Imfinzi®

Durvalumab 50 mg/ml

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.

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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.
- IMFINZI in combination with tremelimumab and platinum-based chemotherapy is indicated for the first-line treatment of adults with metastatic NSCLC with no sensitising EGFR mutations or ALK positive mutations.

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)

1.5 Hepatocellular Carcinoma

IMFINZI in combination with tremelimumab is indicated for the first line treatment of adults with advanced or unresectable hepatocellular carcinoma (HCC).

2. DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended dosages for IMFINZI as a single agent and IMFINZI in combination with other therapeutic agents are presented in Table 1.

Administer IMFINZI as an intravenous infusion after dilution as recommended [see Dosage and Administration (2.3)] .

Table 1. Recommended Dosages of IMFINZI

Indication	Recommended IMFINZI dosage	Duration of Therapy
Urothelial Carcinoma	Patients with a body weight of ≥30 kg: 10 mg/kg every 2 weeks or 1,500 mg every 4 weeks Patients with a body weight of <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: 10 mg/kg every 2 weeks Or 1,500 mg every 4 weeks Patients with a body weight of <30 kg: 10 mg/kg every 2 weeks or 20 mg/kg every 4 weeks	Until disease progression, unacceptable toxicity, or a maximum of 12 months
ES-SCLC	Patients with a body weight of ≥30 kg 1,500 mg in combination with chemotherapy* every 3 weeks (21 days) for 4 cycles, followed by 1,500 mg every 4 weeks as a single agent Patients with a body weight of <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: 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 <30 kg: 20 mg/kg in combination with chemotherapy* every 3 weeks (21 days) followed by 20 mg/kg	Until disease progression or until unacceptable toxicity

	every 4 weeks as a single agent	

uHCC	Patients with a body weight of ≥30 kg:
	
	• IMFINZI 1,500 mg following a single dose of tremelimumab $ 300 mg at Day 1 of Cycle 1;
	  • Continue IMFINZI 1,500 mg as a single agent every 4 weeks
	Patients with a body weight of <30 kg:
	
	  • IMFINZI 20 mg/kg following a single dose of tremelimumab $ 4 mg/kg at Day 1 of Cycle 1;
	• Continue IMFINZI 20 mg/kg as a single agent every 4 weeks
		After Cycle 1 of combination therapy, administer IMFINZI as a single agent every 4 weeks until disease progression or 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.

[$] Administer tremelimumab prior to IMFINZI on the same day. When tremelimumab is administered in combination with IMFINZI, refer to the Prescribing Information for tremelimumab dosing information.

IMFINZI in Combination with Tremelimumab and Platinum-Based Chemotherapy

The recommended dosage schedule and regimens for IMFINZI for the treatment of metastatic non-small cell lung cancer (NSCLC) are provided in Tables 2 and 3.

Weigh patients prior to each infusion.

Calculate the appropriate dose using Table 3 below based on the patient's weight and tumor histology.

Table 2: Recommended Dosage Schedule

	Week*,$																								
	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
Cycle:	1			2			3			4			5				6				7				8
IMFINZI*,¶	X			X			X			X			X				X				X				X
Tremelimumab¶,#	X			X			X			X							X								
Chemotherapy	X			X			X			X			Xᵖ				Xᵖ				Xᵖ				Xᵖ

* continue IMFINZI until disease progression or intolerable toxicity.
$ Note the dosing interval change from every 3 weeks to every 4 weeks starting at cycle 5.
¶ intravenous infusion over 60 minutes *[see Dosage and Administration (2.3)]*.
# if patients receive fewer than 4 cycles of platinum-based chemotherapy, the remaining cycles of tremelimumab (up to a total of 5) should be given after the platinum-based chemotherapy phase, in combination with IMFINZI, every 4 weeks.
ᵖ optional pemetrexed therapy from week 12 until disease progression or intolerable toxicity for patients with non-squamous disease who received treatment with pemetrexed and carboplatin/cisplatin.

Table 3: Recommended Regimen and Dosage

Tumor Histology	Patient Weight	IMFINZI Dosage	Tremelimumab Dosage*	Platinum-based Chemotherapy Regimen*
Non-Squamous	≥30kg	1,500 mg	75 mg	• carboplatin & nab-paclitaxel OR • carboplatin or cisplatin & pemetrexed
	<30kg	20 mg/kg	1 mg/kg	
Squamous	≥30kg	1,500 mg	75 mg	• carboplatin & nab-paclitaxel OR • carboplatin or cisplatin & gemcitabine
	<30kg	20 mg/kg	1 mg/kg	

* Refer to the Prescribing Information for dosing information.

2.2 Dose Modifications for Adverse Reactions

No dose reductions are recommended. Withhold and/or discontinue IMFINZI or IMFINZI in combination with tremelimumab and platinum-based chemotherapy to manage adverse reactions as described in Table 4.

Table 4. 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 (5.1)]	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 (5.1)]	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
Hyperthyroidism or thyroiditis [see Warnings and Precautions (5.1)]	Grade 2-4	Withhold dose until clinically stable
Adrenal insufficiency or Hypophysitis/Hypopituitarism [see Warnings and Precautions (5.1)]	Grade 2-4	Withhold dose until clinically stable
Type 1 Diabetes Mellitus [see Warnings and Precautions (5.1)]	Grade 2-4	Withhold dose until clinically stable
Nephritis [see Warnings and Precautions (5.1)]	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 (5.1)]	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 (5.1)]	Grade 3 or 4	Withhold dose until clinically stable
Infusion-related reactions [see Warnings and Precautions (5.2)]	Grade 1 or 2	Interrupt or slow the rate of infusion
	Grade 3 or 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

Neurological Toxicities	Grade 2	Withhold

[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.

2.3 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.

<u>Administration</u>

- 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.

- Use separate infusion bags and filters for each drug product.

  IMFINZI in Combination with Other Products

  • Administer all drug products as separate intravenous infusions.

  • Do not co-administer other drugs through the same infusion line.

  • For platinum-based chemotherapy, refer to Prescribing Information for administration information.

  • For pemetrexed therapy, refer to Prescribing Information for administration information.

<u>Combination Regimens: Order of Infusions</u>

IMFINZI in combination with tremelimumab

• Infuse tremelimumab first, followed by IMFINZI on the same day of dosing.

IMFINZI in Combination with Tremelimumab and Platinum-Based Chemotherapy

• Infuse tremelimumab first, followed by IMFINZI and then platinum-based chemotherapy on the day of dosing.

IMFINZI in Combination with Tremelimumab and Pemetrexed Therapy

• Infuse tremelimumab first, followed by IMFINZI and then pemetrexed therapy on the day of dosing.

<u>Combination Regimens: Infusion Instructions</u>

IMFINZI in Combination with Tremelimumab

• Administer tremelimumab over 60 minutes followed by a 60 minute observation period. Then administer IMFINZI as a separate intravenous infusion over 60 minutes on the same day.

IMFINZI in Combination with Tremelimumab and Platinum-Based Chemotherapy/ Pemetrexed Therapy

Cycle 1

- Infuse tremelimumab over 1 hour. One to two hours after completion of tremelimumab infusion, infuse IMFINZI over 1 hour. One to two hours after completion of IMFINZI infusion, administer platinum-based chemotherapy.

Subsequent Cycles

- If there are no infusion reactions during cycle 1, subsequent cycles of IMFINZI can be given immediately after tremelimumab. The time between the end of the IMFINZI infusion and the start of chemotherapy can be reduced to 30 minutes.

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.

The incidence and severity of immune-mediated adverse reactions were similar when IMFINZI was administered as a single agent or in combination with chemotherapy or in combination with tremelimumab and platinum-based chemotherapy, unless otherwise noted.

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.

IMFINZI as a Single Agent
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 IMFINZI 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.

