PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrIMFINZI®

durvalumab for injection

solution, 50 mg / mL, intravenous infusion

antineoplastic agent, monoclonal antibody

IMFINZI (durvalumab) indicated for the treatment of patients with:

- Locally advanced or metastatic urothelial carcinoma who:
  - Have disease progression during or following platinum-containing chemotherapy
  - Have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy

has been issued marketing authorization **with** conditions, pending the results of trials to verify its clinical benefit. Patients should be advised of the nature of the authorization. *For further information for IMFINZI, please refer to Health Canada's Notice of Compliance with conditions - drug products web site: http://www.hc-sc.gc.ca/dhp-mps/prodpharma/notices-avis/conditions/index-eng.php.*

IMFINZI indicated for the treatment of patients with:

- Locally advanced, unresectable, Stage III non-small cell lung cancer (NSCLC) whose disease has not progressed following platinum-based chemoradiation therapy

has been issued marketing authorization **without** conditions.

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Date of Initial Approval:
November 03, 2017

Date of Revision:
August 23, 2019

Submission Control No: 222188

This product has been authorized under the Notice of Compliance with Conditions (NOC/c) for one or all of its indicated uses.

What is a Notice of Compliance with Conditions (NOC/c)?

An NOC/c is a form of market approval granted to a product on the basis of **promising** evidence of clinical effectiveness following review of the submission by Health Canada.

Products authorized under Health Canada's NOC/c policy are intended for the treatment, prevention or diagnosis of a serious, life-threatening or severely debilitating illness. They have demonstrated promising benefit, are of high quality and possess an acceptable safety profile based on a benefit/risk assessment. In addition, they either respond to a serious unmet medical need in Canada or have demonstrated a significant improvement in the benefit/risk profile over existing therapies. Health Canada has provided access to this product on the condition that sponsors carry out additional clinical trials to verify the anticipated benefit within an agreed upon time frame.

What will be different about this Product Monograph?

The following Product Monograph will contain boxed text at the beginning of each major section clearly stating the nature of the market authorization. Sections for which NOC/c status holds particular significance will be identified in the left margin by the symbol NOC/c. These sections may include, but are not limited to, the following:

- Indications;
- Action and Clinical Pharmacology;
- Warnings and Precautions;
- Adverse Reactions;
- Dosage and Administration; and
- Clinical Trials.

Adverse Drug Reaction Reporting and Re-Issuance of the Product Monograph

Health care providers are encouraged to report Adverse Drug Reactions associated with normal use of these and all drug products to Health Canada's Canada Vigilance Program at 1-866-234-2345. The Product Monograph will be re-issued in the event of serious safety concerns previously unidentified or at such time as the sponsor provides the additional data in support of the product's clinical benefit. Once the latter has occurred, and in accordance with the NOC/c policy, the conditions associated with market authorization will be removed.

RECENT MAJOR LABEL CHANGES

INDICATIONS (1)	05-2019
DOSAGE AND ADMINISTRATION (3)	05-2019
WARNINGS AND PRECAUTIONS (7)	05-2018
WARNINGS AND PRECAUTIONS (7)	05-2019

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- Locally advanced, unresectable, Stage III non-small cell lung cancer (NSCLC) whose disease has not progressed following platinum-based chemoradiation therapy

has been issued marketing authorization **without** conditions.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

NOC/c

Urothelial Carcinoma

IMFINZI (durvalumab) is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma who:

- Have disease progression during or following platinum-containing chemotherapy
- Have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy

Marketing authorization with conditions was based on a promising tumour response rate and durability of response. An improvement in survival or disease-related symptoms has not been established (see CLINICAL TRIALS).

Locally Advanced, Unresectable, Stage III Non-Small Cell Lung Cancer

IMFINZI is indicated for the treatment of patients with locally advanced, unresectable, Stage III non-small cell lung cancer (NSCLC) whose disease has not progressed following platinum-based chemoradiation therapy.

1.1 Pediatrics

Pediatrics (**<18 years of age)**: The safety and efficacy of IMFINZI in patients younger than 18 years of age have not been established.

1.2 Geriatrics

Geriatrics (≥65 years of age): No overall differences in safety or efficacy were reported between elderly patients (≥65 years of age) and younger patients (<65 years of age) (see WARNINGS AND PRECAUTIONS, Geriatrics).

NOC/c 2 CONTRAINDICATIONS

IMFINZI (durvalumab) is contraindicated in patients who are hypersensitive to durvalumab or to any ingredient in the formulation or component of the container. For a complete listing of ingredients, see DOSAGE FORMS, STRENGTHS, COMPOSITION and PACKAGING section of the Product Monograph.

NOC/c 3 DOSAGE AND ADMINISTRATION

3.1 Recommended Dose and Dosage Adjustment

Recommended Dose

Urothelial Carcinoma

The recommended dose of IMFINZI (durvalumab) is 10 mg/kg administered as an intravenous infusion over 60 minutes every 2 weeks as long as clinical benefit is observed or until unacceptable toxicity.

For previously treated patients in the pivotal study, treatment with IMFINZI was permitted until one or more criteria for discontinuation were met including:

- Adverse event (AE) experienced that contraindicates further dosing
- Pregnancy or intent to become pregnant
- Any AE that met criteria for discontinuation
- AE related to drug that is Grade ≥3, with the exception of toxicities that did not meet criteria for discontinuation
- Grade ≥3 infusion reaction
- Confirmation of progressive disease and investigator determination that the patient no longer benefited from treatment

Locally Advanced, Unresectable, Stage III Non-Small Cell Lung Cancer (NSCLC)

The recommended dose of IMFINZI is 10 mg/kg administered as an intravenous infusion over 60 minutes every 2 weeks for one year or until disease progression or unacceptable toxicity.

Dosage Adjustment

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 WARNINGS AND PRECAUTIONS for further monitoring and evaluation information.

Table 1 Recommended Treatment Modifications for IMFINZI

Adverse Reactions	Severity[a]	IMFINZI Treatment Modification	Corticosteroid Treatment Unless Otherwise Specified
Immune-mediated pneumonitis	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	Initiate 1 to 4 mg/kg/day prednisone or equivalent followed by a taper
Immune-mediated hepatitis	Grade 2 with ALT or AST >3-5xULN and/or total bilirubin >1.5-3xULN	Withhold dose[b]	Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
	Grade 3 with AST or ALT ≤8xULN or total bilirubin ≤5xULN		
	Grade 3 with AST or ALT >8xULN or total bilirubin >5xULN	Permanently discontinue	
	Concurrent ALT or AST >3xULN and total bilirubin >2xULN with no other cause		
Immune-mediated colitis or diarrhea	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 endocrinopathies: Hyperthyroidism	Grade 2-4	Withhold dose until clinically stable	Symptomatic management
Immune-mediated endocrinopathies: Hypothyroidism	Grade 2-4	No change	Initiate thyroid hormone replacement as clinically indicated

Adverse Reactions	**Severity**[a]	**IMFINZI Treatment Modification**	**Corticosteroid Treatment Unless Otherwise Specified**
Immune-mediated endocrinopathies: 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 endocrinopathies: Type 1 diabetes mellitus	Grade 2-4	Withhold dose until clinically stable	Initiate treatment with insulin as clinically indicated
Immune-mediated nephritis	Grade 2 with serum creatinine >1.5-3x (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 >3x baseline or >3-6xULN; Grade 4 with serum creatinine >6xULN	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	
Infection	Grade 3 or 4	Withhold dose	Symptomatic management; treat with anti-infectives for suspected or confirmed infections
Immune-mediated myocarditis	Grade 2	Withhold dose[d]	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[e]	Initiate 2 to 4 mg/kg/day prednisone or equivalent followed by a taper
	Grade 4	Permanently discontinue	

Adverse Reactions	Severity[a]	IMFINZI Treatment Modification	Corticosteroid Treatment Unless Otherwise Specified
Infusion-related reactions	Grade 1 or 2	Interrupt or slow the rate of infusion[c]	May consider pre-medications for prophylaxis of subsequent infusion reactions
	Grade 3 or 4	Permanently discontinue	
Other immune-mediated adverse reactions	Grade 3	Withhold dose[b]	Symptomatic management
	Grade 4	Permanently discontinue	Consider initial dose of 1 mg/kg/day to 4 mg/kg/day prednisone or equivalent followed by taper

[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 (see Table 1) if there is worsening or no improvement. Upon improvement to ≤Grade 1, corticosteroid taper should be initiated and continued over at least 1 month. 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] In case of infusion-related reactions, infusion rate of IMFINZI may be decreased by 50% or be temporarily interrupted until resolution of event.

[d] 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.

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

Special Populations

A population pharmacokinetic (PK) analysis, could not detect any effect on the clearance (CL) parameter in the model due to patient age, body weight, gender and race, therefore no dose adjustment of IMFINZI is recommended (see ACTION AND CLINICAL PHARMACOLOGY).

Pediatrics (<18 years of age): The safety and efficacy of IMFINZI in patients younger than 18 years of age have not been established.

Geriatrics (≥65 years of age): No dose adjustment is recommended for elderly patients (≥65 years of age) (see ACTION AND CLINICAL PHARMACOLOGY).

Renal Impairment: A population PK analysis could not detect any effect of mild to moderate renal impairment on the CL parameter in the model, therefore no dose adjustment of IMFINZI is recommended for patients. The effect of severe renal impairment (CrCL 15 to 29 mL/min) on the PK of durvalumab is unknown (see ACTION AND CLINICAL PHARMACOLOGY).

Hepatic Impairment: A population PK analysis could not detect any effect of mild hepatic impairment on the CL parameter in the model, therefore no dose adjustment of IMFINZI is

recommended for patients. IMFINZI has not been studied in patients with moderate or severe hepatic impairment (see ACTION AND CLINICAL PHARMACOLOGY).

3.2 Administration

Preparation of Infusion Solution

IMFINZI is only to be administered by intravenous infusion.

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

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

- Withdraw the required volume from the vial(s) of IMFINZI and transfer into an intravenous (IV) bag containing 0.9% Sodium Chloride Injection or 5% Dextrose Injection. Mix diluted solution by gentle inversion. The final concentration of the diluted solution should be between 1 mg / mL and 15 mg / mL.

- Do not freeze or shake the solution.

- No incompatibilities between IMFINZI and 0.9% Sodium Chloride or 5% Dextrose have been observed.

- IMFINZI must not be mixed with other drug products except those mentioned above.

- 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.

Storage of Infusion Solution

IMFINZI does not contain a preservative.

Administer infusion solution 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 under refrigeration at 2°C to 8°C, or

- 12 hours at room temperature at 15°C to 30°C

Administration of Infusion Solution

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

- Do not co-administer other drugs through the same infusion line. After each dose, flush the infusion line.

4 OVERDOSAGE

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

For management of a suspected drug overdose, contact your regional poison control centre.

5 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 2 Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Intravenous infusion	Single-use vial solution of: • 120 mg durvalumab / 2.4 mL (nominal concentration of 50 mg/mL) • 500 mg durvalumab / 10 mL (nominal concentration of 50 mg/mL)	L-histidine, L-histidine hydrochloride monohydrate, Polysorbate 80, α,α-trehalose dihydrate, and Water for Injection.

Dosage Form Description
IMFINZI (durvalumab) injection is a sterile, preservative-free, clear to opalescent, colourless to slightly yellow solution, free from visible particles.

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

2.4 mL of concentrate in a 10 mL Type 1 glass vial with an elastomeric stopper and a gray flip-off aluminum seal contains 120 mg durvalumab. Pack size of 1 vial.

