Australian Government
Department of Health and Aged Care
Therapeutic Goods Administration

Australian Public Assessment Report for Imjudo

Active ingredient: Tremelimumab

Sponsor: AstraZeneca Pty Ltd

December 2023

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- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and Aged Care and is responsible for regulating therapeutic goods, including medicines, medical devices, and biologicals.
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- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to the Australian public outweigh any risks associated with the use of therapeutic goods.
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About AusPARs

- The Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission. Further information can be found in Australian Public Assessment Report (AusPAR) guidance.
- AusPARs are prepared and published by the TGA.
- AusPARs are static documents that provide information that relates to a submission at a particular point in time. The publication of an AusPAR is an important part of the transparency of the TGA's decision-making process.
- A new AusPAR may be provided to reflect changes to indications or major variations to a prescription medicine subject to evaluation by the TGA.

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List of abbreviations

Abbreviation	Meaning
ACM	Advisory Committee on Medicines
ADA	Anti-drug antibody
AE	Adverse event
AEPI	Adverse event of potential interest
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ARTG	Australian Register of Therapeutic Goods
ASA	Australia-specific annex
BCLC	Barcelona clinic liver cancer
CD	Cluster of differentiation
CI	Confidence interval
CMI	Consumer Medicines Information
CPD	Certified Product Details
CTLA	Cytotoxic T-lymphocyte-associated antigen
D	Durvalumab 1500 mg every 4 weeks
DLP	Data lock point
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organization for Research and Treatment of Cancer
FDA	Food and Drug Administration (United States of America)
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HR	Hazard ratio
IgG	Immunoglobulin G
imAE	Immune-mediated adverse event
irAEs	Immune-related adverse event
OS	Overall survival
PD-1	Programmed cell death-1
PD-L1	Programmed cell death ligand-1
PFS	Progression-free survival
PK	Pharmacokinetic(s)

Abbreviation	Meaning
PI	Product Information
PS	Performance Status
ΔQTcF	Change in the QT interval corrected for heart rate according to Fridericia's formula
PSUR	Periodic safety update report
RECIST	Response Evaluation Criteria in Solid Tumours
RMP	Risk management plan
S	Sorafenib 400 mg twice daily
SAE	Serious adverse event
SMQ	Standardised Medical Dictionary for Regulatory Activities (MedDRA) query
STRIDE	Single tremelimumab regular interval durvalumab
T300+D	Tremelimumab 300 mg for a single priming dose and durvalumab 1500 mg every 4 weeks
T75+D	Tremelimumab 75 mg every 4 weeks × 4 doses plus durvalumab 1500 mg every 4 weeks
TGA	Therapeutic Goods Administration
TKI	Tyrosine kinase inhibitor
uHCC	Unresectable hepatocellular carcinoma
V1	Central volume of distribution
V2	Peripheral volume of distribution
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor

Product submission

Submission details

Type of submission:	New biological entity
Product name:	Imjudo
Active ingredient:	Tremelimumab
Decision:	Approved
Date of decision:	19 June 2023
Date of entry onto ARTG:	23 June 2023
ARTG numbers:	387299, 387300
, *Black Triangle Scheme*	Yes.
for the current submission:	This product will remain in the scheme for 5 years, starting on the date the product is first supplied in Australia.
Sponsor's name and address:	AstraZeneca Pty Ltd PO Box 131, North Ryde, NSW, 1670
Dose form:	Concentrated solution for injection
Strengths:	25 mg/1.25 mL and 300 mg/15 mL
Container:	Vial
Pack size:	One
Approved therapeutic use for the current submission:	***Hepatocellular Carcinoma (HCC)*** *Imjudo in combination with durvalumab is indicated for the treatment of adult patients with unresectable hepatocellular carcinoma (uHCC) who have not received prior treatment with a PD-1/PD-L1 inhibitor.*
Route of administration:	Intravenous infusion
Dosage:	The recommended dosage is 300 mg as a single priming dose in combination with durvalumab 1500 mg at Cycle 1/Day 1, followed by durvalumab monotherapy every 4 weeks until disease progression or unacceptable toxicity. 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. Administer Imjudo prior to durvalumab on the same day. Imjudo is administered as an intravenous infusion over one hour and for single use in one patient only. Discard any residue. The proposed combination should be administered and monitored under the supervision of physicians experienced with the use of immunotherapy. For further information regarding dosage, refer to the Product Information.

Pregnancy category:	D
	Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.
	The use of any medicine during pregnancy requires careful consideration of both risks and benefits by the treating health professional. This must not be used as the sole basis of decision making in the use of medicines during pregnancy. The TGA does not provide advice on the use of medicines in pregnancy for specific cases. More information is available from obstetric drug information services in your State or Territory.

