1. NAME OF THE MEDICINAL PRODUCT

IMFINZI 50 mg/mL concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion (sterile concentrate).

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

Imfinzi is a human immunoglobulin (IgG1κ) monoclonal antibody.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Treatment must be initiated and monitored by an experience oncologist.

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

Posology
The recommended dose of IMFINZI is 10 mg/kg administered as an intravenous infusion over 60 minutes every 2 weeks, until disease progression or unacceptable toxicity, or a maximum of 12 months.
Instructions for use
For intravenous administration.

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

Dose escalation or reduction is not recommended. Dose withholding or discontinuation may be required based on individual safety and tolerability.

Guidelines for management of immune-mediated adverse reactions are described in Table 1. Refer to section 4.4 for further monitoring and evaluation information.

Table 1. Recommended treatment modifications for IMFINZI and management recommendations

Adverse reactions	Severity[a]	IMFINZI treatment modification	Corticosteroid treatment unless otherwise specified
Immune-mediated pneumonitis/interstitial lung disease	Grade 2	Withhold dose[b]	Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
	Grade 3 or 4	Permanently discontinue	1 to 4 mg/kg/day prednisone or equivalent followed by a taper
Immune-mediated hepatitis	Grade 2 with ALT or AST > 3-5 x ULN and/or total bilirubin > 1.5-3 x ULN	Withhold dose[b]	Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
	Grade 3 with AST or ALT > 5-≤ 8 x ULN or total bilirubin > 3-≤ 5x ULN		
	Grade 3 with AST or ALT > 8 x ULN or total bilirubin > 5 x ULN	Permanently discontinue	
	Concurrent ALT or AST > 3 x ULN and total bilirubin > 2 x ULN with no other cause		
Immune-mediated colitis or diarrhoea	Grade 2	Withhold dose[b]	Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
	Grade 3 or 4	Permanently discontinue	
Immune-mediated hyperthyroidism	Grade 2-4	Withhold dose until clinically stable	Symptomatic treatment, see section 4.8
Immune-mediated hypothyroidism	Grade 2-4	No changes	Initiate thyroid hormone replacement as clinically indicated
Immune-mediated adrenal insufficiency or hypophysitis/hypopituitarism	Grade 2-4	Withhold dose until clinically stable	Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper and hormone replacement as clinically indicated

Reference: Doc ID-003864015 v2.0

Adverse reactions	Severity[a]	IMFINZI treatment modification	Corticosteroid treatment unless otherwise specified
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[b]	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	Grade 2 for > 1 week	Withhold dose[b]	Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
	Grade 3		
	Grade 4	Permanently discontinue	
Immune-mediated myocarditis	Grade 2	Withold dose[c]	Initiate 2 to 4 mg/kg/day prednisone or equivalent followed by a taper
	Grade 3 or 4, or any Grade with positive biopsy	Permanently discontinue	
Immune-mediated myositis/polymyositis	Grade 2 or 3	Withhold dose	Initiate 1 to 4 mg/kg/day prednisone or equivalent followed by a taper
	Grade 4	Permanently discontinue[d]	
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	
Infection	Grade 3 or 4	Withold dose until clinically stable	
Other immune-mediated adverse reactions	Grade 3	Withhold dose	Consider initial dose of 1 mg/kg/day to 4 mg/kg/day prednisone or equivalent followed by taper
	Grade 4	Permanently discontinue	

Reference: Doc ID-003864015 v2.0

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

[b] Based on severity of the adverse reactions. IMFINZI should be withheld and corticosteroids administered. Consider increasing dose of corticosteroids and/or using other systemic immunosuppressants if there is worsening or no improvement. Upon improvement to ≤Grade 1, corticosteroid taper should be initiated and continued over at least 1 month.
After withhold, IMFINZI can be resumed if the adverse reactions improved to ≤Grade 1 and the corticosteroid dose has been reduced to ≤10 mg prednisone or equivalent per day.

[c] If no improvement within 3 to 5 days despite corticosteroids, promptly start additional immunosuppressive therapy. Upon resolution (Grade 0), corticosteroid taper should be initiated and continued over at least 1 month, after which IMFINZI can be resumed based on clinical judgment.