6 DESCRIPTION

IMFINZI (durvalumab) is a fully human immunoglobulin G1 kappa (IgG1κ) monoclonal antibody that blocks the interaction of PD-L1 with PD-1 and CD80 (B7.1). Blockade of PD-L1/PD-1 and PD-L1/CD80 interactions releases the inhibition of immune responses, without inducing antibody dependent cell mediated cytotoxicity (ADCC).

NOC/c 7 WARNINGS AND PRECAUTIONS

General
IMFINZI (durvalumab) should be administered under the supervision of healthcare practitioners experienced in the treatment of cancer.

Driving and Operating Machinery

If patients experience adverse reactions affecting their ability to concentrate and react, they should be advised not to drive or operate machinery.

Immune-Mediated Adverse Reactions
Adverse reactions observed with immunotherapies such as IMFINZI may differ from those observed with non-immunotherapies and may require immunosuppression. Early identification of adverse reactions and timely intervention are an important part of the safe use of IMFINZI. In clinical trials, most immune-mediated adverse reactions were reversible and managed with interruptions of IMFINZI, administration of corticosteroids and/or supportive care. Refer to DOSAGE AND ADMINISTRATION, Table 1 for recommended treatment modifications and management of immune-mediated adverse reactions.

Immune-Mediated Pneumonitis
Cases of immune-mediated pneumonitis or interstitial lung disease, including fatal cases, defined as requiring use of systemic corticosteroids and with no clear alternate etiology, occurred in patients receiving IMFINZI in clinical studies (see ADVERSE REACTIONS, Immune-Mediated Pneumonitis). Patients should be monitored for signs and symptoms of pneumonitis. Patients with suspected pneumonitis should be evaluated with radiographic imaging and managed as recommended in DOSAGE AND ADMINISTRATION, Table 1.

Pneumonitis is frequently observed in patients receiving radiation therapy to the lung and the clinical presentation of radiation pneumonitis is very similar to other forms of pneumonitis. The PACIFIC study enrolled patients with locally advanced unresectable, Stage III non-small cell lung cancer (NSCLC) who had completed chemoradiation therapy within 1 to 42 days prior to initiation of the trial. More cases of pneumonitis, including both immune-mediated pneumonitis and radiation pneumonitis, occurred in patients receiving IMFINZI compared to patients receiving placebo (see ADVERSE REACTIONS, Clinical Trial Adverse Reactions). The median time to onset in the IMFINZI-treated group was 55 days (range: 1-406 days) vs. 55 days (range: 1-255 days) in the placebo group.

Immune-Mediated Hepatitis
Cases of immune-mediated hepatitis, including fatal cases, defined as requiring use of systemic corticosteroids and with no clear alternate etiology, occurred in patients receiving IMFINZI in clinical studies (see ADVERSE REACTIONS, Immune-Mediated Hepatitis). Patients should be monitored for abnormal liver function tests prior to each infusion with IMFINZI. Immune-mediated hepatitis should be managed as recommended in DOSAGE AND ADMINISTRATION, Table 1.

Immune-Mediated Colitis
Immune-mediated colitis or diarrhea, defined as requiring use of systemic corticosteroids and with no clear alternate etiology, occurred in patients receiving IMFINZI in clinical studies (see ADVERSE REACTIONS, Immune-Mediated Colitis). Patients should be monitored for signs and symptoms of colitis or diarrhea and managed as recommended in DOSAGE AND ADMINISTRATION, Table 1.

Immune-Mediated Endocrinopathies
Hypothyroidism:
Immune-mediated hypothyroidism occurred in patients receiving IMFINZI in clinical studies (see ADVERSE REACTIONS, Immune-Mediated Endocrinopathies, *Hypothyroidism*). Patients should be monitored for abnormal thyroid function tests prior to each infusion or at least once per month during treatment. Manage hypothyroidism as recommended in DOSAGE AND

ADMINISTRATION, Table 1.

Hyperthyroidism:
Immune-mediated hyperthyroidism (including thyroiditis) occurred in patients receiving IMFINZI in clinical studies (see ADVERSE REACTIONS, Immune-Mediated Endocrinopathies, *Hyperthyroidism)*. Patients should be monitored for abnormal thyroid function tests prior to each infusion or at least once per month during treatment. Symptomatic hyperthyroidism should be managed as per institutional guidelines. See DOSAGE AND ADMINISTRATION, Table 1.

Adrenal Insufficiency:
Immune-mediated adrenal insufficiency occurred in patients receiving IMFINZI in clinical studies (see ADVERSE REACTIONS, Immune-Mediated Endocrinopathies, *Adrenal Insufficiency)*. Patients should be monitored for clinical signs and symptoms of adrenal insufficiency. For symptomatic adrenal insufficiency, patients should be managed as recommended in DOSAGE AND ADMINISTRATION, Table 1.

Hypophysitis/Hypopituitarism:
Immune-mediated hypophysitis or hypopituitarism have been observed in clinical studies of products that target PD-1/PD-L1, including IMFINZI (see ADVERSE REACTIONS, Immune-Mediated Endocrinopathies, *Hypophysitis*). Patients should be monitored for clinical signs and symptoms of hypophysitis. For symptomatic hypophysitis or hypopituitarism, patients should be managed as recommended in DOSAGE AND ADMINISTRATION, Table 1.

Type I Diabetes Mellitus:
Immune-mediated Type 1 diabetes mellitus (T1DM) has been observed in clinical studies of products that target PD-1/PD-L1, including IMFINZI (see ADVERSE REACTIONS, Immune-Mediated Endocrinopathies, *Type 1 Diabetes Mellitus*). Patients should be monitored for clinical signs and symptoms of T1DM. For symptomatic T1DM, patients should be managed as recommended in DOSAGE AND ADMINISTRATION, Table 1.

Immune-Mediated Nephritis
Immune-mediated nephritis, defined as requiring use of systemic corticosteroids and with no clear alternate etiology, occurred in patients receiving IMFINZI in clinical studies (see ADVERSE REACTIONS, Immune-Mediated Nephritis). Patients should be monitored for abnormal renal function tests prior to and periodically during treatment with IMFINZI and managed as recommended in DOSAGE AND ADMINISTRATION, Table 1.

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 in clinical studies (see ADVERSE REACTIONS, Immune-Mediated Rash). Patients should be monitored for signs and symptoms of rash or dermatitis and managed as recommended in DOSAGE AND ADMINISTRATION, Table 1.

Other Immune-Mediated Adverse Reactions
Given the mechanism of action of IMFINZI, other potential immune-mediated adverse reactions may occur. In clinical studies (n=1889), rare cases (<0.1%) of potentially immune-related aseptic meningitis, immune thrombocytopenic purpura (fatal), myocarditis, pancreatitis (0.3%), uveitis and myositis (0.2%) were observed. Polymyositis with a fatal outcome (<0.1%) was reported in a patient treated with IMFINZI from an ongoing clinical study. Patients should be

monitored for signs and symptoms of immune-mediated adverse reactions and managed as recommended in DOSAGE AND ADMINISTRATION, Table 1.

Infections
Severe infections, including sepsis, necrotizing fasciitis, and osteomyelitis, occurred in patients receiving IMFINZI in clinical studies (see ADVERSE REACTIONS, Infections). Patients should be monitored for signs and symptoms of infection and treated with anti-infectives for suspected or confirmed infections as recommended in DOSAGE AND ADMINSTRATION, Table 1.

Infusion Related Reactions
Severe infusion related reactions have been reported in patients receiving IMFINZI in clinical studies (see ADVERSE REACTIONS). Patients should be monitored for signs and symptoms of infusion related reactions as recommended in DOSAGE AND ADMINISTRATION, Table 1. In patients with prior infusion related reactions to IMFINZI, pre-medication prior to administration may be considered.

Sexual Health

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 (see NON-CLINICAL TOXICOLOGY).

7.1 Special Populations

7.1.1 Pregnant Women

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 fetal harm when administered to a pregnant woman.

Human immunoglobulin G1 (IgG1) is known to cross the placental barrier. IMFINZI is not recommended during pregnancy. Women of childbearing potential should use effective contraception during treatment with IMFINZI and for at least 3 months after the last dose.

In animal reproduction studies, administration of IMFINZI to pregnant cynomolgus monkeys 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 IMFINZI (based on AUC) was associated with premature delivery, fetal loss (abortion and stillbirth) and an increase in neonatal deaths compared to concurrent control (see NON-CLINICAL TOXICOLOGY).

7.1.2 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 of lactating cynomolgus monkeys, and was associated with premature neonatal death compared to concurrent control (see NON-CLINICAL TOXICOLOGY). Because of the potential for adverse reactions in breastfed infants from durvalumab, breastfeeding is not recommended during treatment with IMFINZI and for at least 3 months after the last dose.

7.1.3 Pediatrics

Pediatrics (<18 years of age): The safety and efficacy of IMFINZI in patients younger than 18 years of age have not been established.

7.1.4 Geriatrics

Geriatrics (≥65 years of age): No dose adjustment is required for elderly patients (≥65 years of age).

Of the 191 patients with urothelial carcinoma (primary efficacy population) treated with IMFINZI, 118 patients (61.8%) were 65 years of age or older. Of the 476 patients with locally advanced, unresectable, Stage III NSCLC (primary efficacy population) treated with IMFINZI, 215 patients (45.1%) were 65 years of age or older. No overall clinically meaningful differences in safety or efficacy were reported between these patients (≥65 years of age) and younger patients (<65 years of age).

NOC/c

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Urothelial Carcinoma

The safety of IMFINZI (durvalumab) was evaluated in the urothelial carcinoma (UC) cohort of Study 1108. This cohort enrolled 191 patients in an open-label, single-arm trial with locally advanced or metastatic UC. Of the 191 patients enrolled, 182 patients had UC that had progressed during or after platinum-based chemotherapy or had progressed within 12 months of platinum-based neoadjuvant or adjuvant chemotherapy. Patients received 10 mg/kg IMFINZI via intravenous infusion every 2 weeks (Q2W) until disease progression or unacceptable toxicity. Treatment was continued for a maximum of 12 months. The median duration of exposure was 12 weeks (range: 1.6 to 54.3 weeks).

IMFINZI monotherapy 10 mg/kg Q2W was generally well tolerated in the UC population. Adverse reactions were generally manageable and reversible with interruption of dosing and treatment with immunosuppressants, such as corticosteroids.

Overall and regardless of relationship to treatment, an adverse event was experienced by 99.0% (189/191) of treated patients. At least one serious adverse event (SAE) was reported in 54.5% (104/191) of patients (for 12 of these patients, disease progression was reported as an SAE) and 9 (4.7%) patients had treatment-related SAE). The most common SAEs (occurring in ≥2% of patients) were back pain (4.7%), urinary tract infection (4.2%), acute kidney injury (4.2%), general physical health deterioration (3.7%), sepsis (3.1%), abdominal pain (2.6%), vomiting (2.6%), hypercalcemia (2.6%), and pyrexia (2.1%). Of the 191 enrolled UC patients, 15 (7.9%) had adverse events that resulted in death, including cardio-respiratory arrest, subileus, general physical deterioration, immune-mediated hepatitis, chronic hepatic failure, sepsis, cerebrovascular accident, acute kidney injury and pneumonitis. Of these, investigators considered one Grade 5 event each of pneumonitis and immune-mediated hepatitis to be related to treatment with durvalumab.

