Proposed packaging material		
Code	Imfinzi 120 mg & 500 mg – PI-07.06	
Regulatory Objective	☐NDA ☐Renewal ☒Variation change detail no.: RO-Change Event-0035381-0000068, RO-Change Event-0040505-0000005	
Code of previous version	PI-05.05	
Reference	☐CDS version: ☐CPIL version:	☒SmPC country/version/date: VV-RIM-04948629 v.10; ☐RAM approval:
Changes	New Indication: DUO-E Study	
Name	ARH	

IMFINZI™

DURVALUMAB

Concentrated Solution for Infusion

1 NAME OF THE MEDICINAL PRODUCT

IMFINZI 120 mg Infusion

IMFINZI 500 mg Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

For the full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM

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

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Non-small cell lung cancer (NSCLC)

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

IMFINZI in combination with tremelimumab and platinum-based chemotherapy is indicated for 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 adult patients with extensive-stage small cell lung cancer (ES-SCLC).

Biliary Tract Cancer (BTC)

IMFINZI in combination with gemcitabine and cisplatin is indicated for treatment of adults with unresectable or metastatic biliary tract cancer (BTC).

Hepatocellular Carcinoma (HCC)

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

Endometrial Cancer

IMFINZI in combination with carboplatin and paclitaxel is indicated for the first-line treatment of adults with primary advanced or recurrent endometrial cancer who are candidates for systemic therapy, followed by maintenance treatment with:

- IMFINZI as monotherapy in endometrial cancer that is mismatch repair deficient (dMMR)
- IMFINZI in combination with olaparib in endometrial cancer that is mismatch repair proficient (pMMR).

4.2 Dose and method of administration

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

MMR testing for patients with endometrial cancer

Patients with endometrial cancer should be evaluated for treatment based on tumour MMR status 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 1500 mg every 4 weeks[a]	Until disease progression, unacceptable toxicity, or a maximum of 12 months[b]
Combination Therapy		
Metastatic NSCLC	During platinum chemotherapy: 1500 mg[c] in combination with tremelimumab 75 mg[c]	Until disease progression or unacceptable toxicity

	and platinum-based chemotherapyevery 3 weeks (21 days) for 4 cycles (12 weeks) Post-platinum chemotherapy: 1500 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	
ES-SCLC	1500 mg[g] in combination with chemotherapy every 3 weeks (21 days) for 4 cycles, followed by 1500 mg every 4 weeks as monotherapy	Until disease progression or unacceptable toxicity
BTC	1500 mg[h] in combination with chemotherapy every 3 weeks (21 days) up to 8 cycles, followed by 1500 mg every 4 weeks as monotherapy	Until disease progression or until unacceptable toxicity
HCC	IMFINZI 1500 mg[i] administered in combination with 300 mg[i] tremelimumab as a single dose at Cycle 1/Day 1, followed by IMFINZI as monotherapy every 4 weeks	Until disease progression or unacceptable toxicity
Endometrial Cancer	1 120 mg in combination with carboplatin and paclitaxel every 3 weeks (21 days) for a minimum of 4 and up to 6 cycles,	Until disease progression or unacceptable toxicity

	followed by IMFINZI 1 500 mg[j] every 4 weeks as monotherapy (dMMR patients) or in combination with olaparib 300 mg twice daily (pMMR patients)	

[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 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

[j] Endometrial cancer patients with a body weight of 30 kg or less during maintenance phase must receive weight-based dosing equivalent to IMFINZI at 20 mg/kg, until weight is greater than 30 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 and non-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 and management recommendations for IMFINZI or IMFINZI in combination with other products

Adverse reactions	**Severity**[a]	**Treatment modification**
Immune-mediated adverse reactions		
Pneumonitis	Grade 2	Withhold dose
	Grade 3 or 4	Permanently discontinue
Hepatitis	ALT or AST >3- ≤ 5 x ULN or total bilirubin >1.5-≤ 3 x ULN	Withhold dose

Adverse reactions	**Severity**[a]	**Treatment modification**
	ALT or AST > 5 - ≤ 10 x ULN	Withhold IMFINZI and permanently discontinue tremelimumab (where appropriate)
	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
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
Endocrinopathies: Hyperthyroidism	Grade 2-4	Withhold dose until clinically stable
Endocrinopathies: Hypothyroidism	Grade 2-4	No changes

Adverse reactions	**Severity**[a]	**Treatment modification**
Endocrinopathies: Adrenal insufficiency, Hypophysitis/hypopituitarism	Grade 2-4	Withhold dose until clinically stable
Immune-mediated Type 1 diabetes mellitus	Grade 2-4	No changes
Nephritis	Grade 2 with serum creatinine >1.5-3x (ULN or baseline)	Withhold dose
	Grade 3 with serum creatinine >3x baseline or >3-6xULN; Grade 4 with serum creatinine >6xULN	Permanently discontinue
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
Myositis/polymyositis/rhabdomyolisis	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
Myasthenia gravis	Grade 2-4	Permanently discontinue
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 -3	Withhold dose
	Grade 4	Permanently discontinue
Non-immune-mediated adverse reactions		

Adverse reactions	Severity[a]	Treatment modification
Pure red cell aplasia (PRCA)[i]	Any Grade	Permanently discontinue
Other 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 tremelimumab 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.
[i] Adverse drug reaction is only associated when olaparib maintenance treatment is used in combination with IMFINZI, following treatment with IMFINZI in combination with platinum-based chemotherapy.

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 patient populations

Renal impairment

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

Hepatic impairment

No dose adjustment 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)

Use in paediatric patients

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

Use in the elderly

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

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).

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 unresectable hepatocellular carcinoma (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 summary of product characteristics (SmPC) for tremelimumab dosing information.

Preparation of solution

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

- Visually inspect drug product for particulate matter and discolouration. IMFINZI is a clear to opalescent, colourless to slightly yellow solution. Discard the vial if the solution is cloudy, discoloured or visible particles are observed. Do not shake the vial.
- Withdraw the required volume from the vial(s) of IMFINZI and transfer into an intravenous (IV) bag containing 0.9% Sodium Chloride Injection, or 5% Dextrose Injection. Mix diluted solution by gentle inversion. The final concentration of the diluted solution should be between 1 mg/mL and 15 mg/mL. Do not freeze or shake the solution.
- Care must be taken to ensure the sterility of prepared solutions.
- Do not re-enter the vial after withdrawal of drug; only withdraw one dose per vial.

- Discard any unused portion left in the vial.
- No incompatibilities between IMFINZI and 9 g/L (0.9%) sodium chloride or 50 g/L (5%) dextrose in polyvinylchloride or polyolefin IV bags have been observed.

After preparation of infusion solution

IMFINZI does not contain a preservative.

Chemical and physical in-use stability has been demonstrated for up to 30 days at 2ºC to 8ºC and for up to 24 hours at room temperature (up to 25ºC) 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 2ºC to 8ºC or 12 hours at room temperature (up to 25ºC), unless dilution has taken place in controlled and validated aseptic conditions

Administration

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

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

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Refer to section 4.2, 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 or IMFINZI in combination with platinum-based chemotherapy followed by IMFINZI in combination with olaparib (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

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

Patients should be monitored for signs and symptoms of pneumonitis. Suspected pneumonitis should be confirmed with radiographic imaging and other infectious and disease-related aetiologies excluded, and managed as recommended in Section 4.2

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/thyroiditis

Immune-mediated hypothyroidism, *hyperthyroidism, or 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 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/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. 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 Adverse effects). 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 Adverse effects. Events of Stevens-Johnson Syndrome (SJS) 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 see 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, myositis, polymyositis, rhabdomyolysis, meningitis, Guillain-Barré syndrome, immune thrombocytopenia, immune-mediated arthritis, uveitis and cystitis noninfective and pancreatitis (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.

Treatment-specific precaution (IMFINZI in combination with olaparib in endometrial cancer)

Haematological toxicity

Pure red cell aplasia (PRCA) (see section 4.8) was reported when olaparib maintenance treatment was used in combination with IMFINZI, following treatment with IMFINZI in combination with platinum-based chemotherapy. If PRCA is confirmed, treatment with IMFINZI and olaparib should be discontinued.

Autoimmune haemolytic anemia (AIHA) was reported when olaparib maintenance treatment was used in combination with IMFINZI, following treatment with IMFINZI in combination with platinum-based chemotherapy. If AIHA is confirmed, treatment with IMFINZI and olaparib should be discontinued.

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 trials

Patients with the following were excluded from clinical trials: 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 Interactions with other medicines and other forms of interactions

Durvalumab is an immunoglobulin, therefore no formal pharmacokinetic drug-drug interaction studies have been conducted. 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.
Furthermore, in the DUO-E study, the exposure to durvalumab was similar in both treatment arms which indicates that there were no clinically meaningful PK drug-drug interactions between durvalumab and olaparib, although exposure to olaparib was not measured throughout the study

4.6 Fertility, pregnancy and lactation

Effects on fertility

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

Use in pregnancy – Category D

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

Animal data
As reported in the literature, the PD-1/PD-L1 pathway plays a central role in preserving pregnancy by maintaining maternal immune tolerance to the foetus. In mouse allogeneic pregnancy models, disruption of PD-L1 signalling was shown to result in an increase in foetal loss. The effects of durvalumab on prenatal and postnatal development were evaluated in reproduction studies in cynomolgus monkeys. Durvalumab was administered from the confirmation of pregnancy through delivery at exposure levels approximately 6 to 20 times higher than those observed in humans at the recommended clinical dose of 10 mg/kg (based on AUC). Administration of durvalumab resulted in

premature delivery, foetal loss (abortion and stillbirth) and increase in neonatal deaths compared to concurrent controls. Durvalumab was detected in infant serum on postpartum Day 1, indicating the presence of placental transfer of durvalumab. Based on its mechanism of action, foetal exposure to durvalumab may increase the risk of developing immune-mediated disorders or altering the normal immune response and immune-mediated disorders have been reported in PD-1 knockout mice.

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

4.7 Effects on ability to drive and use machines

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

4.8 Adverse effects (undesirable effects)

Summary of the safety profile

IMFINZI as monotherapy

The safety of IMFINZI as monotherapy is based on pooled data in 3006 patients across multiple tumour types. IMFINZI was administered at a dose of 10 mg/kg every 2 weeks or 20 mg/kg every 4 weeks. The most common (>10%) adverse reactions were cough/productive cough (21.5%), diarrhoea (16.3%), rash (16.0%), pyrexia (13.8%), upper respiratory tract infections (13.5%), abdominal pain (12.7%), pruritus (10.8%), and hypothyroidism (10.1%). The most common (> 2%) Grade ≥ 3 adverse reactions were pneumonia (3.5%) and aspartate aminotransferase increased/alanine aminotransferase increased (2.3%).

IMFINZI was discontinued due to adverse reactions in 3.6% of patients. The most common adverse reaction leading to treatment discontinuation was pneumonitis (1.1%) and pneumonia (0.8%).

IMFINZI was delayed or interrupted due to adverse reactions in 13.7% of patients. The most common adverse reactions leading to dose delay or interruption were pneumonia (2.7%) and aspartate aminotransferase increased/alanine aminotransferase increased (1.7%).

IMFINZI in combination with chemotherapy

The safety of IMFINZI in combination with chemotherapy is based on pooled data in 838 patients from 3 studies (TOPAZ-1, CASPIAN and DUO-E). The most common (> 10%) adverse reactions were neutropenia (47.3%), anaemia (44.9%), fatigue (38.8%), nausea (38.4%), thrombocytopenia (28.0%), alopecia (27.4%), constipation (25.9%), decreased appetite (21.2%), neuropathy peripheral (21.2%), abdominal pain (20.3%), diarrhoea (19.1%), rash (18.5%), vomiting (18.0%), leukopenia (17.2%), pyrexia (13.4%), arthralgia (12.4%), cough/productive cough (12.4%), pruritus (11.8%), hypothyroidism (11.0%), aspartate aminotransferase increased/alanine aminotransferase increased (10.7%) and oedema peripheral (10.1%).

The most common (> 2%) Grade ≥ 3 adverse reactions were neutropenia neutropenia (30.7%), anaemia (17.1%), thrombocytopenia (9.9%), leukopenia (6.4%), fatigue (4.5%), febrile neutropenia

(2.9%), aspartate aminotransferase increased/alanine aminotransferase increased (2.1%) and pneumonia (2.0%).

IMFINZI was discontinued due to adverse reactions in 3.6% of patients. The most common adverse reactions leading to treatment discontinuation were anaemia (0.5%), rash (0.5%) and fatigue (0.5%).

IMFINZI was delayed or interrupted due to adverse reactions in 31.0% of patients. The most common adverse reactions leading to dose delay or interruption were neutropenia (15.0%), thrombocytopenia (6.8%), anaemia (5.1%) and leukopenia (2.9%).

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%) 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) are 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 are colitis (2.6%), diarrhoea (2.4%), pneumonia (2.2%), and hepatitis (1.7%).

The frequency of treatment discontinuation due to adverse reactions is 6.5%. The most common adverse reactions leading to treatment discontinuation are 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.

IMFINZI in combination with platinum-based chemotherapy followed by IMFINZI in combination with olaparib 300 mg twice daily

The safety of IMFINZI given in combination with platinum-based chemotherapy followed by IMFINZI in combination with olaparib 300 mg twice daily is based on data in 238 patients with endometrial cancer. The most common (> 20%) adverse reactions were anaemia (61.8%), nausea (54.6%), fatigue (54.2%), neuropathy peripheral (51.7%), alopecia (50.8%), neutropenia (39.5%), constipation (32.8%), thrombocytopenia (29.8%), diarrhoea (28.2%), vomiting (25.6%), arthralgia (24.4%), rash (23.5%), abdominal pain (23.5%), decreased appetite (23.1%) and leukopenia (20.2%).

The most common (> 2%) NCI CTCAE Grade ≥ 3 adverse reactions were neutropenia (25.2%), anaemia (23.5%), leukopenia (6.7%), thrombocytopenia (5.9%), fatigue (5.5%), febrile neutropenia (3.4%), nausea (2.9%), aspartate aminotransferase increased / alanine aminotransferase increased (2.9%) and neuropathy peripheral (2.5%).

IMFINZI was discontinued in 4.6% of patients. The most common adverse reaction leading to treatment discontinuation was pneumonitis (1.7%).

IMFINZI was interrupted in 38.2% of patients. The most common adverse reactions leading to dose interruption were anaemia (13.4%), thrombocytopenia (11.8%), neutropenia (10.1%), leukopenia (2.9%), hypothyroidism (2.1%) and upper respiratory tract infection (2.1%).