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

For suspected immune-mediated adverse reactions, adequate evaluation should be performed to confirm etiology or exclude alternate etiologies. 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, consider withholding IMFINZI for Grade 2 and 3 adverse reactions ; Imfinzi should be discontinued for Grade 4 adverse reactions. Adverse reactions should be treated according to institutional standard.

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

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

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

Elderly (≥65 years)
Based on a population PK analysis, no dose adjustment is required for elderly patients (≥65 years of age) (see sections 5.1). Of the 476 patients with locally advanced, unresectable NSCLC (primary efficacy population) treated with IMFINZI, 215 patients were 65 years or older. No overall clinically meaningful differences in safety were reported between patients ≥65 years of age and younger patients. Data from patients 75 years of age or older in the Pacific Study (7.6%) are too limited to draw conclusions on this population.

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

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Refer to section Posology and method of administration, Table 1 for recommended treatment modifications and management of immune-mediated adverse reactions .

Immune-mediated pneumonitis
Immune-mediated pneumonitis or interstitial lung disease, defined as requiring use of systemic corticosteroids and with no clear alternate etiology, occurred in patients receiving IMFINZI (see section 4.8).

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. Patients should be monitored for signs and symptoms of pneumonitis or radiation pneumonitis. Patients with suspected pneumonitis should be evaluated with radiographic imaging and managed as recommended in section 4.2.

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

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

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

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

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

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

Hypophysitis/hypopituitarism

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

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

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

Other immune-mediated adverse reactions
Given the mechanism of action of IMFINZI, other potential immune-mediated adverse reactions may occur. Patients should be monitored for signs and symptoms and managed as recommended for other immune-mediated adverse reactions, in section 4.2. In patients treated with IMFINZI as a single agent across the clinical trials (n = 1889), the following clinically significant immune-mediated adverse reactions occurred: aseptic meningitis (<1%), hemolytic anemia (<1%), immune thrombocytopenic purpura (<1%), myocarditis (<1%), myositis (<0.2%), and ocular inflammatory toxicity (<1%), including uveitis and keratitis. Polymyositis with fatal outcome (<0.1%) was reported in a patient treated with IMFINZI from an ongoing clinical study.

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

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

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

4.5 Interaction with other medicinal products and other forms of interaction

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

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

4.6 Pregnancy and lactation

Pregnancy
In animal reproduction studies, administration of durvalumab to pregnant cynomolgus monkeys from the confirmation of pregnancy through delivery at exposure levels approximately 6-20 times higher than those observed at the clinical dose of 10 mg/kg of durvalumab (based on AUC) was associated with premature delivery, fetal loss (abortion and stillbirth) and an increase in neonatal deaths compared to concurrent control (see section 5.3).

There are no data on the use of durvalumab in pregnant women. Based on its mechanism of action, durvalumab has the potential to impact maintenance of pregnancy and may cause fetal harm when administered to a pregnant woman. Human IgG1 is known to cross the placental barrier. Imfinzi cannot be used during pregnancy, unless this is absolutely required. Women of childbearing potential should be use effective contraception during treatment with IMFINZI and for at least 3 months after the last dose.

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Imfinzi is most commonly associated with immune-mediated adverse reactions. Most of these, including severe reactions, resolved following initiation of appropriate medical therapy or withdrawal of Imfinzi (see "Description of selected adverse reactions" below). Below are the incidences of adverse reactions listed, which have been reported with Imfinzi at a dose of 10 mg/kg.
In the pooled dataset with durvalumab 10 mg/kg monotherapy (n=1889), the most frequent adverse reaction (≥20%) was cough (26.5%).

Adverse drug reactions are listed according to system organ class in MedDRA. Within each system organ class, the adverse drug reactions are presented in decreasing frequency. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. The corresponding frequency category for each ADR is defined as: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1000); very rare (<1/10,000); not known (cannot be estimated from available data).

