Summary Report of Benefit-Risk Assessment

IMJUDO CONCENTRATE FOR SOLUTION FOR INFUSION 20MG/ML

NEW DRUG APPLICATION

Active Ingredient(s)	Tremelimumab
Product Registrant	Astrazeneca Singapore Pte Ltd
Product Registration Number	SIN16845P
Application Route	Full evaluation
Date of Approval	25 August 2023

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A INTRODUCTION

Imjudo in combination with durvalumab is indicated for the treatment of patients with unresectable hepatocellular carcinoma (uHCC) who have not received prior systemic therapy.

The active substance, tremelimumab, is a human immunoglobulin G2 monoclonal antibody (IgG2 mAb) directed against cytotoxic T lymphocyte-associated antigen 4 (CTLA-4). The blockade of CTLA-4 leads to prolongation and enhancement of T-cell activation and proliferation resulting in increased T-cell diversity and enhanced antitumour activity. The combination use of tremelimumab with the programmed cell death protein 1 (PD-1) inhibitor, durvaluamab, results in dual checkpoint blockade and leads to potential additive antitumour effect with a longer duration of immune activation.

Imjudo is available as a concentrate for solution for infusion containing 20mg/ml of tremelimumab. Other ingredients in the vial are L-histidine, L-histidine hydrochloride monohydrate, α,α-trehalose dihydrate, disodium edetate dihydrate, polysorbate 80 and water for injection.

B ASSESSMENT OF PRODUCT QUALITY

The drug substance, tremelimumab, is manufactured at Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach an der Riss, Germany. The drug product, Imjudo concentrate for solution for infusion 20mg/ml, is manufactured at Vetter Pharma-Fertigung GmbH & Co. KG, Ravensburg, Germany.

Drug substance:

Adequate controls have been presented for the cell banks and raw materials. The in-process control tests and acceptance criteria applied during the manufacturing of the drug substance are considered appropriate. The drug substance manufacturer is compliant with Good Manufacturing Practice (GMP). Process validation is conducted on four consecutive production-scale batches.

The characterisation of the drug substance and its impurities have been appropriately performed. Potential and actual impurities are adequately controlled in the specification.

The drug substance specifications were established in accordance with ICH Q6B and the impurity limits were appropriately qualified. The analytical methods used were adequately described and non-compendial methods have been validated in accordance with ICH Q2 guideline, with information on the reference standards used for identity, assay and impurities testing presented.

The stability data presented was adequate to support the storage of drug substance at -50°C to -30°C in stainless steel vessels up to 48 months, followed by 2°C to 8°C in ethylene vinyl acetate (EVA) bags up to 24 months.

Drug product:

The manufacturing process involves pooling and homogenisation of the formulated drug substance, followed by prefiltration, sterile filtration and aseptic filling. This is considered a standard manufacturing process.

The manufacturing site involved is compliant with GMP. Proper development and validation studies were conducted. It has been demonstrated that the manufacturing process is reproducible and consistent. Adequate in-process controls are in place.

The specifications have been established in accordance with ICH Q6B guideline and impurity limits were adequately qualified. The analytical methods used were adequately described and non-compendial methods have been appropriately validated in accordance with ICH Q2 guideline, with information on the reference standards used for identity, assay and impurities testing presented.

The stability data submitted was adequate to support the approved shelf-life of 48 months when stored between 2°C and 8°C, as well as in-use period after dilution of 28 days at 2°C to 8°C or 48 hours at room temperature (up to 30°C). The container closure system is type I glass vial with an elastomeric stopper.

C ASSESSMENT OF CLINICAL EFFICACY

The clinical efficacy of tremelimumab in combination with durvalumab in the treatment of uHCC patients who have not received prior systemic therapy was based primarily on one pivotal Phase III study (D419CC00002), referred to as the HIMALAYA study. This was a multicentre, open-label, randomised study in patients with confirmed uHCC who have not received prior systemic treatment for HCC. Patients included had Barcelona Clinic Liver Cancer (BCLC) Stage B (not eligible for locoregional therapy) or Stage C, and Child-Pugh Score Class A liver disease.

