

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.

1. INDICATIONS AND USAGE

1.1 Urothelial Carcinoma

IMFINZI is indicated for the treatment of patients with PD-L1 high (Tumor cell $\geq 25\%$ or IC $\geq 25\%$) 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, as a single agent, is indicated for the treatment of adult patients with limited-stage small cell lung cancer (LS-SCLC) whose disease has not progressed following concurrent platinum-based chemotherapy and radiation therapy (cCRT).
- 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).

1.6 Endometrial Cancer

IMFINZI in combination with carboplatin and paclitaxel followed by IMFINZI as a single agent, for the treatment of adult patients with primary advanced or recurrent endometrial cancer that is mismatch repair deficient (dMMR).

1.7 Bladder Cancer

IMFINZI in combination with gemcitabine and cisplatin as neoadjuvant treatment, followed by single agent IMFINZI as adjuvant treatment following radical cystectomy, is indicated for the treatment of adult patients with muscle invasive bladder cancer (MIBC).

The NIAGARA study was not designed to analyze and assess the efficacy of IMFINZI in the neoadjuvant and adjuvant treatment phase separately (see section 14). The additional adjuvant therapy with IMFINZI compared to the neoadjuvant treatment phase alone was associated with additional toxicity (see "Warnings and precautions").

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. The recommended dosage schedule and regimens for IMFINZI for the treatment of metastatic NSCLC are provided in Tables 2 and 3 [*see Indications and Usage (1.2)*].

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
Limited Stage SCLC	Following concurrent platinum-based chemotherapy and radiation therapy: Patients with a body weight of ≥ 30 kg: 1,500 mg every 4 weeks Patients with a body weight of < 30 kg: 20 mg/kg every 4 weeks	Until disease progression, unacceptable toxicity, or a maximum of 24 months
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
Extensive Stage 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

Indication	Recommended IMFINZI dosage	Duration of Therapy
BTC	<p>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</p> <p>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 every 4 weeks as a single agent</p>	Until disease progression or until unacceptable toxicity
uHCC	<p>Patients with a body weight of ≥ 30 kg:</p> <ul style="list-style-type: none"> 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 <p>Patients with a body weight of < 30 kg:</p> <ul style="list-style-type: none"> 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
Endometrial Cancer	1,120 mg in combination with carboplatin and paclitaxel every 3 weeks (21 days) for a minimum of 4 and up to 6 cycles, followed by IMFINZI 1,500 ^l mg every 4 weeks as monotherapy	Until disease progression or unacceptable toxicity
Neoadjuvant and Adjuvant Treatment of MIBC	<p>Patients with a body weight of ≥ 30 kg:</p> <p>Neoadjuvant: 1,500 mg in combination with gemcitabine and cisplatin* every 3 weeks for 4 cycles prior to surgery</p> <p>Adjuvant: IMFINZI 1,500 mg as a single agent every 4 weeks for up to 8 cycles after surgery</p> <p>Patients with a body weight of < 30 kg:</p> <p>Neoadjuvant: 20 mg/kg in combination</p>	Until disease progression that precludes definitive surgery, recurrence, or unacceptable toxicity or a maximum of 8 cycles after surgery

Indication	Recommended IMFINZI dosage	Duration of Therapy
	<p>with gemcitabine and cisplatin* every 3 weeks for 4 cycles prior to surgery</p> <p>Adjuvant: IMFINZI 20 mg/kg as a single agent every 4 weeks for up to 8 cycles after surgery</p>	

* 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.

† Endometrial cancer patients with a body weight of 30 kg or less during maintenance phase must receive weight-based dosing equivalent to IMFINZI at 20 mg/kg, until weight is greater than 30 kg.

MMR testing for patients with endometrial cancer

Patients with endometrial cancer should be evaluated for treatment based on tumour MMR status confirmed by a validated test (see section 5.1).

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 for Metastatic NSCLC

	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			X ^b				X ^b				X ^b				X ^b

* 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.

Ⓟ 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 for Metastatic NSCLC

Tumor Histology	Patient Weight	IMFINZI Dosage	Tremelimumab Dosage*	Platinum-based Chemotherapy Regimen*
Non-Squamous	≥30kg	1,500 mg	75 mg	<ul style="list-style-type: none"> carboplatin & nab-paclitaxel OR
	<30kg	20 mg/kg	1 mg/kg	<ul style="list-style-type: none"> carboplatin or cisplatin & pemetrexed
Squamous	≥30kg	1,500 mg	75 mg	<ul style="list-style-type: none"> carboplatin & nab-paclitaxel OR
	<30kg	20 mg/kg	1 mg/kg	<ul style="list-style-type: none"> carboplatin or cisplatin & gemcitabine

* 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	Severity¹	Dosage Modification
Pneumonitis [see <i>Warnings and Precautions (5.1)</i>]	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

Adverse Reactions	Severity ¹	Dosage Modification
Hepatitis [<i>see Warnings and Precautions (5.1)</i>]	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 [<i>see Warnings and Precautions (5.1)</i>]	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 [<i>see Warnings and Precautions (5.1)</i>]	Grade 2-4	Withhold dose until clinically stable

Adverse Reactions	Severity¹	Dosage Modification
Adrenal insufficiency or Hypophysitis/Hypopituitarism [<i>see Warnings and Precautions (5.1)</i>]	Grade 2-4	Withhold dose until clinically stable
Type 1 Diabetes Mellitus [<i>see Warnings and Precautions (5.1)</i>]	Grade 2-4	Withhold dose until clinically stable
Nephritis [<i>see Warnings and Precautions (5.1)</i>]	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) [<i>see Warnings and Precautions (5.1)</i>]	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 [<i>see Warnings and Precautions (5.1)</i>]	Grade 3 or 4	Withhold dose until clinically stable
	Grade 1 or 2	Interrupt or slow the rate of infusion

Adverse Reactions	Severity¹	Dosage Modification
Infusion-related reactions [<i>see Warnings and Precautions (5.2)</i>]	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 \leq 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.

Administration

- Administer infusion solution intravenously over 60 minutes through an intravenous line containing a sterile, low-protein binding 0.2 or 0.22 micron in-line filter.
- Use separate infusion bags and filters for each drug product.

IMFINZI in Combination with Other Products

- Administer all intravenous drug products as separate infusions.
- Do not co-administer other intravenous 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.

Combination Regimens: Order of Infusions

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.

IMFINZI in Combination with Chemotherapy

- Infuse IMFINZI first and then chemotherapy on the same day of dosing.

Combination Regimens: Infusion Instructions

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 60 minutes. One to two hours after completion of tremelimumab infusion, infuse IMFINZI over 60 minutes. 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/2.4 mL (50 mg/mL) and 500 mg/10 mL (50 mg/mL) clear to opalescent, colorless to slightly yellow solution in a single-dose vial.

4. CONTRAINDICATIONS

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/PD-L1 blocking antibody. While immune-mediated adverse reactions usually manifest during treatment with PD-1/PD-L1 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 studies 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.

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.

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% had a fatal adverse reaction and 2.7% had Grade 3 adverse reactions. Events resolved in 50 of the 87 (57%) patients and resulted in permanent discontinuation in 27 of the 87 (31%) 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 incidence of pneumonitis (including radiation pneumonitis) in patients with LS-SCLC following chemoradiation within 42 days prior to initiation of IMFINZI in ADRIATIC was 14% (37/262) in patients receiving IMFINZI and 6% (16/265) in patients receiving placebo. Of the patients who received IMFINZI

(262), 0.4% had a fatal adverse reaction and 2.7% had Grade 3 adverse reactions. Events resolved in 19 of the 37 (51%) patients and resulted in permanent discontinuation in 18 of the 37 (49%) patients. Systemic corticosteroids were required in all patients, while 1 patient required use of infliximab with high-dose steroids.

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) of 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 Tremelimumab 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.

IMFINZI with Carboplatin and Paclitaxel

Immune-mediated hypothyroidism occurred in 14% (34/235) of patients receiving IMFINZI in combination with carboplatin and paclitaxel. Events resolved in 8 of the 34 patients. Endocrine therapy was required in 34 of the 34 patients.

Type 1 Diabetes Mellitus, which can present with diabetic ketoacidosis

Monitor patients for hyperglycemia or other signs and symptoms of diabetes. Initiate treatment with insulin as clinically indicated. Withhold or permanently discontinue IMFINZI based on the severity [see *Dosage and Administration (2.2)*].

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 Tremelimumab 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.

Immune-Mediated Nephritis with Renal Dysfunction

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 2.6% (10/388) 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 1,889 patients enrolled in the PACIFIC study (a randomized, placebo-controlled study that enrolled 475 patients with unresectable 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 study (ATLANTIC Study) that enrolled 444 patients with advanced solid tumors, including NSCLC. In these studies, 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 1,500 mg every 4 weeks as a single agent in 262 patients from the ADRIATIC study (a randomized, double-blind study in patients with LS-SCLC) and to IMFINZI in combination with chemotherapy in 265 patients from the CASPIAN study (a randomized, open-label study in patients with ES-SCLC) and 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 also reflect exposure to IMFINZI 1,120 mg in combination with carboplatin and paclitaxel (every 3 weeks for up to 6 cycles) followed by IMFINZI 1,500 mg (every 4 weeks) as a single agent in 235 patients in DUO-E (a randomized, placebo-controlled trial in endometrial cancer). Among the 235 patients, 77% (181 patients) were exposed to IMFINZI for 6 months or more and 41% (96 patients) for 12 months or more.

The data 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 unresectable Stage III NSCLC enrolled in the PACIFIC study, in patients with metastatic NSCLC enrolled in the POSEIDON study, in patients with LS-SCLC enrolled in the ADRIATIC study, in patients with ES-SCLC enrolled in the CASPIAN study, in patients with BTC enrolled in the TOPAZ-1 study, in patients with uHCC included in the HIMALAYA study, in patients with dMMR endometrial cancer enrolled in the DUO-E study, and in patients with MIBC enrolled in the NIAGARA 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 ($\geq 15\%$) 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 ($\geq 3\%$) 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 $\geq 10\%$ of patients, while Table 6 summarizes the Grade 3 - 4 laboratory abnormalities that occurred in $\geq 1\%$ of patients treated with IMFINZI in the urothelial carcinoma cohort of Study 1108.

