ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

IMJUDO 20 mg/ml concentrate for solution for infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of concentrate for solution for infusion contains 20 mg of tremelimumab.
One vial of 1.25 ml of concentrate contains 25 mg of tremelimumab.
One vial of 15 ml of concentrate contains 300 mg of tremelimumab.

Tremelimumab is a human anti-cytotoxic T-lymphocyte antigen 4 (CTLA-4) immunoglobulin G2 IgG2a monoclonal antibody produced in murine myeloma cells by recombinant DNA technology.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion (sterile concentrate).

Clear to slightly opalescent, colourless to slightly yellow solution, free from or practically free from visible particles. The solution has a pH of approximately 5.5 and an osmolality of approximately 285 mOsm/kg.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

IMJUDO in combination with durvalumab and platinum-based chemotherapy is indicated for the first-line treatment of adults with metastatic non-small cell lung cancer (NSCLC) with no sensitising EGFR mutations or ALK positive mutations.

4.2 Posology and method of administration

Treatment must be initiated and supervised by a physician experienced in the treatment of cancer.

Posology

The recommended dose of IMJUDO is presented in Table 1. IMJUDO is administered as an intravenous infusion over 1 hour.

When IMJUDO is administered in combination with other therapeutic agents, refer to the summary of product characteristics (SmPC) of the therapeutic agents for further information.

Table 1. Recommended dose of IMJUDO

Indication	Recommended IMJUDO dosage	Duration of Therapy
Advanced or unresectable HCC	IMJUDO 300 mg[a] as a single dose administered in combination with durvalumab 1500 mg[a] at Cycle 1/Day 1, followed by durvalumab monotherapy every 4 weeks.	Until disease progression or unacceptable toxicity.
Metastatic NSCLC	<u>During platinum chemotherapy:</u> 75 mg[b] in combination with durvalumab 1500 mg and platinum-based chemotherapy every 3 weeks (21 days) for 4 cycles (12 weeks). <u>Post-platinum chemotherapy:</u> Durvalumab 1500 mg every 4 weeks and histology-based pemetrexed maintenance [c] therapy every 4 weeks. A fifth dose of IMJUDO 75 mg[d,e] should be given at week 16 alongside durvalumab dose 6.	Up to a maximum of 5 doses. Patients may receive less than five doses of IMJUDO in combination with durvalumab 1500 mg and platinum-based chemotherapy if there is disease progression or unacceptable toxicity.

[a] For IMJUDO, HCC patients with a body weight of 40 kg or less must receive weight-based dosing, equivalent to IMJUDO 4 mg/kg until weight is greater than 40 kg. For durvalumab, patients with a body weight of 30 kg or less must receive weight-based dosing, equivalent to durvalumab 20 mg/kg until weight is greater than 30 kg.

[b] For IMJUDO, metastatic NSCLC patients with a body weight of 34 kg or less must receive weight-based dosing, equivalent to 1 mg/kg of IMJUDO until the weight improves to greater than 34 kg. For durvalumab, patients with a body weight of 30 kg or less must receive weight-based dosing, equivalent to durvalumab 20 mg/kg until the weight improves to greater than 30 kg.

[c] Consider maintenance administration of pemetrexed for patients with non-squamous tumours who received treatment with pemetrexed and carboplatin/cisplatin during the platinum-based chemotherapy stage.

[d] In the case of dose delay(s), a fifth dose of IMJUDO can be given after Week 16, alongside durvalumab.

[e] If patients receive fewer than 4 cycles of platinum-based chemotherapy, the remaining cycles of IMJUDO (up to a total of 5) alongside durvalumab should be given during the post-platinum chemotherapy phase.

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

Guidelines for management of immune-mediated adverse reactions are described in Table 2 (refer to section 4.4 for further management recommendations, monitoring, and evaluation information). Refer also to the SmPC for durvalumab.

Table 2. Treatment modifications for IMJUDO in combination with durvalumab

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 durvalumab and permanently discontinue IMJUDO (where appropriate)
	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	
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 durvalumab and permanently discontinue IMJUDO (where appropriate)
	ALT or AST > 7 x BLV or > 20 x ULN whichever occurs first or bilirubin > 3 x ULN	Permanently discontinue
Immune-mediated colitis or diarrhoea	Grade 2	Withhold dose[b]
	Grade 3 or 4	Permanently discontinue[e]
Intestinal perforation	ANY grade	Permanently discontinue

Adverse reactions	**Severity**[a]	**Treatment modification**
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
Immune-mediated rash or dermatitis (including pemphigoid)	Grade 2 for > 1 week or Grade 3	Withhold dose[b]
	Grade 4	Permanently discontinue
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
Infusion-related reactions	Grade 1 or 2	Interrupt or slow the rate of infusion
	Grade 3 or 4	Permanently discontinue
Immune-mediated myasthenia gravis	Grade 2-4	Permanently discontinue
Immune-mediated myelitis transverse	Any grade	Permanentely discontinue
Immune-mediated meningitis	Grade 2	Withhold dose[b]

Adverse reactions	**Severity**[a]	**Treatment modification**
	Grade 3 or 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
Non-immune-mediated adverse reactions	Grade 2 and 3	Withhold dose until ≤ Grade 1 or return to baseline
	Grade 4	Permanently discontinue[h]

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

[b] After withholding, IMJUDO and/or 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. IMJUDO and 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] Permanently discontinue IMJUDO for Grade 3; however, treatment with durvalumab can be resumed once event has resolved.

[f] Permanently discontinue IMJUDO and 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, cystitis noninfective, immune-mediated arthritis, uveitis and polymyalgia rheumatica.

[h] With the exception of Grade 4 laboratory abnormalities, about which the decision to discontinue treatment should be based on accompanying clinical signs/symptoms and clinical judgment.

Special populations

Elderly
No dose adjustment is required for elderly patients (≥ 65 years of age) (see section 5.2). Data on patients aged 75 years or older with metastatic NSCLC are limited (see section 4.4).

Renal impairment
No dose adjustment of IMJUDO is recommended in patients with mild or moderate renal impairment. Data from patients with severe renal impairment are too limited to draw conclusions on this population (see section 5.2).

Hepatic impairment
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 section 5.2).

Paediatric population
The safety and efficacy of IMJUDO in children and adolescents below 18 years of age has not been established with regard to HCC and NSCLC. No data are available. Outside its authorised indications,

IMJUDO in combination with durvalumab has been studied in children aged 1 to 17 years with neuroblastoma, solid tumour and sarcoma, however the results of the study did not allow to conclude that the benefits of such use outweigh the risks. Currently available data are described in sections 5.1 and 5.2.

Method of administration

IMJUDO is for intravenous use, it is administered as an intravenous infusion after dilution, over 1 hour (see section 6.6).

For instructions on dilution of the medicinal product before administration, see section 6.6.

IMJUDO in combination with durvalumab

For advanced or uHCC, when IMJUDO is given in combination with durvalumab, administer IMJUDO as a separate intravenous infusion prior to durvalumab on the same day. Refer to the SmPC for durvalumab administration information.

IMJUDO in combination with durvalumab and platinum-based chemotherapy

For NSCLC, when IMJUDO is given in combination with durvalumab and platinum-based chemotherapy, IMJUDO is given first, followed by durvalumab and then platinum-based chemotherapy on the day of dosing.

When IMJUDO is given as a fifth dose in combination with durvalumab and pemetrexed maintenance therapy at week 16, IMJUDO is given first, followed by durvalumab and then pemetrexed maintenance therapy on the day of dosing.

IMJUDO, durvalumab, and platinum-based chemotherapy are administered as separate intravenous infusions. IMJUDO and durvalumab are each given over 1 hour. For platinum-based chemotherapy, refer to the SmPC for administration information. For pemetrexed maintenance therapy, refer to the SmPC for administration information. Separate infusion bags and filters for each infusion should be used.

During cycle 1, IMJUDO is to be followed by durvalumab starting approximately 1 hour (maximum 2 hours) after the end of the IMJUDO infusion. Platinum-based chemotherapy infusion should start approximately 1 hour (maximum 2 hours) after the end of the durvalumab infusion. If there are no clinically significant concerns during cycle 1, then at the physician's discretion, subsequent cycles of durvalumab can be given immediately after IMJUDO and the time period between the end of the durvalumab infusion and the start of chemotherapy can be reduced to 30 minutes.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Refer to section 4.2, Table 2 for recommended treatment modifications. For suspected immune-mediated adverse reactions, adequate evaluation should be performed to confirm aetiology or exclude alternate aetiologies. 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.

Traceability

In order to improve the traceability of biological medicinal products, the tradename and the batch number of the administered product should be clearly recorded.

Immune-mediated pneumonitis

Immune-mediated pneumonitis or interstitial lung disease, defined as requiring use of systemic corticosteroids and with no clear alternate aetiology, occurred in patients receiving tremelimumab in combination with durvalumab, or with durvalumab and chemotherapy (see section 4.8). Patients should be monitored for signs and symptoms of pneumonitis. Suspected pneumonitis should be confirmed with radiographic imaging and other infectious and disease-related aetiologies excluded, and managed as recommended in section 4.2. 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 aetiology, occurred in patients receiving tremelimumab in combination with durvalumab, or with durvalumab and chemotherapy (see section 4.8). Monitor alanine aminotransferase, aspartate aminotransferase, total bilirubin, and alkaline phosphatase levels prior to initiation of treatment and prior to each subsequent infusion. Additional monitoring is to be considered based on clinical evaluation. Immune-mediated hepatitis should be managed as recommended in section 4.2. 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 diarrhoea, defined as requiring use of systemic corticosteroids and with no clear alternate aetiology, occurred in patients receiving tremelimumab in combination with durvalumab, or with durvalumab and chemotherapy (see section 4.8). Intestinal perforation and large intestine perforation were reported in patients receiving tremelimumab in combination with durvalumab. Patients should be monitored for signs and symptoms of colitis/diarrhoea and intestinal perforation and managed as recommended in section 4.2. 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 and thyroiditis

Immune-mediated hypothyroidism, hyperthyroidism and thyroiditis occurred in patients receiving tremelimumab in combination with durvalumab, or with durvalumab and chemotherapy, and hypothyroidism may follow hyperthyroidism (see section 4.8). Patients should be monitored for abnormal thyroid function tests prior to and periodically during treatment and as indicated based on clinical evaluation. Immune-mediated hypothyroidism, hyperthyroidism, and thyroiditis should be managed as recommended in section 4.2. 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 tremelimumab in combination with durvalumab, or with durvalumab and chemotherapy (see section 4.8). Patients should be monitored for clinical signs and symptoms of adrenal insufficiency. For symptomatic adrenal insufficiency, patients should be managed as recommended in section 4.2. 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, which can first present as diabetic ketoacidosis that can be fatal if not detected early, occurred in patients receiving tremelimumab in combination with durvalumab, or with durvalumab and chemotherapy (see section 4.8). Patients should be monitored for clinical signs and symptoms of type 1 diabetes mellitus. For symptomatic type 1 diabetes mellitus, patients should be managed as recommended in section 4.2. 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 tremelimumab in combination with durvalumab, or with durvalumab and chemotherapy (see section 4.8). Patients should be monitored for clinical signs and symptoms of hypophysitis or hypopituitarism. For symptomatic hypophysitis or hypopituitarism, patients should be managed as recommended in section 4.2. 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 nephritis

Immune-mediated nephritis, defined as requiring use of systemic corticosteroids and with no clear alternate aetiology, occurred in patients receiving tremelimumab in combination with durvalumab, or with durvalumab and chemotherapy (see section 4.8). Patients should be monitored for abnormal renal function tests prior to and periodically during treatment and managed as recommended in section 4.2. 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 aetiology, occurred in patients receiving tremelimumab in combination with durvalumab, or with durvalumab and chemotherapy (see section 4.8). Events of Stevens-Johnson Syndrome or toxic epidermal necrolysis have been reported in patients treated with PD-1 and CTLA-4 inhibitors. Patients should be monitored for signs and symptoms of rash or dermatitis and managed as recommended in section 4.2. 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 tremelimumab in combination with durvalumab, or with durvalumab and chemotherapy (see section 4.8). Patients should be monitored for signs and symptoms of immune-mediated myocarditis and managed as recommended in section 4.2. 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.

