

IMFINZI- durvalumab injection, solution
AstraZeneca Pharmaceuticals LP

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use IMFINZI safely and effectively. See full prescribing information for IMFINZI.

IMFINZI® (durvalumab) injection, for intravenous use
Initial U.S. Approval: 2017

----- **RECENT MAJOR CHANGES** -----

Dosage and Administration, Preparation and Administration (2.4) 08/2019

----- **INDICATIONS AND USAGE** -----

IMFINZI is a programmed death-ligand 1 (PD-L1) blocking antibody indicated for the treatment of patients with:

- Locally advanced or metastatic urothelial carcinoma who:
 - have disease progression during or following platinum-containing chemotherapy. (1.1)
 - have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy. (1.1)

This indication is approved under accelerated approval based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials. (1.1)

- Unresectable, Stage III non-small cell lung cancer (NSCLC) whose disease has not progressed following concurrent platinum-based chemotherapy and radiation therapy. (1.2)

----- **DOSAGE AND ADMINISTRATION** -----

- Urothelial Carcinoma: 10 mg/kg every 2 weeks. (2.1)
- Stage III NSCLC: 10 mg/kg every 2 weeks. (2.2)

----- **DOSAGE FORMS AND STRENGTHS** -----

- Injection: 500 mg/10 mL (50 mg/mL) solution in a single-dose vial. (3)
- Injection: 120 mg/2.4 mL (50 mg/mL) solution in a single-dose vial. (3)

----- **CONTRAINDICATIONS** -----

None. (4)

----- **WARNINGS AND PRECAUTIONS** -----

- Immune-Mediated Pneumonitis: Withhold for moderate and permanently discontinue for severe or life-threatening pneumonitis. (2.3, 5.1)
- Immune-Mediated Hepatitis: Monitor for changes in liver function. Withhold for moderate and permanently discontinue for severe or life-threatening transaminase or total bilirubin elevation. (2.3, 5.2)
- Immune-Mediated Colitis: Withhold for moderate and permanently discontinue for severe or life-threatening colitis. (2.3, 5.3)
- Immune-Mediated Endocrinopathies: Withhold for moderate, severe or life-threatening. (2.3, 5.4)
- Immune-Mediated Nephritis: Monitor for changes in renal function. Withhold for moderate and permanently discontinue for severe or life-threatening nephritis. (2.3, 5.5)
- Immune-Mediated Dermatologic Reactions: Withhold for moderate and permanently discontinue for severe or life-threatening rash. (2.3, 5.6)
- Infection: Withhold for severe or life-threatening infection. (2.3, 5.8)
- Infusion-Related Reactions: Interrupt or slow the rate of infusion for mild or moderate and permanently discontinue for severe or life-threatening infusion-related reactions. (2.3, 5.9)
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and use of effective contraception. (5.10, 8.1, 8.3)

-----ADVERSE REACTIONS-----

- Most common adverse reactions ($\geq 15\%$ of patients with urothelial carcinoma) were fatigue, musculoskeletal pain, constipation, decreased appetite, nausea, peripheral edema, and urinary tract infection. (6.1)
- Most common adverse reactions ($\geq 20\%$ of patients with unresectable, Stage III NSCLC) were cough, fatigue, pneumonitis/radiation pneumonitis, upper respiratory tract infections, dyspnea, and rash. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact AstraZeneca at 1-800-236-9933 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

-----USE IN SPECIFIC POPULATIONS-----

Lactation: Advise not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 8/2019

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Urothelial Carcinoma

IMFINZI 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.

This indication is approved under accelerated approval based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials [see *Clinical Studies (14.1)*].

1.2 Non-Small Cell Lung Cancer

IMFINZI is indicated for the treatment of patients with unresectable Stage III non-small cell lung cancer (NSCLC) whose disease has not progressed following concurrent platinum-based chemotherapy and radiation therapy.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage for Urothelial Carcinoma

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

2.2 Recommended Dosage for NSCLC

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

2.3 Dosage Modifications for Adverse Reactions

No dose reductions are recommended. Withhold or discontinue IMFINZI to manage adverse reactions as described in Table 1.

Table 1. Recommended Dosage Modifications for Adverse Reactions

Adverse Reaction	Severity*	Dosage Modification
		Withhold dose until Grade 1 or

Pneumonitis [see Warnings and Precautions (5.1)]	Grade 2	resolved and corticosteroid dose is less than or equal to prednisone 10 mg per day (or equivalent).
	Grade 3 or 4	Permanently discontinue
Hepatitis [see Warnings and Precautions (5.2)]	For ALT or AST greater than 3 but less than or equal to 8 times the ULN or Total bilirubin greater than 1.5 but less than or equal to 5 times the ULN	Withhold dose until Grade 1 or resolved and corticosteroid dose is less than or equal to prednisone 10 mg per day (or equivalent).
	ALT or AST greater than 8 times the ULN or total bilirubin greater than 5 times the ULN or Concurrent ALT or AST greater than 3 times the ULN and total bilirubin greater than 2 times the ULN with no other cause	Permanently discontinue
Colitis or diarrhea [see Warnings and Precautions (5.3)]	Grade 2	Withhold dose until Grade 1 or resolved and corticosteroid dose is less than or equal to prednisone 10 mg per day (or equivalent).
	Grade 3 or 4	Permanently discontinue
Hyperthyroidism [see Warnings and Precautions (5.4)]	Grade 2-4	Withhold dose until clinically stable
Adrenal insufficiency or Hypophysitis/Hypopituitarism [see Warnings and Precautions (5.4)]	Grade 2-4	Withhold dose until clinically stable
Type 1 Diabetes Mellitus [see Warnings and Precautions (5.4)]	Grade 2-4	Withhold dose until clinically stable
Nephritis [see Warnings and Precautions (5.5)]	For Creatinine greater than 1.5 to 3 times the ULN	Withhold dose until Grade 1 or resolved and corticosteroid dose is less than or equal to prednisone 10 mg per day (or equivalent).
	For Creatinine greater than 3 times the ULN	Permanently discontinue
Rash or dermatitis [see Warnings and Precautions (5.6)]	Grade 2 for longer than 1 week or Grade 3	Withhold dose until Grade 1 or resolved and corticosteroid dose is less than or equal to prednisone 10 mg per day (or equivalent).
	Grade 4	Permanently discontinue
Infection [see Warnings and Precautions (5.8)]	Grade 3 or 4	Withhold dose until clinically stable
Infusion-related reactions [see Warnings and Precautions (5.9)]	Grade 1 or 2	Interrupt or slow the rate of infusion
	Grade 3 or 4	Permanently discontinue
Other immune-mediated adverse reactions [see Warnings and Precautions (5.7)]	Grade 3	Withhold dose until Grade 1 or resolved and corticosteroid dose is less than or equal to prednisone 10 mg per day (or equivalent).
	Grade 4	Permanently discontinue

Persistent Grade 2 or 3 adverse reaction (excluding endocrinopathies)	Grade 2 or 3 adverse reaction that does not recover to Grade 0 or 1 within 12 weeks after last IMFINZI dose	Permanently discontinue
Inability to taper corticosteroid	Inability to reduce to less than or equal to prednisone 10 mg per day (or equivalent) within 12 weeks after the last IMFINZI dose	Permanently discontinue
Recurrent Grade 3 or 4 adverse reaction	Recurrent Grade 3 or 4 (severe or life-threatening) adverse reaction	Permanently discontinue

* National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03. ALT: alanine aminotransferase; AST: aspartate aminotransferase; ULN: upper limit of normal.

2.4 Preparation and Administration

Preparation

- Visually inspect drug product for particulate matter and discoloration prior to administration, whenever solution and container permit. Discard the vial if the solution is cloudy, discolored, 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 bag containing 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP. Mix diluted solution by gentle inversion. Do not shake the solution. The final concentration of the diluted solution should be between 1 mg/mL and 15 mg/mL.
- Discard partially used or empty vials of IMFINZI.

Storage of Infusion Solution

- IMFINZI does not contain a preservative.
- Administer infusion solution immediately once prepared. If infusion solution is not administered immediately and needs to be stored, the total time from vial puncture to the start of the administration should not exceed:
 - 24 hours in a refrigerator at 2°C to 8°C (36°F to 46°F)
 - 8 hours at room temperature up to 25°C (77°F)
- Do not freeze.
- Do not shake.