Table 5. Adverse Reactions in $\geq 10\%$ 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		

	IMFINZI (N=182)	
Adverse Reaction	All Grades (%)	Grades 3 – 4 (%)
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

Unresectable 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% of 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 ¹ /Radiation Pneumonitis	34	3.4	25	3
Dyspnea ²	25	1.5	25	2.6
Gastrointestinal Disorders				
Diarrhea	18	0.6	19	1.3
Abdominal pain ³	10	0.4	6	0.4
Endocrine Disorders				
Hypothyroidism ⁴	12	0.2	1.7	0
Skin and Subcutaneous Tissue Disorders				
Rash ⁵	23	0.6	12	0
Pruritus ⁶	12	0	6	0
General Disorders				
Fatigue ⁷	34	0.8	32	1.3
Pyrexia	15	0.2	9	0
Infections				
Upper respiratory tract infections ⁸	26	0.4	19	0
Pneumonia ⁹	17	7	12	6

¹ includes acute interstitial pneumonitis, interstitial lung disease, pneumonitis, pulmonary fibrosis

² includes dyspnea and exertional dyspnea

³ includes abdominal pain, abdominal pain lower, abdominal pain upper, and flank pain

⁴ includes autoimmune hypothyroidism and hypothyroidism

⁵ includes rash erythematous, rash generalized, rash macular, rash maculopapular, rash papular, rash pruritic, rash pustular, erythema, eczema, rash, and dermatitis

⁶ includes pruritus generalized and pruritus

⁷ includes asthenia and fatigue

⁸ includes laryngitis, nasopharyngitis, peritonsillar abscess, pharyngitis, rhinitis, sinusitis, tonsillitis, tracheobronchitis, and upper respiratory tract infection

⁹ 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 $\geq 20\%$ of Patients in the PACIFIC Study

	IMFINZI		Placebo	
Laboratory Abnormality	All Grades ¹ (%) ²	Grade 3 or 4 (%)	All Grades ¹ (%) ²	Grade 3 or 4 (%)
Chemistry				
Hyperglycemia	52	8	51	8
Hypocalcemia	46	0.2	41	0
Increased ALT	39	2.3	22	0.4
Increased AST	36	2.8	21	0.4
Hyponatremia	33	3.6	30	3.1
Hyperkalemia	32	1.1	29	1.8

Increased GGT	24	3.4	22	1.7
Hematology				
Lymphopenia	43	17	39	18

¹ Graded according to NCI CTCAE version 4.0

² Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: IMFINZI (range: 464 to 470) and placebo (range: 224 to 228)

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 study. 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 study 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 (COPD) (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 $\geq 20\%$ of patients) were nausea, fatigue, musculoskeletal pain, decreased appetite, rash, and diarrhea. Grade 3 or 4 laboratory abnormalities ($\geq 10\%$) were neutropenia, anemia, leukopenia, lymphocytopenia, lipase increased, hyponatremia and thrombocytopenia.

Table 9 summarizes the adverse reactions in POSEIDON.

Table 9. Adverse Reactions ($\geq 10\%$) 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				
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

	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 (%)
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 [‡]	10	0	10	0.6
Musculoskeletal and connective tissue disorders				
Musculoskeletal Pain [§]	29	0.6	22	1.5
Metabolism and nutrition disorders				
Decreased appetite	28	1.5	25	1.2
Infections and Infestations				
Pneumonia [‡]	17	8	12	4.2
Upper respiratory tract infections [§]	15	0.6	9	0.9
Nervous system disorders				
Headache [¶]	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.

[‡] Includes face edema, localized edema, and edema peripheral.

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

[‡] Includes lower respiratory tract infection, pneumocystis jirovecii pneumonia, pneumonia, pneumonia aspiration, pneumonia bacterial.

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

[¶] Includes headache and 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	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
Bilirubinemia	16	0.9	8	0.3
Hematology				
Neutropenia	71	37	69	32
Anemia	84	24	84	25
Leukopenia	77	21	81	18

Laboratory Abnormality*	IMFINZI with tremelimumab and platinum-based chemotherapy†		Platinum-based chemotherapy§	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
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

Limited Stage Small Cell Lung Cancer – ADRIATIC

The safety of IMFINZI as a single agent in patients with LS-SCLC without disease progression following completion of concurrent platinum-based chemoradiotherapy (60-66 Gy once daily over 6 weeks or 45 Gy twice daily over 3 weeks) within 42 days prior to initiation of study drug, was evaluated in the ADRIATIC study, a multicenter, randomized, double-blind, placebo-controlled study [see *Clinical Studies (14.2)*]. A total of 262 patients received IMFINZI 1,500 mg every 4 weeks until disease progression or unacceptable toxicity or a maximum of 24 months. The study excluded patients with Stage I or II LS-SCLC who were considered medically operable and patients with active or prior autoimmune disease or with medical conditions that required systemic corticosteroids or immunosuppressants.

The study population characteristics were: median age of 62 years (range: 28 to 84); 39% age 65 years or older, 6% age 75 years or older; 69% male; 50% white, 48% Asian, 1.3% other races; 4.2% Hispanic or Latino; 68% former smoker, 22% current smoker; and 51% had WHO performance status of 1. Sixty-seven percent of patients received a total radiation dose of 60 Gy to 66 Gy once daily and 27% of patients received a total radiation dose of 45 Gy twice daily. The median duration of exposure to IMFINZI was 9.2 months (range: 0.92 to 25) in the IMFINZI arm.

Serious adverse reactions occurred in 30% of patients receiving IMFINZI. The most frequent serious adverse reactions reported in $\geq 1\%$ of patients receiving IMFINZI were pneumonitis or radiation pneumonitis (12%), and pneumonia (5%). Fatal adverse reactions occurred in 2.7% of patients who received IMFINZI

including pneumonia (1.5%), cardiac failure, encephalopathy and pneumonitis (0.4% each). Permanent discontinuation of IMFINZI due to adverse reactions occurred in 16% of the patients. Adverse reactions which resulted in permanent discontinuation of IMFINZI in $\geq 1\%$ of patients included pneumonitis or radiation pneumonitis (9%) and pneumonia (1.5%). Dosage interruptions of IMFINZI due to an adverse reaction occurred in 35% of patients. Adverse reactions which required dosage interruption in $\geq 5\%$ of patients included pneumonitis or radiation pneumonitis (17%). The most common adverse reactions occurring in $\geq 20\%$ of patients receiving IMFINZI were pneumonitis or radiation pneumonitis (38%), and fatigue (21%).

Table 11 summarizes the adverse reactions that occurred in patients treated with IMFINZI in the ADRIATIC study.

Table 11. Adverse Reactions ($\geq 10\%$) in Patients with LS-SCLC Who Received IMFINZI in the ADRIATIC Study

	IMFINZI (n=262)		Placebo (n=265)	
Adverse Reaction	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Respiratory, thoracic and mediastinal disorders				
Pneumonitis or Radiation pneumonitis*	38	3.1	30	2.6
Cough/Productive Cough	17	0	14	0
Dyspnea†	11	0.4	7	0
General disorders				
Fatigue‡	21	0.4	20	2.3
Skin and subcutaneous tissue disorders				
Rash‡	18	0.4	11	0
Pruritus	13	0	7	0
Endocrine disorders				
Hypothyroidism¶	17	0	4.9	0
Hyperthyroidism #	12	0	1.9	0
Metabolism and nutrition disorders				
Decreased appetite	17	0	13	0
Nervous system disorders				
Dizziness§	14	0	9	0
Infections and Infestations				
Pneumonia§	13	3.1	9	4.2

	IMFINZI (n=262)		Placebo (n=265)	
Adverse Reaction	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Gastrointestinal disorders				
Nausea	13	0	11	0
Diarrhea	11	1.9	8	0
Constipation	10	0	10	0

* Includes pneumonitis, immune-mediated lung disease, interstitial lung disease, radiation pneumonitis, and lung radiation fibrosis.

† Includes dyspnea and exertional dyspnea.

‡ Includes fatigue and asthenia.

§ Includes dermatitis, acneiform dermatitis, eczema, rash, maculo-papular rash, papular rash, pruritic rash, and skin exfoliation.

¶ Includes hypothyroidism, increased blood thyroid stimulating hormone, and decreased thyroxine free.

Includes hyperthyroidism, decreased blood thyroid stimulating hormone, increased thyroxine free, increased thyroxine, increased tri-iodothyronine free, and increased tri-iodothyronine.

§ Includes pneumonia, atypical pneumonia, lower respiratory tract infection, bacterial pneumonia, pneumocystis jirovecii pneumonia, legionella pneumonia, and viral pneumonia.

‡ Includes dizziness, postural dizziness, vertigo, and positional vertigo.

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

Table 12. Select Laboratory Abnormalities (≥ 20%) That Worsened from Baseline in Patients with LS-SCLC Who Received IMFINZI in the ADRIATIC Study

Laboratory Abnormality*	IMFINZI†		Placebo‡	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Chemistry				
Hypocalcemia	43	0	43	0.8
Hyperglycemia	38	3.2	45	1.5
ALT increased	36	2.3	29	2.3
AST increased	33	2.3	28	1.5
Gamma Glutamyl Transferase increased	32	7	27	2.9
Hyponatremia	32	5	29	6.2
Hyperkalemia	23	1.2	17	0.8

Laboratory Abnormality*	IMFINZI†		Placebo‡	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Creatinine increased*	21	0	17	0.8
Hematology				
Lymphocytes decreased	34	10	33	10
Leukocytes decreased	26	0.4	33	1.1

* Graded according to NCI CTCAE version 4.03, except creatinine increased which is graded according to NCI CTCAE version 5.0.

† The denominator used to calculate the rate varied from 63 to 259 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 65 to 262 based on the number of patients with a baseline value and at least one post-treatment value.

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 study. 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 study 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 $\geq 20\%$ of patients) were nausea, fatigue/asthenia and alopecia.

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

Table 13. Adverse Reactions Occurring in $\geq 10\%$ 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 14 summarizes the laboratory abnormalities that occurred in at least 20% of patients treated with IMFINZI plus chemotherapy.

Table 14. Laboratory Abnormalities Worsening from Baseline Occurring in $\geq 20\%$ ¹ of Patients in the CASPIAN study

	IMFINZI with Etoposide and either Carboplatin or Cisplatin	Etoposide and either Carboplatin or Cisplatin
Laboratory Abnormality	Grade² 3 or 4 (%)³	Grade² 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 \geq 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 with 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) and upper gastrointestinal hemorrhage (2 patients). The most common adverse reactions (occurring in $\geq 20\%$ of patients) were fatigue, nausea, constipation, decreased appetite, abdominal pain, rash and pyrexia. Table 15 summarizes the adverse reactions that occurred in patients treated with IMFINZI plus chemotherapy.

Table 15. Adverse Reactions Occurring in $\geq 10\%$ 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 16 summarizes the laboratory abnormalities in patients treated with IMFINZI plus chemotherapy.

Table 16. Laboratory Abnormalities Worsening from Baseline Occurring in $\geq 20\%$ * 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 with gemcitabine/cisplatin (range: 312 to 335) and Placebo with gemcitabine/cisplatin (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 (14.5)*]. 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, pruritus, 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 17 summarizes the adverse reactions that occurred in patients treated with IMFINZI in combination with tremelimumab in the HIMALAYA study.

