ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

IMFINZI 50 mg/ml concentrate for solution for infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Durvalumab is produced in mammalian (Chinese hamster ovary) cells by recombinant DNA technology.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion (sterile concentrate).

Clear to opalescent, colourless to slightly yellow solution, free from visible particles. The solution has a pH of approximately 6.0 and an osmolality of approximately 400 mOsm/kg.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Non-Small Cell Lung Cancer (NSCLC)
IMFINZI as monotherapy is indicated for the treatment of locally advanced, unresectable non-small cell lung cancer (NSCLC) in adults whose tumours express PD-L1 on ≥ 1% of tumour cells and whose disease has not progressed following platinum-based chemoradiation therapy (see section 5.1).

IMFINZI in combination with tremelimumab and platinum-based chemotherapy is indicated for the first-line treatment of adults with metastatic NSCLC with no sensitising EGFR mutations or ALK positive mutations.

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

Biliary Tract Cancer (BTC)
IMFINZI in combination with gemcitabine and cisplatin is indicated for the first-line treatment of adults with unresectable or metastatic biliary tract cancer (BTC).

Hepatocellular Carcinoma (HCC)
IMFINZI as monotherapy is indicated for the first line treatment of adults with advanced or unresectable hepatocellular carcinoma (HCC).

IMFINZI in combination with tremelimumab is indicated for the first line treatment of adults with advanced or unresectable hepatocellular carcinoma (HCC).

4.2 Posology and method of administration

Treatment must be initiated and supervised by a physician experienced in the treatment of cancer.

PD-L1 testing for patients with locally advanced NSCLC
Patients with locally advanced NSCLC should be evaluated for treatment based on the tumour expression of PD-L1 confirmed by a validated test (see section 5.1).

Posology
The recommended dose for IMFINZI monotherapy and IMFINZI combination therapy is presented in Table 1. IMFINZI is administered as an intravenous infusion over 1 hour.

When IMFINZI is administered in combination with other therapeutic agents, refer to the summary of product characteristics (SmPC) of the therapeutic agents for further information.

Table 1. Recommended dose of IMFINZI monotherapy and combination therapy

Indication	Recommended IMFINZI dose	Duration of therapy
Monotherapy		
Locally Advanced NSCLC	10 mg/kg every 2 weeks or 1 500 mg every 4 weeks[a]	Until disease progression, unacceptable toxicity, or a maximum of 12 months[b]
HCC	1 500 mg every 4 weeks[a]	Until disease progression or until unacceptable toxicity
Combination therapy		
Metastatic NSCLC	During platinum chemotherapy: 1 500 mg[c] in combination with tremelimumab 75 mg[c] and platinum-based chemotherapy every 3 weeks (21 days) for 4 cycles (12 weeks) Post-platinum chemotherapy: 1 500 mg every 4 weeks as monotherapy and histology-based pemetrexed maintenance[d] therapy every 4 weeks A fifth dose of tremelimumab 75 mg[e,f] should be given at week 16 alongside IMFINZI	Until disease progression or unacceptable toxicity
ES-SCLC	1 500 mg[g] in combination with chemotherapy every 3 weeks (21 days) for 4 cycles, followed by 1 500 mg every 4 weeks as monotherapy	Until disease progression or unacceptable toxicity
BTC	1 500 mg[h] in combination with chemotherapy every 3 weeks (21 days) up to 8 cycles, followed by 1 500 mg every 4 weeks as monotherapy	Until disease progression or until unacceptable toxicity
HCC	IMFINZI 1 500 mg[j] administered in combination with 300 mg[j] tremelimumab as a single dose at Cycle 1/Day 1,	Until disease progression or unacceptable toxicity

Indication	Recommended IMFINZI dose	Duration of therapy
	followed by IMFINZI as monotherapy every 4 weeks	

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

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

[c] Metastatic NSCLC patients with a body weight of 30 kg or less must receive weight-based dosing, equivalent to IMFINZI 20 mg/kg until weight is greater than 30 kg. Patients with a body weight of 34 kg or less must receive weight based dosing equivalent to tremelimumab 1 mg/kg until weight is greater than 34 kg.

[d] Consider maintenance administration of pemetrexed for patients with non-squamous tumours who received treatment with pemetrexed and carboplatin/cisplatin during the platinum-based chemotherapy stage.

[e] In the case of dose delay(s), a fifth dose of tremelimumab can be given after Week 16, alongside IMFINZI.

[f] If patients receive fewer than 4 cycles of platinum-based chemotherapy, the remaining cycles of tremelimumab (up to a total of 5) alongside IMFINZI should be given during the post-platinum chemotherapy phase.

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

[h] BTC patients with a body weight of 36 kg or less must receive weight-based dosing of IMFINZI at 20 mg/kg. In combination with chemotherapy dose every 3 weeks (21 days), followed by 20 mg/kg every 4 weeks as monotherapy until weight increases to greater than 36 kg.

[i] HCC patients with a body weight of 30 kg or less must receive weight-based dosing, equivalent to IMFINZI 20 mg/kg until weight is greater than 30 kg. Patients with a body weight of 40 kg or less must receive weight-based dosing, equivalent to tremelimumab 4 mg/kg until weight is greater than 40 kg.

Dose escalation or reduction is not recommended. Treatment withholding or discontinuation may be required based on individual safety and tolerability, see Table 2.

Guidelines for management of immune-mediated adverse reactions are described in Table 2 (refer to section 4.4 for further management recommendations, monitoring and evaluation information).

Table 2. Treatment modifications for IMFINZI or IMFINZI in combination with tremelimumab

Adverse reactions	Severity[a]	Treatment modification
Immune-mediated pneumonitis/interstitial lung disease	Grade 2	Withhold dose
	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
	ALT or AST > 5 - ≤ 10 x ULN	Withhold IMFINZI and permanently discontinue tremelimumab (where appropriate)

Adverse reactions	**Severity**[a]	**Treatment modification**
	Concurrent ALT or AST > 3 x ULN and total bilirubin > 2 x ULN[b]	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)[c]	ALT or AST > 2.5 - ≤ 5 x BLV and ≤ 20 x ULN	Withhold dose
	ALT or AST > 5 - 7 x BLV and ≤ 20 x ULN or concurrent ALT or AST 2.5 - 5 x BLV and ≤ 20 x ULN and total bilirubin > 1.5 - < 2 x ULN[b]	Withhold IMFINZI and permanently discontinue tremelimumab (where appropriate).
	ALT or AST > 7 x BLV or > 20 ULN whichever occurs first or bilirubin > 3 X ULN	Permanently discontinue
Immune-mediated colitis or diarrhoea	Grade 2	Withhold dose
	Grade 3 for IMFINZI monotherapy	Withhold dose
	Grade 3 for IMFINZI + tremelimumab	Permanently discontinue tremelimumab[e]
	Grade 4	Permanently discontinue
Intestinal perforation[d]	Any grade	Permanently discontinue
Immune-mediated hyperthyroidism, thyroiditis	Grade 2-4	Withhold dose until clinically stable

Adverse reactions	**Severity**[a]	**Treatment modification**
Immune-mediated hypothyroidism	Grade 2-4	No changes
Immune-mediated adrenal insufficiency or hypophysitis/hypopituitarism	Grade 2-4	Withhold dose until clinically stable
Immune-mediated type 1 diabetes mellitus	Grade 2-4	No changes
Immune-mediated nephritis	Grade 2 with serum creatinine > 1.5 - 3 x (ULN or baseline)	Withhold dose
	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	Withhold dose
	Grade 3	
	Grade 4	Permanently discontinue
Immune-mediated myocarditis	Grade 2-4	Permanently discontinue
Immune-mediated myositis/polymyositis	Grade 2 or 3	Withhold dose[f]
	Grade 4	Permanently discontinue
Infusion-related reactions	Grade 1 or 2	Interrupt or slow the rate of infusion
	Grade 3 or 4	Permanently discontinue
Infection	Grade 3 or 4	Withhold dose until clinically stable
Immune-mediated myasthenia gravis	Grade 2-4	Permanently discontinue

Adverse reactions	Severity[a]	Treatment modification
Immune-mediated Myelitis transverse	Any grade	Permanently discontinue
Immune-mediated meningitis	Grade 2	Withhold dose
	Grade 3 or 4	Permanently discontinue
Immune-mediated encephalitis	Grade 2-4	Permanently discontinue
Immune-mediated Guillain-Barré syndrome	Grade 2-4	Permanently discontinue
Other immune-mediated adverse reactions[h]	Grade 2 or 3	Withhold dose
	Grade 4	Permanently discontinue
Non-immune-mediated adverse reactions	Grade 2 and 3	Withhold dose until ≤ Grade 1 or return to baseline
	Grade 4	Permanently discontinue[g]

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

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

[c] 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.

[d] Adverse drug reaction is only associated with IMFINZI in combination with tremelimumab.

[e] Permanently discontinue trememlimumab for Grade 3; however, treatment with durvalumab can be resumed once event has resolved.

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

[g] 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.

[h] Includes immune thrombocytopenia, pancreatitis, immune-mediated arthritis, uveitis and cystitis noninfective.

Based on the severity of the adverse reaction, IMFINZI and/or tremelimumab should be withheld and corticosteroids administered (refer to section 4.4). After withhold, IMFINZI and/or tremelimumab 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 and tremelimumab should be permanently discontinued for recurrent Grade 3 (severe) immune-mediated adverse reactions and for any Grade 4 (life-threatening) immune-mediated adverse reactions, except for endocrinopathies that are controlled with replacement hormones.

Special populations

Elderly

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

Renal impairment

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

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

Paediatric population
The safety and efficacy of IMFINZI in children and adolescents aged below 18 years of age has not been established with regard to NSCLC, SCLC, BTC and HCC. No data are available. Outside its authorised indications, IMFINZI in combination with tremelimumab has been studied in children aged 1 to 17 years with neuroblastoma, solid tumour and sarcoma, however the results of the study did not allow to conclude that the benefits of such use outweigh the risks. Currently available data are described in sections 5.1 and 5.2.

Method of administration
IMFINZI is for intravenous use. It is to be administered as an intravenous infusion solution over 1 hour (see section 6.6).

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

IMFINZI in combination with chemotherapy
For NSCLC, ES-SCLC and BTC, when IMFINZI is administered in combination with chemotherapy, administer IMFINZI prior to chemotherapy on the same day.

IMFINZI in combination with tremelimumab and platinum-based chemotherapy
When IMFINZI is administered in combination with tremelimumab and platinum-based chemotherapy, tremelimumab is given first, followed by IMFINZI and then platinum-based chemotherapy on the same day of dosing.

When IMFINZI is administered in combination with a fifth dose of tremelimumab and pemetrexed maintenance therapy at week 16, tremelimumab is given first, followed by IMFINZI and then pemetrexed maintenance therapy on the same day of dosing.

IMFINZI, tremelimumab, and platinum-based chemotherapy are administered as separate intravenous infusions. IMFINZI and tremelimumab are each given over 1 hour. For platinum-based chemotherapy, refer to the SmPC for administration information. For pemetrexed maintenance therapy, refer to the SmPC for administration information. Separate infusion bags and filters for each infusion should be used.

During cycle 1, tremelimumab is to be followed by IMFINZI starting approximately 1 hour (maximum 2 hours) after the end of the tremelimumab infusion. Platinum-based chemotherapy infusion should start approximately 1 hour (maximum 2 hours) after the end of the IMFINZI infusion. If there are no clinically significant concerns during cycle 1, then at the physician's discretion, subsequent cycles of IMFINZI can be given immediately after tremelimumab and the time period between the end of the IMFINZI infusion and the start of chemotherapy can be reduced to 30 minutes.

IMFINZI in combination with tremelimumab
For uHCC, when IMFINZI is administered in combination with tremelimumab, administer tremelimumab prior to IMFINZI on the same day. IMFINZI and tremelimumab are administered as separate intravenous infusions. Refer to the SmPC for tremelimumab dosing information.

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 4.2, Table 2 for recommended treatment modifications.

For suspected immune-mediated adverse reactions, adequate evaluation should be performed to confirm etiology or exclude alternate etiologies. Based on the severity of the adverse reaction, IMFINZI or IMFINZI in combination with tremelimumab should be withheld or permanently discontinued. Treatment with corticosteroids or endocrine therapy should be initiated. For events requiring corticosteroid therapy, and upon improvement to ≤ Grade 1, corticosteroid taper should be initiated and continued over at least 1 month. Consider increasing dose of corticosteroids and/or using additional systemic immunosuppressants if there is worsening or no improvement.

Traceability
In order to improve the traceability of biological medicinal products, the tradename and the batch number of the administered product should be clearly recorded.

Immune-mediated pneumonitis
Immune-mediated pneumonitis or interstitial lung disease, defined as requiring use of systemic corticosteroids and with no clear alternate aetiology, occurred in patients receiving IMFINZI or IMFINZI in combination with tremelimumab (see section 4.8). For Grade 2 events, an initial dose of 1-2 mg/kg/day prednisone or equivalent should be initiated followed by a taper. For Grade 3 or 4 events, an initial dose of 2-4 mg/kg/day methylprednisolone or equivalent should be initiated followed by a taper.

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 at least 2 cycles of concurrent chemoradiation within 1 to 42 days prior to initiation of the study, pneumonitis or radiation pneumonitis occurred in 161 (33.9%) patients in the IMFINZI-treated group and 58 (24.8%) in the placebo group, including Grade 3 (3.4% vs. 3.0%) and Grade 5 (1.1% vs. 1.7%).

Patients should be monitored for signs and symptoms of pneumonitis or radiation 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.

Immune-mediated hepatitis
Immune-mediated hepatitis, defined as requiring use of systemic corticosteroids and with no clear alternate aetiology, occurred in patients receiving IMFINZI or IMFINZI in combination with tremelimumab (see section 4.8). Monitor alanine aminotransferase, aspartate aminotransferase, total bilirubin, and alkaline phosphatase levels prior to initiation of treatment and prior to each subsequent infusion. Additional monitoring is to be considered based on clinical evaluation. Immune-mediated hepatitis should be managed as recommended in section 4.2. Corticosteroids should be administered with an initial dose of 1-2 mg/kg/day prednisone or equivalent followed by taper for all grades.

Immune-mediated colitis
Immune-mediated colitis or diarrhoea, defined as requiring use of systemic corticosteroids and with no clear alternate aetiology, occurred in patients receiving IMFINZI or IMFINZI in combination with tremelimumab (see section 4.8). Adverse drug reactions of intestinal perforation and large intestine perforation were reported in patients receiving IMFINZI in combination with tremelimumab. Patients should be monitored for signs and symptoms of colitis/diarrhoea and intestinal perforation and managed as recommended in section 4.2. Corticosteroids should be administered at an initial dose of 1-2 mg/kg/day prednisone or equivalent followed by a taper for Grades 2-4. Consult a surgeon immediately if intestinal perforation of ANY grade is suspected.

Immune-mediated endocrinopathies
Immune-mediated hypothyroidism, hyperthyroidism and thyroiditis

Immune-mediated hypothyroidism, hyperthyroidism and thyroiditis occurred in patients receiving IMFINZI or IMFINZI in combination with tremelimumab, and hypothyroidism may follow hyperthyroidism (see section 4.8). Patients should be monitored for abnormal thyroid function tests prior to and periodically during treatment and as indicated based on clinical evaluation. Immune-mediated hypothyroidism, hyperthyroidism, and thyroiditis should be managed as recommended in section 4.2. For immune-mediated hypothyroidism, initiate thyroid hormone replacement as clinically indicated for Grades 2-4. For immune-mediated hyperthyroidism/thyroiditis, symptomatic management can be implemented for Grades 2-4.

Immune-mediated adrenal insufficiency
Immune-mediated adrenal insufficiency occurred in patients receiving IMFINZI or IMFINZI in combination with tremelimumab (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. Corticosteroids should be administered with an initial dose of 1-2 mg/kg/day prednisone or equivalent followed by taper and a hormone replacement as clinically indicated for Grades 2-4.

Immune-mediated type 1 diabetes mellitus
Immune-mediated type 1 diabetes mellitus, which can first present as diabetic ketoacidosis that can be fatal if not detected early, occurred in patients receiving IMFINZI or IMFINZI in combination with tremelimumab (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. Treatment with insulin can be initiated as clinically indicated for Grades 2-4.

Immune-mediated hypophysitis/hypopituitarism
Immune-mediated hypophysitis or hypopituitarism occurred in patients receiving IMFINZI or IMFINZI in combination with tremelimumab (see section 4.8). Patients should be monitored for clinical signs and symptoms of hypophysitis or hypopituitarism. For symptomatic hypophysitis or hypopituitarism, patients should be managed as recommended in section 4.2. Corticosteroids should be administered with an initial dose of 1-2 mg/kg/day prednisone or equivalent followed by taper and a hormone replacement as clinically indicated for Grades 2-4.

Immune-mediated nephritis
Immune-mediated nephritis, defined as requiring use of systemic corticosteroids and with no clear alternate aetiology, occurred in patients receiving IMFINZI or IMFINZI in combination with tremelimumab (see section 4.8). Patients should be monitored for abnormal renal function tests prior to and periodically during treatment with IMFINZI or IMFINZI in combination with tremelimumab and managed as recommended in section 4.2. Corticosteroids should be administered with an initial dose of 1-2 mg/kg/day prednisone or equivalent followed by taper for Grades 2-4.

Immune-mediated rash
Immune-mediated rash or dermatitis (including pemphigoid), defined as requiring use of systemic corticosteroids and with no clear alternate aetiology, occurred in patients receiving IMFINZI or IMFINZI in combination with tremelimumab (see section 4.8). Events of Stevens-Johnson Syndrome or toxic epidermal necrolysis have been reported in patients treated with PD-1 inhibitors. Patients should be monitored for signs and symptoms of rash or dermatitis and managed as recommended in section 4.2. Corticosteroids should be administered with an initial dose of 1-2 mg/kg/day prednisone or equivalent followed by taper for Grade 2 > 1 week or Grade 3 and 4.

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. Corticosteroids should be administered with an initial dose of 2-4 mg/kg/day prednisone or equivalent

followed by taper for Grades 2-4. 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.

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

Other immune-mediated adverse reactions
Given the mechanism of action of IMFINZI or IMFINZI in combination with tremelimumab, other potential immune-mediated adverse reactions may occur. The following immune-related adverse reactions have been observed in patients treated with IMFINZI monotherapy or IMFINZI in combination with tremelimumab: myasthenia gravis, myelitis transverse, myositis, polymyositis, meningitis, encephalitis, Guillain-Barré syndrome, immune thrombocytopenia, immune-mediated arthritis, uveitis and cystitis noninfective (see section 4.8). Patients should be monitored for signs and symptoms and managed as recommended in section 4.2. Corticosteroids should be administered with an initial dose of 1-2 mg/kg/day prednisone or equivalent followed by taper for Grades 2-4.

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). Infusion-related reactions should be managed as recommended in section 4.2. For Grade 1 or 2 severity, may consider pre-medications for prophylaxis of subsequent infusion reactions. For Grade 3 or 4, manage severe infusion-related reactions per insititutional standard, appropriate clinical practice guidelines and/or society guidelines.