The most common adverse events regardless of relationship to treatment (any Grade; occurring in ≥10% of patients) were fatigue (35.6%), constipation (25.7%), decreased appetite (22.5%), nausea (22.0%), anemia (18.3%), diarrhea (16.8%), back pain (16.8%), urinary tract infection (16.2%), fever (15.7%), peripheral edema (14.1%), vomiting (13.1%), cough (11.5%), dyspnea

(11.5%), increased blood creatinine (11.0%), arthralgia (10.5%) and asthenia (10.5%). The majority of adverse events were Grade 1 or 2 (mild to moderate) in severity; Grade 3 or 4 adverse events were reported in 52 (27.2%) patients. The most common Grade 3 or 4 adverse events (>3% of patients) were anemia (9.9%), hyponatremia (5.8%), acute kidney injury (4.7%), urinary tract infection (4.2%), back pain (4.2%), fatigue, sepsis, hypercalcemia and asthenia (3.1% each). Treatment-related Grade 3 or 4 adverse events were reported in 6.8% of patients; the most common (≥1%) were increased AST (1.6%), increased ALT (1.0%), and increased GGT (1.0%), all of which were generally manageable and reversible.

Adverse events (excluding disease progression) leading to the delay, interruption or discontinuation of IMFINZI occurred in 68 (35.6%), 3 (1.6%), and 9 (4.7%) patients, respectively; the most common reasons for dose delay (occurring in >1% of patients) were back pain (3.7%), urinary tract infection (2.6%), acute kidney injury (1.6%), AST increased (1.6%), GGT increased (1.6%), and pneumonia (1.6%). The most common reason for dose discontinuation (occurring in ≥1% of patients) was general physical health deterioration in 2 (1.0%) patients.

Locally Advanced, Unresectable, Stage III Non-Small Cell Lung Cancer

The safety of IMFINZI in patients with locally advanced, unresectable, Stage III non-small lung cancer (NSCLC) was evaluated in a randomized, double-blind, placebo-controlled, multicenter study (PACIFIC). Patients received 10 mg/kg IMFINZI (n=475) or placebo (n=234) via intravenous infusion every 2 weeks (Q2W) (see CLINICAL TRIALS).

IMFINZI monotherapy 10 mg/kg Q2W was generally well tolerated in this patient population. Adverse reactions were generally manageable and reversible with interruption of dosing and treatment with immunosuppressants, such as corticosteroids.

The most common adverse reactions (any Grade; occurring in ≥10% of patients) reported for IMFINZI vs. placebo, respectively were cough (40.2% vs. 30.3%), pneumonitis/radiation pneumonitis (33.9% vs 24.8%), upper respiratory tract infections (26.1% vs. 19.2%), rash (21.7% vs. 12.0%), diarrhea (18.3% vs. 18.8%), pneumonia (17.1% vs. 11.5%), pyrexia (14.7% vs. 9.0%), pruritus (12.4% vs 5.6%), hypothyroidism (11.6% vs. 1.7%), abdominal pain (10.1% vs. 6.0%). The majority of adverse reactions were Grade 1 or 2 (mild to moderate) in severity; Grade 3 or 4 adverse reactions were reported in 12.8% of patients receiving IMFINZI vs 9.8% receiving placebo, with no event occurring with more than a 2-percentage-point difference between the treatment groups. The most common Grade 3 or 4 adverse reactions (occurring in >3% of patients) were pneumonia (6.5% of patients on IMFINZI vs. 5.6% on placebo).

The incidence of Grade 3 pneumonitis and radiation pneumonitis was similar between IMFINZI-treated patients and patients receiving placebo (3.4% vs. 3.0%, respectively). No Grade 4 events of pneumonitis or radiation pneumonitis were reported in either group. The incidence of Grade 5 pneumonitis and radiation pneumonitis was also similar between IMFINZI-treated patients and placebo-treated patients (1.1% vs. 1.7%, respectively).

Serious adverse reactions occurred in 12.8% of patients on IMFINZI and 11.1% of patients on placebo. The most frequent serious adverse reactions (occurring in >1% of patients) were pneumonia (8.2% of patients on IMFINZI vs. 7.3% on placebo), and pneumonitis/radiation pneumonitis (7.2% of patients on IMFINZI vs. 5.1% on placebo).

Adverse drug reactions with a fatal outcome occurred in 1.5% patients on IMFINZI and 2.6% patients on placebo, including pneumonitis in 0.8% patients on IMFINZI vs. 1.3% on placebo, and pneumonia in 0.6% patients on IMFINZI vs. 1.7% patients on placebo.

Adverse drug reactions leading to dose delay or interruption occurred in 24.4% of patients on IMFINZI vs. 14.5% of patients on placebo; the most common (occurring in >5% of patients) reasons in the IMFINZI and placebo groups were pneumonia (8.0% vs. 4.7%, respectively) and pneumonitis (5.1% vs. 3.0%, respectively). Treatment was discontinued for adverse drug reactions in 8.2% patients (n=39) on IMFINZI vs. 5.6% patients (n=13) on placebo. The most common (occurring in >1% of patients) reasons for discontinuation of study treatment in the IMFINZI and placebo groups were pneumonitis (4.8% vs. 2.6%, respectively) and pneumonia (1.9% vs. 2.1%, respectively).

Immune-mediated adverse drug reactions requiring systemic corticosteroids occurred in 14.3% of patients on IMFINZI vs. 5.6% on placebo, high dose corticosteroids (at least 40 mg prednisone or equivalent per day) in 8.2% of patients on IMFINZI vs. 4.3% on placebo, endocrine therapy occurred in 10.7% of patients on IMFINZI vs. 1.3% on placebo. Other immunosuppressants were required in 2 (0.4%) patients on IMFINZI (infliximab for both), and 1 (0.4%) patient on placebo (cyclophosphamide and tacrolimus).

8.2 Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Urothelial Carcinoma

Table 3 lists the adverse drug reactions, with incidences regardless of investigators assessment of causality, reported in patients with UC (n=191) treated with IMFINZI 10 mg/kg Q2W.

Table 3 Adverse Drug Reactions in the Urothelial Carcinoma Patients Treated with IMFINZI at 10 mg/kg Q2W (Study 1108)

	IMFINZI (N=191)			
System Organ Class Preferred Term[a]	**Any Grade N (%)**	**Grade 1 N (%)**	**Grade 2 N (%)**	**Grade 3 or 4 N (%)**
Cardiac disorders				
Myocarditis	Not reported[c]			
Endocrine disorders				
Hypothyroidism[d]	13 (6.8)	4 (2.1)	9 (4.7)	0
Hyperthyroidism[d]	9 (4.7)	7 (3.7)	2 (1.0)	0
Adrenal insufficiency	1 (0.5)	1 (0.5)	0	0
Hypophysitis/Hypopituitarism	Not reported[c]			
Diabetes insipidus	Not reported[c]			
Type 1 diabetes mellitus	Not reported[c]			

	IMFINZI (N=191)			
System Organ Class Preferred Term[a]	**Any Grade N (%)**	**Grade 1 N (%)**	**Grade 2 N (%)**	**Grade 3 or 4 N (%)**
Gastrointestinal disorders				
Diarrhea	32 (16.8)	22 (11.5)	9 (4.7)	1 (0.5)
Colitis[d]	2 (1.0)	1 (0.5)	1 (0.5)	0
Hepatobiliary disorders				
Hepatitis[b,d]	3 (1.6)	1 (0.5)	0	1 (0.5)
Aspartate aminotransferase increased[d]	16 (8.4)	8 (4.2)	3 (1.6)	5 (2.6)
Alanine aminotransferase increased[d]	16 (8.4)	10 (5.2)	3 (1.6)	3 (1.6)
Injury, poisoning and procedural complications				
Infusion related reaction	2 (1.0)	1 (0.5)	0	1 (0.5)
Musculoskeletal and connective tissue disorders				
Myositis	1 (0.5)	0	1 (0.5)	0
Renal and urinary disorders				
Blood creatinine increased	21 (11.0)	14 (7.3)	6 (3.1)	1 (0.5)
Nephritis[d]	1 (0.5)	0	0	1 (0.5)
Respiratory, thoracic and mediastinal disorders				
Pneumonitis[b]	2 (1.0)	1 (0.5)	0	0
Interstitial lung disease	Not reported[c]			
Skin and subcutaneous tissue disorders				
Rash[d]	27 (14.1)	20 (10.5)	6 (3.1)	1 (0.5)
Pruritus[d]	12 (6.3)	9 (4.7)	3 (1.6)	0
Dermatitis	1 (0.5)	0	1 (0.5)	0

[a] Incidences presented in this table are based on reports of drug-related adverse events.

[b] Including a fatal outcome.

[c] Adverse Drug Reactions not reported in the UC cohort but reported from other clinical studies (N=1889) included interstitial lung disease: uncommon (≥1/1,000 to <1/100) in any grade, and uncommon in Grade 3 or 4. Type 1 diabetes mellitus, hypopituitarism including diabetes insipidus, myocarditis: rare (≥1/10,000 to <1/1000) in any grade, rare in Grade 3 or 4.

[d] Included additional preferred terms: aspartate aminotransferase increased or alanine aminotransferase increased included transaminase increased and hepatic enzyme increased; colitis included enterocolitis, proctitis and enteritis; hepatitis included autoimmune hepatitis, hepatitis toxic, hepatocellular injury, hepatitis acute and hepatotoxicity; hypothyroidism included autoimmune hypothyroidism; hyperthyroidism included autoimmune thyroiditis, thyroiditis, thyroiditis subacute, Basedow's disease; rash included rash erythematous, rash generalized, rash macular, rash maculopapular, rash papular, rash pruritic, rash pustular, erythema, and eczema; pruritus included pruritus generalized; nephritis included autoimmune nephritis, glomerulonephritis, tubulointerstitial nephritis.

Table 4 lists the incidences of very common (occurring in ≥10% of patients) adverse events, regardless of investigators assessment of causality, reported in patients with UC (n=191) treated with IMFINZI 10 mg/kg Q2W.

Table 4 Adverse Events Reported in ≥10% in Urothelial Carcinoma Patients Treated with IMFINZI at 10 mg/kg Q2W (Study 1108)

	IMFINZI (N =191)			
System Organ Class Preferred Term[a]	**Any Grade N (%)**	**Grade 1 N (%)**	**Grade 2 N (%)**	**Grade 3 or 4 N (%)**
Blood and lymphatic system disorders				
Anemia	35 (18.3)	3 (1.6)	13 (6.8)	19 (9.9)
Gastrointestinal disorders				
Constipation	49 (25.7)	35 (18.3)	11 (5.8)	3 (1.6)
Nausea	41 (21.5)	25 (13.1)	12 (6.3)	4 (2.1)
Vomiting	25 (13.1)	13 (6.8)	8 (4.2)	4 (2.1)
General disorders and administration site conditions				
Fatigue	68 (35.6)	33 (17.3)	29 (15.2)	6 (3.1)
Pyrexia	30 (15.7)	25 (13.1)	5 (2.6)	0
Edema peripheral	27 (14.1)	17 (8.9)	7 (3.7)	3 (1.6)
Asthenia	20 (10.5)	9 (4.7)	5 (2.6)	6 (3.1)
Infections and infestations				
Urinary tract infection	31 (16.3)	3 (1.6)	20 (10.5)	8 (4.2)
Metabolism and nutrition disorders				
Decreased appetite	43 (22.5)	21 (11.0)	21 (11.0)	1 (0.5)
Musculoskeletal and connective tissue disorders				
Back pain	32 (16.8)	7 (3.7)	17 (8.9)	8 (4.2)
Arthralgia	20 (10.5)	12 (6.3)	7 (3.7)	1 (0.5)
Respiratory, thoracic and mediastinal disorders				
Dyspnea	22 (11.6)	8 (4.2)	11 (5.8)	3 (1.6)
Cough	21 (11.5)	19 (9.9)	3 (1.6)	0

[a] The terms presented in the table are adverse events reported regardless of the investigators assessment of relationship to treatment.