IMFINZI with Tremelimumab

Immune-mediated pneumonitis occurred in 1.3% (5/388) of patients receiving IMFINZI in combination with tremelimumab, including fatal (0.3%) and Grade 3 (0.2%) adverse reactions. Events resolved in 3 of the 5 patients and resulted in permanent discontinuation in 1 patient. Systemic corticosteroids were required in all patients; of these, 4 patients required high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). One patient (1/5) required other immunosuppressants.

IMFINZI with Tremelimumab and Platinum-Based Chemotherapy

Immune-mediated pneumonitis occurred in 3.5% (21/596) of patients receiving IMFINZI in combination with tremelimumab and platinum-based chemotherapy, including fatal (0.5%), and Grade 3 (1%) adverse reactions. Events resolved in 11 of the 21 patients and resulted in permanent discontinuation in 7 patients. Systemic corticosteroids were required in all patients with immune-mediated pneumonitis, while 1 patient (1/21) required other immunosuppressants.

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.

IMFINZI as a Single Agent

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).

IMFINZI with Tremelimumab

Immune-mediated colitis or diarrhea occurred in 6% (23/388) of patients receiving IMFINZI in combination with tremelimumab, including Grade 3 (3.6%) adverse reactions. Events resolved in 22 of the 23 patients and resulted in permanent discontinuation in 5 patients. All patients received systemic corticosteroids, and 20 of the 23 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). Three patients also received other immunosuppressants.

Intestinal perforation has been observed in other studies of IMFINZI in combination with tremelimumab.

IMFINZI with Tremelimumab and Platinum-Based Chemotherapy

Immune-mediated colitis occurred in 6.5% (39/596) of patients receiving IMFINZI in combination with tremelimumab including fatal (0.2%) and Grade 3 (2.5%) adverse reactions. Events resolved in 33 of 39 patients and resulted in permanent discontinuation in 11 patients. Systemic corticosteroids were required in all patients with immune-mediated colitis, while 4 patients (4/39) required other corticosteroids.

Intestinal perforation and large intestine perforation were reported in 0.1% of patients receiving IMFINZI in combination with tremelimumab.

Immune-Mediated Hepatitis

IMFINZI can cause immune-mediated hepatitis.

IMFINZI as a Single Agent

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.

IMFINZI with Tremelimumab

Immune-mediated hepatitis occurred in 7.5% (29/388) of patients receiving IMFINZI in combination with tremelimumab, including fatal (0.8%), Grade 4 (0.3%), and Grade 3 (4.1%) adverse reactions. Events resolved in 12 of the 29 patients and resulted in permanent discontinuation in 9 patients. Systemic corticosteroids were required in all 29 patients and all 29 patients required high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). Eight patients (8/29) required other immunosuppressants.

IMFINZI with Tremelimumab and Platinum-Based Chemotherapy

Immune-mediated hepatitis occurred in 3.9% (23/596) of patients receiving IMFINZI in combination with tremelimumab, including fatal (0.3%), Grade 4 (0.5%), and Grade 3 (2.0%) adverse reactions. Events resolved in 12 of the 23 patients and resulted in permanent discontinuation in 10 patients. Systemic corticosteroids were required in all patients with immune-mediated hepatitis, while 2 patients (2/23) required use of other immunosuppressants.

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)].

IMFINZI as a Single Agent

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.

IMFINZI with Tremelimumab

Immune-mediated adrenal insufficiency occurred in 1.5% (6/388) of patients receiving IMFINZI in combination with tremelimumab, including Grade 3 (0.3%) adverse reactions. Events resolved in 2 of the 6 patients. Systemic corticosteroids were required in all 6 patients, and of these, 1 patient required high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day).

IMFINZI with Tremelimumab and Platinum-Based Chemotherapy

Immune-mediated adrenal insufficiency occurred in 2.2% (13/596) of patients receiving IMFINZI in combination with tremelimumab, including Grade 3 (0.8%) adverse reactions. Events resolved in 2 of the 13 patients and resulted in permanent discontinuation in 1 patient. Systemic corticosteroids were required in all patients with adrenal insufficiency. One patient also required endocrine therapy.

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)].

IMFINZI as a Single Agent

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.

IMFINZI with Tremelimumab

Immune-mediated hypophysitis/hypopituitarism occurred in 1% (4/388) of patients receiving IMFINZI in combination with tremelimumab. Events resolved in 2 of the 4 patients. Systemic corticosteroids were required in 3 patients, and of these, 1 patient received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). Two patients also required endocrine therapy.

IMFINZI with Tremelimumab and Platinum-Based Chemotherapy

Immune-mediated hypophysitis occurred in 1.3% (8/596) of patients receiving IMFINZI in combination with tremelimumab, including Grade 3 (0.5%) adverse reactions. Events resulted in permanent discontinuation in 1 patient. Systemic corticosteroids were required in 6 patients with immune-mediated hypophysitis; of these, 2

of the 8 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). Four patients also required endocrine therapy.

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

IMFINZI as a Single Agent
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.

IMFINZI with Tremelimumab
Immune-mediated thyroiditis occurred in 1.5% (6/388) of patients receiving IMFINZI in combination with tremelimumab. Events resolved in 2 of the 6 patients. Systemic corticosteroids were required in 2 patients (2/6) with immune-mediated thyroiditis; of these, 1 patient required high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). All patients required other therapy including hormone replacement therapy, thiamazole, carbimazole, propylthiouracil, perchlorate, calcium channel blocker, or beta-blocker.

IMFINZI with and Platinum-Based Chemotherapy
Immune-mediated thyroiditis occurred in 1.2% (7/596) of patients receiving IMFINZI in combination with tremelimumab. Events resolved in 2 of the 7 patients and one resulted in permanent discontinuation. Systemic corticosteroids were required in 2 patients (2/7) with immune-mediated thyroiditis, while all patients required endocrine therapy.

Hyperthyroidism:

IMFINZI as a Single Agent

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.

IMFINZI with Tremelimumab

Immune-mediated hyperthyroidism occurred in 4.6% (18/388) of patients receiving IMFINZI in combination with tremelimumab, including Grade 3 (0.3%) adverse reactions. Events resolved in 15 of the 18 patients. Two patients (2/18) required high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). Seventeen patients required other therapy (thiamazole, carbimazole, propylthiouracil, perchlorate, calcium channel blocker, or beta-blocker).

IMFINZI with Tremelimumab and Platinum-Based Chemotherapy

Immune-mediated hyperthyroidism occurred in 5% (30/596) of patients receiving IMFINZI in combination with tremelimumab, including Grade 3 (0.2%) adverse reactions. Events resolved in 21 of the 30 patients. Systemic corticosteroids were required in 5 patients (5/30) with immune-mediated hyperthyroidism, while 28 patients (28/30) required endocrine therapy.

Hypothyroidism:
IMFINZI as a Single Agent

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.

IMFINZI with Tremelimumab

Immune-mediated hypothyroidism occurred in 11% (42/388) of patients receiving IMFINZI in combination with tremelimumab. Events resolved in 5 of the 42 patients. One patient received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). All patients required other therapy (thiamazole, carbimazole, propylthiouracil, perchlorate, calcium channel blocker, or beta-blocker).

IMFINZI with Tremelimumab and Platinum-Based Chemotherapy

Immune-mediated hypothyroidism occurred in 8.6% (51/596) of patients receiving IMFINZI in combination with tremelimumab, including Grade 3 (0.5%) adverse reactions. Systemic corticosteroids were required in 2 patients (2/51) and all patients required endocrine therapy.

<u>*Type 1 Diabetes Mellitus* which can present with diabetic ketoacidosis</u>:

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)]*.

IMFINZI as a Single Agent

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.

IMFINZI with Tremelimumab

Two patients (0.5%, 2/388) had events of hyperglycemia requiring insulin therapy that had not resolved at last follow-up.