Tabulated list of adverse reactions

Table 3 lists the incidence of adverse reactions in the IMFINZI monotherapy pooled safety dataset and in patients treated with IMFINZI in combination with chemotherapy (N=838) and in patients treated with IMFINZI in combination with platinum-based chemotherapy followed by IMFINZI in combination with olaparib (platinum-based chemotherapy + IMFINZI + olaparib) (N=238). 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 < 1/1000); 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**	**Platinum-based chemotherapy + IMFINZI + olaparib***
Infections and infestations			
Very common	Upper respiratory tract infections[a]		Upper respiratory tract infection[a]
Common	Pneumonia[b,c], Influenza, Oral candidiasis, Dental and oral soft tissue infections[d]	Pneumonia[b,c], Upper respiratory tract infections[a] Dental and oral soft tissue infections[d]	Pneumonia, Oral candidiasis, Dental and oral soft tissue infections[d]

Uncommon		Oral candidiasis, Influenza,	Influenza
Blood and lymphatic system disorders			
Very Common		Anaemia, Leukopenia[e], Neutropenia[f], Thrombocytopenia[g]	Anaemia[h], Leukopenia[h] Neutropenia[h], Thrombocytopenia[h]
Common		Febrile neutropenia, Pancytopenia[c]	Aplasia pure red cell, Febrile neutropenia[h], Lymphopenia[i]
Uncommon		Immune thrombocytopenia	Pancytopenia[h]
Rare	Immune thrombocytopenia[c]		
Immune system disorders			
Common			Hypersensitivity[i,j]
Endocrine disorders			
Very common	Hypothyroidism[k]	Hypothyroidism[k]	Hypothyroidism
Common	Hyperthyroidism[l]	Hyperthyroidism[l] Thyroiditis[m]	Hyperthyroidism, Thyroiditis
Uncommon	Thyroiditis[m], Adrenal insufficiency	Adrenal insufficiency, Type 1 diabetes mellitus	
Rare	Type 1 diabetes mellitus, Hypophysitis/Hypopituitarism, Diabetes insipidus		
Eye Disorder			
Uncommon		Uveitis	Uveitis
Rare	Uveitis		
Metabolism and nutrition disorders			
Very common		Decreased appetite	Decreased appetite[h]
Nervous System Disorders			
Very Common		Neuropathy peripheral[n]	Neuropathy peripheral, Dizziness[i], Headache[i], Dysgeusia[i,o]
Uncommon		Myasthenia gravis	
Rare	Myasthenia gravis, Meningitis[p]		
Not known	Noninfective encephalitis[q], Guillain-Barré syndrome, Myelitis transverse[r]		
Vascular disorders			
Common			Venous thromboembolic events[i,s]
Cardiac disorders			
Uncommon	Myocarditis		
Respiratory, thoracic and mediastinal disorders			
Very common	Cough/Productive Cough	Cough/Productive Cough	Cough/Productive cough, Dyspnoea[i,t]
Common	Pneumonitis[c], Dysphonia	Pneumonitis	Pneumonitis, Dysphonia

Uncommon	Interstitial lung disease	Interstitial lung disease, Dysphonia	Interstitial lung disease
Gastrointestinal disorders			
Very common	Diarrhoea, Abdominal pain[u]	Diarrhoea, Abdominal pain[u], Constipation, Nausea, Vomiting	Diarrhoea, Abdominal pain[u], Constipation[h], Nausea[h], Vomiting[h], Stomatitis[h]
Common		Stomatitis[v]	Dyspepsia[i], Colitis[w]
Uncommon	Colitis[w], Pancreatitis[x]	Colitis[w], Pancreatitis[x]	
Rare	Coeliac disease[r]	Coeliac disease[r]	
Hepatobiliary disorders			
Very common		Aspartate aminotransferase increased or Alanine aminotransferase increased[y]	Aspartate aminotransferase increased or Alanine aminotransferase increased
Common	Hepatitis[c,z], Aspartate aminotransferase increased or Alanine aminotransferase increased[c,y]	Hepatitis[z]	
Uncommon			Hepatitis[z]
Skin and subcutaneous tissue disorders			
Very common	Rash[aa], Pruritus	Rash[aa], Alopecia, Pruritus	Rash[aa], Alopecia[h], Pruritus
Common	Night sweats	Dermatitis	Dermatitis[bb]
Uncommon	Dermatitis, Psoriasis, Pemphigoid[cc]	Pemphigoid[cc], Night sweats, Psoriasis	Night sweats
Musculoskeletal and connective tissue disorders			
Very common	Arthralgia	Arthralgia	Arthralgia[h], Myalgia
Common	Myalgia	Myalgia	
Uncommon	Myositis[dd]	Immune-mediated arthritis, Myositis	Myositis
Rare	Polymyositis[ee], Immune-mediated arthritis		
Renal and urinary disorders			
Very common			Blood creatinine increased
Common	Blood creatinine increased, Dysuria	Blood creatinine increased, Dysuria	Dysuria
Uncommon	Nephritis[ff]	Cystitis noninfective	Cystitis noninfective[h]
Rare	Cystitis noninfective		
General disorders and administration site conditions			
Very common	Pyrexia	Pyrexia, Fatigue[gg], Peripheral oedema[hh]	Pyrexia, Fatigue[h], Peripheral oedema[hh]
Common	Peripheral oedema[hh]		
Injury, poisoning and procedural complications			
Common	Infusion-related reaction[ii]	Infusion-related reaction[ii]	Infusion-related reaction

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.

* overall study of treatment with up to six 21-day cycles with platinum-based chemotherapy in combination with IMFINZI, followed by IMFINZI in combination with olaparib.

[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] adverse reaction only applies to chemotherapy ADRs in the DUO-E study.

[i] adverse reaction only applies to olaparib ADRs in the DUO-E study.

[j] includes drug hypersensitivity and hypersensitivity

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

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

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

[n] Includes neuropathy peripheral, paraesthesia and peripheral sensory neuropathy.

[o] includes dysgeusia and taste disorder

[p] includes meningitis and noninfective meningitis.

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

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

[s] includes deep vein thrombosis, embolism, embolism venous, pelvic venous thrombosis, superficial vein thrombosis and thrombosis.

[t] includes dyspnoea and dyspnoea exertional

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

[v] includes stomatitis and mucosal inflammation.

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

[x] includes pancreatitis and pancreatitis acute.

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

[z] includes hepatitis, autoimmune hepatitis, hepatitis toxic, hepatic cytolysis, hepatocellular injury, hepatitis acute, hepatotoxicity and immune-mediated hepatitis

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

[bb] includes dermatitis and immune-mediated dermatitis.

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

[dd] Includes rhabdomyolysis, myositis, and polymyositis.

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

[ff] includes autoimmune nephritis, tubulointerstitial nephritis, nephritis, glomerulonephritis and glomerulonephritis membranous

[gg] includes fatigue and asthenia

[hh] includes oedema peripheral and peripheral swelling

[ii] 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	

	IMFINZI in combination with tremelimumab 75 mg and platinum-based chemotherapy	IMFINZI in combination with tremelimumab 300 mg
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]
Common	Stomatitis[d,r], Amylase increased, Abdominal pain[q], Lipase increased, Colitis[s], Pancreatitis[t]	Lipase increased, Amylase increased, Colitis[s], Pancreatitis[t],
Rare	Coeliac disease[n]	Coeliac disease[h]
Not known	Intestinal perforation[m], Large intestine perforation[m]	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	

	IMFINZI in combination with tremelimumab 75 mg and platinum-based chemotherapy	IMFINZI in combination with tremelimumab 300 mg
Common	Myalgia	Myalgia
Uncommon	Myositis[y], Polymyositis[y], Immune-mediated arthritis[n]	Myositis[y], Polymyositis[y], Immune-mediated arthritis
Renal and urinary disorders		
Common	Blood creatinine increased, Dysuria	Blood creatinine increased, Dysuria
Uncommon	Nephritis, Cystitis noninfective	Nephritis[z]
Not known		Cystitis noninfective[h]
General disorders and administration site conditions		
Very common	Fatigue[d], Pyrexia	Pyrexia, Oedema peripheral[aa]
Common	Oedema peripheral[aa]	
Injury, poisoning and procedural complications		
Common	Infusion-related reaction[bb]	Infusion-related reaction[bb]

[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 rhabdomyolysis, myositis, and polymyositis.
[z] Includes autoimmune nephritis and immune-mediated nephritis.
[aa] Includes oedema peripheral and peripheral swelling.
[bb] 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 or withdrawal and/or treatment modifications. The data for the following immune-mediated adverse reactions reflect IMFINZI monotherapy the combined safety database of 3006 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 1500 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 2280 patients who received IMFINZI 20 mg/kg every 4 weeks in combination with tremelimumab 1 mg/kg or IMFINZI 1500 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 1500 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 = 3006 multiple tumour types), immune-mediated pneumonitis occurred in 92 (3.1%) patients, including Grade 3 in 25 (0.8%) patients, Grade 4 in 2 (< 0.1%) patient and Grade 5 in 6 (0.2%) patients. The median time to onset was 55 days (range: 2-785 days). Sixty-nine of the 92 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day), and 2 patients also received infliximab infliximab and 1 patient also received cyclosporine. IMFINZI was discontinued in 38 patients. Resolution occurred in 53 patients.

Immune-mediated pneumonitis occurred more frequently in the PACIFIC study who had completed treatment with concurrent chemoradiation within 1 to 42 days prior to initiation of the study (9.9%), than in the other patients in the combined safety database (1.8%).

In the PACIFIC Study, (n = 475 in the IMFINZI arm, and n = 234 in the placebo arm) immune-mediated pneumonitis occurred in 47 (9.9%) patients in the IMFINZI-treated group and 14 (6.0%) patients in the placebo group, including Grade 3 in 9 (1.9%) patients on IMFINZI vs. 6 (2.6%) patients on placebo and Grade 5 (fatal) in 4 (0.8%) patients on IMFINZI vs. 3 (1.3%) patients on placebo. The median time to onset in the IMFINZI-treated group was 46 days (range: 2-342 days) vs. 57 days (range: 26-253 days) in the placebo group. In the IMFINZI-treated group, 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=2280), 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.

In the DUO-E Study, out of 238 patients treated with platinum-based chemotherapy in combination with IMFINZI, followed by IMFINZI in combination with olaparib (platinum-based chemotherapy + IMFINZI + olaparib arm) immune-mediated pneumonitis occurred in 5 (2.1%) patients, including Grade 3 in 3 (1.3%) patients. The median time to onset was 85 days (range: 65-321 days). Five patients received systemic corticosteroids, including 4 patients who received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). Resolution occurred in all 5 patients.

Immune-mediated hepatitis

In the combined safety database with IMFINZI monotherapy, immune-mediated hepatitis occurred in 68 (2.3%) patients, including Grade 3 in 35 (1.2%) patient, Grade 4 in 6 (0.2%) and Grade 5 (fatal) in 4 (0.1%) patients. The median time to onset was 33 days (range: 3-333 days). Forty-five of the 68 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). Three patients also received mycophenolate treatment. IMFINZI was discontinued in 9 patients. Resolution occurred in 31 patients.

In the combined safety database with IMFINZI in combination with tremelimumab (n=2280), 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 58 (1.9%) patients, including Grade 3 in 9 (0.3%) patients and Grade 4 in 2 (<0.1%) patient. The median time to onset was 70 days (range: 1-394 days). Thirty-eight of the 58 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). One patient also received infliximab treatment and 1 patient also received mycophenolate. IMFINZI was discontinued in 9 patients. Resolution occurred in 43 patients.

In the combined safety database with IMFINZI in combination with tremelimumab (n=2280), 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 245 (8.2%) patients, including Grade 3 in 4 (0.1%) patients. The median time to onset was 85 days (range: 1-562 days). Of the 245 patients, 240 patients received hormone replacement therapy and 6 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.

In the combined safety database with IMFINZI in combination with tremelimumab (n=2280), 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 50 (1.7%) patients, there were no Grade 3 or 4 cases. The median time to onset was 43 days (range: 1-196 days). Forty-six of the 50 patients received medical therapy (thiamazole, carbimazole, propylthiouracil, perchlorate, calcium channel blocker, or beta-blocker), 11 patients received systemic corticosteroids and 4 of the 11 patients received high-dose systemic corticosteroid treatment (at least 40 mg prednisone or equivalent per day). One patient discontinued IMFINZI due to immune-mediated hyperthyroidism. Resolution occurred in 39 patients. Twenty patients experienced hypothyroidism following hyperthyroidism.

In the combined safety database with IMFINZI in combination with tremelimumab (n=2280), 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 12 (0.4%) patients, including Grade 3 in 2 (<0.1%) patients. The median time to onset was 49 days (range: 14-106 days). Of the 12 patients, 10 patients received hormone replacement therapy and 1 patient received high-dose corticosteroids (at least 40 mg prednisone or equivalent per day). One patient discontinued IMFINZI due to immune-mediated thyroiditis. Three patients experienced hypothyroidism following thyroiditis.

In the combined safety database with IMFINZI in combination with tremelimumab (n=2280), 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 14 (0.5%) patients, including Grade 3 in 3 (<0.1%) patients. The median time to onset was 146 days (range: 20-547 days). All 14 patients received systemic corticosteroids; 4 of the 14 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). No patients discontinued IMFINZI due to immune-mediated adrenal insufficiency. Resolution occurred in 3 patients.

In the combined safety database with IMFINZI in combination with tremelimumab (n=2280), 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 one study with 475 locally advance, unresectable NSCLC patients, Grade-3 immune-mediated type 1 diabetes mellitus occurred in 1 (<0.1%) patient. The time to onset was 43 days. This patient recovered with sequelae, required long-term insulin therapy and IMFINZI was permanently discontinued due to immune-mediated type 1 diabetes mellitus.

In the combined safety database with IMFINZI in combination with tremelimumab (n=2280), 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 2 (<0.1%) patients, both Grade 3. The time to onset for the events was 44 days and 50 days. Both patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day) and one patient discontinued IMFINZI due to immune-mediated hypophysitis/hypopituitarism.

In the combined safety database with IMFINZI in combination with tremelimumab (n=2280), 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 14 (0.5%) patients, including Grade 3 in 2 (< 0.1%) patients. The median time to onset was 71 days (range: 4-393 days). Nine patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day) and 1 patient also received mycophenolate. IMFINZI was discontinued in 5 patients. Resolution occurred in 8 patients.

In the combined safety database with IMFINZI in combination with tremelimumab (n=2280), 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 occurred in 50 (1.7%) patients, including Grade 3 in 12 (0.4%) patients. The median time to onset was 43 days (range: 4-333 days). Twenty-three of the 50 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). IMFINZI was discontinued in 3 patients. Resolution occurred in 32 patients.