Locally Advanced, Unresectable, Stage III Non-Small Cell Lung Cancer

Table 5 lists the incidence of treatment-emergent adverse events reported in at least 5% of patients in the PACIFIC study regardless of investigator assessed causality.

Table 5 Treatment-Emergent Adverse Events in Locally Advanced, Unresectable, Stage III NSCLC Patients Reported in the PACIFIC Study Treated with IMFINZI at 10 mg/kg Q2W or Placebo

	IMFINZI (N=475)			Placebo (N=234)		
MedDRA System Organ Class Preferred Term	**All Grades n (%)**	**Grades 3 n (%)**	**Grades 4 n (%)**	**All Grades n (%)**	**Grades 3 n (%)**	**Grades 4 n (%)**
Blood and lymphatic system disorders						
Anemia	36 (7.6)	14 (2.9)	0	25 (10.7)	8 (3.4)	0
Endocrine disorders						
Hyperthyroidism[a]*	39 (8.2)	0	0	5 (2.1)	0	0
Hypothyroidism[b]*	55 (11.6)	1 (0.2)	0	4 (1.7)	0	0
Gastrointestinal disorders						
Abdominal pain[c]*	48 (10.1)	2 (0.4)	0	14 (6.0)	1 (0.4)	0
Constipation	56 (11.8)	1 (0.2)	0	20 (8.5)	0	0
Diarrhea*	87 (18.3)	3 (0.6)	0	44 (18.8)	3 (1.3)	0
Nausea	66 (13.9)	0	0	31 (13.2)	0	0
Vomiting	37 (7.8)	1 (0.2)	0	19 (8.1)	0	0
General disorders and administration site conditions						
Asthenia	51 (10.7)	3 (0.6)	0	31 (13.2)	1 (0.4)	0
Edema peripheral*	37 (7.8)	0	0	9 (3.8)	0	0
Fatigue	113 (23.8)	1 (0.2)	0	48 (20.5)	3 (1.3)	0
Non-cardiac chest pain	35 (7.4)	1 (0.2)	0	22 (9.4)	1 (0.4)	0
Pyrexia*	70 (14.7)	1 (0.2)	0	21 (9.0)	0	0
Hepatobiliary disorders						
Aspartate aminotransferase increased or Alanine aminotransferase increase[d]*	29 (6.1)	9 (1.9)	0	4 (1.7)	0	0
Infections and infestations						
Bronchitis	33 (6.9)	1 (0.2)	0	19 (8.1)	1 (0.4)	0
Nasopharyngitis	41 (8.6)	0	0	14 (6.0)	0	0
Pneumonia[e]*	81 (17.1)	30 (6.3)	1 (0.2)	27 (11.5)	13 (5.6)	0
Upper respiratory tract infections[f]*	124 (26.1)	2 (0.4)	0	45 (19.2)	0	0
Urinary tract infection	28 (5.9)	0	0	13 (5.6)	0	0
Metabolism and nutrition disorders						
Decreased appetite	68 (14.3)	1 (0.2)	0	30 (12.8)	1 (0.4)	1 (0.4)
Hypokalemia	24 (5.1)	5 (1.1)	0	12 (5.1)	5 (2.1)	0
Musculoskeletal and connective tissue disorders						
Arthralgia	59 (12.4)	0	0	26 (11.1)	0	0
Back pain	50 (10.5)	1 (0.2)	0	27 (11.5)	1 (0.4)	0
Musculoskeletal chest pain	25 (5.3)	0	0	18 (7.7)	0	0
Musculoskeletal pain	39 (8.2)	3 (0.6)	0	24 (10.3)	1 (0.4)	0

Myalgia*	38 (8.0)	1 (0.2)	0	10 (4.3)	0	0
Pain in extremity	32 (6.7)	0	0	12 (5.1)	1 (0.4)	0
Nervous system disorders						
Dizziness	33 (6.9)	1 (0.2)	0	21 (9.0)	0	0
Headache	52 (10.9)	1 (0.2)	0	21 (9.0)	2 (0.9)	0
Paresthesia	20 (4.2)	0	0	12 (5.1)	0	0
Psychiatric disorders						
Insomnia	45 (9.5)	0	0	16 (6.8)	0	0
Respiratory, thoracic and mediastinal disorders						
Cough/ Productive Cough*	191 (40.2)	3 (0.6)	0	71 (30.3)	1 (0.4)	0
Dyspnea	106 (22.3)	7 (1.5)	0	56 (23.9)	6 (2.6)	0
Pneumonitis[g]*/Radiation Pneumonitis	161 (33.9)	16 (3.4)	0	58 (24.8)	7 (3.0)	0
Skin and subcutaneous tissue disorders						
Dry skin	37 (7.8)	0	0	12 (5.1)	0	0
Pruritus[h]*	59 (12.4)	0	0	13 (5.6)	0	0
Rash[i]*	103 (21.7)	3 (0.6)	0	28 (12.0)	0	0
Vascular disorders						
Hypertension	27 (5.7)	9 (1.9)	1 (0.2)	8 (3.4)	2 (0.9)	0

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* These adverse events are considered drug-related.

[a] includes hyperthyroidism, autoimmune thyroiditis, thyroiditis, thyroiditis subacute and Basedow's disease.

[b] includes autoimmune hypothyroidism and hypothyroidism.

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

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

[e] includes lung infection, pneumocystis jirovecii pneumonia, pneumonia, pneumonia adenoviral, pneumonia bacterial, pneumonia cytomegaloviral, pneumonia haemophilus, pneumonia klebsiella, pneumonia necrotising, pneumonia pneumococcal and pneumonia streptococcal.

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

[g] includes acute interstitial pneumonitis, interstitial lung disease, pneumonitis and pulmonary fibrosis.

[h] includes pruritus generalized and pruritus.

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

Less Common Clinical Trial Adverse Reactions (<5%)

The following additional adverse reactions considered drug-related were reported in less than 5% of IMFINZI-treated patients in the PACIFIC study. Adverse reactions presented elsewhere are excluded.

Endocrine disorders: adrenal insufficiency (0.2%), type 1 diabetes mellitus (0.2%)

Gastrointestinal disorders: colitis (includes colitis, enteritis, enterocolitis and proctitis) (1.1%)

Hepatobiliary disorders: hepatitis (includes hepatitis, autoimmune hepatitis, hepatitis toxic, hepatocellular injury, hepatitis acute and hepatotoxicity) (0.6%)

Infections and infestations: dental and oral soft tissue infections (includes gingivitis, oral infection, periodontitis, pulpitis dental, tooth abscess and tooth infection) (3.6%), oral candidiasis (3.2%), influenza (2.5%)

Injury, poisoning and procedural complications: infusion related reaction (includes infusion related reaction and urticaria with onset on the day of dosing or 1 day after dosing) (1.9%)

Musculoskeletal and connective tissue disorders: myositis (0.4%)

Renal and urinary disorders: blood creatinine increased (4.6%), dysuria (2.3%), nephritis (includes autoimmune nephritis, tubulointerstitial nephritis, nephritis, glomerulonephritis and glomerulonephritis membranous) (0.4%)

Respiratory, thoracic and mediastinal disorders: dysphonia (3.8%)

Skin and subcutaneous tissue disorders: night sweats (2.3%), dermatitis (1.5%)

Additional Information on Selected Adverse Reactions

The data for the following immune-mediated adverse reactions, defined as requiring the use of systemic corticosteroids/hormone replacement therapy with no clear alternate etiology, reflect exposure to IMFINZI, as a single agent, in Study 1108 (UC cohort (n=191)), PACIFIC study (n=475) and overall population (n= 1889) (see CLINICAL TRIALS). The management guidelines for these adverse reactions are described in WARNINGS AND PRECAUTIONS and DOSAGE AND ADMINISTRATION.

Immune-Mediated Pneumonitis

In the UC cohort (n=191) of Study 1108, immune-mediated pneumonitis occurred in 1 (0.5%) patient (Grade 5).

In the PACIFIC study, in patients with locally advanced, unresectable, Stage III NSCLC (n=475 in the IMFINZI arm, and n=234 in the placebo arm) who had completed treatment with 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.

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 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 UC cohort (n=191) of Study 1108, immune-mediated hepatitis occurred in 4 (2.1%) patients, with Grade 3 in 2 (1.0%) patients, and Grade 5 in 1 (0.5%) patient.

In the PACIFIC study, immune-mediated hepatitis occurred in 3 (0.6%) patients treated with IMFINZI. 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 UC cohort (n=191) of Study 1108, immune-mediated colitis or diarrhea occurred in 4 (2.1%) patients (diarrhea in 4 patients [2.1%, Grade 1 or 2]) and colitis occurred in 1 patient (0.5%, Grade 2).

In the PACIFIC study, immune-mediated colitis or diarrhea occurred in 5 (1.1%) patients treated with IMFINZI, 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 UC cohort (n=191) of Study 1108, immune-mediated hypothyroidism occurred in 10 (5.2%) patients, there were no Grade 3 or 4 cases.

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 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 UC cohort (n=191) of Study 1108, immune-mediated hyperthyroidism occurred in 2 (1.0%) patients (Grade 2).

In the PACIFIC study, immune-mediated hyperthyroidism occurred in 13 (2.7%) patients treated with IMFINZI. 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. Resolution occurred in 23 patients. Eight patients experienced hypothyroidism following hyperthyroidism.

Adrenal Insufficiency
In the UC cohort (n=191) of Study 1108, immune-mediated adrenal insufficiency occurred in 1 (0.5%) patient (Grade 1).

In the PACIFIC study, immune-mediated adrenal insufficiency occurred in 1 (0.2%) patient treated with IMFINZI. 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.

Hypophysitis/*Hypopituitarism*
In clinical studies, hypopituitarism (including diabetes insipidus) was observed in one patient (<0.1%, Grade 3) treated with IMFINZI. This patient received high dose corticosteroid (at least 40 mg prednisone or equivalent per day) and did not discontinue IMFINZI.

Type I Diabetes Mellitus
In clinical studies, Type I diabetes mellitus was observed in one patient (<0.1%, Grade 3) treated with IMFINZI. The time to onset was 42 days. This patient received insulin treatment and discontinued IMFINZI.

Immune-Mediated Nephritis
In the UC cohort (n=191) of Study 1108, immune-mediated nephritis occurred in 1 (0.5%) patient (Grade 3).

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

In the combined safety database with IMFINZI monotherapy, immune-mediated nephritis occurred in in 3 (0.2%) patients, including Grade 3 in 1 (<0.1%) patients. 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 UC cohort (n=191) of Study 1108, immune-mediated rash or dermatitis occurred in 2 (1%) patients, including Grade 3 in 1 (0.5%) patient.

In the PACIFIC study immune-mediated rash or dermatitis occurred in 9 (1.9%) patients in the IMFINZI-treated group and in 1 (0.4%) patient in the placebo group, including Grade 3 in 2 (0.4%) patients on IMFINZI vs. no 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 treated with IMFINZI 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.

8.3 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Urothelial Carcinoma
Changes in laboratory parameters were predominantly Grade 1 or 2 in severity, and the incidence of any grade worsening to Grade 3 or 4 was generally low (Table 6Table 6).