Administration

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

3 DOSAGE FORMS AND STRENGTHS

Injection: 120 mg/2.4 mL (50 mg/mL) and 500 mg/10 mL (50 mg/mL) clear to opalescent, colorless to slightly yellow solution in a single-dose vial.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Immune-Mediated Pneumonitis

IMFINZI can cause immune-mediated pneumonitis, defined as requiring use of corticosteroids. Fatal cases have been reported.

Monitor patients for signs and symptoms of pneumonitis. Evaluate patients with suspected pneumonitis with radiographic imaging. Administer corticosteroids, prednisone 1 to 2 mg per kg per day or equivalent for moderate (Grade 2) pneumonitis or prednisone 1 to 4 mg per kg per day or equivalent for more severe (Grade 3-4) pneumonitis, followed by taper. Interrupt or permanently discontinue IMFINZI based on the severity [*see Dosage and Administration (2.3)*].

In clinical studies enrolling 1889 patients with various cancers who received IMFINZI [*see Adverse Reactions (6.1)*], pneumonitis occurred in 5% of patients, including Grade 3 (0.8%), Grade 4 (< 0.1%), and Grade 5 (0.3%) immune-mediated pneumonitis. The median time to onset was 1.8 months (range: 1 day to 13.9 months) and the median time to resolution was 4.9 months (range: 0 days to 13.7 months). Pneumonitis led to discontinuation of IMFINZI in 1.5% of the 1889 patients. Pneumonitis resolved in 54% of patients. Systemic corticosteroids were required in 3.5% of the 1889 patients, with 2.5% requiring high-dose corticosteroids (prednisone \geq 40 mg per day or equivalent) and 0.1% requiring infliximab.

The incidence of pneumonitis (including radiation pneumonitis) was higher in patients in the PACIFIC study who completed treatment with definitive chemoradiation within 42 days prior to initiation of IMFINZI (34%) compared to patients in other clinical studies (2.3%) in which radiation therapy was generally not administered immediately prior to initiation of IMFINZI.

In the PACIFIC study, the incidence of Grade 3 pneumonitis was 3.4% and the incidence of Grade 5 pneumonitis was 1.1% in the IMFINZI arm. The median time to onset of pneumonitis was 1.8 months and the median duration was 2.1 months (range: 3 days to 18.7 months). Pneumonitis led to discontinuation of IMFINZI in 6% of patients. Pneumonitis resolved in 47% of patients experiencing pneumonitis. Systemic corticosteroids were required in 21% of patients, with 12% requiring high-dose corticosteroids and 0.1% requiring infliximab.

5.2 Immune-Mediated Hepatitis

IMFINZI can cause immune-mediated hepatitis, defined as requiring use of corticosteroids. Fatal cases have been reported.

Monitor patients for signs and symptoms of hepatitis, during and after discontinuation of IMFINZI, including clinical chemistry monitoring. Administer corticosteroids, prednisone 1 to 2 mg per kg per day or equivalent, followed by taper for Grade 2 or higher elevations of ALT, AST, and/or total bilirubin. Interrupt or permanently discontinue IMFINZI based on the severity [*see Dosage and Administration (2.3)*].

In clinical studies enrolling 1889 patients with various cancers who received IMFINZI [*see Adverse Reactions (6.1)*], hepatitis occurred in 12% of patients, including Grade 3 (4.4%), Grade 4 (0.4%), and Grade 5 (0.2%) immune-mediated hepatitis. The median time to onset was 1.2 months (range: 1 day to 13.6 months). Hepatitis led to discontinuation of IMFINZI in 0.7% of the 1889 patients. Hepatitis resolved in 49% of patients. Systemic corticosteroids were required in 2.7% of patients, with 1.7% requiring high-dose corticosteroids and 0.1% requiring mycophenolate.

5.3 Immune-Mediated Colitis

IMFINZI can cause immune-mediated colitis, defined as requiring use of corticosteroids.

Monitor patients for signs and symptoms of diarrhea or colitis. Administer corticosteroids, prednisone 1 to 2 mg per kg per day or equivalent, for moderate (Grade 2) or more severe (Grade 3-4) colitis, followed by taper. Interrupt or permanently discontinue IMFINZI based on the severity [see *Dosage and Administration* (2.3)].

In clinical studies enrolling 1889 patients with various cancers who received IMFINZI [see *Adverse Reactions* (6.1)], diarrhea or colitis occurred in 18% of patients, including Grade 3 (1%) and Grade 4 (0.1%) immune-mediated colitis. The median time to onset was 1.4 months (range: 1 day to 14 months). Diarrhea or colitis lead to discontinuation of IMFINZI in 0.4% of the 1889 patients. Diarrhea or colitis resolved in 78% of the patients. Systemic corticosteroids were required in 1.9% of patients, with 1% requiring high-dose corticosteroids and 0.1% requiring other immunosuppressants (e.g., infliximab, mycophenolate).

5.4 Immune-Mediated Endocrinopathies

IMFINZI can cause immune-mediated endocrinopathies, including thyroid disorders, adrenal insufficiency, type 1 diabetes mellitus, and hypophysitis/hypopituitarism.

Thyroid Disorders: Monitor thyroid function prior to and periodically during treatment with IMFINZI. Initiate hormone replacement therapy or medical management of hyperthyroidism as clinically indicated. Continue IMFINZI for hypothyroidism and interrupt for hyperthyroidism based on the severity [see *Dosage and Administration* (2.3)].

In clinical studies enrolling 1889 patients who received IMFINZI [see *Adverse Reactions* (6.1)], hypothyroidism occurred in 11% of patients and hyperthyroidism occurred in 7% of patients. Thyroiditis occurred in 0.9% of patients, including Grade 3 (< 0.1%) thyroiditis. Hypothyroidism was preceded by thyroiditis or hyperthyroidism in 25% of patients.

Adrenal Insufficiency: Monitor patients for clinical signs and symptoms of adrenal insufficiency. For Grade 2 or higher adrenal insufficiency, initiate prednisone 1 to 2 mg per kg per day or equivalent, followed by corticosteroid taper and hormone replacement as clinically indicated. Interrupt IMFINZI based on the severity [see *Dosage and Administration* (2.3)].

In clinical studies enrolling 1889 patients who received IMFINZI, adrenal insufficiency occurred in 0.7% of patients, including Grade 3 (< 0.1%) adrenal insufficiency. Systemic corticosteroids were required in 0.4% of patients, including 0.1% of patients who required high-dose corticosteroids.

Type 1 Diabetes Mellitus: Monitor patients for hyperglycemia or other signs and symptoms of diabetes. Initiate treatment with insulin as clinically indicated. Interrupt IMFINZI based on the severity [see *Dosage and Administration* (2.3)].

In clinical studies enrolling 1889 patients who received IMFINZI, type 1 diabetes mellitus occurred in < 0.1% of patients. The median time to onset was 1.4 months.

Hypophysitis: For Grade 2 or higher hypophysitis, initiate prednisone 1 to 2 mg per kg per day or equivalent, followed by corticosteroid taper and hormone replacement therapy as clinically indicated. Interrupt IMFINZI based on the severity [see *Dosage and Administration* (2.3)].

Hypopituitarism leading to adrenal insufficiency and diabetes insipidus occurred in < 0.1% of 1889 patients who received IMFINZI in clinical studies.

5.5 Immune-Mediated Nephritis

IMFINZI can cause immune-mediated nephritis, defined as evidence of renal dysfunction requiring use of corticosteroids. Fatal cases have occurred.

Monitor patients for abnormal renal function tests prior to and periodically during treatment with IMFINZI. Initiate prednisone 1 to 2 mg per kg per day or equivalent, for moderate (Grade 2) or severe

(Grade 3-4) nephritis, followed by taper. Interrupt or permanently discontinue IMFINZI based on the severity [see *Dosage and Administration* (2.3)].