Table 17. 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 18 summarizes the laboratory abnormalities that occurred in patients treated with IMFINZI in combination with tremelimumab in the HIMALAYA study.

Table 18. Laboratory Abnormalities Worsening from Baseline Occurring in $\geq 20\%$ 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).

Endometrial Cancer

Advanced or Recurrent dMMR Endometrial Cancer – DUO-E

The safety of IMFINZI in combination with carboplatin and paclitaxel followed by IMFINZI as a single agent was evaluated in 44 patients with dMMR advanced or recurrent endometrial cancer in DUO-E, a randomized, double-blind, placebo-controlled trial [*See Clinical Studies (14.6)*]. Patients received IMFINZI 1,120 mg with carboplatin and paclitaxel every 3 weeks for up to six 21-day cycles followed by IMFINZI 1,500 mg every 4 weeks or carboplatin and paclitaxel every 3 weeks for up to six 21-day cycles alone. Treatment was continued until disease progression or unacceptable toxicity. The median duration of exposure to IMFINZI with carboplatin and paclitaxel was 14.8 months (range: 0.7 to 31.7).

Serious adverse reactions occurred in 30% of patients who received IMFINZI with carboplatin and paclitaxel. The most common serious adverse reactions ($\geq 4\%$) were constipation (4.5%) and rash (4.5%).

Permanent discontinuation of IMFINZI due to adverse reactions occurred in 11% of patients. The adverse reaction which resulted in permanent discontinuation of IMFINZI ($\geq 4\%$) was rash (4.5%).

Dosage interruptions of IMFINZI due to adverse reactions occurred in 52% of patients. Adverse reactions which required dosage interruptions of IMFINZI ($\geq 4\%$) were anemia (11%), thrombocytopenia (9%), neutropenia (9%), COVID-19 (9%), increased ALT (4.5%), and pneumonitis (4.5%).

The most common adverse reactions ($>20\%$), including laboratory abnormalities, were peripheral neuropathy, musculoskeletal pain, nausea, alopecia, fatigue, abdominal pain, constipation, rash, decreased magnesium, increased ALT, increased AST, diarrhea, vomiting, cough, decreased potassium, dyspnea, headache, increased alkaline phosphatase, and decreased appetite.

Tables 19 and 20 summarize adverse reactions and laboratory abnormalities in DUO-E, respectively.

Table 19. Adverse Reactions Occurring in $\geq 10\%$ of Patients with dMMR tumors in DUO-E

Adverse Reactions	IMFINZI with Carboplatin and Paclitaxel (N=44)		Carboplatin and Paclitaxel (N=46)	
	All Grades (%)	Grade 3-4 (%)	All Grades (%)	Grade 3-4 (%)
Nervous system disorders				
Peripheral neuropathy ^a	61	2.3	61	4.3
Headache	23	0	17	0
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain ^b	59	2.3	52	2.2
Gastrointestinal disorders				
Nausea	59	0	48	2.2
Abdominal pain ^c	39	0	24	2.2
Constipation ^d	39	4.5	35	2.2
Diarrhea	27	2.3	24	2.2
Vomiting	27	0	22	4.3
Skin and subcutaneous tissue disorders				
Alopecia	52	0	41	0
Rash ^e	39	2.3	17	2.2
Pruritus	16	0	11	0
General disorders and administration site conditions				
Fatigue ^f	41	4.5	57	11
Peripheral edema ^g	16	0	13	2.2
Respiratory, thoracic and mediastinal disorders				
Cough / productive cough	27	0	20	0
Dyspnea ^h	25	2.3	9	0
Metabolism and nutrition disorders				

Decreased appetite	18	0	18	0
Infections and infestations				
Upper respiratory tract infection ⁱ	14	0	4.3	0
Endocrine disorders				
Hypothyroidism ^j	11	0	4.3	0

^a Includes neuropathy peripheral, peripheral sensory neuropathy, hypoesthesia, peripheral motor neuropathy, and parasthesia.

^b Includes arthralgia, pain in extremity, back pain, non-cardiac chest pain, myalgia, musculoskeletal pain, musculoskeletal chest pain, arthritis, bone pain, musculoskeletal stiffness, neck pain, musculoskeletal discomfort, and spinal pain.

^c Includes abdominal pain, abdominal pain lower, flank pain, abdominal discomfort, and abdominal pain upper.

^d Includes constipation and fecaloma.

^e Includes eczema, rash, rash erythematous, rash maculo-papular, dermatitis, rash pustular, skin exfoliation, and symmetrical drug-related intertriginous, and flexural exanthema.

^f Includes asthenia and fatigue.

^g Includes peripheral edema, peripheral swelling, and edema.

^h Includes dyspnea and exertional dyspnea.

ⁱ Includes nasopharyngitis, pharyngitis, rhinitis, sinusitis, tracheobronchitis, and upper respiratory tract infection.

^j Includes blood thyroid stimulating hormone increased, and hypothyroidism.

Clinically relevant adverse reactions in < 10% of patients who received IMFINZI with carboplatin and paclitaxel included autoimmune hemolytic anemia, colitis, immune-mediated thyroiditis, infusion related reaction, interstitial lung disease, myositis, pneumonitis, pulmonary embolism, and sepsis.

Table 20 summarizes the laboratory abnormalities that occurred in patients treated with IMFINZI with carboplatin and paclitaxel followed by IMFINZI as a single agent.

Table 20. Select Laboratory Abnormalities Worsening from Baseline Occurring in ≥ 20% of Patients with dMMR tumors in DUO-E

Laboratory Abnormality	IMFINZI with Carboplatin and Paclitaxel [‡]		Carboplatin and Paclitaxel [‡]	
	All Grades (%)	Grade 3-4 (%)	All Grades (%)	Grade 3-4 (%)
Chemistry				

Magnesium decreased	36	0	30	2.5
ALT increased	32	2.3	22	2.2
AST increased	30	2.3	22	0
Potassium decreased	25	0	24	2.2
Alkaline phosphatase increased	20	0	16	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 with carboplatin and paclitaxel (range: 40 to 44), and carboplatin and paclitaxel (range: 37 to 46).

Muscle Invasive Bladder Cancer (MIBC)

Neoadjuvant and adjuvant treatment of MIBC – NIAGARA

The safety of IMFINZI in combination with neoadjuvant gemcitabine and cisplatin followed by surgery and continued IMFINZI treatment as adjuvant, single-agent therapy was evaluated in NIAGARA, a randomized, open-label, multicenter trial. Patients received IMFINZI in combination with chemotherapy (n=530) or received chemotherapy alone (n=526) [see *Clinical Studies (14.7)*].

The median duration of exposure to IMFINZI 1,500 mg every 3 weeks in the neoadjuvant phase was 12 weeks (range: 1.1 to 84 weeks). The median duration of exposure to IMFINZI 1,500 mg every 4 weeks in the adjuvant phase was 32 weeks (range: 2.4 to 50 weeks).

The most common adverse reactions, including laboratory abnormalities, in the overall study (occurring in $\geq 20\%$ of patients) were decreased hemoglobin, decreased neutrophils, increased blood creatinine, decreased sodium, nausea, increased ALT, decreased calcium, decreased platelets, fatigue, increased potassium, decreased lymphocytes, increased AST, constipation, decreased magnesium, decreased appetite, increased alkaline phosphate, rash, pyrexia, diarrhea, vomiting, and abdominal pain.

Table 21 summarizes the adverse reactions that occurred in patients treated with IMFINZI plus chemotherapy.

Table 21. Adverse Reactions Occurring in $\geq 10\%$ of Patients in the NIAGARA Study

	IMFINZI with gemcitabine and cisplatin N = 530		Gemcitabine and cisplatin N = 526	
Adverse Reaction	All Grades* (%)	Grade* 3-4 (%)	All Grades* (%)	Grade* 3-4 (%)
Gastrointestinal disorders				
Nausea	54	1.5	48	1
Constipation	39	0.8	39	0.8
Diarrhea	21	1.5	14	0.4
Vomiting†	20	0.9	19	0.2
Abdominal pain†	20	0.9	13	1
General disorders and administration site conditions				
Fatigue†	52	2.3	49	3
Pyrexia†	22	0.4	17	0
Edema†	13	0.4	13	0
Metabolism and nutrition disorders				
Decreased appetite	27	0.6	25	0.6
Skin and subcutaneous tissue disorders				
Rash†	23	1.3	12	0.6
Pruritus	15	0	7	0
Nervous system disorders				
Peripheral neuropathy†	16	0.2	14	0
Headache†	11	0	11	0
Dizziness†	11	0	10	0.2
Endocrine disorders				
Hypothyroidism†	13	0.4	2.3	0
Vascular disorders				

Hypertension†	12	4.5	9	2.9
Hemorrhage†	11	0.9	10	2.1

* Graded according to NCI CTCAE version 5.0.

† Includes multiple similar terms.

Table 22 summarizes the laboratory abnormalities in patients treated with IMFINZI plus chemotherapy.

Table 22. Select Laboratory Abnormalities That Worsened from Baseline in ≥ 20% of Patients Who Received IMFINZI with Chemotherapy in the NIAGARA study

Laboratory Abnormality	IMFINZI with gemcitabine and cisplatin‡		Gemcitabine and cisplatin ‡	
	All Grades† (%)	Grade† 3 or 4 (%)	All Grades† (%)	Grade† 3 or 4 (%)
Chemistry				
Increased blood creatinine	63	9	58	7
Decreased sodium	54	9	55	10
Increased ALT	53	2.3	54	4.0
Decreased calcium	52	1.3	43	1.2
Increased potassium	51	4.2	49	4.4
Increased AST	42	1.5	39	2.1
Decreased magnesium	38	1.9	37	2.3
Increased alkaline phosphate	26	0.8	25	0.4
Hematology				
Decreased hemoglobin	88	13	87	13
Decreased neutrophils	76	31	74	34
Decreased platelets	52	6	50	7

Decreased lymphocytes	44	10	40	8
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‡ Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: IMFINZI plus chemotherapy (range: 482 to 528), and chemotherapy (range: 467 to 521).

† Graded per NCI CTCAE V5.

Neoadjuvant Phase of NIAGARA

A total of 530 patients received at least 1 dose of IMFINZI in combination with chemotherapy as neoadjuvant treatment in the IMFINZI treatment arm, and 526 patients received at least 1 dose of chemotherapy as neoadjuvant treatment in the chemotherapy treatment arm. In the neoadjuvant phase, serious adverse reactions occurred in 24% of patients who received IMFINZI in combination with chemotherapy; the most frequent ($\geq 1\%$) serious adverse reactions were pulmonary embolism (1.9%), febrile neutropenia (1.5%), acute kidney injury (1.3%), thrombocytopenia (1.3%), urinary tract infection (1.3%) and pneumonia (1.3%). Fatal adverse reactions occurred in 1.1% of patients including sepsis (0.2%), myocardial infarction (0.2%), and pulmonary embolism (0.2%). One fatal adverse reaction of pneumonia was reported in 1 (0.2%) patient in the post-surgery phase before adjuvant treatment started.

