Proposed packaging material		
Code	IMJUDO 25 mg & 300 mg - PI – 02.03	
Regulatory Objective	☐NDA ☐Renewal ☒Variation change detail no.: RO-Change Event-0044206-0000003	
Code of previous version	PI – 01. 04	
Reference	☐CDS version: ☐CPIL version:	☒SmPC country/version/date: VV-RIM-05752223, v5.0; VV-RIM-04950657, v4.0. ☐GRL approval:
Changes	CDS v9 Rhabdomyolysis + PRAC Tranverse Myletis + Corticosteroid	
Name	ARH	

IMJUDO

Tremelimumab

Concentrate Solution for Infusion, 20 mg/mL

To access electronic Product Information
please scan 2D barcode on the carton
using BPOM Mobile Apps

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

Hepatocellular Carcinoma (HCC)

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

Non-Small Cell Lung Cancer (NSCLC)

IMJUDO in combination with durvalumab and platinum-based chemotherapy is 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	During platinum chemotherapy: 75 mg[b] in combination with durvalumab 1500 mg and platinum-based chemotherapy every 3 weeks (21 days) for 4 cycles (12 weeks). Post-platinum chemotherapy: 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)

Adverse reactions	**Severity**[a]	**Treatment modification**
	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
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]

Adverse reactions	**Severity**[a]	**Treatment modification**
	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	Permanently discontinue
Immune-mediated meningitis	Grade 2	Withhold dose[b]
	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 and pancreatitis.

[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

Paediatric population
The safety and efficacy of IMJUDO in children and adolescents below 18 years of age have not been established. No data are available.

Elderly
No dose adjustment is required for elderly patients (≥ 65 years of age) (see section 5.2).

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).

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 or 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 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 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 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 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 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 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 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 for with an initial dose of 1-2 mg/kg/day prednisone or equivalent followed by taper and a hormone replacement as clinically indicated for Grades 2-4.

Immune-mediated nephritis

Immune-mediated nephritis, defined as requiring use of systemic corticosteroids and with no clear alternate aetiology, occurred in patients receiving tremelimumab in combination with durvalumab, or 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 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 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 durvalumab and chemotherapy: myasthenia gravis, myelitis transverse, myositis, polymyositis, rhabdomyolysis, meningitis, encephalitis, Guillain-Barré syndrome, immune thrombocytopenia, cystitis noninfective and pancreatitis (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, tremelimumab has the potential to impact maintenance of pregnancy and may cause foetal harm when administered to a pregnant woman. In animal reproduction studies, administration of tremelimumab to

pregnant cynomolgus monkeys during the period of organogenesis was not associated with maternal toxicity or any effects on maintenance of pregnancy or embryofoetal development (see section 5.3). Human IgG2 is known to cross the placental barrier. Tremelimumab is not recommended during pregnancy and in women of childbearing potential not using effective contraception during treatment and for at least 3 months after the last dose.

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 excreted in human milk. Because of the potential for adverse reactions from tremelimumab in breast-fed infants, breast-feeding women are advised not to breast-feed during treatment 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%), oedema peripheral (10.4%) and lipase increased (10.0%) (see Table 3).

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

The most common serious adverse reactions are colitis (2.6%), diarrhoea (2.4%), pneumonia (2.2%), and hepatitis (1.7%).

The frequency of treatment discontinuation due to adverse reactions is 6.5%. The most common adverse reactions leading to treatment discontinuation are 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 (> 20%) adverse reactions were anaemia (49.7%), nausea (41.5%), neutropenia (41.2%), fatigue (36.1%), rash (25.8%) thrombocytopenia (24.5%), and diarrhoea (21.5%).

The most common (> 2%) NCI CTCAE Grade ≥ 3 adverse reactions were neutropenia (23.9%), anaemia (20.6%), pneumonia (9.4%), thrombocytopenia (8.2%), leukopenia (5.5%), fatigue (5.2%), lipase increased (3.9%), amylase increased (3.6%), febrile neutropenia (2.4%), colitis (2.1%) and aspartate aminotransferase increased/alanine aminotransferase increased (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%).

The severity of adverse drug reactions was assessed based on the CTCAE, defining grade 1=mild, grade 2=moderate, grade 3=severe, grade 4=life threatening and grade 5=death.

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 drug 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

	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 (%)
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						
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

	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 (%)
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
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[cc]	Uncommon	0.6	0	Uncommon	0.6	0.4
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[dd]	Common	8.5	0	Very common	10.4	0.4
Injury, poisoning and procedural complications						
Infusion-related reaction[ee]	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 abdominal pain, abdominal pain lower, abdominal pain upper and flank pain.

[u] Includes mucosal inflammation and stomatitis.

[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] Includes autoimmune nephritis and immune-mediated nephritis.
[dd] Includes oedema peripheral and peripheral swelling.
[ee] 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 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. 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). Six 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 (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%.

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 efficacy and 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. Neutralizing 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.

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 antitumour 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. In murine syngeneic tumour models, dual blockade of PD-L1 and CTLA-4 resulted in enhanced anti-tumour activity.