IMFINZI with and Platinum-Based Chemotherapy

Immune-mediated Type 1 diabetes mellitus occurred in 0.5% (3/596) of patients receiving IMFINZI in combination with tremelimumab, including Grade 3 (0.3%) adverse reactions. All patients required endocrine therapy.

<u>Immune-Mediated Nephritis with Renal Dysfunction</u>

IMFINZI can cause immune-mediated nephritis.

IMFINZI as a Single Agent

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.

IMFINZI with Tremelimumab

Immune-mediated nephritis occurred in 1% (4/388) of patients receiving IMFINZI in combination with tremelimumab, including Grade 3 (0.5%) adverse reactions. Events resolved in 3 of the 4 patients and resulted in permanent discontinuation in 2 patients. Systemic corticosteroids were required in all patients with immune-mediated nephritis; of these, 3 patients required high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day).

IMFINZI with Tremelimumab and Platinum-Based Chemotherapy

Immune-mediated nephritis occurred in 0.7% (4/596) of patients receiving IMFINZI in combination with tremelimumab, including Grade 3 (0.2%) adverse reactions. Events resolved in 1 of the 4 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)]

IMFINZI as a Single Agent

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.

IMFINZI with Tremelimumab

Immune-mediated rash or dermatitis occurred in 4.9% (19/388) of patients receiving IMFINZI in combination with tremelimumab, including Grade 4 (0.3%) and Grade 3 (1.5%) adverse reactions. Events resolved in 13 of the 19 patients and resulted in permanent discontinuation in 2 patients. Systemic corticosteroids were required in all patients with immune-mediated rash or dermatitis; of these, 12 patients required high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). One patient received other immunosuppressants.

IMFINZI with Tremelimumab and Platinum-Based Chemotherapy

Immune-mediated rash or dermatitis occurred in 7.2% (43/596) of patients receiving IMFINZI in combination with tremelimumab, including Grade 3 (0.3%) adverse reactions. Events resolved in 32 of the 43 patients and resulted in permanent discontinuation in 2 patients. Systemic corticosteroids were required in all patients with immune-mediated rash or dermatitis.

Immune-Mediated Pancreatitis

IMFINZI in combination with tremelimumab can cause immune-mediated pancreatitis.

IMFINZI with Tremelimumab

Immune-mediated pancreatitis occurred in 2.3% (9/388) of patients receiving IMFINZI in combination with tremelimumab, including Grade 4 (0.3%) and Grade 3 (1.5%) adverse reactions. Events resolved in 6 of the 9 patients. Systemic corticosteroids were required in all 9 patients and of these 7 patients required high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day).

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 IMFINZI in combination with tremelimumab 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, other transplant (including corneal graft) rejection.

Disease-specific precaution
Metastatic NSCLC
Limited data are available in elderly patients (≥ 75 years) treated with IMFINZI in combination with tremelimumab and platinum-based chemotherapy (see sections 8.5 and 14). Careful consideration of the potential benefit/risk of this regimen on an individual basis is recommended.

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.

IMFINZI as a Single Agent

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

IMFINZI in Combination with Tremelimumab

Infusion-related reactions occurred in 10 (2.6%) patients receiving IMFINZI in combination with tremelimumab.

IMFINZI with Tremelimumab and Platinum-Based Chemotherapy

Infusion-related reactions occurred in 2.9% (17/596) of patients receiving IMFINZI in combination with tremelimumab, 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 as a single agent in a total of 1889 patients enrolled in 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 (ATLANTIC Study) that enrolled 444 patients with advanced solid tumors, including NSCLC. 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 the Warnings and Precautions also reflect exposure to IMFINZI 1,500 mg in combination with tremelimumab 300 mg in 388 patients in HIMALAYA. In the HIMALAYA study patients received IMFINZI 1,500 mg in combination with tremelimumab as a single intravenous infusion of 300 mg, followed by IMFINZI 1,500 mg every 4 weeks. The pooled safety population (N=596) described in the Warnings and Precautions section reflect exposure to IMFINZI 1,500 mg in combination with tremelimumab 75 mg and histology-based platinum chemotherapy regimens in 330 patients in POSEIDON *[see Clinical Studies (14.2)]* and 266 patients with ES-SCLC in CASPIAN who received up to four cycles of platinum-etoposide plus IMFINZI 1,500 mg with tremelimumab 75 mg every 3 weeks followed by IMFINZI 1,500 mg every 4 weeks (an unapproved regimen for extensive stage small cell

lung cancer). Among the 596 patients, 55% were exposed to IMFINZI for 6 months or more and 24% were exposed for 12 months or more.

The data described in this section reflect exposure to IMFINZI in patients with Stage III NSCLC enrolled in the PACIFIC study, in patients with metastatic NSCLC enrolled in the POSEIDON study, in patients with ES-SCLC enrolled in the CASPIAN study, in patients with BTC enrolled in the TOPAZ-1 study and in patients with uHCC included in the HIMALAYA 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 5 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 5. Adverse Reactions in ≥10% of Patients in study 1108 Urothelial Carcinoma Cohort

Adverse Reaction	IMFINZI (N=182)	
	All Grades (%)	Grades 3 – 4 (%)
Gastrointestinal Disorders		
Constipation	21	1.1
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

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 6. 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

Stage III NSCLC - PACIFIC

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

Table 7. Adverse Reactions Occurring in ≥ 10% Patients in the PACIFIC Study

	IMFINZI N=475		Placebo 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 8 summarizes the laboratory abnormalities that occurred in at least 20% of patients treated with IMFINZI.

Table 8. Laboratory Abnormalities Worsening From Baseline Occurring in ≥ 20% of Patients in the PACIFIC Study

Laboratory Abnormality	IMFINZI		Placebo	
	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)

Metastatic NSCLC - POSEIDON

The safety of IMFINZI in combination with tremelimumab and platinum-based chemotherapy in patients with metastatic NSCLC was evaluated in POSEIDON (NCT03164616), a randomized, open-label, multicenter, active-controlled trial. A total of 330 patients received IMFINZI 1,500 mg in combination with tremelimumab (≥ 30 kg body weight received 75 mg and < 30 kg body weight received 1 mg/kg) and histology-based platinum chemotherapy regimens *[see Clinical Studies (14.2)]*. Of these patients, 66% received the maximum 5 doses of tremelimumab and 79% received at least 4 doses. Treatment was continued with IMFINZI as a single agent (or with IMFINZI and histologically-based pemetrexed for non-squamous patients based on the investigator's decision) 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)]*.

The median age of patients who received IMFINZI in combination with tremelimumab and platinum-based chemotherapy was 63 years (range: 27 to 87); 80% male; 61% White, 29% Asian, 58% former smoker, 25% current smoker, and 68% ECOG performance of 1.

Serious adverse reactions occurred in 44% of patients receiving IMFINZI in combination with tremelimumab and platinum-based chemotherapy. The most frequent serious adverse reactions reported in at least 2% of patients were pneumonia (11%), anemia (5%), diarrhea (2.4%), thrombocytopenia (2.4%), pyrexia (2.4%), and febrile neutropenia (2.1%). Fatal adverse reactions occurred in a total of 4.2% of patients receiving IMFINZI in combination with tremelimumab and platinum-based chemotherapy. These include hepatitis, nephritis, myocarditis, pancreatitis (all in the same patient), death (2 patients), sepsis (2 patients), pneumonitis (2 patients), acute kidney injury (2 patients), febrile neutropenia (1 patient), chronic obstructive pulmonary disease (1 patient), dyspnea (1 patient), sudden death (1 patient), and ischemic stroke (1 patient).

Permanent discontinuation of IMFINZI or tremelimumab due to an adverse reaction occurred in 17% of the patients. Adverse reactions which resulted in permanent discontinuation of IMFINZI or tremelimumab in > 2% of patients included pneumonia.