In clinical studies enrolling 1889 patients with various cancers who received IMFINZI [see *Adverse Reactions* (6.1)], nephritis (reported as any of the following increased creatinine or urea, acute kidney injury, renal failure, decreased glomerular filtration rate, tubulointerstitial nephritis, decreased creatinine clearance, glomerulonephritis, and nephritis) occurred in 6.3% of patients including Grade 3 (1.1%), Grade 4 (0.2%), and Grade 5 (0.1%) immune-mediated nephritis. The median time to onset was 2 months (range: 1 day to 14.2 months). IMFINZI was discontinued in 0.3% of the 1889 patients. Nephritis resolved in 50% of patients. Systemic corticosteroids were required in 0.6% of patients, with 0.4% receiving high-dose corticosteroids.

5.6 Immune-Mediated Dermatologic Reactions

IMFINZI can cause immune-mediated rash; bullous dermatitis, Stevens Johnson Syndrome (SJS)/toxic epidermal necrolysis (TEN) have occurred with other products in this class [see *Warnings and Precautions* (5.7)].

Monitor for signs and symptoms of rash. Initiate prednisone 1 to 2 mg per kg per day or equivalent, for moderate (Grade 2) rash or dermatitis lasting for more than 1 week or severe (Grade 3-4) rash or dermatitis, followed by taper. Interrupt or permanently discontinue IMFINZI based on the severity [see *Dosage and Administration* (2.3)].

In clinical studies enrolling 1889 patients with various cancers who received IMFINZI [see *Adverse Reactions* (6.1)], 26% of patients developed rash or dermatitis and 0.4% of the patients developed vitiligo. Rash or dermatitis led to discontinuation of IMFINZI in 0.1% of the 1889 patients. Rash resolved in 62% of patients. Systemic corticosteroids were required in 2% of patients, including high-dose corticosteroids in 1% of patients.

5.7 Other Immune-Mediated Adverse Reactions

IMFINZI can cause severe and fatal immune-mediated adverse reactions. These immune-mediated reactions may involve any organ system. While immune-mediated reactions usually manifest during treatment with IMFINZI, immune-mediated adverse reactions can also manifest after discontinuation of IMFINZI.

For suspected Grade 2 immune-mediated adverse reactions, exclude other causes and initiate corticosteroids as clinically indicated. For severe (Grade 3 or 4) adverse reactions, administer corticosteroids, prednisone 1 to 4 mg per kg per day or equivalent, followed by taper. Interrupt or permanently discontinue IMFINZI, based on the severity of the reaction [see *Dosage and Administration* (2.3)]. If uveitis occurs in combination with other immune-mediated adverse reactions, evaluate for Vogt-Koyanagi-Harada syndrome, which has been observed with other products in this class and may require treatment with systemic steroids to reduce the risk of permanent vision loss.

The following clinically significant, immune-mediated adverse reactions occurred at an incidence of less than 1% each in 1889 patients who received IMFINZI: aseptic meningitis, hemolytic anemia, immune thrombocytopenic purpura, myocarditis, myositis, and ocular inflammatory toxicity, including uveitis and keratitis [see *Adverse Reactions* (6.1)]. The following clinically significant, immune-mediated adverse reactions have been reported with other products in this class: bullous dermatitis, Stevens Johnson Syndrome (SJS)/toxic epidermal necrolysis (TEN), pancreatitis, systemic inflammatory response syndrome, rhabdomyolysis, myasthenia gravis, histiocytic necrotizing lymphadenitis, vasculitis, hemolytic anemia, iritis, encephalitis, facial and abducens nerve paresis, demyelination, polymyalgia rheumatica, autoimmune neuropathy, Guillain-Barré syndrome, and Vogt-Koyanagi-Harada syndrome.

5.8 Infection

IMFINZI can cause serious infections, including fatal cases.

Monitor patients for signs and symptoms of infection. For Grade 3 or higher infections, withhold IMFINZI and resume once clinically stable [see *Dosage and Administration (2.3)*].

In clinical studies enrolling 1889 patients with various cancers who received IMFINZI [see *Adverse Reactions (6.1)*], infections occurred in 43% of patients, including Grade 3 (8%), Grade 4 (1.9%), and Grade 5 (1%). In the urothelial carcinoma cohort in Study 1108 the most common Grade 3 or higher infection was urinary tract infections, which occurred in 4% of patients. In the PACIFIC study, the most common Grade 3 or higher infection was pneumonia, which occurred in 5% of patients. The overall incidence of infections in IMFINZI-treated patients (56%) in the PACIFIC study was higher compared to patients in other studies (38%) in which radiation therapy was generally not administered immediately prior to initiation of IMFINZI.

5.9 Infusion-Related Reactions

IMFINZI can cause severe or life-threatening infusion-related reactions.

Monitor for signs and symptoms of infusion-related reactions. Interrupt, slow the rate of, or permanently discontinue IMFINZI based on the severity [see *Dosage and Administration (2.3)*]. For Grade 1 or 2 infusion-related reactions, consider using pre-medications with subsequent doses.

In clinical studies enrolling 1889 patients with various cancers [see *Adverse Reactions (6.1)*], infusion-related reactions occurred in 2.2% of patients, including Grade 3 (0.3%).

5.10 Embryo-Fetal Toxicity

Based on its mechanism of action and data from animal studies, IMFINZI can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of durvalumab to cynomolgus monkeys from the onset of organogenesis through delivery resulted in increased premature delivery, fetal loss and premature neonatal death. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with IMFINZI and for at least 3 months after the last dose of IMFINZI [see *Use in Specific Populations (8.1, 8.3)*].

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the labeling.

- Immune-Mediated Pneumonitis [see *Warnings and Precautions (5.1)*].
- Immune-Mediated Hepatitis [see *Warnings and Precautions (5.2)*].
- Immune-Mediated Colitis [see *Warnings and Precautions (5.3)*].
- Immune-Mediated Endocrinopathies [see *Warnings and Precautions (5.4)*].
- Immune-Mediated Nephritis [see *Warnings and Precautions (5.5)*].
- Immune-Mediated Dermatologic Reactions [see *Warnings and Precautions (5.6)*].
- Other Immune-Mediated Adverse Reactions [see *Warnings and Precautions (5.7)*].
- Infection [see *Warnings and Precautions (5.8)*].
- Infusion-Related Reactions [see *Warnings and Precautions (5.9)*].

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data described in the Warnings and Precautions section reflect exposure to IMFINZI in 1889 patients from the PACIFIC study (a randomized, placebo-controlled study that enrolled 475 patients with Stage III NSCLC), Study 1108 (an open-label, single-arm, multicohort study that enrolled 191 patients

with urothelial carcinoma and 779 patients with various other solid tumors), and an additional open-label, single-arm trial that enrolled 444 patients with metastatic lung cancer, an indication for which durvalumab is not approved. Across all studies, IMFINZI was administered at a dose of 10 mg/kg intravenously every 2 weeks. Among the 1889 patients, 38% were exposed for 6 months or more and 18% were exposed for 12 months or more.

The data described in this section reflect exposure to IMFINZI in patients with locally advanced or metastatic urothelial carcinoma enrolled in Study 1108 and in patients with Stage III NSCLC enrolled in the PACIFIC study.

Urothelial Carcinoma

The safety data described in Table 2 reflect exposure to IMFINZI in 182 patients with locally advanced or metastatic urothelial carcinoma in the urothelial carcinoma cohort of Study 1108 whose disease has progressed during or after one standard platinum-based regimen. Patients received IMFINZI 10 mg/kg intravenously every 2 weeks [see *Clinical Studies (14.1)*]. The median duration of exposure was 2.3 months (range: 1 day to 12.1 months).

Thirty-one percent (31%) of patients had a drug delay or interruption for an adverse reaction. The most common (> 2%) were liver injury (4.9%), urinary tract infection (3.3%), acute kidney injury (3.3%), and musculoskeletal pain (2.7%).

The most common adverse reactions (≥ 15%) were fatigue (39%), musculoskeletal pain (24%), constipation (21%), decreased appetite (19%), nausea (16%), peripheral edema (15%), and urinary tract infection (15%). The most common Grade 3 or 4 adverse reactions (≥ 3%) were fatigue, urinary tract infection, musculoskeletal pain, abdominal pain, dehydration, and general physical health deterioration.