Product background

This AusPAR describes the submission by AstraZeneca Pty Ltd (the sponsor) to register Imjudo (tremelimumab) 25 mg/1.25 mL and 300 mg/15 mL, concentrated solution for injection, vial for the following proposed indication:[1]

Hepatocellular carcinoma (HCC)

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

Hepatocellular carcinoma

Primary liver cancer is a major global health problem accounting for approximately 906,000 new cases and 830,000 deaths per year globally. Hepatocellular carcinoma (HCC) represents about 90% of primary liver cancers.[2] The incidence of HCC increases progressively with advancing age in all populations, reaching a peak at 70 years[3] with 2 to 3 times higher incidence or mortality observed in men compared to women in most regions.[4]

Majority of the HCC cases are due to hepatitis B virus (HBV; 75% to 80%) and hepatitis B virus (HCV; 10% to 20%). Other risk factors of HCC include fungal metabolite aflatoxin B1 exposure, excessive alcohol consumption, and non-alcoholic fatty liver disease (linked to the growing prevalence of obesity and type 2 diabetes).[5] The major risk factors vary across geographic region, and this is reflected in incidence of HCC which is higher in East Asia and Sub-Saharan Africa compared to rates observed in Europe and North America.[6]

[1] This is the original indication proposed by the sponsor when the TGA commenced the evaluation of this submission. It may differ to the final indication approved by the TGA and registered on the Australian Register of Therapeutic Goods.

[2] European Association for the Study of the Liver (EASL). Clinical Practice Guidelines: Management of hepatocellular carcinoma. *J Hepatol*, 2018;69(1):182-236.

[3] White DL et al. Incidence of hepatocellular carcinoma in all 50 United States, from 2000 through 2012. *Gastroenterology*, 2017;152:812-820, e5.

[4] Sung H et al. Global Cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*, 2021;71:209-49.

[5] Vogel A et al. Hepatocellular carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*, 2019;30(5):871-3.

[6] World Health Organization (WHO). Global Cancer Observatory. Cancer Fact Sheets – Liver and intrahepatic bile ducts (C22). Available at URL: http://gco.iarc.fr/today/data/factsheets/cancers/11-Liver-fact-sheet.pdf (Accessed 7 October 2019)

The HCC prognosis and treatment depend on factors such as tumour burden, degree of liver dysfunction and clinical performance status.[5] HCC classically develops and grows silently with majority of patients usually diagnosed late in its course. The median survival following diagnosis is approximately 6 to 20 months[7] and the 5-year survival rate for HCC is less than 20%.[8,9] Presence of underlying cirrhosis and other liver disease in majority of patients makes unresectable HCC a difficult-to-treat disease. The majority of patients will ultimately die of either HCC or complications of liver disease.

In Australia, it was estimated that there would be 2,832 new cases of liver cancer diagnosed (2,050 males and 782 females) in 2021 representing 1.9% of all new diagnosed cancers in Australia. The incidence of HCC has increased from 1.38 cases per 100,000 in 1982 to 4.96 cases per 100,000 in 2014 and HCC is a leading cause of cancer deaths in Australia.[10] However, there are significant regional variation in incidence with 2.4-fold higher rates of diagnosis and mortality in Indigenous Australians compared with non-Indigenous populations.[11] In Australia, HCC is also more common in migrants from countries with a higher rate of HBV infection such as Asia, Pacific Islands and Africa.[12]

Current treatment options

More than 75% of patients with early-stage HCC are not suitable for either surgical resection or liver transplantation because of underlying severity of disease, clinically significant portal hypertension, significant comorbidity or age. Surgical therapies including liver resection are indicated and recommended for HCC in patients in whom the tumour is confined to the liver and can be completely removed. Liver transplantation in selected patients may be a treatment option for patients with early-stage HCC as it eliminates both the tumour and the liver disease.

Systemic therapies are indicated in patients with advanced HCC, with vascular invasion and/extrahepatic disease, or in patients with unresectable HCC, when locoregional therapies have failed to control disease or cannot be delivered. However, systemic therapy is restricted to patients with preserved liver function, non-cirrhotic patients, or those with Child-Pugh class[13] A cirrhosis.[14]

First-line systemic therapies for HCC include sorafenib, lenvatinib and combination of atezolizumab and bevacizumab.[15]

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[7] McGlynn KA et al. Global epidemiology of hepatocellular carcinoma: an emphasis on demographic and regional variability. *Clin Liver Dis*, 2015;19(2):223-38.

[8] Sarveazad A et al. Predictors of 5 year survival rate in hepatocellular carcinoma patients. *J Res Med Sci*, 2019;24:86.

[9] Villanueva A. Hepatocellular carcinoma. *N Engl J Med,* 2019;380(15):1450-62.

[10] Australian Government Cancer Australia Website. Liver cancer. Available at: https://www.canceraustralia.gov.au/cancer-types/liver-cancer/statistics (Accessed 3 February 2022)

[11] Australian Institute of Health and Welfare. Cancer in Australia 2019 (Cat. No. CAN 123) Canberra: AIHW; 2019. Available at: https://www.aihw.gov.au/reports/cancer/cancer-in-australia-2019/contents/table%20-of-contents (Accessed 3 February 2022)

[12] Cancer Council Australia website. Liver Cancer Fact Sheet. Available at: https://www.cancer.org.au/cancer-information/types-of-cancer/breast-cancer (Accessed 3 February 2022).

[13] The **Child-Pugh score** is used to assess the prognosis of chronic liver disease. The score employs five clinical measures of liver disease. Each measure is scored 1 to 3, with 3 indicating most severe derangement. Class A: 5 to 6 points, least severe liver disease, one to five year survival rate of 95%. Class B: 7 to 9 points, moderately severe liver disease, one to five year survival of 75%. Class C: 10 to 15 points, most severe liver disease, 1 to 5 year survival rate 50%.

