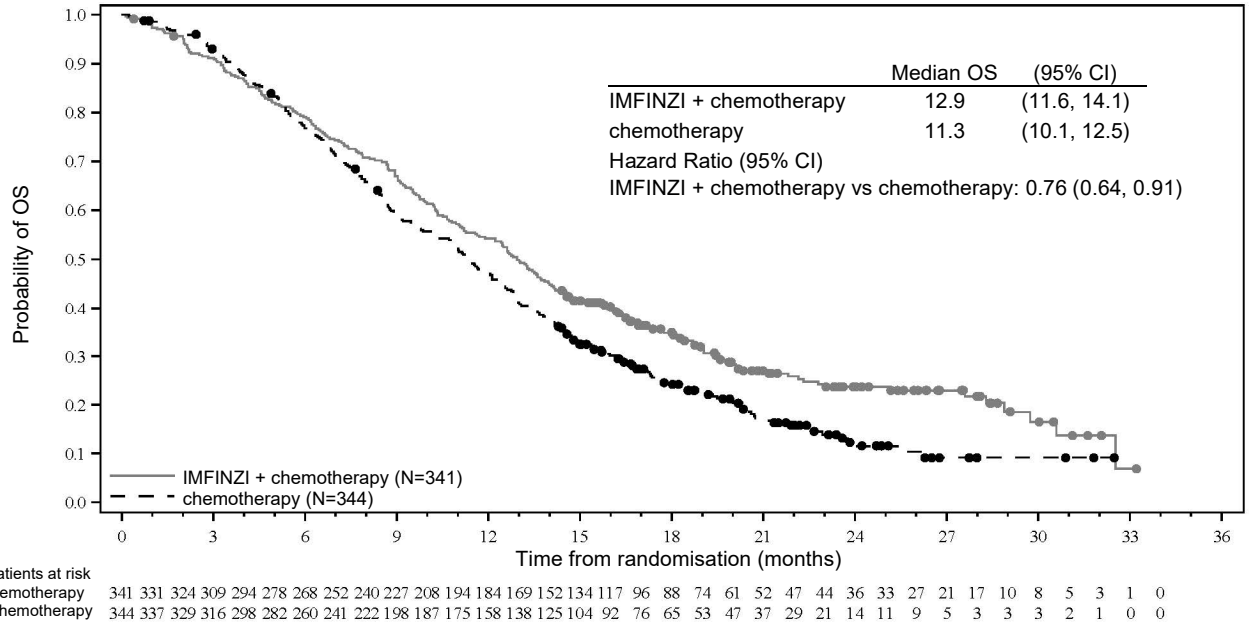
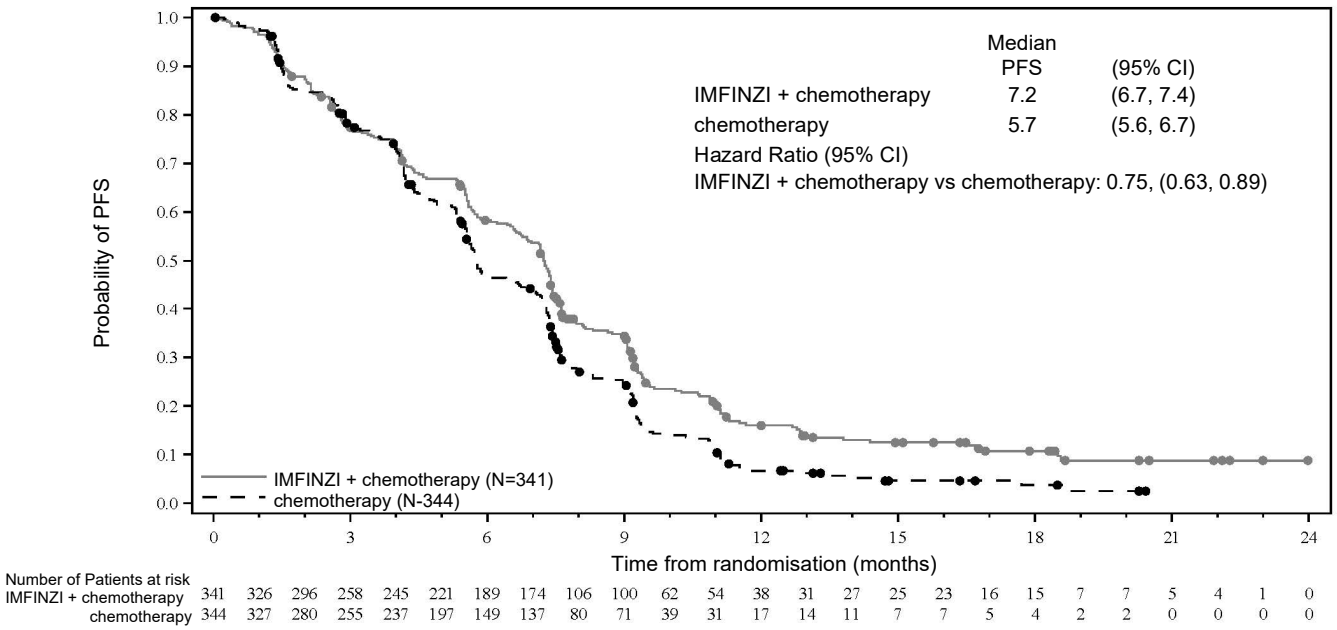


