

PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

 **IMFINZI**[®]

durvalumab for injection

Concentrate for solution for infusion, 50 mg / mL, Intravenous

Professed

Antineoplastic agent, monoclonal antibody
(Anatomical Therapeutic Chemical code: L01FF03)

Imfinzi, indicated for:

- Treatment of patients with locally advanced or metastatic urothelial carcinoma who:
 - Have disease progression during or following platinum-containing chemotherapy
 - Have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy

has been issued market authorization with conditions, pending the results of trials to verify its clinical benefit. Patients should be advised of the nature of the authorization. For further information for Imfinzi please refer to Health Canada's Notice of Compliance with conditions - drug products web site: <https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/notice-compliance/conditions.html>

Imfinzi, indicated for:

- Treatment of patients with locally advanced, unresectable, Stage III non-small cell lung cancer (NSCLC) whose disease has not progressed following platinum-based chemoradiation therapy
- First-line treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC) in combination with etoposide and either carboplatin or cisplatin
- Treatment of patients with locally advanced or metastatic biliary tract cancer (BTC) in combination with gemcitabine-based chemotherapy
- First-line treatment of adult patients with unresectable hepatocellular carcinoma (uHCC) who require systemic therapy, in combination with tremelimumab
- First-line treatment of adult patients with uHCC who require systemic therapy, as monotherapy

has been issued market authorization without conditions.

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Date of Initial Authorization:
NOV 03, 2017

Date of Revision:
OCT 8, 2024

Submission Control Number: 281318

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What is a Notice of Compliance with Conditions (NOC/c)?

An NOC/c is a form of market approval granted to a product on the basis of promising evidence of clinical effectiveness following review of the submission by Health Canada.

Products authorized under Health Canada's NOC/c policy are intended for the treatment, prevention or diagnosis of a serious, life-threatening or severely debilitating illness. They have demonstrated promising benefit, are of high quality and possess an acceptable safety profile based on a benefit/risk assessment. In addition, they either respond to a serious unmet medical need in Canada or have demonstrated a significant improvement in the benefit/risk profile over existing therapies. Health Canada has provided access to this product on the condition that sponsors carry out additional clinical trials to verify the anticipated benefit within an agreed upon time frame.

RECENT MAJOR LABEL CHANGES

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

Urothelial Carcinoma

IMFINZI® (durvalumab for injection) is indicated for:

- the treatment of patients with locally advanced or metastatic urothelial carcinoma who:
 - have disease progression during or following platinum-containing chemotherapy
 - have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy

Marketing authorization with conditions was based on a promising tumour response rate and durability of response. An improvement in survival or disease-related symptoms has not been established (see [14 CLINICAL TRIALS](#)).

Locally Advanced, Unresectable, Stage III Non-Small Cell Lung Cancer

Imfinzi is indicated for the treatment of patients with locally advanced, unresectable, Stage III non-small cell lung cancer (NSCLC) whose disease has not progressed following platinum-based chemoradiation therapy.

Extensive-Stage Small Cell Lung Cancer

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

Locally Advanced or Metastatic Biliary Tract Cancer

Imfinzi in combination with gemcitabine-based chemotherapy is indicated for the treatment of patients with locally advanced or metastatic biliary tract cancer (BTC).

Unresectable Hepatocellular Carcinoma

Imfinzi in combination with tremelimumab is indicated for the first-line treatment of adult patients with unresectable hepatocellular carcinoma (uHCC) who require systemic therapy.

- When using Imfinzi in combination with tremelimumab, consult the Product Monograph for IMJUDO (tremelimumab) for further information on this drug.

Imfinzi, as monotherapy, is indicated for the first-line treatment of adult patients with uHCC who require systemic therapy.

1.1 Pediatrics

Pediatrics (<18 years of age): The safety and efficacy of Imfinzi in patients younger than 18 years of age have not been established. Therefore, Health Canada has not authorized an indication for pediatric use (See [7.1.3 Pediatrics](#)).

1.2 Geriatrics

Geriatrics (≥65 years of age): No overall differences in safety or efficacy were reported between elderly patients (≥65 years of age) and younger patients (<65 years of age) who received Imfinzi. (see [7.1.4 Geriatrics](#)).

Of the 462 patients with uHCC treated with Imfinzi and tremelimumab, 236 (51%) patients were older than 65 years of age, 173 (37.4%) patients were ≥ 65 years to < 75 years and 63 (13.6%) patients were 75 years or older. Evidence from clinical studies and experience suggests there were no overall differences in efficacy between patients 65 years or older and younger patients. Evidence from clinical studies suggests the use in the geriatric population may be associated with differences in safety in the uHCC population. See [7.1.4 Geriatrics](#).

2 CONTRAINDICATIONS

Imfinzi (durvalumab) is contraindicated in patients who are hypersensitive to durvalumab or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing of ingredients, see [6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING](#).

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- Imfinzi in combination with tremelimumab or as monotherapy can cause severe and fatal immune-mediated adverse reactions, including enterocolitis, intestinal perforation, hepatitis, dermatitis, Stevens-Johnson syndrome, endocrinopathy, pneumonitis, interstitial lung disease, myocarditis, neuropathy, encephalitis, myasthenia gravis, as well as toxicities in other organ systems (See [7 WARNINGS AND PRECAUTIONS](#) and [8 ADVERSE REACTIONS](#)). Immune-mediated adverse reactions have occurred at lower frequencies when Imfinzi was administered as monotherapy compared with Imfinzi in combination with tremelimumab.

4 DOSAGE AND ADMINISTRATION

4.2 Recommended Dose and Dosage Adjustment

The recommended dose of Imfinzi depends on the indication. Imfinzi is administered as an intravenous infusion over 60 minutes.

Urothelial Carcinoma

The recommended dose of Imfinzi is 10 mg/kg every 2 weeks or 1500 mg every 4 weeks. Therapy should continue as long as clinical benefit is observed or until unacceptable toxicity.

Patients with a body weight of 30 kg or less must receive weight-based dosing, equivalent to Imfinzi 10 mg/kg every 2 weeks as a monotherapy until weight increases to greater than 30 kg.

For previously treated patients in the pivotal study, treatment with Imfinzi was permitted until one or more criteria for discontinuation were met including:

- Adverse event (AE) experienced that contraindicates further dosing
- Pregnancy or intent to become pregnant
- Any AE that met criteria for discontinuation
- AE related to drug that is Grade ≥ 3 , with the exception of toxicities that did not meet criteria for discontinuation
- Grade ≥ 3 infusion reaction

- Confirmation of progressive disease and investigator determination that the patient no longer benefited from treatment

Locally Advanced, Unresectable, Stage III Non-Small Cell Lung Cancer

The recommended dose of Imfinzi is 10 mg/kg every 2 weeks or 1500 mg every 4 weeks. Therapy should continue for one year or until disease progression or unacceptable toxicity.

Patients with a body weight of 30 kg or less must receive weight-based dosing, equivalent to Imfinzi 10 mg/kg every 2 weeks as a monotherapy until weight increases to greater than 30 kg.

Extensive-Stage Small Cell Lung Cancer

The recommended dose of Imfinzi is 1500 mg in combination with chemotherapy (etoposide and either carboplatin or cisplatin, see [14 CLINICAL TRIALS](#)) every 3 weeks (21 days) for 4 cycles, followed by 1500 mg every 4 weeks as monotherapy until disease progression or unacceptable toxicity.

Patients with a body weight of 30 kg or less must receive weight-based dosing, equivalent to Imfinzi 20 mg/kg in combination with chemotherapy every 3 weeks (21 days) for 4 cycles, followed by 20 mg/kg every 4 weeks as monotherapy until weight increases to greater than 30 kg.

Please also refer to the full prescribing information for the appropriate chemotherapeutic agents, in their respective Product Monographs.

Locally Advanced or Metastatic Biliary Tract Cancer

The recommended dose of Imfinzi is 1500 mg in combination with gemcitabine-based chemotherapy every 3 weeks (21 days), followed by 1500 mg every 4 weeks as monotherapy until disease progression or unacceptable toxicity (see [14 CLINICAL TRIALS](#)).

Patients with a body weight of 30 kg or less must receive weight-based dosing of Imfinzi at 20 mg/kg in combination with chemotherapy dose every 3 weeks (21 days), followed by monotherapy at 20 mg/kg every 4 weeks until weight increases to greater than 30 kg.

Please also refer to the full prescribing information for the appropriate chemotherapeutic agents, in their respective Product Monographs.

Unresectable Hepatocellular Carcinoma

Imfinzi in combination with tremelimumab

The recommended dose of tremelimumab is 300 mg as a single dose, followed by Imfinzi 1500 mg at Day 1 of Cycle 1. Continue Imfinzi 1500 mg as a single agent every 4 weeks.

Patients with a body weight of 30 kg or less must receive weight-based dosing, equivalent to tremelimumab 4 mg/kg as a single dose followed by Imfinzi 20 mg/kg at Day 1 of Cycle 1; continue Imfinzi 20 mg/kg as a single agent every 4 weeks.

Treatment should continue until disease progression or unacceptable toxicity.

When using Imfinzi in combination with tremelimumab, consult the Product Monograph for Imjudo (tremelimumab) for further information on this drug.

Imfinzi as monotherapy

The recommended dose of Imfinzi is 1500 mg every 4 weeks.

Patients with a body weight of 30 kg or less must receive weight-based dosing, equivalent to Imfinzi 20 mg/kg every 4 weeks as a monotherapy until weight increases to greater than 30 kg.

Treatment should continue until disease progression or unacceptable toxicity.

Dosage Adjustment

Dose withholding or discontinuation may be required based on individual safety and tolerability. No dose reduction or escalation for Imfinzi is recommended. In general, withhold Imfinzi for severe (Grade 3) immune-mediated adverse reactions. Permanently discontinue Imfinzi for life-threatening (Grade 4) immune-mediated adverse reactions, recurrent severe (Grade 3) immune-mediated reactions that require systemic immunosuppressive treatment, or an inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks of initiating corticosteroids.

Immune-mediated adverse reactions requiring specific management are summarized in Table 1. Refer to [7 WARNINGS AND PRECAUTIONS](#) for further management recommendations, monitoring and evaluation information.

Table 1 Recommended Treatment Modifications for Imfinzi for Immune-Mediated Adverse Reactions

Adverse Reactions	Severity^a	Imfinzi Treatment Modification
Immune-mediated pneumonitis/ interstitial lung disease	Grade 2	Withhold dose ^b
	Grade 3 or 4	Permanently discontinue
Immune-mediated hepatitis	ALT or AST >3 – ≤5 x ULN or total bilirubin >1.5 – ≤3 x ULN	Withhold dose ^b
	ALT or AST >5 – ≤10 x ULN	Withhold dose ^b
	Concurrent ALT or AST >3 x ULN and total bilirubin >2 x ULN ^c	Permanently discontinue

Adverse Reactions	Severity ^a	Imfinzi Treatment Modification
	ALT or AST >10 x ULN or total bilirubin >3 x ULN	
Immune-mediated hepatitis in HCC (or secondary tumour involvement of the liver with abnormal baseline values) ^d	ALT or AST >2.5 – ≤5 x BLV and ≤20 x ULN	Withhold dose ^b
	ALT or AST >5 – ≤7 x BLV and ≤20 x ULN or Concurrent ALT or AST >2.5 – ≤5 x BLV and ≤20 x ULN and total bilirubin >1.5 – <2 x ULN ^c	Withhold dose ^b
	ALT or AST >7 x BLV or >20 x ULN whichever occurs first or Total bilirubin >3 x ULN	Permanently discontinue
Immune-mediated colitis or diarrhea	Grade 2 or 3	Withhold dose ^b
	Grade 4 or recurrent Grade 3	Permanently discontinue
	Intestinal perforation of ANY grade	Permanently discontinue
Immune-mediated endocrinopathies: Hyperthyroidism, Thyroiditis	Grade 2 – 4	Withhold dose until clinically stable
Immune-mediated endocrinopathies: Hypothyroidism	Grade 2 – 4	No change

Adverse Reactions	Severity^a	Imfinzi Treatment Modification
Immune-mediated endocrinopathies: Adrenal insufficiency, Hypophysitis/ Hypopituitarism	Grade 2 – 4	Withhold dose until clinically stable
Immune-mediated endocrinopathies: Type 1 diabetes mellitus	Grade 2 – 4	No change
Immune-mediated nephritis	Grade 2 with serum creatinine >1.5 – 3 x (ULN or baseline)	Withhold dose ^b
	Grade 3 with serum creatinine >3 x baseline or >3 – 6 x ULN; Grade 4 with serum creatinine >6 x ULN	Permanently discontinue
Immune-mediated rash or dermatitis (including pemphigoid)	Grade 2 for >1 week or Grade 3	Withhold dose ^b
	Grade 4 or recurrent Grade 3	Permanently discontinue
Infection	Grade 3 or 4	Withhold dose
Immune-mediated myocarditis	Grade 2 – 4	Permanently discontinue
Immune-mediated myositis/ polymyositis/ rhabdomyolysis	Grade 2 or 3	Withhold dose ^{b,e}
	Grade 4 or recurrent Grade 3	Permanently discontinue
Infusion-related reactions	Grade 1 or 2	Interrupt or slow the rate of infusion

Adverse Reactions	Severity^a	Imfinzi Treatment Modification
	Grade 3 or 4	Permanently discontinue
Immune-mediated myasthenia gravis	Grade 2 – 4	Permanently discontinue
Immune-mediated encephalitis	Grade 2 – 4	Permanently discontinue
Immune-mediated Guillain-Barré syndrome	Grade 2 – 4	Permanently discontinue
Other immune-mediated adverse reactions (including immune thrombocytopenia, pancreatitis, immune-mediated arthritis, and uveitis)	Grade 2 or 3	Withhold dose ^b
	Grade 4 or recurrent Grade 3	Permanently discontinue

^a Common Terminology Criteria for Adverse Events, version 4.03. ALT: alanine aminotransferase; AST: aspartate aminotransferase; BLV: baseline value; ULN: upper limit of normal.

^b After withholding, Imfinzi can be resumed within 12 weeks if the adverse reactions improved to ≤Grade 1 and the corticosteroid dose has been reduced to ≤10 mg prednisone or equivalent per day.

^c For patients with alternative cause follow the recommendations for AST or ALT increases without concurrent bilirubin elevations.

^d If AST and ALT are less than or equal to ULN at baseline in patients with liver involvement, withhold or permanently discontinue Imfinzi based on recommendations for hepatitis with no liver involvement.

^e Permanently discontinue Imfinzi if adverse reaction does not resolve to ≤Grade 1 within 30 days or if there are signs of respiratory insufficiency.

For suspected immune-mediated adverse reactions, adequate evaluation should be performed to confirm etiology or exclude alternate etiologies.

For non-immune-mediated adverse reactions, withhold Imfinzi for Grade 2 and 3 adverse reactions until ≤Grade 1 or baseline. Imfinzi should be discontinued for Grade 4 adverse reactions (with the exception of Grade 4 laboratory abnormalities, about which the decision to discontinue should be based on accompanying clinical signs/symptoms and clinical judgement).

Special Populations

A population pharmacokinetic (PK) analysis, could not detect any clinically significant effect on the clearance (CL) parameter in the model due to patient age, body weight, gender and race, therefore no dose adjustment of Imfinzi is recommended (see [10 CLINICAL](#))

[PHARMACOLOGY](#)).

Pediatrics (<18 years of age): The safety and efficacy of Imfinzi in patients younger than 18 years of age have not been established. Therefore, Health Canada has not authorized an indication for pediatric use.

Geriatrics (≥65 years of age): No dose adjustment is recommended for elderly patients (≥65 years of age) (see [10 CLINICAL PHARMACOLOGY](#)).

Renal Impairment: A population PK analysis could not detect any clinically significant effect of mild to moderate renal impairment on the CL parameter in the model, therefore no dose adjustment of Imfinzi is recommended for patients. The effect of severe renal impairment (CrCL 15 to 29 mL/min) on the PK of durvalumab is unknown (see [10 CLINICAL PHARMACOLOGY](#)).

Hepatic Impairment: A population PK analysis could not detect any clinically significant effect of mild or moderate hepatic impairment on the CL parameter in the model, therefore no dose adjustment of Imfinzi is recommended for patients. Imfinzi has not been studied in patients with severe hepatic impairment (see [10 CLINICAL PHARMACOLOGY](#)).

4.4 Administration

Imfinzi is only to be administered by intravenous infusion.

When Imfinzi is administered in combination with chemotherapy on the same day, administer Imfinzi prior to chemotherapy.

Imfinzi is supplied as a single-use vial and does not contain any preservatives, therefore, aseptic technique must be observed.

- Visually inspect drug product for particulate matter and discoloration. Imfinzi is a clear to opalescent, colourless to slightly yellow solution. Discard the vial if the solution is cloudy, discoloured 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 (IV) bag containing 0.9% Sodium Chloride Injection or 5% Dextrose Injection. Mix diluted solution by gentle inversion. The final concentration of the diluted solution should be between 1 mg / mL and 15 mg / mL.
- Do not freeze or shake the solution.
- No incompatibilities between Imfinzi and 0.9% Sodium Chloride or 5% Dextrose have been observed.
- Imfinzi must not be mixed with other drug products except those mentioned above.
- Care must be taken to ensure the sterility of prepared solutions.
- Do not re-enter the vial after withdrawal of drug. Only administer one dose per vial.
- Administer infusion solution once prepared. Discard any unused portion left in the vial (see [11 STORAGE, STABILITY AND DISPOSAL](#)).
- Administer infusion solution intravenously over 60 minutes through an intravenous line containing a sterile, low-protein binding 0.2 or 0.22 micron in-line filter.
- Do not co-administer other drugs through the same infusion line. After each dose, flush the infusion line.

Imfinzi in combination with tremelimumab

- When Imfinzi is administered in combination with tremelimumab, administer tremelimumab prior to Imfinzi on the same day of cycle 1. Observing patient for 60 minutes is recommended following completion of tremelimumab infusion. Imfinzi and tremelimumab are administered as separate intravenous infusions.
- When using Imfinzi in combination with tremelimumab, consult the Product Monograph for Imjudo (tremelimumab) for further information on this drug.

4.5 Missed dose

If a dose of Imfinzi is missed, the appointment should be rescheduled as soon as possible.

5 OVERDOSAGE

There is no specific treatment in the event of Imfinzi overdose, and symptoms of overdose are not established. In the event of an overdose, healthcare practitioners should follow general supportive measures and should treat symptomatically.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

To help ensure the traceability of biologic products, including biosimilars, health professionals should recognize the importance of recording both the brand name and the non-proprietary (active ingredient) name as well as other product-specific identifiers such as the Drug Identification Number (DIN) and the batch/lot number of the product supplied.

Table 2 Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Intravenous infusion	Single-use vial solution of: <ul style="list-style-type: none">• 120 mg durvalumab / 2.4 mL (nominal concentration of 50 mg/mL)• 500 mg durvalumab / 10 mL (nominal concentration of 50 mg/mL)	L-histidine, L-histidine hydrochloride monohydrate, Polysorbate 80, α,α -trehalose dihydrate, and Water for Injection.

Imfinzi is a sterile, preservative-free, clear to opalescent, colourless to slightly yellow solution, free from visible particles.

Packaging

10 mL of concentrate in a 10 mL Type 1 glass vial with an elastomeric stopper and a white flip-off aluminum seal contains 500 mg durvalumab. Pack size of 1 vial.

2.4 mL of concentrate in a 10 mL Type 1 glass vial with an elastomeric stopper and a gray flip-off aluminum seal contains 120 mg durvalumab. Pack size of 1 vial.

7 WARNINGS AND PRECAUTIONS

General

Imfinzi (durvalumab) should be administered under the supervision of healthcare practitioners experienced in the treatment of cancer.

When using Imfinzi in combination with tremelimumab, consult the Imjudo (tremelimumab) Product Monograph for further information on this drug.

Driving and Operating Machinery

If patients experience adverse reactions affecting their ability to concentrate and react, they should be advised not to drive or operate machinery.

Hepatic/Biliary/Pancreatic

Hepatocellular Carcinoma

In unresectable hepatocellular carcinoma, there are no clinical data available for Child-Pugh Class B patients and Child-Pugh Class C patients (see [14 CLINICAL TRIALS](#)).

Immune

Immune-Mediated Adverse Reactions

For suspected immune-mediated adverse reactions, adequate evaluation should be performed to confirm etiology or exclude alternate etiologies. Based on the severity of the adverse reaction, Imfinzi should be withheld or permanently discontinued. Treatment with corticosteroids or endocrine therapy should be initiated. For events requiring corticosteroid therapy, and upon improvement to \leq Grade 1, corticosteroid taper should be initiated and continued over at least 1 month. Consider increasing dose of corticosteroids and/or using additional systemic immunosuppressants if there is worsening or no improvement.

Adverse reactions observed with immunotherapies such as Imfinzi may differ from those observed with non-immunotherapies and may require immunosuppression. Immune-mediated adverse reactions have occurred at higher frequencies when Imfinzi was administered in combination with tremelimumab compared with Imfinzi as monotherapy. Early identification of adverse reactions and timely intervention are an important part of the safe use of Imfinzi and Imfinzi in combination with tremelimumab.

Monitor patients continuously (even after the last dose) for signs, symptoms and laboratory abnormalities indicative of immune-mediated adverse reactions. Evaluate suspected immune-mediated adverse reactions to exclude other causes. In clinical trials, most immune-mediated adverse reactions were reversible and managed with interruptions of Imfinzi, administration of corticosteroids and/or supportive care. Refer to [4 DOSAGE AND ADMINISTRATION](#), Table 1 for recommended treatment modifications.

Immune-Mediated Pneumonitis

Cases of immune-mediated pneumonitis or interstitial lung disease, including fatal cases, defined as requiring use of systemic corticosteroids and with no clear alternate etiology, occurred in patients receiving Imfinzi or Imfinzi in combination with tremelimumab in clinical studies (see [8 ADVERSE REACTIONS](#) – [Immune Mediated Pneumonitis](#)

Immune-Mediated Pneumonitis). Patients should be monitored for signs and symptoms of pneumonitis. Suspected pneumonitis should be confirmed with radiographic imaging and other infectious and disease-related etiologies excluded, and managed as recommended in [4](#)

[DOSAGE AND ADMINISTRATION](#), Table 1. For Grade 2 events, an initial dose of 1 – 2 mg/kg/day prednisone or equivalent should be initiated followed by a taper. For Grade 3 or 4 events, an initial dose of 2 – 4 mg/kg/day methylprednisolone or equivalent should be initiated followed by a taper.

Pneumonitis and Radiation Pneumonitis

Pneumonitis is frequently observed in patients receiving radiation therapy to the lung and the clinical presentation of radiation pneumonitis is very similar to other forms of pneumonitis. The PACIFIC study enrolled patients with locally advanced unresectable, Stage III non-small cell lung cancer (NSCLC) who had completed chemoradiation therapy within 1 to 42 days prior to initiation of the trial. More cases of pneumonitis and radiation pneumonitis occurred in patients receiving Imfinzi compared to patients receiving placebo (see [8.2 Clinical Trial Adverse Reactions](#)). The median time to onset in the Imfinzi-treated group was 55 days (range: 1-406 days) vs. 55 days (range: 1-255 days) in the placebo group.

Immune-Mediated Hepatitis

Cases of immune-mediated hepatitis, including fatal cases, defined as requiring use of systemic corticosteroids and with no clear alternate etiology, occurred in patients receiving Imfinzi or Imfinzi in combination with tremelimumab in clinical studies (see [8 ADVERSE REACTIONS – Immune Mediated Hepatitis](#)). Patients should be monitored for abnormal liver function tests prior to each infusion with Imfinzi. Immune-mediated hepatitis should be managed as recommended in [4 DOSAGE AND ADMINISTRATION](#), Table 1. Corticosteroids should be administered with an initial dose of 1 – 2 mg/kg/day prednisone or equivalent followed by taper for all grades.

Immune-Mediated Colitis

Immune-mediated colitis or diarrhea, defined as requiring use of systemic corticosteroids and with no clear alternate etiology, occurred in patients receiving Imfinzi or Imfinzi in combination with tremelimumab in clinical studies (see [8 ADVERSE REACTIONS – Immune Mediated Colitis](#)). Intestinal perforation and large intestine perforation were reported in patients receiving Imfinzi in combination with tremelimumab. Patients should be monitored for signs and symptoms of colitis, diarrhea and intestinal perforation and managed as recommended in [4 DOSAGE AND ADMINISTRATION](#), Table 1. Corticosteroids should be administered at an initial dose of 1 – 2 mg/kg/day prednisone or equivalent followed by a taper for Grades 2 – 4. Consult a surgeon immediately if intestinal perforation of ANY grade is suspected.