Dosage interruption or delay of IMFINZI and tremelimumab due to an adverse reaction occurred in 41% of patients. Adverse reactions which required dosage interruption or delay of IMFINZI and tremelimumab in > 1% of patients included anemia, leukopenia/white blood cell count decreased, pneumonia, pneumonitis, colitis, diarrhea, hepatitis, rash, asthenia, amylase increased, alanine aminotransferase increased, aspartate aminotransferase increased, lipase increased, neutropenia/neutrophil count decreased, and thrombocytopenia/platelet count decreased.

The most common adverse reactions (occurring in ≥ 20% of patients) were nausea, fatigue, musculoskeletal pain, decreased appetite, rash, and diarrhea. Grade 3 or 4 laboratory abnormalities (≥ 10%) were neutropenia, anemia, leukopenia, lymphocytopenia, lipase increased, hyponatremia and thrombocytopenia.

Table 9 summarizes the adverse reactions in POSEIDON.

Table 9. Adverse Reactions (≥ 10%) in Patients with NSCLC Who Received IMFINZI in the POSEIDON Study

	IMFINZI with tremelimumab and platinum-based chemotherapy N = 330		Platinum-based chemotherapy N = 333	
Adverse Reaction	**All Grades (%)**	**Grade 3 or 4 (%)**	**All Grades (%)**	**Grade 3 or 4 (%)**
Respiratory, thoracic and mediastinal disorders				

Adverse Reaction	IMFINZI with tremelimumab and platinum-based chemotherapy N = 330		Platinum-based chemotherapy N = 333	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Cough/Productive Cough[*]	12	0	8	0.3
Gastrointestinal disorders				
Nausea	42	1.8	37	2.1
Diarrhea	22	1.5	15	1.5
Constipation	19	0	24	0.6
Vomiting	18	1.2	14	1.5
Stomatitis[†]	10	0	6	0.3
Endocrine disorders				
Hypothyroidism[‡]	13	0	2.1	0
Skin and subcutaneous tissue disorders				
Rash[§]	27	2.4	10	0.6
Alopecia	10	0	6	0
Pruritus	11	0	4.5	0
General disorders and administration site conditions				
Fatigue/Asthenia[¶]	36	5	32	4.5
Pyrexia[#]	19	0	8	0
Edema[þ]	10	0	10	0.6
Musculoskeletal and connective tissue disorders				
Musculoskeletal Pain[ß]	29	0.6	22	1.5
Metabolism and nutrition disorders				
Decreased appetite	28	1.5	25	1.2
Infections and Infestations				
Pneumonia [à]	17	8	12	4.2
Upper respiratory tract infections[è]	15	0.6	9	0.9
Nervous system disorders				
Headache[ð]	11	0	8	0.6

[*] Includes cough and productive cough.

† Includes mucosal inflammation and stomatitis.

‡ Includes blood thyroid stimulating hormone increased and hypothyroidism.

§ Includes eczema, erythema, dermatitis, drug eruption, erythema multiforme, pemphigoid, rash, rash maculo-papular, rash papular,

rash pruritic, and rash pustular.

¶ Includes asthenia and fatigue.

Includes body temperature increased, hyperpyrexia, hyperthermia, and pyrexia.

Þ Includes face edema, localized edema, and edema peripheral.

ß Includes arthralgia, arthritis, back pain, bone pain, musculoskeletal chest pain, musculoskeletal pain, myalgia, neck pain, non-cardiac chest pain, spinal pain.

à Includes lower respiratory tract infection, pneumocystis jirovecii pneumonia, pneumonia, pneumonia aspiration, pneumonia bacterial.

è Includes laryngitis, nasopharyngitis, pharyngitis, rhinitis, sinusitis, tonsillitis, tracheobronchitis and upper respiratory tract infection.

ð Includes headache, migraine.

Table 10 summarizes the laboratory abnormalities in POSEIDON.

Table 10. Select Laboratory Abnormalities (≥ 10%) That Worsened from Baseline in Patients with NSCLC Who Received IMFINZI in the POSEIDON Study

Laboratory Abnormality[*]	IMFINZI with tremelimumab and platinum-based chemotherapy[†]		Platinum-based chemotherapy[§]	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Chemistry				
Lipase increased	35	14	25	5
Hyponatremia	55	13	50	11
Hypernatremia	15	0	14	0
Amylase increased	41	9	25	6
Hypokalemia	21	7	17	2.8
Hyperglycemia	42	6	37	3.1
Increased ALT	64	6	56	4.7
Increased AST	63	5	55	2.2
Blood creatinine increased	89	4.0	83	1.9
Increased Alkaline Phosphatase	33	3.4	26	1.2
Gamma Glutamyl Transferase increased	38	2.2	35	4.7
Hyperkalemia	49	2.2	35	2.8
Albumin decreased	27	1.9	18	0.9
Hypocalcemia	58	0.9	49	0.9
Hypomagnesemia	12	4	23	0

Laboratory Abnormality[*]	IMFINZI with tremelimumab and platinum-based chemotherapy[†]		Platinum-based chemotherapy[§]	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Bilirubinemia	16	0.9	8	0.3
Hematology				
Neutropenia	71	37	69	32
Anemia	84	24	84	25
Leukopenia	77	21	81	18
Lymphocytopenia	67	20	60	19
Thrombocytopenia	53	11	54	12

[*] Graded according to NCI CTCAE version 4.03.

[†] The denominator used to calculate the rate varied from 45 to 326 based on the number of patients with a baseline value and at least one post-treatment value.

[§] The denominator used to calculate the rate varied from 43 to 323 based on the number of patients with a baseline value and at least one post-treatment value.

Small Cell Lung Cancer

Extensive Stage Small Cell Lung Cancer – CASPIAN

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 (14.3)].

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

Table 11. 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 12 summarizes the laboratory abnormalities that occurred in at least 20% of patients treated with IMFINZI plus chemotherapy.

Table 12. Laboratory Abnormalities Worsening from Baseline Occurring in ≥ 20%[1] of Patients in the CASPIAN study

	IMFINZI with Etoposide and either Carboplatin or	Etoposide and either Carboplatin or Cisplatin

	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

Locally advanced or metastatic BTC -TOPAZ-1

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 (14.4)].

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

Table 13. 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 14 summarizes the laboratory abnormalities in patients treated with IMFINZI plus chemotherapy.

Table 14. 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
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).

Hepatocellular Carcinoma

Unresectable HCC - HIMALAYA

The safety of IMFINZI in combination with tremelimumab was evaluated in a total of 388 patients with uHCC in HIMALAYA, a randomized, open-label, multicenter study *[see Clinical Studies (14.1)]*. Patients received IMFINZI 1,500 mg administered as a single intravenous infusion in combination with tremelimumab 300 mg on the same day, followed by IMFINZI every 4 weeks or sorafenib 400 mg given orally twice daily.

Serious adverse reactions occurred in 41% of patients who received IMFINZI in combination with tremelimumab. Serious adverse reactions in > 1% of patients included hemorrhage (6%), diarrhea (4%), sepsis (2.1%), pneumonia (2.1%), rash (1.5%), vomiting (1.3%), acute kidney injury (1.3%), and anemia (1.3%). Fatal adverse reactions occurred in 8% of patients who received IMFINZI in combination with tremelimumab, including death (1%), hemorrhage intracranial (0.5%), cardiac arrest (0.5%), pneumonitis (0.5%), hepatic failure (0.5%), and

immune-mediated hepatitis (0.5%). The most common adverse reactions (occurring in ≥ 20% of patients) were rash, diarrhea, fatigue, pruritis, musculoskeletal pain, and abdominal pain.

Permanent discontinuation of treatment regimen due to an adverse reaction occurred in 14% of patients; the most common adverse reactions leading to treatment discontinuation (≥ 1%) were hemorrhage (1.8%), diarrhea (1.5%), AST increased (1%), and hepatitis (1%).