[14] Wallace MC et al. Hepatocellular carcinoma in Australia 1982–2014: increasing incidence and improving survival. *Liver Int*. 2019; 39: 522–530.

[15] Gastrointestinal Society of Australia (GESA). Australian recommendations for management of hepatocellular carcinoma: a consensus statement. (2020). Available at: https://www.gesa.org.au/resources/hepatocellular-carcinoma-hcc-management-consensus/

Sorafenib, an oral tyrosine-kinase inhibitor (TKI) targeting multiple kinases, including vascular endothelial growth factor receptor (VEGFR)-1, -2, and -3 and BRAF was the standard of care for advanced HCC in the first-line setting (since its approval in 2007 until 2020). Median overall survival (OS) ranged from 10.7 to 13.4 months following sorafenib treatment in various studies.[16,17,18]

Lenvatinib, another multiple kinase inhibitor (against VEGFR-1, -2, and -3 and fibroblast growth factor receptor (FGFR)-1, -2, -3, and -4) was approved as first-line treatment for advanced HCC in patients without main portal vein invasion and Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) 0 to 1.[19] It was approved in 2018 and demonstrated non-inferiority to sorafenib.[20]

Atezolizumab (a programmed cell death ligand-1 (PD-L1) inhibitor) in combination with bevacizumab (an angiogenesis inhibitor targeting vascular endothelial growth factor A) has been approved in the first-line setting, after the Phase III IMbrave150 trial demonstrated statistically significant and clinically meaningful improvements in OS and progression-free survival (PFS) compared to sorafenib.[16,21] Atezolizumab is now the preferred first-line treatment for HCC in the updated ESMO guidelines.[22,23,24]

In patients with HCC, a second-line systemic therapy is recommended for suitable patients who have radiological progression while being treated with multi-kinase inhibitors but have preserved liver function and good performance status. Second line treatments approved by the TGA include two oral targeted therapies (regorafenib and cabozantinib) and nivolumab (an anti-programmed cell death-1 (anti-PD-1) monoclonal antibodies) administered by intravenous infusion.

Regorafenib is an oral multi-kinase inhibitor that blocks the activity of protein kinases involved in angiogenesis, oncogenesis, metastasis and tumour immunity (RAF, KIT, RET and platelet derived growth factor receptors, VEGFR 1 and TIE2). Regorafenib was TGA-approved on 18

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[16] Finn RS et al. IMbrave150: Updated overall survival (OS) data from a global, randomized, open-label phase III study of atezolizumab (atezo) + bevacizumab (bev) versus sorafenib (sor) in patients (pts) with unresectable hepatocellular carcinoma (HCC). *J Clin Oncol*, 2021;39(3):Suppl 267.

[17] Llovet JM et al. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med*, 2008;359(4):378-90.

[18] Yamashita T et al. REFLECT – a phase 3 trial comparing efficacy and safety of lenvatinib to sorafenib for the treatment of unresectable hepatocellular carcinoma: an analysis of Japanese subset. *J Gastroenterol.* 2020:55:113-22.

[19] **Eastern Cooperative Oncology Group Performance Status (ECOG PS)**: The ECOG has developed criteria used by doctors and researchers to assess how a patient's disease is progressing, assess how the disease affects the daily living abilities of the patient, and determine appropriate treatment and prognosis. The following are used:
0 - Fully active, able to carry on all pre-disease performance without restriction
1- Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, for example, light house work, office work
2 - Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3 - Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4 - Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5 – Dead

[20] Kudo M et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomized Phase 3 non-inferiority trial. *Lancet*, 2018;391(10126):1163-73.

[21] Finn RS et al. Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. *N Engl J Med 2020*; 382: 1894-1905.

[22] Vogel A and Martinelli E, on behalf of the ESMO Guidelines Committee. Updated treatment recommendations for hepatocellular carcinoma (HCC) from the ESMO Clinical Practice Guidelines. *Ann Oncol*, 2021;32(6):801-5.

[23] NCCN Clinical Practice Guidelines in Oncology: Hepatobiliary Cancers V.5.2021. Available from: https://www.nccn.org/professionals/physician_gls/pdf/hepatobiliary.pdf (Accessed 29 November 2021)

[24] Kudo M et al. Management of hepatocellular carcinoma in Japan: JSH consensus statements and recommendations 2021 update. *Liver Cancer*, 2021;10:181-223.

December 2017 for second-line treatment of advanced HCC that has progressed during treatment with sorafenib. Second-line treatment with regorafenib is not appropriate for patients who are intolerant to sorafenib.

Cabozantinib inhibits multiple receptor tyrosine kinases, including MET (hepatocyte growth factor receptor protein), vascular endothelial growth factor (VEGF), the Gas6 receptor (Axl), RET, Tyro3 and Mer. Cabozantinib was approved by the TGA for HCC on 28 May 2019. It is indicated as monotherapy in adults with HCC who have previously been treated with sorafenib. Cabozantinib is administered as an oral tablet with a recommended dose of 60 mg daily.