Patients in the study were randomised in a 1:1:1 ratio to receive one of the following regimens:
- durvalumab 1500 mg every 4 weeks (D); or
- tremelimumab 300 mg as a single priming dose + durvalumab 1500 mg, followed by durvalumab 1500 mg every 4 weeks (T300+D); or
- sorafenib 400 mg twice daily (S).

Randomisation was stratified by macrovascular invasion (yes vs no), aetiology of liver disease (confirmed hepatitis B virus [HBV] vs confirmed hepatitis C virus [HCV] vs others), and ECOG performance status (0 vs 1). Treatment was continued until disease progression or unacceptable toxicity. Sorafenib was an appropriate active control as it was one of the standard of care for patients with uHCC who are not eligible for locoregional therapy and have not received prior systemic therapy for HCC.

The primary efficacy objective was to assess overall survival (OS) superiority of T300+D compared to S. The key secondary objective was to assess OS non-inferiority of D compared to S, followed by OS superiority if non-inferiority was demonstrated. The progression-free survival (PFS), objective response rate (ORR) and duration of response (DoR) were assessed as secondary endpoints of the study. The statistical methods employed were appropriate for the endpoints studied. Two analyses of OS were planned (Interim Analysis and Final Analysis).

Appropriate control for the Type I error was applied using the Lan DeMets approach for the two planned OS analyses for the primary comparison and hierarchical testing was applied for the primary and key secondary objectives.

A total of 1,171 patients were randomised in the study and were included in the Full Analysis Set (FAS) for efficacy analysis: 389 patients in the D group, 393 patients in the T300+D group and 389 patients in the S group. The demographics and baseline disease characteristics were generally representative for patients with uHCC. The median age was 64.0 years (range: 18 to 88 years), 83.7% of patients were male, and 44.6% and 50.7% of patients were White and Asian, respectively. A total of 38.9% of the patients were PD-L1 positive (i.e., Tumour and Immune Cell Positivity ≥ 1%). The majority of the patients (80.8%) had BCLC score of "C" and 74.8% of the patients had no macrovascular invasion (MVI). Extrahepatic spread (EHS) was reported in the 53.4% of the patients and only 34.1% of the patients had no MVI and EHS at baseline.

Summary of key efficacy results (FAS; final analysis)