Immune-Mediated Endocrinopathies

Immune-Mediated Hypothyroidism/Hyperthyroidism/Thyroiditis:

Immune-mediated hypothyroidism, hyperthyroidism and thyroiditis occurred in patients receiving Imfinzi or Imfinzi in combination with tremelimumab in clinical studies (see [8 ADVERSE REACTIONS – Immune-Mediated Hypothyroidism, Immune-Mediated Hyperthyroidism, Immune-Mediated Thyroiditis](#)). Patients should be monitored for abnormal thyroid function tests prior to each infusion or at least once per month during treatment. Manage hypothyroidism as recommended in [4 DOSAGE AND ADMINISTRATION](#), Table 1. For immune-mediated hypothyroidism, initiate thyroid hormone replacement as clinically indicated for Grades 2 – 4. For immune-mediated hyperthyroidism/thyroiditis, symptomatic management can be implemented for Grades 2 – 4. Symptomatic hyperthyroidism should be managed as per institutional guidelines. See [4 DOSAGE AND ADMINISTRATION](#), Table 1.

Immune-Mediated Adrenal Insufficiency:

Immune-mediated adrenal insufficiency occurred in patients receiving Imfinzi or Imfinzi in combination with tremelimumab in clinical studies (see [8 ADVERSE REACTIONS – Immune-Mediated Adrenal Insufficiency](#)). Patients should be monitored for clinical signs and symptoms of adrenal insufficiency. For symptomatic adrenal insufficiency, patients should be managed as recommended in [4 DOSAGE AND ADMINISTRATION](#), Table 1. Corticosteroids should be administered with an initial dose of 1 – 2 mg/kg/day prednisone or equivalent followed by taper and a hormone replacement as clinically indicated for Grades 2 – 4.

Immune-Mediated Hypophysitis/Hypopituitarism:

Immune-mediated hypophysitis or hypopituitarism have been observed in clinical studies of products that target PD-1/PD-L1, including Imfinzi or Imfinzi in combination with tremelimumab (see [8 ADVERSE REACTIONS – Immune-Mediated Hypophysitis/Hypopituitarism](#)). Patients should be monitored for clinical signs and symptoms of hypophysitis. For symptomatic hypophysitis or hypopituitarism, patients should be managed as recommended in [4 DOSAGE AND ADMINISTRATION](#), Table 1. Corticosteroids should be administered with an initial dose of 1 – 2 mg/kg/day prednisone or equivalent followed by taper and a hormone replacement as clinically indicated for Grades 2 – 4.

Immune-Mediated Type 1 Diabetes Mellitus:

Immune-mediated Type 1 diabetes mellitus (T1DM), which can present with diabetic ketoacidosis, has been observed in clinical studies of products that target PD-1/PD-L1, including Imfinzi or Imfinzi in combination with tremelimumab (see [8 ADVERSE REACTIONS – Immune-Mediated Type 1 Diabetes Mellitus](#)). Patients should be monitored for clinical signs and symptoms of T1DM. For symptomatic T1DM, patients should be managed as recommended in [4 DOSAGE AND ADMINISTRATION](#), Table 1. Treatment with insulin can be initiated as clinically indicated for Grades 2 – 4.

Immune-Mediated Nephritis

Immune-mediated nephritis, defined as requiring use of systemic corticosteroids and with no clear alternate etiology, occurred in patients receiving Imfinzi or Imfinzi in combination with tremelimumab in clinical studies (see [8 ADVERSE REACTIONS – Immune-Mediated Nephritis](#)). Patients should be monitored for abnormal renal function tests prior to and periodically during treatment with Imfinzi or Imfinzi in combination with tremelimumab and managed as recommended in [4 DOSAGE AND ADMINISTRATION](#), Table 1. Corticosteroids should be administered with an initial dose of 1 – 2 mg/kg/day prednisone or equivalent followed by taper for Grades 2 – 4.

Immune-Mediated Rash

Immune-mediated rash or dermatitis (including pemphigoid), defined as requiring use of systemic corticosteroids and with no clear alternate etiology, occurred in patients receiving Imfinzi or Imfinzi in combination with tremelimumab in clinical studies (see [8 ADVERSE REACTIONS – Immune-Mediated Rash](#)). Patients should be monitored for signs and symptoms of rash or dermatitis and managed as recommended in [4 DOSAGE AND ADMINISTRATION](#), Table 1. Corticosteroids should be administered with an initial dose of 1 – 2 mg/kg/day prednisone or equivalent followed by taper for Grade 2 > 1 week or Grade 3 and 4.

Immune-mediated Myocarditis

Immune-mediated myocarditis, which can be fatal, occurred in patients receiving Imfinzi or Imfinzi in combination with tremelimumab (see [8.2 Clinical Trial Adverse Reactions](#)). Patients should be monitored for signs and symptoms of immune-mediated myocarditis and managed as recommended in [4 DOSAGE AND ADMINISTRATION](#), Table 1. Corticosteroids should be administered with an initial dose of 2 – 4 mg/kg/day prednisone or equivalent followed by taper for Grades 2 – 4. If no improvement within 2 to 3 days despite corticosteroids, promptly start additional immunosuppressive therapy. Upon resolution (Grade 0), corticosteroid taper should be initiated and continued over at least 1 month.

Other Immune-Mediated Adverse Reactions

Given the mechanism of action of Imfinzi or Imfinzi in combination with tremelimumab, other potential immune-mediated adverse reactions may occur. The following immune-mediated adverse reactions have been observed: immune-related thrombocytopenia (of which one was fatal), pancreatitis, aseptic meningitis, uveitis, myositis, polymyositis (fatal), immune-mediated arthritis, myasthenia gravis, Guillain-Barré syndrome, aplastic anemia, encephalitis, Stevens-Johnson Syndrome (SJS), hypoparathyroidism, rhabdomyolysis, and myelitis transverse (see [8 ADVERSE REACTIONS](#)).

The following clinically significant immune-mediated adverse reactions have been reported in patients who received other immune-checkpoint inhibitor blocking antibodies: meningitis, toxic epidermal necrolysis (TEN), demyelinating polyneuropathy, autoimmune hemolytic anemia, sarcoidosis, and retinal detachment. Patients should be monitored for signs and symptoms of immune-mediated adverse reactions and managed as recommended in [4 DOSAGE AND ADMINISTRATION](#), Table 1. Corticosteroids should be administered with an initial dose of 1 – 2 mg/kg/day prednisone or equivalent followed by taper for Grades 2 – 4.

Infections

Severe infections, including sepsis, necrotizing fasciitis, and osteomyelitis, occurred in patients receiving Imfinzi in clinical studies (see [8 ADVERSE REACTIONS](#)). Patients should be monitored for signs and symptoms of infection as recommended in [4 DOSAGE AND ADMINISTRATION](#), Table 1. Treat patients with anti-infectives for suspected or confirmed infections.

Infusion Related Reactions

Severe infusion related reactions have been reported in patients receiving Imfinzi or Imfinzi in combination with tremelimumab in clinical studies (see [8 ADVERSE REACTIONS](#)). Patients should be monitored for signs and symptoms of infusion related reactions as recommended in [4 DOSAGE AND ADMINISTRATION](#), Table 1. For Grade 1 or 2 severity, consider pre-medication for prophylaxis of subsequent infusion reactions. For Grade 3 or 4, manage severe infusion-related reactions per institutional standard, appropriate clinical practice guidelines and/or society guidelines.

Monitoring and Laboratory Tests

Monitor AST, ALT, bilirubin, renal, and thyroid function prior to and as indicated based on clinical evaluation.

Reproductive Health: Female and Male Potential

- **Fertility**

There are no data on the potential effects of Imfinzi on fertility in humans. In repeat-dose toxicology studies with Imfinzi in sexually mature cynomolgus monkeys of up to 3 months duration, there were no notable effects on the male and female reproductive organs (see [16 NON-CLINICAL TOXICOLOGY](#)).

7.1 Special Populations

7.1.1 Pregnant Women

There are no data on the use of Imfinzi in pregnant women. Based on its mechanism of action, Imfinzi has the potential to impact maintenance of pregnancy and may cause fetal harm when administered to a pregnant woman.

Human immunoglobulin G1 (IgG1) is known to cross the placental barrier. Imfinzi is not recommended during pregnancy. Women of childbearing potential should use effective contraception during treatment with Imfinzi and for at least 3 months after the last dose.

In animal reproduction studies, administration of Imfinzi 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 of Imfinzi (based on AUC) was associated with premature delivery, fetal loss (abortion and stillbirth) and an increase in neonatal deaths compared to concurrent control (see [16 NON-CLINICAL TOXICOLOGY](#)).

7.1.2 Breast-feeding

There is no information regarding the presence of durvalumab in human milk, the absorption and effects on the breastfed infant, or the effects on milk production. Human IgG is excreted in human milk. In animal reproduction studies, administration of durvalumab to pregnant cynomolgus monkeys was associated with dose-related low level excretion of durvalumab in breast milk of lactating cynomolgus monkeys, and was associated with premature neonatal death compared to concurrent control (see [16 NON-CLINICAL TOXICOLOGY](#)). Because of the potential for adverse reactions in breastfed infants from durvalumab, breastfeeding is not recommended during treatment with Imfinzi and for at least 3 months after the last dose.

7.1.3 Pediatrics

Pediatrics (<18 years of age): The safety and efficacy of Imfinzi in patients younger than 18 years of age have not been established. Therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

Geriatrics (≥65 years of age): No dose adjustment is required for elderly patients (≥65 years of age).

Of the 191 patients with urothelial carcinoma (primary efficacy population) treated with Imfinzi, 118 patients (61.8%) were 65 years of age or older. Of the 476 patients with locally advanced, unresectable, Stage III NSCLC (primary efficacy population) treated with Imfinzi, 215 patients (45.1%) were 65 years of age or older. No overall clinically meaningful differences in safety or

efficacy were reported between these patients (≥65 years of age) and younger patients (<65 years of age).

Of the 265 patients with ES-SCLC treated with Imfinzi in combination with chemotherapy, 101 (38%) patients were 65 years or older. There were no overall clinically meaningful differences in safety or efficacy between patients ≥65 years of age and younger patients.

Of the 338 patients with BTC treated with Imfinzi in combination with chemotherapy, 158 (46.7%) patients were 65 years or older. There were no overall clinically meaningful differences in safety or effectiveness between patients ≥65 years of age and younger patients.

Of the 462 patients with uHCC treated with Imfinzi in combination with tremelimumab, 173 patients were ≥65 years to <75 years, 63 patients were 75 years or older. No overall clinically meaningful differences in efficacy were reported between patients ≥ 65 years of age and younger patients. The rates of adverse events were higher with increasing age. Adverse events possibly related to treatment were 72.1%, 79.8%, and 85.7% for patients younger than 65 years, ≥65 years to <75 years, and 75 years or older, respectively. There was a higher rate of adverse events with outcome of death in patients 65 years or older (10.6%) relative to patients who were younger than 65 years (4.0%). In addition, there was a higher discontinuation rate due to adverse events in patients 65 years or older (18.6%) relative to patients who were younger than 65 years (8.4%).

Of the 492 patients with uHCC treated with Imfinzi monotherapy, 163 patients were ≥65 years to <75 years and 75 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.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Urothelial Carcinoma

The safety of Imfinzi was evaluated in the urothelial carcinoma (UC) cohort of Study 1108. This cohort enrolled 191 patients in an open-label, single-arm trial with locally advanced or metastatic UC. Of the 191 patients enrolled, 182 patients had UC that had progressed during or after platinum-based chemotherapy or had progressed within 12 months of platinum-based neoadjuvant or adjuvant chemotherapy. Patients received 10 mg/kg Imfinzi via intravenous infusion every 2 weeks (Q2W) until disease progression or unacceptable toxicity. Treatment was continued for a maximum of 12 months. The median duration of exposure was 12 weeks (range: 1.6 to 54.3 weeks).

Imfinzi monotherapy 10 mg/kg Q2W was generally well tolerated in the UC population. Adverse reactions were generally manageable and reversible with interruption of dosing and treatment with immunosuppressants, such as corticosteroids.

Overall and regardless of relationship to treatment, an adverse event was experienced by 99.0% (189/191) of treated patients. At least one serious adverse event (SAE) was reported in 54.5% (104/191) of patients (for 12 of these patients, disease progression was reported as an SAE) and 9 (4.7%) patients had treatment-related SAE). The most common SAEs (occurring in ≥2% of patients) were back pain (4.7%), urinary tract infection (4.2%), acute kidney injury (4.2%), general physical health deterioration (3.7%), sepsis (3.1%), abdominal pain (2.6%), vomiting (2.6%), hypercalcemia (2.6%), and pyrexia (2.1%). Of the 191 enrolled UC patients, 15 (7.9%) had adverse events that resulted in death, including cardio-respiratory arrest, subileus, general physical health deterioration, immune-mediated hepatitis, chronic hepatic failure, sepsis,

cerebrovascular accident, acute kidney injury and pneumonitis. Of these, investigators considered one Grade 5 event each of pneumonitis and immune-mediated hepatitis to be related to treatment with durvalumab.

The most common adverse events regardless of relationship to treatment (any Grade; occurring in $\geq 10\%$ of patients) were fatigue (35.6%), constipation (25.7%), decreased appetite (22.5%), nausea (22.0%), anemia (18.3%), diarrhea (16.8%), back pain (16.8%), urinary tract infection (16.2%), fever (15.7%), peripheral edema (14.1%), vomiting (13.1%), cough (11.5%), dyspnea (11.5%), increased blood creatinine (11.0%), arthralgia (10.5%) and asthenia (10.5%). The majority of adverse events were Grade 1 or 2 (mild to moderate) in severity; Grade 3 or 4 adverse events were reported in 52 (27.2%) patients. The most common Grade 3 or 4 adverse events ($>3\%$ of patients) were anemia (9.9%), hyponatremia (5.8%), acute kidney injury (4.7%), urinary tract infection (4.2%), back pain (4.2%), fatigue, sepsis, hypercalcemia and asthenia (3.1% each). Treatment-related Grade 3 or 4 adverse events were reported in 6.8% of patients; the most common ($\geq 1\%$) were increased AST (1.6%), increased ALT (1.0%), and increased GGT (1.0%), all of which were generally manageable and reversible.

Adverse events (excluding disease progression) leading to the delay, interruption or discontinuation of Imfinzi occurred in 68 (35.6%), 3 (1.6%), and 9 (4.7%) patients, respectively; the most common reasons for dose delay (occurring in $>1\%$ of patients) were back pain (3.7%), urinary tract infection (2.6%), acute kidney injury (1.6%), AST increased (1.6%), GGT increased (1.6%), and pneumonia (1.6%). The most common reason for dose discontinuation (occurring in $\geq 1\%$ of patients) was general physical health deterioration in 2 (1.0%) patients.

Locally Advanced, Unresectable, Stage III Non-Small Cell Lung Cancer

The safety of Imfinzi in patients with locally advanced, unresectable, Stage III non-small lung cancer (NSCLC) was evaluated in a randomized, double-blind, placebo-controlled, multicenter study (PACIFIC). Patients received 10 mg/kg Imfinzi (n=475) or placebo (n=234) via intravenous infusion every 2 weeks (Q2W) (see [14 CLINICAL TRIALS](#)).

Imfinzi monotherapy 10 mg/kg Q2W was generally well tolerated in this patient population. Adverse reactions were generally manageable and reversible with interruption of dosing and treatment with immunosuppressants, such as corticosteroids.

The most common adverse reactions (any Grade; occurring in $\geq 10\%$ of patients) reported for Imfinzi vs. placebo, respectively were cough (40.2% vs. 30.3%), pneumonitis/radiation pneumonitis (33.9% vs 24.8%), upper respiratory tract infections (26.1% vs. 19.2%), rash (21.7% vs. 12.0%), diarrhea (18.3% vs. 18.8%), pneumonia (17.1% vs. 11.5%), pyrexia (14.7% vs. 9.0%), pruritus (12.4% vs 5.6%), hypothyroidism (11.6% vs. 1.7%), abdominal pain (10.1% vs. 6.0%). The majority of adverse reactions were Grade 1 or 2 (mild to moderate) in severity; Grade 3 or 4 adverse reactions were reported in 12.8% of patients receiving Imfinzi vs 9.8% receiving placebo, with no event occurring with more than a 2-percentage-point difference between the treatment groups. The most common Grade 3 or 4 adverse reactions (occurring in $>3\%$ of patients) were pneumonia (6.5% of patients on Imfinzi vs. 5.6% on placebo).

The incidence of Grade 3 pneumonitis and radiation pneumonitis was similar between Imfinzi-treated patients and patients receiving placebo (3.4% vs. 3.0%, respectively). No Grade 4 events of pneumonitis or radiation pneumonitis were reported in either group. The incidence of Grade 5 pneumonitis and radiation pneumonitis was also similar between Imfinzi-treated patients and placebo-treated patients (1.1% vs. 1.7%, respectively).

Serious adverse reactions occurred in 12.8% of patients on Imfinzi and 11.1% of patients on placebo. The most frequent serious adverse reactions (occurring in $>1\%$ of patients) were

pneumonia (8.2% of patients on Imfinzi vs. 7.3% on placebo), and pneumonitis/radiation pneumonitis (7.2% of patients on Imfinzi vs. 5.1% on placebo).

Adverse drug reactions with a fatal outcome occurred in 1.5% patients on Imfinzi and 2.6% patients on placebo, including pneumonitis in 0.8% patients on Imfinzi vs. 1.3% on placebo, and pneumonia in 0.6% patients on Imfinzi vs. 1.7% patients on placebo.

Adverse drug reactions leading to dose delay or interruption occurred in 24.4% of patients on Imfinzi vs. 14.5% of patients on placebo; the most common (occurring in >5% of patients) reasons in the Imfinzi and placebo groups were pneumonia (8.0% vs. 4.7%, respectively) and pneumonitis (5.1% vs. 3.0%, respectively). Treatment was discontinued for adverse drug reactions in 8.2% patients (n=39) on Imfinzi vs. 5.6% patients (n=13) on placebo. The most common (occurring in >1% of patients) reasons for discontinuation of study treatment in the Imfinzi and placebo groups were pneumonitis (4.8% vs. 2.6%, respectively) and pneumonia (1.9% vs. 2.1%, respectively).

Immune-mediated adverse drug reactions requiring systemic corticosteroids occurred in 14.3% of patients on Imfinzi vs. 5.6% on placebo, high dose corticosteroids (at least 40 mg prednisone or equivalent per day) in 8.2% of patients on Imfinzi vs. 4.3% on placebo, endocrine therapy occurred in 10.7% of patients on Imfinzi vs. 1.3% on placebo. Other immunosuppressants were required in 2 (0.4%) patients on Imfinzi (infliximab for both), and 1 (0.4%) patient on placebo (cyclophosphamide and tacrolimus).

Extensive-Stage Small Cell Lung Cancer

The safety of Imfinzi in combination with etoposide and either carboplatin or cisplatin in patients with treatment-naïve extensive-stage small cell lung cancer (ES-SCLC) was evaluated in CASPIAN, a randomized, open-label, multicenter active-controlled study (see [14 CLINICAL TRIALS](#)). Patients received Imfinzi 1500 mg in combination with chemotherapy every 3 weeks for 4 cycles followed by Imfinzi 1500 mg every 4 weeks until disease progression or unacceptable toxicity, or chemotherapy alone every 3 weeks for up to 6 cycles.

In the Imfinzi in combination with chemotherapy group, 87% of patients received 4 cycles of chemotherapy. In the chemotherapy alone group, 85% of patients received 4 cycles of chemotherapy, and 57% of patients received 6 cycles of chemotherapy; additionally, 8% of patients received prophylactic cranial irradiation (PCI).

The most common adverse events (any Grade; occurring in ≥10% of patients) reported for the Imfinzi + chemotherapy arm were neutropenia, anemia, nausea, fatigue, alopecia, thrombocytopenia, leukopenia, decreased appetite, constipation, cough/productive cough, vomiting, and dyspnoea.

Grade 3 or 4 adverse events were reported in 61.5% of patients in the Imfinzi + chemotherapy arm versus 62.4% of patients in the chemotherapy arm. Adverse events leading to dose delay or interruption of study treatment were reported in 41.9% of patients treated with Imfinzi in combination with chemotherapy versus 37.6% of patients treated with chemotherapy alone. Imfinzi dose was delayed due to adverse events in 41.1% of patients. Adverse events leading to discontinuation of study treatment were reported in 9.4% of patients in both groups. Imfinzi was discontinued due to adverse events in 6.8% of the patients receiving Imfinzi in combination with chemotherapy. These include pneumonitis, hepatotoxicity, neurotoxicity, sepsis, diabetic ketoacidosis and pancytopenia (1 patient each).

Serious adverse events occurred in 30.9% of patients treated with Imfinzi in combination with chemotherapy versus 36.1% of patients treated with chemotherapy alone. The most frequent serious adverse events reported in at least 1% of patients in the Imfinzi + chemotherapy arm

were febrile neutropenia (4.5%), pneumonia (2.3%), anemia (1.9%), pancytopenia (1.5%), chronic obstructive pulmonary disease (1.1%) and pneumonitis (1.1%). Serious adverse events with an outcome of death occurred in 4.9% of patients in the Imfinzi + chemotherapy arm and 5.6% in the chemotherapy arm. Fatal adverse events in the Imfinzi + chemotherapy arm include sepsis, septic shock, pancytopenia, dehydration, cardiac arrest, acute respiratory failure, aspiration, hypoxia, pulmonary artery thrombosis, pulmonary embolism, and hepatotoxicity (1 patient each), and sudden death (2 patients).

Immune-mediated adverse reactions were reported in 19.6% of patients treated with Imfinzi in combination with chemotherapy (Grade 3 or 4 events 4.5%). Immune-mediated adverse reactions requiring systemic corticosteroids were reported in 9.4% of patients, and endocrine therapy in 14.7% of patients. The most commonly reported immune-mediated adverse reactions were hypothyroidism (9.1%) and hyperthyroidism (5.3%). At the time of analysis, immune-mediated adverse events were unresolved in 10.9% of patients.

Locally Advanced or Metastatic Biliary Tract Cancer

The safety of Imfinzi in combination with gemcitabine and cisplatin in patients with locally advanced or metastatic biliary tract cancer (BTC) was evaluated in TOPAZ-1, a randomized, double-blind, placebo-controlled, multicentre, international study (see [14 CLINICAL TRIALS](#)). Patients received either Imfinzi 1500 mg (n=338) in combination with gemcitabine and cisplatin every 3 weeks, followed by 1500 mg every 4 weeks as monotherapy, or placebo (n=342) in combination with gemcitabine and cisplatin every 3 weeks, followed by placebo every 4 weeks, until disease progression or unacceptable toxicity. The median duration of exposure to durvalumab in combination with chemotherapy was 7.33 months [range 0.1 to 24.5], corresponding to 10 treatment cycles [range 1 to 29]. Treatment with Imfinzi + chemotherapy in patients with BTC demonstrated a tolerable and manageable safety profile. Overall, the incidence of adverse events and their severity were comparable between the Imfinzi + chemotherapy and placebo + chemotherapy groups, and in-line with the known safety profiles of either durvalumab monotherapy or the chemotherapy regimens.

The most commonly reported adverse events (any Grade; occurring in $\geq 10\%$ of patients) for Imfinzi + chemotherapy arm compared to the placebo + chemotherapy arm were anaemia (48.2% vs 44.7%), nausea (40.2% vs 34.2%), constipation (32.0% vs 28.9%), neutropenia (31.7% vs 29.8%), fatigue (26.9% vs 26.3%), neutrophil count decreased (26.9% vs 31.0%), decreased appetite (25.7% vs 23.1%), platelet count decreased (20.7% vs 23.1%), pyrexia (20.1% vs 16.4%), vomiting (18.3% vs 18.1%), diarrhea (16.9% vs 14.9%), asthenia (14.2% vs 14.0%), abdominal pain (13.9% vs 17.0%), thrombocytopenia (12.7% vs 13.2%), pruritus (11.2% vs 8.2%), rash (11.2% vs 7.9%), white blood cell count decreased (10.9% vs 13.5%), abdominal pain upper (10.4% vs 8.8%), insomnia (9.5% vs 10.5%), and alanine aminotransferase increased (8.6% vs 10.2%).

