PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

# PrIMFINZI®

durvalumab for injection

Concentrate for solution for infusion, 50 mg / mL, Intravenous

Professed

Antineoplastic agent, monoclonal antibody

IMFINZI, indicated for:

- 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 market 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: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/notice-compliance/conditions.html"

IMFINZI, indicated for:

- 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

- First-line treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC) in combination with etoposide and either carboplatin or cisplatin

has been issued market authorization without conditions.

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**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.*

## RECENT MAJOR LABEL CHANGES

| | |
|---|---|
| 1 INDICATIONS | 09/2020 |
| 4 DOSAGE AND ADMINISTRATION, 4.1 | 09/2020 |
| 4 DOSAGE AND ADMINISTRATION, 4.2 | 09/2021 |
| 7 WARNINGS AND PRECAUTIONS, 7.1.4 | 09/2020 |
| 7 WARNINGS AND PRECAUTIONS | 03/2021 |

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**Sections or subsections that are not applicable at the time of authorization are not listed.**

## PART I: HEALTH PROFESSIONAL INFORMATION

## 1 INDICATIONS

### Urothelial Carcinoma

IMFINZI (durvalumab for injection) 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 14 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.

### Extensive-Stage Small Cell Lung Cancer

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

### 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 7 WARNINGS AND PRECAUTIONS, 7.1.4 Geriatrics).

## 2 CONTRAINDICATIONS

IMFINZI (durvalumab) is contraindicated in patients who are hypersensitive to durvalumab or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing of ingredients, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

## 4 DOSAGE AND ADMINISTRATION

### 4.2 Recommended Dose and Dosage Adjustment

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

### Urothelial Carcinoma

The recommended dose of IMFINZI (durvalumab) is 10 mg/kg 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

The recommended dose of IMFINZI is 10 mg/kg every 2 weeks for one year or until disease progression or unacceptable toxicity.

### Extensive-Stage Small Cell Lung Cancer

The recommended dose of IMFINZI is 1500 mg in combination with chemotherapy (etoposide and either carboplatin or cisplatin, see 14 CLINICAL TRIALS) every 3 weeks (21 days) for 4 cycles, followed by 1500 mg every 4 weeks as monotherapy until disease progression or unacceptable toxicity.

Patients with a body weight of 30 kg or less must receive weight-based dosing, equivalent to IMFINZI 20 mg/kg in combination with chemotherapy every 3 weeks (21 days) for 4 cycles, followed by 20 mg/kg every 4 weeks as monotherapy until weight increases to greater than 30 kg.

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

Please also refer to the full prescribing information for etoposide, carboplatin or cisplatin, in their respective Product Monographs.

### Dosage Adjustment

Dose withholding or discontinuation may be required based on individual safety and tolerability. No dose reduction or escalation for IMFINZI is recommended. In general, withhold IMFINZI for severe (Grade 3) immune-mediated adverse reactions. Permanently discontinue IMFINZI for life-threatening (Grade 4) immune-mediated adverse reactions, recurrent severe (Grade 3) immune-mediated reactions that require systemic immunosuppressive treatment, or an inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks of initiating corticosteroids.

Immune-mediated adverse reactions requiring specific management are summarized in Table 1. Refer to 7 WARNINGS AND PRECAUTIONS for further monitoring and evaluation information.

**Table 1 Recommended Treatment Modifications for IMFINZI for Immune-Mediated Adverse Reactions**

| Adverse Reactions | Severity[a] | IMFINZI Treatment Modification | Corticosteroid Treatment Unless Otherwise Specified[b] |
|---|---|---|---|
| Immune-mediated pneumonitis/ interstitial lung disease | Grade 2 | Withhold dose[c] | Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper |
| | Grade 3 or 4 | Permanently discontinue | |
| Immune-mediated hepatitis | Grade 2 with ALT or AST >3-5xULN and/or total bilirubin >1.5-3xULN | Withhold dose[c] | Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper |
| | Grade 3 with AST or ALT >5-≤8xULN or total bilirubin >3-≤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 or 3 | Withhold dose[c] | Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper |
| | Grade 4 | Permanently discontinue | |
| Immune-mediated endocrinopathies: Hyperthyroidism, Thyroiditis | 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[b] |
|---|---|---|---|
| Immune-mediated endocrinopathies:<br>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 | No change | Initiate treatment with insulin as clinically indicated |
| Immune-mediated nephritis | Grade 2 with serum creatinine >1.5-3x (ULN or baseline) | Withhold dose[c] | Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper |
| | Grade 3 with serum creatinine >3x baseline or >3-6xULN; Grade 4 with serum creatinine >6xULN | Permanently discontinue | |
| Immune-mediated rash or dermatitis (including pemphigoid) | Grade 2 for >1 week or Grade 3 | Withhold dose[c] | Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper |
| | Grade 4 | Permanently discontinue | |
| 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 1 to 2 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[c,e] | Initiate 1 to 2 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[b] |
|---|---|---|---|
| Infusion-related reactions | Grade 1 or 2 | Interrupt or slow the rate of infusion | May consider pre-medications for prophylaxis of subsequent infusion reactions |
| | Grade 3 or 4 | Permanently discontinue | |
| Myasthenia gravis | Grade 3 | Withhold dose[c]<br>Permanently discontinue if not resolved to ≤Grade 1 within 30 days or if signs of respiratory or autonomic insufficiency | Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper |
| | Grade 4 or any Grade with signs of respiratory or autonomic insufficiency | Permanently discontinue | |
| Other immune-mediated adverse reactions[f] | Grade 3 | Withhold dose[c] | Initiate 1 mg/kg/day to 2 mg/kg/day prednisone or equivalent followed by a taper |
| | Grade 4 | Permanently discontinue | |

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

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

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

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

[f] Includes immune thrombocytopenia.

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

### Special Populations

A population pharmacokinetic (PK) analysis, could not detect any clinically significant 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 10 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 10 CLINICAL PHARMACOLOGY).

**Renal Impairment:** A population PK analysis could not detect any clinically significant 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 10 CLINICAL PHARMACOLOGY).

**Hepatic Impairment:** A population PK analysis could not detect any clinically significant 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 10 CLINICAL PHARMACOLOGY).

## 4.4 Administration

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.

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.

## 4.7 Instructions for Preparation and Use

- 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.
- Administer infusion solution once prepared. Discard any unused portion left in the vial (see 11 STORAGE, STABILITY AND DISPOSAL).

## 5 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.

## 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

To help ensure the traceability of biologic products, including biosimilars, health professionals should recognise the importance of recording both the brand name and the non-proprietary (active ingredient) name as well as other product-specific identifiers such as the Drug Identification Number (DIN) and the batch/lot number of the product supplied.

**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:<br>• 120 mg durvalumab / 2.4 mL (nominal concentration of 50 mg/mL)<br>• 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. |

### 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.

## 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**

**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 4 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 8 ADVERSE REACTIONS, Immune-Mediated Pneumonitis). Patients should be monitored for signs and symptoms of pneumonitis. Suspected pneumonitis should be confirmed with radiographic imaging and other infectious and disease-related etiologies excluded, and managed as recommended in 4 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 8 ADVERSE REACTIONS, 8.2 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 8 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 4 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 8 ADVERSE REACTIONS, Immune-Mediated Colitis). Patients should be monitored for signs and symptoms of colitis or diarrhea and managed as recommended in 4 DOSAGE AND ADMINISTRATION, Table 1.

Immune-Mediated Endocrinopathies

*Immune-Mediated Hypothyroidism/Hyperthyroidism/Thyroiditis:*

Immune-mediated hypothyroidism, hyperthyroidism and thyroiditis occurred in patients receiving IMFINZI in clinical studies (see 8 ADVERSE REACTIONS, Immune-Mediated Endocrinopathies, Immune-Mediated Hypothyroidism, Immune-Mediated Hyperthyroidism, Immune-Mediated Thyroiditis). 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 4 DOSAGE AND ADMINISTRATION, Table 1.

Symptomatic hyperthyroidism should be managed as per institutional guidelines. See 4 DOSAGE AND ADMINISTRATION, Table 1.

