1. NAME OF THE MEDICINAL PRODUCT

- IMJUDO™, 25 mg (25 mg/1.25 mL) for intravenous infusion.
- IMJUDO™, 300 mg (300 mg/15 mL) for intravenous infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL contains 20 mg of IMJUDO.

Each vial of 1.25 mL contains 25 mg of tremelimumab.

Each vial of 15 mL contains 300 mg of tremelimumab.

IMJUDO is a human anti-cytotoxic T-lymphocyte antigen 4 (CTLA-4)- immunoglobulin G2 (IgG2a) monoclonal antibody.

For a full list of excipient(s), see section 6.1.

3. PHARMACEUTICAL FORM

Injection (US) or concentrate for solution for infusion (EU); 20 mg/mL in a single-dose vial for intravenous administration.

Sterile, preservative-free, clear to slightly opalescent, colourless to slightly yellow solution, free from or practically free from visible particles.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Non-Small Cell Lung Cancer (NSCLC)

IMJUDO in combination with durvalumab and platinum-based chemotherapy is indicated for the first-line treatment of patients with metastatic NSCLC with no sensitising epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) genomic tumour aberrations.

Hepatocellular Carcinoma (HCC)

IMJUDO in combination with durvalumab is indicated for the treatment of patients with unresectable hepatocellular carcinoma (uHCC).

4.2 Posology and method of administration

The recommended dose of IMJUDO is presented in Table 1.

IMJUDO is administered as an intravenous infusion over 1 hour.

Table 1: Recommended dosage of IMJUDO

Indication	Recommended IMJUDO dosage	Duration of Therapy
Metastatic NSCLC	During chemotherapy: 75 mg[a,b] in combination with durvalumab 1500 mg[c] and platinum-based chemotherapy[d] every 3 weeks (21 days) for 4 cycles Post-platinum chemotherapy: Durvalumab 1500 mg[b,c] every 4 weeks as monotherapy and histology-based pemetrexed maintenance[d.e] therapy every 4 weeks and, a fifth dose of 75 mg[f,g] alongside durvalumab dose 6 at week 16	Up to a maximum of 5 doses unless there was disease progression or unacceptable toxicity
uHCC	Single Tremelimumab Regular Interval Durvalumab (STRIDE): 300 mg[h] as a single priming dose in combination with durvalumab 1500 mg[h,i] at Cycle 1/Day 1, followed by durvalumab monotherapy every 4 weeks	As long as clinical benefit is observed or until unacceptable toxicity

[a] Patients with a body weight of 30 kg or less must receive weight-based dosing, equivalent to IMJUDO 1 mg/kg and durvalumab 20 mg/kg until the weight improves to greater than 30 kg.

[b] Administer IMJUDO first; followed by durvalumab and then chemotherapy on the day of dosing, when applicable.

[c] When IMJUDO is administered in combination with durvalumab and chemotherapy, refer to the Prescribing Information for durvalumab for dosing information.

[d] When IMJUDO is administered in combination with durvalumab and platinum-based chemotherapy, refer to the Prescribing Information for nab-paclitaxel, gemcitabine, pemetrexed and carboplatin or cisplatin for dosing information.

[e] Based on investigator decision for non-squamous patients who received treatment with pemetrexed and carboplatin/cisplatin.

[f] In the case of dose delay(s), a fifth dose of IMJUDO can be given after Week 16, alongside durvalumab.
[g] 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.
[h] Patients with a body weight of 30 kg or less must receive weight-based dosing, equivalent to IMJUDO 4 mg/kg and durvalumab 20 mg/kg until weight is greater than 30 kg.
[i] Administer IMJUDO prior to durvalumab on the same day. Refer to the Prescribing Information for durvalumab dosing information.

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

Immune-mediated adverse reactions requiring specific treatment modification and management are summarized in Table 2. Refer to section 4.4 for further monitoring and evaluation information.

Table 2. Treatment modifications and management recommendations for IMJUDO in combination with durvalumab

Adverse Reactions	**Severity**[a]	**Treatment Modification**	**Corticosteroid Treatment Unless Otherwise Specified**[b]
Immune-mediated pneumonitis/interstitial lung disease	Grade 2	Withhold dose[c]	Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
	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[c]	Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
	ALT or AST > 5-≤ 10 x ULN	Withhold durvalumab and permanently discontinue tremelimumab	

Adverse Reactions	**Severity**[a]	**Treatment Modification**	**Corticosteroid Treatment Unless Otherwise Specified**[b]
	Concurrent ALT or AST > 3 x ULN and total bilirubin > 2 x ULN[d]	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)[e]	ALT or AST > 2.5- ≤ 5X BLV and ≤ 20xULN	Withhold dose[c]	Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
	ALT or AST >5-7X BLV and ≤ 20X ULN OR concurrent 2.5-5X BLV and ≤ 20XULN AND total bilirubin > 1.5 - < 2 x ULN[d]	Withhold durvalumab and permanently discontinue tremelimumab	
	ALT or AST > 7 X BLV OR > 20 ULN whichever occurs first OR bilirubin > 3ULN	Permanently discontinue	
Immune-mediated colitis or diarrhoea	Grade 2	Withhold dose[c]	Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
	Grade 3 or 4	Permanently discontinue	
	Intestinal perforation of ANY grade	Permanently discontinue	Consult a surgeon immediately if an intestinal perforation is suspected

Adverse Reactions	**Severity**[a]	**Treatment Modification**	**Corticosteroid Treatment Unless Otherwise Specified**[b]
Immune-mediated hyperthyroidism, thyroiditis	Grade 2-4	Withhold dose until clinically stable	Symptomatic management
Immune-mediated hypothyroidism	Grade 2-4	No changes	Initiate thyroid hormone replacement as clinically indicated
Immune-mediated adrenal insufficiency, hypophysitis/hypopituitarism	Grade 2-4	Withhold dose until clinically stable	Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper and hormone replacement as clinically indicated
Immune-mediated Type 1 diabetes mellitus	Grade 2-4	No changes	Initiate treatment with insulin as clinically indicated
Immune-mediated nephritis	Grade 2 with serum creatinine > 1.5-3 x (ULN or baseline)	Withhold dose[c]	Initiate 1 to 2 mg/kg/day prednisone or equivalent

Adverse Reactions	Severity[a]	Treatment Modification	Corticosteroid Treatment Unless Otherwise Specified[b]
	Grade 3 with serum creatinine > 3 x baseline or > 3-6 x ULN; Grade 4 with serum creatinine > 6 x ULN	Permanently discontinue	followed by a taper
Immune-mediated rash or dermatitis (including pemphigoid)	Grade 2 for > 1 week or Grade 3	Withhold dose[c]	Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
	Grade 4	Permanently discontinue	
Immune-mediated myocarditis	Grade 2-4	Permanently discontinue	Initiate 2 to 4 mg/kg/day prednisone or equivalent followed by a taper[f]
Immune-mediated myositis/polymyositis	Grade 2 or 3	Withhold dose[c,g]	Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
	Grade 4	Permanently discontinue	
Infusion-related reactions	Grade 1 or 2	Interrupt or slow the rate of infusion	May consider pre-medications for prophylaxis of subsequent infusion reactions
	Grade 3 or 4	Permanently discontinue	Manage severe infusion-related reactions per

Adverse Reactions	**Severity**[a]	**Treatment Modification**	**Corticosteroid Treatment Unless Otherwise Specified**[b]
			institutional standard, appropriate clinical practice guidelines and/or society guidelines
Immune-mediated myasthenia gravis	Grade 2-4	Permanently discontinue	Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
Immune-mediated encephalitis	Grade 2-4	Permanently discontinue	Initiate 1 mg/kg/day to 2 mg/kg/day prednisone or equivalent followed by a taper
Other immune-mediated adverse reactions[h]	Grade 2 or 3	Withhold dose[c]	Initiate 1 mg/kg/day to 2 mg/kg/day prednisone or equivalent followed by a taper
	Grade 4	Permanently discontinue	

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

[b] 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.

[c] 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.

[d] For patients with alternative cause follow the recommendations for AST or ALT increases without concurrent bilirubin elevations.

[e] 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.

[f] 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.

[g] 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.

[h] Includes immune thrombocytopenia and pancreatitis.

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

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

Special patient populations

Based on a population pharmacokinetic analysis, no dose adjustment of IMJUDO is recommended based on patient age, body weight, gender and race (see section 5.2).

