IMFINZI®
(durvalumab)

1. NAME OF THE MEDICINAL PRODUCT

- IMFINZI, 500 mg (500 mg/10 mL) in 10 mL vial for intravenous infusion.
- IMFINZI, 120 mg (120 mg/2.4 mL) in 10 mL vial for intravenous infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL contains 50 mg of IMFINZI.

Each vial of 2.4 mL contains 120 mg of durvalumab.

Each vial of 10 mL contains 500 mg of durvalumab.

IMFINZI is a human immunoglobulin (IgG1κ) monoclonal antibody.

For a full list of excipient(s), see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion; 50 mg/mL in single-dose vial for intravenous administration.

Sterile, preservative-free, clear to opalescent, colourless to slightly yellow solution, free from visible particles.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Locally Advanced Non-small Cell Lung Cancer (NSCLC)

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

Small Cell Lung Cancer (SCLC)

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

Biliary Tract Cancer (BTC)

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

4.2 Posology and method of administration

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**
Monotherapy		
Locally Advanced NSCLC	10 mg/kg every 2 weeks or 1500 mg every 4 weeks[a]	Until disease progression or unacceptable toxicity
Combination Therapy		
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) up to 8 cycles, followed by 1500 mg every 4 weeks as monotherapy	Until disease progression or until unacceptable toxicity

[a] Patients with a body weight of less than 30 kg must receive weight-based dosing of IMFINZI at 10 mg/kg every 2 weeks as monotherapy until weight increases to 30 kg and more.

[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.

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

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 for further monitoring and evaluation information.

Table 2 Recommended treatment modifications for IMFINZI and management recommendations

Adverse Reactions	**Severity**[a]	**IMFINZI Treatment Modification**	**Corticosteroid Treatment Unless Otherwise Specified**[b]
Immune-mediated pneumonitis/interstitial lung disease	Grade 2	Withhold dose[c]	Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
	Grade 3 or 4	Permanently discontinue	
Immune-mediated hepatitis	Grade 2 with ALT or AST > 3-5 x ULN and/or total bilirubin > 1.5-3 x ULN	Withhold dose[c]	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	
	Concurrent ALT or AST > 3 x ULN and total bilirubin > 2 x ULN with no other cause		
Immune-mediated colitis or diarrhoea	Grade 2 or 3	Withhold dose[c]	Initiate 1 to 2 mg/kg/day prednisone or

Adverse Reactions	Severity[a]	IMFINZI Treatment Modification	Corticosteroid Treatment Unless Otherwise Specified[b]
	Grade 4	Permanently discontinue	equivalent followed by a taper
Immune-mediated endocrinopathies: hyperthyroidism, thyroiditis	Grade 2-4	Withhold dose until clinically stable	Symptomatic management
Immune-mediated endocrinopathies: hypothyroidism	Grade 2-4	No changes	Initiate thyroid hormone replacement as clinically indicated
Immune-mediated endocrinopathies: adrenal insufficiency, hypophysitis/hypopituitarism	Grade 2-4	Withhold dose until clinically stable	Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper and hormone replacement as clinically indicated
Immune-mediated endocrinopathies: Type 1 diabetes mellitus	Grade 2-4	No changes	Initiate treatment with insulin as clinically indicated
Immune-mediated nephritis	Grade 2 with serum creatinine > 1.5-3 x (ULN or baseline)	Withhold dose[c]	Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
	Grade 3 with serum creatinine > 3 x baseline or > 3-6 x ULN; Grade 4 with serum creatinine > 6 x ULN	Permanently discontinue	
Immune-mediated rash or dermatitis (including pemphigoid)	Grade 2 for > 1 week or Grade 3	Withhold dose[c]	Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
	Grade 4	Permanently discontinue	

Adverse Reactions	Severity[a]	IMFINZI Treatment Modification	Corticosteroid Treatment Unless Otherwise Specified[b]
Immune-mediated myocarditis	Grade 2-4, or any Grade with positive biopsy	Permanently discontinue	Initiate 2 to 4 mg/kg/day prednisone or equivalent followed by a taper[d]
Immune-mediated myositis/polymyositis	Grade 2 or 3	Withhold dose[c,e]	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	
Myasthenia gravis	Grade 2	Withhold dose[c]	Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
	Grade 3 or 4 or any Grade with signs of respiratory or autonomic insufficiency	Permanently discontinue	
Other immune-mediated adverse reactions[f]	Grade 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] 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.

[c] 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.

[d] 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.

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

[f] Includes immune thrombocytopenia, pancreatitis and encephalitis.

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

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

Based on a population pharmacokinetic analysis, no dose adjustment of IMFINZI is recommended based on patient age, body weight, gender and race (see section 5.2).

Paediatric and adolescents

The safety and effectiveness of IMFINZI have not been established in children and adolescents aged less than 18 years.

Elderly (≥ 65 years)

No dose adjustment is required for elderly patients (≥ 65 years of age) (see sections 5.1 and 5.2).

Renal impairment

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

Hepatic impairment

Based on a population pharmacokinetic analysis, no dose adjustment of IMFINZI is recommended for patients with mild hepatic impairment. IMFINZI has not been studied in patients with moderate or severe hepatic impairment (see section 5.2).

Method of administration

For intravenous administration.

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

4.3 Contraindications

Hypersensitivity to the active ingredient or to any of the excipients.

4.4 Special warnings and special precautions for use

Refer to section 4.2, Table 2 for recommended treatment modifications and management of immune-mediated adverse reactions.

Immune-mediated pneumonitis

Immune-mediated pneumonitis or interstitial lung disease, defined as requiring use of systemic corticosteroids and with no clear alternate etiology, occurred in patients receiving IMFINZI (see section 4.8). Patients should be monitored for signs and symptoms of pneumonitis. Suspected pneumonitis should be confirmed with radiographic imaging and other infectious and disease-related etiologies excluded, and managed as recommended in section 4.2.

Pneumonitis and radiation pneumonitis

Radiation pneumonitis is frequently observed in patients receiving radiation therapy to the lung and the clinical presentation of pneumonitis and radiation pneumonitis is very similar. In the PACIFIC Study, in patients who had completed treatment with concurrent chemoradiation within 1 to 42 days prior to initiation of the trial, pneumonitis and radiation pneumonitis occurred in patients receiving IMFINZI. 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 in 16 (3.4%) patients on IMFINZI vs. 7 (3.0%) patients on placebo and Grade 5 in 5 (1.1%) patients on IMFINZI vs. 4 (1.7%) patients on placebo. The median time to onset in the IMFINZI-treated group was 55 days (range: 1-406 days) vs. 55 days (range: 1-255 days) in the placebo group.

Immune-mediated hepatitis

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

Immune-mediated colitis

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

Immune-mediated endocrinopathies

Immune-mediated hypothyroidism/hyperthyroidism/thyroiditis

Immune-mediated hypothyroidism, hyperthyroidism or thyroiditis have occurred in patients receiving IMFINZI (see section 4.8). Patients should be monitored for abnormal thyroid function tests prior to and periodically during treatment and managed as recommended in section 4.2.

Immune-mediated adrenal insufficiency

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

Immune-mediated type 1 diabetes mellitus

Immune-mediated type 1 diabetes mellitus, which can present with diabetic ketoacidosis, occurred in patients receiving IMFINZI (see section 4.8). Patients should be monitored for clinical signs and symptoms of type 1 diabetes mellitus. For symptomatic type 1 diabetes mellitus, patients should be managed as recommended in section 4.2.

Immune-mediated hypophysitis/hypopituitarism

Immune-mediated hypophysitis or hypopituitarism occurred in patients receiving IMFINZI (see section 4.8). Patients should be monitored for clinical signs and symptoms of hypophysitis or

hypopituitarism. For symptomatic hypophysitis or hypopituitarism, patients should be managed as recommended in section 4.2.

Immune-mediated nephritis

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

Immune-mediated rash

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

Other immune-mediated adverse reactions

Given the mechanism of action of IMFINZI, other potential immune-mediated adverse reactions may occur. Patients should be monitored for signs and symptoms and managed as recommended in section 4.2. Other immune-mediated adverse reactions are myasthenia gravis, myocarditis, myositis, polymyositis, immune thrombocytopenia, pancreatitis and encephalitis.

