PROFESSIONAL INFORMATION

SCHEDULING STATUS: S4

1 NAME OF THE MEDICINE

IMFINZI 120 mg concentrate for solution for infusion

IMFINZI 500 mg concentrate for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

IMFINZI 120 mg: Each vial of 2,4 ml contains 120 mg of durvalumab

IMFINZI 500 mg: Each vial of 10 ml contains 500 mg of durvalumab

Sugar free.

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

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

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Urothelial Carcinoma

IMFINZI in combination with cisplatin-based chemotherapy as neoadjuvant treatment, followed by IMFINZI as monotherapy adjuvant treatment after radical cystectomy, is indicated for the treatment of patients with muscle invasive bladder cancer (MIBC).

Non-Small Cell Lung Cancer (NSCLC)

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

IMFINZI in combination with tremelimumab and platinum-based chemotherapy is indicated for the first-line treatment of patients with metastatic NSCLC with no sensitising epidermal growth factor (EGFR) mutations or anaplastic lymphoma kinase (ALK) genomic tumour aberrations.

IMFINZI in combination with chemotherapy as neoadjuvant treatment, followed by IMFINZI as monotherapy after surgery, is indicated for the treatment of patients with resectable (tumours ≥ 4 cm and/or node positive) NSCLC and no known EGFR mutations or ALK rearrangements.

Small Cell Lung Cancer (SCLC)

IMFINZI is indicated for the treatment of patients with limited-stage small cell lung cancer (LS-SCLC) whose disease has not progressed following platinum-based chemoradiation therapy (CRT).

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

Hepatocellular Carcinoma (HCC)

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

Biliary Tract Cancer (BTC)

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

Gastric or Gastroesophageal Junction Adenocarcinoma (GC/GEJC)

IMFINZI in combination with FLOT (Fluorouracil, Leucovorin, Oxaliplatin, and Docetaxel) chemotherapy as neoadjuvant and adjuvant treatment, followed by adjuvant IMFINZI monotherapy, is indicated for the treatment of patients with resectable gastric or gastroesophageal junction adenocarcinoma.

4.2 Posology and method of administration

Posology

The recommended dose of IMFINZI depends on the indication as presented in Table 1. IMFINZI is administered as an intravenous infusion over 60 minutes.

Table 1. Recommended dosage of IMFINZI

Indication	Recommended IMFINZI dosage	Duration of Therapy
LS-SCLC	1500 mg[b] every 4 weeks	Until disease progression, unacceptable toxicity or a maximum of 24 months.
Locally Advanced NSCLC	10 mg/kg every 2 weeks or 1500 mg every 4 weeks[a,b]	Until disease progression or unacceptable toxicity
Metastatic NSCLC	During chemotherapy: 1500 mg[f,g] in combination with tremelimumab 75 mg[h] and platinum-based chemotherapy[i] every 3 weeks (21 days) for 4 cycles Post-platinum chemotherapy: 1500 mg[g,h] every 4 weeks as monotherapy and histology-based pemetrexed maintenance[i,j] therapy every 4 weeks and, a fifth dose of tremelimumab[k,l] alongside IMFINZI dose 6 at week 16	Until disease progression or unacceptable toxicity
Resectable NSCLC	1500 mg[o] in combination with chemotherapy[d,i] every 3 weeks for up to 4 cycles prior to surgery, followed by 1500 mg monotherapy every 4 weeks for up to 12 cycles after surgery.	Until disease is deemed unresectable, recurrence, unacceptable toxicity, or a maximum of 12 cycles after surgery
ES-SCLC	1500 mg[c] in combination with chemotherapy[d,e] every 3 weeks (21 days) for 4 cycles, followed	Until disease progression or unacceptable toxicity

	by 1500 mg every 4 weeks as monotherapy	
uHCC	Single Tremelimumab Regular Interval Durvalumab (STRIDE): 300 mg[f] tremelimumab as a single priming dose in combination with IMFINZI 1500 mg[f,g] at Cycle 1/Day 1, followed by IMFINZI as monotherapy every 4 weeks	As long as clinical benefit is observed or until unacceptable toxicity
BTC	1500 mg[c] in combination with chemotherapy[h] every 3 weeks (21 days), followed by 1500 mg every 4 weeks as monotherapy	Until disease progression or until unacceptable toxicity
MIBC	1500 mg[d] in combination with chemotherapy every 3 weeks (21 days) for 4 cycles prior to surgery, followed by 1500 mg[d] every 4 weeks as monotherapy for up to 8 cycles after surgery.	Until disease progression that precludes definitive surgery, recurrence, unacceptable toxicity, or a maximum of 8 cycles after surgery
GC/GEJC	1500 mg[p] in combination with FLOT chemotherapy every 4 weeks for up to 2 cycles prior to surgery, followed by 1500 mg[p], with FLOT chemotherapy, every 4 weeks for up to 2 cycles and then as 1500 mg[p] monotherapy every 4 weeks for up to 10 cycles, for a total of up to 12 cycles after surgery	Neoadjuvant phase: until disease progression that precludes definitive surgery or unacceptable toxicity Adjuvant phase: until progression or recurrence, unacceptable toxicity, or a maximum of 12 cycles after surgery