Permanent discontinuation of IMFINZI due to an adverse reaction in the neoadjuvant phase occurred in 9% of patients while receiving IMFINZI in combination with chemotherapy. The most frequent ($\geq 0.5\%$) adverse reactions that led to permanent discontinuation of IMFINZI were blood creatinine increased (0.9%), neutropenia (0.6%), acute kidney injury (0.6%), asthenia (0.6%) and fatigue (0.6%).

Of the 530 patients in the IMFINZI treatment arm and 526 patients in the chemotherapy treatment arm who received neoadjuvant treatment, 1 (0.2%) patient in each treatment arm did not receive surgery due to adverse reactions. The adverse reaction that led to cancellation of surgery in the IMFINZI treatment arm was interstitial lung disease.

Of the 469 patients in the IMFINZI treatment arm who underwent radical cystectomy, 4 (0.8%) patients experienced delay of surgery (defined as occurring more than 56 days after the last dose of neoadjuvant treatment) due to adverse reactions.

Adjuvant Phase of NIAGARA

A total of 383 patients (72%) in the IMFINZI treatment arm received at least 1 dose of adjuvant treatment.

Serious adverse reactions occurred in 26% of patients receiving IMFINZI as adjuvant treatment. The most frequent serious adverse reactions (occurring in $\geq 1\%$ of patients) were urinary tract infection (7%), acute kidney injury (3.7%), hydronephrosis (2.1%), pyelonephritis (2.1%), urosepsis (1.8%), and sepsis (1.6%). Fatal adverse reactions occurred in 1.8% of patients, including COVID-19 (0.3%), severe acute respiratory syndrome (0.3%), cardiopulmonary failure (0.3%), gastrointestinal haemorrhage (0.3%), and chronic hepatic failure (0.3%).

Permanent discontinuation of adjuvant IMFINZI due to an adverse reaction occurred in 5% of patients. The most frequent ($\geq 0.5\%$) adverse reactions that led to permanent discontinuation of adjuvant IMFINZI were nephritis (0.8%), fatigue (0.5%), diarrhea (0.5%), decreased appetite (0.5%) and pneumonitis (0.5%).

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 with unresectable, Stage III NSCLC 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 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 262 patients with LS-SCLC treated with IMFINZI, 103 (39%) patients were 65 years or older and 15 (6%) patients were 75 years or older. There were no clinically meaningful differences in safety and efficacy between patients 65 years or older and 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 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.

Of the 235 patients with endometrial cancer treated with IMFINZI with carboplatin and paclitaxel, 49% of patients were 65 years of age or older and 12% 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.

Of the 530 patients with MIBC treated with IMFINZI in combination with gemcitabine and cisplatin in the NIAGARA study, 272 (51%) patients were 65 years or older, and 57 (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.

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 (IgG1 κ) monoclonal antibody that is produced by recombinant DNA technology in Chinese Hamster Ovary (CHO) cell suspension culture.

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

Each 500 mg vial of IMFINZI contains 500 mg of durvalumab in 10 mL solution. Each mL contains durvalumab, 50 mg, 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 (IgG1 κ) monoclonal antibody that binds to PD-L1 and blocks the interaction of PD-L1 with PD-1 and CD80 (B7.1). Blockade of PD-L1/PD-1 and PD-L1/CD80 interactions releases the inhibition of immune responses, without inducing antibody dependent cell-mediated cytotoxicity (ADCC).

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

12.2 Pharmacodynamics

The steady state AUC, C_{trough}, and C_{max} 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 < 3 mg/kg (0.3 times the approved recommended dosage) and dose proportionally at doses \geq 3 mg/kg every 2 weeks. Steady state was achieved at approximately 16 weeks.

The pharmacokinetics of durvalumab is similar when assessed as a single agent, when in combination with chemotherapy, 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 (V_{ss}) 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 (CL_{ss}) of 8 mL/h (39%) at day 365; the decrease in CL_{ss} is not considered clinically relevant. The geometric mean (CV%) terminal half-life, based on baseline CL was approximately 21 (26%) days.

Specific Populations

There were no clinically significant differences in pharmacokinetics of durvalumab based on body weight (31 to 175 kg), age (18 to 96 years), sex, race (White, Black, Asian, Native Hawaiian, Pacific Islander, or Native American), albumin levels (4 to 57 g/L), lactate dehydrogenase levels (18 to 15,800 U/L), soluble PD-L1 (67 to 3,470 pg/mL), tumor type (NSCLC, SCLC, BTC and HCC), mild or moderate renal impairment (CL_{cr} 30 to 89

mL/min), and mild or moderate hepatic impairment (bilirubin \leq 3xULN 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 or of other durvalumab products.

In clinical trials of patients who received IMFINZI for 10 to 48 week at dosages of 1,500 mg every 4 weeks, 10 mg/kg every 2 weeks, 20 mg/kg every 4 weeks as a single agent or 1,120 mg every 3 weeks, or 1,500 mg every 3 weeks in the combination therapies, 3.1% (159/5121) of evaluable patients tested positive for treatment-emergent anti-durvalumab antibodies, and 10% (16/159) of treatment-emergent ADA positive patients had neutralizing antibodies against durvalumab. There were no identified clinically significant effects of ADAs on durvalumab pharmacokinetics or safety; however, the effect of these ADAs on the effectiveness of IMFINZI is unknown.

13. NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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

13.2 Animal Toxicology and/or Pharmacology

In animal models, inhibition of PD-L1/PD-1 signaling increased the severity of some infections and enhanced inflammatory responses. *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 and mice receiving PD-L1 blocking antibody 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 $\geq 25\%$ or IC $\geq 25\%$; if ICs involve $\leq 1\%$ of the tumor area, TC $\geq 25\%$ 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 23 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 23. 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	NR	NR	12.3	NR
months (range)	(0.9+, 19.9+)	(0.9+, 19.9+)	(1.9+, 12.3)	(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 24 and Figure 1 summarizes the efficacy results for PACIFIC.

Table 24. 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

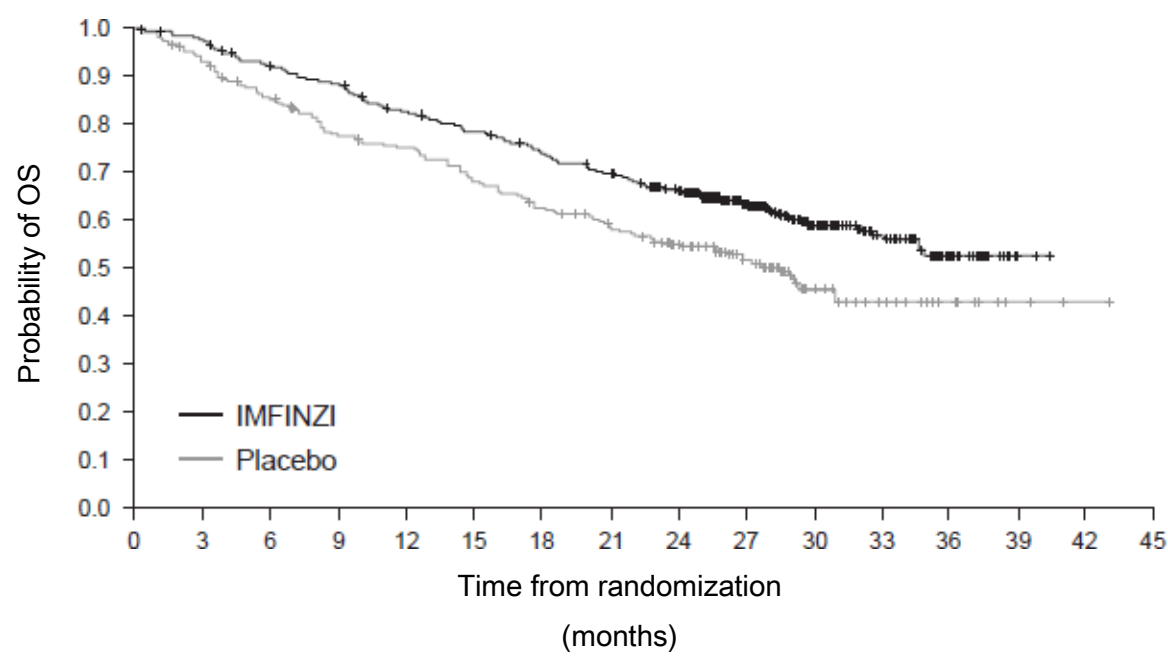
⁵ As assessed by BICR RECIST v1.1

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 OS in the PACIFIC Study



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

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 \geq 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/m² with carboplatin AUC 5-6 or cisplatin 75 mg/m² every 3 weeks for 4 cycles.
- Squamous NSCLC
 - Gemcitabine 1,000 or 1,250 mg/m² on Days 1 and 8 with cisplatin 75 mg/m² or carboplatin AUC 5-6 on Day 1 every 3 weeks for 4 cycles.
- Non-squamous and Squamous NSCLC
 - Nab-paclitaxel 100 mg/m² 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 \geq 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 \geq 50%, 71% PD-L1 expression TC $<$ 50%.

Efficacy results are summarized in Table 25 and Figure 2.