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 randomized 1171 patients 1:1:1 to receive:

- D: durvalumab 1500 mg every 4 weeks
- IMJUDO 300 mg as a single dose + durvalumab 1500 mg; followed by durvalumab 1500 mg every 4 weeks
- S: 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). 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. S

	IMJUDO 300 mg + durvalumab (n= 393)	**S (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) (95% CI)	16.4 (14.2, 19.6)	13.8 (12.3, 16.1)
HR (95% CI)	0.78 (0.66, 0.92)	
p-value[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

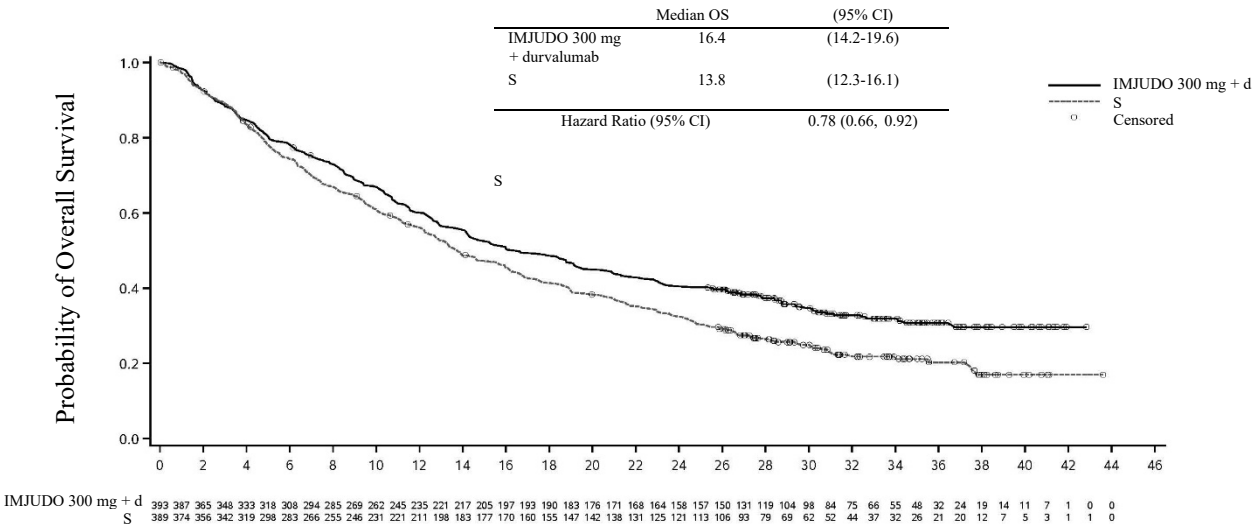
[a] Calculated using reverse the Kaplan-Meier technique (with censor indicator reversed).

[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. S 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/m² with carboplatin AUC 5-6 or cisplatin 75 mg/m² every 3 weeks. Unless contraindicated by the investigator, pemetrexed maintenance could be given.
- Squamous NSCLC
  - Gemcitabine 1000 or 1250 mg/m² on Days 1 and 8 with cisplatin 75 mg/m² or carboplatin AUC 5-6 on Day 1 every 3 weeks.
- Non-squamous or squamous NSCLC
  - Nab-paclitaxel 100 mg/m² 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%), 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%), 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.

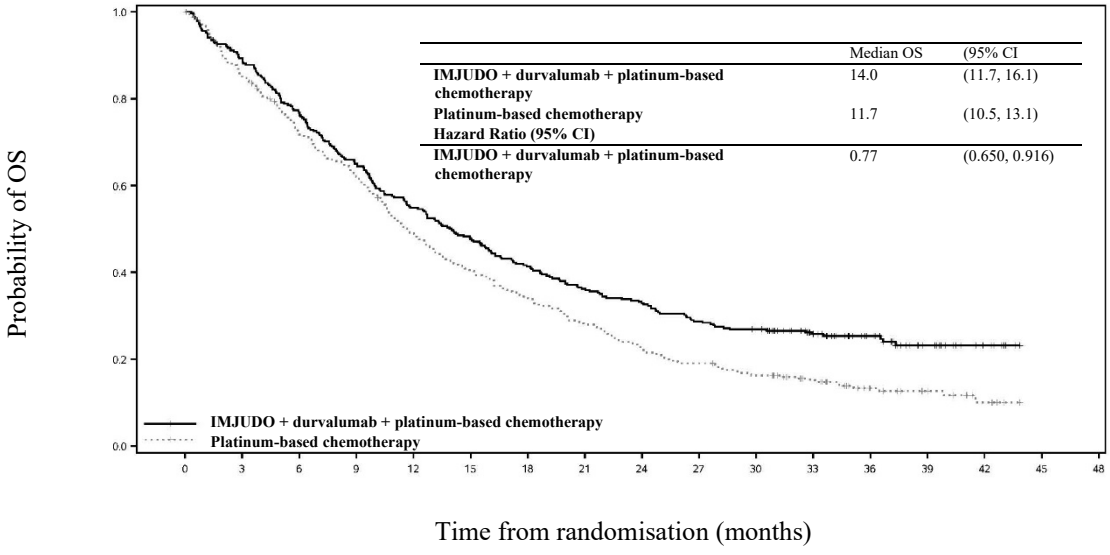
Table 4. Efficacy results for the POSEIDON study