Infusion-related reactions

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

4.5 Interaction with other medicinal products 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 with durvalumab 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 Pregnancy and lactation

Pregnancy

In animal reproduction studies, administration of durvalumab to pregnant cynomolgus monkeys from the confirmation of pregnancy through delivery at exposure levels approximately 22 times higher than those observed at the clinical dose of 10 mg/kg of durvalumab (based on AUC) was not associated with maternal toxicity or effects on embryofoetal development, pregnancy outcome or postnatal development (see section 5.3). 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. Durvalumab is not recommended during

pregnancy and in women of childbearing potential not using effective contraception during treatment and for at least 3 months after the last dose.

Breast-feeding

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. Because of the potential for adverse reactions in breast-fed infants from durvalumab, advise a lactating woman not to breast-feed during treatment and for at least 3 months after the last dose.

Fertility

There are no data on the potential effects of durvalumab on fertility in humans. In repeat-dose toxicology studies with durvalumab in sexually mature cynomolgus monkeys of up to 3 months duration, there were no notable effects on the male and female reproductive organs.

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%)
	Colitis[e]	Uncommon	28 (0.9%)	Uncommon	10 (0.3%)
	Pancreatitis[f]	Uncommon	6 (0.23%)	Uncommon	5 (0.17%)
Endocrine disorders	Hypothyroidism[g]	Very common	305 (10.1%)	Uncommon	5 (0.2%)
	Hyperthyroidism[h]	Common	137 (4.6%)		0
	Thyroiditis[i]	Uncommon	23 (0.8%)	Rare	2 (< 0.1%)
	Adrenal insufficiency	Uncommon	18 (0.6%)	Rare	3 (< 0.1%)
	Hypophysitis/	Rare	2 (< 0.1%)	Rare	2 (< 0.1%)

System Organ Class	Adverse Drug Reaction	Frequency of any Grade		Frequency of Grade 3-4	
	Hypopituitarism				
	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[j]	Uncommon	9 (0.3%)	Rare	2 (< 0.1%)
Skin and subcutaneous tissue disorders	Rash[k]	Very common	480 (16.0%)	Uncommon	18 (0.6%)
	Pruritus[l]	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[m]	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[n]	Common	291 (9.7%)	Uncommon	9 (0.3%)
Infections and infestations	Upper respiratory tract infections[o]	Very common	407 (13.5%)	Uncommon	6 (0.2%)
	Pneumonia[a,p]	Common	269 (8.9%)	Common	106 (3.5%)

System Organ Class	Adverse Drug Reaction	Frequency of any Grade		Frequency of Grade 3-4	
	Oral candidiasis	Common	64 (2.1%)		0
	Dental and oral soft tissue infections[q]	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[r]		Not determined[r]	
Nervous system disorders	Myasthenia gravis	Not determined[s]		Not determined[s]	
	Encephalitis	Not determined[t]		Not determined[t]	
Blood and lymphatic system disorders	Immune thrombocytopenia[a]	Rare	2 (< 0.1%)	Rare	1 (< 0.1%)
Injury, poisoning and procedural complications	Infusion-related reaction[u]	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 pancreatitis and pancreatitis acute.
[g] Includes autoimmune hypothyroidism and hypothyroidism.
[h] Includes hyperthyroidism and Basedow's disease.
[i] Includes autoimmune thyroiditis, thyroiditis, and thyroiditis subacute.
[j] Includes autoimmune nephritis, tubulointerstitial nephritis, nephritis, glomerulonephritis and glomerulonephritis membranous.
[k] Includes rash erythematous, rash generalised, rash macular, rash maculopapular, rash papular, rash pruritic, rash pustular, erythema, eczema and rash.

[l] Includes pruritus generalised and pruritus.
[m] Includes pemphigoid, dermatitis bullous and pemphigus. Reported frequency from completed and ongoing trials is uncommon.
[n] Includes oedema peripheral and peripheral swelling.
[o] Includes laryngitis, nasopharyngitis, peritonsillar abscess, pharyngitis, rhinitis, sinusitis, tonsillitis, tracheobronchitis, and upper respiratory tract infection.
[p] Includes lung infection, pneumocystis jirovecii pneumonia, pneumonia, candida pneumonia, pneumonia legionella, pneumonia adenoviral, pneumonia bacterial, pneumonia cytomegaloviral, pneumonia haemophilus, pneumonia pneumococcal and pneumonia streptococcal.
[q] Includes gingivitis, oral infection, periodontitis, pulpitis dental, tooth abscess and tooth infection.
[r] 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.
[s] Reported frequency from AstraZeneca-sponsored clinical studies outside of the pooled dataset is rare, with no events at Grade > 2.
[t] 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.
[u] Includes infusion-related reaction and urticaria with onset on the day of dosing or 1 day after dosing.

Table 4 lists the incidence of laboratory abnormalities reported in the IMFINZI monotherapy safety dataset.

Table 4 Laboratory abnormalities worsening from baseline in patients treated with IMFINZI monotherapy

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 ≤ ULN at baseline	3006	566 (18.8%)	NA
TSH decreased < LLN and ≥ LLN at 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. Refer to Table 5 for details.

Table 5 Adverse drug reactions in ES-SCLC patients treated with IMFINZI with etoposide and either carboplatin or cisplatin

	IMFINZI with etoposide and either carboplatin or cisplatin (n = 265)			Etoposide and either carboplatin or cisplatin (n = 266)		
Term	**Any Grade**		**Grade 3-4**	**Any Grade**		**Grade 3-4**
Blood and Lymphatic System Disorders						
Neutropenia[a]	Very common	129 (48.7)	77 (29.1)	Very common	150 (56.4)	104 (39.1)
Anaemia	Very common	102 (38.5)	24 (9.1)	Very common	125 (47.0)	48 (18.0)
Thrombocytopenia[b]	Very common	56 (21.1)	18 (6.8)	Very common	66 (24.8)	31 (11.7)
Leukopenia[c]	Very common	53 (20.0)	21 (7.9)	Very common	49 (18.4)	20 (7.5)
Febrile neutropenia	Common	17 (6.4)	14 (5.3)	Common	17 (6.4)	17 (6.4)
Pancytopenia	Common	8 (3.0)	4 (1.5)	Common	3 (1.1)	2 (0.8)
Respiratory thoracic and mediastinal disorders						
Cough/ Productive Cough[d]	Very common	39 (14.7)	2 (0.8)	Common	23 (8.6)	0
Pneumonitis	Common	7 (2.6)	2 (0.8)	Common	5 (1.9)	1 (0.4)
Dysphonia	Uncommon	2 (0.8)	0	Common	4 (1.5)	0
Interstitial lung disease	Uncommon	2 (0.8)	0			
Hepatobiliary disorders						
Aspartate aminotransferase increased or Alanine aminotransferase increased[e]	Common	23 (8.7)	5 (1.9)	Common	15 (5.6)	4 (1.5)

	IMFINZI with etoposide and either carboplatin or cisplatin (n = 265)			Etoposide and either carboplatin or cisplatin (n = 266)		
Term	**Any Grade**		**Grade 3-4**	**Any Grade**		**Grade 3-4**
Hepatitis[f]	Common	5 (1.9)	3 (1.1)	Uncommon	1 (0.4)	0
Gastrointestinal disorders						
Diarrhoea	Common	26 (9.8)	3 (1.1)	Very common	30 (11.3)	3 (1.1)
Abdominal pain[g]	Common	23 (8.7)	1 (0.4)	Common	12 (4.5)	0
Colitis[h]	Uncommon	2 (0.8)	0	Uncommon	1 (0.4)	0
Nausea	Very common	89 (33.6)	1 (0.4)	Very common	89 (33.5)	5 (1.9)
Constipation	Very common	44 (16.6)	2 (0.8)	Very common	51 (19.2)	0
Vomiting	Very common	39 (14.7)	0	Very common	44 (16.5)	3 (1.1)
Stomatitis[i]	Common	16 (6.0)	1 (0.4)	Common	12 (4.5)	0
Endocrine disorders						
Hypothyroidism	Common	25 (9.4)	0	Common	4 (1.5)	0
Hyperthyroidism	Common	26 (9.8)	0	Uncommon	1 (0.4)	0
Thyroiditis[j]	Common	4 (1.5)	0			
Adrenal insufficiency	Common	3 (1.1)	0			
Type 1 diabetes mellitus	Uncommon	2 (0.8)	2 (0.8)			
Renal and urinary disorders						