Table 25. Efficacy Results for the POSEIDON Study

	IMFINZI with tremelimumab and platinum-based chemotherapy (n=338)	Platinum-based chemotherapy (n=337)
OS¹		
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	
PFS²		
Number of events (%)	238 (70)	258 (77)
Median PFS (months)	6.2	4.8

	IMFINZI with tremelimumab and platinum-based chemotherapy (n=338)	Platinum-based chemotherapy (n=337)
(95% CI)	(5.0, 6.5)	(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)

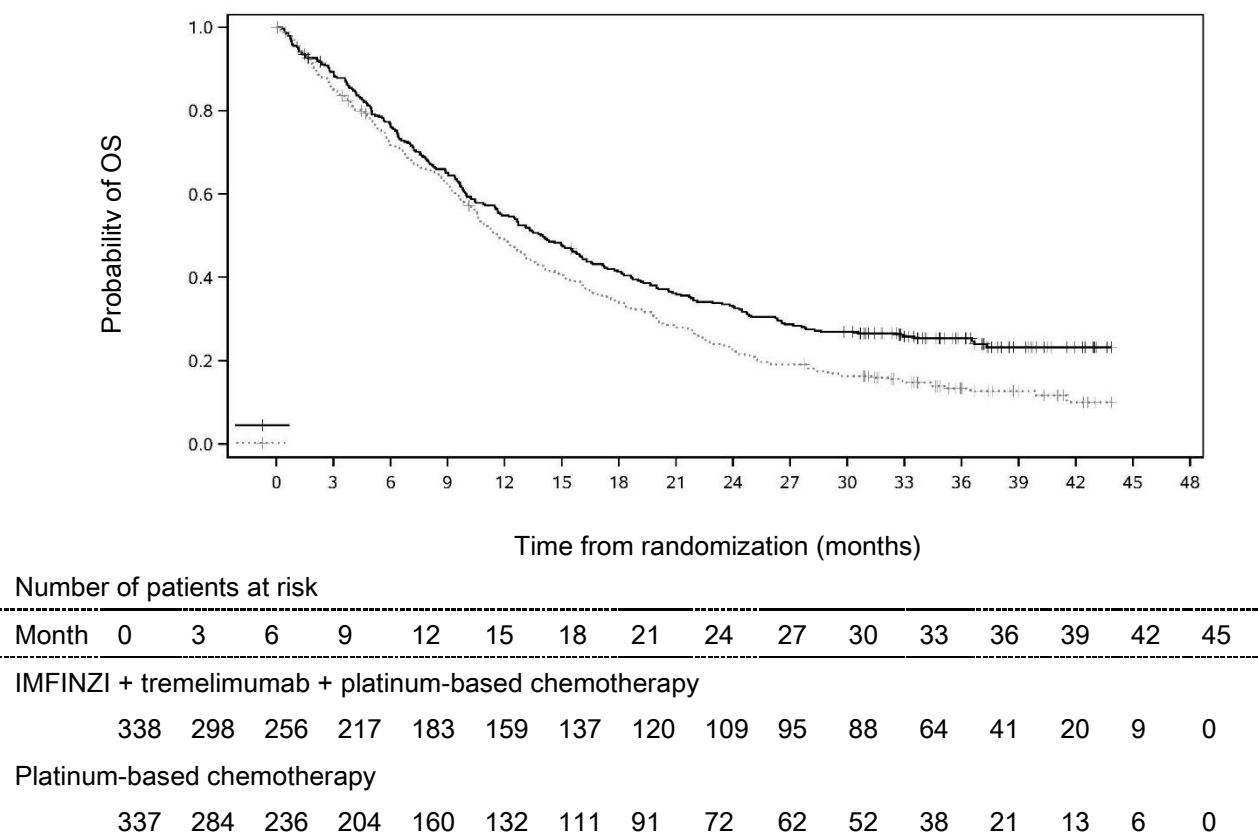
¹ PFS/OS results are based on planned analyses which occurred 25/45 months respectively after study initiation.

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.

³ Confirmed responses with 95% Clopper-Pearson confidence interval.

NR=Not Reached, CI=Confidence Interval

Figure 2. Kaplan-Meier curves of OS in the POSEIDON study



14.3 Small Cell Lung Cancer (SCLC)

Limited-stage SCLC – ADRIATIC

The efficacy of IMFINZI was evaluated in the ADRIATIC Study (NCT03703297), a randomized, double-blind, placebo-controlled, multicenter study in 730 patients with histologically or cytologically confirmed LS-SCLC (Stage I to III according to AJCC, 8th edition) whose disease had not progressed following concurrent chemoradiation therapy (cCRT). Patients who had Stage I or II disease had to be medically inoperable as determined by the investigator. Eligible patients completed cCRT consisting of 4 cycles of platinum-based chemotherapy and either 60-66 Gy once daily over 6 weeks or 45 Gy twice daily over 3 weeks radiation therapy within 42 days prior to the first dose of IMFINZI or placebo. Prophylactic cranial irradiation (PCI) could be delivered at the discretion of the investigator after cCRT and had to be completed within 42 days prior to the first dose of IMFINZI or placebo. Patients with active or prior documented autoimmune disease within 5 years of initiation into the study; a history of active primary immunodeficiency; a history of Grade ≥ 2 pneumonitis or active tuberculosis or hepatitis B or C or HIV infection; active interstitial lung disease were ineligible. Patients with mixed SCLC and NSCLC histology were also ineligible. Randomization was stratified by stage (I/II versus III) and receipt of PCI (yes versus no).

Patients were randomized 1:1:1 to receive IMFINZI as a single agent, IMFINZI in combination with another agent, or placebo. All study medications were administered intravenously. The evaluation of efficacy for LS-SCLC relied on comparison between:

- Arm 1: IMFINZI 1,500 mg in combination with placebo every 4 weeks for 4 cycles, followed by IMFINZI 1,500 mg every 4 weeks.
- Arm 2: Placebo in combination with a second placebo every 4 weeks for 4 cycles, followed by a single placebo every 4 weeks.

A total of 530 patients were randomized between Arms 1 and 2, 264 patients to the IMFINZI arm and 266 patients to the placebo arm. Treatment continued until disease progression, until unacceptable toxicity, or for a maximum of 24 months. Tumor assessments were conducted every 8 weeks for the first 72 weeks, then every 12 weeks up to 96 weeks and then every 24 weeks thereafter.

The major efficacy outcome measures were OS and PFS assessed by BICR according to RECIST v1.1.

The baseline demographics and disease characteristics for patients in the IMFINZI and placebo arms were as follows: male (69%); age ≥ 65 years (39%); White (50%), Black or African-American (0.8%), Asian (48%), other race (1.3%); Hispanic or Latino (4.2%); current smoker (22%), past-smoker (68%), never smoker (9%); WHO/ECOG PS 0 (49%), WHO/ECOG PS 1 (51%); and Stage I (3.6%), Stage II (9%), Stage III (87%).

Prior to randomization, all patients received platinum-based chemotherapy (66% cisplatin-etoposide, 34% carboplatin-etoposide) with 88% of patients receiving 4 cycles; 72% of patients received once daily radiation (of which 92% received $\geq 60 - \leq 66$ Gy QD); 28% received twice daily radiation (of which 97% received 45 Gy twice daily) and 54% of patients received PCI.

Efficacy results are presented in Table 26 and Figure 3.

Table 26. Efficacy Results for the ADRIATIC study

	IMFINZI (n=264)	Placebo (n=266)
OS		
Number of deaths (%)	115 (44)	146 (55)
Median OS (months) (95% CI)†	55.9 (37.3, NR)	33.4 (25.5, 39.9)
HR (95% CI)‡	0.73 (0.57, 0.93)	
p-value§	0.0104	
PFS¶		
Number of events (%)	139 (53)	169 (64)
Median PFS (months) (95% CI)†	16.6 (10.2, 28.2)	9.2 (7.4, 12.9)
HR (95% CI)#	0.76 (0.61, 0.95)	
p-value§	0.0161	

[†] Calculated using the Kaplan Meier technique. CI for median derived based on Brookmeyer-Crowley method.

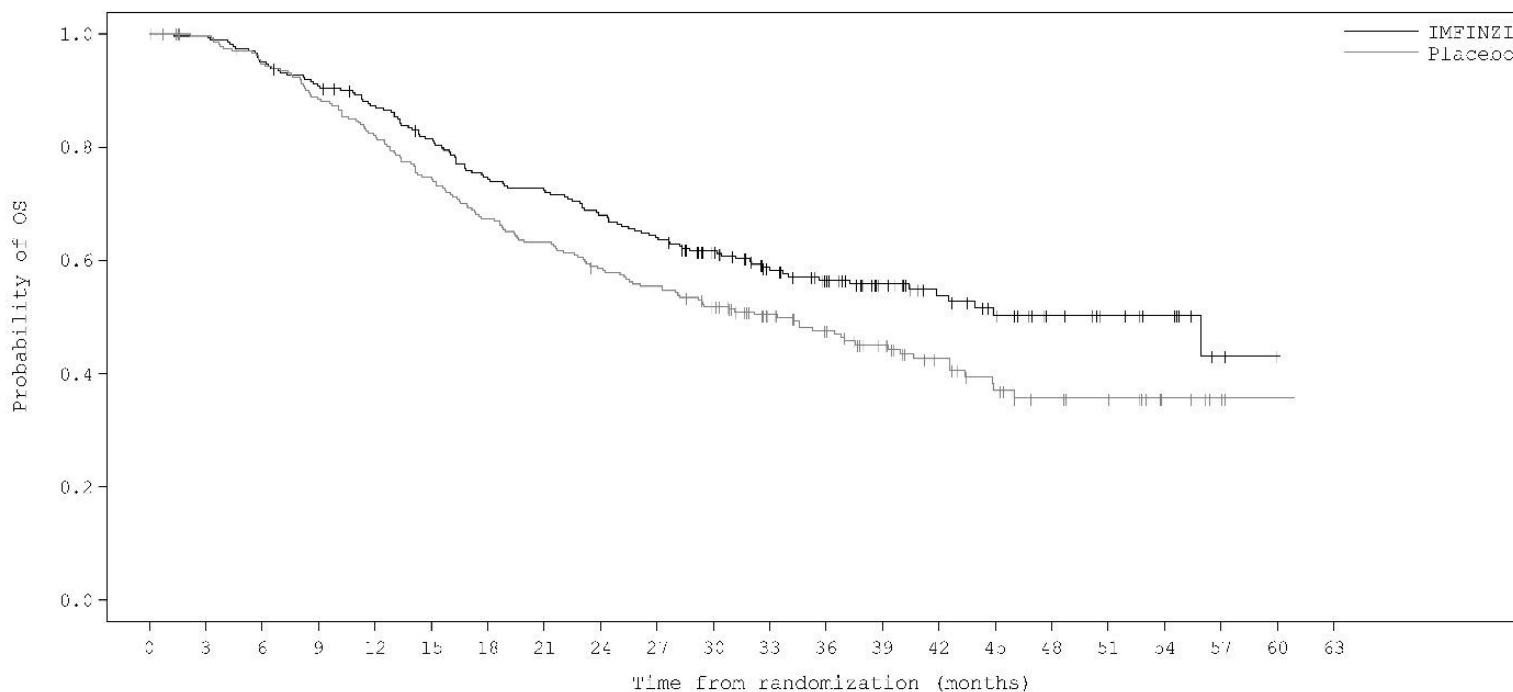
[‡] Based on Cox proportional hazards model stratified by receipt of PCI.

[§] Compared with allocated alpha of 0.0168 for OS and 0.0280 for PFS (Lan-DeMets spending function approximating O'Brien Fleming boundary) for interim analysis.

[¶] Assessed by BICR according to RECIST v1.1.

Based on Cox proportional hazards model stratified by TNM stage and receipt of PCI.