In the combined safety database with IMFINZI in combination with tremelimumab (n=2280), 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.

In the DUO-E Study, out of 238 patients treated with platinum-based chemotherapy in combination with IMFINZI, followed by IMFINZI in combination with olaparib (platinum-based chemotherapy + IMFINZI + olaparib arm) immune-mediated rash occurred in 8 (3.4%) patients, including Grade 3 in 2 (0.8%) patients. The median time to onset was 155 days (range: 2-308 days). All patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). Resolution occurred in all 8 patients.

Infusion-related reactions

In the combined safety database with IMFINZI monotherapy, infusion-related reactions occurred in 49 (1.6%) patients, including Grade 3 in 5 (0.2%) patients. There were no Grade 4 or 5 events.

In the combined safety database with IMFINZI in combination with tremelimumab (n=2280), 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.

In the DUO-E Study, out of 238 patients treated with platinum-based chemotherapy in combination with IMFINZI, followed by IMFINZI in combination with olaparib (platinum-based chemotherapy + IMFINZI + olaparib arm), infusion-related reactions occurred in 13 (5.5%) patients, including Grade 3 in 1 (0.4%) patient. There were no Grade 4 or 5 events.

Pure Red Cell Aplasia

Pure Red Cell Aplasia (PRCA) has been reported when IMFINZI has been used in combination with olaparib. In a clinical study of patients with endometrial cancer treated with IMFINZI in combination with olaparib, the incidence of PRCA was 1.6%. All events were CTCAE Grade 3 or 4. Events were manageable following discontinuation of both IMFINZI and olaparib. The majority of events were managed with blood transfusion and immunosuppression and recovered; there were no fatal events. For management see section 4.4.

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: 2.4% for alanine aminotransferase increased, 3.6% for aspartate aminotransferase increased, 0.5% for blood creatinine increased, 5.7% for amylase increased and 5.6% for lipase increased. The proportion of patients who experienced a TSH shift from baseline that was ≤ ULN to any grade > ULN was 18.8% and a TSH shift from baseline that was ≥ LLN to any grade < LLN was 18.1%.

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%.

In patients treated with platinum-based chemotherapy in combination with IMFINZI, followed by IMFINZI either as monotherapy (platinum-based chemotherapy + IMFINZI arm) or in combination with olaparib (platinum-based chemotherapy + IMFINZI + olaparib arm), the proportion of patients who experienced a shift from baseline to a Grade 3 or 4 laboratory abnormality was as follows in the platinum-based chemotherapy + IMFINZI arm: 3.5% for alanine aminotransferase increased, 3.0% for aspartate aminotransferase increased and 0.4% for blood creatinine increased, and as follows in the platinum-based chemotherapy + IMFINZI + olaparib arm: 3.8% for alanine aminotransferase increased, 3.4% for aspartate aminotransferase increased and 1.7% for blood creatinine increased. The proportion of patients who experienced a TSH shift from baseline that was ≤ ULN to > ULN was 27.2% and a TSH shift from baseline that was ≥ LLN to < LLN was 24.3% in the platinum-based chemotherapy + IMFINZI arm and the proportion of patients who experienced a TSH shift from baseline that was ≤ ULN to > ULN was 28.6% and a TSH shift from baseline that was ≥ LLN to < LLN was 20.1% in the platinum-based chemotherapy + IMFINZI + olaparib arm.

Immune checkpoint inhibitor class effects
There have been cases of the following adverse reactions reported during treatment with other immune checkpoint inhibitors which might also occur during treatment with durvalumab: pancreatic exocrine insufficiency

Immunogenicity
Immunogenicity of IMFINZI as monotherapy is based on pooled data in 2280 patients who were treated with IMFINZI 10 mg/kg every 2 weeks, or 20 mg/kg every 4 weeks as a single-agent and evaluable for the presence of anti-drug antibodies (ADAs). Sixty nine patients (3.0%) tested

positive for treatment emergent ADAs. Neutralising antibodies (nAb) against durvalumab were detected in 0.5% (12/2280) of patients. The presence of ADAs did not have a clinically relevant effect on safety. There are insufficient number of patients to determine ADA impact on efficacy. Based on population PK analysis, slightly lower exposure are expected in ADA-positive patients however, the reduction of PK exposure is less than 30% compared to a typical patient and is not considered clinically relevant.

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 and TOPAZ-1 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 registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions.

4.9 Overdose

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Durvalumab is a fully human, high affinity, immunoglobulin G1 kappa (IgG1κ) monoclonal antibody that blocks the interaction of PD-L1 with PD-1 and CD80 (B7.1). Durvalumab does not

induce antibody dependent cell-mediated cytotoxicity (ADCC). Blockade of PD-L1/PD-1 and PD-L1/CD80 interactions enhances antitumour immune responses. These antitumour responses may result in tumour elimination.

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.

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

Clinical trials

Durvalumab doses of 10 mg/kg every 2 weeks, 1120 mg every 3 weeks or 1500 mg every 4 weeks were evaluated in NSCLC, ES-SCLC and endometrial cancer clinical studies. Based on the modelling 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, 1120 mg every 3 weeks or 1500 mg every 4 weeks.

Non-small cell lung cancer (NSCLC)

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

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

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

The demographics and baseline disease characteristics were well balanced between study arms. Baseline demographics of the overall study population were as follows: male (70%), age ≥ 65 years

(45%), white (69%), Asian (27%), other (4%), current smoker (16%), past-smoker (75%), and never smoker (9%), WHO/ECOG PS 0 (49%), WHO/ECOG PS 1 (51%). Disease characteristics were as follows: Stage IIIA (53%), Stage IIIB (45%), histological sub-groups of squamous (46%), non-squamous (54%). Of 451 patients with PD L1 expression available, 67% were TC ≥ 1% [PD-L1 TC 1-24% (32%), PD L1 TC ≥ 25% (35%)] and 33% were TC < 1%.

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

The study demonstrated a statistically significant improvement in PFS 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. Kaplan-Meier curves for OS and PFS from the 5 year follow-up analysis are presented in Figures 1 and 2.

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%, 61.8%)	66.3% (61.8%, 70.4%)	55.3% (48.6%, 61.4%)
p-value	0.005			
OS at 48 months (%) (95% CI)	N/A		49.7% (45.0%, 54.2%)	36.3% (30.1%, 42.6%)
OS at 60 months (%) (95% CI)	N/A		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%)

	Primary Analysis[a]		5 Year Follow-up Analysis[b]	
	IMFINZI (n = 476)	**Placebo (n = 237)**	**IMFINZI (n = 476)**	**Placebo (n = 237)**
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)	N/A	N/A	35.0% (29.9%, 40.1%)	19.9% (14.4%, 26.1%
PFS at 60 months (%) (95% CI)	N/A	N/A	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)	N/A	N/A
HR (95% CI)	0.58 (0.46, 0.73)		N/A	N/A
p-value	p < 0.0001		N/A	

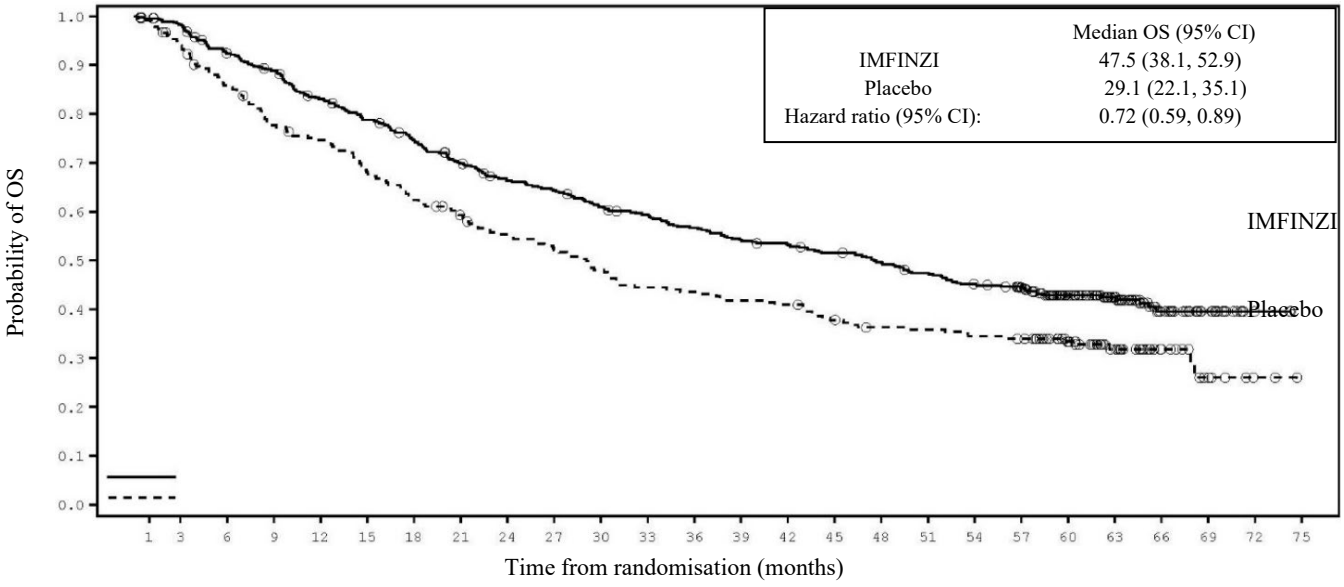
[a]Primary analysis of PFS at data cut-off 13 February 2017. Primary analysis of OS and PFS2 at data cut-off 22 March 2018.

[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

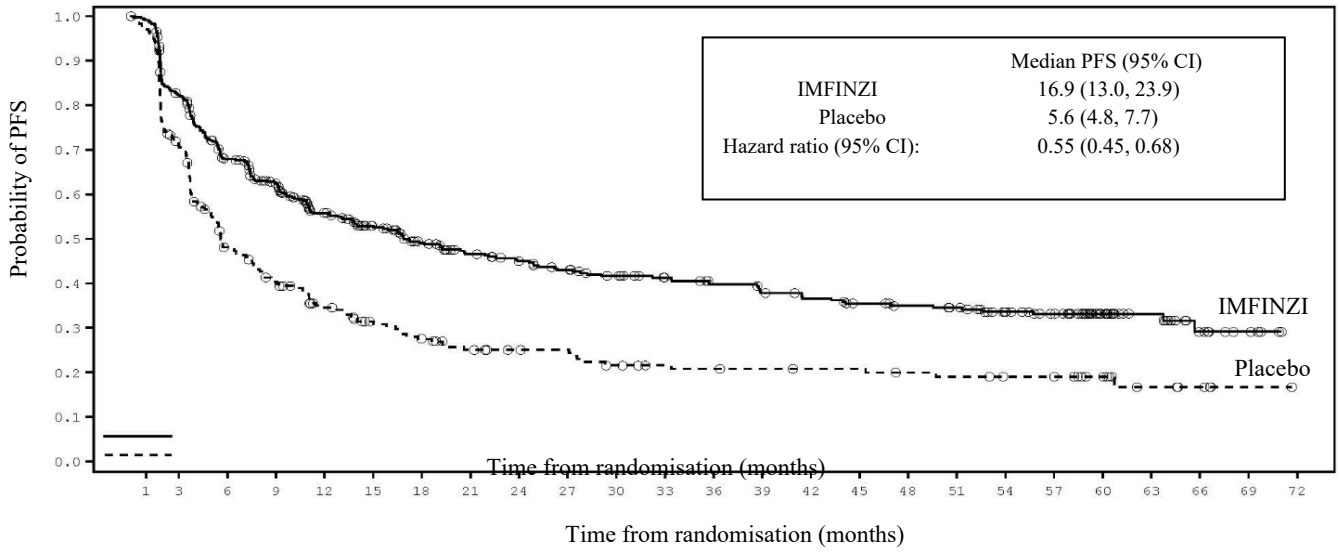
Figure 1. Kaplan-Meier curve of OS (PACIFIC study)



Number of patients at risk

Month	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54	57	60	63	66	69	72	75
IMFINZI	476	464	431	415	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 (PACIFIC study)



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. ALK mutation status was not analysed in this study.

Post-hoc subgroup analysis by PD-L1 expression
Additional subgroup analyses were conducted to evaluate the efficacy by tumour PD-L1 expression (≥ 25%, 1-24%, ≥ 1%, < 1%) and for patients whose PD-L1 status could not be established (PD-L1 unknown). PFS and OS results from the 5 year follow-up analysis are summarised in Figures 3 and 4. Overall the safety profile of durvalumab in PD-L1 TC ≥1% subgroup was consistent with the intent to treat population, as was the PD-L1 TC <1% subgroup.