[a] Patients with a body weight of 30 kg or less must receive weight-based dosing, equivalent to IMFINZI10 mg/kg every 2 weeks or 20 mg/kg every 4 weeks as monotherapy until weight increases to greater than 30 kg

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

[c] Patients with a body weight of 30 kg or less must receive weight-based dosing, equivalent to IMFINZI 20 mg/kg in combination with chemotherapy every 3 weeks (21 days) for 4 cycles, followed by 20 mg/kg

every 4 weeks as monotherapy until weight increases to greater than 30 kg.

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

[e] When IMFINZI is administered in combination with chemotherapy, refer to the Professional Information for etoposide and carboplatin or cisplatin for dosing information.

[f] Patients with a body weight of 30 kg or less must receive weight-based dosing, equivalent to IMFINZI 20 mg/kg and tremelimumab 4 mg/kg until weight ~~is~~ increases to greater than 30 kg.

[g] Administer tremelimumab first; followed by IMFINZI and then chemotherapy on the day of dosing, when applicable.

[h] When IMFINZI is administered in combination with tremelimumab and chemotherapy, refer to the Professional Information for tremelimumab for dosing information.

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

[j] Based on investigator decision for non-squamous patients who received treatment with pemetrexed and carboplatin/cisplatin.

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

[l] 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-chemotherapy phase.

[m] Patients with a body weight of 30 kg or less must receive weight-based dosing, equivalent to IMFINZI 20 mg/kg and tremelimumab 4 mg/kg until weight ~~is~~ increases to greater than 30 kg.

[n] Administer tremelimumab prior to IMFINZI on the same day. When IMFINZI is administered in combination with tremelimumab, refer to the Prescribing Information for tremelimumab dosing information.

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

[p] Patients with a body weight of 30 kg or less must receive weight-based dosing of IMFINZI at 20 mg/kg. In combination with FLOT chemotherapy or as monotherapy, dose at 20 mg/kg every 4 weeks until weight increases to greater than 30 kg.

Dose escalation or reduction is not recommended. Dose withholding or discontinuation may be required based on individual safety and tolerability. In general, withhold IMFINZI for severe (Grade 3) immune-mediated adverse reactions. Permanently discontinue IMFINZI for life-threatening (Grade 4) immune-mediated adverse reactions, recurrent severe (Grade 3) immune-mediated reactions that require systemic immunosuppressive treatment, or an inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks of initiating corticosteroids.

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

Table 2. Recommended Treatment Modifications for IMFINZI and Management Recommendations

Adverse Reactions	**Severity**[a]	**IMFINZI Treatment Modification**	**Corticosteroid Treatment Unless Otherwise Specified**[b]
Immune-mediated pneumonitis/interstitial lung disease	Grade 2	Withhold dose[c]	Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper.
	Grade 3 or 4	Permanently discontinue	
Immune-mediated hepatitis	ALT or AST >3 - ≤ 5 x ULN or total bilirubin >1.5 ≤3 x ULN	Withhold dose[c]	Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
	ALT or AST > 5 ≤10 x ULN	Withhold IMFINZI And permanently Discontinue tremelimumab	
	Concurrent ALT or AST >3 x ULN and total bilirubin >2 x ULN	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	ALT or AST > 2.5 ≤5 X BLV and ≤ 20 X ULN	Withhold dose[c]	
	ALT or AST >5 - 7X 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	Withhold IMFINZI And permanently discontinue tremelimumab	
	ALT or AST > 7 x BLV or > 20 x ULN whichever occurs first or bilirubin > 3 x ULN	Permanently discontinue	
Immune-mediated colitis or diarrhoea	Grade 2	Withhold dose[c]	Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
	Grade 3 for IMFINZI monotherapy	Withhold dose[c]	
	Grade 3 for IMFINZI + tremelimumab	Permanently discontinue	
	Grade 4	Permanently discontinue	
	Intestinal perforation of any grade	Permanently discontinue	Consult a surgeon immediately if an intestinal perforation is suspected
Immune-mediated hyperthyroidism or thyroiditis	Grade 2-4	Withhold dose until clinically stable	Symptomatic management
Immune-mediated hypothyroidism	Grade 2-4	No changes	Initiate thyroid hormone replacement as clinically