Patients with pre-existing autoimmune disease
In patients with pre-existing autoimmune disease (AID), data from observational studies suggest an increased risk of immune-related adverse reactions following immune-checkpoint inhibitor therapy as compared with patients without pre-existing AID. In addition, flares of the underlying AID were frequent, but the majority were mild and manageable

Disease-specific precaution (BTC)
Cholangitis and biliary tract infections
Cholangitis and biliary tract infections are not uncommon in patients with advanced BTC. Cholangitis events were reported in TOPAZ-1 in both treatment groups (14.5% [IMFINZI + chemotherapy] vs. 8.2% [placebo + chemotherapy]); these were mostly in association with biliary stents and were not immune-mediated in aetiology. Patients with BTC (especially those with biliary stents) should be closely monitored for development of cholangitis or biliary tract infections before initiation of treatment and, regularly, thereafter.

Metastatic NSCLC
Limited data are available in elderly patients (≥ 75 years) treated with IMFINZI in combination with tremelimumab and platinum-based chemotherapy (see sections 4.8 and 5.1). Careful consideration of the potential benefit/risk of this regimen on an individual basis is recommended.

Patients excluded from clinical studies
Patients with the following were excluded from clinical studies: a baseline ECOG performance score ≥ 2; active or prior documented autoimmune disease within 2 years of initiation of the study; a history of immunodeficiency; a history of severe immune-mediated adverse reactions; medical conditions that required systemic immunosuppression, except physiological dose of systemic corticosteroids (≤ 10 mg/day prednisone or equivalent); uncontrolled intercurrent illnesses; active tuberculosis or hepatitis B or C or HIV infection or patients receiving live attenuated vaccine within 30 days before or

after the start of IMFINZI. In the absence of data, durvalumab should be used with caution in these populations after careful consideration of the potential benefit/risk on an individual basis.
The safety of concurrent prophylactic cranial irradiation (PCI) with IMFINZI in patients with ES-SCLC is unknown.

For more information on exclusion criteria for each specific study see section 5.1.

4.5 Interaction with other medicinal products and other forms of interaction

The use of systemic corticosteroids or immunosuppressants before starting durvalumab, except physiological dose of systemic corticosteroids (≤ 10 mg/day prednisone or equivalent), is not recommended because of their potential interference with the pharmacodynamic activity and efficacy of durvalumab. However, systemic corticosteroids or other immunosuppressants can be used after starting durvalumab to treat immune-related adverse reactions (see section 4.4).

No formal pharmacokinetic (PK) drug-drug interaction studies have been conducted with durvalumab. Since the primary elimination pathways of durvalumab are protein catabolism via reticuloendothelial system or target-mediated disposition, no metabolic drug-drug interactions are expected. PK drug-drug interaction between durvalumab and chemotherapy was assessed in the CASPIAN study and showed concomitant treatment with durvalumab did not impact the PK of etoposide, carboplatin or cisplatin. Additionally, based on population PK analysis, concomitant chemotherapy treatment did not meaningfully impact the PK of durvalumab. PK drug-drug interactions between durvalumab in combination with tremelimumab and platinum-based chemotherapy were assessed in the POSEIDON study and showed no clinically meaningful PK interactions between tremelimumab, durvalumab, nab-paclitaxel, gemcitabine, pemetrexed, carboplatin or cisplatin in the concomitant treatment.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception
Women of childbearing potential should use effective contraception during treatment with durvalumab and for at least 3 months after the last dose of durvalumab.

Pregnancy
There are no data on the use of durvalumab in pregnant women. Based on its mechanism of action, durvalumab has the potential to impact maintenance of pregnancy, and in a mouse allogeneic pregnancy model, disruption of PD-L1 signaling was shown to result in an increase in foetal loss. Animal studies with durvalumab are not indicative of reproductive toxicity (see section 5.3). Human IgG1 is known to cross the placental barrier and placental transfer of durvalumab was confirmed in animal studies. Durvalumab may cause foetal harm when administered to a pregnant woman and is not recommended during pregnancy and in women of childbearing potential not using effective contraception during treatment and for at least 3 months after the last dose.

Breast-feeding
It is unknown whether durvalumab is secreted in human breast milk. Available toxicological data in cynomolgus monkeys have shown low levels of durvalumab in breast milk on day 28 after birth (see section 5.3). In humans, antibodies may be transferred to breast milk, but the potential for absorption and harm to the newborn is unknown. However, a potential risk to the breast-fed child cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue or abstain from durvalumab therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility
There are no data on the potential effects of durvalumab on fertility in humans or animals.

4.7 Effects on ability to drive and use machines

Durvalumab has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

IMFINZI as monotherapy

The safety of IMFINZI as monotherapy is based on pooled data in 4 045 patients across multiple tumour types. IMFINZI was administered at a dose of 10 mg/kg every 2 weeks, 20 mg/kg every 4 weeks or 1 500 mg every 4 weeks. The most common (> 10%) adverse reactions were cough/productive cough (18.7%), diarrhoea (16.1%), rash (15.5%), arthralgia (13.8%), pyrexia (13.0%), abdominal pain (13.0%), upper respiratory tract infections (12.1%), pruritus (11.4%), and hypothyroidism (10.9%). The most common (> 2%) NCI CTCAE Grade ≥ 3 adverse reactions were pneumonia (3.6%) and aspartate aminotransferase increased/alanine aminotransferase increased (2.9%).

IMFINZI was discontinued due to adverse reactions in 3.7% of patients. The most common adverse reaction leading to treatment discontinuation was pneumonitis (0.9%) and pneumonia (0.7%).

IMFINZI was delayed or interrupted due to adverse reactions in 13.0% of patients. The most common adverse reactions leading to dose delay or interruption were pneumonia (2.2%) and aspartate aminotransferase increased/alanine aminotransferase increased (2.2%).

The safety of IMFINZI as monotherapy in patients treated for HCC is based on data in 492 patients and was consistent with the overall safety profile in the IMFINZI monotherapy pool (N = 4 045). The most common (> 10%) adverse reactions were AST increased/ALT increased (20.3%), abdominal pain (17.9%), diarrhoea (15.9%), pruritus (15.4%), and rash (15.2%). The most common (> 2%) Grade ≥ 3 adverse reactions were AST increased/ALT increased (8.1%) and abdominal pain (2.2%).

IMFINZI was discontinued due to adverse reactions in 3.7% of patients. The most common adverse reactions leading to treatment discontinuation were AST increased/ALT increased (0.8%) and hepatitis (0.6%).

IMFINZI was delayed or interrupted due to adverse reactions in 11.6% of patients. The most common adverse reaction leading to dose delay or interruption was AST increased/ALT increased (5.9%).

IMFINZI in combination with chemotherapy

The safety of IMFINZI in combination with chemotherapy is based on pooled data in 603 patients from 2 studies (TOPAZ-1 and CASPIAN). The most common (> 10%) adverse reactions were neutropenia (53.1%), anaemia (43.9%), nausea (37.5%), fatigue (36.8%), thrombocytopenia (28.0%), constipation (25.4%), decreased appetite (22.6%), abdominal pain (18.4%), alopecia (18.4%), leukopenia (17.2%), vomiting (16.9%), pyrexia (15.1%), rash (14.8%), diarrhoea (13.8%), aspartate aminotransferase increased or alanine aminotransferase increased (10.9%), cough/productive cough (10.8%), and pruritus (10.4%).The most common (> 2%) NCI CTCAE Grade ≥ 3 adverse reactions were neutropenia (35.2%), anaemia (17.4%), thrombocytopenia (11.1%), leukopenia (7.1%), fatigue (5.0%), febrile neutropenia (3.0%), aspartate aminotransferase increased or alanine aminotransferase increased (2.8%) and pneumonia (2.5%).

IMFINZI was discontinued due to adverse reactions in 2.0% of patients. The most common adverse reaction leading to treatment discontinuation was fatigue (0.3%).

IMFINZI was delayed or interrupted due to adverse reactions in 29.2% of patients. The most common adverse reactions leading to dose delay or interruption were neutropenia (17.1%), anaemia (3.8%), thrombocytopenia (4.3%), leukopenia (3.5%), fatigue (1.7%) and pyrexia (1.3).

IMFINZI in combination with tremelimumab 75 mg and platinum-based chemotherapy

The safety of IMFINZI given in combination with tremelimumab 75 mg and chemotherapy is based on data in 330 patients with metastatic NSCLC. The most common (> 20%) adverse reactions were anaemia (49.7%), nausea (41.5%), neutropenia (41.2%), fatigue (36.1%), rash (25.8%), thrombocytopenia (24.5%) and diarrhoea (21.5%). The most common (> 2%) NCI CTCAE Grade ≥ 3 adverse reactions were neutropenia (23.9%), anaemia (20.6%), pneumonia (9.4%), thrombocytopenia (8.2%), leukopenia (5.5%), fatigue (5.2%), lipase increased (3.9%), amylase increased (3.6%), febrile neutropenia (2.4%), colitis (2.1%) and aspartate aminotransferase increased/alanine aminotransferase increased (2.1%).

IMFINZI was discontinued due to adverse reactions in 8.5% of patients. The most common adverse reactions leading to treatment discontinuation were pneumonia (2.1%) and colitis (1.2%).

IMFINZI was interrupted due to adverse reactions in 49.4% of patients. The most common adverse reactions leading to dose interruption were neutropenia (16.1%), anaemia (10.3%), thrombocytopenia (7.3%), leukopenia (5.8%), pneumonia (5.2%), aspartate aminotransferase increased/alanine aminotransferase increased (4.8%), colitis (3.3%) and pneumonitis (3.3%).

IMFINZI in combination with tremelimumab 300 mg

The safety of IMFINZI given in combination with a single dose of tremelimumab 300 mg is based on pooled data (HCC pool) in 462 HCC patients from the HIMALAYA Study and another study in HCC patients, Study 22. The most common (> 10%) adverse reactions were rash (32.5%), pruritus (25.5%), diarrhoea (25.3%), abdominal pain (19.7%), aspartate aminotransferase increased/alanine aminotransferase increased (18.0%), pyrexia (13.9%), hypothyroidism (13.0%), cough/productive cough (10.8%), oedema peripheral (10.4%) and lipase increased (10.0%) (see Table 4). The most common severe adverse reactions (NCI CTCAE Grade ≥ 3) were aspartate aminotransferase increased/alanine aminotransferase increased (8.9%), lipase increased (7.1%), amylase increased (4.3%) and diarrhoea (3.9%).

The most common serious adverse reactions were colitis (2.6%), diarrhoea (2.4%), pneumonia (2.2%), and hepatitis (1.7%).

The frequency of treatment discontinuation due to adverse reactions was 6.5%. The most common adverse reactions leading to treatment discontinuation were hepatitis (1.5%) and aspartate aminotransferase increased/alanine aminotransferase increased (1.3%).

The severity of adverse drug reactions was assessed based on the CTCAE, defining grade 1=mild, grade 2=moderate, grade 3=severe, grade 4=life threatening and grade 5=death.

Tabulated list of adverse reactions

Table 3 lists the incidence of adverse reactions in the IMFINZI monotherapy pooled safety dataset (N=4 045) and in patients treated with IMFINZI in combination with chemotherapy (N=603). Unless otherwise stated, Table 4 lists the incidence of adverse reactions in patients treated with IMFINZI in combination with tremelimumab 75 mg and platinum-based chemotherapy in the POSEIDON study (N=330) and in patients treated with IMFINZI in combination with a single dose of tremelimumab 300 mg in the HCC pool (N=462). Adverse reactions are listed according to system organ class in MedDRA. Within each system organ class, the adverse reactions are presented in decreasing frequency. The corresponding frequency category for each ADR is defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1 000 to < 1/100); rare (≥ 1/10 000 to < 1/1 000); very rare (< 1/10 000); not known (cannot be estimated from available data). Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness.

Table 3. Adverse drug reactions in patients treated with IMFINZI

	IMFINZI as monotherapy	**IMFINZI in combination with chemotherapy**
Infections and infestations		
Very common	Upper respiratory tract infections[a]	
Common	Pneumonia[b,c], Influenza, Oral candidiasis, Dental and oral soft tissue infections[d]	Pneumonia[b,c], Upper respiratory tract infections[a]
Uncommon		Oral candidiasis, Influenza, Dental and oral soft tissue infections[d]
Blood and lymphatic system disorders		
Very Common		Anaemia, Leukopenia[e], Neutropenia[f], Thrombocytopenia[g]
Common		Febrile neutropenia, Pancytopenia[c]
Rare	Immune thrombocytopenia[c]	
Endocrine disorders		
Very common	Hypothyroidism[h]	
Common	Hyperthyroidism[i]	Adrenal insufficiency, Hyperthyroidism[i], Hypothyroidism[h]
Uncommon	Thyroiditis[j], Adrenal insufficiency	Thyroiditis[j], Type 1 diabetes mellitus
Rare	Type 1 diabetes mellitus, Hypophysitis/Hypopituitarism, Diabetes insipidus	
Eye disorders		
Rare	Uveitis	Uveitis
Metabolism and nutrition disorders		
Very common		Decreased appetite
Nervous System Disorders		
Common		Neuropathy peripheral[k]
Rare	Myasthenia gravis, Meningitis[l]	
Not known	Noninfective encephalitis[m], Guillain-Barré syndrome, Myelitis transverse[n]	
Cardiac disorders		
Uncommon	Myocarditis	
Respiratory, thoracic and mediastinal disorders		
Very common	Cough/Productive Cough	Cough/Productive Cough
Common	Pneumonitis[c], Dysphonia	Pneumonitis
Uncommon	Interstitial lung disease	Interstitial lung disease, Dysphonia
Gastrointestinal disorders		
Very common	Diarrhoea, Abdominal pain[o]	Diarrhoea, Abdominal pain[o], Constipation, Nausea, Vomiting
Common		Stomatitis[p]
Uncommon	Colitis[q], Pancreatitis[r]	Colitis[q], Pancreatitis[r]
Hepatobiliary disorders		
Very common		Aspartate aminotransferase increased or Alanine aminotransferase increased[s]
Common	Hepatitis[c,t], Aspartate aminotransferase increased or Alanine aminotransferase increased[c,s]	Hepatitis[c,t]
Skin and subcutaneous tissue disorders		
Very common	Rash[u], Pruritus	Rash[u], Alopecia, Pruritus
Common	Night sweats	Dermatitis

	IMFINZI as monotherapy	IMFINZI in combination with chemotherapy
Uncommon	Dermatitis, Psoriasis, Pemphigoid[v]	Pemphigoid[v], Night sweats, Psoriasis
Musculoskeletal and connective tissue disorders		
Very common	Arthralgia	
Common	Myalgia	Myalgia, Arthralgia
Uncommon	Myositis	Immune-mediated arthritis
Rare	Polymyositis[w], Immune-mediated arthritis	
Renal and urinary disorders		
Common	Blood creatinine increased, Dysuria	Blood creatinine increased, Dysuria
Uncommon	Nephritis[x]	
Rare	Cystitis noninfective	
General disorders and administration site conditions		
Very common	Pyrexia	Pyrexia, Fatigue[y]
Common	Peripheral oedema[z]	Peripheral oedema[z]
Injury, poisoning and procedural complications		
Common	Infusion-related reaction[aa]	Infusion-related reaction[aa]

Adverse reaction frequencies may not be fully attributed to durvalumab alone but may contain contributions from the underlying disease or from other medicinal products used in a combination.

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

[b] includes pneumocystis jirovecii pneumonia, pneumonia, pneumonia adenoviral, pneumonia bacterial, pneumonia cytomegaloviral, pneumonia haemophilus, pneumonia pneumococcal, pneumonia streptococcal, candida pneumonia and pneumonia legionella.

[c] including fatal outcome.

[d] includes gingivitis, oral infection, periodontitis, pulpitis dental, tooth abscess and tooth infection.

[e] includes leukopenia and white blood cell count decreased.

[f] includes neutropenia and neutrophil count decreased.

[g] includes thrombocytopenia and platelet count decreased.

[h] includes autoimmune hypothyroidism, hypothyroidism, immune-mediated hypothyroidism, blood thyroid stimulating hormone increased.

[i] includes hyperthyroidism, Basedow's disease, immune-mediated hyperthyroidism and blood thyroid stimulating hormone decreased.

[j] includes autoimmune thyroiditis, immune-mediated thyroiditis, thyroiditis, and thyroiditis subacute.

[k] includes neuropathy peripheral, paraesthesia and peripheral sensory neuropathy.

[l] includes meningitis and noninfective meningitis.

[m] reported frequency from ongoing AstraZeneca-sponsored clinical studies outside of the pooled dataset is rare and includes fatal outcome.

[n] events were reported from post-marketing data.

[o] includes abdominal pain, abdominal pain lower, abdominal pain upper and flank pain.

[p] includes stomatitis and mucosal inflammation.

[q] includes colitis, enteritis, enterocolitis, and proctitis.

[r] includes pancreatitis and pancreatitis acute.

[s] includes alanine aminotransferase increased, aspartate aminotransferase increased, hepatic enzyme increased and transaminases increased.

[t] includes hepatitis, autoimmune hepatitis, hepatitis toxic, hepatocellular injury, hepatitis acute, hepatotoxicity and immune-mediated hepatitis.

[u] includes rash erythematous, rash macular, rash maculopapular, rash papular, rash pruritic, rash pustular, erythema, eczema and rash.

[v] includes pemphigoid, dermatitis bullous and pemphigus. Reported frequency from completed and ongoing studies is uncommon.

[w] polymyositis (fatal) was observed in a patient treated with IMFINZI from an ongoing sponsored clinical study outside of the pooled dataset.

[x] includes autoimmune nephritis, tubulointerstitial nephritis, nephritis, glomerulonephritis and glomerulonephritis membranous.

[y] includes fatigue and asthenia.

[z] includes oedema peripheral and peripheral swelling.

[aa] includes infusion-related reaction and urticaria with onset on the day of dosing or 1 day after dosing.