Immune-mediated pancreatitis

Immune-mediated pancreatitis, occurred in patients receiving tremelimumab in combination with durvalumab and chemotherapy (see section 4.8). Patients should be monitored for signs and symptoms of immune-mediated pancreatitis and managed as recommended in section 4.2.

Other immune-mediated adverse reactions

Given the mechanism of action of tremelimumab in combination with durvalumab, other potential immune-mediated adverse reactions may occur. The following immune-related adverse reactions have been observed in patients treated with tremelimumab in combination with durvalumab, or with durvalumab and chemotherapy: myasthenia gravis, myelitis transverse, myositis, polymyositis, rhabdomyolysis, meningitis, encephalitis, Guillain-Barré syndrome, immune thrombocytopenia, cystitis noninfective, immune-mediated arthritis, uveitis and polymyalgia rheumatica (see section 4.8). Patients should be monitored for signs and symptoms and managed as recommended in section 4.2. Corticosteroids should be administered with 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. Severe infusion-related reactions have been reported in patients receiving tremelimumab in combination with durvalumab (see section 4.8). Infusion-related reactions should be managed as recommended in section 4.2. 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 insititutional standard, appropriate clinical practice guidelines and/or society guidelines.

Disease-specific precaution

Metastatic NSCLC

Limited data are available in elderly patients (≥ 75 years) treated with tremelimumab in combination with durvalumab and platinum-based chemotherapy (see sections 4.8 and 5.1). Careful consideration of the potential benefit/risk of this regimen on an individual basis is recommended.

Patients excluded from clinical studies

Advanced or unresectable HCC

Patients with the following were excluded from clinical studies: Child-Pugh Score B or C, main portal vein thrombosis, liver transplant, uncontrolled hypertension, history of, or current brain metastases, spinal cord compression, co-infection of viral hepatitis B and hepatitis C, active or prior documented gastrointestinal (GI) bleeding within 12 months, ascites requiring non-pharmacologic intervention within 6 months, hepatic encephalopathy within 12 months before the start of treatment, active or prior documented autoimmune or inflammatory disorders. In the absence of data, tremelimumab should be used with caution in these populations after careful consideration of the potential benefit/risk on an individual basis.

Metastatic NSCLC

Patients with the following were excluded from clinical studies: active or prior documented autoimmune disease; active and/or untreated brain metastases; a history of immunodeficiency; administration of systemic immunosuppression within 14 days before the start of tremelimumab or durvalumab, except physiological dose of systemic corticosteroids (≤ 10 mg/day prednisone or equivalent); uncontrolled intercurrent illness; 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 tremelimumab or durvalumab. In the absence of data, tremelimumab should be used with caution in these populations after careful consideration of the potential benefit/risk on an individual basis.

Sodium content

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

The use of systemic corticosteroids or immunosuppressants before starting tremelimumab, except physiological dose of systemic corticosteroids (≤ 10 mg/day prednisone or equivalent), is not recommended because of their potential interference with the pharmacodynamic activity and efficacy of tremelimumab. However, systemic corticosteroids or other immunosuppressants can be used after starting tremelimumab to treat immune-related adverse reactions (see section 4.4).

No formal pharmacokinetic (PK) drug-drug interaction studies have been conducted with tremelimumab. Since the primary elimination pathways of tremelimumab are protein catabolism via reticuloendothelial system or target-mediated disposition, no metabolic drug-drug interactions are expected. PK drug-drug interactions between tremelimumab in combination with durvalumab and platinum-based chemotherapy were assessed in the POSEIDON study and showed no clinically meaningful PK interactions between tremelimumab, durvalumab, nab-paclitaxel, gemcitabine, pemetrexed, carboplatin or cisplatin in the concomitant treatment.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception

Women of childbearing potential should use effective contraception during treatment with tremelimumab and for at least 3 months after the last dose of tremelimumab.

Pregnancy

There are no data on the use of tremelimumab in pregnant women. Based on its mechanism of action, and placental transfer of human IgG2, tremelimumab has the potential to impact maintenance of pregnancy and may cause foetal harm when administered to a pregnant woman. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). IMJUDO 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.

Breast-feeding

There is no information regarding the presence of tremelimumab in human milk, the absorption and effects on the breast-fed infant, or the effects on milk production. Human IgG2 is known to be excreted in human milk. A risk to the breastfed child cannot be excluded. Breast-feeding should be discontinued during treatment with IMJUDO and for at least 3 months after the last dose.

Fertility

There are no data on the potential effects of tremelimumab on fertility in humans or animals. However, mononuclear cell infiltration in prostate and uterus was observed in repeat-dose toxicity studies (see Section 5.3). The clinical relevance of these findings for fertility is unknown.

4.7 Effects on ability to drive and use machines

Tremelimumab has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

IMJUDO in combination with durvalumab

The safety of tremelimumab 300 mg as a single dose in combination with durvalumab, is based on pooled data in 462 HCC patients (HCC pool) from the HIMALAYA Study and another study in HCC patients, Study 22. The most common (> 10%) adverse reactions were rash (32.5%), pruritus (25.5%), diarrhoea (25.3%), abdominal pain (19.7%), aspartate aminotransferase increased/alanine aminotransferase increased (18.0%), pyrexia (13.9%), hypothyroidism (13.0%), cough/productive cough (10.8%) and oedema peripheral (10.4%) (see Table 3).

The most common (> 3%) severe adverse reactions (NCI CTCAE Grade ≥ 3) were aspartate aminotransferase increased/alanine aminotransferase increased (8.9%), lipase increased (7.1%), amylase increased (4.3%) and diarrhoea (3.9%).

The most common (> 2%) serious adverse reactions were colitis (2.6%), diarrhoea (2.4%) and pneumonia (2.2%).

The frequency of treatment discontinuation due to adverse reactions is 6.5%. The most common adverse reactions leading to treatment discontinuation were hepatitis (1.5%) and aspartate aminotransferase increased/alanine aminotransferase increased (1.3%).

IMJUDO in combination with durvalumab and chemotherapy

The safety of tremelimumab given in combination with durvalumab and chemotherapy is based on data in 330 patients with metastatic NSCLC. The most common (> 10%) adverse reactions were anaemia (49.7%), nausea (41.5%), neutropenia (41.2%), fatigue (36.1%), decreased appetite (28.2%), rash (25.8%), thrombocytopenia (24.5%), diarrhoea (21.5%), leukopenia (19.4%), constipation (19.1%), vomiting (18.2%), aspartate aminotransferase increased/alanine aminotransferase increased (17.6%), pyrexia (16.1%), upper respiratory tract infections (15.5%), pneumonia (14.8%), hypothyroidism (13.3%), arthralgia (12.4%), cough/productive cough (12.1%) and pruritus (10.9%).

The most common (> 3%) severe adverse reactions (NCI CTCAE Grade ≥ 3) were neutropenia (23.9%), anaemia (20.6%), pneumonia (9.4%), thrombocytopenia (8.2%), leukopenia (5.5%), fatigue (5.2%), lipase increased (3.9%) and amylase increased (3.6%).

The most common (> 2%) serious adverse reactions were pneumonia (11.5%), anaemia (5.5%), thrombocytopenia (3%), colitis (2.4%), diarrhoea (2.4%), pyrexia (2.4%) and febrile neutropenia (2.1%).

Tremelimumab was discontinued due to adverse reactions in 4.5% of patients. The most common adverse reactions leading to treatment discontinuation were pneumonia (1.2%) and colitis (0.9%).

Tremelimumab was interrupted due to adverse reactions in 40.6% of patients. The most common adverse reactions leading to dose interruption were neutropenia (13.6%), thrombocytopenia (5.8%), leukopenia (4.5%), diarrhoea (3.0%), pneumonia (2.7%), aspartate aminotransferase increased/alanine aminotransferase increased (2.4%), fatigue (2.4%), lipase increased (2.4%), colitis (2.1%), hepatitis (2.1%) and rash (2.1%).

Tabulated list of adverse reactions

Table 3, unless otherwise stated, lists the incidence of adverse reactions (ADRs) in patients treated with tremelimumab 300 mg in combination with durvalumab in the HCC pool of 462 patients, and IMJUDO in combination with durvalumab and platinum-based chemotherapy in the POSEIDON Study, in which 330 patients received tremelimumab. In the POSEIDON study, patients were exposed to tremelimumab during a median of 20 weeks.

Adverse reactions are listed according to system organ class in MedDRA. Within each system organ class, the ADRs are presented in decreasing frequency. The corresponding frequency category for each ADR is defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1000); very rare (< 1/10,000); not known (cannot be estimated from

available data). Within each frequency grouping, ADRs are presented in order of decreasing seriousness.