*Immune-Mediated Adrenal Insufficiency:*

Immune-mediated adrenal insufficiency occurred in patients receiving IMFINZI in clinical studies (see 8 ADVERSE REACTIONS, Immune-Mediated Endocrinopathies, Immune-Mediated 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 4 DOSAGE AND ADMINISTRATION, Table 1.

*Immune-Mediated Hypophysitis/Hypopituitarism:*

Immune-mediated hypophysitis or hypopituitarism have been observed in clinical studies of products that target PD-1/PD-L1, including IMFINZI (see 8 ADVERSE REACTIONS, Immune-Mediated Endocrinopathies, Immune-Mediated Hypophysitis). Patients should be monitored for clinical signs and symptoms of hypophysitis. For symptomatic hypophysitis or hypopituitarism, patients should be managed as recommended in 4 DOSAGE AND ADMINISTRATION, Table 1.

*Immune-Mediated Type I Diabetes Mellitus:*

Immune-mediated Type 1 diabetes mellitus (T1DM), which can present with diabetic ketoacidosis, has been observed in clinical studies of products that target PD-1/PD-L1, including IMFINZI (see 8 ADVERSE REACTIONS, Immune-Mediated Endocrinopathies, Immune-Mediated 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 4 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 8 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 4 DOSAGE AND ADMINISTRATION, Table 1.

Immune-Mediated Rash

Immune-mediated rash or dermatitis (including pemphigoid), defined as requiring use of systemic corticosteroids and with no clear alternate etiology, occurred in patients receiving IMFINZI in clinical studies (see 8 ADVERSE REACTIONS, Immune-Mediated Rash). Patients should be monitored for signs and symptoms of rash or dermatitis and managed as recommended in 4 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, rare cases of potentially immune-related thrombocytopenia (of which one was fatal), myocarditis, pancreatitis, aseptic meningitis, uveitis, myositis and polymyositis (fatal) were observed. In clinical studies outside of the pooled dataset, rare cases of potentially immune-mediated myasthenia gravis were observed.

The following clinically significant rare immune-mediated adverse reactions have been reported in patients who received IMFINZI or other PD-L1 blocking antibodies: Stevens Johnson Syndrome (SJS)/toxic epidermal necrolysis (TEN), rhabdomyolysis, encephalitis, demyelinating polyneuropathy, autoimmune hemolytic anemia and Guillain-Barré syndrome. Patients should be monitored for signs and symptoms of immune-mediated adverse reactions and managed as recommended in 4 DOSAGE AND ADMINISTRATION, Table 1.

**Infections**

Severe infections, including sepsis, necrotizing fasciitis, and osteomyelitis, occurred in patients receiving IMFINZI in clinical studies (see 8 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 4 DOSAGE AND ADMINISTRATION, Table 1.

**Infusion Related Reactions**

Severe infusion related reactions have been reported in patients receiving IMFINZI in clinical studies (see 8 ADVERSE REACTIONS). Patients should be monitored for signs and symptoms of infusion related reactions as recommended in 4 DOSAGE AND ADMINISTRATION, Table 1. In patients with prior infusion related reactions to IMFINZI, pre-medication prior to administration may be considered.

**Reproductive Health: Female and Male Potential**

- **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 16 NON-CLINICAL TOXICOLOGY).

### 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 16 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 16 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).

Of the 265 patients with ES-SCLC treated with IMFINZI in combination with chemotherapy, 101 (38%) patients were 65 years or older. There were no overall clinically meaningful differences in safety or efficacy between patients ≥ 65 years of age and younger patients.

## 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 14 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).

**Extensive-Stage Small Cell Lung Cancer**

The safety of IMFINZI in combination with etoposide and either carboplatin or cisplatin in patients with treatment-naive extensive-stage small cell lung cancer (ES-SCLC) was evaluated in CASPIAN, a randomized, open-label, multicenter active-controlled study (see 14 CLINICAL TRIALS). Patients received IMFINZI 1500 mg in combination with chemotherapy every 3 weeks for 4 cycles followed by IMFINZI 1500 mg every 4 weeks until disease progression or unacceptable toxicity, or chemotherapy alone every 3 weeks for up to 6 cycles.

In the IMFINZI in combination with chemotherapy group, 87% of patients received 4 cycles of chemotherapy. In the chemotherapy alone group, 85% of patients received 4 cycles of chemotherapy, and 57% of patients received 6 cycles of chemotherapy; additionally, 8% of patients received prophylactic cranial irradiation (PCI).

The most common adverse events (any Grade; occurring in ≥10% of patients) reported for the IMFINZI + chemotherapy arm were neutropenia, anemia, nausea, fatigue, alopecia, thrombocytopenia, leukopenia, decreased appetite, constipation, cough/productive cough, vomiting, and dyspnoea.

Grade 3 or 4 adverse events were reported in 61.5% of patients in the IMFINZI + chemotherapy arm versus 62.4% of patients in the chemotherapy arm. Adverse events leading to dose delay or interruption of study treatment were reported in 41.9% of patients treated with IMFINZI in combination with chemotherapy versus 37.6% of patients treated with chemotherapy alone. IMFINZI dose was delayed due to adverse events in 41.1% of patients. Adverse events leading to discontinuation of study treatment were reported in 9.4% of patients in both groups. IMFINZI was discontinued due to adverse events in 6.8% of the patients receiving IMFINZI in combination with chemotherapy. These include pneumonitis, hepatotoxicity, neurotoxicity, sepsis, diabetic ketoacidosis and pancytopenia (1 patient each).

Serious adverse events occurred in 30.9% of patients treated with IMFINZI in combination with chemotherapy versus 36.1% of patients treated with chemotherapy alone. The most frequent serious adverse events reported in at least 1% of patients in the IMFINZI + chemotherapy arm were febrile neutropenia (4.5%), pneumonia (2.3%), anemia (1.9%), pancytopenia (1.5%), chronic obstructive pulmonary disease (1.1%) and pneumonitis (1.1%). Serious adverse events with an outcome of death occurred in 4.9% of patients in the IMFINZI + chemotherapy arm and 5.6% in the chemotherapy arm. Fatal adverse events in the IMFINZI + chemotherapy arm include sepsis, septic shock, pancytopenia, dehydration, cardiac arrest, acute respiratory failure, aspiration, hypoxia, pulmonary artery thrombosis, pulmonary embolism, and hepatotoxicity (1 patient each), and sudden death (2 patients).

Immune-mediated adverse reactions were reported in 19.6% of patients treated with IMFINZI in combination with chemotherapy (Grade 3 or 4 events 4.5%). Immune-mediated adverse reactions requiring systemic corticosteroids were reported in 9.4% of patients, and endocrine therapy in 14.7% of patients. The most commonly reported immune-mediated adverse reactions were hypothyroidism (9.1%) and hyperthyroidism (5.3%). At the time of analysis, immune-mediated adverse events were unresolved in 10.9% of patients.

### 8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates

observed in the clinical trials; therefore, 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 may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

**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] | | | |
| **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** | | | | |

| | IMFINZI (N=191) | | | |
|---|---|---|---|---|
| **System Organ Class Preferred Term[a]** | **Any Grade N (%)** | **Grade 1 N (%)** | **Grade 2 N (%)** | **Grade 3 or 4 N (%)** |
| 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) |

| | IMFINZI (N =191) | | | |
|---|---|---|---|---|
| **System Organ Class Preferred Term[a]** | **Any Grade N (%)** | **Grade 1 N (%)** | **Grade 2 N (%)** | **Grade 3 or 4 N (%)** |
| **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 |

| | 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 (%)** |
| **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.

### Extensive-Stage Small Cell Lung Cancer

Table 6 lists the incidence of adverse reactions in at least 1% of patients in the CASPIAN study.

Adverse reactions known to occur with IMFINZI or chemotherapies given alone may occur during treatment with these medicinal products in combination, even if these reactions were not reported in clinical trials with combination therapy.

