PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

IMJUDO®

tremelimumab for injection

Concentrate for solution for infusion, 20 mg / mL, Intravenous

Antineoplastic
(Anatomical Therapeutic Code: L01FX20)

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Date of Initial Authorization:
AUG 31, 2023

Date of Revision:
May 13, 2024

Submission Control Number: 282758

RECENT MAJOR LABEL CHANGES

4 DOSAGE AND ADMINISTRATION, 4.2 Recommended Dose and Dosage Adjustment	03-2024
7 WARNINGS AND PRECAUTIONS	03-2024

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

IMJUDO® (tremelimumab for injection) in combination with durvalumab is indicated for the first-line treatment of adult patients with unresectable hepatocellular carcinoma (uHCC) who require systemic therapy (see 14 CLINICAL TRIALS).

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

1.1 Pediatrics

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

1.2 Geriatrics

Of the 462 patients with uHCC treated with Imjudo and durvalumab, 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 WARNINGS AND PRECAUTIONS, Special Populations.

2 CONTRAINDICATIONS

Imjudo is contraindicated in patients who are hypersensitive to tremelimumab or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- Imjudo in combination with durvalumab 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).

4 DOSAGE AND ADMINISTRATION

4.2 Recommended Dose and Dosage Adjustment

Hepatocellular Carcinoma

Imjudo in combination with durvalumab
The recommended dose of Imjudo is 300 mg as a single dose, followed by durvalumab 1500 mg at Day 1 of Cycle 1. Continue durvalumab 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 Imjudo 4 mg/kg as a single dose followed by durvalumab 20 mg/kg at Day 1 of Cycle 1; continue durvalumab 20 mg/kg as a single agent every 4 weeks.

Treatment should continue until disease progression or unacceptable toxicity.

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

Dose reduction or escalation is not recommended during treatment with Imjudo in combination with durvalumab. Treatment withholding or discontinuation may be required based on individual safety and tolerability.

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

Table 1 Treatment modifications for Imjudo in combination with durvalumab in patients with uHCC

Adverse Reactions	Severity[a]	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
	ALT or AST >10 x ULN or total bilirubin >3 x ULN	

Adverse Reactions	Severity[a]	Treatment Modification
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 bilirubin >3 x ULN	Permanently discontinue
Immune-mediated colitis or diarrhea	Grade 2 or 3	Withhold dose[b]
	Grade 4	Permanently discontinue
	Intestinal perforation of ANY grade	Permanently discontinue
Immune-mediated hyperthyroidism, thyroiditis	Grade 2 – 4	Withhold dose until clinically stable
Immune-mediated hypothyroidism	Grade 2 – 4	No changes
Immune-mediated adrenal insufficiency, hypophysitis/hypopituitarism	Grade 2 – 4	Withhold dose until clinically stable
Immune-mediated Type 1 diabetes mellitus	Grade 2 – 4	No changes
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

Adverse Reactions	Severity[a]	Treatment Modification
Immune-mediated rash or dermatitis (including pemphigoid)	Grade 2 for >1 week or Grade 3	Withhold dose[b]
	Grade 4	Permanently discontinue
Infection	Grade 3 or 4	Withhold dose[e]
Immune-mediated myocarditis	Grade 2 – 4	Permanently discontinue
Immune-mediated myositis/polymyositis/ rhabdomyolysis	Grade 2 or 3	Withhold dose[b,f]
	Grade 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[g]	Grade 2 or 3	Withhold dose[b]
	Grade 4	Permanently discontinue
Infusion-related reactions	Grade 1 or 2	Interrupt or slow the rate of infusion
	Grade 3 or 4	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, durvalumab 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. Durvalumab should be permanently discontinued for recurrent Grade 3 adverse reactions, as applicable.

[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 durvalumab based on recommendations for hepatitis with no liver involvement.

[e] Symptomatic management; treat with anti-infectives for suspected or confirmed infections

[f] Permanently discontinue durvalumab if the adverse reaction does not resolve to ≤ Grade 1 within 30 days or if there are signs of respiratory insufficiency.

[g] Includes immune thrombocytopenia, pancreatitis, immune-mediated arthritis, and uveitis.

For non-immune-mediated adverse reactions, withhold durvalumab for Grade 2 and 3 adverse reactions until ≤ Grade 1 or return to baseline. Durvalumab should be discontinued for Grade 4 adverse reactions (except for Grade 4 laboratory abnormalities, for which the decision to discontinue should be based on accompanying clinical signs/symptoms and clinical judgment).

Special patient populations
Based on a population pharmacokinetic analysis, no dose adjustment of Imjudo is recommended based on patient age, body weight, gender, and race (see 10 CLINICAL PHARMACOLOGY).

Pediatrics (<18 years of age): The safety and effectiveness of Imjudo have not been established in children and adolescents aged less than 18 years.

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

Renal Impairment: Based on a population pharmacokinetic analysis, no dose adjustment of Imjudo is recommended in patients with renal impairment. Imjudo has not been studied in patients with severe renal impairment (see 10 CLINICAL PHARMACOLOGY).