Table 6 Laboratory Abnormalities Worsened from Baseline Occurring in ≥1% (Grade 3 or 4) of IMFINZI-Treated Patients with Urothelial Carcinoma (Study 1108)

	IMFINZI (N =191)			
Laboratory Test	**N**	**Grades 1 N (%)**	**Grades 2 N (%)**	**Grade 3 or 4[a] N (%)**
Anemia	180	25 (13.9)	38 (21.1)	22 (12.2)
Hyponatremia	179	62 (34.6)	0	19 (10.6)
Lymphocyte count decreased	180	20 (11.1)	41 (22.8)	19 (10.6)
Hypermagnesemia	176	13 (7.4)	0	7 (4.0)
Alkaline phosphatase increased	179	28 (15.6)	15 (8.4)	7 (3.9)
Aspartate aminotransferase increased	179	35 (19.6)	5 (2.8)	7 (3.9)
Hypercalcemia	176	16 (9.1)	4 (2.3)	6 (3.4)

	IMFINZI (N =191)			
Laboratory Test	**N**	**Grades 1 N (%)**	**Grades 2 N (%)**	**Grade 3 or 4[a] N (%)**
Hyperglycemia	178	47 (26.4)	26 (14.6)	6 (3.4)
Blood bilirubin increased	179	9 (5.0)	6 (3.4)	4 (2.2)
Hyperkalemia	179	21 (11.7)	8 (4.5)	4 (2.2)
Creatinine increased	180	40 (22.2)	16 (8.9)	4 (2.2)
Alanine aminotransferase increased	180	27 (15.0)	6 (3.3)	2 (1.1)
Neutrophil count decreased	178	5 (2.8)	7 (3.9)	2 (1.1)
Hypoalbuminemia	179	34 (19.0)	31 (17.3)	2 (1.1)
Hypokalemia	179	16 (8.9)	0	2 (1.1)

[a] Frequency of lab abnormalities for Grade 1 and Grade 2 are provided for those lab abnormalities reported in ≥1% patients with Grade 3 and Grade 4 severity.

Locally Advanced, Unresectable, Stage III Non-Small Cell Lung Cancer

Table 7Table 7 lists the incidence of laboratory abnormalities reported in patients with locally advanced unresectable, Stage III NSCLC in the PACIFIC study.

Table 7 Laboratory Abnormalities Worsening from Baseline Occurring More Frequently (≥5% Higher Incidence vs. Placebo) in IMFINZI-Treated Locally Advanced, Unresectable, Stage III NSCLC Patients in the PACIFIC Study

Laboratory Abnormalities	IMFINZI			Placebo		
	N	**Any Grade n (%)**	**Grade 3 or 4 n (%)**	**N**	**Any Grade n (%)**	**Grade 3 or 4 n (%)**
Alanine aminotransferase increased	470	181 (38.5)	11 (2.3)	228	49 (21.5)	1 (0.4)
Aspartate aminotransferase increased	469	169 (36.0)	13 (2.8)	228	48 (21.1)	1 (0.4)
Creatinine increased	465	76 (16.3)	0	226	23 (10.2)	0
TSH elevated >ULN and above baseline	464	123 (26.5)	NA	224	30 (13.4)	NA
TSH decreased <LLN and below baseline	464	148 (31.9)	NA	224	35 (15.6)	NA

NA - not applicable TSH - thyroid stimulating hormone ULN - upper limit of normal LLN - lower limit of normal

Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity.

Due to assay deficiencies, the immunogenicity of IMFINZI has not yet been adequately established. Of 1570 patients who were treated with IMFINZI 10 mg/kg every 2 weeks across trials and evaluable for the presence of anti-drug antibodies (ADAs), 2.9% (45/1570) patients tested positive for treatment-emergent ADAs. Neutralizing antibodies against durvalumab were detected in 0.5% (8/1570) patients. A population PK analysis could not detect any clinically relevant effect of ADAs on the PK parameters in the model.

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

concomitant medications and underlying disease. For these reasons, comparison of incidence of antibodies to IMFINZI with the incidence of antibodies to other products may be misleading.

9 DRUG INTERACTIONS

The drug interaction potential of IMFINZI (durvalumab) is unknown. No formal pharmacokinetic drug-drug interaction studies have been conducted with durvalumab as durvalumab is an immunoglobulin.

NOC/c 10 ACTION AND CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

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

IMFINZI (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. IMFINZI 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.

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

10.2 Pharmacokinetics

The pharmacokinetics (PK) of IMFINZI was studied in 1902 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 1310 patients (dose ≥10 mg/kg), the mean steady-state clearance, steady state volume of distribution, and terminal half-life were 8.24 mL/h, 5.6 L, and approximately 17 days, respectively. Following multiple doses, the systemic accumulation in area under the curve (AUC), maximum concentration (C_{max}) and trough concentration (C_{min}) was 2.6, 1.9, and 3.2-fold, respectively.

Durvalumab clearance decreases over time, with a mean maximal reduction (% coefficient of variation [CV%]) from baseline values of approximately 22.9% (46.3%). The decrease in CLss was not considered clinically relevant.

Special Populations and Conditions

The covariate of 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, 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), or ECOG/WHO status were shown to have no clinically significant effect on the pharmacokinetics parameters in the population PK model of durvalumab.

Hepatic Insufficiency: 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.

Renal Insufficiency: The effect of severe renal impairment (CrCL 15 to 29 mL/min) on the pharmacokinetics of durvalumab is unknown.

11 STORAGE, STABILITY AND DISPOSAL

Store IMFINZI (durvalumab) under refrigeration at 2°C to 8°C. Protect IMFINZI from light by storing in the original package until time of use. Do not freeze or shake. For storage conditions after preparation of the infusion, see DOSAGE AND ADMINISTRATION, Storage of Infusion Solution.

12 SPECIAL HANDLING INSTRUCTIONS

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

PART II: SCIENTIFIC INFORMATION

IMFINZI (durvalumab) indicated for the treatment of patients with:

- Locally advanced or metastatic urothelial carcinoma who:
  - Have disease progression during or following platinum-containing chemotherapy
  - Have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy

has been issued marketing authorization **with** conditions, pending the results of trials to verify its clinical benefit. Patients should be advised of the nature of the authorization. *For further information for IMFINZI, please refer to Health Canada's Notice of Compliance with conditions - drug products web site: http://www.hc-sc.gc.ca/dhp-mps/prodpharma/notices-avis/conditions/index-eng.php.*

IMFINZI indicated for the treatment of patients with:

- Locally advanced, unresectable, Stage III non-small cell lung cancer (NSCLC) whose disease has not progressed following platinum-based chemoradiation therapy

has been issued marketing authorization **without** conditions.

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Durvalumab

Structure: Durvalumab is a fully human monoclonal antibody of the immunoglobulin (Ig) G1 kappa subclass composed of 2 identical heavy chains and 2 identical light chains.

Molecular formula and molecular mass: Approximately 149 kDa, including oligosaccharides.

Physicochemical properties: The durvalumab drug substance is a clear to opalescent, colourless to slightly yellow liquid with a density of 1.054 g/mL. The durvalumab drug substance liquid is formulated in buffer (26 mM histidine/histidine-HCl, 275 mM trehalose dihydrate, 0.02% (w/v) polysorbate 80, pH 6.0) at a concentration of 50 mg/mL (nominal). The pI of durvalumab is 8.1-8.8.

14 CLINICAL TRIALS

NOC/c

Urothelial Carcinoma

The efficacy of IMFINZI (durvalumab), in terms of tumour response rate, was evaluated in a Phase I/II, global, multicenter, multi-cohort, open-label, single-arm clinical trial, Study 1108. In the urothelial carcinoma (UC) cohort, 191 patients received IMFINZI 10 mg/kg every 2 weeks (Q2W). Patients were followed for at least 16 weeks as of the data cut-off date (had tumour assessments at Weeks 6, 12 and 16). The reported efficacy is based on 182 patients with

locally advanced or metastatic UC who had progressed during or after a platinum-based therapy, including those patients who progressed within 12 months of receiving therapy in a neo-adjuvant or adjuvant setting (2L+ UC). The remaining 9 patients were treatment naïve/first line. The median duration of follow-up for the 182 patients who had received prior platinum-based chemotherapy was 5.57 months (range: 0.4 to 25.9 months).

IMFINZI 10 mg/kg was administered by intravenous infusion every 2 weeks for up to 12 months or until unacceptable toxicity or confirmed disease progression. In the absence of clinical deterioration, patients in the UC cohort were permitted to continue to receive IMFINZI after confirmed progression of disease if investigators considered that they continued to derive a clinical benefit. The primary efficacy endpoint was Objective Response Rate (ORR) according to RECIST v1.1 as assessed by Blinded Independent Central Review (BICR). The trial excluded patients with a history of immunodeficiency; medical conditions that required systemic immunosuppression; history of severe immune-mediated adverse reactions; untreated CNS metastases; HIV; active tuberculosis, or hepatitis B or C infection. Additional efficacy endpoints included Duration of Response (DoR), Disease-Control Rate (DCR) and Overall Survival (OS).

In Study 1108, tumour specimens were evaluated for PD-L1 expression using the VENTANA PD-L1 (SP263 clone) immunohistochemical assay. Testing was performed prospectively at a central laboratory by pathologists trained in the use of the SP263 assay for the evaluation of PD-L1 expression. The test detects membrane and cytoplasmic PD-L1 expression by tumour cells (TC) and tumour-associated immune cells (IC). PD-L1 status was determined by the percentage of TC with any membrane PD-L1 staining above background or by the percentage of IC with PD-L1 staining (IC+) at any intensity above background. The percent of tumour area occupied by any tumour-associated immune cells (Immune Cells Present, ICP) is used to determine IC+, which is the percent area of ICP exhibiting PD-L1 positive immune cell staining. PD-L1 status is considered high if any of the following are met:

- ≥25% of tumour cells exhibit membrane staining; or,
- ICP >1% and IC+ ≥25%; or,
- ICP ≤1% and IC+ = 100%

If none of these criteria were met, PD-L1 status was considered low/negative.

Of the 182 patients that had received prior platinum-based chemotherapy, 95 were classified as PD-L1 high, 73 as PD-L1 low/negative and 14 patients were not evaluable for PD-L1 status.

Trial Design and Study Demographics

Table 8 Summary of Patient Demographics in the UC cohort of Study 1108 (N=182)

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
CD-ON-MEDI4736-1108	Phase I/II, multicenter, open-label, first-time-in-human, dose-escalation, dose-exploration, and dose-expansion study	10 mg/kg Q2W, intravenous, 12 months	182	66.2 years old	F: 51 (28.0%) M: 131 (72.0%)

In the UC cohort (n = 182), 70% of patients received prior cisplatin, 30% had prior carboplatin and 35% received 2 or more prior lines of systemic therapy. Seventy-four patients (42%) had a baseline creatinine clearance of <60 mL/min. The median age of patients was 67 years (range: 34 to 88), 72% were male, 71% were Caucasian, 22% were Asian, 4% were Black/African American and 3% were Other. Based on combined independent radiographic assessment and investigator reported data, ninety-two percent (92%) had visceral metastases at study entry, including 43% with liver metastases. Lymph-node-only metastases were present in 8% of patients. Most patients had an ECOG performance status of 1 (66.5%), the remaining had ECOG status of 0 (33.5%). The Bellmunt risk score (which includes ECOG score, baseline hemoglobin, and liver metastases) was 0 in 22%, 1 in 38%, 2 in 30%, and 3 in 11% of patients.

Study Results

Table 9 summarizes the efficacy results for pre-specified analyses.