	IMFINZI with etoposide and either carboplatin or cisplatin (n = 265)			Etoposide and either carboplatin or cisplatin (n = 266)		
Term	**Any Grade**		**Grade 3-4**	**Any Grade**		**Grade 3-4**
Blood creatinine increased	Common	5 (1.9)	0	Common	6 (2.3)	0
Dysuria	Common	5 (1.9)	0	Common	6 (2.3)	0
Skin and subcutaneous tissue disorders						
Rash[k]	Common	25 (9.4)	0	Common	15 (5.6)	0
Pruritus	Common	20 (7.5)	0	Common	10 (3.8)	0
Night sweats	Uncommon	1 (0.4)	0			
Dermatitis	Common	4 (1.5)	0			
Alopecia	Very common	83 (31.3)	3 (1.1)	Very common	91 (34.2)	2 (0.8)
General disorders and administration site conditions						
Pyrexia	Common	22 (8.3)	0	Common	17 (6.4)	1 (0.4)
Oedema peripheral[l]	Common	17 (6.4)	2 (0.8)	Common	11 (4.1)	0
Fatigue[m]	Very common	85 (32.1)	9 (3.4)	Very common	84 (31.6)	6 (2.3)
Infections and infestations						
Upper respiratory tract infections[n]	Common	24 (9.1)	1 (0.4)	Common	16 (6.0)	0
Pneumonia[o]	Common	15 (5.7)	5 (1.9)	Common	22 (8.3)	11 (4.1)
Oral candidiasis	Uncommon	2 (0.8)	0	Common	5 (1.9)	0

	IMFINZI with etoposide and either carboplatin or cisplatin (n = 265)			Etoposide and either carboplatin or cisplatin (n = 266)		
Term	**Any Grade**		**Grade 3-4**	**Any Grade**		**Grade 3-4**
Dental and oral soft tissue infections[p]	Common	3 (1.1)	0	Common	3 (1.1)	0
Influenza	Uncommon	1 (0.4)	0			
Musculoskeletal and connective tissue disorders						
Myalgia	Common	9 (3.4)	0	Common	6 (2.3)	0
Injury, poisoning and procedural complications						
Infusion-related reaction[q]	Common	5 (1.9)	1 (0.4)	Common	3 (1.1)	0
Metabolism and nutrition disorders						
Decreased appetite	Very common	48 (18.1)	2 (0.8)	Very common	46 (17.3)	2 (0.8)

[a] Includes neutropenia and neutrophil count decreased.
[b] Includes thrombocytopenia and platelet count decreased.
[c] Includes leukopenia and white blood cell count decreased.
[d] Includes cough and productive cough.
[e] Includes alanine aminotransferase increased, aspartate aminotransferase increased, hepatic enzyme increased and transaminases increased.
[f] Includes hepatitis, hepatotoxicity and hepatocellular injury.
[g] Includes abdominal pain, abdominal pain lower, abdominal pain upper and flank pain.
[h] Includes colitis, enteritis and proctitis.
[i] Includes stomatitis and mucosal inflammation.
[j] Includes autoimmune thyroiditis and thyroiditis.
[k] Includes rash erythematous, rash macular, rash maculopapular, erythema and rash.
[l] Includes oedema peripheral and peripheral swelling.
[m] Includes fatigue and asthenia.
[n] Includes nasopharyngitis, pharyngitis, rhinitis, sinusitis, tonsillitis, tracheobronchitis, and upper respiratory tract infection.
[o] Includes lung infection, pneumonia and pneumonia bacterial.
[p] Includes periodontitis, pulpitis dental, tooth abscess and tooth infection.
[q] Includes infusion-related reaction and urticaria with onset on the day of dosing or 1 day after dosing.

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. Refer to Table 6 for details.

Table 6 Adverse drug reactions in BTC patients treated with IMFINZI in combination with gemcitabine and cisplatin

	IMFINZI with gemcitabine and cisplatin (n = 338)			Placebo with gemcitabine and cisplatin (n = 342)		
Term	**Any Grade**		**Grade 3-4**	**Any Grade**		**Grade 3-4**
Blood and Lymphatic System Disorders						
Neutropenia[a,b]	Very common	191 (56.5)	135 (39.9)	Very common	197 (57.6)	154 (45.0)
Anaemia[a]	Very common	163 (48.2)	80 (23.7)	Very common	153 (44.7)	77 (22.5)
Thrombocytopenia[a,c]	Very common	113 (33.4)	49 (14.5)	Very common	119 (34.8)	46 (13.5)
Leukopenia[a,d]	Very Common	51 (15.1)	22 (6.5)	Very Common	61 (17.8)	23 (6.7)
Febrile neutropenia[a]	Common	4 (1.2)	4 (1.2)	Common	6 (1.8)	6 (1.8)
Cardiac disorders						
Tachycardia[a]	Uncommon	2 (0.6)	0	Common	4 (1.2)	0
Ear and labyrinth disorders						
Tinnitus[a]	Common	10 (3.0)	0	Uncommon	3 (0.9)	0
Endocrine disorders						
Hypothyroidism[e]	Common	25 (7.4)	0	Common	11 (3.2)	0
Hyperthyroidism[f]	Common	9 (2.7)	0	Common	4 (1.2)	0
Adrenal insufficiency	Common	4 (1.2)	0	Uncommon	1 (0.3)	0
Thyroiditis[g]	Uncommon	1 (0.3)	0		0	0

	IMFINZI with gemcitabine and cisplatin (n = 338)			Placebo with gemcitabine and cisplatin (n = 342)		
Term	**Any Grade**		**Grade 3-4**	**Any Grade**		**Grade 3-4**
Type 1 diabetes mellitus	Uncommon	1 (0.3)	0		0	0
Gastrointestinal disorders						
Nausea[a]	Very common	136 (40.2)	5 (1.5)	Very common	117 (34.2)	6 (1.8)
Constipation[a]	Very common	108 (32.0)	2 (0.6)	Very common	99 (28.9)	1 (0.3)
Abdominal pain[h]	Very common	80 (23.7)	2 (0.6)	Very common	80 (23.4)	10 (2.9)
Vomiting[a]	Very common	62 (18.3)	5 (1.5)	Very common	62 (18.1)	7 (2.0)
Diarrhoea	Very common	57 (16.9)	4 (1.2)	Very common	51 (14.9)	6 (1.8)
Stomatitis[a,i]	Common	23 (6.8)	0	Common	22 (6.4)	0
Amylase increased[a,j]	Common	16 (4.7)	3 (0.9)	Common	16 (4.7)	4 (1.2)
Pancreatitis[k]	Uncommon	3 (0.9)	2 (0.6)	Uncommon	2 (0.6)	0
Colitis[l]	Uncommon	1 (0.3)	1 (0.3)	Uncommon	2 (0.6)	1 (0.3)
General disorders and administration site conditions						
Fatigue[a,m]	Very common	133 (39.3)	21 (6.2)	Very common	134 (39.2)	19 (5.6)
Pyrexia	Very common	68 (20.1)	5 (1.5)	Very common	56 (16.4)	2 (0.6)
Oedema peripheral[n]	Common	30 (8.9)	0	Common	20 (5.8)	0

	IMFINZI with gemcitabine and cisplatin (n = 338)			Placebo with gemcitabine and cisplatin (n = 342)		
Term	**Any Grade**		**Grade 3-4**	**Any Grade**		**Grade 3-4**
Chills[a]	Common	11 (3.3)	0	Common	8 (2.3)	0
Oedema[a]	Common	11 (3.3)	1 (0.3)	Common	5 (1.5)	0
Malaise[a]	Common	10 (3.0)	0	Common	14 (4.1)	0
Hepatobiliary disorders						
Aspartate aminotransferase or Alanine aminotransferase increased[o]	Very common	41 (12.1)	10 (3.0)	Very common	44 (12.9)	6 (1.8)
Blood Bilirubin increased[a,p]	Common	13 (3.8)	6 (1.8)	Common	28 (8.2)	14 (4.1)
Gamma-Glutamyltransferase increased[a]	Common	12 (3.6)	3 (0.9)	Common	18 (5.3)	8 (2.3)
Hepatitis[q]	Common	10 (3.0)	3 (0.9)	Uncommon	3 (0.9)	1 (0.3)
Infections and infestations						
Upper respiratory tract infections[r]	Common	22 (6.5)	0	Common	19 (5.6)	0
Pneumonia[s]	Common	15 (4.4)	10 (3.0)	Common	10 (2.9)	6 (1.8)
Sepsis[a]	Common	15 (4.4)	12 (3.6)	Common	9 (2.6)	8 (2.3)
Oral candidiasis	Common	4 (1.2)	0		0	0