Hepatic Impairment: Based on a population pharmacokinetic analysis, no dose adjustment of Imjudo is recommended for patients with mild or moderate hepatic impairment. Imjudo has not been studied in patients with severe hepatic impairment (see 10 CLINICAL PHARMACOLOGY).

4.4 Administration

Imjudo is only to be administered by intravenous infusion.

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

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 and infusion bag. After each dose, flush the infusion line.

Administer Imjudo prior to durvalumab on the same day of Cycle 1. Observing patient for 60 minutes is recommended following completion of Imjudo infusion. Imjudo and durvalumab are administered as separate intravenous infusions.

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

4.7 Instructions for Preparation and Use

- Visually inspect drug product for particulate matter and discolouration. Imjudo is a clear to slightly 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 Imjudo 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 0.1 mg/mL and 10 mg/mL.
- Do not freeze or shake the solution.
- No incompatibilities between Imjudo and 0.9% Sodium Chloride or 5% Dextrose in polyvinylchloride or polyolefin IV bags have been observed.
- This drug product must not be mixed with other drug products during its preparation.
- Care must be taken to ensure the sterility of prepared solutions.
- Do not re-enter the vial after withdrawal of drug.
- Discard any unused portion left in the vial.

5 OVERDOSAGE

There is no specific treatment in the event of an Imjudo overdose, and symptoms of overdose are not established. In the event of an overdose, physicians 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

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: • 25 mg tremelimumab / 1.25 mL (20 mg/mL) • 300 mg tremelimumab / 15 mL (20 mg/mL)	Disodium edetate dihydrate, L-histidine, L-histidine hydrochloride monohydrate, Polysorbate 80, α,α-Trehalose dihydrate, and Water for Injection

Description
Imjudo is a sterile, preservative-free, clear to slightly opalescent, colourless to slightly yellow solution, free from or practically free from visible particles.

Packaging

1.25 mL (a total of 25 mg tremelimumab) concentrate in a Type I glass vial with an elastomeric stopper and a violet flip-off aluminum seal. Pack size of 1 single-dose vial.

15 mL (a total of 300 mg tremelimumab) concentrate in a Type I glass vial with an elastomeric stopper and a dark blue flip-off aluminum seal. Pack size of 1 single-dose vial.

7 WARNINGS AND PRECAUTIONS

General
Imjudo (tremelimumab) should be administered under the supervision of healthcare practitioners experienced in the treatment of cancer.

When using Imjudo in combination with durvalumab, consult the Imfinzi (durvalumab) 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 TRIAL).

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, Imjudo in combination with durvalumab should be withheld and corticosteroids administered. Upon improvement to ≤ 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 Imjudo in combination with durvalumab may differ from those observed with non-immunotherapies and may require immunosuppression. Immune-mediated adverse reactions have occurred at higher frequencies when Imjudo was administered in combination with durvalumab compared with durvalumab as monotherapy. Early identification of adverse reactions and timely intervention are an important part of the safe use of Imjudo in combination with durvalumab.

Immune-mediated adverse reactions may involve any organ system or tissue and may affect more than one body system simultaneously. Immune-mediated adverse reactions can manifest at any time during treatment with Imjudo in combination with durvalumab; however, immune-mediated adverse reactions can occur after discontinuation of treatment. Important immune-mediated adverse reactions listed in this section are not inclusive of all possible severe and fatal immune-mediated reactions.

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. Immune-mediated adverse reactions are managed with treatment modification, administration of corticosteroids and/or supportive care. Refer to 4 DOSAGE AND ADMINISTRATION, Table 1 for recommended treatment modifications.

Immune-mediated pneumonitis

Immune-mediated pneumonitis or interstitial lung disease, defined as requiring use of systemic corticosteroids and with no clear alternate etiology, occurred in patients receiving Imjudo in combination with durvalumab, including fatal cases (8 ADVERSE REACTIONS, 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 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.

Immune-mediated hepatitis

Immune-mediated hepatitis, defined as requiring use of systemic corticosteroids and with no clear alternate etiology, occurred in patients receiving Imjudo in combination with durvalumab, including fatal cases (8 ADVERSE REACTIONS, Immune-mediated hepatitis). Patients should be monitored for abnormal liver tests prior to and periodically during treatment with Imjudo in combination with durvalumab. Immune-mediated hepatitis should be managed as recommended in 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 Imjudo in combination with durvalumab (8 ADVERSE REACTIONS, Immune-mediated colitis). Intestinal perforation and large intestine perforation were reported in patients receiving Imjudo in combination with durvalumab. Patients should be monitored for signs and symptoms of colitis/diarrhea and intestinal perforation and managed as recommended in 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 or thyroiditis have occurred in patients receiving Imjudo in combination with durvalumab (8 ADVERSE REACTIONS, Immune-mediated endocrinopathies). Patients should be monitored for abnormal thyroid function tests prior to and periodically during treatment and managed as recommended in 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.