Table 3. Adverse reactions in patients treated with tremelimumab in combination with durvalumab

	Tremelimumab 75 mg in combination with durvalumab and platinum-based chemotherapy			**Tremelimumab 300 mg in combination with durvalumab**		
	Any Grade (%)		**Grade 3-4 (%)**	**Any Grade (%)**		**Grade 3-4 (%)**
Infections and infestations						
Upper respiratory tract infections[a]	Very common	15.5	0.6	Common	8.4	0
Pneumonia[b]	Very common	14.8	7.3	Common	4.3	1.3
Influenza	Common	3.3	0	Common	2.2	0
Oral candidiasis	Common	2.4	0.3	Uncommon	0.6	0
Dental and oral soft tissue infections[c]	Uncommon	0.6	0.3	Common	1.3	0
Blood and lymphatic system disorders						
Anaemia[d]	Very common	49.7	20.6			
Neutropenia[d,e]	Very common	41.2	23.9			
Thrombocytopenia[d,f]	Very common	24.5	8.2			
Leukopenia[d,g]	Very common	19.4	5.5			
Febrile neutropenia[d]	Common	3.0	2.1			
Pancytopenia[d]	Common	1.8	0.6			
Immune thrombocytopenia	Uncommon	0.3	0	Uncommon[h]	0.3	0
Endocrine disorders						
Hypothyroidism[i]	Very common	13.3	0	Very common	13.0	0
Hyperthyroidism[j]	Common	6.7	0	Common	9.5	0.2
Adrenal insufficiency	Common	2.1	0.6	Common	1.3	0.2
Hypopituitarism/ Hypophysitis	Common	1.5	0.3	Uncommon	0.9	0
Thyroiditis[k]	Common	1.2	0	Common	1.7	0
Diabetes insipidus	Uncommon	0.3	0.3	Rare[l]	<0.1	0
Type 1 diabetes mellitus	Uncommon	0.3	0.3	Uncommon[l]	0.3	<0.1
Eye disorders						
Uveitis	Uncommon	0.3	0	Rare[l]	<0.1	0
Metabolism and nutrition disorders						
Decreased appetite[d]	Very common	28.2	1.5			
Nervous system disorders						
Neuropathy peripheral[d,m]	Common	6.4	0			
Encephalitis[n]	Uncommon	0.6	0.6	Rare[l]	<0.1	0
Myasthenia gravis	Rare[o]	<0.1	<0.1	Uncommon	0.4	0
Guillain-Barré syndrome	Rare[p]	<0.1	0	Rare[p]	<0.1	0
Meningitis	Rare[o]	0.1	0	Uncommon	0.2	0.2
Myelitis transverse[q]	Not known	-	-	Not known	-	-
Cardiac disorders						
Myocarditis[r]	Uncommon	0.3	0	Uncommon	0.4	0
Respiratory, thoracic, and mediastinal disorders						

	Tremelimumab 75 mg in combination with durvalumab and platinum-based chemotherapy			Tremelimumab 300 mg in combination with durvalumab		
	Any Grade (%)		**Grade 3-4 (%)**	**Any Grade (%)**		**Grade 3-4 (%)**
Cough/Productive cough	Very common	12.1	0	Very common	10.8	0.2
Pneumonitis[s]	Common	4.2	1.2	Common	2.4	0.2
Dysphonia	Common	2.4	0	Uncommon	0.9	0
Interstitial lung disease	Uncommon	0.6	0	Uncommon	0.2	0
Gastrointestinal disorders						
Nausea[d]	Very common	41.5	1.8			
Diarrhoea	Very common	21.5	1.5	Very common	25.3	3.9
Constipation[d]	Very common	19.1	0			
Vomiting[d]	Very common	18.2	1.2			
Stomatitis[d,t]	Common	9.7	0			
Amylase increased	Common[o]	8.5	3.6	Common	8.9	4.3
Abdominal pain[u]	Common	7.3	0	Very common	19.7	2.2
Lipase increased	Common[o]	6.4	3.9	Common	10.0	7.1
Colitis[v]	Common	5.5	2.1	Common	3.5	2.6
Pancreatitis[w]	Common	2.1	0.3	Common	1.3	0.6
Intestinal perforation	Rare[p]	<0.1	<0.1	Rare[p]	<0.1	<0.1
Large intestine perforation	Uncommon[p]	0.1	<0.1	Uncommon[p]	0.1	<0.1
Coeliac disease	Rare[p]	0.03	0.03	Rare[p]	0.03	0.03
Hepatobiliary disorders						
Aspartate aminotransferase increased/Alanine aminotransferase increased[x]	Very common	17.6	2.1	Very common	18.0	8.9
Hepatitis[y]	Common	3.9	0.9	Common	5.0	1.7
Skin and subcutaneous tissue disorders						
Alopecia[d]	Very common	10.0	0			
Rash[z]	Very common	25.8	1.5	Very common	32.5	3.0
Pruritus	Very common	10.9	0	Very common	25.5	0
Dermatitis[aa]	Uncommon	0.6	0	Common	1.3	0
Night sweats	Uncommon	0.6	0	Common	1.3	0
Pemphigoid	Uncommon	0.3	0.3	Uncommon	0.2	0
Musculoskeletal and connective tissue disorders						
Arthralgia	Very common	12.4	0.3			
Myalgia	Common	4.2	0	Common	3.5	0.2
Myositis[bb]	Uncommon	0.3	0.3	Uncommon	0.6	0.2
Polymyositis[bb]	Uncommon	0.3	0.3	Uncommon	0.2	0.2
Immune-mediated arthritis	Uncommon[o]	0.2	0	Uncommon	0.6	0
Polymyalgia rheumatica	Not known[cc]	-	-	Uncommon	0.6	0.2
Renal and urinary disorders						
Blood creatinine increased	Common	6.4	0.3	Common	4.5	0.4
Dysuria	Common	1.5	0	Common	1.5	0
Nephritis[dd]	Uncommon	0.6	0	Uncommon	0.6	0.4

	Tremelimumab 75 mg in combination with durvalumab and platinum-based chemotherapy			Tremelimumab 300 mg in combination with durvalumab		
	Any Grade (%)		Grade 3-4 (%)	Any Grade (%)		Grade 3-4 (%)
Cystitis noninfective	Uncommon	0.3	0	Rare[l]	<0.1	0
General disorders and administration site conditions						
Fatigue[d]	Very common	36.1	5.2			
Pyrexia	Very common	16.1	0	Very common	13.9	0.2
Oedema peripheral[ee]	Common	8.5	0	Very common	10.4	0.4
Injury, poisoning and procedural complications						
Infusion-related reaction[ff]	Common	3.9	0.3	Common	1.3	0

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

[b] Includes pneumocystis jirovecii pneumonia, pneumonia and pneumonia bacterial.

[c] Includes periodontitis, pulpitis dental, tooth abscess and tooth infection.

[d] Adverse reaction only applies to chemotherapy ADRs in the Poseidon study.

[e] Includes neutropenia and neutrophil count decreased.

[f] Includes platelet count decreased and thrombocytopenia.

[g] Includes leukopenia and white blood cell count decreased.

[h] Reported in studies outside of the HCC pool. Frequency is based on the POSEIDON study.

[I] Includes blood thyroid stimulating hormone increased, hypothyroidism and immune-mediated hypothyroidism.

[j] Includes blood thyroid stimulating hormone decreased and hyperthyroidism.

[k] Includes autoimmune thyroiditis, immune-mediated thyroiditis, thyroiditis and thyroiditis subacute.

[l] Reported in studies outside of the HCC pool. Frequency is based on a pooled data set of patients treated with tremelimumab in combination with durvalumab.

[m] Includes neuropathy peripheral, parasthesia and peripheral sensory neuropathy.

[n] Includes encephalitis and encephalitis autoimmune.

[o] Reported in studies outside of the POSEIDON study. Frequency is based on a pooled data set of patients treated with tremelimumab in combination with durvalumab.

[p] Reported in studies outside of the POSEIDON study and HCC pool. Frequency is based on a pooled data set of patients treated with tremelimumab in combination with durvalumab.

[q] Reported in studies outside of the POSEIDON study and HCC pool.

[r] Includes autoimmune myocarditis.

[s] Includes immune-mediated pneumonitis and pneumonitis.

[t] Includes mucosal inflammation and stomatitis.

[u] Includes abdominal pain, abdominal pain lower, abdominal pain upper and flank pain.

[v] Includes colitis, enteritis and enterocolitis.

[w] Includes autoimmune pancreatitis, pancreatitis and pancreatitis acute.

[x] Includes alanine aminotransferase increased, aspartate aminotransferase increased, hepatic enzyme increased and transaminases increased.

[y] Includes autoimmune hepatitis, hepatitis, hepatocellular injury, hepatotoxicity, hepatitis acute and immune-mediated hepatitis.

[z] Includes eczema, erythema, rash, rash macular, rash maculopapular, rash papular, rash pruritic and rash pustular.

[aa] Includes dermatitis and immune-mediated dermatitis.

[bb] Includes rhabdomyolysis, myositis, and polymyositis.

[cc] Adverse reaction was not observed in the POSEIDON study but was reported in patients treated with tremelimumab in combination with durvalumab in clinical studies outside of the POSEIDON dataset.

[dd] Includes autoimmune nephritis and immune-mediated nephritis.

[ee] Includes oedema peripheral and peripheral swelling.

[ff] Includes infusion-related reaction and urticaria.

Description of selected adverse reactions

Tremelimumab is associated with immune-mediated adverse reactions. Most of these, including severe reactions, resolved following initiation of appropriate medical therapy or withdrawal of tremelimumab. The data for the following immune-mediated adverse reactions are based on 2280 patients from nine studies across multiple tumour types who received tremelimumab 75 mg every 4 weeks or 1 mg/kg every 4 weeks in combination with durvalumab 1500 mg every 4 weeks, 20 mg/kg every 4 weeks or 10 mg/kg every 2 weeks. This combined safety dataset excludes the POSEIDON Study (and patients treated with tremelimumab in combination with durvalumab and platinum-based chemotherapy). Details for the significant adverse reactions for tremelimumab when given in combination with durvalumab and platinum-based chemotherapy are presented if clinically relevant differences were noted in comparison to tremelimumab in combination with durvalumab.

The data below also reflects information for significant adverse reactions for tremelimumab 300 mg in combination with durvalumab in the HCC pool (n=462).

The management guidelines for these adverse reactions are described in section 4.4.

Immune-mediated pneumonitis

In the combined safety database with tremelimumab in combination with durvalumab (n=2280), immune-mediated pneumonitis occurred in 86 (3.8%) patients, including Grade 3 in 30 (1.3%) patients, Grade 4 in 1 (< 0.1%) patient, and Grade 5 (fatal) in 7 (0.3%) patients. The median time to onset was 57 days (range: 8 - 912 days). All patients received systemic corticosteroids and 79 of the 86 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). Seven patients also received other immunosuppressants. Treatment was discontinued in 39 patients. Resolution occurred in 51 patients.

In the HCC pool (n=462), 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 the combined safety database with tremelimumab in combination with durvalumab (n=2280), immune-mediated hepatitis occurred in 80 (3.5%) patients, including Grade 3 in 48 (2.1%) patients, Grade 4 in 8 (0.4%) patients and Grade 5 (fatal) in 2 (< 0.1%) patients. The median time to onset was 36 days (range: 1 - 533 days). All patients received systemic corticosteroids and 68 of the 80 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). Eight patients also received other immunosuppressants. Treatment was discontinued in 27 patients. Resolution occurred in 47 patients.

In the HCC pool (n=462), 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 the combined safety database with tremelimumab in combination with durvalumab (n=2280), immune-mediated colitis or diarrhoea occurred in 167 (7.3%) patients, including Grade 3 in 76 (3.3%)

patients and Grade 4 in 3 (0.1%) patients. The median time to onset was 57 days (range: 3 - 906 days). All patients received systemic corticosteroids and 151 of the 167 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). Twenty-two patients also received other immunosuppressants. Treatment was discontinued in 54 patients. Resolution occurred in 141 patients.