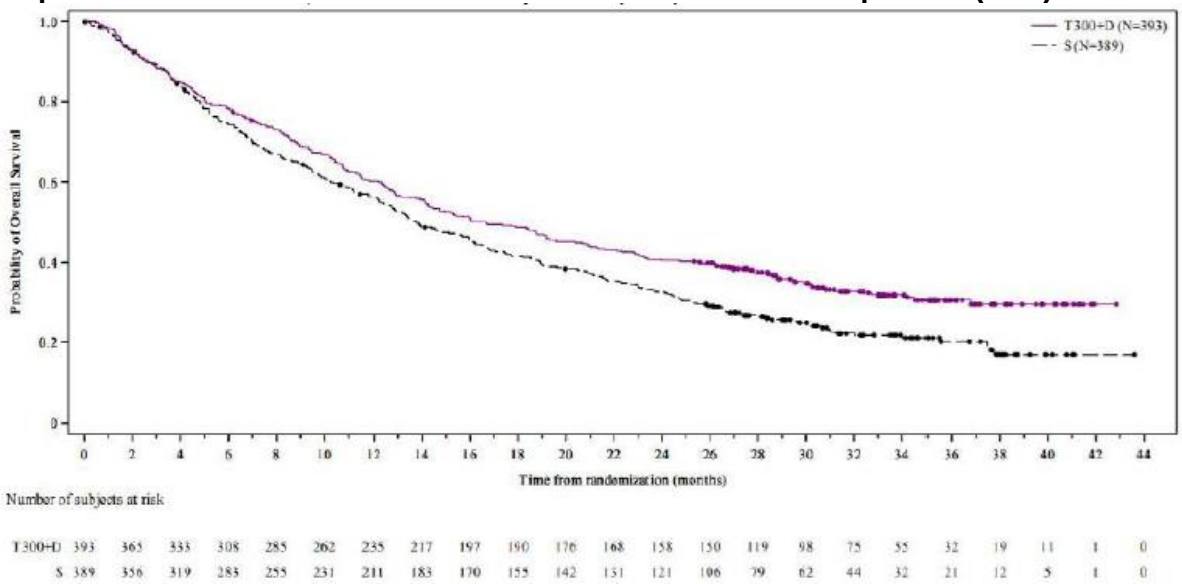
	T300+D (N = 393)	**S (N = 389)**	**D (N = 389)**
Follow-up duration (months)			
Median follow-up	33.18	32.23	32.56
(95% CI)	(31.74, 34.53)	(30.42, 33.71)	(31.57, 33.71)
OS			
Number of deaths (%)	262 (66.7)	293 (75.3)	280 (72.0)
Median OS (months) (95% CI)	16.43 (14.16, 19.58)	13.77 (12.25, 16.13)	16.56 (14.06, 19.12)
HR (96.02% CI)	0.78 (0.65, 0.93)		-
p-value[a]	0.0035		-
HR (95.67% CI)	-	0.86 (0.73, 1.03)	
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)
PFS based on investigator assessment			
Number of events (%)	335 (85.2)	327 (84.1)	345 (88.7)
Median PFS (months) (95% CI)	3.78 (3.68, 5.32)	4.07 (3.75, 5.49)	3.65 (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 based on investigator assessment			

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 (OR) (95% CI)	4.69 (2.85, 8.04)		-
p-value[c]	<0.0001		-
Odds ratio (OR) (95% CI)	-	3.80 (2.29, 6.57)	
p-value[c]	-	<0.0001	
DoR			
Median DoR (months)	22.34	18.43	16.82
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 T300 + D 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.
[d] Responses include only confirmed responses.
NR=Not Reached, CI=Confidence Interval

The primary analysis of OS demonstrated a statistically significant improvement for subjects in the T300+D arm compared to S arm (HR: 0.78; 96.02% CI: 0.65, 0.93; p = 0.0035). The median duration of OS was 16.43 months in the T300+D arm compared to 13.77 months in the S arm, which was an approximately 2.7-month difference. The OS Kaplan-Meier curves separated at approximately Month 4 and remained separated through the remainder of patient follow-up indicating the observed OS benefit in the T300+D arm was sustained over time where at Month 36 the proportion of patients surviving was higher with the T300+D arm compared with the S arm (30.7% vs 20.2%).

Kaplan-Meier Curves of Overall Survival for T300+D vs S Comparison (FAS)



Treatment with T300+D showed no PFS benefit over S (HR: 0.90; 95% CI: 0.77, 1.05; nominal p = 0.1625) with the median PFS of 3.78 months in the T300+D arm compared to 4.07 months in the S arm. Nonetheless, tumour-related responses were better with the T300+D arm compared to the S arm. The ORR was higher in the T300+D arm compared to the S arm (20.1% vs 5.1%; OR: 4.69; 95% CI: 2.85, 8.04; nominal p < 0.0001) and median DoR was also longer with the T300+D arm compared to the S arm (22.34 months vs 18.43 months).

OS with the D arm was non-inferior to the S arm as the upper 95.67% CI of 1.03 was less than the pre-defined non-inferiority limit of 1.08. However, the D arm did not achieve OS superiority over the S arm (p-value of 0.0674 was greater than the pre-specified alpha of 0.0433).

The study was not planned to compare the OS benefit of T300+D compared to D. Nonetheless, given that OS superiority over sorafenib was demonstrated only for T300+D and not D, this supported the benefit of adding a single-priming dose of tremelimumab to the durvalumab regimen in order to achieve the treatment effect.