**Table 6 Adverse Reactions (>1%) in ES-SCLC Patients Reported in the CASPIAN Study Treated with IMFINZI with Etoposide and Either Carboplatin or Cisplatin**

| | IMFINZI with etoposide and either carboplatin or cisplatin (n=265) | | Etoposide and either carboplatin or cisplatin (n=266) | |
|---|---|---|---|---|
| **MedDRA System Organ Class Preferred Term[a]** | **All Grades n(%)** | **Grade 3 or 4 n(%)** | **All Grades n(%)** | **Grade 3 or 4 n(%)** |
| **Blood and Lymphatic System Disorder** | | | | |
| Neutropenia[b] | 129 (48.7) | 77 (29.1) | 150 (56.4) | 104 (39.1) |
| Anemia | 102 (38.5) | 24 (9.1) | 125 (47.0) | 48 (18.0) |
| Thrombocytopenia[c] | 56 (21.1) | 18 (6.8) | 66 (24.8) | 31 (11.7) |
| Leukopenia[d] | 53 (20.0) | 21 (7.9) | 49 (18.4) | 20 (7.5) |
| Febrile neutropenia | 17 (6.4) | 14 (5.3) | 17 (6.4) | 17 (6.4) |
| Pancytopenia[e] | 8 (3.0) | 4 (1.5) | 3 (1.1) | 2 (0.8) |
| **Endocrine Disorders** | | | | |
| Hyperthyroidism | 26 (9.8) | 0 | 1 (0.4) | 0 |
| Hypothyroidism | 25 (9.4) | 0 | 4 (1.5) | 0 |
| Thyroiditis[f] | 4 (1.5) | 0 | - | - |
| Adrenal insufficiency | 3 (1.1) | 0 | - | - |
| **Gastrointestinal Disorders** | | | | |
| Nausea | 89 (33.6) | 1 (0.4) | 89 (33.5) | 5 (1.9) |
| Constipation | 44 (16.6) | 2 (0.8) | 51 (19.2) | 0 |
| Vomiting | 39 (14.7) | 0 | 44 (16.5) | 3 (1.1) |
| Diarrhea | 26 (9.8) | 3 (1.1) | 30 (11.3) | 3 (1.1) |
| Abdominal pain[g] | 23 (8.7) | 1 (0.4) | 12 (4.5) | 0 |
| Stomatitis[h] | 16 (6.0) | 1 (0.4) | 12 (4.5) | 0 |
| **General disorders and administration site conditions** | | | | |
| Fatigue[i] | 85 (32.1) | 9 (3.4) | 84 (31.6) | 6 (2.3) |
| Pyrexia | 22 (8.3) | 0 | 17 (6.4) | 1 (0.4) |
| Edema peripheral[j] | 17 (6.4) | 2 (0.8) | 11 (4.1) | 0 |

| | IMFINZI with etoposide and either carboplatin or cisplatin (n=265) | | Etoposide and either carboplatin or cisplatin (n=266) | |
|---|---|---|---|---|
| **MedDRA System Organ Class Preferred Term[a]** | **All Grades n(%)** | **Grade 3 or 4 n(%)** | **All Grades n(%)** | **Grade 3 or 4 n(%)** |
| **Hepatobiliary disorders** | | | | |
| Aspartate aminotransferase increased or Alanine aminotransferase increased[k] | 23 (8.7) | 5 (1.9) | 15 (5.6) | 4 (1.5) |
| Hepatitis[e, l] | 5 (1.9) | 3 (1.1) | 1 (0.4) | 0 |
| **Infections and infestations** | | | | |
| Upper respiratory tract infections[m] | 24 (9.1) | 1 (0.4) | 16 (6.0) | 0 |
| Pneumonia[n] | 15 (5.7) | 5 (1.9) | 22 (8.3) | 11 (4.1) |
| Dental and oral soft tissue infections[o] | 3 (1.1) | 0 | 3 (1.1) | 0 |
| **Injury, poisoning and procedural complications** | | | | |
| Infusion-related reaction[p] | 5 (1.9) | 1 (0.4) | 3 (1.1) | 0 |
| **Metabolism and nutrition disorders** | | | | |
| Decreased appetite | 48 (18.1) | 2 (0.8) | 46 (17.3) | 2 (0.8) |
| **Musculoskeletal and connective tissue disorders** | | | | |
| Myalgia | 9 (3.4) | 0 | 6 (2.3) | 0 |
| **Renal and urinary disorders** | | | | |
| Blood creatinine increased | 5 (1.9) | 0 | 6 (2.3) | 0 |
| Dysuria | 5 (1.9) | 0 | 6 (2.3) | 0 |
| **Respiratory thoracic and mediastinal disorders** | | | | |
| Cough/ Productive Cough[q] | 39 (14.7) | 2 (0.8) | 23 (8.6) | 0 |
| Pneumonitis | 7 (2.6) | 2 (0.8) | 5 (1.9) | 1 (0.4) |
| **Skin and subcutaneous tissue disorders** | | | | |
| Alopecia | 83 (31.3) | 3 (1.1) | 91 (34.2) | 2 (0.8) |
| Rash[r] | 25 (9.4) | 0 | 15 (5.6) | 0 |
| Pruritus | 20 (7.5) | 0 | 10 (3.8) | 0 |
| Dermatitis | 4 (1.5) | 0 | - | - |

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

[b] Includes neutropenia and neutrophil count decreased.

[c] Includes thrombocytopenia and platelet count decreased.

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

[e] Includes a fatal outcome

[f] Includes autoimmune thyroiditis and thyroiditis.

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

[h] Includes stomatitis and mucosal inflammation.

[l] Includes fatigue and asthenia.

[j] Includes oedema peripheral and peripheral swelling.

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

[l] Includes hepatitis and hepatocellular injury.

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

[n] Includes lung infection, pneumonia and pneumonia bacterial.

[o] Includes periodontitis, pulpitis dental, tooth abscess and tooth infection.
[p] Includes infusion-related reaction and urticaria with onset on the day of dosing or 1 day after dosing.
[q] Includes cough and productive cough.
[r] Includes rash erythematous, rash macular, rash maculopapular erythema and rash.

### 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 a pooled dataset across multiple tumour types (n=3006) from 9 studies including Study 1108 (UC cohort [n=191]) and PACIFIC (n=475) (see 14 CLINICAL TRIALS). The management guidelines for these adverse reactions are described in 7 WARNINGS AND PRECAUTIONS and 4 DOSAGE AND ADMINISTRATION.

### Immune-Mediated Pneumonitis

In patients receiving IMFINZI monotherapy, immune-mediated pneumonitis occurred in 92 (3.1%) patients, including Grade 3 in 25 (0.8%) patients, Grade 4 in 2 (< 0.1%) patients, and Grade 5 in 6 (0.2%) patients. The median time to onset was 55 days (range: 2-785 days). Sixty-nine of the 92 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day), 2 patients also received infliximab and 1 patient also received cyclosporine. IMFINZI was discontinued in 38 patients. Resolution occurred in 53 patients. Immune-mediated pneumonitis occurred more frequently in patients in the PACIFIC Study who had completed treatment with concurrent chemoradiation within 1 to 42 days prior to initiation of the study (9.9%), compared to the other patients in the combined safety database (1.8%).

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 47 (9.9%) patients in the IMFINZI-treated group and 14 (6.0%) patients in the placebo group, including Grade 3 in 9 (1.9%) patients on IMFINZI vs. 6 (2.6%) patients on placebo and Grade 5 in 4 (0.8%) patients on IMFINZI vs. 3 (1.3%) patients on placebo. The median time to onset in the IMFINZI-treated group was 46 days (range: 2-342 days) vs. 57 days (range: 26-253 days) in the placebo group. In the IMFINZI-treated group, 30 patients who received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day), and 2 patients also received infliximab. In the placebo group, 12 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day) and 1 patient also received cyclophosphamide and tacrolimus. Resolution occurred for 29 patients in the IMFINZI treated group vs 6 in placebo.