Nivolumab (Opdivo)[25], a PD-1-targeting monoclonal antibody has been approved by the TGA as monotherapy for the treatment of patients with HCC after prior sorafenib therapy. It is noted that this approval was granted based on improvement in objective response rate and duration of response (Checkmate 04 trial); improvement in survival or reduction in disease-related symptoms was not shown.

Another agent with Phase III clinical trial evidence for improved survival in patients whose disease has progressed while taking, or who are intolerant to sorafenib is ramucirumab (in patients with alpha-fetoprotein level >400 ng/mL). However, ramucirumab[26] is not approved in Australia for treatment of HCC.

Pembrolizumab (Keytruda)[27] is a high affinity antibody against PD-1, which exerts ligand blockade of the PD-1 pathway, including PD-L1 and PD-L2, on antigen presenting or tumour cells. It was granted accelerated approval by the US Food and Drug Administration in November 2018, based on a non-randomised, multicentre, open-label, Phase II trial in 104 patients with disease progression while or after taking sorafenib or with intolerance to sorafenib. However, pembrolizumab is not approved for unresectable hepatocellular carcinoma (uHCC) in Australia.

Clinical rationale

While sorafenib demonstrated a manageable tolerability profile in advanced HCC patients, the quality of life was limited by certain adverse events (AEs) such as diarrhea, hand-foot skin reaction, and fatigue which occur frequently in sorafenib-treated patients. First-line combination therapy with intravenous atezolizumab (anti-PD-L1) and bevacizumab (anti-VEGF) has also been associated with a higher incidence of bleeding, including fatal bleeding, infections, discontinuations, and dose interruptions due to AEs. Furthermore, the toxicity of systemic therapies particularly VEGFR TKI can exacerbate the pre-existing hepatopathy and increase the risk of liver-related AEs.[28]

Hence, there is a need for effective and safe/tolerable first-line systemic therapies in patients with uHCC. Increased expression of immunosuppressive cell populations, such as regulatory T-cells and myeloid-derived suppressor cells, and inhibitory signalling molecules, such as cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and PD-1, have been observed in

[25] *Opdivo (Nivolumab) Australian Product Information. Available at:* https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2016-PI-01052-1&d=20220830172310101

[26] *ramucirumab is only approved in Australia for treatment of advanced or metastatic gastric or gastro-oesophageal junction adenocarcinoma with disease progression after prior platinum and fluoropyrimidine chemotherapy (either as monotherapy or in combination with paclitaxel).*

[27] *Keytruda (pembrolizumab) Australian Product Information. Available at:* https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2015-PI-01639-1&d=20220830172310101

[28] Cheng AL et al. Challenges of combination therapy with immune checkpoint inhibitors for hepatocellular carcinoma. *J Hepatol*, 2020;72(2):307-19.

HCC[29,30,31] and is also associated with HBV and HCV infection. Furthermore, overexpression of PD-L1 has been shown to be associated with tumour aggressiveness, progressive disease and high mortality in HCC patients.[29] Therefore, therapeutic agents that block PD-L1 and CTLA-4 may potentially improve clinical outcomes by reversing the immunosuppressive nature of HCC tumours and restoring the immune function of 'exhausted' T-cells against HCC tumour cells.

Tremelimumab is a human immunoglobulin G (IgG)2 monoclonal antibodies directed against CTLA-4, a critical regulatory signal for T-cell expansion and activation following an immune response, and it serves as a natural braking mechanism that maintains T-cell homeostasis. T-cell activation upregulates CTLA-4, which binds to cluster of differentiation (CD)80 and CD86 ligands on antigen-presenting cells, sending an inhibitory signal and preventing CD28-mediated T-cell co-stimulation, thus limiting T-cell activation. Tremelimumab blocks these events, leading to prolongation and enhancement of T-cell activation and expansion.

Expression of PD-L1 can be induced by inflammatory signals and expressed on both tumour cells and tumour-associated immune cells in the tumour microenvironment. Programmed cell death ligand-1 blocks T-cell function and activation through interactions with PD-1 and CD80 (B7.1). By binding to its receptors, PD-L1 reduces cytotoxic T-cell activity, proliferation, and cytokine production. Durvalumab is a human IgG1 kappa monoclonal antibodies that binds to PD-L1 and blocks the interaction of PD-L1 with PD-1 and CD80 (B7.1). Blockade of PD-L1/PD-1 and PD-L1/CD80 interactions releases the inhibition of immune responses, without inducing antibody-dependent cell-mediated cytotoxicity.

Targeting both the PD-1 and CTLA-4 pathways using dual checkpoint blockade could result in a potential additive antitumour effect with a longer duration of immune activation because the mechanisms of action of these pathways are non-redundant and utilised at different times of immune activation and at different locations in the body.[32,33]

Regulatory status

This product is considered a new biological entity for Australian regulatory purposes.

At the time the TGA considered this submission, a similar submission had been approved in European Union on 20 February 2023, Japan on 23 December 2022, and United States of America on 21 October 2022. Similar submissions were under consideration in Canada (submitted on 24 March 2022), Singapore (submitted on 25 February 2022), Switzerland (submitted on 22 April 2022), and United Kingdom (submitted on 20 December 2022).

The following table summarises these submissions and provides the indications where approved.

[29] Gao YW et al. Increased expression of cyclooxygenase-2 and increased infiltration of regulatory T cells in tumors of patients with hepatocellular carcinoma. *Digestion*, 2009;79(3):169-76.