Overall, the efficacy of the tremelimumab plus durvalumab combination in patients with uHCC was adequately demonstrated in the HIMALAYA study. The primary endpoint was met as treatment with T300+D showed a statistically significant improvement in overall survival compared to the standard of care, sorafenib. This was further supported by the secondary endpoints in terms of a higher ORR and numerically longer DoR compared to sorafenib.

D ASSESSMENT OF CLINICAL SAFETY

The clinical safety of the combination of tremelimumab and durvalumab in patients with uHCC was based primarily on pooled safety data from the pivotal Phase III HIMALAYA study and the supportive open-label study 22 with the primary objective to assess the safety and tolerability of durvalumab, tremelimumab and their combination. In total, 462 patients (n = 388 from study HIMALAYA and n = 74 from study 22) contributed to the safety data for the T300+D pool while 489 patients (n = 388 from study HIMALAYA and n = 101 from study 22) contributed to the safety data for the D pool. The safety data for sorafenib was based on the 374 patients treated in study HIMALAYA.

The median duration of exposure was 20.0 weeks (range: 2 to 185 weeks) in the T300+D pool and 19.9 weeks (range: 1 to 193 weeks) in the D pool. The median duration of treatment in the sorafenib arm was 16.4 weeks (range: 0.4, 154.4 weeks).

Overview of safety profile

AE	T300+D Pool (N = 462) n (%)	Sorafenib (N = 374) n (%)	D Pool (N = 492) n (%)
Any adverse event (AE)	451 (97.6)	357 (95.5)	443 (90.0)
Any AE possibly related to any study treatment	355 (76.8)	317 (84.8)	267 (54.3)
Any AE possibly related to durvalumab	349 (75.5)	0	267 (54.3)
Any AE possibly related to tremelimumab	224 (48.5)	0	0
Any AE of CTCAE Grade 3 or 4	222 (48.1)	196 (52.4)	188 (38.2)
Any serious AE (SAE)	189 (40.9)	111 (29.7)	161 (32.7)

Any AE leading to treatment discontinuations	63 (13.6)	63 (16.8)	47 (9.6)
Any AE with outcome of death	34 (7.4)	27 (7.2)	30 (6.1)

Almost all subjects in the T300+D pool arm (97.6%) and in the D pool arm (90.0%) experienced an AE. The AE profiles between the T300+D pool arm and the D pool arm were similar. The most common AEs occurring in ≥ 10% of patients were pruritus (25.5% in T300+D pool arm and 15.4% in D pool arm), diarrhoea (25.3% and 15.9%), rash (24.9 % and 10.8%), fatigue (18.0 % and 12.6%), decreased appetite (16.5% and 13.8%), AST increased (15.4% and 17.3%), pyrexia (13.9% and 8.9%), abdominal pain (12.6% and 11.0%), nausea (12.3% and 10.0%), hypothyroidism (11.9% and 6.7%), ALT increased (11.5% and 14.2%), lipase-increased (10.0% and 5.7%), constipation (9.7% and 11.0%), asthenia (9.1% and 10.6%), and back pain (6.5% and 10.2%). Grade 3 or 4 events that occurred in ≥ 5% of the patients were AST increased (7.4% and 7.3%) and lipase increased (7.1% and 3.5%).

Due to the differences in the mechanism of action (i.e. immune checkpoint inhibition vs tyrosine kinase inhibition), the AEs reported in the S arm were different from the other two durvalumab-containing study arms. Palmar-plantar erythrodysaesthesia syndrome (46.5%), diarrhoea (44.7%), fatigue (19.0%), hypertension (18.2%), decreased appetite (17.9%) abdominal pain (16.8%), nausea (14.2%), alopecia (14.2%), rash (13.6%) and asthenia (11.8%) were events occurring in ≥ 10% of the patients in the S arm, while Grade 3 or 4 events that occurred in ≥ 5% of the patients were palmar-plantar erythrodysaesthesia syndrome (9.1%) and hypertension (6.1%).