	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)	6.2	4.8

	Arm 1: IMJUDO+durvalumab+ platinum-based chemotherapy (n=338)	Arm 3: Platinum-based chemotherapy (n=337)
(95% CI)	(5.0, 6.5)	(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. 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

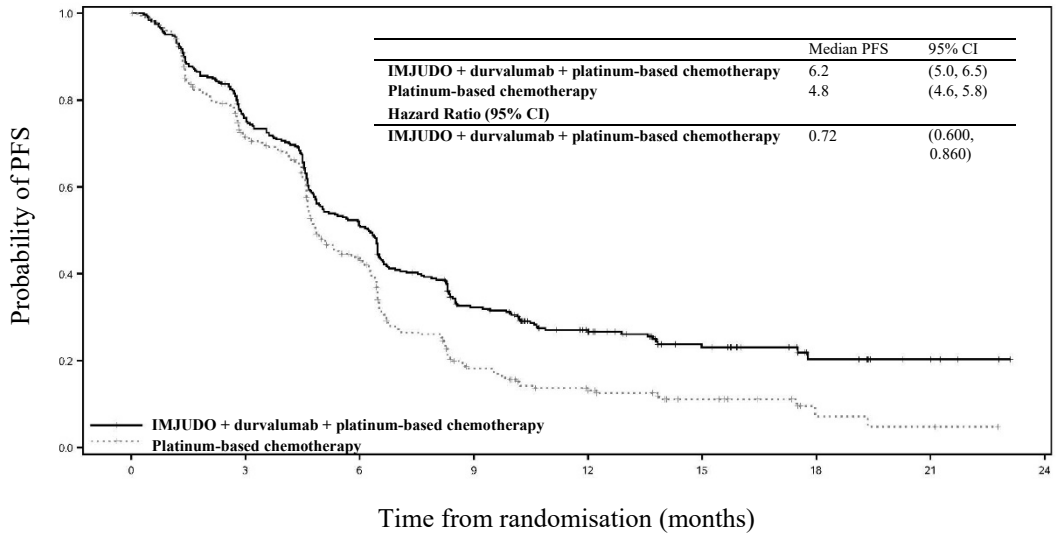


Time from randomisation (months)

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

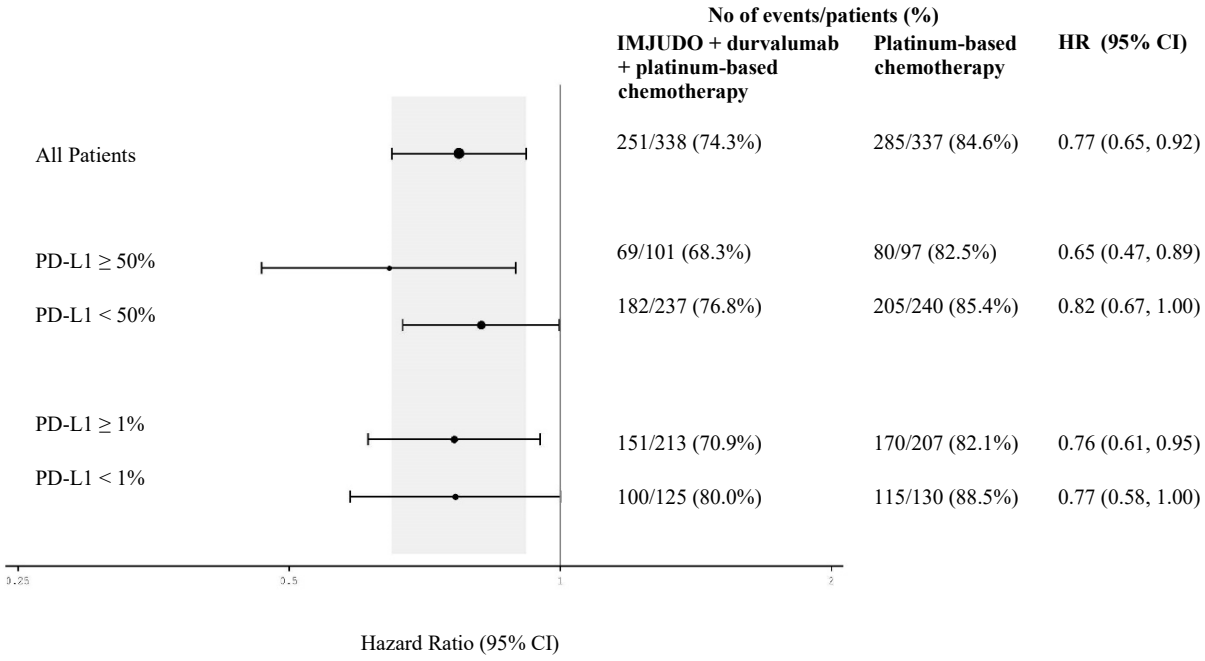


Number of patients at risk

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.