Paediatric and adolescents

The safety and effectiveness of IMJUDO have not been established in children and adolescents aged less than 18 years.

Elderly (≥ 65 years)

No dose adjustment is required for elderly patients (≥ 65 years of age) (see sections 5.1 and 5.2).

Renal Impairment

Based on a population pharmacokinetic analysis, no dose adjustment of IMJUDO is recommended in patients with renal impairment. IMJUDO has not been studied in patients with severe renal impairment (see section 5.2).

Hepatic Impairment

Based on a population pharmacokinetic analysis, no dose adjustment of IMJUDO is recommended for patients with mild or moderate hepatic impairment. IMJUDO has not been studied in patients with severe hepatic impairment (see section 5.2).

Method of Administration
For metastatic NSCLC, 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.

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

4.3 Contraindications
None.

4.4 Special warnings and special precautions for use
Refer to section 4.2, Table 2 for recommended treatment modifications and management of immune-mediated adverse reactions.

Immune-mediated pneumonitis
Immune-mediated pneumonitis or interstitial lung disease, defined as requiring use of systemic corticosteroids and with no clear alternate etiology, occurred in patients receiving IMJUDO in combination with durvalumab (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 etiologies excluded, and managed as recommended in section 4.2.

Immune-mediated hepatitis
Immune-mediated hepatitis, defined as requiring use of systemic corticosteroids and with no clear alternate etiology, occurred in patients receiving IMJUDO in combination with durvalumab (see section 4.8). Patients should be monitored for abnormal liver tests prior to and periodically during treatment with IMJUDO in combination with durvalumab. Immune-mediated hepatitis should be managed as recommended in section 4.2.

Immune-mediated colitis
Immune-mediated colitis or diarrhoea, defined as requiring use of systemic corticosteroids and with no clear alternate etiology, occurred in patients receiving IMJUDO in combination with

durvalumab (see section 4.8). Intestinal perforation and large intestine perforation were reported in patients receiving IMJUDO in combination with durvalumab. Patients should be monitored for signs and symptoms of colitis/diarrhoea and intestinal perforation and managed as recommended in section 4.2.

Immune-mediated endocrinopathies

Immune-mediated hypothyroidism/hyperthyroidism/thyroiditis

Immune-mediated hypothyroidism, hyperthyroidism or thyroiditis have occurred in patients receiving IMJUDO in combination with durvalumab (see section 4.8). Patients should be monitored for abnormal thyroid function tests prior to and periodically during treatment and managed as recommended in section 4.2.

Immune-mediated adrenal insufficiency

Immune-mediated adrenal insufficiency occurred in patients receiving IMJUDO in combination with durvalumab (see section 4.8). Patients should be monitored for clinical signs and symptoms of adrenal insufficiency and managed as recommended in section 4.2.

Immune-mediated type 1 diabetes mellitus

Immune-mediated type 1 diabetes mellitus, which can present with diabetic ketoacidosis, occurred in patients receiving IMJUDO in combination with durvalumab (see section 4.8). Patients should be monitored for clinical signs and symptoms of type 1 diabetes mellitus and managed as recommended in section 4.2.

Immune-mediated hypophysitis/hypopituitarism

Immune-mediated hypophysitis or hypopituitarism occurred in patients receiving IMJUDO in combination with durvalumab (see section 4.8). Patients should be monitored for clinical signs and symptoms of hypophysitis or hypopituitarism and managed as recommended in section 4.2.

Immune-mediated nephritis

Immune-mediated nephritis, defined as requiring use of systemic corticosteroids and with no clear alternate etiology, occurred in patients receiving IMJUDO in combination with durvalumab (see section 4.8). Patients should be monitored for abnormal renal function tests prior to and periodically during treatment with IMJUDO in combination with durvalumab and managed as recommended in section 4.2.

Immune-mediated rash

Immune-mediated rash or dermatitis (including pemphigoid), defined as requiring use of systemic corticosteroids and with no clear alternate etiology, occurred in patients receiving IMJUDO in combination with durvalumab (see section 4.8). Patients should be monitored for signs and symptoms of rash or dermatitis and managed as recommended in section 4.2.

Immune-mediated myocarditis

Immune-mediated myocarditis, which can be fatal, occurred in patients receiving IMJUDO in combination with durvalumab (see section 4.8). Patients should be monitored for signs and symptoms of immune-mediated myocarditis and managed as recommended in section 4.2.

Other immune-mediated adverse reactions

Given the mechanism of action of IMJUDO and durvalumab, other potential immune-mediated adverse reactions may occur in patients receiving the combination of IMJUDO with durvalumab. The following immune-mediated adverse reactions have been observed: myasthenia gravis, myositis, polymyositis, immune thrombocytopenia, pancreatitis, and encephalitis (see section 4.8). Patients should be monitored for signs and symptoms and managed as recommended in section 4.2.

Infusion-related reactions

Patients should be monitored for signs and symptoms of infusion-related reactions and managed as recommended in section 4.2. Severe infusion-related reactions have been reported in patients receiving IMJUDO in combination with durvalumab (see section 4.8).

4.5 Interaction with other medicinal products and other forms of interaction

Tremelimumab is an immunoglobulin and the primary elimination pathways of tremelimumab are protein catabolism via reticuloendothelial system or target-mediated disposition; therefore, no formal pharmacokinetic (PK) drug-drug interaction studies have been conducted with tremelimumab since no metabolic drug-drug interactions are expected. PK drug-drug interaction between tremelimumab in combination with durvalumab and platinum-based chemotherapy was assessed in the POSEIDON study, and no clinically meaningful PK drug-drug interaction was identified. PK drug-drug interaction between tremelimumab in combination with durvalumab was assessed in the HIMALAYA study and no clinically meaningful PK drug-drug interaction was identified.

4.6 Pregnancy and lactation

Pregnancy

In animal reproduction studies, administration of tremelimumab to pregnant cynomolgus monkeys during the period of organogenesis was not associated with maternal toxicity or any effects on pregnancy maintenance or embryofoetal development (see section 5.3). There are no data on the use of tremelimumab in pregnant women. Based on its mechanism of action, tremelimumab has the potential to impact pregnancy maintenance and may cause foetal harm when administered to a pregnant woman. Human IgG2 is known to cross the placental barrier. Tremelimumab is not recommended during pregnancy and in women of childbearing potential not using effective contraception during treatment and for at least 3 months after the last dose.

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

Fertility
There are no data on the potential effects of tremelimumab on fertility in humans.

4.7 Effects on ability to drive and use machines
Based on its pharmacodynamic properties, tremelimumab is unlikely to affect the ability to drive and use machines. However, if patients experience adverse reactions affecting their ability to concentrate and react, they should be advised to use caution when driving or operating machinery.

4.8 Undesirable effects
Overall summary of adverse drug reactions
The safety of IMJUDO in combination with durvalumab and platinum-based chemotherapy is based on data in 330 patients from the POSEIDON (metastatic NSCLC) study.

The safety of STRIDE is based on data in 462 patients from the HIMALAYA study and Study 22 (uHCC, HCC pool).

Tabulated list of adverse reactions
Table 3 lists the incidence of adverse reactions (ADRs) in patients treated with IMJUDO in combination with durvalumab and platinum-based chemotherapy in the POSEIDON study. Table 4 lists the incidence of ADRs in patients treated with STRIDE in the HCC pool. Adverse drug reactions are listed according to system organ class in MedDRA. Within each system organ class, the adverse drug reactions are presented in decreasing frequency. Within each frequency grouping, ADRs are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each ADR is based on the CIOMS III convention and 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 determined (cannot be estimated from available data).