The most commonly reported Grade 3 or 4 adverse events occurring with a frequency $>2\%$ possibly related to any study medication for Imfinzi + chemotherapy arm compared to the placebo + chemotherapy arm were neutrophil count decreased (20.7% vs 25.4%), neutropenia (19.2% vs 20.2%), anaemia (18.9% vs 18.7%), platelet count decreased (8.0% vs 7.6%), white blood cell count decreased (4.1% vs 5.8%), thrombocytopenia (3.6% vs 5.3%), fatigue (2.7% vs 2.3%), leukopenia (2.1% vs 0.6%) and asthenia (1.2% vs 2.0%).

Grade 3 or 4 adverse events were reported in 73.7% of patients in the Imfinzi + chemotherapy arm versus 75.1% of patients in the placebo + chemotherapy arm. Adverse events leading to dose delay or interruption of study treatment were reported in 59.2% of patients treated with Imfinzi in combination with chemotherapy versus 62.3% of patients treated with chemotherapy

alone. Imfinzi dose was delayed due to adverse events in 36.1% of patients, in the comparator arm the placebo dose was delayed due to adverse events in 34.5%.

Serious adverse reactions occurred in 47.3% of patients on Imfinzi + chemotherapy arm and 43.6% of patients in the placebo + chemotherapy arm. The most frequent serious adverse reactions (occurring in >2% of patients in either treatment group;) were cholangitis (7.4% vs 5.0%), pyrexia (3.8% vs. 2.3%), anaemia (3.6% vs 1.2%), sepsis (3.3% vs. 2.6%), acute kidney injury (2.4% vs 1.2%), and biliary obstruction (1.8% vs 2.0%). Adverse events leading to death were reported for 3.6% patients in the Imfinzi + chemotherapy group and 4.1% patients in the placebo + chemotherapy group. The adverse events leading to death that were considered causally-related occurred in 2 (0.6%) patients in the Imfinzi + chemotherapy group (due to ischemic stroke and hepatic failure) and 1 (0.3%) patient in the placebo + chemotherapy group (due to polymyositis).

Adverse events leading to discontinuation of study treatment were reported in 13.0% of patients treated with Imfinzi + chemotherapy group versus 15.2% of patients treated with placebo + chemotherapy. Imfinzi was discontinued due to adverse events in 6.2% of the patients receiving Imfinzi + chemotherapy. These include biliary tract infection, Covid-19, gastroenteritis Escherichia coli, sepsis, thrombocytopenia, ischaemic stroke, interstitial lung disease, ascites, melaena, pancreatitis, upper gastrointestinal haemorrhage, vomiting, biliary obstruction, hepatic failure, rash maculo-papular, asthenia, fatigue, and alanine aminotransferase increased.

Immune-mediated adverse events were reported in 12.7% of patients in the Imfinzi + chemotherapy arm (Grade 3 or 4 events 2.4%) and 4.7% of patients in the placebo + chemotherapy arm (Grade 3 or 4 event 1.5%). Immune-mediated adverse reactions requiring systemic corticosteroids were reported in 8.0% of patients in the Imfinzi + chemotherapy arm and 3.5% in the placebo + chemotherapy arm. The frequency of discontinuations of study treatment due to immune-mediated adverse reactions was consistent between study groups. The most commonly reported immune-mediated adverse reactions (>1%) in the Imfinzi + chemotherapy group were hypothyroidism (5.6%), rash maculo-papular (1.8%), and adrenal insufficiency (1.2%).

Unresectable hepatocellular carcinoma (uHCC)

The safety of Imfinzi monotherapy, and Imfinzi in combination with tremelimumab in patients with unresectable hepatocellular carcinoma (uHCC) were evaluated in the HIMALAYA study, a randomized, open-label, multicenter study. Patients received Imfinzi in combination with tremelimumab (N=388), Imfinzi as a single agent (N=388) or sorafenib 400 mg orally twice daily (N=374). Patients on the combination therapy of Imfinzi plus tremelimumab received a single dose of tremelimumab 300 mg in combination with Imfinzi 1500 mg, followed by Imfinzi 1500 mg as a single agent every 4 weeks. Patients on Imfinzi monotherapy received Imfinzi 1500 mg as a single agent every 4 weeks. Patients were treated until disease progression or unacceptable toxicity. For the Imfinzi in combination with tremelimumab arm all of the 388 patients received the initial single dose of tremelimumab; the median duration of exposure to tremelimumab in combination with durvalumab was 5.5 months (range 0.4 to 41.9). For the patients in the Imfinzi monotherapy arm the median duration of exposure was 5.5 months (range 0.2 to 44.4).

For patients receiving Imfinzi in combination with tremelimumab, the most commonly reported adverse events (reported by $\geq 10\%$ patients) were pruritus, diarrhoea, rash, fatigue, decreased appetite, pyrexia, AST increased, hypothyroidism, nausea, abdominal pain, insomnia and asthenia. For patients receiving Imfinzi monotherapy, the most commonly reported adverse events (reported in $\geq 10\%$ patients) were diarrhoea, pruritus, AST increased, decreased appetite, asthenia, ALT increased, rash and constipation.

In patients receiving Imfinzi in combination with tremelimumab 50.5% reported grade 3 or 4 adverse events, and the most common adverse events (occurring in $\geq 5\%$ of patients) were lipase increase and AST increased. In patients receiving Imfinzi monotherapy 37.1% reported grade 3 or 4 adverse events, and the most common adverse event (occurring in $\geq 5\%$ of patients) was AST increased. In patients receiving sorafenib 52.4% reported grade 3 or 4 adverse events, and the most common adverse events (occurring in $\geq 5\%$ of patients) were hypertension and palmar-plantar erythrodysesthesia syndrome.

In patients receiving Imfinzi in combination with tremelimumab 34.5% reported adverse events leading to dose delays or interruption of any study treatment, and the most common of these adverse events (occurring in $\geq 3\%$ of patients) were ALT increased, amylase increased, diarrhoea and AST increased. In patients receiving Imfinzi monotherapy 24.5% reported adverse events leading to dose delays or interruption of any study treatment and the most common of these adverse events (occurring in $\geq 3\%$ of patients) were AST increased and ALT increased. In patients receiving sorafenib 47.6% reported adverse events leading to dose delays or interruption of any study treatment and the most common of these adverse events (occurring in $\geq 3\%$ of patients) were palmar-plantar erythrodysesthesia.

In patients receiving Imfinzi in combination with tremelimumab 13.7% reported discontinuation due to adverse events and the most common adverse events (occurring in $\geq 1\%$ of patients) were hepatitis and AST increased. In patients receiving Imfinzi monotherapy 8.2% reported discontinuation due to adverse events. In patients receiving sorafenib 16.8% reported discontinuation due to adverse events and the most common adverse events (occurring in $\geq 1\%$ of patients) were palmar-plantar erythrodysesthesia-syndrome, diarrhea and abdominal pain.

Serious adverse events occurred in 40.5% of patients receiving Imfinzi in combination with tremelimumab, and the most commonly reported serious adverse events (reported in $\geq 1\%$ patients) were pneumonia (1.8%), anaemia (1.3%), diabetes mellitus (1%), pneumonitis (1%), ascites (1%), upper gastro-intestinal haemorrhage (1.8%), sepsis (2.1%), diarrhea (2.3%), death (1%), and pyrexia (1%). Serious adverse events occurred in 29.6% of patients receiving Imfinzi monotherapy, and the most commonly reported events (reported in $\geq 1\%$ patients) were sepsis (1%), gastro-intestinal haemorrhage (1.3%), esophageal varices haemorrhage (1%), death (2.1%), hepatic function abnormal (1.3%) and pyrexia (1.5%). Serious adverse events occurred in 29.7% of patients receiving sorafenib, and the most commonly reported events (reported in $\geq 1\%$ patients) were pneumonia (2.1%), urinary tract infection (1.1%), dyspnea (1.1%), abdominal pain (1.6%), diarrhea (1.6%), upper gastro-intestinal haemorrhage (1.1%), hepatic failure (1.3%), and death (1.3%).

Adverse events with outcome of death occurred in 7.7% of patients treated with Imfinzi in combination with tremelimumab versus 6.7% of patients treated with Imfinzi monotherapy and 7.2% of patients treated with sorafenib. Fatal adverse events possibly related to treatment as assessed by the investigator in Imfinzi in combination with tremelimumab occurred in 2.3% of patients and included hepatitis, myocarditis, immune-mediated hepatitis (2 patients), pneumonitis, myasthenia gravis, nervous system disorder, acute respiratory distress syndrome, and hepatic failure. The majority of these events were attributed to disease progression, metastases or viral etiology but the role of study treatment could not be definitively ruled out. With the Imfinzi monotherapy no fatal events were assessed as being possibly related to treatment.

Immune-mediated adverse reactions were reported in 35.8% of patients treated with Imfinzi in combination with tremelimumab (Grade 3 or 4 events 12.6%) and 16.5% of patients treated with Imfinzi alone (Grade 3 or 4 events 6.4%). In the Imfinzi plus tremelimumab arm, immune-mediated adverse reactions requiring systemic corticosteroids were reported in 24.7% of

patients, and endocrine therapy in 17.0% of patients. In the Imfinzi monotherapy arm, immune-mediated adverse reactions requiring systemic corticosteroids were reported in 10.8% of patients, and endocrine therapy in 6.7% of patients.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Urothelial Carcinoma

Table 3 lists the adverse drug reactions, with incidences regardless of investigators assessment of causality, reported in patients with UC (n=191) treated with Imfinzi 10 mg/kg Q2W.

Table 3 Adverse Drug Reactions in the Urothelial Carcinoma Patients Treated with Imfinzi at 10 mg/kg Q2W (Study 1108)

System Organ Class Preferred Term ^a	Imfinzi (N=191)			
	Any Grade N (%)	Grade 1 N (%)	Grade 2 N (%)	Grade 3 or 4 N (%)
Cardiac disorders				
Myocarditis	Not reported ^c			
Endocrine disorders				
Hypothyroidism ^d	13 (6.8)	4 (2.1)	9 (4.7)	0
Hyperthyroidism ^d	9 (4.7)	7 (3.7)	2 (1.0)	0
Adrenal insufficiency	1 (0.5)	1 (0.5)	0	0
Hypophysitis/Hypopituitarism	Not reported ^c			
Diabetes insipidus	Not reported ^c			
Type 1 diabetes mellitus	Not reported ^c			
Gastrointestinal disorders				
Diarrhea	32 (16.8)	22 (11.5)	9 (4.7)	1 (0.5)
Colitis ^d	2 (1.0)	1 (0.5)	1 (0.5)	0
Hepatobiliary disorders				
Hepatitis ^{b,d}	3 (1.6)	1 (0.5)	0	1 (0.5)
Aspartate aminotransferase increased ^d	16 (8.4)	8 (4.2)	3 (1.6)	5 (2.6)
Alanine aminotransferase increased ^d	16 (8.4)	10 (5.2)	3 (1.6)	3 (1.6)
Injury, poisoning and procedural complications				
Infusion related reaction	2 (1.0)	1 (0.5)	0	1 (0.5)

	Imfinzi (N=191)			
System Organ Class Preferred Term ^a	Any Grade N (%)	Grade 1 N (%)	Grade 2 N (%)	Grade 3 or 4 N (%)
Musculoskeletal and connective tissue disorders				
Myositis	1 (0.5)	0	1 (0.5)	0
Renal and urinary disorders				
Blood creatinine increased	21 (11.0)	14 (7.3)	6 (3.1)	1 (0.5)
Nephritis ^d	1 (0.5)	0	0	1 (0.5)
Respiratory, thoracic and mediastinal disorders				
Pneumonitis ^b	2 (1.0)	1 (0.5)	0	0
Interstitial lung disease	Not reported ^c			
Skin and subcutaneous tissue disorders				
Rash ^d	27 (14.1)	20 (10.5)	6 (3.1)	1 (0.5)
Pruritus ^d	12 (6.3)	9 (4.7)	3 (1.6)	0
Dermatitis	1 (0.5)	0	1 (0.5)	0

^a Incidences presented in this table are based on reports of drug-related adverse events.

^b Including a fatal outcome.

^c Adverse Drug Reactions not reported in the UC cohort but reported from other clinical studies (N=1889) included interstitial lung disease: uncommon ($\geq 1/1,000$ to $< 1/100$) in any grade, and uncommon in Grade 3 or 4. Type 1 diabetes mellitus, hypopituitarism including diabetes insipidus, myocarditis: rare ($\geq 1/10,000$ to $< 1/1000$) in any grade, rare in Grade 3 or 4.

^d Included additional preferred terms: aspartate aminotransferase increased or alanine aminotransferase increased included transaminase increased and hepatic enzyme increased; colitis included enterocolitis, proctitis and enteritis; hepatitis included autoimmune hepatitis, hepatitis toxic, hepatocellular injury, hepatitis acute and hepatotoxicity; hypothyroidism included autoimmune hypothyroidism; hyperthyroidism included autoimmune thyroiditis, thyroiditis, thyroiditis subacute, Basedow's disease; rash included rash erythematous, rash generalized, rash macular, rash maculopapular, rash papular, rash pruritic, rash pustular, erythema, and eczema; pruritus included pruritus generalized; nephritis included autoimmune nephritis, glomerulonephritis, tubulointerstitial nephritis.

Table 4 lists the incidences of very common (occurring in $\geq 10\%$ of patients) adverse events, regardless of investigators assessment of causality, reported in patients with UC (n=191) treated with Imfinzi 10 mg/kg Q2W.

Table 4 Adverse Events Reported in $\geq 10\%$ in Urothelial Carcinoma Patients Treated with Imfinzi at 10 mg/kg Q2W (Study 1108)

	Imfinzi (N =191)			
System Organ Class Preferred Term ^a	Any Grade N (%)	Grade 1 N (%)	Grade 2 N (%)	Grade 3 or 4 N (%)
Blood and lymphatic system disorders				
Anemia	35 (18.3)	3 (1.6)	13 (6.8)	19 (9.9)

System Organ Class Preferred Term ^a	Imfinzi (N =191)			
	Any Grade N (%)	Grade 1 N (%)	Grade 2 N (%)	Grade 3 or 4 N (%)
Gastrointestinal disorders				
Constipation	49 (25.7)	35 (18.3)	11 (5.8)	3 (1.6)
Nausea	41 (21.5)	25 (13.1)	12 (6.3)	4 (2.1)
Vomiting	25 (13.1)	13 (6.8)	8 (4.2)	4 (2.1)
General disorders and administration site conditions				
Fatigue	68 (35.6)	33 (17.3)	29 (15.2)	6 (3.1)
Pyrexia	30 (15.7)	25 (13.1)	5 (2.6)	0
Edema peripheral	27 (14.1)	17 (8.9)	7 (3.7)	3 (1.6)
Asthenia	20 (10.5)	9 (4.7)	5 (2.6)	6 (3.1)
Infections and infestations				
Urinary tract infection	31 (16.3)	3 (1.6)	20 (10.5)	8 (4.2)
Metabolism and nutrition disorders				
Decreased appetite	43 (22.5)	21 (11.0)	21 (11.0)	1 (0.5)
Musculoskeletal and connective tissue disorders				
Back pain	32 (16.8)	7 (3.7)	17 (8.9)	8 (4.2)
Arthralgia	20 (10.5)	12 (6.3)	7 (3.7)	1 (0.5)
Respiratory, thoracic and mediastinal disorders				
Dyspnea	22 (11.6)	8 (4.2)	11 (5.8)	3 (1.6)
Cough	21 (11.5)	19 (9.9)	3 (1.6)	0

^a The terms presented in the table are adverse events reported regardless of the investigators assessment of relationship to treatment.

Locally Advanced, Unresectable, Stage III Non-Small Cell Lung Cancer

Table 5 lists the incidence of treatment-emergent adverse events reported in at least 5% of patients in the PACIFIC study regardless of investigator assessed causality.

Table 5 Treatment-Emergent Adverse Events in Locally Advanced, Unresectable, Stage III NSCLC Patients Reported in the PACIFIC Study Treated with Imfinzi at 10 mg/kg Q2W or Placebo

MedDRA System Organ Class Preferred Term	Imfinzi (N=475)			Placebo (N=234)		
	All Grades n (%)	Grades 3 n (%)	Grades 4 n (%)	All Grades n (%)	Grades 3 n (%)	Grades 4 n (%)
Blood and lymphatic system disorders						
Anemia	36 (7.6)	14 (2.9)	0	25 (10.7)	8 (3.4)	0
Endocrine disorders						
Hyperthyroidism ^{a*}	39 (8.2)	0	0	5 (2.1)	0	0
Hypothyroidism ^{b*}	55 (11.6)	1 (0.2)	0	4 (1.7)	0	0

MedDRA System Organ Class Preferred Term	Imfinzi (N=475)			Placebo (N=234)		
	All Grades n (%)	Grades 3 n (%)	Grades 4 n (%)	All Grades n (%)	Grades 3 n (%)	Grades 4 n (%)
Gastrointestinal disorders						
Abdominal pain ^{c*}	48 (10.1)	2 (0.4)	0	14 (6.0)	1 (0.4)	0
Constipation	56 (11.8)	1 (0.2)	0	20 (8.5)	0	0
Diarrhea*	87 (18.3)	3 (0.6)	0	44 (18.8)	3 (1.3)	0
Nausea	66 (13.9)	0	0	31 (13.2)	0	0
Vomiting	37 (7.8)	1 (0.2)	0	19 (8.1)	0	0
General disorders and administration site conditions						
Asthenia	51 (10.7)	3 (0.6)	0	31 (13.2)	1 (0.4)	0
Edema peripheral*	37 (7.8)	0	0	9 (3.8)	0	0
Fatigue	113 (23.8)	1 (0.2)	0	48 (20.5)	3 (1.3)	0
Non-cardiac chest pain	35 (7.4)	1 (0.2)	0	22 (9.4)	1 (0.4)	0
Pyrexia*	70 (14.7)	1 (0.2)	0	21 (9.0)	0	0
Hepatobiliary disorders						
Aspartate aminotransferase increased or Alanine aminotransferase increase ^{d*}	29 (6.1)	9 (1.9)	0	4 (1.7)	0	0
Infections and infestations						
Bronchitis	33 (6.9)	1 (0.2)	0	19 (8.1)	1 (0.4)	0
Nasopharyngitis	41 (8.6)	0	0	14 (6.0)	0	0
Pneumonia ^{e*}	81 (17.1)	30 (6.3)	1 (0.2)	27 (11.5)	13 (5.6)	0
Upper respiratory tract infections ^{f*}	124 (26.1)	2 (0.4)	0	45 (19.2)	0	0
Urinary tract infection	28 (5.9)	0	0	13 (5.6)	0	0
Metabolism and nutrition disorders						
Decreased appetite	68 (14.3)	1 (0.2)	0	30 (12.8)	1 (0.4)	1 (0.4)
Hypokalemia	24 (5.1)	5 (1.1)	0	12 (5.1)	5 (2.1)	0
Musculoskeletal and connective tissue disorders						
Arthralgia	59 (12.4)	0	0	26 (11.1)	0	0
Back pain	50 (10.5)	1 (0.2)	0	27 (11.5)	1 (0.4)	0
Musculoskeletal chest pain	25 (5.3)	0	0	18 (7.7)	0	0
Musculoskeletal pain	39 (8.2)	3 (0.6)	0	24 (10.3)	1 (0.4)	0
Myalgia*	38 (8.0)	1 (0.2)	0	10 (4.3)	0	0
Pain in extremity	32 (6.7)	0	0	12 (5.1)	1 (0.4)	0
Nervous system disorders						
Dizziness	33 (6.9)	1 (0.2)	0	21 (9.0)	0	0
Headache	52 (10.9)	1 (0.2)	0	21 (9.0)	2 (0.9)	0
Paresthesia	20 (4.2)	0	0	12 (5.1)	0	0
Psychiatric disorders						
Insomnia	45 (9.5)	0	0	16 (6.8)	0	0

MedDRA System Organ Class Preferred Term	Imfinzi (N=475)			Placebo (N=234)		
	All Grades n (%)	Grades 3 n (%)	Grades 4 n (%)	All Grades n (%)	Grades 3 n (%)	Grades 4 n (%)
Respiratory, thoracic and mediastinal disorders						
Cough/ Productive Cough*	191 (40.2)	3 (0.6)	0	71 (30.3)	1 (0.4)	0
Dyspnea	106 (22.3)	7 (1.5)	0	56 (23.9)	6 (2.6)	0
Pneumonitis ^g /Radiation Pneumonitis	161 (33.9)	16 (3.4)	0	58 (24.8)	7 (3.0)	0
Skin and subcutaneous tissue disorders						
Dry skin	37 (7.8)	0	0	12 (5.1)	0	0
Pruritus ^h *	59 (12.4)	0	0	13 (5.6)	0	0
Rash ⁱ *	103 (21.7)	3 (0.6)	0	28 (12.0)	0	0
Vascular disorders						
Hypertension	27 (5.7)	9 (1.9)	1 (0.2)	8 (3.4)	2 (0.9)	0

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* These adverse events are considered drug-related.

a includes hyperthyroidism, autoimmune thyroiditis, thyroiditis, thyroiditis subacute and Basedow's disease.

b includes autoimmune hypothyroidism and hypothyroidism.

c includes abdominal pain, abdominal pain lower, abdominal pain upper and flank pain.

d includes alanine aminotransferase increased, aspartate aminotransferase increased, hepatic enzyme increased, and transaminases increased.

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

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

g includes acute interstitial pneumonitis, interstitial lung disease, pneumonitis and pulmonary fibrosis.

h includes pruritus generalized and pruritus.

i includes rash erythematous, rash generalized, rash macular, rash maculopapular, rash papular, rash pruritic, rash pustular, erythema, eczema and rash.

Extensive-Stage Small Cell Lung Cancer

Table 6 lists the incidence of adverse reactions in at least 1% of patients in the CASPIAN study.

Adverse reactions known to occur with Imfinzi or chemotherapies given alone may occur during treatment with these medicinal products in combination, even if these reactions were not reported in clinical trials with combination therapy.

Table 6 Adverse Reactions ($\geq 1\%$) in ES-SCLC Patients Reported in the CASPIAN Study Treated with Imfinzi with Etoposide and Either Carboplatin or Cisplatin

MedDRA System Organ Class Preferred Term ^a	Imfinzi with etoposide and either carboplatin or cisplatin (n=265)		Etoposide and either carboplatin or cisplatin (n=266)	
	All Grades n(%)	Grade 3 or 4 n(%)	All Grades n(%)	Grade 3 or 4 n(%)
Blood and Lymphatic System Disorder				
Neutropenia ^b	129 (48.7)	77 (29.1)	150 (56.4)	104 (39.1)
Anemia	102 (38.5)	24 (9.1)	125 (47.0)	48 (18.0)
Thrombocytopenia ^c	56 (21.1)	18 (6.8)	66 (24.8)	31 (11.7)
Leukopenia ^d	53 (20.0)	21 (7.9)	49 (18.4)	20 (7.5)
Febrile neutropenia	17 (6.4)	14 (5.3)	17 (6.4)	17 (6.4)
Pancytopenia ^e	8 (3.0)	4 (1.5)	3 (1.1)	2 (0.8)
Endocrine Disorders				
Hyperthyroidism	26 (9.8)	0	1 (0.4)	0
Hypothyroidism	25 (9.4)	0	4 (1.5)	0
Thyroiditis ^f	4 (1.5)	0	-	-
Adrenal insufficiency	3 (1.1)	0	-	-
Gastrointestinal Disorders				
Nausea	89 (33.6)	1 (0.4)	89 (33.5)	5 (1.9)
Constipation	44 (16.6)	2 (0.8)	51 (19.2)	0
Vomiting	39 (14.7)	0	44 (16.5)	3 (1.1)
Diarrhea	26 (9.8)	3 (1.1)	30 (11.3)	3 (1.1)
Abdominal pain ^g	23 (8.7)	1 (0.4)	12 (4.5)	0
Stomatitis ^h	16 (6.0)	1 (0.4)	12 (4.5)	0
General disorders and administration site conditions				
Fatigue ⁱ	85 (32.1)	9 (3.4)	84 (31.6)	6 (2.3)
Pyrexia	22 (8.3)	0	17 (6.4)	1 (0.4)
Edema peripheral ^j	17 (6.4)	2 (0.8)	11 (4.1)	0
Hepatobiliary disorders				
Aspartate aminotransferase increased or Alanine aminotransferase increased ^k	23 (8.7)	5 (1.9)	15 (5.6)	4 (1.5)
Hepatitis ^{e, l}	5 (1.9)	3 (1.1)	1 (0.4)	0
Infections and infestations				
Upper respiratory tract infections ^m	24 (9.1)	1 (0.4)	16 (6.0)	0
Pneumonia ⁿ	15 (5.7)	5 (1.9)	22 (8.3)	11 (4.1)
Dental and oral soft tissue infections ^o	3 (1.1)	0	3 (1.1)	0
Injury, poisoning and procedural complications				
Infusion-related reaction ^p	5 (1.9)	1 (0.4)	3 (1.1)	0
Metabolism and nutrition disorders				
Decreased appetite	48 (18.1)	2 (0.8)	46 (17.3)	2 (0.8)

MedDRA System Organ Class Preferred Term ^a	Imfinzi with etoposide and either carboplatin or cisplatin (n=265)		Etoposide and either carboplatin or cisplatin (n=266)	
	All Grades n(%)	Grade 3 or 4 n(%)	All Grades n(%)	Grade 3 or 4 n(%)
Musculoskeletal and connective tissue disorders				
Myalgia	9 (3.4)	0	6 (2.3)	0
Renal and urinary disorders				
Blood creatinine increased	5 (1.9)	0	6 (2.3)	0
Dysuria	5 (1.9)	0	6 (2.3)	0
Respiratory thoracic and mediastinal disorders				
Cough/ Productive Cough ^q	39 (14.7)	2 (0.8)	23 (8.6)	0
Pneumonitis	7 (2.6)	2 (0.8)	5 (1.9)	1 (0.4)
Skin and subcutaneous tissue disorders				
Alopecia	83 (31.3)	3 (1.1)	91 (34.2)	2 (0.8)
Rash ^f	25 (9.4)	0	15 (5.6)	0
Pruritus	20 (7.5)	0	10 (3.8)	0
Dermatitis	4 (1.5)	0	-	-

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^a The terms presented in the table are adverse reactions reported regardless of the investigators assessment of relationship to treatment.