	IMFINZI with gemcitabine and cisplatin (n = 338)			Placebo with gemcitabine and cisplatin (n = 342)		
Term	**Any Grade**		**Grade 3-4**	**Any Grade**		**Grade 3-4**
Dental and oral soft tissue infections[t]	Uncommon	3 (0.9)	0	Common	5 (1.5)	1 (0.3)
Injury, poisoning and procedural complications						
Infusion related reaction[u]	Common	9 (2.7)	0	Common	5 (1.5)	0
Metabolism and nutrition disorders						
Decreased appetite[a]	Very common	87 (25.7)	7 (2.1)	Very common	79 (23.1)	3 (0.9)
Hypomagnesaemia[a,v]	Common	33 (9.8)	6 (1.8)	Common	33 (9.6)	3 (0.9)
Hypokalaemia[a]	Common	28 (8.3)	10 (3.0)	Common	17 (5.0)	4 (1.2)
Hyponatraemia[a,w]	Common	23 (6.8)	7 (2.1)	Common	22 (6.4)	8 (2.3)
Dehydration[a]	Common	9 (2.7)	0	Common	7 (2.0)	1 (0.3)
Hypocalcaemia[a,x]	Common	7 (2.1)	1 (0.3)	Common	8 (2.3)	2 (0.6)
Hypophosphataemia[a]	Common	6 (1.8)	0	Uncommon	1 (0.3)	0
Musculoskeletal and connective tissue disorders						
Back Pain[a]	Common	29 (8.6)	1 (0.3)	Common	23 (6.7)	1 (0.3)
Myalgia	Common	15 (4.4)	0	Common	19 (5.6)	0
Muscle Spasms[a]	Common	4 (1.2)	0	Common	5 (1.5)	0
Polymyositis		0	0	Uncommon	1 (0.3)	0

	IMFINZI with gemcitabine and cisplatin (n = 338)			Placebo with gemcitabine and cisplatin (n = 342)		
Term	**Any Grade**		**Grade 3-4**	**Any Grade**		**Grade 3-4**
Nervous system disorders						
Headache[a]	Common	23 (6.8)	0	Common	14 (4.1)	0
Neuropathy peripheral[a,y]	Common	29 (8.6)	1 (0.3)	Common	28 (8.2)	1 (0.3)
Psychiatric disorders						
Insomnia[a]	Common	32 (9.5)	0	Very common	36 (10.5)	0
Renal and urinary disorders						
Acute Kidney Injury[a]	Common	13 (3.8)	11 (3.3)	Common	7 (2.0)	5 (1.5)
Blood creatinine increased	Common	10 (3.0)	0	Common	34 (9.9)	1 (0.3)
Dysuria	Common	4 (1.2)	0	Common	6 (1.8)	0
Proteinuria[a]	Uncommon	3 (0.9)	1 (0.3)	Common	4 (1.2)	0
Nephritis		0	0	Uncommon	2 (0.6)	0
Respiratory, thoracic and mediastinal disorders						
Cough/ Productive cough	Common	26 (7.7)	1 (0.3)	Common	20 (5.8)	0
Dyspnoea[a]	Common	22 (6.5)	4 (1.2)	Common	19 (5.6)	1 (0.3)
Pulmonary embolism[a]	Common	16 (4.7)	8 (2.4)	Common	13 (3.8)	7 (2.0)
Hiccups[a]	Common	11 (3.3)	1 (0.3)	Common	6 (1.8)	0

	IMFINZI with gemcitabine and cisplatin (n = 338)			Placebo with gemcitabine and cisplatin (n = 342)		
Term	**Any Grade**		**Grade 3-4**	**Any Grade**		**Grade 3-4**
Pneumonitis	Uncommon	3 (0.9)	1 (0.3)	Common	5 (1.5)	1 (0.3)
Dysphonia	Uncommon	3 (0.9)	0		0	0
Interstitial lung disease	Uncommon	1 (0.3)	0	Uncommon	1 (0.3)	0
Skin and subcutaneous tissue disorders						
Rash[z]	Very common	62 (18.3)	3 (0.9)	Very common	42 (12.3)	0
Pruritus	Very common	38 (11.2)	0	Common	28 (8.2)	0
Alopecia[a]	Common	28 (8.3)	1 (0.3)	Common	15 (4.4)	0
Dermatitis	Common	6 (1.8)	0	Uncommon	1 (0.3)	0
Night sweats	Uncommon	2 (0.6)	0		0	0
Pemphigoid[aa]	Uncommon	1 (0.3)	0		0	0
Vascular disorders						
Hypotension[a]	Common	6 (1.8)	2 (0.6)	Common	5 (1.5)	2 (0.6)

[a] Adverse reaction only applies to chemotherapy ADRs in the TOPAZ-1 study.
[b] Includes neutropenia and neutrophil count decreased.
[c] Includes thrombocytopenia and platelet count decreased.
[d] Includes leukopenia and white blood cell count decreased.
[e] Includes hypothyroidism, immune-mediated hypothyroidism, blood thyroid stimulating hormone increased.
[f] Includes hyperthyroidism and blood thyroid stimulating hormone decreased.
[g] Reported term autoimmune thyroiditis.
[h] Includes abdominal pain, abdominal pain lower, abdominal pain upper and flank pain.
[i] Includes stomatitis and mucosal inflammation.
[j] Includes amylase increased and hyperamylasaemia.
[k] Includes pancreatitis and pancreatitis acute.
[l] Includes colitis, enterocolitis, and immune-mediated enterocolitis.
[m] Includes fatigue and asthenia.

[n] Includes oedema peripheral and peripheral swelling.
[o] Includes alanine aminotransferase increased, aspartate aminotransferase increased, hepatic enzyme increased and transaminases increased.
[p] Includes blood bilirubin increased and hyperbilirubinaemia.
[q] Includes hepatitis, immune-mediated hepatitis, autoimmune hepatitis, hepatic cytolysis, and hepatotoxicity.
[r] Includes nasopharyngitis, rhinitis, sinusitis, tonsillitis, and upper respiratory tract infection.
[s] Includes pneumonia and pneumocystis jirovecii pneumonia.
[t] Includes gingivitis, tooth abscess and tooth infection.
[u] Includes infusion-related reaction and urticaria with onset on the day of dosing or 1 day after dosing.
[v] Includes blood magnesium decreased and hypomagnesaemia.
[w] Includes blood sodium decreased and hyponatraemia.
[x] Includes hypocalcaemia and blood calcium decreased.
[y] Includes neuropathy peripheral, paraesthesia,and peripheral sensory neuropathy.
[z] Includes rash, rash macular, rash maculopapular, rash papular, rash pruritic, rash pustular, rash erythematous, eczema and erythema.
[aa] Reported term dermatitis bullous.

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, in patients with locally advanced, unresectable NSCLC (n = 475 in the IMFINZI arm, and n = 234 in the placebo arm) who had completed treatment with concurrent chemoradiation within 1 to 42 days prior to initiation of the study, 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 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 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: 14-253 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.

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

Expression of programmed cell death ligand-1 (PD-L1) protein is an adaptive immune response that helps tumours evade detection and elimination by the immune system. PD-L1 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 selectively blocks the interaction of PD-L1 with PD-1 and CD80 (B7.1) while leaving PD-1/PD-L2 interaction intact. Durvalumab does not induce antibody dependent cell-mediated cytotoxicity (ADCC). Selective blockade of PD-L1/PD-1 and PD-L1/CD80 interactions enhances antitumour immune responses. These antitumour responses may result in tumour elimination.

In preclinical studies, PD-L1 blockade led to increased T-cell activation and decreased tumour size.

Clinical efficacy and safety

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

Locally advanced NSCLC – PACIFIC study

The efficacy of IMFINZI was evaluated in the PACIFIC Study, a randomised, double-blind, placebo-controlled, multicentre study in 713 patients with histologically or cytologically confirmed locally advanced, unresectable NSCLC. Patients had completed at least 2 cycles of definitive platinum-based chemoradiation within 1 to 42 days prior to initiation of the study and had a ECOG performance status of 0 or 1. Ninety-two percent of patients had received a total dose of 54 to 66 Gy of radiation. The study excluded patients who had progressed following chemoradiation therapy, patients with 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 overall survival (OS) and progression-free survival (PFS) of IMFINZI vs. placebo. Secondary efficacy endpoints included Objective Response Rate (ORR), Duration of Response (DoR) and Time to Death or Distant Metastasis (TTDM). PFS, ORR, DoR and TTDM were assessed by Blinded Independent Central Review (BICR) according to RECIST v1.1.

