Imfinzi®

Durvalumab 50 mg/1ml

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.

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.

1.3 Small Cell Lung Cancer

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

1.4 Biliary Tract Cancers

IMFINZI in combination with gemcitabine and cisplatin is indicated for the first-line treatment of adults with locally advanced, unresectable, or metastatic biliary tract cancer (BTC)

2. DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended dosages for IMFINZI as a single agent and IMFINZI in combination with chemotherapy are presented in Table 1 *[see Clinical Studies (14)]*.

IMFINZI is administered as an intravenous infusion over 60 minutes after dilution.

Table 1. Recommended Dosages of IMFINZI

Indication	**Recommended IMFINZI dosage**	**Duration of Therapy**
Urothelial Carcinoma	Patients with a body weight of 30 kg and more: 10 mg/kg every 2 weeks or 1500 mg every 4 weeks Patients with a body weight of less than 30 kg: 10 mg/kg every 2 weeks	Until disease progression or unacceptable toxicity
Unresectable stage III NSCLC	Patients with a body weight of 30 kg and more: 10 mg/kg every 2 weeks Or 1500 mg every 4 weeks Patients with a body weight of less than 30 kg:	Until disease progression, unacceptable toxicity, or a maximum of 12 months

	10 mg/kg every 2 weeks or 20 mg/kg every 4 weeks	
ES-SCLC	Patients with a body weight of 30 kg and more: 1500 mg in combination with chemotherapy[1] every 3 weeks (21 days) for 4 cycles, followed by 1500 mg every 4 weeks as a single agent Patients with a body weight of less than 30 kg: 20 mg/kg in combination with chemotherapy every 3 weeks (21 days) for 4 cycles, followed by 20 mg/kg every 4 weeks as a single agent	Until disease progression or unacceptable toxicity
BTC	Patients with a body weight of 30 kg and more: 1,500 mg in combination with chemotherapy* every 3 weeks (21 days) followed by 1,500 mg every 4 weeks as a single agent Patients with a body weight of less than 30 kg: 20 mg/kg in combination with chemotherapy* every 3 weeks (21 days). followed by 20 mg/kg every 4 weeks as a single agent	Until disease progression or until unacceptable toxicity

* Administer IMFINZI prior to chemotherapy on the same day. When IMFINZI is administered in combination with chemotherapy, refer to the Prescribing Information for appropriate

chemotherapeutic agent for dosing information.

2.2 Dose Modifications for Adverse Reactions

No dose reductions are recommended. Withhold and/or discontinue IMFINZI to manage adverse reactions as described in Table 2.

Table 2. Recommended Treatment Modifications for IMFINZI

Adverse Reactions	**Severity[1]**	**Dosage Modification**
Pneumonitis [see Warnings and Precautions (5.1)]	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

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 or thyroiditis [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 (including Pemphigoid) [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)[2] .
	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

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

[2] For myasthenia gravis permanently discontinue IMFINZI if the adverse reaction does not resolve to ≤ Grade 1 within 30 days or if there are signs of respiratory and/or autonomic insufficiency.

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 the infusion solution is not administered immediately and needs to be stored, the time from preparation until the completion of the infusion should not exceed:
    - 30 days in a refrigerator at 2°C to 8°C
    - 12 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 Adverse Reactions

IMFINZI is a monoclonal antibody that belongs to a class of drugs that bind to either the programmed death-receptor 1 (PD-1) or the PD-ligand 1 (PD-L1), blocking the PD-1/PD-L1 pathway, thereby removing inhibition of the immune response, potentially breaking peripheral tolerance and inducing immune-mediated adverse reactions. Important immune-mediated adverse reactions listed under Warnings and Precautions may not include all possible severe and fatal immune-mediated reactions.

Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue. Immune-mediated adverse reactions can occur at any time after starting treatment with a PD-1/PDL1 blocking antibody. While immune-mediated adverse reactions usually manifest during treatment with PD-1/PDL1 blocking antibodies, immune-mediated adverse reactions can also manifest after discontinuation of PD-1/PD-L1 blocking antibodies.

Early identification and management of immune-mediated adverse reactions are essential to ensure safe use of PD-1/PD-L1 blocking antibodies. Monitor patients closely for symptoms and signs that may be clinical manifestations of underlying immune-mediated adverse reactions. Evaluate liver enzymes, creatinine, and thyroid function at baseline and periodically during treatment. In cases of suspected immune-mediated adverse reactions, initiate appropriate workup to exclude alternative etiologies, including infection. Institute medical management promptly, including specialty consultation as appropriate.

Withhold or permanently discontinue IMFINZI depending on severity [see Dosage and Administration (2.2)]. In general, if IMFINZI requires interruption or discontinuation, administer systemic corticosteroid therapy (1 mg to 2 mg/kg/day prednisone or equivalent) until improvement to Grade 1 or less. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Consider administration of other systemic immunosuppressants in patients whose immune-mediated adverse reactions are not controlled with corticosteroid therapy.

Toxicity management guidelines for adverse reactions that do not necessarily require systemic steroids (e.g., endocrinopathies and dermatologic reactions) are discussed below.

Immune-Mediated Pneumonitis

IMFINZI can cause immune-mediated pneumonitis The incidence of pneumonitis is higher in patients who have received prior thoracic radiation.

In Patients Who did Not Receive Recent Prior Radiation

In patients who received IMFINZI on clinical trials in which radiation therapy was generally not administered immediately prior to initiation of IMFINZI, the incidence of immune-mediated pneumonitis was 2.4% (34/1414), , including fatal (<0.1%), and Grade 3-4 (0.4%) adverse reactions. Events resolved in 19 of the 34 patients and resulted in permanent discontinuation in 5 patients. Systemic corticosteroids were required in 19 patients (19/34) with pneumonitis who did not receive chemoradiation prior to initiation of IMFINZI.