Table 4. Adverse drug reactions in patients treated with IMFINZI in combination with tremelimumab

	IMFINZI in combination with tremelimumab 75 mg and platinum-based chemotherapy	**IMFINZI in combination with tremelimumab 300 mg**
Infections and infestations		
Very common	Upper respiratory tract infections[a], Pneumonia[b]	
Common	Influenza, Oral candidiasis	Upper respiratory tract infections[a], Pneumonia[b], Influenza, Dental and oral soft tissue infections[c]
Uncommon	Dental and oral soft tissue infections[c]	Oral candidiasis
Blood and lymphatic system disorders		
Very Common	Anaemia[d], Neutropenia[d,e], Thrombocytopenia[d,f], Leukopenia[d,g]	
Common	Febrile neutropenia[d], Pancytopenia[d]	
Uncommon	Immune thrombocytopenia	
Not known		Immune thrombocytopenia[h]
Endocrine disorders		
Very common	Hypothyroidism[i]	Hypothyroidism[i]
Common	Hyperthyroidism[j], Adrenal insufficiency, Hypopituitarism/ Hypophysitis, Thyroiditis[k]	Hyperthyroidism[j], Thyroiditis[k], Adrenal insufficiency
Uncommon	Diabetes insipidus, Type 1 diabetes mellitus	Hypopituitarism/Hypophysitis
Not known		Diabetes insipidus[h], Type 1 diabetes mellitus[h]
Eye disorders		
Uncommon	Uveitis	
Rare		Uveitis[h]
Metabolism and nutrition disorders		
Very common	Decreased appetite[d]	
Nervous system disorders		
Common	Neuropathy peripheral[d,l]	
Uncommon	Encephalitis[m],	Myasthenia gravis, Meningitis
Not known	Myasthenia gravis[n], Guillain-Barre syndrome[n], Meningitis[n]	Guillain-Barré syndrome[h], Encephalitis[h]
Cardiac disorders		
Uncommon	Myocarditis[o]	Myocarditis
Respiratory, thoracic, and mediastinal disorders		
Very common	Cough/Productive Cough	Cough/Productive cough
Common	Pneumonitis[p], Dysphonia	Pneumonitis[p]
Uncommon	Interstitial lung disease	Dysphonia, Intersitial lung disease
Gastrointestinal disorders		
Very common	Nausea[d], Diarrhoea, Constipation[d], Vomiting[d]	Diarrhoea, Abdominal pain[q]

	IMFINZI in combination with tremelimumab 75 mg and platinum-based chemotherapy	IMFINZI in combination with tremelimumab 300 mg
Common	Stomatitis[d,r], Amylase increased, Abdominal pain[q], Lipase increased, Colitis[s], Pancreatitis[t]	Lipase increased, Amylase increased, Colitis[s], Pancreatitis[t],
Not known	Intestinal perforation[n], Large intestine perforation[n]	Intestinal perforation[h], Large intestinal perforation[h]
Hepatobiliary disorders		
Very common	Aspartate aminotransferase increased/Alanine aminotransferase increased[u]	Aspartate aminotransferase increased/Alanine aminotransferase increased[u]
Common	Hepatitis[v]	Hepatitis[v]
Skin and subcutaneous tissue disorders		
Very common	Alopecia[d], Rash[w], Pruritus	Rash[w], Pruritus
Common		Dermatitis[x], Night sweats,
Uncommon	Dermatitis, Night sweats, Pemphigoid	Pemphigoid
Musculoskeletal and connective tissue disorders		
Very common	Arthralgia	
Common	Myalgia	Myalgia
Uncommon	Myositis, Polymyositis, Immune-mediated arthritis[n]	Myositis, Polymyositis, Immune-mediated arthritis
Renal and urinary disorders		
Common	Blood creatinine increased, Dysuria	Blood creatinine increased, Dysuria
Uncommon	Nephritis, Cystitis noninfective	Nephritis[y]
Not known		Cystitis noninfective[h]
General disorders and administration site conditions		
Very common	Fatigue[d], Pyrexia	Pyrexia, Oedema peripheral[z]
Common	Oedema peripheral[z]	
Injury, poisoning and procedural complications		
Common	Infusion-related reaction[aa]	Infusion-related reaction[aa]

[a] Includes laryngitis, nasopharyngitis, pharyngitis, rhinitis, sinusitis, tonsillitis, tracheobronchitis and upper respiratory tract infection.

[b] Includes pneumocystis jirovecii pneumonia, pneumonia and pneumonia bacterial.

[c] Includes periodontitis, pulpitis dental, tooth abscess and tooth infection.

[d] Adverse reaction only applies to chemotherapy ADRs in the Poseidon study.

[e] Includes neutropenia and neutrophil count decreased.

[f] Includes platelet count decreased and thrombocytopenia.

[g] Includes leukopenia and white blood cell count decreased.

[h] Adverse reaction was not observed in the HCC pool, but was reported in patients treated with IMFINZI or IMFINZI+tremelimumab in AstraZeneca-sponsored clinical studies.

[i] Includes blood thyroid stimulating hormone increased, hypothyroidism and immune-mediated hypothyroidism.

[j] Includes blood thyroid stimulating hormone decreased and hyperthyroidism.

[k] Includes autoimmune thyroiditis, immune-mediated thyroiditis, thyroiditis and thyroiditis subacute.

[l] Includes neuropathy peripheral, parasthesia and peripheral sensory neuropathy.

[m] Includes encephalitis and encephalitis autoimmune.

[n] Adverse reaction was not observed in the POSEIDON study but was reported in patients treated with IMFINZI or IMFINZI+tremelimumab in clinical studies outside of the POSEIDON dataset.

[o] Includes autoimmune myocarditis.

[p] Includes immune-mediated pneumonitis and pneumonitis.

[q] Includes abdominal pain, abdominal pain lower, abdominal pain upper and flank pain.

[r] Includes mucosal inflammation and stomatitis.

[s] Includes colitis, enteritis and enterocolitis.

[t] Includes autoimmune pancreatitis, pancreatitis and pancreatitis acute.
[u] Includes alanine aminotransferase increased, aspartate aminotransferase increased, hepatic enzyme increased and transaminases increased.
[v] Includes autoimmune hepatitis, hepatitis, hepatocellular injury, hepatotoxicity, hepatitis acute and immune-mediated hepatitis.
[w] Includes eczema, erythema, rash, rash macular, rash maculopapular, rash papular, rash pruritic and rash pustular.
[x] Includes dermatitis and immune-mediated dermatitis.
[y] Includes autoimmune nephritis and immune-mediated nephritis.
[z] Includes oedema peripheral and peripheral swelling.
[aa] Includes infusion-related reaction and urticaria.

Description of selected adverse reactions

IMFINZI is associated with immune-mediated adverse reactions. Most of these, including severe reactions, resolved following initiation of appropriate medical therapy and/or treatment modifications. The data for the following immune-mediated adverse reactions reflect the IMFINZI monotherapy combined safety database of 4 045 patients which includes the PACIFIC Study and additional studies in patients with various solid tumours, in indications for which durvalumab is not approved. Across all studies, IMFINZI was administered at a dose of 10 mg/kg every 2 weeks, 20 mg/kg every 4 weeks or 1 500 mg every 3 or 4 weeks. Details for the significant adverse reactions for IMFINZI when given in combination with chemotherapy are presented if clinically relevant differences were noted in comparison to IMFINZI monotherapy.

The data for the following immune-mediated adverse reactions are also based on 2 280 patients who received IMFINZI 20 mg/kg every 4 weeks in combination with tremelimumab 1 mg/kg or IMFINZI 1 500 mg in combination with tremelimumab 75 mg every 4 weeks. Details for the significant adverse reactions for IMFINZI when given in combination with tremelimumab and platinum-based chemotherapy are presented if clinically relevant differences were noted in comparison to IMFINZI in combination with tremelimumab.

The data for the following immune-mediated adverse reactions also reflect the IMFINZI in combination with tremelimumab 300 mg combined safety database of 462 patients with HCC (the HCC pool). In these two studies, IMFINZI was administered at a dose of 1 500 mg in combination with tremelimumab 300 mg every 4 weeks.

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

Immune-mediated pneumonitis

In the combined safety database with IMFINZI monotherapy, (n=4 045 multiple tumour types), immune-mediated pneumonitis occurred in 103 (2.5%) patients, including Grade 3 in 27 (0.7%) patients, Grade 4 in 2 (< 0.1%) patients and Grade 5 in 7 (0.2%) patients. The median time to onset was 56 days (range: 2-814 days). Seventy-five of the 103 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 40 patients. Resolution occurred in 61 patients.

Immune-mediated pneumonitis occurred more frequently in patients in the PACIFIC Study who had completed treatment with concurrent chemoradiation within 1 to 42 days prior to initiation of the study (10.7%), than in the other patients in the combined safety database (1.0%).

In the PACIFIC Study, (n=475 in the IMFINZI arm, and n=234 in the placebo arm) immune-mediated pneumonitis occurred in 47 (9.9%) patients in the IMFINZI-treated group and 14 (6.0%) patients in the placebo group, including Grade 3 in 9 (1.9%) patients on IMFINZI vs. 6 (2.6%) patients on placebo and Grade 5 (fatal) in 4 (0.8%) patients on IMFINZI vs. 3 (1.3%) patients on placebo. The median time to onset in the IMFINZI-treated group was 46 days (range: 2-342 days) vs. 57 days (range:

26-253 days) in the placebo group. In the IMFINZI-treated group, all patients received systemic corticosteroids, including 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, all patients received systemic corticosteroids, including 12 patients who received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day) and 1 patient also received cyclophosphamide and tacrolimus. Resolution occurred for 29 patients in the IMFINZI treated group vs. 6 in placebo.

In the combined safety database with IMFINZI in combination with tremelimumab (n=2 280), 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 (fatal) 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.

In the HCC pool (n=462), 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 the combined safety database with IMFINZI monotherapy, immune-mediated hepatitis occurred in 112 (2.8%) patients, including Grade 3 in 65 (1.6%) patients, Grade 4 in 8 (0.2%) patients and Grade 5 (fatal) in 6 (0.1%) patients. The median time to onset was 31 days (range: 1-644 days). Eighty-six of the 112 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). Seven patients also received mycophenolate treatment. IMFINZI was discontinued in 26 patients. Resolution occurred in 54 patients.

In the combined safety database with IMFINZI in combination with tremelimumab (n=2 280), 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 (fatal) 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 immunosuppressants. Treatment was discontinued in 27 patients. Resolution occurred in 47 patients.

In the HCC pool (n=462), 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

In the combined safety database with IMFINZI monotherapy, immune-mediated colitis or diarrhoea occurred in 77 (1.9%) patients, including Grade 3 in 15 (0.4%) patients and Grade 4 in 2 (< 0.1%) patients. The median time to onset was 71 days (range: 1-920 days). Fifty-five of the 77 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). Two patient also received infliximab treatment and 1 patient also received mycophenolate. IMFINZI was discontinued in 13 patients. Resolution occurred in 54 patients.

In the combined safety database with IMFINZI in combination with tremelimumab (n=2 280), 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 immunosuppressants. Treatment was discontinued in 54 patients. Resolution occurred in 141 patients.
Intestinal perforation and large intestine perforation were uncommonly reported in patients receiving IMFINZI in combination with tremelimumab.

In the HCC pool (n=462), 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 observed in patients receiving IMFINZI in combination with tremelimumab (rare) in studies outside of the HCC pool.

Immune-mediated endocrinopathies
Immune-mediated hypothyroidism
In the combined safety database with IMFINZI monotherapy, immune-mediated hypothyroidism occurred in 307 (7.6%) patients, including Grade 3 in 3 (< 0.1%) patients. The median time to onset was 86 days (range: 1-951 days). Of the 307 patients, 303 patients received hormone replacement therapy and 5 patients received high-dose corticosteroids (at least 40 mg prednisone or equivalent per day) for immune-mediated hypothyroidism. No patients discontinued IMFINZI due to immune-mediated hypothyroidism. Resolution occurred in 61 patients.

In the combined safety database with IMFINZI in combination with tremelimumab (n=2 280), 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 received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). Treatment 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.

In the HCC pool (n=462), 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 including hormone replacement therapy. Resolution occurred in 6 patients. Immune-mediated hypothyroidism was preceded by immune-mediated hyperthyroidism in 4 patients.

Immune-mediated hyperthyroidism
In the combined safety database with IMFINZI monotherapy, immune-mediated hyperthyroidism occurred in 64 (1.6%) patients, including Grade 3 in 1 (< 0.1%) patient. The median time to onset was 43 days (range: 1-253 days). Fifty-nine of the 64 patients received medical therapy (thiamazole, carbimazole, propylthiouracil, perchlorate, calcium channel blocker or beta-blocker), 13 patients received systemic corticosteroids and 5 of the 13 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 47 patients. Twenty-two patients experienced hypothyroidism following hyperthyroidism.

In the combined safety database with IMFINZI in combination with tremelimumab (n=2 280), 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 coticosteroids, 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 beta-blocker), One patient discontinued treatment due to hyperthyroidism. Resolution occurred in 47 patients.

In the HCC pool (n=462), 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 corticosteriods, 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 the combined safety database with IMFINZI monotherapy, immune-mediated thyroiditis occurred in 16 (0.4%) patients, including Grade 3 in 2 (< 0.1%) patients. The median time to onset was 49 days (range: 14-217 days). Of the 16 patients, 13 patients received hormone replacement therapy and 3 patients received high-dose corticosteroids (at least 40 mg prednisone or equivalent per day). One patient discontinued IMFINZI due to immune-mediated thyroiditis. Resolution occurred in 5 patients. Three patients experienced hypothyroidism following thyroiditis.

In the combined safety database with IMFINZI in combination with tremelimumab (n=2 280), 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 therapy, thiamazole, carbimazole, propylthiouracil, perchlorate, calcium channel blocker, or beta-blocker. No patients discontinued treatment due to immune-mediated thyroiditis. Resolution occurred in 5 patients.

In the HCC pool (n=462), 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. Resolution occurred in 2 patients.

Immune-mediated adrenal insufficiency
In the combined safety database with IMFINZI monotherapy, immune-mediated adrenal insufficiency occurred in 20 (0.5%) patients, including Grade 3 in 6 (0.1%) patients. The median time to onset was 157.5 days (range: 20-547 days). All 20 patients received systemic corticosteroids; 7 of the 20 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 6 patients.

In the combined safety database with IMFINZI in combination with tremelimumab (n=2 280), 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 high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). Treatment was discontinued in one patient. Resolution occurred in 11 patients.

In the HCC pool (n=462), 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 the combined safety database with IMFINZI monotherapy, immune-mediated type 1 diabetes mellitus occurred in 3 (< 0.1%) patients, including Grade 3 in 2 (< 0.1%) patients and Grade 4 in 1 (< 0.1%) patient. The time to onset was 43 days (range: 42-518 days). All three patients required long-term insulin therapy. IMFINZI was permanently discontinued in one patient. One patient recovered and one patient recovered with sequelae.

In the combined safety database with IMFINZI in combination with tremelimumab (n=2 280), immune-mediated type 1 diabetes mellitus 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 for 1 patient. Resolution occurred in 1 patient.

Immune mediated hypophysitis/hypopituitarism
In the combined safety database with IMFINZI monotherapy, immune-mediated hypophysitis/hypopituitarism occurred in 4 (< 0.1%) patients, including Grade 3 in 3 (< 0.1%) patients. The time to onset for the events was 74 days (range: 44-225 days). Two patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day), two patients discontinued IMFINZI due to immune-mediated hypophysitis/hypopituitarism and resolution occurred in 1 patient.

In the combined safety database with IMFINZI in combination with tremelimumab (n=2 280), immune-mediated hypophysitis/hypopituitarism occurred in 16 (0.7%) patients, including Grade 3 in 8 (0.4%) patients. The median time to onset for the events 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.

In the HCC pool (n=462), 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 the combined safety database with IMFINZI monotherapy, immune-mediated nephritis occurred in 18 (0.4%) patients, including Grade 3 in 4 (< 0.1%) patients and Grade 4 in 1 (< 0.1%) patient. The median time to onset was 77.5 days (range: 4-393 days). Thirteen 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 7 patients. Resolution occurred in 9 patients.

In the combined safety database with IMFINZI in combination with tremelimumab (n=2 280), 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.

In the HCC pool (n=462), 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 the combined safety database with IMFINZI monotherapy, immune-mediated rash or dermatitis (including pemphigoid) occurred in 65 (1.6%) patients, including Grade 3 in 17 (0.4%) patients. The median time to onset was 54 days (range: 4-576 days). Thirty-three of the 65 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). IMFINZI was discontinued in 5 patients. Resolution occurred in 43 patients.

In the combined safety database with IMFINZI in combination with tremelimumab (n=2 280), 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.

In the HCC pool (n=462), 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%) patient. 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 the combined safety database with IMFINZI monotherapy, infusion-related reactions occurred in 55 (1.4%) patients, including Grade 3 in 5 (0.1%) patients. There were no Grade 4 or 5 events.

In the combined safety database with IMFINZI in combination with tremelimumab (n=2 280), infusion-related reactions occurred in 45 (2.0%) patients, including Grade 3 in 2 (< 0.1%) patients. There were no Grade 4 or 5 events.

Laboratory abnormalities
In patients treated with durvalumab monotherapy, the proportion of patients who experienced a shift from baseline to a Grade 3 or 4 laboratory abnormality was as follows: 3.8% for alanine aminotransferase increased, 6.1% for aspartate aminotransferase increased, 0.9% for blood creatinine increased, 5.4% for amylase increased and 8.4% for lipase increased. The proportion of patients who experienced a TSH shift from baseline that was ≤ ULN to any grade > ULN was 19.3% and a TSH shift from baseline that was ≥ LLN to any grade < LLN was 17.5%.

In patients treated with durvalumab in combination with chemotherapy, the proportion of patients who experienced a shift from baseline to a Grade 3 or 4 laboratory abnormality was as follows: 6.4% for alanine aminotransferase increased, 6.5% for aspartate aminotransferase increased, 4.2% for blood creatinine increased, 6.4% for amylase increased, and 11.7% for lipase increased. The proportion of patients who experienced a TSH shift from baseline that was ≤ ULN to any grade > ULN was 20.3% and a TSH shift from baseline that was ≥ LLN to any grade < LLN was 24.1%.

In patients treated with IMFINZI in combination with tremelimumab and platinum-based chemotherapy, the proportion of patients who experienced a shift from baseline to a Grade 3 or 4 laboratory abnormality was as follows: 6.2% for alanine aminotransferase increased, 5.2% for aspartate aminotransferase increased, 4.0% for blood creatinine increased, 9.4% for amylase increased and 13.6% for lipase increased. The proportion of patients who experienced a TSH shift from baseline that was ≤ ULN to > ULN was 24.8% and a TSH shift from baseline that was ≥ LLN to < LLN was 32.9%.

In patients treated with IMFINZI in combination with tremelimumab, the proportion of patients who experienced a shift from baseline to a Grade 3 or 4 laboratory abnormality was as follows: 5.1% for alanine aminotransferase increased, 5.8% for aspartate aminotransferase, 1.0% for blood creatinine increased, 5.9% for amylase increased and 11.3% for lipase increased. The proportion of patients who

experienced a TSH shift from baseline that was ≤ ULN to > ULN was 4.2% and a TSH shift from baseline that was ≥ LLN to < LLN was 17.2%.

Immunogenicity
Immunogenicity of IMFINZI as monotherapy is based on pooled data in 3 069 patients who were treated with IMFINZI 10 mg/kg every 2 weeks, or 20 mg/kg every 4 weeks as a single-agent and evaluable for the presence of anti-drug antibodies (ADAs). Eighty-four patients (2.7%) tested positive for treatment emergent ADAs. Neutralising antibodies (nAb) against durvalumab were detected in 0.5% (16/3 069) of patients. The presence of ADAs did not have a clinically relevant effect on pharmacokinetics or safety. There are insufficient number of patients to determine ADA impact on efficacy.

Across multiple phase III studies, in patients treated with IMFINZI in combination with other therapeutic agents, 0% to 10.1% of patients developed treatment-emergent ADAs. Neutralizing antibodies against durvalumab were detected in 0% to 1.7% of patients treated with IMFINZI in combination with other therapeutic agents. The presence of ADAs did not have an apparent effect on pharmacokinetics or safety.