			indicated
Immune-mediated adrenal insufficiency, hypophysitis/hypopituitarism	Grade 2-4	Withhold dose until clinically stable	Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper and hormone replacement as clinically indicated
Immune-mediated Type 1 diabetes mellitus	Grade 2-4	No changes	Initiate treatment with insulin as clinically indicated
Immune-mediated nephritis	Grade 2 with serum creatinine >1.5 – 3 x (ULN or baseline)	Withhold dose[c]	Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
	Grade 3 with serum creatinine >3 x baseline or >3 - 6 x ULN; Grade 4 with serum creatinine >6 x ULN	Permanently discontinue	
Immune-mediated rash or dermatitis (including pemphigoid)	Grade 2 for >1 week or Grade 3	Withhold dose[c]	Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
	Grade 4	Permanently discontinue	
Immune-mediated myocarditis	Grade 2- 4	Permanently discontinue	Initiate 2 to 4 mg/kg/day prednisone or equivalent followed by a taper[f]
Immune-mediated myositis/polymyositis	Grade 2 or 3	Withhold dose[c,g]	Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
	Grade 4	Permanently discontinue	
Infusion-related reactions	Grade 1 or 2	Interrupt or slow the rate of infusion	May consider pre-medications for prophylaxis of subsequent infusion

			reactions
	Grade 3 or 4	Permanently discontinue	Manage severe infusion-related reactions per institutional standard, appropriate clinical practice guidelines and/or society guidelines
Immune-mediated - myasthenia gravis	Grade 2 - 4	Permanently discontinue	Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
Immune-mediated encephalitis	Grade 2-4	Permanently discontinue	Initiate 1 mg/kg/day to 2 mg/kg/day prednisone or equivalent followed by a taper
Immune-mediated Guillain-Barré syndrome	Grade 2-4	Permanently discontinue	Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
Other immune-mediated adverse reactions[h]	Grade 2 or 3	Withhold dose[c]	Initiate 1 mg/kg/day to 2 mg/kg/day prednisone or equivalent followed by a taper
	Grade 4	Permanently discontinue	

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

[b] Upon improvement to ≤ Grade 1, corticosteroid taper should be initiated and continued over at least 1 month. Consider increasing dose of corticosteroids and/or using additional systemic immunosuppressants if there is worsening or no improvement.

[c] After withholding, IMFINZI can be resumed within 12 weeks if the adverse reactions improved to ≤ Grade 1 and the corticosteroid dose has been reduced to ≤ 10 mg prednisone or equivalent per day. IMFINZI should be permanently discontinued for recurrent Grade 3 adverse reactions, as applicable.

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

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

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

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

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

For suspected immune-mediated adverse reactions, adequate evaluation should be performed to confirm aetiology or exclude alternate aetiologies. For other immune-mediated adverse reactions not included in Table 1, IMFINZI should be discontinued for Grade 4 adverse reactions. Withholding of IMFINZI should be considered for Grade 3 immune- mediated adverse reactions, unless clinical judgment indicates discontinuation. Systemic corticosteroids should be considered.

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

Special patient populations

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

Paediatric and adolescents:

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

Elderly (≥ 65 years):

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

Renal Impairment:

Based on a population pharmacokinetic analysis, no dose adjustment of IMFINZI is recommended in patients with mild or moderate renal impairment (see section 5.2).

Hepatic Impairment:

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

Method of Administration

For intravenous administration.

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

4.3 Contraindications

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

4.4. Special warnings and precautions for use

Immune-mediated pneumonitis:

Immune-mediated pneumonitis or interstitial lung disease, defined as requiring use of systemic corticosteroids and with no clear alternate aetiology, occurred in patients receiving IMFINZI or IMFINZI in combination with tremelimumab (see section 4.8). Patients should be monitored for signs and symptoms of pneumonitis.

Patients with suspected pneumonitis should be evaluated and the diagnosis should be confirmed with radiographic imaging and other infections and disease-related aetiologies (example tuberculosis) excluded and managed as recommended in section 4.2.

Pneumonitis and radiation pneumonitis

Radiation pneumonitis is frequently observed in patients receiving radiation therapy to the lung and the clinical presentation of pneumonitis and radiation pneumonitis is very similar.