The incidence of SAEs was higher in the T300+D pool arm (40.9%) compared to the S arm (29.7%) and D pool arm (32.7%). The SAEs reported by ≥ 2% patients in the T300+D pool arm were pneumonia (2.2% in T300+D pool, 0.8% in D pool and 2.1% in S arm), colitis (2.2%, 0.2% and 0%), and diarrhoea (2.4%, 1.0% and 1.6%). The majority of SAEs had the outcome reported as recovered/resolved.

The incidences of fatal AEs were similar between the treatment arms. The majority of the fatal AEs in the T300+D pool arm were single events. Cardiac arrest (0.4% in T300+D pool, 0.2% in D pool and 0.5% in S arm), haemorrhage intracranial (0.4%, 0% and 0%), hepatic failure (0.4%, 0.6% and 1.1%), immune-mediated hepatitis (0.4%, 0% and 0%), pneumonia (0.4%, 0% and 0.5%) and pneumonitis (0.4%, 0.2% and 0%) occurred in 2 subjects each in the T300+D pool arm. While deaths due to haemorrhage intracranial occurred solely in the T300+D pool arm, no conclusion could be drawn from this observation considering the small number of events.

The rates of treatment discontinuation were lower in the T300+D pool arm compared to the S arm (13.6% vs 16.8%), suggesting that AEs with T300+D were more tolerable than S and more patients were able to stay on treatment with T300+D than S. The most commonly reported AEs leading to discontinuation with T300+D were immune-mediated AEs of pneumonitis (0.4%), colitis (0.4%) and AST increased (1.1%); nonetheless, the rates of these AEs were low.

Adverse events of special interest for T300+D pool included immune-mediated AEs (imAEs) and as expected from the dual immune checkpoint inhibition by both tremelimumab and durvalumab, the occurrence of imAEs were much more common in the T300+D pool and D pool arms compared to the S arm (35.7% in T300+D pool, 17.1% in D pool vs 8.0% in S arm). Serious imAEs occurred in 10.6% of the patients in the T300+D pool compared to 5.5% in the D pool and 1.1% in the S arm. Few patients (5.6%) in the T300+D pool discontinued treatment

due to imAEs, suggesting that the imAEs were generally well-tolerated and could possibly be managed by the toxicity management guidelines. The imAEs reported by patients in the T300+D pool and D pool arms included dermatitis/rash (5.6% in T300+D pool and 0.6% in D pool), pneumonitis (1.3% and 0.8%), diarrhoea/colitis (6.7% and 1.4%), adrenal insufficiency (1.3% and 1.2%), hyperthyroid events (4.5% and 1.0%), hypothyroid events (10.0% and 5.9%), hypophysitis/hypopituitarism (1.1% and 0.2%), thyroiditis (1.3% and 0.4%), hepatic events (7.4% and 6.1%), myocarditis (0.4% and 0.2%), myositis/polymyositis (0.6% and 0.2%), renal events (0.9% and 0%), pancreatic events (1.9% and 0.4%), and myasthenia gravis (0.4% and 0.2%). The imAEs have been adequately described in the package insert.

Overall, the safety profile in patients who received tremelimumab in combination with durvalumab is generally consistent with the known safety profiles of immune checkpoint therapies with no new or unexpected safety events in patients with unresectable HCC. The AEs (including imAEs) were generally well-tolerated by patients or can be managed according to the toxicity management guidelines allowing most of the patients to continue with the treatment.

E ASSESSMENT OF BENEFIT-RISK PROFILE

The current standard of care for uHCC patients who have not received prior systemic therapy includes treatment with sorafenib and lenvatinib, and more recently atezolizumab in combination with bevacizumab. Despite these agents, the disease remains difficult to treat, and new therapeutic options are required to improve outcomes, particularly in terms of overall survival.