### Immune-Mediated Hepatitis

In patients receiving IMFINZI monotherapy, immune-mediated hepatitis occurred in 67 (2.2%) patients, including Grade 3 in 35 (1.2%) patients, Grade 4 in 6 (0.2%) patients and Grade 5 in 4 (0.1%) patients. The median time to onset was 36 days (range: 3-333 days). Forty-four of the 67 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). Three patients also received mycophenolate treatment. IMFINZI was discontinued in 9 patients. Resolution occurred in 29 patients.

### Immune-Mediated Colitis

In patients receiving IMFINZI monotherapy, immune-mediated colitis or diarrhea occurred in 58 (1.9%) patients, including Grade 3 in 9 (0.3%) patients and Grade 4 in 2 (<0.1%) patients. The median time to onset was 70 days (range: 1-394 days). Thirty-eight of the 58 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). One

patient also received infliximab treatment and one patient also received mycophenolate treatment. IMFINZI was discontinued in 9 patients. Resolution occurred in 43 patients.

**Immune-Mediated Endocrinopathies**

*Immune-Mediated Hypothyroidism*

In patients receiving IMFINZI monotherapy, immune-mediated hypothyroidism occurred in 245 (8.2%) patients, including Grade 3 in 4 (0.1%) patients. The median time to onset was 85 days (range: 1-562 days). Of the 245 patients, 240 patients received hormone replacement therapy, 6 patients received high-dose corticosteroids (at least 40 mg prednisone or equivalent per day) for immune-mediated hypothyroidism followed by hormone replacement. No patients discontinued IMFINZI due to immune-mediated hypothyroidism. Immune-mediated hypothyroidism was preceded by immune-mediated hyperthyroidism in 20 patients or immune-mediated thyroiditis in 3 patients.

*Immune-Mediated Hyperthyroidism*

In patients receiving IMFINZI monotherapy, immune-mediated hyperthyroidism occurred in 50 (1.7%) patients, there were no Grade 3 or 4 cases. The median time to onset was 43 days (range: 14-253 days). Forty-six of the 50 patients received medical therapy (thiamazole, carbimazole, propylthiouracil, perchlorate, calcium channel blocker, or beta-blocker), 11 patients received systemic corticosteroids and 4 of the 11 patients received high-dose systemic corticosteroid treatment (at least 40 mg prednisone or equivalent per day). One patient discontinued IMFINZI due to immune-mediated hyperthyroidism. Resolution occurred in 39 patients.

*Immune-Mediated Thyroiditis*

In patients receiving IMFINZI monotherapy, immune-mediated thyroiditis occurred in 12 (0.4%) patients, including Grade 3 in 2 (<0.1%) patients. The median time to onset was 49 days (range: 14-106 days). Of the 12 patients, 10 patients received hormone replacement therapy, 1 patient received high-dose corticosteroids (at least 40 mg prednisone or equivalent per day). One patient discontinued IMFINZI due to immune-mediated thyroiditis.

*Immune-Mediated Adrenal Insufficiency*

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

*Immune-Mediated Hypophysitis/Hypopituitarism*

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

*Immune-Mediated Type I Diabetes Mellitus*

In patients receiving IMFINZI monotherapy, Grade 3 immune-mediated type 1 diabetes mellitus occurred in 1 (<0.1%) patient. This patient required long-term insulin therapy and IMFINZI was permanently discontinued due to immune-mediated type 1 diabetes mellitus.

**Immune-Mediated Nephritis**

In patients receiving IMFINZI monotherapy, immune-mediated nephritis occurred in 14 (0.5%) patients, including Grade 3 in 2 (<0.1%) patients. The median time to onset was 71 days (range: 4-393 days). Nine patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day) and 1 patient also received mycophenolate. IMFINZI was discontinued in 5 patients. Resolution occurred in 8 patients.

**Immune-Mediated Rash**

In patients receiving IMFINZI monotherapy, immune-mediated rash or dermatitis (including pemphigoid) occurred in 50 (1.7%) patients, including Grade 3 in 12 (0.4%) patients. The median time to onset was 43 days (range: 4-333 days). Twenty-four of the 50 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). IMFINZI was discontinued in 3 patients. Resolution occurred in 31 patients.

**Infusion Related Reactions**

In patients receiving IMFINZI monotherapy, infusion related reactions occurred in 49 (1.6%) patients, including Grade 3 in 5 (0.2%) patients. There were no Grade 4 or 5 events.

### 8.3 Less Common Clinical Trial Adverse Reactions

**Less Common Clinical Trial Adverse Reactions (<5%) in the PACIFIC Study**

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 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%)

**Less Common Clinical Trial Adverse Reactions (<1%) in the CASPIAN Study**

The following additional adverse reactions were reported in less than 1% of patients treated with IMFINZI in combination with chemotherapy in the CASPIAN study.

**Endocrine Disorders:** type 1 diabetes mellitus (0.8%)
**Gastrointestinal Disorders:** colitis (includes colitis, enteritis and proctitis) (0.8%)
**Infections and Infestations:** oral candidiasis (0.8%), influenza (0.4%)
**Respiratory Thoracic and Mediastinal Disorders:** dysphonia (0.8%), interstitial lung disease (0.8%)
**Skin and Subcutaneous Tissue Disorders:** night sweats (0.4%)

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

**Clinical Trial Findings**

**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 7).

**Table 7 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) |
| 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 8 lists the incidence of laboratory abnormalities reported in patients with locally advanced unresectable, Stage III NSCLC in the PACIFIC study.

**Table 8 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 | 469 | 169 (36.0) | 13 (2.8) | 228 | 48 (21.1) | 1 (0.4) |

| Laboratory Abnormalities | IMFINZI | | | Placebo | | |
|---|---|---|---|---|---|---|
| | N | Any Grade n (%) | Grade 3 or 4 n (%) | N | Any Grade n (%) | Grade 3 or 4 n (%) |
| increased | | | | | | |
| 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

**Extensive-Stage Small Cell Lung Cancer**

Table 9 lists the incidence of laboratory abnormalities reported in patients with IMFINZI in the CASPIAN study.

**Table 9 Laboratory Abnormalities Worsening from Baseline in IMFINZI-Treated Patients in the CASPIAN Study**

| Laboratory Abnormalities | IMFINZI with Etoposide and either Carboplatin or Cisplatin (N=265) | | Etoposide and either Carboplatin or Cisplatin (N=266) | |
|---|---|---|---|---|
| | Any Grade (%) | Grade 3 or 4 (%) | Any Grade (%) | Grade 3 or 4 (%) |
| Blood creatinine increased | 84.8 | 3.4 | 83.5 | 1.1 |
| Hypocalcaemia | 52.3 | 3.5 | 54.9 | 2.4 |
| Hypomagnesaemia | 50.0 | 11.1 | 43.8 | 6.3 |
| Hyponatraemia | 46.0 | 11.4 | 39.5 | 13.0 |
| Hyperkalaemia | 43.0 | 1.5 | 42.9 | 3.1 |
| Hyperglycaemia | 41.3 | 5.4 | 38.4 | 5.4 |
| Alanine aminotransferase increased | 37.3 | 4.9 | 36.2 | 2.7 |
| Increased Alkaline phosphatase | 37.3 | 4.9 | 34.9 | 3.5 |
| Aspartate aminotransferase increased | 34.2 | 4.6 | 29.2 | 1.2 |
| TSH decreased <LLN and ≥LLN at baseline | 31.3 | 0 | 16.5 | 0 |
| Amylase increased | 26.2 | 4.8 | 20.2 | 5.0 |
| Lipase increased | 20.0 | 8.1 | 13.7 | 3.1 |
| TSH elevated >ULN and ≤ULN at baseline | 17.7 | 0 | 7.5 | 0 |

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. Immunogenicity of IMFINZI as monotherapy is based on pooled data in 2280 patients who were treated with

IMFINZI 10 mg/kg every 2 weeks or 20 mg/kg every 4 weeks as a single-agent and evaluable for the presence of anti-drug antibodies (ADA). Sixty-nine patients (3.0%) tested positive for treatment emergent ADA. Neutralizing antibodies against durvalumab were detected in 0.5% (12/2280) patients. The presence of ADAs did not appear to have a clinically relevant effect on pharmacokinetics, pharmacodynamics or safety.