In the HCC pool (n=462), immune-mediated colitis or diarrhoea 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 observed in patients receiving tremelimumab in combination with durvalumab (rare) in studies outside of the HCC pool.

Immune-mediated endocrinopathies

Immune-mediated hypothyroidism
In the combined safety database with tremelimumab in combination with durvalumab (n=2280), immune-mediated hypothyroidism occurred in 209 (9.2%) patients, including Grade 3 in 6 (0.3%) patients. The median time to onset was 85 days (range: 1 - 624 days). Thirteen patients received systemic corticosteroids and 8 of the 13 received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). Treatment discontinued in 3 patients. Resolution occurred in 52 patients. Immune-mediated hypothyroidism was preceded by immune-mediated hyperthyroidism in 25 patients or immune-mediated thyroiditis in 2 patients.

In the HCC pool (n=462), 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 including hormone replacement therapy. Resolution occurred in 6 patients. Immune-mediated hypothyroidism was preceded by immune-mediated hyperthyroidism in 4 patients.

Immune-mediated hyperthyroidism
In the combined safety database with tremelimumab in combination with durvalumab (n=2280), immune-mediated hyperthyroidism occurred in 62 (2.7%) patients, including Grade 3 in 5 (0.2%) patients. The median time to onset was 33 days (range: 4 - 176 days). Eighteen patients received systemic corticosteroids, and 11 of the 18 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). Fifty-three patients required other therapy (thiamazole, carbimazole, propylthiouracil, perchlorate, calcium channel blocker or beta-blocker). One patient discontinued treatment due to hyperthyroidism. Resolution occurred in 47 patients.

In the HCC pool (n=462), 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 corticosteriods, and all of the four patients received 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 the combined safety database with tremelimumab in combination with durvalumab (n=2280), immune-mediated thyroiditis occurred in 15 (0.7%) patients, including Grade 3 in 1 (< 0.1%) patient. The median time to onset was 57 days (range: 22 - 141 days). Five patients received systemic corticosteroids and 2 of the 5 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). Thirteen patients required other therapy including, hormone replacement therapy, thiamazole, carbimazole, propylthiouracil, perchlorate, calcium channel blocker,

or beta-blocker. No patients discontinued treatment due to immune-mediated thyroiditis. Resolution occurred in 5 patients.

In the HCC pool (n=462), 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. Resolution occurred in 2 patients.

Immune-mediated adrenal insufficiency
In the combined safety database with tremelimumab in combination with durvalumab (n=2280), immune-mediated adrenal insufficiency occurred in 33 (1.4%) patients, including Grade 3 in 16 (0.7%) patients and Grade 4 in 1 (< 0.1%) patient. The median time to onset was 105 days (range: 20-428 days). Thirty-two patients received systemic corticosteroids, and 10 of the 32 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). Treatment was discontinued in one patient. Resolution occurred in 11 patients.

In the HCC pool (n=462), 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 the combined safety database with tremelimumab in combination with durvalumab (n=2280), immune-mediated type 1 diabetes mellitus occurred in 6 (0.3%) patients, including Grade 3 in 1 (< 0.1%) patient and Grade 4 in 2 (< 0.1%) patients. The median time to onset was 58 days (range: 7 - 220 days). All patients required insulin. Treatment was discontinued for 1 patient. Resolution occurred in 1 patient.

Immune-mediated type 1 diabetes mellitus was observed in patients receiving tremelimumab in combination with durvalumab (uncommon) in studies outside of the HCC pool.

Immune-mediated hypophysitis/hypopituitarism
In the combined safety database with tremelimumab in combination with durvalumab (n=2280), immune-mediated hypophysitis/hypopituitarism occurred in 16 (0.7%) patients, including Grade 3 in 8 (0.4%) patients. The median time to onset for the events was 123 days (range: 63 - 388 days). All patients received systemic corticosteroids and 8 of the 16 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). Four patients also required endocrine therapy. Treatment was discontinued in 2 patients. Resolution occurred in 7 patients.

In the HCC pool (n=462), 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 the combined safety database with tremelimumab in combination with durvalumab (n=2280), immune-mediated nephritis occurred in 9 (0.4%) patients, including Grade 3 in 1 (< 0.1%) patient. The median time to onset was 79 days (range: 39 - 183 days). All patients received systemic corticosteroids and 7 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). Treatment was discontinued in 3 patients. Resolution occurred in 5 patients.

In the HCC pool (n=462), 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 patients 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 the combined safety database with tremelimumab in combination with durvalumab (n=2280), immune-mediated rash or dermatitis (including pemphigoid) occurred in 112 (4.9%) patients, including Grade 3 in 17 (0.7%) patients. The median time to onset was 35 days (range: 1 - 778 days). All patients received systemic corticosteroids, and 57 of the 112 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). Treatment was discontinued in 10 patients. Resolution occurred in 65 patients.

In the HCC pool (n=462), 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.

Infusion-related reactions

In the combined safety database with tremelimumab in combination with durvalumab (n=2280), infusion-related reactions occurred in 45 (2.0%) patients, including Grade 3 in 2 (< 0.1%) patients. There were no Grade 4 or 5 events.

Laboratory abnormalities

In patients treated with tremelimumab in combination with durvalumab and platinum-based chemotherapy in the POSEIDON study (n=330), the proportion of patients who experienced a shift from baseline to a Grade 3 or 4 laboratory abnormality was as follows: 6.2% for alanine aminotransferase increased, 5.2% for aspartate aminotransferase increased, 4.0% for blood creatinine increased, 9.4% for amylase increased and 13.6% for lipase increased. The proportion of patients who experienced a TSH shift from baseline that was ≤ ULN to > ULN was 24.8% and a TSH shift from baseline that was ≥ LLN to < LLN was 32.9%.

Immune checkpoint inhibitor class effects

There have been cases of the following adverse reactions reported during treatment with other immune checkpoint inhibitors which might also occur during treatment with tremelimumab: pancreatic exocrine insufficiency.

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 tremelimumab 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. Neutralising 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 safety.

In the HIMALAYA study, of the 182 patients who were treated with tremelimumab 300 mg as a single dose in combination with durvalumab and evaluable for the presence of ADAs against tremelimumab, 20 (11.0%) patients tested positive for treatment-emergent ADAs. Neutralising 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.

In the POSEIDON study, of the 278 patients who were treated with tremelimumab 75 mg in combination with durvalumab 1500 mg every 3 weeks and platinum-based chemotherapy and evaluable for the presence of ADAs, 38 (13.7%) patients tested positive for treatment-emergent ADAs. Neutralising antibodies against tremelimumab were detected in 11.2% (31/278) of patients. The presence of ADAs did not have an apparent effect on pharmacokinetics or safety.

Elderly

Data from HCC patients 75 years of age or older are limited.

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

There is no information on overdose with tremelimumab. In case of overdose, patients should be closely monitored for signs or symptoms of adverse reactions, and appropriate symptomatic treatment instituted immediately.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other monoclonal antibodies and antibody drug conjugates. ATC code: L01FX20

Mechanism of action

Cytotoxic T lymphocyte-associated antigen (CTLA-4) is primarily expressed on the surface of T lymphocytes. 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, resulting in increased T-cell diversity and enhanced anti-tumour activity.

The combination of tremelimumab, a CTLA-4 inhibitor and durvalumab, a PD-L1 inhibitor results in improved anti-tumour responses in metastatic non-small cell lung cancer and hepatocellular carcinoma.

Clinical efficacy

HCC - HIMALAYA Study

The efficacy of IMJUDO 300 mg as a single dose in combination with durvalumab was evaluated in the HIMALAYA Study, a randomised, open-label, multicentre study in patients with confirmed uHCC who did not receive prior systemic treatment for HCC. The study included patients with Barcelona Clinic Liver Cancer (BCLC) Stage C or B (not eligible for locoregional therapy) and Child-Pugh Score Class A.

The study excluded patients with brain metastases or a history of brain metastases, co-infection of viral hepatitis B and hepatitis C; active or prior documented gastro-intestinal (GI) bleeding within 12 months; ascites requiring non-pharmacologic intervention within 6 months; hepatic encephalopathy within 12 months before the start of treatment; active or prior documented autoimmune or inflammatory disorders.

Patients with esophageal varices were included except those with active or prior documented GI bleeding within 12 months prior to study entry.

Randomisation was stratified by macrovascular invasion (MVI) (yes vs. no), aetiology of liver disease (confirmed hepatitis B virus vs. confirmed hepatitis C virus vs. others) and ECOG performance status (0 vs. 1). The HIMALAYA study randomised 1171 patients 1:1:1 to receive:

- Durvalumab 1500 mg every 4 weeks
- IMJUDO 300 mg as a single dose + durvalumab 1500 mg; followed by durvalumab 1500 mg every 4 weeks
- Sorafenib 400 mg twice daily

Tumour assessments were conducted every 8 weeks for the first 12 months and then every 12 weeks thereafter. Survival assessments were conducted every month for the first 3 months following treatment discontinuation and then every 2 months.

The primary endpoint was Overall Survival (OS) for the comparison of IMJUDO 300 mg as a single dose in combination with durvalumab vs. sorafenib. Secondary endpoints included Progression-Free Survival (PFS), Investigator-assessed Objective Response Rate (ORR) and Duration of Response (DoR) according to RECIST v1.1.

The demographics and baseline disease characteristics were well balanced between study arms. The baseline demographics of the overall study population were as follows: male (83.7%), age < 65 years (50.4%), White (44.6%), Asian (50.7%), Black or African American (1.7%), Other race (2.3%), ECOG PS 0 (62.6%); Child-Pugh Class score A (99.5%), macrovascular invasion (25.2%), extrahepatic spread (53.4%), baseline AFP < 400 ng/ml (63.7%), baseline AFP ≥ 400 ng/ml (34.5%), viral aetiology; hepatitis B (30.6%), hepatitis C (27.2%), uninfected (42.2%), evaluable PD-L1 data (86.3%), PD-L1 Tumour area positivity (TAP) ≥ 1% (38.9%), PD-L1 TAP < 1% (48.3%) [Ventana PD-L1 (SP263) assay].

Results are presented in Table 4 and Figure 1.