In the PACIFIC Study, in patients who had completed treatment with concurrent chemoradiation within 1 to 42 days prior to initiation of study treatment, pneumonitis including both immune-mediated pneumonitis and radiation pneumonitis, occurred in patients receiving IMFINZI Pneumonitis or radiation pneumonitis occurred in 161 (33,9 %) patients in the IMFINZI treated group and 58 (24,8 %) in the placebo group; including Grade 3 in 16 (3,4 %) patients on IMFINZI vs. 7 (3,0 %) patients on placebo and Grade 5 in 5 (1,1 %) patients on IMFINZI vs. 4 (1,7 %) patients on placebo.
The median time to onset in the IMFINZI treated group was 55 days (range: 1-406 days) vs. 55 days (range: 1-255 days) in the placebo group.

In the ADRIATIC Study, in patients who had completed treatment with chemoradiation within 1 to 42 days prior to initiation of study treatment, pneumonitis or radiation pneumonitis occurred in 100 (38,2 %) patients in the IMFINZI treated group and 80 (30,2 %) in the placebo group; including Grade 3 in 8 (3,1 %) patients on IMFINZI vs 6 (2,3 %) patients on placebo, and Grade 5 in 1 (0,4 %) patient on IMFINZI vs 0 patients on placebo.

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).
Patients should be monitored for abnormal liver tests prior to and periodically during treatment with IMFINZI. Immune-mediated hepatitis should be managed as recommended in section 4.2.

Immune-mediated colitis:

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

Immune-mediated endocrinopathies:

Immune-mediated hypothyroidism hyperthyroidism/thyroiditis

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

Immune-mediated Adrenal insufficiency

Immune-mediated adrenal insufficiency occurred in patients receiving IMFINZI 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.

Immune-mediated Type 1 diabetes mellitus

Immune-mediated type 1 diabetes mellitus, which can present with diabetic ketoacidosis 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.

Immune-mediated Hypophysitis/hypopituitarism

Immune-mediated hypophysitis or hypopituitarism occurred in patients receiving IMFINZI or IMFINZI in combination with tremelimumab (see section 4.8). Patients should be monitored for

clinical signs and symptoms of hypophysitis or hypopituitarism. For symptomatic hypophysitis or hypopituitarism, patients should be managed as recommended in section 4.2.

Immune-mediated nephritis

Immune-mediated nephritis, defined as requiring use of systemic corticosteroids and with no clear alternate aetiology, occurred in patients receiving IMFINZI or IMFINZI in combination with tremelimumab (see section 4.8).

Patients should be monitored for abnormal renal function tests prior to and periodically during treatment with IMFINZI and managed as recommended in section 4.2.

Immune-mediated rash

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

Immune-mediated myocarditis

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

Other immune mediated adverse reactions:

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

(see section 4.8).

Human Immunodeficiency Virus (HIV):

Safety and efficacy in patients with HIV have not been established.

Infusion related reactions:

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

4.5 interaction with other medicines and other forms of interaction

IMFINZI is an immunoglobulin, therefore no formal pharmacokinetic (PK) medicine-medicine interaction studies have been conducted with IMFINZI.

PK drug-drug interaction between durvalumab in combination with tremelimumab was assessed in the HIMALAYA study and no clinically meaningful PK drug-drug interaction was identified.

4.6 Fertility, pregnancy and lactation

Pregnancy

In animal reproduction studies, administration of IMFINZI to pregnant cynomolgus monkeys from the confirmation of pregnancy through delivery at exposure levels approximately 22 times higher than those observed at the clinical dose of 10 mg/kg of IMFINZI (based on AUC) was not associated with maternal toxicity or effects on embryofoetal development, pregnancy outcome or postnatal development. There are no data on the use of IMFINZI in pregnant women. Based on its mechanism of action, IMFINZI 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. IMFINZI is not recommended during pregnancy and in women of childbearing potential not using effective contraception during treatment and for at least 3 months after the last dose.

Lactation

There is no information regarding the presence of IMFINZI 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 IMFINZI to pregnant cynomolgus monkeys was associated with dose-related low level excretion of IMFINZI in breast milk. Because of the potential for adverse reactions in breastfed infants from IMFINZI, advise a lactating woman not to breastfeed during treatment and for at least 3 months after the last dose.

Fertility

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

The safety of IMFINZI as monotherapy is based on pooled data in 3006 patients from 9 studies across multiple tumour types the most frequent adverse reaction were cough, diarrhoea and rash.