In Patients Who Received Recent Prior Radiation

The incidence of pneumonitis (including radiation pneumonitis) in patients with unresectable Stage III NSCLC following definitive chemoradiation within 42 days prior to initiation of IMFINZI in PACIFIC was 18.3% (87/475) in patients receiving IMFINZI and 12.8% (30/234) in patients receiving placebo. Of the patients who received IMFINZI (475), 1.1% were fatal and 2.7% were Grade 3 adverse reactions. Events resolved in 50 of the 87 patients and resulted in permanent discontinuation in 27 patients.

Systemic corticosteroids were required in 64 patients (64/87) with pneumonitis who had received chemoradiation prior to initiation of IMFINZI, while 2 patients required use of infliximab with high-dose steroids.

The frequency and severity of immune-mediated pneumonitis in patients who did not receive definitive chemoradiation prior to IMFINZ were similar whether IMFINZI was given as a single agent in patients with various cancers in a pooled data set or in patients with ES-SCLC or BTC when given in combination with chemotherapy.

Immune-Mediated Colitis

IMFINZI can cause immune-mediated colitis that is frequently associated with diarrhea. Cytomegalovirus (CMV) infection/reactivation has been reported in patients with corticosteroid-refractory immune-mediated colitis. In cases of corticosteroid-refractory colitis, consider repeating infectious workup to exclude alternative etiologies.

Immune-mediated colitis occurred in 2% (37/1889) of patients receiving IMFINZI, including Grade 4 (<0.1%) and Grade 3 (0.4%) adverse reactions. Events resolved in 27 of the 37 patients and resulted in permanent discontinuation in 8

patients. Systemic corticosteroids were required in all patients with immune-mediated colitis, while 2 patients (2/37) required other immunosuppressants (e.g. infliximab, mycophenolate).

Immune-Mediated Hepatitis
IMFINZI can cause immune-mediated hepatitis.

Immune-mediated hepatitis occurred in 2.8% (52/1889) of patients receiving IMFINZI, including fatal (0.2%), Grade 4 (0.3%) and Grade 3 (1.4%) adverse reactions. Events resolved in 21 of the 52 patients and resulted in permanent discontinuation of IMFINZI in 6 patients. Systemic corticosteroids were required in all patients with immune-mediated hepatitis, while 2 patients (2/52) required use of mycophenolate with high-dose steroids.

Immune-Mediated Endocrinopathies

Adrenal Insufficiency

IMFINZI can cause primary or secondary adrenal insufficiency. For Grade 2 or higher adrenal insufficiency, initiate symptomatic treatment, including hormone replacement as clinically indicated. Withhold or permanently discontinue IMFINZI based on the severity [see Dosage and Administration (2.2)].

Immune-mediated adrenal insufficiency occurred in 0.5% (9/1889) of patients receiving IMFINZI, including Grade 3 (<0.1%) adverse reactions. Events resolved in 1 of the 9 patients and did not lead to permanent discontinuation of IMFINZI in any patients. Systemic corticosteroids were required in all patients with adrenal insufficiency; of these, the majority remained on systemic corticosteroids.

Hypophysitis

IMFINZI can cause immune-mediated hypophysitis. Hypophysitis can present with acute symptoms associated with mass effect such as headache, photophobia, or visual field cuts. Hypophysitis can cause hypopituitarism. Initiate symptomatic treatment including hormone replacement as clinically indicated. Withhold or permanently discontinue IMFINZI depending on severity [see Dosage and Administration (2.2)].

Grade 3 hypophysitis / hypopituitarism occurred in <0.1% (1/1889) patients who received IMFINZI. Treatment with systemic corticosteroids was administered in this patient. The event did not lead to permanent

discontinuation of IMFINZI.

Thyroid Disorders

IMFINZI can cause immune-mediated thyroid disorders. Thyroiditis can present with or without endocrinopathy. Hypothyroidism can follow hyperthyroidism. Initiate hormone replacement therapy for hypothyroidism or institute medical management of hyperthyroidism as clinically indicated. Withhold or discontinue IMFINZI based on the severity [see Dosage and Administration (2.2)].

Thyroiditis: Immune-mediated thyroiditis occurred in 0.5% (9/1889) of patients receiving IMFINZI, including Grade 3 (<0.1%) adverse reactions. Events resolved in 4 of the 9 patients and resulted in permanent discontinuation in 1 patient. Systemic corticosteroids were required in 3 patients (3/9) with immune-mediated thyroiditis, while 8 patients (8/9) required endocrine therapy.

Hyperthyroidism: Immune-mediated hyperthyroidism occurred in 2.1% (39/1889) of patients receiving IMFINZI. Events resolved in 30 of the 39 patients and did not lead to permanent discontinuation of IMFINZI in any patients. Systemic corticosteroids were required in 9 patients (9/39) with immune mediated hyperthyroidism, while 35 patients (35/39) required endocrine therapy.

Hypothyroidism: Immune-mediated hypothyroidism occurred in 8.3% (156/1889) of patients receiving IMFINZI, including Grade 3 (<0.1%) adverse reactions. Events resolved in 31 of the 156 patients and did not lead to permanent discontinuation of IMFINZI in any patients. Systemic corticosteroids were required in 11 patients (11/156) and the majority of patients (152/156) required long-term thyroid hormone replacement.

Type 1 Diabetes Mellitus which can present with diabetic ketoacidosis: Monitor patients for hyperglycemia or other signs and symptoms of diabetes. Initiate treatment with insulin as clinically indicated. Withhold or permanently discontinue IMFINZI based on the severity *[see Dosage and Administration (2.2)].*

Grade 3 immune-mediated type 1 diabetes mellitus occurred in <0.1% (1/1889) of patients receiving IMFINZI. This patient required long-term insulin therapy and IMFINZI was permanently discontinued. Two additional patients (0.1%, 2/1889) had events of hyperglycemia requiring insulin therapy that did not resolve at the time of reporting.

Immune-Mediated Nephritis with Renal Dysfunction

IMFINZI can cause immune-mediated nephritis.