Infections and infestations

Very common: Upper respiratory tract infections[l] (15.2%) (CTCAE grade 3 and above: uncommon [0.3%])

Common: Pneumonia[m] (9.2%) (CTCAE grade 3 and above: common [3.6%]), Dental and oral soft tissue infections[n] (1.9%) (CTCAE grade 3 and above: very rare [0%]), Oral candidiasis (2.6%) (CTCAE grade 3 and above: very rare [0%]), Influenza (1.4%) (CTCAE grade 3 and above: very rare [0%])

Endocrine disorders

Common: Hypothyroidism[g] (9.5%) (CTCAE grade 3 and above: uncommon [0.1%]), Hyperthyroidism[h] (6.1%) (CTCAE grade 3 and above: rare [<0.1%]), TSH decreased (1.0%) (CTCAE grade 3 and above: very rare [0%]), TSH increased (1.4%) (CTCAE grade 3 and above: very rare [0%])

Uncommon: Adrenal insufficiency (0.7%) (CTCAE grade 3 and above: uncommon [0.1%])

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

Cardiac disorders

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

Respiratory, thoracic and mediastinal disorders

Very common: Cough/ Productive cough[a] (26.5%) (CTCAE grade 3 and above: uncommon [0.5%])

Common: Pneumonitis[b] (4.7%) (CTCAE grade 3 and above: uncommon [0.7%]), Dysphonia (3.3%) (CTCAE grade 3 and above: uncommon [0.1%])

Uncommon: Interstitial lung disease (0.4%) (CTCAE grade 3 and above: very rare [0%])

Gastrointestinal disorders

Very common: Diarrhoea (17.4%) (CTCAE grade 3 and above: uncommon [0.7%]), Abdominal pain[e] (15.9%) (CTCAE grade 3 and above: common [2.4%])

Common: Colitis[f] (1.1%) (CTCAE grade 3 and above: uncommon [0.4%])

Hepatobiliary disorders

Common: Aspartate aminotransferase increased or Alanine aminotransferase increased[c] (9.8%) (CTCAE grade 3 and above: common [3.2%])

Uncommon: Hepatitis[a,d] (0.7%) (CTCAE grade 3 and above: uncommon [0.3%])

Skin and subcutaneous tissue disorders

Very common: Rash[j] (17%) (CTCAE grade 3 and above: uncommon [0.6%]), Pruritus[k] (11.9%) (CTCAE grade 3 and above: rare [<0.1%])

Common: Night sweats (2%) (CTCAE grade 3 and above: rare [<0.1%])

Uncommon: Dermatitis (0.8%) (CTCAE grade 3 and above: rare [<0.1%])

Musculoskeletal and connective tissue disorders

Common: Myalgia (7.4%) (CTCAE grade 3 and above: uncommon [0.1%])

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

Very rare: Polymyositis[o] (0%) (frequency of CTCAE grade 3 and above: very rare [0%])

Renal and urinary disorders

Common: Blood creatinine increased (4%) (CTCAE grade 3 and above: uncommon [0.2%]), Dysuria (1.6%) (CTCAE grade 3 and above: very rare [0%])

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

General disorders and administration site conditions

Very common: Pyrexia (15.2%) (CTCAE grade 3 and above: uncommon [0.2%]), Peripheral oedema (10.5%) (CTCAE grade 3 and above: uncommon [0.4%])

Common: Infusion related reaction[p] (1.4%) (CTCAE grade 3 and above: uncommon [0.3%])

[a] Includes cough and productive cough

[b] fatal pneumonitis and fatal pneumonia were reported at similar rate between the IMFINZI-treated group and placebo group in the PACIFIC Study; fatal hepatitis was reported in other trials
[c] Included alanine aminotransferase increased, aspartate aminotransferase increased, hepatic enzyme increased, and transaminases increased
[d] Includes hepatitis, autoimmune hepatitis, hepatitis toxic, hepatocellular injury, hepatitis acute, and hepatoxicity
[e] Includes abdominal pain, abdominal pain lower, abdominal pain upper and flank pain
[f] Includes colitis, enteritis, enterocolitis, and proctitis
[g] Includes autoimmune hypothyroidism and hypothyroidism
[h] Includes hyperthyroidism, autoimmune thyroiditis, thyroiditis, thyroiditis subacute and Basedow's disease
[i] Includes autoimmune nephritis, tubulointerstitial nephritis, nephritis, glomerulonephritis and glomerulonephritis membranous
[j] Includes rash erythematous, rash generalized, rash macular, rash maculopapular, rash papular, rash pruritic, rash pustular, erythema, eczema and rash
[k] Includes pruritus generalized and pruritus
[l] Includes laryngitis, nasopharyngitis, peritonsillar abscess, pharyngitis, rhinitis, sinusitis, tonsillitis, tracheobronchitis, and upper respiratory tract infection
[m] Includes lung infection, pneumocystis jirovecii pneumonia, pneumonia, pneumonia adenoviral, pneumonia bacterial, pneumonia cytomegaloviral, pneumonia haemophilus, pneumonia klebsiella, pneumonia necrotising, pneumonia pneumococcal and pneumonia streptococcal
[n] Includes gingivitis, oral infection, periodontitis, pulpitis dental, tooth abscess and tooth infection
[o] Polymyositis (fatal) was observed in a patient treated with IMFINZI from an ongoing clinical study outside of the pooled dataset.
[p] Includes infusion related reaction and urticaria with onset on the day of dosing or 1 day after dosing