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

The safety of IMFINZI in combination with chemotherapy as neoadjuvant treatment in patients

with resectable NSCLC, is based on data in 401 patients from the AEGEAN study and was consistent with known IMFINZI monotherapy and known chemotherapy safety profiles.
The safety of IMFINZI in combination with chemotherapy in patients with BTC is based on data in 338 patients from the TOPAZ-1 study and was consistent with IMFINZI monotherapy and known chemotherapy safety profiles.

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

The safety of STRIDE treatment in patients with uHCC is based on data in 462 patients from the HCC pool and was consistent with known IMFINZI + tremelimumab safety profile.
The safety of IMFINZI monotherapy in patients with LS-SCLC is based on data in 262 patients from the ADRIATIC study. The safety profile was consistent with IMFINZI monotherapy.
The safety of IMFINZI in combination with chemotherapy in patients with MIBC is based on data in 530 patients from the NIAGARA study and was consistent with IMFINZI monotherapy and known chemotherapy safety profiles.
The safety of IMFINZI in combination with FLOT chemotherapy as neoadjuvant and adjuvant treatment, followed by adjuvant IMFINZI monotherapy, in patients with GC/GEJC is based on data in 475 patients from the MATTERHORN study and was consistent with IMFINZI monotherapy and known FLOT chemotherapy safety profiles.

Tabulated list of adverse reactions

Adverse reactions are listed according to system organ class in MedDRA. Within each system organ class, the adverse drug reactions are presented in decreasing frequency. The corresponding frequency category is based on the CIOMS III convention and is defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1000); very rare (< 1/10,000); not determined (cannot be estimated from

available data).

Table 3. Adverse drug reactions in patients treated with IMFINZI at 10 mg/kg

System Organ Class	Adverse Drug Reaction	Frequency of any Grade		Frequency of Grade 3-4	
Respiratory, thoracic and mediastinal disorders	Cough/ Productive Cough	Very common	646 (21,5 %)	Uncommon	11 (0,4 %)
	Pneumonitis[a]	Common	114 (3,8 %)	Uncommon	26 (0,9 %)
	Dysphonia	Common	93 (3,1 %)	Rare	2 (<0,1 %)
	Interstitial lung disease	Uncommon	18 (0,6 %)	Uncommon	4 (0,1 %)
Hepatobiliary disorders	Aspartate aminotransferase increased or Alanine aminotransferase increased[a,b]	Common	244 (8,1 %)	Common	69 (2,3 %)
	Hepatitis[a,c]	Uncommon	25 (0,8 %)	Uncommon	12 (0,4 %)
Gastrointestinal disorders	Abdominal pain[d]	Very common	383 (12,7 %)	Common	53 (1,8 %)
	Diarrhoea	Very common	491 (16,3 %)	Uncommon	19 (0,6 %)
	Colitis[e]	Uncommon	28 (0,9 %)	Uncommon	10 (0,3 %)
	Pancreatitis[f]	Uncommon	6 (0,2 %)	Uncommon	5 (0,17 %)
Endocrine disorders	Hypothyroidism[g]	Very common	305 (10,1 %)	Uncommon	5 (0,2 %)
	Hyperthyroidism[h]	Common	137 (4,6 %)		0
	Thyroiditis[i]	Uncommon	23 (0,8 %)	Rare	2 (<0,1 %)
	Adrenal insufficiency	Uncommon	18 (0,6 %)	Rare	3 (<0,1 %)

System Organ Class	Adverse Drug Reaction	Frequency of any Grade		Frequency of Grade 3-4	
	Hypophysitis/ Hypopituitarism	Rare	2 (<0,1 %)	Rare	2 (<0,1 %)
	Type 1 diabetes mellitus	Rare	1 (<0,1 %)	Rare	1 (<0,1 %)
	Diabetes insipidus	Rare	1 (<0,1 %)	Rare	1 (<0,1 %)
Eye disorders	Uveitis	Rare	1 (<0,1 %)		0
Renal and urinary disorders	Blood creatinine increased	Common	105 (3,5 %)	Rare	3 (<0,1 %)
	Dysuria	Common	39 (1,3 %)		0
	Nephritis[j]	Uncommon	9 (0,3 %)	Rare	2 (<0,1 %)
Skin and subcutaneous tissue disorders	Rash[k]	Very common	480 (16,0 %)	Uncommon	18 (0,6 %)
	Pruritus[l]	Very common	325 (10,8 %)	Rare	1 (<0,1 %)
	Night sweats	Common	47 (1,6 %)	Rare	1 (<0,1 %)
	Dermatitis	Uncommon	22 (0,7 %)	Rare	2 (<0,1 %)
	Pemphigoid[m]	Rare	3 (<0,1 %)		0
Cardiac disorders	Myocarditis	Rare	1 (<0,1 %)	Rare	1 (<0,1 %)
General disorders and administration site conditions	Pyrexia	Very common	414 (13,8 %)	Uncommon	10 (0,3 %)
	Oedema peripheral[n]	Common	291 (9,7 %)	Uncommon	9 (0,3 %)
Infections and infestations	Upper respiratory tract infections[o]	Very common	407 (13,5 %)	Uncommon	6 (0,2 %)
	Pneumonia[a,p]	Common	269 (8,9 %)	Common	106 (3,5 %)
	Oral candidiasis	Common	64 (2,1 %)		0
	Dental and oral soft tissue	Common	50 (1,7 %)	Rare	1 (<0,1 %)