The study demonstrated a statistically significant and clinically meaningful improvement in OS in the IMFINZI-treated group compared with the placebo group [HR = 0.68 (95% CI: 0.53, 0.87), p=0.00251]. Median OS was not reached in the IMFINZI-treated group and was 28.7 months in the placebo group. The study demonstrated a statistically significant and clinically meaningful improvement in PFS in the IMFINZI-treated group compared with the placebo group [hazard ratio (HR) = 0.52 (95% CI: 0.42, 0.65), p < 0.0001]. Median PFS was 16.8 months in the IMFINZI-treated group and 5.6 months in the placebo group. See Table 7 and Figure 1 and 2.

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 OS (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)	16.8	5.6

	IMFINZI (n = 476)	Placebo (n = 237)
(95% CI)	(13.0, 18.1)	(4.6, 7.8)
HR (95% CI)	0.52 (0.42, 0.65)	
p-value	p < 0.0001	
PFS at 12 months (%) (95% CI)	55.9% (51.0%, 60.4%)	35.3% (29.0%, 41.7%)
PFS at 18 months (%) (95% CI)	44.2% (37.7%, 50.5%)	27.0% (19.9%, 34.5%)
PFS2[b]		
Number of events (%)	217 (45.6%)	144 (60.8%)
Median PFS2 (months) (95% CI)	28.3 (25.1, 34.7)	17.1 (14.5, 20.7)
HR (95% CI)	0.58 (0.46, 0.73)	
p-value	p < 0.0001	
TTDM[c]		
Number of events (%)	182 (38.2%)	126 (53.2%)
Median TTDM (months) (95% CI)	28.3 (24.0, 34.9)	16.2 (12.5, 21.1)
HR (95% CI)	0.53 (0.41, 0.68)	
p-value	p < 0.0001	
TFST[d]		
Number of events (%)	267 (56.1%)	169 (71.3%)
Median TFST (months) (95% CI)	21.0 (16.6, 25.5)	10.4 (8.3, 12.5)
HR (95% CI)	0.58 (0.47, 0.72)	
p-value	p < 0.0001	
ORR[e] n (%) (95% CI)	133 (30.0%) (25.79%, 34.53%)	38 (17.8%) (12.95%, 23.65%)
p-value	p < 0.001	
Complete Response n (%)	8 (1.8%)	1 (0.5%)
Partial Response n (%)	125 (28.2%)	37 (17.4%)
Median DoR (months) (95% CI)	NR (27.4, NR)	18.4 (6.7, 24.5)

[a] The analysis of OS, PFS2 and an updated analysis of TTDM, TFST, ORR and DoR 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.

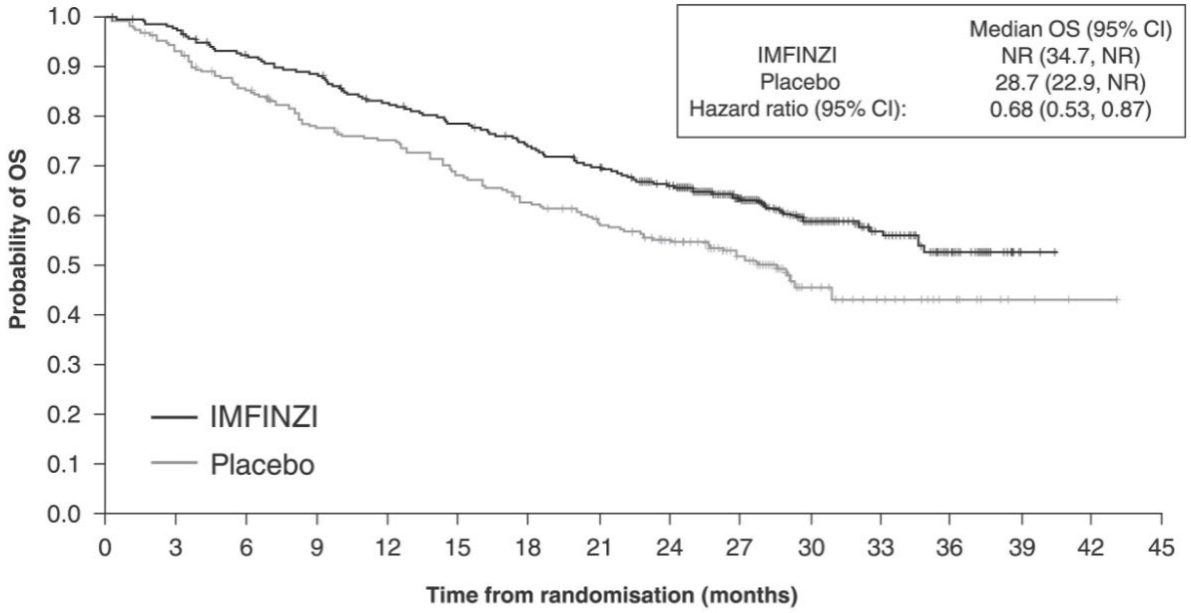
[c] TTDM is defined as the time from the date of randomisation until the first date of distant metastasis or death in the absence of distant metastasis. Distant metastasis is defined as any new lesion that is outside of the radiation field according to RECIST v1.1 or proven by biopsy.

[d] TFST is defined as the time from randomisation to the start date of the first subsequent therapy after discontinuation of treatment, or death.

[e] Based on sub-group of ITT population with measurable disease at baseline according to RECIST v1.1; IMFINZI (n = 443), Placebo (n = 213) assessed within 0-42 days after concurrent chemoradiation and before the start of study drug.

NR = Not Reached

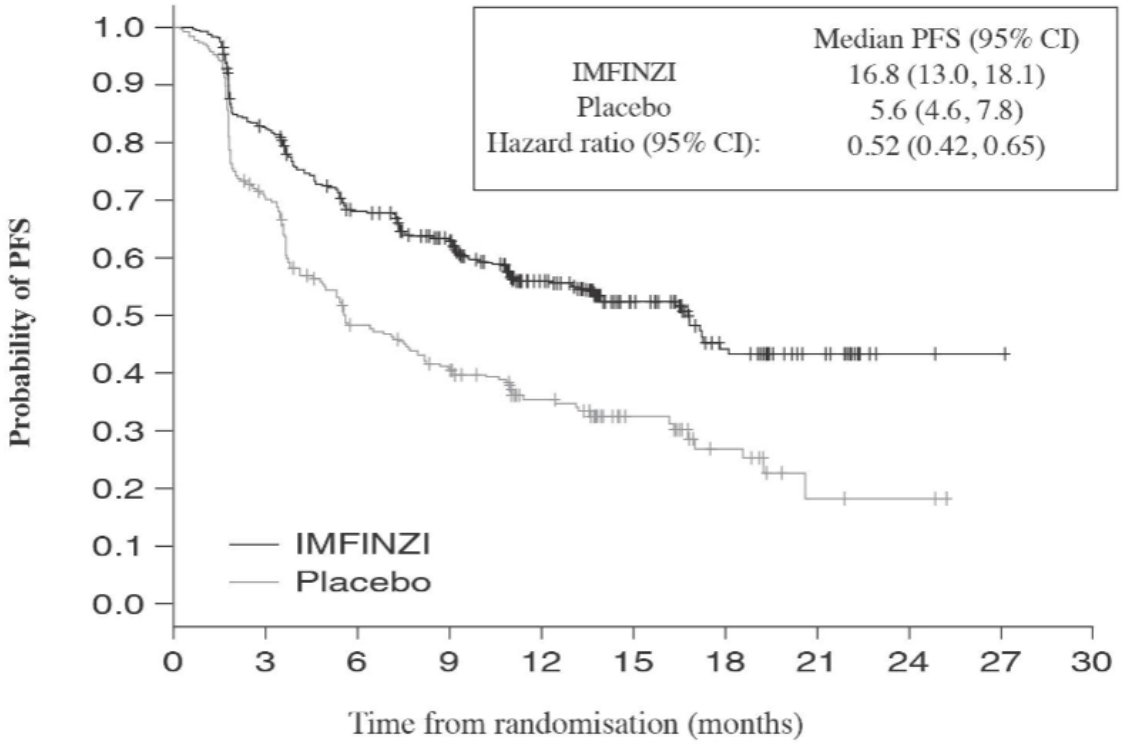
Figure 1 Kaplan-Meier curve of OS



Number of patients at risk

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

Figure 2 Kaplan-Meier curve of PFS



Number of patients at risk

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

The improvements in OS and PFS in favour of patients receiving IMFINZI compared to those receiving placebo were consistently observed across predefined subgroups analysed. Sensitivity analyses of OS and PFS demonstrated a consistent treatment effect with that observed in the primary analysis.