Immune-mediated adrenal insufficiency

Immune-mediated adrenal insufficiency occurred in patients receiving Imjudo in combination with durvalumab (8 ADVERSE REACTIONS, Immune-mediated adrenal insufficiency). Patients should be monitored for clinical signs and symptoms of adrenal insufficiency and managed as recommended in Table 1. Corticosteroids should be administered for 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, which can present with diabetic ketoacidosis, occurred in patients receiving Imjudo in combination with durvalumab (8 ADVERSE REACTIONS, Immune-mediated type 1 diabetes mellitus). Patients should be monitored for clinical signs and symptoms of type 1 diabetes mellitus and managed as recommended in Table 1. Treatment with insulin can be initiated as clinically indicated for Grades 2 – 4.

Immune-mediated hypophysitis/hypopituitarism

Immune-mediated hypophysitis or hypopituitarism occurred in patients receiving Imjudo in combination with durvalumab (8 ADVERSE REACTIONS, Immune-mediated hypophysitis/hypopituitarism). Patients should be monitored for clinical signs and symptoms of hypophysitis or hypopituitarism and managed as recommended in Table 1. Corticosteroids should be administered for 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 nephritis

Immune-mediated nephritis, defined as requiring use of systemic corticosteroids and with no clear alternate etiology, occurred in patients receiving Imjudo in combination with durvalumab (8 ADVERSE REACTIONS, Immune-mediated nephritis). Patients should be monitored for abnormal renal function tests prior to and periodically during treatment with Imjudo in combination with durvalumab and managed as recommended in 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 Imjudo in combination with durvalumab (8 ADVERSE REACTIONS, Immune-mediated rash). Patients should be monitored for signs and symptoms of rash or dermatitis and managed as recommended in 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 Imjudo in combination with durvalumab (see 8 ADVERSE REACTIONS, Other immune-mediated adverse reactions). Patients should be monitored for signs and symptoms of immune-mediated myocarditis and managed as recommended in 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 Imjudo and durvalumab, other potential immune-mediated adverse reactions may occur in patients receiving the combination of Imjudo with durvalumab. The following immune-mediated adverse reactions have been observed: myasthenia gravis, myositis, polymyositis, rhabdomyolysis, Guillain-Barré Syndrome, immune-mediated arthritis, uveitis, immune thrombocytopenia, pancreatitis, encephalitis, Stevens-Johnson syndrome, and

hypoparathyroidism. The following clinically significant immune-mediated adverse reactions have been observed in patients who received other immune-checkpoint inhibitors: meningitis, demyelination, toxic epidermal necrolysis, hemolytic anemia, sarcoidosis and retinal detachment. Patients should be monitored for signs and symptoms and managed as recommended in Table 1. Corticosteroids should be administered an initial dose of 1 – 2 mg/kg/day prednisone or equivalent followed by taper for Grades 2 – 4.

Infusion-related reactions
Patients should be monitored for signs and symptoms of infusion-related reactions and managed as recommended in 4.2 Recommended Dose and Dosage Adjustment. Severe infusion-related reactions have been reported in patients receiving Imjudo in combination with durvalumab (8 ADVERSE REACTIONS, Infusion-related reactions). For Grade 1 or 2 severity, may consider pre-medications 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 starting treatment and as indicated based on clinical evaluation.

Reproductive Health: Female and Male Potential
There are no data on the potential effects of tremelimumab on fertility in humans.

7.1 Special Populations

7.1.1 Pregnant Women

In animal reproduction studies, administration of tremelimumab to pregnant cynomolgus monkeys during the period of organogenesis was not associated with maternal toxicity or any effects on pregnancy maintenance or embryofetal development (16 NON-CLINICAL TOXICOLOGY). There are no data on the use of tremelimumab in pregnant women. Based on its mechanism of action, tremelimumab has the potential to impact pregnancy maintenance and may cause fetal harm when administered to a pregnant woman. Human IgG2 is known to cross the placental barrier. Tremelimumab is not recommended during pregnancy and in women of childbearing potential not using effective contraception during treatment and for at least 3 months after the last dose.

7.1.2 Breast-feeding

There is no information regarding the presence of tremelimumab in human milk, the absorption and effects on the breastfed infant, or the effects on milk production. Human IgG2 is excreted in human milk. Because of the potential for adverse reactions from tremelimumab in breastfed infants, lactating women are advised not to breastfeed during treatment and for at least 3 months after the last dose.

7.1.3 Pediatrics

Pediatrics (<18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

Geriatrics (≥ 65 years): No dose adjustment is required for elderly patients (≥ 65 years of age). Of the 462 patients with uHCC treated with Imjudo in combination with durvalumab, 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%).

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Unresectable hepatocellular carcinoma (uHCC)

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

For patients receiving Imjudo in combination with durvalumab, the most commonly reported adverse events (reported by ≥ 10% patients) were pruritus, diarrhea, rash, fatigue, decreased appetite, pyrexia, AST increased, hypothyroidism, nausea, abdominal pain, insomnia and asthenia.

In patients receiving Imjudo in combination with durvalumab 50.5% reported grade 3 or 4 adverse events, and the most common adverse events (occurring in ≥ 5% of patients) were lipase increase and AST increased. In patients receiving durvalumab monotherapy 37.1% reported grade 3 or 4 adverse events, and the most common adverse event (occurring in ≥ 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 ≥ 5% of patients) were hypertension and palmar-plantar erythrodysaesthesia syndrome.