System Organ Class	Adverse Drug Reaction	Frequency of any Grade		Frequency of Grade 3-4	
	infections[q]				
	Influenza	Common	47 (1,6 %)	Rare	2 (<0,1 %)
Musculoskeletal and connective tissue disorders	Myalgia	Common	178 (5,9 %)	Rare	2 (<0,1 %)
	Myositis	Uncommon	6 (0,2 %)	Rare	1 (<0,1 %)
	Polymyositis	Not determined[r]		Not determined[r]	
	Immune-mediated arthritis	Not determined[s]		Not determined[s]	
Nervous system disorders	Myasthenia gravis	Not determined[s]		Not determined[s]	
	Encephalitis	Not determined		Not determined[t]	
	Guillain-Barré syndrome[a]	Not determined[s]		Not determined[s]	
Blood and lymphatic system disorders	Immune thrombocytopenia[a]	Rare	2 (<0,1 %)	Rare	1 (<0,1 %)
Injury, poisoning and procedural complications	Infusion-related reaction[u]	Common	49 (1,6 %)	Uncommon	5 (0,2 %)

[a] Including fatal outcome.

[b] Includes alanine aminotransferase increased, aspartate aminotransferase increased, hepatic enzyme increased, and transaminases increased.

[c] Includes hepatitis, autoimmune hepatitis, hepatitis toxic, hepatocellular injury, hepatitis acute, hepatotoxicity and immune-mediated hepatitis.

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

[e] Includes colitis, enteritis, enterocolitis, and proctitis.

[f] Includes pancreatitis and pancreatitis acute.

System Organ Class	Adverse Drug Reaction	Frequency of any Grade	Frequency of Grade 3-4

[g] Includes autoimmune hypothyroidism and hypothyroidism.

[h] Includes hyperthyroidism and Basedow's disease.

[i] Includes autoimmune thyroiditis, thyroiditis, and thyroiditis subacute.

[j] Includes autoimmune nephritis, tubulointerstitial nephritis, nephritis, glomerulonephritis and glomerulonephritis membranous.

[k] Includes rash erythematous, rash generalized, rash macular, rash maculopapular, rash papular, rash pruritic, rash pustular, erythema, eczema and rash.

[l] Includes pruritus generalized and pruritus.

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

[n] Includes oedema peripheral and peripheral swelling.

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

[p] Includes lung infection, pneumocystis jirovecii pneumonia, pneumonia, candida pneumonia, pneumonia legionella, pneumonia adenoviral, pneumonia bacterial, pneumonia cytomegaloviral, pneumonia haemophilus, pneumonia pneumococcal and pneumonia streptococcal.

[q] Includes gingivitis, oral infection, periodontitis, pulpitis dental, tooth abscess and tooth infection.

[r] Polymyositis (fatal) was observed in a patient treated with IMFINZI from an ongoing sponsored clinical study outside of the pooled dataset: rare in any grade, rare in Grade 3 or 4 or 5.

[s] Reported frequency from AstraZeneca-sponsored clinical studies outside of the pooled dataset is rare.

[t] Reported frequency from ongoing AstraZeneca-sponsored clinical studies outside of the pooled dataset is rare and includes two events of encephalitis, one was Grade 5 (fatal) and one was Grade 2.

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

Worsening laboratory abnormalities including increased alanine aminotransferase, increased aspartate aminotransferase, increases blood creatinine and thyroid stimulating hormone (TSH) changes were observed in patients treated with IMFINZI.

Description of selected adverse reactions

See section 4.4 for selected adverse reactions and the management guidelines for these adverse reactions are described in sections 4.2.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website

4.9 Overdose

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, monoclonal antibodies. ATC code: L01XC28

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

Durvalumab is a fully human, high affinity, immunoglobulin G1 kappa (IgG1κ) monoclonal antibody that selectively blocks the interaction of PD-L1 with PD-1 and CD80 (B7.1) while

leaving PD-1/PD-L2 interaction intact. Durvalumab does not induce antibody dependent cell-mediated cytotoxicity (ADCC).