Figure 3. Forest plot of OS by PD-L1 expression (PACIFIC study)

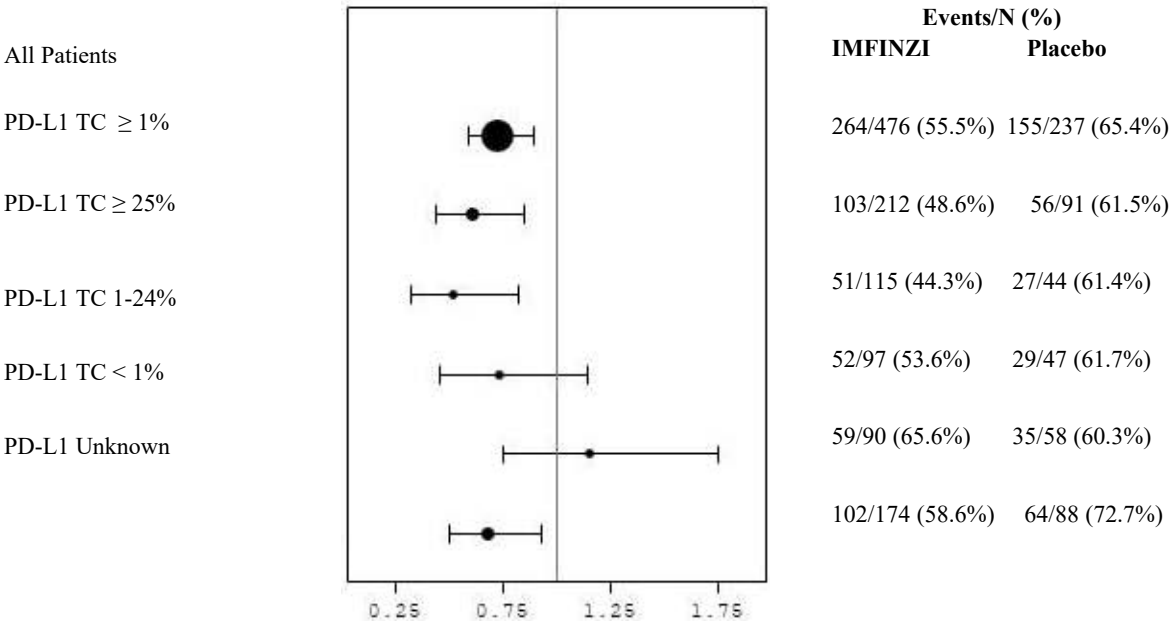
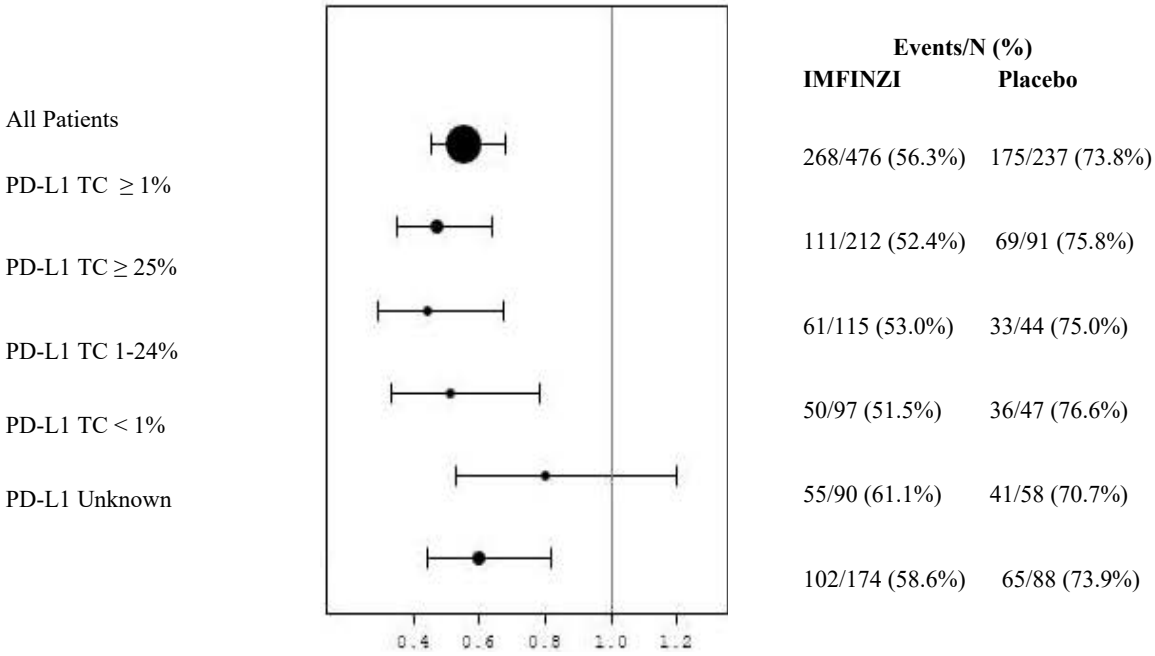


Figure 4. Forest plot of PFS by PD-L1 expression (PACIFIC study)



Patient reported outcomes

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

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

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 $\geq$ 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 1500 mg with tremelimumab 75 mg and platinum-based chemotherapy every 3 weeks for 4 cycles followed by, IMFINZI 1500 mg every 4 weeks as monotherapy. A fifth dose of tremelimumab 75 mg was given at Week 16 alongside IMFINZI dose 6.
- Arm 2: IMFINZI 1500 mg and platinum-based chemotherapy every 3 weeks for 4 cycles, followed by IMFINZI 1500 mg every 4 weeks as monotherapy.
- Arm 3: Platinum-based chemotherapy every 3 weeks for 4 cycles. 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 1000 or 1250 mg/m^2 on Days 1 and 8 with cisplatin 75 mg/m^2 or carboplatin AUC 5-6 on Day 1 every 3 weeks.
- Non-squamous 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 progression-free survival (PFS) and overall survival (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 Blinded Independent Central Review (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

	Arm 1: IMFINZI+tremelimumab +platinum-based chemotherapy (n=338)	Arm 3: Platinum-based chemotherapy (n=337)
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.

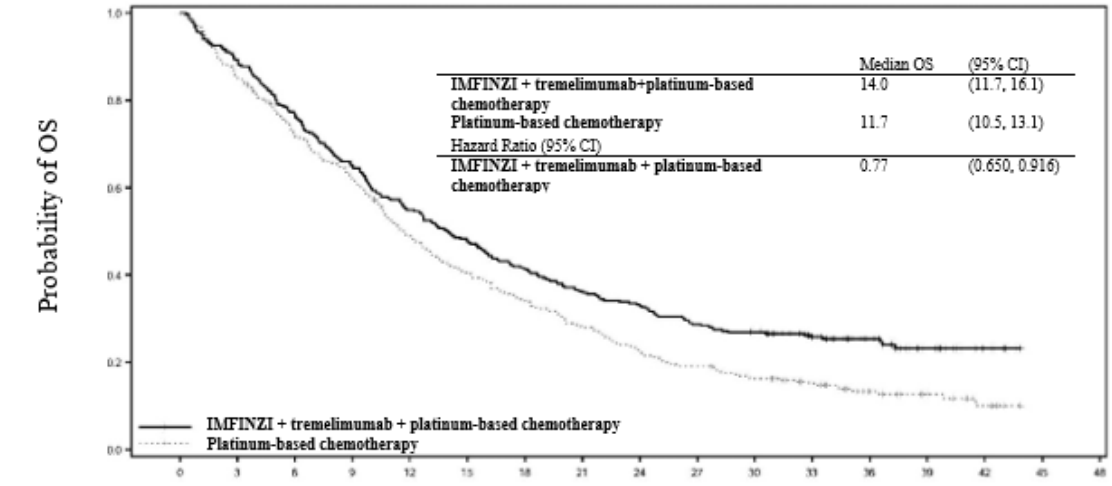
[c] 2-sided p-value based on a log-rank test stratified by PD-L1, histology and disease stage.

[d] Confirmed Objective Response.

[e] Post-hoc analysis.

NR = Not Reached, CI = Confidence Interval

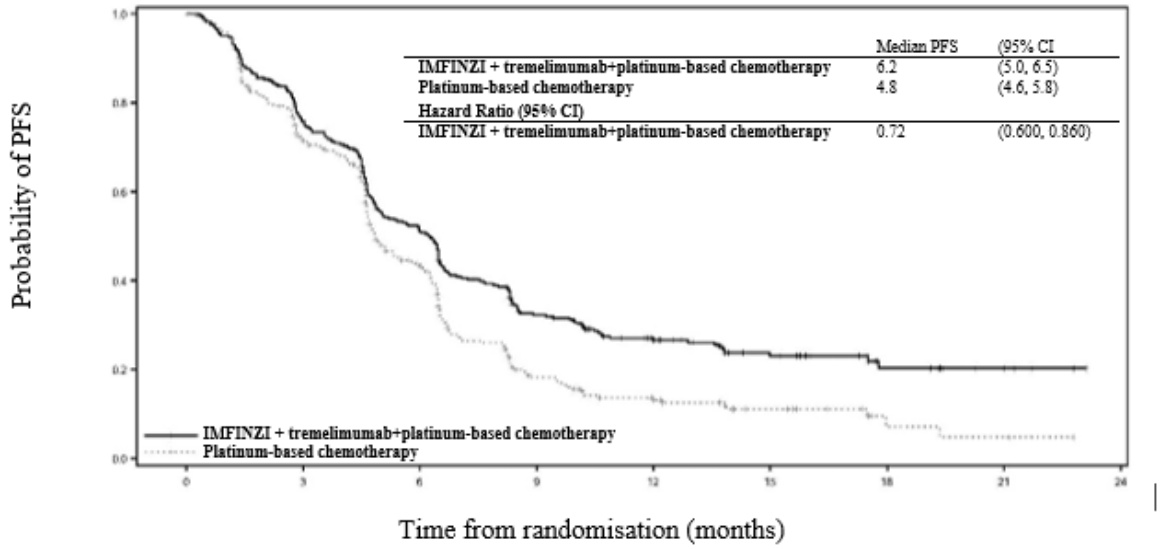
Figure 5. Kaplan-Meier curve of OS



Number of patients at risk

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

Figure 6. Kaplan-Meier curve of PFS

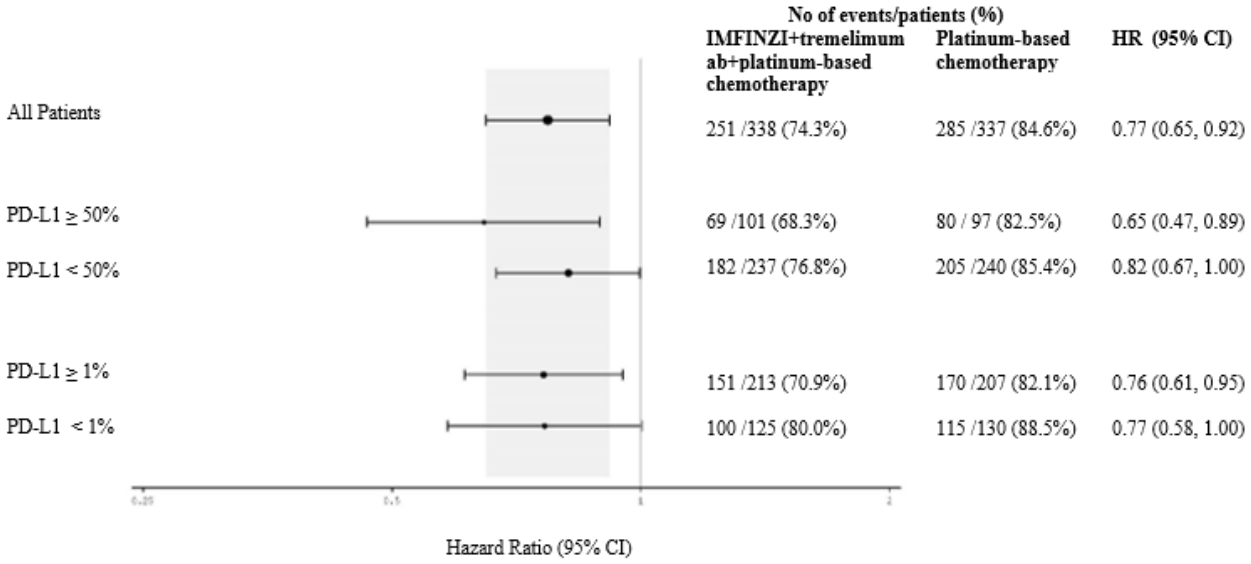


Number of patients at risk

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

Figure 7 summarises efficacy results of OS by tumour PD-L1 expression in prespecified subgroup analyses.

Figure 7. 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, multicenter study in 805 treatment naïve ES-SCLC patients with WHO/ECOG Performance status of 0 or 1, suitable to receive a platinum-based chemotherapy regimen as first-line treatment for SCLC, with life expectancy ≥12 weeks, at least one target lesion by RECIST 1.1 and adequate organ and bone marrow function. Patients with asymptomatic or treated brain metastases were eligible. The study excluded patients with a history of chest radiation therapy; a history of active primary immunodeficiency; autoimmune disorders including paraneoplastic syndrome (PNS); active or prior documented autoimmune or inflammatory disorders; use of systemic immunosuppressants within 14 days before the first dose of the treatment except physiological dose of systemic corticosteroids; active tuberculosis or hepatitis B or C or HIV infection; or patients receiving live attenuated vaccine within 30 days before or after the start of IMFINZI.

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

Patients were randomised 1:1:1 to receive:

- Arm 1: IMFINZI 1500 mg + tremelimumab 75 mg + etoposide and either carboplatin or cisplatin
- Arm 2: IMFINZI 1500 mg + etoposide and either carboplatin or cisplatin

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

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

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

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

The primary endpoints of the study were OS of IMFINZI + chemotherapy (Arm 2) vs. chemotherapy alone (Arm 3) and IMFINZI + tremelimumab + chemotherapy (Arm 1) vs. chemotherapy alone (Arm 3). The key secondary endpoint was PFS. Other secondary endpoints were Objective Response Rate (ORR), OS and PFS landmarks and Patient-Reported Outcomes (PRO). PFS and ORR were assessed using Investigator assessments according to RECIST v1.1.

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 + plantinum alone (Arm 3) [HR=0.73 (95% CI: 0.591, 0.909), p=0.0047]. IMFINZI + etoposide + plantinum demonstrated an improvement in PFS vs. etoposide + plantinum 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 9.

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 curves for OS is presented in Figures 8.