^b Includes neutropenia and neutrophil count decreased.

^c Includes thrombocytopenia and platelet count decreased.

^d Includes leukopenia and white blood cell count decreased.

^e Includes a fatal outcome

^f Includes autoimmune thyroiditis and thyroiditis.

^g Includes abdominal pain, abdominal pain lower, abdominal pain upper and flank pain.

^h Includes stomatitis and mucosal inflammation.

ⁱ Includes fatigue and asthenia.

^j Includes oedema peripheral and peripheral swelling.

^k Includes alanine aminotransferase increased, aspartate aminotransferase increased, hepatic enzyme increased, and transaminases increased.

^l Includes hepatitis, hepatocellular injury and hepatotoxicity.

^m Includes nasopharyngitis, pharyngitis, rhinitis, sinusitis, tonsillitis, tracheobronchitis, and upper respiratory tract infection.

ⁿ Includes lung infection, pneumonia and pneumonia bacterial.

^o Includes periodontitis, pulpitis dental, tooth abscess and tooth infection.

^p Includes infusion-related reaction and urticaria with onset on the day of dosing or 1 day after dosing.

^q Includes cough and productive cough.

^r Includes rash erythematous, rash macular, rash maculopapular erythema and rash.

Locally Advanced or Metastatic Biliary Tract Cancer

Adverse reactions known to occur with durvalumab or chemotherapy given alone, may occur during treatment with these medicinal products in combination, even if these reactions were not reported in clinical trials with combination therapy.

Please also refer to the full prescribing information for the chemotherapeutic agents in their respective Product Monographs.

Table 7 Adverse drug reactions in BTC patients treated with Imfinzi in combination with chemotherapy

Term	Imfinzi with gemcitabine and cisplatin (n = 338)		Placebo with gemcitabine and cisplatin (n = 342)	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Blood and Lymphatic System Disorders				
Neutropenia ^{a,b}	191 (56.5)	135 (39.9)	197 (57.6)	154 (45.0)
Anaemia ^a	163 (48.2)	80 (23.7)	153 (44.7)	77 (22.5)
Thrombocytopenia ^{a,c}	113 (33.4)	49 (14.5)	119 (34.8)	46 (13.5)
Leukopenia ^{a,d}	51 (15.1)	22 (6.5)	61 (17.8)	23 (6.7)
Febrile neutropenia ^a	4 (1.2)	4 (1.2)	6 (1.8)	6 (1.8)
Ear and labyrinth disorders				
Tinnitus ^a	10 (3.0)	0	3 (0.9)	0
Endocrine disorders				
Hypothyroidism ^e	25 (7.4)	0	11 (3.2)	0
Hyperthyroidism ^f	9 (2.7)	0	4 (1.2)	0
Adrenal insufficiency	4 (1.2)	0	1 (0.3)	0
Gastrointestinal disorders				
Nausea ^a	136 (40.2)	5 (1.5)	117 (34.2)	6 (1.8)
Constipation ^a	108 (32.0)	2 (0.6)	99 (28.9)	1 (0.3)
Abdominal pain ^g	80 (23.7)	2 (0.6)	80 (23.4)	10 (2.9)
Vomiting ^a	62 (18.3)	5 (1.5)	62 (18.1)	7 (2.0)
Diarrhoea	57 (16.9)	4 (1.2)	51 (14.9)	6 (1.8)
Stomatitis ^{a,j}	23 (6.8)	0	22 (6.4)	0
Amylase increased ^{a,k}	16 (4.7)	3 (0.9)	16 (4.7)	4 (1.2)
General disorders and administration site conditions				
Fatigue ^{a,l}	133 (39.3)	21 (6.2)	134 (39.2)	19 (5.6)
Pyrexia	68 (20.1)	5 (1.5)	56 (16.4)	2 (0.6)
Oedema peripheral ^m	30 (8.9)	0	20 (5.8)	0
Chills ^a	11 (3.3)	0	8 (2.3)	0
Oedema ^a	11 (3.3)	1 (0.3)	5 (1.5)	0
Malaise ^a	10 (3.0)	0	14 (4.1)	0
Hepatobiliary disorders				
Aspartate aminotransferase or Alanine aminotransferase increased ⁿ	41 (12.1)	10 (3.0)	44 (12.9)	6 (1.8)
Blood Bilirubin increased ^{a,o}	13 (3.8)	6 (1.8)	28 (8.2)	14 (4.1)
Gamma-Glutamyltransferase increased ^a	12 (3.6)	3 (0.9)	18 (5.3)	8 (2.3)
Hepatitis ^p	10 (3.0)	3 (0.9)	3 (0.9)	1 (0.3)
Infections and infestations				
Upper respiratory tract infections ^q	22 (6.5)	0	19 (5.6)	0

Term	Imfinzi with gemcitabine and cisplatin (n = 338)		Placebo with gemcitabine and cisplatin (n = 342)	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Pneumonia ^r	15 (4.4)	10 (3.0)	10 (2.9)	6 (1.8)
Sepsis ^a	15 (4.4)	12 (3.6)	9 (2.6)	8 (2.3)
Oral candidiasis	4 (1.2)	0	0	0
Injury, poisoning and procedural complications				
Infusion related reaction ^s	9 (2.7)	0	5 (1.5)	0
Metabolism and nutrition disorders				
Decreased appetite ^a	87 (25.7)	7 (2.1)	79 (23.1)	3 (0.9)
Hypomagnesaemia ^{a,t}	33 (9.8)	6 (1.8)	33 (9.6)	3 (0.9)
Hypokalaemia ^a	28 (8.3)	10 (3.0)	17 (5.0)	4 (1.2)
Hyponatraemia ^{a,u}	23 (6.8)	7 (2.1)	22 (6.4)	8 (2.3)
Dehydration ^a	9 (2.7)	0	7 (2.0)	1 (0.3)
Hypocalcaemia ^{a,v}	7 (2.1)	1 (0.3)	8 (2.3)	2 (0.6)
Hypophosphataemia ^a	6 (1.8)	0	1 (0.3)	0
Musculoskeletal and connective tissue disorders				
Back Pain ^a	29 (8.6)	1 (0.3)	23 (6.7)	1 (0.3)
Myalgia	15 (4.4)	0	19 (5.6)	0
Muscle Spasms ^a	4 (1.2)	0	5 (1.5)	0
Nervous system disorders				
Headache ^a	23 (6.8)	0	14 (4.1)	0
Neuropathy peripheral ^{a,w}	29 (8.6)	1 (0.3)	28 (8.2)	1 (0.3)
Psychiatric disorders				
Insomnia ^a	32 (9.5)	0	36 (10.5)	0
Renal and urinary disorders				
Acute Kidney Injury ^a	13 (3.8)	11 (3.3)	7 (2.0)	5 (1.5)
Blood creatinine increased	10 (3.0)	0	34 (9.9)	1 (0.3)
Dysuria	4 (1.2)	0	6 (1.8)	0
Respiratory, thoracic and mediastinal disorders				
Cough/ Productive cough	26 (7.7)	1 (0.3)	20 (5.8)	0
Dyspnoea ^a	22 (6.5)	4 (1.2)	19 (5.6)	1 (0.3)
Pulmonary embolism ^a	16 (4.7)	8 (2.4)	13 (3.8)	7 (2.0)
Hiccups ^a	11 (3.3)	1 (0.3)	6 (1.8)	0
Skin and subcutaneous tissue disorders				
Rash ^x	62 (18.3)	3 (0.9)	42 (12.3)	0
Pruritus	38 (11.2)	0	28 (8.2)	0
Alopecia ^a	28 (8.3)	1 (0.3)	15 (4.4)	0
Dermatitis	6 (1.8)	0	1 (0.3)	0
Vascular disorders				
Hypotension ^a	6 (1.8)	2 (0.6)	5 (1.5)	2 (0.6)

^a Adverse reaction only applies to chemotherapy ADRs in the TOPAZ-1 study.

^b Includes neutropenia and neutrophil count decreased.

^c Includes thrombocytopenia and platelet count decreased.

^d Includes leukopenia and white blood cell count decreased.

^e Includes hypothyroidism, immune-mediated hypothyroidism, blood thyroid stimulating hormone increased.

- ^f Includes hyperthyroidism and blood thyroid stimulating hormone decreased.
- ^g Includes abdominal pain, abdominal pain lower, abdominal pain upper and flank pain.
- ^j Includes stomatitis and mucosal inflammation.
- ^k Includes amylase increased and hyperamylasaemia.
- ^l Includes fatigue and asthenia.
- ^m Includes oedema peripheral and peripheral swelling.
- ⁿ Includes alanine aminotransferase increased, aspartate aminotransferase increased, hepatic enzyme increased and transaminases increased.
- ^o Includes blood bilirubin increased and hyperbilirubinaemia.
- ^p Includes hepatitis, immune-mediated hepatitis, autoimmune hepatitis, hepatic cytolysis, and hepatotoxicity.
- ^q Includes nasopharyngitis, rhinitis, sinusitis, tonsillitis, and upper respiratory tract infection.
- ^r Includes pneumonia and pneumocystis jirovecii pneumonia.
- ^s Includes infusion-related reaction and urticaria with onset on the day of dosing or 1 day after dosing.
- ^t Includes blood magnesium decreased and hypomagnesaemia.
- ^u Includes blood sodium decreased and hyponatraemia.
- ^v Includes hypocalcaemia and blood calcium decreased.
- ^w Includes neuropathy peripheral, paraesthesia, and peripheral sensory neuropathy.
- ^x Includes rash, rash macular, rash maculopapular, rash papular, rash pruritic, rash pustular, rash erythematous, eczema and erythema.

Unresectable hepatocellular carcinoma (uHCC)

Table 8 lists the incidence of adverse drug reactions found in at least 1% of patients with uHCC treated with Imfinzi in combination with tremelimumab or Imfinzi monotherapy in the HIMALAYA study.

Table 8 Adverse Drug Reactions Occurring in ≥1% of Patients with Hepatocellular Carcinoma receiving Imfinzi in combination with tremelimumab or Imfinzi Monotherapy Compared to Sorafenib in HIMALAYA

Adverse Drug Reaction	Imfinzi + tremelimumab (n=388)		Imfinzi Monotherapy (n=388)		Sorafenib (n=374)	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Endocrine disorders						
Adrenal insufficiency	6 (1.5%)	0	6 (1.5%)	3 (0.8%)	0	0
Hyperthyroidism ^a	38 (9.8%)	1 (0.3%)	10 (2.6%)	0	2 (0.5%)	0
Hypothyroidism ^b	52 (13.4%)	0	27 (7.0%)	0	21 (5.6%)	0
Thyroiditis ^c	8 (2.1%)	0	4 (1.0%)	0	2 (0.5%)	-
Gastrointestinal disorders						
Abdominal pain ^d	75 (19.3%)	7 (1.8%)	62 (16.0%)	8 (2.1%)	87 (23.2%)	15 (4.0%)
Amylase increased ^e	29 (7.5%)	14 (3.6%)	9 (2.3%)	3 (0.8%)	10 (2.7%)	3 (0.8%)
Colitis ^f	10 (2.6%)	6 (1.5%)	3 (0.8%)	0	2 (0.5%)	0
Diarrhoea	103 (26.5%)	17 (4.4%)	58 (14.9%)	6 (1.5%)	167 (44.7%)	16 (4.3%)
Lipase increased ^e	34 (8.8%)	24 (6.2%)	23 (5.9%)	16 (4.1%)	15 (4.0%)	11 (2.9%)
Pancreatitis ^g	5 (1.3%)	2 (0.5%)	1 (0.3%)	0	2 (0.5%)	1 (0.3%)

General disorders and administration site conditions						
Oedema peripheral ^h	36 (9.3%)	2 (0.5%)	24 (6.2%)	1 (0.3%)	24 (6.4%)	0
Pyrexia	50 (12.9%)	1 (0.3%)	36 (9.3%)	7 (1.8)	33 (8.8%)	0
Hepatobiliary disorders						
Aspartate aminotransferase increased /Alanine aminotransferase increased ⁱ	58 (14.9%)	25 (6.4%)	67 (17.3%)	30 (7.7%)	35 (9.4%)	15 (4.0%)
Hepatitis ^j	23 (5.9%)	7 (1.8%)	9 (2.3%)	2 (0.5%)	1 (0.3%)	0
Infections and infestations						
Dental and oral soft tissue infections ^k	6 (1.5%)	0	3 (0.8%)	0	2 (0.5%)	-
Influenza	10 (2.6%)	0	7 (1.8%)	1 (0.3%)	4 (1.1%)	1 (0.3%)
Pneumonia ^l	17 (4.4%)	4 (0.1%)	15 (3.9%)	3 (0.8%)	13 (3.5%)	6 (1.6%)
Upper respiratory tract infections ^m	32 (8.2%)	0	21 (5.4%)	0	15 (4.0%)	-
Injury, poisoning and procedural complications						
Infusion-related reaction ⁿ	6 (1.5%)	0	4 (1.0%)	0	2 (0.5%)	0
Musculoskeletal and connective tissue disorders						
Myalgia	12 (3.1%)	1 (0.3%)	8 (2.1%)	0	10 (2.7%)	0
Renal and urinary disorders						
Blood creatinine increased	14 (3.6%)	1 (0.3%)	8 (2.1%)	0	5 (1.3%)	1 (0.3%)
Dysuria	6 (1.5%)	0	3 (0.8%)	0	3 (0.8%)	-
Respiratory, thoracic and mediastinal disorders						
Cough/Productive cough	34 (8.8%)	0	35 (9.0%)	0	26 (7.0%)	1 (0.3%)
Dysphonia	3 (0.8%)	0	4 (1.0%)	0	26 (7.0%)	0
Pneumonitis	10 (2.6%)	0	5 (1.3%)	0	2 (0.5%)	0
Skin and subcutaneous tissue disorders						
Dermatitis ^o	6 (1.5%)	0	4 (1.0%)	0	6 (1.6%)	1 (0.3%)
Night sweats	4 (1.0%)	0	3 (0.8%)	0	2 (0.5%)	-
Pruritus	89 (22.9%)	0	56 (14.4%)	0	24 (6.4%)	1 (0.3%)
Rash ^p	116 (29.9%)	9 (2.3%)	55 (14.2%)	1 (0.3%)	80 (21.4%)	8 (2.1%)

^a Includes blood thyroid stimulating hormone decreased and hyperthyroidism.

^b Includes blood thyroid stimulating hormone increased, hypothyroidism and immune-mediated hypothyroidism.

^c Includes autoimmune thyroiditis, immune-mediated thyroiditis, thyroiditis and thyroiditis subacute.

^d Includes abdominal pain, abdominal pain lower, abdominal pain upper and flank pain.

^e Adverse drug reaction only for combination of Imfinzi + tremelimumab

^f Includes colitis, enteritis and enterocolitis.

^g Includes pancreatitis and pancreatitis acute.

^h Includes oedema peripheral and peripheral swelling.

ⁱ Includes alanine aminotransferase increased, aspartate aminotransferase increased, hepatic enzyme increased and transaminases increased.

- j Includes autoimmune hepatitis, hepatitis, hepatocellular injury, hepatotoxicity and immune-mediated hepatitis.
- k Includes periodontitis, pulpitis dental, tooth abscess and tooth infection.
- l Includes pneumocystis jirovecii pneumonia and pneumonia.
- m Includes nasopharyngitis, pharyngitis, rhinitis, tracheobronchitis and upper respiratory tract infection.
- n Includes infusion-related reaction and urticaria.
- o Includes dermatitis and immune-mediated dermatitis.
- p Includes eczema, erythema, rash, rash macular, rash maculo-papular, rash papular and rash pruritic.

Additional Information on Selected Adverse Reactions

The data for the following immune-mediated adverse reactions, defined as requiring the use of systemic corticosteroids/hormone replacement therapy with no clear alternate etiology, reflect exposure to Imfinzi, as a single agent, in a pooled dataset across multiple tumour types (n=3006) from 9 studies including Study 1108 (UC cohort [n=191]) and PACIFIC (n=475). For Imfinzi in combination with tremelimumab the following selected adverse reactions are based on 462 patients from the HIMALAYA study and Study 22 (N=74), an open-label, multi-part, multicenter study (see [14 CLINICAL TRIALS](#)). The management guidelines for these adverse reactions are described in [7 WARNINGS AND PRECAUTIONS](#) and [4 DOSAGE AND ADMINISTRATION](#).

Immune-Mediated Pneumonitis

In patients receiving Imfinzi monotherapy, immune-mediated pneumonitis occurred in 92 (3.1%) patients, including Grade 3 in 25 (0.8%) patients, Grade 4 in 2 (<0.1%) patients, and Grade 5 in 6 (0.2%) patients. The median time to onset was 55 days (range: 2-785 days). Sixty-nine of the 92 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day), 2 patients also received infliximab and 1 patient also received cyclosporine. Imfinzi was discontinued in 38 patients. Resolution occurred in 53 patients. Immune-mediated pneumonitis occurred more frequently in patients in the PACIFIC Study who had completed treatment with concurrent chemoradiation within 1 to 42 days prior to initiation of the study (9.9%), compared to the other patients in the combined safety database (1.8%).

In the PACIFIC study, in patients with locally advanced, unresectable, Stage III NSCLC (n=475 in the Imfinzi arm, and n=234 in the placebo arm) who had completed treatment with chemoradiation within 1 to 42 days prior to initiation of the study, immune-mediated pneumonitis occurred in 47 (9.9%) patients in the Imfinzi-treated group and 14 (6.0%) patients in the placebo group, including Grade 3 in 9 (1.9%) patients on Imfinzi vs. 6 (2.6%) patients on placebo and Grade 5 in 4 (0.8%) patients on Imfinzi vs. 3 (1.3%) patients on placebo. The median time to onset in the Imfinzi-treated group was 46 days (range: 2-342 days) vs. 57 days (range: 26-253 days) in the placebo group. In the Imfinzi-treated group, 30 patients who received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day), and 2 patients also received infliximab. In the placebo group, 12 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day) and 1 patient also received cyclophosphamide and tacrolimus. Resolution occurred for 29 patients in the Imfinzi treated group vs 6 in placebo.

In patients receiving Imfinzi in combination with tremelimumab in uHCC, immune-mediated pneumonitis occurred in 6 (1.3%) patients, including Grade 3 in 1 (0.2%) patient and Grade 5 (fatal) in 1 (0.2%) patient. The median time to onset was 29 days (range: 5-774 days). All patients received systemic corticosteroids, and 5 of the 6 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). One patient also

received other immunosuppressants. Treatment was discontinued in 2 patients. Resolution occurred in 3 patients.

Immune-Mediated Hepatitis

In patients receiving Imfinzi monotherapy, immune-mediated hepatitis occurred in 67 (2.2%) patients, including Grade 3 in 35 (1.2%) patients, Grade 4 in 6 (0.2%) patients and Grade 5 in 4 (0.1%) patients. The median time to onset was 36 days (range: 3-333 days). Forty-four of the 67 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). Three patients also received mycophenolate treatment. Imfinzi was discontinued in 9 patients. Resolution occurred in 29 patients.

In patients receiving Imfinzi in combination with tremelimumab in uHCC, immune-mediated hepatitis occurred in 34 (7.4%) patients, including Grade 3 in 20 (4.3%) patients, Grade 4 in 1 (0.2%) patient and Grade 5 (fatal) in 3 (0.6%) patients. The median time to onset was 29 days (range: 13-313 days). All patients received systemic corticosteroids, and 32 of the 34 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). Nine patients also received other immunosuppressants. Treatment was discontinued in 10 patients. Resolution occurred in 13 patients.

Immune-Mediated Colitis

In patients receiving Imfinzi monotherapy, immune-mediated colitis or diarrhea occurred in 58 (1.9%) patients, including Grade 3 in 9 (0.3%) patients and Grade 4 in 2 (<0.1%) patients. The median time to onset was 70 days (range: 1-394 days). Thirty-eight of the 58 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). One patient also received infliximab treatment and one patient also received mycophenolate treatment. Imfinzi was discontinued in 9 patients. Resolution occurred in 43 patients.

In patients receiving Imfinzi in combination with tremelimumab in uHCC, immune-mediated colitis or diarrhea occurred in 31 (6.7%) patients, including Grade 3 in 17 (3.7%) patients. The median time to onset was 23 days (range: 2-479 days). All patients received systemic corticosteroids, and 28 of the 31 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). Four patients also received other immunosuppressants. Treatment was discontinued in 5 patients. Resolution occurred in 29 patients.

Intestinal perforation was not observed in patients receiving Imfinzi in combination with tremelimumab in uHCC but it was observed in clinical trials of patients receiving Imfinzi in combination with tremelimumab.

Immune-Mediated Endocrinopathies

Immune-Mediated Hypothyroidism

In patients receiving Imfinzi monotherapy, immune-mediated hypothyroidism occurred in 245 (8.2%) patients, including Grade 3 in 4 (0.1%) patients. The median time to onset was 85 days (range: 1-562 days). Of the 245 patients, 240 patients received hormone replacement therapy, 6 patients received high-dose corticosteroids (at least 40 mg prednisone or equivalent per day) for immune-mediated hypothyroidism followed by hormone replacement. No patients discontinued Imfinzi due to immune-mediated hypothyroidism. Immune-mediated hypothyroidism was preceded by immune-mediated hyperthyroidism in 20 patients or immune-mediated thyroiditis in 3 patients.

In patients receiving Imfinzi in combination with tremelimumab in uHCC, immune-mediated hypothyroidism occurred in 46 (10.0%) patients. The median time to onset was 85 days (range: 26-763 days). 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). Resolution occurred in 6 patients. Immune-mediated hypothyroidism was preceded by immune-mediated hyperthyroidism in 4 patients.

Immune-Mediated Hyperthyroidism

In patients receiving Imfinzi monotherapy, immune-mediated hyperthyroidism occurred in 50 (1.7%) patients, there were no Grade 3 or 4 cases. The median time to onset was 43 days (range: 14-253 days). Forty-six of the 50 patients received medical therapy (thiamazole, carbimazole, propylthiouracil, perchlorate, calcium channel blocker, or beta-blocker), 11 patients received systemic corticosteroids and 4 of the 11 patients received high-dose systemic corticosteroid treatment (at least 40 mg prednisone or equivalent per day). One patient discontinued Imfinzi due to immune-mediated hyperthyroidism. Resolution occurred in 39 patients.