Eight patients (4.4%) who were treated with IMFINZI experienced Grade 5 adverse reactions of cardiorespiratory arrest, general physical health deterioration, sepsis, ileus, pneumonitis, or immune-mediated hepatitis. Three additional patients were experiencing infection and disease progression at the time of death. IMFINZI was discontinued for adverse reactions in 3.3% of patients. Serious adverse reactions occurred in 46% of patients. The most frequent serious adverse reactions (> 2%) were acute kidney injury (4.9%), urinary tract infection (4.4%), musculoskeletal pain (4.4%), liver injury (3.3%), general physical health deterioration (3.3%), sepsis, abdominal pain, and pyrexia/tumor associated fever (2.7% each).

Table 2 summarizes the adverse reactions that occurred in ≥ 10% of patients, while Table 3 summarizes the Grade 3 - 4 laboratory abnormalities that occurred in ≥ 1% of patients treated with IMFINZI in the urothelial carcinoma cohort of Study 1108.

Table 2. Adverse Reactions in ≥ 10% of Patients in Study 1108 Urothelial Carcinoma Cohort

Adverse Reaction	IMFINZI N = 182	
	All Grades (%)	Grades 3 – 4 (%)
Gastrointestinal Disorders		
Constipation	21	1
Nausea	16	2
Abdominal pain*	14	3
Diarrhea/Colitis	13	1
General Disorders and Administration		
Fatigue [†]	39	6
Peripheral edema [‡]	15	2
Pyrexia/Tumor associated fever	14	1
Infections		

Urinary tract infection [§]	15	4
Metabolism and Nutrition Disorders		
Decreased appetite/Hypophagia	19	1
Musculoskeletal and Connective Tissue Disorders		
Musculoskeletal pain [¶]	24	4
Respiratory, Thoracic, and Mediastinal Disorders		
Dyspnea/Exertional Dyspnea	13	2
Cough/Productive Cough	10	0
Skin and Subcutaneous Tissue Disorders		
Rash [#]	11	1

* Includes abdominal pain upper, abdominal pain lower, and flank pain

† Includes asthenia, lethargy, and malaise

‡ Includes edema, localized edema, edema peripheral, lymphedema, peripheral swelling, scrotal edema, and scrotal swelling

§ Includes cystitis, candiduria, and urosepsis

¶ Includes back pain, musculoskeletal chest pain, musculoskeletal pain and discomfort, myalgia, and neck pain

Includes dermatitis, dermatitis acneiform, dermatitis psoriasiform, psoriasis, rash maculo-papular, rash pruritic, rash papular, rash pustular, skin toxicity, eczema, erythema, erythema multiforme, rash erythematous, acne, and lichen planus

Table 3. Grade 3-4 Laboratory Abnormalities Worsened from Baseline Occurring in $\geq 1\%$ Patients in Study 1108 Urothelial Carcinoma Cohort

Laboratory Abnormality	Grades 3 - 4 %
Hyponatremia	12
Lymphopenia	11
Anemia	8
Increased alkaline phosphatase	4
Hypermagnesemia	4
Hypercalcemia	3
Hyperglycemia	3
Increased AST	2
Increased ALT	1
Hyperbilirubinemia	1
Increased creatinine	1
Neutropenia	1
Hyperkalemia	1
Hypokalemia	1
Hypoalbuminemia	1

Non-Small Cell Lung Cancer

The safety of IMFINZI in patients with Stage III NSCLC who completed concurrent platinum-based chemoradiotherapy within 42 days prior to initiation of study drug was evaluated in the PACIFIC study, a multicenter, randomized, double-blind, placebo-controlled study. A total of 475 patients received IMFINZI 10 mg/kg intravenously every 2 weeks. The study excluded patients who had disease progression following chemoradiation, with active or prior autoimmune disease within 2 years of initiation of the study or with medical conditions that required systemic immunosuppression [see *Clinical Studies (14.2)*].

The study population characteristics were: median age of 64 years (range: 23 to 90), 45% age 65 years or older, 70% male, 69% White, 27% Asian, 75% former smoker, 16% current smoker, and 51% had WHO performance status of 1. All patients received definitive radiotherapy as per protocol, of which 92% received a total radiation dose of 54 Gy to 66 Gy. The median duration of exposure to IMFINZI was 10 months (range: 0.2 to 12.6).

IMFINZI was discontinued due to adverse reactions in 15% of patients. The most common adverse reactions leading to IMFINZI discontinuation were pneumonitis or radiation pneumonitis in 6% of patients. Serious adverse reactions occurred in 29% of patients receiving IMFINZI. The most frequent serious adverse reactions reported in at least 2% of patients were pneumonitis or radiation pneumonitis (7%) and pneumonia (6%). Fatal pneumonitis or radiation pneumonitis and fatal pneumonia occurred in < 2% of patients and were similar across arms. The most common adverse reactions (occurring in $\geq 20\%$ of patients) were cough, fatigue, pneumonitis or radiation pneumonitis, upper respiratory tract infections, dyspnea, and rash.

Table 4 summarizes the adverse reactions that occurred in at least 10% of patients treated with IMFINZI.

Table 4. Adverse Reactions Occurring in $\geq 10\%$ Patients in the PACIFIC Study

Adverse Reaction	IMFINZI N = 475		Placebo* N = 234	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Respiratory, Thoracic, and Mediastinal Disorders				
Cough/Productive Cough	40	0.6	30	0.4
Pneumonitis [†] /Radiation Pneumonitis	34	3.4	25	3.0
Dyspnea [‡]	25	1.5	25	2.6
Gastrointestinal Disorders				
Diarrhea	18	0.6	19	1.3
Abdominal pain [§]	10	0.4	6	0.4
Endocrine Disorders				
Hypothyroidism [¶]	12	0.2	1.7	0
Skin and Subcutaneous Tissue Disorders				
Rash [#]	23	0.6	12	0
Pruritus [Ⓓ]	12	0	6	0
General Disorders				
Fatigue ^β	34	0.8	32	1.3
Pyrexia	15	0.2	9	0
Infections				
Upper respiratory tract infections ^α	26	0.4	19	0
Pneumonia ^ε	17	7	12	6

* The PACIFIC study was not designed to demonstrate statistically significant difference in adverse reaction rates for IMFINZI, as compared to placebo, for any specific adverse reaction listed in Table 4

[†] includes acute interstitial pneumonitis, interstitial lung disease, pneumonitis, pulmonary fibrosis

[‡] includes dyspnea, and exertional dyspnea

[§] includes abdominal pain, abdominal pain lower, abdominal pain upper, and flank pain

[¶] includes autoimmune hypothyroidism and hypothyroidism

[#] includes rash erythematous, rash generalized, rash macular, rash maculopapular, rash papular, rash pruritic, rash pustular, erythema, eczema, rash, and dermatitis

[Ⓓ] includes pruritus generalized and pruritus

β includes asthenia and fatigue

à includes laryngitis, nasopharyngitis, peritonsillar abscess, pharyngitis, rhinitis, sinusitis, tonsillitis, tracheobronchitis, and upper respiratory tract infection

è includes lung infection, pneumocystis jirovecii pneumonia, pneumonia, pneumonia adenoviral, pneumonia bacterial, pneumonia cytomegaloviral, pneumonia haemophilus, pneumonia klebsiella, pneumonia necrotising, pneumonia pneumococcal, and pneumonia streptococcal

Other adverse reactions occurring in less than 10% of patients treated with IMFINZI were dysphonia, dysuria, night sweats, peripheral edema, and increased susceptibility to infections.

Table 5 summarizes the laboratory abnormalities that occurred in at least 20% of patients treated with IMFINZI.

Table 5. Laboratory Abnormalities Worsening from Baseline Occurring in ≥ 20% of Patients in the PACIFIC Study

Laboratory Abnormality	IMFINZI		Placebo	
	All Grades* (%)†	Grade 3 or 4 (%)	All Grades* (%)†	Grade 3 or 4 (%)
Chemistry				
Hyperglycemia	52	8	51	8
Hypocalcemia	46	0.2	41	0
Increased ALT	39	2.3	22	0.4
Increased AST	36	2.8	21	0.4
Hyponatremia	33	3.6	30	3.1
Hyperkalemia	32	1.1	29	1.8
Increased GGT	24	3.4	22	1.7
Hematology				
Lymphopenia	43	17	39	18

* Graded according to NCI CTCAE version 4.0

† Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: IMFINZI (range: 464 to 470) and placebo (range: 224 to 228)

6.2 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to durvalumab to the incidence of antibodies to other products may be misleading.