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 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.

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

Animal fertility studies have not been conducted with tremelimumab. 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 clinical 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

Please refer to expiry date on the outer carton

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. PACK SIZE

Tremelimumab 25 mg : Dus, 1 vial @ 1.25 mL, Reg No: DKI2451304849A1
Tremelimumab 300 mg: Dus, 1 vial @ 15 mL, Reg No: DKI2451304849B1

HARUS DENGAN RESEP DOKTER

Manufactured by:
Vetter Pharma-Fertigung GmbH & Co. KG
Mooswiesen 2
88214 Ravensburg
Jerman

Released by:
AstraZeneca AB
Gärtunavägen
Södertälje
Swedia

Imported by:
PT AstraZeneca Indonesia
Cikarang, Bekasi - Indonesia

Suspected side effects of PT AstraZeneca Indonesia's products can be reported online via the link http://contactazmedical.astrazeneca.com or by scanning the following QR code:

Reporting suspected product side effects to PT AstraZeneca Indonesia **does not replace medical consultation or treatment by a doctor**. For medical advice, diagnosis or treatment, please consult your doctor or healthcare professional.

Reporting of suspected adverse drug events can also be sent to Pusat Farmakovigilans/MESO Nasional Badan Pengawas Obat dan Makanan (BPOM) by filling out the online form: https://e-meso.pom.go.id/ADR or via email pv-center@pom.go.id

or by direct reporting addressed to:
Pusat Farmakovigilans/MESO Nasional Badan Pengawas Obat dan Makanan (BPOM)
Direktorat Pengawasan Keamanan, Mutu, dan Ekspor Impor Obat, Narkotika, Psikotropika, Prekursor dan Zat Adiktif
Badan Pengawas Obat dan Makanan RI
Jl. Percetakan Negara No. 23
Jakarta 10560

Date of revision of the text: 23 October 2025

Doc Number: VV-RIM-07523912

Proposed packaging material		
Code	IMJUDO 25 mg & 300 mg - PIL - 02.02	
Submission	☒NDA ☐Renewal ☐Variation change detail no.:	
Code of previous version	PIL - 01.02	
Reference	☐CDS version: ☐CPIL version:	☒SmPC country/version/date: VV-RIM-05752223, v5.0 ☐GRL approval:
Changes	CDS v9 Rhabdomyolysis + PRAC Tranverse Myletis	
Name	ARH	

Leaflet Informasi Pasien
IMJUDO
Tremelimumab
Larutan Konsentrat untuk Infus 20 mg/ml

Baca seluruh isi leaflet ini dengan seksama sebelum Anda menggunakan obat ini karena informasi ini penting untuk Anda.
- Simpan leaflet ini. Anda mungkin butuh membacanya lagi.
- Jika Anda memiliki pertanyaan lebih lanjut, tanyakan pada dokter Anda.
- Jika Anda mengalami efek samping, beri tahu dokter Anda. Termasuk efek samping yang mungkin tidak tercantum dalam leaflet ini. Lihat bagian 4.

Informasi di dalam leaflet ini

1. IMJUDO dan kegunaannya
2. Hal yang harus diketahui sebelum menggunakan IMJUDO
3. Cara menggunakan IMJUDO
4. Efek samping yang mungkin dialami
5. Cara penyimpanan IMJUDO
6. Isi kemasan dan informasi lainnya

1. IMJUDO DAN KEGUNAANNYA

IMJUDO adalah obat anti-kanker. Obat ini mengandung zat aktif tremelimumab, yaitu sejenis obat yang disebut *antibodi monoklonal.* Obat ini dirancang dapat mengenali zat spesifik yang menjadi target dalam tubuh. IMJUDO bekerja membantu sistem kekebalan tubuh Anda dalam melawan kanker.

IMJUDO dalam kombinasi dengan durvalumab digunakan untuk mengobati sejenis kanker hati/lever, yang disebut karsinoma hepatoseluler (HCC) stadium lanjut atau yang tidak dapat dioperasi. Obat tersebut digunakan saat HCC Anda:
- tidak dapat dihilangkan dengan operasi (*unresectable*) dan
- mungkin telah menyebar di organ hati Anda atau ke bagian lain dari tubuh.

IMJUDO digunakan untuk mengobati sejenis kanker paru-paru yang disebut kanker paru-paru non-sel kecil tingkat lanjut pada orang dewasa. Obat ini nantinya digunakan dalam kombinasi dengan obat anti kanker lainnya (durvalumab dan kemoterapi).

Karena IMJUDO akan diberikan dalam kombinasi dengan obat anti kanker lainnya, maka penting bagi Anda untuk membaca leaflet dari obat-obatan lain tersebut. Jika Anda memiliki pertanyaan tentang obat-obatan tersebut, tanyakan pada dokter Anda.