In patients receiving Imfinzi in combination with tremelimumab in uHCC, immune-mediated hyperthyroidism occurred in 21 (4.5%) patients, including Grade 3 in 1 (0.2%) patient. The median time to onset was 30 days (range: 13-60 days). Four patients received systemic corticosteroids and high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). Twenty patients required other therapy (thiamazole, carbimazole, propylthiouracil, perchlorate, calcium channel blocker, or beta-blocker). One patient discontinued treatment due to hyperthyroidism. Resolution occurred in 17 patients.

Immune-Mediated Thyroiditis

In patients receiving Imfinzi monotherapy, immune-mediated thyroiditis occurred in 12 (0.4%) patients, including Grade 3 in 2 (<0.1%) patients. The median time to onset was 49 days (range: 14-106 days). Of the 12 patients, 10 patients received hormone replacement therapy, 1 patient received high-dose corticosteroids (at least 40 mg prednisone or equivalent per day). One patient discontinued Imfinzi due to immune-mediated thyroiditis.

In patients receiving Imfinzi in combination with tremelimumab in uHCC, immune-mediated thyroiditis occurred in 6 (1.3%) patients. The median time to onset was 56 days (range: 7-84 days). Two patients received systemic corticosteroids, and 1 of the 2 patients received 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. Resolution occurred in 2 patients.

Immune-Mediated Adrenal Insufficiency

In patients receiving Imfinzi monotherapy, immune-mediated adrenal insufficiency occurred in 14 (0.5%) patients, including Grade 3 in 3 (<0.1%) patients. The median time to onset was 146 days (range: 20-547 days). All 14 patients received systemic corticosteroids; 4 of the 14 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). No patients discontinued Imfinzi due to immune-mediated adrenal insufficiency. Resolution occurred in 3 patients.

In patients receiving Imfinzi in combination with tremelimumab in uHCC, immune-mediated adrenal insufficiency occurred in 6 (1.3%) patients, including Grade 3 in 1 (0.2%) patient. The median time to onset was 64 days (range: 43-504 days). All patients received systemic

corticosteroids, and 1 of the 6 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). Resolution occurred in 2 patients.

Immune-Mediated Hypophysitis/Hypopituitarism

In patients receiving Imfinzi monotherapy, immune-mediated hypophysitis/hypopituitarism occurred in 2 (<0.1%) patients (both Grade 3). The time to onset for the events was 44 days and 50 days. Both patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day) and one patient discontinued Imfinzi due to immune-mediated hypophysitis/hypopituitarism.

In patients receiving Imfinzi in combination with tremelimumab in uHCC, immune-mediated hypophysitis/hypopituitarism occurred in 5 (1.1%) patients. The median time to onset for the events was 149 days (range: 27-242 days). Four patients received systemic corticosteroids, and 1 of the 4 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). Three patients also required endocrine therapy. Resolution occurred in 2 patients.

Immune-Mediated Type 1 Diabetes Mellitus

In patients receiving Imfinzi monotherapy, Grade 3 immune-mediated type 1 diabetes mellitus occurred in 1 (<0.1%) patient. This patient required long-term insulin therapy and Imfinzi was permanently discontinued due to immune-mediated type 1 diabetes mellitus.

In patients receiving Imfinzi in combination with tremelimumab in uHCC, immune-mediated type 1 diabetes mellitus was not observed but was observed in clinical trials of patients receiving Imfinzi in combination with tremelimumab.

Immune-Mediated Nephritis

In patients receiving Imfinzi monotherapy, immune-mediated nephritis occurred in 14 (0.5%) patients, including Grade 3 in 2 (<0.1%) patients. The median time to onset was 71 days (range: 4-393 days). Nine patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day) and 1 patient also received mycophenolate. Imfinzi was discontinued in 5 patients. Resolution occurred in 8 patients.

In patients receiving Imfinzi in combination with tremelimumab in uHCC, immune-mediated nephritis occurred in 4 (0.9%) patients, including Grade 3 in 2 (0.4%) patients. The median time to onset was 53 days (range: 26-242 days). All patients received systemic corticosteroids, and 3 of the 4 received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). Treatment was discontinued in 2 patients. Resolution occurred in 3 patients.

Immune-Mediated Rash

In patients receiving Imfinzi monotherapy, immune-mediated rash or dermatitis (including pemphigoid) occurred in 50 (1.7%) patients, including Grade 3 in 12 (0.4%) patients. The median time to onset was 43 days (range: 4-333 days). Twenty-four of the 50 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). Imfinzi was discontinued in 3 patients. Resolution occurred in 31 patients.

In patients receiving Imfinzi in combination with tremelimumab in uHCC, immune-mediated rash or dermatitis (including pemphigoid) occurred in 26 (5.6%) patients, including Grade 3 in 9 (1.9%) patients and Grade 4 in 1 (0.2%) patient. The median time to onset was 25 days (range: 2-933 days). All patients received systemic corticosteroids and 14 of the 26 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). One

patient received other immunosuppressants. Treatment was discontinued in 3 patients. Resolution occurred in 19 patients.

Immune-mediated pancreatitis

In patients receiving Imfinzi in combination with tremelimumab in uHCC, immune-mediated pancreatitis occurred in 9 (1.9%) patients, including Grade 3 - 4 in 7 (1.5%) patients. The median time to onset was 37 days (range: 27 to 534 days). All patients received systemic corticosteroids and 7 of the 9 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). Resolution occurred in 6 patients.

Other immune-mediated adverse reactions

The following clinically significant, immune-mediated adverse reactions occurred at an incidence of less than 1% of 462 patients with uHCC treated with Imfinzi in combination with tremelimumab in clinical trials: myocarditis (fatal), myositis, myasthenia gravis (fatal), Stevens-Johnson syndrome and hypoparathyroidism.

The following immune-mediated adverse reactions occurred at an incidence of less than 1% in clinical trials of patients receiving Imfinzi in combination with tremelimumab: Guillain-Barre syndrome.

Infusion Related Reactions

In patients receiving Imfinzi monotherapy, infusion related reactions occurred in 49 (1.6%) patients, including Grade 3 in 5 (0.2%) patients. There were no Grade 4 or 5 events.

In patients receiving Imfinzi in combination with tremelimumab in uHCC, infusion-related reactions occurred in 7 (1.5%) patients.

8.3 Less Common Clinical Trial Adverse Reactions

Less Common Clinical Trial Adverse Reactions (<5%) in the PACIFIC Study

The following additional adverse reactions considered drug-related were reported in less than 5% of Imfinzi-treated patients in the PACIFIC study. Adverse reactions presented elsewhere are excluded.

Endocrine disorders: adrenal insufficiency (0.2%), type 1 diabetes mellitus (0.2%)

Gastrointestinal disorders: colitis (includes colitis, enteritis and proctitis) (1.1%)

Hepatobiliary disorders: hepatitis (includes hepatitis, autoimmune hepatitis, hepatitis toxic, hepatocellular injury, hepatitis acute and hepatotoxicity) (0.6%)

Infections and infestations: dental and oral soft tissue infections (includes gingivitis, oral infection, periodontitis, pulpitis dental, tooth abscess and tooth infection) (3.6%), oral candidiasis (3.2%), influenza (2.5%)

Injury, poisoning and procedural complications: infusion related reaction (includes infusion related reaction and urticaria with onset on the day of dosing or 1 day after dosing) (1.9%)

Musculoskeletal and connective tissue disorders: myositis (0.4%)

Renal and urinary disorders: blood creatinine increased (4.6%), dysuria (2.3%), nephritis (includes autoimmune nephritis, tubulointerstitial nephritis, nephritis, glomerulonephritis and glomerulonephritis membranous) (0.4%)

Respiratory, thoracic and mediastinal disorders: dysphonia (3.8%)

Skin and subcutaneous tissue disorders: night sweats (2.3%), dermatitis (1.5%)

Less Common Clinical Trial Adverse Reactions (<1%) in the CASPIAN Study

The following additional adverse reactions were reported in less than 1% of patients treated with Imfinzi in combination with chemotherapy in the CASPIAN study.

Endocrine Disorders: type 1 diabetes mellitus (0.8%)

Gastrointestinal Disorders: colitis (includes colitis, enteritis and proctitis) (0.8%)

Infections and Infestations: oral candidiasis (0.8%), influenza (0.4%)

Musculoskeletal and connective tissue disorders: immune-mediated arthritis (0.8%)

Respiratory Thoracic and Mediastinal Disorders: dysphonia (0.8%), interstitial lung disease (0.8%)

Skin and Subcutaneous Tissue Disorders: night sweats (0.4%)

Less Common Clinical Trial Adverse Reactions (<1%) in the TOPAZ-1 Study

The following additional adverse reactions were reported in less than 1% of patients treated with Imfinzi in combination with chemotherapy in the TOPAZ-1 study.

Cardiac disorders: tachycardia (0.6%)

Endocrine disorders: thyroiditis (0.3%), type 1 diabetes mellitus (0.3%)

Gastrointestinal disorders: pancreatitis (0.9%), colitis (0.3%)

Infections and infestations: dental and oral soft tissue infections (0.9%)

Renal and urinary disorders: proteinuria (0.9%)

Respiratory, thoracic and mediastinal disorders: pneumonitis (0.9%), dysphonia (0.9%), interstitial lung disease (0.3%)

Skin and subcutaneous tissue disorders: night sweats (0.6%), pemphigoid (0.3%)

Less Common Clinical Trial Adverse Reactions (<1%) in the HIMALAYA Study

The following additional adverse reactions considered drug-related were reported in less than 1% of patients treated with Imfinzi in combination with tremelimumab in the HIMALAYA study. Adverse reactions presented elsewhere are excluded.

Cardiovascular disorders: myocarditis (0.5%)

Endocrine disorders: hypopituitarism/hypophysitis (0.8%)

Eye disorders: retinal detachment (0.5%)

Infections and infestations: oral candidiasis (0.8%)

Musculoskeletal and connective tissue disorders: myositis (0.8%), polymyositis (0.3%)

Nervous system disorders: myasthenia gravis (0.5%)

Renal and urinary disorders: nephritis (0.8%)

Respiratory, thoracic and mediastinal disorders: interstitial lung disease (0.3%)

Skin and subcutaneous tissue disorders: pemphigoid (0.3%)

The following additional adverse reactions considered drug-related were reported in less than 1% of patients treated with Imfinzi monotherapy in the HIMALAYA study. Adverse reactions presented elsewhere are excluded.

Cardiovascular disorders: myocarditis (0.3%)

Endocrine disorders: type 1 diabetes mellitus (0.3%)

Nervous Systems Disorders: myasthenia gravis (0.3%)

Respiratory thoracic and mediastinal disorders: interstitial lung disease (0.3%)

Skin and subcutaneous tissue disorders: pemphigoid (0.3%)

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Clinical Trial Findings

Urothelial Carcinoma

Changes in laboratory parameters were predominantly Grade 1 or 2 in severity, and the incidence of any grade worsening to Grade 3 or 4 was generally low (Table 9).

Table 9 Laboratory Abnormalities Worsened from Baseline Occurring in ≥1% (Grade 3 or 4) of Imfinzi-Treated Patients with Urothelial Carcinoma (Study 1108)

Laboratory Test	Imfinzi (N =191)			
	N	Grades 1 N (%)	Grades 2 N (%)	Grade 3 or 4 ^a N (%)
Anemia	180	25 (13.9)	38 (21.1)	22 (12.2)
Hyponatremia	179	62 (34.6)	0	19 (10.6)
Lymphocyte count decreased	180	20 (11.1)	41 (22.8)	19 (10.6)
Hypermagnesemia	176	13 (7.4)	0	7 (4.0)
Alkaline phosphatase increased	179	28 (15.6)	15 (8.4)	7 (3.9)
Aspartate aminotransferase increased	179	35 (19.6)	5 (2.8)	7 (3.9)
Hypercalcemia	176	16 (9.1)	4 (2.3)	6 (3.4)
Hyperglycemia	178	47 (26.4)	26 (14.6)	6 (3.4)
Blood bilirubin increased	179	9 (5.0)	6 (3.4)	4 (2.2)
Hyperkalemia	179	21 (11.7)	8 (4.5)	4 (2.2)
Creatinine increased	180	40 (22.2)	16 (8.9)	4 (2.2)
Alanine aminotransferase increased	180	27 (15.0)	6 (3.3)	2 (1.1)
Neutrophil count decreased	178	5 (2.8)	7 (3.9)	2 (1.1)
Hypoalbuminemia	179	34 (19.0)	31 (17.3)	2 (1.1)
Hypokalemia	179	16 (8.9)	0	2 (1.1)

^a Frequency of lab abnormalities for Grade 1 and Grade 2 are provided for those lab abnormalities reported in ≥1% patients with Grade 3 and Grade 4 severity.

Locally Advanced, Unresectable, Stage III Non-Small Cell Lung Cancer

Table 10 lists the incidence of laboratory abnormalities reported in patients with locally advanced unresectable, Stage III NSCLC in the PACIFIC study.

Table 10 Laboratory Abnormalities Worsening from Baseline Occurring More Frequently (≥5% Higher Incidence vs. Placebo) in Imfinzi-Treated Locally Advanced, Unresectable, Stage III NSCLC Patients in the PACIFIC Study

Laboratory Abnormalities	Imfinzi			Placebo		
	N	Any Grade n (%)	Grade 3 or 4 n (%)	N	Any Grade n (%)	Grade 3 or 4 n (%)
Alanine aminotransferase increased	470	181 (38.5)	11 (2.3)	228	49 (21.5)	1 (0.4)
Aspartate aminotransferase increased	469	169 (36.0)	13 (2.8)	228	48 (21.1)	1 (0.4)
Creatinine increased	465	76 (16.3)	0	226	23 (10.2)	0
TSH elevated >ULN and above baseline	464	123 (26.5)	NA	224	30 (13.4)	NA
TSH decreased <LLN and below baseline	464	148 (31.9)	NA	224	35 (15.6)	NA

NA - not applicable TSH - thyroid stimulating hormone ULN - upper limit of normal LLN - lower limit of normal

Extensive-Stage Small Cell Lung Cancer

Table 11 lists the incidence of laboratory abnormalities reported in patients with Imfinzi in the CASPIAN study.

Table 11 Laboratory Abnormalities Worsening from Baseline in Imfinzi-Treated Patients in the CASPIAN Study

Laboratory Abnormalities	Imfinzi with Etoposide and either Carboplatin or Cisplatin (N=265)		Etoposide and either Carboplatin or Cisplatin (N=266)	
	Any Grade (%)	Grade 3 or 4 (%)	Any Grade (%)	Grade 3 or 4 (%)
Blood creatinine increased	84.8	3.4	83.5	1.1
Hypocalcaemia	52.3	3.5	54.9	2.4
Hypomagnesaemia	50.0	11.1	43.8	6.3
Hyponatraemia	46.0	11.4	39.5	13.0
Hyperkalaemia	43.0	1.5	42.9	3.1
Hyperglycaemia	41.3	5.4	38.4	5.4

Laboratory Abnormalities	Imfinzi with Etoposide and either Carboplatin or Cisplatin (N=265)		Etoposide and either Carboplatin or Cisplatin (N=266)	
	Any Grade (%)	Grade 3 or 4 (%)	Any Grade (%)	Grade 3 or 4 (%)
Alanine aminotransferase increased	37.3	4.9	36.2	2.7
Increased Alkaline phosphatase	37.3	4.9	34.9	3.5
Aspartate aminotransferase increased	34.2	4.6	29.2	1.2
TSH decreased <LLN and ≥LLN at baseline	31.3	0	16.5	0
Amylase increased	26.2	4.8	20.2	5.0
Lipase increased	20.0	8.1	13.7	3.1
TSH elevated >ULN and ≤ULN at baseline	17.7	0	7.5	0

TSH - thyroid stimulating hormone ULN - upper limit of normal LLN - lower limit of normal

Locally Advanced or Metastatic Biliary Tract Cancer

Table 12 lists the incidence of laboratory abnormalities reported in patients with locally advanced or metastatic BTC in the TOPAZ-1 study.

Table 12 Laboratory Abnormalities Worsening from Baseline in Imfinzi-Treated Patients in the TOPAZ-1 Study (occurring in ≥20% of Patients)

Laboratory Abnormalities	Imfinzi with gemcitabine and cisplatin (n = 338)		Placebo with gemcitabine and cisplatin (n = 342)	
	Any Grade (%)	Grade 3 or 4 (%)	Any Grade (%)	Grade 3 or 4 (%)
Hematology				
Anemia	89.6	30.7	88.9	27.6
Leukopenia	83.6	27.8	80.9	28.2
Neutropenia	74.9	47.8	74.5	49.3
Thrombocytopenia	70.7	17.7	67.4	17.6
Lymphopenia	69.4	23.1	56.1	15.4
Chemistry				
Hyponatraemia	56.1	17.6	48.8	12.9
Hypocalcaemia	51.7	1.8	48.4	2.4
Alanine aminotransferase increased	50.7	6.6	48.7	6.2
Aspartate aminotransferase increased	41.0	7.5	38.1	7.9

Laboratory Abnormalities	Imfinzi with gemcitabine and cisplatin (n = 338)		Placebo with gemcitabine and cisplatin (n = 342)	
	Any Grade (%)	Grade 3 or 4 (%)	Any Grade (%)	Grade 3 or 4 (%)
Hypomagnesaemia	40.7	4.5	37.5	2.2
Hyperkalaemia	38.8	2.1	36.8	2.1
Lipase increased	36.1	13.8	25.6	11.0
Hypoalbuminemia	36.0	3.6	30.0	2.9
Creatinine increased	35.8	5.1	35.8	2.1
Amylase increased	31.4	6.3	24.4	5.9
Hyperbilirubinemia	25.4	9.6	32.0	13.5
Gamma-glutamyltransferase increased	24.6	11.5	24.5	12.9
Hypokalaemia	21.2	7.8	20.9	4.4
Increased Alkaline phosphatase	21.0	1.8	23.9	3.8

Unresectable hepatocellular carcinoma (uHCC)

Table 13 summarizes the laboratory abnormalities that occurred in patients treated with Imfinzi in combination with tremelimumab or Imfinzi monotherapy in the HIMALAYA study.

Table 13 Laboratory Abnormalities Worsening from Baseline Occurring in $\geq 20\%$ ¹ of Patients in the HIMALAYA study

Laboratory Abnormality	Imfinzi + tremelimumab (n = 388)		Imfinzi monotherapy (n = 388)		Sorafenib (n = 374)	
	Any grade ² (%) ³	Grade 3 ² or 4 (%) ³	Any grade ² (%) ³	Grade 3 ² or 4 (%) ³	Any grade ² (%) ³	Grade 3 ² or 4 (%) ³
Chemistry						
Aspartate Aminotransferase increased	63.1	26.8	55.1	23.1	54.6	21.1
Alanine Aminotransferase increased	56.2	17.8	51.9	13.1	52.6	12.2
Sodium decreased	46.0	15.3	37.5	6.7	39.8	11.1
Bilirubin increased	41.4	8.2	40.9	7.5	47.4	10.5
Alkaline Phosphatase increased	41.2	8.3	39.1	8.1	44.4	5.4
Glucose increased	38.9	13.5	38.6	8.4	29.1	3.7
Calcium decreased	33.5	0	35.4	0.3	43.0	0.3
Albumin decreased	31.3	0.5	24.1	0.5	37.1	1.7
Potassium increased	28.4	3.8	25.5	4.6	21.3	2.6
Creatinine increased	20.9	1.3	18.8	0.3	14.8	0.9
Hematology						
Hemoglobin decreased	51.6	4.8	42.4	4.8	40.3	6.0
Lymphocytes decreased	41.4	11.1	43.1	8.6	39.3	10.0
Platelets decreased	28.8	1.6	29.0	2.2	34.7	3.1
Leukocytes decreased	20.2	0.8	30.3	1.4	30.1	1.1

¹The frequency cut-off is based on any grade change from baseline for Imfinzi in combination with tremelimumab.

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 with tremelimumab (range: 367-378) and sorafenib (range:344-352).

8.5 Post-Market Adverse Reactions

The following adverse reactions have been identified during post-approval use of Imfinzi:

Gastrointestinal disorders: pancreatitis (includes pancreatitis and pancreatitis acute)

Musculoskeletal and connective tissue disorders: rhabdomyolysis

Nervous system disorders: encephalitis, Guillain-Barré syndrome

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

Durvalumab is an immunoglobulin and the primary elimination pathways of durvalumab is protein catabolism, therefore no formal pharmacokinetic drug-drug interaction studies have been conducted with durvalumab since no metabolic drug-drug interactions are expected.

9.3 Drug-Behavioural Interactions

Drug-Behavioural Interactions have not been established.

9.4 Drug-Drug Interactions

PK drug-drug interaction between durvalumab and chemotherapy was explored in the CASPIAN study and no clinically meaningful PK drug-drug interaction was identified.

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Expression of programmed cell death ligand-1 (PD-L1) protein is an adaptive immune response that helps tumours evade detection and elimination by the immune system. PD-L1 expression can be induced by inflammatory signals (e.g., IFN-gamma) and can be expressed on both tumour cells and tumour-associated immune cells present in the tumour microenvironment. Through its interactions with PD-1 and CD80 (B7.1), PD-L1 reduces cytotoxic T-cell activity, proliferation, and cytokine production.

Imfinzi is a fully human, high affinity, immunoglobulin G1 kappa (IgG1 κ) monoclonal antibody that selectively blocks the interaction of PD-L1 with PD-1 and CD80 (B7.1) while leaving PD-1/PD-L2 interaction intact. Imfinzi does not induce antibody dependent cell-mediated cytotoxicity (ADCC). Selective blockade of PD-L1/PD-1 and PD-L1/CD80 interactions releases the inhibition of immune responses and enhances antitumour immune responses.

In preclinical studies, PD-L1 blockade led to increased T-cell activation and delayed tumour growth.

10.2 Pharmacodynamics

Durvalumab 10 mg/kg every 2 weeks was evaluated in UC and NSCLC clinical studies, whereas durvalumab 1500 mg every 4 weeks was evaluated in an ES-SCLC clinical study. Based on the modeling and simulation of exposure, exposure-safety relationships and

exposure-efficacy data comparisons, there are no anticipated clinically significant differences in efficacy and safety between durvalumab doses of 10 mg/kg every 2 weeks or 1500 mg every 4 weeks.

10.3 Pharmacokinetics

The PK of durvalumab was assessed for both Imfinzi as a single agent and in combination with chemotherapy.

The pharmacokinetics of Imfinzi was studied as a single agent in 2903 patients with solid tumours with doses ranging from 0.1 to 20 mg/kg administered once every two, three or four weeks. PK exposure increased more than dose-proportionally (non-linear PK) at doses <3 mg/kg and dose proportionally (linear PK) at doses ≥ 3 mg/kg. Steady state was achieved at approximately 16 weeks.

The PK of durvalumab as a single agent and in combination with chemotherapy is similar.

Distribution

Based on population PK analysis that included 1878 patients in the dose range of ≥ 10 mg/kg Q2W, the geometric mean, steady state volume of distribution (V_{ss}) was 5.64 L.

Elimination

Based on population PK analysis, durvalumab clearance (CL) decreased over time resulting in a geometric mean steady state clearance (CL_{ss}) of 8.16 mL/h at Day 365; the decrease in CL_{ss} was not considered clinically relevant. The terminal half-life ($t_{1/2}$), based on baseline CL, was approximately 18 days.

Special Populations and Conditions

The covariate of age (19–96 years), body weight (31-149 kg), gender, positive anti-drug antibody (ADA) status, albumin levels, LDH levels, creatinine levels, soluble PD-L1, tumour type, race, mild renal impairment (creatinine clearance (CrCL) 60 to 89 mL/min), moderate renal impairment (creatinine clearance (CrCL) 30 to 59 mL/min), mild hepatic impairment (bilirubin \leq ULN and AST $>$ ULN or bilirubin >1.0 to $1.5 \times$ ULN and any AST), or ECOG/WHO status were shown to have no clinically significant effect on the pharmacokinetics parameters in the population PK model of durvalumab.

- **Hepatic Insufficiency:** The effect of moderate hepatic impairment (bilirubin >1.5 to $3 \times$ ULN and any AST) or severe hepatic impairment (bilirubin $>3.0 \times$ ULN and any AST) on the pharmacokinetics of durvalumab is unknown.
- **Renal Insufficiency:** The effect of severe renal impairment (CrCL 15 to 29 mL/min) on the pharmacokinetics of durvalumab is unknown.