[30] Hato T et al. Immune checkpoint blockade in hepatocellular carcinoma: current progress and future directions. *Hepatology*, 2014;60(5):1776-82.

[31] Pardee AD et al. Immunotherapy of hepatocellular carcinoma: unique challenges and clinical opportunities. *Oncoimmunology* 2012;1(1):48-55.

[32] Buchbinder EI and Desai A. CTLA-4 and PD-1 pathways: similarities, differences, and implications of their inhibition. *Am J Clin Oncol*, 2016;39(1):98-106.

[33] Wu Y et al. PD-L1 distribution and perspective for cancer immunotherapy-blockade, knockdown, or inhibition. *Front Immunol*, 2019;10:2022.

Table 1: International regulatory status

Region	Submission date	Status	Approved indications
Canada	24 March 2022	Under consideration	Under consideration
European Union	4 March 2022	20 February 2023	*Imjudo in combination with durvalumab is indicated for the first line treatment of adults with advanced or unresectable hepatocellular carcinoma (HCC).*
Japan	25 February 2022	23 December 2022	*Unresectable hepatocellular carcinoma (uHCC)*
Singapore	25 February 2022	Under consideration	Under consideration
Switzerland	22 April 2022	Under consideration	Under consideration
United Kingdom	20 December 2022	Under consideration	Under consideration
United States of America	23 February 2022	21 October 2022	*Imjudo, in combination with durvalumab, is indicated for the treatment of adult patients with unresectable hepatocellular carcinoma (uHCC).*

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI and Consumer Medicines Information (CMI), please refer to the TGA PI/CMI search facility.

Registration timeline

The following table captures the key steps and dates for this submission.

This submission was evaluated under the standard prescription medicines registration process.

Table 2: Timeline for Submission PM-2022-01514-1-4

Description	Date
Submission dossier accepted and first round evaluation commenced	31 May 2022
First round evaluation completed	22 November 2022

Description	Date
Sponsor provides responses on questions raised in first round evaluation	23 December 2022
Second round evaluation completed	15 February 2023
Delegate's Overall benefit-risk assessment and request for Advisory Committee advice	27 February 2023
Sponsor's pre-Advisory Committee response	13 March 2023
Advisory Committee meeting	30 and 31 March 2023
Registration decision (Outcome)	19 June 2023
Administrative activities and registration on the ARTG completed	23 June 2023
Number of working days from submission dossier acceptance to registration decision*	219

*Statutory timeframe for standard submissions is 255 working days

Submission overview and risk/benefit assessment

A summary of the TGA's assessment for this submission is provided below.

Quality

There were no objections on quality grounds to the approval of Imjudo tremelimumab (25 mg and 300 mg presentations) concentrated injection vial.

Imjudo (tremelimumab, also known as CP-675,206, MEDI1123, PF2-01) is a human anti-CTLA-4 IgG2a monoclonal antibody comprising two heavy chains and two light chains covalently linked with six inter-chain disulphide bonds.

The recommended shelf life for the drug product is 2°C to 8°C (long term storage condition) for 48 months and the drug product should be stored in original carton to protect from light.

Sufficient evidence has been provided to demonstrate that the risks related to adventitious agents in the manufacturing of Imjudo (tremelimumab) have been managed to an acceptable level.

The evaluation recommends that Imjudo (tremelimumab) 25 mg/1.25 mL concentrated injection vial and Imjudo (tremelimumab) 300 mg/15 mL concentrated injection vial are acceptable for registration with respect to container safety.

There are no further objections, from a microbiological point of view for approval of the application to register Imjudo (tremelimumab) 25 mg/1.25 mL and 300 mg/15 mL concentrated injection vial presentations.

Nonclinical

The following conclusion and recommendations from the nonclinical evaluation are noted:

- The pharmacology studies support the proposed indication.
- Immune-mediated toxicities in the gastrointestinal tract, skin, lymphoid system and thyroid are expected in clinical scenarios.
- Based on mechanism of action of CTLA-4 inhibitors, the proposed Pregnancy Category D[34] is acceptable.
- There are no nonclinical objections to registration.

Clinical

Summary of clinical studies

The clinical dossier to support this submission and the concurrent durvalumab Submission PM-2022-01573-1-4 consisted of:

- a pivotal Phase III Study: Study D419CC00002 (also known as the HIMALAYA trial)
- a supportive Phase I/II study: D4190C00022 (also known as Study 22).
- PK data from a number of supporting studies, relating to other indications, were also provided for comparative purposes.
- a single population pharmacokinetics (PK)/exposure-response study: Study D419CC00002, characterises the PK of durvalumab and tremelimumab using the HIMALAYA trial and Study 22 data combined with data from five previous clinical trials that study the drugs in various indications.

Pharmacology

Pharmacokinetic/population pharmacokinetics

The conduct of the PK studies that were provided in support of the current submission was satisfactory. The data analyses undertaken were appropriate. The analytical methods used to measure exposure levels were validated.

Absorption, distribution, metabolism and excretion

- Imjudo (20 mg/mL) aqueous solution is to be administered via intravenous infusion.
- The clinical trial formulation and the to-be-marketed formulation are identical with the only difference being the volume of solution contained in the vials.
- In patients with uHCC, tremelimumab exposure increased approximately dose-proportionally with increasing weight-based doses from 1 to 10 mg/kg and fixed doses from 75 to 750 mg, respectively.