2. HAL YANG HARUS DIKETAHUI SEBELUM MENGGUNAKAN IMJUDO

Anda tidak boleh menggunakan IMJUDO
Jika alergi terhadap tremelimumab atau bahan lain dari obat ini (tercantum di bagian 6). Konsultasikan dengan dokter jika Anda tidak yakin.

Peringatan dan pencegahan
Konsultasikan dengan dokter sebelum Anda menggunakan IMJUDO jika:
- Anda memiliki penyakit autoimun (suatu penyakit dimana sistem kekebalan tubuh menyerang selnya sendiri)
- Anda pernah menjalani transplantasi organ
- Anda menderita gangguan pada paru-paru atau pernapasan
- Anda menderita gangguan pada hati/lever.

Berkonsultasilah dengan dokter sebelum menggunakan IMJUDO jika salah satu hal di atas terjadi pada Anda.

Saat menggunakan IMJUDO, Anda dapat mengalami beberapa **efek samping serius**.

Dokter Anda mungkin memberi obat lain untuk mencegah komplikasi yang lebih parah dan membantu mengurangi gejala-gejala yang muncul. Dokter Anda mungkin menunda pemberan dosis IMJUDO berikutnya atau menghentikan pengobatan Anda dengan IMJUDO. **Segera beri tahu dokter** jika Anda mengalami efek samping berikut ini:
- Batuk yang baru muncul atau yang memburuk; sesak napas; nyeri dada (dapat menjadi tanda radang **paru-paru**)
- Merasa tidak enak badan (mual) atau muntah; rasa lapar berkurang; sakit perut di sisi kanan; kulit atau bagian putih mata menguning; kantuk; urin gelap, atau pendarahan, atau memar lebih mudah muncul dari biasanya (dapat menjadi tanda radang **hati**)
- Diare atau lebih banyak buang air besar dari biasanya; tinja berwarna hitam, lembap atau lengket dengan darah atau lendir; sakit perut yang parah atau nyeri tekan (dapat menjadi tanda radang **usus** atau ada lubang di usus)
- Detak jantung cepat; kelelahan ekstrim; berat badan bertambah atau berkurang; pusing atau pingsan; rambut rontok; meriang; konstipasi/sembelit; sakit kepala yang tidak kunjung sembuh atau sakit kepala yang tidak biasa (dapat menjadi tanda ada **kelenjar** yang meradang, terutama kelenjar tiroid, adrenal, hipofisis, atau pankreas)
- Merasa lebih lapar atau lebih haus dari biasanya; buang air kecil lebih sering dari biasanya; gula darah tinggi; pernapasan cepat dan dalam; kebingungan; bau manis pada napas; rasa manis atau rasa seperti logam di mulut, atau bau yang berbeda pada urin atau keringat Anda (dapat menjadi tanda **diabetes**)
- Penurunan jumlah urin yang Anda keluarkan (dapat menjadi tanda radang pada **ginjal**)
- Ruam; gatal; kulit melepuh atau bisul di mulut atau di permukaan lembab lainnya (dapat menjadi tanda ada peradangan di **kulit**)
- Nyeri dada; sesak napas; detak jantung tidak teratur (dapat menjadi tanda radang **otot jantung**)

- Nyeri otot atau lemas atau otot cepat lelah (dapat menjadi tanda ada peradangan atau masalah pada **otot** lainnya)
- Menggigil atau gemetar, gatal atau ruam, kemerahan, sesak napas atau mengi, pusing atau demam (dapat menjadi tanda-tanda **reaksi terkait infus**)
- Kejang; leher kaku; sakit kepala; demam, menggigil; muntah; mata sensitif terhadap cahaya; kebingungan dan kantuk (dapat menjadi tanda radang **otak** atau selaput di sekitar otak dan **sumsum tulang belakang**)
- **Radang sumsum tulang belakang** (mielitis transversal) gejalanya dapat berupa nyeri, mati rasa, kesemutan, atau kelemahan pada lengan atau tungkai; masalah kandung kemih atau usus termasuk perlu buang air kecil lebih sering, tidak mampu menahan buang air kecil, kesulitan buang air kecil, dan sembelit;
- Nyeri; lemas dan kelumpuhan di tangan, kaki, atau lengan (dapat menjadi tanda radang **saraf**, sindrom Guillain-Barré)
- Pendarahan (dari hidung atau gusi) dan/atau memar (dapat menjadi tanda **trombosit darah rendah**).

Segera beri tahu dokter jika Anda mengalami gejala apapun seperti yang tercantum di atas.

Anak-anak dan remaja
IMJUDO tidak boleh diberikan pada anak-anak dan remaja di bawah usia 18 tahun karena belum pernah diteliti pada pasien usia tersebut.

Obat-obatan lain dan IMJUDO
Beri tahu dokter jika Anda sedang mengonsumsi, baru saja mengonsumsi, atau mungkin mengonsumsi obat lain. Termasuk obat herbal dan obat-obatan lain yang diperoleh tanpa resep dokter.