In the PACIFIC Study, in patients who had completed treatment with concurrent chemoradiation within 1 to 42 days prior to initiation of the trial, the most common (≥10%) ADRs (in IMFINZI vs placebo arm) were cough/productive cough (40.2% vs 30.3%), upper respiratory tract infection (26.1% vs 19.2%), rash (21.7% vs 12.0%), diarrhoea (18.3% vs 18.8%), pneumonia (17.1% vs 11.5%) and pyrexia (14.7% vs 9.0%). The most common (≥1%) Grade 3-4 ADRs (in IMFINZI vs placebo arm) were pneumonia (6.5% vs 5.6%) and pneumonitis (1.7% vs 1.7%).

Description of selected adverse reactions

Immune-mediated pneumonitis

In the PACIFIC Study, in patients with locally advanced, unresectable NSCLC (n=475 in the IMFINZI arm, and n=234 in the placebo arm) who had completed treatment with concurrent chemoradiation within 1 to 42 days prior to initiation of the study, immune-mediated pneumonitis occurred in 51 (10.7%) patients in the IMFINZI-treated group and 16 (6.8%) patients in the placebo group, including Grade 3 in 8 (1.7%) patients on IMFINZI vs. 6 (2.6%) patients on placebo and Grade 5 in 4 (0.8%) patients on IMFINZI vs. 3 (1.3%) patients on placebo. The median time to onset in the IMFINZI-treated group was 53 days (range: 1-341 days) vs. 55.5 days (range: 0-231 days) in the placebo group. In the IMFINZI-treated group, 44 of the 51 patients received systemic corticosteroids, including 28 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, 11 of the 16 patients received systemic corticosteroids, including 9 patients who received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). Resolution occurred for 27 patients in the IMFINZI treated group vs 6 in placebo.

Radiation pneumonitis is frequently observed in patients receiving radiation therapy to the lung and the clinical presentation of pneumonitis and radiation pneumonitis is very similar. In the PACIFIC study, pneumonitis including both immune-mediated pneumonitis and radiation pneumonitis, occurred in 161 (33.9%) patients in the IMFINZI-treated group and 58 (24.8%) in the placebo group including grade 3 (3.4% vs. 3.0% respectively) and grade 5 (1.1 vs. 1.7%).

In the combined safety database with IMFINZI monotherapy, (n=1889 multiple tumor types), immune-mediated pneumonitis occurred in 79 (4.2%) patients, including Grade 3 in 12 (0.6%) patients, Grade 4 in 1 (<0.1%) patient, and Grade 5 in 5 (0.3%) patients. The median time to onset was 53 days (range: 1-341 days). Forty-five of the 79 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day), and 2 patients also received infliximab. IMFINZI

was discontinued in 26 patients. Resolution occurred in 42 patients. Immune-mediated pneumonitis occurred more frequently in patients in the PACIFIC Study who had completed treatment with concurrent chemoradiation within 1 to 42 days prior to initiation of the study (10.7%), than in the other patients in the combined safety database (2.0%).

Immune-mediated hepatitis
In the PACIFIC Study, immune-mediated hepatitis occurred in 3 (0.6%) patients. There were no Grade 3 or higher cases.

In the combined safety database with IMFINZI monotherapy, immune-mediated hepatitis occurred in 19 (1.0%) patients, including Grade 3 in 11 (0.6%) patients and Grade 5 in 1 (< 0.1%) patient. The median time to onset was 70.0 days (range: 15-312 days). Thirteen of the 19 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). One patient also received mycophenolate treatment. IMFINZI was discontinued in 4 patients. Resolution occurred in 12 patients.