Post-hoc subgroup analysis by PD-L1 expression

Additional subgroup analyses were conducted to evaluate the efficacy by tumour PD-L1 expression (≥ 25%, 1-24%, ≥ 1%, < 1%) and for patients whose PD-L1 status cannot be established (PD-L1 unknown). PFS and OS results are summarised in Figures 3 and 4.

Overall the safety profile of durvalumab in PD-L1 TC ≥ 1% subgroup was consistent with the intent to treat population, as was the PD-L1 TC < 1% subgroup.

Figure 3 Forest plot of OS by PD-L1 expression

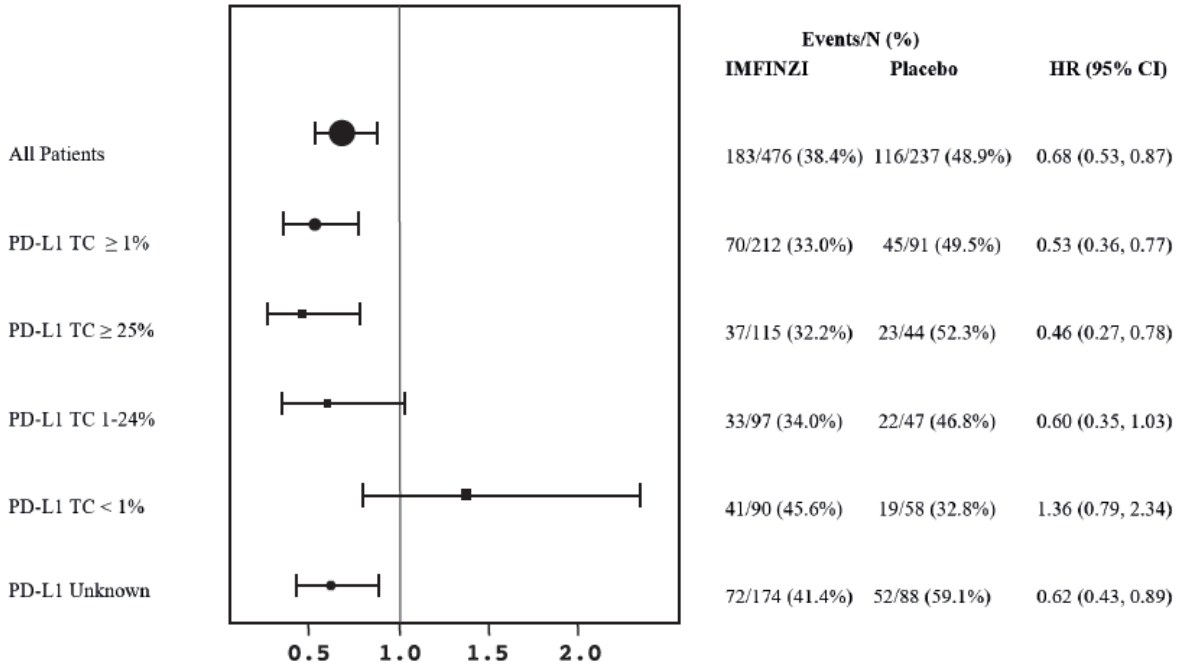
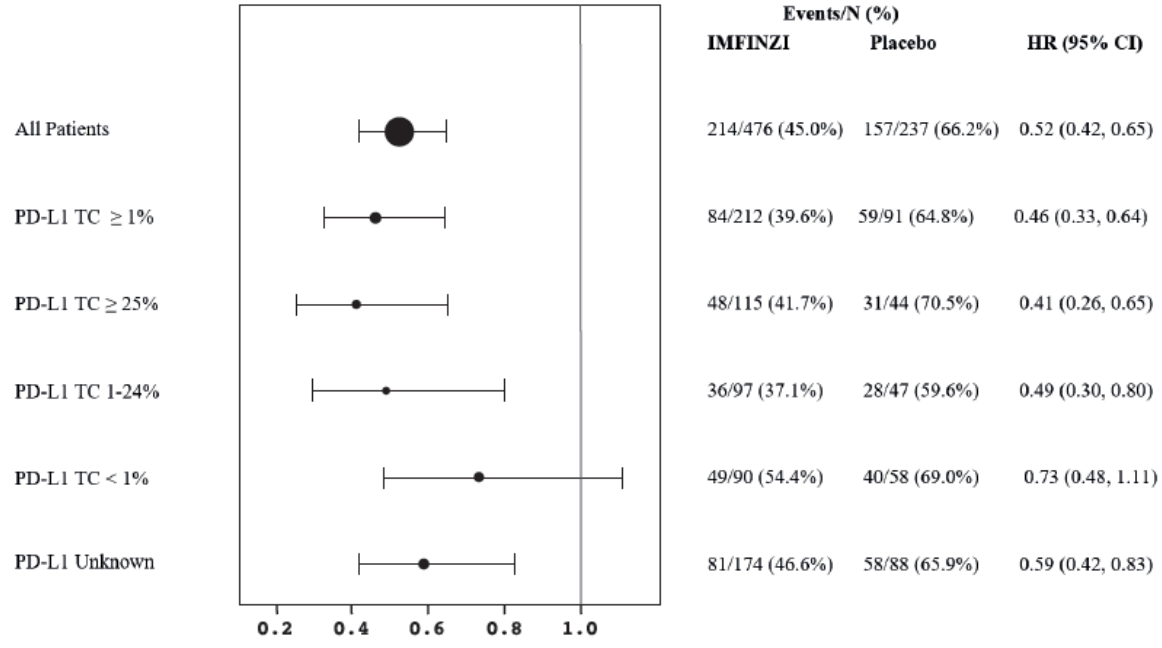


Figure 4 Forest plot of PFS by PD-L1 expression



Patient-reported outcomes

Patient-reported symptoms, function and health-related quality of life (HRQoL) were collected using the EORTC QLQ-C30 and its lung cancer module (EORTC QLQ-LC13). The LC13 and C30 were assessed at baseline, every 4 weeks for the first 8 weeks, followed by every 8 weeks

until completion of the treatment period or discontinuation of study drug due to toxicity or disease progression. Compliance was high and very similar between the IMFINZI and placebo treatment groups.

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

SCLC – CASPIAN Study

CASPIAN was a study designed to evaluate the efficacy of IMFINZI with or without tremelimumab in combination with etoposide and either carboplatin or cisplatin. CASPIAN was a randomised, open-label, multicentre 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/m^2) on Day 1 and etoposide (80-100 mg/m^2) intravenously on Days 1, 2, and 3 of each 21-day cycle for between 4 – 6 cycles.

For patients randomised to Arm 1 and 2, etoposide and either carboplatin or cisplatin was limited to 4 cycles on an every 3 week schedule subsequent to randomisation. IMFINZI monotherapy continued 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. In 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 8 and Figures 5 and 6.

Table 8 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		

	Arm 2: IMFINZI + etoposide and either carboplatin or cisplatin (n=268)	Arm 3: etoposide and either carboplatin or cisplatin (n=269)
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.