In patients receiving Imjudo in combination with durvalumab 34.5% reported adverse events leading to dose delays or interruption of any study treatment, and the most common adverse events (occurring in ≥ 3% of patients) were ALT increased, amylase increased, diarrhea and AST increased. In patients receiving durvalumab monotherapy 24.5% reported adverse events leading to dose delays or interruption of any study treatment and the most common adverse

events (occurring in ≥ 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 adverse events (occurring in ≥ 3% of patients) were palmar-plantar erythrodysaesthesia.

In patients receiving Imjudo in combination with durvalumab 13.7% reported discontinuation due to adverse events and the most common adverse events (occurring in ≥ 1% of patients) was hepatitis and AST increased. In patients receiving durvalumab 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 ≥ 1% of patients) were palmar-plantar erythrodysaesthesia-syndrome, diarrhea and abdominal pain.

Serious adverse events occurred in 40.5% of patients receiving Imjudo in combination with durvalumab, and the most commonly reported serious adverse event (reported in ≥ 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 durvalumab monotherapy, and the most commonly reported events (reported in ≥ 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 ≥ 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 Imjudo in combination with durvalumab versus 6.7% of patients treated with durvalumab monotherapy and 7.2% of patients treated with sorafenib. Fatal adverse events possibly related to treatment as assessed by the investigator in Imjudo in combination with durvalumab 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.

Immune-mediated adverse reactions were reported in 35.8% of patients treated with Imjudo in combination with durvalumab (Grade 3 or 4 events 12.6%) and 16.5% of patients treated with durvalumab alone (Grade 3 or 4 events 6.4%). In the Imjudo plus durvalumab 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 durvalumab 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.

Table 3 lists the incidence of adverse drug reactions found in at least 1% of patients with uHCC treated with Imjudo in combination with durvalumab in the HIMALAYA study.

Table 3 Adverse Drug Reactions Occurring in ≥1% of Patients with Hepatocellular Carcinoma receiving Imjudo in combination with durvalumab Compared to Sorafenib in HIMALAYA

	Imjudo + durvalumab (n=388)		Sorafenib (n=374)	
Adverse Drug Reaction	**Frequency of any Grade**	**Frequency of Grade 3-4**	**Frequency of any Grade**	**Frequency of Grade 3-4**
Endocrine disorders				
Adrenal insufficiency	6 (1.5%)	0	0	0
Hyperthyroidism[a]	38 (9.8%)	1 (0.3%)	2 (0.5%)	0
Hypothyroidism[b]	52 (13.4%)	0	21 (5.6%)	0
Thyroiditis[c]	8 (2.1%)	0	2 (0.5%)	-
Gastrointestinal disorders				
Abdominal pain[d]	75 (19.3%)	7 (1.8%)	87 (23.2%)	15 (4.0%)
Amylase increased	29 (7.5%)	14 (3.6%)	10 (2.7%)	3 (0.8%)
Colitis[e]	10 (2.6%)	6 (1.5%)	2 (0.5%)	0
Diarrhea	103 (26.5%)	17 (4.4%)	167 (44.7%)	16 (4.3%)
Lipase increased	34 (8.8%)	24 (6.2%)	15 (4.0%)	11 (2.9%)
Pancreatitis[f]	5 (1.3%)	2 (0.5%)	2 (0.5%)	1 (0.3%)
General disorders and administration site conditions				
Oedema peripheral[g]	36 (9.3%)	2 (0.5%)	24 (6.4%)	0
Pyrexia	50 (12.9%)	1 (0.3%)	33 (8.8%)	0
Hepatobiliary disorders				
Aspartate aminotransferase increased /Alanine aminotransferase increased[h]	58 (14.9%)	25 (6.4%)	35 (9.4%)	15 (4.0%)
Hepatitis[i]	23 (5.9%)	7 (1.8%)	1 (0.3%)	0
Infections and infestations				
Dental and oral soft tissue infections[j]	6 (1.5%)	0	2 (0.5%)	-
Influenza	10 (2.6%)	0	4 (1.1%)	1 (0.3%)
Pneumonia[k]	17 (4.4%)	4 (0.1%)	13 (3.5%)	6 (1.6%)
Upper respiratory tract infections[l]	32 (8.2%)	0	15 (4.0%)	-
Injury, poisoning and procedural complications				
Infusion-related reaction[m]	6 (1.5%)	0	2 (0.5%)	0
Musculoskeletal and connective tissue disorders				
Myalgia	12 (3.1%)	1 (0.3%)	10 (2.7%)	0
Renal and urinary disorders				
Blood creatinine increased	14 (3.6%)	1 (0.3%)	5 (1.3%)	1 (0.3%)
Dysuria	6 (1.5%)	0	3 (0.8%)	-
Respiratory, thoracic and mediastinal disorders				