Immune-mediated colitis
In the PACIFIC Study, immune-mediated colitis or diarrhoea occurred in 5 (1.1%) patients, including Grade 3 in 2 (0.4%) patients.
In the combined safety database with IMFINZI monotherapy, immune-mediated colitis or diarrhea occurred in 31 (1.6%) patients, including Grade 3 in 6 (0.3%) patients and Grade 4 in 1 (<0.1%) patient. The median time to onset was 74 days (range: 1-365 days). Sixteen of the 31 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). One patient also received infliximab treatment. IMFINZI was discontinued in 8 patients. Resolution occurred in 23 patients.

Immune-mediated endocrinopathies
Hypothyroidism
In the PACIFIC Study, immune-mediated hypothyroidism occurred in 44 (9.3%) patients in the IMFINZI-treated group and 3 (1.3%) patients in the placebo group, including Grade 3 in 1 (0.2%) patient on IMFINZI vs. 0 patients on placebo. The median time to onset in the IMFINZI-treated group was 106.5 days (range: 13-377 days) vs. 98 days (range: 0-99 days) in the placebo group. In the IMFINZI-treated group, 41 patients received received hormone replacement therapy. In the placebo group, all 3 patients received hormone replacement therapy.

In the combined safety database with IMFINZI monotherapy, immune-mediated hypothyroidism occurred in 137 (7.3%) patients, including Grade 3 in 1 (< 0.1%) patient. The median time to onset was 85 days (range: 9-378 days). Of the 137 patients, 134 patients received hormone replacement therapy, 2 patients received high-dose corticosteroids (at least 40 mg prednisone or equivalent per day) for hypothyroidism followed by hormone replacement. No patients discontinued IMFINZI due to hypothyroidism .

Hyperthyroidism
In the PACIFIC Study immune-mediated hyperthyroidism occurred in 13 (2.7%) patients. There were no Grade 3-4 cases.

In the combined safety database with IMFINZI monotherapy, immune-mediated hyperthyroidism occurred in 34 (1.8%) patients, there were no Grade 3 or 4 cases. The median time to onset was 41 days (range: 14-195 days). Twenty-six of the 34 patients received medical therapy (thiamazole, carbimazole, propylthiouracil or beta-blocker), 12 patients received thyroxine when hyperthyroidism transitioned to hypothyroidism, 12 patients received systemic corticosteroids and 3 of the 12 patients received high-dose systemic corticosteroid treatment (at least 40 mg prednisone or equivalent per day). No patients discontinued IMFINZI due to hyperthyroidism. Eight patients experienced hypothyroidism following hyperthyroidism.

Adrenal insufficiency

In the PACIFIC Study immune-mediated adrenal insufficiency occurred in 1 (0.2%) patients. There were no Grade 3-4 cases.

In the combined safety database with IMFINZI monotherapy, immune-mediated adrenal insufficiency occurred in 7 (0.4%) patients, including Grade 3 in 1 (<0.1%) patient. The median time to onset was 141 days (range: 70-265 days). All 7 patients received systemic corticosteroids; 2 of the 7 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). No patients discontinued IMFINZI due to adrenal insufficiency. Resolution occurred in 1 patient.

Type 1 diabetes mellitus
In the PACIFIC Study immune-mediated type 1 diabetes mellitus occurred in 1 (0.2%) patient (Grade 3). IMFINZI was discontinued due to type 1 diabetes mellitus. The time to onset was 42 days. This 1 patient received insulin.

Hypophysitis/Hypopituitarism
In the combined safety database with IMFINZI monotherapy, immune-mediated hypopituitarism occurred in 1 (< 0.1%) patient (Grade 3). This 1 patient received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day) and did not discontinue IMFINZI.

Immune-mediated nephritis
In the PACIFIC Study, immune-mediated nephritis occurred in 1 (0.2%) patient. There were no Grade 3-4 cases.

In the combined safety database with IMFINZI monotherapy, immune-mediated nephritis occurred in 3 (0.2%) patients, including Grade 3 in 1 (< 0.1%) patient. The median time to onset was 95 days (range: 28-239 days). Two (0.1%) patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). IMFINZI was discontinued in all 3 patients. Resolution occurred in 2 patients.