In the CASPIAN study, of the 201 patients who were treated with IMFINZI 1500 mg every 3 weeks in combination with chemotherapy and evaluable for the presence of ADAs, no patients tested positive for treatment-emergent ADAs.

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

### 9.2 Drug Interactions Overview

Durvalumab is an immunoglobulin and the primary elimination pathways of durvalumab is protein catabolism, therefore no formal pharmacokinetic drug-drug interaction studies have been conducted with durvalumab since no metabolic drug-drug interactions are expected.

### 9.4 Drug-Drug Interactions

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

### 9.5 Drug-Food Interactions

Interactions with food have not been established.

### 9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

### 9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

## 10 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 releases the inhibition of immune responses and enhances antitumour immune responses.

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

### 10.3 Pharmacokinetics

The PK of durvalumab was assessed for both IMFINZI as a single agent and in combination with chemotherapy.

The pharmacokinetics of IMFINZI was studied as a single agent in 2903 patients with solid tumours with doses ranging from 0.1 to 20 mg/kg administered once every two, three or four weeks. PK exposure increased more than dose-proportionally (non-linear PK) at doses <3 mg/kg and dose proportionally (linear PK) at doses ≥3 mg/kg. Steady state was achieved at approximately 16 weeks.

Based on population PK analysis that included 1878 patients in the dose range of ≥ 10 mg/kg Q2W, the geometric mean, steady state volume of distribution (Vss) was 5.64 L. Durvalumab clearance (CL) decreased over time resulting in a geometric mean steady state clearance (CLss) of 8.16 mL/h at Day 365; the decrease in CLss was not considered clinically relevant. The terminal half-life (t1/2), based on baseline CL, was approximately 18 days.

The PK of durvalumab as a single agent and in combination with chemotherapy is similar.

**Special Populations and Conditions**

The covariate of age (19–96 years), body weight (31-149 kg), gender, positive anti-drug antibody (ADA) status, albumin levels, LDH levels, creatinine levels, soluble PD-L1, tumour type, race, mild renal impairment (creatinine clearance (CrCL) 60 to 89 mL/min), moderate renal impairment (creatinine clearance (CrCL) 30 to 59 mL/min), mild hepatic impairment (bilirubin ≤ ULN and AST >ULN or bilirubin >1.0 to 1.5 × ULN and any AST), 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. 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

## 12 SPECIAL HANDLING INSTRUCTIONS

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

## PART II: SCIENTIFIC INFORMATION

## 13 PHARMACEUTICAL INFORMATION

### Drug Substance

Proper name: Durvalumab

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

Structural formula: 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.

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.

Pharmaceutical standard: Professed

## 14 CLINICAL TRIALS

### 14.1 Clinical Trials by Indication

#### 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 10 Summary of Patient Demographics in the UC Cohort of Study 1108 (N=182)**

| Study # | Study 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%)<br>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 11 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 11 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
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 12 Summary of Patient Demographics in Locally Advanced, Unresectable, Stage III NSCLC (PACIFIC)**

| Study # | Study 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 13).

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 13 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 13 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) |

**Table 13 Patient Demographics and Baseline Disease Characteristics, PACIFIC (Full analysis set)**

| | PACIFIC | |
|---|---|---|
| **Demographic/Disease Characteristic** | **IMFINZI (N=476)** | **Placebo (N=237)** |
| ≥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 14 and Figure 1 and Figure 2.

**Table 14 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)<br>(95% CI) | NR<br>(34.7, NR) | 28.7<br>(22.9, NR) |
| HR (95% CI) | 0.68 (0.53, 0.87) | |
| 2-sided p-value[d] | 0.00251 | |
| OS at 24 months<br>(95% CI) | 66.3<br>(61.7, 70.4) | 55.6<br>(48.9, 61.8) |
| p-value[f] | 0.005 | |
| PFS[b] | | |
| Number of events (%) | 214 (45.0) | 157 (66.2) |

| | | |
|---|---|---|
| Median PFS (months)<br>(95% CI) | 16.8<br>(13.0, 18.1) | 5.6<br>(4.6, 7.8) |
| HR (95% CI) | 0.52 (0.42, 0.65) | |
| p-value[e] | p<0.0001 | |
| ORR[c] n (%)<br>(95% CI) | 133 (30.0)<br>(25.8, 34.5) | 38 (17.8)<br>(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)<br>(95% CI) | NR<br>(27.4, NR) | 18.4<br>(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.

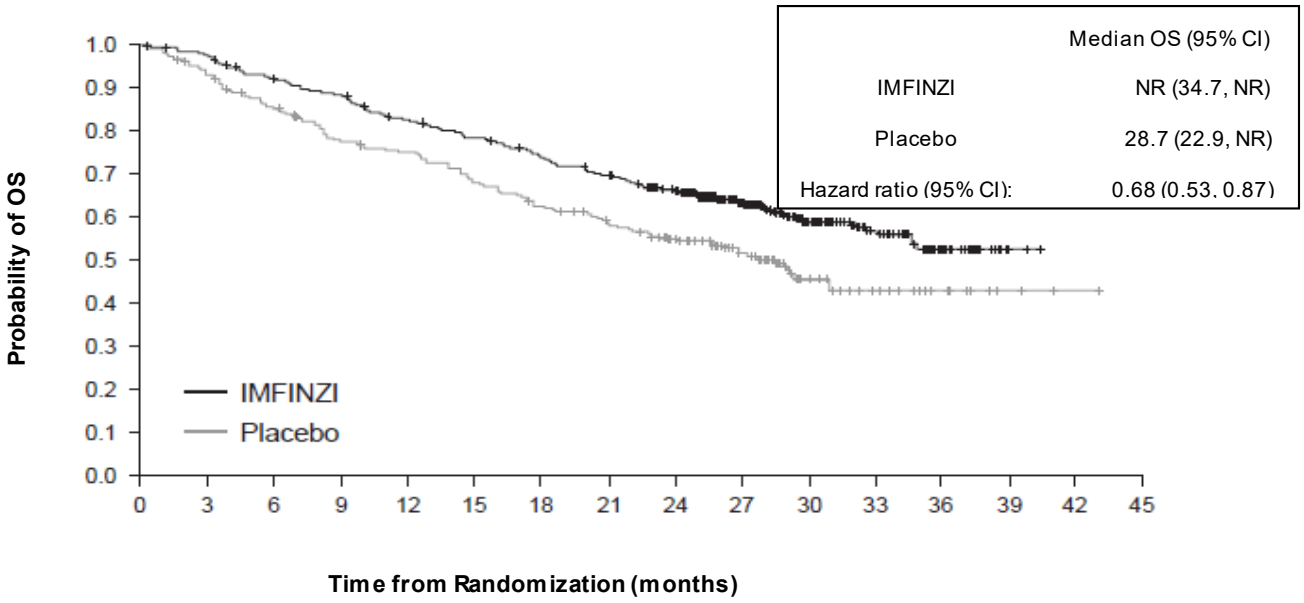
[d] Compared with allocated α of 0.00274 (Lan DeMets spending function approximating O'Brien Fleming boundary) for interim analysis