Table 3. Adverse drug reactions in metastatic NSCLC patients treated with IMJUDO in combination with durvalumab and platinum-based chemotherapy

	IMJUDO with durvalumab and platinum-based chemotherapy (n = 330)		
Adverse Drug Reaction[a]	**Frequency of any Grade**		**Frequency of Grade 3-4**
Blood and Lymphatic System Disorders			
Anaemia[b]	Very common	164 (49.7%)	68 (20.6%)
Febrile neutropenia[b]	Common	10 (3.0%)	7 (2.1%)
Immune thrombocytopenia	Uncommon	1 (0.3%)	0
Leukopenia[b,c]	Very common	64 (19.4%)	18 (5.5%)
Neutropenia[b,d]	Very common	136 (41.2%)	79 (23.9%)
Pancytopenia[b]	Common	6 (1.8%)	2 (0.6%)
Thrombocytopenia[b,e]	Very common	81 (24.5%)	27 (8.2%)
Cardiac disorders			
Myocarditis[f]	Uncommon	1 (0.3%)	0
Endocrine disorders			
Adrenal insufficiency	Common	7 (2.1%)	2 (0.6%)
Diabetes insipidus	Uncommon	1 (0.3%)	1 (0.3%)
Hyperthyroidism[g]	Common	22 (6.7%)	0
Hypopituitarism/ Hypophysitis	Common	5 (1.5%)	1 (0.3%)
Hypothyroidism[h]	Very common	44 (13.3%)	0
Thyroiditis[i]	Common	4 (1.2%)	0
Type 1 diabetes mellitus	Uncommon	1 (0.3%)	1 (0.3%)
Gastrointestinal disorders			
Abdominal pain[j]	Common	24 (7.3%)	0
Amylase increased	Common	28 (8.5%)	12 (3.6%)
Colitis[l]	Common	18 (5.5%)	7 (2.1%)
Constipation[b]	Very common	63 (19.1%)	0
Diarrhoea	Very common	71 (21.5%)	5 (1.5%)
Intestinal perforation	Not determined[k]		
Large intestine perforation	Not determined[k]		
Lipase increased	Common	21 (6.4%)	13 (3.9%)
Nausea[b]	Very common	137 (41.5%)	6 (1.8%)
Pancreatitis[m]	Common	7 (2.1%)	1 (0.3%)
Stomatitis[b,n]	Common	32 (9.7%)	0
Vomiting[b]	Very common	60 (18.2%)	4 (1.2%)

References: US PI and CDS version 5.0 (25 Aug 2022)

	IMJUDO with durvalumab and platinum-based chemotherapy (n = 330)		
Adverse Drug Reaction[a]	**Frequency of any Grade**		**Frequency of Grade 3-4**
General disorders and administration site conditions			
Fatigue[b,o]	Very common	119 (36.1%)	17 (5.2%)
Oedema peripheral[p]	Common	28 (8.5%)	0
Pyrexia	Very common	53 (16.1%)	0
Hepatobiliary disorders			
Aspartate aminotransferase increased/Alanine aminotransferase increased[q]	Very common	58 (17.6%)	7 (2.1%)
Hepatitis[r]	Common	13 (3.9%)	3 (0.9%)
Infections and infestations			
Dental and oral soft tissue infections[s]	Uncommon	2 (0.6%)	1 (0.3%)
Influenza	Common	11 (3.3%)	0
Oral candidiasis	Common	8 (2.4%)	1 (0.3%)
Pneumonia[t]	Very common	49 (14.8%)	24 (7.3%)
Upper respiratory tract infections[u]	Very common	51 (15.5%)	2 (0.6%)
Injury, poisoning and procedural complications			
Infusion-related reaction[v]	Common	13 (3.9%)	1 (0.3%)
Metabolism and nutrition disorders			
Decreased appetite[b]	Very common	93 (28.2%)	5 (1.5%)
Musculoskeletal and connective tissue disorders			
Myalgia	Common	14 (4.2%)	0
Myositis	Uncommon	1 (0.3%)	1 (0.3%)
Polymyositis	Uncommon	1 (0.3%)	1 (0.3%)
Nervous system disorders			
Encephalitis[w]	Uncommon	2 (0.6%)	2 (0.6%)
Myasthenia gravis	Not determined[k]		
Neuropathy peripheral[b,z]	Common	21 (6.4%)	0
Renal and urinary disorders			

	IMJUDO with durvalumab and platinum-based chemotherapy (n = 330)		
Adverse Drug Reaction[a]	**Frequency of any Grade**		**Frequency of Grade 3-4**
Blood creatinine increased	Common	21 (6.4%)	1 (0.3%)
Dysuria	Common	5 (1.5%)	0
Nephritis	Uncommon	2 (0.6%)	0
Respiratory, thoracic, and mediastinal disorders			
Cough/Productive cough	Very common	40 (12.1%)	0
Dysphonia	Common	8 (2.4%)	0
Interstitial lung disease	Uncommon	2 (0.6%)	0
Pneumonitis[x]	Common	14 (4.2%)	4 (1.2%)
Skin and subcutaneous tissue disorders			
Alopecia[b]	Very common	33 (10.0%)	0
Dermatitis	Uncommon	2 (0.6%)	0
Night sweats	Uncommon	2 (0.6%)	0
Pemphigoid	Uncommon	1 (0.3%)	1 (0.3%)
Pruritus	Very common	36 (10.9%)	0
Rash[y]	Very common	85 (25.8%)	5 (1.5%)

[a] Refer to the durvalumab monotherapy pool in the IMFINZI CDS for a completed list of grouped terms preferred terms for the ADR concepts.

[b]Adverse reaction only applies to chemotherapy ADRs in the POSEIDON study.

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

[d] Includes neutropenia and neutrophil count decreased.

[e] Includes platelet count decreased and thrombocytopenia.

[f] Includes autoimmune myocarditis.

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

[h] Includes blood thyroid stimulating hormone increased and hypothyroidism.

[i] Includes autoimmune thyroiditis and thyroiditis.

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

[k] Adverse reaction was not observed in the POSEIDON study but was reported in patients treated with IMJUDO + durvalumab in AstraZeneca-sponsored clinical studies included in the pan-tumour pooled dataset.

[l] Includes colitis, enteritis and enterocolitis.

[m] Includes autoimmune pancreatitis and pancreatitis.

[n] Includes mucosal inflammation and stomatitis.

[o] Includes asthenia and fatigue.

[p] Includes oedema peripheral and peripheral swelling.
[q] Includes alanine aminotransferase increased, aspartate aminotransferase increased, hepatic enzyme increased and transaminases increased.
[r] Includes autoimmune hepatitis, hepatitis, hepatotoxicity and immune-mediated hepatitis.
[s] Includes tooth abscess and tooth infection.
[t] Includes pneumocystis jirovecii pneumonia, pneumonia and pneumonia bacterial.
[u] Includes laryngitis, nasopharyngitis, pharyngitis, rhinitis, sinusitis, tonsillitis, tracheobronchitis and upper respiratory tract infection.
[v] Includes infusion-related reaction and urticaria.
[w] Includes encephalitis and encephalitis autoimmune.
[x] Includes immune-mediated pneumonitis and pneumonitis.
[y] Includes eczema, erythema, rash, rash macular, rash maculopapular, rash papular, rash pruritic and rash pustular.
[z] Includes neuropathy peripheral, parasthesia and peripheral sensory neuropathy.

Table 4. Adverse Drug Reactions in patients with uHCC treated with STRIDE

	STRIDE (n=462)			
Adverse Drug Reaction[a]	**Frequency of any Grade**		**Frequency of Grade 3-4**	
Blood and Lymphatic System Disorders				
Immune thrombocytopenia	Not determined[b]			
Cardiac disorders				
Myocarditis	Uncommon	2 (0.4%)		0
Endocrine disorders				
Adrenal insufficiency	Common	6 (1.3%)	Uncommon	1 (0.2%)
Diabetes insipidus	Not determined[b]			
Hyperthyroidism[c]	Common	44 (9.5%)	Uncommon	1 (0.2%)
Hypopituitarism/Hypophysitis	Uncommon	4 (0.9%)		0
Hypothyroidism[d]	Very common	60 (13.0%)		0
Thyroiditis[e]	Common	8 (1.7%)		0
Type 1 diabetes mellitus	Not determined[b]			
Gastrointestinal disorders				
Abdominal pain[f]	Very common	91 (19.7%)	Common	10 (2.2%)
Amylase increased	Common	41 (8.9%)	Common	20 (4.3%)
Colitis[g]	Common	16 (3.5%)	Common	12 (2.6%)