Immune-mediated rash
In the PACIFIC Study immune-mediated rash or dermatitis occurred in 9 (1.9%) patients in the IMFINZI-treated group and 1 (0.4%) patient in the placebo group, including Grade 3 in 2 (0.4%) patients on IMFINZI vs. 0 patients on placebo. The median time to onset in the IMFINZI-treated group was 36 days (range: 5-110 days) vs. 110 days in the one placebo patient. In the IMFINZI-treated group, all 9 patients received systemic corticosteroids, including 5 patients who received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). In the placebo group, the 1 patient received systemic corticosteroids.

In the combined safety database with IMFINZI monotherapy, immune-mediated rash or dermatitis occurred in 30 (1.6%) patients, including Grade 3 in 7 (0.4%) patients. The median time to onset was 74 days (range: 1-365 days). Eleven of the 30 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). IMFINZI was discontinued in 2 patients. Resolution occurred in 18 patients.

Infusion related reactions
Infusion related reactions occurred in 9 (1.9%) patients in the PACIFIC Study. In the combined safety database with IMFINZI monotherapy, infusion related reactions occurred in 35 (1.9%) patients, including Grade 3 in 5 (0.3%) patients. There were no Grade 4 or 5 events.

Immunogenicity
As with all therapeutic proteins, there is a potential for immunogenicity. Of the 1570 patients who were treated with IMFINZI 10 mg/kg every 2 weeks and evaluable for the presence of anti-drug antibodies (ADAs), 2.9% (45/1570) of patients tested positive for treatment-emergent ADAs. Neutralising antibodies against durvalumab were detected in 0.5% (8/1570) of patients. Development of ADAs was associated with lower durvalumab serum concentrations. The lower concentrations are

considered as not clinically relevant. There are insufficient numbers of patients with ADA to determine whether ADA alters the safety or efficacy of durvalumab.

Immunogenicity assay results are highly dependent on several factors, including assay sensitivity and specificity, assay methodology, sample handling, timing of sample collection, concomitant medications and underlying disease. Due to the limitations in assay performance, the incidence of antibody development in patients receiving IMFINZI may be underestimated and comparison of incidence of antibodies to IMFINZI with the incidence of antibodies to other products may be misleading.

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Durvalumab is a fully human, high affinity, immunoglobulin G1 kappa (IgG1κ) monoclonal antibody that selectively blocks the interaction of PD-L1 with PD-1 and CD80 (B7.1) while leaving PD-1/PD-L2 interaction intact. Durvalumab does not induce antibody dependent cell-mediated cytotoxicity (ADCC). Selective blockade of PD-L1/PD-1 and PD-L1/CD80 interactions enhances antitumour immune responses. These antitumour responses may result in tumour elimination.

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

Clinical efficacy and safety

PACIFIC Study

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

The demographics and baseline disease characteristics were well balanced between study arms. Baseline demographics of the overall study population were as follows: male (70%), age ≥ 65 years (45%), white (69%), asian (27%), other (4%), current smoker (16%), past-smoker (75%), and never smoker (9%), WHO/ECOG PS 0 (49%), WHO/ECOG PS 1 (50%). Disease characteristics were as follows: Stage IIIA (54%), Stage IIIB (44%), histological sub-groups of squamous (47%), non-

squamous (53%), PD-L1 expression TC≥25% (22%), PD-L1 expression TC<25% (41%). (PD-L1 status was retrospectively analysed using the Ventana PD-L1 (SP263) Assay in 451 patients with available samples, taken prior to concurrent chemoradiation therapy).

The co-primary endpoints of the study were progression-free survival (PFS) and overall survival (OS) of IMFINZI vs. placebo.

At the time of the interim PFS analysis by Blinded Independent Central Review (BICR) according to RECIST 1.1 the study demonstrated a statistically significant and clinically meaningful improvement in PFS in the IMFINZI-treated group (16.8 months) compared with the placebo group (5.6 months) [hazard ratio (HR) = 0.52 (0.42, 0.65), p < 0.0001]. PFS at 12 months was 55.9% in the IMFINZI-treated group and 35.5% in the placebo group. PFS at 18 months was 44.2% in the IMFINZI-treated group and 27.0% in the placebo group. The improvements in PFS in favor of patients receiving IMFINZI compared to those receiving placebo were consistently observed in all predefined subgroups analysed.