[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

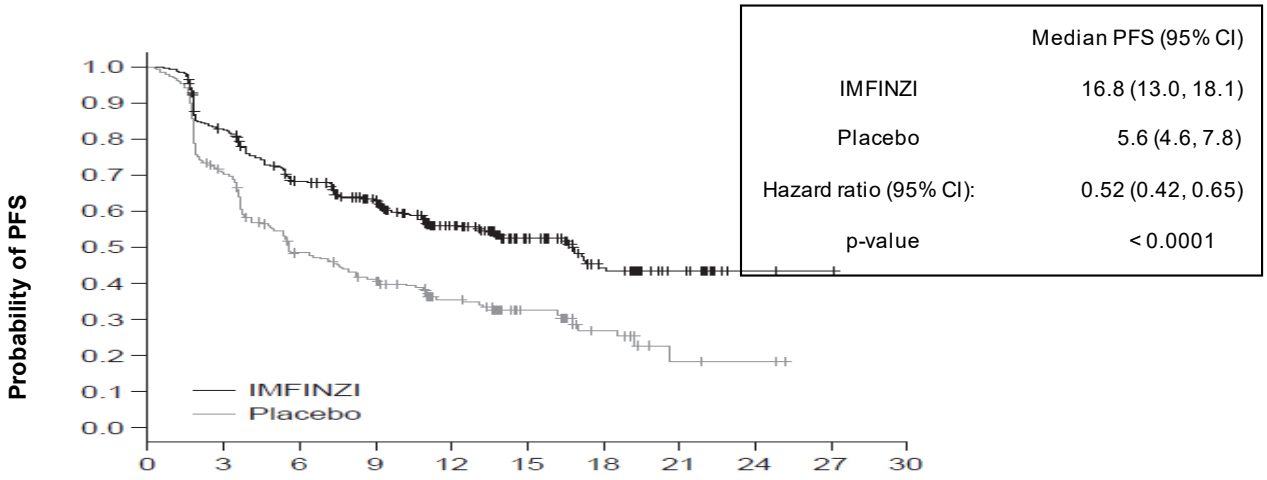
**Figure 1 Kaplan-Meier curve of OS (PACIFIC ) (Full analysis set)**




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 ) (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**

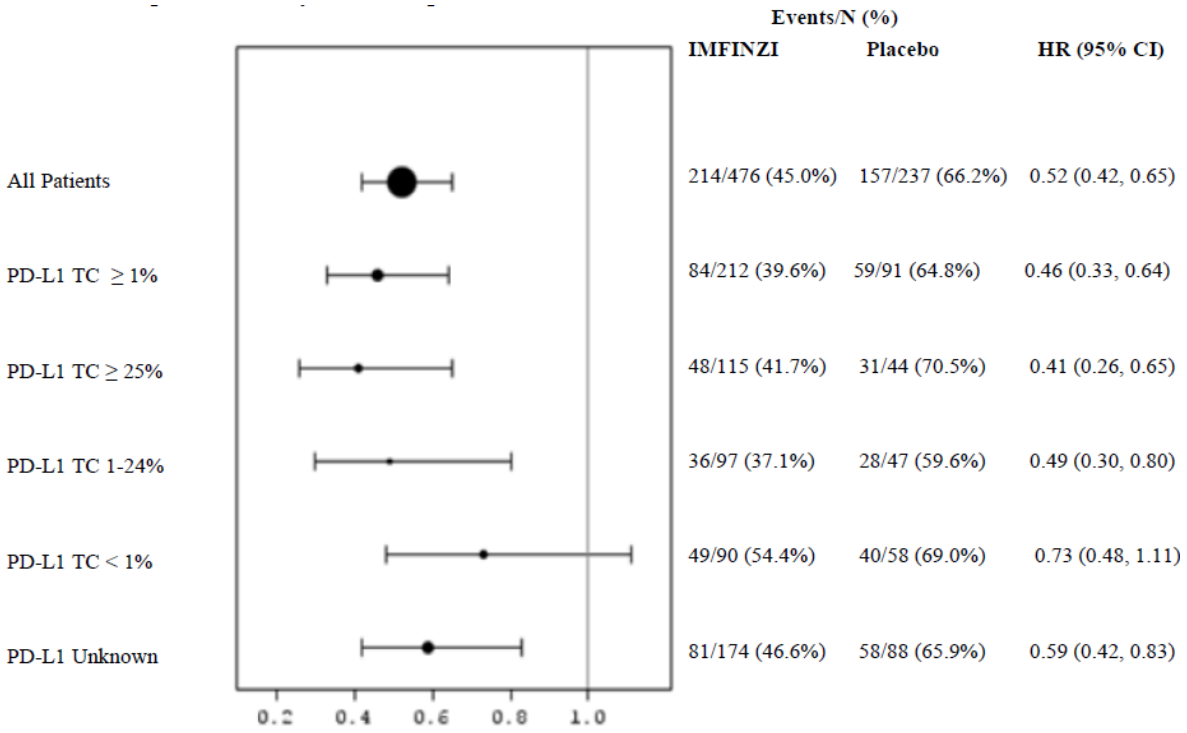
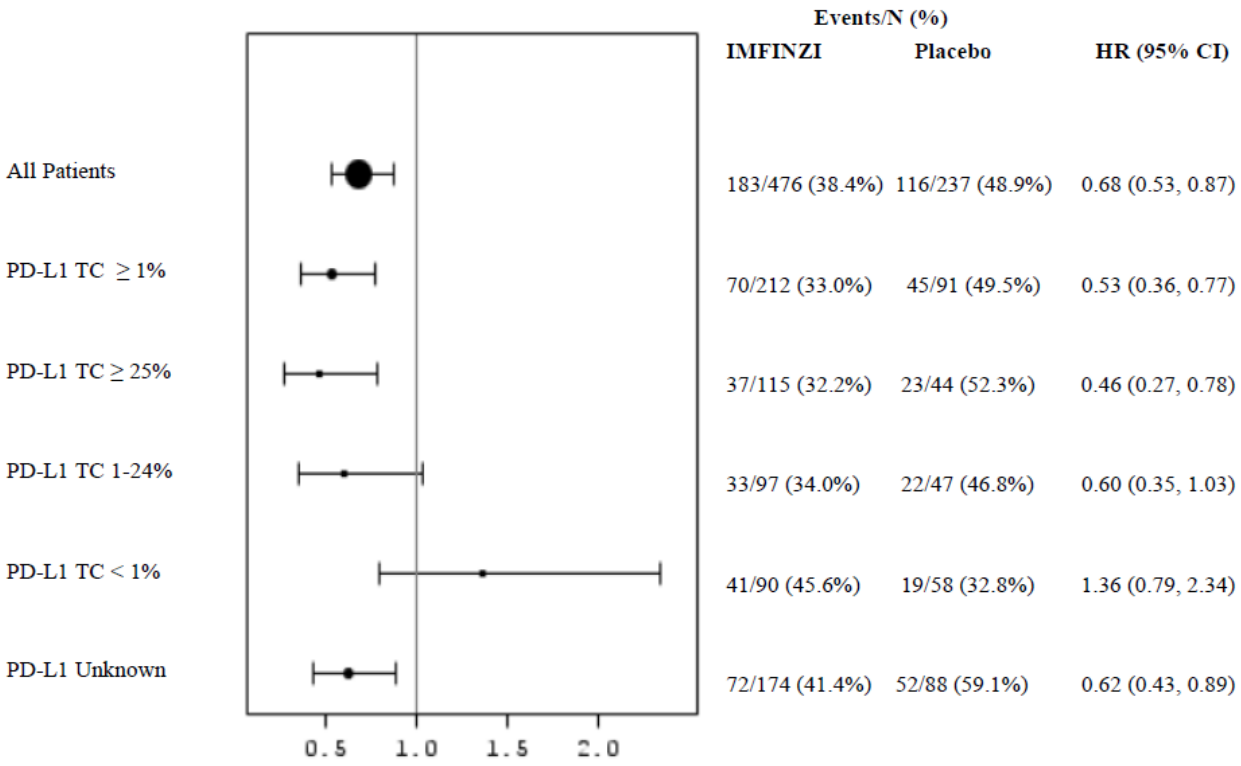


**Figure 4 Forest Plot of OS by PD-L1 expression**




**Extensive-Stage Small Cell Lung Cancer (ES-SCLC)**

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

Randomization (see Table 15) was stratified by the planned platinum-based therapy in cycle 1 (carboplatin or cisplatin).

Administration of IMFINZI monotherapy was permitted beyond disease progression if the patient was clinically stable and deriving clinical benefit as determined by the investigator.