Diarrhoea	Very common	117 (25.3%)	Common	18 (3.9%)
Intestinal perforation	Not determined[b]			
Large intestine perforation	Not determined[b]			
Lipase increased	Common	46 (10.0%)	Common	33 (7.1%)
Pancreatitis[h]	Common	6 (1.3%)	Uncommon	3 (0.6%)
General disorders and administration site conditions				
Oedema peripheral[i]	Very common	48 (10.4%)	Uncommon	2 (0.4%)
Pyrexia	Very common	64 (13.9%)	Uncommon	1 (0.2%)
Hepatobiliary disorders				
Aspartate aminotransferase increased/Alanine aminotransferase increased[j]	Very common	83 (18.0%)	Common	41 (8.9%)
Hepatitis[k]	Common	23 (5.0%)	Common	8 (1.7%)
Infections and infestations				
Dental and oral soft tissue infections[l]	Common	6 (1.3%)		0
Influenza	Common	10 (2.2%)		0
Oral candidiasis	Uncommon	3 (0.6%)		0
Pneumonia[m]	Common	20 (4.3%)	Common	6 (1.3%)
Upper respiratory tract infections[n]	Common	39 (8.4%)		0
Injury, poisoning and procedural complications				
Infusion-related reaction[o]	Common	6 (1.3%)		0
Musculoskeletal and connective tissue disorders				
Myalgia	Common	16 (3.5%)	Uncommon	1 (0.2%)
Myositis	Uncommon	3 (0.6%)	Uncommon	1 (0.2%)
Polymyositis	Uncommon	1 (0.2%)	Uncommon	1 (0.2%)
Nervous system disorders				
Myasthenia gravis	Uncommon	2 (0.4%)		0
Encephalitis	Not determined[b]			
Renal and urinary disorders				

Blood creatinine increased	Common	21 (4.5%)	Uncommon	2 (0.4%)
Dysuria	Common	7 (1.5%)		0
Nephritis[p]	Uncommon	3 (0.6%)	Uncommon	2 (0.4%)
Respiratory, thoracic and mediastinal disorders				
Cough/Productive cough	Very common	50 (10.8%)	Uncommon	1 (0.2%)
Dysphonia	Uncommon	4 (0.9%)		0
Interstitial lung disease	Uncommon	1 (0.2%)		0
Pneumonitis[q]	Common	11 (2.4%)	Uncommon	1 (0.2%)
Skin and subcutaneous tissue disorders				
Dermatitis[r]	Common	6 (1.3%)		0
Night sweats	Common	6 (1.3%)		0
Pemphigoid	Uncommon	1 (0.2%)		0
Pruritus	Very common	118 (25.5%)		0
Rash[s]	Very common	150 (32.5%)	Common	14 (3.0%)

[a] Refer to the durvalumab monotherapy pool in the IMFINZI CDS for a completed list of grouped terms preferred terms for the ADR concepts.

[b] Adverse reaction was not observed in the HCC pool, but was reported in patients treated with durvalumab and/or IMJUDO + durvalumab in AstraZeneca-sponsored clinical studies.

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

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

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

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

[g] Includes colitis, enteritis and enterocolitis.

[h] Includes pancreatitis and pancreatitis acute.

[i] Includes oedema peripheral and peripheral swelling.

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

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

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

[m] Includes pneumocystis jirovecii pneumonia and pneumonia.

[n] Includes nasopharyngitis, pharyngitis, rhinitis, tracheobronchitis and upper respiratory tract infection.

[o] Includes infusion-related reaction and urticaria.

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

[q] Includes immune-mediated pneumonitis and pneumonitis.

[r] Includes dermatitis and immune-mediated dermatitis.

[s] Includes eczema, erythema, rash, rash macular, rash maculo-papular, rash papular and rash pruritic.

The safety of IMJUDO in combination with durvalumab and platinum-based chemotherapy is based on data in 330 patients from the POSEIDON (metastatic NSCLC) study and was consistent with known IMJUDO + durvalumab (refer to Appendix II for details) and known chemotherapy safety profile.

The safety of STRIDE is based on data in 462 patients from the HCC pool (uHCC) and was consistent with known IMJUDO + durvalumab safety profile. Refer to Appendix II for details.

Description of selected adverse reactions

The data below reflects information for significant adverse reactions for IMJUDO (75 mg Q4W) in combination with durvalumab in the pooled studies across various tumour types (n=2280) and STRIDE in the HCC pool (n=462).

The management guidelines for these adverse reactions are described in sections 4.2 and 4.4.

Immune-mediated pneumonitis

IMFINZI + tremelimumab pan-tumour pool

In patients receiving IMJUDO in combination with durvalumab, 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 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.

HCC pool

In patients receiving STRIDE, immune-mediated pneumonitis occurred in 6 (1.3%) patients, including Grade 3 in 1 (0.2%) patient and Grade 5 (fatal) in 1 (0.2%) patient. The median time to onset was 29 days (range: 5-774 days). All patients received systemic corticosteroids, and 5 of the 6 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). One patient also received other immunosuppressants. Treatment was discontinued in 2 patients. Resolution occurred in 3 patients.

Immune-mediated hepatitis

IMFINZI + tremelimumab pan-tumour pool

In patients receiving IMJUDO in combination with durvalumab, 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 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.

HCC pool
In patients receiving STRIDE, 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
IMFINZI + tremelimumab pan-tumour pool
In patients receiving IMJUDO in combination with durvalumab, 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.

Intestinal perforation was observed in patients receiving IMJUDO in combination with durvalumab.

HCC pool
In patients receiving STRIDE, 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 not observed in patients receiving STRIDE.

Immune-mediated endocrinopathies
Immune-mediated hypothyroidism

IMFINZI + tremelimumab pan-tumour pool
In patients receiving IMJUDO in combination with durvalumab, 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 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). Two-hundred and five patients required endocrine therapy. Treatment was 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.

HCC pool
In patients receiving STRIDE, immune-mediated hypothyroidism occurred in 46 (10.0%) patients. The median time to onset was 85 days (range: 26-763 days). One patient received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). All patients required other therapy (thiamazole, carbimazole, propylthiouracil, perchlorate, calcium channel blocker, or beta-blocker). Resolution occurred in 6 patients. Immune-mediated hypothyroidism was preceded by immune-mediated hyperthyroidism in 4 patients.

Immune-mediated hyperthyroidism
IMFINZI + tremelimumab pan-tumour pool
In patients receiving IMJUDO in combination with durvalumab, 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). Treatment was discontinued in 1 patient. Resolution occurred in 47 patients.

HCC pool
In patients receiving STRIDE, 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 coticosteriods, 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
IMFINZI + tremelimumab pan-tumour pool

In patients receiving IMJUDO in combination with durvalumab, 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.

HCC pool
In patients receiving STRIDE, immune-mediated thyroiditis occurred in 6 (1.3%) patients. The median time to onset was 56 days (range: 7-84 days). Two patients received systemic corticosteroids, and 1 of the 2 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). All patients required other therapy including hormone replacement therapy, thiamazole, carbimazole, propylthiouracil, perchlorate, calcium channel blocker, or beta-blocker. Resolution occurred in 2 patients.

Immune-mediated adrenal insufficiency
IMFINZI + tremelimumab pan-tumour pool
In patients receiving IMJUDO in combination with durvalumab, 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). Seven patients required endocrine therapy. Treatment was discontinued in 1 patient. Resolution occurred in 11 patients.

HCC pool
In patients receiving STRIDE, 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
IMFINZI + tremelimumab pan-tumour pool
In patients receiving IMJUDO in combination with durvalumab, 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 in 1 patient. Resolution occurred in 1 patient.

HCC pool
In patients receiving STRIDE, immune-mediated type 1 diabetes mellitus was not observed.

Immune-mediated hypophysitis/hypopituitarism
IMFINZI + tremelimumab pan-tumour pool
In patients receiving IMJUDO in combination with durvalumab, immune-mediated hypophysitis/hypopituitarism occurred in 16 (0.7%) patients, including Grade 3 in 8 (0.4%) patients. The median time to onset 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.

HCC pool
In patients receiving STRIDE, 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
IMFINZI + tremelimumab pan-tumour pool
In patients receiving IMJUDO in combination with durvalumab, 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.

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

Immune-mediated rash
IMFINZI + tremelimumab pan-tumour pool

In patients receiving IMJUDO in combination with durvalumab, 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.

HCC pool
In patients receiving STRIDE, 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%) patients. 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
IMFINZI + tremelimumab pan-tumour pool
In patients receiving IMJUDO in combination with durvalumab, 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.

HCC pool
In patients receiving STRIDE, infusion-related reactions occurred in 7 (1.5%) patients.