Selective blockade of PD-L1/PD-1 and PD-L1/CD80 interactions enhances antitumour immune responses. These antitumour responses may result in tumour elimination.

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

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

5.2 Pharmacokinetic properties

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

The pharmacokinetics of durvalumab was studied in 2903 patients with solid tumours with doses ranging from 0,1 to 20 mg/kg administered once every two, three or four weeks. PK exposure increased more than dose-proportionally (non-linear PK) at doses < 3 mg/kg and dose proportionally (linear PK) at doses ≥ 3 mg/kg.

Steady state was achieved at approximately 16 weeks. Based on population PK analysis that included 1878 patients in the dose range of ≥ 10 mg/kg Q2W, geometric mean, steady state volume of distribution (Vss) was 5,64 L. Durvalumab clearance (CL) decreased over time resulting in a geometric mean steady state clearance (CLss) of 8,16 ml/h at Day 365; the decrease in CLss was not considered clinically relevant. The terminal half-life (t1/2), based on baseline CL, was approximately 18 days.

There was no clinically meaningful difference between the PK of durvalumab as a single agent and in combination with chemotherapy or in combination with tremelimumab.

Special Populations:

Age (19–96 years), body weight (31-149 kg), gender, positive anti-drug antibody (ADA) status,

albumin levels, LDH levels, creatinine levels, soluble PD-L1, tumour type, race, mild renal impairment (creatinine clearance (CRCL) 60 to 89 ml/min), moderate renal impairment (creatinine clearance (CRCL) 30 to 59 ml/min), mild hepatic impairment (bilirubin ≤ ULN and AST > ULN or bilirubin > 1,0 to 1,5 × ULN and any AST), moderate hepatic impairment (bilirubin > 1.5 to 3 x ULN and any AST) or ECOG/WHO status had no clinically significant effect on the pharmacokinetics of durvalumab.

The effect of severe renal impairment (CRCL 15 to 29 ml/min) or severe hepatic impairment (bilirubin > 3,0 x ULN and any AST) on the pharmacokinetics of durvalumab is unknown.

Elderly:

No dose adjustment is required for elderly patients (≥65 years of age). Of the 476 patients with locally advanced, unresectable NSCLC (primary efficacy population) treated with durvalumab, 215 patients were 65 years or older. Of the 265 patients with ES-SCLC treated with durvalumab in combination with chemotherapy, 101 (38%) patients were 65 years or older. No overall clinically meaningful differences in safety were reported between patients ≥65 years of age and younger patients.

Of the 462 patients with uHCC treated with STRIDE, 173 (37.4%) patients were 65 years or older and 63 (13.6%) patients were 75 years or older. There were no clinically meaningful differences in safety or efficacy between patients 65 years or older and younger patients.

Of the 401 patients with resectable NSCLC treated with IMFINZI in combination with chemotherapy in the AEGEAN study, 209 (52%) patients were 65 years or older and 49 (12%) patients were 75 years or older. There were no overall clinically meaningful differences in safety or effectiveness between patients ≥ 65 years of age and younger patients.

Of the 262 patients with LS-SCLC treated with IMFINZI, 103 (39,3 %) patients were 65 years or older. There were no overall clinically meaningful differences in safety or effectiveness between patients ≥ 65 years of age and younger patients.

Of the 338 patients with metastatic NSCLC treated with IMFINZI in combination with

tremelimumab and platinum-based chemotherapy, 147 (43%) patients were 65 years or older. There were no overall clinically meaningful differences in safety or effectiveness between patients ≥ 65 years of age and younger patients. (See section 4.2).

Of the 533 patients with MIBC treated with IMFINZI in combination with chemotherapy, 275 (51,6 %) patients were 65 years or older. There were no overall clinically meaningful differences in safety or effectiveness between patients ≥ 65 years of age and younger patients.

Of the 475 patients with resectable GC/GEJC treated with IMFINZI in combination with FLOT chemotherapy as neoadjuvant and adjuvant treatment, then as adjuvant IMFINZI monotherapy in the MATTERHORN study, 184 (38,7 %) patients were 65 years or older and 37 (7,8 %) patients were 75 years or older. There were no overall clinically meaningful differences in safety or effectiveness between patients ≥ 65 years of age and younger patients.