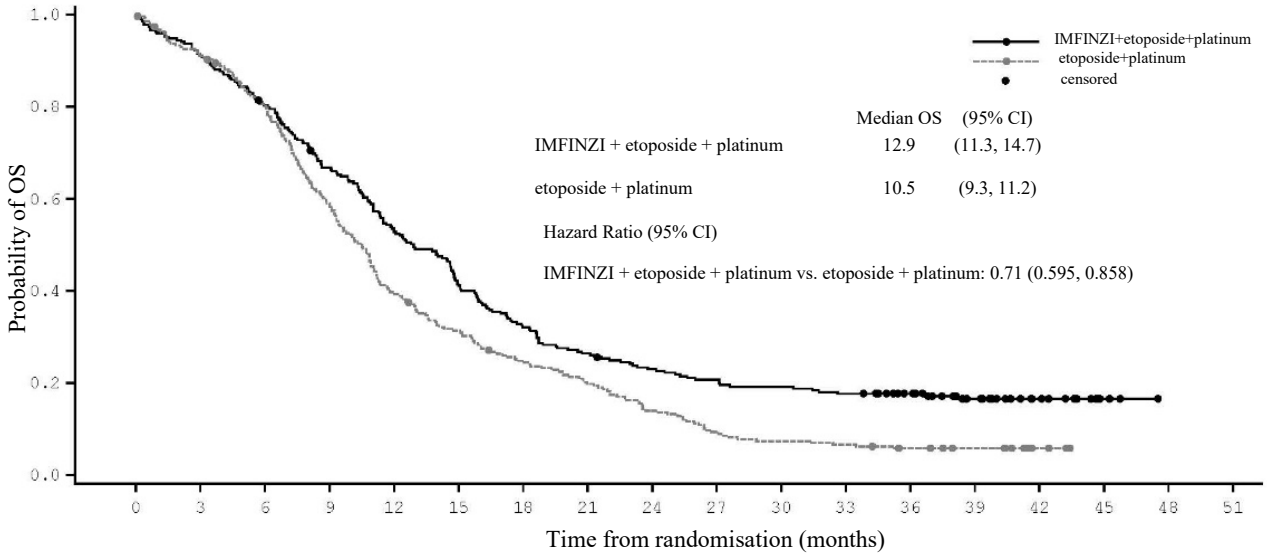
Table 7. Efficacy Results for the CASPIAN Study

	Final analysis[a]		**Long-term follow-up analysis[b]**	
	Arm 2: IMFINZI + etoposide and	**Arm 3: etoposide and either**	**Arm 2: IMFINZI +**	**Arm 3: etoposide and either**

	either carboplatin or cisplatin (n=268)	carboplatin or cisplatin (n=269)	etoposide and either carboplatin or cisplatin (n=268)	carboplatin or cisplatin (n=269)
OS				
Number of deaths (%)	210 (78.4)	231 (85.9)	221 (82.5)	248 (92.2)
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)[bc]	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 (%)[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)		

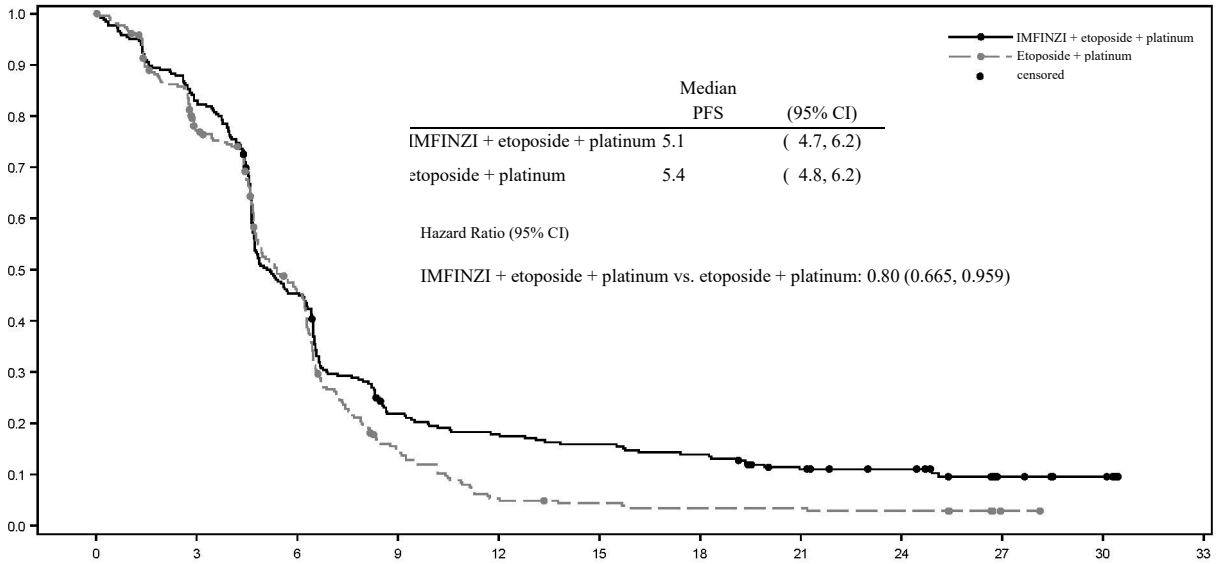
[a] Final OS, PFS, ORR and DoR analysis at data cut-off 27 January 2020
[b] Long-term follow-up OS analysis at data cut-off 22 March 2021
[c] The analysis was performed using the stratified log-rank test, adjusting for planned platinum therapy in Cycle 1 (carboplatin or cisplatin), and using the rank 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 8. 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	6	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 9. 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 favor of patients receiving IMFINZI + chemotherapy compared to those receiving chemotherapy alone, were consistently observed across the prespecified subgroups

based on demographics, geographical region, carboplatin or cisplatin use and disease characteristics.

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 1500 mg administered on Day 1 + gemcitabine 1000 mg/m^2 and cisplatin 25 mg/m^2 (each administered on Days 1 and 8) every 3 weeks (21 days) for up to 8 cycles, followed by IMFINZI 1500 mg every 4 weeks until disease progression or unacceptable toxicity, or

- Arm 2: Placebo administered on Day 1 + gemcitabine 1000 mg/m^2 and cisplatin 25 mg/m^2 (each administered on Days 1 and 8) every 3 weeks (21 days) for up to 8 cycles, followed by placebo every 4 weeks 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, Duration of Response (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 10. 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 tumor 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 medium follow-up increased to 12 months.

Figure 10: Kaplan-Meier curve of OS, follow-up OS analysis at data cut-off 25 February 2022

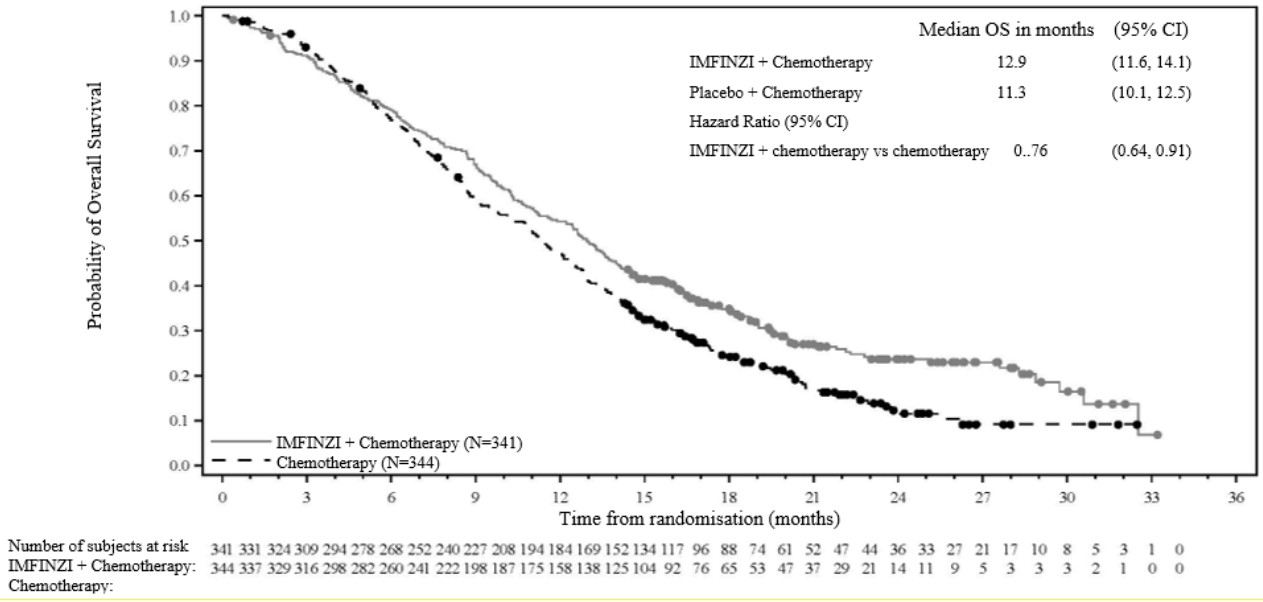
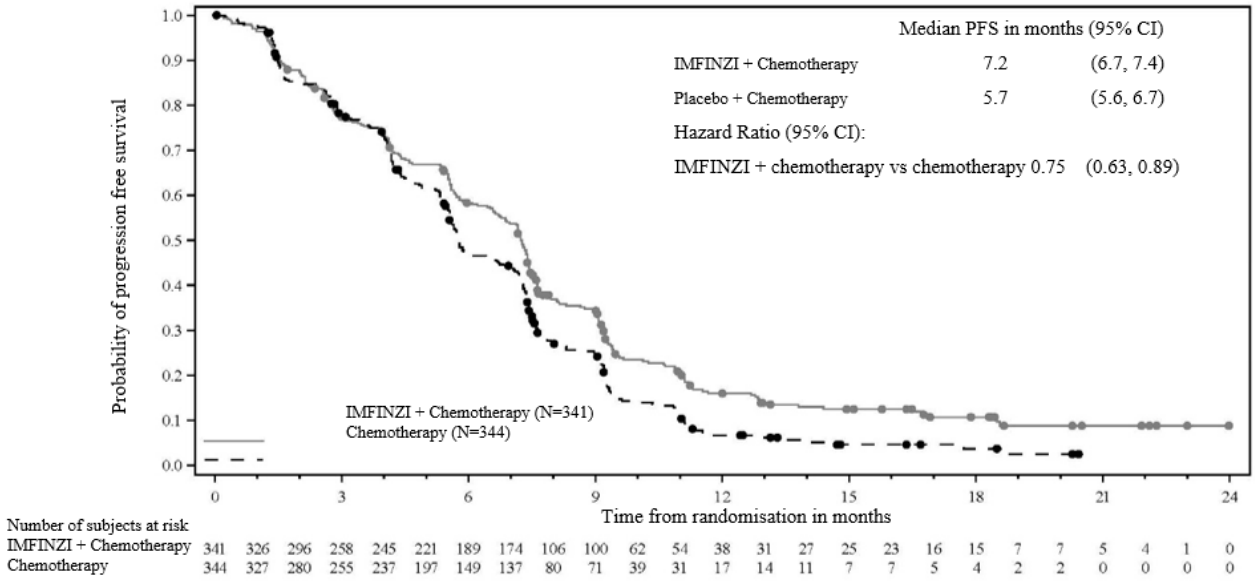


Figure 11: Kaplan-Meier curve of PFS, inferential (primary) analysis at data cut-off 11 August 2021



HCC - HIMALAYA Study

The efficacy of IMFINZI 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 1500 mg every 4 weeks
- Tremelimumab 300 mg as a single dose + IMFINZI 1500 mg; followed by IMFINZI 1500 mg every 4 weeks
- S: 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. Secondary endpoints included PFS, Investigator-assessed ORR and DoR according to RECIST v1.1.

The demographics and baseline disease characteristics were well balanced between 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 and Figure 12.

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

	IMFINZI + tremelimumab 300 mg (n=393)	**S (n=389)**
Follow-up duration		
Median follow-up (months)[a]	33.2	32.2
OS		
Number of deaths (%)	262 (66.7)	293 (75.3)
Median OS (months) (95% CI)	**16.4 (14.2, 19.6)**	**13.8 (12.3, 16.1)**
HR (95% CI)	0.78 (0.66, 0.92)	
p-value[b]	0.0035	
PFS		
Number of events (%)	335 (85.2)	327 (84.1)
Median PFS (months) (95% CI)	3.78 (3.68, 5.32)	4.07 (3.75, 5.49)

	IMFINZI + tremelimumab 300 mg (n=393)	S (n=389)
HR (95% CI)	0.90 (0.77, 1.05)	
ORR		
ORR n (%)[c]	79 (20.1)	20 (5.1)
Complete Response n (%)	12 (3.1)	0
Partial Response n (%)	67 (17.0)	20 (5.1)
DoR		
Median DoR (months)	22.3	18.4

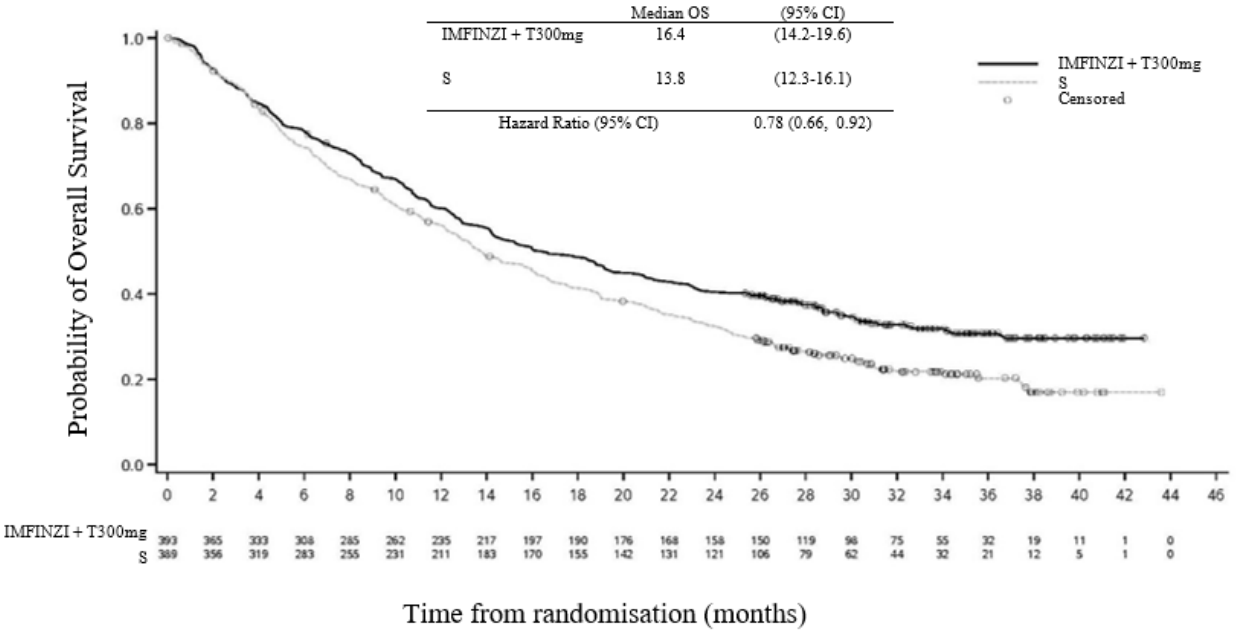
[a] Calculated using reverse the Kaplan-Meier technique (with censor indicator reversed).

[b] 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. S was 0.0398 (Lan◦and◦DeMets 1983).

[c] Confirmed complete response.

NR=Not Reached, CI=Confidence Interval

Figure 12. Kaplan-Meier curve of OS



Endometrial Cancer – DUO-E Study

DUO-E was a randomised, multicentre, double-blind, placebo-controlled Phase III study of first-line platinum-based chemotherapy in combination with IMFINZI, followed by IMFINZI with or without olaparib in patients with advanced or recurrent endometrial cancer. Patients had to have endometrial cancer in one of the following categories: newly diagnosed Stage III disease (measurable disease per RECIST v1.1 following surgery or diagnostic biopsy), newly diagnosed Stage IV disease (with or without disease following surgery or diagnostic biopsy), or recurrence of disease (measurable or non-measurable disease per RECIST v1.1) where the potential for cure by surgery alone or in combination is poor. For patients with recurrent disease, prior chemotherapy was allowed only if it was administered in the adjuvant setting and there was at least 12 months from the date of last dose of chemotherapy administered to the date of subsequent relapse. The

study included patients with epithelial endometrial carcinomas of all histologies, including carcinosarcomas. Patients with endometrial sarcoma were excluded.