Elderly
No overall differences in safety were reported between elderly (≥ 65 years) and younger patients.

In studies PACIFIC, CASPIAN, TOPAZ-1 and HIMALAYA data on safety for patients 75 years and older are too limited to draw a conclusion on this population.

In first line metastatic NSCLC patients in the POSEIDON study, some differences in safety were reported between elderly (≥ 65 years) and younger patients. The safety data from patients 75 years of age or older are limited to a total of 74 patients. There was a higher frequency of serious adverse reactions and discontinuation rate of any study treatment due to adverse reactions in 35 patients aged 75 years of age or older treated with IMFINZI in combination with tremelimumab and platinum-based chemotherapy (45.7% and 28.6%, respectively) relative to 39 patients aged 75 years of age or older who received platinum-based chemotherapy only (35.9% and 20.5%, respectively).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

There is no information on overdose with durvalumab. In case of overdose, patients should be closely monitored for signs or symptoms of adverse reactions, and appropriate symptomatic treatment instituted immediately.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, monoclonal antibodies and antibody drug conjugates, PD-1/PDL-1 (Programmed cell death protein 1/death ligand 1) inhibitors. ATC code: L01FF03.

Mechanism of action
Expression of programmed cell death ligand-1 (PD-L1) protein is an adaptive immune response that helps tumours evade detection and elimination by the immune system. PD-L1 can be induced by

inflammatory signals (e.g., IFN-gamma) and can be expressed on both tumour cells and tumour-associated immune cells in tumour microenvironment. PD-L1 blocks T-cell function and activation through interaction with PD-1 and CD80 (B7.1). By binding to its receptors, PD-L1 reduces cytotoxic T-cell activity, proliferation and cytokine production.

Durvalumab is a fully human, immunoglobulin G1 kappa (IgG1κ) monoclonal antibody that selectively blocks the interaction of PD-L1 with PD-1 and CD80 (B7.1). Durvalumab does not induce antibody dependent cell-mediated cytotoxicity (ADCC). Selective blockade of PD-L1/PD-1 and PD-L1/CD80 interactions enhances antitumour immune responses and increases T-cell activation.

The combination of tremelimumab, a CTLA-4 inhibitor and durvalumab, a PD-L1 inhibitor functions to enhance anti-tumour T-cell activation and function at multiple stages of the immune response resulting in improved anti-tumour responses. In murine syngeneic tumour models, dual blockade of PD-L1 and CTLA-4 resulted in enhanced anti-tumour activity.

Clinical efficacy and safety

Durvalumab doses of 10 mg/kg every 2 weeks or 1 500 mg every 4 weeks were evaluated in NSCLC and ES-SCLC clinical studies. Based on the modeling and simulation of exposure, exposure-safety relationships and exposure-efficacy data comparisons, there are no anticipated clinically significant differences in efficacy and safety between durvalumab doses of 10 mg/kg every 2 weeks or 1 500 mg every 4 weeks.

NSCLC – PACIFIC Study

The efficacy of IMFINZI was evaluated in the PACIFIC Study, a randomised, double-blind, placebo-controlled, multicentre study in 713 patients with locally advanced, unresectable NSCLC. Patients had completed at least 2 cycles of definitive platinum-based chemotherapy with radiation therapy within 1 to 42 days prior to initiation of the study and had a ECOG performance status of 0 or 1. Ninety-two percent of patients had received a total dose of 54 to 66 Gy of radiation. The study excluded patients who had progressed following chemoradiation therapy, patients with prior exposure to any anti-PD-1 or anti-PD-L1 antibody, patients with active or prior documented autoimmune disease within 2 years of initiation of the study; a history of immunodeficiency; a history of severe immune-mediated adverse reactions; medical conditions that required systemic immunosuppression, except physiological dose of systemic corticosteroids; active tuberculosis or hepatitis B or C or HIV infection or patients receiving live attenuated vaccine within 30 days before or after the start of IMFINZI. Patients were randomised 2:1 to receive 10 mg/kg IMFINZI (n=476) or 10 mg/kg placebo (n=237) via intravenous infusion every 2 weeks for up to 12 months or until unacceptable toxicity or confirmed disease progression. Randomisation was stratified by gender, age (< 65 years vs. ≥ 65 years) and smoking status (smoker vs. non-smoker). Patients with disease control at 12 months were given the option to be re-treated upon disease progression. Tumour assessments were conducted every 8 weeks for the first 12 months and then every 12 weeks thereafter.

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

The demographics and baseline disease characteristics were well balanced between study arms. Baseline demographics of the overall study population were as follows: male (70%), age ≥ 65 years (45%), age ≥ 75 years (8%), White (69%), Asian (27%), other (4%), current smoker (16%), past-smoker (75%), never smoker (9%), ECOG Performance Status 0 (49%), ECOG Performance Status 1 (51%). Disease characteristics were as follows: Stage IIIA (53%), Stage IIIB (45%), histological sub-groups of squamous (46%), non-squamous (54%). Of 451 patients with PD-L1 expression available, 67% were TC ≥ 1% [PD-L1 TC 1-24% (32%), PD-L1 TC ≥ 25% (35%)] and 33% were TC < 1%.

The two primary endpoints of the study were progression-free survival (PFS) and overall survival (OS) of IMFINZI vs. placebo. Secondary efficacy endpoints included PFS at 12 months (PFS 12) and 18 months (PFS 18) from randomisation and Time from Randomisation to Second Progression (PFS2). PFS was assessed by Blinded Independent Central Review (BICR) according to RECIST v1.1.

The study demonstrated a statistically significant improvement in PFS in the IMFINZI-treated group compared with the placebo group [hazard ratio (HR) = 0.52 (95% CI: 0.42, 0.65), p < 0.0001]. The study demonstrated a statistically significant improvement in OS in the IMFINZI-treated group compared with the placebo group [HR = 0.68 (95% CI: 0.53, 0.87), p = 0.00251].

In the 5 year follow-up analysis, with a median follow-up of 34.2 months, IMFINZI continued to demonstrate improved OS and PFS compared to placebo. The OS and PFS results from the primary analysis and the follow-up analysis are summarized in Table 5.

Table 5. Efficacy results for the PACIFIC Study

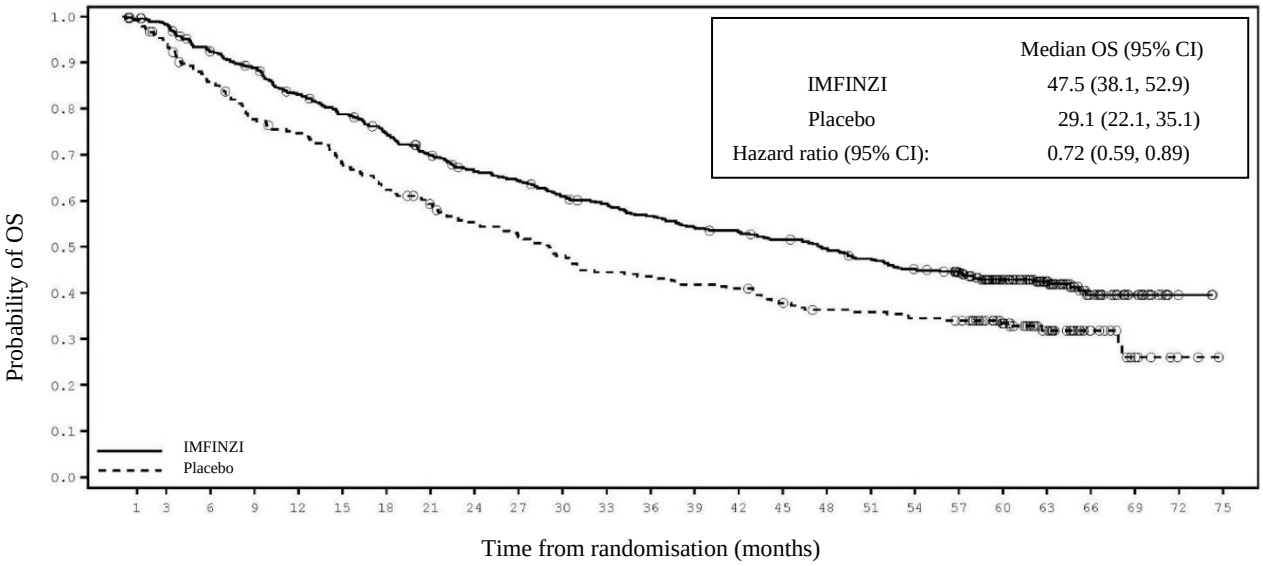
	Primary analysis[a]		**5 year follow-up analysis[b]**	
	IMFINZI (n=476)	**Placebo (n=237)**	**IMFINZI (n=476)**	**Placebo (n=237)**
OS				
Number of deaths (%)	183 (38.4%)	116 (48.9%)	264 (55.5%)	155 (65.4%)
Median (months) (95% CI)	NR (34.7, NR)	28.7 (22.9, NR)	47.5 (38.1, 52.9)	29.1 (22.1, 35.1)
HR (95% CI)	0.68 (0.53, 0.87)		0.72 (0.59, 0.89)	
2- sided p-value	0.00251			
OS at 24 months (%) (95% CI)	66.3% (61.7%, 70.4%)	55.6% (48.9%, 61.3%)	66.3% (61.8%, 70.4%)	55.3% (48.6%, 61.4%)
p-value	0.005			
OS at 48 months (%) (95% CI)			49.7% (45.0%, 54.2%)	36.3% (30.1%, 42.6%)
OS at 60 months (%) (95% CI)			42.9% (38.2%, 47.4%)	33.4% (27.3%, 39.6%)
PFS				
Number of events (%)	214 (45.0%)	157 (66.2%)	268 (56.3%)	175 (73.8%)
Median PFS (months) (95% CI)	16.8 (13.0, 18.1)	5.6 (4.6, 7.8)	16.9 (13.0, 23.9)	5.6 (4.8, 7.7)
HR (95% CI)	0.52 (0.42, 0.65)		0.55 (0.45, 0.68)	
p-value	p < 0.0001			
PFS at 12 months (%) (95% CI)	55.9% (51.0%, 60.4%)	35.3% (29.0%, 41.7%)	55.7% (51.0%, 60.2%)	34.5% (28.3%, 40.8%)
PFS at 18 months (%) (95% CI)	44.2% (37.7%, 50.5%)	27.0% (19.9%, 34.5%)	49.1% (44.2%, 53.8%)	27.5% (21.6%, 33.6%)
PFS at 48 months (%) (95% CI)			35.0% (29.9%, 40.1%)	19.9% (14.4%, 26.1%)
PFS at 60 months (%) (95% CI)			33.1% (28.0%, 38.2%)	19.0% (13.6%, 25.2%)
PFS2[c]				
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			

[a] Primary analysis of PFS at data cut-off 13 February 2017. Primary analysis of OS and PFS2 at data cut-off 22 March 2018.

[b] Follow-up OS and PFS analysis at data cut-off 11 January 2021.
[c] PFS2 is defined as the time from the date of randomisation until the date of second progression (defined by local standard clinical practice) or death.
NR: Not Reached

Kaplan-Meier curves for OS and PFS from the 5 year follow-up analysis are presented in Figures 1 and 2.

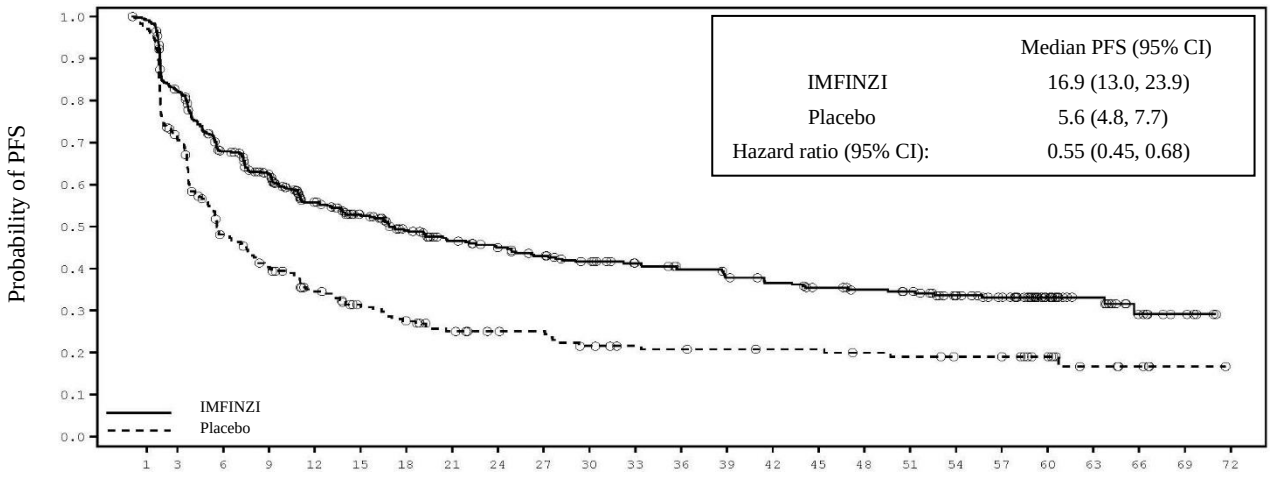
Figure 1. Kaplan-Meier curve of OS



Number of patients at risk

Month	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54	57	60	63	66	69	72	75
IMFINZI	476	464	431	414	385	364	343	319	298	289	273	264	252	241	236	227	218	207	196	183	134	91	40	18	2	0
Placebo	237	220	199	179	171	156	143	133	123	116	107	99	97	93	91	83	78	77	74	72	56	33	16	7	2	0

Figure 2. Kaplan-Meier curve of PFS



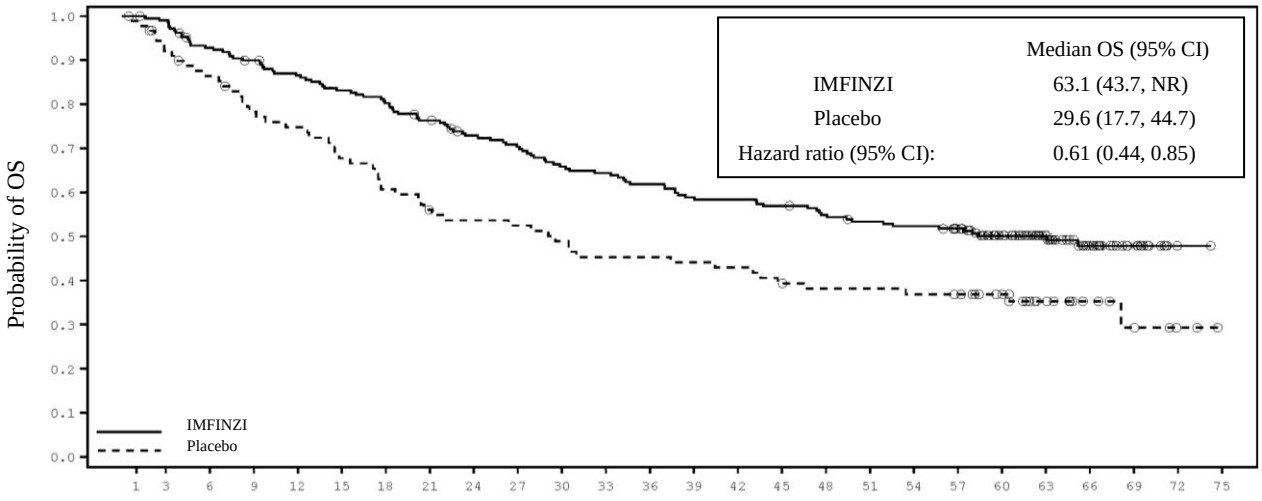
Number of patients at risk

Month	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54	57	60	63	66	69	72
IMFINZI	476	377	301	267	215	190	165	147	137	128	119	110	103	97	92	85	81	78	67	57	34	22	11	5	0
Placebo	237	164	105	87	68	56	48	41	37	36	30	27	26	25	24	24	22	21	19	19	14	6	4	1	0

The improvements in PFS and OS in favour of patients receiving IMFINZI compared to those receiving placebo were consistently observed in all predefined subgroups analysed, including ethnicity, age, gender, smoking history, EGFR mutation status and histology.

Post-hoc subgroup analysis by PD-L1 expression
Additional subgroup analyses were conducted to evaluate the efficacy by tumour PD-L1 expression (≥ 25%, 1-24%, ≥ 1%, < 1%) and for patients whose PD-L1 status cannot be established (PD-L1 unknown). PFS and OS results from the 5 year follow-up analysis are summarised in Figures 3, 4, 5 and 6.