Figure 3: Kaplan-Meier Curves of OS in the ADRIATIC Study



Number of subjects at risk

IMFINZI	264	261	248	236	223	207	189	183	172	162	141	110	93	68	51	39	27	19	11	5	1	0
Placebo	266	260	247	231	214	195	175	164	151	143	123	97	80	62	44	31	23	19	8	5	1	0

Subgroup efficacy analyses for PFS and OS by time from the end of cCRT to randomization are presented in Table 27

Table 27. OS and PFS Using BICR Assessments According to RECIST 1.1, by Time from End of cCRT to Randomization (FAS)

	FAS*		< 28 days		28-42 days		> 42 days	
	D (N = 264)	Placebo (N = 266)	D (N = 111)	Placebo (N = 112)	D (N = 146)	Placebo (N = 152)	D (N = 7)	Placebo (N = 2)
Overall Survival								
Death, n (%)	115 (43.6)	146 (54.9)	51 (45.9)	75 (67.0)	62 (42.5)	70 (46.1)	2 (28.6)	1 (50.0)
Median OS, months	55.9 (37.3, NR)	33.4 (25.5, 39.9)	42.5 (31.2, NR)	23.1 (17.6, 25.7)	NR (33.0, NR)	42.5 (34.6, NR)	NR (1.3, NR)	NR (37.0, NR)

	FAS*		< 28 days		28-42 days		> 42 days	
	D	Placebo	D	Placebo	D	Placebo	D	Placebo
	(N = 264)	(N = 266)	(N = 111)	(N = 112)	(N = 146)	(N = 152)	(N = 7)	(N = 2)
(95% CI)								
OS HR, D vs placebo ^a (95% CI)	0.73 (0.569, 0.928)		0.56 (0.387, 0.791)		0.90 (0.639, 1.268)		NC	
Progression-Free Survival								
Total PFS events, n (%)	139 (52.7)	169 (63.5)	61 (55.0)	77 (68.8)	75 (51.4)	91 (59.9)	3 (42.9)	2 (50.0)
Median PFS, months (95% CI) ^b	16.6 (10.2, 28.2)	9.2 (7.4, 12.9)	9.5 (7.3, 21.0)	7.3 (5.6, 9.2)	27.6 (12.0, 37.3)	12.9 (9.2, 17.0)	NR (1.3, NR)	NR (37.0, NR)
PFS HR, D vs placebo (95% CI) ^a	0.76 (0.606, 0.950)		0.74 (0.525, 1.030)		0.78 (0.572, 1.056)		NC	

CI=Confidence Interval; D=durvalumab; HR= Hazard Ratio; NC=Not Calculated; NR=Not Reached; OS=Overall Survival; PFS=Progression Free Survival

^a The HR and CI were calculated using an unstratified Cox proportional hazards model, with treatment as only covariate and ties handled by Efron approach.

A HR< 1 favors durvalumab to be associated with a longer event-free survival than placebo.

^b Patients who had not progressed or died, or who progressed or died after 2 or more missed visits were censored at the latest evaluable RECIST assessment, or Day 1 if there were no evaluable visits. Patients with RECIST progression within 2 visits of baseline who did not have any evaluable visits or did not have a baseline assessment were censored at Day 1.

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 study (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/m²) on Day 1 and etoposide (80-100 mg/m²) intravenously on Days 1, 2, and 3 of each 21-day cycle for 4 cycles, followed by IMFINZI 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/m²) on Day 1 and etoposide (80-100 mg/m²) intravenously on Days 1, 2, and 3 of each 21-day cycle, up to 6 cycles. After completion of chemotherapy, prophylactic cranial irradiation (PCI) 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 28 and Figure 4.

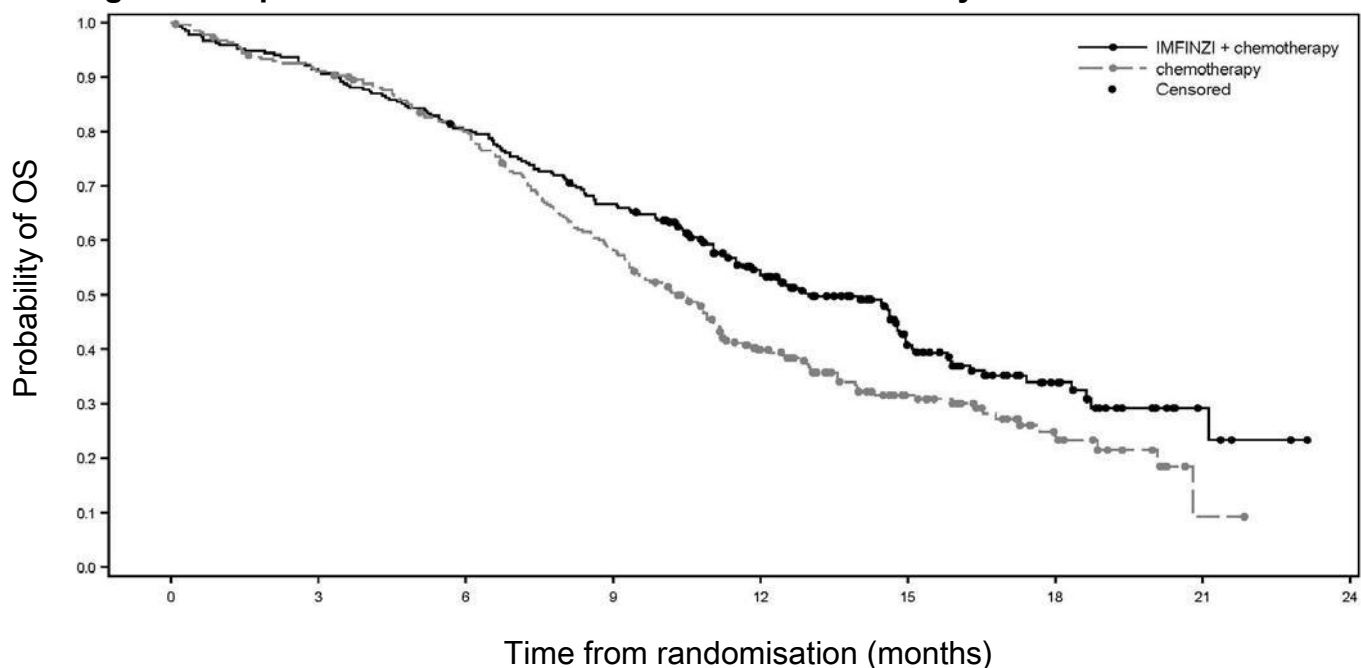
Table 28. OS Results for the CASPIAN Study

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 4. Kaplan-Meier Curves of OS 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 study 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 v1.1. 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/m² and cisplatin 25 mg/m² 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/m² and cisplatin 25 mg/m² 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 study 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 29 summarizes the efficacy results for TOPAZ-1.

Table 29. 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.

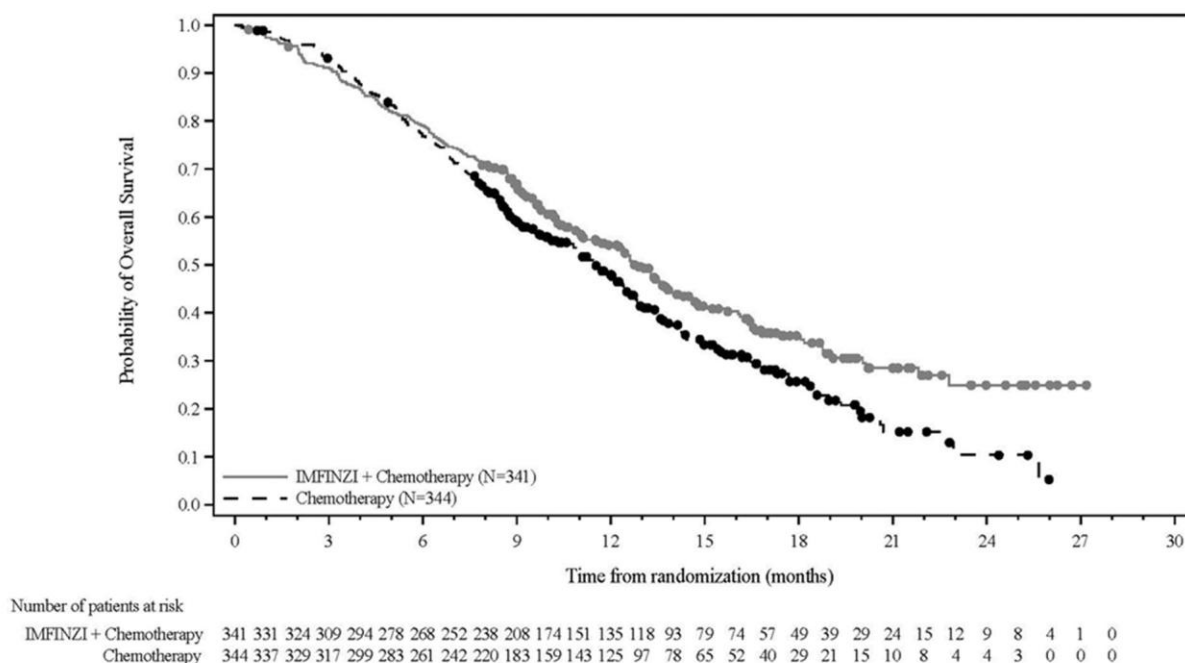
† Based on Cox proportional hazards model stratified by disease status and primary tumor location

‡ 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 5: Kaplan-Meier Curve of OS in TOPAZ-1 Study



14.5 Hepatocellular Carcinoma (HCC)

Unresectable HCC -HIMALAYA

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 tremelimumab 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 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 30 and Figure 6.

Table 30. 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 (IMFINZI and tremelimumab vs. sorafenib) based on the stratified Cox proportional hazard model.

† Based on a stratified log-rank test.

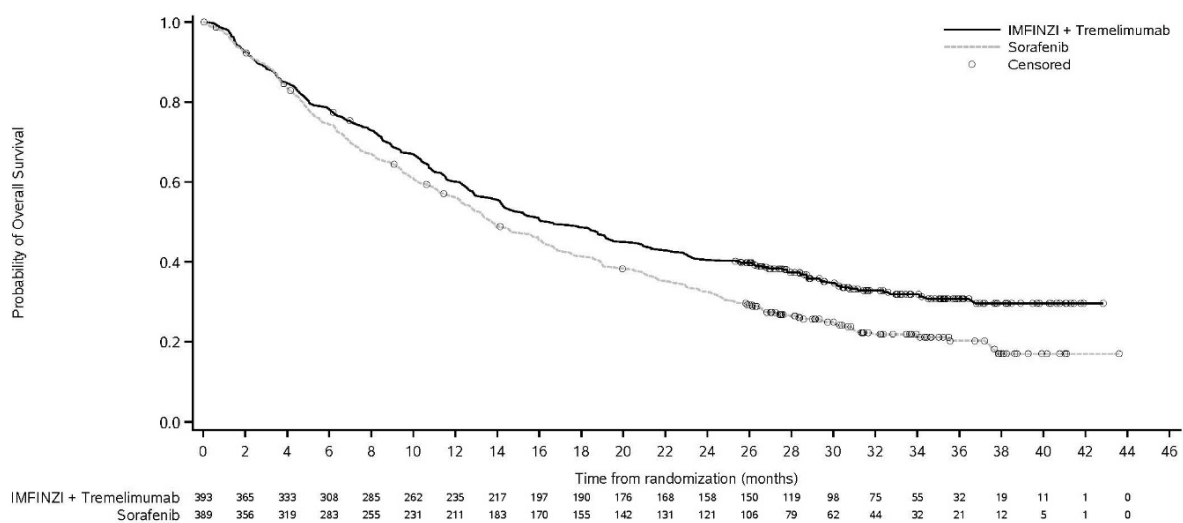
‡ Based on a Lan-DeMets alpha spending function with O'Brien Fleming type boundary and the actual number of events observed, the boundary for declaring statistical significance for IMFINZI and tremelimumab vs. sorafenib was 0.0398 (Lan and DeMets 1983).