Dosage interruptions or delay of the treatment regimen due to an adverse reaction occurred in 35% of patients. Adverse reactions which required dosage interruption or delay in ≥ 1% of patients included ALT increased (3.6%), diarrhea (3.6%), rash (3.6%), amylase increased (3.4%), AST increased (3.1%), lipase increased (2.8%), pneumonia (1.5%), hepatitis (1.5%), pyrexia (1.5%), anemia (1.3%), thrombocytopenia (1%), hyperthyroidism (1%), pneumonitis (1%), and blood creatinine increased (1%).

Table 15 summarizes the adverse reactions that occurred in patients treated with IMFINZI in combination with tremelimumab in the HIMALAYA study.

Table 15. Adverse Reactions Occurring in ≥ 10% of Patients in the HIMALAYA study

	IMFINZI and Tremelimumab (N=388)		Sorafenib (N=374)	
Adverse Reaction	**All Grades (%)**	**Grade 3-4 (%)**	**All Grades (%)**	**Grade 3-4 (%)**
Gastrointestinal disorders				
Diarrhea*	27	6	45	4.3
Abdominal pain*	20	1.8	24	4
Nausea	12	0	14	0
Skin and subcutaneous tissue disorders				
Rash*	32	2.8	57	12

Pruritus	23	0	6	0.3
Metabolism and nutrition disorders				
Decreased appetite	17	1.3	18	0.8
General disorders and administration site conditions				
Fatigue[*]	26	3.9	30	6
Pyrexia[*]	13	0.3	9	0.3
Psychiatric disorders				
Insomnia	10	0.3	4.3	0
Endocrine disorders				
Hypothyroidism[*]	14	0	6	0
Musculoskeletal and Connective Tissue Disorders				
Musculoskeletal pain[*]	22	2.6	17	0.8

[*] Represents a composite of multiple related terms.

Table 16 summarizes the laboratory abnormalities that occurred in patients treated
with IMFINZI in combination with tremelimumab in the HIMALAYA study.

Table 16. Laboratory Abnormalities Worsening from Baseline Occurring in ≥ 20% of Patients in the HIMALAYA study

	IMFINZI and Tremelimumab		Sorafenib	
Laboratory Abnormality	**Any grade[†] (%)[‡]**	**Grade 3[†] or 4 (%)[‡]**	**Any grade[†] (%)[‡]**	**Grade 3[†] or 4 (%)[‡]**
Chemistry				
Aspartate Aminotransferase increased	63	27	55	21
Alanine Aminotransferase increased	56	18	53	12

Sodium decreased	46	15	40	11
Bilirubin increased	41	8	47	11
Alkaline Phosphatase increased	41	8	44	5
Glucose increased	39	14	29	4
Calcium decreased	34	0	43	0.3
Albumin decreased	31	0.5	37	1.7
Potassium increased	28	3.8	21	2.6
Creatinine increased	21	1.3	15	0.9
Hematology				
Hemoglobin decreased	52	4.8	40	6
Lymphocytes decreased	41	11	39	10
Platelets decreased	29	1.6	35	3.1
Leukocytes decreased	20	0.8	30	1.1

[†] Graded according to NCI CTCAE version 4.03.

[‡] Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: IMFINZI with tremelimumab (range: 367-378) and sorafenib (range:344-352).

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 findings from animal studies and its mechanism of action, IMFINZI can cause fetal harm when administered to a pregnant woman [see Clinical Pharmacology (12.1)]. There are no available 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 area under the curve (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 to 4% and 15 to 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 a 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 are no data on the presence of durvalumab in human milk, its effects on the breastfed child, or the effects on milk production. Maternal IgG is known to be present in human milk. The effects of local gastrointestinal exposure and limited systemic exposure in the breastfed child to IMFINZI are unknown. 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 a breastfed child, advise women not to breastfeed during treatment with IMFINZI and for 3 months after the last dose. Refer to the Prescribing Information for the agents administered in combination with IMFINZI for recommended duration to not breastfeed, as appropriate.

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

Pregnancy testing

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

Contraception

Females

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 3 months following the last dose of IMFINZI. Refer to the Prescribing Information for the agents administered in combination with IMFINZI for recommended contraception duration, as appropriate.

8.4 Pediatric Use

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

8.5 Geriatric Use

No dose adjustment is required for elderly patients (≥ 65 years of age) (see section 14).

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.

Of the 265 patients with ES-SCLC treated with IMFINZI in combination with chemotherapy 101 (38%) patients were 65 years or older and 19 (7.2%) patients were 75 years or older. There were no clinically meaningful differences in safety or efficacy between patients 65 years or older and younger patients.

Of the 330 patients with metastatic NSCLC treated with IMFINZI in combination with tremelimumab and platinum-based chemotherapy, 143 (43%) patients were 65 years or older and 35 (11%) patients were 75 years or older. There were no clinically meaningful differences in safety or efficacy between patients 65 years or older and younger patients.

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.

Of the 393 patients with uHCC treated with IMFINZI in combination with tremelimumab, 50% of patients were 65 years of age or older and 13% of patients were 75 years of age 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.

In studies PACIFIC, CASPIAN and TOPAZ-1 data on safety for patients 75 years and older are too limited to draw a conclusion on this population.

In first line metastatic NSCLC patients in the POSEIDON study, some differences in safety were reported between elderly (≥ 65 years) and younger patients. The safety data from patients 75 years of age or older are limited to a total of 74 patients. There was a higher frequency of serious adverse reactions and discontinuation rate of any study treatment due to adverse reactions in 35 patients aged 75 years of age or older treated with IMFINZI in combination with tremelimumab and platinum-based chemotherapy (45.7% and 28.6%, respectively) relative to 39 patients aged 75 years of age or older who received platinum-based chemotherapy only (35.9% and 20.5%, respectively).

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 1,500 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 1,500 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, when in combination with chemotherapy and when in combination with tremelimumab and when in combination with tremelimumab and platinum-based chemotherapy.

Distribution

The geometric mean (% coefficient of variation [CV%]) steady state volume of distribution (Vss) was 5.4 (13.1%) 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 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 21 (26%) days.

Specific Populations

There were no clinically significant differences in pharmacokinetics of durvalumab based on age (18-96 years), body weight (31-175 kg), sex, race (White, Black, Asian, Native Hawaiian, Pacific Islander, or Native American), albumin levels (4-57 g/L), lactate dehydrogenase levels (18-15,800 U/L), soluble PD-L1 (67-3,470 pg/mL), tumor type (NSCLC, SCLC, BTC and HCC), 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).

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.

12.4 Immunogenicity

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

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

During the 12 week treatment period in the HIMALAYA study, of the 294 patients who received IMFINZI once every 4 weeks in combination with a single dose of tremelimumab and who were evaluated for the presence of ADAs against IMFINZI at predose week 0, week 4 and week 12, 3.1% (9/294) of patients tested positive for anti-durvalumab-antibodies. Among the 9 patients who tested positive for ADA, 55.6% (5/9) tested positive for neutralizing antibodies against durvalumab. There was no identified clinically significant effect of anti-durvalumab antibodies on the safety of durvalumab; however, the effect of ADAs on the pharmacokinetics and effectiveness of durvalumab is unknown.

During 16 weeks of treatment during the POSEIDON study, among 286 patients who received IMFINZI 1,500 mg in combination with tremelimumab 75 mg every 3 weeks for five doses and chemotherapy for four cycles followed by IMFINZI 1,500 mg every 4 weeks 10% (29/286) of patients tested positive for anti-durvalumab antibodies with predose sampling at week 0, week 3 and week 12. Among the 29 patients who tested positive for ADAs, 10% (3/29) tested positive for neutralizing antibodies against durvalumab. The geometric mean of durvalumab concentration in patients with ADA positive was 46 mcg/mL compared to 89 mcg/mL in patients with ADA negative. There was no clinically significant effect of anti-durvalumab antibodies on the safety of durvalumab; however, there is insufficient data to assess whether the observed ADA associated pharmacokinetic changes reduce effectiveness of durvalumab.