Overall, the ORR in the UC cohort was 17.6%. Patients with PD-L1 high tumours were associated with numerically increased ORR (27.4%).

Responses occurred early in the treatment. Median time to response was 1.40 months (range: 1.2 to 3.2 months), which coincides with the first protocol-specified imaging assessment. Responses appear durable; median DoR has not yet been reached (range: 0.9+ to 19.9+ months). Among the total 32 responding patients, 75.0% (24/32) had ongoing responses at the time of analysis for ORR (patients with ≥13 weeks follow-up), 15 (46.9%) patients had ongoing responses of 6 months or longer in duration, 10 (31.3%) patients had ongoing responses of 9 months or longer in duration and 5 (15.6%) patients had ongoing response of 12 months or longer in duration. Eight patients in the UC cohort did not have ongoing responses at the time of analysis. Seven patients progressed per BICR after an initial response. Of the 7 patients who progressed per BICR after an initial response, 3 patients continued on IMFINZI, and 4 patients completed 12 months of treatment with IMFINZI.

Table 9 Efficacy Results of Study 1108 in the UC Cohort (N=182) and by PD-L1 Status

Efficacy Parameter[a]	All Patients (N=182)	PD-L1 High (N=95)	PD-L1 Low/Negative (N=73)	PD-L1 NE (N=14)
Number of confirmed responders by BICR	32	26	3	3
Objective Response Rate (95% CI)	17.6% (12.3%, 23.9%)	27.4% (18.7%, 37.5%)	4.1% (0.9%, 11.5%)	21.4% (4.7%, 50.8%)
CR, n (%)	6 (3.3%)	4 (4.2%)	1 (1.4%)	1 (7.1%)
PR, n (%)	26 (14.3%)	22 (23.2%)	2 (2.7%)	2 (14.3%)
Median DoR, months, range	NR (0.9+, 19.9+)	NR (0.9+, 19.9+)	12.25 (1.9+, 12.3)	NR (2.3+, 2.6+)

CR = Complete Response; PR = Partial Response; BICR = Blinded Independent Central Review; DoR = Duration of Response; TC = Tumour Cell; IC = Immune Cell; NE = Not Estimable; NR = Not Reached

[a] Overall Response Rate and Duration of Response determined by RECIST v1.1.

Locally Advanced, Unresectable, Stage III Non-Small Cell Lung Cancer

The efficacy of IMFINZI was evaluated in the PACIFIC study, a Phase III, randomized, double-blind, placebo-controlled, multicenter study that enrolled 713 patients with locally advanced, unresectable, Stage III non-small cell lung cancer (NSCLC). Eligible patients had completed at least 2 cycles of definitive platinum-based chemoradiation within 1 to 42 days prior to initiation of the study and had a WHO performance status of 0 or 1. Ninety-two percent of patients had received a total dose of 54 to 66 Gy of radiation.

The study excluded patients who had progressed following chemoradiation therapy, patients with active or prior documented autoimmune disease within 2 years of initiation of the study; a history of immunodeficiency; a history of severe immune-mediated adverse reactions; medical conditions that required systemic immunosuppression; active tuberculosis or hepatitis B or C or HIV infection or patients receiving live attenuated vaccine within 30 days before or after receiving 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 disease progression. Randomization was stratified by gender, age (<65 years vs. ≥65 years) and smoking status (smoker vs. non- smoker). Tumour assessments were conducted every 8 weeks for the first 12 months and then every 12 weeks thereafter.

Trial Design and Study Demographics

Table 10 Summary of patient demographics in locally advanced, unresectable, Stage III NSCLC (PACIFIC Study)

Study No.	Trial design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
D4191C00001 (PACIFIC)	Phase III, randomized, double-blind, placebo-controlled, multicenter, international study	IMFINZI, Double arm 10 mg/kg Q2W or placebo (2:1) Intravenous infusion	IMFINZI: 476 Placebo: 237	63 years (23-90 years)	Male (70%)

The demographics and baseline disease characteristics were well balanced between study arms (see Table 11).

Patients were enrolled regardless of their tumour PD-L1 expression level. Where available, archival tumour tissue specimens, taken prior to chemoradiation therapy, were retrospectively tested for PD-L1 expression on tumour cells (TC) using the VENTANA PD-L1 (SP263) IHC assay. Of the 713 patients randomized, 63% (n=451) of patients provided a tissue sample of sufficient quality and quantity to determine PD-L1 expression and 37% (n=262) were unknown. Of 451 patients with PD-L1 expression available, 67% were TC ≥1% [PD-L1 TC 1-24% (32%), PD-L1 TC ≥25% (35%)] and 33% were TC <1%.

Table 11 Patient Demographics and Baseline Disease Characteristics, PACIFIC (Full analysis set)

	PACIFIC	
Demographic/Disease Characteristic	**IMFINZI (N=476)**	**Placebo (N=237)**
Age (years)		
N	476	237
Mean	63.0	62.6
SD	8.66	9.64
Median	64.0	64.0
Min, max	31, 84	23, 90
Age group (years), n (%)		
<50	30 (6.3)	22 (9.3)
≥50 to <65	231 (48.5)	108 (45.6)
≥65 to <75	178 (37.4)	88 (37.1)
≥75	37 (7.8)	19 (8.0)
Sex, n (%)		
Male	334 (70.2)	166 (70.0)
Female	142 (29.8)	71 (30.0)
Race, n (%)		
Caucasian	337 (70.8)	157 (66.2)

Table 11 Patient Demographics and Baseline Disease Characteristics, PACIFIC (Full analysis set)

	PACIFIC	
Demographic/Disease Characteristic	**IMFINZI (N=476)**	**Placebo (N=237)**
Black or African-American	12 (2.5)	2 (0.8)
Asian	120 (25.2)	72 (30.4)
Other	5 (1.0)	6 (2.5)
Missing	1 (0.2)	0
Weight (kg)		
N	475	236
Mean	71.9	69.4
SD	17.39	15.73
Median	69.0	69.0
Min, Max	34, 175	38, 128
Weight group (kg), n (%)		
<70	243 (51.1)	124 (52.3)
≥70 to ≤90	174 (36.6)	93 (39.2)
>90	58 (12.2)	19 (8.0)
Missing	1 (0.2)	1 (0.4)
Smoking history, n (%)		
Current/Former smoker	433 (91.0)	216 (91.1)
Never smoker	43 (9.0)	21 (8.9)
Baseline WHO, n (%)		
0	234 (49.2)	114 (48.1)
1	240 (50.4)	122 (51.5)
2	0	0
Missing	2 (0.4)	1 (0.4)
Histology type		
Squamous	224 (47.1)	102 (43.0)
Non-squamous	252 (52.9)	135 (57.0)
Staging		
IA/IB	1 (0.2)	2 (0.8)
IIA/IIB	7 (1.4)	3 (1.2)
IIIA	252 (52.9)	125 (52.7)
IIIB	212 (44.5)	107 (45.1)
IV	4 (0.8)	0
Baseline hemoglobin concentration, n (%)		
<10 g/dL	80 (16.8)	35 (15.0)
≥10 g/dL	395 (83.2)	199 (85.0)
Missing	0	0

Max Maximum; Min Minimum; SD Standard deviation

Study Results

Overall survival (OS) and progression-free survival (PFS) were the primary endpoints of the PACIFIC study. Secondary efficacy endpoints included Objective Response Rate (ORR) and Duration of Response (DoR). PFS, ORR and DoR were assessed by Blinded Independent Central Review (BICR) according to RECIST v1.1. Analysis of ORR was based on a sub-group of the intent to treat (ITT) population [IMFINZI (N=443), Placebo (N=213)] with measurable disease at baseline, assessed within 0 – 42 days after chemoradiation and before the start of study drug. Data obtained up to progression or the last evaluable assessment in the absence of progression, were included in the assessment of ORR.

The study demonstrated a statistically significant and clinically meaningful improvement in OS in the IMFINZI-treated group compared with the placebo group [HR = 0.68 (95% CI: 0.53, 0.87), p = 0.00251]. Median OS was not reached in the IMFINZI-treated group and was 28.7 months in the placebo group. The study demonstrated a statistically significant and clinically meaningful improvement in PFS in the IMFINZI-treated group compared with the placebo group [hazard ratio (HR) = 0.52 (95% CI: 0.42, 0.65), p<0.0001]. Median PFS was 16.8 months in the IMFINZI-treated group and 5.6 months in the placebo group. See Table 12 and Figures 1 and 2.

Table 12 Efficacy Results in Locally Advanced, Unresectable, Stage III NSCLC, PACIFIC (Full analysis set)[a]

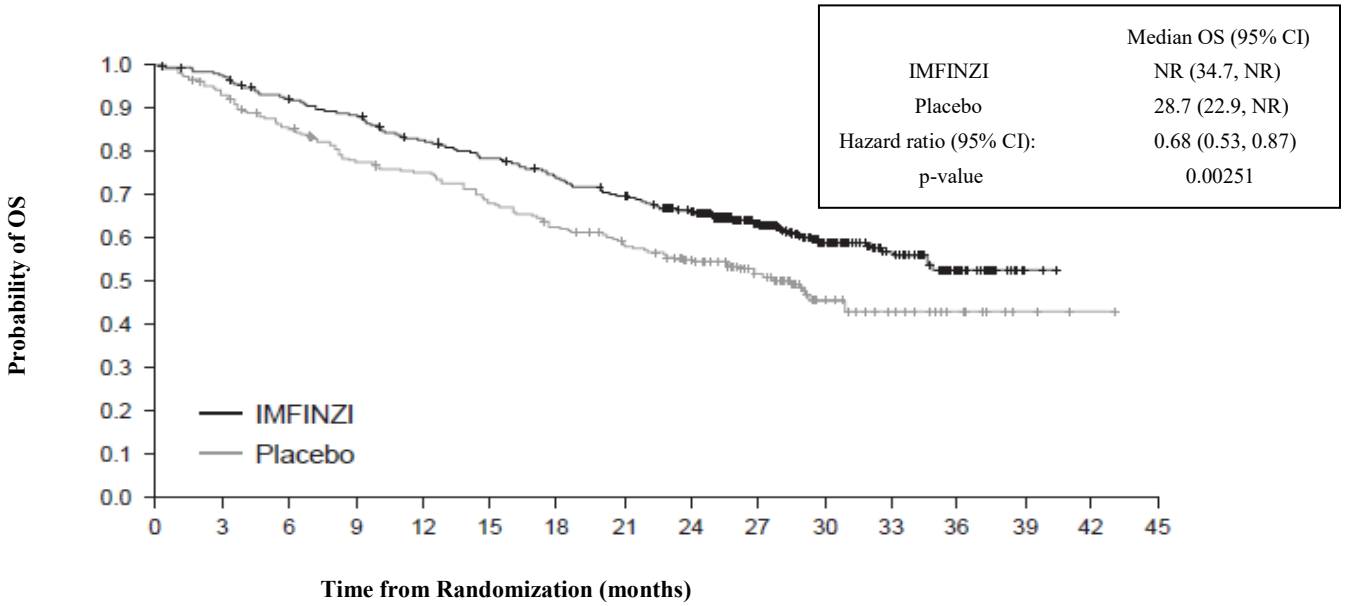
	IMFINZI (N=476)	**Placebo (N=237)**
OS		
Number of deaths (%)	183 (38.4)	116 (48.9)
Median OS (months) (95% CI)	NR (34.7, NR)	28.7 (22.9, NR)
HR (95% CI)	0.68 (0.53, 0.87)	
2-sided p-value[d]	0.00251	
OS at 24 months (95% CI)	66.3 (61.7, 70.4)	55.6 (48.9, 61.8)
p-value[f]	0.005	
PFS[b]		
Number of events (%)	214 (45.0)	157 (66.2)
Median PFS (months) (95% CI)	16.8 (13.0, 18.1)	5.6 (4.6, 7.8)
HR (95% CI)	0.52 (0.42, 0.65)	
p-value[e]	p<0.0001	
ORR[c] n (%) (95% CI)	133 (30.0) (25.8, 34.5)	38 (17.8) (13.0, 23.7)
Complete Response n (%)	8 (1.8)	1 (0.5)
Partial Response n (%)	125 (28.2)	37 (17.4)
Median DoR (months) (95% CI)	NR (27.4, NR)	18.4 (6.7, 24.5)

[a] The analysis of OS and an updated analysis of ORR and DoR was performed approximately 13 months after the primary analysis of PFS.