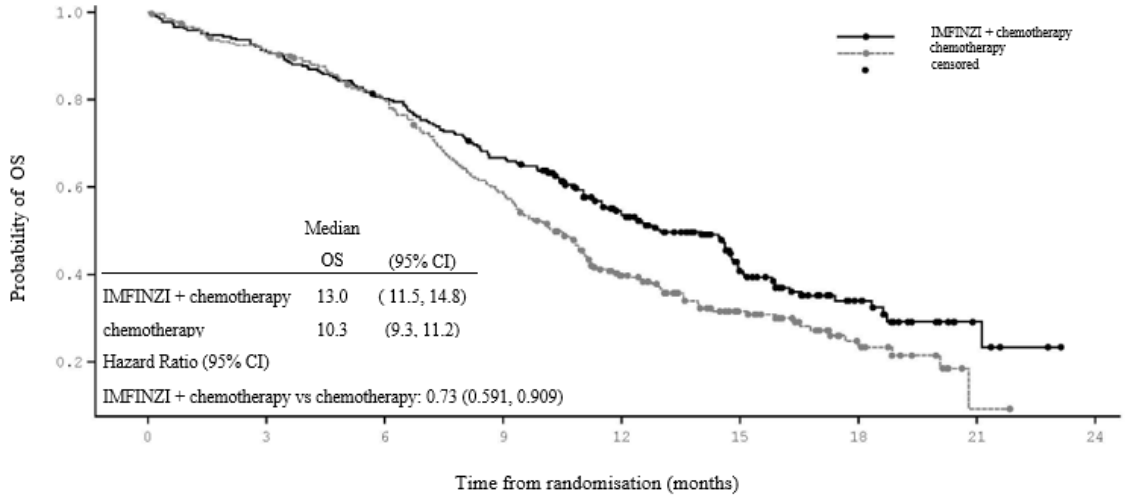
[b] Nominal p-value. PFS was included in the Multiple Testing Procedure (MTP) hierarchy at the second level. It was not able to be tested within the MTP as both Arm 1 and Arm 2 were required to achieve statistical significance prior to stepping down to PFS. ORR was not included in the MTP.

[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.

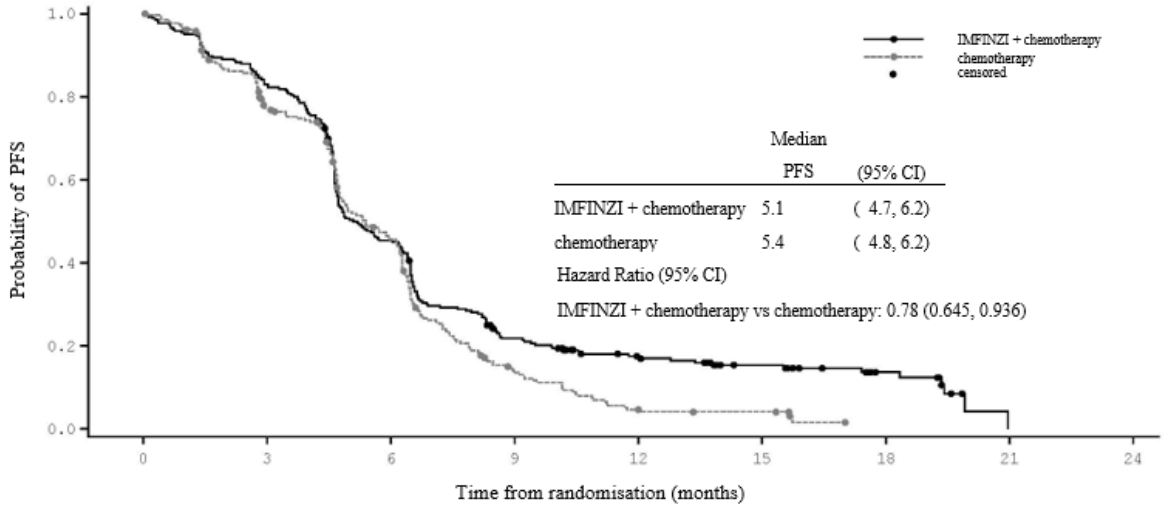
[e] The analysis was performed using a logistic regression model adjusting for planned platinum therapy in Cycle 1 (carboplatin or cisplatin) with 95% CI calculated by profile likelihood.

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 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 9 and 10).

Table 9 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 10 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

Symptom scale	Delay in time to deterioration (months) Arm 2 (N=261) vs. Arm 3 (N=260)
	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
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 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 are presented in Table 11. PFS is also presented in Figure 8.

An additional OS analysis was performed 6.5 months after the interim analysis with an OS maturity of 76.9%. The observed treatment effect was consistent with the interim analysis. The OS HR was 0.76 (95% CI: 0.64, 0.91) and median survival was 12.9 months (95% CI: 11.6, 14.1).

Table 11 Efficacy Results for the TOPAZ-1 Study

	IMFINZI + gemcitabine and cisplatin (n=341)	**Placebo + gemcitabine and cisplatin (n=344)**
OS (DCO: 11 Aug 2021)		
Number of deaths (%)	198 (58.1)	226 (65.7)
Median OS (months) (95% CI)[a]	12.8 (11.1, 14)	11.5 (10.1, 12.5)
HR (95% CI)[b]	0.80 (0.66, 0.97)	
OS at 12 months (%) (95% CI)[a]	54.1 (48.4, 59.4)	48 (42.4, 53.4)
OS at 18 months (%) (95% CI)[a]	35.1 (29.1, 41.2)	25.6 (19.9, 31.7)
OS at 24 months (%) (95% CI)[a]	24.9 (17.9, 32.5)	10.4 (4.7, 18.8)
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: 11 Aug 2021)

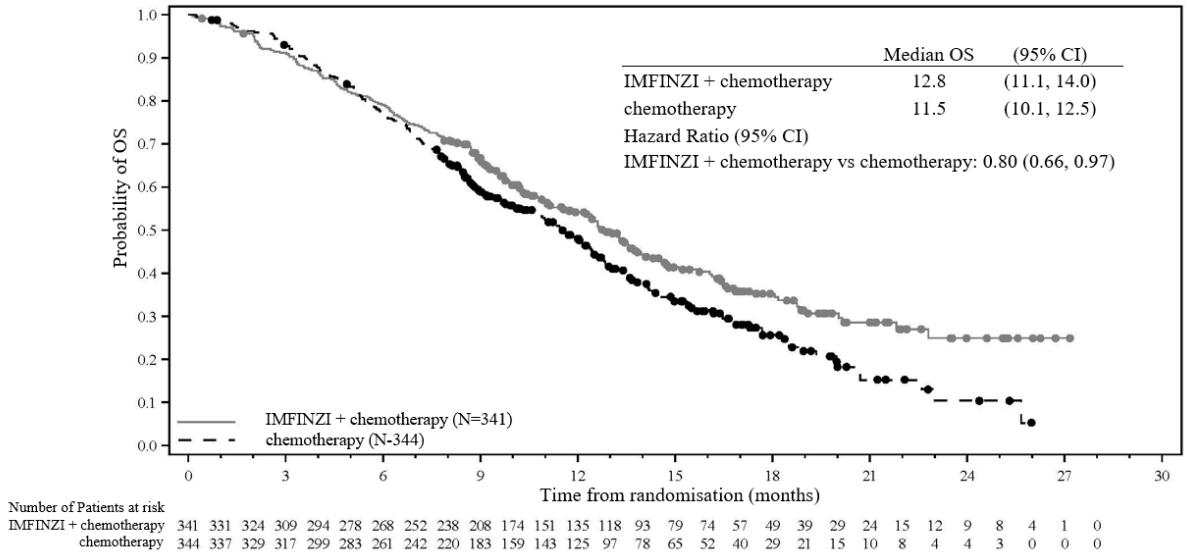
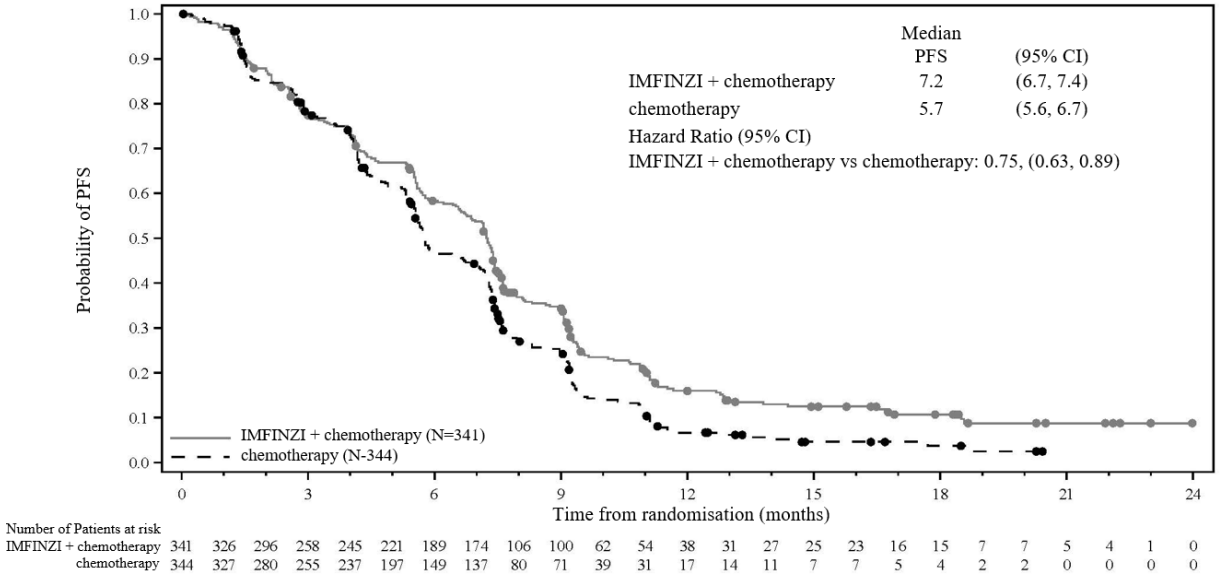


Figure 8 Kaplan-Meier curve of PFS (DCO: 11 Aug 2021)



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 (see Tables 12 and 13).