11 STORAGE, STABILITY AND DISPOSAL

Store Imfinzi under refrigeration at 2°C to 8°C. Protect Imfinzi from light by storing in the original package until time of use. Do not freeze or shake. If the prepared infusion solution is not administered immediately, it can be stored in the IV bag:

- for up to 30 days under refrigeration at 2°C to 8°C, or
- for up to 12 hours at room temperature at 15°C to 30°C from the time of preparation.

12 SPECIAL HANDLING INSTRUCTIONS

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Durvalumab

Molecular formula and molecular mass: Approximately 149 kDa, including oligosaccharides.

Structural formula: Durvalumab is a fully human monoclonal antibody of the immunoglobulin (Ig) G1 kappa subclass composed of 2 identical heavy chains and 2 identical light chains.

Physicochemical properties: The durvalumab drug substance is a clear to opalescent, colourless to slightly yellow liquid with a density of 1.054 g/mL. The durvalumab drug substance liquid is formulated in buffer (26 mM histidine/histidine-HCl, 275 mM trehalose dihydrate, 0.02% (w/v) polysorbate 80, pH 6.0) at a concentration of 50 mg/mL (nominal). The pI of durvalumab is 8.1-8.8.

Product Characteristics: durvalumab is a human immunoglobulin G1 kappa (IgG1κ) monoclonal antibody that is produced by recombinant DNA technology in Chinese Hamster Ovary (CHO) cell suspension culture.

Pharmaceutical standard: Professed

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Urothelial Carcinoma

The efficacy of IMFINZI (durvalumab for injection), in terms of tumour response rate, was evaluated in a Phase I/II, global, multicenter, multi-cohort, open-label, single-arm clinical trial, Study 1108. In the urothelial carcinoma (UC) cohort, 191 patients received Imfinzi 10 mg/kg every 2 weeks (Q2W). Patients were followed for at least 16 weeks as of the data cut-off date (had tumour assessments at Weeks 6, 12 and 16). The reported efficacy is based on 182 patients with locally advanced or metastatic UC who had progressed during or after a platinum-based therapy, including those patients who progressed within 12 months of receiving therapy in a neo-adjuvant or adjuvant setting (2L+ UC). The remaining 9 patients were treatment naïve/first line. The median duration of follow-up for the 182 patients who had received prior platinum-based chemotherapy was 5.57 months (range: 0.4 to 25.9 months).

Imfinzi 10 mg/kg was administered by intravenous infusion every 2 weeks for up to 12 months or until unacceptable toxicity or confirmed disease progression. In the absence of clinical deterioration, patients in the UC cohort were permitted to continue to receive Imfinzi after confirmed progression of disease if investigators considered that they continued to derive a clinical benefit. The primary efficacy endpoint was Objective Response Rate (ORR) according to RECIST v1.1 as assessed by Blinded Independent Central Review (BICR). The trial excluded patients with a history of immunodeficiency; medical conditions that required systemic immunosuppression; history of severe immune-mediated adverse reactions; untreated CNS metastases; HIV; active tuberculosis, or hepatitis B or C infection. Additional efficacy endpoints included Duration of Response (DoR), Disease-Control Rate (DCR) and Overall Survival (OS).

In Study 1108, tumour specimens were evaluated for PD-L1 expression using the VENTANA PD-L1 (SP263 clone) immunohistochemical assay. Testing was performed prospectively at a

central laboratory by pathologists trained in the use of the SP263 assay for the evaluation of PD-L1 expression. The test detects membrane and cytoplasmic PD-L1 expression by tumour cells (TC) and tumour-associated immune cells (IC). PD-L1 status was determined by the percentage of TC with any membrane PD-L1 staining above background or by the percentage of IC with PD-L1 staining (IC+) at any intensity above background. The percent of tumour area occupied by any tumour-associated immune cells (Immune Cells Present, ICP) is used to determine IC+, which is the percent area of ICP exhibiting PD-L1 positive immune cell staining. PD-L1 status is considered high if any of the following are met:

- $\geq 25\%$ of tumour cells exhibit membrane staining; or,
- ICP $> 1\%$ and IC+ $\geq 25\%$; or,
- ICP $\leq 1\%$ and IC+ = 100%

If none of these criteria were met, PD-L1 status was considered low/negative.

Of the 182 patients that had received prior platinum-based chemotherapy, 95 were classified as PD-L1 high, 73 as PD-L1 low/negative and 14 patients were not evaluable for PD-L1 status.

Trial Design and Study Demographics

Table 14 Summary of Patient Demographics in the UC Cohort of Study 1108 (N=182)

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
CD-ON-MEDI4736-1108	Phase I/II, multicenter, open-label, first-time-in-human, dose-escalation, dose-exploration, and dose-expansion study	10 mg/kg Q2W, intravenous, 12 months	182	66.2 years old	F: 51 (28.0%) M: 131 (72.0%)

In the UC cohort (n = 182), 70% of patients received prior cisplatin, 30% had prior carboplatin and 35% received 2 or more prior lines of systemic therapy. Seventy-four patients (42%) had a baseline creatinine clearance of < 60 mL/min. The median age of patients was 67 years (range: 34 to 88), 72% were male, 71% were Caucasian, 22% were Asian, 4% were Black/African American and 3% were Other. Based on combined independent radiographic assessment and investigator reported data, ninety-two percent (92%) had visceral metastases at study entry, including 43% with liver metastases. Lymph-node-only metastases were present in 8% of patients. Most patients had an ECOG performance status of 1 (66.5%), the remaining had ECOG status of 0 (33.5%). The Bellmunt risk score (which includes ECOG score, baseline hemoglobin, and liver metastases) was 0 in 22%, 1 in 38%, 2 in 30%, and 3 in 11% of patients.

Study Results

Table 15 summarizes the efficacy results for pre-specified analyses.

Overall, the ORR in the UC cohort was 17.6%. Patients with PD-L1 high tumours were associated with numerically increased ORR (27.4%).

Responses occurred early in the treatment. Median time to response was 1.40 months (range: 1.2 to 3.2 months), which coincides with the first protocol-specified imaging assessment. Responses appear durable; median DoR has not yet been reached (range: 0.9+ to 19.9+ months). Among the total 32 responding patients, 75.0% (24/32) had ongoing responses at the time of analysis for ORR (patients with ≥ 13 weeks follow-up), 15 (46.9%) patients had ongoing responses of 6 months or longer in duration, 10 (31.3%) patients had ongoing responses of 9 months or longer in duration and 5 (15.6%) patients had ongoing response of 12 months or longer in duration. Eight patients in the UC cohort did not have ongoing responses at the time of analysis. Seven patients progressed per BICR after an initial response. Of the 7 patients who progressed per BICR after an initial response, 3 patients continued on Imfinzi, and 4 patients completed 12 months of treatment with Imfinzi.

Table 15 Efficacy Results of Study 1108 in the UC Cohort (N=182) and by PD-L1 Status

Efficacy Parameter ^a	All Patients (N=182)	PD-L1 High (N=95)	PD-L1 Low/Negative (N=73)	PD-L1 NE (N=14)
Number of confirmed responders by BICR	32	26	3	3
Objective Response Rate (95% CI)	17.6% (12.3%, 23.9%)	27.4% (18.7%, 37.5%)	4.1% (0.9%, 11.5%)	21.4% (4.7%, 50.8%)
CR, n (%)	6 (3.3%)	4 (4.2%)	1 (1.4%)	1 (7.1%)
PR, n (%)	26 (14.3%)	22 (23.2%)	2 (2.7%)	2 (14.3%)
Median DoR, months, range	NR (0.9+, 19.9+)	NR (0.9+, 19.9+)	12.25 (1.9+, 12.3)	NR (2.3+, 2.6+)

CR = Complete Response; PR = Partial Response; BICR = Blinded Independent Central Review; DoR = Duration of Response; TC = Tumour Cell; IC = Immune Cell; NE = Not Estimable; NR = Not Reached

Overall Response Rate and Duration of Response determined by RECIST v1.1.

Locally Advanced, Unresectable, Stage III Non-Small Cell Lung Cancer

The efficacy of Imfinzi was evaluated in the PACIFIC study, a Phase III, randomized, double-blind, placebo-controlled, multicenter study that enrolled 713 patients with locally advanced, unresectable, Stage III non-small cell lung cancer (NSCLC). Eligible patients had completed at least 2 cycles of definitive platinum-based chemoradiation within 1 to 42 days prior to initiation of the study and had a WHO performance status of 0 or 1. Ninety-two percent of patients had received a total dose of 54 to 66 Gy of radiation.

The study excluded patients who had progressed following chemoradiation therapy, patients with active or prior documented autoimmune disease within 2 years of initiation of the study; a history of immunodeficiency; a history of severe immune-mediated adverse reactions; medical conditions that required systemic immunosuppression; active tuberculosis or hepatitis B or C or HIV infection or patients receiving live attenuated vaccine within 30 days before or after receiving Imfinzi.

Patients were randomized 2:1 to receive 10 mg/kg Imfinzi (n=476) or placebo (n=237) via intravenous infusion every 2 weeks for up to 12 months or until unacceptable toxicity or disease progression. Randomization was stratified by gender, age (<65 years vs. ≥65 years) and smoking status (smoker vs. non-smoker). Tumour assessments were conducted every 8 weeks for the first 12 months and then every 12 weeks thereafter.

Trial Design and Study Demographics

Table 16 Summary of Patient Demographics in Locally Advanced, Unresectable, Stage III NSCLC (PACIFIC)

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
D4191C00001 (PACIFIC)	Phase III, randomized, double-blind, placebo-controlled, multicenter, international study	Imfinzi, Double arm 10 mg/kg Q2W or placebo (2:1) Intravenous infusion	Imfinzi: 476 Placebo: 237	63 years (23-90 years)	Male (70%)

The demographics and baseline disease characteristics were well balanced between study arms (see Table 17).

Patients were enrolled regardless of their tumour PD-L1 expression level. Where available, archival tumour tissue specimens, taken prior to chemoradiation therapy, were retrospectively tested for PD-L1 expression on tumour cells (TC) using the VENTANA PD-L1 (SP263) IHC assay. Of the 713 patients randomized, 63% (n=451) of patients provided a tissue sample of sufficient quality and quantity to determine PD-L1 expression and 37% (n=262) were unknown. Of 451 patients with PD-L1 expression available, 67% were TC ≥1% [PD-L1 TC 1-24% (32%), PD-L1 TC ≥25% (35%)] and 33% were TC <1%.

Table 17 Patient Demographics and Baseline Disease Characteristics, PACIFIC (Full analysis set)

Demographic/Disease Characteristic	PACIFIC	
	Imfinzi (N=476)	Placebo (N=237)
Age (years)		
N	476	237
Mean	63.0	62.6
SD	8.66	9.64
Median	64.0	64.0
Min, max	31, 84	23, 90
Age group (years), n (%)		
<50	30 (6.3)	22 (9.3)
≥50 to <65	231 (48.5)	108 (45.6)

Demographic/Disease Characteristic	PACIFIC	
	Imfinzi (N=476)	Placebo (N=237)
≥65 to <75	178 (37.4)	88 (37.1)
≥75	37 (7.8)	19 (8.0)
Sex, n (%)		
Male	334 (70.2)	166 (70.0)
Female	142 (29.8)	71 (30.0)
Race, n (%)		
Caucasian	337 (70.8)	157 (66.2)
Black or African-American	12 (2.5)	2 (0.8)
Asian	120 (25.2)	72 (30.4)
Other	5 (1.0)	6 (2.5)
Missing	1 (0.2)	0
Weight (kg)		
N	475	236
Mean	71.9	69.4
SD	17.39	15.73
Median	69.0	69.0
Min, Max	34, 175	38, 128
Weight group (kg), n (%)		
<70	243 (51.1)	124 (52.3)
≥70 to ≤90	174 (36.6)	93 (39.2)
>90	58 (12.2)	19 (8.0)
Missing	1 (0.2)	1 (0.4)
Smoking history, n (%)		
Current/Former smoker	433 (91.0)	216 (91.1)
Never smoker	43 (9.0)	21 (8.9)
Baseline WHO, n (%)		
0	234 (49.2)	114 (48.1)
1	240 (50.4)	122 (51.5)
2	0	0
Missing	2 (0.4)	1 (0.4)
Histology type		
Squamous	224 (47.1)	102 (43.0)
Non-squamous	252 (52.9)	135 (57.0)

Demographic/Disease Characteristic	PACIFIC	
	Imfinzi (N=476)	Placebo (N=237)
Staging		
IA/IB	1 (0.2)	2 (0.8)
IIA/IIB	7 (1.4)	3 (1.2)
IIIA	252 (52.9)	125 (52.7)
IIIB	212 (44.5)	107 (45.1)
IV	4 (0.8)	0
Baseline hemoglobin concentration, n (%)		
<10 g/dL	80 (16.8)	35 (15.0)
≥10 g/dL	395 (83.2)	199 (85.0)
Missing	0	0

Max Maximum; Min Minimum; SD Standard deviation

Study Results

Overall survival (OS) and progression-free survival (PFS) were the primary endpoints of the PACIFIC study. Secondary efficacy endpoints included Objective Response Rate (ORR) and Duration of Response (DoR). PFS, ORR and DoR were assessed by Blinded Independent Central Review (BICR) according to RECIST v1.1. Analysis of ORR was based on a sub-group of the intent to treat (ITT) population [Imfinzi (N=443), Placebo (N=213)] with measurable disease at baseline, assessed within 0 – 42 days after chemoradiation and before the start of study drug. Data obtained up to progression or the last evaluable assessment in the absence of progression, were included in the assessment of ORR.

The study demonstrated a statistically significant and clinically meaningful improvement in OS in the Imfinzi-treated group compared with the placebo group [HR = 0.68 (95% CI: 0.53, 0.87), p = 0.00251]. Median OS was not reached in the Imfinzi-treated group and was 28.7 months in the placebo group. The study demonstrated a statistically significant and clinically meaningful improvement in PFS in the Imfinzi-treated group compared with the placebo group [hazard ratio (HR) = 0.52 (95% CI: 0.42, 0.65), p<0.0001]. Median PFS was 16.8 months in the Imfinzi-treated group and 5.6 months in the placebo group. See Table 18 and Figure 1 and Figure 2.

Table 18 Efficacy Results in Locally Advanced, Unresectable, Stage III NSCLC, PACIFIC (Full analysis set)^a

	Imfinzi (N=476)	Placebo (N=237)
OS		
Number of deaths (%)	183 (38.4)	116 (48.9)
Median OS (months) (95% CI)	NR (34.7, NR)	28.7 (22.9, NR)

	Imfinzi (N=476)	Placebo (N=237)
HR (95% CI)	0.68 (0.53, 0.87)	
2-sided p-value ^d	0.00251	
OS at 24 months (95% CI)	66.3 (61.7, 70.4)	55.6 (48.9, 61.8)
p-value ^f	0.005	
PFS^b		
Number of events (%)	214 (45.0)	157 (66.2)
Median PFS (months) (95% CI)	16.8 (13.0, 18.1)	5.6 (4.6, 7.8)
HR (95% CI)	0.52 (0.42, 0.65)	
p-value ^e	p<0.0001	
ORR ^c n (%) (95% CI)	133 (30.0) (25.8, 34.5)	38 (17.8) (13.0, 23.7)
Complete Response n (%)	8 (1.8)	1 (0.5)
Partial Response n (%)	125 (28.2)	37 (17.4)
Median DoR (months) (95% CI)	NR (27.4, NR)	18.4 (6.7, 24.5)

^a The analysis of OS and an updated analysis of ORR and DoR was performed approximately 13 months after the primary analysis of PFS.

^b PFS is defined as the time from the date of randomization until the date of objective disease progression (using BICR according to RECIST 1.1) or death.

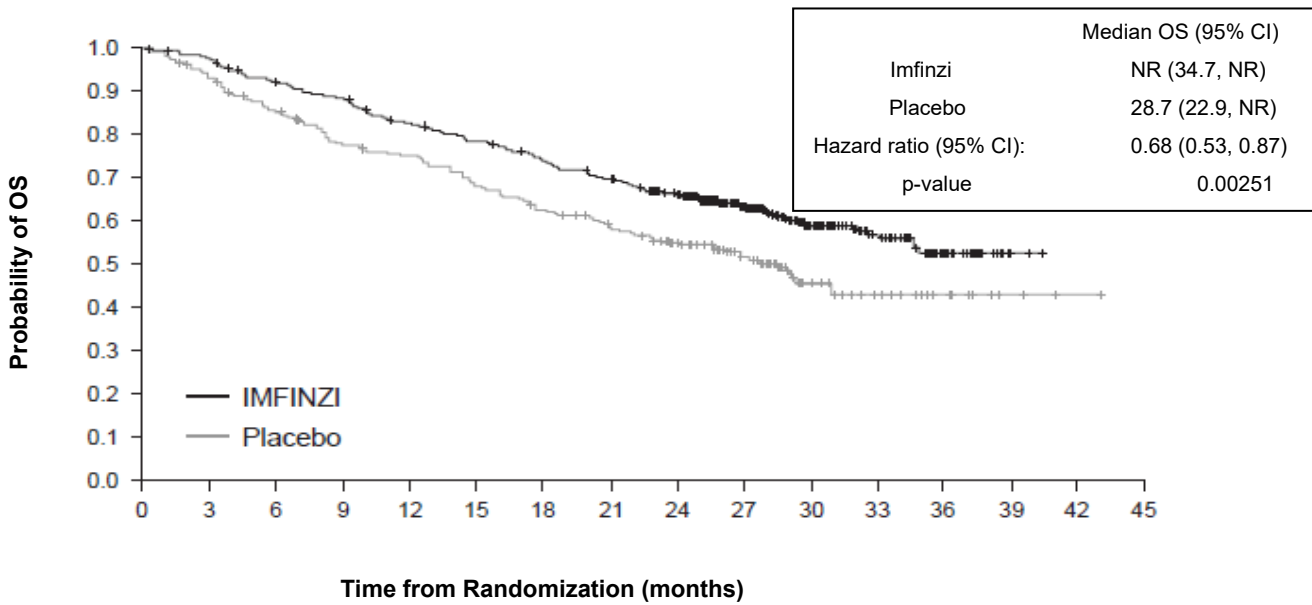
^c Based on sub-group of ITT population with measurable disease at baseline according to RECIST v1.1; Imfinzi (N=443), Placebo (N=213) assessed within 0-42 days after concurrent chemoradiation and before the start of study drug.

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

^e Compared with allocated α of 0.011035 (Lan DeMets spending function approximating O'Brien Fleming boundary) for interim analysis

^f Compared with α of 0.05 following statistically significant PFS and OS at interim analyses
NR = not reached

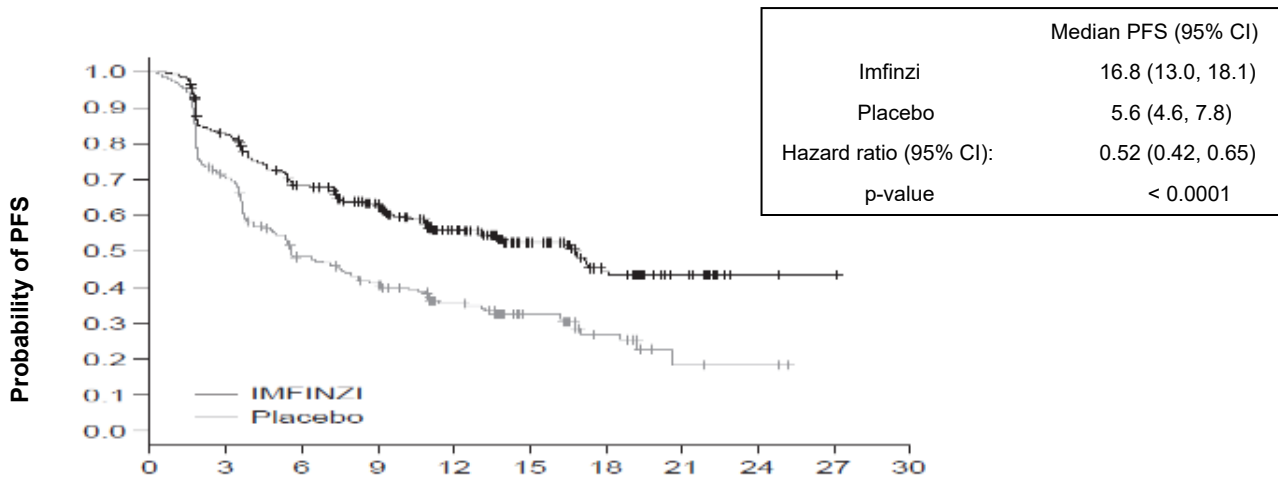
Figure 1 Kaplan-Meier curve of OS (PACIFIC) (Full analysis set)



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

Figure 2 Kaplan-Meier curve of PFS (PACIFIC) (Full analysis set)



Time from Randomization (months)

Number of patients at risk											
Month	0	3	6	9	12	15	18	21	24	27	30
Imfinzi	476	377	301	264	159	86	44	21	4	1	0
Placebo	237	163	106	87	52	28	15	4	3	0	0

The improvements in OS and PFS, in favour of patients receiving Imfinzi compared to those receiving placebo, were consistently observed across all prespecified subgroups.

There were no clinically meaningful differences between Imfinzi-treated vs. placebo-treated patients in disease-related symptoms deterioration and health-related quality of life.

Exploratory post-hoc subgroup analysis by PD-L1 expression

Additional exploratory post-hoc subgroup analyses were conducted to evaluate efficacy by pre-chemoradiation tumour PD-L1 expression ($\geq 25\%$, 1-24%, $\geq 1\%$, $< 1\%$) and for patients whose PD-L1 status could not be established (PD-L1 unknown). Due to the overall exploratory nature of this subgroup analysis performed without any pre-specified statistical adjustment, definitive conclusions cannot be drawn. PFS and OS results, by PD-L1 expression level, are summarized in Figures 3 and 4, respectively.

Several limitations are associated with exploratory, post-hoc analyses. Limitations include the absence of methods to control the type I error rate, small sample sizes and the potential for low event rates by subgroup. In addition, subgroups are not protected by randomization and may be subject to bias due to imbalances in patient demographics and disease characteristics. The results should be interpreted with caution. Imfinzi is indicated for locally advanced, unresectable Stage III NSCLC regardless of PD-L1 status based on statistically significant and clinically meaningful improvements in OS and PFS observed in the ITT population.

Overall the safety profile of durvalumab in PD-L1 TC $\geq 1\%$ subgroup was consistent with the intent to treat population, as was the PD-L1 TC $< 1\%$ subgroup.