Cough/Productive cough	34 (8.8%)	0	26 (7.0%)	1 (0.3%)
Pneumonitis	10 (2.6%)	0	2 (0.5%)	0
Skin and subcutaneous tissue disorders				
Dermatitis[n]	6 (1.5%)	0	6 (1.6%)	1 (0.3%)
Night sweats	4 (1.0%)	0	2 (0.5%)	-
Pruritus	89 (22.9%)	0	24 (6.4%)	1 (0.3%)
Rash[o]	116 (29.9%)	9 (2.3%)	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] Includes colitis, enteritis and enterocolitis.
[f] Includes pancreatitis and pancreatitis acute.
[g] Includes oedema peripheral and peripheral swelling.
[h] Includes alanine aminotransferase increased, aspartate aminotransferase increased, hepatic enzyme increased and transaminases increased.
[i] Includes autoimmune hepatitis, hepatitis, hepatocellular injury, hepatotoxicity and immune-mediated hepatitis.
[j] Includes periodontitis, pulpitis dental, tooth abscess and tooth infection.
[k] Includes pneumocystis jirovecii pneumonia and pneumonia.
[l] Includes nasopharyngitis, pharyngitis, rhinitis, tracheobronchitis and upper respiratory tract infection.
[m] Includes infusion-related reaction and urticaria.
[n] Includes dermatitis and immune-mediated dermatitis.
[o] Includes eczema, erythema, rash, rash macular, rash maculo-papular, rash papular and rash pruritic.

Additional Information on Selected Adverse Reactions

Imjudo 300 mg as a single dose, in combination with durvalumab 1500 mg in uHCC:
The data for the following selected adverse reactions is based on 462 patients from the HIMALAYA study and Study 22 (N=74), an open-label, multi-part, multicenter study.

Immune-mediated pneumonitis
In patients receiving Imjudo in combination with durvalumab 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 Imjudo in combination with durvalumab 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 Imjudo in combination with durvalumab 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 Imjudo in combination with durvalumab in uHCC but it was observed in clinical trials of patients receiving Imjudo in combination with durvalumab.

Immune-mediated endocrinopathies

Immune-mediated hypothyroidism
In patients receiving Imjudo in combination with durvalumab 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 Imjudo in combination with durvalumab 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 Imjudo in combination with durvalumab 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 Imjudo in combination with durvalumab 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 type 1 diabetes mellitus

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

Immune-mediated hypophysitis/hypopituitarism
In patients receiving Imjudo in combination with durvalumab 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 nephritis
In patients receiving Imjudo in combination with durvalumab 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 Imjudo in combination with durvalumab 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 Imjudo in combination with durvalumab 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 Imjudo in combination with durvalumab 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 Imjudo in combination with durvalumab: Guillain-Barré Syndrome.

Infusion-related reactions
In patients receiving Imjudo in combination with durvalumab in uHCC, infusion-related reactions occurred in 7 (1.5%) patients.

8.3 Less Common Clinical Trial Adverse Reactions

The following additional adverse reactions considered drug-related were reported in less than 1% of patients treated with Imjudo in combination with durvalumab 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: dysphonia (0.8%), 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

Table 4 summarizes the laboratory abnormalities that occurred patients treated with Imjudo in combination with durvalumab in the HIMALAYA study.

Table 4 Laboratory Abnormalities Worsening from Baseline Occurring in ≥ 20%[1] of Patients in the HIMALAYA study

	Imjudo +durvalumab (n = 388)		Sorafenib (n = 374)	
Laboratory Abnormality	**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	54.6	21.1
Alanine Aminotransferase increased	56.2	17.8	52.6	12.2
Sodium decreased	46.0	15.3	39.8	11.1
Bilirubin increased	41.4	8.2	47.4	10.5
Alkaline Phosphatase increased	41.2	8.3	44.4	5.4
Glucose increased	38.9	13.5	29.1	3.7
Calcium decreased	33.5	0	43.0	0.3
Albumin decreased	31.3	0.5	37.1	1.7
Potassium increased	28.4	3.8	21.3	2.6
Creatinine increased	20.9	1.3	14.8	0.9
Hematology				
Hemoglobin decreased	51.6	4.8	40.3	6.0
Lymphocytes decreased	41.4	11.1	39.3	10.0
Platelets decreased	28.8	1.6	34.7	3.1
Leukocytes decreased	20.2	0.8	30.1	1.1

[1]The frequency cut-off is based on any grade change from baseline for Imjudo in combination with durvalumab.

[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: Imjudo with durvalumab (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 Imjudo in combination with durvalumab:

Eye disorders: uveitis

Musculoskeletal and connective tissue disorders: immune-mediated arthritis, rhabdomyolysis

Nervous system disorders: Guillain-Barré syndrome

9 DRUG INTERACTIONS

9.4 Drug-Drug Interactions

Tremelimumab is an immunoglobulin and the primary elimination pathways of tremelimumab are protein catabolism via reticuloendothelial system or target-mediated disposition; therefore, no formal pharmacokinetic (PK) drug-drug interaction studies have been conducted with tremelimumab since no metabolic drug-drug interactions are expected.

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

CTLA-4 is primarily expressed on the surface of T lymphocytes and is a negative regulator of T-cell activity. Interaction of CTLA-4 with its ligands, CD80 and CD86, limits effector T-cell activation, through a number of potential mechanisms, but primarily by limiting co-stimulatory signalling through CD28. Tremelimumab is a selective, fully human IgG2 antibody that blocks CTLA-4 interaction with CD80 and CD86, thus enhancing T-cell activation and proliferation, which may result in increased T-cell diversity and enhanced antitumour immune activity.

