1. NAME OF THE MEDICINAL PRODUCT

IMFINZI 50 mg/mL concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion (sterile concentrate).

Imfinzi is a sterile, preservative-free, clear to opalescent, colourless to slightly yellow solution, free from visible particles.

Imfinzi is a human immunoglobulin (IgG1κ) monoclonal antibody.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Locally Advanced Non-small Cell Lung Cancer (NSCLC)

- IMFINZI as monotherapy is indicated for the treatment of locally advanced, unresectable NSCLC whose disease has not progressed following definitive platinum-based chemoradiation therapy.
- IMFINZI, in combination with tremelimumab and platinum-based chemotherapy, is indicated for the treatment of adult patients with metastatic NSCLC with no sensitizing epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) genomic tumor aberrations.

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

Hepatocellular Carcinoma (HCC)
IMFINZI in combination with tremelimumab is indicated for the treatment of adult patients with unresectable hepatocellular carcinoma (uHCC).

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

4.2 Posology and method of administration

Treatment must be initiated and monitored by an experience oncologist.

To ensure tracebility of biotechnically manufactured medicinal treatment, it is recommended to keep record of brand name and batch number from each treatment.

Posology
The recommended dosages for IMFINZI as a single agent and IMFINZI in combination with other therapeutic agents are presented in Table 1, 2 and 3.

IMFINZI is administered as an intravenous infusion over 60 minutes.

Table 1. Recommended dosage of IMFINZI

Indication	**Recommended IMFINZI dosage**	**Duration of Therapy**
Locally Advanced NSCLC	Patients with a body weight of 30 kg and more: 10 mg/kg every 2 weeks or 1500 mg every 4 weeks Patients with a body weight of less than 30 kg: 10 mg/kg every 2 weeks	Until disease progression, unacceptable toxicity, or a maximum of 12 months
ES-SCLC	Patients with a body weight of 30 kg and more: 1500 mg in combination with chemotherapy* every 3 weeks (21 days) for 4 cycles, followed by 1500 mg every 4 weeks as a single agent Patients with a body weight of less than 30 kg: 20 mg/kg in combination with chemotherapy* every 3 weeks (21 days) for 4 cycles, followed by 10 mg/kg every 2 weeks as a single agent	Until disease progression or unacceptable toxicity
uHCC	Patients with a body weight of ≥ 30 kg: • IMFINZI 1,500 mg following a single dose of tremelimumab$ 300 mg at Day 1 of Cycle 1; • Continue IMFINZI 1,500 mg as a single agent every 4 weeks Patients with a body weight of < 30 kg: • IMFINZI 20 mg/kg following a single dose of tremelimumab$ 4 mg/kg at Day 1 of Cycle 1; • Continue IMFINZI 20 mg/kg as a single agent every 4 weeks	After Cycle 1 of combination therapy, administer IMFINZI as a single agent every 4 weeks until disease progression or unacceptable toxicity

BTC	Patients with a body weight of ≥ 30 kg: 1,500 mg in combination with chemotherapy* every 3 weeks (21 days) up to 8 cycles followed by 1,500 mg every 4 weeks as a single agent Patients with a body weight of < 30 kg: 20 mg/kg in combination with chemotherapy* every 3 weeks (21 days) up to 8 cycles followed by 20 mg/kg every 4 weeks as a single agent	Until disease progression or until unacceptable toxicity

* Administer IMFINZI prior to chemotherapy on the same day. Refer to the Prescribing Information for the agent administered in combination with IMFINZI for recommended dosage information, as appropriate.

$ Administer tremelimumab prior to IMFINZI on the same day. When tremelimumab is administered in combination with IMFINZI, refer to the Prescribing Information for tremelimumab-actl dosing information.

IMFINZI in Combination with Tremelimumab and Platinum-Based Chemotherapy

The recommended dosage schedule and regimens for IMFINZI for the treatment of metastatic non-small cell lung cancer (NSCLC) are provided in Tables 2 and 3.

Weigh patients prior to each infusion.

Calculate the appropriate dose using Table 3 below based on the patient's weight and tumor histology.

Table 2: Recommended Dosage Schedule

	Week*,$																							
	0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**
Cycle:	**1**			**2**			**3**			**4**			**5**				**6**				**7**				**8**
IMFINZI*,¶	**X**			**X**			**X**			**X**			**X**				**X**				**X**				**X**
Tremelimumab¶,#	**X**			**X**			**X**			**X**							**X**								
Chemotherapy	**X**			**X**			**X**			**X**			**X**þ				**X**þ				**X**þ				**X**þ

* continue IMFINZI until disease progression or intolerable toxicity.

$ Note the dosing interval change from every 3 weeks to every 4 weeks starting at cycle 5.

¶ intravenous infusion over 60 minutes.

if patients receive fewer than 4 cycles of platinum-based chemotherapy, the remaining cycles of tremelimumab (up to a total of 5) should be given after the platinum-based chemotherapy phase, in combination with IMFINZI, every 4 weeks.

þ optional pemetrexed therapy from week 12 until disease progression or intolerable toxicity for patients with non-squamous disease who received treatment with pemetrexed and carboplatin/cisplatin.

Table 3: Recommended Regimen and Dosage

Tumor Histology	**Patient Weight**	**IMFINZI Dosage**	**Tremelimumab Dosage***	**Platinum-based Chemotherapy Regimen***
Non-Squamous	≥30kg	1,500 mg	75 mg	• carboplatin & nab-paclitaxel OR
	<30kg	20 mg/kg	1 mg/kg	

Tumor Histology	Patient Weight	IMFINZI Dosage	Tremelimumab Dosage*	Platinum-based Chemotherapy Regimen*
				• carboplatin or cisplatin & pemetrexed
Squamous	≥30kg	1,500 mg	75 mg	• carboplatin & nab-paclitaxel OR • carboplatin or cisplatin & gemcitabine
	<30kg	20 mg/kg	1 mg/kg	

* Refer to the Prescribing Information for dosing information.

Instructions for use
For intravenous administration.

For instructions on dilution of the medicinal product before administration, see section "Instructions for use, handling and disposal".

No dose reduction 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.

Dosage modifications for IMFINZI for adverse reactions that require management different from these general guidelines are summarized in Table 4. Refer to section 4.4 for further monitoring and evaluation information.

Table 4. 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	ALT or AST > 3 - ≤5 x ULN 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
	ALT or AST > 5-≤ 10 x ULN	Withhold durvaluamb and permanently discontinue tremelimumab	

Adverse reactions	**Severity**[a]	**IMFINZI treatment modification**	**Corticosteroid treatment unless otherwise specified**[b]
	Concurrent ALT or AST > 3 x ULN and total bilirubin > 2 x ULN[d]	Permanently discontinue	
	ALT or AST > 10 x ULN OR total bilirubin > 3 x ULN		
Immune-mediated hepatitis in HCC (or secondary tumour involvement of the liver with abnormal baseline values)[e]	ALT or AST > 2.5-≤ 5X BLV and ≤ 20xULN	Withhold dose[c]	Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
	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 durvalumab and permanently discontinue tremelimumab	
	ALT or AST > 7 X BLV OR > 20 ULN whichever occurs first OR bilirubin > 3ULN	Permanently discontinue	
Immune-mediated colitis or diarrhoea	Grade 2	Withhold dose[c]	Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
	Grade 3 for IMFINZI monotherapy	Withhold dose[c]	
	Grade 3 for IMFINZI +tremelimumab	Permanently discontinue	
	Grade 4	Permanently discontinue	
	Intestinal perforation of ANY grade	Permanently discontinue	Consult a surgeon immediately if an intestinal perforation is suspected
Immune-mediated hyperthyroidism, thyroiditis	Grade 2-4	Withhold dose until clinically stable	Symptomatic management
Immune-mediated hypothyroidism	Grade 2-4	No changes	Initiate thyroid hormone replacement as clinically indicated
Immune-mediated adrenal insufficiency or hypophysitis/hypopituitarism	Grade 2-4	Withhold dose until clinically stable	Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper and hormone replacement as clinically indicated
Immune-mediated type 1 diabetes mellitus	Grade 2-4	No changes	Initiate treatment with insulin as clinically indicated

Adverse reactions	**Severity**[a]	**IMFINZI treatment modification**	**Corticosteroid treatment unless otherwise specified**[b]
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	
Immune-mediated myocarditis	Grade 2 - 4	Permanently discontinue	Initiate 2 to 4 mg/kg/day prednisone or equivalent followed by a taper[f]
Immune-mediated myositis/polymyositis	Grade 2 or 3	Withhold dose[c,g]	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 infusionrelated reactions per institutional standard, appropriate clinical practice guidelines and/or society guidelines

Adverse reactions	Severity[a]	IMFINZI treatment modification	Corticosteroid treatment unless otherwise specified[b]
Immune-mediated myasthenia gravis	Grade 2-4	Permanently discontinue	Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
Immune-mediated encephalitis	Grade 2-4	Permanently discontinue	Initiate 1 mg/kg/day to 2 mg/kg/day prednisone or equivalent followed by a taper
Other immune-mediated adverse reactions[h]	Grade 2 or 3	Withhold dose[c]	Initiate 1 mg/kg/day 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 other systemic immunosuppressants if there is worsening or no improvement.

[c] After withholding, 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] 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] 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.

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

[h] Includes immune thrombocytopenia and pancreatitis.

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

For non-immune-mediated adverse reactions, consider withholding IMFINZI for Grade 2 and 3 adverse reactions until ≤ Grade 1 or baseline. IMFINZI should be discontinued for Grade 4 adverse reactions (with the exception of Grade 4 laboratory abnormalities, about which the decision to discontinue should be based on accompanying clinical signs/symptoms and clinical judgment).

Special populations

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).

Renal impairment
Safety and Efficacy of Imfinzi have not been studied in patients with renal impairment. Based on the population pharmacokinetic (PK) results, no dose adjustment of IMFINZI is recommended in patients with mild or moderate renal impairment (see section 5.2). Data from patients with severe renal impairment are too limited to draw conclusions on this population .

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

Elderly (≥65 years)
Based on a population PK analysis, no dose adjustment is required for elderly patients (≥65 years of age) (see sections 5.1). 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. Data from patients 75 years of age or older in the Pacific Study (7.6%) are too limited to draw conclusions on this population.

Of the 265 patients with ES-SCLC treated with IMFINZI in combination with chemotherapy, 101 (38%) patients were 65 years or older and 19 (7.2%) patients were 75 years or older. There were no clinically meaningful differences in safety or efficacy between patients 65 years or older and younger patients.

Paediatric population
Safety and efficacy of IMFINZI have not been established in children and adolescents aged less than 18 years. No data are available.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Refer to section Posology and method of administration, 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 aetiologies 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, including fatal cases, 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 hyperthyroidism (including thyroiditis) 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. 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.

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 IMFINZI, other potential immune-mediated adverse reactions may occur. Patients should be monitored for signs and symptoms and managed as recommended for other immune-mediated adverse reactions, in section 4.2. Other immune mediated adverse reaction are myasthenia gravis, myositis, polymyositis, immune thrombocytopenia, pancreatitis and encephalitis (see section 4.8).