Immune-mediated nephritis occurred in 0.5% (10/1889) of patients receiving IMFINZI, including Grade 3 (<0.1%) adverse reactions. Events resolved in 5 of the 10 patients and resulted in permanent discontinuation in 3 patients. Systemic corticosteroids were required in all patients with immune mediated nephritis.

Immune-Mediated Dermatologic Reactions

IMFINZI can cause immune-mediated rash or dermatitis. Exfoliative dermatitis including Stevens Johnson Syndrome (SJS) drug rash with eosinophilia and systemic symptoms (DRESS), and toxic epidermal necrolysis (TEN) has occurred with PD-1/L-1 blocking antibodies. Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate non-exfoliative rashes. Withhold or permanently discontinue IMFINZI depending on severity [see Dosage and Administration (2.2)]

Immune-mediated rash or dermatitis occurred in 1.8% (34/1889) of patients receiving IMFINZI, including Grade 3 (0.4%) adverse reactions. Events resolved in 19 of the 34 patients and resulted in permanent discontinuation in 2 patients. Systemic corticosteroids were required in all patients with immune-mediated rash or dermatitis.

Other Immune-Mediated Adverse Reactions

The following clinically significant, immune-mediated adverse reactions occurred at an incidence of less than 1% each in patients who received IMFINZI or were reported with the use of other PD-1/PD-L1 blocking antibodies:

Cardiac/vascular: Myocarditis, pericarditis, vasculitis.

Nervous system: Meningitis, encephalitis, myelitis and demyelination, myasthenic syndrome/myasthenia gravis (including exacerbation), Guillain-Barré syndrome, nerve paresis, autoimmune neuropathy.

Ocular: Uveitis, iritis, and other ocular inflammatory toxicities can occur. Some cases can be associated with retinal detachment. Various grades of visual impairment to include blindness can occur. If uveitis occurs in

combination with other immune-mediated adverse reactions, consider a Vogt-Koyanagi-Harada like syndrome, as this may require treatment with systemic steroids to reduce the risk of permanent vision loss.

Gastrointestinal: Pancreatitis including increases in serum amylase and lipase levels, gastritis, duodenitis.

Musculoskeletal and connective tissue disorders: Myositis/polymyositis, rhabdomyolysis and associated sequelae including renal failure, arthritis, polymyalgia rheumatic.

Endocrine: Hypoparathyroidism

Other (hematologic/immune): Hemolytic anemia, aplastic anemia, hemophagocytic lymphohistiocytosis, systemic inflammatory response syndrome, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immune thrombocytopenia, solid organ transplant rejection.

5.2 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 (2.2)]*. For Grade 1 or 2 infusion-related reactions, consider using pre-medications with subsequent doses.

infusion- related reactions occurred in 2.2% (42/1889) of patients receiving IMFINZI, including Grade 3 (0.3%) adverse reactions.

5.3 Complications of Allogeneic HSCT after IMFINZI

Fatal and other serious complications can occur in patients who receive allogeneic hematopoietic stem cell transplantation (HSCT) before or after being treated with a PD-1/L-1 blocking antibody. Transplant related complications include hyperacute graft-versus-host-disease (GVHD), acute GVHD, chronic GVHD, hepatic veno-occlusive disease (VOD) after reduced intensity conditioning, and steroid-requiring febrile syndrome (without an identified infectious cause). These complications may occur despite intervening therapy between PD-1/L-1 blockade and allogeneic HSCT.

Follow patients closely for evidence of transplant-related complications and intervene promptly.

Consider the benefit versus risks of treatment with a PD-1/L-1 blocking antibody prior to or after an allogeneic HSCT.

5.4 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 Adverse Reactions [see Warnings and Precautions (5.1)].
- Infusion-Related Reactions [see Warnings and Precautions (5.2)].

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 970 patients with advanced 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. In these trials, IMFINZI was administered at a dose of 10 mg/kg 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 also reflect exposure to IMFINZI in combination with chemotherapy in 265 patients from the CASPIAN study (a randomized, open-label study in patients with ES-SCLC), in 338 patients from the TOPAZ-1 study (a randomized, double-blind study in patients with BTC). In the CASPIAN and TOPAZ-1

studies, IMFINZI was administered at a dose of 1,500 mg every 3 or 4 weeks.

The data described in this section reflect exposure to IMFINZI in patients with Stage III NSCLC enrolled in the PACIFIC study, in patients with ES-SCLC enrolled in the CASPIAN study and in patients with BTC enrolled in the TOPAZ-1 study.

Urothelial Carcinoma

The safety of IMFINZI was evaluated 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 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 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 3 summarizes the adverse reactions that occurred in ≥10% of patients, while Table 4 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 3. Adverse Reactions in ≥10% of Patients in study 1108 Urothelial Carcinoma Cohort

	IMFINZI (N=182)	
Adverse Reaction	All Grades (%)	Grades 3 – 4 (%)
Gastrointestinal Disorders		
Constipation	21	1.1
Nausea	16	1.6
Abdominal pain[1]	14	2.7
Diarrhea/Colitis	13	1.1
General Disorders and Administration		
Fatigue[2]	39	6
Peripheral edema[3]	15	1.6
Pyrexia/Tumor associated fever	14	0.5
Infections		
Urinary tract infection[4]	15	4.4
Metabolism and Nutrition Disorders		
Decreased appetite/Hypophagia	19	0.5
Musculoskeletal and Connective Tissue Disorders		
Musculoskeletal pain[5]	24	3.8
Respiratory, Thoracic, and Mediastinal Disorders		
Dyspnea/Exertional Dyspnea	13	2.2
Cough/Productive Cough	10	0
Skin and Subcutaneous Tissue Disorders		
Rash[6]	11	0.5

1 Includes abdominal pain upper, abdominal pain lower and flank pain Includes asthenia, lethargy, and malaise

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

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

Laboratory Abnormality	Grade 3 – 4 %
Hyponatremia	12
Lymphopenia	11
Anemia	8
Increased alkaline phosphatase	4.1
Hypermagnesemia	4.2
Hypercalcemia	3
Hyperglycemia	3
Increased AST	2.4
Increased ALT	0.6
Hyperbilirubinemia	1.2
Increased creatinine	1.2
Neutropenia	1.2
Hyperkalemia	1.2
Hypokalemia	1.2
Hypoalbuminemia	1.2

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

Table 5. 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
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

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

Table 6. 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)

Small Cell Lung Cancer

The safety of IMFINZI in combination with etoposide and either carboplatin or cisplatin in previously untreated ES-SCLC was evaluated in CASPIAN, a randomized, open-label, multicenter, active-controlled trial. A total of 265 patients received IMFINZI 1,500 mg in combination with chemotherapy every 3 weeks for 4 cycles followed by IMFINZI 1,500 mg every 4 weeks until disease progression or unacceptable toxicity. The trial excluded patients with active or prior autoimmune disease or with medical conditions that required systemic corticosteroids or immunosuppressants [see Clinical Studies (14.2)].