Randomisation was stratified by tumour tissue's mismatch repair (MMR) status (proficient versus deficient), disease status (recurrent versus newly diagnosed), and geographic region (Asia versus rest of the world). Patients were randomised 1:1:1 to one of the following arms:

- Arm 1 (Platinum-based chemotherapy): Platinum-based chemotherapy (paclitaxel and carboplatin) every 3 weeks for a maximum of 6 cycles with durvalumab placebo every 3 weeks. Following completion of chemotherapy treatment, patients without objective disease progression received durvalumab placebo every 4 weeks and olaparib placebo tablets twice daily as maintenance treatment until disease progression.
- Arm 2 (Platinum-based chemotherapy + IMFINZI): Platinum-based chemotherapy (paclitaxel and carboplatin) every 3 weeks for a maximum of 6 cycles with 1 120 mg durvalumab every 3 weeks. Following completion of chemotherapy treatment, patients without objective disease progression received 1 500 mg durvalumab every 4 weeks with olaparib placebo tablets twice daily as maintenance treatment until disease progression.
- Arm 3 (Platinum-based chemotherapy + IMFINZI + olaparib): Platinum-based chemotherapy (paclitaxel and carboplatin) every 3 weeks for a maximum of 6 cycles with 1 120 mg durvalumab every 3 weeks. Following completion of chemotherapy treatment, patients without objective disease progression received 1 500 mg durvalumab every 4 weeks with 300 mg olaparib tablets twice daily as maintenance treatment until disease progression.

Patients who discontinued either product (IMFINZI/placebo or olaparib/placebo) for reasons other than disease progression could continue treatment with the other product if appropriate based on toxicity considerations and investigator discretion.

Treatment was continued until RECIST v1.1-defined progression of disease or unacceptable toxicity. Assessment of tumour status was performed every 9 weeks for the first 18 weeks relative to randomisation and every 12 weeks thereafter.

The primary endpoint was PFS, determined by investigator assessment using RECIST v1.1. Secondary efficacy endpoints included OS, ORR and DoR.

The study demonstrated a statistically significant improvement in PFS in the ITT population, for patients treated with platinum-based chemotherapy + IMFINZI + olaparib compared to platinum-based chemotherapy [HR=0.55 (95% CI: 0.43, 0.69), p=<0.0001], and for patients treated with platinum-based chemotherapy + IMFINZI compared to platinum-based chemotherapy [HR=0.71 (95% CI: 0.57, 0.89), p=0.003]. At the time of PFS analysis, interim OS data were 28% mature with events in 199 of 718 patients.

Mismatch repair (MMR) status was determined centrally using an MMR immunohistochemistry panel assay. Of a total of 718 patients randomized in the study, 575 (80%) patients had MMR-proficient (pMMR) tumour status and 143 (20%) patients had MMR-deficient (dMMR) tumour status.

Patients with MMR-deficient (dMMR) endometrial cancer
Among patients with dMMR tumour status, demographic and baseline characteristics were generally well balanced between the treatment arms. Baseline demographics across all three arms were as follows: median age of 62 years (range: 34 to 85), 41% age 65 or older, 1.5% age 75 or older, 62% White, 29% Asian, and 2% Black or African American. Disease characteristics were as follows: ECOG PS of 0 (58%) or 1 (42%), 46% newly diagnosed and 54% recurrent disease. The

histologic subtypes were endometrioid (83%), mixed epithelial (5%), serous (3%), carcinosarcoma (3%), undifferentiated (2%), and other (3%).

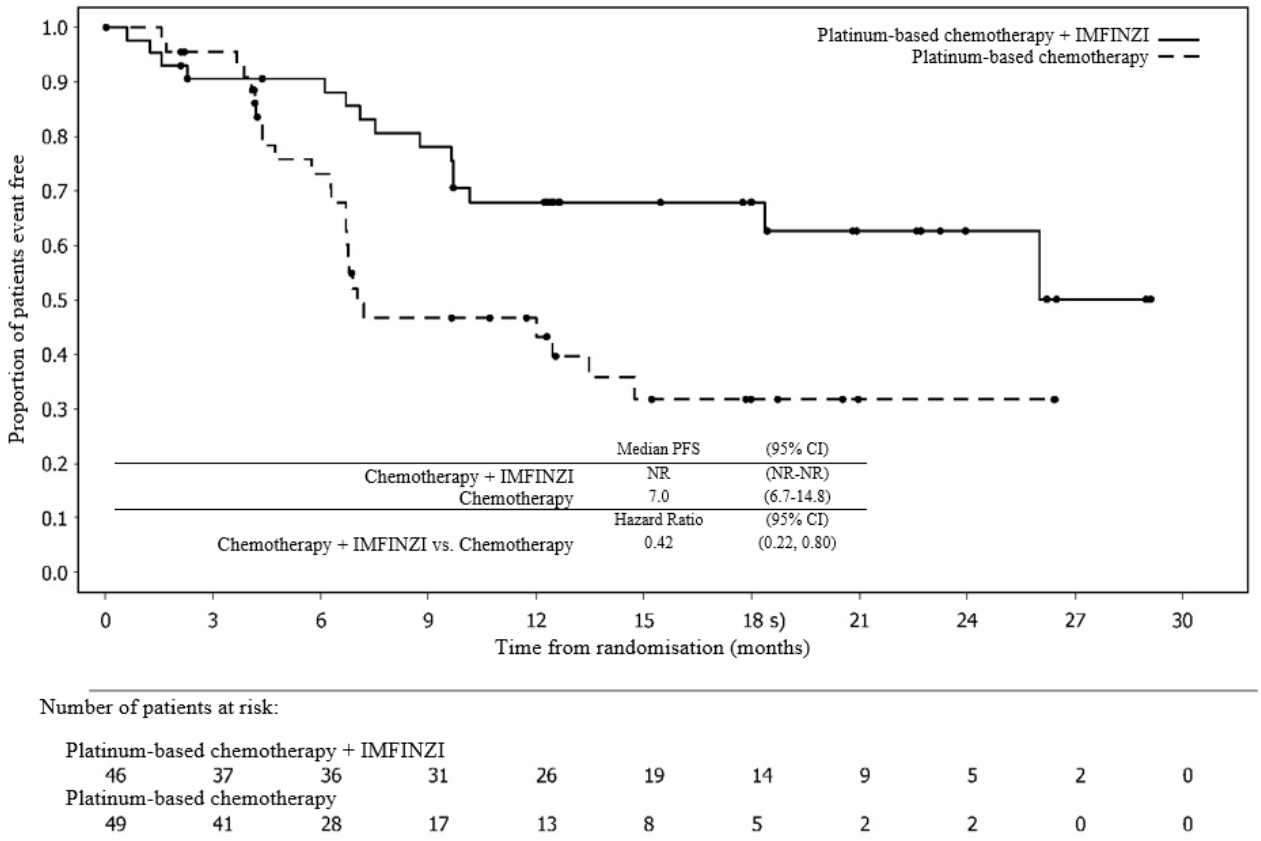
In patients with dMMR tumour status, the results are summarised in Table 10 and Figure 13. The median follow-up time for PFS in censored patients with dMMR tumour status was 15.5 months in the platinum-based chemotherapy + IMFINZI arm and 10.2 months in the platinum-based chemotherapy arm. At the time of PFS analysis, interim OS data were 26% mature with events in 25 of 95 patients treated with platinum-based chemotherapy + IMFINZI and platinum-based chemotherapy.

Table 10. Efficacy results for the DUO-E Study (Patients with dMMR tumour status)

	Platinum-based chemotherapy + IMFINZI N=46	**Platinum-based chemotherapy N=49**
PFS[a,b]		
Number of events (%)	15 (32.6)	25 (51.0)
Median PFS (months) (95% CI)[c]	NR (NR, NR)	7.0 (6.7, 14.8)
HR (95% CI)	0.42 (0.22, 0.80)	-
OS[b]		
Number of events (%)	7 (15.2)	18 (36.7)
Median OS (months) (95% CI)[c]	NR (NR, NR)	23.7 (16.9, NR)
HR (95% CI)	0.34 (0.13, 0.79)	-
ORR[b]		
ORR[d] n (%)	30 (71.4)	17 (40.5)
DoR[b]		
Median DoR (months) (95% CI)[c]	NR (NR, NR)	10.5 (4.3, NR)

[a] Investigator assessed.
[b] Results are based on the first interim analysis (DCO: 12 April 2023).
[c] Calculated using the Kaplan-Meier technique.
[d] Response: Best objective response as confirmed complete response or partial response. Based on number of patients in treatment group with measurable disease at baseline (N=42 in platinum-based chemotherapy + IMFINZI arm, N=42 in platinum-based chemotherapy arm).
CI=Confidence Interval, HR=Hazard Ratio, NR=Not Reached

Figure 13. Kaplan-Meier curve of PFS in DUO-E (Patients with dMMR tumour status)



Patients with MMR-proficient (pMMR) endometrial cancer

Among patients with pMMR tumour status, demographic and baseline characteristics were generally well balanced between the treatment arms. Baseline demographics across all three arms were as follows: median age of 64 years (range: 22 to 86), 48% age 65 or older, 8.1% age 75 or older, 56% White, 30% Asian, and 6% Black or African American. Disease characteristics were as follows: ECOG PS of 0 (69%) or 1 (31%), 47% newly diagnosed and 53% recurrent disease. The histologic subtypes were endometrioid (54%), serous (26%), carcinosarcoma (8%), mixed epithelial (4%), clear cell (3%), undifferentiated (2%), mucinous (<1%), and other (3%).

Results in patients with pMMR tumour status are summarised in Table 11 and Figure 14. The median follow-up time in censored patients with pMMR tumour status was 15.2 months in the platinum-based chemotherapy + IMFINZI + olaparib arm, and 12.8 months in the platinum-based chemotherapy arm. At the time of PFS analysis, interim OS data were 29% mature with events in 110 of 383 patients treated with platinum-based chemotherapy + IMFINZI + olaparib and platinum-based chemotherapy.

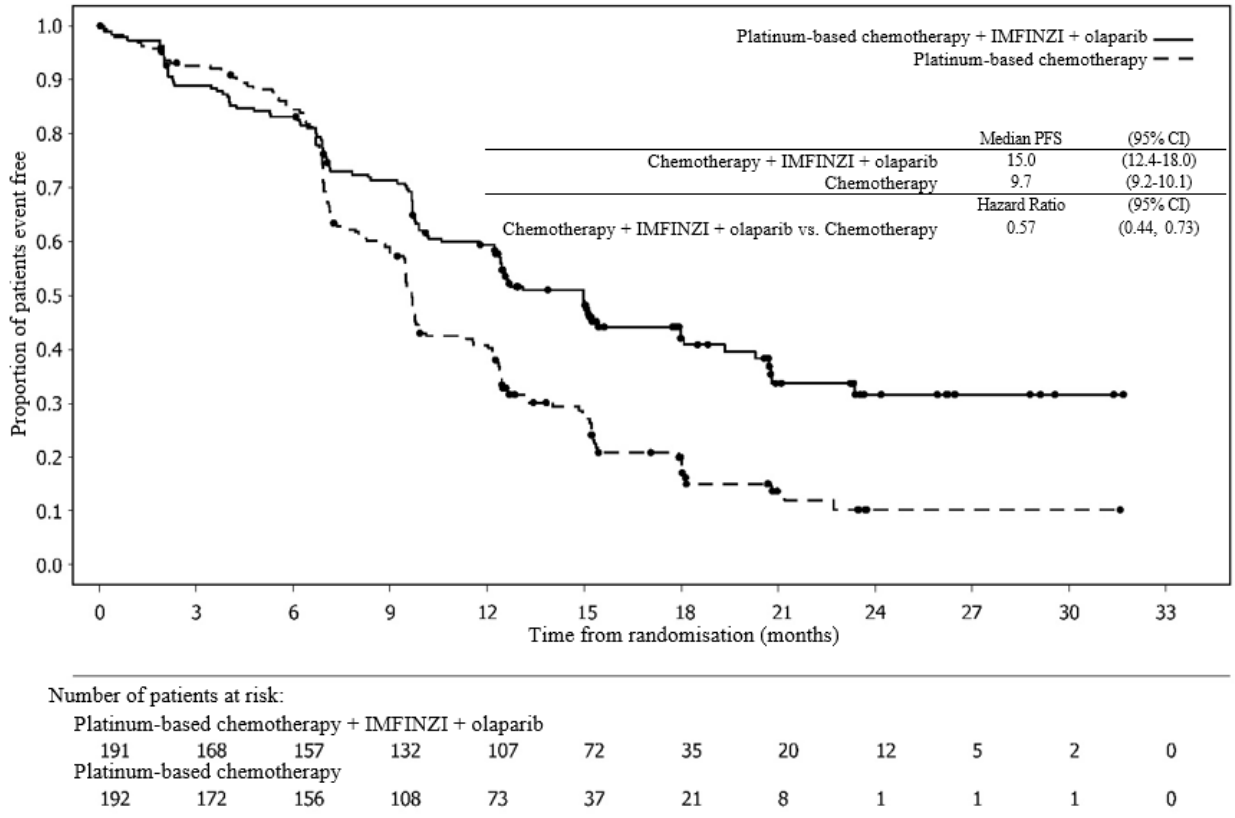
Table 11. Efficacy results for the DUO-E Study (Patients with pMMR tumour status)

	Platinum-based chemotherapy + IMFINZI + olaparib N=191	**Platinum-based chemotherapy N=192**
PFS[a,b]		
Number of events (%)	108 (56.5)	148 (77.1)

Median PFS (months) (95% CI)[c]	15.0 (12.4, 18.0)	9.7 (9.2, 10.1)
HR (95% CI)	0.57 (0.44, 0.73)	-
OS[b]		
Number of events (%)	46 (24.1)	64 (33.3)
Median OS (months) (95% CI)[c]	NR (NR, NR)	25.9 (25.1, NR)
HR (95% CI)	0.69 (0.47, 1.00)	-
ORR[b]		
ORR[d] n (%)	90 (61.2)	92 (59.0)
DoR[b]		
Median DoR (months) (95% CI)[c]	18.7 (10.5, NR)	7.6 (7.1, 10.2)

[a] Investigator assessed.
[b] Results are based on the first interim analysis (DCO: 12 April 2023).
[c] Calculated using the Kaplan-Meier technique.
[d] Response: Best objective response as confirmed complete response or partial response. Based on number of patients in treatment group with measurable disease at baseline (N=147 in platinum-based chemotherapy + IMFINZI + olaparib arm, N=156 in platinum-based chemotherapy arm).
CI=Confidence Interval, HR=Hazard Ratio, NR=Not Reached

Figure 14. Kaplan-Meier curve of PFS in DUO-E (Patients with pMMR tumour status)



Among patients with pMMR tumour status, the PFS HRs were 0.44 (95% CI: 0.31, 0.61) in patients with PD-L1 expression positive status (236/383; 62%) and 0.87 (95% CI: 0.59, 1.28) in patients with PD-L1 expression negative status (140/383; 37%), for the platinum-based chemotherapy + IMFINZI + olaparib arm compared to the platinum-based chemotherapy arm. PD-L1 expression positive was defined as tumour area positive (TAP) ≥ 1%.