Figure 3 Forest Plot of PFS by PD-L1 expression

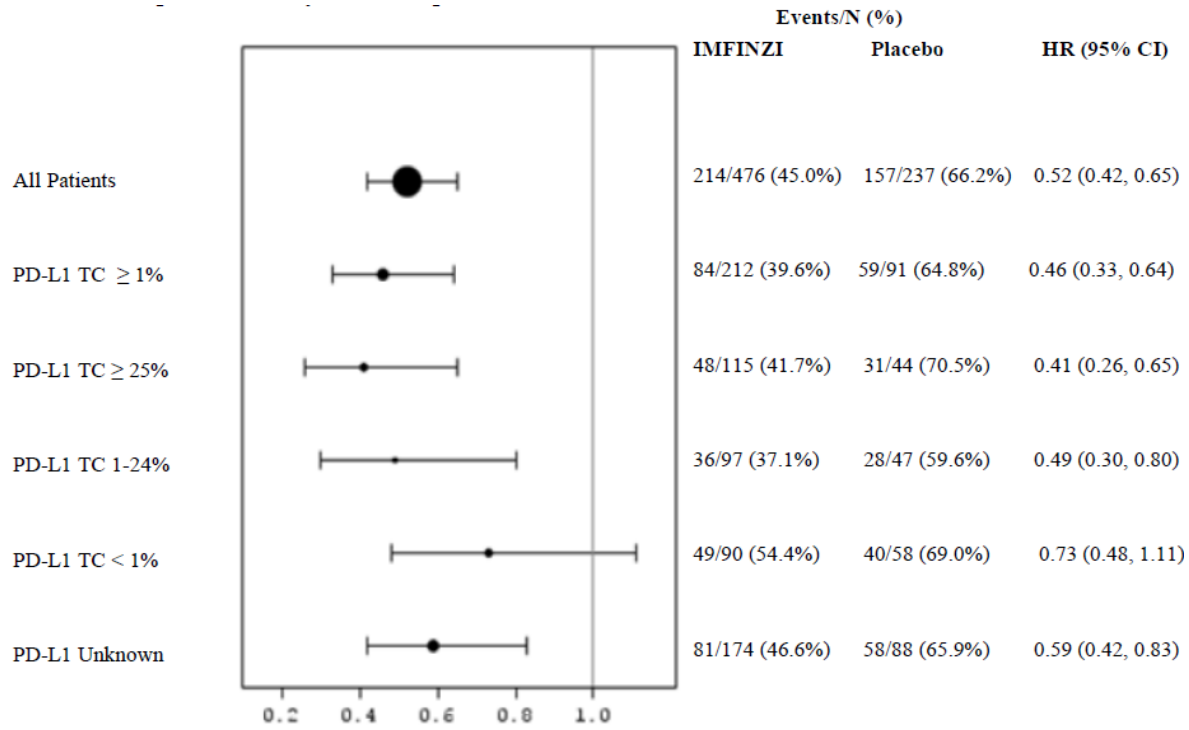
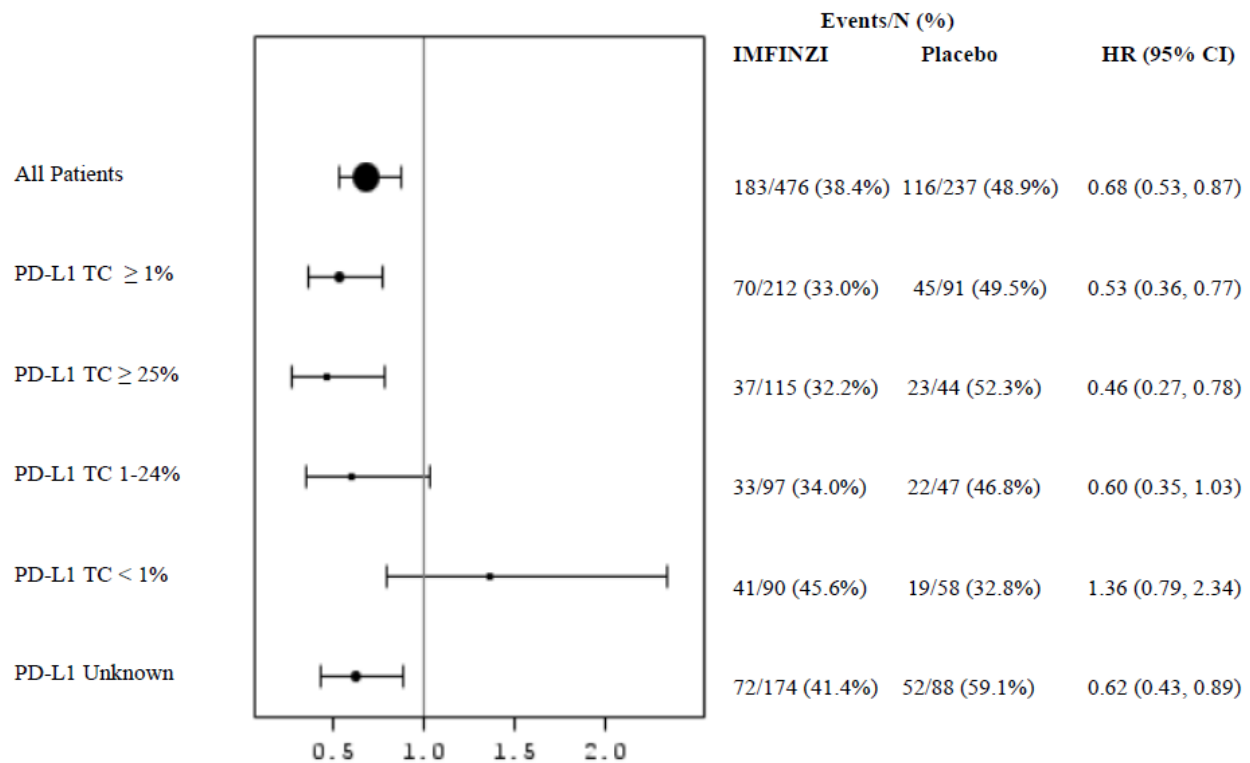


Figure 4 Forest Plot of OS by PD-L1 expression



Extensive-Stage Small Cell Lung Cancer (ES-SCLC)

The efficacy of Imfinzi in combination with etoposide and either carboplatin or cisplatin was investigated in CASPIAN, a randomized, open-label, multicenter study in treatment-naïve ES-SCLC patients. Eligible patients had WHO/ECOG Performance status of 0 or 1, suitable to receive a platinum-based chemotherapy regimen as first-line treatment for SCLC, a life expectancy \geq 12 weeks, at least one target lesion by RECIST 1.1 and adequate organ and bone marrow function. Patients with asymptomatic or treated brain metastases were eligible. The study excluded patients with a history of chest radiation therapy; prior exposure to immune checkpoint inhibitors; a history of allogeneic organ transplantation; a history of active primary immunodeficiency; autoimmune disorders including paraneoplastic syndrome (PNS); 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; active tuberculosis or hepatitis B or C or HIV infection; or patients receiving live attenuated vaccine within 30 days before or after the start of Imfinzi.

Randomization (see Table 19) was stratified by the planned platinum-based therapy in cycle 1 (carboplatin or cisplatin).

Administration of Imfinzi monotherapy was permitted beyond disease progression if the patient was clinically stable and deriving clinical benefit as determined by the investigator.

Trial Design and Study Demographics

Table 19 Summary of Patient Demographics in ES-SCLC (CASPIAN)

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
D419QC00001 (CASPIAN)	Phase III, randomized, open-label, multicenter study	Imfinzi 1500 mg + etoposide and either carboplatin or cisplatin ^a or etoposide and either carboplatin or cisplatin ^b	537	63 years (28-82 years)	M: 374 (69.6%) F: 163 (30.4%)

^a Imfinzi 1500 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 1500 mg every 4 weeks until disease progression or unacceptable toxicity

^b 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) may be administered per investigator discretion.

Additional demographics and baseline disease characteristics are presented in Table 20.

Table 20 Patient Demographics and Baseline Disease Characteristics, CASPIAN (Full Analysis Set)

Demographic/Disease Characteristic	CASPIAN	
	Imfinzi + etoposide and either carboplatin or cisplatin (N=268)	etoposide and either carboplatin or cisplatin (N=269)
Age group (years), n (%)		
<50	10 (3.7)	20 (7.4)
≥50 to <65	157 (58.6)	137 (50.9)
≥65 to <75	82 (30.6)	90 (33.5)
≥75	19 (7.1)	22 (8.2)
Race, n (%)		
Caucasian	229 (85.4)	221 (82.2)
Black or African-American	2 (0.7)	3 (1.1)
Asian	36 (13.4)	42 (15.6)
Other	1 (0.4)	2 (0.7)
Missing	0	1 (0.4)
Smoking/nicotine history, n (%)		
Current smoker	120 (44.8)	126 (46.8)
Former smoker	126 (47.0)	128 (47.6)
Never smoker	22 (8.2)	15 (5.6)

Demographic/Disease Characteristic	CASPIAN	
	Imfinzi + etoposide and either carboplatin or cisplatin (N=268)	etoposide and either carboplatin or cisplatin (N=269)
WHO/ECOG performance status, n (%)		
(0) Normal activity	99 (36.9)	90 (33.5)
(1) Restricted activity	169 (63.1)	179 (66.5)
Brain/CNS metastases	28 (10.4)	27 (10.0)
Staging ^a		
III ^b	1 (0.4)	0
IIIA	5 (1.9)	3 (1.1)
IIIB	22 (8.2)	21 (7.8)
IV	240 (89.6)	245 (91.1)

^a AJCC staging: Stage IV combines Stage IV/Stage IVA/Stage IVB from eCRF [PATHGEN] module.

^b For the 1 Stage III patient, the TNM indicated Stage IIIb although the data were not reported this way.

Of all randomized patients, 24.6% received cisplatin and 74.1% received carboplatin. In the chemotherapy group, 56.8% of the patients received 6 cycles of treatment and 7.8% of patients received PCI.

Study Results

The primary efficacy endpoint supporting the ES-SCLC indication was overall survival (OS) of Imfinzi + chemotherapy versus chemotherapy alone. Additional efficacy outcome measures include progression-free survival (PFS) and investigator-assessed objective response rate (ORR), per RECIST v1.1.

The study demonstrated a statistically significant improvement in OS with Imfinzi + chemotherapy vs. chemotherapy alone (HR=0.73 [95% CI: 0.591, 0.909], p=0.0047).

The OS results are summarized in Table 21.

Table 21 OS Results in ES-SCLC Patients Treated with Imfinzi in Combination with Etoposide and Carboplatin or Cisplatin in the CASPIAN Study

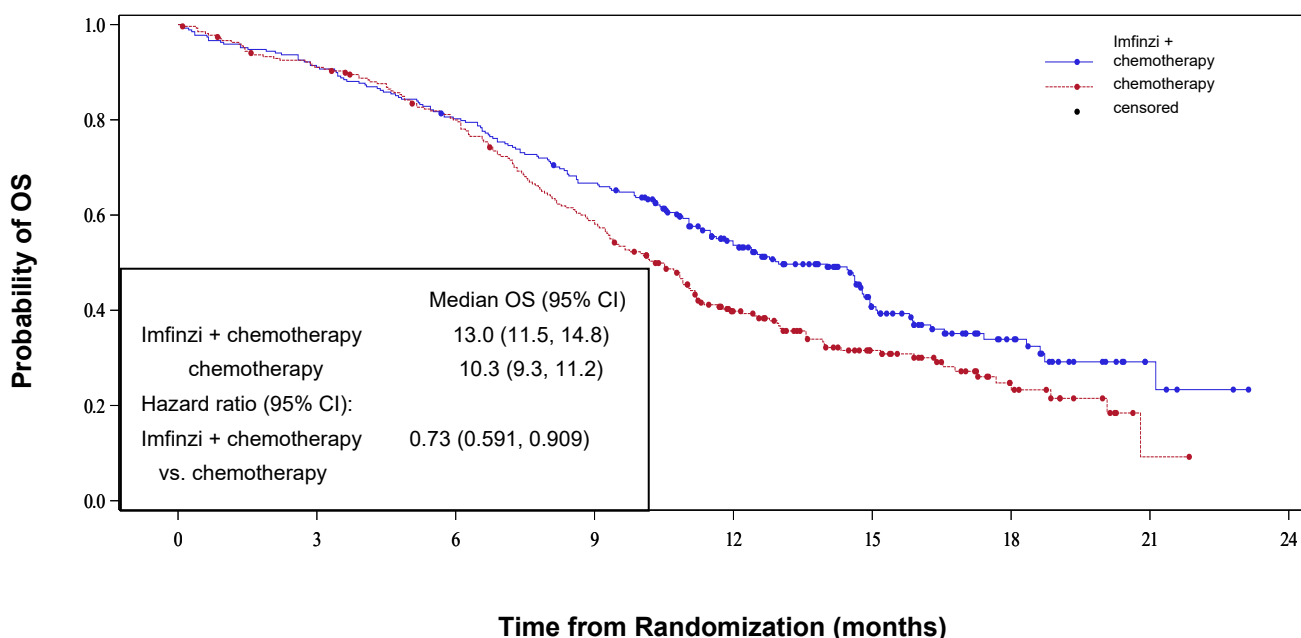
	Imfinzi + etoposide and either carboplatin or cisplatin (N=268)	Etoposide and either carboplatin or cisplatin (N=269)
OS		
Number of deaths (%)	155 (57.8)	181 (67.3)
Median OS (months) (95% CI)	13.0 (11.5, 14.8)	10.3 (9.3, 11.2)

HR (95% CI) ^a	0.73 (0.591, 0.909)
p-value ^b	0.0047

^a 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.

^b 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.

Figure 5 Kaplan-Meier curve of OS (CASPIAN)



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 an 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.

Locally Advanced or Metastatic Biliary Tract Cancer

TOPAZ-1 (D933AC00001) was a study designed to evaluate the efficacy of Imfinzi in combination with chemotherapy (gemcitabine and cisplatin). TOPAZ-1 was a phase III, randomised, double-blind, placebo-controlled, multicentre study in 685 patients with histologically confirmed locally advanced or metastatic BTC and ECOG performance status of 0 or 1. Patients who developed recurrent disease more than 6 months after surgery and/or completion of adjuvant therapy were included. Patients must have had at least one target lesion by RECIST v1.1 and adequate organ and bone marrow function.

The study excluded patients with ampullary carcinoma, active or prior documented autoimmune or inflammatory disorders, HIV infection or active infections, including tuberculosis or hepatitis C or patients with current or prior use of immunosuppressive medication within 14 days before the first dose of Imfinzi.

Randomisation (see Table 22) was stratified by disease status and primary tumour location.

Tumour assessments were conducted every 6 weeks for the first 24 weeks after the date of randomisation, and then every 8 weeks until confirmed objective disease progression.

Trial Design and Study Demographics

Table 22 Summary of Patient Demographics in BTC (TOPAZ-1)

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
D933AC00001 (TOPAZ-1)	Phase III, randomized, double-blind placebo controlled, multi-centre, international study	gemcitabine and cisplatin + Imfinzi 1500 mg ^a or gemcitabine and cisplatin + Placebo ^b	685	62 years (20-84 years)	M: 345 (50.4%) F: 340 (49.6%)

^a Imfinzi 1500 mg administered intravenously on Day 1+ gemcitabine 1000 mg/m² and cisplatin 25 mg/m² (each administered on Days 1 and 8) every 3 weeks (21 days) for up to 8 cycles, followed by Imfinzi 1500 mg every 4 weeks as long as clinical benefit is observed or until unacceptable toxicity

^b Placebo administered intravenously on Day 1+ gemcitabine 1000 mg/m² and cisplatin 25 mg/m² (each administered on Days 1 and 8) every 3 weeks (21 days) for up to 8 cycles, followed by placebo every 4 weeks as long as clinical benefit is observed or until unacceptable toxicity.

The demographics and baseline disease characteristics were well balanced between the two study arms (341 patients in Arm 1 and 344 patients in Arm 2). Baseline demographics of the overall study population were as follows: male (50.4%), age <65 years (53.3%), white (37.2%), Asian (56.4%), black or African American (2.0%), other (4.2%), ECOG PS 0 (49.1%), vs. PS 1 (50.9%), primary tumour location [intrahepatic cholangiocarcinoma(55.9%), extrahepatic cholangiocarcinoma (19.1%) and gallbladder cancer (25.0%)], disease status [recurrent (19.1%) vs. initially unresectable (80.7%), metastatic (86.0%) vs locally advanced (13.9%)].

The primary endpoint of the study was OS and the key secondary endpoint was PFS. Other secondary endpoints were ORR, DoR and PRO. PFS, ORR and DoR were Investigator assessed according to RECIST v1.1.

Study Results

Imfinzi + chemotherapy (Arm 1) demonstrated a clinically meaningful and statistically significant improvement vs. placebo + chemotherapy (Arm 2) in OS [HR=0.80, (95% CI: 0.66, 0.97), p=0.021] and in PFS [HR=0.75, (95% CI: 0.63, 0.89), p=0.001]. Results are summarized in Table 23 and Figure 6.

Table 23 Efficacy Results for the TOPAZ-1 Study

	Imfinzi + gemcitabine and cisplatin (n=341)	Placebo + gemcitabine and cisplatin (n=344)
OS		
Number of deaths (%)	198 (58.1)	226 (65.7)
Median OS (months) (95% CI)^a	12.8 (11.1, 14)	11.5 (10.1, 12.5)
HR (95% CI) ^b	0.80 (0.66, 0.97)	
p-value ^b	0.021	
PFS		
Number of events (%)	276 (80.9)	297 (86.3)
Median PFS (months) (95% CI)^a	7.2 (6.7, 7.4)	5.7 (5.6, 6.7)
HR (95% CI) ^b	0.75 (0.63, 0.89)	
p-value ^b	0.001	
ORR n (%)^c	91 (26.7)	64 (18.7)

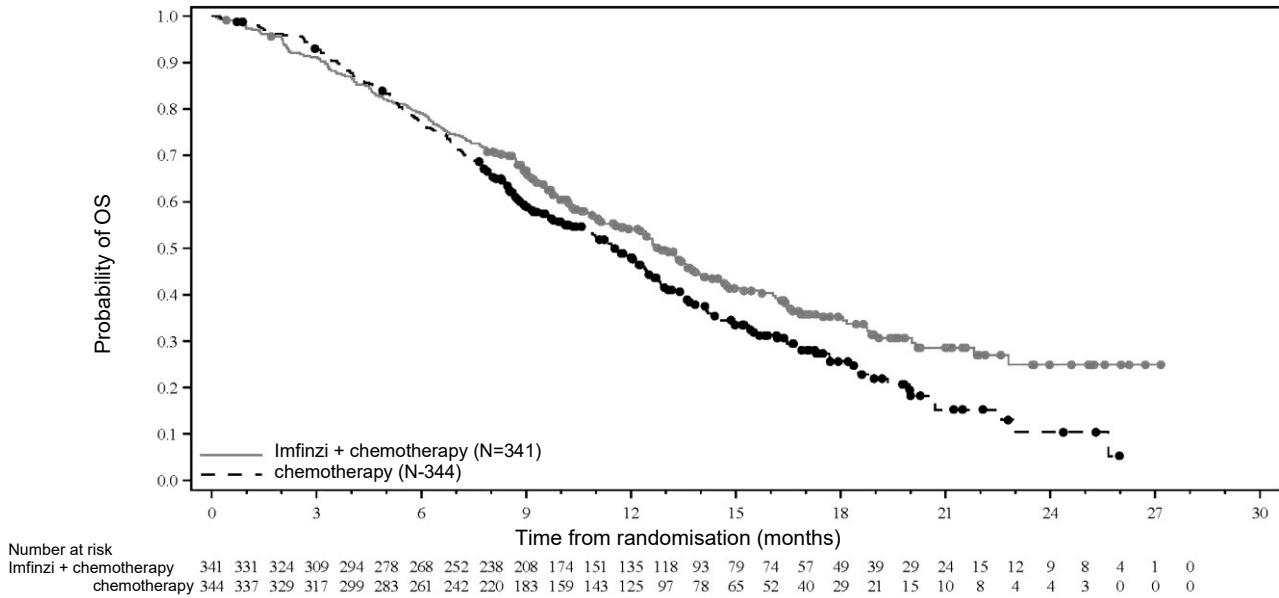
OS and PFS were formally tested at a pre-planned interim analysis. The maturity for OS was 62% and the maturity for PFS was 84%.

^a Calculated using the Kaplan-Meier technique. CI for median derived based on Brookmeyer-Crowley method.

^b The analysis for HR was performed using a stratified Cox proportional hazards model and 2-sided p-value is based on a stratified log-rank test, both are adjusted for disease status and primary tumor location.

^c Confirmed objective response

Figure 6 Kaplan-Meier curve of OS (IA2)



Unresectable Hepatocellular Carcinoma

Trial Design and Study Demographics

The efficacy of Imfinzi and Imfinzi in combination with tremelimumab was evaluated in the HIMALAYA study, a randomised, open-label, multicenter study in patients with confirmed uHCC who did not receive prior systemic treatment for HCC. The study included patients with BCLC Stage C or B (not eligible for locoregional therapy), Child-Pugh Score Class A, and ECOG performance status of 0 or 1.

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; main portal vein thrombosis; history of or current brain metastases or spinal cord compression; active or prior documented autoimmune or inflammatory disorders; history of allogeneic organ transplantation (e.g., liver transplant), and Child-Pugh Score Class B and C. Patients did not require an esophagogastroduodenoscopy prior to enrollment. For patients with a history of GI bleeding for more than 12 months or assessed as high risk for esophageal varices by the Investigator, adequate endoscopic therapy according to institutional standards was required.

Patients were randomized (1:1:1) to the Imfinzi plus tremelimumab arm, the Imfinzi alone arm and the sorafenib arm (See Table 24). Randomisation was stratified by macrovascular invasion (MVI) (yes vs. no), etiology of liver disease (confirmed hepatitis B virus vs. confirmed hepatitis C virus vs. others) and ECOG performance status (0 vs. 1).

Table 24 Summary of Patient Demographics in Unresectable Hepatocellular Carcinoma (HIMALAYA)

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (range)	Sex
D419CC00002 (HIMALAYA)	Phase III, randomized, open-label, multicenter, international study	Imfinzi in combination with tremelimumab: tremelimumab 300 mg as a single priming dose + Imfinzi 1500 mg; followed by Imfinzi 1500 mg every 4 weeks, intravenous Or Imfinzi 1500 mg every 4 weeks, intravenous Or sorafenib 400 mg twice daily, oral	Imfinzi in combination with tremelimumab: 393 Imfinzi monotherapy: 389 sorafenib: 389	63 years (18-88 years)	Male: 987/1171 (84.3%) Female: 184/1171 (15.7%)

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

The primary objective was to assess the overall survival (OS) between the Imfinzi plus tremelimumab arm versus the sorafenib arm for superiority. The key secondary objectives were to assess OS between the Imfinzi arm versus the sorafenib arm for non-inferiority followed by superiority. Other secondary endpoints included investigator-assessed progression-free survival (PFS) according to RECIST v 1.1. Tumor assessments were conducted every 8 weeks for the first 12 months and then every 12 weeks thereafter.

The baseline demographics of the overall study population were as follows: male (83.7%), age <65 years (50.4%), median age of 64 years (range: 18 to 88 years), white (44.6%), Asian (50.7%), black or African American (1.7%), ECOG PS 1 (37.2%), Child-Pugh Class score A (99.5%), BCLC Stage B (19.2%), BCLC Stage C (80.8%), macrovascular invasion (25.2%), extrahepatic spread (53.4%), viral etiology [hepatitis B (30.6%), hepatitis C (27.2%), uninfected (42.2%)], Albumin-Bilirubin (ALBI) score 2 (46.8%), ALBI score 3 (0.5%) and alpha-fetoprotein (AFP) ≥ 400 ng/mL (34.5%).

Study Results

The efficacy results for Imfinzi plus tremelimumab vs sorafenib, and Imfinzi monotherapy vs sorafenib are presented in Table 25 and Figure 7.

Table 25 Efficacy Results in Unresectable Hepatocellular Carcinoma, HIMALAYA (Full analysis set)

	Imfinzi plus tremelimumab (n=393)	Imfinzi monotherapy (n=389)	Sorafenib (n=389)
Follow up duration			
Median follow up (months)	33.2	32.6	32.2
Range	31.7-34.5	31.6-33.7	30.4-33.7
OS			
Number of deaths (%)	262 (66.7)	280 (72.0)	293 (75.3)
Median OS (months) (95% CI)	16.4 (14.2-19.6)	16.6 (14.1-19.1)	13.8 (12.3-16.1)
HR vs sorafenib (95% CI) ^a	0.76 (0.64, 0.90)	0.83 (0.70, 0.98)	-
p-value ^b	0.0013 ^c	0.0293 ^{d,e}	-
PFS			
Number of events (%)	335 (85.2)	345 (88.7)	327 (84.1)
Median PFS (months) (95% CI)	3.78 (3.68-5.32)	3.65 (3.19-3.75)	4.07 (3.75-5.49)
HR vs sorafenib (95% CI) ^a	0.89 (0.76, 1.04)	1.00 (0.86, 1.17)	-

^a Based on a stratified Cox proportional hazard model adjusting for baseline covariates (Extrahepatic Spread, Albumin-Bilirubin score, Alpha Fetoprotein, and Barcelona Clinic Liver Cancer Staging).

^b A hierarchical procedure was used to control overall type I error.