Among 265 patients receiving IMFINZI, 49% were exposed for 6 months or longer and 19% were exposed for 12 months or longer.

Among 266 patients receiving chemotherapy alone, 57% of the patients received 6 cycles of chemotherapy and 8% of the patients received prophylactic cranial irradiation (PCI) after chemotherapy.

IMFINZI was discontinued due to adverse reactions in 7% of the patients receiving IMFINZI plus chemotherapy. These include pneumonitis, hepatotoxicity, neurotoxicity, sepsis, diabetic ketoacidosis and pancytopenia (1 patient each). Serious adverse reactions occurred in 31% of patients receiving IMFINZI plus chemotherapy. The most frequent serious adverse reactions reported in at least 1% of patients were febrile neutropenia (4.5%), pneumonia (2.3%), anemia (1.9%), pancytopenia (1.5%), pneumonitis (1.1%) and COPD (1.1%). Fatal adverse reactions occurred in 4.9% of patients receiving IMFINZI plus chemotherapy. These include pancytopenia, sepsis, septic shock, pulmonary artery thrombosis, pulmonary embolism, and hepatitis (1 patient each) and sudden death (2 patients). The most common adverse reactions (occurring in ≥ 20% of patients) were nausea, fatigue/asthenia and alopecia.

Table 7 summarizes the adverse reactions that occurred in patients treated with IMFINZI plus chemotherapy.

Table 7. Adverse Reactions Occurring in ≥ 10% of Patients in the CASPIAN study

	IMFINZI with etoposide and either carboplatin or cisplatin N = 265		**Etoposide and either carboplatin or cisplatin N = 266**	
Adverse Reaction	**All Grades (%)**	**Grade 3-4 (%)**	**All Grades (%)**	**Grade 3-4 (%)**
Respiratory, thoracic and mediastinal disorders				
Cough/Productive Cough	**15**	**0.8**	**9**	**0**
Gastrointestinal disorders				
Nausea	**34**	**0.4**	**34**	**1.9**
Constipation	**17**	**0.8**	**19**	**0**
Vomiting	**15**	**0**	**17**	**1.1**
Diarrhea	**10**	**1.1**	**11**	**1.1**
Endocrine disorders				

Hyperthyroidism[a]	**10**	**0**	**0.4**	**0**
Skin and subcutaneous tissue disorders				
Alopecia	**31**	**1.1**	**34**	**0.8**
Rash[b]	**11**	**0**	**6**	**0**
General disorders and administration site conditions				
Fatigue/Asthenia	**32**	**3.4**	**32**	**2.3**
Metabolism and nutrition disorders				
Decreased appetite	**18**	**0.8**	**17**	**0.8**

[a] Includes hyperthyroidism and Basedow's disease

[b] Includes rash erythematous, rash generalized, rash macular, rash maculopapular, rash papular, rash pruritic, rash pustular, erythema, eczema, rash and dermatitis

Table 8 summarizes the laboratory abnormalities that occurred in at least 20% of patients treated with IMFINZI plus chemotherapy.

Table 8. Laboratory Abnormalities Worsening from Baseline Occurring in ≥ 20%[1] of Patients in the CASPIAN study

	IMFINZI with Etoposide and either Carboplatin or Cisplatin	**Etoposide and either Carboplatin or Cisplatin**
Laboratory Abnormality	**Grade[2] 3 or 4 (%)[3]**	**Grade[2] 3 or 4 (%)[3]**
Chemistry		

Hyponatremia	11	13
Hypomagnesemia	11	6
Hyperglycemia	5	5
Increased Alkaline Phosphatase	4.9	3.5
Increased ALT	4.9	2.7
Increased AST	4.6	1.2
Hypocalcemia	3.5	2.4
Blood creatinine increased	3.4	1.1
Hyperkalemia	1.5	3.1
TSH decreased < LLN[4] and ≥ LLN at baseline	NA	NA
Hematology		
Neutropenia	41	48
Lymphopenia	14	13
Anemia	13	22
Thrombocytopenia	12	15

[1] The frequency cut off is based on any grade change from baseline

[2] Graded according to NCI CTCAE version 4.03

[3] 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: 258 to 263) and chemotherapy (range: 253 to 262) except magnesium IMFINZI + chemotherapy(18) and chemotherapy(16)

[4] LLN = lower limit of normal

Biliary Tract Cancer

The safety of IMFINZI in combination with gemcitabine and cisplatin in locally advanced or metastatic BTC was evaluated in TOPAZ-1, a randomized, double-blind, placebo-controlled,

multicenter trial. A total of 338 patients received IMFINZI 1,500 mg in combination with gemcitabine and cisplatin every 3 weeks up to 8 cycles followed by IMFINZI 1,500 mg every 4 weeks until disease progression or unacceptable toxicity. Patients with active or prior documented autoimmune or inflammatory disorders, HIV infection or other active infections, including tuberculosis or hepatitis C were ineligible [see Clinical Studies (14.3)].