Of 1570 patients enrolled in Study 1108, the PACIFIC study or an additional open-label study, who received IMFINZI 10 mg/kg every 2 weeks and were evaluable for the presence of anti-drug antibodies (ADAs), 45 (2.9%) patients tested positive for treatment-emergent ADAs. The development of treatment-emergent ADA against durvalumab appears to have no clinically relevant effect on its pharmacokinetic profile. There are insufficient numbers of patients with ADA to determine whether ADA alters the safety or efficacy of durvalumab.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk summary

Based on its mechanism of action and data from animal studies, IMFINZI can cause fetal harm when administered to a pregnant woman [see *Clinical Pharmacology (12.1)*]. There are no data on the use of IMFINZI in pregnant women.

In animal reproduction studies, administration of durvalumab to pregnant cynomolgus monkeys from the confirmation of pregnancy through delivery resulted in an increase in premature delivery, fetal loss, and premature neonatal death (see *Data*). Human immunoglobulin G1 (IgG1) is known to cross the placental barrier; therefore, durvalumab has the potential to be transmitted from the mother to the developing fetus. Apprise pregnant women of the potential risk to a fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

As reported in the literature, the PD-1/PD-L1 pathway plays a central role in preserving pregnancy by maintaining maternal immune tolerance to the fetus. In mouse allogeneic pregnancy models, disruption of PD-L1 signaling was shown to result in an increase in fetal loss. The effects of durvalumab on prenatal and postnatal development were evaluated in reproduction studies in cynomolgus monkeys. Durvalumab was administered from the confirmation of pregnancy through delivery at exposure levels approximately 6 to 20 times higher than those observed at the recommended clinical dose of 10 mg/kg (based on AUC). Administration of durvalumab resulted in premature delivery, fetal loss (abortion and stillbirth), and increase in neonatal deaths. Durvalumab was detected in infant serum on postpartum Day 1, indicating the presence of placental transfer of durvalumab. Based on its 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 PD-1 knockout mice.

8.2 Lactation

Risk Summary

There is no information regarding the presence of durvalumab in human milk, the effects on the breastfed infant, or the effects on milk production. Human IgG1 is excreted in human milk. Durvalumab was present in the milk of lactating cynomolgus monkeys and was associated with premature neonatal death (see *Data*).

Because of the potential for adverse reactions in breastfed infants, advise women not to breastfeed during treatment with IMFINZI and for at least 3 months after the last dose.

Data

In lactating cynomolgus monkeys, durvalumab was present in breast milk at about 0.15% of maternal serum concentrations after administration of durvalumab from the confirmation of pregnancy through delivery at exposure levels approximately 6 to 20 times higher than those observed at the recommended clinical dose of 10 mg/kg (based on AUC). Administration of durvalumab resulted in premature neonatal death.

8.3 Females and Males of Reproductive Potential

Contraception

Females

Based on its mechanism of action and data from animal studies, IMFINZI can cause fetal harm when administered to a pregnant woman [see *Use in Specific Populations (8.1)*]. Advise females of reproductive potential to use effective contraception during treatment with IMFINZI and for at least 3 months following the last dose of IMFINZI.

8.4 Pediatric Use

The safety and effectiveness of IMFINZI have not been established in pediatric patients.

8.5 Geriatric Use

Of the 182 patients treated with IMFINZI in patients with urothelial carcinoma, 112 patients were 65 years or older and 34 patients were 75 years or older. The overall response rate in patients 65 years or older was 15% (17/112) and was 12% (4/34) in patients 75 years or older. Grade 3 or 4 adverse reactions occurred in 38% (42/112) of patients 65 years or older and 35% (12/34) of patients 75 years or older.

Of the 476 patients treated with IMFINZI in the PACIFIC study, 45% were 65 years or older, while 7.6% were 75 years or older. No overall differences in safety or effectiveness were observed between patients 65 years or older and younger patients. The PACIFIC study did not include sufficient numbers of patients aged 75 years and over to determine whether they respond differently from younger patients.

10 OVERDOSAGE

There is no information on overdose with IMFINZI.

11 DESCRIPTION

Durvalumab is a programmed cell death ligand 1 (PD-L1) blocking antibody. Durvalumab is a human immunoglobulin G1 kappa (IgG1 κ) monoclonal antibody that is produced by recombinant DNA technology in Chinese Hamster Ovary (CHO) cell suspension culture.

IMFINZI (durvalumab) Injection for intravenous use is a sterile, preservative-free, clear to opalescent, colorless to slightly yellow solution, free from visible particles.

Each 500 mg vial of IMFINZI contains 500 mg of durvalumab in 10 mL solution. Each mL contains durvalumab, 50 mg, L-histidine (2 mg), L-histidine hydrochloride monohydrate (2.7 mg), α,α -trehalose dihydrate (104 mg), Polysorbate 80 (0.2 mg), and Water for Injection, USP.

Each 120 mg vial of IMFINZI contains 120 mg of durvalumab in 2.4 mL solution. Each mL contains durvalumab, 50 mg, L-histidine (2 mg), L-histidine hydrochloride monohydrate (2.7 mg), α,α -trehalose dihydrate (104 mg), Polysorbate 80 (0.2 mg), and Water for Injection, USP.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Expression of programmed cell death ligand-1 (PD-L1) can be induced by inflammatory signals (e.g., IFN- γ) and can be expressed on both tumor cells and tumor-associated immune cells in the tumor microenvironment. PD-L1 blocks T-cell function and activation through interaction with PD-1 and CD80 (B7.1). By binding to its receptors, PD-L1 reduces cytotoxic T-cell activity, proliferation, and cytokine production.

Durvalumab is a human immunoglobulin G1 kappa (IgG1 κ) monoclonal antibody that binds to PD-L1 and blocks the interaction of PD-L1 with PD-1 and CD80 (B7.1). Blockade of PD-L1/PD-1 and PD-L1/CD80 interactions releases the inhibition of immune responses, without inducing antibody dependent cell-mediated cytotoxicity (ADCC).

PD-L1 blockade with durvalumab led to increased T-cell activation in vitro and decreased tumor size in co-engrafted human tumor and immune cell xenograft mouse models.

12.3 Pharmacokinetics

The pharmacokinetics of durvalumab was studied in 1902 patients with doses ranging from 0.1 mg/kg (0.01 times the approved recommended dosage) to 20 mg/kg (2 times the approved recommended dosage) administered once every two, three, or four weeks.

PK exposure increased more than dose-proportionally at doses < 3 mg/kg (0.3 times the approved recommended dosage) and dose proportionally at doses \geq 3 mg/kg every 2 weeks. Steady state was achieved at approximately 16 weeks.

Distribution

The geometric mean (% coefficient of variation [CV%]) steady state volume of distribution was 5.6 (18%) L.

Elimination

Durvalumab clearance decreases over time, with a mean maximal reduction (CV%) from baseline values of approximately 23% (57%) resulting in a geometric mean (CV%) steady state clearance (CL_{ss}) of 8.2 mL/h (39%) at day 365; the decrease in CL_{ss} is not considered clinically relevant. The geometric mean (CV%) terminal half-life, based on baseline CL was approximately 18 (24%) days.

Specific Populations

Age (19–96 years), body weight (34-149 kg), sex, albumin levels, lactate dehydrogenase (LDH) levels, creatinine levels, soluble PD-L1, tumor type, race, mild renal impairment (creatinine clearance (CL_{cr}) 60 to 89 mL/min), moderate renal impairment (CL_{cr} 30 to 59 mL/min), mild hepatic impairment (bilirubin \leq ULN and AST > ULN or bilirubin > 1 to 1.5x ULN and any AST), or ECOG/WHO performance status had no clinically significant effect on the pharmacokinetics of durvalumab.

The effect of severe renal impairment (CL_{cr} 15 to 29 mL/min) or moderate hepatic impairment (bilirubin > 1.5 to 3x ULN and any AST) or severe hepatic impairment (bilirubin > 3x ULN and any AST) on the pharmacokinetics of durvalumab is unknown.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

Animal fertility studies have not been conducted with durvalumab. In repeat-dose toxicology studies with durvalumab in sexually mature cynomolgus monkeys of up to 3 months duration, there were no notable effects on the male and female reproductive organs.

13.2 Animal Toxicology and/or Pharmacology

In animal models, inhibition of PD-L1/PD-1 signaling increased the severity of some infections and enhanced inflammatory responses. M. tuberculosis-infected PD-1 knockout mice exhibit markedly decreased survival compared with wild-type controls, which correlated with increased bacterial proliferation and inflammatory responses in these animals. PD-L1 and PD-1 knockout mice have also shown decreased survival following infection with lymphocytic choriomeningitis virus.

14 CLINICAL STUDIES

14.1 Urothelial Carcinoma

The efficacy of IMFINZI was evaluated in the urothelial carcinoma cohort of Study 1108 (NCT01693562), a multicenter, multi-cohort, open-label clinical trial. In Study 1108, 182 patients with locally advanced or metastatic urothelial carcinoma were enrolled. Patients had progressed while on or after a platinum-based therapy, including those who progressed within 12 months of receiving therapy in a neo-adjuvant or adjuvant setting. These patients had initiated IMFINZI at least 13 weeks prior to the

data cut-off date. The trial excluded patients with a history of immunodeficiency; medical conditions that required systemic immunosuppression (not to exceed 10 mg per day of prednisone or equivalent); history of severe autoimmune disease; untreated CNS metastases; HIV; active tuberculosis, or hepatitis B or C infection. All patients received IMFINZI 10 mg/kg intravenously every 2 weeks for up to 12 months or until unacceptable toxicity or disease progression. Tumor assessments were performed at Weeks 6, 12, and 16, then every 8 weeks for the first year and every 12 weeks thereafter. The major efficacy outcome measures were confirmed Overall Response Rate (ORR) according to RECIST v1.1 as assessed by Blinded Independent Central Review (BICR), and duration of response (DoR).

The median age was 67 years (range: 34 to 88), 72% were male, 64% were White. Sixty six percent (66%) of patients had visceral metastasis (bone, liver, or lung), including 34% with liver metastasis. Lymph node only metastasis were present in 13% of patients. Sixty-six percent (66%) of patients had ECOG score of 1 and 41% of patients had a baseline creatinine clearance < 60 mL/min. The Bellmunt risk score (which includes ECOG score, baseline hemoglobin, and liver metastases) was 0 in 23%, 1 in 38%, 2 in 29%, and 3 in 9% of patients. Twenty percent (20%) of patients had disease progression following platinum containing neoadjuvant or adjuvant chemotherapy as their only prior line of therapy. Seventy percent (70%) of patients received prior cisplatin, 30% prior carboplatin and 35% received ≥ 2 prior lines of systemic therapy.

Tumor specimens were evaluated prospectively for PD-L1 expression on tumor cells (TC) and immune cells (IC) at a central laboratory using the VENTANA PD-L1 (SP263) Assay. Of the 182 patients, 52% were classified as PD-L1 high (if ICs involve > 1% of the tumor area, TC ≥ 25% or IC ≥ 25%; if ICs involve ≤ 1% of the tumor area, TC ≥ 25% or IC = 100%), 40% as PD-L1 low/negative (did not meet criterion for PD L1 high), and samples for 8% were not evaluable.

Table 6 summarizes the results in the urothelial carcinoma cohort of Study 1108. The median follow-up time was 5.6 months. In 37 patients who had received only neoadjuvant or adjuvant therapy prior to study entry, 24% responded.

Among the total 31 responding patients, 45% had ongoing responses of 6 months or longer and 16% had ongoing responses of 12 months or longer.

Table 6. Efficacy Results for Study 1108 Urothelial Carcinoma Cohort

	All Patients N = 182	PD-L1 High N = 95	PD-L1 Low/Negative N = 73	PD-L1 NE N = 14
Overall Response Rate by BICR n (%) (95% CI)	31 (17%) (11.9, 23.3)	25 (26%) (17.8, 36.4)	3 (4%) (0.9, 11.5)	3 (21%) (4.7, 50.8)
Complete Response	5	3	1	1
Partial Response	26	22	2	2
Median Duration of Response months (range)	NR (0.9+, 19.9+)	NR (0.9+, 19.9+)	12.3 (1.9+, 12.3)	NR (2.3+, 2.6+)

BICR = Blinded Independent Central Review; NE = Not Evaluable; NR = Not Reached; + denotes a censored value

14.2 Non-Small Cell Lung Cancer (NSCLC)

The efficacy of IMFINZI was evaluated in the PACIFIC study (NCT02125461), a multicenter, randomized, double-blind, placebo-controlled study in patients with unresectable Stage III NSCLC who completed at least 2 cycles of concurrent platinum-based chemotherapy and definitive radiation within 42 days prior to initiation of the study drug and had a WHO performance status of 0 or 1. The study excluded patients who had progressed following concurrent chemoradiation, patients with active or prior documented autoimmune disease within 2 years of initiation of the study or patients with medical

conditions that required systemic immunosuppression. Randomization was stratified by sex, age (< 65 years vs. ≥ 65 years), and smoking history (smoker vs. non-smoker). Patients were randomized 2:1 to receive IMFINZI 10 mg/kg or placebo intravenously every 2 weeks for up to 12 months or until unacceptable toxicity or confirmed RECIST v1.1-defined progression. Assessment of tumor status was performed every 8 weeks. The major efficacy outcome measures were progression-free survival (PFS) as assessed by a BICR RECIST v1.1, and overall survival (OS). Additional efficacy outcome measures included ORR and DoR assessed by BICR.

A total of 713 patients were randomized: 476 patients to the IMFINZI arm and 237 to the placebo arm. The study population characteristics were: median age of 64 years (range: 23 to 90); 70% male; 69% White and 27% Asian; 16% current smokers, 75% former smokers, and 9% never smokers; 51% WHO performance status of 1; 53% with Stage IIIA and 45% were Stage IIIB; 46% with squamous and 54% with non-squamous histology. All patients received definitive radiotherapy as per protocol, of which 92% received a total radiation dose of 54 Gy to 66 Gy; 99% of patients received concomitant platinum-based chemotherapy (55% cisplatin-based, 42% carboplatin-based chemotherapy, and 2% switched between cisplatin and carboplatin).

At a pre-specified interim analysis for OS based on 299 events (61% of total planned events), the study demonstrated a statistically significant improvement in OS in patients randomized to IMFINZI compared to placebo. The pre-specified interim analysis of PFS based on 371 events (81% of total planned events) demonstrated a statistically significant improvement in PFS in patients randomized to IMFINZI compared to placebo. Table 7 and Figure 1 summarizes the efficacy results for PACIFIC.

Table 7. Efficacy Results for the PACIFIC Study

Endpoint	IMFINZI (N = 476)*	Placebo (N = 237)*
Overall Survival (OS)†		
Number of deaths	183 (38%)	116 (49%)
Median in months (95% CI)	NR (34.7, NR)	28.7 (22.9, NR)
Hazard Ratio (95% CI)‡	0.68 (0.53, 0.87)	
p-value‡§	0.0025	
Progression-Free Survival (PFS)¶#		
Number (%) of patients with event	214 (45%)	157 (66%)
Median in months (95% CI)	16.8 (13.0, 18.1)	5.6 (4.6, 7.8)
Hazard Ratio (95% CI)‡¶	0.52 (0.42, 0.65)	
p-value‡§	< 0.0001	

* Among the ITT population, 7% in the IMFINZI arm and 10% in the placebo arm had non-measurable disease as assessed by BICR according to RECIST v1.1

† OS results are based on the interim OS analysis conducted at 299 OS events which occurred 46 months after study initiation