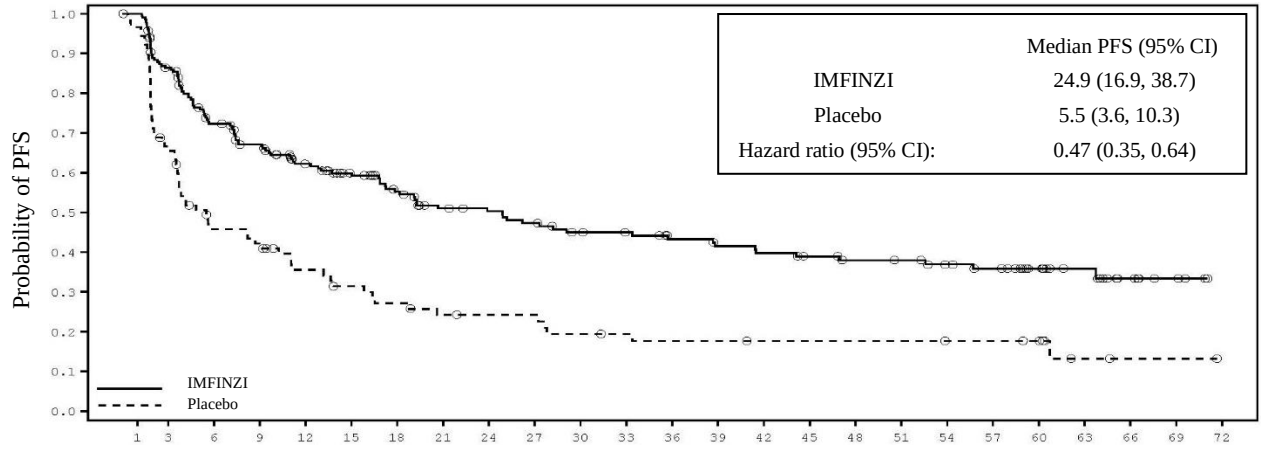
Figure 3. Kaplan-Meier curve of OS for PD-L1 TC ≥ 1%



Number of patients at risk

Month	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54	57	60	63	66	69	72	75
IMFINZI	212	208	193	186	178	171	165	156	146	141	132	129	124	118	117	114	109	105	103	98	74	52	29	14	1	0
Placebo	91	81	75	67	64	58	52	47	45	44	41	38	38	37	36	33	31	31	30	29	24	14	8	5	2	0

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



Number of patients at risk

Month	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54	57	60	63	66	69	72
IMFINZI	212	175	142	127	107	95	82	70	67	63	57	55	50	47	45	42	39	38	34	31	22	15	8	4	0
Placebo	91	59	38	34	26	22	19	16	15	15	12	11	10	10	9	9	9	9	8	8	7	2	1	1	0

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

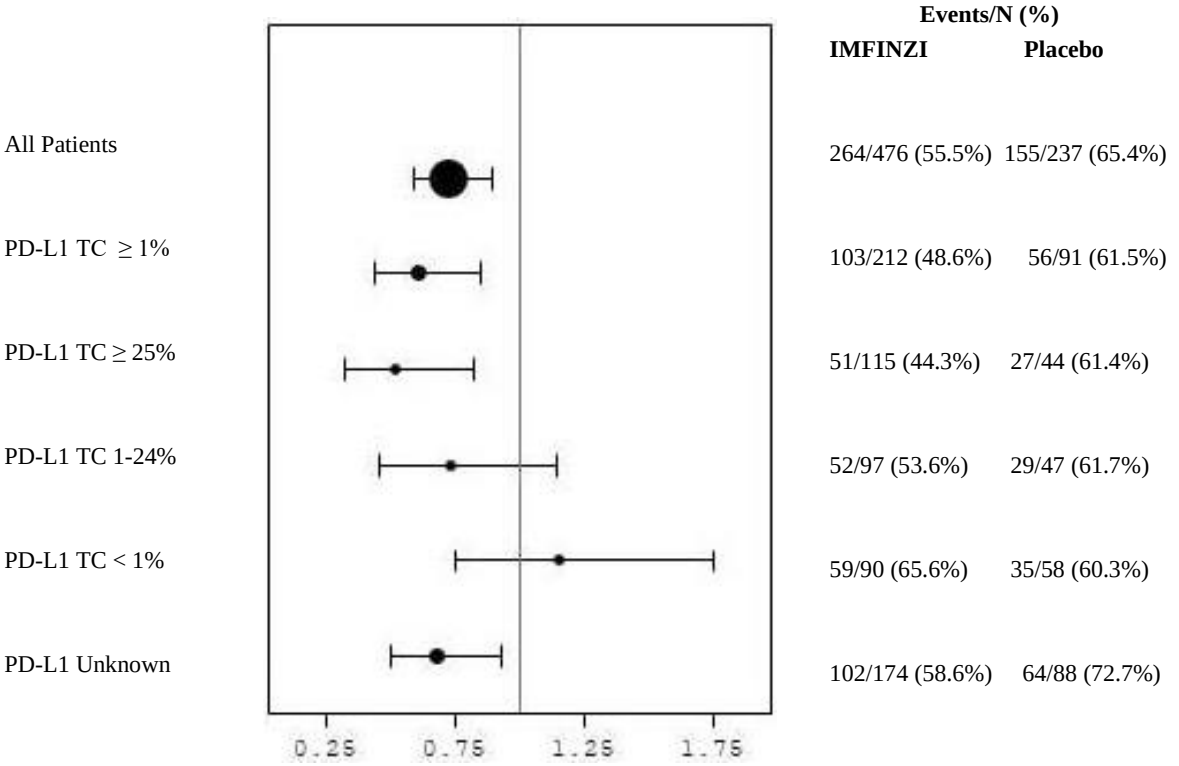
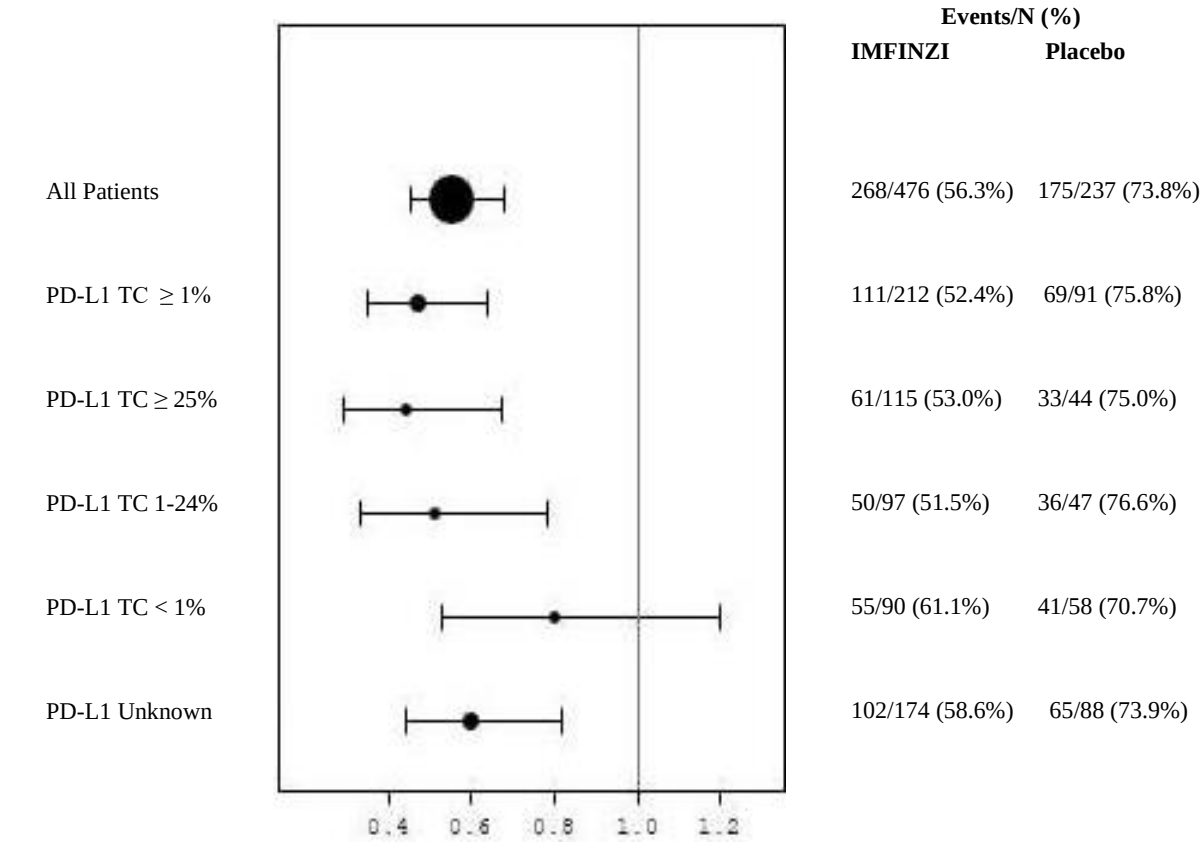


Figure 6. Forest plot of PFS by PD-L1 expression



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

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

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

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, multicenter study in 1013 metastatic NSCLC patients with no sensitising epidermal growth factor receptor (EGFR) mutation or anaplastic lymphoma kinase (ALK) genomic tumour aberrations. Patients with 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 (WHO)/Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 at enrolment.

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 (see section 4.4).

Randomisation was stratified by tumour cells (TC) PD-L1 expression (TC ≥ 50% vs. TC < 50%), disease stage (Stage IVA vs. Stage IVB, per the 8th edition of American Joint Committee on Cancer), and histology (non-squamous vs. squamous).

Patients were randomised 1:1:1 to receive:
- Arm 1: IMFINZI 1 500 mg with tremelimumab 75 mg and platinum-based chemotherapy every 3 weeks for 4 cycles followed by, IMFINZI 1 500 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 1 500 mg and platinum-based chemotherapy every 3 weeks for 4 cycles, followed by IMFINZI 1 500 mg every 4 weeks as monotherapy.
- Arm 3: Platinum-based chemotherapy every 3 weeks for 4 cycles. Patients could receive 2 additional cycles (a total of 6 cycles post-randomisation), as clinically indicated, at the 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 1 000 or 1 250 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 or 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.

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 vs. platinum-based chemotherapy alone. The key secondary endpoints of the study were PFS and OS for IMFINZI + tremelimumab + platinum-based chemotherapy and platinum-based chemotherapy alone. The secondary endpoints included objective response rate (ORR) and Duration of Response (DoR). PFS, ORR, and DoR, were assessed using BICR according to RECIST v1.1

The demographics and baseline disease characteristics were well-balanced between study arms. Baseline demographics of the overall study population were as follows: male (76.0%), age ≥ 65 years (47.1%), age ≥ 75 years (11.3%) median age 64 years (range: 27 to 87 years), 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%), 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%), brain metastases (10.5%), PD-L1 expression TC≥ 50% (28.8%), PD-L1 expression TC < 50% (71.1%).

The study showed a statistically significant improvement in OS with IMFINZI + tremelimumab + platinum-based chemotherapy vs. platinum-based chemotherapy. IMFINZI + tremelimumab + platinum-based chemotherapy showed a statistically significant improvement in PFS vs. platinum-based chemotherapy alone. The results are summarised below.

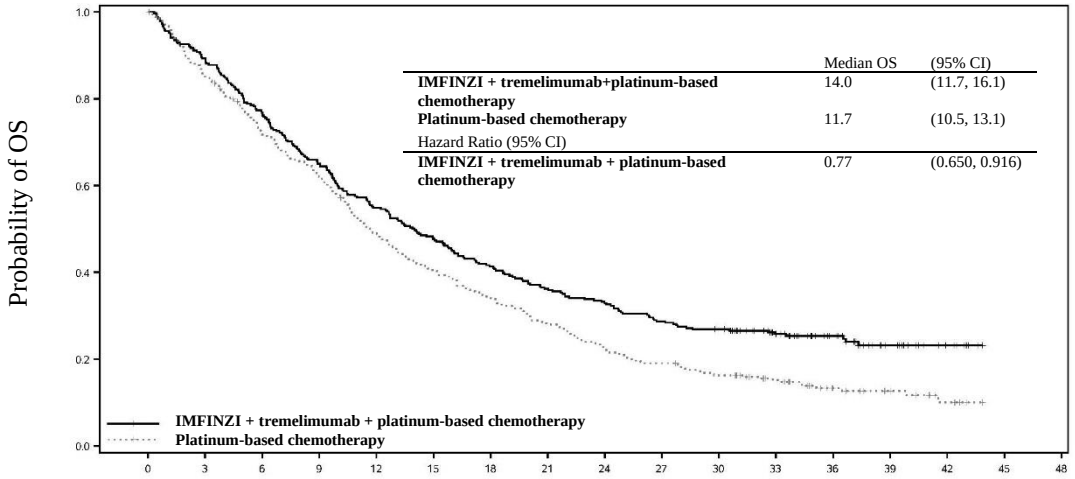
Table 6. Efficacy results for the POSEIDON study

	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) [b]	0.77 (0.650, 0.916)	
p-value[c]	0.00304	
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)[b]	0.72 (0.600, 0.860)	
p-value[c]	0.00031	
ORR n (%)[d,e]	130 (38.8)	81 (24.4)
Complete Response n (%)	2 (0.6)	0
Partial Response n (%)	128 (38.2)	81 (24.4)
Median DoR (months) (95% CI)[d,e]	9.5 (7.2, NR)	5.1 (4.4, 6.0)

[a] Analysis of PFS at data cut off 24 July 2019 (median follow up 10.15 months). Analysis of OS at data cut off 12 March 2021 (median follow up 34.86 months). The boundaries for declaring efficacy (Arm 1 vs. Arm 3:

PFS 0.00735, OS 0.00797; 2-sided) were determined by a Lan-DeMets alpha spending function that approximates an O'Brien Fleming approach. PFS was assessed by BICR according to RECIST v1.1.
[b] HR are derived using a Cox pH model stratified by PD-L1, histology and disease stage.
[c] 2-sided p-value based on a log-rank test stratified by PD-L1, histology and disease stage.
[d] Confirmed Objective Response.
[e] Post-hoc analysis.
NR = Not Reached, CI = Confidence Interval

Figure 7. Kaplan-Meier curve of OS

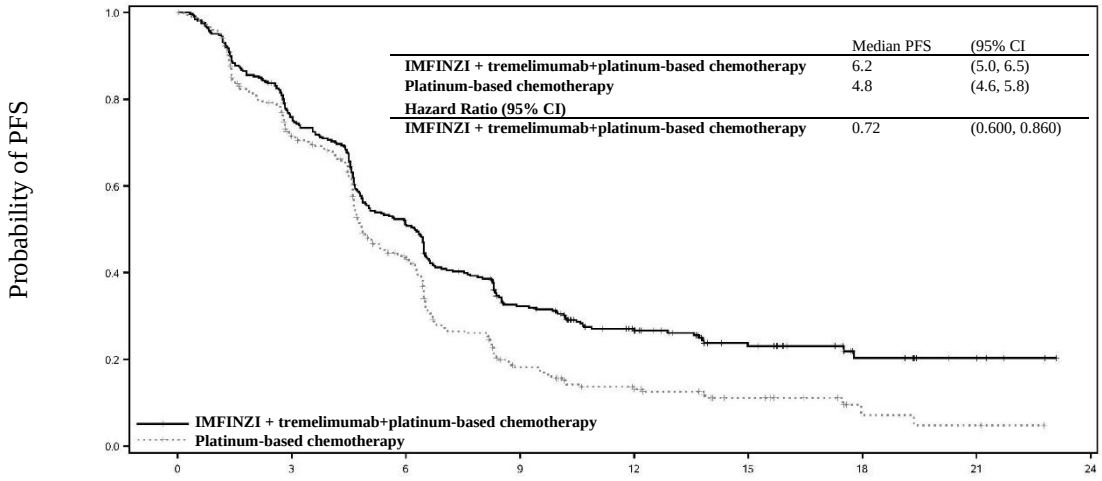


Time from randomisation (months)

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 8. Kaplan-Meier curve of PFS



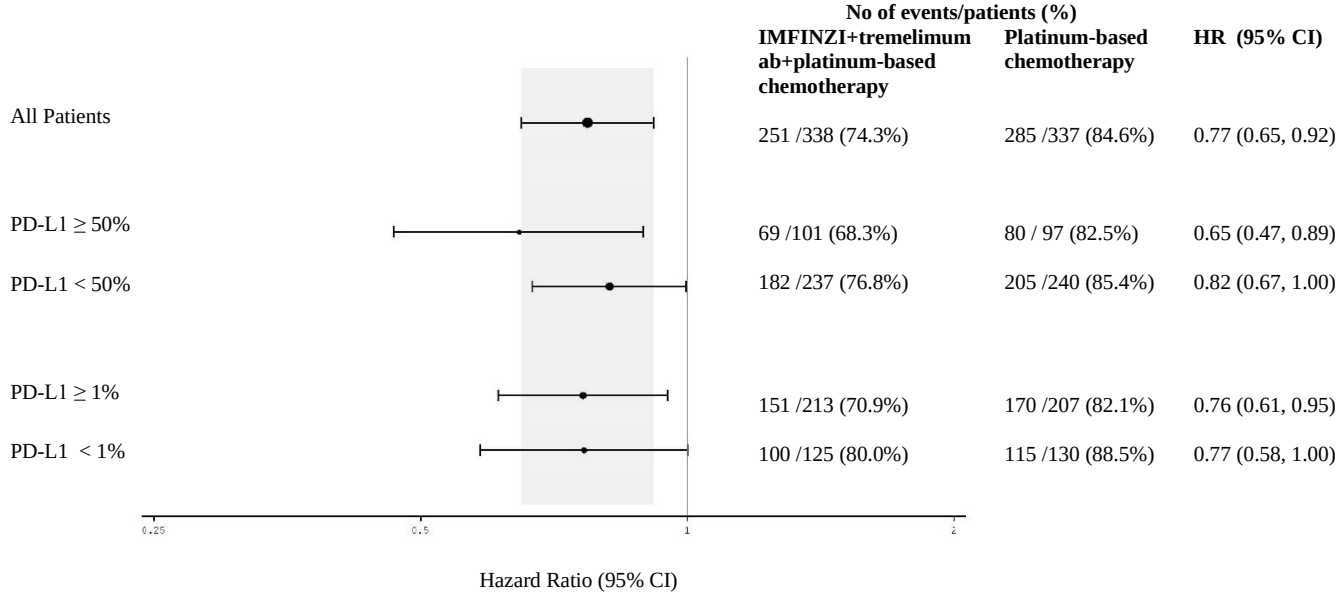
Time from randomisation (months)

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

Figure 9 summarises efficacy results of OS by tumour PD-L1 expression in prespecified subgroup analyses.

Figure 9. Forest plot of OS by PD-L1 expression for IMFINZI+tremelimumab+platinum-based chemotherapy vs. platinum-based chemotherapy



Elderly population

A total of 75 patients aged ≥ 75 years were enrolled in the IMFINZI in combination with tremelimumab and chemotherapy (n=35) and platinum-based chemotherapy only (n=40) arms of the POSEIDON study. An exploratory HR of 1.05 (95% CI: 0.64, 1.71) for OS was observed for the IMFINZI in combination with tremelimumab and platinum-based chemotherapy vs. platinum-based chemotherapy within this study subgroup. Due to the exploratory nature of this subgroup analysis no definitive conclusions can be drawn, but caution is suggested when considering this regimen for elderly patients.

SCLC – CASPIAN Study

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

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

Patients were randomised 1:1:1 to receive:

- Arm 1: IMFINZI 1 500 mg + tremelimumab 75 mg + etoposide and either carboplatin or cisplatin.
- Arm 2: IMFINZI 1 500 mg + etoposide and either carboplatin or cisplatin.
- Arm 3: Either carboplatin (AUC 5 or 6 mg/ml/min) or cisplatin (75-80 mg/m^2) on Day 1 and etoposide (80-100 mg/m^2) intravenously on Days 1, 2, and 3 of each 21-day cycle for between 4 – 6 cycles.

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

Patients randomised to Arm 3 were permitted to receive a total of up to 6 cycles of etoposide and either carboplatin or cisplatin. After completion of etoposide + platinum, PCI was permitted only in Arm 3 per investigator discretion.

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

The primary endpoints of the study were OS of IMFINZI + etoposide + platinum (Arm 2) vs. etoposide + platinum alone (Arm 3) and IMFINZI + tremelimumab + etoposide + platinum (Arm 1) vs. etoposide + platinum alone (Arm 3). The key secondary endpoint was PFS. Other secondary endpoints were ORR, OS and PFS landmarks and PRO. PFS and ORR were assessed using Investigator assessments according to RECIST v1.1.

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

At a planned interim (primary) analysis the study demonstrated a statistically significant improvement in OS with IMFINZI + etoposide + platinum (Arm 2) vs. etoposide + platinum alone (Arm 3) [HR=0.73 (95% CI: 0.591, 0.909), p=0.0047]. Although not formally tested for significance, IMFINZI + etoposide + platinum demonstrated an improvement in PFS vs. etoposide + platinum alone [HR=0.78 (95% CI: 0.645, 0.936)].

The PFS, ORR and DoR results from the planned final analysis (DCO: 27 Jan 2020) are summarized in Table 7. Kaplan-Meier curve for PFS is presented in Figure 11.

The OS results with the planned long-term OS follow-up analysis (DCO: 22 March 2021) (median follow-up: 39.3 months) are presented in Table 7. IMFINZI + etoposide + platinum (Arm 2) vs. etoposide + platinum (Arm 3) continued to demonstrate sustained improvement in OS. Kaplan-Meier curve for OS is presented in Figure 10.