[b] PFS is defined as the time from the date of randomization until the date of objective disease progression (using BICR according to RECIST 1.1) or death.

[c] Based on sub-group of ITT population with measurable disease at baseline according to RECIST v1.1; IMFINZI (N=443), Placebo (N=213) assessed within 0-42 days after concurrent chemoradiation and before the start of study drug.
[d] Compared with allocated α of 0.00274 (Lan DeMets spending function approximating O'Brien Fleming boundary) for interim analysis
[e] Compared with allocated α of 0.011035 (Lan DeMets spending function approximating O'Brien Fleming boundary) for interim analysis
[f] Compared with α of 0.05 following statistically significant PFS and OS at interim analyses
NR = not reached

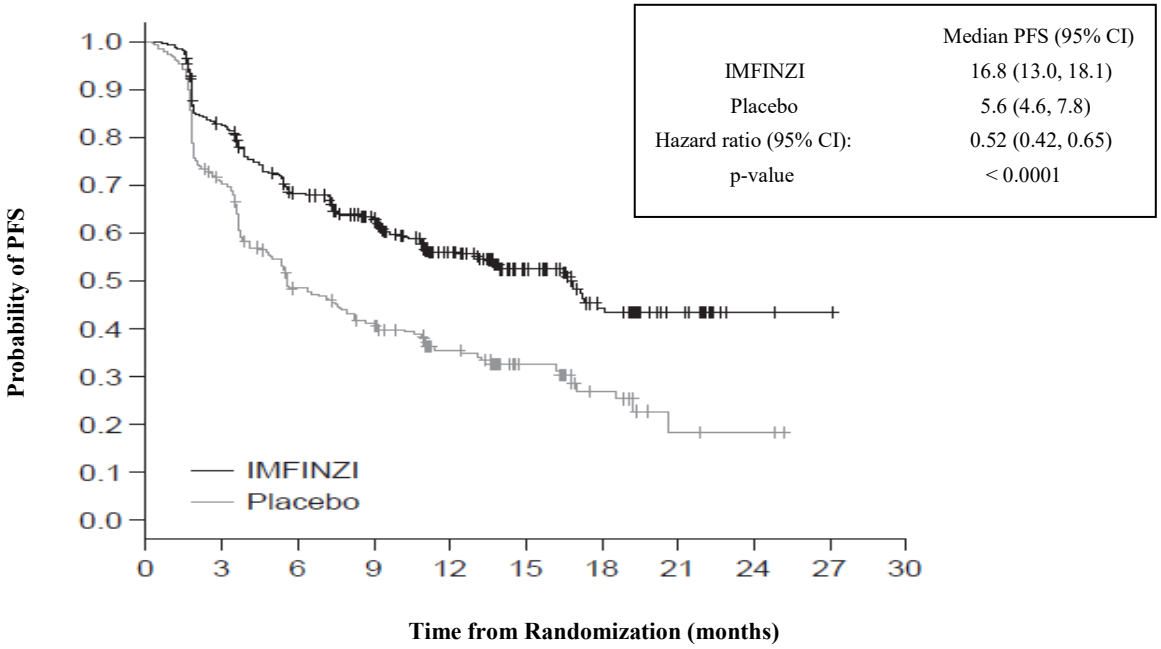
Figure 1 Kaplan-Meier curve of OS (PACIFIC Study) (Full analysis set)



Number of patients at risk

Month	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45
IMFINZI	476	464	431	415	385	364	343	319	274	210	115	57	23	2	0	0
Placebo	237	220	198	178	170	155	141	130	117	78	42	21	9	3	1	0

Figure 2 Kaplan-Meier curve of PFS (PACIFIC Study) (Full analysis set)



Number of patients at risk

Month	0	3	6	9	12	15	18	21	24	27	30
IMFINZI	476	377	301	264	159	86	44	21	4	1	0
Placebo	237	163	106	87	52	28	15	4	3	0	0

The improvements in OS and PFS, in favour of patients receiving IMFINZI compared to those receiving placebo, were consistently observed across all prespecified subgroups.

There were no clinically meaningful differences between IMFINZI-treated vs. placebo-treated patients in disease-related symptoms deterioration and health-related quality of life.

Exploratory post-hoc subgroup analysis by PD-L1 expression

Additional exploratory post-hoc subgroup analyses were conducted to evaluate efficacy by pre-chemoradiation tumour PD-L1 expression (≥25%, 1-24%, ≥1%, <1%) and for patients whose PD-L1 status could not be established (PD-L1 unknown). Due to the overall exploratory nature of this subgroup analysis performed without any pre-specified statistical adjustment, definitive conclusions cannot be drawn. PFS and OS results, by PD-L1 expression level, are summarized in Figures 3 and 4, respectively.

Several limitations are associated with exploratory, post-hoc analyses. Limitations include the absence of methods to control the type I error rate, small sample sizes and the potential for low event rates by subgroup. In addition, subgroups are not protected by randomization and may be subject to bias due to imbalances in patient demographics and disease characteristics. The results should be interpreted with caution. IMFINZI is indicated for locally advanced, unresectable Stage III NSCLC regardless of PD-L1 status based on statistically significant and clinically meaningful improvements in OS and PFS observed in the ITT population.

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

Figure 3 Forest Plot of PFS by PD-L1 expression

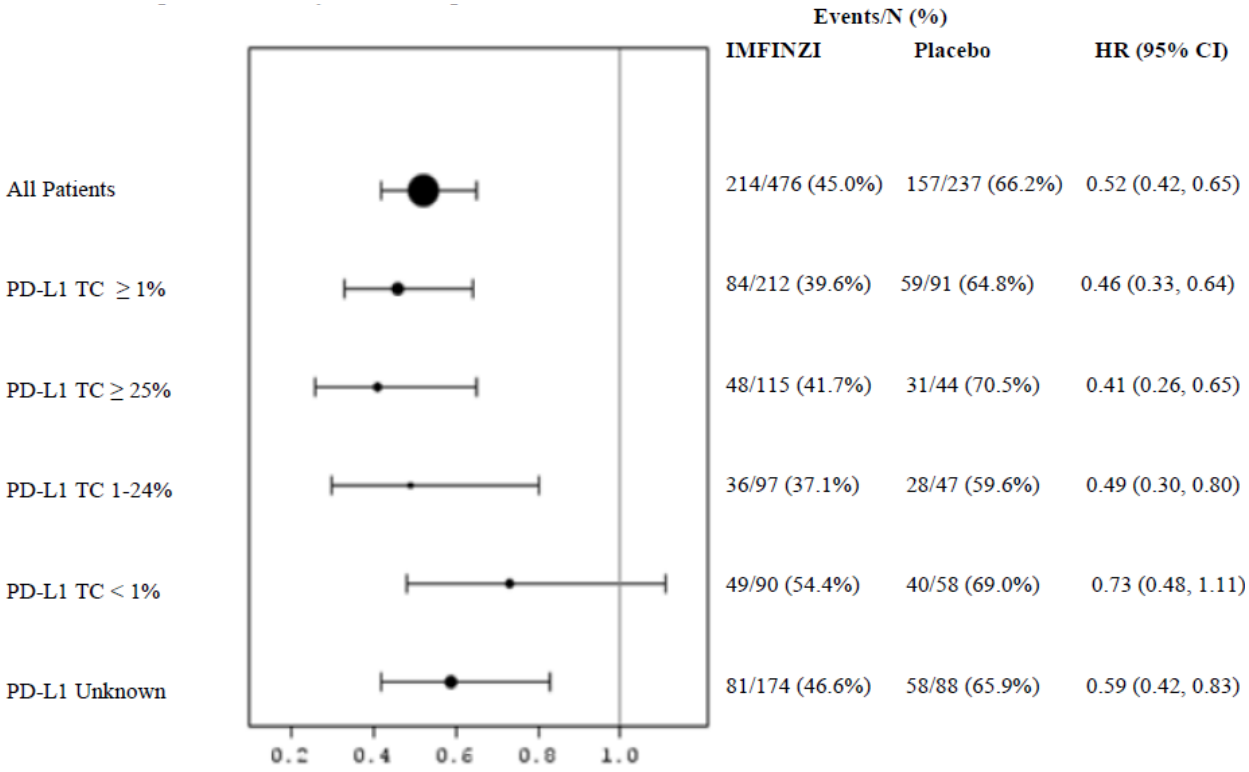
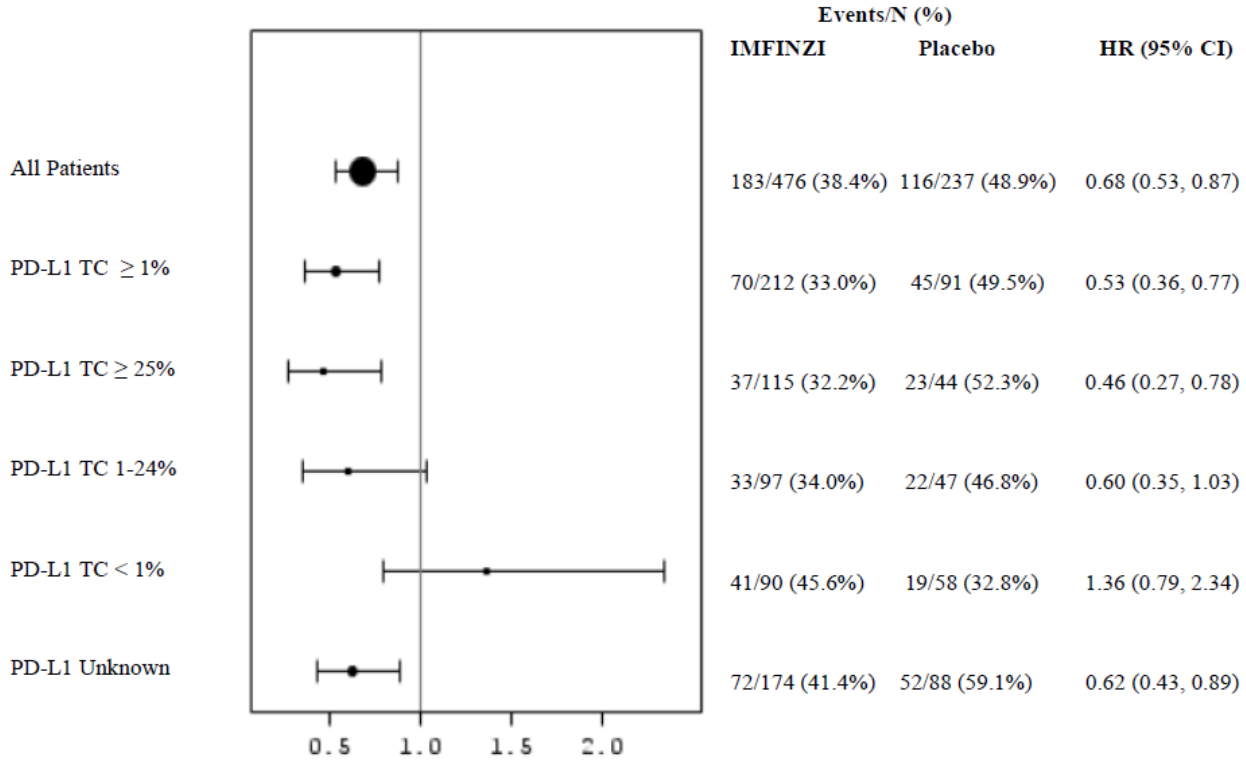


Figure 4 Forest Plot of OS by PD-L1 expression



15 NON-CLINICAL TOXICOLOGY

Carcinogenicity and Mutagenicity: The carcinogenic and genotoxic potential of durvalumab have not been evaluated.