4.9 Overdose
There is no specific treatment in the event of tremelimumab overdose, and symptoms of overdose are not established. In the event of an overdose, physicians should follow general supportive measures and should treat symptomatically.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action
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 immune activity.

The combination of durvalumab, a PD-L1 inhibitor, and tremelimumab functions to enhance anti-tumour T-cell activation and function at multiple stages of the immune response, maximizing anti-tumour immunity.

The effect of STRIDE on the quantities of proliferative cytotoxic CD8+ T cells was evaluated in Study 22 in patients with uHCC using a CD8+Ki67+ assay. At Day 15 a marked increase of proliferating CD8+ T cell populations was observed in the STRIDE arm compared to the durvalumab monotherapy arm. Patients receiving STRIDE also experienced a higher Objective Response Rate (ORR) compared to other treatment arms and responders across all arms exhibited higher median proliferative cytotoxic CD8+ T cell when compared to non-responding patients.

Clinical efficacy and safety

Metastatic 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 sensitizing epidermal growth factor receptor (EGFR) mutation or anaplastic lymphoma kinase (ALK) genomic tumour aberrations. Patients with a 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/Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.

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.

Randomisation was stratified by tumour cells (TC) PD-L1 expression (TC≥50% vs. TC<50%), disease stage (Stage IVA vs. Stage IVB), 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 as monotherapy.

Patients could receive additional 2 cycles (a total of 6 cycles post-randomisation), as clinically indicated, at Investigator's discretion.

In the 3 treatment arms, patients received one of the following histology-based chemotherapy regimens:

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

IMJUDO was given up to a maximum of 5 doses unless there was disease progression or unacceptable toxicity. Durvalumab and histology-based pemetrexed maintenance therapy (when applicable) was continued until disease progression or unacceptable toxicity. Administration of durvalumab monotherapy was permitted beyond disease progression if the patient was clinically stable and deriving clinical benefit as determined by the investigator. Patients with disease progression during durvalumab monotherapy were given the option to be retreated with 4 additional cycles of IMJUDO alongside durvalumab.

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) vs. 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. At planned analyses for OS and PFS, IMJUDO + durvalumab + platinum-based chemotherapy (Arm 1) vs. platinum-based

chemotherapy (Arm 3) met the efficacy boundaries for the endpoints of OS and PFS. The results are summarised below.

The demographics and baseline disease characteristics were generally well-balanced between study arms. Baseline demographics of the overall study population were as follows: male (76.0%), age ≥ 65 years (47.1%), 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%), and never smoker (21.9%), 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%), PD-L1 expression TC≥50% (28.8%), PD-L1 expression TC <50% (71.1%).

The study demonstrated a statistically significant and clinically meaningful improvement in OS in the IMJUDO + durvalumab + platinum-based chemotherapy (Arm 1) vs. platinum-based chemotherapy alone (Arm 3) [HR=0.77 (95% CI: 0.650, 0.916), p=0.00304]. IMJUDO + durvalumab + platinum-based chemotherapy demonstrated a statistically significant and clinically meaningful improvement in PFS vs. platinum-based chemotherapy alone (Arm 3) [HR=0.72 (95% CI: 0.600, 0.860), p=0.00031]. See Table 4 and Figures 1 and 2.

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[1]		
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)	0.77 (0.650, 0.916)	
p-value[2]	0.00304	
OS at 12 months (%) (95% CI)	54.8 (49.3, 60.0)	49.1 (43.6, 54.4)
OS at 24 months (%) (95% CI)	32.9 (27.9, 37.9)	22.1 (17.8, 26.8)
OS at 36 months (%) (95% CI)	25.3 (20.8, 30.2)	13.3 (9.8, 17.4)
PFS[1]		
Number of events (%)	238 (70.4)	258 (76.6)
Median PFS (months) (95% CI)	6.2 (5.0, 6.5)	4.8 (4.6, 5.8)

HR (95% CI)	0.72 (0.600, 0.860)	
p-value[2]	0.00031	
PFS at 12 months (%) (95% CI)	26.6 (21.7, 31.7)	13.1 (9.3, 17.6)
ORR n (%)[3]	130 (38.8)	81 (24.4)
Complete Response n (%)	2 (0.6)	0
Partial Response n (%)	128 (38.2)	81 (24.4)
Odds ratio (95% CI)	2.00 (1.428, 2.807)	
p-value	<0.001	
Median DoR (months) (95% CI)	9.5 (7.2, NR)	5.1 (4.4, 6.0)

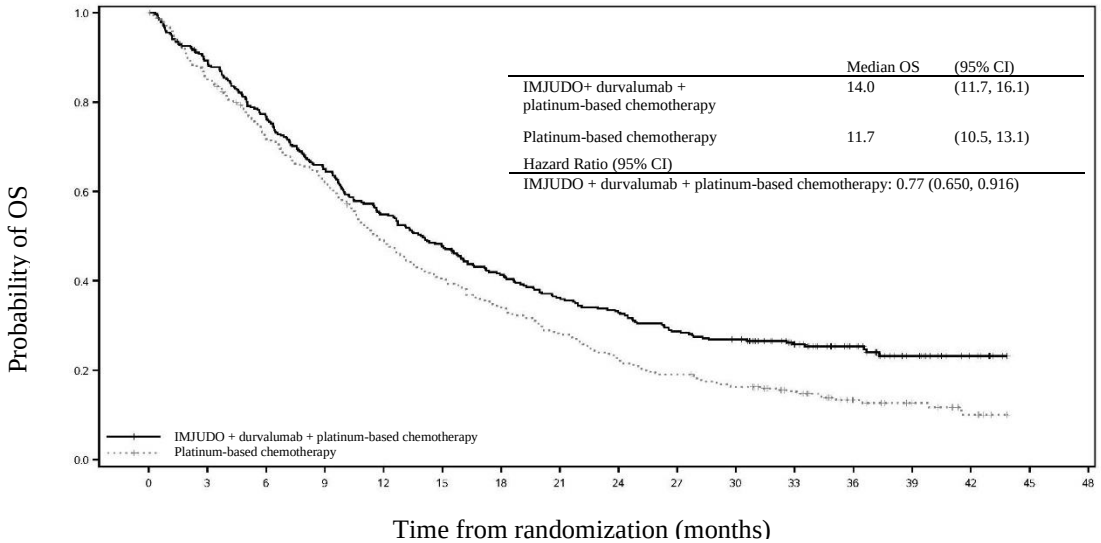
[1] PFS/OS results are based on planned analyses which occurred 25/45 months respectively after study initiation. The boundaries for declaring efficacy (PFS 0.00735, OS 0.00797 2-sided) were determined by a Lan-DeMets alpha spending function that approximates an O'Brien Fleming approach.

[2] 2-sided p-value based on a log-rank test stratified by PD-L1, histology and disease stage.

[3] Confirmed Objective Response.

NR=Not Reached, CI=Confidence Interval

Figure 1. Kaplan-Meier curve of OS



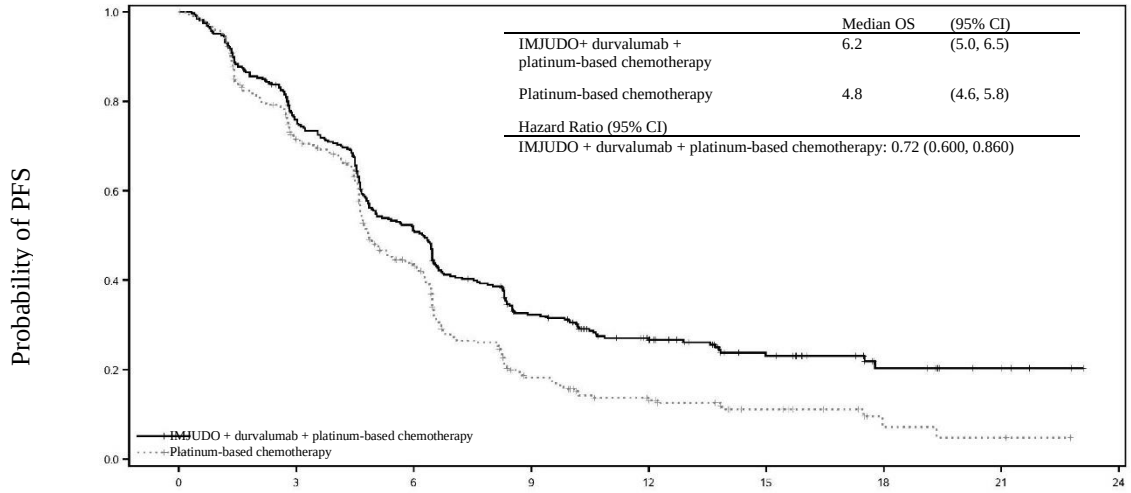
Number of patients at risk

Month	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45
IMJUDO + durvalumab + platinum-based chemotherapy	338	298	256	217	183	159	137	120	109	95	88	64	41	20	9	0
Platinum-based chemotherapy																

References: US PI and CDS version 5.0 (25 Aug 2022)

337	284	236	204	160	132	111	91	72	62	52	38	21	13	6	0

Figure 2. 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

Subgroup analysis

The improvements in OS and PFS favour patients receiving IMJUDO + durvalumab + platinum-based chemotherapy compared to those receiving platinum-based chemotherapy alone and were consistently observed across the pre-specified subgroups based on demographic and baseline characteristics, biomarker status, histology, planned chemotherapy, and disease characteristics. An exception was noted in the never smoker subgroup for OS. However, due to the small numbers of patients, no definitive conclusions can be drawn from these data.