Figure 8: Kaplan-Meier curve of PFS (DCO: 11 Aug 2021)



Subgroup analysis
The improvements in OS and PFS in favour of patients receiving Imfinzi + chemotherapy compared to those receiving placebo + chemotherapy, were consistently observed across the prespecified subgroups based on demographics, geographical region, primary tumour location, disease status, ECOG PS, and PD-L1 expression levels.

Patient-Reported Outcomes
Patient-reported symptoms, function and global health status/QoL (GHS/QoL) were collected using the EORTC QLQ-C30 and its biliary tract cancer module (EORTC QLQ-BIL21). At baseline, patient-reported symptoms, functioning and GHS/QoL scores were comparable between the study arms. Time to deterioration and change from baseline analyses were consistent with no detriment in symptoms, function and GHS/QoL per EORTC QLQ-C30 and EORTC QLQ-BIL21 in the IMFINZI + chemotherapy group compared to the placebo + chemotherapy group.

5.2 PHARMACOKINETIC PROPERTIES

The pharmacokinetics (PK) of durvalumab was assessed for both IMFINZI as a single agent and in combination with chemotherapy. There was no clinically meaningful difference between the PK of durvalumab as a single agent and in combination with chemotherapy.
The pharmacokinetics of durvalumab was studied in 2903 patients with solid tumours with doses ranging from 0.1 to 20 mg/kg administered once every two, three or four weeks.

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), moderate hepatic impairment (bilirubin > 1.5 to 3 x 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 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. Immunogenicity of IMFINZI as monotherapy is based on pooled data in 2280 patients who were treated with IMFINZI 10 mg/kg every 2 weeks or 20 mg/kg every 4 weeks as a single-agent and evaluable for the presence of anti-drug antibodies (ADAs). Sixty nine patients (3.0%) tested positive for treatment-emergent ADAs. Neutralising antibodies against durvalumab were detected in 0.5% (12/2280) patients. The presence of ADAs did not have a clinically relevant effect on pharmacokinetics, pharmacodynamics or safety.

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

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

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

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

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

Carcinogenicity

The carcinogenic potential of durvalumab has not been evaluated.

Reproductive Toxicity

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.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

- histidine
- histidine hydrochloride monohydrate
- trehalose dihydrate
- polysorbate 80
- water for injection.

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: 36 months

Diluted 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:

- 30 days at 2°C to 8°C and for up to
- 12 hours at room temperature (up to 25°C) from the time of preparation.

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.

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

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 AND OTHER HANDLING

For dilution and administration instructions see Section 4.2 Dose and Method of Administration.

Return unused and expired medicines to your local pharmacy for disposal.

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

AstraZeneca Limited
PO Box 87453
Meadowbank
Auckland 1742.
Telephone: (09) 306 5650

9. DATE OF FIRST APPROVAL

10 October 2019

10. DATE OF REVISION OF THE TEXT

21 March 2023

IMFINZI is a registered trademark of the AstraZeneca group of companies.

Doc ID-004154649 v11.0

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.2 and 6.3	In-use storage conditions updated.