§ Confirmed complete response or partial response.

¶ Based on Clopper-Pearson method.

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

Figure 6. Kaplan-Meier curve of OS in the Himalaya Study



14.6 Endometrial cancer

Advanced or Recurrent dMMR Endometrial Cancer - DUO-E

IMFINZI was evaluated in combination with carboplatin and paclitaxel in DUO-E (NCT04269200), a randomized, multicenter, double-blind, placebo-controlled study in patients with advanced or recurrent endometrial cancer. The trial enrolled patients with newly diagnosed Stage III disease (with measurable disease per RECIST v1.1), or newly diagnosed Stage IV disease. The trial also enrolled patients with recurrent disease with a low potential for cure by radiation therapy or surgery. For patients with recurrent disease, prior chemotherapy was allowed only if it was administered in the adjuvant setting and at least 12 months had elapsed from the date of last dose of chemotherapy to the date of relapse. The trial included patients with epithelial endometrial carcinomas of all histologies, including carcinosarcomas. Patients with endometrial sarcoma were excluded, and patients who had active autoimmune disease or a medical condition that required immunosuppression were ineligible.

Randomization was stratified by tumor mismatch repair (MMR) status (proficient or deficient), disease status (recurrent or newly diagnosed), and geographic region (Asia or rest of the world). MMR status was assessed using an FDA-approved test.

Patients were randomized (1:1:1) to one of the following treatment arms:

- IMFINZI 1,120 mg in combination with carboplatin and paclitaxel every 3 weeks for a maximum of 6 cycles. Following completion of chemotherapy treatment, patients received IMFINZI 1,500 mg every 4 weeks as maintenance treatment until disease progression.
- Placebo in combination with carboplatin and paclitaxel every 3 weeks for a maximum of 6 cycles.

Following completion of chemotherapy treatment, patients received placebo every 4 weeks as maintenance treatment until disease progression.

- An additional investigational combination regimen.

Treatment was continued until Response Evaluation Criteria in Solid Tumors (RECIST) v1.1-defined progression of disease or unacceptable toxicity. Assessment of tumor status was performed every 9 weeks for the first 18 weeks and every 12 weeks thereafter.

The major efficacy outcome measure was progression-free survival (PFS), determined by investigator assessment using RECIST 1.1. Additional efficacy outcome measures included overall response rate (ORR), duration of response (DOR) and overall survival (OS).

Among 95 patients with dMMR tumor, the baseline characteristics were median age of 63 years (range: 34 to 85); 47% age 65 or older; 62% White, 31% Asian, 2% Black or African American; 7% Hispanic or Latino, 1% American Indian or Alaska Native, and 4% other or not reported; ECOG PS of 0 (55%) or 1 (45%); 48% newly diagnosed (11% Stage III and 38% Stage IV) and 52% recurrent disease. The histologic subtypes were endometrioid (78%), mixed epithelial (6%), carcinosarcoma (5%), serous (4%), undifferentiated (1%), and other (5%).

While a statistically significant improvement in PFS was observed in the overall population for IMFINZI with carboplatin and paclitaxel compared to carboplatin and paclitaxel alone, based on an exploratory analysis by MMR status, the PFS improvement in the overall population was primarily attributed to patients with dMMR tumors.

Efficacy results for DUO-E are summarized in Table 31 and Figure 7 for patients with dMMR tumors.

OS data in this subpopulation at the time of PFS analysis were immature with 26% of patients who died.

Table 31. Efficacy Results for Patients with dMMR Tumors in the DUO-E Study

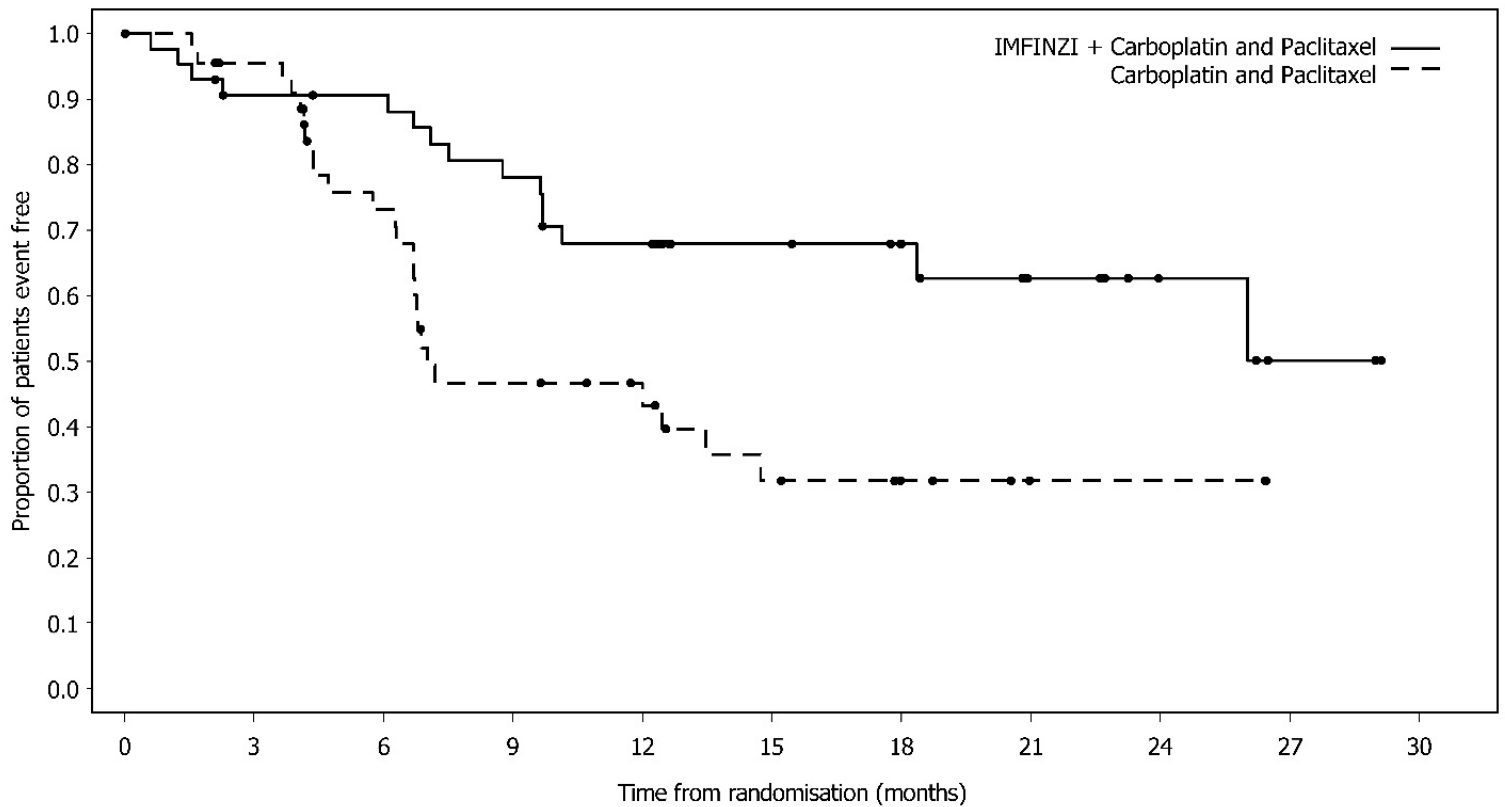
Endpoint	IMFINZI with Carboplatin and Paclitaxel N=46	Carboplatin and Paclitaxel N=49
PFS*		
Number of events (%)	15 (32.6)	25 (51.0)
Median in months (95% CI)‡	NR (NR, NR)	7.0 (6.7, 14.8)
HR (95% CI)	0.42 (0.22, 0.80)	
ORR	N=42	N=42
ORR % (95% CI)	71.4 (55.4, 84.3)	40.5 (25.6, 56.7)
Complete response %	12 (28.6)	4 (9.5)
Partial response %	18 (42.9)	13 (31.0)
DOR		
Median in months (range)	NR (2.4+, 26.9+)	10.5 (2.1+, 25.2+)

*Investigator assessed.

‡ Calculated using the Kaplan-Meier technique.

CI=Confidence Interval, HR=Hazard Ratio, NR=Not Reached, + = response ongoing at last assessment.

Figure 7. Kaplan-Meier curves of PFS for Patients with dMMR Tumors in the DUO-E Study



Number of patients at risk:

IMFINZI + Carboplatin and Paclitaxel	46	37	36	31	26	19	14	9	5	2	0
Carboplatin and Paclitaxel	49	41	28	17	13	8	5	2	2	0	0

14.7 Muscle invasive bladder cancer (MIBC)

MIBC – NIAGARA Study

The efficacy of neoadjuvant IMFINZI in combination with gemcitabine and cisplatin followed by adjuvant IMFINZI as a single agent in patients with MIBC was evaluated in NIAGARA (NCT03732677), a randomized, open-label, multicenter study. The study randomized (1:1) 1,063 patients who were candidates for radical cystectomy and who had not received prior systemic chemotherapy or immunemediated therapy for the treatment of NMIBC or MIBC. The study excluded patients with pure non-urothelial histology, any small cell histology and primary non-bladder (i.e., ureter, urethral, or renal pelvis) cancer of the urothelium.

Randomization was stratified by clinical tumor stage T2N0 vs. > T2N0 (including T2N1, T3, and T4a), renal function (creatinine clearance [CrCl] ≥ 60 mL/min vs. CrCl ≥ 40

mL/min to < 60 mL/min), and PDL-1 expression (high vs. low/negative). Patients received:

- Neoadjuvant IMFINZI 1,500 mg plus gemcitabine 1,000 mg/m² and cisplatin 70 mg/m² every 3 weeks for 4 cycles prior to surgery, followed by IMFINZI 1,500 mg every 4 weeks as a single agent adjuvant treatment for up to 8 cycles after surgery, or
- Neoadjuvant gemcitabine 1,000 mg/m² and cisplatin 70 mg/m² every 3 weeks for 4 cycles prior to surgery, without adjuvant treatment.