Table 12 Time to deterioration in global health status/ QoL and function (EORTC QLQ-C30)[a]

	Time to deterioration (months) : median, HR (95% CI); p-value Arm A (N=318) vs. Arm B (N=328)
Global health status/QoL	7.4 vs. 6.7 0.87 (0.69, 1.12); p=0.279
Physical	6.6 vs. 7.7 1.05 (0.83, 1.35); p=0.678
Cognitive	6.0 vs. 7.7 1.09 (0.86, 1.39); p=0.487
Role	5.6 vs. 6.5 1.08 (0.85, 1.36); p=0.558
Emotional	10.1 vs. 10.0 0.98 (0.75, 1.30); p=0.914
Social	6.0 vs. 6.8 0.98 (0.77, 1.25); p=0.865

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

Table 13 Time to deterioration in symptoms (EORTC QLQ-C30 and EORTC QLQ-BIL21)[a]

Symptom scale	**Time to deterioration (months): median, HR (95% CI); p-value**
Fatigue	3.0 vs 3.5 0.97 (0.78,1.20); p=0.759

Symptom scale	Time to deterioration (months): median, HR (95% CI); p-value
Pain (QLQ-C30)	6.5 vs 7.0 0.98 (0.77, 1.25); p=0.848
Nausea/Vomiting	6.6 vs 6.6 0.95 (0.74, 1.21); p=0.645
Abdominal pain	11.1 vs 8.5 0.92 (0.69, 1.23); p=0.575
Pruritus	9.8 vs 8.9 1.00 (0.75, 1.33); p=0.991
Jaundice (single-item)	NC vs. 14.2 0.88 (0.62, 1.25); p=0.474
Weight loss	11.7 vs.11.5 1.11 (0.82, 1.50); p=0.522
Eating	7.4 vs 8.0 1.09 (0.84, 1.42); p=0.512
Jaundice (multiple symptoms)	8.9 vs. 8.4 1.00 (0.76, 1.32); p=0.966
Pain (QLQ- BIL21)	10.9 vs.11.2 0.93 (0.70, 1.25); p=0.637
Anxiety	10.9 vs. 9.1 0.99 (0.74, 1.32); p=0.941
Tiredness	3.5 vs. 3.7 1.04 (0.82, 1.31); p=0.767

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

5.2 Pharmacokinetic properties

The pharmacokinetics (PK) of durvalumab was assessed for both IMFINZI 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. 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 geometric mean, steady state volume of distribution (Vss) was 5.64 L. 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 ($t_{1/2}$), based on baseline CL, was approximately 18 days. There was no clinically meaningful difference between the PK of durvalumab as a single agent and in combination with chemotherapy.

Special populations

Age (19–96 years), body weight (31-149 kg), gender, positive anti-drug antibody (ADA) status, albumin levels, LDH levels, creatinine levels, soluble PD-L1, tumour type, race, mild renal impairment (creatinine clearance (CrCL) 60 to 89 mL/min), moderate renal impairment (creatinine clearance (CrCL) 30 to 59 mL/min), mild hepatic impairment (bilirubin ≤ ULN and AST > ULN or bilirubin > 1.0 to 1.5 × ULN and any AST), or 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 hepatic impairment (bilirubin > 1.5 to 3 x ULN and any AST) or severe hepatic impairment (bilirubin > 3.0 x ULN and any AST) on the pharmacokinetics of durvalumab is unknown.

Elderly

No dose adjustment is required for elderly patients (≥ 65 years of age).

Of the 476 patients with locally advanced, unresectable NSCLC (primary efficacy population) treated with IMFINZI, 215 patients were 65 years or older. No overall clinically meaningful differences in safety were reported between patients ≥ 65 years of age and younger patients.

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.

Drug interaction studies

PK drug-drug interaction between durvalumab and chemotherapy was assessed in the CASPIAN study and no clinically meaningful PK drug-drug interaction was identified.

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 (ADA). Sixty-nine patients (3.0%) tested positive for treatment emergent ADA. Neutralizing 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.

In the TOPAZ-1 study, of the 240 patients who were treated with IMFINZI 1500 mg every 3 weeks in combination with chemotherapy, followed by IMFINZI 1500 mg every 4 weeks and evaluable for the presence of ADAs, 2 (0.8%) patients tested positive for treatment-emergent ADAs. There were insufficient numbers of patients with treatment emergent ADAs or neutralizing antibodies (2 patients each) to determine whether ADAs have an impact on pharmacokinetics and clinical safety of durvalumab.

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

Carcinogenicity and mutagenicity

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

Reproductive toxicology

As reported in the literature, the PD-1/PD-L1 pathway plays a central role in preserving pregnancy by maintaining maternal immune tolerance to the foetus, and in mouse allogeneic pregnancy models disruption of PD-L1 signalling was shown to result in an increase in foetal loss. In reproduction studies in cynomolgus monkeys, administration of durvalumab from the confirmation of pregnancy through delivery at exposure levels approximately 22 times higher than those observed at the clinical dose of 10 mg/kg of durvalumab (based on AUC) was not associated with maternal toxicity or effects on embryofoetal development, pregnancy outcome or postnatal development.

Animal toxicology and/or pharmacology

Repeat dose toxicity studies in sexually mature cynomolgus monkeys with durvalumab of up to 3 months duration were not associated with any adverse effects that were considered of relevance to humans.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

L-histidine

L-histidine hydrochloride monohydrate

α,α-Trehalose dihydrate

Polysorbate 80

Water for Injection

6.2 Incompatibilities

Durvalumab

No incompatibilities between IMFINZI and 9 g/L (0.9%) sodium chloride or 50 g/L (5%) dextrose in polyvinylchloride or polyolefin intravenous (IV) bags have been observed.

This drug product must not be mixed with other drug products except those mentioned in section 6.6.

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

6.3 Shelf-life

Unopened Vial

Please refer to expiry date on the outer carton.

Store at 2°C-8°C.

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, follow the below recommendations:

Chemical and physical stability of the prepared solution for infusion, in the IV bag, has been demonstrated for up to 30 days at 2°C to 8°C and for up to 24 hours at room temperature (up to 25°C) from the time of preparation.

From a microbiological point of view, the prepared solution for infusion, in the IV bag, should be used immediately. If not used immediately, post-dilution storage times and conditions prior to use are the responsibility of the user and the product may be stored for a maximum of 30 days at 2°C to 8°C or 12 hours at room temperature (up to 25°C). If dilution has taken place in controlled and validated aseptic conditions, the product may be stored for the time defined by the chemical and physical stability described above.

6.4 Special precautions for storage

Unopened vial

Store vials under refrigeration at 2°C to 8°C in original carton to protect from light.

Do not freeze.

Do not shake.

Diluted Solution

For storage conditions after preparation of the infusion, see section 6.3.

6.5 Nature and contents of container

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

2.4 mL of concentrate in a 10 mL Type 1 glass vial with an elastomeric stopper and a gray flip-off aluminum seal contains 120 mg durvalumab. Pack size of 1 vial.

Not all pack sizes may be marketed.

6.6 Instructions for use, handling and disposal

Preparation of solution

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

- Visually inspect drug product for particulate matter and discolouration. IMFINZI is clear to opalescent, colourless to slightly yellow solution. Discard the vial if the solution is cloudy, discoloured or visible particles are observed. Do not shake the vial.
- Withdraw the required volume from the vial(s) of IMFINZI and transfer into an 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 administer one dose per vial.
- Discard any unused portion left in the vial.

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.

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

Product owner

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