Reproductive Toxicology: As reported in the literature, the PD-1/PD-L1 pathway plays a central role in preserving pregnancy by maintaining maternal immune tolerance to the fetus, and in mouse allogeneic pregnancy models disruption of PD-L1 signaling was shown to result in an increase in fetal loss. In reproduction studies in cynomolgus monkeys, administration of IMFINZI (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 IMFINZI (based on AUC) was associated with premature delivery, fetal loss (abortion and stillbirth) and an increase in neonatal deaths compared to concurrent control. Based on the mechanism of action, fetal exposure to durvalumab may increase the risk of developing immune-mediated disorders or altering the normal immune response, and immune-mediated disorders have been reported in the literature in PD-1 knockout mice. In animal models reported in the literature, inhibition of PD-L1/PD-1 signaling increased the severity of some infections and enhanced inflammatory responses.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

PrIMFINZI® (im-FIN-zee)
durvalumab for injection, intravenous infusion

Read this information carefully before you start treatment with **IMFINZI** and each time you get an infusion. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **IMFINZI**.

What is IMFINZI used for?
IMFINZI (durvalumab) is a medicine used to treat adults with a bladder cancer (called urothelial carcinoma) including cancer of the ureter, urethra or kidney pelvis. It is used when:

- Your cancer has spread and cannot be removed by surgery and,
- You have received chemotherapy, and it did not work or is no longer working.

IMFINZI is also used to treat adults with a type of lung cancer called non-small cell lung cancer. It is used when:

- Your cancer has grown within your lung and cannot be removed by surgery and,
- Your cancer has responded or stabilized after treatment with chemotherapy and radiation therapy.

IMFINZI contains the active substance durvalumab which belongs to the monoclonal antibody class of anticancer medicines. Refer to the NOC/c summary box below for additional detail.

For the following indication, IMFINZI has been approved **with** conditions (NOC/c). This means it has passed Health Canada's review and can be bought and sold in Canada, but the manufacturer has agreed to complete more studies to make sure the drug works the way it should. For more information, talk to your healthcare professional.

IMFINZI (durvalumab) is used to treat adults with a bladder cancer (called urothelial carcinoma) including cancer of the ureter, urethra or kidney pelvis. It is used when:

- Your cancer has spread and cannot be removed by surgery and,
- You have received chemotherapy, and it did not work or is no longer working.

For the following indication, IMFINZI has been approved **without** conditions. This means it has passed Health Canada's review and can be bought and sold in Canada.

IMFINZI is used to treat adults with a type of lung cancer called non-small cell lung cancer. It is used when:

- Your cancer has grown within your lung and cannot be removed by surgery and,
- Your cancer has responded or stabilized after treatment with chemotherapy and radiation therapy.

What is a Notice of Compliance with Conditions (NOC/c)?

A Notice of Compliance with Conditions (NOC/c) is a type of approval to sell a drug in Canada.

Health Canada only gives an NOC/c to a drug that treats, prevents, or helps identify a serious or life-threatening illness. The drug must show promising proof that it works well, is of high quality, and is reasonably safe. Also, the drug must either respond to a serious medical need in Canada, or be much safer than existing treatments.

Drug makers must agree in writing to clearly state on the label that the drug was given an NOC/c, to complete more testing to make sure the drug works the way it should, to actively monitor the drug's performance after it has been sold, and to report their findings to Health Canada.

How does IMFINZI work?
- IMFINZI works by helping your immune system fight your cancer.
- IMFINZI can help slow or stop your cancer from growing. It can also help shrink the tumour.
    - The average time to respond to IMFINZI for a bladder cancer patient is approximately 1.5 months. However, this may vary from patient to patient.

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

What are the ingredients in IMFINZI?
Medicinal ingredient: durvalumab.
Non-medicinal ingredients: L-histidine, L-histidine hydrochloride monohydrate, α,α-trehalose dihydrate, polysorbate 80, and water for injection.

IMFINZI comes in the following dosage forms:
A solution in 10 mL single-use glass vials containing either 2.4 mL or 10 mL of 50 mg/mL durvalumab. After further dilution and preparation, IMFINZI is administered as an intravenous infusion.

Do not use IMFINZI if:
- You are allergic to durvalumab or any other ingredients in IMFINZI.

To help avoid unnecessary side effects and ensure proper use, talk to your healthcare professional before you take IMFINZI. Talk about any health conditions or problems you may have, including if you:
- Have immune system problems such as Crohn's disease, ulcerative colitis, or lupus
- Have had an organ transplant
- Have lung or breathing problems
- Have liver problems
- Have problems with hormone producing glands such as your thyroid, pituitary, adrenal glands or pancreas
- Have diabetes
- Are taking medicine(s) that affect the immune system such as a steroid

If you have any questions about your medical condition, talk to your healthcare professional.

When you receive IMFINZI, you can have some serious side effects.
IMFINZI can cause your immune system to attack normal organs and tissues in your body and can affect the way they work.

Other warnings you should know about:
Pregnancy
- If you are pregnant, think you may be pregnant or are planning to have a baby, tell your doctor before taking this medicine. You should not use IMFINZI if you are pregnant.
- IMFINZI can harm your unborn baby.
- If you are a woman who could become pregnant, you should use an effective method of birth control during your treatment and for at least 3 months after the last dose of IMFINZI.

Breastfeeding
- If you are breastfeeding or plan to breastfeed, tell your doctor.
- Do not breastfeed during treatment and for at least 3 months after the last dose of IMFINZI. It is not known if IMFINZI passes into your breast milk.

Driving and using machines
If you experience side effects affecting your ability to concentrate and react, do not drive or use machines until you feel better.

Tell your healthcare professional about all the medicines you take, have recently taken or might take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

How to take IMFINZI:
- IMFINZI will be given to you in a hospital or clinic under the supervision of an experienced healthcare professional. Your healthcare professional will give you IMFINZI through an intravenous infusion into your vein for about 60 minutes.
- IMFINZI is typically given every 2 weeks.
- Your doctor will decide how many treatments you need.

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

Usual dose:
The recommended dose is 10 mg of durvalumab per kilogram of your body weight.

It is not known if IMFINZI is safe and effective in children less than 18 years of age.

Overdose:

If you think you have been given too much IMFINZI, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed Dose or Appointment to get IMFINZI:
It is very important that you keep all your appointments to get IMFINZI. If you miss an appointment, call your doctor as soon as possible to discuss next steps.

What are possible side effects from using IMFINZI?
Like all medicines, this medicine can cause side effects, although not everybody gets them. These are not all the possible side effects you may feel when taking IMFINZI. If you get any side effects, talk to your doctor, pharmacist or nurse. If you experience any side effects not listed here, contact your healthcare professional.

The following side effects have been reported in clinical trials with IMFINZI in patients with bladder cancer:

Most frequent serious side effects:
- urinary tract infection
- acute kidney injury
- back pain
- general physical health deterioration

Very common side effects (≥ 10%):
- feeling tired
- decreased appetite
- diarrhea
- joint pain
- fever
- feeling sick (nausea)
- cough
- difficulty breathing
- rash or itchiness
- constipation

The following side effects have been reported in clinical trials with IMFINZI in patients with lung cancer:

Most frequent serious side effects:
- lung infection
- lung inflammation

Very common side effects (≥ 10%):
- cough
- upper respiratory tract infection
- rash
- diarrhea
- fever

When you get IMFINZI, you can have some serious side-effects. See table below. If you have any of the following, call or see your healthcare professional right away. Your healthcare professional may give you other medicines in order to prevent more severe complications and reduce your symptoms. Your healthcare professional may withhold the next dose of IMFINZI or stop your treatment with IMFINZI.

Serious side effects and what to do about them		
Symptom / effect	Talk to your healthcare professional	
	Only if severe	In all cases
Lung inflammation (pneumonitis). Signs and symptoms of pneumonitis may include: • new or worsening cough • shortness of breath • chest pain		√
Liver problems (hepatitis). Signs and symptoms of hepatitis may include: • yellowing of your skin or the whites of your eyes • severe nausea or vomiting • pain on the right side of your stomach area (abdomen) • drowsiness • dark urine (tea coloured) • bleeding or bruising more easily than normal • feeling less hungry than usual		√
Intestinal problems (colitis) that can lead to tears or holes in your intestine. Signs and symptoms of colitis may include: • diarrhea or more bowel movements than usual • stools that are black, tarry, sticky, or have blood or mucus • severe stomach area (abdomen) pain or tenderness		√
Hormone gland problems (especially the thyroid, adrenals, pituitary and pancreas). Signs and symptoms that your hormone glands especially the thyroid gland is not working properly may include: • headaches that will not go away or unusual headaches • extreme tiredness • weight gain or weight loss • dizziness or fainting • feeling more hungry or thirsty than usual • hair loss • feeling cold • constipation • changes to your voice • urinating more often than usual • nausea or vomiting		√

Serious side effects and what to do about them		
Symptom / effect	Talk to your healthcare professional	
	Only if severe	In all cases
• stomach area (abdomen) pain • changes in mood or behaviour, such as decreased sex drive, irritability, or forgetfulness		
Kidney problems, including inflammation (nephritis) and kidney failure. Signs of kidney problems may include: • decrease in the amount of urine • blood in your urine • swelling in your ankles • loss of appetite		√
Skin or mouth problems. Signs of these problems may include: • rash • itching • skin blistering • ulcers in mouth or other mucous membranes		√
Problems in other organs. Signs of these problems may include: • changes in eyesight • severe or persistent muscle or joint pains • chest pain, shortness of breath, irregular heartbeat (myocarditis)		√
Muscle problems. Signs of these problems may include: • severe muscle weakness • tiredness • pain in one or more areas of your body		√
Severe infusion reactions. Signs and symptoms of severe infusion reactions may include: • chills or shaking • itching or rash • flushing • shortness of breath or wheezing dizziness • fever • feeling like passing out • back or neck pain • facial swelling		√

If you have a side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your healthcare professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage of IMFINZI for Healthcare Professional:
IMFINZI should not be used after the expiry date which is stated on the label and carton. IMFINZI should be stored in a refrigerator (2° to 8°C) in the original package in order to protect from light. Do not freeze or shake. Any unused medicine or waste material should be disposed of in accordance with local requirements.

Keep medication out of reach and sight of children.

If you want more information about IMFINZI:

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (http://hc-sc.gc.ca/index-eng.php); the manufacturer's website www.astrazeneca.ca, or by calling 1-800-668-6000.
- This Patient Medication Information is current at the time of printing. The most up-to-date version can be found at www.astrazeneca.ca.

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