**Trial Design and Study Demographics**

**Table 15 Summary of Patient Demographics in ES-SCLC (CASPIAN)**

| Study # | Study design | Dosage, route of administration and duration | Study subjects (n) | Mean age (Range) | Sex |
|---|---|---|---|---|---|
| D419QC00001 (CASPIAN) | Phase III, randomized, open-label, multicenter study | IMFINZI 1500 mg + etoposide and either carboplatin or cisplatin[a]<br>or<br>etoposide and either carboplatin or cisplatin[b] | 537 | 63 years (28-82 years) | M: 374 (69.6%)<br>F: 163 (30.4%) |

[a] IMFINZI 1500 mg, and investigator's choice of carboplatin (AUC 5 or 6 mg/mL/min) or cisplatin (75-80 mg/m2) on Day 1 and etoposide (80-100 mg/m2) intravenously on Days 1, 2, and 3 of each 21-day cycle for 4 cycles, followed by IMFINZI 1500 mg every 4 weeks until disease progression or unacceptable toxicity

[b] Investigator's choice of carboplatin (AUC 5 or 6 mg/mL/min) or cisplatin (75-80 mg/m2) on Day 1 and etoposide (80-100 mg/m2) intravenously on Days 1, 2, and 3 of each 21-day cycle, up to 6 cycles. After completion of chemotherapy, prophylactic cranial irradiation (PCI) may be administered per investigator discretion.

Additional demographics and baseline disease characteristics are presented in Table 16.

**Table 16 Patient Demographics and Baseline Disease Characteristics, CASPIAN (Full Analysis Set)**

| Demographic/Disease Characteristic | CASPIAN | |
|---|---|---|
| | IMFINZI + etoposide and either carboplatin or cisplatin (N=268) | etoposide and either carboplatin or cisplatin (N=269) |
| Age group (years), n (%) | | |
| <50 | 10 (3.7) | 20 (7.4) |
| ≥50 to <65 | 157 (58.6) | 137 (50.9) |
| ≥65 to <75 | 82 (30.6) | 90 (33.5) |
| ≥75 | 19 (7.1) | 22 (8.2) |
| Race, n (%) | | |
| Caucasian | 229 (85.4) | 221 (82.2) |
| Black or African-American | 2 (0.7) | 3 (1.1) |
| Asian | 36 (13.4) | 42 (15.6) |
| Other | 1 (0.4) | 2 (0.7) |
| Missing | 0 | 1 (0.4) |
| Smoking/nicotine history, n (%) | | |
| Current smoker | 120 944.8) | 126 (46.8) |
| Former smoker | 126 (47.0) | 128 (47.6) |
| Never smoker | 22 (8.2) | 15 (5.6) |
| WHO/ECOG performance status, n (%) | | |
| (0) Normal activity | 99 (36.9) | 90 (33.5) |
| (1) Restricted activity | 169 (63.1) | 179 (66.5) |

| Demographic/Disease Characteristic | CASPIAN | |
|---|---|---|
| | IMFINZI + etoposide and either carboplatin or cisplatin (N=268) | etoposide and either carboplatin or cisplatin (N=269) |
| Brain/CNS metastases | 28 (10.4) | 27 (10.0) |
| Staging[a] | | |
| III[b] | 1 (0.4) | 0 |
| IIIA | 5 (1.9) | 3 (1.1) |
| IIIB | 22 (8.2) | 21 (7.8) |
| IV | 240 (89.6) | 245 (91.1) |

[a] AJCC staging: Stage IV combines Stage IV/Stage IVA/Stage IVB from eCRF [PATHGEN] module.
[b] For the 1 Stage III patient, the TNM indicated Stage IIIb although the data were not reported this way.

Of all randomized patients, 24.6% received cisplatin and 74.1% received carboplatin. In the chemotherapy group, 56.8% of the patients received 6 cycles of treatment and 7.8% of patients received PCI.

### Study Results

The primary efficacy endpoint supporting the ES-SCLC indication was overall survival (OS) of IMFINZI + chemotherapy versus chemotherapy alone. Additional efficacy outcome measures include progression-free survival (PFS) and investigator-assessed objective response rate (ORR), per RECIST v1.1.

The study demonstrated a statistically significant improvement in OS with IMFINZI + chemotherapy vs. chemotherapy alone (HR=0.73 [95% CI: 0.591, 0.909], p=0.0047).

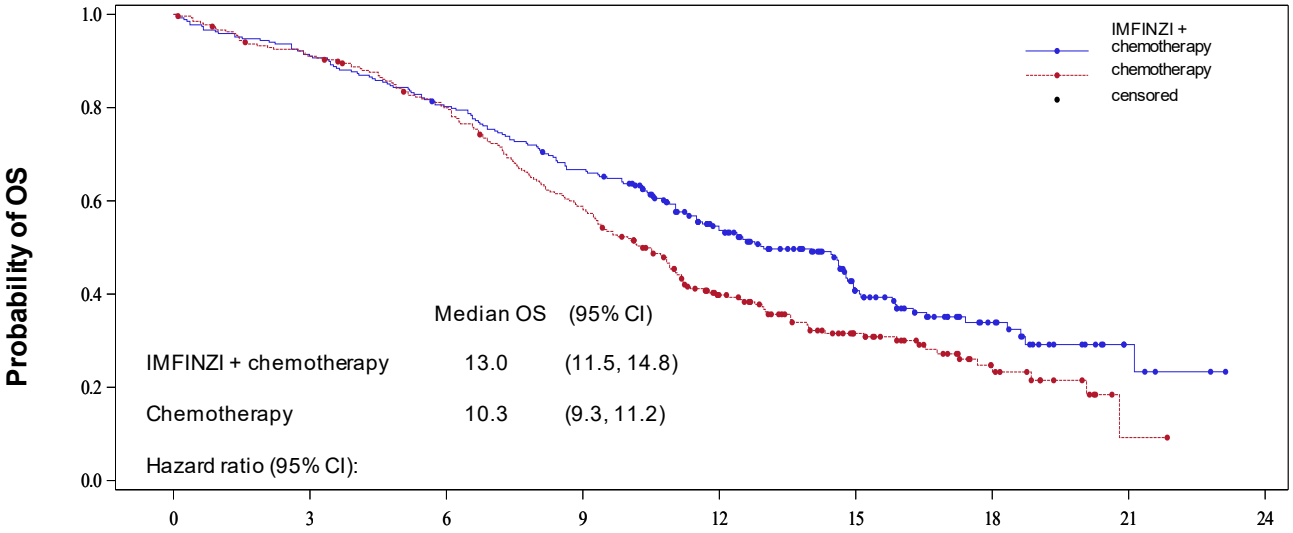
The OS results are summarized in Table 17.

**Table 17 OS Results in ES-SCLC Patients Treated with IMFINZI in Combination with Etoposide and Carboplatin or Cisplatin in the CASPIAN Study**

| | IMFINZI + etoposide and either carboplatin or cisplatin (N=268) | Etoposide and either carboplatin or cisplatin (N=269) |
|---|---|---|
| **OS** | | |
| Number of deaths (%) | 155 (57.8) | 181 (67.3) |
| **Median OS (months) (95% CI)** | 13.0 (11.5, 14.8) | 10.3 (9.3, 11.2) |
| HR (95% CI)[a] | 0.73 (0.591, 0.909) | |
| p-value[b] | 0.0047 | |

[a] The analysis was performed using the stratified log-rank test, adjusting for planned platinum therapy in Cycle 1 (carboplatin or cisplatin), and using the rank tests of association approach.
[b] At a pre-specified interim analysis, 336 OS events (79% of total planned events) were observed, and the boundary for declaring efficacy (0.0178) was determined by a Lan-Demets alpha spending function with O'Brien Fleming type boundary.