Table 7. Efficacy Results for the CASPIAN Study

	Final analysis[a]		**Long-term follow-up analysis[b]**	
	Arm 2: IMFINZI + etoposide and either carboplatin or cisplatin (n=268)	**Arm 3: etoposide + and either carboplatin or cisplatin (n=269)**	**Arm 2: IMFINZI + etoposide and either carboplatin or cisplatin (n=268)**	**Arm 3: etoposide + and either carboplatin or cisplatin (n=269)**
OS				
Number of deaths (%)	210 (78.4)	231 (85.9)	221 (82.5)	248 (92.2)

	Final analysis[a]		Long-term follow-up analysis[b]	
	Arm 2: IMFINZI + etoposide and either carboplatin or cisplatin (n=268)	**Arm 3: etoposide + and either carboplatin or cisplatin (n=269)**	**Arm 2: IMFINZI + etoposide and either carboplatin or cisplatin (n=268)**	**Arm 3: etoposide + and either carboplatin or cisplatin (n=269)**
Median OS (months) (95% CI)	12.9 (11.3, 14.7)	10.5 (9.3, 11.2)	12.9 (11.3, 14.7)	10.5 (9.3, 11.2)
HR (95% CI)[b,c]	0.75 (0.625, 0.910)		0.71 (0.595, 0.858)	
p-value[d]	0.0032		0.0003	
OS at 18 months (%) (95% CI)	32.0 (26.5, 37.7)	24.8 (19.7, 30.1)	32.0 (26.5, 37.7)	24.8 (19.7, 30.1)
OS at 36 months (%) (95% CI)			17.6 (13.3, 22.4)	5.8 (3.4, 9.1)
PFS				
Number of events (%)	234 (87.3)	236 (87.7)		
Median PFS (months) (95% CI)	5.1 (4.7, 6.2)	5.4 (4.8, 6.2)		
HR (95% CI)[c]	0.80 (0.665, 0.959)			
PFS at 6 months (%) (95% CI)	45.4 (39.3, 51.3)	45.8 (39.5, 51.9)		
PFS at 12 months (%) (95% CI)	17.9 (13.5, 22.8)	5.3 (2.9, 8.8)		
ORR n (%) (95% CI)[e]	182 (67.9) (62.0, 73.5)	156 (58.0) (51.8, 64.0)		
Complete Response n (%)	7 (2.6)	2 (0.7)		
Partial Response n (%)	175 (65.3)	154 (57.2)		
Median DoR (months) (95% CI)[e,f]	5.1 (4.9, 5.3)	5.1 (4.8, 5.3)		

[a] Final PFS, ORR and DoR analysis at data cut-off 27 January 2020.

[b] Long-term follow-up OS analysis at data cut-off 22 March 2021.

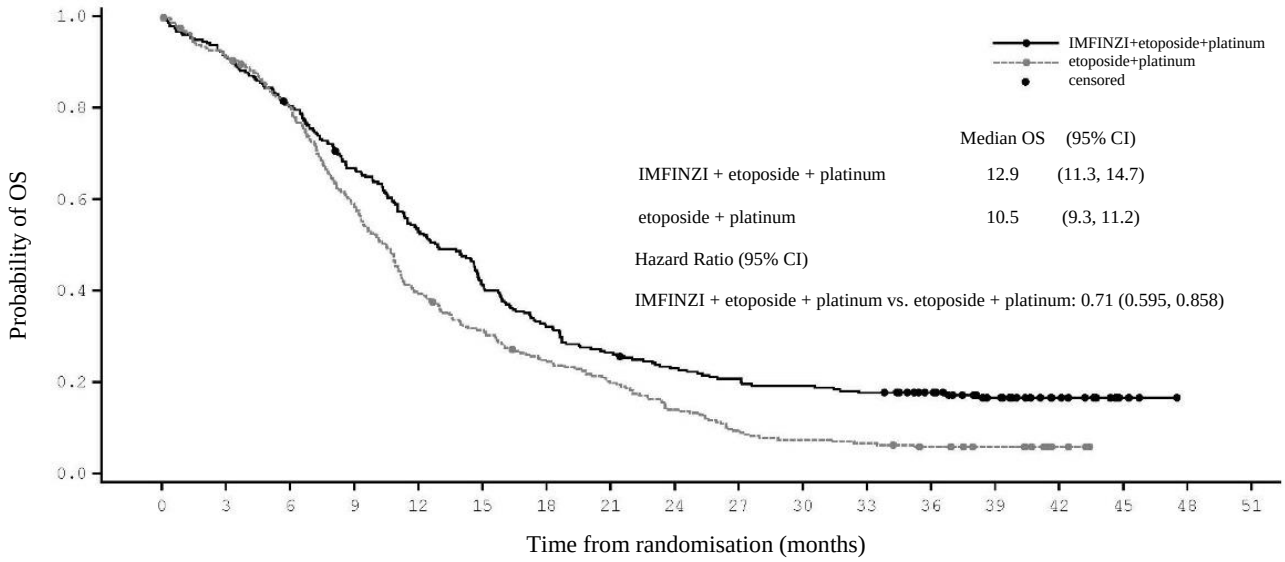
[c] The analysis was performed using the stratified log-rank test, adjusting for planned platinum therapy in Cycle 1 (carboplatin or cisplatin), and using the rank tests of association approach.

[d] At the interim analysis (data cut-off 11 March 2019) the OS p-value was 0.0047, which met the boundary for declaring statistical significance of 0.0178 for a 4% overall 2-sided alpha, based on a Lan-DeMets alpha spending function with O'Brien Fleming type boundary with the actual number of events observed.

[e] Confirmed Objective Response.

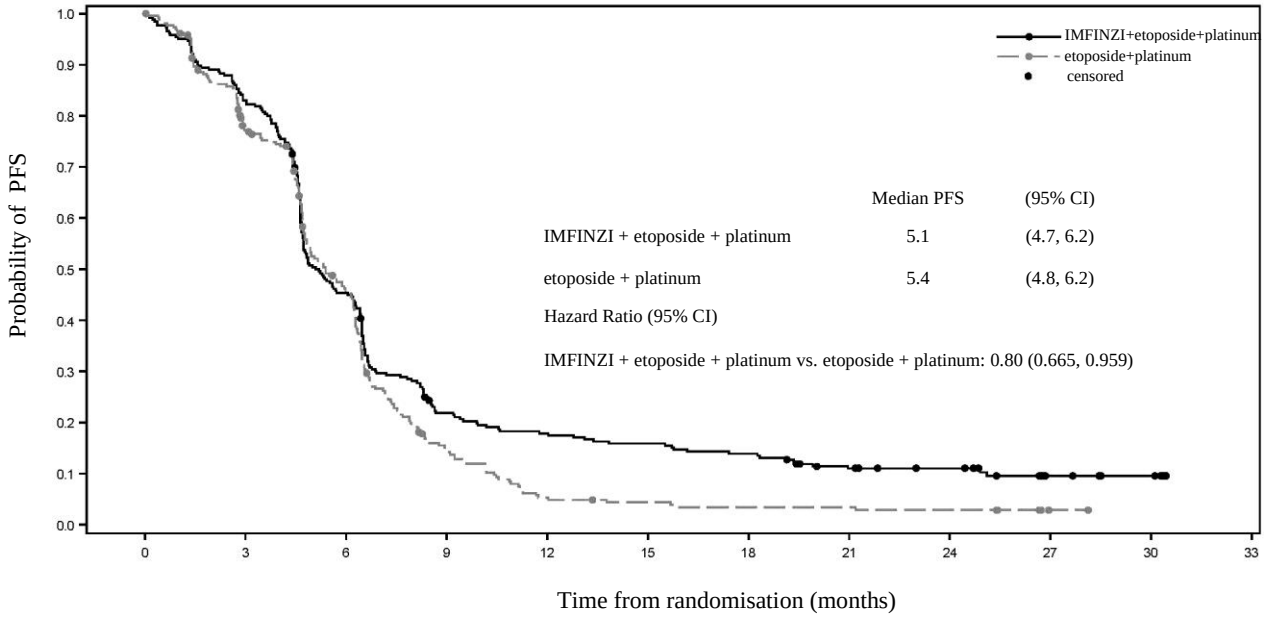
[f] Post-hoc analysis.

Figure 10. Kaplan-Meier curve of OS



Number of patients at risk	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51
IMFINZI + etoposide + platinum	268	244	214	177	140	109	85	70	60	54	50	46	39	25	13	3	0	0
etoposide + platinum	269	243	212	156	104	82	64	51	36	24	19	17	13	10	3	0	0	0

Figure 11. Kaplan-Meier curve of PFS



Number of patients at risk	0	3	6	9	12	15	18	21	24	27	30	33
IMFINZI + etoposide + platinum	268	220	119	55	45	40	35	24	18	8	5	0
etoposide + platinum	269	195	110	33	12	9	7	7	6	1	0	0

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

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 unresectable or metastatic BTC (including intrahepatic and extrahepatic cholangiocarcinoma and gallbladder carcinoma) and ECOG Performance status of 0 or 1. Patients had not received previous therapy in the advanced/unresectable setting. Patients who developed recurrent disease > 6 months after surgery and/or completion of adjuvant therapy were included. Patients must have had an adequate organ and bone marrow function, and have had acceptable serum bilirubin levels (≤ 2.0 x the upper limit of normal (ULN)), and any clinically significant biliary obstruction had to be resolved before randomisation.

The study excluded patients with ampullary carcinoma, with brain metastases, 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. Patients with active HBV were allowed to participate if they were on antiviral therapy.

Randomisation was stratified by disease status (initially unresectable vs. recurrent) and primary tumour location (intrahepatic cholangiocarcinoma vs. extrahepatic cholangiocarcinoma vs. gallbladder carcinoma).

Patients were randomised 1:1 to receive:

- Arm 1: IMFINZI 1 500 mg administered on Day 1 + gemcitabine 1 000 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 1 500 mg every 4 weeks until disease progression or unacceptable toxicity, or
- Arm 2: Placebo administered on Day 1 + gemcitabine 1 000 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 until disease progression or 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, 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 bile duct 55.9%, extrahepatic bile duct 19.1% and gallbladder 25.0%), disease status [recurrent (19.1%) vs. unresectable (80.7%), metastatic (86.0%) vs. locally advanced (13.9%)]. PD-L1 expression was evaluated on tumour and immune cells using the Ventana PD-L1 (SP263) assay and the TAP (tumour area positivity) algorithm, 58.7% patients had TAP ≥ 1% and 30.1% TAP < 1%.

OS and PFS were formally tested at a pre-planned interim analysis (data cut-off 11 Aug 2021) after a median follow-up of 9.8 months. Efficacy results are shown in Table 8 and Figure 13. The maturity for OS was 62% and the maturity for PFS was 84%. IMFINZI + chemotherapy (Arm 1) showed statistically significant improvement vs. placebo + chemotherapy (Arm 2) in OS and in PFS.

Table 8. Efficacy Results for the TOPAZ-1 Study[a]

	IMFINZI + gemcitabine and cisplatin (n=341)	**Placebo + gemcitabine and cisplatin (n=344)**
OS		
Number of deaths (%)	198 (58.1)	226 (65.7)
Median OS (months) (95% CI)[b]	12.8 (11.1, 14.0)	11.5 (10.1, 12.5)
HR (95% CI)[c]	0.80 (0.66, 0.97)	
p-value[c,d]	0.021	
Median follow-up in all patients (months)	10.2	9.5
PFS		
Number of events (%)	276 (80.9)	297 (86.3)
Median PFS (months) (95% CI)[b]	7.2 (6.7, 7.4)	5.7 (5.6, 6.7)
HR (95% CI)[c]	0.75 (0.63, 0.89)	
p-value[c,e]	0.001	
Median follow-up in all patients (months)	7.2	5.6
ORR[f]	91 (26.7)	64 (18.7)
Complete Response n (%)	7 (2.1)	2 (0.6)
Partial Response n (%)	84 (24.6)	62 (18.1)
DoR		
Median DoR (months) (95% CI)[b]	6.4 (5.9, 8.1)	6.2 (4.4, 7.3)

[a] Analysis at data cut-off 11 August 2021.
[b] Calculated using the Kaplan-Meier technique. CI for median derived based on Brookmeyer-Crowley method.
[c] 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 tumour location.
[d] At the interim analysis (data cut-off 11 August 2021) the OS p-value was 0.021, which met the boundary for declaring statistical significance of 0.03 for a 4.9% overall 2-sided alpha, based on a Lan-DeMets alpha spending function with O'Brien Fleming type boundary with the actual number of events observed.
[e] At the interim analysis (data cut-off 11 August 2021) the PFS p-value was 0.001, which met the boundary for declaring statistical significance of 0.0481 for a 4.9% overall 2-sided alpha, based on a Lan-DeMets alpha spending function with Pocock-type boundary with the actual number of events observed.
[f] Confirmed objective response.

An additional planned follow-up analysis of OS (data cut-off 25 Feb 2022) was performed 6.5 months after the interim analysis with an OS maturity of 77%. IMFINZI + chemotherapy continued to demonstrate improved OS vs. chemotherapy alone [HR=0.76, (95% CI: 0.64, 0.91)] and the median follow-up increased to 12 months.

Figure 12: Kaplan-Meier curve of OS, follow-up OS analysis at data cut-off 25 February 2022

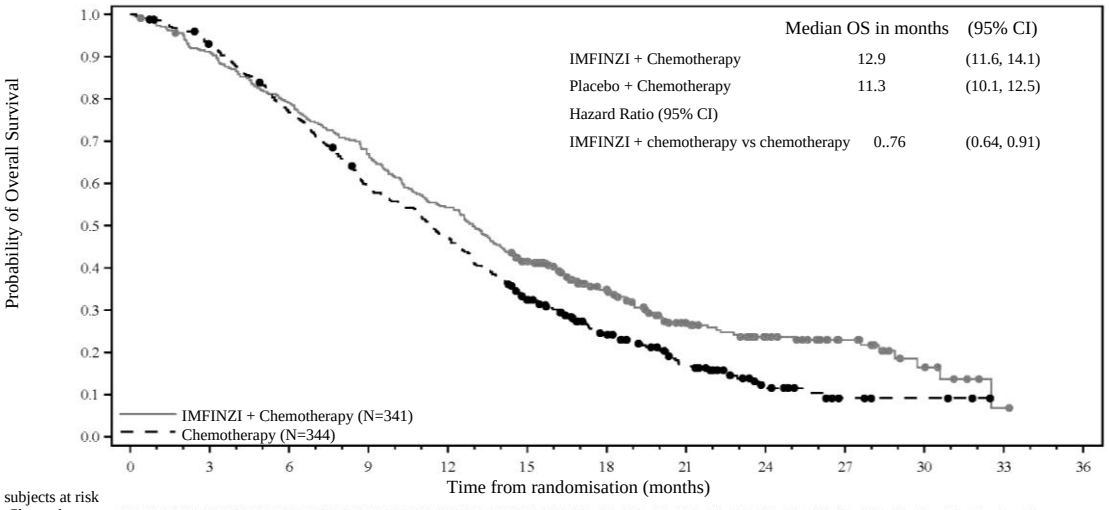
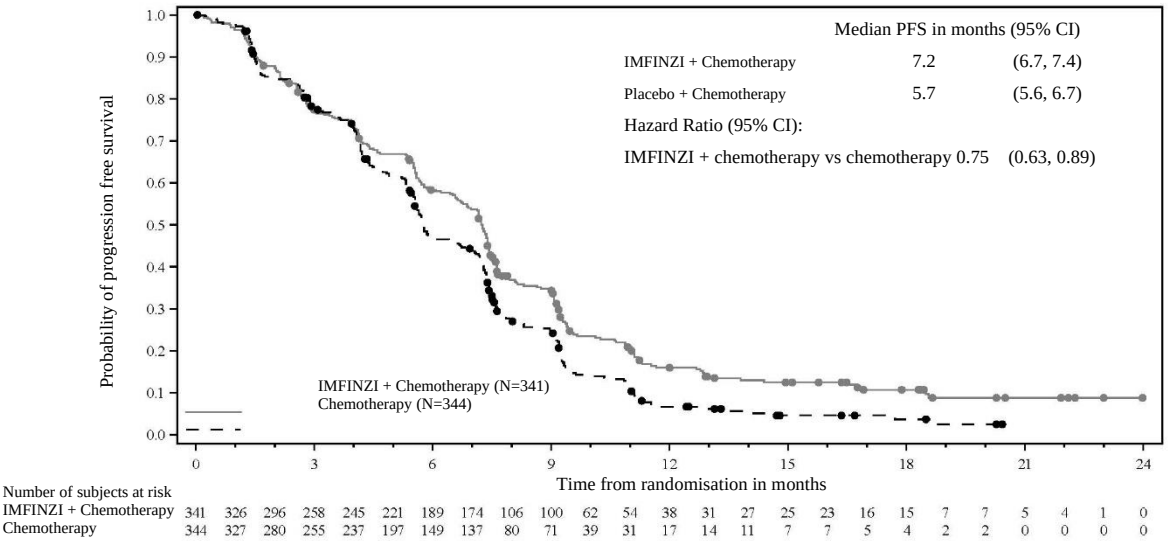


Figure 13: Kaplan-Meier curve of PFS, inferential (primary) analysis at data cut-off 11 August 2021



HCC - HIMALAYA Study

The efficacy of IMFINZI as monotherapy and given in combination with a single dose of tremelimumab 300 mg was evaluated in the HIMALAYA Study, a randomised, open-label, multicentre study in patients with confirmed uHCC who did not receive prior systemic treatment for HCC. The study included patients with Barcelona Clinic Liver Cancer (BCLC) Stage C or B (not eligible for locoregional therapy) and Child-Pugh Score Class A.

The study excluded patients with brain metastases or a history of brain metastases, co-infection of viral hepatitis B and hepatitis C; active or prior documented gastrointestinal (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 oesophageal 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), aetiology 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 1 500 mg every 4 weeks.
- Tremelimumab 300 mg as a single dose + IMFINZI 1 500 mg; followed by IMFINZI 1 500 mg every 4 weeks.
- Sorafenib 400 mg twice daily.

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 superiority for the comparison of IMFINZI given in combination with a single dose of tremelimumab vs. Sorafenib. The key secondary objectives were OS non-inferiority followed by superiority for the comparison of IMFINZI vs. Sorafenib. Other secondary endpoints included PFS, Investigator-assessed ORR and DoR according to RECIST v1.1.

The demographics and baseline disease characteristics were well balanced among study arms. 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 race (2.3%), ECOG PS 0 (62.6%); Child-Pugh Class score A (99.5%), macrovascular invasion (25.2%), extrahepatic spread (53.4%), baseline AFP < 400 ng/ml (63.7%), baseline AFP ≥ 400 ng/ml (34.5%), viral aetiology; hepatitis B (30.6%), hepatitis C (27.2%), uninfected (42.2%), evaluable PD-L1 data (86.3%), PD-L1 Tumour area positivity (TAP) ≥ 1% (38.9%), PD-L1 TAP < 1% (48.3%) [Ventana PD-L1 (SP263) assay].