Kehamilan dan kesuburan
Obat ini **tidak direkomendasikan digunakan saat hamil**. Beri tahu dokter jika Anda sedang hamil, kemungkinan bisa hamil, atau berencana memiliki bayi. Jika Anda seorang wanita yang bisa hamil, Anda harus menggunakan kontrasepsi yang efektif saat sedang diobati dengan IMJUDO dan setidaknya 3 bulan setelah dosis terakhir Anda.

Menyusui
Beri tahu dokter jika Anda sedang menyusui. Belum diketahui apakah IMJUDO mengalir masuk ke ASI. Anda mungkin disarankan untuk tidak menyusui selama pengobatan dan setidaknya 3 bulan setelah dosis terakhir Anda.

Menyetir dan mengoperasikan mesin
IMJUDO kemungkinan tidak akan memengaruhi Anda yang sedang mengemudi atau mengoperasikan mesin. Namun, jika Anda mengalami efek samping yang memengaruhi kemampuan dalam berkonsentrasi dan bereaksi, berhati-hatilah saat mengemudi atau mengoperasikan mesin.

IMJUDO memiliki kandungan natrium yang rendah
IMJUDO mengandung kurang dari 1 mmol natrium (23 mg) pada tiap dosisnya, yang pada dasarnya dapat dikatakan sama dengan bebas sodium.

3. CARA MENGGUNAKAN IMJUDO

IMJUDO akan diberikan pada Anda di rumah sakit atau klinik di bawah pengawasan dokter yang berpengalaman. Dokter Anda akan memasukkan IMJUDO melalui infus ke pembuluh darah Anda dan berlangsung sekitar satu jam.

IMJUDO diberikan dalam kombinasi dengan durvalumab untuk kanker hati.
Dosis yang direkomendasikan
- Jika berat badan Anda 40 kg atau lebih, dosis yang diberikan adalah 300 mg sebagai dosis tunggal sekali pakai.
- Jika berat badan Anda kurang dari 40 kg, dosis yang digunakan adalah 4 mg per kg berat badan Anda.

Ketika IMJUDO diberikan dalam kombinasi dengan durvalumab untuk kanker hati yang Anda alami, Anda akan diberikan IMJUDO terlebih dahulu, kemudian durvalumab.

IMJUDO diberikan dalam kombinasi dengan durvalumab dan kemoterapi untuk kanker paru-paru.

Dosis yang direkomendasikan:
- Jika berat badan Anda 34 kg atau lebih dosis yang diberikan adalah 75 mg setiap 3 minggu.
- Jika berat badan Anda kurang dari 34 kg, dosis yang diberikan menjadi 1 mg per kg dari berat badan Anda setiap 3 minggu.

Anda biasanya akan menggunakan total 5 dosis IMJUDO. 4 dosis pertama diberikan di minggu 1, 4, 7, dan 10. Dosis kelima biasanya diberikan di minggu ke-6 setelahnya atau minggu ke-16. Dokter Anda akan menentukan dengan tepat seberapa banyak pengobatan yang Anda butuhkan.

Ketika IMJUDO diberikan dalam kombinasi dengan durvalumab dan kemoterapi, Anda akan diberikan IMJUDO terlebih dahulu kemudian durvalumab dan kemudian kemoterapi.

Jika Anda melewatkan janji temu dengan dokter Anda
Jangan melewatkan dosis obat, ini sangat penting bagi Anda. Jika Anda melewatkan janji temu, **segera hubungi dokter Anda** untuk menjadwalkan ulang janji temu Anda.

Jika memiliki pertanyaan lebih lanjut tentang pengobatan Anda, tanyakan pada dokter Anda.

4. EFEK SAMPING YANG MUNGKIN DIALAMI

Seperti semua obat, obat ini bisa menimbulkan efek samping, meski tidak semua orang mengalaminya.

Saat Anda menggunakan IMJUDO, Anda dapat mengalami beberapa efek samping yang serius. **Lihat bagian 2** untuk daftar terperinci**.**

Segera beri tahu dokter jika Anda mendapatkan salah satu dari efek samping berikut, yang mana telah dilaporkan dalam studi klinis pada pasien penerima IMJUDO dalam kombinasi dengan durvalumab.

Efek samping berikut telah dilaporkan dalam uji klinis pada pasien yang menggunakan IMJUDO dalam kombinasi dengan durvalumab:

Sangat umum (dapat dialami lebih dari 1 dari 10 orang)

- Kelenjar tiroid kurang aktif yang dapat menyebabkan kelelahan atau penambahan berat badan
- Batuk
- Diare
- Nyeri perut
- Uji hati abnormal (aspartat aminotransferase meningkat; alanin aminotransferase meningkat)
- Ruam kulit
- Gatal-gatal
- Demam
- Bengkak pada kaki (edema perifer)

Umum (dapat dialami hingga 1 dari 10 orang)