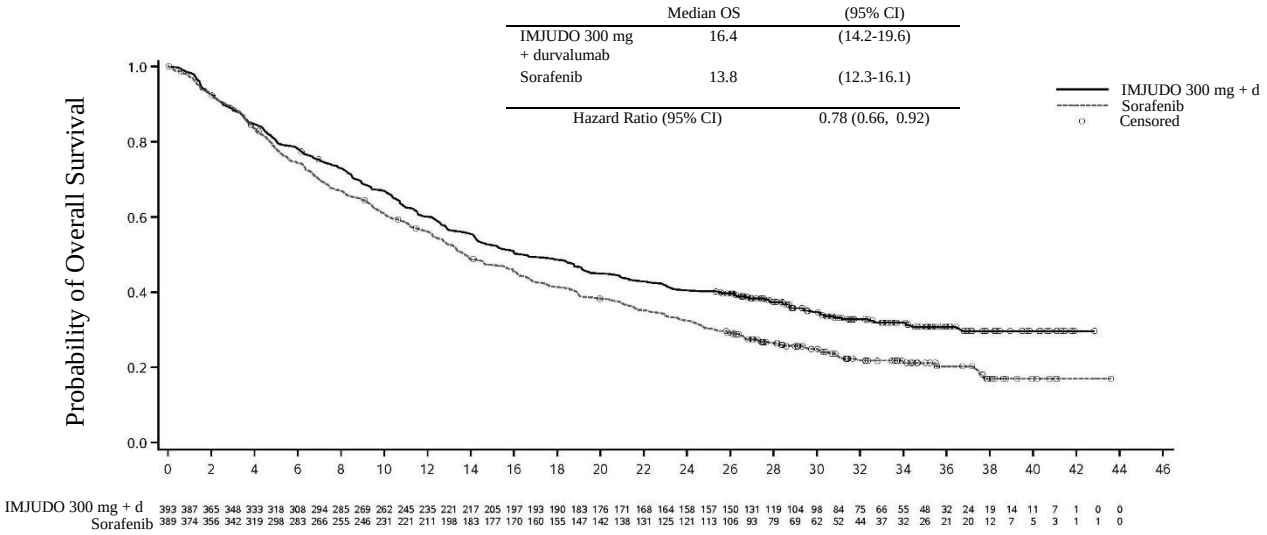
Table 4. Efficacy results for the HIMALAYA study for IMJUDO 300 mg with durvalumab vs. Sorafenib

	IMJUDO 300 mg + durvalumab (n= 393)	**Sorafenib (n= 389)**
Follow-up duration		
Median follow-up (months)[a]	33.2	32.2
OS		
Number of deaths (%)	262 (66.7)	293 (75.3)
Median OS (months)	16.4	13.8

	IMJUDO 300 mg + durvalumab (n= 393)	Sorafenib (n= 389)
(95% CI)	(14.2, 19.6)	(12.3, 16.1)
HR (95% CI)	0.78 (0.66, 0.92)	
p-value[b]	0.0035	
PFS		
Number of events (%)	335 (85.2)	327 (84.1)
Median PFS (months) (95% CI)	3.78 (3.68, 5.32)	4.07 (3.75, 5.49)
HR (95% CI)	0.90 (0.77, 1.05)	
ORR		
ORR n (%)[c]	79 (20.1)	20 (5.1)
Complete Response n (%)	12 (3.1)	0
Partial Response n (%)	67 (17.0)	20 (5.1)
DoR		
Median DoR (months)	22.3	18.4

[a] Calculated using the reverse Kaplan-Meier technique (with censor indicator reversed).
[b] Based on a Lan-DeMets alpha spending function with O'Brien Fleming type boundary and the actual number of events observed, the boundary for declaring statistical significance for IMJUDO 300 mg + durvalumab vs. Sorafenib was 0.0398 (Lan◦and◦DeMets 1983).
[c] Confirmed complete response.
CI=Confidence Interval

Figure 1. Kaplan-Meier curve of OS



NSCLC – POSEIDON study

POSEIDON was a study designed to evaluate the efficacy of durvalumab with or without IMJUDO in combination with platinum-based chemotherapy. POSEIDON was a randomised, open-label, multicentre study in 1013 metastatic NSCLC patients with no sensitising epidermal growth factor receptor (EGFR) mutation or anaplastic lymphoma kinase (ALK) genomic tumour aberrations. Patients with histologically or cytologically documented metastatic NSCLC were eligible for enrolment. Patients had no prior chemotherapy or any other systemic therapy for metastatic NSCLC. Prior to randomisation, patients had tumour PD-L1 status confirmed by using the Ventana PD-L1

(SP263) assay. Patients had a World Health Organization (WHO)/Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 at enrolment.

The study excluded patients with active or prior documented autoimmune disease; active and/or untreated brain metastases; a history of immunodeficiency; administration of systemic immunosuppression within 14 days before the start of IMJUDO or durvalumab, 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 IMJUDO and/or durvalumab (see section 4.4).

Randomisation was stratified by tumour cells (TC) PD-L1 expression (TC ≥ 50% vs. TC < 50%), disease stage (Stage IVA vs. Stage IVB, per the 8th edition of American Joint Committee on Cancer), and histology (non-squamous vs. squamous).

Patients were randomised 1:1:1 to receive:

- Arm 1: IMJUDO 75 mg with durvalumab 1500 mg and platinum-based chemotherapy every 3 weeks for 4 cycles, followed by durvalumab 1500 mg every 4 weeks as monotherapy. A fifth dose of IMJUDO 75 mg was given at Week 16 alongside durvalumab dose 6.
- Arm 2: Durvalumab 1500 mg and platinum-based chemotherapy every 3 weeks for 4 cycles, followed by durvalumab 1500 mg every 4 weeks as monotherapy.
- Arm 3: Platinum-based chemotherapy every 3 weeks for 4 cycles. Patients could receive 2 additional cycles (a total of 6 cycles post-randomisation), as clinically indicated, at investigator's discretion.

Patients received one of the following platinum-based chemotherapy regimens:

- Non-squamous NSCLC
    - Pemetrexed 500 mg/m^2 with carboplatin AUC 5-6 or cisplatin 75 mg/m^2 every 3 weeks. Unless contraindicated by the investigator, pemetrexed maintenance could be given.
- Squamous NSCLC
    - Gemcitabine 1000 or 1250 mg/m^2 on Days 1 and 8 with cisplatin 75 mg/m^2 or carboplatin AUC 5-6 on Day 1 every 3 weeks.
- Non-squamous or squamous NSCLC
    - Nab-paclitaxel 100 mg/m^2 on Days 1, 8, and 15 with carboplatin AUC 5-6 on Day 1 every 3 weeks.

IMJUDO was given up to a maximum of 5 doses unless there was disease progression or unacceptable toxicity. Durvalumab and histology-based pemetrexed maintenance therapy (when applicable) was continued until disease progression or unacceptable toxicity.

Tumour assessments were conducted at Week 6 and Week 12 from the date of randomisation, and then every 8 weeks until confirmed objective disease progression. Survival assessments were conducted every 2 months following treatment discontinuation.

The dual primary endpoints of the study were progression-free survival (PFS) and overall survival (OS) for durvalumab + platinum-based chemotherapy (Arm 2) vs. platinum-based chemotherapy alone (Arm 3). The key secondary endpoints of the study were PFS and OS for IMJUDO + durvalumab + platinum-based chemotherapy (Arm 1) and platinum-based chemotherapy alone (Arm 3). The secondary endpoints included objective response rate (ORR) and duration of response (DoR). PFS, ORR, and DoR were assessed using Blinded Independent Central Review (BICR) according to RECIST v1.1.

The demographics and baseline disease characteristics were well-balanced between study arms. Baseline demographics of the overall study population were as follows: male (76.0%), age ≥ 65 years (47.1%), age ≥ 75 years (11.3%) median age 64 years (range: 27 to 87 years), White (55.9%), Asian (34.6%), Black or African American (2.0%), other (7.6%), non-Hispanic or Latino (84.2%), current smoker or past-smoker (78.0%), WHO/ECOG PS 0 (33.4%) and WHO/ECOG PS 1 (66.5%). Disease

characteristics were as follows: Stage IVA (50.0%), Stage IVB (49.6%), histological sub-groups of squamous (36.9%), non-squamous (62.9%), brain metastases (10.5%), PD-L1 expression TC ≥ 50% (28.8%) and PD-L1 expression TC < 50% (71.1%).

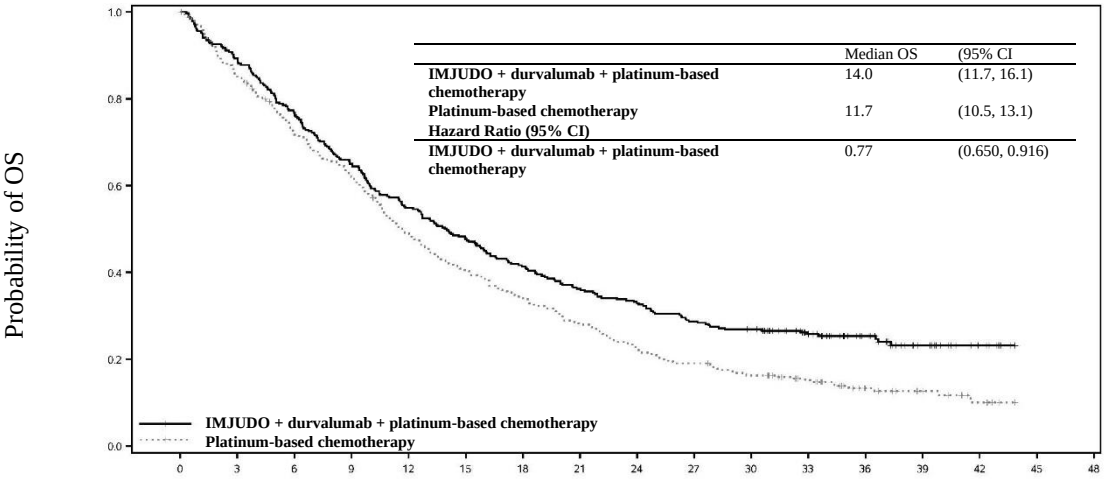
The study showed a statistically significant improvement in OS with IMJUDO + durvalumab + platinum-based chemotherapy (Arm 1) vs. platinum-based chemotherapy alone (Arm 3). IMJUDO + durvalumab + platinum-based chemotherapy showed a statistically significant improvement in PFS vs. platinum-based chemotherapy alone. The results are summarised below.