Patients with CrCl ≥ 40 mL/min to < 60 mL/min in both arms received split-dose cisplatin of 35 mg/m² on days 1 and 8 of each cycle.

A RECIST 1.1 tumor assessment was performed at baseline and upon completion of neoadjuvant therapy (prior to surgery). After surgery, tumor assessments were performed every 12 weeks for the first 24 months, then every 24 weeks for 36 months, and then every 52 weeks thereafter until progression, the end of study, or death.

The major efficacy outcome measure was EFS by BICR assessment. OS was an additional efficacy outcome measure.

Baseline demographics were: male (82%), median age 65 years (range: 32 to 84), age ≥65 years (53%), White (67%), Asian (28%), Black or African American (0.9%), other (0.8%), Hispanic or Latino (8%), and ECOG PS 0 (78%) vs. PS 1 (22%). Disease characteristics were: tumor stage T2N0 (40%) and >T2N0 (60%), regional lymph nodes N0 (95%) and N1 (5%), adequate renal function (81%) and borderline renal function (19%). The histologic subtypes included urothelial carcinoma (85%) and urothelial carcinoma with variant histology (15%).

In the overall population, 469 (88%) patients in the IMFINZI plus gemcitabine and

cisplatin arm and 441 (83%) patients in the gemcitabine and cisplatin arm underwent radical cystectomy.

At a pre-specified interim analysis, the study demonstrated a statistically significant improvement in EFS and OS in the IMFINZI plus gemcitabine and cisplatin arm compared to the gemcitabine and cisplatin arm. The trial was not designed to isolate the effect of IMFINZI in each phase (neoadjuvant or adjuvant) of treatment. See Table 32 and Figures 8 and 9.

Table 32. Efficacy Results for the NIAGARA Study

	IMFINZI plus gemcitabine and cisplatin (N=533)	Gemcitabine and cisplatin (N = 530)
EFS*		
Number of events (%)	187 (35.1)	246 (46.4)
Median EFS (months) (95% CI)	NR (NR, NR)	46.1 (32.2, NR)
HR (95% CI)†	0.68 (0.56, 0.82)	
2-sided p-value§.#	<0.0001	
Overall Survival (OS)		
Number of events (%)	136 (25.5)	169 (31.9)
Median OS (months) (95% CI)	NR (NR, NR)	NR (NR, NR)
HR (95% CI)†	0.75 (0.59, 0.93)	
2-sided p-value§.#	0.0106	

* EFS is defined as the time from randomization to the first recurrence of disease after radical cystectomy, the time of first documented progression in patients who are medically precluded from a radical cystectomy, or time of expected surgery in patients who refuse to undergo a radical cystectomy or failure to undergo a radical cystectomy in participants with residual disease, or the time of death due to any cause, whichever occurs first.

† Based on stratified Cox proportional hazard model.

§ Based on stratified log-rank test.

Alpha allocated at the interim analysis was 0.0412 for EFS and 0.0154 for OS.

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

Figure 8. Kaplan-Meier Curve of EFS

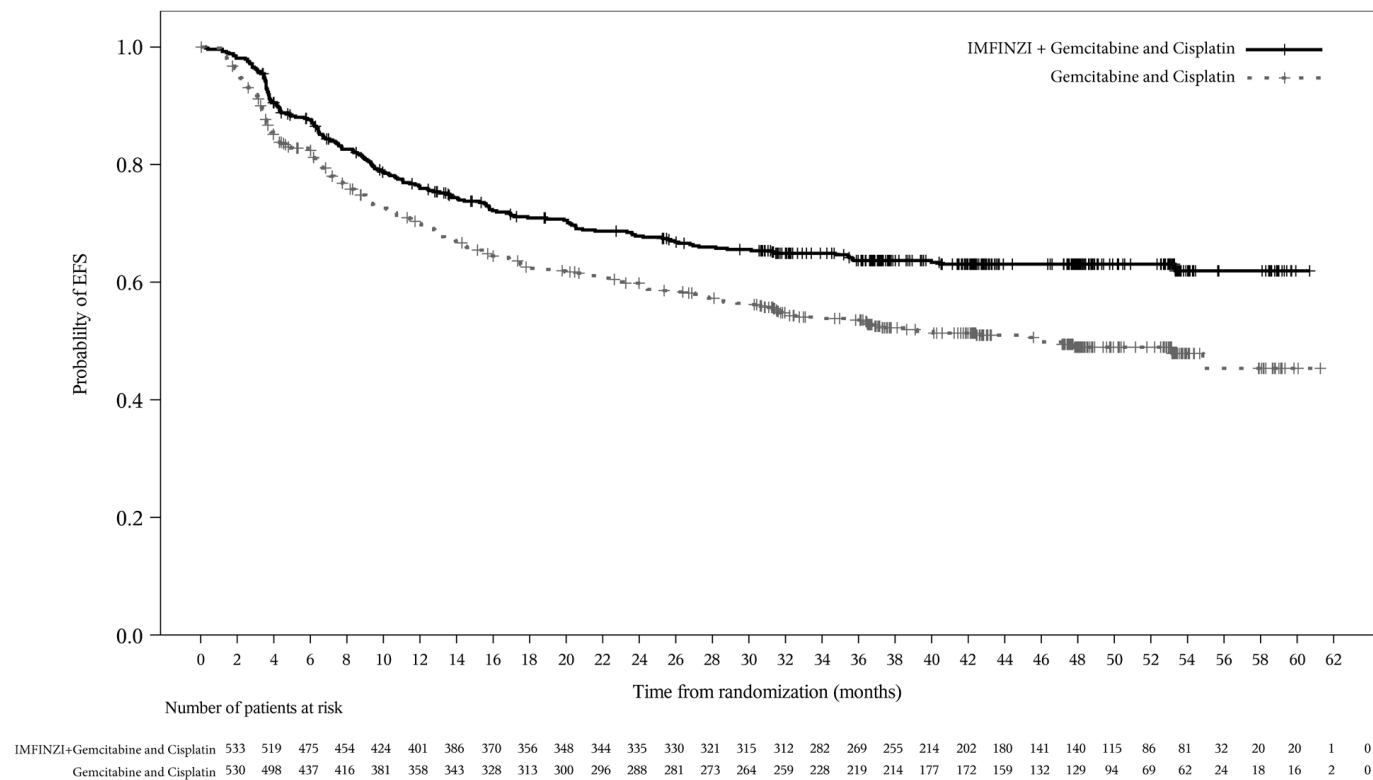
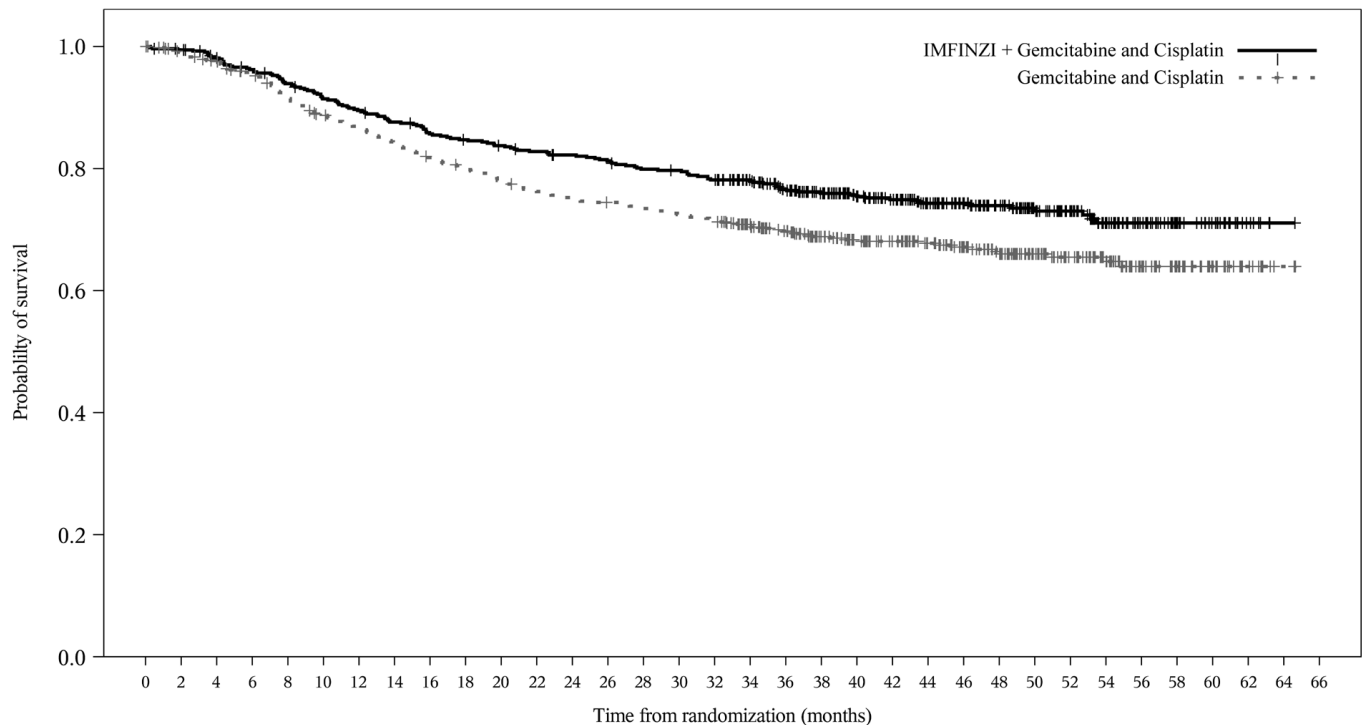


Figure 9. Kaplan-Meier Curve of OS



Number of patients at risk

IMFINZI+Gemcitabine and Cisplatin	533	528	517	505	492	478	468	457	446	440	434	428	423	418	410	408	400	375	349	321	295	271	238	207	182	152	125	96	68	34	21	7	1	0
Gemcitabine and Cisplatin	530	516	507	490	467	450	438	425	413	402	392	383	378	373	368	363	358	334	311	281	259	239	215	194	174	141	113	90	60	38	21	10	2	0

Subgroup analysis

In an exploratory analysis by tumour stage, the EFS HR was 0.61 (95% CI: 0.48, 0.78) in the subgroup of patients with clinical stage > T2N0 (N=635) and 0.81 (95% CI: 0.60, 1.10) in the subgroup of patients with clinical stage T2N0 (N=428). The OS HR was 0.67 (95% CI: 0.50, 0.89) in the subgroup of patients with clinical stage > T2N0 and 0.89 (95% CI: 0.62, 1.29) in patients with clinical stage T2N0.

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

17. License holder and importer:

AstraZeneca (Israel) Ltd.,

1 Atirei Yeda St., Kfar Saba 4464301.

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