In the pivotal Phase III HIMALAYA study, the improvement in OS of 2.7 months for T300+D compared to sorafenib (median OS 16.43 vs 13.77 months; HR: 0.78; 96.02% CI: 0.65, 0.93; $p = 0.0035$) was considered clinically relevant for patients with uHCC given the poor prognosis. The efficacy was further supported by a higher ORR (20.1% vs 5.1%; OR: 4.69; 95% CI: 2.85, 8.04; nominal $p < 0.0001$) and numerically longer median DoR (22.34 vs 18.43 months) for the T300+D regimen compared to sorafenib.

The safety profile of T300+D was consistent with the known safety profiles of immune checkpoint therapies. The immune-mediated adverse events reported with T300+D were known to be associated with immune checkpoint therapies and could be managed based on the toxicity management guidelines in the package insert.

Overall, the benefit-risk profile of tremelimumab in combination with durvalumab for the treatment of adult patients with uHCC who have not received prior systemic therapy was considered favourable.

F CONCLUSION

Based on the review of quality, safety and efficacy data, the benefit-risk balance of Imjudo in combination with durvalumab for the treatment of patients with uHCC who have not received prior systemic therapy was deemed favourable and approval of the product registration was granted on 25 August 2023.

APPROVED PACKAGE INSERT AT REGISTRATION

IMJUDO®
(tremelimumab)

1. NAME OF THE MEDICINAL PRODUCT

- IMJUDO CONCENTRATE FOR SOLUTION FOR INFUSION 20MG/ML, 25 mg (25 mg/1.25 mL) for intravenous infusion.
- IMJUDO CONCENTRATE FOR SOLUTION FOR INFUSION 20MG/ML, 300 mg (300 mg/15 mL) for intravenous infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL contains 20 mg of tremelimumab.

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 produced in murine myeloma cells by recombinant DNA technology.

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

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion; 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

Hepatocellular Carcinoma (HCC)

IMJUDO in combination with durvalumab is indicated for the treatment of patients with unresectable hepatocellular carcinoma (uHCC) who have not received prior systemic therapy.

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 Combination Therapy
uHCC	Single Tremelimumab Regular Interval Durvalumab (STRIDE): 300 mg[a] as a single priming dose in combination with durvalumab 1500 mg[a,b] at Cycle 1/Day 1, followed by durvalumab monotherapy every 4 weeks	Until disease progression or until unacceptable toxicity

[a] 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.

[b] 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

<table>
<tr><th>Adverse Reactions</th><th>Severity[a]</th><th>Treatment Modification</th><th colspan="2">Corticosteroid Treatment Unless Otherwise Specified[b]</th></tr>
<tr><td rowspan="2">Immune-mediated pneumonitis/interstitial lung disease</td><td>Grade 2</td><td>Withhold dose[c]</td><td colspan="2" rowspan="2">Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper</td></tr>
<tr><td>Grade 3 or 4</td><td>Permanently discontinue</td></tr>
<tr><td rowspan="2">Immune-mediated hepatitis</td><td colspan="2">ALT or AST > 3 ≤ 5 x ULN or total bilirubin > 1.5 ≤ 3 x ULN</td><td>Withhold dose[c]</td><td rowspan="2">Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper</td></tr>
<tr><td colspan="2">ALT or AST > 5-≤ 10 x ULN</td><td>Withhold durvalumab and permanently discontinue tremelimumab</td></tr>
</table>

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-≤ 5 X BLV and ≤ 20 x ULN		Withhold dose[c]	Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
	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[d]		Withhold durvalumab and permanently discontinue tremelimumab	
	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[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	
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	

Adverse Reactions	Severity[a]	Treatment Modification	Corticosteroid Treatment Unless Otherwise Specified[b]
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 followed by a taper
	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[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	

Adverse Reactions	Severity[a]	Treatment Modification	Corticosteroid Treatment Unless Otherwise Specified[b]
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 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
Immune-mediated Guillain-Barré syndrome	Grade 2-4	Permanently discontinue	Initiate 1 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; BLV: baseline value.

[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 pancreatitis, immune-mediated arthritis, and uveitis.

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 mild to moderate 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 instructions on dilution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

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 prior to initiation of treatment and prior to each subsequent infusion. 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). Cytomegalovirus (CMV) infection/reactivation has been reported in patients with corticosteroid-refractory immune-mediated colitis. In cases of corticosteroid-refractory colitis, consider repeating infectious workup to exclude alternative etiologies. 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 that can be fatal if not detected early, 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). 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.

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, Guillain-Barré syndrome, meningitis, cystitis noninfective, immune thrombocytopenia, pancreatitis, hemophagocytic lymphohistiocytosis, autoimmune hemolytic anemia, aplastic anemia, immune-mediated arthritis, uveitis, and encephalitis (see section 4.8). Iritis, and other ocular inflammatory toxicities can occur. Some cases can be associated with retinal detachment. Various grades of visual impairment to include blindness can occur. If uveitis occurs in combination with other immune-mediated adverse reactions, consider a Vogt-Koyanagi-Harada-like syndrome, as this may require treatment with systemic steroids to reduce the risk of permanent vision loss. 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 was assessed in the HIMALAYA study and no clinically meaningful PK drug-drug interaction was identified.

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.

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 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 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 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]			

	STRIDE (n=462)			
Adverse Drug Reaction[a]	**Frequency of any Grade**		**Frequency of Grade 3-4**	
Eye disorders				
Uveitis	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[t]			
Large intestine perforation	Not determined[t]			
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				

	STRIDE (n=462)			
Adverse Drug Reaction[a]	**Frequency of any Grade**		**Frequency of Grade 3-4**	
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%)
Immune-mediated arthritis	Uncommon	3 (0.6%)		0
Nervous system disorders				
Myasthenia gravis	Uncommon	2 (0.4%)		0
Meningitis	Uncommon	1 (0.2%)	Uncommon	1 (0.2%)
Encephalitis	Not determined[b]			
Guillain-Barré syndrome	Not determined[b]			
Renal and urinary disorders				
Blood creatinine increased	Common	21 (4.5%)	Uncommon	2 (0.4%)

	STRIDE (n=462)			
Adverse Drug Reaction[a]	**Frequency of any Grade**		**Frequency of Grade 3-4**	
Dysuria	Common	7 (1.5%)		0
Nephritis[p]	Uncommon	3 (0.6%)	Uncommon	2 (0.4%)
Cystitis noninfective	Not determined[b]			
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 Prescribing Information 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.
[t] Adverse reaction was not observed in the HCC pool, but was reported in patients treated with IMJUDO + durvalumab in AstraZeneca-sponsored clinical studies.

Description of selected adverse reactions

The data below reflects information for significant adverse reactions for 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

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

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

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 but was observed in patients receiving tremelimumab in combination with durvalumab (rare) in studies outside of the HCC pool..

Immune-mediated endocrinopathies

Immune-mediated hypothyroidism

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

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

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

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

HCC pool

In patients receiving STRIDE, immune-mediated type 1 diabetes mellitus was not observed but was observed patients receiving tremelimumab in combination with durvalumab (uncommon) in studies outside of the HCC pool.

Immune-mediated hypophysitis/hypopituitarism

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

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

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

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

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 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, enhancing 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

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 brain metastases or a history of brain metastases, 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

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%), 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].

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 4 and Figure 1.

Table 4 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)

	STRIDE (n=393)	S (n=389)	D (n=389)
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) (95% CI)	3.78 (3.68-5.32)	4.07 (3.75-5.49)	3.65 (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).