10.2 Pharmacodynamics

The pharmacodynamic response and exposure-response relationships of tremelimumab in combination with durvalumab have not been fully characterized in patients with uHCC.

The effect on ECG intervals has been evaluated in a phase 1, open label study of tremelimumab (at 1, 3 or 10 mg/kg) in combination with durvalumab (at 3, 10, 15 or 20 mg/kg) administered to patients with advanced non-small cell lung cancer, and no relationship was observed between tremelimumab concentration and QTc intervals.

10.3 Pharmacokinetics

The pharmacokinetics of tremelimumab was studied in patients with solid tumours following administration of doses 1 mg/kg, 3 mg/kg and 10 mg/kg administered intravenously once every 4 weeks for 4 doses. The pharmacokinetics of tremelimumab as a single dose of 300 mg were evaluated in patients with uHCC.

The AUC of tremelimumab increased proportionally from 1mg/kg to 10 mg/kg every 4 weeks and steady state was achieved at approximately 12 weeks. There was no clinically meaningful difference between the PK of tremelimumab as monotherapy or in combination with durvalumab.

Table 5 Summary of Tremelimumab Pharmacokinetic Parameters in patients with solid tumors including uHCC

	Cmax (µg/mL)	**$T_{½}$ (day)**	**AUC_{dose1} (ug•day/mL)**	**CL (L/day)**	**V1 (L)**	**V2 (L)**
300 mg (Single dose) **Geometric Mean (CV) [n]**	86.5 (23.9%) [2406]	16.9 (18.5%) [2406]	763 (28.0%) [2406]	0.286 (32.3%) [2406]	3.45 (24.0%) [2406]	2.66 (33.9%) [2406]

Based on Population PK analysis.
Abbreviations: Cmax, maximum serum concentration; $T_{1/2}$, terminal elimination half-life; AUC_{dose1}, area under the serum concentration-time curve after single tremelimumab infusion to day 28; CL, clearance; V1, central volume of distribution; V2, peripheral volume of distribution

Absorption
Tremelimumab in combination with durvalumab is administered via the intravenous route and therefore is immediately and expected to be completely bioavailable.

Distribution
Based on the population pharmacokinetic analysis, the geometric mean (% coefficient of variation [CV%]) of tremelimumab for central (V1) and peripheral (V2) volume of distribution was 3.45 (24%) and 2.66 (34%) L, respectively.

Metabolism
Tremelimumab is a humanized IgG with a large molecular weight and is eliminated by widely distributed proteolytic enzymes. It is not subject to hepatic elimination pathway.

Elimination
Tremelimumab PK monotherapy was well characterized by a 2-compartment model with linear clearance components. Based on the population pharmacokinetic analysis, the geometric mean (CV%) terminal half-life of tremelimumab was 16.9 days (19%) after a single dose of 300 mg and 18.2 days (19%) during steady state. The geometric mean (CV%) clearance of tremelimumab was 0.286 L/day (32%) after a single dose and 0.263 L/day (32%) during steady state.

Special Populations and Conditions
Based on a population PK analysis, age, body weight, gender, positive anti-drug antibody (ADA) status, albumin levels, LDH levels, creatinine levels, 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 ≤ ULN and AST > ULN or bilirubin >1.0 to 1.5 × ULN and any AST), moderate hepatic impairment (bilirubin >1.5 to 3 x ULN and any AST) or ECOG/WHO status had no clinically significant effect on the PK of tremelimumab.

- **Geriatrics:** No dose adjustment is required for elderly patients (≥65 years of age). Of the 462 patients with uHCC treated with Imjudo in combination with durvalumab, 173 patients were ≥65 years to <75 years and 63 patients were 75 years or older. No overall clinically meaningful differences in PK were reported between patients ≥ 65 years of age and younger patients.

- **Hepatic Insufficiency:** The effect of severe hepatic impairment (bilirubin >3.0 x ULN and any AST) on the PK of tremelimumab is unknown.

- **Renal Insufficiency:** The effect of severe renal impairment (CrCL 15 to 29 mL/min) on the PK of tremelimumab is unknown.

11 STORAGE, STABILITY AND DISPOSAL

Store unopened vials of Imjudo under refrigeration at 2°C to 8°C in the original carton to protect from light. Do not freeze or shake.

Imjudo does not contain a preservative. Administer infusion solution immediately once prepared. If infusion solution is not administered immediately, it can be stored in the IV bag:

- For up to 24 hours under refrigeration at 2°C to 8°C, or
- For up to 24 hours at room temperature up 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: Tremelimumab

Molecular formula and molecular mass: The molecular weight for tremelimumab is 149,145 Da

Structural formula: Tremelimumab is a human anti-cytotoxic T-lymphocyte antigen 4 (CTLA-4)-immunoglobulin G2 (IgG2a) monoclonal antibody.

Physicochemical properties: The tremelimumab drug substance is a clear to slightly opalescent, colourless to slightly yellow liquid with a density of 1.034 g/mL. The tremelimumab drug substance is formulated in 20 mM histidine/histidine-HCl monohydrate, 222 mM trehalose dihydrate, 0.27 mM disodium edetate dihydrate, 0.02% (w/v) Polysorbate 80, pH 5.5 at a concentration of 20 mg/mL (nominal).