Of the patients receiving durvalumab, 21 (4.4%) patients had an AE with the outcome of death. Of the patients receiving placebo, 14 (6.0%) patients had an AE with the outcome of death.

At the time of analysis the results for Overall survival (OS) were not mature.

5.2 Pharmacokinetic properties

The pharmacokinetics of durvalumab was studied in 1902 patients with solid tumors with doses ranging from 0.1 to 20 mg/kg administered once every two, three or four weeks.

Absorption:

PK exposure increased more than dose-proportionally (non-linear PK) at doses <3 mg/kg and dose proportionally (linear PK) at doses ≥ 3 mg/kg.

Distribution:

Steady state was achieved at approximately 16 weeks. Based on population PK analysis that included 1878 patients in the dose range of ≥ 10 mg/kg Q2W, the geometric mean, steady state volume of distribution (Vss) was 5.64 L.

Metabolism:

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

Elimination:

Durvalumab clearance (CL) decreased over time resulting in a geometric mean steady state clearance (CLss) of 8.16 mL/h at Day 365; the decrease in CLss was not considered clinically relevant. The terminal half-life (t1/2), based on baseline CL, was approximately 18 days. The primary elimination pathways of durvalumab are protein catabolism via reticuloendothelial system or target mediated disposition.

Special Populations

As assessed by population PK analysis, Age (19–96 years), body weight (34-149 Kg), gender, positive anti-drug antibody (ADA) status, albumin levels, LDH levels, creatinine levels, soluble PD-L1, tumor type, race, or ECOG/WHO status had no clinically significant effect on the pharmacokinetics of durvalumab.

Elderly

A population PK analysis showed that age (19–96 years) had no clinically significant effect on the pharmacokinetics of durvalumab. Therefore, elderly patients (≥65 years) require no dose adjustment.

Renal insufficiency

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

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

5.3 Preclinical safety data

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

Reproductive toxicology
There are no data on the potential effects of durvalumab on fertility in humans. As reported in the literature, the PD-1/PD-L1 pathway plays a central role in preserving pregnancy by maintaining maternal immune tolerance to the fetus, and in mouse allogeneic pregnancy models disruption of PD-L1 signalling was shown to result in an increase in fetal loss. In reproduction studies in cynomolgus monkeys, administration of durvalumab from the confirmation of pregnancy through delivery at exposure levels approximately 6 to 20 times higher than those observed at the clinical dose of 10 mg/kg of durvalumab (based on AUC) was associated with premature delivery, fetal loss (abortion and stillbirth) and an increase in neonatal deaths compared to concurrent control.

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Histidine
Histidine hydrochloride monohydrate
Trehalose dihydrate
Polysorbate 80
Water for injections

6.2 Incompatibilities

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

6.3 Shelf life

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

6.4 Special precautions for storage

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

Do not freeze.

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

6.5 Nature and contents of container

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

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

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

- 24 hours at 2°C to 8°C
- 4 hours at room temperature up to 25°C

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

- Visually inspect the medicinal product for particulate matter and discolouration. IMFINZI is clear to opalescent, colourless to slightly yellow solution. Discard the vial if the solution is cloudy, discoloured or visible particles are observed. Do not shake the vial.
- Withdraw the required volume from the vial(s) of IMFINZI and transfer into an intravenous (IV) bag containing sodium chloride 9 mg/mL (0.9%) solution for injection, or glucose 50 mg/mL (5%) solution for injection. Mix diluted solution by gentle inversion. The final concentration of the diluted solution should be between 1 mg/mL and 15 mg/mL. Do not freeze or shake the solution.
- Care must be taken to ensure the sterility of prepared solutions.
- Do not re-enter the vial after withdrawal of drug; only administer one dose per vial.
- Discard any unused portion left in the vial.

Administration
- Administer the infusion solution intravenously over 60 minutes through an intravenous line containing a sterile, low-protein binding 0.2 or 0.22 micron in-line filter.
- Do not co-administer other medicinal products through the same infusion line.

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

7. MARKETING AUTHORISATION HOLDER

AstraZeneca (Thailand) Ltd., Bangkok, Thailand

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

17 April 2019