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, in combination with tremelimumab, and in combination with platinum-based chemotherapy followed by IMFINZI in combination with olaparib.

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, in combination with tremelimumab and in combination with platinum-based chemotherapy followed by IMFINZI in combination with olaparib. 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.

5.3 Preclinical safety data

Genotoxicity

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

Carcinogenicity

The carcinogenic potential of durvalumab has not been evaluated.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Histidine,
Histidine hydrochloride monohydrate,
Trehalose dihydrate,
Polysorbate 80,
Water for injection.

6.2 Incompatibilities

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

6.3 Shelf life

36 months

6.4 Special precautions for storage

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

6.5 PACK SIZE

120 mg: Box, 1 vial @ 2.4 ml, Reg No: DKI2051303949A1
500 mg: Box, 1 vial @ 10 ml, Reg No: DKI2051303949A1

HARUS DENGAN RESEP DOKTER

Manufactured and released by
AstraZeneca AB, Gärtunavägen, Södertälje Sweden

Imported by:
PT AstraZeneca Indonesia
Cikarang, Bekasi - Indonesia

DATE OF FIRST AUTHORISATION

18 November 2019

DATE OF REVISION OF THE TEXT

9 September 2025

Document number: VV-RIM-07252680

Anda dapat melaporkan efek samping secara langsung melalui:

PT AstraZeneca Indonesia

Apabila Anda ingin melaporkan dugaan efek samping produk AstraZeneca menanyakan/ meminta informasi medis terkait produk AstraZeneca mohon dikirimkan dengan mengisi form elektronik pada tautan berikut ini: http://contactazmedical.astrazeneca.com
Pusat Farmakovigilans/MESO Nasional Direktorat Pengawasan Keamanan, Mutu, dan Ekspor Impor Obat, Narkotika, Psikotropika, Prekursor , dan Zat Adiktif Badan Pengawas Obat dan Makanan Jl. Percetakan Negara No.23, Jakarta Pusat, 10560 Email: pv-center@pom.go.id Webiste: https://e-meso.pom.go.id/

Proposed packaging material		
Code	Imfinzi 120 mg & 500 mg – PIL-04.05	
Regulatory Objective	☐NDA ☐Renewal ☒Variation change detail no.: RO-Change Event-0035381-0000068; RO-Change Event-0040505-0000005	
Code of previous version	PI-03.01	
Reference	☐CDS version: ☐CPIL version:	☒SmPC country/version/date: VV-RIM-04948629 v.10 ☐RAM approval:
Changes	New Indication: DUO-E Study	
Name	ARH	

Leaflet Informasi Pasien
IMFINZI
Durvalumab
Larutan Konsentrat untuk Infus 50 mg/ml

Bacalah seluruh isi leaflet dengan seksama sebelum Anda mulai menggunakan obat ini

- Leaflet ini menjawab beberapa pertanyaan umum tentang IMFINZI. Leaflet ini tidak mencantumkan semua informasi yang tersedia dan tidak untuk menggantikan konsultasi dengan dokter atau apoteker.
- Semua obat memiliki risiko dan manfaat. Dokter Anda akan menimbang risiko penggunaan IMFINZI terhadap manfaat yang diharapkan untuk Anda.
- Jika Anda memiliki pertanyaan tentang pemakaian obat ini, tanyakan pada dokter Anda.
- Simpan leaflet ini, Anda mungkin perlu untuk membacanya lagi.

Informasi di leaflet ini:

IMFINZI, cairan injeksi 120/2.4 dan 500/10 miligram/mililiter, mengandung zat aktif durvalumab, histidine, histidine hidroklorida monohidrat, trehalose dihidrate, polisorbat 80, air untuk injeksi sebagai bahan lainnya.

1. IMFINZI DAN KEGUNAANNYA

IMFINZI digunakan untuk mengobati sejenis kanker paru yang disebut kanker paru-paru non-sel kecil (NSCLC) pada pasien dewasa. Obat ini akan diresepkan sendiri pada NSCLC Anda bila:

- Kanker Anda telah menyebar di dalam paru-paru Anda dan tidak dapat diangkat dengan pembedahan, dan
- Anda telah mencoba radiasi dan kemoterapi yang mengandung platinum, dan kanker anda telah menyusut atau tidak memburuk.

Obat ini akan dikombinasikan dengan tremelimumab dan kemoterapi pada NSCLC Anda bila:

- Telah menyebar pada kedua paru-paru Anda (dan/atau bagian tubuh lainnya) dan tidak dapat dilakukan operasi

- Tidak ada perubahan (mutasi) pada gen yang disebut EGFR (Epidermal Growth Factor receptor) atau ALK (Anaplastic Lymphoma kinase)

IMFINZI dikombinasikan dengan kemoterapi digunakan untuk mengobati jenis kanker paru-paru yang disebut kanker paru-paru sel kecil stadium lanjut (ES-SCLC) pada pasien dewasa. Ini digunakan ketika SCLC Anda:

- telah menyebar ke dalam paru-paru Anda (atau ke bagian tubuh lainnya) dan
- belum menerima pengobatan sebelumnya.

IMFINZI dikombinasikan dengan kemoterapi digunakan pada pasien dewasa untuk mengobati kanker saluran empedu (cholangiocarcinoma) dan kantung empedu yang disebut dengan Biliary Tract Cancer (BTC). Obat ini diresepkan pada Anda bila:

- Kanker Anda telah menyebar dalam saluran empedu dan kantung empedu (atau ke bagian tubuh lainnya) atau tidak dapat dioperasi.

IMFINZI dikombinasikan dengan tremelimumab digunakan untuk mengobati kanker pada hati yang disebut Hepatocellular Carcinoma (HCC) stadium lanjut yang tidak dapat dioperasi pada pasien dewasa. Obat ini diresepkan pada HCC Anda bila:

- Tidak dapat dioperasi, dan
- Telah menyebar pada organ hati Anda atau bagian tubuh lainnya

IMFINZI digunakan untuk mengobati jenis kanker rahim (kanker endometrium) yang telah menyebar dari lokasi awal tumor atau ketika mengalami kekambuhan pada orang dewasa. Obat ini digunakan dalam kombinasi dengan kemoterapi (karboplatin dan paclitaxel), diikuti oleh:

- Terapi hanya dengan IMFINZI apabila tumor Anda kekurangan MMR (dMMR), atau
- Terapi kombinasi IMFINZI dengan olaparib bila tumor Anda cukup MMR (pMMR).

Perlu dilakukan uji untuk mengetahui status MMR kanker endometrium Anda

Ketika IMFINZI diberikan secara kombinasi dengan obat anti-kanker lainnya, penting untuk pasien membaca Informasi untuk Pasien dari obat lainnya. Jika Anda memiliki pertanyaan tentang obat-obatan ini, tanyakan kepada dokter Anda.

IMFINZI merupakan antibodi monoklonal, yaitu sejenis protein. IMFINZI adalah sejenis immunotherapy dan termasuk dalam golongan obat *immune checkpoint inhibitor* yang bekerja dengan membantu sistem kekebalan tubuh Anda untuk menghancurkan kanker Anda.
Tanyakan kepada dokter Anda jika ada pertanyaan tentang mengapa obat ini telah diresepkan untuk Anda.

2. HAL YANG PERLU DIKETAHUI SEBELUM MENGGUNAKAN IMFINZI

Anda tidak boleh diberikan obat ini bila Anda alergi terhadap durvalumab atau salah satu bahan yang disebutkan di bagian awal leaflet ini.
Beberapa gejala reaksi alergi dapat meliputi:

- Sesak napas
- Mengi atau kesulitan bernapas
- Pembengkakan pada wajah, bibir, lidah atau bagian tubuh lainnya
- Ruam, gatal, atau gatal-gatal pada kulit.

Peringatan dan Pencegahan
Beritahu dokter sebelum Anda menggunakan IMFINZI bila:

- Anda memiliki penyakit Autoimun (penyakit yang mengganggu system kekebalan tubuh);
- Anda menjalani transplantasi organ;
- Anda memiliki masalah pada paru-paru dan masalah pernafasan;
- Anda memiliki penyakit hati

Apabila Anda mengalami masalah di atas (atau Anda tidak yakin), katakana pada dokter sebelum Anda diberikan IMFINZI.

Ketika Anda diberikan IMFINZI, Anda dapat mengalami efek samping yang serius.

Apabila Anda mengalami berikut ini, hubungi dokter Anda segera. Dokter Anda mungkin memberikan pengobatan lain yang dapat mencegah komplikasi memburuk dan membantu Anda untuk mengurangi gejala Anda. Dokter Anda mungkin menunda dosis selanjutnya untuk IMFINZI atau menghentikan pengobatan dengan IMFINZI, bila Anda:

- **Peradangan pada paru-paru :** gejala dapat berupa batuk atau batuk yang semakin parah, sesak nafas atau nyeri dada
- **Peradangan pada hati :** gejela dapat berupa mual atau muntah, merasa sedikit lapar, nyeri di sisi kanan perut, menguningnya kulit atau bagian putih mata, mengantuk, urine berwarna gelap atau berdarah.
- **Peradangan pada usus :** gejala dapat berupa diare atau buang air besar lebih banyak dari biasanya, atau tinja berwarna hitam, lengket dengan darah atau lender, sakit atau nyeri perut yang parah, atau terdapat lubang pada usus.
- **Peradangan pada kelenjar** (terutama tiroid, adrenal, pituitary, dan pancreas) : gejela dapat berupa detak jantung cepat, kelelahan ekstrem, penambahan atau penurunan berat badan, pusing atau pingsan, rambut rontok, rasa dingin, sembelit, sakit kepala yang tidak kunjung sembuh atau sakit kepala yang tidak biasa, sakit perut, mual, dan muntah
- **Diabetes tipe 1 :** gejala dapat berupa gula darah tinggi, merasa lebih lapar atau haus dari biasanya, buang air kecil lebih sering dari biasanya, napas cepat dan dalam kebingungan atau bau napas manis, rasa manis atau logam di mulut, atau bau urin atau keringat yang berbeda.
- **Peradangan pada ginjal :** gejala dapat berupa penurunan dalam jaumlah urin yang Anda keluarkan
- **Peradangan pada kulit :** gejala dapat berupa ruam, gatal, kulit melepuh atau bisul di mulut atau pada permukaan lembab lainnya
- **Peradangan pada otot jantung :** gejala dapat berupa nyeri dada, sesak napas, atau detak jantung tidak teratur.
- **Peradangan pada otot :** gejala dapat berupa nyeri otot, atau kelemahan atau kelelahan otot yang cepat.
- **Peradangan pada sumsum tulang belakang (myelitis transversal) :** gejala dapat berupa nyeri, mati rasa, kesemutan atau kelemahan pada lengan atau tungkai; masalah kandung kemih atau usus termasuk perlu melakukan buang air kecil lebih sering, kesulitan buang air kecil dan sembelit
- **Reaksi terkait infus :** gejala dapat berupa menggigil atau gemetar, gatal atau ruam, kemerahan, sesak napas atau mengi, pusing atau demam.

- **Peradangan pada otak** (ensefalitis) atau **radang selaput di sekitar sumsum tulang belakang dan ot**ak (meningitis) : gejala dapat berupa kejang, leher kaku, sakit kepala, demam, menggigil, muntah, kepekaan mata terhadap cahaya, kebingungan dan kantuk;
- **Peradangan pada saraf :** gejala dapat berupa nyeri, kelemahan dan kelumpuhan pada ekstremitas (sindrom Guillain- Barré);
- **Peradangan pada sendi:** tanda dan gejala termasuk nyeri sendi, pembengkakan, dan/atau kekakuan (radang sendi yang dimediasi oleh imun)
- **Peradangan pada mata:** tanda dan gejala termasuk kemerahan pada mata, nyeri mata, sensitivitas cahaya, dan/atau perubahan penglihatan (uveitis)
- **Jumlah trombosit yang rendah :** gejala dapat berupa pendarahan (hidung atau pendarahan gusi) dan/atau memar.
- **Kadar Angka Sel Darah Merah yang Rendah**: Gejala mencakup sesak napas, kelelahan, kulit pucat dan/atau detak jantung cepat. Ketika IMFINZI digunakan dalam kombinasi dengan obat anti kanker lain (olaparib), jumlah sel darah merah yang rendah bisa menjadi tanda 'aplasia sel darah merah murni' (PRCA), yaitu suatu kondisi di mana tidak ada sel darah merah yang diproduksi, atau ‘anemia hemolitik autoimun’ (AIHA), yaitu kerusakan sel darah merah yang berlebihan

Apabila Anda memiliki gejala yang telah disebutkan di atas, hubungi dokter segera.

Imfinzi bekerja pada sistem kekebalan tubuh Anda. Hal ini dapat menyebabkan peradangan di beberapa bagian tubuh Anda. Risiko Anda terhadap efek samping ini mungkin lebih tinggi jika Anda sudah memiliki penyakit autoimun (suatu kondisi di mana tubuh menyerang sel-selnya sendiri). Anda juga dapat sering mengalami flare (kekambuhan dengan derajat yang berat) pada penyakit autoimun Anda, namun sebagian besar kasusnya bersifat ringan.

Anak
IMFINZI tidak digunakan untuk pasien anak dibawah 18 tahun.

Pengobatan lain dan IMFINZI
Katakan pada dokter apabila Anda sedang, sudah, atau berencana menggunakan pengobatan lain. Ini termasuk pengobatan herbal dan obat yang didapatkan tanpa resep dokter.
Durvalumab adalah jenis antibodi yang tidak memiliki interaksi signifikan dengan obat lain berdasarkan studi yang telah dilakukan. Berdasarkan penelitian, penggunaan durvalumab bersamaan dengan kemoterapi atau obat-obatan seperti etoposide, carboplatin, cisplatin, tremelimumab, nab-paclitaxel, gemcitabine, pemetrexed, dan olaparib tidak menunjukkan adanya perubahan yang berarti terhadap kadar obat di dalam tubuh.