[34] **Pregnancy Category D**: Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.

- There appeared to be no accumulation in tremelimumab exposure following multiple doses in either patients with HCC or other tumour types. In addition, steady-state appears to be attained by week 12 following every 4 weeks dosing.
- The estimated central volume of distribution (V1) and peripheral volume of distribution (V2) for tremelimumab were 3.59 L and 2.69 L, respectively.
- In-line with other antibodies, tremelimumab is not primarily cleared via hepatic or renal pathways; instead, the primary elimination pathways are protein catabolism via RES or target-mediated disposition.
- Tremelimumab clearance is estimated to be 0.295 L/day.

Inter-subject variability

The estimated inter-subject variability values on tremelimumab clearance, V1 and V2 were 0.108 L/day, 0.062 L and 0.212 L, respectively. The proportional and additive components of the associated residual variability were 0.285 and 0.369, respectively.

Special populations

With the exception of low serum albumin concentrations, which results in a 22% increase in tremelimumab clearance, the effects of all of the other covariates tested appear to induce changes in tremelimumab clearance or V1 of <20%. Overall, none of the covariates are considered to have a clinically significant impact on estimated tremelimumab clearance and V1.

Population pharmacokinetics

Tremelimumab PK data could be described by a 2-compartment model with both linear and time-dependent elimination (for monotherapy, elimination was linear only).

Tremelimumab exposure was similar between anti-drug antibody (ADA)-positive and ADA-negative patients.

Drug-drug interaction

No formal drug-drug interaction studies have been conducted. However, adverse drug-drug interactions are not anticipated with tremelimumab given its elimination pathways. Moreover, it is not expected to induce or inhibit the major drug metabolising cytochrome P450[35] pathways. Population PK analyses indicate that there is no clinically significant effect on tremelimumab clearance when tremelimumab is co-administered with durvalumab alone or when co-administered with durvalumab and another chemotherapeutic agent.

Pharmacodynamics

Tremelimumab is a selective, fully human IgG2 antibody that blocks CTLA-4 interaction with CD80 and CD86, thus enhancing T-cell activation and proliferation, resulting in increased T-cell diversity and enhanced anti-tumour immune activity.

[35] **Cytochrome P450 (CYP)** enzymes are the major enzymes involved in drug metabolism, accounting for large part of the total metabolism. Most drugs undergo deactivation by CYPs, either directly or by facilitated excretion from the body. Also, many substances are bioactivated by CYPs to form their active compounds.
Many drugs may increase or decrease the activity of various CYP isozymes either by inducing the biosynthesis of an isozyme (enzyme induction) or by directly inhibiting the activity of the CYP (enzyme inhibition). This is a major source of adverse drug interactions, since changes in CYP enzyme activity may affect the metabolism and clearance of various drugs. Such drug interactions are especially important to take into account when using drugs of vital importance to the patient, drugs with important side-effects and drugs with small therapeutic windows, but any drug may be subject to an altered plasma concentration due to altered drug metabolism.

Primary pharmacodynamics

Substantial and consistent increases in CD4 + Ki67 + T-cells were observed following treatment with T75+D, T300+D or tremelimumab 750 mg every 4 weeks monotherapy that were associated with increasing tremelimumab dose. Moreover, patients receiving T300+D or tremelimumab monotherapy exhibited the highest elevations in CD8 + Ki67 + T-cells that correspond with the best objective responses of complete or partial response.

Secondary pharmacodynamics

In the HIMALAYA trial, ADA prevalence was 15.9% in the T300+D arm and 29.4% in the T75+D arm, whereas ADA incidence was 11.0% and 22.5%, respectively. Maximum ADA titres to tremelimumab in treatment-emergent ADA-positive patients were low and close to the limit of detection. There was no clear evidence that the presence of tremelimumab ADA had any potential impact on the efficacy or safety. Overall, these results support a low immunogenicity risk of tremelimumab.

There was no clear relationship between tremelimumab concentration and change in the QT interval corrected for heart rate according to Fridericia's formula (ΔQTcF).[36] Moreover, following doses of 15 mg/kg tremelimumab plus 10 mg/kg durvalumab, the upper bound of the 90% confidence interval (CI) for ΔQTcF was less than 10 ms and the highest observed concentration of tremelimumab had a predicted mean ΔQTcF of less than 5 ms.

Exposure-response

- There were no relationships between simulated tremelimumab exposure metrics and OS or PFS.
- There were no relationships between simulated tremelimumab exposure and >Grade 3 drug-related AEs or >Grade 3 drug-related adverse events of special interest (AESIs).

Dose finding for pivotal studies

Pharmacokinetic/pharmacodynamic data from Phase I/II studies and simulation data were used to guide selection of the combination of single dose of tremelimumab 300 mg and durvalumab 1500 mg, followed by durvalumab 1500 mg monotherapy every 4 weeks. The pivotal study compared the combination of durvalumab plus tremelimumab with durvalumab monotherapy. The proposed dose of durvalumab plus tremelimumab was used in this study. Fixed dosing rather than weight-based dosing was used to potentially improve ease of administration and avoid dosing errors. Overall, the dosing regimen used in the pivotal HIMALAYA trial was justified.