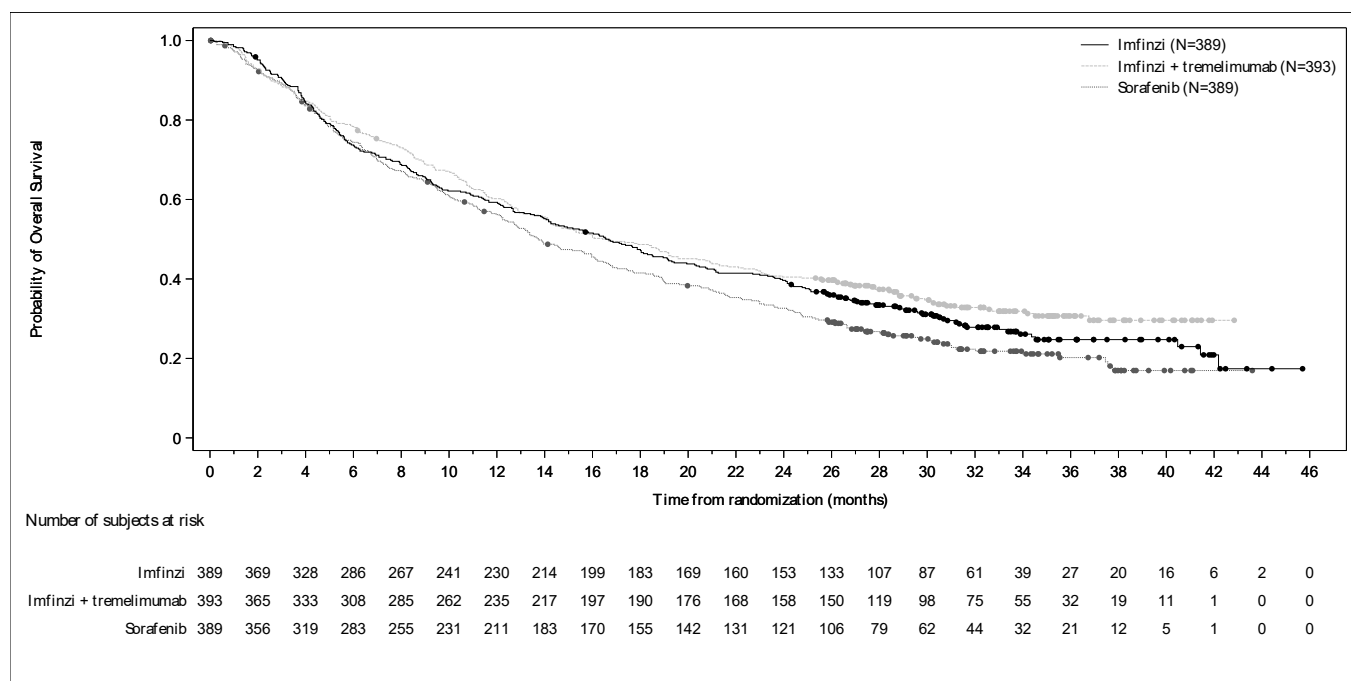
^c Statistically significant superiority for Imfinzi in combination with tremelimumab compared with sorafenib.

^d When compared to sorafenib, Imfinzi monotherapy met the pre-defined non-inferiority margin of 1.08.

^e Additional analysis, which adjusted for baseline covariates, demonstrated clinically meaningful treatment benefit in terms of OS for Imfinzi monotherapy compared to sorafenib.

NR=Not Reached, CI=Confidence Interval

Figure 7 Kaplan-Meier curve of OS for Imfinzi monotherapy and Imfinzi in combination with tremelimumab vs sorafenib (Full analysis set)



In an exploratory OS analysis, controlling for EHS, ALBI, Alpha-Fetoprotein and BCLC staging, between the Imfinzi plus tremelimumab arm versus the sorafenib arm for the subgroups defined by the stratification factor of etiology status (HCV, HBV and Others), the HRs are 0.92 (95% CI: 0.65, 1.30), 0.60 (95% CI: 0.44, 0.81) and 0.78 (95% CI: 0.60, 1.01), respectively. In an exploratory OS analysis, controlling for EHS, ALBI, Alpha-Fetoprotein and BCLC staging, between the Imfinzi monotherapy arm versus the sorafenib arm for the subgroups defined by the stratification factor of etiology status (HCV, HBV and Others), the HRs are 0.94 (95% CI: 0.67, 1.32), 0.77 (95% CI: 0.57, 1.03) and 0.80 (95% CI: 0.62, 1.03), respectively.

14.4 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. Immunogenicity of Imfinzi as monotherapy is based on pooled data in 2280 patients who were treated with Imfinzi 10 mg/kg every 2 weeks or 20 mg/kg every 4 weeks as a single-agent and evaluable for the presence of anti-drug antibodies (ADA). Sixty-nine patients (3.0%) tested positive for treatment emergent ADA. Neutralizing antibodies against durvalumab were detected in 0.5% (12/2280) patients. The presence of ADAs did not appear to have a clinically relevant effect on pharmacokinetics, pharmacodynamics or safety.

In the CASPIAN study, of the 201 patients who were treated with Imfinzi 1500 mg every 3 weeks in combination with chemotherapy and evaluable for the presence of ADAs, no patients tested positive for treatment-emergent ADAs.

In the TOPAZ-1 study, 240 patients were treated with Imfinzi 1500 mg every 3 weeks in combination with chemotherapy followed by Imfinzi 1500 mg every 4 weeks, and were evaluable for the presence of ADAs. Within that group of patients 2 (0.8%) tested positive for treatment-emergent ADAs. There were insufficient numbers of patients with treatment emergent

ADAs (2 patients) or neutralizing antibodies (2 patients) to determine whether ADAs have an impact on pharmacokinetics and clinical safety of durvalumab.

In the HIMALAYA study, of the 294 patients who were treated with Imfinzi in combination with tremelimumab and evaluable for the presence of ADAs, 9 (3.1%) patients tested positive for treatment-emergent ADAs. Neutralizing antibodies against durvalumab were detected in 1.7% (5/294) patients. The presence of ADAs did not have an apparent effect on pharmacokinetics or safety.

In the HIMALAYA study, of the 282 patients who were treated with Imfinzi monotherapy and evaluable for the presence of ADAs, 8 (2.8%) patients tested positive for treatment-emergent ADAs. Neutralizing antibodies against durvalumab were detected in 0.7% (2/282) patients. The presence of ADAs did not have an apparent effect on the pharmacokinetics or safety.

Immunogenicity assay results are highly dependent on several factors, including assay sensitivity and specificity, assay methodology, sample handling, timing of sample collection, concomitant medications and underlying disease. For these reasons, comparison of incidence of antibodies to Imfinzi with the incidence of antibodies to other products may be misleading.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

Carcinogenicity: The carcinogenic potential of durvalumab have not been evaluated.

Genotoxicity: The genotoxic potential of durvalumab have not been evaluated.

Reproductive and Developmental Toxicology: 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, and in mouse allogeneic pregnancy models disruption of PD-L1 signaling was shown to result in an increase in fetal loss. In reproduction studies in cynomolgus monkeys, administration of Imfinzi (durvalumab) from the confirmation of pregnancy through delivery at exposure levels approximately 6 to 20 times higher than those observed at the clinical dose of 10 mg/kg of Imfinzi (based on AUC) was associated with premature delivery, fetal loss (abortion and stillbirth) and an increase in neonatal deaths compared to concurrent control. Based on the 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 the literature in PD-1 knockout mice. In animal models reported in the literature, inhibition of PD-L1/PD-1 signaling increased the severity of some infections and enhanced inflammatory responses.

17 SUPPORTING PRODUCT MONOGRAPHS

1. Carboplatin Injection BP (sterile solution, 10 mg/mL), submission control number 274117, Product Monograph, Pfizer Canada ULC. (Aug 23, 2023)
2. Cisplatin Injection BP (sterile solution, 1 mg/mL), submission control number 275069, Product Monograph, Pfizer Canada ULC. (Oct 24, 2023)
3. Vepesid (etoposide capsules, 50 mg), submission control number 233295, Product Monograph, CHEPLAPHARM Arzneimittel GmbH. (Dec 18, 2019)

4. Imjudo (tremelimumab for injection, concentrate for solution for infusion, 20 mg/mL), submission control 282758, Product Monograph, AstraZeneca Canada Inc. May 13, 2024)

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE



durvalumab for injection, intravenous infusion

Read this carefully before you start treatment with **IMFINZI** and each time you get an infusion. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **Imfinzi**.

Serious Warnings and Precautions

Imfinzi in combination with tremelimumab or alone can cause serious side effects which can lead to death. These serious side effects may include: inflammation of the intestines (enterocolitis) that can cause tears or holes (perforation) in the intestines; inflammation of the liver (hepatitis) that can lead to liver failure; inflammation of the skin that can lead to severe skin reaction (Stevens-Johnson syndrome); inflammation of hormone glands that may affect how these glands work; inflammation of the lung tissue (pneumonitis or interstitial lung disease); inflammation of the heart muscle (myocarditis); inflammation of the brain (encephalitis); neuromuscular disease that leads to skeletal muscle weakness (myasthenia gravis). Side effects have occurred at lower frequencies when Imfinzi was given alone compared with Imfinzi in combination with tremelimumab. Please see **What are possible side effects from using Imfinzi?**

What is Imfinzi used for?

Bladder Cancer

Imfinzi is a medicine used to treat a type of bladder cancer (called urothelial carcinoma) including cancer of the ureter, urethra or kidney pelvis. It is used when:

- Your cancer has spread and cannot be removed by surgery and,
- You have received chemotherapy, and it did not work or is no longer working.

Lung Cancer

Imfinzi is used to treat a type of lung cancer called non-small cell lung cancer. It is used when:

- Your cancer has grown within your lung and cannot be removed by surgery and,
- Your cancer has responded or stabilized after treatment with chemotherapy and radiation therapy.

Imfinzi is used to treat adults with a type of lung cancer called extensive-stage small cell lung cancer (ES-SCLC). It is used when:

- Your cancer has spread within your lungs (or to other parts of the body) and,
- You have not previously been treated.

Imfinzi will be given in combination with chemotherapy for SCLC. It is important that you also read the package insert for the specific chemotherapy you may be receiving. If you have any questions about these medicines, ask your doctor.

Biliary Tract Cancer

Imfinzi is used to treat adults with a type of cancer called biliary tract cancer (BTC), including cancer of the bile ducts (cholangiocarcinoma) and gallbladder. It is used when your BTC

- Has spread within these regions or to other parts of the body

Imfinzi will be given in combination with chemotherapy for BTC. It is important that you also read the package insert for the specific chemotherapy you may be receiving. If you have any questions about these medicines, ask your doctor.

Imfinzi contains the active substance durvalumab which belongs to the monoclonal antibody class of anticancer medicines. Refer to the NOC/c summary box below for additional detail.

Liver Cancer

Imfinzi alone or in combination with tremelimumab is used to treat a type of liver cancer, called hepatocellular carcinoma (HCC), when your liver cancer:

- cannot be removed by surgery (unresectable) and requires medication,
- may have spread within your liver or to other parts of the body, and
- you have not received other medicines to treat your liver cancer.

If you are given Imfinzi in combination with IMJUDO (tremelimumab), it is important that you also read the PATIENT MEDICATION INFORMATION for both medications.

For the following indication, Imfinzi has been approved with conditions (NOC/c). This means it has passed Health Canada's review and can be bought and sold in Canada, but the manufacturer has agreed to complete more studies to make sure the drug works the way it should. For more information, talk to your healthcare professional.

Imfinzi is used to treat a type of bladder cancer (called urothelial carcinoma) including cancer of the ureter, urethra or kidney pelvis. It is used when:

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- You have received chemotherapy, and it did not work or is no longer working.

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- You have not previously been treated.

Imfinzi is used to treat a type of cancer called biliary tract cancer (BTC), including cancer of the bile ducts (cholangiocarcinoma) and gallbladder. It is used when your BTC:

- Has spread within these regions or to other parts of the body.

Imfinzi alone or in combination with tremelimumab is used to treat a type of liver cancer, called hepatocellular carcinoma (HCC), when your liver cancer:

- cannot be removed by surgery (unresectable) and requires medication,
- may have spread within your liver or to other parts of the body, and
- you have not received other medicines to treat your liver cancer.

Imfinzi will be given in combination with chemotherapy for SCLC and BTC. It is important that you also read the package insert for the specific chemotherapy you may be receiving. If you have any questions about these medicines, ask your doctor.

What is a Notice of Compliance with Conditions (NOC/c)?

A Notice of Compliance with Conditions (NOC/c) is a type of approval to sell a drug in Canada.

Health Canada only gives an NOC/c to a drug that treats, prevents, or helps identify a serious or life-threatening illness. The drug must show promising proof that it works well, is of high quality, and is reasonably safe. Also, the drug must either respond to a serious medical need in Canada, or be much safer than existing treatments.

Drug makers must agree in writing to clearly state on the label that the drug was given an NOC/c, to complete more testing to make sure the drug works the way it should, to actively monitor the drug's performance after it has been sold, and to report their findings to Health Canada.

How does Imfinzi work?

- Imfinzi works by helping your immune system fight your cancer.
- Imfinzi can help slow or stop your cancer from growing. It can also help shrink the tumour.
 - The average time to respond to Imfinzi for a bladder cancer patient is approximately 1.5 months. However, this may vary from patient to patient.

If you have any questions about how Imfinzi works or why this medicine has been prescribed for you, ask your healthcare professional.

What are the ingredients in Imfinzi?

Medicinal ingredient: durvalumab.

Non-medicinal ingredients: L-histidine, L-histidine hydrochloride monohydrate, α , α -trehalose dihydrate, polysorbate 80, and water for injection.

Imfinzi comes in the following dosage forms:

A solution in 10 mL single-use glass vials containing either 2.4 mL or 10 mL of 50 mg/mL durvalumab. After further dilution and preparation, Imfinzi is administered as an intravenous infusion.

Do not use Imfinzi if:

- You are allergic to durvalumab or any other ingredients in Imfinzi.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Imfinzi. Talk about any health conditions or problems you may have, including if you:

- Have immune system problems such as Crohn's disease, ulcerative colitis, or lupus
- Have had an organ transplant
- Have lung or breathing problems
- Have liver problems
- Have problems with hormone producing glands such as your thyroid, pituitary, adrenal glands or pancreas
- Have diabetes
- Are taking medicine(s) that affect the immune system such as a steroid

When you receive Imfinzi, you can have some serious side effects.

Imfinzi can cause your immune system to attack normal organs and tissues in your body and can affect the way they work.

Other warnings you should know about:

Pregnancy

- If you are pregnant, think you may be pregnant or are planning to have a baby, tell your doctor before taking this medicine. You should not use Imfinzi if you are pregnant.
- Imfinzi can harm your unborn baby.
- If you are a woman who could become pregnant, you should use an effective method of birth control during your treatment and for at least 3 months after the last dose of Imfinzi.

Breastfeeding

- If you are breastfeeding or plan to breastfeed, tell your doctor.

- Do not breastfeed during treatment and for at least 3 months after the last dose of Imfinzi. It is not known if Imfinzi passes into your breast milk.

Driving and using machines

If you experience side effects affecting your ability to concentrate and react, do not drive or use machines until you feel better.

Tell your healthcare professional about all the medicines you take including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with Imfinzi:

No drug-drug interactions are expected with Imfinzi.

How to take Imfinzi:

- Imfinzi will be given to you in a hospital or clinic under the supervision of an experienced healthcare professional. Your healthcare professional will give you Imfinzi through an intravenous infusion into your vein for about 60 minutes.
- Your doctor will decide how many treatments you need.

If you have any questions about your treatment, ask your doctor.

Usual dose:

Urothelial carcinoma

The recommended dose is 10 mg of durvalumab per kg of your body weight every 2 weeks or 1500 mg every 4 weeks. Imfinzi is given on its own.

Non-small cell lung cancer

The recommended dose is 10 mg of durvalumab per kg of your body weight every 2 weeks or 1500 mg every 4 weeks. Imfinzi is given on its own.

Extensive-stage small cell lung cancer (ES-SCLC)

The recommended dose is 1500 mg of durvalumab every 3 weeks for a total of 4 doses in combination with chemotherapy. Thereafter, Imfinzi is given on its own and the recommended dose of Imfinzi is 1500 mg every 4 weeks.

Biliary Tract Cancer (BTC)

The recommended dose is 1500 mg of durvalumab in combination with chemotherapy every 3 weeks. Thereafter, Imfinzi is given on its own and the recommended dose is 1500 mg every 4 weeks.

Liver Cancer

Imfinzi in combination with tremelimumab:

The recommended dose of tremelimumab is 300 mg as a single dose, followed by durvalumab 1500 mg at Day 1 of Cycle 1. Continue durvalumab 1500 mg on its own every 4 weeks.

When using Imfinzi in combination with tremelimumab, consult the Product Monograph for IMJUDO (tremelimumab) for further information on this drug.

Imfinzi alone:

The recommended dose of durvalumab is 1500 mg every 4 weeks. Imfinzi is given on its own.

It is not known if Imfinzi is safe and effective in children less than 18 years of age.

Overdose:

If you think you, or a person you are caring for, have been given too much Imfinzi, contact a healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed Dose or Appointment to get Imfinzi:

It is very important that you keep all your appointments to get Imfinzi. If you miss an appointment, call your doctor as soon as possible to discuss next steps.

What are possible side effects from using Imfinzi?

These are not all the possible side effects you may have when taking Imfinzi. If you experience any side effects not listed here, tell your healthcare professional.

The following side effects have been reported in clinical trials with patients receiving Imfinzi alone or in combination tremelimumab or with chemotherapy; ask your doctor for more information regarding side effects of your chemotherapy:

Very common side effects ($\geq 10\%$):

- nausea
- hair loss
- decreased appetite
- feeling tired or weak
- constipation
- vomiting
- cough
- diarrhea
- stomach or abdominal pain
- skin rash or itchiness
- fever
- swelling of the legs
- upper respiratory tract infection
- abnormal liver tests (aspartate aminotransferase increased; alanine aminotransferase increased)
- underactive thyroid gland that can cause tiredness or weight gain
- abnormal pancreas test

When you get Imfinzi either alone or in combination with tremelimumab or chemotherapy, you can have some serious side-effects. See table below. If you have any of the following, call or see your healthcare professional right away. Your healthcare professional may give you other medicines in order to prevent more severe complications and reduce your symptoms. Your healthcare professional may withhold the next dose of Imfinzi or stop your treatment with Imfinzi.

Serious side effects and what to do about them				
Symptom / effect		Talk to your healthcare professional		Stop taking drug and get immediate medical help
		Only if severe	In all cases	
Very Common (combination with chemotherapy)	Leukopenia or Neutropenia (low white blood cells, low neutrophils): fever or infection, fatigue, flu-like symptoms.		✓	

Serious side effects and what to do about them				
Symptom / effect		Talk to your healthcare professional		Stop taking drug and get immediate medical help
		Only if severe	In all cases	
Very Common (combination with chemotherapy)	Anemia (low red blood cells): being short of breath, feeling very tired, having pale skin, fast heartbeat, loss of energy, or weakness.		✓	
Very Common (monotherapy, combination with tremelimumab) Common (combination with chemotherapy)	Skin or mouth problems: rash, itching, skin blistering; ulcers in mouth or other mucous membranes when in combination with chemotherapy.		✓	
Very Common (monotherapy, combination with tremelimumab) Common (combination with chemotherapy)	Hormone gland problems (especially the thyroid, adrenals, pituitary and pancreas): headaches that will not go away or unusual headaches, extreme tiredness, weight gain or weight loss, dizziness or fainting, feeling more hungry or thirsty than usual, hair loss, feeling cold, constipation, changes to your voice, urinating more often than usual, nausea or vomiting, stomach area (abdomen) pain, changes in mood or behaviour, such as decreased sex drive, irritability, or forgetfulness, fast and deep breathing, confusion, a sweet smell to your breath, a sweet or metallic taste in your mouth, a different odour to your urine or sweat, increased frequency of urination (peeing) or feeling unusually thirsty.		✓	
Common (monotherapy, combination with chemotherapy, combination with tremelimumab)	Pneumonia (infection in the lungs): cough with or without mucus, fever, chills, shortness of breath, chest pain including difficult and painful breathing.		✓	
Common (combination with chemotherapy)	Febrile neutropenia (low number of white blood cells with signs of fever): fever or infection, fatigue, flu-like symptoms.		✓	
Common (monotherapy, combination with chemotherapy, combination with tremelimumab)	Lung inflammation (pneumonitis): new or worsening cough, shortness of breath, chest pain.		✓	

Serious side effects and what to do about them				
Symptom / effect		Talk to your healthcare professional		Stop taking drug and get immediate medical help
		Only if severe	In all cases	
Common (combination with chemotherapy)	Pancytopenia (low number of red blood cells, white blood cells, and platelets): Leukopenia or Neutropenia: fever or infection, fatigue, flu-like symptoms. Anemia: being short of breath, feeling very tired, having pale skin, fast heartbeat, loss of energy, or weakness. Thrombocytopenia: bruising or bleeding for longer than usual if you hurt yourself, fatigue and weakness.		✓	
Common (monotherapy, combination with chemotherapy, combination with tremelimumab)	Severe infusion reactions: chills or shaking, itching or rash, flushing, shortness of breath or wheezing dizziness, fever, feeling like passing out, back or neck pain, facial swelling.		✓	
Uncommon (monotherapy, combination with chemotherapy) Common (combination with tremelimumab)	Intestinal problems (colitis) that can lead to tears or holes in your intestine: diarrhea or more bowel movements than usual, stools that are black, tarry, sticky, or have blood or mucus, severe stomach area (abdomen) pain or tenderness.		✓	
Uncommon (monotherapy) Common (combination with chemotherapy, combined with tremelimumab)	Liver problems (hepatitis): yellowing of your skin or the whites of your eyes, severe nausea or vomiting, pain on the right side of your stomach area (abdomen), drowsiness, dark urine (tea coloured), bleeding or bruising more easily than normal, feeling less hungry than usual.		✓	
Uncommon (monotherapy, combination with tremelimumab) (combination with chemotherapy – not reported)	Kidney problems, including inflammation (nephritis) and kidney failure: decrease in the amount of urine, blood in your urine, swelling in your ankles, loss of appetite.		✓	

Serious side effects and what to do about them				
Symptom / effect		Talk to your healthcare professional		Stop taking drug and get immediate medical help
		Only if severe	In all cases	
<p>Uncommon (<i>monotherapy</i>)</p> <p>Common (combination with tremelimumab)</p> <p>(<i>combination with chemotherapy – not reported</i>)</p>	<p>Muscle problems: muscle weakness, tiredness and/or pain, rapid fatigue of the muscles in one or more areas of your body.</p>		✓	
<p>Uncommon (<i>monotherapy, combined with tremelimumab</i>)</p> <p>(<i>combination with chemotherapy – not reported</i>)</p>	<p>Problems in other organs: changes in eyesight, blurry vision, double vision, cloudy vision or other vision problems including temporary loss of vision, severe or persistent muscle or joint pains, chest pain, shortness of breath.</p>		✓	
<p>Uncommon (<i>monotherapy, combined with tremelimumab</i>)</p>	<p>Inflammation of the Heart: chest pain, shortness of breath or irregular heartbeat.</p>		✓	
<p>Uncommon (<i>monotherapy, combination with chemotherapy</i>)</p>	<p>Inflammation of the joints (Arthritis): joint pain, swelling, and/or stiffness</p>		✓	
<p>Rare (<i>monotherapy, combination with tremelimumab</i>)</p> <p>Very Common (<i>combination with chemotherapy</i>)</p>	<p>Thrombocytopenia (low blood platelets): bruising or bleeding (e.g. nose or gums) more easily than normal.</p>		✓	
<p>Rare (<i>combination with chemotherapy, combination with tremelimumab</i>)</p> <p>(<i>monotherapy – not reported</i>)</p>	<p>Inflammation of the brain (encephalitis): seizures, headache, fever, chills, vomiting, confusion and sleepiness.</p>		✓	
<p>Rare (<i>monotherapy, combination with chemotherapy</i>)</p>	<p>Inflammation of the eye (Uveitis): eye redness, eye pain, light sensitivity, and/or changes in vision.</p>		✓	

Serious side effects and what to do about them				
Symptom / effect		Talk to your healthcare professional		Stop taking drug and get immediate medical help
		Only if severe	In all cases	
Unknown (<i>monotherapy, combination with chemotherapy</i>)	Inflammation of the nerves (Guillain-Barré syndrome): pain, weakness and paralysis in the hands, feet or arms.		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (<https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html>) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your healthcare professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage of Imfinzi for Healthcare Professional:

Imfinzi should not be used after the expiry date which is stated on the label and carton.

Imfinzi should be stored in a refrigerator (2° to 8°C) in the original package in order to protect from light. Do not freeze or shake. Any unused medicine or waste material should be disposed of in accordance with local requirements.

Keep out of reach and sight of children.

If you want more information about Imfinzi:

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html>); the manufacturer's website www.astrazeneca.ca, or by calling 1-800-668-6000.
- This Patient Medication Information is current at the time of printing. The most up-to-date version can be found at www.astrazeneca.ca.

This leaflet was prepared by AstraZeneca Canada Inc., Mississauga, Ontario L4Y 1M4.

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Last Revised:

