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Imfinzi® 120 mg/2.4 ml

Imfinzi® 500 mg/10 ml

Durvalumab 120 mg, 500 mg

Solution for infusion

Patient safety information card

The marketing of Imfinzi is subject to a risk management plan (RMP) including a 'patient alert card'. The 'patient alert card', emphasizes important safety information that the patient should be aware of before and during treatment. Please explain to the patient the need to review the card before starting treatment.

HCP guide

This product is marketed with HCP guide providing important safety information. Please ensure you are familiar with this material as it contains important safety information.

1. INDICATIONS AND USAGE

1.1 Urothelial Carcinoma

IMFINZI is indicated for the treatment of patients with PD-L1 high (Tumor cell ≥ 25% or IC ≥ 25%) 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.

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 Dosing 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 Dose Modifications

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

Table 1. Recommended Treatment Modifications for IMFINZI

Adverse Reactions	**Severity[a]**	**IMFINZI Treatment Modification**	**Corticosteroid Treatment Unless Otherwise Specified**
Pneumonitis [see Warnings and Precautions (5.1)]	Grade 2	Withhold dose[b]	Initial dose of 1 mg/kg/day to 2 mg/kg/day prednisone or equivalent followed by a taper
	Grade 3 or 4	Permanently discontinue	Initial dose of 1 mg/kg/day to 4 mg/kg/day prednisone or equivalent followed by a taper

Hepatitis [see Warnings and Precautions (5.2)]	Grade 2 ALT or AST >3-5xULN or total bilirubin >1.5-3xULN	Withhold dose[b]	Initial dose of 1 mg/kg/day to 2 mg/kg/day prednisone or equivalent followed by a taper
	Grade 3 ALT or AST ≤8xULN or total bilirubin ≤5xULN		
	Grade 3 ALT or AST >8xULN or total bilirubin >5xULN	Permanently discontinue	
	Concurrent ALT or AST >3xULN and total bilirubin >2xULN with no other cause		
Colitis or diarrhea [see Warnings and Precautions (5.3)]	Grade 2	Withhold dose[b]	Initial dose of 1 mg/kg/day to 2 mg/kg/day prednisone or equivalent followed by a taper
	Grade 3 or 4	Permanently discontinue	
Hypothyroidism [see Warnings and Precautions (5.4)]	Grade 2-4		Initiate thyroid hormone replacement as clinically indicated
Hyperthyroidism [see Warnings and Precautions (5.4)]	Grade 2-4	Withhold dose until clinically stable	Symptomatic management
Adrenal insufficiency, Hypophysitis/Hypopituitarism [see Warnings and Precautions (5.4)]	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

Type 1 Diabetes Mellitus [see Warnings and Precautions (5.4)]	Grade 2-4	Withhold dose until clinically stable	Initiate treatment with insulin as clinically indicated
Nephritis [see Warnings and Precautions (5.5)]	Grade 2 Creatinine >1.5-3x ULN	Withhold dose[b]	Initial dose of 1 mg/kg/day to 2 mg/kg/day prednisone or equivalent followed by a taper
	Grade 3 Creatinine >3-6x ULN	Permanently discontinue	
	Grade 4 Creatinine >6x ULN		
Rash or dermatitis [see Warnings and Precautions (5.5)]	Grade 2 for >1 week	Withhold dose[b]	Consider initial dose of 1 mg/kg/day to 2 mg/kg/day prednisone or equivalent followed by a taper
	Grade 3		
	Grade 4	Permanently discontinue	
Infection [see Warnings and Precautions (5.6)]	Grade 3 or 4	Withhold dose	Symptomatic management; treat with anti-infectives for suspected or confirmed infections
Infusion-related reactions [see Warnings and Precautions (5.7)]	Grade 1 or 2	Interrupt or slow the rate of infusion	Consider pre-medications with subsequent doses
	Grade 3 or 4	Permanently discontinue	
Other	Grade 3	Withhold dose[b]	Symptomatic management
	Grade 4	Permanently discontinue	Consider initial dose of 1 mg/kg/day to 4 mg/kg/day prednisone or equivalent followed by taper

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

[b] Based on severity of the adverse reactions, IMFINZI should be withheld and corticosteroids administered. Consider increasing dose of corticosteroids and/or other systemic immunosuppressants if there is worsening or no improvement. Corticosteroid taper should be initiated when adverse reaction improves to < Grade 1 and should be continued over at least 1 month. For adverse reactions that do not result in permanent discontinuation, resume treatment when adverse reaction returns to ≤ Grade 1 and the corticosteroid dose has been reduced to <10 mg prednisone or equivalent per day.

2.4 Preparation and Administration

Preparation

- Visually inspect drug product for particulate matter and discoloration. IMFINZI is clear to opalescent, colorless to slightly yellow solution, free from visible particles. 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
- 4 hours at room temperature up to 25°C

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

4 CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients listed in section 11.

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 ≥ 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 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 diarrhoea 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, requirement for 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 2.0% 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 (1.0%). 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 Study 1108 whose disease has progressed during or after one standard platinum-based regimen. Patients received 10 mg/kg IMFINZI via intravenous infusion 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 events 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, 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 UC Cohort

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

Metabolism and Nutrition Disorders		
Decreased appetite/Hypophagia	19	1
Musculoskeletal and Connective Tissue Disorders		
Musculoskeletal pain[5]	24	4
Respiratory, Thoracic, and Mediastinal Disorders		
Dyspnea/Exertional Dyspnea	13	2
Cough/Productive Cough	10	0
Skin and Subcutaneous Tissue Disorders		
Rash[6]	11	1

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

2 Includes asthenia, lethargy, and malaise

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

4 Includes cystitis, candiduria and urosepsis

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

6 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 ≥1% Patients in UC Cohort Study 1108

Laboratory Test	Grade 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 ≥ 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 ≥ 10% Patients in the PACIFIC Study

	IMFINZI N=475		**Placebo[1] N=234**	
Adverse Reaction	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[2]/Radiation Pneumonitis	34	3.4	25	3.0
Dyspnea[3]	25	1.5	25	2.6
Gastrointestinal Disorders				
Diarrhea	18	0.6	19	1.3
Abdominal pain[4]	10	0.4	6	0.4
Endocrine Disorders				
Hypothyroidism[5]	12	0.2	1.7	0
Skin and Subcutaneous Tissue Disorders				
Rash[6]	23	0.6	12	0
Pruritus[7]	12	0	6	0
General Disorders				

Fatigue[8]	34	0.8	32	1.3
Pyrexia	15	0.2	9	0
Infections				
Upper respiratory tract infections[9]	26	0.4	19	0
Pneumonia[10]	17	7	12	6

[1] 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

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

[3] includes dyspnea and exertional dyspnea

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

[5] includes autoimmune hypothyroidism and hypothyroidism

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

[7] includes pruritus generalized and pruritus

[8] includes asthenia and fatigue

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

[10] 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

	IMFINZI		Placebo	
Laboratory Abnormality	**All Grades [1] (%)[2]**	**Grade 3 or 4 (%)**	**All Grades [1] (%)[2]**	**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

[1] Graded according to NCI CTCAE version 4.0
[2] 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 IMFINZI 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 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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il)

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 increased 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 clinical dose of 10 mg/kg of durvalumab (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 (IgG1κ) 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, α,α-trehalose dihydrate (104 mg), L-histidine hydrochloride monohydrate (2.7 mg), L-histidine (2 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, α,α-trehalose dihydrate (104 mg), L-histidine hydrochloride monohydrate (2.7 mg), L-histidine (2 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-gamma) 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 (IgG1κ) 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.

12.2 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 less than 3 mg/kg (0.3 times the approved recommended dosage) and dose proportionally at doses greater than or equal to 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 (CLss) of 8.2 mL/h (39%) at day 365; the decrease in CLss 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 (CLcr) 60 to 89 mL/min), moderate renal impairment (CLcr 30 to 59 mL/min), mild hepatic impairment (bilirubin less than or equal to ULN and AST greater than ULN or bilirubin greater than 1.0 to 1.5 times 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 (CLcr 15 to 29 mL/min) or moderate hepatic impairment (bilirubin greater than 1.5 to 3.0 times ULN and any AST) or severe hepatic

impairment (bilirubin greater than 3.0 times 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 urothelial carcinoma cohort of Study 1108(NCT01693562) a multicenter, multicohort, 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 durvalumab therapy 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/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 of <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 neo-adjuvant 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 1.1-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 1.1 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)[1]**	**Placebo (N = 237)[1]**
Overall Survival (OS)[2]		
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)[3]	0.68 (0.53, 0.87)	
p-value[3,4]	0.0025	
Progression-Free Survival (PFS)[5,6]		
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)[3,7]	0.52 (0.42, 0.65)	
p-value[3,8]	< 0.0001	

[1] 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

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

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

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

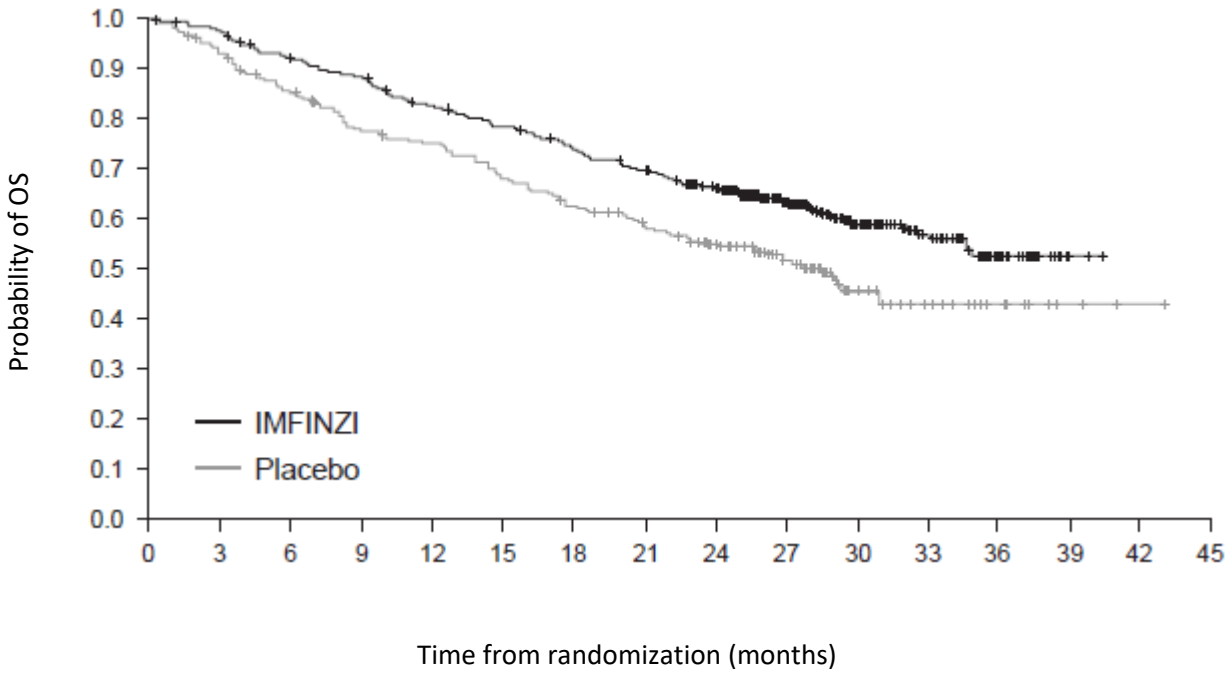
[5] As assessed by BICR RECIST v1.1

[6] PFS results are based on the interim PFS analysis conducted at 371 PFS events which occurred 33 months after study initiation

[7] Pike estimator

[8] 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 (159-98-35281-00)
- 120 mg/2.4 mL (159-97-35280-00)

Store in a refrigerator at 2°C to 8°C in original carton to protect from light.

Do not freeze. Do not shake.

Shelf life

The expiry date of the product is indicated on the packaging materials.

Manufacture:

Catalent Indiana LLC, USA

1300 South Patterson Drive Bloomington, IN 47403

USA

License holder:

AstraZeneca (Israel) Ltd.,

P.O.B 1455, Hod Hasharon 4524075.