The following clinically significant, immune-mediated adverse reactions have been reported with other products in this class: bullous dermatitis, Stevens Johnson Syndrome (SJS)/toxic epidermal necrolysis (TEN), pancreatitis, systemic inflammatory response syndrome, rhabdomyolysis, myasthenia gravis, histiocytic necrotizing lymphadenitis, demyelination, vasculitis, hemolytic anemia, iritis, encephalitis, facial and abducens nerve paresis, polymyalgia rheumatica, autoimmune neuropathy, Guillain-Barré syndrome and Vogt-Koyanagi-Harada syndrome.

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 or IMFINZI in combination with tremelimumab (see section 4.8).

Adverse reactions in transplant recipients
In patients treated with PD-1 / PD-L1 inhibitors, solid organ transplant rejection has been observed in the postmarketing setting. In these patients, the benefit of treatment with PD-1/PD-L1 inhibitors including Durvalumab should be weighed against the risk of possible organ rejection.

4.5 Interaction with other medicinal products and other forms of interaction

Durvalumab is an immunoglobulin, therefore no formal pharmacokinetic drug-drug interaction studies have been conducted with durvalumab. PK drug-drug interaction of durvalumab with other medicinal products are not anticipated given durvalumab is not primarily cleared via hepatic/renal pathways but instead the primary elimination pathways are protein catabolism via reticuloendothelial system or target-mediated disposition. Durvalumab is not expected to induce or inhibit the major drug metabolizing cytochrome P450 pathways.

The pharmacokinetics of durvalumab is similar when assessed as a single agent and when in combination with chemotherapy.

The use of systemic corticosteroids or immunosuppressants before starting durvalumab should be avoided because of their potential interference with the pharmacodynamic activity and efficacy of durvalumab. However, systemic corticosteroids or other immunosuppressants can be used after starting durvalumab to treat immune-related adverse reactions (see section 4.4).

PK drug-drug interaction between durvalumab and chemotherapy was assessed in the CASPIAN study and no clinically meaningful PK drug-drug interaction was identified. PK drug-drug interaction between durvalumab in combination with tremelimumab and platinum-based chemotherapy was assessed in the POSEIDON study and no clinically meaningful PK drug-drug interaction was identified. PK drug-drug interaction between durvalumab in combination with tremelimumab was assessed in the HIMALAYA study and no clinically meaningful PK drugdrug 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 6-20 times higher than those observed at the clinical dose of 10 mg/kg of durvalumab (based on AUC) was associated with premature delivery, fetal loss (abortion and stillbirth) and an increase in neonatal deaths compared to concurrent control (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 fetal harm when administered to a pregnant woman. Human IgG1 is known to cross the placental barrier. Imfinzi cannot be used during pregnancy, unless this is absolutely required. Women of childbearing potential should be use effective contraception during treatment with IMFINZI 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. Because of the potential for adverse reactions in breastfed infants from durvalumab, advise a lactating women not to breastfeed during treatment and for at least 3 months after the last dose.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

The safety of IMFINZI as monotherapy is based on pooled data in 3006 patients from 9 studies across multiple tumor types the most frequent adverse reaction were cough (21.5%), diarrhoea (16.3%) and rash (16.0%).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. The corresponding frequency category for each ADR is defined as: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1000); very rare (<1/10,000); not known (cannot be estimated from available data).

Infections and infestations

Very common: Upper respiratory tract infections[o] (13.5%) (CTCAE grade 3 and above: uncommon [0.2%])

Common: Pneumonia[a,p] (8.9%) (CTCAE grade 3 and above: common [3.5%]), Dental and oral soft tissue infections[q] (1.7%) (CTCAE grade 3 and above: rare [<0.1%]), Oral candidiasis (2.1%) (CTCAE grade 3 and above: very rare [0%]), Influenza (1.6%) (CTCAE grade 3 and above: rare [<0.1%])

Endocrine disorders

Very common: Hypothyroidism[g] (10.1%) (CTCAE grade 3 and above: uncommon [0.2%]),

Common: Hyperthyroidism[h] (4.6%) (CTCAE grade 3 and above: very rare [0%])

Uncommon: Adrenal insufficiency (0.6%) (CTCAE grade 3 and above: rare [<0.1%]).Thyroiditis[i] (0.8%) (CTCAE grade 3 and above: rare[<0.1%])

Rare: Type 1 diabetes mellitus (<0.1%) (CTCAE grade 3 and above: rare [<0.1%]), Hypophysitis/ Hypopituitarism (<0.1%) (CTCAE grade 3 and above: rare [<0.1%]), Diabetes insipidus (<0.1%) (CTCAE grade 3 and above: [<0.1%])

Cardiac disorders

Rare: Myocarditis (<0.1%) (CTCAE grade 3 and above: rare [<0.1%])

Respiratory, thoracic and mediastinal disorders

Very common: Cough/ Productive cough[a] (21.5%) (CTCAE grade 3 and above: uncommon [0.4%])

Common: Pneumonitis[a] (3.8%) (CTCAE grade 3 and above: uncommon [0.9%]), Dysphonia (3.1%) (CTCAE grade 3 and above: rare [<0.1%])

Uncommon: Interstitial lung disease (0.6%) (CTCAE grade 3 and above: uncommon [<0.1%])

Gastrointestinal disorders

Very common: Diarrhoea (16.3%) (CTCAE grade 3 and above: uncommon [0.6%]), Abdominal pain[d] (12.7%) (CTCAE grade 3 and above: common [1.8%])

Uncommon: Colitis[e] (0.9%) (CTCAE grade 3 and above: uncommon [0.3%]), Pancreatitis[f] (0.23%) (CTCAE grade 3 and above: uncommon [0.17%])

Hepatobiliary disorders

Common: Aspartate aminotransferase increased or Alanine aminotransferase increased[a,b] (8.1%) (CTCAE grade 3 and above: common [2.3%])

Uncommon: Hepatitis[a,c] (0.8%) (CTCAE grade 3 and above: uncommon [0.4%])

Skin and subcutaneous tissue disorders

Very common: Rash[k] (16%) (CTCAE grade 3 and above: uncommon [0.6%]), Pruritus[l] (10.8%) (CTCAE grade 3 and above: rare [<0.1%])

Common: Night sweats (1.6%) (CTCAE grade 3 and above: rare [<0.1%])

Uncommon: Dermatitis (0.7%) (CTCAE grade 3 and above: rare [<0.1%])

Rare: Pemphigoid[m] (0.1%) (CTCAE grade 3 and above: very rare [0%])

Musculoskeletal and connective tissue disorders

Common: Myalgia (5.9%) (CTCAE grade 3 and above: rare [<0.1%])

Uncommon: Myositis (0.2%) (CTCAE grade 3 and above: rare [<0.1%])

Very rare: Polymyositis (Not determined[r]) (frequency of CTCAE grade 3 and above: very rare [Not determined[r]])

Renal and urinary disorders

Common: Blood creatinine increased (3.5%) (CTCAE grade 3 and above: rare [<0.1%]), Dysuria (1.3%) (CTCAE grade 3 and above: very rare [0%])

Uncommon: Nephritis[j] (0.3%) (CTCAE grade 3 and above: rare [<0.1%])

General disorders and administration site conditions

Very common: Pyrexia (13.8%) (CTCAE grade 3 and above: uncommon [0.3%])

*Common:*Oedema peripheral[n] (9.7%) (CTCAE grade 3 and above: uncommon [0.3%])

Nervous system disorders

Not known: Myasthenia gravis (Not determined[s]) (CTCAE grade 3 and above: [Not determined[s]]), Encephalitis (Not determined[t]) (CTCAE grade 3 and above: [Not determined[t]]

Blood and lymphatic system disorders

Rare: Immune thrombocytopenia[a] (<0.1%) (CTCAE grade 3 and above: rare [<0.1%])

Injury, poisoning and procedural complications

Infusion related reaction[u] (1.6%) (CTCAE grade 3 and above: uncommon [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 generalized, rash macular, rash maculopapular, rash papular, rash pruritic, rash pustular, erythema, eczema and rash.
[l] Includes pruritus generalized 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

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.

The safety of IMFINZI in combination with tremelimumab and platinum-based chemotherapy is based on data in 330 patients from the POSEIDON (metastatic NSCLC) study and was consistent with known IMFINZI + tremelimumab and known chemotherapy safety profiles.

The safety of STRIDE is based on data in 462 patients from the HCC pool (uHCC) and was consistent with known IMFINZI + tremelimumab safety profile.

Description of selected adverse reactions

The data below reflect information for significant adverse reactions for IMFINZI as monotherapy in the pooled safety dataset across tumor types (n=3006). IMFINZI in combination with tremelimumab (75 mg Q4W; pan-tumour pool) in the pooled safety dataset across tumour types (n=2280) and STRIDE in the HCC pool (n=462).

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 who received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day), and 2 patients also received infliximab. In the placebo group 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.

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, pneumonitis including both immune-mediated pneumonitis and 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% respectively) and grade 5 (1.1 vs. 1.7%).

IMFINZI + tremelimumab pan-tumour pool
In patients receiving IMFINZI in combination with tremelimumab, immune-mediated pneumonitis occurred in 86 (3.8%) patients, including Grade 3 in 30 (1.3%) patients, Grade 4 in 1 (<0.1%) patient, and Grade 5 in 7 (0.3%) patients. The median time to onset was 57 days (range: 8-912 days). All patients received systemic corticosteroids, and 79 of the 86 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). Seven patients also received other immunosuppressants. Treatment was discontinued in 39 patients. Resolution occurred in 51 patients.

HCC pool
In patients receiving STRIDE, immune--mediated pneumonitis occurred in 6 (1.3%) patients, including Grade 3 in 1 (0.2%) patient and Grade 5 (fatal) in 1 (0.2%) patient. The median time to onset was 29 days (range: 5-774 days). Six patients received systemic corticosteroids, and 5 of the 6 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). One patient also received other immunosuppressants. Treatment was discontinued in 2 patients. Resolution occurred in 3 patients.

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). Fourty-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.

IMFINZI + tremelimumab pan-tumour pool
In patients receiving IMFINZI in combination with tremelimumab, immune-mediated hepatitis occurred in 80 (3.5%) patients, including Grade 3 in 48 (2.1%) patients, Grade 4 in 8 (0.4%) patients, and Grade 5 in 2 (<0.1%) patients. The median time to onset was 36 days (range: 1-533 days). All patients received systemic corticosteroids, and 68 of the 80 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). Eight patients also received other immunosuppresants. Treatment was discontinued in 27 patients. Resolution occurred in 47 patients.

HCC pool
In patients receiving STRIDE, immune-mediated hepatitis occurred in 34 (7.4%) patients, including Grade 3 in 20 (4.3%) patients, Grade 4 in 1 (0.2%) patient and Grade 5 (fatal) in 3 (0.6%) patients. The median time to onset was 29 days (range: 13-313 days). All patients received systemic corticosteroids, and 32 of the 34 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or

equivalent per day). Nine patients also received other immunosuppressants. Treatment was discontinued in 10 patients. Resolution occurred in 13 patients.

Immune-mediated colitis
IMFINZI monotherapy, immune-mediated colitis or diarrhea occurred in 58 (1.9%) patients, including Grade 3 in 9 (0.3%) patients and Grade 4 in 2 (<0.1%) patient. 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.