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. *Mycobacterium* 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-1 blockade using a primate anti-PD-1 antibody was also shown to exacerbate *M. tuberculosis* infection in rhesus macaques. 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 17 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 17. 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)

Unresectable Stage III NSCLC - PACIFIC

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 18 and Figure 1 summarizes the efficacy results for PACIFIC.

Table 18. 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

Probability of OS

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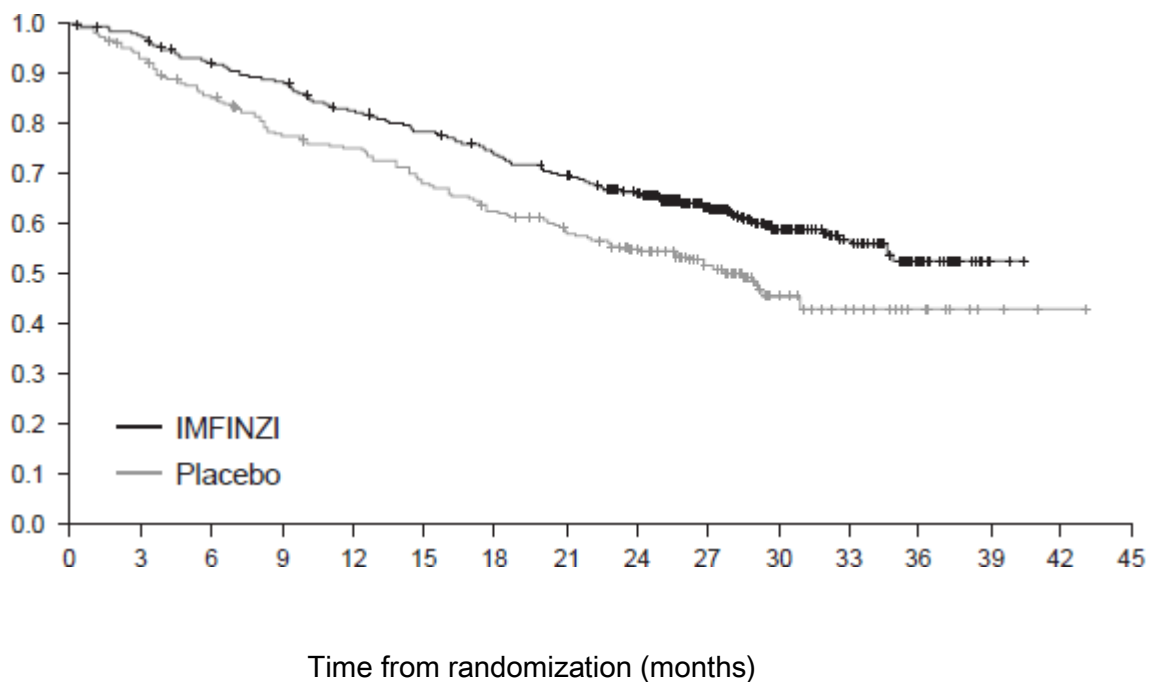
Number of patients at risk															
Month	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45
IMFINZI	476	464	431	415	385	364	343	319	274	210	115	57	23	2	0	0
Placebo	237	220	198	178	170	155	141	130	117	78	42	21	9	3	1	0

Metastatic NSCLC - POSEIDON

The efficacy of IMFINZI in combination with tremelimumab and platinum-based chemotherapy in previously untreated metastatic NSCLC patients with no sensitizing epidermal growth factor receptor (EGFR) mutation or anaplastic lymphoma kinase (ALK) genomic tumor aberrations was investigated in POSEIDON, a randomized, multicenter, active-controlled, open-label trial (NCT03164616). Eligible patients had Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1 and must have had no prior chemotherapy or any other systemic therapy for metastatic NSCLC. Choice of platinum-based chemotherapy was at the investigator's discretion, taking into consideration the calculated creatinine clearance. Patients with active and/or untreated brain metastases; a history of active primary immunodeficiency; autoimmune disorders including 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 tumor cells (TC) PD-L1 expression (TC ≥ 50% vs. TC < 50%), disease stage (Stage IVA vs. Stage IVB), and histology (non-squamous vs. squamous).

Patients were randomized 1:1:1 to receive IMFINZI in combination with tremelimumab and platinum-based chemotherapy according to the regimens listed below, IMFINZI and platinum-based chemotherapy (an unapproved regimen for metastatic NSCLC), or platinum-based chemotherapy. The evaluation of efficacy for metastatic NSCLC relied on comparison between:

- IMFINZI 1,500 mg with tremelimumab 75 mg (or 1 mg/kg for patients < 30 kg) and platinum-based chemotherapy every 3 weeks for 4 cycles, followed by IMFINZI 1,500 mg every 4 weeks as a single agent. A fifth dose of tremelimumab 75 mg (or 1 mg/kg for patients < 30 kg) was given at Week 16 in combination with IMFINZI dose 6.

- Platinum-based chemotherapy every 3 weeks as monotherapy for 4 cycles. Patients could receive an additional 2 cycles (a total of 6 cycles post-randomization), as clinically indicated, at investigator's discretion.

Patients received IMFINZI in combination with tremelimumab with one of the following platinum-based chemotherapy regimens:

- Non-squamous NSCLC
    - Pemetrexed 500 mg/m^2 with carboplatin AUC 5-6 or cisplatin 75 mg/m^2 every 3 weeks for 4 cycles.
- Squamous NSCLC
    - Gemcitabine 1,000 or 1,250 mg/m^2 on Days 1 and 8 with cisplatin 75 mg/m^2 or carboplatin AUC 5-6 on Day 1 every 3 weeks for 4 cycles.
- Non-squamous and Squamous NSCLC
    - Nab-paclitaxel 100 mg/m^2 on Days 1, 8, and 15 with carboplatin AUC 5-6 on Day 1 every 3 weeks for 4 cycles.

Tremelimumab was given up to a maximum of 5 doses. IMFINZI and histology-based pemetrexed continued every 4 weeks until disease progression or unacceptable toxicity. Administration of IMFINZI monotherapy was permitted beyond disease progression if the patient was clinically stable and deriving clinical benefit as determined by the investigator. Patients with disease progression during IMFINZI monotherapy were given the option to be retreated with 4 additional cycles of tremelimumab in combination with IMFINZI. Tumor assessments were performed at Week 6, Week 12, and then every 8 weeks thereafter.

The major efficacy outcome measures were progression free survival (PFS) and overall survival (OS) of

IMFINZI and tremelimumab in combination with platinum-based chemotherapy compared to platinum-based chemotherapy alone. Additional efficacy outcome measures were overall response rate (ORR) and duration of response (DoR). PFS, ORR, and DoR were assessed using Blinded Independent Central Review (BICR) according to RECIST v1.1.

A total of 675 patients were randomized to receive either IMFINZI with tremelimumab and platinum-based-chemotherapy (n=338) or platinum-based chemotherapy (n=337). The median age was 63 years (range: 27 to 87), 46% of patients age ≥ 65 years, 77% male, 57% White, 34% Asian, 0.3% Native Hawaiian or Other Pacific Islander, 3% American Indian or Alaska Native, 2% Black or African American, 4% Other Race, 79% former or current smoker, 34% ECOG PS 0, and 66% ECOG PS 1. Thirty-six percent had squamous histology, 63% non-squamous histology, 29% PD-L1 expression TC ≥ 50%, 71% PD-L1 expression TC < 50%.

Efficacy results are summarized in Table 19 and Figure 2.