IMFINZI was discontinued due to adverse reactions in 6% of the patients receiving IMFINZI plus chemotherapy. The most frequently reported events resulting in discontinuation were sepsis (3 patients) and ischemic stroke (2 patients). The remaining events were dispersed across system organ classes and reported in 1 patient each. Serious adverse reactions occurred in 47% of patients receiving IMFINZI plus chemotherapy. The most frequent serious adverse reactions reported in at least 2% of patients were cholangitis (7%), pyrexia (3.8%), anemia (3.6%), sepsis (3.3%) and acute kidney injury (2.4%). Fatal adverse reactions occurred in 3.6% of patients receiving IMFINZI plus chemotherapy. These include ischemic or hemorrhagic stroke (4 patients), sepsis (2 patients), upper gastrointestinal hemorrhage (2 patients). The most common adverse reactions (occurring in ≥ 20% of patients) were fatigue, nausea, constipation, decreased appetite, abdominal pain, rash and pyrexia. Table 9 summarizes the adverse reactions that occurred in patients treated with IMFINZI plus chemotherapy.

Table 9. Adverse Reactions Occurring in ≥ 10% of Patients in the TOPAZ-1 Study

	IMFINZI with Gemcitabine and Cisplatin N = 338		**Placebo with Gemcitabine and Cisplatin N = 342**	
Adverse Reaction	**All Grades* (%)**	**Grade* 3-4 (%)**	**All Grades* (%)**	**Grade* 3-4 (%)**
General disorders and administration site conditions				
Fatigue†	42	6	43	6
Pyrexia	20	1.5	16	0.6
Gastrointestinal disorders				
Nausea	40	1.5	34	1.8

Constipation	32	0.6	29	0.3
Abdominal pain‡	24	0.6	23	2.9
Vomiting	18	1.5	18	2.0
Diarrhea	17	1.2	15	1.8
Metabolism and nutrition disorders				
Decreased appetite	26	2.1	23	0.9
Skin and subcutaneous tissue disorders				
Rash§	23	0.9	14	0
Pruritus	11	0	8	0
Psychiatric disorders				
Insomnia	10	0	11	0

* Graded according to NCI CTCAE version 5.0

† Includes fatigue, malaise, cancer fatigue and asthenia.

‡ Includes abdominal pain, abdominal pain lower, abdominal pain upper and flank pain.

§ Includes rash macular, rash maculopapular, rash morbilliform, rash papular, rash pruritic, rash pustular, rash erythematous, dermatitis acneiform, dermatitis bullous, drug eruption, eczema, erythema, dermatitis and rash.

Table 10 summarizes the laboratory abnormalities in patients treated with IMFINZI plus chemotherapy.

Table 10. Laboratory Abnormalities Worsening from Baseline Occurring in ≥ 20%* of Patients in the TOPAZ-1 study

	IMFINZI with Gemcitabine and Cisplatin	**Placebo with Gemcitabine and Cisplatin**
Laboratory Abnormality	**Grade† 3 or 4 (%)**	**Grade† 3 or 4 (%)**
Chemistry		
Hyponatremia	18	13
Gamma-glutamyltransferase increased	12	13
Increased bilirubin	10	14
Hypokalemia	8	4.4
Increased AST	8	8
Increased ALT	7	6

	IMFINZI with Gemcitabine and Cisplatin	Placebo with Gemcitabine and Cisplatin
Laboratory Abnormality	**Grade† 3 or 4 (%)**	**Grade† 3 or 4 (%)**
Blood creatinine increased	5	2.1
Hypomagnesemia	4.5	2.2
Hypoalbuminemia	3.6	2.9
Hyperkalemia	2.1	2.1
Increased Alkaline Phosphatase	1.8	3.8
Hypocalcemia	1.8	2.4
Hematology		
Neutropenia	48	49
Anemia	31	28
Leukopenia	28	28
Lymphopenia	23	15
Thrombocytopenia	18	18

* The frequency cut off is based on any grade change from baseline

† Graded according to NCI CTCAE version 5.0. Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: IMFINZI + Gem/Cis (range: 312 to 335) and Placebo + Gem/Cis (range: 319 to 341).

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: https://sideeffects.health.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 at exposure levels approximately 6 to 20 times higher than those observed at the clinical dose of 10 mg/kg (based on AUC), 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 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

IMFINZI can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*.

Pregnancy testing

Verify pregnancy status of females of reproductive potential prior to initiating treatment with IMFINZI.

Contraception

Females

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 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.

Safety and efficacy were similar for patients age 65 years and younger and those older than 65 in patients with ES-SCLC treated with IMFINZI in combination with chemotherapy. Of the 265 patients with ES- SCLC 101 (38%) patients were 65 years or older and 19 (7.2%) patients were 75 years or older. Of the 338 patients with BTC treated with IMFINZI in combination with chemotherapy in the TOPAZ-1 study, 158 (47%) patients were 65 years or older and 38 (11%) patients were 75 years or older. No overall differences in safety or effectiveness of IMFINZI have been observed between patients 65 years of age and older and younger adult 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 Pharmacodynamics

The steady state AUC, Ctrough, and Cmax in patients administered with 1500 mg every 4 weeks are 6% higher, 19% lower, and 55% higher than those administered with 10 mg/kg every 2 weeks, respectively. Based on the modeling of pharmacokinetic data and exposure relationships for safety,

there are no anticipated clinically meaningful differences in efficacy and safety for the doses of 1500 mg every 4 weeks compared to 10 mg/kg every 2 weeks in patients weighing > 30 kg with NSCLC.

12.3 Pharmacokinetics

The pharmacokinetics of durvalumab as a single agent was studied in 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 ≥ 3 mg/kg every 2 weeks. Steady state was achieved at approximately 16 weeks.
The pharmacokinetics of durvalumab is similar when assessed as a single agent and when in combination with chemotherapy.