Medicine Interaction Studies:

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

Immunogenicity:

As with all therapeutic proteins, there is a potential for immunogenicity. Of the 2280 patients who were treated with durvalumab 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), 3 % (69/2280) patients tested positive for treatment-emergent ADAs. Neutralising antibodies against durvalumab were detected in 0,5 % (12/2280) patients. The presence of ADAs did not have a clinically relevant effect on pharmacokinetics or safety.

In the ADRIATIC study, of the 206 patients who were treated with IMFINZI monotherapy and evaluable for the presence of ADAs, 7 (3,4 %) patients tested positive for treatment-emergent ADAs. Neutralising antibodies against durvalumab were detected in 1 % (2/206) patients. The

presence of ADAs did not have an apparent effect on the pharmacokinetics or safety.

In the AEGEAN study, of the 375 patients who were treated with durvalumab 1500 mg in combination with chemotherapy every 3 weeks prior to surgery, followed by durvalumab 1500 mg every 4 weeks following surgery, and were evaluable for the presence of ADAs, 25 (6.7%) patients tested positive for treatment emergent ADAs. Neutralizing antibodies against durvalumab were detected in 2 patients (0.5%). The presence of ADAs did not have an apparent effect on the pharmacokinetics or safety of durvalumab.
In the CASPIAN study, of the 201 patients who were treated with IMFINZI 1500 mg every 3 weeks in combination with chemotherapy and evaluable for the presence of ADAs, 0 (0%) patients tested positive for treatment-emergent ADAs.

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

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

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

In the NIAGARA study, of the 453 patients who were treated with IMFINZI 1500 mg in combination with chemotherapy every 3 weeks prior to surgery followed by IMFINZI 1500 mg every 4 weeks following surgery and were evaluable for the presence of ADAs, 8 (1,8 %) patients tested positive for treatment-emergent ADAs. Neutralising antibodies against durvalumab were detected in 6 (1,3 %) patients. The presence of ADAs did not have an apparent effect on the pharmacokinetics or safety.

In the MATTERHORN study, of the 441 patients who were treated with IMFINZI 1500 mg in combination with FLOT chemotherapy as neoadjuvant and adjuvant treatment, then continued as adjuvant IMFINZI monotherapy, and were evaluable for the presence of ADAs, 40 (9,1 %) patients tested positive for treatment emergent ADAs. Neutralising antibodies against durvalumab were detected in 2 patients (0,5 %). The presence of ADAs did not have an apparent effect on the pharmacokinetics or safety of IMFINZI.

Immunogenicity assay results are highly dependent on several factors, including assay sensitivity and specificity, assay methodology, sample handling, timing of sample collection, concomitant medications and underlying disease.
For these reasons, comparison of incidence of antibodies to durvalumab with the incidence of antibodies to other medicines may be misleading.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

L-histidine,

L-histidine hydrochloride monohydrate,

α,α-trehalose dihydrate,

polysorbate 80

Water for Injection

6.2 Incompatibilities

No incompatibilities between IMFINZI and 9 g/L (0,9 %) sodium chloride or 50 g/L (5 %) dextrose in polyvinylchloride or polyolefin intravenous (IV) bags have been observed.

IMFINZI must not be mixed with other medicinal products except those mentioned in section 6.6, Instructions for use and handling.

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

6.3 Shelf Life

36 months

6.4 Special precautions for storage

Unopened Vial

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

Diluted Solution

IMFINZI does not contain a preservative. Administer infusion solution immediately once prepared. If infusion solution is not administered immediately and it needs to be stored, the total time from vial puncture to the start of administration should not exceed:

- 30 days at 2 °C - 8 °C
- 12 hours at or below 25 °C, up to 24 hours if dilution took place in controlled and validated aseptic conditions.

6.5 Nature and contents of container

IMFINZI 120 mg/2,4 ml: 2,4 ml of concentrate in a 10 ml Type 1 glass vial with an elastomeric stopper and a grey flip-off aluminium seal contains 120 mg durvalumab. Pack size of 1 vial.

IMFINZI 500 mg/10 ml: 10 ml of concentrate in a 10 ml Type 1 glass vial with an elastomeric stopper and a white flip-off aluminium seal contains 500 mg durvalumab. Pack size of 1 vial.

6.6 Special precautions for disposal and other handling

Preparation of solution:

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

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

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 medicines through the same infusion line.

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

7 HOLDER OF CERTIFICATE OF REGISTRATION

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8 REGISTRATION NUMBERS

IMFINZI 120 mg: 54/30.1/0001

IMFINZI 500 mg: 54/30.1/0002

9 DATE OF FIRST AUTHORISATION

23 February 2021

10 DATE OF REVISION OF THE TEXT

13 January 2026

AstraZeneca Logo

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