- Infeksi saluran pernapasan atas
- Infeksi paru-paru (pneumonia)
- Badan seperti terserang flu
- Infeksi jaringan halus pada mulut dan gigi
- Kelenjar tiroid terlalu aktif yang dapat menyebabkan detak jantung cepat atau penurunan berat badan
- Peradangan kelenjar tiroid (tiroiditis)
- Penurunan sekresi hormon yang dihasilkan oleh kelenjar adrenal yang dapat menyebabkan kelelahan
- Radang paru-paru (pneumonitis)
- Uji fungsi pankreas abnormal
- Radang usus besar atau usus kecil (kolitis)
- Radang pankreas (pankreatitis)
- Radang hati (hepatitis)
- Radang kulit
- Berkeringat di malam hari
- Nyeri otot (myalgia)
- Uji fungsi ginjal abnormal (kreatinin darah meningkat)
- Nyeri saat berkemih (dysuria)
- Reaksi terhadap obat dalam infus yang menyebabkan demam atau kemerahan

Jarang (dapat dialami hingga 1 dari 100 orang)

- Infeksi jamur pada mulut
- Jumlah trombosit rendah dengan tanda-tanda perdarahan dan memar yang berlebihan (trombositopenia imun)
- Kelenjar hipofisis kurang aktif; radang kelenjar hipofisis
- Diabetes mellitus tipe 1
- Suatu kondisi yang mana otot melemah dan terjadi kelelahan otot yang cepat (myasthenia gravis)
- Radang selaput di sekitar sumsum tulang belakang dan otak (meningitis)
- Radang jantung (miokarditis)
- Suara serak (disfonia)
- Jaringan parut pada paru-paru
- Kulit melepuh
- Radang otot (myositis)
- Radang pada otot dan pembuluh darah
- Radang ginjal (nefritis) yang dapat menurunkan jumlah urin

- Radang sendi (artritis yang dimediasi imun)

Langka (dapat dialami hingga 1 dari 1000 orang)
- Diabetes insipidus
- Radang mata (uveitis)
- Radang saraf (Guillain-Barré syndrome)
- Radang otak (ensefalitis)
- Lubang di usus (perforasi usus)
- Radang kandung kemih (sistitis). Tanda dan gejala mungkin termasuk buang air kecil yang sering dan/atau nyeri, keinginan untuk buang air kecil, darah dalam urin, nyeri atau tekanan di perut bagian bawah.

Efek samping lain yang telah dilaporkan dengan frekuensi tidak diketahui (tidak dapat diperkirakan dari data yang tersedia)
- Peradangan pada bagian sumsum tulang belakang (mielitis transversal)

Efek samping berikut telah dilaporkan dalam uji klinis pada pasien yang memakai IMJUDO dalam kombinasi dengan durvalumab dan kemoterapi berbasis platinum:

Sangat umum (dapat dialami lebih dari 1 dari 10 orang)
- Infeksi saluran pernapasan atas
- Infeksi paru-paru (pneumonia)
- Jumlah sel darah merah rendah
- Jumlah sel darah putih rendah
- Jumlah trombosit rendah
- Kelenjar tiroid kurang aktif yang dapat menyebabkan kelelahan atau penambahan berat badan
- Nafsu makan berkurang
- Batuk
- Mual
- Diare
- Muntah
- Konstipasi
- Uji hati abnormal (aspartat aminotransferase meningkat; alanin aminotransferase meningkat)
- Rambut rontok
- Ruam kulit
- Gatal-gatal
- Nyeri sendi (arthralgia)
- Merasa letih atau lesu
- Demam

Umum (dapat dialami hingga 1 dari 10 orang)
- Badan seperti terserang flu
- Infeksi jamur pada mulut
- Jumlah sel darah putih yang rendah dengan tanda-tanda demam
- Rendahnya jumlah sel darah merah, sel darah putih, dan trombosit (pansitopenia)
- Kelenjar tiroid terlalu aktif yang dapat menyebabkan detak jantung cepat atau penurunan berat badan

- Penurunan kadar hormon yang diproduksi oleh kelenjar adrenal yang dapat menyebabkan kelelahan
- Kelenjar hipofisis kurang aktif; radang kelenjar hipofisis
- Radang kelenjar tiroid (tiroiditis)
- Radang saraf yang menyebabkan mati rasa, lemas, kesemutan, atau nyeri panas pada lengan dan tungkai kaki (neuropati perifer)
- Radang paru-paru (pneumonitis)
- Suara serak (disfonia)
- Radang pada mulut atau bibir
- Uji fungsi pankreas abnormal
- Nyeri perut
- Radang usus besar atau usus kecil (kolitis)
- Radang pankreas (pankreatitis)
- Radang hati yang dapat menyebabkan mual atau rasa kurang lapar (hepatitis)
- Nyeri otot (myalgia)
- Tes fungsi ginjal abnormal (peningkatan kreatinin darah)
- Nyeri saat berkemih (dysuria)
- Bengkak pada kaki (edema perifer)
- Reaksi terhadap infus obat yang dapat menyebabkan demam atau kemerahan

Jarang (dapat dialami hingga 1 dari 100 orang)