Table 19. Efficacy Results for POSEIDON

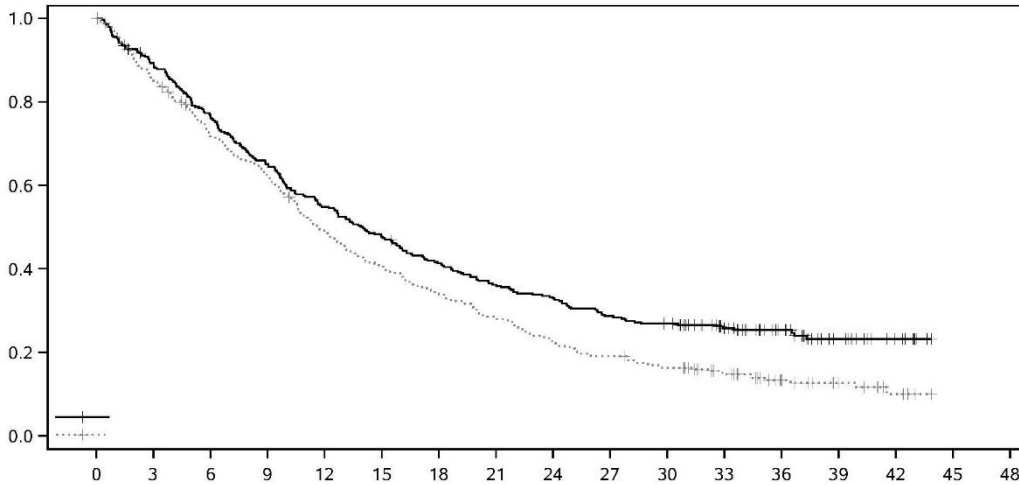|	IMFINZI with tremelimumab and platinum-based chemotherapy (n=338)	Platinum-based chemotherapy (n=337)
OS[1]		
Number of deaths (%)	251 (74)	285 (85)
Median OS (months) (95% CI)	14.0 (11.7, 16.1)	11.7 (10.5, 13.1)
HR (95% CI)	0.77 (0.65, 0.92)	
p-value[2]	0.00304	
PFS[2]		
Number of events (%)	238 (70)	258 (77)
Median PFS (months) (95% CI)	6.2 (5.0, 6.5)	4.8 (4.6, 5.8)
HR (95% CI)	0.72 (0.60, 0.86)	
p-value[2]	0.00031	
ORR % (95% CI) [3]	39 (34, 44)	24 (20, 29)
Median DoR (months) (95% CI)	9.5 (7.2, NR)	5.1 (4.4, 6.0)

[1] PFS/OS results are based on planned analyses which occurred 25/45 months respectively after study initiation.

[2] 2-sided p-values based on log-rank tests stratified by PD-L1, histology and disease stage and compared to a boundary value of 0.00735 for PFS and 0.00797 for OS.

NR=Not Reached, CI=Confidence Interval

Figure 2. Kaplan-Meier curves of OS in POSEIDON

Number of patients at risk

Month	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45
IMFINZI + tremelimumab + platinum-based chemotherapy																
	338	298	256	217	183	159	137	120	109	95	88	64	41	20	9	0
Platinum-based chemotherapy																
	337	284	236	204	160	132	111	91	72	62	52	38	21	13	6	0

14.3   Small Cell Lung Cancer (SCLC)

Extensive-stage SCLC – CASPIAN

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 20 and Figure 3.

Table 20. 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 3. Kaplan-Meier Curves of Overall Survival in the CASPIAN Study
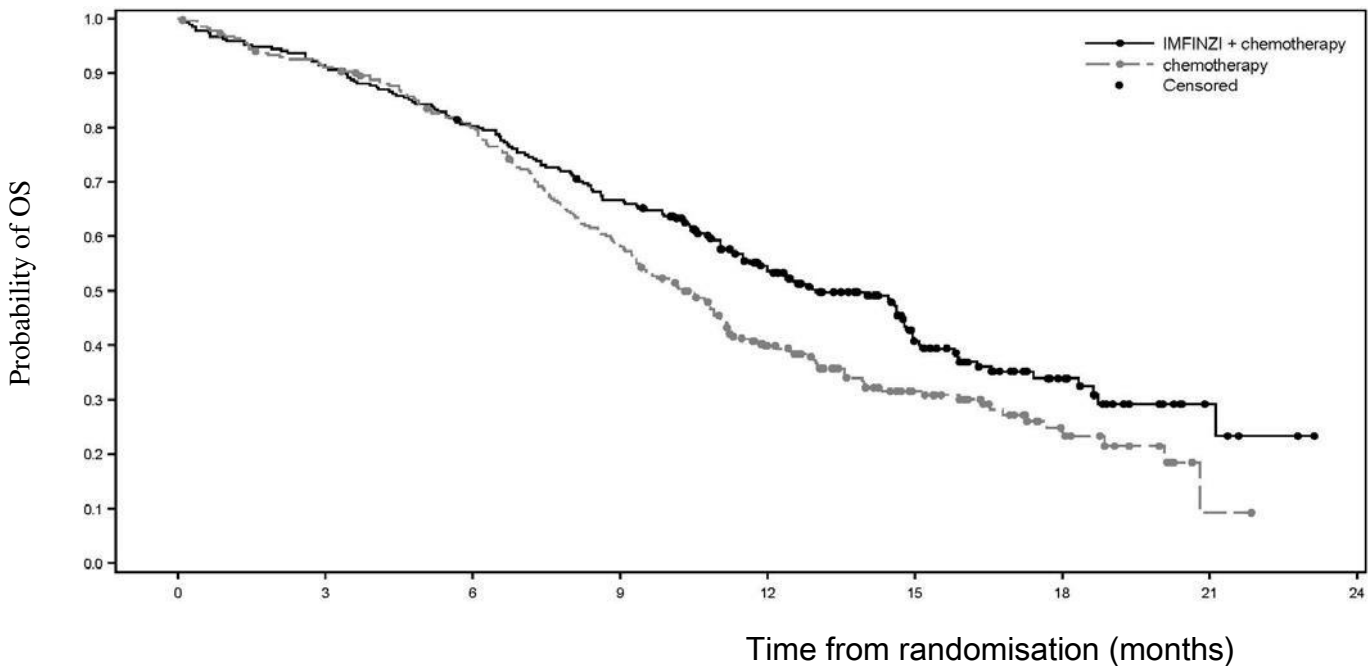
Number of patients at risk	0	3	6	9	12	15	18	21	24
IMFINZI + chemotherapy	268	244	214	177	116	57	25	5	0
chemotherapy	269	242	209	153	82	44	17	1	0

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)

Locally advanced or metastatic BTC -TOPAZ-1 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 21 summarizes the efficacy results for TOPAZ-1.

Table 21. 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	

* 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 4: Kaplan-Meier Curve of OS in TOPAZ-1 Study
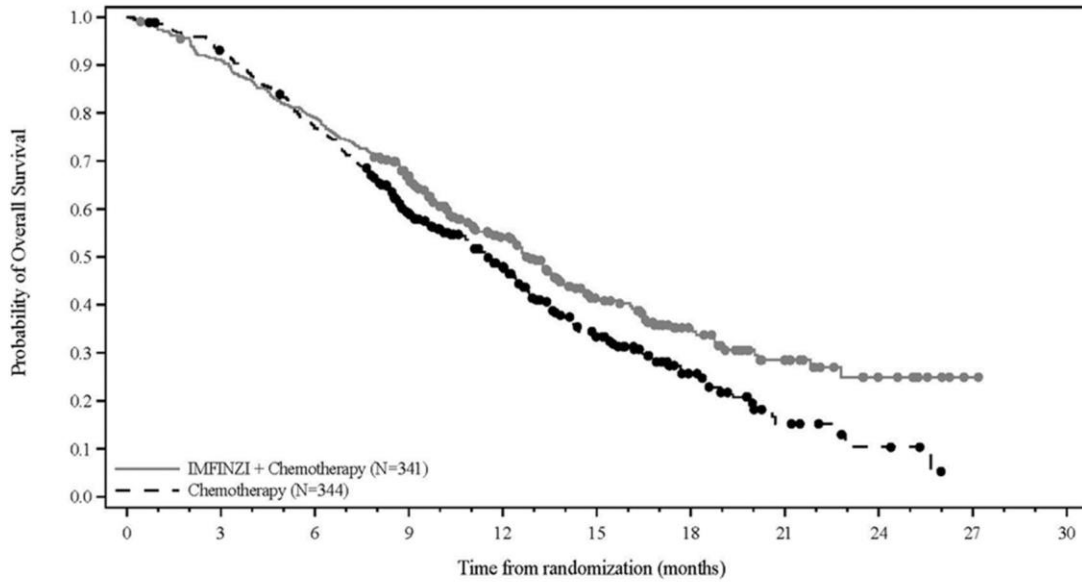
Number of patients at risk