Table 5. Efficacy results for the POSEIDON study

	Arm 1: IMJUDO+durvalumab+ platinum-based chemotherapy (n=338)	**Arm 3: Platinum-based chemotherapy (n=337)**
OS[a]		
Number of deaths (%)	251 (74.3)	285 (84.6)
Median OS (months) (95% CI)	14.0 (11.7, 16.1)	11.7 (10.5, 13.1)
HR (95% CI)[b]	0.77 (0.650, 0.916)	
p-value[c]	0.00304	
PFS[a]		
Number of events (%)	238 (70.4)	258 (76.6)
Median PFS (months) (95% CI)	6.2 (5.0, 6.5)	4.8 (4.6, 5.8)
HR (95% CI)[b]	0.72 (0.600, 0.860)	
p-value[c]	0.00031	
ORR n (%)[d,e]	130 (38.8)	81 (24.4)
Complete Response n (%)	2 (0.6)	0
Partial Response n (%)	128 (38.2)	81 (24.4)
Median DoR (months) (95% CI)[d,e]	9.5 (7.2, NR)	5.1 (4.4, 6.0)

[a] Analysis of PFS at data cut off 24 July 2019 (median follow up 10.15 months). Analysis of OS at data cut off 12 March 2021 (median follow up 34.86 months). The boundaries for declaring efficacy (Arm 1 vs. Arm 3: PFS 0.00735, OS 0.00797; 2-sided) were determined by a Lan-DeMets alpha spending function that approximates an O'Brien Fleming approach. PFS was assessed by BICR according to RECIST v1.1.
[b] HR are derived using a Cox pH model stratified by PD-L1, histology and disease stage.
[c] 2-sided p-value based on a log-rank test stratified by PD-L1, histology and disease stage.
[d] Confirmed Objective Response.
[e] Post-hoc analysis.
NR=Not Reached, CI=Confidence Interval

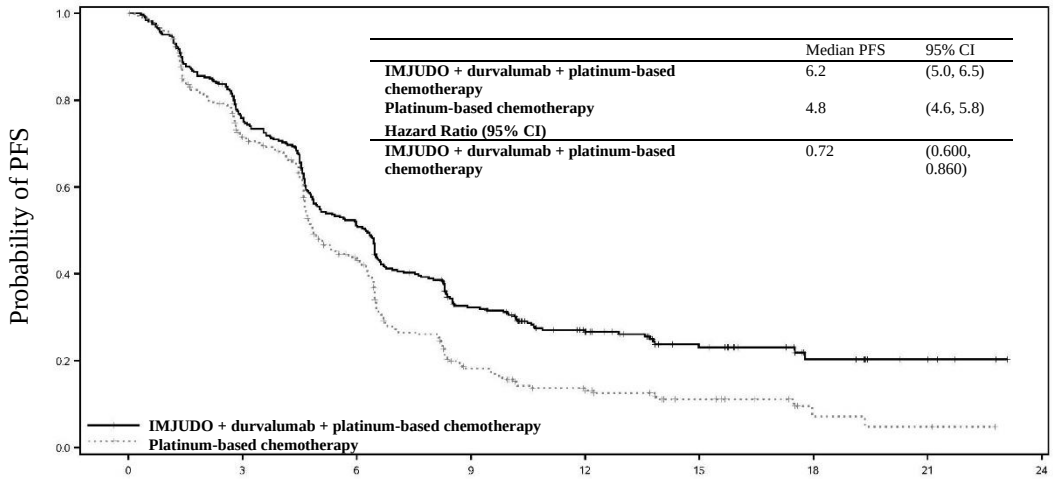
Figure 2. Kaplan-Meier curve of OS



Number of patients at risk

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

Figure 3. Kaplan-Meier curve of PFS

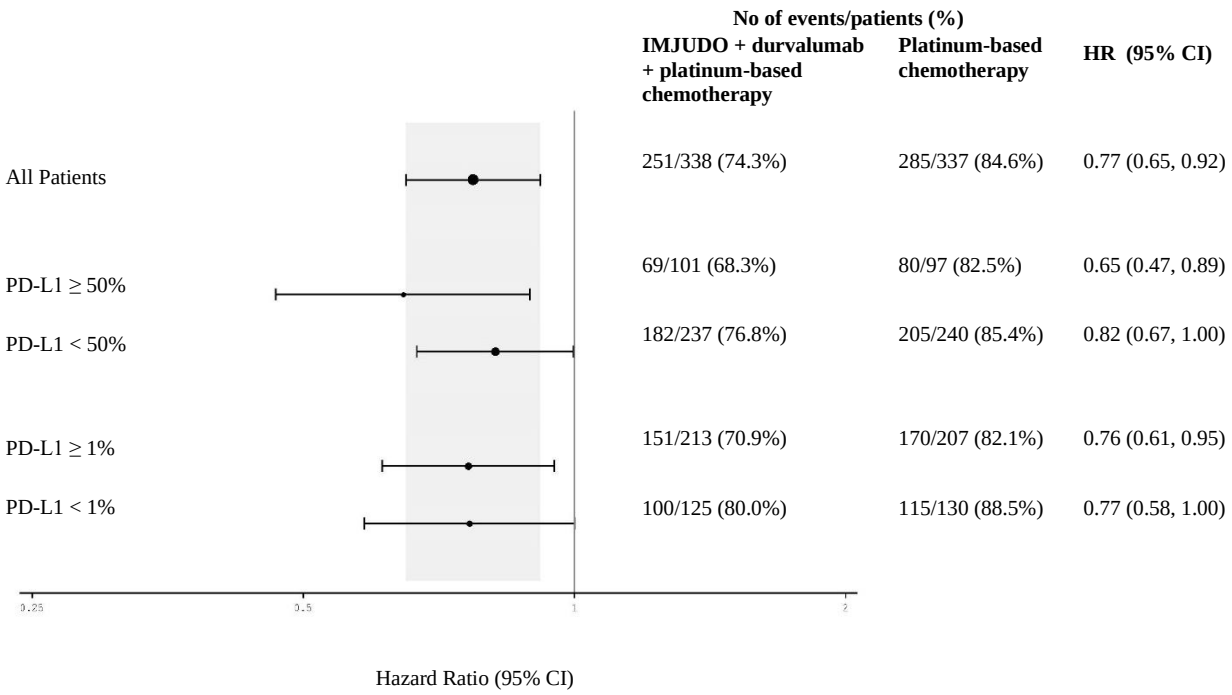


Number of patients at risk

Month	0	3	6	9	12	15	18	21	24
IMJUDO + durvalumab + platinum-based chemotherapy	338	243	161	94	56	32	13	5	0
Platinum-based chemotherapy	337	219	121	43	23	12	3	2	0

Figure 4 summarises efficacy results of OS by tumour PD-L1 expression in prespecified subgroup analyses.

Figure 4. Forest plot of OS by PD-L1 expression for IMJUDO + durvalumab + platinum-based chemotherapy vs. platinum-based chemotherapy



Elderly population
A total of 75 patients aged ≥ 75 years were enrolled in the IMJUDO in combination with durvalumab and platinum-based chemotherapy (n=35) and platinum-based chemotherapy only (n=40) arms of the POSEIDON study. An exploratory HR of 1.05 (95% CI: 0.64, 1.71) for OS was observed for IMJUDO in combination with durvalumab and platinum-based chemotherapy vs. platinum-based chemotherapy within this study subgroup. Due to the exploratory nature of this subgroup analysis no definitive conclusions can be drawn, but caution is suggested when considering this regimen for elderly patients.

Paediatric population

The safety and efficacy of IMJUDO in combination with durvalumab in children and adolescents aged less than 18 years has not been established. Study D419EC00001 was a multi centre, open-label dose finding and dose expansion study to evaluate the safety, preliminary efficacy and pharmacokinetics of IMJUDO in combination with durvalumab followed by durvalumab monotherapy in paediatric patients with advanced malignant solid tumours (except primary central nervous system tumours) who had disease progression and for whom no standard of care treatment exists. The study enrolled 50 paediatric patients with an age range from 1 to 17 years with primary tumour categories: neuroblastoma, solid tumour and sarcoma. Patients received IMJUDO 1 mg/kg either in combination with durvalumab 20 mg/kg or durvalumab 30 mg/kg every 4 weeks for 4 cycles, followed by durvalumab as monotherapy every 4 weeks. In the dose finding phase, IMJUDO and durvalumab combination therapy was preceded by a single cycle of durvalumab; 8 patients in this phase however discontinued treatment prior to receiving IMJUDO. Thus, of the 50 patients enrolled in the study, 42 received IMJUDO in combination with durvalumab and 8 received durvalumab only. In the dose-expansion phase, an ORR of 5.0% (1/20 patients) was reported in the evaluable for response analysis set. No new safety signals were observed relative to the known safety profiles of IMJUDO and durvalumab in adults. See section 4.2 for information on paediatric use.

5.2 Pharmacokinetic properties

The pharmacokinetics (PK) of tremelimumab was assessed for tremelimumab as monotherapy,in combination with durvalumab and in combination with platinum-based chemotherapy.

The PK of tremelimumab was studied in patients with doses ranging from 75 mg to 750 mg or 10 mg/kg administered intravenously once every 4 or 12 weeks as monotherapy, or at a single dose of 300 mg. PK exposure increased dose proportionally (linear PK) at doses ≥ 75 mg. Steady state was achieved at approximately 12 weeks. Based on population PK analysis that included patients (n = 1605) who received tremelimumab monotherapy or in combination with other medicinal products in the dose range of ≥ 75 mg (or 1 mg/kg) every 3 or 4 weeks, the estimated tremelimumab clearance (CL) and volume of distribution (Vd) were 0.309 l/day and 6.33 l, respectively. The terminal half-life was approximately 14.2 days. The primary elimination pathways of tremelimumab are protein catabolism via reticuloendothelial system or target mediated disposition.

Special populations

Age (18–87 years), body weight (34-149 kg), gender, positive anti-drug antibody (ADA) status, albumin levels, LDH levels, creatinine levels, tumour type, race or ECOG/WHO status had no clinically significant effect on the PK of tremelimumab.

Renal impairment

Mild (creatinine clearance (CrCL) 60 to 89 ml/min) and moderate renal impairment (creatinine clearance (CrCL) 30 to 59 ml/min) had no clinically significant effect on the PK of tremelimumab. The effect of severe renal impairment (CrCL 15 to 29 ml/min) on the PK of tremelimumab is unknown; the potential need for dose adjustment cannot be determined. However, as IgG monoclonal antibodies are not primarily cleared via renal pathways, a change in renal function is not expected to influence tremelimumab exposure.

Hepatic impairment

Mild hepatic impairment (bilirubin ≤ ULN and AST > ULN or bilirubin > 1.0 to 1.5 × ULN and any AST) and moderate hepatic impairment (bilirubin > 1.5 to 3 x ULN and any AST) had no clinically significant effect on the PK of tremelimumab. The effect of severe hepatic impairment (bilirubin > 3.0 x ULN and any AST) on the PK of tremelimumab is unknown; the potential need for dose adjustment cannot be determined. However, as IgG monoclonal antibodies are not primarily cleared via hepatic pathways, a change in hepatic function is not expected to influence tremelimumab exposure.

Paediatric population

The PK of tremelimumab in combination with durvalumab was evaluated in a study of 50 paediatric patients with an age range from 1 to 17 years in study D419EC00001. Patients received tremelimumab 1 mg/kg either in combination with durvalumab 20 mg/kg or in combination with durvalumab 30 mg/kg every 4 weeks for 4 cycles, followed by durvalumab as monotherapy every 4 weeks. Based on population PK analysis, tremelimumab systemic exposure in paediatric patients ≥ 35kg receiving tremelimumab 1 mg/kg every 4 weeks was similar to exposure in adults receiving 1 mg/kg every 4 weeks, whereas in paediatric patients < 35kg, exposure was lower relative to adults.

5.3 Preclinical safety data

Animal toxicology

In the chronic 6-month study in cynomolgus monkeys, treatment with tremelimumab was associated with dose-related incidence in persistent diarrhoea and skin rash, scabs and open sores, which were dose-limiting. These clinical signs were also associated with decreased appetite and body weight and swollen peripheral lymph nodes. Histopathological findings correlating with the observed clinical signs included reversible chronic inflammation in the cecum and colon, mononuclear cell infiltration in the skin and hyperplasia in lymphoid tissues.