- Infeksi jaringan halus pada mulut dan gigi
- Jumlah trombosit yang rendah dengan tanda-tanda perdarahan dan memar yang berlebihan (trombositopenia imun)
- Diabetes insipidus
- Diabetes mellitus tipe 1
- Radang otak (ensefalitis)
- Radang jantung (miokarditis)
- Jaringan parut pada paru-paru
- Kulit melepuh
- Berkeringat di malam hari
- Radang kulit
- Radang otot (myositis)
- Radang pada otot dan pembuluh darah
- Radang ginjal (nefritis) yang dapat menurunkan jumlah urin
- Radang kandung kemih (sistitis). Tanda dan gejala mungkin termasuk buang air kecil yang sering dan/atau nyeri, keinginan untuk buang air kecil, darah dalam urin, nyeri atau tekanan di perut bagian bawah.
- Radang mata (uveitis)
- Radang sendi (artritis yang dimediasi imun)

Langka (dapat dialami hingga 1 dari 1000 orang)

- Suatu kondisi yang mana otot melemah dan terjadi kelelahan otot yang cepat (myasthenia gravis)
- Radang saraf (guillain-barré syndrome)
- Radang selaput di sekitar sumsum tulang belakang dan otak (meningitis)
- Lubang di usus (perforasi usus)

Efek samping lain yang telah dilaporkan dengan frekuensi tidak diketahui (tidak dapat diperkirakan dari data yang tersedia)

- Peradangan pada bagian sumsum tulang belakang (mielitis transversal)

Segera beri tahu dokter jika Anda mengalami efek samping yang tercantum di atas.

Pelaporan efek samping
Jika Anda mengalami efek samping apa pun, **beri tahu dokter Anda**. Termasuk efek samping yang mungkin tidak tercantum dalam selebaran ini. Dengan melaporkan efek samping, Anda dapat membantu memberikan informasi lebih lanjut tentang keamanan obat ini.

5. Cara penyimpanan IMJUDO

IMJUDO akan diberikan pada Anda di rumah sakit atau klinik dan tenaga kesehatan profesional akan bertanggung jawab atas penyimpanannya.

Jauhkan obat ini dari pandangan dan jangkauan anak-anak.

Jangan gunakan obat ini setelah lewat tanggal kedaluwarsa yang tertera pada karton dan label vial setelah kode EXP. Tanggal kedaluwarsa mengacu pada hari terakhir bulan yang tecantum.

Simpan dalam lemari pendingin (2°C–8°C).
Jangan dibekukan.
Simpan dalam kemasan asli agar terlindung dari cahaya.

Jangan gunakan jika obat keruh, berubah warna, atau mengandung partikel yang terlihat.

Jangan menyimpan sisa larutan infus untuk digunakan kembali. Setiap obat atau bahan limbah yang tidak terpakai harus dibuang sesuai dengan persyaratan daerah setempat.

6. ISI KEMASAN DAN INFORMASI LAINNYA

Kandungan IMJUDO
Mengandung bahan aktif tremelimumab.

Tiap ml larutan konsentrat untuk infus mengandung 20 mg tremelimumab.

Satu vial mengandung 300 mg tremelimumab dalam 15 ml konsentrat atau 25 mg tremelimumab dalam 1,25 ml konsentrat.

Bahan lainnya adalah: histidine, histidine hydrochloride monohydrate, trehalose dihydrate, disodium edetate dihydrate (lihat bagian 2 “IMJUDO memiliki kandungan natrium yang rendah”), polysorbate 80 dan water for injections.

Tampilan IMJUDO dan isi kemasan
IMJUDO larutan konsentrat untuk infus (konsentrat steril) adalah larutan bebas pengawet, jernih hingga agak opalesen (buram), tidak berwarna hingga agak kekuningan, bebas dari partikel terlihat.

Tersedia dalam kemasan 1 vial kaca yang berisi 1,25 ml konsentrat atau 1 vial kaca yang berisi 15 ml konsentrat.

Tidak semua ukuran kemasan dipasarkan.

Diproduksi oleh:
Vetter Pharma-Fertigung GmbH & Co. KG
Mooswiesen 2
88214 Ravensburg
Jerman

Dirilis oleh:
AstraZeneca AB
Gärtunavägen
Södertälje
Swedia

Diimpor oleh:
PT AstraZeneca Indonesia
Cikarang, Bekasi-Indonesia

HARUS DENGAN RESEP DOKTER

Nomor Izin Edar **: DKI2451304849A1 (25 mg)**
DKI2451304849B1 (300 mg)

Dugaan efek samping produk obat PT. AstraZeneca Indonesia dapat dilaporkan secara online melalui link http://contactazmedical.astrazeneca.com atau dengan *scan QR code* berikut:

Pelaporan dugaan efek samping produk kepada PT. AstraZeneca Indonesia tidak menggantikan konsultasi atau penanganan medis oleh dokter. Untuk mendapatkan saran medis, diagnosis, atau pengobatan, tetap konsultasikan keluhan pasien kepada dokter atau tenaga kesehatan profesional.

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