Distribution

The geometric mean (% coefficient of variation [CV%]) steady state volume of distribution (Vss) 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

There were no clinically significant difference in pharmacokinetic of durvalumab based on age (19-96 years), body weight (34-149 kg), sex, race (White, Black, Asian, Native Hawaiian, Pacific Islander, or American Indian), albumin levels (4-

57 g/L), lactate dehydrogenase levels (18-15,800 U/L), creatinine levels, soluble PD-L1 (67-3,470 pg/mL), tumor type (NSCLC, SCLC and BTC), varying degrees of organ impairment including mild to moderate renal impairment (CLcr 30 to 89 mL/min), mild to moderate hepatic impairment (bilirubin ≤ 3*ULN and any AST), or ECOG/WHO performance status.

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

12.6 Immunogenicity

The observed incidence of anti-drug antibodies is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparison of the incidence of anti-drug antibodies (ADAs) in the studies described below with the incidence of ADAs in other studies.

Of the 2,280 patients who received IMFINZI 10 mg/kg every 2 weeks or 20 mg/kg every 4 weeks as a single-agent, 69 patients (3%) tested positive for ADAs and 12 (0.5%) tested positive for neutralizing antibodies. The development of ADAs against durvalumab appears to have no clinically relevant effect on its pharmacokinetics or safety.

Of the 201 patients in the CASPIAN study who received IMFINZI 1,500 mg every 3 weeks in combination with chemotherapy for four doses followed by IMFINZI 1,500 mg every 4 weeks, no patients tested positive for treatment-emergent ADAs.

Of the 240 patients in the TOPAZ-1 study who received IMFINZI 1,500 mg every 3 weeks in combination with chemotherapy up to 8 cycles followed by IMFINZI 1,500 mg every 4 weeks, 2 (0.8%) patients tested positive for treatment-emergent ADAs and neutralizing antibodies, respectively. There were insufficient numbers of patients with treatment-emergent ADAs or neutralizing antibodies

(2 patients each) to determine whether ADAs have an impact on pharmacokinetics, pharmacodynamics, safety and/or effectiveness of IMFINZI

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, 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 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 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 9 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 9. 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; 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 10 and Figure 1 summarizes the efficacy results for PACIFIC.

Table 10. 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

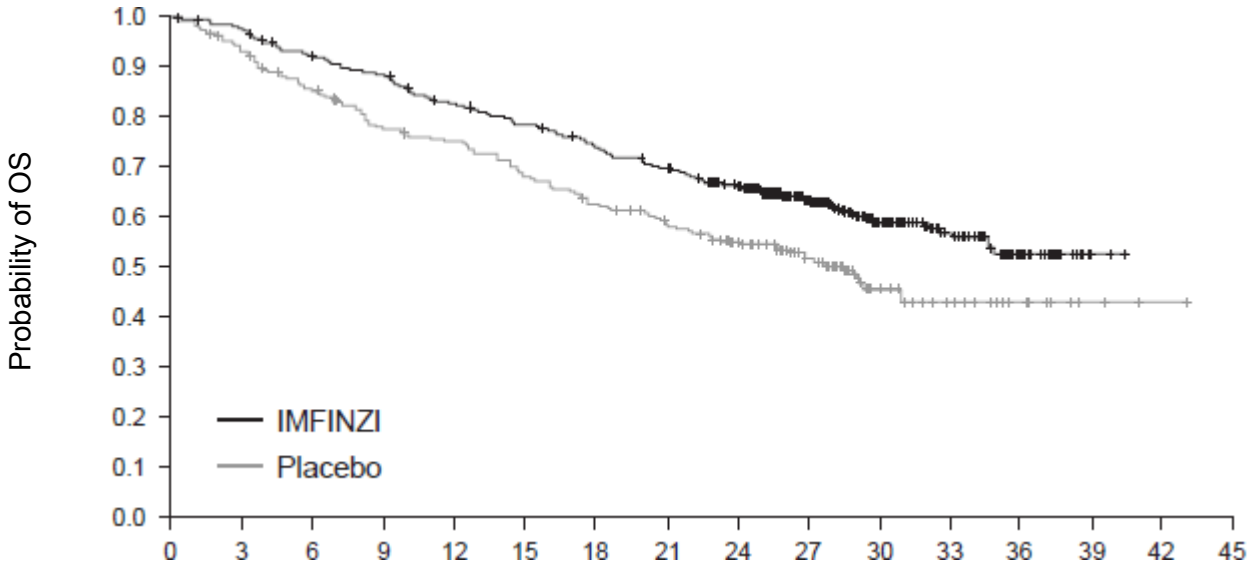
[5] As assessed by BICR RECIST v1.1

[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



Time from randomization (months)

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	80	42	21	9	3	1	0

14.3 Small Cell Lung Cancer (SCLC)

The efficacy of IMFINZI in combination with etoposide and either carboplatin or cisplatin in previously untreated ES-SCLC was investigated in CASPIAN, a randomized, multicenter, active-controlled, open-label trial (NCT03043872). Eligible patients had WHO Performance Status of 0 or 1 and were suitable to receive a platinum-based chemotherapy regimen as first-line treatment for SCLC. Patients with asymptomatic or treated brain metastases were eligible. Choice of platinum agent was at the investigator's discretion, taking into consideration the calculated creatinine clearance. Patients with history of chest radiation therapy; a history of active primary immunodeficiency; autoimmune disorders including paraneoplastic syndrome;

active or prior documented autoimmune or inflammatory disorders; use of systemic immunosuppressants within 14 days before the first dose of the treatment except physiological dose of systemic corticosteroids were ineligible.
Randomization was stratified by the planned platinum-based therapy in cycle 1 (carboplatin or cisplatin). The evaluation of efficacy for ES-SCLC relied on comparison between:

IMFINZI 1,500 mg, and investigator's choice of carboplatin (AUC 5 or 6 mg/mL/min) or cisplatin (75-80 mg/m^2) on Day 1 and etoposide (80-100 mg/m^2) intravenously on Days 1, 2, and 3 of each 21-day cycle for 4 cycles, followed by IMFINZI 1,500 mg every 4 weeks until disease progression or unacceptable toxicity, or

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

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

The major efficacy outcome measure was overall survival (OS) of IMFINZI plus chemotherapy vs. chemotherapy alone. Additional efficacy outcome measures were investigator-assessed progression-free survival (PFS) and objective response rate (ORR), per RECIST v1.1.