Pharmaceutical standard: Professed

Product Characteristics

Tremelimumab is a fully human anti-human Cytotoxic T Lymphocyte-associated Antigen 4 (CTLA-4 or CD152) monoclonal antibody of the IgG2a isotype. Tremelimumab is produced in mouse cells by recombinant DNA technology.

14 CLINICAL TRIALS

14.1 Clinical Trial by Indication

Hepatocellular Carcinoma

Trial Design and Study Demographics

The efficacy of IMJUDO (tremelimumab for injection) in combination with durvalumab 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 Imjudo plus durvalumab arm, the durvalumab alone arm and the sorafenib arm (See Table 5). 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 6 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	Imjudo in combination with durvalumab: Imjudo 300 mg as a single priming dose + durvalumab 1500 mg; followed by durvalumab 1500 mg every 4 weeks, intravenous Or durvalumab 1500 mg every 4 weeks, intravenous Or sorafenib 400 mg twice daily, oral	Imjudo in combination with durvalumab: 393 durvalumab 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 Imjudo plus durvalumab arm versus the sorafenib arm. The secondary objective was to assess OS between the durvalumab arm versus the sorafenib arm. Key secondary endpoints were investigator-assessed progression-free survival (PFS), objective response rate (ORR) 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

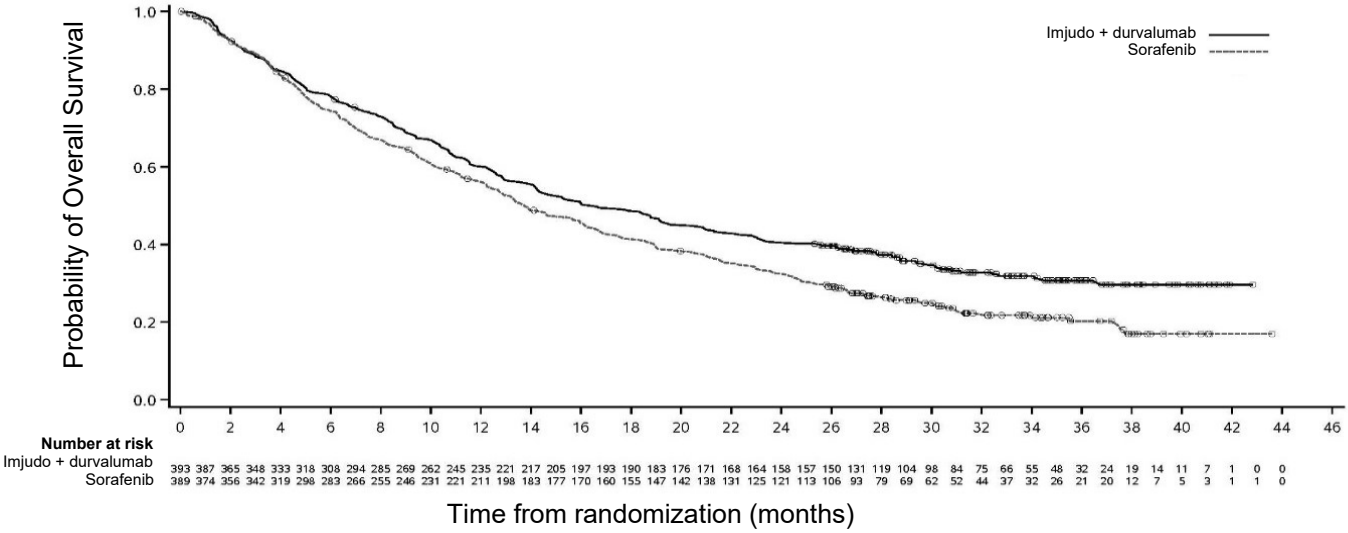
The efficacy results for the combination of Imjudo plus durvalumab vs. sorafenib are presented in Table 7 and Figure 1. The study met the primary pre-specified objective of statistically significant improvement in overall survival for Imjudo in combination with durvalumab compared with sorafenib.

Table 7 Efficacy Results in Unresectable Hepatocellular Carcinoma, HIMALAYA (Full analysis set)

	Imjudo + durvalumab (n=393)	**Durvalumab 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	0.0013	0.0293	-
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).
CI=Confidence Interval

Figure 1 Kaplan-Meier curve of OS for Imjudo in combination with durvalumab vs. sorafenib (Full analysis set)



In an exploratory OS analysis, controlling for EHS, ALBI, Alpha-Fetoprotein and BCLC staging, between the Imjudo plus durvalumab 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.

14.3 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity.

Immunogenicity of tremelimumab is based on pooled data in 2075 patients who were treated with Imjudo 75 mg or 1 mg/kg and evaluable for the presence of anti-drug antibodies (ADAs). Two-hundred fifty-two patients (12.1%) tested positive for treatment-emergent ADAs. Neutralizing antibodies against tremelimumab were detected in 10.0% (208/2075) patients. The presence of ADAs did not impact tremelimumab pharmacokinetics, and there was no apparent effect on efficacy and safety.