Patient-Reported Outcomes

Patient-reported symptoms, function and health-related quality of life (HRQoL) were collected using the EORTC QLQ-C30 and its lung cancer module (EORTC QLQ-LC13). Both questionnaires were administered up to second disease progression (PFS2) or death (whichever came first). At baseline, patient-reported symptoms, functioning or HRQoL scores were comparable between the study arms.

<u>Delay in time to deterioration (TTD) of symptoms, functioning, and global health status/QoL:</u>

T+D+SoC prolonged the median TTD in patient-reported symptoms, functioning and global health status/QoL compared to SoC alone (see Tables 5 and 6). Nominally significant differences in TTD in favor of T + D + SoC compared to SoC alone were observed for the pre-specified domains of interest of global health status/QoL, physical functioning and dyspnoea (EORTC QLQ-LC13) (HRs ranging from 0.75 to 0.78; nominal p-values <0.05).

Table 5: Median time to deterioration in global health status/QoL and function (EORTC QLQ-C30)[a]

PRO domain	Statistic	D +T+SoC (N=338)	SoC (N=337)
Global health status/QoL[a]	n[b]	319	318
	Median time to deterioration (months)	8.3	5.6
	HR[c] (95% CI)	0.78 (0.631, 0.961)	
	p-value[d]	0.021	
Physical[a]	n[b]	323	320
	Median time to deterioration (months)	7.7	5.3
	HR[c] (95% CI)	0.75 (0.610, 0.920)	
	p-value[d]	0.006	
Cognitive	n[b]	323	318
	Median time to deterioration (months)	7.6	5.8
	HR[c] (95% CI)	0.79 (0.644, 0.975)	
	p-value[d]	0.028	
Role	n[b]	314	304
	Median time to deterioration (months)	6.6	4.8
	HR[c] (95% CI)	0.81 (0.664, 0.999)	
	p-value[d]	0.049	
Emotional	n[b]	322	315
	Median time to deterioration (months)	8.5	7.5
	HR[c] (95% CI)	0.87 (0.697, 1.082)	
	p-value[d]	0.208	
Social	n[b]	320	314
	Median time to deterioration (months)	6.4	5.7
	HR[c] (95% CI)	0.85 (0.687, 1.045)	
	p-value[d]	0.120	

[a] Pre-specified PRO domains of interest

[b] Number of patients with a baseline global health status/QoL or function score ≥10 that were included in the time to deterioration analysis

[c] A hazard ratio <1 favours D+T+SoC

[d] p-values for time to deterioration based on stratified log-rank test adjusting for PD-L1 (PD-L1 ≥50% vs PD-L1 <50%), histology (squamous vs non-squamous), and disease stage (Stage IVA vs Stage IVB). They were not adjusted for multiplicity

Table 6: Median time to deterioration in symptoms (EORTC QLQ-C30 and QLQ-LC13)[a]

PRO domain	Statistic	D +T+SoC (N=338)	SoC (N=337)
Coughing[a]	n[b]	302	295
	Median time to deterioration (months)	9.7	8.8
	HR[c] (95% CI)	0.91 (0.722, 1.146)	
	p-value[d]	0.418	
Dyspnoea (QLQ-C30)	n[b]	310	301
	Median time to deterioration (months)	7.9	6.7
	HR[c] (95% CI)	0.84 (0.678, 1.047)	
	p-value[d]	0.123	
Dyspnoea (QLQ-LC13)[a]	n[b]	325	316
	Median time to deterioration (months)	5.4	3.6
	HR[c] (95% CI)	0.77 (0.635, 0.936)	
	p-value[d]	0.009	
Pain	n[b]	316	298
	Median time to deterioration (months)	8.9	5.7
	HR[c] (95% CI)	0.70 (0.563, 0.862)	
	p-value[d]	<0.001	
Chest pain[a]	n[b]	319	309
	Median time to deterioration (months)	10.0	8.6
	HR[c] (95% CI)	0.85 (0.681, 1.066)	
	p-value[d]	0.163	
Arm or shoulder pain	n[b]	312	310
	Median time to deterioration (months)	8.9	8.8
	HR[c] (95% CI)	0.93 (0.745, 1.161)	
	p-value[d]	0.517	
Pain in other parts of body	n[b]	312	306
	Median time to deterioration (months)	9.7	5.8
	HR[c] (95% CI)	0.74 (0.597, 0.921)	
	p-value[d]	0.007	
Fatigue[a]	n[b]	317	314
	Median time to deterioration (months)	3.7	2.8

PRO domain	Statistic	D +T+SoC (N=338)	SoC (N=337)
	HR[c] (95% CI)	0.90 (0.746, 1.084)	
	p-value[d]	0.272	
Insomnia	n[b]	311	301
	Median time to deterioration (months)	8.3	5.8
	HR[c] (95% CI)	0.74 (0.598, 0.921)	
	p-value[d]	0.007	
Appetite loss[a]	n[b]	308	305
	Median time to deterioration (months)	7.2	7.0
	HR[c] (95% CI)	0.94 (0.754, 1.169)	
	p-value[d]	0.570	
Constipation	n[b]	315	306
	Median time to deterioration (months)	9.2	6.1
	HR[c] (95% CI)	0.78 (0.627, 0.972)	
	p-value[d]	0.026	
Diarrhoea	n[b]	324	320
	Median time to deterioration (months)	11.0	10.8
	HR[c] (95% CI)	1.00 (0.792, 1.260)	
	p-value[d]	0.986	
Nausea/vomiting	n[b]	322	319
	Median time to deterioration (months)	7.8	5.6
	HR[c] (95% CI)	0.81 (0.655, 0.994)	
	p-value[d]	0.045	
Haemoptysis	n[b]	325	318
	Median time to deterioration (months)	17.8	11.4
	HR[c] (95% CI)	0.77 (0.598, 0.984)	
	p-value[d]	0.036	

[a] Pre-specified PRO domains of interest

[b] Number of patients with a baseline symptom score ≤90 that were included in the time to deterioration analysis

[c] A hazard ratio <1 favours D+T+SoC

[d] p-values for time to deterioration based on stratified log-rank test adjusting for PD-L1 (PD-L1 ≥50% vs PD-L1 <50%), histology (squamous vs non-squamous), and disease stage (Stage IVA vs Stage IVB). They were not adjusted for multiplicity.

HCC - HIMALAYA Study

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

The study excluded patients with co-infection of viral hepatitis B and hepatitis C; active or prior documented 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), etiology 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
- STRIDE: IMJUDO 300 mg as a single priming dose + durvalumab 1500 mg; followed by durvalumab 1500 mg every 4 weeks
- S: Sorafenib 400 mg twice daily

Treatment continued as long as clinical benefit was observed or until unacceptable toxicity. Patients in all arms could continue to receive treatment after evidence of disease progression if, in the Investigator's opinion, they were benefiting from study drug and met all inclusion and exclusion criteria for treatment beyond progression. In addition, patients in the STRIDE arm who continued treatment beyond progression were allowed to be rechallenged once with an additional single dose of IMJUDO 300 mg after cycle five of durvalumab. Of the 182 patients enrolled to the STRIDE arm who received durvalumab beyond progression, the median OS was 19.5 months (95% CI: 15.4, 23.4). Of the 30 patients who were enrolled to the STRIDE arm who were rechallenged with IMJUDO, the median OS was 30.4 months (95% CI: 23.4, NR).

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 OS. Key secondary endpoints were PFS, Investigator assessed ORR and DoR according to RECIST v1.1. Patient-Reported Outcomes (PROs) were also assessed.

The demographics and baseline disease characteristics were generally representative for patients with uHCC. 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 (2.3%), ECOG PS 0 (62.6%); Child-Pugh Class score A (99.5%), macrovascular invasion (25.2%), extrahepatic spread (53.4%), viral etiology; hepatitis B (30.6%), hepatitis C (27.2%), uninfected (42.2%).

The study demonstrated a statistically significant and clinically meaningful improvement in OS with STRIDE vs. S [HR=0.78 [95% CI 0.66, 0.92]; p=0.0035].
See Table 7 and Figure 3.

Table 7. Efficacy Results for the HIMALAYA Study for STRIDE vs. S and D vs. S

	STRIDE (n=393)	**S (n=389)**	**D (n=389)**
Follow up duration			
Median follow up	33.2	32.2	32.6
Range	(31.7-34.5)	(30.4-33.7)	(31.6-33.7)
OS			
Number of deaths (%)	262 (66.7)	293 (75.3)	280 (72.0)
Median OS (months) (95% CI)	16.4 (14.2-19.6)	13.8 (12.3-16.1)	16.6 (14.1-19.1)
HR (95% CI)	0.78 (0.66, 0.92)		-
p-value[a]	0.0035		-
HR (95% CI)	-	0.86 (0.73, 1.02)	
p-value[b]	-	0.0674	
OS at 12 months (%) (95% CI)	60.2 (55.2 - 64.9)	56.2 (51.0 - 61.0)	59.3 (54.2-64.0)
OS at 18 months (%) (95% CI)	48.7 (43.6-53.5)	41.5 (36.5-46.4)	47.4 (42.4-52.3)
OS at 24 months (%) (95% CI)	40.5 (35.6-45.3)	32.6 (27.9-37.4)	39.6 (34.8-44.5)
OS at 36 months (%) (95% CI)	30.7 (25.8-35.7)	20.2 (15.8-25.1)	24.7 (20.0-29.8)
p-value	0.0029		0.1926
Number of patients treated beyond progression	182	192	188
PFS			
Number of events (%)	335 (85.2)	327 (84.1)	345 (88.7)
Median PFS (months)	3.78	4.07	3.65

(95% CI)	(3.68-5.32)	(3.75-5.49)	(3.19-3.75)
HR (95% CI)	0.90 (0.77 - 1.05)		-
p-value[c]	0.1625		-
HR (95% CI)	-	1.02 (0.88-1.19)	
p-value[c]	-	0.7736	
ORR			
ORR n (%)[c,d]	79 (20.1)	20 (5.1)	66 (17.0)
Complete Response n (%)	12 (3.1)	0	6 (1.5)
Partial Response n (%)	67 (17.0)	20 (5.1)	60 (15.4)
Odds ratio 95% CI	4.69 (2.85, 8.04)		3.8 (2.3, 6.6)
p-value	<0.0001[c]		<0.0001[c]
DoR			
Median DoR (months)	22.3	18.4	16.9
Sample size (n)	79	20	66
% with duration ≥6 months	82.3	78.9	81.8
% with duration ≥12 months	65.8	63.2	57.8

[a] 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 STRIDE vs. S was 0.0398 (Lan◦and◦DeMets 1983).

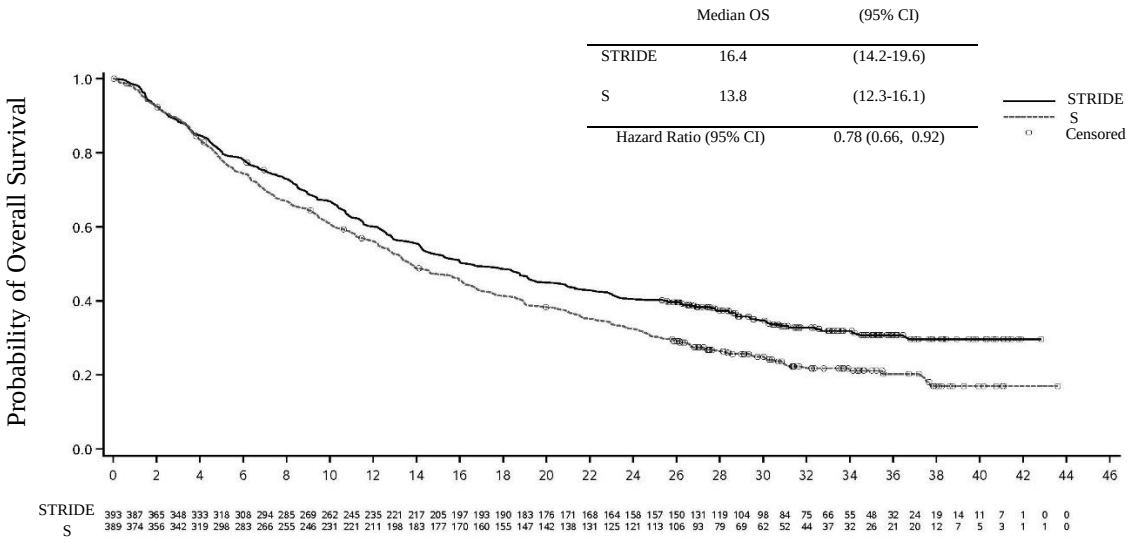
[b] p-value is for the superiority test of D vs. S. Based on a Lan-DeMets alpha spending function with O'Brien Fleming type boundary and the actual number of events observed, the boundary for declaring statistical significance for D vs. S was 0.0433 (Lan◦and◦DeMets 1983).

[c] Nominal p-value. PFS and ORR were not included in the Multiple Testing Procedure (MTP).

[d] Confirmed complete response.

NR=Not Reached, CI=Confidence Interval

Figure 3. Kaplan-Meier curve of OS



Patient reported outcomes

Patient-reported symptoms, function and health-related quality of life (HRQoL) were collected using the EORTC QLQ-C30 and its hepatocellular carcinoma module (EORTC QLQ-HCC18). At baseline, patient-reported symptoms, functioning or HRQoL scores were comparable between the study arms.

<u>Delay in time to deterioration of symptoms, functioning, and global health status/QoL:</u>

STRIDE vs. S demonstrated a clinically meaningful improvement by delaying time to deterioration in a broad range of patient-reported symptoms, function, and global health status/QoL compared to S. Longer time to deterioration (median in months) was observed in the STRIDE arm compared to S for the following symptoms: Global Health Status (7.5 vs. 5.7 months, HR 0.76, p = 0.0306); physical functioning (12.9 vs. 7.4 months, HR 0.68; p = 0.0020), fatigue (7.4 vs. 5.4 months, HR 0.71; p = 0.0026), nausea (25.0 vs. 11.0 months, HR 0.65; p = 0.0033), appetite loss (12.6 vs. 6.9 months, HR 0.59; p <0.0001), abdominal pain (16.8 vs. 8.9 months, HR 0.61; p = 0.0008) and abdominal swelling (20.9 vs. 11.1 months, HR 0.74; p = 0.0431.

<u>Change from baseline in patient-reported symptoms (mixed model for repeated measures)</u>:

STRIDE improved patient-reported HRQoL functioning and diarrhoea by demonstrating a nominal difference and clinically meaningful mean change from baseline vs. S from randomisation until 8 months (Estimated mean difference at 8 months: -18.5 95% CI: -23.24, -13.84 and p-value: <0.0001).

Patient-reported outcome results should be interpreted in the context of the open-label study design.

HCC – Study 22

The safety and efficacy of STRIDE was evaluated in Study 22, an open-label, multi-part, multicenter study in 75 immunotherapy naïve patients with uHCC who had progressed on, are intolerant to, or have refused sorafenib. The study included patients with BCLC Stage C or B (not eligible for locoregional therapy), ECOG performance status of 0 or 1 and Child-Pugh Score Class A.

The study excluded patients with co-infection of viral hepatitis B and hepatitis C; active or prior documented 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.