Efficacy

The pivotal data for efficacy come from Study D419CC00002 (HIMALAYA trial), a randomised, open-label, multi-centre Phase III study of durvalumab and tremelimumab as first-line treatment in patients with advanced hepatocellular carcinoma.

Supportive data was provided from D4190C00022 (Study 22), a study of safety, tolerability, and clinical activity of durvalumab and tremelimumab administered as monotherapy, or durvalumab

[36] The QT interval is the time from the start of the QRS wave complex to the end of the corresponding T wave. It approximates to the time taken for ventricular depolarisation and repolarisation, that is to say, the period of ventricular systole from ventricular isovolumetric contraction to isovolumetric relaxation.
The corrected QT interval (QTc) estimates the QT interval at a standard heart rate. This allows comparison of QT values over time at different heart rates and improves detection of patients at increased risk of arrhythmias.
The **QTcF** is the QT interval corrected for heart rate according to Fridericia's formula.

in combination with tremelimumab or bevacizumab in subjects with advanced hepatocellular carcinoma.

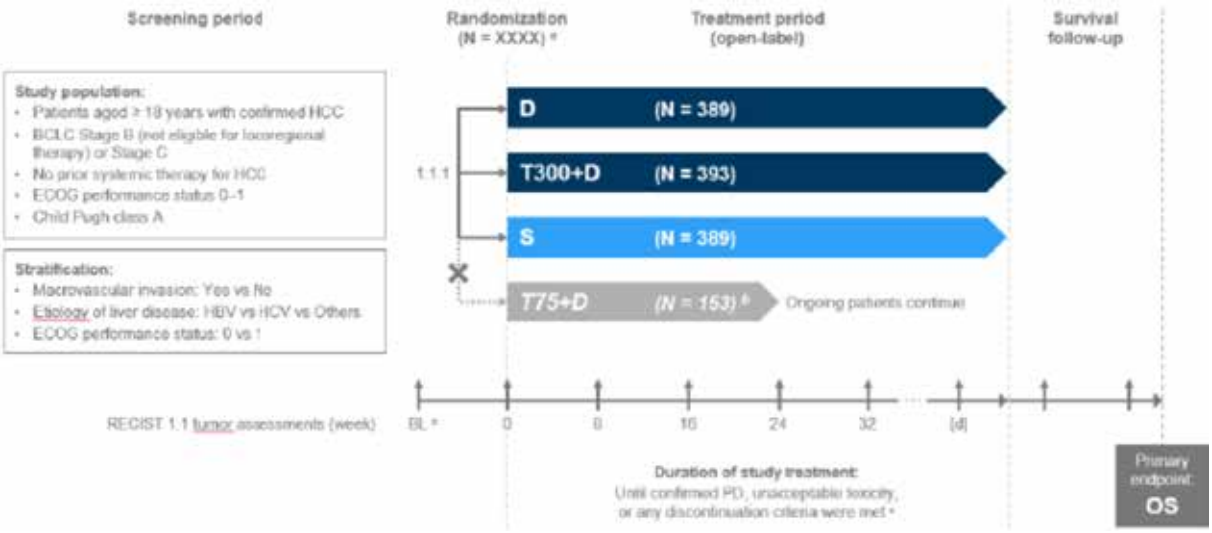
The Delegate also notes the publication by Abou-Alfa et al. (2022).[37]

Study D419CC00002 (HIMALAYA trial)

Study design

Study D419CC00002 (also known as the HIMALAYA trial) is a Phase III randomised, open-label, multi-centre, global study in patients with uHCC who have not received prior systemic therapy (See Figure 1 below).

Figure 1: Study D419CC00002 (HIMALAYA trial) Study design



Abbreviations: BCLC = Barcelona Clinic Liver Cancer; BL = baseline; D = durvalumab 1500 mg (20 mg/kg) every 4 weeks; ECOG = Eastern Cooperative Oncology Group; HBV = hepatitis B virus; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; N = total number of patients; OS = overall survival; PD = progressive disease; RECIST 1.1 = Response Evaluation Criteria in Solid Tumours version 1.1; S = sorafenib 400 mg twice daily; T300+D = tremelimumab 300 mg (4 mg/kg) × 1 dose + durvalumab 1500 mg (20 mg/kg) every 4 weeks; T75+D = tremelimumab 75 mg (1 mg/kg) every 4 weeks × 4 doses + durvalumab 1500 mg (20 mg/kg) every 4 weeks, followed by durvalumab 1500 mg (20 mg/kg) every 4 weeks.

a Patient numbers shown correspond to the actual enrolment.

b Enrolment into the T75+D arm was closed following protocol edition 4.0 (29 November 2018). Patients randomized to T75+D prior to protocol amendment 3 could continue on their assigned study treatment, provided the Investigator and patient agreed this was in the patient's best interest. Patients randomized to T75+D arm who had not completed or started all 4 doses of tremelimumab could either complete the full schedule or continue with durvalumab monotherapy only.