Results are presented in Table 9, Figure 14 and Figure 15.

Table 9. Efficacy Results for the HIMALAYA Study for IMFINZI given in combination with a single dose of tremelimumab 300 mg and IMFINZI as monotherapy vs. Sorafenib

	IMFINZI + tremelimumab 300 mg (n=393)	**Sorafenib (n=389)**	**IMFINZI (n=389)**
Follow up duration			
Median follow up (months)[a]	33.2	32.2	32.6
OS			
Number of deaths (%)	262 (66.7)	293 (75.3)	280 (72.0)

	IMFINZI + tremelimumab 300 mg (n=393)	Sorafenib (n=389)	IMFINZI (n=389)
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)[b,c]	0.78 (0.66, 0.92)		-
p-value[d]	0.0035		-
HR (95% CI)[b,c,e]	-	0.86 (0.73, 1.03)	
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)		-
HR (95% CI)	-	1.02 (0.88, 1.19)	
ORR			
ORR n (%)[f]	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)
DoR			
Median DoR (months)	22.3	18.4	16.8

[a] Calculated using reverse the Kaplan-Meier technique (with censor indicator reversed).

[b] Based on stratified Cox-model adjusting for treatment, etiology of liver disease (HBV versus HCV versus others), ECOG (0 versus 1).

[c] Performed using stratified log-rank test adjusting for treatment, etiology of liver disease (HBV versus HCV versus others), ECOG (0 versus 1), and macro-vascular invasion (yes versus no).

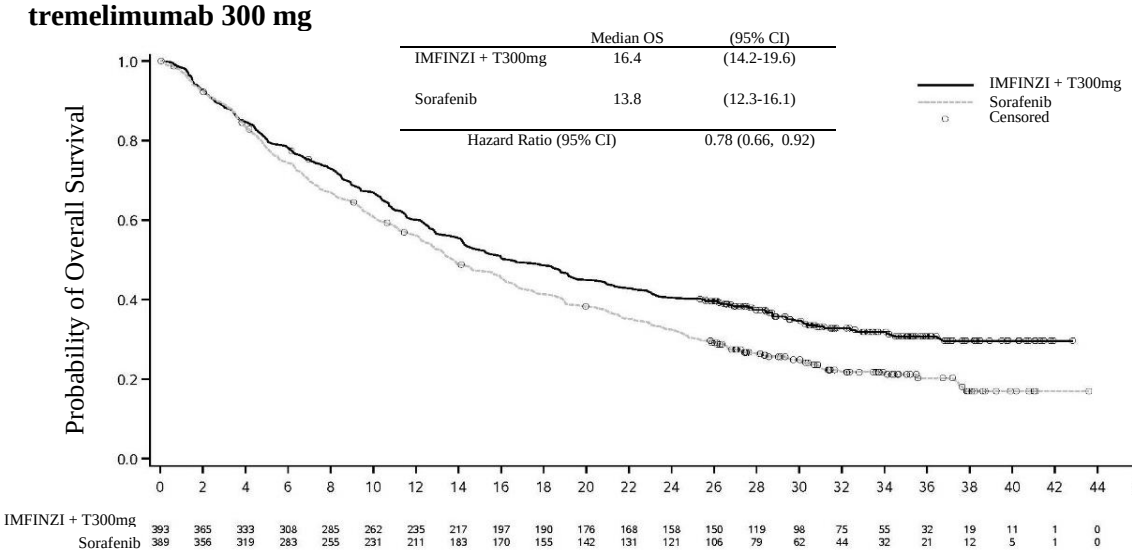
[d] Based on a Lan-DeMets alpha spending function with O'Brien Fleming type boundary and the actual number of events observed, the boundary for declaring statistical significance for IMFINZI + tremelimumab 300 mg vs. Sorafenib was 0.0398 (Lan◦and◦DeMets 1983).

[e] Non-inferiority margin for HR (IMFINZI vs Sorafenib) is 1.08 using a 95.67% confidence interval 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). P-value based on superiority testing of IMFINZI vs. Sorafenib was 0.0674 and did not reach statistical significance.

[f] Confirmed complete response.

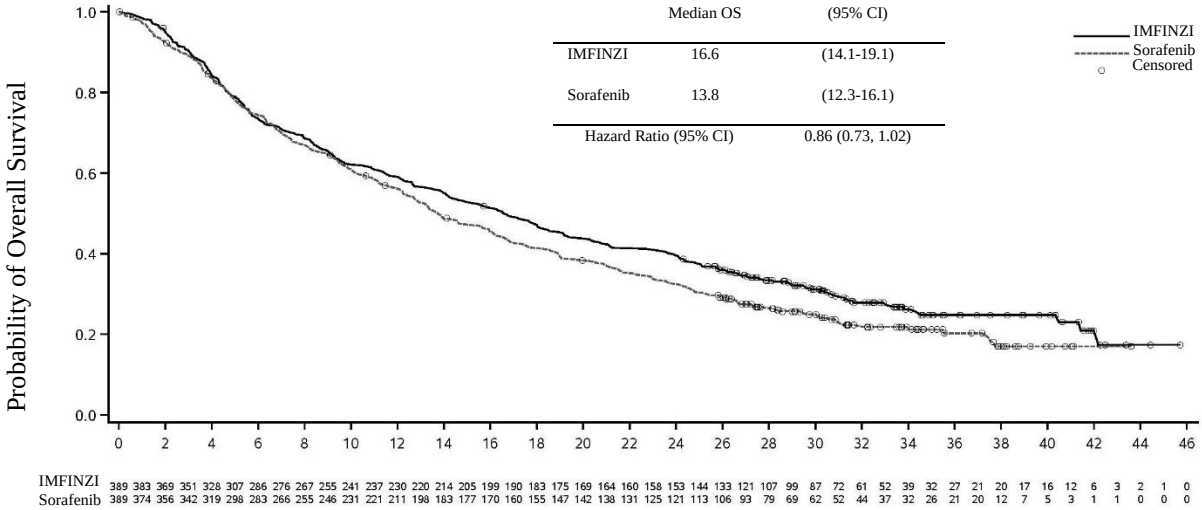
CI=Confidence Interval

Figure 14. Kaplan-Meier curve of OS of IMFINI given in combination with a single dose of tremelimumab 300 mg



Time from randomisation (months)

Figure 15. Kaplan-Meier curve of OS of IMFINZI given as monotherapy



Time from randomisation (months)

Paediatric population

The safety and efficacy of IMFINZI in combination with tremelimumab in children and adolescents aged less than 18 years has not been established. Study D419EC00001 was a multi-centre, open-label dose finding and dose expansion study to evaluate the safety, preliminary efficacy and pharmacokinetics of IMFINZI in combination with tremelimumab followed by IMFINZI monotherapy, in paediatric patients with advanced malignant solid tumours (except primary central nervous system tumours) who had disease progression and for whom no standard of care treatment exists. The study enrolled 50 paediatric patients with an age range from 1 to 17 years with primary tumour categories: neuroblastoma, solid tumour and sarcoma. Patients received either IMFINZI 20 mg/kg in combination with tremelimumab 1 mg/kg or IMFINZI 30 mg/kg in combination with tremelimumab 1 mg/kg intravenously every 4 weeks for 4 cycles, followed by IMFINZI as monotherapy every 4 weeks. In the dose finding phase, IMFINZI and tremelimumab combination therapy was preceded by a single cycle of IMFINZI monotherapy; 8 patients in this phase however discontinued treatment prior to receiving tremelimumab. Thus, of the 50 patients enrolled in the study,

42 received IMFINZI in combination with tremelimumab and 8 received IMFINZI only. In the dose-expansion phase, an ORR of 5.0% (1/20 patients) was reported in the evaluable for response analysis set. No new safety signals were observed relative to the known safety profiles of IMFINZI and tremelimumab in adults. See section 4.2 for information on paediatric use.

5.2 Pharmacokinetic properties

The pharmacokinetics (PK) of durvalumab was assessed for IMFINZI as a single agent, in combination with chemotherapy, in combination with tremelimumab and platinum-based chemotherapy and in combination with tremelimumab.

The PK of durvalumab was studied in 2903 patients with solid tumours with doses ranging from 0.1 to 20 mg/kg administered intravenously once every two, three or four weeks as monotherapy. PK exposure increased more than dose-proportionally (non-linear PK) at doses < 3 mg/kg, and dose proportionally (linear PK) at doses ≥ 3 mg/kg. Steady state was achieved at approximately 16 weeks. Based on population PK analysis that included 1878 patients who received durvalumab monotherapy in the dose range of ≥ 10 mg/kg every 2 weeks, the geometric mean steady state volume of distribution (V_{ss}) was 5.64 L. Durvalumab clearance (CL) decreased over time resulting in a geometric mean steady state clearance (CL_{ss}) of 8.16 ml/h at Day 365; the decrease in CL_{ss} was not considered clinically relevant. The terminal half-life ($t_{1/2}$), based on baseline CL, was approximately 18 days. There was no clinically meaningful difference between the PK of durvalumab as a single agent, in combination with chemotherapy, in combination with tremelimumab and platinum-based chemotherapy and in combination with tremelimumab. The primary elimination pathways of durvalumab are protein catabolism via reticuloendothelial system or target mediated disposition.

Special populations
Age (19-96 years), body weight (31-149 kg), gender, positive anti-drug antibody (ADA) status, albumin levels, LDH levels, creatinine levels, soluble PD-L1, tumour type, race or ECOG status had no clinically significant effect on the PK of durvalumab.

Renal impairment
Mild (creatinine clearance (CrCL) 60 to 89 ml/min) and moderate renal impairment (creatinine clearance (CrCL) 30 to 59 ml/min) had no clinically significant effect on the PK of durvalumab. The effect of severe renal impairment (CrCL 15 to 29 ml/min) on the PK of durvalumab is unknown; however, as IgG monoclonal antibodies are not primarily cleared via renal pathways, a change in renal function is not expected to influence durvalumab exposure.

Hepatic impairment
Mild hepatic impairment (bilirubin ≤ ULN and AST > ULN or bilirubin > 1.0 to 1.5 x ULN and any AST) or moderate hepatic impairment (bilirubin > 1.5 to 3 x ULN and any AST) had no clinically significant effect on the PK of durvalumab. The effect of severe hepatic impairment (bilirubin > 3.0 x ULN and any AST) on the pharmacokinetics of durvalumab is unknown; however, as IgG monoclonal antibodies are not primarily cleared via hepatic pathways, a change in hepatic function is not expected to influence durvalumab exposure.

Paediatric population
The PK of durvalumab in combination with tremelimumab was evaluated in a study of 50 paediatric patients with an age range from 1 to 17 years in study D419EC00001. Patients received either durvalumab 20 mg/kg in combination with tremelimumab 1 mg/kg or durvalumab 30 mg/kg in combination with tremelimumab 1 mg/kg intravenously every 4 weeks for 4 cycles, followed by durvalumab as monotherapy every 4 weeks. Based on population PK analysis, durvalumab systemic exposure in paediatric patients ≥ 35kg receiving durvalumab 20 mg/kg every 4 weeks was similar to exposure in adults receiving durvalumab 20 mg/kg every 4 weeks, whereas in paediatric patients (≥ 35kg) receiving durvalumab 30mg/kg every 4 weeks, exposure was approximately 1.5 fold higher compared to exposure in adults receiving durvalumab 20 mg/kg every 4 weeks. In paediatric patients

< 35kg receiving durvalumab 30 mg/kg every 4 weeks, the systemic exposure was similar to exposure in adults receiving durvalumab 20 mg/kg every 4 weeks.

5.3 Preclinical safety data

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

Reproductive toxicology
As reported in the literature, the PD-1/PD-L1 pathway plays a central role in preserving pregnancy by maintaining maternal immune tolerance to the foetus, and in mouse allogeneic pregnancy models disruption of PD-L1 signalling was shown to result in an increase in foetal loss. In animal reproduction studies, administration of durvalumab to pregnant cynomolgus monkeys from the confirmation of pregnancy through delivery, at exposure levels approximately 18-times higher than those observed at the clinical dose of 10 mg/kg of durvalumab (based on AUC), was associated with placental transfer but not with maternal toxicity or effects on embryofoetal development, pregnancy outcome or postnatal development. Negligible levels of durvalumab was found in milk of cynomolgous monkey on Day 28 after birth.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Histidine
Histidine hydrochloride monohydrate
Trehalose dihydrate
Polysorbate 80
Water for injections

6.2 Incompatibilities

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

6.3 Shelf life

Unopened vial
3 years.

Diluted solution

Chemical and physical in-use stability has been demonstrated for up to 30 days at 2 °C to 8 °C and for up to 24 hours at room temperature (up to 25 °C) from the time of preparation.

From a microbiological point of view, the prepared solution for infusion should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 °C to 8 °C or 12 hours at room temperature (up to 25 °C), unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

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

Do not freeze.

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

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

6.5 Nature and contents of container

Two pack sizes of IMFINZI are available:

2.4 ml (a total of 120 mg durvalumab) of 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) of 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

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

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

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

- Discard any unused portion left in the vial.

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

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

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

7. MARKETING AUTHORISATION HOLDER

AstraZeneca AB
SE-151 85 Södertälje
Sweden

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1322/002 120 mg vial

EU/1/18/1322/001 500 mg vial

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21 September 2018
Date of latest renewal: 24 April 2023

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers of the biological active substance

AstraZeneca Pharmaceuticals LP
Frederick Manufacturing Center (FMC)
633 Research Court
Frederick,
Maryland
21703
United States

Samsung Biologics Co. Ltd
300, Songdo bio-daero
Yeonsu-gu,
Incheon, 21987
Korea, Republic of

Name and address of the manufacturers responsible for batch release

AstraZeneca AB
Gärtunavägen
SE-152 57 Södertälje
Sweden

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

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

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;

- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

IMFINZI 50 mg/ml concentrate for solution for infusion
durvalumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One ml of concentrate contains 50 mg of durvalumab.
One vial of 2.4 ml of concentrate contains 120 mg of durvalumab.
One vial of 10 ml of concentrate contains 500 mg of durvalumab.

3. LIST OF EXCIPIENTS

Excipients: histidine, histidine hydrochloride monohydrate, trehalose dihydrate, polysorbate 80, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion

120 mg/2.4 ml
500 mg/10 ml
1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intravenous use.
Read the package leaflet before use.
For single use only.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

AstraZeneca AB
SE-151 85 Södertälje
Sweden

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1322/002 120 mg vial
EU/1/18/1322/001 500 mg vial

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

IMFINZI 50 mg/ml sterile concentrate
durvalumab
IV

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

120 mg/2.4 ml
500 mg/10 ml

6. OTHER

AstraZeneca AB

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

IMFINZI 50 mg/ml concentrate for solution for infusion
durvalumab

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What IMFINZI is and what it is used for

IMFINZI contains the active substance durvalumab which is a monoclonal antibody, a type of protein designed to recognise a specific target substance in the body. IMFINZI works by helping your immune system fight your cancer.

IMFINZI is used to treat a type of lung cancer called non-small cell lung cancer (NSCLC) in adults. It is used alone when your NSCLC:
- has spread within your lung and cannot be removed by surgery, and
- has responded or stabilised after initial treatment with chemotherapy and radiotherapy.

It is used in combination with tremelimumab and chemotherapy when your NSCLC:
- has spread within both your lungs (and/or to other parts of the body), cannot be removed by surgery and
- has shown no changes (mutations) in genes called EGFR (epidermal growth factor receptor) or ALK (anaplastic lymphoma kinase).

IMFINZI in combination with chemotherapy is used to treat a type of lung cancer called extensive-stage small cell lung cancer (ES-SCLC) in adults. It is used when your SCLC:
- has spread within your lungs (or to other parts of the body) and
- has not previously been treated.

IMFINZI in combination with chemotherapy is used in adults to treat a type of cancer of the bile ducts (cholangiocarcinoma) and gallbladder that are collectively referred to as biliary tract cancers (BTC). It is used when your BTC:
- has spread within your bile ducts and gallbladder (or to other parts of the body).

IMFINZI is used alone or in combination with tremelimumab to treat a type of liver cancer called advanced or unresectable hepatocellular carcinoma (HCC) in adults. It is used when your HCC:
- cannot be removed by surgery (unresectable), and
- may have spread within your liver or to other parts of the body.

If you have any questions about how IMFINZI works or why this medicine has been prescribed for you, ask your doctor or pharmacist.

When IMFINZI is given in combination with other anti-cancer medicines, it is important that you also read the package leaflet for these other medicines. If you have any questions about these medicines, ask your doctor.

2. What you need to know before you are given IMFINZI

You should not be given IMFINZI

- if you are allergic to durvalumab or any of the other ingredients of this medicine (listed in section 6 "Contents of the pack and other information"). Talk to your doctor if you are not sure.

Warnings and precautions

Talk to your doctor before you are given IMFINZI if:

- you have an autoimmune disease (an illness where the body's immune system attacks its own cells);
- you have had an organ transplant;
- you have lung problems or breathing problems;
- you have liver problems.

If any of the above apply to you (or you are not sure), talk to your doctor before you are given IMFINZI.

When you are given IMFINZI, you can have some serious side effects.

If you have any of the following, call or see your doctor straight away. Your doctor may give you other medicines that prevent more severe complications and to help reduce your symptoms. Your doctor may delay the next dose of IMFINZI or stop your treatment with IMFINZI, if you have:

- **inflammation of the lungs**: symptoms may include new or worsening cough, shortness of breath or chest pain;
- **inflammation of the liver**: symptoms may include nausea or vomiting, feeling less hungry, pain on the right side of your stomach, yellowing of skin or whites of eyes, drowsiness, dark urine or bleeding or bruising more easily than normal;
- **inflammation of the intestines**: symptoms may include diarrhoea or more bowel movements than usual, or stools that are black, tarry or sticky with blood or mucus, severe stomach pain or tenderness, hole in the bowel;
- **inflammation of glands** (especially the thyroid, adrenal, pituitary and pancreas): symptoms may include fast heart rate, extreme tiredness, weight gain or weight loss, dizziness or fainting, hair loss, feeling cold, constipation, headaches that will not go away or unusual headaches, abdominal pain, nausea and vomiting;
- **type 1 diabetes**: symptoms may include high blood sugar, feeling more hungry or thirsty than usual, passing urine more often than usual, fast and deep breathing, confusion, or a sweet smell to your breath, a sweet or metallic taste in your mouth or a different odour to your urine or sweat;
- **inflammation of the kidneys**: symptoms may include decrease in the amount of urine you pass;
- **inflammation of the skin**: symptoms may include rash, itching, skin blistering or ulcers in the mouth or on other moist surfaces;
- **inflammation of the heart muscle**: symptoms may include chest pain, shortness of breath, or irregular heartbeat;
- **inflammation or problems of the muscles**: symptoms may include muscle pain, or weakness or rapid fatigue of the muscles;

- **inflammation of the spinal cord** (transverse myelitis): symptoms may include pain, numbness, tingling, or weakness in the arms or legs; bladder or bowel problems including needing to urinate more frequently, urinary incontinence, difficulty urinating and constipation;
- **infusion-related reactions**: symptoms may include chills or shaking, itching or rash, flushing, shortness of breath or wheezing, dizziness or fever;
- **inflammation of the brain** (encephalitis) **or inflammation of the membrane around the spinal cord and brain** (meningitis): symptoms may include seizures, neck stiffness, headache, fever, chills, vomiting, eye sensitivity to light, confusion and sleepiness;
- **inflammation of the nerves:** symptoms may include pain, weakness, and paralysis in the extremities (Guillain-Barré syndrome);
- **inflammation of the joints**: signs and symptoms include joint pain, swelling, and/or stiffness (immune-mediated arthritis);
- **inflammation of the eye**: signs and symptoms include eye redness, eye pain, light sensitivity, and/or changes in vision (uveitis);
- **low number of platelets:** symptoms may include bleeding (nose or gum bleeding) and/or bruising.