IMFINZI + Chemotherapy	341	331	324	309	294	278	268	252	238	208	174	151	135	118	93	79	74	57	49	39	29	24	15	12	9	8	4	1	0
Chemotherapy	344	337	329	317	299	283	261	242	220	183	159	143	125	97	78	65	52	40	29	21	15	10	8	4	4	3	0	0	0

14.5 Hepatocellular Carcinoma (HCC)

The efficacy of IMFINZI in combination with tremelimumab was evaluated in the HIMALAYA study (NCT03298451), a randomized (1:1:1), open-label, multicenter study in patients with confirmed uHCC who had not received prior systemic treatment for HCC. Patients were randomized to one of two investigational arms (IMFINZI plus trememlimumab or IMFINZI) or sorafenib. Study treatment consisted of IMFINZI 1,500 mg in combination with tremelimumab as a one-time single intravenous infusion of 300 mg on the same day, followed by IMFINZI every 4 weeks; IMFINZI 1,500 mg every 4 weeks; or sorafenib 400 mg given orally twice daily, until disease progression or unacceptable toxicity. The efficacy assessment of IMFINZI is based on patients randomized to the IMFINZI plus tremelimumab arm versus the sorafenib arm. Randomization was stratified by macrovascular invasion (MVI) (yes or no), etiology of liver disease (hepatitis B virus vs. hepatitis C virus vs. others) and ECOG performance status (0 vs. 1).

The study enrolled patients with BCLC Stage C or B (not eligible for locoregional therapy). The study excluded patients with co-infection of viral hepatitis B and hepatitis

65

C; active or prior documented gastrointestinal (GI) bleeding within 12 months; ascites requiring non-pharmacologic intervention within 6 months; hepatic encephalopathy within 12 months before the start of treatment; active or prior documented autoimmune or inflammatory disorders. Esophagogastroduodenoscopy was not mandated prior to enrollment but adequate endoscopic therapy, according to institutional standards, was required for patients with history of esophageal variceal bleeding or those assessed as high risk for esophageal variceal bleeding by the treating physician.

Study treatment 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) between the IMFINZI plus tremelimumab arm versus the sorafenib arm. Additional efficacy outcomes were investigator- assessed progression-free survival (PFS), objective response rate (ORR) and duration of response (DoR) according to RECIST v1.1. Tumor assessments were conducted every 8 weeks for the first 12 months and then every 12 weeks thereafter.

The baseline demographics of the IMFINZI plus tremelimumab and sorafenib arms were as follows: male (85%), age < 65 years (50%), median age of 65 years (range: 18 to 88 years), White (46%), Asian (49%), Black or African American (2%), Native Hawaiian or other Pacific Islander (0.1%), race Unknown (2%), Hispanic or Latino (5%), Not Hispanic or Latino (94%), ethnicity Unknown (1%), ECOG PS 0 (62%); Child-Pugh Class score A (99%), macrovascular invasion (26%), extrahepatic spread (53%), viral etiology; hepatitis B (31%), hepatitis C (27%), uninfected (42%).

Efficacy results are presented in Table 22 and Figure 5.

Table 22. Efficacy Results for the HIMALAYA Study

Endpoint	IMFINZI and Tremelimumab (N=393)	Sorafenib (N=389)
OS		
Number of deaths (%)	262 (66.7)	293 (75.3)
Median OS (months) (95% CI)	16.4 (14.2, 19.6)	13.8 (12.3, 16.1)
HR (95% CI) [*]	0.78 (0.66, 0.92)	
p-value[†, ‡]	0.0035	
PFS		
Number of events (%)	335 (85.2)	327 (84.1)
Median PFS (months) (95% CI)	3.8 (3.7, 5.3)	4.1 (3.7, 5.5)
HR (95% CI)[*]	0.90 (0.77, 1.05)	
ORR		
ORR % (95% CI)[§, ¶]	20.1 (16.3, 24.4)	5.1 (3.2, 7.8)
Complete Response n (%)	12 (3.1)	0
Partial Response n (%)	67 (17.0)	20 (5.1)
DoR		
Median DoR (months) (95% CI)	22.3 (13.7, NR)	18.4 (6.5, 26.0)
% with duration ≥ 6 months	82.3	78.9
% with duration ≥ 12 months	65.8	63.2

[*] HR (IMJUDO and durvalumab vs. sorafenib) based on the stratified Cox proportional hazard model.

[†] Based on a stratified log-rank test.

[‡] Based on a Lan-DeMets alpha spending function with O'Brien Fleming type boundary and the actual number of events observed, the boundary for declaring statistical significance for IMJUDO and durvalumab vs. sorafenib was 0.0398 (Lan and DeMets 1983).

[§] Confirmed complete response or partial response.

[¶] Based on Clopper-Pearson method.

CI=Confidence Interval, HR=Hazard Ratio, NR=Not Reached

Figure 5. Kaplan-Meier curve of OS
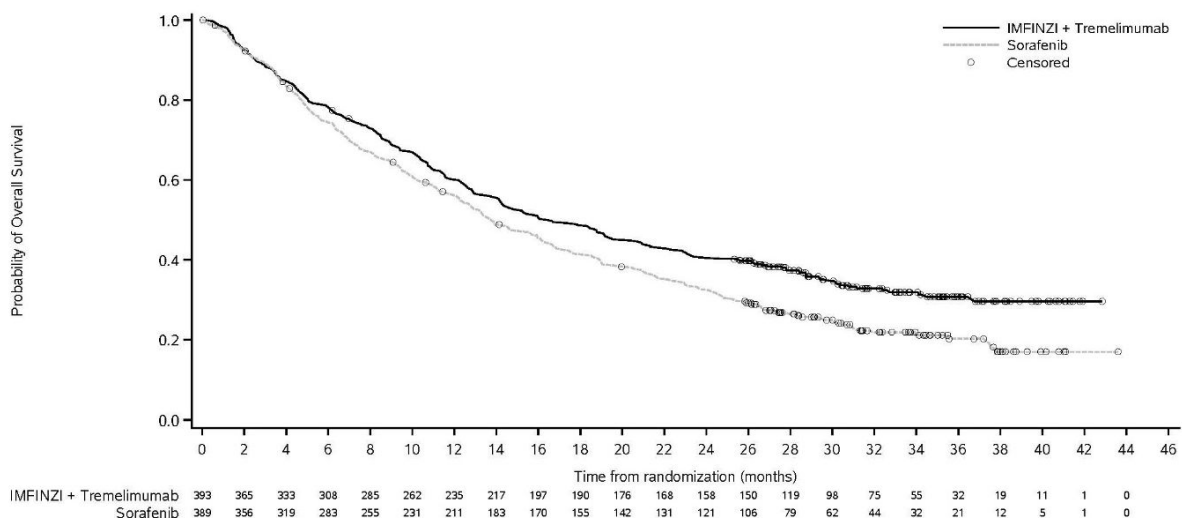
15. HOW SUPPLIED/STORAGE AND HANDLING

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)
- 120 mg/2.4 mL (50 mg/mL)

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.

16. License Number

159-97-35280-00

16. License holder and importer:

AstraZeneca (Israel) Ltd.,

1 Atirei Yeda St., Kfar Saba 4464301.

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