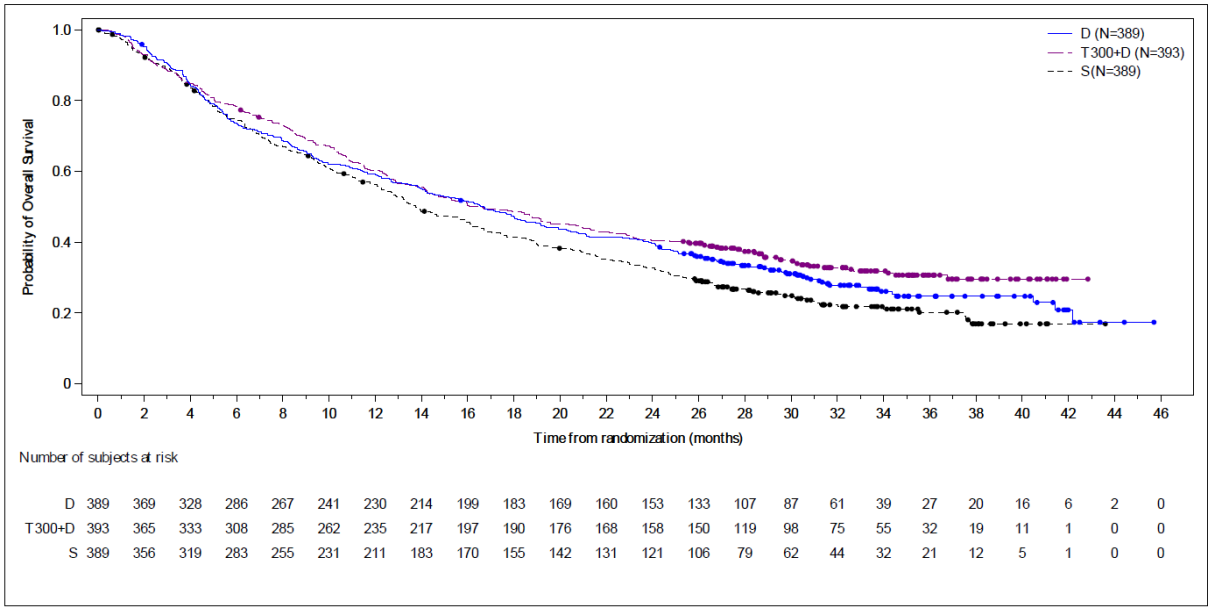
[b] p-value is for the superiority test of D vs. S. Based on a Lan-DeMets alpha spending function with O'Brien Fleming type boundary and the actual number of events observed, the boundary for declaring statistical significance for D vs. S was 0.0433 (Lan◦and◦DeMets 1983).

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

[d] Confirmed complete response.

CI=Confidence Interval

Figure 1 Kaplan-Meier curve of OS



D = Durva 1500 mg, T300+D = Treme 300 mg x1 dose + Durva 1500 mg, S = Sora 400 mg BID

5.2 Pharmacokinetic properties

The pharmacokinetics (PK) of tremelimumab was assessed for IMJUDO in combination with durvalumab.

The pharmacokinetics of tremelimumab was studied in patients with solid tumours at a single priming dose of 300 mg.

There was no clinically meaningful difference between the PK of tremelimumab as monotherapy or in combination with durvalumab.

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, 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 462 patients with uHCC treated with STRIDE, 173 (37.4%) patients were 65 years or older and 63 (13.6%) patients were 75 years or older. No overall clinically meaningful differences in safety or efficacy were reported between patients ≥ 65 years of age and younger patients.

Immunogenicity

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

In the HIMALAYA study, of the 182 patients who were treated with 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 on pregnancy losses, foetal weights, or external, visceral, skeletal abnormalities or weights of selected foetal organs at exposure levels approximately 4 to 31-times higher than those observed at a recommended dose range of 75 mg to 300 mg based on area under the curve (AUC).

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.

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 observed adverse effect level (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 to clinical relevant exposure.

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 intravenous (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

Please refer to expiry date on outer carton.

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 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 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.

Product Owner

AstraZeneca AB
SE-151 85
Södertälje
Sweden

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