If you have any of the symptoms listed above, call or see your doctor straight away.

IMFINZI acts on your immune system. It may cause inflammation in parts of your body. Your risk of these side effects may be higher if you already have an autoimmune disease (a condition where the body attacks its own cells). You may also experience frequent flares of your autoimmune disease, which in the majority of cases are mild.

Children and adolescents
IMFINZI should not be used in children and adolescents below 18 years of age as it has not been studied in these patients.

Other medicines and IMFINZI
Tell your doctor if you are taking, have recently taken or might take any other medicines. This includes herbal medicines and medicines obtained without a prescription.

Pregnancy
- This medicine is not recommended during pregnancy.
- Tell your doctor if you are pregnant, think you may be pregnant or are planning to have a baby.
- If you are a woman who could become pregnant you must use effective birth control while you are being treated with IMFINZI and for at least 3 months after your last dose.

Breast-feeding
- Tell your doctor if you are breast-feeding.
- Ask your doctor if you can breast-feed during or after treatment with IMFINZI.
- It is not known if IMFINZI passes into human breast milk.

Driving and using machines
IMFINZI is not likely to affect you being able to drive and use machines.

However, if you have side effects that affect your ability to concentrate and react, you should be careful when driving or operating machines.

3. How you are given IMFINZI

IMFINZI will be given to you in a hospital or clinic under the supervision of an experienced doctor.
- The recommended dose of IMFINZI is 10 mg per kg of your body weight every 2 weeks or 1 500 mg every 3 or 4 weeks.
- Your doctor will give you IMFINZI through an infusion (drip) into your vein for about 1 hour.

- Your doctor will decide how many treatments you need.
- Depending on your type of cancer, IMFINZI may be given in combination with other anti-cancer medicines.
- When IMFINZI is given in combination with tremelimumab and chemotherapy for your lung cancer, you will first be given tremelimumab followed by IMFINZI and then chemotherapy.
- When IMFINZI is given in combination with chemotherapy for your lung cancer, you will first be given IMFINZI followed by chemotherapy.
- When IMFINZI is given in combination with tremelimumab for your liver cancer, you will first be given tremelimumab followed by IMFINZI.
- Please refer to the package leaflet of the other anti-cancer medicines in order to understand the use of these other medicines. If you have questions about these medicines, ask your doctor.

If you miss an appointment to get IMFINZI
- Call your doctor straight away to reschedule your appointment.
- It is very important that you do not miss a dose of this medicine.

If you have any further questions about your treatment, ask your doctor.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

When you get IMFINZI, you can have some serious side effects (see section 2).

Talk to your doctor straight away if you get any of the following side effects, that have been reported in clinical studies with patients receiving IMFINZI alone:

Very common (may affect more than 1 in 10 people)
- infections of the upper respiratory tract
- underactive thyroid gland that can cause tiredness or weight gain
- cough
- diarrhoea
- stomach pain
- skin rash or itchiness
- fever
- joint pain (arthralgia)

Common (may affect up to 1 in 10 people)
- serious lung infections (pneumonia)
- fungal infection in the mouth
- tooth and mouth soft tissue infections
- flu-like illness
- overactive thyroid gland that can cause fast heart rate or weight loss
- inflammation of the lungs (pneumonitis)
- hoarse voice (dysphonia)
- abnormal liver tests (aspartate aminotransferase increased; alanine aminotransferase increased)
- night sweats
- muscle pain (myalgia)
- abnormal kidney function tests (blood creatinine increased)
- painful urination (dysuria)
- swelling of the legs (oedema peripheral)
- reaction to the infusion of the medicine that can cause fever or flushing
- inflammation of the liver that can cause nausea or feeling less hungry (hepatitis)

Uncommon (may affect up to 1 in 100 people)
- inflammation of thyroid gland (thyroiditis)
- decreased secretion of hormones produced by the adrenal glands that can cause tiredness
- scarring of lung tissue
- blistering of the skin
- inflammation of the gut or intestine (colitis)
- inflammation of the muscle (myositis)
- inflammation of the heart (myocarditis)
- inflammation of the kidneys (nephritis) that can decrease the amount of your urine
- inflammation of the pancreas (pancreatitis)
- red, itchy, dry, scaly patches of thickened skin (psoriasis)

Rare (may affect up to 1 in 1 000 people)
- a condition leading to high blood sugar levels (type 1 diabetes mellitus)
- underactive function of pituitary gland (hypopituitarism including diabetes insipidus) that can cause tiredness, an increase in the amount of your urine
- a condition in which the muscles become weak and there is a rapid fatigue of the muscles (myasthenia gravis)
- inflammation of the membrane around the spinal cord and brain (meningitis)
- low number of platelets caused by an immune reaction (immune thrombocytopenia)
- Inflammation of the bladder (cystitis). Signs and symptoms may include frequent and/or painful urination, urge to pass urine, blood in urine, pain or pressure in lower abdomen
- inflammation of the eye (uveitis)
- inflammation of the joints (immune-mediated arthritis)

Other side effects that have been reported with frequency not known (cannot be estimated from the available data)
- inflammation of the nerves: (Guillain-Barré syndrome)

The following side effects have been reported in clinical studies in patients taking IMFINZI in combination with chemotherapy (the frequency and severity of side effects may vary depending on chemotherapeutic agents received):

Very common (may affect more than 1 in 10 people)
- low number of white blood cells
- low number of red blood cells
- low number of platelets
- nausea; vomiting; constipation, stomach pain, diarrhoea
- abnormal liver tests (aspartate aminotransferase increased; alanine aminotransferase increased)
- hair loss
- rash, red raised rash, dry or itchy skin; inflammation of the skin
- fever
- feeling less hungry
- feeling tired or weak
- cough

Common (may affect up to 1 in 10 people)
- low number of white blood cells with signs of fever
- underactive thyroid gland; overactive thyroid gland; inflammation of thyroid gland
- lack of energy; general feeling of discomfort or illness
- inflammation of the nerves causing numbness, weakness, tingling or burning pain of the arms and legs (neuropathy peripheral)
- shortness of breath
- serious lung infections (pneumonia)

- tooth and mouth soft tissue infections
- swelling (oedema)
- swelling of legs (oedema peripheral)
- inflammation of the mouth or lips
- muscle pain (myalgia)
- inflammation of the lungs (pneumonitis)
- blood clot in the lung (pulmonary embolism)
- infection of the upper respiratory tract
- low number of red blood cells, white blood cells, and platelets (pancytopenia)
- decreased secretion of hormones produced by the adrenal glands that can cause tiredness
- inflammation of the liver that can cause nausea or feeling less hungry (hepatitis)
- abnormal kidney function tests (blood creatinine increased)
- painful urination (dysuria)
- reaction to the infusion of the medicine that can cause fever or flushing
- fungal infection in the mouth
- joint pain (arthralgia)

Uncommon (may affect up to 1 in 100 people)
- flu-like illness
- type 1 diabetes mellitus
- hoarse voice (dysphonia)
- scarring of lung tissue
- inflammation of the gut or intestine (colitis)
- night sweats
- red, itchy, dry, scaly patches of thickened skin (psoriasis)
- inflammation of the pancreas (pancreatitis)
- blistering of the skin
- inflammation of the joints (immune-mediated arthritis)

Rare (may affect up to 1 in 1 000 people)
- inflammation of the eye (uveitis)

The following side effects have been reported in clinical studies in patients taking IMFINZI in combination with tremelimumab and platinum-based chemotherapy (the frequency and severity of side effects may vary depending on chemotherapeutic agents received):

Very common (may affect more than 1 in 10 people)
- infection of the upper respiratory tract
- lung infection (pneumonia)
- low number of red blood cells
- low number of white blood cells
- low number of platelets
- underactive thyroid gland that can cause tiredness or weight gain
- decrease in appetite
- cough
- nausea
- diarrhoea
- constipation
- vomiting
- abnormal liver tests (aspartate aminotransferase increased; alanine aminotransferase increased)
- hair loss
- skin rash
- itchiness
- joint pain (arthralgia)

- feeling tired or weak
- fever

Common (may affect up to 1 in 10 people)
- flu-like illness
- fungal infection in the mouth
- low number of white blood cells with signs of fever
- low number of red blood cells, white blood cells, and platelets (pancytopenia)
- overactive thyroid gland that can cause fast heart rate or weight loss
- decreased levels of hormones produced by the adrenal glands that can cause tiredness
- underactive pituitary gland; inflammation of pituitary gland
- inflammation of thyroid gland (thyroiditis)
- inflammation of the nerves causing numbness, weakness, tingling or burning pain of the arms and legs (neuropathy peripheral)
- inflammation of the lungs (pneumonitis)
- hoarse voice (dysphonia)
- inflammation of the mouth or lips
- abnormal pancreas function tests
- stomach pain
- inflammation of the gut or intestine (colitis)
- inflammation of the pancreas (pancreatitis)
- inflammation of the liver that can cause nausea or feeling less hungry (hepatitis)
- muscle pain (myalgia)
- abnormal kidney function tests (blood creatinine increased)
- painful urination (dysuria)
- swelling of legs (oedema peripheral)
- reaction to the infusion of the medicine that can cause fever or flushing

Uncommon (may affect up to 1 in 100 people)
- tooth and mouth soft tissue infections
- low number of platelets with signs of excessive bleeding and bruising (immune thrombocytopenia)
- diabetes insipidus
- type 1 diabetes mellitus
- inflammation of the brain (encephalitis)
- inflammation of the heart (myocarditis)
- scarring of lung tissue
- blistering of the skin
- night sweats
- inflammation of the skin
- inflammation of the muscles (myositis)
- inflammation of the muscles and vessels
- inflammation of the kidneys (nephritis) that can decrease the amount of your urine
- inflammation of the bladder (cystitis). Signs and symptoms may include frequent and/or painful urination, urge to pass urine, blood in urine, pain or pressure in lower abdomen
- inflammation of the eye (uveitis)
- inflammation of the joints (immune-mediated arthritis)

Other side effects that have been reported with frequency not known (cannot be estimated from the available data)
- a condition in which the muscles become weak and there is a rapid fatigue of the muscles (myasthenia gravis)
- inflammation of the nerves (Guillain-Barré syndrome)
- inflammation of the membrane around the spinal cord and brain (meningitis)

- hole in the bowel (intestinal perforation)

The following side effects have been reported in clinical studies in patients taking IMFINZI in combination with tremelimumab:

Very common (may affect more than 1 in 10 people)
- underactive thyroid gland that can cause tiredness or weight gain
- cough
- diarrhoea
- stomach pain
- abnormal liver tests (aspartate aminotransferase increased; alanine aminotransferase increased)
- skin rash
- itchiness
- fever
- swelling of legs (oedema peripheral)

Common (may affect up to 1 in 10 people)
- infection of the upper respiratory tract
- lung infection (pneumonia)
- flu-like illness
- tooth and mouth soft tissue infections
- overactive thyroid gland that can cause fast heart rate or weight loss
- inflammation of the thyroid gland (thyroiditis)
- decreased secretion of hormones produced by the adrenal glands that can cause tiredness
- inflammation of the lungs (pneumonitis)
- abnormal pancreas function tests
- inflammation of the gut or intestine (colitis)
- inflammation of the pancreas (pancreatitis)
- inflammation of the liver (hepatitis)
- inflammation of the skin
- night sweats
- muscle pain (myalgia)
- abnormal kidney function test (blood creatinine increased)
- painful urination (dysuria)
- reaction to the infusion of the medicine that can cause fever or flushing

Uncommon (may affect up to 1 in 100 people)
- fungal infection in the mouth
- underactive pituitary gland; inflammation of pituitary gland
- a condition in which the muscles become weak and there is a rapid fatigue of the muscles (myasthenia gravis)
- inflammation of the membrane around the spinal cord and brain (meningitis)
- inflammation of the heart (myocarditis)
- hoarse voice (dysphonia)
- scarring of lung tissue
- blistering of the skin
- inflammation of the muscles (myositis)
- inflammation of the muscles and vessels
- inflammation of the kidneys (nephritis) that can decrease the amount of your urine
- inflammation of the joints (immune-mediated arthritis)

Rare (may affect up to 1 in 1,000 people)
- inflammation of the eye (uveitis)

Other side effects that have been reported with frequency not known (cannot be estimated from the available data)

- low number of platelets with signs of excessive bleeding and bruising (immune thrombocytopenia)
- diabetes insipidus
- type 1 diabetes mellitus
- inflammation of the nerves: (Guillain-Barré syndrome)
- inflammation of the brain (encephalitis)
- hole in the bowel (intestinal perforation)
- inflammation of the bladder (cystitis). Signs and symptoms may include frequent and/or painful urination, urge to pass urine, blood in urine, pain or pressure in lower abdomen.

Talk to your doctor straight away if you get any of the side effects listed above.

Reporting of side effects
If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store IMFINZI

IMFINZI will be given to you in a hospital or clinic and the healthcare professional will be responsible for its storage. The storage details are as follows:
Keep this medicine out of the sight and reach of children.
Do not use this medicine after the expiry date which is stated on the carton and vial label after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2 °C to 8 °C).
Do not freeze.
Store in the original package in order to protect from light.
Do not use if this medicine is cloudy, discoloured or contains visible particles.

Do not store any unused portion of the infusion solution for re-use. Any unused medicine or waste material should be disposed of in accordance with local requirements.

6. Contents of the pack and other information

What IMFINZI contains
The active substance is durvalumab.

Each ml of concentrate for solution for infusion contains 50 mg of durvalumab.

Each vial contains either 500 mg of durvalumab in 10 ml of concentrate or 120 mg of durvalumab in 2.4 ml of concentrate.

The other ingredients are: histidine, histidine hydrochloride monohydrate, trehalose dihydrate, polysorbate 80, water for injections.

What IMFINZI looks like and contents of the pack
IMFINZI concentrate for solution for infusion (sterile concentrate) is a preservative-free, clear to opalescent, colourless to slightly yellow solution, free from visible particles.

It is available in packs containing either 1 glass vial of 2.4 ml of concentrate or 1 glass vial of 10 ml of concentrate.

Marketing Authorisation Holder
AstraZeneca AB
SE-151 85 Södertälje
Sweden

Manufacturer
AstraZeneca AB
Gärtunavägen
SE-152 57 Södertälje
Sweden

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
AstraZeneca S.A./N.V.
Tel: +32 2 370 48 11

България
АстраЗенека България ЕООД
Тел.: +359 24455000

Česká republika
AstraZeneca Czech Republic s.r.o.
Tel: +420 222 807 111

Danmark
AstraZeneca A/S
Tlf: +45 43 66 64 62

Deutschland
AstraZeneca GmbH
Tel: +49 40 809034100

Eesti
AstraZeneca
Tel: +372 6549 600

Ελλάδα
AstraZeneca A.E.
Τηλ: +30 210 6871500

España
AstraZeneca Farmacéutica Spain, S.A.
Tel: +34 91 301 91 00

France
AstraZeneca
Tél: +33 1 41 29 40 00

Hrvatska
AstraZeneca d.o.o.
Tel: +385 1 4628 000

Ireland

Lietuva
UAB AstraZeneca Lietuva
Tel: +370 5 2660550

Luxembourg/Luxemburg
AstraZeneca S.A./N.V.
Tél/Tel: +32 2 370 48 11

Magyarország
AstraZeneca Kft.
Tel.: +36 1 883 6500

Malta
Associated Drug Co. Ltd
Tel: +356 2277 8000

Nederland
AstraZeneca BV
Tel: +31 85 808 9900

Norge
AstraZeneca AS
Tlf: +47 21 00 64 00

Österreich
AstraZeneca Österreich GmbH
Tel: +43 1 711 31 0

Polska
AstraZeneca Pharma Poland Sp. z o.o.
Tel.: +48 22 245 73 00

Portugal
AstraZeneca Produtos Farmacêuticos, Lda.
Tel: +351 21 434 61 00

România
AstraZeneca Pharma SRL
Tel: +40 21 317 60 41

Slovenija
AstraZeneca UK Limited

AstraZeneca Pharmaceuticals (Ireland) DAC
Tel: +353 1609 7100

Ísland
Vistor hf.
Sími: +354 535 7000

Italia
AstraZeneca S.p.A.
Tel: +39 02 00704500

Κύπρος
Αλέκτωρ Φαρμακευτική Λτδ
Τηλ: +357 22490305

Latvija
SIA AstraZeneca Latvija
Tel: +371 67377100

Tel: +386 1 51 35 600

Slovenská republika
AstraZeneca AB, o.z.
Tel: +421 2 5737 7777

Suomi/Finland
AstraZeneca Oy
Puh/Tel: +358 10 23 010

Sverige
AstraZeneca AB
Tel: +46 8 553 26 000

United Kingdom (Northern Ireland)
AstraZeneca UK Ltd
Tel: +44 1582 836 836

This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu

---

The following information is intended for healthcare professionals only:

Preparation and administration of the infusion

- Parenteral medicinal products should be inspected visually for particulate matter and discolouration prior to administration. The concentrate is a clear to opalescent, colourless to slightly yellow solution, free from visible particles. Discard the vial if the solution is cloudy, discoloured or visible particles are observed.
- Do not shake the vial.
- Withdraw the required volume of concentrate from the vial(s) and transfer into an intravenous bag containing sodium chloride 9 mg/ml (0.9%) solution for injection, or glucose 50 mg/ml (5%) solution for injection, to prepare a diluted solution with a final concentration ranging from 1 to 15 mg/ml. Mix diluted solution by gentle inversion.
- The medicinal product, once diluted, should be used immediately. The diluted solution must not be frozen. Chemical and physical in-use stability has been demonstrated for up to 30 days at 2 ºC to 8 ºC and for up to 24 hours at room temperature (up to 25 ºC) from the time of preparation.
- From a microbiological point of view, the prepared solution for infusion should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 ºC to 8 ºC or 12 hours at room temperature (up to 25 ºC), unless dilution has taken place in controlled and validated aseptic conditions.
- If refrigerated, intravenous bags must be allowed to come to room temperature prior to use. Administer the infusion solution intravenously over 1 hour using a sterile, low-protein binding 0.2 or 0.22 micron in-line filter.

- Do not co-administer other medicinal products through the same infusion line.
- IMFINZI is single-dose. Discard any unused portion left in the vial.

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