The study population characteristics were: median age of 63 years (range: 28 to 82); 40% age 65 or older; 70% male; 84% White, 15% Asian, and 0.9% Black; 65% WHO/ECOG PS of 1; and 93% were former/current smokers. Ninety percent of patients had Stage IV disease and 10% had brain metastasis at baseline. A total of 25% of the patients received cisplatin and 74% of the patients received carboplatin. In the chemotherapy alone arm, 57% of the patients received 6 cycles of chemotherapy, and 8% of the patients received PCI.
The OS results are summarized in Table 11 and Figure 2.

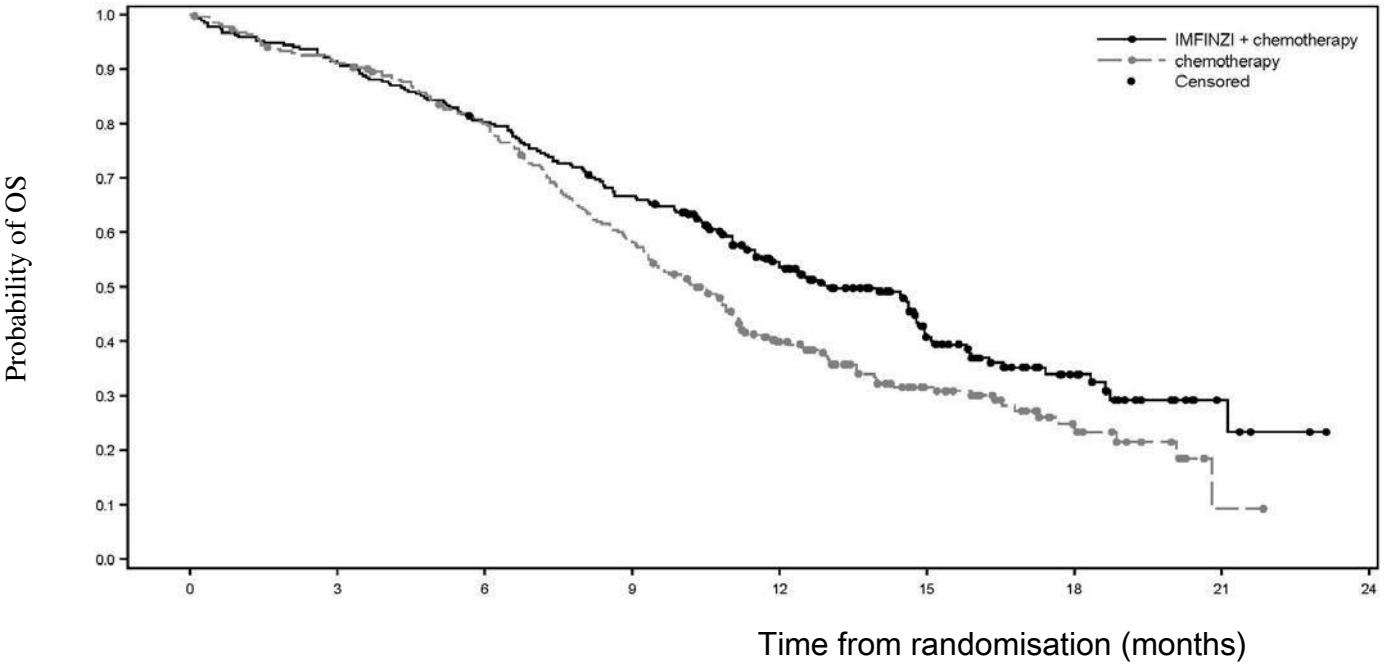
Table 11. OS Result for the CASPIAN Study

Endpoint	IMFINZI with Etoposide and either Carboplatin or Cisplatin (n=268)	Etoposide and either Carboplatin or Cisplatin (n=269)
Overall Survival (OS)		
Number of deaths (%)[1]	**155 (58)**	**181 (67)**
Median OS (months) (95% CI)	**13.0 (11.5, 14.8)**	**10.3 (9.3, 11.2)**
Hazard Ratio (95% CI)[2]	**0.73 (0.59, 0.91)**	
p-value[1]	**0.0047**	

[1] At a pre-specified interim analysis, 336 OS events (79% of total planned events) were observed, and the boundary for declaring efficacy (0.0178) was determined by a Lan-Demets alpha spending function with O'Brien Fleming type boundary

[2] The analysis was performed using the stratified log-rank test, adjusting for planned platinum therapy in Cycle 1 (carboplatin or cisplatin) and using the rank tests of association approach

Figure 2. Kaplan-Meier Curves of Overall Survival in the CASPIAN Study



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

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

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

14.4 Biliary Tract Cancer (BTC)

The efficacy of IMFINZI in combination with gemcitabine and cisplatin in patients with locally advanced or metastatic BTC was investigated in TOPAZ-1 (NCT03875235), a randomized, double-blind, placebo- controlled, multicenter trial that enrolled 685 patients with histologically confirmed locally advanced unresectable or metastatic BTC who have not previously received systemic therapy. Patients with recurrent disease >6 months after surgery and/or completion of adjuvant therapy were eligible. Patients had an ECOG Performance status of 0 and 1 and least one target lesion by RECIST 1.1. Patients with ampullary carcinoma; active or prior documented autoimmune or inflammatory disorders; HIV infection or active infections, including tuberculosis or hepatitis C; current or prior use of immunosuppressive medication within 14 days before the first dose of IMFINZI were ineligible.

Randomization was stratified by disease status (recurrent vs. initially unresectable) and primary tumor location (intrahepatic cholangiocarcinoma [ICCA] vs. extrahepatic cholangiocarcinoma [ECCA] vs. gallbladder cancer [GBC]). Patients were randomized 1:1 to receive:

- IMFINZI 1,500 mg on Day 1+ gemcitabine 1,000 mg/m^2 and cisplatin 25 mg/m^2 on Days 1 and 8 of each 21-day cycle up to 8 cycles, followed by IMFINZI 1,500 mg every 4 weeks, or
- Placebo on Day 1+ gemcitabine 1,000 mg/m^2 and cisplatin 25 mg/m^2 on Days 1 and 8 of each 21-day cycle up to 8 cycles, followed by placebo every 4 weeks.