A dose-dependent increase in the incidence and severity of mononuclear cell infiltration with or without mononuclear cell inflammation was observed in the salivary gland, pancreas (acinar), thyroid, parathyroid, adrenal, heart, esophagus, tongue, periportal liver area, skeletal muscle, prostate, uterus, pituitary, eye (conjunctiva, extra ocular muscles), and choroid plexus of the brain. No NOAEL was found in this study with animals treated with the lowest dose of 5 mg/kg/week, however the intermediate dose of 15 mg/kg week was considered the highest non-severely toxic dose (HNSTD). This dose provided an exposure-based safety margin of 1.77-5.33 to clinical relevant exposure based on the clinical dosing regimen of either a 300 mg single dose or 75 mg every three weeks.

Carcinogenicity and mutagenicity

The carcinogenic and genotoxic potential of tremelimumab has not been evaluated.

Reproductive toxicology

Mononuclear cell infiltration in prostate and uterus was observed in repeat dose toxicity studies. Since animal fertility studies have not been conducted with tremelimumab, the relevance of these findings for fertility is unknown. In reproduction studies, administration of tremelimumab to pregnant cynomolgus monkeys during the period of organogenesis was not associated with maternal toxicity or effects on pregnancy losses, foetal weights, or external, visceral, skeletal abnormalities or weights of selected foetal organs.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Histidine
Histidine hydrochloride monohydrate
Trehalose dihydrate
Disodium edetate dihydrate
Polysorbate 80
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

Unopened vial

4 years at 2 °C - 8 °C.

Diluted solution

Chemical and physical in-use stability has been demonstrated for up to 28 days at 2 °C to 8 °C and for up to 48 hours at room temperature (up to 25 °C) from the time of preparation.

From a microbiological point of view, the prepared solution for infusion should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 °C to 8 °C or 12 hours at room temperature (up to 25 °C), unless dilution has taken place in controlled and validated aseptic conditions.

Lack of microbial growth in the prepared solution for infusion has been demonstrated for up to 28 days at 2 °C to 8 °C and for up to 48 hours at room temperature (up to 25 °C) from the time of preparation.

6.4 Special precautions for storage

Store in a refrigerator (2 °C - 8 °C).

Do not freeze.

Store in the original package in order to protect from light.

For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Two pack sizes of IMJUDO are available:

- 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.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Preparation of solution

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

- Visually inspect medicinal product for particulate matter and discolouration. IMJUDO is 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 bag containing sodium chloride 9 mg/ml (0.9%) solution for injection, or glucose 50 mg/ml (5%) solution for 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.

- Care must be taken to ensure the sterility of the prepared solution.

- Do not re-enter the vial after withdrawal of the medicinal product.

- Discard any unused portion left in the vial.

Administration

- Administer the 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 medicinal products through the same infusion line.

Disposal

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

7. MARKETING AUTHORISATION HOLDER

AstraZeneca AB
SE-151 85 Södertälje
Sweden

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/22/1713/001 25 mg vial
EU/1/22/1713/002 300 mg vial

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20 February 2023

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

Boehringer Ingelheim Pharma GmBH & Co. KG
Birkendorfer Strasse 65
88397, Biberach An Der Riss
Germany

Name and address of the manufacturers responsible for batch release

AstraZeneca AB
Gärtunavägen
SE-152 57 Södertälje
Sweden

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Prior to the launch of IMJUDO in each Member State the MAH will agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority. The additional risk minimisation measure is aimed at increasing awareness and providing information concerning the symptoms of immune-mediated adverse reactions.

The MAH shall ensure that in each Member State where IMJUDO is marketed, all physicians who are expected to use IMJUDO have access to/are provided with the following to provide to their patients:

Patient card

Key messages of the Patient Card include:

- A warning that immune-mediated adverse reactions (in lay terms) may occur and that they can be serious.
- A description of the symptoms of immune-mediated adverse reactions.
- A reminder to contact a healthcare professional provider immediately to discuss signs and symptoms.
- Space for contact details of the prescriber.
- A reminder to carry the card at all times.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

IMJUDO 20 mg/ml concentrate for solution for infusion
tremelimumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One ml of concentrate contains 20 mg of tremelimumab.
One vial of 1.25 ml of concentrate contains 25 mg of tremelimumab.
One vial of 15 ml of concentrate contains 300 mg of tremelimumab.

3. LIST OF EXCIPIENTS

Excipients: histidine, histidine hydrochloride monohydrate, trehalose dihydrate, disodium edetate dihydrate, polysorbate 80, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion

25 mg/1.25 ml
300 mg/15 ml
1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intravenous use
Read the package leaflet before use.
For single use only

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

AstraZeneca AB
SE-151 85 Södertälje
Sweden

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/22/1713/001 25 mg vial
EU/1/22/1713/002 300 mg vial

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

IMJUDO 20 mg/ml sterile concentrate
tremelimumab
IV

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

25 mg/1.25 ml
300 mg/15 ml

6. OTHER

AstraZeneca

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

IMJUDO 20 mg/ml concentrate for solution for infusion
tremelimumab

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What IMJUDO is and what it is used for

IMJUDO is an anti-cancer medicine. It contains the active substance tremelimumab, which is a type of medicine called a *monoclonal antibody*. This medicine is designed to recognise a specific target substance in the body. IMJUDO works by helping your immune system fight your cancer.

IMJUDO in combination with durvalumab is used to treat a type of liver cancer, called advanced or unresectable hepatocellular carcinoma (HCC). It is used when your HCC:
- cannot be removed by surgery (unresectable), and
- may have spread within your liver or to other parts of the body.

IMJUDO is used to treat a type of lung cancer called advanced non-small cell lung cancer in adults. It will be used in combination with other anti-cancer medicines (durvalumab and chemotherapy).

As IMJUDO will be given in combination with other anti-cancer medicines, it is important that you also read the package leaflet for these other medicines. If you have any questions about these medicines, ask your doctor.

2. What you need to know before you are given IMJUDO

You should not be given IMJUDO
if you are allergic to tremelimumab or any of the other ingredients of this medicine (listed in section 6). Talk to your doctor if you are not sure.

Warnings and precautions
Talk to your doctor before you are given IMJUDO if:

- you have an autoimmune disease (an illness where the body’s immune system attacks its own cells)

- you have had an organ transplant
- you have lung or breathing problems
- you have liver problems.

Talk to your doctor before you are given IMJUDO if any of these could apply to you.

When you are given IMJUDO, you can have some **serious side effects**.

Your doctor may give you other medicines that prevent more severe complications and to help reduce your symptoms. Your doctor may delay the next dose of IMJUDO or stop your treatment with IMJUDO. **Talk to your doctor straight away** if you get any of the following side effects:

- new or worsening cough; shortness of breath; chest pain (may be signs of **lung** inflammation)
- feeling sick (nausea) or vomiting; feeling less hungry; pain on the right side of your stomach; yellowing of skin or whites of eyes; drowsiness; dark urine or bleeding or bruising more easily than normal may be signs of **liver** inflammation)
- diarrhoea or more bowel movements than usual; stools that are black, tarry or sticky with blood or mucus; severe stomach pain or tenderness (may be signs of **bowel** inflammation, or a hole in the bowel)
- fast heart rate; extreme tiredness; weight gain or weight loss; dizziness or fainting; hair loss; feeling cold; constipation; headaches that will not go away or unusual headaches (may be signs of **glands** being inflamed, especially the thyroid, adrenal, pituitary or pancreas)
- feeling more hungry or thirsty than usual; passing urine more often than usual; high blood sugar; fast and deep breathing; confusion; a sweet smell to your breath; a sweet or metallic taste in your mouth or a different odour to your urine or sweat (may be signs of **diabetes**)
- decrease in the amount of urine you pass (may be sign of **kidney** inflammation)
- rash; itching; skin blistering or ulcers in the mouth or on other moist surfaces (may be signs of **skin** inflammation)
- chest pain; shortness of breath; irregular heartbeat (may be signs of **heart muscle** inflammation)
- muscle pain or stiffness or weakness or rapid tiring of the muscles (may be signs of inflammation or other problems of the **muscles**)
- chills or shaking, itching or rash, flushing, shortness of breath or wheezing, dizziness or fever (may be signs of **infusion-related reactions)**
- seizures; neck stiffness; headache; fever, chills; vomiting; eye sensitivity to light; confusion and sleepiness (may be signs of inflammation of the **brain** or the membrane around the brain and **spinal cord)**
- **inflammation of the spinal cord** (transverse myelitis): symptoms may include pain, numbness, tingling, or weakness in the arms or legs; bladder or bowel problems including needing to urinate more frequently, urinary incontinence, difficulty urinating and constipation;
- pain; weakness and paralysis in the hands, feet or arms (may be signs of inflammation of the **nerves**, Guillain-Barré syndrome)
- joint pain, swelling, and/or stiffness (may be signs of inflammation of the **joints**, immune-mediated arthritis)
- eye redness, eye pain, light sensitivity, and/or changes in vision (may be signs and symptoms of inflammation of the **eye**, uveitis)
- bleeding (from the nose or gums) and/or bruising (may be signs of **low blood platelets**).

Talk to your doctor straight away if you have any of the symptoms listed above.

Children and adolescents
IMJUDO should not be given to children and adolescents below 18 years of age as it has not been studied in these patients.

Other medicines and IMJUDO
Tell your doctor if you are taking, have recently taken or might take any other medicines. This includes herbal medicines and medicines obtained without a prescription.

Pregnancy and fertility
This medicine is **not recommended during pregnancy**. Tell your doctor if you are pregnant, think you may be pregnant or are planning to have a baby. If you are a woman who could become pregnant, you must use effective contraception while you are being treated with IMJUDO and for at least 3 months after your last dose.

Breast-feeding
Tell your doctor if you are breast-feeding. It is not known if IMJUDO passes into human breast milk. You may be advised to not breast-feed during treatment and for at least 3 months after your last dose.

Driving and using machines
IMJUDO is not likely to affect your driving or use of machines. However, if you have side effects that affect your ability to concentrate and react, be careful when driving or operating machines.

IMJUDO has a low sodium content
IMJUDO contains less than 1 mmol sodium (23 mg) in each dose, that is to say essentially sodium-free.

IMJUDO contains polysorbate
This medicine contains 0.3 mg of polysorbate 80 in a 1.25 ml vial, or 3 mg of polysorbate 80 in a 15 ml vial, which is equivalent to 0.2 mg/ml. Polysorbates may cause allergic reactions. Tell your doctor if you have any known allergies.

3. How you are given IMJUDO

IMJUDO will be given to you in a hospital or clinic under the supervision of an experienced doctor. Your doctor will give you IMJUDO as a drip into your vein (infusion) lasting about an hour.

It is given in combination with durvalumab for liver cancer.

The recommended dose
- If you weigh 40 kg or more, the dose is 300 mg as a one-time single dose.
- If you weigh less than 40 kg, the dose will be 4 mg per kg of your body weight.