In the HIMALAYA study, of the 182 patients who were treated with Imjudo in combination with durvalumab and evaluable for the presence of ADAs against tremelimumab, 20 (11.0%) patients tested positive for treatment-emergent ADAs. Neutralizing antibodies against tremelimumab were detected in 4.4% (8/182) patients. The presence of ADAs did not have an apparent effect on pharmacokinetics or safety; however, due to the low incidence the possible effect on the efficacy could not be determined.

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 tremelimumab 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 and genotoxic potential of tremelimumab have not been evaluated.

Reproductive and Developmental Toxicology: Animal fertility studies have not been conducted with tremelimumab.

17 SUPPORTING PRODUCT MONOGRAPHS

IMFINZI (durvalumab for injection, concentrate for solution for infusion, 50 mg/mL), submission control 278423, Product Monograph, AstraZeneca Canada Inc. (DEC 27, 2023)

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

℞IMJUDO®
tremelimumab for injection, intravenous infusion

Read this carefully before you start treatment with IMJUDO. 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 Imjudo.

Serious Warnings and Precautions

Imjudo in combination with durvalumab 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). Please see **What are possible side effects from using Imjudo?**

What is Imjudo used for?
Imjudo in combination with durvalumab is used to treat a type of liver cancer, called hepatocellular carcinoma (HCC). Imjudo is used with another drug, durvalumab 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 Imjudo in combination with IMFINZI (durvalumab), it is important that you also read the PATIENT MEDICATION INFORMATION for both medications.

How does Imjudo work?
Tremelimumab is a monoclonal antibody, which is a type of protein designed to recognise and attach to a specific target substance in the body. Imjudo together with Imfinzi (durvalumab) are medicines that may treat your liver cancer by working with your immune system to attack the cancer cells.

Imjudo will only be prescribed to you by a doctor with experience in the use of medicines for cancer.

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

What are the ingredients in Imjudo?
Medicinal ingredient: tremelimumab
Non-medicinal ingredients: disodium edetate dihydrate, L-histidine, L-histidine hydrochloride monohydrate, polysorbate 80, α,α-Trehalose dihydrate, and water for injection

Imjudo comes in the following dosage forms:
A solution in single-use glass vials containing either 1.25 mL or 15 mL of 20 mg/mL tremelimumab.
After further dilution and preparation, Imjudo is administered as an intravenous infusion.

Do not use Imjudo if:
- You are allergic to tremelimumab or any other ingredients in Imjudo.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Imjudo. Talk about any health conditions or problems you may have, including if you:
- Have had an organ transplant.
- Have lung or breathing problems.
- Have liver problems.
- Have immune system problems such as Crohn's disease, ulcerative colitis, or lupus.
- Have problems with hormone producing glands such as your thyroid, pituitary, adrenal glands, or pancreas.
- Have diabetes.

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.
- 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 Imjudo.

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 Imjudo. It is not known if Imjudo 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 Imjudo:
No drug-drug interactions are expected with Imjudo.

How to take Imjudo:
- Imjudo will be given to you in a hospital or clinic under the supervision of an experienced healthcare professional.

- Your healthcare professional will give you Imjudo through an intravenous infusion into your vein for about 60 minutes.

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

Usual dose:
The recommended dose of Imjudo 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.

If you have a body weight of 30 kg or less, you must receive weight-based dosing, equivalent to Imjudo 4 mg/kg as a single dose, followed by durvalumab 20 mg/kg at Day 1 of Cycle 1. Continue durvalumab 20 mg/kg on its own every 4 weeks.

Overdose:

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

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

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

Very common side effects (≥ 10%):
- Underactive thyroid gland that can cause tiredness or weight gain
- Stomach pain
- Diarrhea
- Abnormal pancreas test
- Swelling of legs
- Fever
- Abnormal liver tests
- Cough
- Itchiness
- Skin rash
- Feeling tired

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			
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.		✓	
Skin problems: rash, itching, skin blistering.		✓	
COMMON			
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.		✓	
Lung inflammation (pneumonitis): new or worsening cough, shortness of breath, chest pain.		✓	
Muscle problems: muscle weakness, tiredness and/or pain, rapid fatigue of the muscles in one or more areas of your body.		✓	
Pneumonia (infection in the lungs): cough with or without mucus, fever, chills, shortness of breath, chest pain including difficult and painful breathing.		✓	
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.		✓	

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**	
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.		✓	
UNCOMMON			
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.		✓	
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.		✓	
Inflammation of the heart: chest pain, shortness of breath or irregular heartbeat.		✓	
RARE			
Low number of platelets: bleeding (e.g., nose or gum bleeding) and/or bruising.		✓	
Inflammation of the brain: seizures, headache, fever, chills, vomiting, confusion, and sleepiness.		✓	
UNKNOWN			
Inflammation of the nerves: signs and symptoms may include pain; weakness and paralysis in the hands, feet, or arms.		✓	
Inflammation of the joints: signs and symptoms may include joint pain, swelling, and/or stiffness.		✓	
Inflammation of the eye: signs and symptoms may include eye redness, eye pain, light sensitivity, and/or changes in vision.		✓	

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

Storage (for Healthcare Professional):

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

Imjudo 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 Imjudo:

- 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

Last Revised