IMFINZI + tremelimumab pan-tumour pool
In patients receiving IMFINZI in combination with tremelimumab, immune-mediated colitis or diarrhoea occurred in 167 (7.3%) patients, including Grade 3 in 76 (3.3%) patients and Grade 4 in 3 (0.1%) patients. The median time to onset was 57 days (range: 3-906 days). All patients received systemic corticosteroids, and 151 of the 167 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). Twenty-two patients also received other immunosuppresants. Treatment was discontinued in 54 patients. Resolution occurred in 141 patients.

Intestinal perforation was observed in patients receiving IMFINZI in combination with tremelimumab.

HCC pool
In patients receiving STRIDE, immune-mediated colitis or diarrhoea occurred in 31 (6.7%) patients, including Grade 3 in 17 (3.7%) patients. The median time to onset was 23 days (range: 2-479 days). All patients received systemic corticosteroids, and 28 of the 31 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). Four patients also received other immunosuppressants. Treatment was discontinued in 5 patients. Resolution occurred in 29 patients.

Intestinal perforation was not observed in patients receiving STRIDE.

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.

IMFINZI + tremelimumab pan-tumour pool
In patients receiving IMFINZI in combination with tremelimumab, immune-mediated hypothyroidism occurred in 209 (9.2%) patients, including Grade 3 in 6 (0.3%) patients. The median time to onset was 85 days (range: 1-624 days). Thirteen patients received systemic corticosteroids, and 8 of the 13 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). Two-hundred and five patients required endocrine therapy. Treatment was discontinued in 3 patients. Resolution occurred in 52 patients. Immune-mediated hypothyroidism was preceded by immune-mediated hyperthyroidism in 25 patients or immune-mediated thyroiditis in 2 patients.

HCC pool
In patients receiving STRIDE, immune-mediated hypothyroidism occurred in 46 (10.0%) patients. The median time to onset was 85 days (range: 26-763 days). One patient received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). All patients required other therapy (thiamazole, carbimazole, propylthiouracil, perchlorate, calcium channel blocker, or beta-blocker).

Resolution occurred in 6 patients. Immunemediated hypothyroidism was preceded by immune-mediated hyperthyroidism in 4 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). Fourty-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.

IMFINZI + tremelimumab pan-tumour pool
In patients receiving IMFINZI in combination with tremelimumab, immune-mediated hyperthyroidism occurred in 62 (2.7%) patients, including Grade 3 in 5 (0.2%) patients. The median time to onset was 33 days (range: 4-176 days). Eighteen patients received systemic corticosteroids, and 11 of the 18 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). Fifty-three patients required other therapy (thiamazole, carbimazole, propylthiouracil, perchlorate, calcium channel blocker, or betablocker). Treatment was discontinued in 1 patient. Resolution occurred in 47 patients.

HCC pool
In patients receiving STRIDE, immune-mediated hyperthyroidism occurred in 21 (4.5%) patients, including Grade 3 in 1 (0.2%) patient. The median time to onset was 30 days (range: 13-60 days). Four patients received systemic coticosteriods, and all of the four patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). Twenty patients required other therapy (thiamazole, carbimazole, propylthiouracil, perchlorate, calcium channel blocker, or beta-blocker). One patient discontinued treatment due to hyperthyroidism. Resolution occurred in 17 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

IMFINZI + tremelimumab pan-tumour pool
In patients receiving IMFINZI in combination with tremelimumab, immune-mediated thyroiditis occurred in 15 (0.7%) patients, including Grade 3 in 1 (<0.1%) patient. The median time to onset was 57 days (range: 22-141 days). Five patients received systemic corticosteroids, and 2 of the 5 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). Thirteen patients required other therapy, including hormone replacement tharapy, thiamazole, carbimazole, propylthiouracil, perchlorate, calcium channel blocker, or beta-blocker. No patients discontinued treatment due to immune-mediated thyroiditis. Resolution occurred in 5 patients.

HCC pool
In patients receiving STRIDE, immune-mediated thyroiditis occurred in 6 (1.3%) patients. The median time to onset was 56 days (range: 7-84 days). Two patients received systemic corticosteroids, and 1 of the 2 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). All patients required other therapy including hormone replacement therapy, thiamazole, carbimazole, propylthiouracil, perchlorate, calcium channel blocker, or beta-blocker. Resolution occurred in 2 patients.

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.

IMFINZI + tremelimumab pan-tumour pool
In patients receiving IMFINZI in combination with tremelimumab, immune-mediated adrenal insufficiency occurred in 33 (1.4%) patients, including Grade 3 in 16 (0.7%) patients and Grade 4 in 1 (<0.1%) patient. The median time to onset was 105 days (range: 20-428 days). Thirty-two patients received systemic corticosteroids, and 10 of the 32 patients received highdose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). Seven patients required endocrine therapy. Treatment was discontinued in 1 patient. Resolution occurred in 11 patients.

HCC pool
In patients receiving STRIDE, immune-mediated adrenal insufficiency occurred in 6 (1.3%) patients, including Grade 3 in 1 (0.2%) patient. The median time to onset was 64 days (range: 43-504 days). All patients received systemic corticosteroids, and 1 of the 6 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). Resolution occurred in 2 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.

IMFINZI + tremelimumab pan-tumour pool
In patients receiving IMFINZI in combination with tremelimumab, immune-mediated type 1 diabetes occurred in 6 (0.3%) patients, including Grade 3 in 1 (<0.1%) patient and Grade 4 in 2 (<0.1%) patients. The median time to onset was 58 days (range: 7-220 days). All patients required insulin. Treatment was discontinued in 1 patient. Resolution occurred in 1 patient.

HCC pool
In patients receiving STRIDE, immune-mediated type 1 diabetes mellitus was not observed.

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.

IMFINZI + tremelimumab pan-tumour pool
In patients receiving IMFINZI in combination with tremelimumab, immune-mediated hypophysitis/hypopituitarism occurred in 16 (0.7%) patients, including Grade 3 in 8 (0.4%) patients. The median time to onset was 123 days (range: 63-388 days). All patients received systemic corticosteroids, and 8 of the 16 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). Four patients also required endocrine therapy. Treatment was discontinued in 2 patients. Resolution occurred in 7 patients.

HCC pool
In patients receiving STRIDE, immune-mediated hypophysitis/hypopituitarism occurred in 5 (1.1%) patients. The median time to onset for the events was 149 days (range: 27-242 days). Four patients received systemic corticosteroids, and 1 of the 4 patients received high-dose corticosteroid treatment

(at least 40 mg prednisone or equivalent per day). Three patients also required endocrine therapy. Resolution occurred in 2 patients.

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.

IMFINZI + tremelimumab pan-tumour pool
In patients receiving IMFINZI in combination with tremelimumab, immune-mediated nephritis occurred in 9 (0.4%) patients, including Grade 3 in 1 (<0.1%) patient. The median time to onset was 79 days (range: 39-183 days). All patients received systemic corticosteroids, and 7 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). Treatment was discontinued in 3 patients. Resolution occurred in 5 patients.

HCC pool
In patients receiving STRIDE, immune-mediated nephritis occurred in 4 (0.9%) patients, including Grade 3 in 2 (0.4%) patients. The median time to onset was 53 days (range: 26-242 days). All patients received systemic corticosteroids, and 3 of the 4 received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). Treatment was discontinued in 2 patients. Resolution occurred in 3 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.

IMFINZI + tremelimumab pan-tumour pool
In patients receiving IMFINZI in combination with tremelimumab, immune-mediated rash or dermatitis (including pemphigoid), occurred in 112 (4.9%) patients, including Grade 3 in 17 (0.7%) patients. The median time to onset was 35 days (range: 1-778 days). All patients received systemic corticosteroids, and 57 of the 112 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). Treatment was discontinued in 10 patients. Resolution occurred in 65 patients

HCC pool
In patients receiving STRIDE, immune-mediated rash or dermatitis (including pemphigoid) occurred in 26 (5.6%) patients, including Grade 3 in 9 (1.9%) patients and Grade 4 in 1 (0.2%) patients. The median time to onset was 25 days (range: 2-933 days). All patients received systemic corticosteroids and 14 of the 26 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). One patient received other immunosuppressants. Treatment was discontinued in 3 patients. Resolution occurred in 19 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.

IMFINZI + tremelimumab pan-tumour pool
In patients receiving IMFINZI in combination with tremelimumab, infusion-related reactions occurred in 45 patients (2.0%), including Grade 3 in 2 (<0.1%) patients. There were no Grade 4 or 5 events.

HCC pool
In patients receiving STRIDE, infusion-related reactions occurred in 13 (2.8%) patients.

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.Neutralising antibodies against durvalumab were detected in 0.5% (12/2280) of 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 types of AEs reported in patients positive for durvalumab ADA were similar to those reported in patients who were negative for durvalumab ADA. 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 treatmentemergent 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.

In the POSEIDON study, of the 286 patients who were treated with IMFINZI 1500 mg in combination with tremelimumab every 3 weeks and platinum-based chemotherapy and evaluable for the presence of ADAs, 29 (10.1%) patients tested positive for treatmentemergent ADAs. Neutralizing antibodies against durvalumab were detected in 1% (3/286) patients. The presence of ADAs did not have an apparent effect on pharmacokinetics or safety.

In the HIMALAYA study, of the 294 patients who were treated with STRIDE and evaluable for the presence of ADAs, 9 (3.1%) patients tested positive for treatment-emergent ADAs. Neutralizing antibodies against durvalumab were detected in 1.7% (5/294) patients. The presence of ADAs did not have an apparent effect on pharmacokinetics or safety.

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

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

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 tumors 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 tumor cells and tumor-associated immune cells in tumor 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 tumor size.

The combination of durvalumab, a PD-L1 inhibitor, and tremelimumab, a CTLA-4 inhibitor functions to enhance anti-tumour T-cell activation and function at multiple stages of the immune response, maximizing anti-tumour immunity.

The steady state AUC, C_{trough}, and C_{max} in patients administered with 1500 mg every 4 weeks are 6% higher, 19% lower, and 55% higher than those administered with 10 mg/kg every 2 weeks, respectively. Based on the modeling of pharmacokinetic data and exposure relationships for safety, there are no anticipated clinically meaningful differences in efficacy and safety for the doses of 1500 mg every 4 weeks compared to 10 mg/kg every 2 weeks in patients weighing > 30 kg with UC and NSCLC.

Clinical efficacy and safety

Locally Advanced NSCLC - PACIFIC Study

The efficacy of IMFINZI was evaluated in the PACIFIC Study, a randomized, double-blind, placebo-controlled, multicenter 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 randomized 2:1 to receive 10 mg/kg IMFINZI (n=476) or placebo (n=237) via intravenous infusion every 2 weeks for up to 12 months or until unacceptable toxicity or confirmed disease progression. Randomization was stratified by gender, age (<65 years vs. ≥ 65 years) and smoking status (smoker vs. non- smoker). Tumour assessments were conducted every 8 weeks for the first 12 months and then every 12 weeks thereafter.

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%), PD-L1 expression TC≥25% (22%), PD-L1 expression TC<25% (41%). (PD-L1 status was retrospectively analysed in 451 patients with available samples, taken prior to concurrent chemoradiation therapy).

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 5 and Figures 1 and 2.

Table 5. 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) (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[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	

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

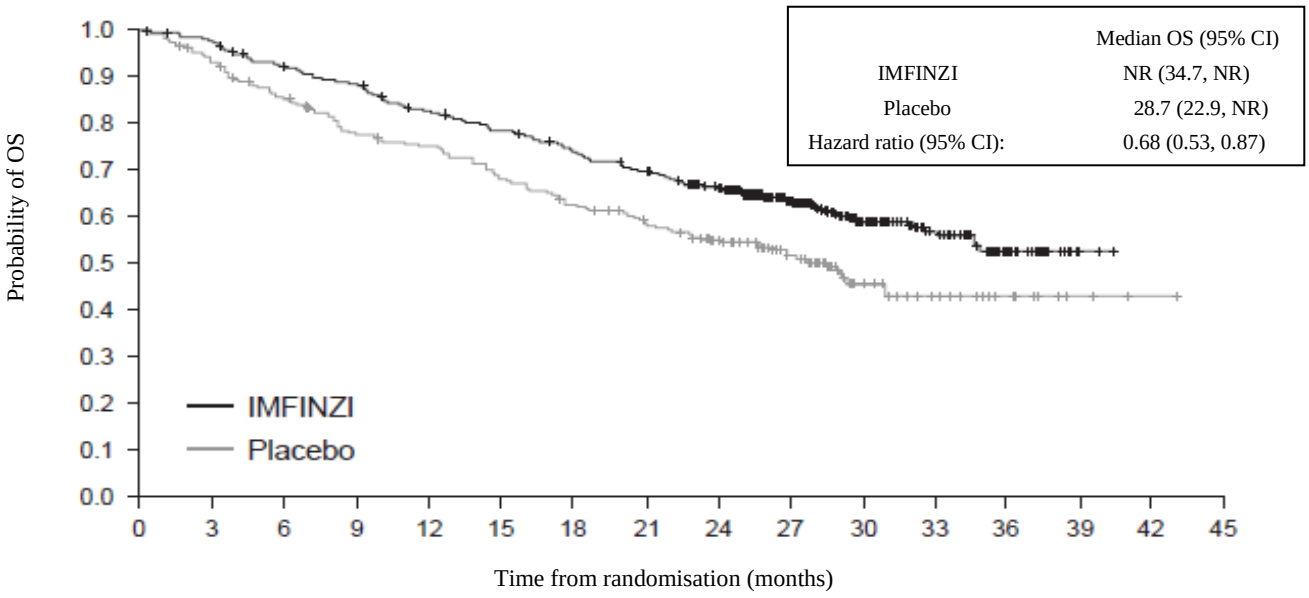
[c] TTDM is defined as the time from the date of randomization until the first date of distant metastasis or death in the absence of distant metastasis. Distant metastasis is defined as any new lesion that is outside of the radiation field according to RECIST v1.1 or proven by biopsy.

[d] TFST is defined as the time from randomization 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

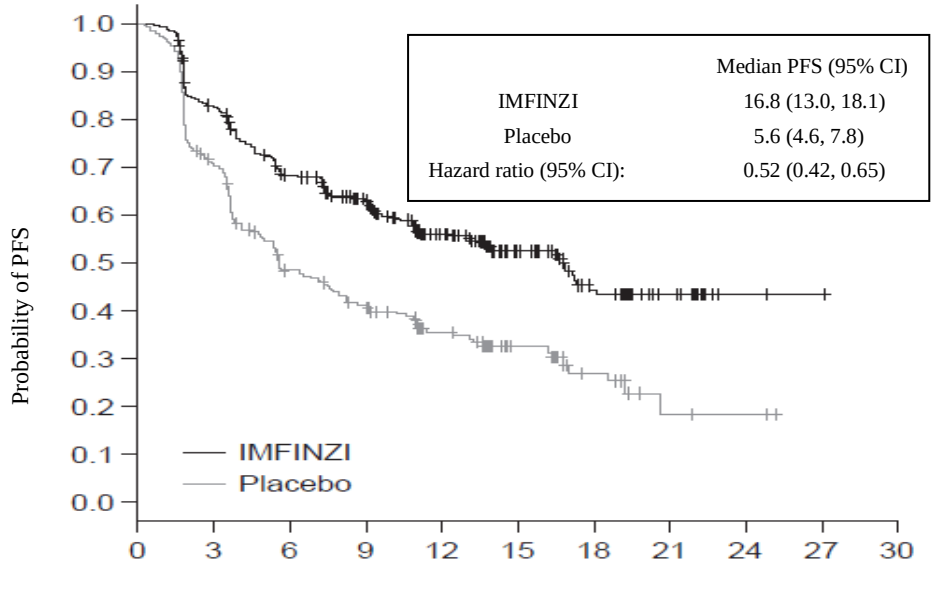
Figure 1. Kaplan-Meier curve of OS



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

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).

Metastatic NSCLC – POSEIDON Study

POSEIDON was a study designed to evaluate the efficacy of IMFINZI with or without tremelimumab in combination with platinum-based chemotherapy. POSEIDON was a randomised, open-label, multicentre study in 1013 metastatic NSCLC patients with no sensitizing epidermal growth factor receptor (EGFR) mutation or anaplastic lymphoma kinase (ALK) genomic tumour aberations. Patients with a histologically or cytologically documented metastatic NSCLC were eligible for enrolment. Patients had no prior chemotherapy or any other systemic therapy for metastatic NSCLC. Prior to randomisation, patients had tumour PD-L1 status confirmed by using the Ventana PD-L1 (SP263) Assay. Patients had a World Health Organization/Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.

The study excluded patients with active or prior documented autoimmune disease; active and/or untreated brain metastases; a history of immunodeficiency; administration of systemic

immunosuppression within 14 days before the start of IMFINZI or tremelimumab, 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 and/or tremelimumab.

Randomisation was stratified by tumour cells (TC) PD-L1 expression (TC≥50% vs. TC<50%), disease stage (Stage IVA vs. Stage IVB), and histology (non-squamous vs. squamous).

Patients were randomised 1:1:1 to receive:

- Arm 1: IMFINZI 1500 mg with tremelimumab 75 mg and platinum-based chemotherapy every 3 weeks for 4 cycles, followed by, IMFINZI 1500 mg every 4 weeks as monotherapy. A fifth dose of tremelimumab 75 mg was given at Week 16 alongside IMFINZI dose 6.
- Arm 2: IMFINZI 1500 mg and platinum-based chemotherapy every 3 weeks for 4 cycles, followed by, IMFINZI 1500 mg every 4 weeks as monotherapy.
- Arm 3: Platinum-based chemotherapy every 3 weeks for 4 cycles as monotherapy. Patients could receive additional 2 cycles (a total of 6 cycles post-randomisation), as clinically indicated, at Investigator's discretion.

In the 3 treatment arms, patients received one of the following histology-based chemotherapy regimens:

- Non-squamous NSCLC
    - Pemetrexed 500 mg/m^2 with carboplatin AUC 5-6 or cisplatin 75 mg/m^2 every 3 weeks, unless contraindicated by the investigator, pemetrexed maintenance could be given
- Squamous NSCLC
    - Gemcitabine 1000 or 1250 mg/m^2 on Days 1 and 8 with cisplatin 75 mg/m^2 or carboplatin AUC 5-6 on Day 1 every 3 weeks
- Non-squamous and Squamous NSCLC
    - Nab-paclitaxel 100 mg/m^2 on Days 1, 8, and 15 with carboplatin AUC 5-6 on Day 1 every 3 weeks

Tremelimumab was given up to a maximum of 5 doses unless there was disease progression or unacceptable toxicity. IMFINZI and histology-based pemetrexed maintenance therapy (when applicable) was 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 with disease progression during IMFINZI monotherapy were given the option to to be retreated with 4 additional cycles of tremelimumab alongside IMFINZI.

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 dual primary endpoints of the study were PFS and OS for IMFINZI + platinum-based chemotherapy (Arm 2) vs. platinum-based chemotherapy alone (Arm 3). The key secondary endpoints of the study were PFS and OS for IMFINZI + tremelimumab + platinum-based chemotherapy (Arm 1) vs. platinum-based chemotherapy alone (Arm 3). The secondary endpoints included ORR and DoR. PFS, ORR, and DoR were assessed using BICR according to RECIST v1.1. At planned analyses for OS and PFS, IMFINZI + tremelimumab + platinum-based chemotherapy (Arm 1) vs. platinum-based chemotherapy (Arm 3) met the efficacy boundaries for the endpoints of OS and PFS. The results are summarised below.

The demographics and baseline disease characteristics were generally well-balanced between study arms. Baseline demographics of the overall study population were as follows: male (76.0%), age ≥ 65 years (47.1%), white (55.9%), Asian (34.6%), black or African American (2.0%), other (7.6%), non-Hispanic or Latino (84.2%), current smoker or past-smoker (78.0%), and never smoker (21.9%), WHO/ECOG PS 0 (33.4%), WHO/ECOG PS 1 (66.5%). Disease characteristics were as follows:

Stage IVA (50.0%), Stage IVB (49.6%), histological sub-groups of squamous (36.9%), non-squamous (62.9%), PD-L1 expression TC≥50% (28.8%), PD-L1 expression TC <50% (71.1%).

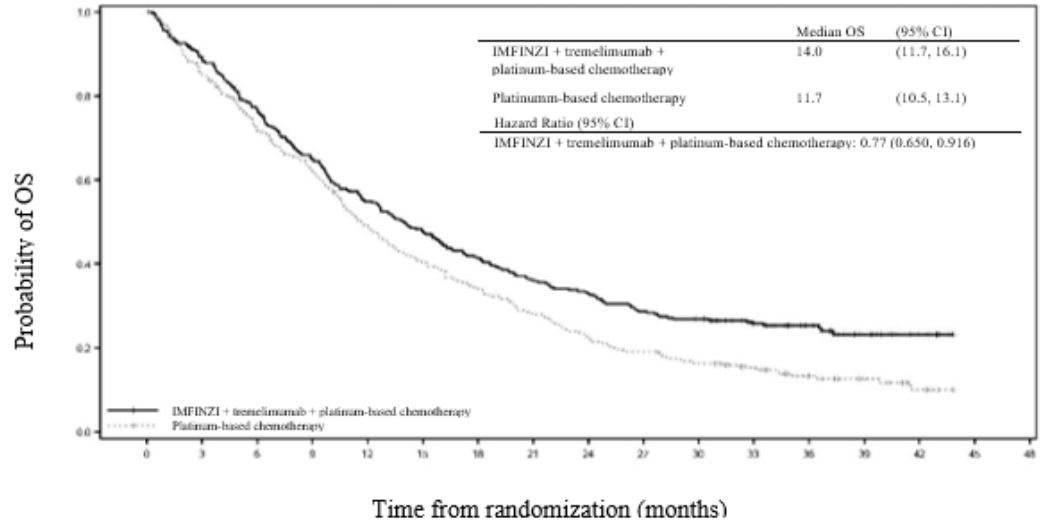
The study demonstrated a statistically significant and clinically meaningful improvement in OS in the IMFINZI + tremelimumab + platinum-based chemotherapy (Arm 1) vs. platinum-based chemotherapy alone (Arm 3) [HR=0.77 (95% CI: 0.650, 0.916), p=0.00304]. IMFINZI + tremelimumab + platinum-based chemotherapy demonstrated a statistically significant and clinically meaningful improvement in PFS vs. platinum-based chemotherapy alone (Arm 3) [HR=0.72 (95% CI: 0.600, 0.860), p=0.00031]. See Table 6 and Figures 3 and 4.

Table 6. Efficacy Results for the POSEIDON Study

	Arm 1: IMFINZI+tremelimumab+ platinum-based chemotherapy (n=338)	**Arm 3: Platinum-based chemotherapy (n=337)**
OS[a]		
Number of deaths (%)	251 (74.3)	285 (84.6)
Median OS (months) (95% CI)	14.0 (11.7, 16.1)	11.7 (10.5, 13.1)
HR (95% CI)	0.77 (0.650, 0.916)	
p-value[b]	0.00304	
OS at 12 months (%) (95% CI)	54.8 (49.3, 60.0)	49.1 (43.6, 54.4)
OS at 24 months (%) (95% CI)	32.9 (27.9, 37.9)	22.1 (17.8, 26.8)
OS at 36 months (%) (95% CI)	25.3 (20.8, 30.2)	13.3 (9.8, 17.4)
PFS[a]		
Number of events (%)	238 (70.4)	258 (76.6)
Median PFS (months) (95% CI)	6.2 (5.0, 6.5)	4.8 (4.6, 5.8)
HR (95% CI)	0.72 (0.600, 0.860)	
p-value[b]	0.00031	
PFS at 12 months (%) (95% CI)	26.6 (21.7, 31.7)	13.1 (9.3, 17.6)
ORR n (%)[c]	130 (38.8)	81 (24.4)
Complete Response n (%)	2 (0.6)	0
Partial Response n (%)	128 (38.2)	81 (24.4)
Odds ratio (95% CI)	2.00 (1.428, 2.807)	
p-value	<0.001	
Median DoR (months) (95% CI)	9.5 (7.2, NR)	5.1 (4.4, 6.0)

[a] PFS/OS results are based on planned analyses which occurred 25/45 months respectively after study initiation. The boundaries for declaring efficacy (PFS 0.00735, OS 0.00797 2-sided) were determined by a Lan-DeMets alpha spending function that approximates an O'Brien Fleming approach.
[b] 2-sided p-value based on a log-rank test stratified by PD-L1, histology and disease stage.
[c] Confirmed Objective Response.
NR=Not Reached, CI=Confidence Interval

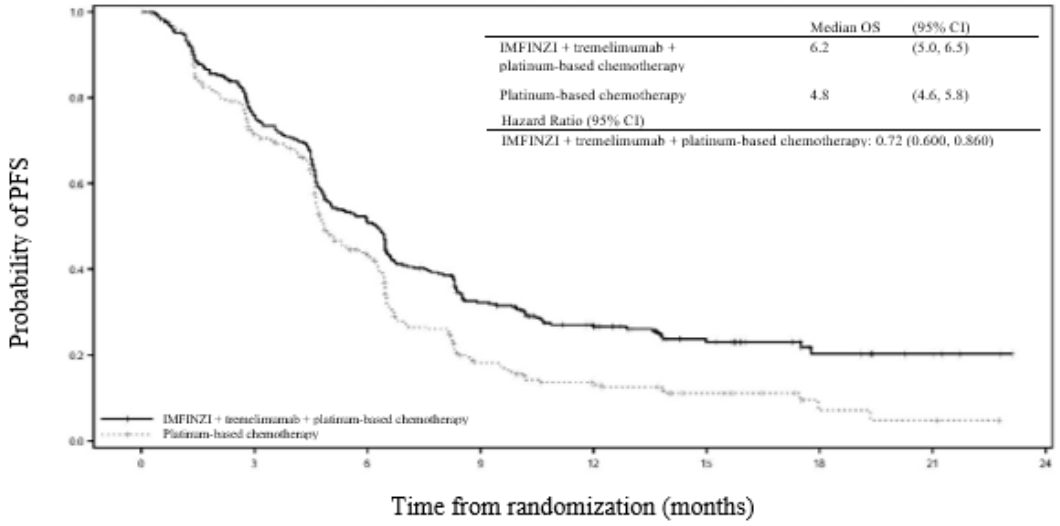
Figure 3. Kaplan-Meier curve of OS



Number of patients at risk

Month															
0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45
IMFINZI + tremelimumab + platinum-based chemotherapy															
338	298	256	217	183	159	137	120	109	95	88	64	41	20	9	0
Platinum-based chemotherapy															
337	284	236	204	160	132	111	91	72	62	52	38	21	13	6	0

Figure 4. Kaplan-Meier curve of PFS



Number of patients at risk

Month								
0	3	6	9	12	15	18	21	24
IMFINZI + tremelimumab + platinum-based chemotherapy								
338	243	161	94	56	32	13	5	0
Platinum-based chemotherapy								
337	219	121	43	23	12	3	2	0

Subgroup analysis

The improvements in OS and PFS favour patients receiving IMFINZI + tremelimumab + platinum-based chemotherapy compared to those receiving platinum-based chemotherapy alone and were consistently observed across the prespecified subgroups based on demographic and baseline characteristics, biomarker status, histology, planned chemotherapy, and disease characteristics. An

exception was noted in the never smoker subgroup for OS. However, due to the small numbers of patients, no definitive conclusions can be drawn from these data.

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. Overall compliance for EORTC QLQ-C30 and EORTC QLQ-L13 were 73.0% and 72.8% in the T + D + SoC arm and 65.0% and 64.8% in the SoC chemotherapy arm.

Delay in time to deterioration (TTD) of symptoms, functioning, and global health status/QoL:
D+T+SoC prolonged the median TTD in patient-reported symptoms, functioning and global health status/QoL compared to SoC alone (see Tables 7 and 8). Nominally significant differences in TTD in favor of T + D + SoC compared to SoC alone were observed for the pre-specified domains of interest of global health status/QoL, physical functioning and dyspnea (EORTC QLQ-LC13) (HRs ranging from 0.75 to 0.78; nominal p-values <0.05).

Table 7: Median time to deterioration in global health status/QoL and function (EORTC QLQ-C30)[a]

PRO domain	Statistic	D +T+SoC (N=338)	SoC (N=337)
Global health status/QoL[a]	n[b]	319	318
	Median time to deterioration (months)	8.3	5.6
	HR[c] (95% CI)	0.78 (0.631, 0.961)	
	p-value[d]	0.021	
Physical[a]	n[b]	323	320
	Median time to deterioration (months)	7.7	5.3
	HR[c] (95% CI)	0.75 (0.610, 0.920)	
	p-value[d]	0.006	
Cognitive	n[b]	323	318
	Median time to deterioration (months)	7.6	5.8
	HR[c] (95% CI)	0.79 (0.644, 0.975)	
	p-value[d]	0.028	
Role	n[b]	314	304
	Median time to deterioration (months)	6.6	4.8
	HR[c] (95% CI)	0.81 (0.664, 0.999)	
	p-value[d]	0.049	
Emotional	n[b]	322	315
	Median time to deterioration (months)	8.5	7.5
	HR[c] (95% CI)	0.87 (0.697, 1.082)	
	p-value[d]	0.208	
Social	n[b]	320	314
	Median time to deterioration (months)	6.4	5.7
	HR[c] (95% CI)	0.85 (0.687, 1.045)	
	p-value[d]	0.120	

[a] Pre-specified PRO domains of interest
[b] Number of patients with a baseline global health status/QoL or function score ≥10 that were included in the time to deterioration analysis
[c] A hazard ratio <1 favours D+T+SoC
[d] p-values for time to deterioration based on stratified log-rank test adjusting for PD-L1 (PD-L1 ≥50% vs PD-L1 <50%), histology (squamous vs non-squamous), and disease stage (Stage IVA vs Stage IVB). They were not adjusted for multiplicity

Table 8: Median time to deterioration in symptoms (EORTC QLQ-C30 and QLQ-LC13)[a]

PRO domain	Statistic	D +T+SoC (N=338)	SoC (N=337)
Coughing[a]	n[b]	302	295
	Median time to deterioration (months)	9.7	8.8
	HR[c] (95% CI)	0.91 (0.722, 1.146)	
	p-value[d]	0.418	
Dyspnoea (QLQ-C30)	n[b]	310	301
	Median time to deterioration (months)	7.9	6.7
	HR[c] (95% CI)	0.84 (0.678, 1.047)	
	p-value[d]	0.123	
Dyspnoea (QLQ-LC13)[a]	n[b]	325	316
	Median time to deterioration (months)	5.4	3.6
	HR[c] (95% CI)	0.77 (0.635, 0.936)	
	p-value[d]	0.009	
Pain	n[b]	316	298
	Median time to deterioration (months)	8.9	5.7
	HR[c] (95% CI)	0.70 (0.563, 0.862)	
	p-value[d]	<0.001	
Chest pain[a]	n[b]	319	309
	Median time to deterioration (months)	10.0	8.6
	HR[c] (95% CI)	0.85 (0.681, 1.066)	
	p-value[d]	0.163	
Arm or shoulder pain	n[b]	312	310
	Median time to deterioration (months)	8.9	8.8
	HR[c] (95% CI)	0.93 (0.745, 1.161)	
	p-value[d]	0.517	
Pain in other parts of body	n[b]	312	306
	Median time to deterioration (months)	9.7	5.8
	HR[c] (95% CI)	0.74 (0.597, 0.921)	
	p-value[d]	0.007	
Fatigue[a]	n[b]	317	314
	Median time to deterioration (months)	3.7	2.8
	HR[c] (95% CI)	0.90 (0.746, 1.084)	
	p-value[d]	0.272	
Insomnia	n[b]	311	301
	Median time to deterioration (months)	8.3	5.8
	HR[c] (95% CI)	0.74 (0.598, 0.921)	
	p-value[d]	0.007	
Appetite loss[a]	n[b]	308	305
	Median time to deterioration (months)	7.2	7.0
	HR[c] (95% CI)	0.94 (0.754, 1.169)	
	p-value[d]	0.570	
Constipation	n[b]	315	306
	Median time to deterioration (months)	9.2	6.1
	HR[c] (95% CI)	0.78 (0.627, 0.972)	
	p-value[d]	0.026	
Diarrhoea	n[b]	324	320
	Median time to deterioration (months)	11.0	10.8
	HR[c] (95% CI)	1.00 (0.792, 1.260)	
	p-value[d]	0.986	
Nausea/vomiting	n[b]	322	319
	Median time to deterioration (months)	7.8	5.6

PRO domain	Statistic	D +T+SoC (N=338)	SoC (N=337)
	HR[c] (95% CI)	0.81 (0.655, 0.994)	
	p-value[d]	0.045	
Haemoptysis	n[b]	325	318
	Median time to deterioration (months)	17.8	11.4
	HR[c] (95% CI)	0.77 (0.598, 0.984)	
	p-value[d]	0.036	

[a] Pre-specified PRO domains of interest
[b] Number of patients with a baseline symptom score ≤90 that were included in the time to deterioration analysis
[c] A hazard ratio <1 favours D+T+SoC
[d] p-values for time to deterioration based on stratified log-rank test adjusting for PD-L1 (PD-L1 ≥50% vs PD-L1 <50%), histology (squamous vs non-squamous), and disease stage (Stage IVA vs Stage IVB). They were not adjusted for multiplicity

SCLC – CASPIAN Study

The efficacy of IMFINZI in combination with etoposide and either carboplatin or cisplatin in previously untreated ES-SCLC was investigated in CASPIAN, a randomized, multicenter, active-controlled, open-label trial (NCT03043872). Eligible patients had WHO Performance Status of 0 or 1 and were suitable to receive a platinum-based chemotherapy regimen as first-line treatment for SCLC. Patients with asymptomatic or treated brain metastases were eligible. Choice of platinum agent was at the investigator's discretion, taking into consideration the calculated creatinine clearance. Patients with history of chest radiation therapy; a history of active primary immunodeficiency; autoimmune disorders including paraneoplastic syndrome; 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 were ineligible.

Randomization was stratified by the planned platinum-based therapy in cycle 1 (carboplatin or cisplatin).
The evaluation of efficacy for ES-SCLC relied on:

- IMFINZI 1500 mg, and investigator's choice of 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 4 cycles, followed by IMFINZI 1500 mg every 4 weeks until disease progression or unacceptable toxicity, or

- Investigator's choice of 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, up to 6 cycles. After completion of chemotherapy, prophylactic cranial irradiation (PCI) as administered per investigator discretion.

Administration of IMFINZI as a single agent was permitted beyond disease progression if the patient was clinically stable and deriving clinical benefit as determined by the investigator.
The major efficacy outcome measure was overall survival (OS) of IMFINZI plus chemotherapy vs. chemotherapy alone. Additional efficacy outcome measures were investigator-assessed progression-free survival (PFS) and objective response rate (ORR), per RECIST v1.1.

The study population characteristics were: median age of 63 years (range: 28 to 82); 40% age 65 or older; 70% male; 84% White, 15% Asian, and 0.9% Black; 65% WHO/ECOG PS of 1; and 93% were former/current smokers. Ninety percent of patients had Stage IV disease and 10% had brain metastasis at baseline. A total of 25% of the patients received cisplatin and 74% of the patients received

carboplatin. In the chemotherapy alone arm, 57% of the patients received 6 cycles of chemotherapy, and 8% of the patients received PCI.

The OS results are summarized in Table 9 and Figure 5.

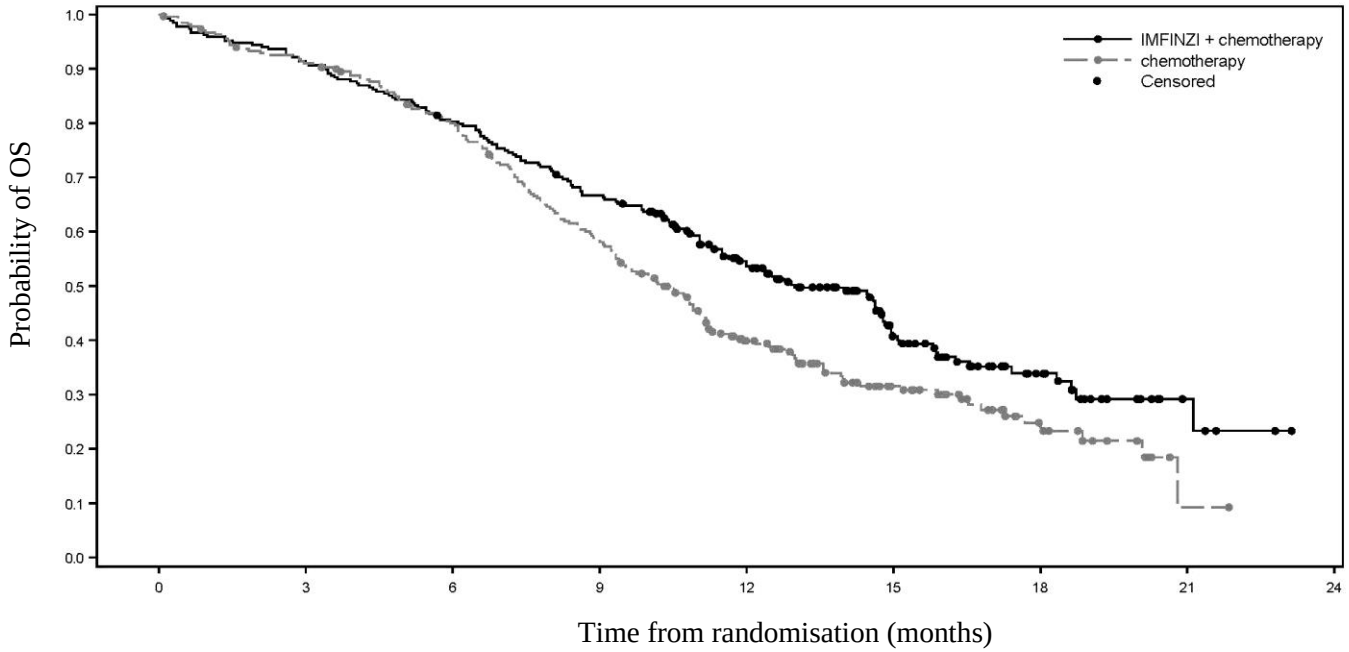
Table 9. OS Result for the CASPIAN Study

Endpoint	**IMFINZI with Etoposide and either Carboplatin or Cisplatin (n=268)**	**Etoposide and either Carboplatin or Cisplatin (n=269)**
Overall Survival (OS)		
Number of deaths (%)[1]	155 (58)	181 (67)
Median OS (months) (95% CI)	13.0 (11.5, 14.8)	10.3 (9.3, 11.2)
Hazard Ratio (95% CI)[2]	0.73 (0.59, 0.91)	
p-value[1]	0.0047	

[1] At a pre-specified interim analysis, 336 OS events (79% of total planned events) were observed, and the boundary for declaring efficacy (0.0178) was determined by a Lan-Demets alpha spending function with O'Brien Fleming type boundary

[2] 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

Figure 5. Kaplan-Meier Curves of Overall Survival in the CASPIAN Study



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

Investigator-assessed PFS (96% of total planned events) showed a HR of 0.78 (95% CI: 0.65, 0.94), with median PFS of 5.1 months (95% CI: 4.7, 6.2) in the IMFINZI plus chemotherapy arm and 5.4 months (95% CI: 4.8, 6.2) in the chemotherapy alone arm. The investigator-assessed confirmed ORR was 68% (95% CI: 62%, 73%) in the IMFINZI plus chemotherapy arm and 58% (95% CI: 52%, 63%) in the chemotherapy alone arm.

In the exploratory subgroup analyses of OS based on the planned platinum chemotherapy received at cycle 1, the HR was 0.70 (95% CI 0.55, 0.89) in patients who received carboplatin, and the HR was 0.88 (95% CI 0.55, 1.41) in patients who received cisplatin.

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 8. PFS is also presented in Figure 7.

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). Results from this analysis for OS are presented in the Table 10 and Figure 6.

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

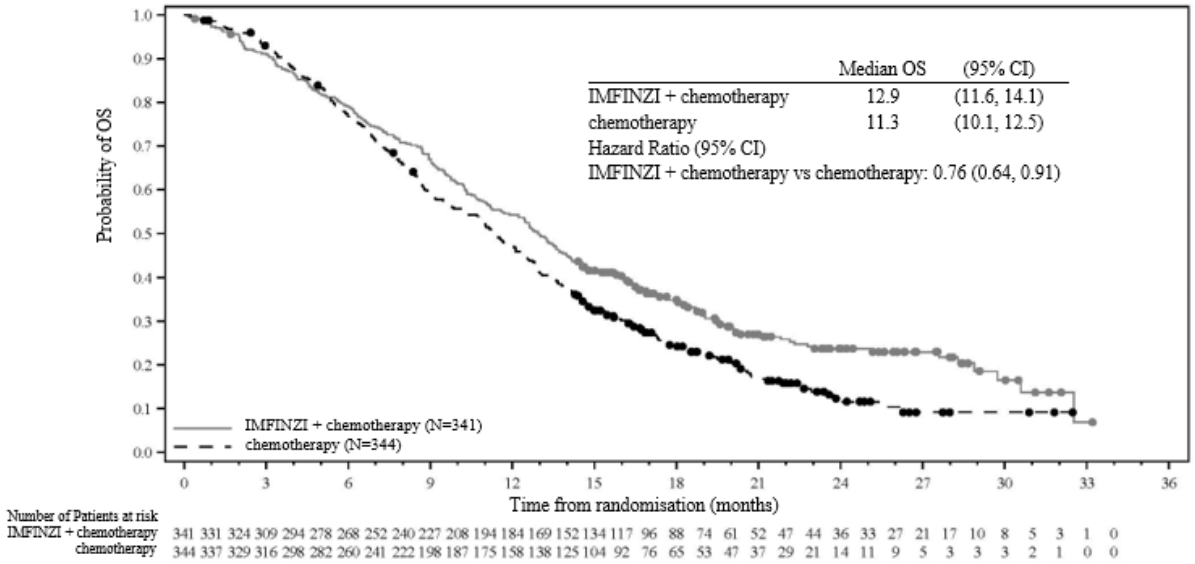
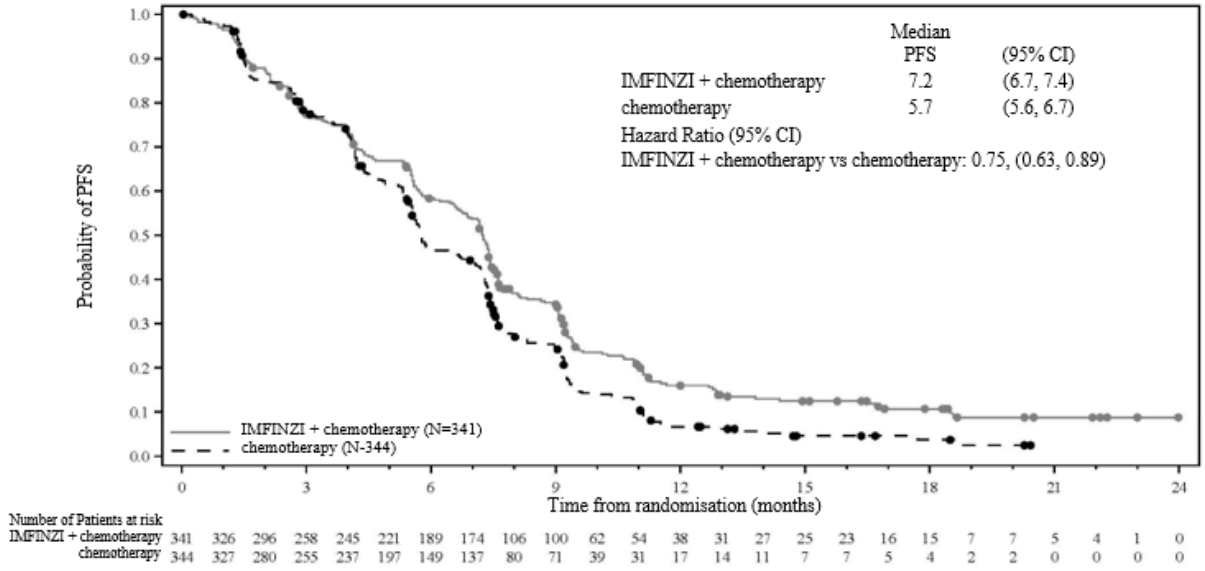


Figure 7: Kaplan-Meier curve of PFS (DCO: 11 Aug 2021)



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.

HCC - HIMALAYA Study

The efficacy of STRIDE was evaluated in the HIMALAYA study, a randomised, open-label, multicenter study in patients with confirmed uHCC who did not receive prior systemic treatment for

HCC. The study included patients with BCLC Stage C or B (not eligible for locoregional therapy) and Child-Pugh Score Class A.

The study excluded patients with co-infection of viral hepatitis B and hepatitis C; active or prior documented GI bleeding within 12 months; ascites requiring non-pharmacologic intervention within 6 months; hepatic encephalopathy within 12 months before the start of treatment; active or prior documented autoimmune or inflammatory disorders.

Patients with esophageal varices were included except those with active or prior documented GI bleeding within 12 months prior to study entry.

Randomisation was stratified by macrovascular invasion (MVI) (yes vs. no), etiology of liver disease (confirmed hepatitis B virus vs. confirmed hepatitis C virus vs. others) and ECOG performance status (0 vs. 1).

The HIMALAYA study randomized 1171 patients 1:1:1 to receive:

- IMFINZI: durvalumab 1500 mg every 4 weeks
- STRIDE: tremelimumab 300 mg as a single priming dose + IMFINZI 1500 mg; followed by IMFINZI 1500 mg every 4 weeks
- S: Sorafenib 400 mg twice daily

Treatment continued as long as clinical benefit was observed or until unacceptable toxicity. Patients in all arms could continue to receive treatment after evidence of disease progression if, in the Investigator's opinion, they were benefiting from study drug and met all inclusion and exclusion criteria for treatment beyond progression. In addition, patients in the STRIDE arm who continued treatment beyond progression were allowed to be rechallenged once with an additional single dose of tremelimumab 300 mg after cycle five of IMFINZI. Of the 182 patients enrolled to the STRIDE arm who received IMFINZI beyond progression, the median OS was 19.5 months (95% CI: 15.4, 23.4). Of the 30 patients who were enrolled to the STRIDE arm who were rechallenged with tremelimumab, the median OS was 30.4 months (95% CI: 23.4, NR).

Tumour assessments were conducted every 8 weeks for the first 12 months and then every 12 weeks thereafter. Survival assessments were conducted every month for the first 3 months following treatment discontinuation and then every 2 months.

The primary endpoint was OS for STRIDE vs. S. The key secondary objective was OS for non-inferiority based on the comparison of IMFINZI vs. S. Key secondary endpoints were Investigator assessed PFS, ORR and DoR according to RECIST v1.1. PROs were also assessed.

The demographics and baseline disease characteristics were generally representative for patients with uHCC. The baseline demographics of the overall study population were as follows: male (83.7%), age <65 years (50.4%), white (44.6%), Asian (50.7%), black or African American (1.7%), other (2.3%), ECOG PS 0 (62.6%); Child-Pugh Class score A (99.5%), macrovascular invasion (25.2%), extrahepatic spread (53.4%), viral etiology; hepatitis B (30.6%), hepatitis C (27.2%), uninfected (42.2%).

The study demonstrated a statistically significant and clinically meaningful improvement in OS with STRIDE vs. S [HR=0.78 [95% CI 0.66, 0.92]; p=0.0035]. The study also met the key secondary objective of OS non-inferiority of IMFINZI to S with the upper limit of the 95.67% CI being below the pre-specified non-inferiority margin of 1.08. See Table 11 Figure 8 and Figure 9.

Table 11. Efficacy Results for the HIMALAYA Study for STRIDE vs. S and IMFINZI vs. S

	STRIDE (n=393)	**S (n=389)**	**IMFINZI (n=389)**
Follow up duration			

Median follow up	33.2	32.2	32.6
Range	(31.7–34.5)	(30.4–33.7)	(31.6–33.7)
OS			
Number of deaths (%)	262 (66.7)	293 (75.3)	280 (72.0)
Median OS (months) (95% CI)	16.4 (14.2-19.6)	13.8 (12.3-16.1)	16.6 (14.1-19.1)
HR (95% CI)	0.78 (0.66, 0.92)		-
p-value[a]	0.0035		-
HR (95% CI)[b]	-	0.86 (0.73, 1.02)	
OS at 12 months (%) (95% CI)	60.2 (55.2 - 64.9)	56.2 (51.0 - 61.0)	59.3 (54.2-64.0)
OS at 18 months (%) (95% CI)	48.7 (43.6-53.5)	41.5 (36.5-46.4)	47.4 (42.4-52.3)
OS at 24 months (%) (95% CI)	40.5 (35.6-45.3)	32.6 (27.9-37.4)	39.6 (34.8-44.5)
OS at 36 months (%) (95% CI)	30.7 (25.8-35.7)	20.2 (15.8-25.1)	24.7 (20.0-29.8)
p-value	0.0029		0.1926
Number of patients treated beyond progression	182	192	188
PFS			
Number of events (%)	335 (85.2)	327 (84.1)	345 (88.7)
Median PFS (months) (95% CI)	3.78 (3.68-5.32)	4.07 (3.75-5.49)	3.65 (3.19-3.75)
HR (95% CI)	0.90 (0.77 - 1.05)		-
p-value[c]	0.1625		-
HR (95% CI)	-	1.02 (0.88 - 1.19)	
p-value[c]	-	0.7736	
ORR			
ORR n (%)[c,d]	79 (20.1)	20 (5.1)	66 (17.0)
Complete Response n (%)	12 (3.1)	0	6 (1.5)
Partial Response n (%)	67 (17.0)	20 (5.1)	60 (15.4)
Odds ratio 95% CI	4.69 (2.85, 8.04)		-
	-	3.8 (2.3, 6.6)	
p-value[c]	<0.0001		-
p-value[c]	-	<0.0001	
DoR[d]			
Median DoR (months)	22.3	18.4	16.9
Sample size (n)	79	20	66
% with duration ≥6 months	82.3	78.9	81.8
% with duration ≥12 months	65.8	63.2	57.8

[a] Based on a Lan-DeMets alpha spending function with O'Brien Fleming type boundary and the actual number of events observed, the boundary for declaring statistical significance for STRIDE vs. S was 0.0398 for a 4.9% overall 2-sided 4.9% (Lan◦and◦DeMets 1983).
[b] Based on stratified Cox-model. Non-inferiority margin for HR (IMFINZI vs S) is 1.08 using a 95.67% confidence interval (alpha-level adjusted based on a Lan-DeMets alpha-spending function).
[c] Nominal p-value. PFS and ORR were not included in the Multiple Testing Procedure (MTP).
[d] Confirmed complete response.
NR=Not Reached, CI=Confidence Interval

Figure 8. Kaplan-Meier curve of OS

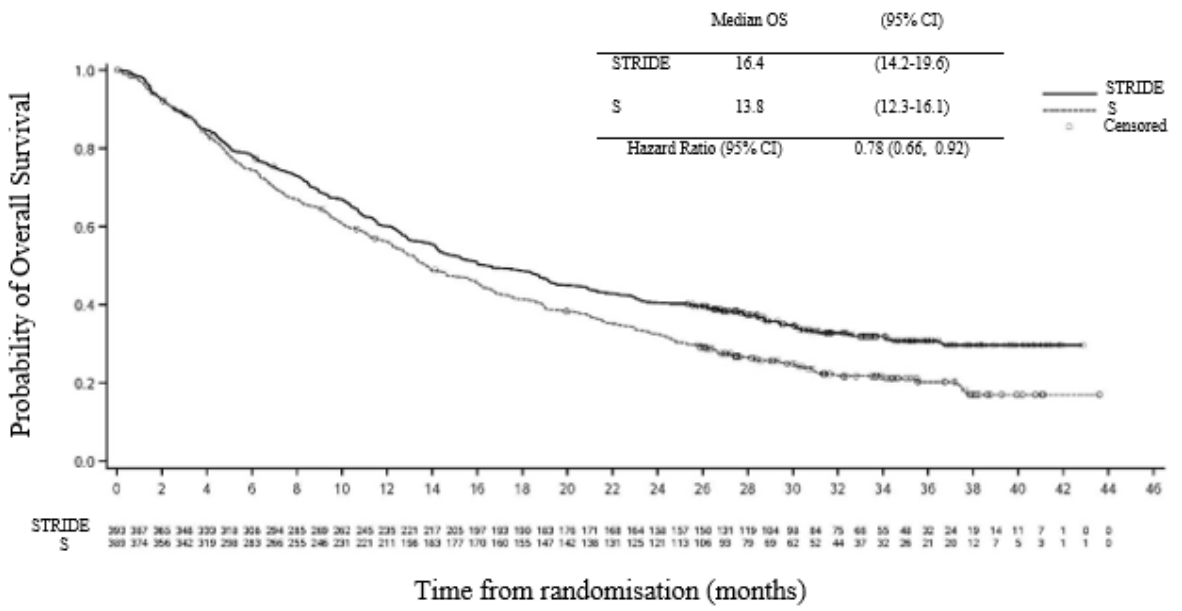
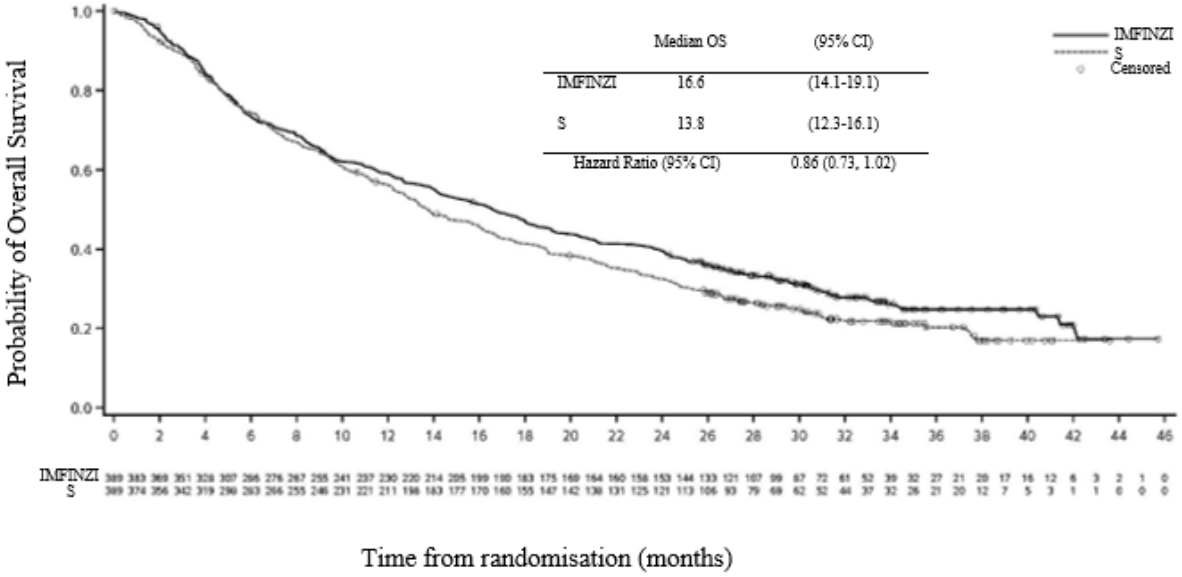


Figure 9. Kaplan-Meier curve of OS



Patient reported outcomes
Patient-reported symptoms, function and health-related quality of life (HRQoL) were collected using the EORTC QLQ-C30 and its hepatocellular carcinoma module (EORTC QLQ-HCC18). At baseline, patient-reported symptoms, functioning or HRQoL scores were comparable between the study arms.

STRIDE vs. S
<u>Delay in time to deterioration of symptoms, functioning, and global health status/QoL:</u>
STRIDE vs. S demonstrated a clinically meaningful improvement by delaying time to deterioration in a broad range of patient-reported symptoms, function, and global health status/QoL compared to S. Longer time to deterioration (median in months) was observed in the STRIDE arm compared to S for the following symptoms: Global Health Status (7.5 vs. 5.7 months, HR 0.76, p = 0.0306); physical functioning (12.9 vs. 7.4 months, HR 0.68; p = 0.0020), fatigue (7.4 vs. 5.4 months, HR 0.71; p = 0.0026), nausea (25.0 vs. 11.0 months, HR 0.65; p = 0.0033), appetite loss (12.6 vs. 6.9 months, HR 0.59; p <0.0001), abdominal pain (16.8 vs. 8.9 months, HR 0.61; p = 0.0008) and abdominal swelling (20.9 vs. 11.1 months, HR 0.74; p = 0.0431.

Change from baseline in patient-reported symptoms (mixed model for repeated measures):
STRIDE improved patient-reported HRQoL functioning and diarrhoea by demonstrating a nominal difference and clinically meaningful mean change from baseline vs. S from randomisation until 8 months (Estimated mean difference at 8 months: -18.5 95% CI: -23.24, -13.84 and p-value: <0.0001).

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

IMFINZI vs. S
Delay in time to deterioration of symptoms, functioning and GHS/QoL:
Treatment with IMFINZI demonstrated a clinically meaningful delay in time to deterioration in a broad range of patient-reported symptoms, function and GHS/QoL compared with S. Longer median time to deterioration was observed in the IMFINZI arm compared to S for the following: EORTC QLQ-C30 appetite loss (11.1 vs. 6.9 months, HR=0.60; p<0.0001), fatigue (6.9 vs. 5.4 months, HR=0.75; p=0.0162), physical functioning (14.1 vs. 7.4 months, HR=0.66; p=0.0008) and GHS/QoL domain (7.4 vs. 5.7 months, HR=0.77; p=0.0300); and EORTC QLQ-HCC18 abdominal pain (14.1 vs. 8.9 months, HR=0.67; p=0.0022).

Change from baseline in patient-reported symptoms (mixed model for repeated measures):
Treatment with IMFINZI also demonstrated fewer patient-reported symptoms, better function and improved GHS/QoL burden over time as evidenced by the change from baseline scores compared with S.

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

HCC – Study 22
The safety and efficacy of STRIDE was evaluated in Study 22, an open-label, multi-part, multicenter study in 75 immunotherapy naïve patients with uHCC who had progressed on, are intolerant to, or have refused sorafenib. The study included patients with BCLC Stage C or B (not eligible for locoregional therapy), ECOG performance status of 0 or 1 and Child-Pugh Score Class A.

The study excluded patients with co-infection of viral hepatitis B and hepatitis C; active or prior documented GI bleeding within 12 months; ascites requiring non-pharmacologic intervention within 6 months; hepatic encephalopathy within 12 months before the start of treatment; active or prior documented autoimmune or inflammatory disorders.

Treatment continued as long as clinical benefit was observed or until unacceptable toxicity. Patients who completed the assigned dosing cycles and were benefiting from study drug in the Investigator's opinion and subsequently had evidence of disease progression during the IMFINZI monotherapy phase could be rechallenged with tremelimumab 300 mg.

Tumour assessments were conducted every 8 weeks.

The primary objective was safety and tolerability. Key secondary endpoints included OS, ORR and DoR. ORR, DoR and PFS were based on Investigator assessments and BICR according to RECIST 1.1.

The baseline demographics of the study population (STRIDE) were as follows: male (86.7%); age <65 years (45.3%), white (36.0%); Asian (58.7%); black or African American (5.3%); other (0%), ECOG PS 0 (61.3%), Child-Pugh Class/Score A/5 (68.0%), Child-Pugh Class/Score A/6 (30.7%), macrovascular invasion (21.3%); extrahepatic spread (70.7%), viral etiology; hepatitis B (36.0%), hepatitis C (28.0%), uninfected (36.0%); prior systemic therapy (73.3%).

Efficacy results are shown in Table 12.

Table 12. Efficacy results for Study 22[a]

	STRIDE (n=75)	D (n=104)
ORR		
ORR n (%)[b,c]	18 (24.0)	12 (11.5)
95% CI	14.9, 35.3	6.1, 19.3
DoR[b]		
Median DoR (months) (95% CI)	18.4 (5.6, 24.0)	15.0 (8.5, NR)
% with duration ≥6 months	71.8	83.3
% with duration ≥12 months	64.6	56.3
OS		
Number of deaths (%)	49 (65.3)	78 (75.0)
Median OS (months) (95% CI)	17.05 (10.6-22.8)	12.9 (8.7-16.8)
OS at 12 months (%) (95% CI)	57.6 (45.5-68.0)	50.4 (40.3-59.7)
OS at 18 months (%) (95% CI)	47.8 (35.9-58.7)	34.0 (24.9-43.3)
OS at 24 months (%) (95% CI)	38.3 (26.9-49.6)	26.2 (17.9-35.3)

[a] DCO of Final analysis: 6 Nov 2020.
[b] Confirmed by BICR per RECIST v1.1.
[c] Confirmed complete response.
NR=Not Reached, CI=Confidence Interval

5.2 Pharmacokinetic properties

The pharmacokinetics of durvalumab as a single agent was studied in patients with solid tumors with doses ranging from 0.1 to 20 mg/kg administered once every two, three or four weeks.

The pharmacokinetics of durvalumab is similar when assessed as a single agent, in combination with chemotherapy, in combination with tremelimumab and platinum-based chemotherapy, and in combination with tremelimumab.

Absorption:
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.

Distribution:
Steady state was achieved at approximately 16 weeks. Based on population PK analysis that included patients in the dose range of 10 mg/kg Q2W, 15 mg/kg Q3W and 20 mg/kg Q4W, the geometric mean, steady state volume of distribution (Vss) was 5.64 L.

Metabolism:
The metabolic pathway of durvalumab has not been characterised. Durvalumab is expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as endogenous IgG.

Elimination:
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. The primary elimination

pathways of durvalumab are protein catabolism via reticuloendothelial system or target mediated disposition.

Special Populations
As assessed by population PK analysis, Age (19–96 years), body weight (314-149 Kg), gender, positive anti-drug antibody (ADA) status, albumin levels, LDH levels, creatinine levels, soluble PD-L1, tumor type, race, or ECOG/WHO status had no clinically significant effect on the pharmacokinetics of durvalumab.

Elderly
No dose adjustment is required for elderly patients (≥ 65 years of age). Of the 191 patients with urothelial carcinoma (primary efficacy population) treated with IMFINZI, 118 patients were 65 years or older. No overall clinically meaningful differences in safety or efficacy were reported between patients ≥ 65 years of age and younger patients.

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 metastatic NSCLC treated with IMFINZI in combination with tremelimumab and platinum-based chemotherapy, 147 (43%) 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 462 patients with uHCC treated with STRIDE, 173 (37.4%) patients were 65 years or older and 63 (13.6%) patients were 75 years or older. There were no clinically meaningful differences in safety or efficacy between patients 65 years or older 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.

Renal insufficiency
As assessed by population PK analysis, mild renal impairment (creatinine clearance (CRCL) 60 to 89 mL/min) and moderate renal impairment (creatinine clearance (CRCL) 30 to 59 mL/min) had no clinically significant effect on the pharmacokinetics of Durvalumab. The effect of severe renal impairment (CRCL 15 to 29 mL/min) on the pharmacokinetics of durvalumab is unknown.

Hepatic insufficiency
As assessed by population PK analysis, mild hepatic impairment (bilirubin ≤ ULN and AST > ULN or bilirubin >1.0 to 1.5 × ULN and any AST) had no clinically significant effect on the pharmacokinetics of Durvalumab. The effect of moderate hepatic impairment (bilirubin >1.5 to 3 x ULN and any AST) or severe hepatic impairment (bilirubin >3.0 x ULN and any AST) on the pharmacokinetics of durvalumab is unknown.

5.3 Preclinical safety data

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

Reproductive toxicology
There are no data on the potential effects of durvalumab on fertility in humans. 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 fetus, and in mouse allogeneic pregnancy models disruption of PD-L1 signalling was shown to result in an increase in fetal loss. In reproduction studies in cynomolgus monkeys, administration of durvalumab from the confirmation of pregnancy through delivery at exposure levels approximately 6 to 20 times higher than those observed at the clinical dose of 10 mg/kg of durvalumab (based on AUC) was associated with premature delivery, fetal loss (abortion and stillbirth) and an increase in neonatal deaths compared to concurrent control.

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

Histidine
Histidine hydrochloride monohydrate
Trehalose dihydrate
Polysorbate 80
Water for injections

6.2 Incompatibilities

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

6.3 Shelf life

The drug product may not be administered after the EXP date printed on the carton.

6.4 Special precautions for storage

Store in a refrigerator (2 °C – 8 °C).

Do not freeze.

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

6.5 Nature and contents of container

Two pack sizes of IMFINZI are available:

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

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

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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 daysat 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 (36°F to 46°F) or 12 hours at room temperature. 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.

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

- Visually inspect the medicinal product for particulate matter and discolouration. IMFINZI is clear to opalescent, colourless to slightly yellow solution. Discard the vial if the solution is cloudy, discoloured or visible particles are observed. Do not shake the vial.

- Withdraw the required volume from the vial(s) of IMFINZI and transfer into an IV bag containing sodium chloride 9 mg/mL (0.9%) solution for injection, or glucose 50 mg/mL (5%) solution for injection. Mix diluted solution by gentle inversion. The final concentration of the diluted solution should be between 1 mg/mL and 15 mg/mL. Do not freeze or shake the solution.

- 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 val.

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

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

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

7. MARKETING AUTHORISATION HOLDER

AstraZeneca (Thailand) Ltd., Bangkok, Thailand

8. MARKETING AUTHORISATION NUMBER(S)

1C 15041/62 (NB)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

3 May 2019

10. DATE OF REVISION OF THE TEXT

July 2023