Hamil
- Katakan pada dokter jika Anda hamil atau berencana untuk memiliki anak.
- Apabila Anda adalah perempuan yang dapat hamil, Anda harus menggunakan alat kontrasepsi selama Anda melakukan pengobatan dengan IMFINZI dan untuk setidaknya 3 bulan setelah dosis terakhir Anda.

Ibu Menyusui
- Katakan pada dokter apabila Anda sedang menyusui

- Tanyakan pada dokter apabila Anda menyusui selama atau setelah pengobatan dengan IMFINZI
- Tidak diketahui apakah IMFINZI masuk ke dalam ASI manusia

Mengemudi
IMFINZI tidak akan mempengaruhi kemampuan Anda untuk mengemudi dan menggunakan mesin. Namun, apabila Anda memiliki efek samping yang dapat mempengaruhi kemampuan Anda untuk konsentrasi, Anda harus hati-hati ketika mengemudi atau menggunakan mesin.

3. CARA MENGGUNAKAN IMFINZI

IMFINZI akan diberikan kepada Anda di rumah sakit atau klinik dalam pengawasan dokter yang telah berpengalaman:

- Dosis yang direkomendasikan untuk IMFINZI adalah 10 mg per kilogram berat badan setiap 2 minggu, 1120 mg setiap 3 minggu atau 1500 mg setiap 3 atau 4 minggu
- IMFINZI akan diberikan kepada Anda sebagai cairan konsentrat untuk infus melalui pembuluh vena Anda (IV).
- Infus memakan waktu sekitar 60 menit dan biasanya akan diberikan setiap 2 minggu.
- Dokter Anda akan memutuskan berapa banyak perawatan yang Anda butuhkan
- Tergantung pada jenis kanker Anda, IMFINZI dapat diberikan dalam kombinasi dengan obat anti kanker lainnya.
- Ketika IMFINZI diberikan dalam kombinasi dengan tremelimumab dan kemoterapi untuk kanker paru-paru Anda, pertama-tama Anda akan diberikan tremelimumab diikuti oleh IMFINZI dan kemudian kemoterapi.
- limumab diikuti oleh IMFINZI dan kemudian kemoterapi.
- Ketika IMFINZI diberikan dalam kombinasi dengan kemoterapi untuk kanker paru-paru atau kanker rahim (kanker endometrial) Anda, Anda akan diberikan IMFINZI terlebih dahulu diikuti dengan kemoterapi.
- Ketika IMFINZI diberikan dalam kombinasi dengan tremelimumab untuk kanker hati Anda, Anda akan diberikan tremelimumab terlebih dahulu diikuti oleh IMFINZI.
- Silakan merujuk ke informasi pasien anti kanker lainnya untuk memahami penggunaan obat lain tersebut. Jika Anda memiliki pertanyaan tentang obat-obatan ini, tanyakan kepada dokter Anda.

Jika Anda melewatkan janji untuk diberikan IMFINZI. Segera hubungi dokter untuk dijadwalkan ulang. Sangat penting untuk tidak melewatkan satu dosis pun. Apabila Anda memiliki pertanyaan lebih lanjut mengenai pengobatan Anda, tanyakan pada dokter.

4. EFEK SAMPING YANG MUNGKIN TERJADI

Jika Anda memiliki salah satu dari gejala berikut ini, hubungi atau temui dokter Anda segera. Yang dilaporkan pada studi klinis oleh pasien yang mendapatkan IMFINZI tanpa dikombinasi:

Sangat umum (dapat mempengaruhi lebih dari 1 dari 10 orang)

- infeksi pada saluran pernapasan bagian atas
- kelenjar tiroid kurang aktif yang dapat menyebabkan kelelahan atau penambahan berat badan
- batuk

- diare
- sakit perut
- ruam kulit atau gatal
- demam
- nyeri sendi (arthralgia)

Umum (dapat mempengaruhi hingga 1 dari 10 orang)

- infeksi paru-paru serius (pneumonia)
- infeksi jamur di mulut
- infeksi jaringan lunak gigi dan mulut
- penyakit seperti flu
- kelenjar tiroid yang terlalu aktif yang dapat menyebabkan detak jantung cepat atau penurunan berat badan
- radang paru-paru (pneumonitis)
- suara serak (disfonia)
- tes hati abnormal (aspartate aminotransferase meningkat; alanine aminotransferase meningkat)
- keringat malam
- nyeri otot (mialgia)
- tes fungsi ginjal abnormal (peningkatan kreatinin darah)
- buang air kecil yang menyakitkan (disuria)
- pembengkakan kaki (edema perifer)
- reaksi terhadap infus obat yang dapat menyebabkan demam atau pembilasan
- radang hati yang dapat menyebabkan mual atau merasa kurang lapar (hepatitis)

Jarang (dapat mempengaruhi hingga 1 dari 100 orang)

- radang kelenjar tiroid (tiroiditis)
- penurunan sekresi hormon yang dihasilkan oleh kelenjar adrenal yang dapat menyebabkan kelelahan
- jaringan parut pada paru-paru
- kulit melepuh (pemphigoid)
- radang kulit (dermatitis)
- radang usus atau usus (kolitis)
- radang otot (myositis)
- radang jantung (miokarditis)
- radang ginjal (nefritis) yang dapat menurunkan jumlah urin Anda
- radang pankreas (pankreatitis)
- merah, gatal, kering, bercak bersisik pada kulit yang menebal (psoriasis)

Langka (dapat mempengaruhi hingga 1 dari 1000 orang)

- suatu kondisi yang menyebabkan kadar gula darah tinggi (diabetes mellitus tipe 1)
- fungsi kelenjar pituitari yang kurang aktif (hipopituitarisme termasuk diabetes insipidus) yang dapat menyebabkan kelelahan, peningkatan jumlah urin Anda
- suatu kondisi dimana otot menjadi lemah dan terjadi kelelahan otot yang cepat (myasthenia gravis)
- radang selaput di sekitar sumsum tulang belakang dan otak (meningitis)
- penyakit celiac (ditandai dengan gejala seperti sakit perut, diare, dan kembung setelah mengonsumsi makanan yang mengandung gluten)
- rendahnya jumlah trombosit yang disebabkan oleh reaksi imun (trombositopenia imun)

- Peradangan kandung kemih (sistitis). Tanda dan gejala mungkin termasuk buang air kecil yang sering dan/atau nyeri, keinginan untuk buang air kecil, darah dalam urin, nyeri atau tekanan di perut bagian bawah.
- radang mata (uveitis)
- radang sendi (arthritis yang dimediasi imun)
- radang otot dan pembuluh darah (polimiositis)

Efek samping lain yang telah dilaporkan dengan frekuensi yang tidak diketahui (tidak bisa diperkirakan dari data yang tersedia)

- radang saraf: (sindrom Guillain-Barré)
- kekurangan atau berkurangnya enzim pencernaan yang dihasilkan oleh pankreas (insufisiensi eksokrin pankreas)
- radang otak (ensefalitis noninfeksi)
- radang bagian sumsum tulang belakang (mielitis transversal)

Efek samping tambahan berikut ini akibat terapi tunggal IMFINZI telah dilaporkan pada studi klinis pada pasien yang mendapatkan IMFINZI dikombinasikan dengan kemoterapi (frekuensi dan keparahan dari efek samping dapat berbeda pada obat kemoterapi yang didapatkan):

Sangat umum (dapat mempengaruhi lebih dari 1 dari 10 orang)

- jumlah sel darah putih yang rendah
- jumlah sel darah merah yang rendah
- jumlah trombosit yang rendah
- mual; muntah; sembelit
- rambut rontok
- merasa kurang lapar
- merasa lelah atau lemah
- radang saraf yang menyebabkan mati rasa, kelemahan, kesemutan atau rasa terbakar di lengan dan kaki (neuropati periferal)

Umum (dapat mempengaruhi hingga 1 dari 10 orang)

- jumlah sel darah putih yang rendah dengan tanda-tanda demam (febrile neutropenia)
- radang mulut atau bibir (stomatitis)
- rendahnya jumlah sel darah merah, sel darah putih, dan trombosit (pancytopenia)

Efek samping tambahan berikut ini akibat terapi tunggal IMFINZI telah dilaporkan dari pasien yang berpartisipasi dalam studi klinis yang mendapatkan IMFINZI dikombinasikan dengan tremelimumab dan kemoterapi (frekuensi dan keparahan dari efek samping dapat berbeda pada obat kemoterapi yang didapatkan):

Sangat umum (dapat mempengaruhi lebih dari 1 dari 10 orang)

- jumlah sel darah merah yang rendah
- jumlah sel darah putih yang rendah
- jumlah trombosit yang rendah
- merasa kurang lapar
- mual, muntah
- sembelit
- rambut rontok
- merasa lelah atau lemah

Umum (dapat mempengaruhi hingga 1 dari 10 orang)

- jumlah sel darah putih yang rendah dengan tanda-tanda demam (febrile neutropenia)
- rendahnya jumlah sel darah merah, sel darah putih, dan trombosit (pansitopenia)
- radang saraf yang menyebabkan mati rasa, lemas, kesemutan atau rasa terbakar di lengan dan kaki (neuropati perifer)
- radang mulut atau bibir (stomatitis)
- tes fungsi pankreas abnormal

Efek samping lain yang telah dilaporkan dengan frekuensi tidak diketahui (tidak dapat diperkirakan dari data yang tersedia)

- lubang di usus (perforasi usus)

Efek samping tambahan berikut ini akibat terapi tunggal IMFINZI telah dilaporkan dari pasien yang berpartisipasi dalam studi klinis yang mendapatkan IMFINZI dikombinasikan dengan tremelimumab

Umum (dapat mempengaruhi hingga 1 dari 10 orang)

- tes fungsi pankreas abnormal

Efek samping lain yang telah dilaporkan dengan frekuensi tidak diketahui (tidak dapat diperkirakan dari data yang tersedia)

- lubang di usus (perforasi usus)

Efek samping tambahan berikut akibat penggunaan IMFINZI saja telah dilaporkan dalam studi klinis pada pasien yang mengonsumsi IMFINZI dalam kombinasi dengan kemoterapi berbasis platinum diikuti oleh IMFINZI dengan olaparib:

Sangat umum (dapat memengaruhi lebih dari 1 dari 10 orang)

- jumlah sel darah merah rendah
- jumlah sel darah putih rendah (neutropenia dan leukopenia)
- jumlah trombosit rendah
- merasa kurang lapar
- radang saraf yang menyebabkan mati rasa, lemas, kesemutan atau nyeri terbakar pada lengan dan kaki (neuropati periferal)
- mual; muntah; sembelit
- pusing
- sakit kepala
- perubahan rasa makanan (disgeusia)
- sesak napas (dispnea)
- radang mulut atau bibir (stomatitis)
- rambut rontok
- merasa lelah atau lemah

Umum (dapat memengaruhi hingga 1 dari 10 orang)

- jumlah sel darah putih yang rendah disertai demam (febrile neutropenia)
- kadar limfosit rendah, salah satu jenis sel darah putih
- reaksi alergi
- gangguan pencernaan atau nyeri ulu hati (dispepsia)
- bekuan darah di vena dalam, biasanya di kaki (trombosis vena) yang dapat menyebabkan gejala seperti nyeri atau pembengkakan pada kaki
- kegagalan memproduksi sel darah merah (aplasia sel darah merah murni) yang dapat menyebabkan gejala seperti sesak napas, kelelahan, kulit pucat, atau detak jantung cepat

Jarang (dapat memengaruhi hingga 1 dari 100 orang)

- rendah jumlah sel darah merah, sel darah putih, dan trombosit (pansitopenia)

Tanyakan dokter Anda bila Anda memiliki pertanyaan terkait efek samping. Beritahu dokter atau Apoteker Anda jika Anda merasakan hal lain yang membuat Anda merasa tidak sehat. Efek samping lain yang tidak tercantum di atas mungkin juga terjadi pada beberapa orang.

Pelaporan Efek Samping

Apabila Anda memiliki efek samping, katakaan pada dokter Anda. Ini termasuk segala kemungkinan efek samping yang tidak terdapat pada *leaflet.* Anda dapat melaporkan efek samping pada dokter atau tenaga kesehatan Anda dan atau secara langsung ke kontak Industri Farmasi pada bagian ”**Informasi lebih lanjut”.** Dengan melaporkan efek samping Anda dapat membantu menyediakan informasi lebih pada keamanan obat ini.

5. CARA PENYIMPANAN IMFINZI

IMFINZI akan diberikan pada Anda di rumah sakit atau klinik dan tenaga Kesehatan akan bertanggung jawab untuk penyimpanannya. Berikut ini merupakan detail penyimpanannya :

Simpan obat ini jauh dari jangkauan anak-anak
Jangan gunakan obat ini setelah tanggal kadaluarsa yang tercantum pada karton dan label vial.
Tanggal kadaluarsa mengacu pada hari terakhir pada bulan tersebut.

Simpan pada suhu 2°C - 8°C didalam kemasan asli untuk menghindari sinar matahari langsung.
Jangan dibekukan. Jangan digunakan apabila obat ini keruh, berubah warna atau terdapat partikel yang terlihat.

Jangan menyimpan bagian larutan infus yang tidak terpakai untuk digunakan kembali. Setiap obat atau bahan limbah yang tidak terpakai harus dibuang sesuai dengan persyaratan setempat.

6. ISI KEMASAN DAN INFORMASI LAINNYA

- IMFINZI adalah larutan konsentrat untuk infus yang jernih hingga *opalescent*, tidak berwarna hingga cairan agak kuning dibotol kaca.
- IMFINZI mengandung zat aktif durvalumab.
- Tiap mL konsentrat untuk larutan infus mengandung 50 mg durvalumab.
- Setiap vial mengandung 500 mg durvalumab dalam 10 mL konsentrat atau 120 mg durvalumab dalam 2,4 mL konsentrat.
- Bahan lainnya adalah: histidin, histidin hidroklorida monohidrat, trehalosa dihidrat, polisorbat 80, air untuk injeksi.
- Bahan lainnya adalah Histidin, Histidin hidroklorida monohidrat, Trehalose dihydrate, Polisorbat 80, dan Air untuk injeksi.

Bentuk IMFINZI dan isi kemasannya

Konsentrat IMFINZI untuk larutan infus adalah larutan steril, bebas pengawet, bening hingga opalescent, tidak berwarna hingga agak kuning, bebas dari partikel yang terlihat.

7. INFORMASI LEBIH LANJUT

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