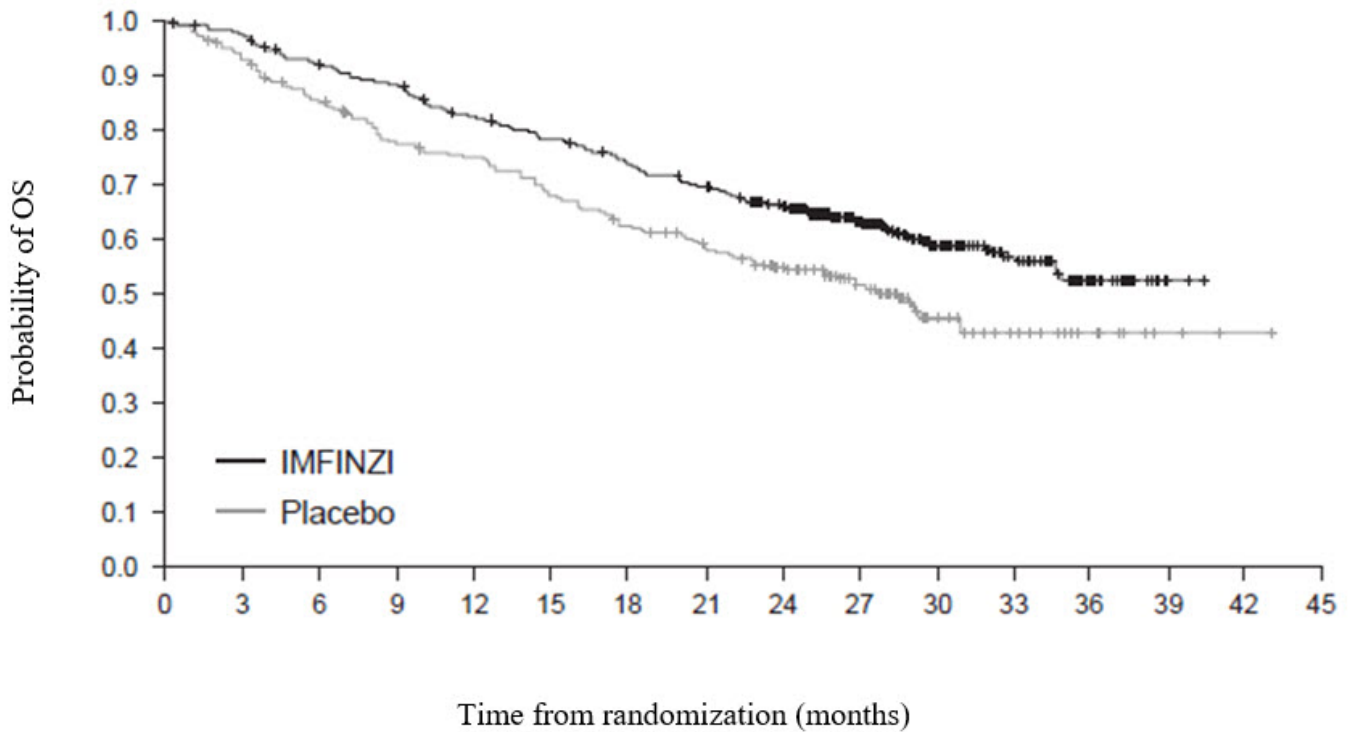
‡ Two-sided p-value based on a log-rank test stratified by sex, age, and smoking history

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

¶ As assessed by BICR RECIST v1.1

- # PFS results are based on the interim PFS analysis conducted at 371 PFS events which occurred 33 months after study initiation
- ▷ Pike estimator
- β Compared with allocated α of 0.011035 (Lan DeMets spending function approximating O'Brien Fleming boundary) for interim analysis

Figure 1 Kaplan-Meier Curves of Overall Survival in the PACIFIC Study



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

16 HOW SUPPLIED/STORAGE AND HANDLING

IMFINZI (durvalumab) Injection is a clear to opalescent, colorless to slightly yellow solution supplied in a carton containing one single-dose vial either as:

- 500 mg/10 mL (NDC 0310-4611-50)
- 120 mg/2.4 mL (NDC 0310-4500-12)

Store in a refrigerator at 2°C to 8°C (36°F to 46°F) in original carton to protect from light.

Do not freeze. Do not shake.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Inform patients of the risk of immune-mediated adverse reactions that may require corticosteroid treatment and interruption or discontinuation of IMFINZI, including:

- Pneumonitis: Advise patients to contact their healthcare provider immediately for any new or worsening cough, chest pain, or shortness of breath [see *Warnings and Precautions (5.1)*].
- Hepatitis: Advise patients to contact their healthcare provider immediately for jaundice, severe nausea or vomiting, pain on the right side of abdomen, lethargy, or easy bruising or bleeding [see *Warnings and Precautions (5.2)*].
- Colitis: Advise patients to contact their healthcare provider immediately for diarrhea, blood or mucus in stools, or severe abdominal pain [see *Warnings and Precautions (5.3)*].
- Endocrinopathies: Advise patients to contact their healthcare provider immediately for signs or symptoms of hypothyroidism, hyperthyroidism, adrenal insufficiency, type 1 diabetes mellitus, or hypophysitis [see *Warnings and Precautions (5.4)*].
- Nephritis: Advise patients to contact their healthcare provider immediately for signs or symptoms of nephritis [see *Warnings and Precautions (5.5)*].
- Dermatological Reactions: Advise patients to contact their healthcare provider immediately for signs or symptoms of severe dermatological reactions [see *Warnings and Precautions (5.6)*].
- Other Immune-Mediated Adverse Reactions: Advise patients to contact their healthcare provider immediately for signs or symptoms of aseptic meningitis, thrombocytopenic purpura, myocarditis, hemolytic anemia, myositis, uveitis, and keratitis [see *Warnings and Precautions (5.7)*].
- Infection: Advise patients to contact their healthcare provider immediately for infection [see *Warnings and Precautions (5.8)*].
- Infusion-Related Reactions: Advise patients to contact their healthcare provider immediately for signs or symptoms of infusion-related reactions [see *Warnings and Precautions (5.9)*].
- Embryo-Fetal Toxicity: Advise females of reproductive potential that IMFINZI can cause harm to a fetus and to inform their healthcare provider of a known or suspected pregnancy [see *Warnings and Precautions (5.10) and Use in Specific Populations (8.1, 8.3)*]. Advise females of reproductive potential to use effective contraception during treatment and for at least 3 months after the last dose of IMFINZI [see *Use in Specific Populations (8.3)*].
- Lactation: Advise female patients not to breastfeed while taking IMFINZI and for at least 3 months after the last dose [see *Warnings and Precautions (5.10) and Use in Specific Populations (8.2)*].

Manufactured for:

AstraZeneca Pharmaceuticals LP
Wilmington, DE 19850

By: AstraZeneca UK Limited
1 Francis Crick Ave.
Cambridge, England CB2 0AA
US License No. 2043

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MEDICATION GUIDE

IMFINZI[®] (im-FIN-zee)

(durvalumab)

Injection

What is the most important information I should know about IMFINZI?

IMFINZI is a medicine that may treat a type of cancer in the bladder and urinary tract or a type of lung cancer by working with your immune system.

IMFINZI can cause your immune system to attack normal organs and tissues and can affect the way they work. These problems can sometimes become serious or life-threatening and can lead to death.

Call or see your healthcare provider right away if you develop any symptoms of the following problems or these symptoms get worse:

Lung problems (pneumonitis). Signs and symptoms of pneumonitis may include:

- new or worsening cough
- shortness of breath
- chest pain

Liver problems (hepatitis). Signs and symptoms of hepatitis may include:

- yellowing of your skin or the whites of your eyes
- severe nausea or vomiting
- pain on the right side of your stomach area (abdomen)
- drowsiness
- dark urine (tea colored)
- bleeding or bruising more easily than normal
- feeling less hungry than usual

Intestinal problems (colitis). Signs and symptoms of colitis may include:

- diarrhea or more bowel movements than usual
- stools that are black, tarry, sticky, or have blood or mucus
- severe stomach area (abdomen) pain or tenderness

Hormone gland problems (especially the thyroid, adrenals, pituitary, and pancreas). Signs and symptoms that your hormone glands are not working properly may include:

- headaches that will not go away or unusual headaches
- extreme tiredness
- weight gain or weight loss
- dizziness or fainting
- feeling more hungry or thirsty than usual
- hair loss
- changes in mood or behavior, such as decreased sex drive, irritability, or forgetfulness
- feeling cold
- constipation
- your voice gets deeper
- urinating more often than usual
- nausea or vomiting
- stomach area (abdomen) pain

Kidney problems, including nephritis and kidney failure. Signs of kidney problems may include:

- decrease in the amount of urine
- blood in your urine
- swelling of your ankles
- loss of appetite

Skin problems. Signs of these problems may include:

- rash
- itching
- skin blistering

Problems in other organs. Signs and symptoms may include:

- neck stiffness
- low red blood cells (anemia)

- headache
- confusion
- fever
- chest pain, shortness of breath, or irregular heartbeat (myocarditis)
- changes in mood or behavior
- excessive bleeding or bruising
- muscle weakness or muscle pain
- blurry vision, double vision, or other vision problem
- eye pain or redness

Severe Infections. Signs and symptoms may include:

- fever
- cough
- frequent urination
- pain when urinating
- flu-like symptoms

Severe infusion reactions. Signs and symptoms of severe infusion reactions may include:

- chills or shaking
- itching or rash
- flushing
- shortness of breath or wheezing
- dizziness
- fever
- feel like passing out
- back or neck pain
- facial swelling

Getting medical treatment right away may help keep these problems from becoming more serious.