**Figure 5 Kaplan-Meier curve of OS (CASPIAN)**




| Number of patients at risk | 0 | 3 | 6 | 9 | 12 | 15 | 18 | 21 | 24 |
|---|---|---|---|---|---|---|---|---|---|
| IMFINZI + chemotherapy | 268 | 244 | 214 | 177 | 116 | 57 | 25 | 5 | 0 |
| chemotherapy | 269 | 242 | 209 | 153 | 82 | 44 | 17 | 1 | 0 |

Investigator-assessed PFS (96% of total planned events) showed a HR of 0.78 (95% CI: 0.65, 0.94), with median PFS of 5.1 months (95% CI: 4.7, 6.2) in the IMFINZI plus chemotherapy arm and 5.4 months (95% CI: 4.8, 6.2) in the chemotherapy alone arm. The investigator-assessed confirmed ORR was 68% (95% CI: 62%, 73%) in the IMFINZI plus chemotherapy arm and 58% (95% CI: 52%, 63%) in the chemotherapy alone arm.

In an exploratory subgroup analyses of OS based on the planned platinum chemotherapy received at cycle 1, the HR was 0.70 (95% CI 0.55, 0.89) in patients who received carboplatin, and the HR was 0.88 (95% CI 0.55, 1.41) in patients who received cisplatin.

## 15 MICROBIOLOGY

No microbiological information is required for this drug product.

## 16 NON-CLINICAL TOXICOLOGY

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

**Reproductive and Developmental 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.

## 17 SUPPORTING PRODUCT MONOGRAPHS


1. Carboplatin Injection BP (sterile solution, 10 mg/mL), submission control number 231317, Product Monograph, Pfizer Canada ULC. (Dec 16, 2019)
2. Cisplatin Injection BP (sterile solution, 1 mg/mL), submission control number 235278, Product Monograph, Pfizer Canada ULC. (Apr 3, 2020)
3. Vepesid (etoposide capsules, 50 mg), submission control number 233295, Product Monograph, CHEPLAPHARM Arzneimittel GmbH. (Dec 18, 2019)

## PATIENT MEDICATION INFORMATION

## READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

**IMFINZI®**
**durvalumab for injection, intravenous infusion**

Read this 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?

### Bladder Cancer

IMFINZI (durvalumab) is a medicine used to treat a type of 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.

### Lung Cancer

IMFINZI is used to treat 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 is used to treat adults with a type of lung cancer called extensive-stage small cell lung cancer (ES-SCLC). It is used when:

- Your cancer has spread within your lungs (or to other parts of the body) and,
- You have not previously been treated.

IMFINZI will be given in combination with chemotherapy for SCLC. It is important that you also read the package insert for the specific chemotherapy you may be receiving. If you have any questions about these medicines, ask your doctor.

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

IMFINZI will be given in combination with chemotherapy for SCLC. It is important that you also read the package insert for the specific chemotherapy you may be receiving. If you have any questions about these medicines, ask your doctor.

***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 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

**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 including any drugs, vitamins, minerals, natural supplements or alternative medicines.**

No drug-drug interactions are expected with IMFINZI.

**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.
- 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 kg of your body weight every 2 weeks or 1500 mg every 3 or 4 weeks.

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

**Overdose:**

If you think you, or a person you are caring for, have been given too much IMFINZI, contact a 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?**
These are not all the possible side effects you may have when taking IMFINZI. If you experience any side effects not listed here, tell your healthcare professional.

The following side effects have been reported in clinical trials with patients receiving IMFINZI alone and in combination with chemotherapy; ask your doctor for more information regarding side effects of your chemotherapy:

Very common side effects (≥ 10%):
- nausea
- hair loss
- decreased appetite
- feeling tired or weak
- constipation
- vomiting
- cough
- diarrhea
- stomach pain
- skin rash or itchiness
- fever
- swelling of the legs
- upper respiratory tract infection

When you get IMFINZI either alone or in combination with chemotherapy, 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** | | **Stop taking drug and get immediate medical help** |
| | | **Only if severe** | **In all cases** | |
| **Very Common** (*combination with chemotherapy*) | **Leukopenia or Neutropenia (low white blood cells, low neutrophils):** fever or infection, fatigue, flu-like symptoms. | | ✓ | |
| **Very Common** (*combination with chemotherapy*) | **Anemia (low red blood cells):** being short of breath, feeling very tired, having pale skin, fast heartbeat, loss of energy, or weakness. | | ✓ | |

| Serious side effects and what to do about them | | | | |
|---|---|---|---|---|
| Symptom / effect | | Talk to your healthcare professional | | Stop taking drug and get immediate medical help |
| | | Only if severe | In all cases | |
| **Very Common** (*monotherapy*)<br><br>**Common** (*combination with chemotherapy*) | **Skin or mouth problems:** rash, itching, skin blistering; ulcers in mouth or other mucous membranes when in combination with chemotherapy. | | ✓ | |
| **Very Common** (*monotherapy*)<br><br>**Common** (*combination with chemotherapy*) | **Hormone gland problems (especially the thyroid, adrenals, pituitary and pancreas):** 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, stomach area (abdomen) pain, changes in mood or behaviour, such as decreased sex drive, irritability, or forgetfulness, fast and deep breathing, confusion, a sweet smell to your breath, a sweet or metallic taste in your mouth, a different odour to your urine or sweat, increased frequency of urination (peeing) or feeling unusually thirsty. | | ✓ | |
| **Common** (*monotherapy, combination with chemotherapy*) | **Pneumonia (infection in the lungs):** cough with or without mucus, fever, chills, shortness of breath, chest pain including difficult and painful breathing. | | ✓ | |
| **Common** (*combination with chemotherapy*) | **Febrile neutropenia (low number of white blood cells with signs of fever):** fever or infection, fatigue, flu-like symptoms. | | ✓ | |
| **Common** (*monotherapy, combination with chemotherapy*) | **Lung inflammation (pneumonitis):** new or worsening cough, shortness of breath, chest pain. | | ✓ | |
| **Common** (*combination with chemotherapy*) | **Pancytopenia (low number of red blood cells, white blood cells, and platelets):**<br>**Leukopenia or Neutropenia:** fever or infection, fatigue, flu-like symptoms.<br>**Anemia:** being short of breath, feeling very tired, having pale skin, fast heartbeat, loss of energy, or weakness.<br>**Thrombocytopenia:** bruising or bleeding for longer than usual if you hurt yourself, fatigue and weakness. | | ✓ | |
| **Common** (*monotherapy, combination with chemotherapy*) | **Severe infusion reactions:** chills or shaking, itching or rash, flushing, shortness of breath or wheezing dizziness, fever, feeling like passing out, back or neck pain, facial swelling. | | ✓ | |

| Serious side effects and what to do about them | | | | |
|---|---|---|---|---|
| Symptom / effect | | Talk to your healthcare professional | | Stop taking drug and get immediate medical help |
| | | Only if severe | In all cases | |
| **Uncommon** (*monotherapy, combination with chemotherapy*) | **Intestinal problems (colitis) that can lead to tears or holes in your intestine:** 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. | | ✓ | |
| **Uncommon** (*monotherapy*)<br><br>**Common** (*combination with chemotherapy*) | **Liver problems (hepatitis):** 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. | | ✓ | |
| **Uncommon** (*monotherapy*)<br><br>(*combination with chemotherapy – not reported*) | **Kidney problems, including inflammation (nephritis) and kidney failure:** decrease in the amount of urine, blood in your urine, swelling in your ankles, loss of appetite. | | ✓ | |
| **Uncommon** (*monotherapy*)<br><br>(*combination with chemotherapy – not reported*) | **Muscle problems:** muscle weakness, tiredness and/or pain, rapid fatigue of the muscles in one or more areas of your body. | | ✓ | |
| **Uncommon** (*monotherapy*)<br><br>(*combination with chemotherapy – not reported*) | **Problems in other organs:** changes in eyesight, severe or persistent muscle or joint pains, chest pain, shortness of breath, irregular heartbeat (myocarditis). | | ✓ | |
| **Rare** (*monotherapy*)<br><br>**Very Common** (*combination with chemotherapy*) | **Thrombocytopenia (low blood platelets):** bruising or bleeding (e.g. nose or gums) more easily than normal. | | ✓ | |

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell 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 (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) 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 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 (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); 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.

This leaflet was prepared by AstraZeneca Canada Inc., Mississauga, Ontario L4Y 1M4.



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AstraZeneca