When IMJUDO is given in combination with durvalumab for your liver cancer, you will be given IMJUDO first, then durvalumab.

It is given in combination with durvalumab and chemotherapy for lung cancer.

The recommended dose:
- If you weigh 34 kg or more the dose is 75 mg every 3 weeks.
- If you weigh less than 34 kg, the dose will be 1 mg per kg of your body weight every 3 weeks.

You will usually have a total of 5 doses of IMJUDO. The first 4 doses are given in week 1, 4, 7 and 10. The fifth dose is usually then given 6 weeks later, in week 16. Your doctor will decide exactly how many treatments you need.

When IMJUDO is given in combination with durvalumab and chemotherapy, you will be given IMJUDO first then durvalumab and then chemotherapy.

If you miss an appointment
It is very important that you do not miss a dose of this medicine. If you miss an appointment, **call your doctor straight away** to reschedule your appointment.

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

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

When you get IMJUDO, you can have some serious side effects. **See section 2** for a detailed list of these**.**

Talk to your doctor straight away if you get any of the following side effects that have been reported in a clinical study with patients receiving IMJUDO in combination with durvalumab.

The following side effects have been reported in clinical trials in patients taking IMJUDO in combination with durvalumab:

Very common (may affect more than 1 in 10 people)
- underactive thyroid gland that can cause tiredness or weight gain
- cough
- diarrhoea
- stomach pain
- abnormal liver tests (aspartate aminotransferase increased; alanine aminotransferase increased)
- skin rash
- itchiness
- fever
- swelling of legs (oedema peripheral)

Common (may affect up to 1 in 10 people)
- infections of the upper respiratory tract
- lung infection (pneumonia)
- flu-like illness
- tooth and mouth soft tissue infections
- overactive thyroid gland that can cause fast heart rate or weight loss
- inflammation of the thyroid gland (thyroiditis)
- decreased secretion of hormones produced by the adrenal glands that can cause tiredness
- inflammation of the lungs (pneumonitis)
- abnormal pancreas function tests
- inflammation of the gut or intestine (colitis)
- inflammation of the pancreas (pancreatitis)
- inflammation of the liver (hepatitis)
- inflammation of the skin
- night sweats
- muscle pain (myalgia)
- abnormal kidney function test (blood creatinine increased)
- painful urination (dysuria)
- reaction to the infusion of the medicine that can cause fever or flushing

Uncommon (may affect up to 1 in 100 people)
- fungal infection in the mouth
- low number of platelets with signs of excessive bleeding and bruising (immune thrombocytopenia)
- underactive pituitary gland; inflammation of pituitary gland
- type 1 diabetes mellitus
- a condition in which the muscles become weak and there is a rapid fatigue of the muscles (myasthenia gravis)
- inflammation of the membrane around the spinal cord and brain (meningitis)

- inflammation of the heart (myocarditis)
- hoarse voice (dysphonia)
- scarring of lung tissue
- blistering of the skin
- inflammation of the muscles (myositis)
- inflammation of the muscles and vessels
- inflammation of the kidneys (nephritis) that can decrease the amount of your urine
- inflammation of the joints (immune-mediated arthritis)
- Inflammation of the muscles causing pain or stiffness (polymyalgia rheumatica)

Rare (may affect up to 1 in 1 000 people)
- diabetes insipidus
- inflammation of the eye (uveitis)
- inflammation of the brain (encephalitis)
- inflammation of the nerves (Guillain-Barré syndrome)
- hole in the bowel (intestinal perforation)
- coeliac disease (characterized by symptoms such as stomach pain, diarrhoea, and bloating after consuming gluten-containing foods)
- inflammation of the bladder (cystitis). Signs and symptoms may include frequent and/or painful urination, urge to pass urine, blood in urine, pain or pressure in lower abdomen.

Other side effects that have been reported with frequency not known (cannot be estimated from the available data)
- inflammation of part of the spinal cord (transverse myelitis)
- lack or reduction of digestive enzymes made by the pancreas (pancreatic exocrine insufficiency)

The following side effects have been reported in clinical trials in patients taking IMJUDO in combination with durvalumab and platinum-based chemotherapy:

Very common (may affect more than 1 in 10 people)
- infections of the upper respiratory tract
- lung infection (pneumonia)
- low number of red blood cells
- low number of white blood cells
- low number of platelets
- underactive thyroid gland that can cause tiredness or weight gain
- decrease in appetite
- cough
- nausea
- diarrhoea
- vomiting
- constipation
- abnormal liver tests (aspartate aminotransferase increased; alanine aminotransferase increased)
- hair loss
- skin rash
- itchiness
- joint pain (arthralgia)
- feeling tired or weak
- fever

Common (may affect up to 1 in 10 people)
- flu-like illness
- fungal infection in the mouth
- low number of white blood cells with signs of fever
- low number of red blood cells, white blood cells, and platelets (pancytopenia)

- overactive thyroid gland that can cause fast heart rate or weight loss
- decreased levels of hormones produced by the adrenal glands that can cause tiredness
- underactive pituitary gland; inflammation of pituitary gland
- inflammation of thyroid gland (thyroiditis)
- inflammation of the nerves causing numbness, weakness, tingling or burning pain of the arms and legs (neuropathy peripheral)
- inflammation of the lungs (pneumonitis)
- hoarse voice (dysphonia)
- inflammation of the mouth or lips
- abnormal pancreas function tests
- stomach pain
- inflammation of the gut or intestine (colitis)
- inflammation of the pancreas (pancreatitis)
- inflammation of the liver that can cause nausea or feeling less hungry (hepatitis)
- muscle pain (myalgia)
- abnormal kidney function tests (blood creatinine increased)
- painful urination (dysuria)
- swelling of legs (oedema peripheral)
- reaction to the infusion of the medicine that can cause fever or flushing

Uncommon (may affect up to 1 in 100 people)
- tooth and mouth soft tissue infections
- low number of platelets with signs of excessive bleeding and bruising (immune thrombocytopenia)
- diabetes insipidus
- type 1 diabetes mellitus
- inflammation of the brain (encephalitis)
- inflammation of the heart (myocarditis)
- scarring of lung tissue
- blistering of the skin
- night sweats
- inflammation of the skin
- inflammation of the muscle (myositis)
- inflammation of the muscles and vessels
- inflammation of the kidneys (nephritis) that can decrease the amount of your urine
- inflammation of the bladder (cystitis). Signs and symptoms may include frequent and/or painful urination, urge to pass urine, blood in urine, pain or pressure in lower abdomen
- inflammation of the eye (uveitis)
- inflammation of the joints (immune-mediated arthritis)

Rare (may affect up to 1 in 1 000 people)
- a condition in which the muscles become weak and there is a rapid fatigue of the muscles (myasthenia gravis)
- inflammation of the nerves (Guillain-Barré syndrome)
- inflammation of the membrane around the spinal cord and brain (meningitis)
- hole in the bowel (intestinal perforation)
- coeliac disease (characterized by symptoms such as stomach pain, diarrhoea, and bloating after consuming gluten-containing foods)

Other side effects that have been reported with frequency not known (cannot be estimated from the available data)
- inflammation of part of the spinal cord (transverse myelitis)
- lack or reduction of digestive enzymes made by the pancreas (pancreatic exocrine insufficiency)
- Inflammation of the muscles causing pain or stiffness (polymyalgia rheumatica)

Talk to your doctor straight away if you get any of the side effects listed above.

Reporting of side effects
If you get any side effects, **talk to your doctor**. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store IMJUDO

IMJUDO will be given to you in a hospital or clinic and the healthcare professional will be responsible for its storage.

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and vial label after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2 °C - 8 °C).
Do not freeze.
Store in the original package in order to protect from light.

Do not use if this medicine is cloudy, discoloured or contains visible particles.

Do not store any unused portion of the infusion solution for re-use. Any unused medicine or waste material should be disposed of in accordance with local requirements.

6. Contents of the pack and other information

What IMJUDO contains
The active substance is tremelimumab.

Each ml of concentrate for solution for infusion contains 20 mg of tremelimumab.

One vial contains either 300 mg of tremelimumab in 15 ml of concentrate or 25 mg of tremelimumab in 1.25 ml of concentrate.

The other ingredients are: histidine, histidine hydrochloride monohydrate, trehalose dihydrate, disodium edetate dihydrate (see section 2 “IMJUDO has a low sodium content”), polysorbate 80 and water for injections.

What IMJUDO looks like and contents of the pack
IMJUDO concentrate for solution for infusion (sterile concentrate) is a preservative-free, clear to slightly opalescent, colourless to slightly yellow solution, free from visible particles.

It is available in packs containing either 1 glass vial of 1.25 ml of concentrate or 1 glass vial of 15 ml of concentrate.

Not all pack sizes may be marketed.

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Manufacturer
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Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu

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The following information is intended for healthcare professionals only:

Preparation and administration of the infusion:

- Parenteral medicinal products should be inspected visually for particulate matter and discolouration prior to administration. The concentrate is a clear to opalescent, colourless to slightly yellow solution, free from visible particles. Discard the vial if the solution is cloudy, discoloured or visible particles are observed.
- Do not shake the vial.
- Withdraw the required volume of concentrate from the vial(s) and transfer into an intravenous bag containing sodium chloride 9 mg/ml (0.9%) solution for injection, or glucose 50 mg/ml (5%) solution for injection, to prepare a diluted solution with a final concentration ranging from 0.1 to 10 mg/ml. Mix diluted solution by gentle inversion.
- Use the medicinal product immediately once diluted. The diluted solution must not be frozen. If not used immediately, the total time from vial puncture to start of the administration should not exceed 24 hours at 2 ºC to 8 ºC or 12 hours at room temperature (up to 25 ºC). If refrigerated, intravenous bags must be allowed to come to room temperature prior to use. Administer the infusion solution intravenously over 1 hour using a sterile, low-protein binding 0.2 or 0.22 micron in-line filter.
- Do not co-administer other medicinal products through the same infusion line.
- IMJUDO is a single dose. Discard any unused portion left in the vial.

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

ANNEX IV

SCIENTIFIC CONCLUSIONS AND GROUNDS FOR THE VARIATION TO THE TERMS OF THE MARKETING AUTHORISATION(S)

Scientific conclusions

Taking into account the PRAC Assessment Report on the PSUR(s) for tremelimumab, the scientific conclusions of PRAC are as follows:

In view of available data on polymyalgia rheumatica, the PRAC considers a causal relationship between tremelimumab in combination with durvalumab and polymyalgia rheumatica is at least a reasonable possibility. The PRAC concluded that the product information of products containing tremelimumab should be amended accordingly.

Having reviewed the PRAC recommendation, the CHMP agrees with the PRAC overall conclusions and grounds for recommendation.

Grounds for the variation to the terms of the marketing authorisation(s)

On the basis of the scientific conclusions for tremelimumab the CHMP is of the opinion that the benefit-risk balance of the medicinal product(s) containing tremelimumab is unchanged subject to the proposed changes to the product information.

The CHMP recommends that the terms of the marketing authorisation(s) should be varied.