Your healthcare provider will check you for these problems during your treatment with IMFINZI. Your healthcare provider may treat you with corticosteroid or hormone replacement medicines. Your healthcare provider may delay or completely stop treatment with IMFINZI, if you have severe side effects.

What is IMFINZI?

IMFINZI is a prescription medicine used to treat:

- a type of cancer in the bladder and urinary tract called urothelial carcinoma. IMFINZI may be used when your urothelial carcinoma:
 - has spread or cannot be removed by surgery, **and**
 - you have tried chemotherapy that contains platinum, and it did not work or is no longer working.
- a type of lung cancer called non-small cell lung cancer (NSCLC). IMFINZI may be used when your NSCLC:
 - has not spread outside your chest
 - cannot be removed by surgery, **and**
 - has responded or stabilized with initial treatment with chemotherapy that contains platinum, given at the same time as radiation therapy.

It is not known if IMFINZI is safe and effective in children.

Before you receive IMFINZI, tell your healthcare provider about all of your medical conditions, 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
- are being treated for an infection
- are pregnant or plan to become pregnant. IMFINZI can harm your unborn baby. If you are able to 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. Talk to your healthcare provider about birth control methods that you can use during this time. Tell your healthcare provider right away if you become pregnant during treatment with IMFINZI.
- are breastfeeding or plan to breastfeed. It is not known if IMFINZI passes into your breast milk. Do not breastfeed during treatment and for at least 3 months after the last dose of IMFINZI.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

How will I receive IMFINZI?

- Your healthcare provider will give you IMFINZI into your vein through an intravenous (IV) line over 60 minutes.
- IMFINZI is usually given every 2 weeks.
- Your healthcare provider will decide how many treatments you need.
- Your healthcare provider will test your blood to check you for certain side effects.
- If you miss any appointments, call your healthcare provider as soon as possible to reschedule your appointment.

What are the possible side effects of IMFINZI?

IMFINZI can cause serious side effects, including:

See "What is the most important information I should know about IMFINZI?"

The most common side effects of IMFINZI in people with urothelial carcinoma include:

- | | |
|-----------------------|----------------------------------|
| • feeling tired | • nausea |
| • muscle or bone pain | • swelling of your arms and legs |
| • constipation | • urinary tract infection |
| • decreased appetite | |

The most common side effects of IMFINZI in people with NSCLC include:

- | | |
|---|--------------------------------------|
| • cough | • upper respiratory tract infections |
| • feeling tired | • shortness of breath |
| • inflammation in the lungs (pneumonitis) | • rash |

Tell your healthcare provider if you have any side effect that bothers you or that does not go away. These are not all the possible side effects of IMFINZI. Ask your healthcare provider or pharmacist for more information.

Call your healthcare provider for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of IMFINZI.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. If you would like more information about IMFINZI, talk with your healthcare provider. You can ask your healthcare provider for information about IMFINZI that is written for health professionals.

What are the ingredients in IMFINZI?

Active ingredient: durvalumab

Inactive ingredients: L-histidine, L-histidine hydrochloride monohydrate, α,α -trehalose dihydrate, polysorbate 80, water for injection, USP.

Manufactured for: AstraZeneca Pharmaceuticals LP, Wilmington, DE 19850

By: AstraZeneca UK Limited

1 Francis Crick Ave.

Cambridge, England CB2 0AA

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IMFINZI is a registered trademark of AstraZeneca group of companies.

For more information, call 1-800-236-9933 or go to www.IMFINZI.com

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This Medication Guide has been approved by the U.S. Food and Drug Administration.

Issued: 7/2019

PACKAGE/LABEL PRINCIPAL DISPLAY PANEL

NDC 0310-4500-12

Rx only

IMFINZI™

(durvalumab)

Injection

120 mg/2.4 mL

(50 mg/mL)

For Intravenous Infusion After Dilution

Single-dose vial. Discard unused portion.

Store at 2° to 8°C (36° to 46°F).

Do not freeze or shake.

Keep vial in original carton to protect from light.

Attention Pharmacist: Dispense the accompanying Medication Guide to each patient.

Do not use if vial seal is broken or missing.

Must dilute before use.

See prescribing information.

AstraZeneca



PACKAGE/LABEL DISPLAY PANEL

NDC 0310-4611-50

Rx only

IMFINZI™
(durvalumab)
Injection

500 mg/10 mL
(50 mg/mL)

For Intravenous Infusion After Dilution
Single-dose vial. Discard unused portion.
Store at 2° to 8°C (36° to 46°F).
Do not freeze or shake.

Keep vial in original carton to protect from light.

Attention Pharmacist: Dispense the accompanying Medication Guide to each patient.
Do not use if vial seal is broken or missing.

Must dilute before use.
See prescribing information.

AstraZeneca



IMFINZI

durvalumab injection, solution

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:0310-4500
Route of Administration	INTRAVENOUS		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
DURVALUMAB (UNII: 28 X28 X9 OKV) (DURVALUMAB - UNII:28 X28 X9 OKV)	DURVALUMAB	120 mg in 2.4 mL

Inactive Ingredients

Ingredient Name	Strength
HISTIDINE (UNII: 4QD397987E)	4.8 mg in 2.4 mL
HISTIDINE MONOHYDROCHLORIDE MONOHYDRATE (UNII: X573657P6P)	6.5 mg in 2.4 mL
TREHALOSE DIHYDRATE (UNII: 7YIN7J07X4)	250 mg in 2.4 mL

POLYSORBATE 80 (UNII: 6OZP39ZG8H)			0.5 mg in 2.4 mL	
WATER (UNII: 059QF0KO0R)				
Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0310-4500-12	1 in 1 CARTON	05/01/2017	
1		2.4 mL in 1 VIAL; Type 0: Not a Combination Product		
Marketing Information				
Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date	
BLA	BLA761069	05/01/2017		

IMFINZI				
durvalumab injection, solution				
Product Information				
Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:0310-4611	
Route of Administration	INTRAVENOUS			
Active Ingredient/Active Moiety				
	Ingredient Name	Basis of Strength	Strength	
	DURVALUMAB (UNII: 28X28X9OKV) (DURVALUMAB - UNII:28X28X9OKV)	DURVALUMAB	500 mg in 10 mL	
Inactive Ingredients				
	Ingredient Name	Strength		
	HISTIDINE (UNII: 4QD397987E)	20 mg in 10 mL		
	HISTIDINE MONOHYDROCHLORIDE MONOHYDRATE (UNII: X573657P6P)	27 mg in 10 mL		
	TREHALOSE DIHYDRATE (UNII: 7YIN7J07X4)	1040 mg in 10 mL		
	POLYSORBATE 80 (UNII: 6OZP39ZG8H)	2 mg in 10 mL		
	WATER (UNII: 059QF0KO0R)			
Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0310-4611-50	1 in 1 CARTON	05/01/2017	
1		10 mL in 1 VIAL; Type 0: Not a Combination Product		
Marketing Information				
Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date	

BLA	BLA761069	05/01/2017	
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Labeler - AstraZeneca Pharmaceuticals LP (054743190)

Registrant - AstraZeneca PLC (230790719)

Revised: 8/2019

AstraZeneca Pharmaceuticals LP