Treatment continued as long as clinical benefit was observed or until unacceptable toxicity. Patients who completed the assigned dosing cycles and were benefiting from study drug in the Investigator's opinion and subsequently had evidence of disease progression during the durvalumab monotherapy phase could be rechallenged with IMJUDO 300 mg.

Tumour assessments were conducted every 8 weeks.

The primary objective was safety and tolerability. Key secondary endpoints included OS, ORR and DoR. ORR and DoR were based on Investigator assessments and BICR according to RECIST 1.1.

The baseline demographics of the study population (STRIDE) were as follows: male (86.7%); age <65 years (45.3%), white (36.0%); Asian (58.7%); black or African American (5.3%); other (0%), ECOG PS 0 (61.3%), Child-Pugh Class/Score A/5 (68.0%), Child-Pugh Class/Score A/6 (30.7%), macrovascular invasion (21.3%); extrahepatic spread (70.7%), viral etiology; hepatitis B (36.0%), hepatitis C (28.0%), uninfected (36.0%); prior systemic therapy (73.3%).

Efficacy results are shown in Table 8.

Table 8. Efficacy results for Study 22[a]

	STRIDE (n=75)	**D (n=104)**
ORR		
ORR n (%)[b,c]	18 (24.0)	12 (11.5)
95% CI	14.9, 35.3	6.1, 19.3

DoR[b]		
Median DoR (months) (95% CI)	18.43 (5.6, 24.0)	15.0 (8.5, NR)
% with duration ≥6 months	71.8	83.3
% with duration ≥12 months	64.6	56.3
OS		
Number of deaths (%)	49 (65.3)	78 (75.0)
Median OS (months) (95% CI)	17.05 (10.6-22.8)	12.9 (8.7-16.8)
OS at 12 months (%) (95% CI)	57.6 (45.5-68.0)	50.4 (40.3-59.7)
OS at 18 months (%) (95% CI)	47.8 (35.9-58.7)	34.0 (24.9-43.3)
OS at 24 months (%) (95% CI)	38.3 (26.9-49.6)	26.2 (17.9-35.3)

[a] DCO of Final analysis: 6 Nov 2020.
[b] Confirmed by BICR per RECIST v1.1.
[c] Confirmed complete response.
NR=Not Reached, CI=Confidence Interval

5.2 Pharmacokinetic properties

The pharmacokinetics (PK) of tremelimumab was assessed for IMJUDO in combination with durvalumab and platinum-based chemotherapy in addition to IMJUDO in combination with durvalumab.

The pharmacokinetics of tremelimumab was studied in patients with solid tumours 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 priming 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 durvalumab with or without chemotherapy in the dose range of ≥ 75 mg (or 1 mg/kg) every 3 or 4 weeks, the geometric mean steady state volume of distribution (V_{ss}) was 5.97 L. Tremelimumab clearance (CL) decreased over time in combination with durvalumab and chemotherapy resulting in a geometric mean steady state clearance (CL_{ss}) of 0.202 L/day at Day 365; the decrease in CL_{ss} was not considered clinically relevant. The geometric mean (CV%) terminal half-life was approximately 20.4 (34.7) days. There was no clinically meaningful difference between the PK of tremelimumab as monotherapy, in combination with durvalumab or in combination with durvalumab and chemotherapy.

Special populations

Age (22–97 years), body weight (34-149 kg), gender, positive anti-drug antibody (ADA) status, albumin levels, LDH levels, creatinine levels, tumour type, race, mild renal impairment (creatinine clearance (CRCL) 60 to 89 mL/min), moderate renal impairment (creatinine clearance (CRCL) 30 to 59 mL/min), mild hepatic impairment (bilirubin ≤ ULN and AST > ULN or bilirubin > 1.0 to 1.5 × ULN and any AST), moderate hepatic impairment (bilirubin > 1.5 to 3 x ULN and any AST) or ECOG/WHO status had no clinically significant effect on the PK of tremelimumab.

The effect of severe renal impairment (CRCL 15 to 29 mL/min) or severe hepatic impairment (bilirubin > 3.0 x ULN and any AST) on the PK of tremelimumab is unknown.

Elderly

No dose adjustment is required for elderly patients (≥ 65 years of age). Of the 338 patients with metastatic NSCLC treated with IMJUDO in combination with durvalumab and platinum-based chemotherapy, 147 patients were 65 years or older. No overall clinically meaningful differences in safety or efficacy were reported between patients ≥ 65 years of age and younger patients.

No dose adjustment is required for elderly patients (≥ 65 years of age). Of the 462 patients with uHCC treated with STRIDE, 173 patients were 65 years or older. No overall clinically meaningful differences in safety or efficacy were reported between patients ≥ 65 years of age and younger patients.

Drug interaction studies

PK drug-drug interaction between tremelimumab and durvalumab and platinum-based chemotherapy was assessed in the POSEIDON study and no clinically meaningful PK drug-drug interaction was identified.

Immunogenicity

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

In the POSEIDON study, of the 278 patients who were treated with IMJUDO 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) patients. The presence of ADAs did not have an apparent effect on pharmacokinetics or safety.

In the HIMALAYA study, of the 182 patients who were treated with STRIDE and evaluable for the presence of ADAs against tremelimumab, 20 (11.0%) patients tested positive for treatment-emergent ADAs. Neutralizing antibodies against tremelimumab were detected in 4.4% (8/182) patients. The presence of ADAs did not have an apparent effect on pharmacokinetics or safety.

Immunogenicity assay results are highly dependent on several factors, including assay sensitivity and specificity, assay methodology, sample handling, timing of sample collection, concomitant medications and underlying disease.

For these reasons, comparison of incidence of antibodies to tremelimumab with the incidence of antibodies to other products may be misleading.

5.3 Preclinical safety data

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. In reproduction studies, administration of tremelimumab to pregnant cynomolgus monkeys during the period of organogenesis was not associated with maternal toxicity or effects pregnancy losses, foetal weights, or external, visceral, skeletal abnormalities or weights of selected foetal organs.

Animal toxicology and/or pharmacology

In the chronic six-month toxicity study in cynomolgus monkeys, weekly intravenous administration of 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, and mononuclear cell infiltration in a wide variety of tissues including the skin and lymphoid tissues, with dose-related incidence and severity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

L-histidine
L-histidine hydrochloride monohydrate
α,α-Trehalose dihydrate

Disodium edetate dihydrate
Polysorbate 80
Water for Injection

6.2 Incompatibilities

Tremelimumab

No incompatibilities between IMJUDO and 9 g/L (0.9%) sodium chloride or 50 g/L (5%) dextrose in polyvinylchloride or polyolefin IV bags have been observed.

This drug product must not be mixed with other drug products except those mentioned in section 6.6.

Do not co-administer other drugs through the same intravenous line.

6.3 Shelf-life

Unopened Vial

4 years at 2°C to 8°C.

After preparation of infusion solution

IMJUDO does not contain a preservative. Administer infusion solution immediately once prepared. If infusion solution is not administered immediately and it needs to be stored, follow the below recommendations:

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 30°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 not be longer than 28 days at 2°C to 8°C or 48 hours at room temperature (up to 30°C).

6.4 Special precautions for storage

Unopened vial

Store vials under refrigeration at 2°C to 8°C (36°F to 46°F) in original carton to protect from light.

Do not freeze.

Do not shake.

Diluted Solution
For storage conditions after preparation of the infusion, 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 Instructions for use, handling and disposal
Preparation of solution
IMJUDO is supplied as a single-dose vial and does not contain any preservatives, aseptic technique must be observed.

- Visually inspect drug 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 (IV) bag containing 0.9% Sodium Chloride Injection, or 5% Dextrose Injection. Mix diluted solution by gentle inversion. The final concentration of the diluted solution should be between 0.1 mg/mL and 10 mg/mL. Do not freeze or shake the solution.
- Care must be taken to ensure the sterility of prepared solutions.
- Do not re-enter the vial after withdrawal of drug.
- Discard any unused portion left in the vial.

Administration

- Administer infusion solution intravenously over 1 hour through an intravenous line containing a sterile, low-protein binding 0.2 or 0.22 micron filter.
- Do not co-administer other drugs through the same infusion line.

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

7. MARKETING AUTHORISATION HOLDER

AstraZeneca (Thailand) Ltd., Bangkok, Thailand.

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

December 2022