Treatment with IMFINZI or placebo continued until disease progression, or unacceptable toxicity. Treatment beyond disease progression was permitted if the patient was clinically stable and deriving clinical benefit as determined by the investigator.

The major efficacy outcome measure was overall survival (OS). Additional efficacy outcome measures were investigator-assessed progression-free survival (PFS), objective response rate (ORR) and duration of response (DoR). Tumor assessments were conducted every 6 weeks for the first 24 weeks after the date of randomization, and then every 8 weeks until confirmed objective disease progression.

The study population characteristics were: 50% male, median age of 64 years (range 20-85), 47% age 65 or older; 56% Asian, 37% White, 2% Black or African American, 0.1% American Indian or Alaskan Native, and 4% other; 51% had an ECOG PS of 1; primary tumor location was ICCA 56%, ECCA 18% and GBC 25%); 20% of patients had recurrent disease; 86% of patients had metastatic and 14% had locally advanced disease.

At a pre-specified interim analysis, the trial demonstrated a statistically significant improvement in OS and PFS in patients randomized to IMFINZI in combination with

chemotherapy compared to placebo in combination with chemotherapy. Table 11 summarizes the efficacy results for TOPAZ-1.

Table 11. Efficacy Results for the TOPAZ-1 Study

Endpoint	**IMFINZI with Gemcitabine and Cisplatin (n=341)**	**Placebo with Gemcitabine and Cisplatin (n=344)**
Overall Survival (OS)		
Number of deaths (%)	198 (58)	226 (66)
Median OS (months) (95% CI)*	12.8 (11.1, 14)	11.5 (10.1, 12.5)
Hazard Ratio (95% CI)†	0.80 (0.66, 0.97)	
p-value‡	0.021	
Progression-Free Survival (PFS)		
Number of patients with event (%)	276 (81)	297 (86)
Median in months (95% CI)*	7.2 (6.7, 7.4)	5.7 (5.6, 6.7)
Hazard Ratio (95% CI)†	0.75 (0.63, 0.89)	
p-value§	0.001	

Endpoint	IMFINZI with Gemcitabine and Cisplatin (n=341)	Placebo with Gemcitabine and Cisplatin (n=344)

* Kaplan-Meier estimated median with 95%CI derived using Brookmeyer-Crowley method.

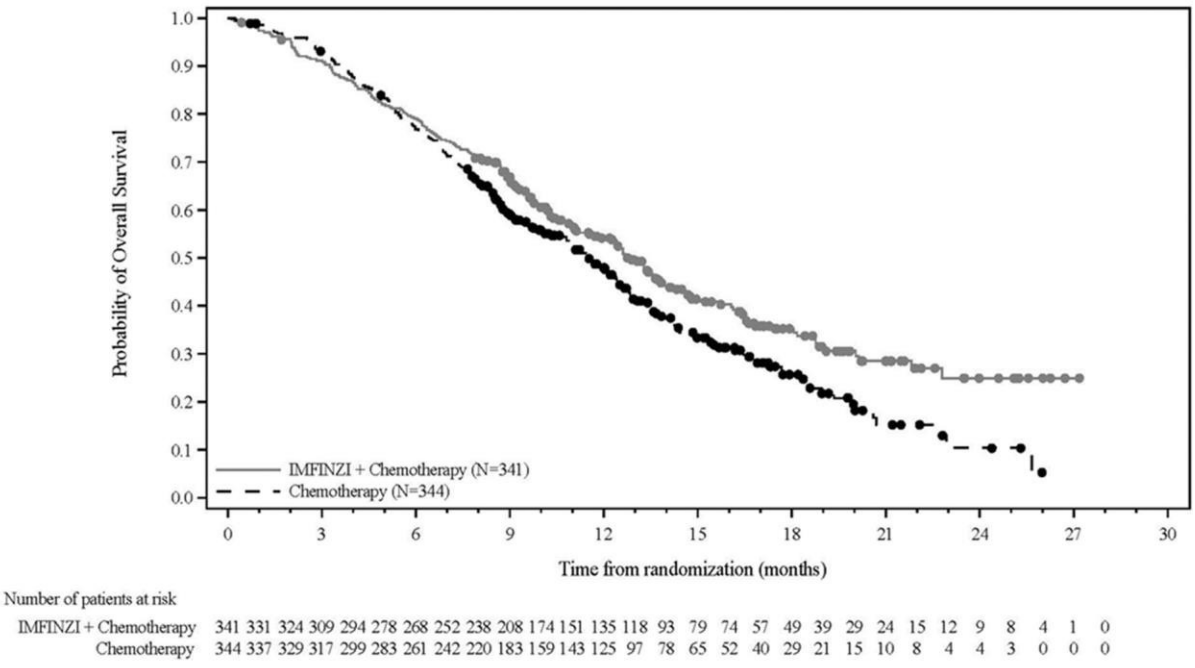
† Based on Cox proportional hazards model stratified by disease status and primary tumor location

‡ 2-sided p-value based on a stratified log rank test compared with alpha boundary of 0.030

§ 2-sided p-value based on a stratified log rank test compared with alpha boundary of 0.048

The investigator-assessed ORR was 27% (95% CI: 22% - 32%) in the IMFINZI plus chemotherapy arm and 19% (95% CI: 15%-23%) in the chemotherapy alone arm.

Figure 3: Kaplan-Meier Curve of OS in TOPAZ-1 Study



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 (50 mg/mL) (159-98-35280-00)
- 120 mg/2.4 mL (50 mg/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.

License holder and importer:

AstraZeneca (Israel) Ltd.,

1 Atirei Yeda St., Kfar Saba 4464301.

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