Eligible patients were randomised in 1:1:1:1 ratio to each of the following four treatment arms:

- Durvalumab arm: durvalumab 1500 mg every 4 weeks
- T300+D arm: tremelimumab 300 mg for a single priming dose and durvalumab 1500 mg every 4 weeks
- T75+D arm: tremelimumab 75 mg every 4 weeks × 4 doses plus durvalumab 1500 mg every 4 weeks
- Sorafenib arm: sorafenib 400 mg twice daily

[37] Abou-Alfa G et al. Tremelimumab plus durvalumab in unresectable hepatocellular carcinoma. *NEJM Evid*, 2022;1(8).

Recruitment in the T75+D treatment arm was closed due to non-meaningful differentiation in terms of efficacy from the durvalumab arm following a benefit-risk assessment based on the results of a pre-planned analysis of Phase II Study 22.

The primary objective was OS for single tremelimumab regular interval durvalumab (STRIDE: tremelimumab 300 plus durvalumab 1500 mg every 4 weeks (T300+D)) compared to sorafenib 400 mg twice daily (for superiority). A key secondary objective was OS for durvalumab versus sorafenib (D versus sorafenib for non-inferiority and then for superiority).

Trial location

The study was conducted from 11 October 2017 to 19 June 2019 at 170 centres in 16 countries: Brazil (13 centres), Canada (9), France (14), Germany (10), Hong Kong (5), India (10), Italy (8), Japan (27), South Korea (8), Russian Federation (10), Spain (6), Taiwan (9), Thailand (9), Ukraine (8), United States of America (21) and Vietnam (3). There were no study sites in Australia.

Inclusion and exclusion criteria, study treatments, efficacy variables and outcomes

The choice of comparator is considered to be appropriate and relevant to Australian clinical practice. A combination of atezolizumab and bevacizumab was not an approved treatment option at the time of study conduct.

Patients

Key inclusion criteria

- Age ≥18 years
- Histologically confirmed hepatocellular carcinoma
- No prior systemic therapy for HCC
- Ineligible for locoregional therapy
- Barcelona clinic liver cancer (BCLC) stage B or C
- Child-Pugh score class A
- Eastern Cooperative Oncology Group Performance Status 0 or 1
- Measurable disease by the Response Evaluation Criteria In Solid Tumours (RECIST) version 1.1.[38]

Key exclusion criteria

- Hepatic encephalopathy within the past 12 months or requirement for medications to prevent or control encephalopathy
- Clinically meaningful ascites (requiring non-pharmacologic intervention) within 6 months

[38] The **Response Evaluation Criteria In Solid Tumours (RECIST)** is a voluntary international standard with unified and easily applicable criteria to define when a patient's tumour has improved ('respond'), stayed the same ('stabilise'), or worsened ('progress') during treatment. The criteria were published in February 2000 by an international collaboration including the European Organisation for Research and Treatment of Cancer (EORTC), National Cancer Institute (NCI) of the United States, and the National Cancer Institute of Canada Clinical Trials Group. Today, the majority of clinical trials evaluating cancer treatments for objective response in solid tumours use RECIST. These criteria were developed and published in February 2000, and subsequently updated in 2009.

- Main portal vein thrombosis
- Active or prior documented gastrointestinal bleeding within 12 months
- Co-infection with HBV and HCV, or HBV and hepatitis D virus (HDV).

Intervention

Randomised 1:1:1 (as amended) to the following:

- T300+D arm: tremelimumab 300 mg for one dose plus 1500 mg durvalumab every 4 weeks (STRIDE regimen)
- Durvalumab arm: durvalumab 1500 mg every 4 weeks
- Sorafenib arm: sorafenib 400 mg twice daily.

Amendment: enrolment to T75+D in the HIMALAYA trial was closed (as no meaningful difference from durvalumab monotherapy in terms of efficacy per Study 22).

Weight-based dosing modifications for durvalumab (20 mg/kg every 4 weeks) and tremelimumab (4 mg/kg for T300+D) were permitted if a patient's weight decreased to ≤30 kg. However, the original fixed dose of durvalumab 1500 mg every 4 weeks with or without tremelimumab was resumed once the patient's weight increased to >30 kg.

Comparator

Sorafenib 400 mg twice daily.

Endpoints

Primary endpoint

- Overall survival of T300+D versus sorafenib, for superiority).

Key Secondary endpoint

- Overall survival of durvalumab versus sorafenib (for non-inferiority)
- Overall survival of durvalumab versus sorafenib (for superiority).

Randomisation and blinding methods

Patients were stratified according to macrovascular invasion (yes versus no), etiology of liver disease (confirmed HBV versus confirmed HCV versus others), and ECOG PS (0 versus 1).

Analysis populations

All efficacy analyses were performed on the full analysis set (intention-to-treat[39] population), which included all randomised patients.

Statistical methods

Two interim analyses (Interim Analyses 1 and 2) and a final analysis were planned for this study.

- Interim Analysis 1: the first interim analysis was performed after 100 subjects per treatment arm had the opportunity for at least 32 weeks of follow-up (that is, randomised ≥ 32 weeks prior to Interim Analysis 1 data cut-off) and after all patients had been enrolled in the study

[39] The randomised clinical trials analysed by the **intention-to-treat (ITT)** approach provide unbiased comparisons among the treatment groups. In the ITT population, none of the subjects are excluded, regardless of treatment compliance or attrition due to dropout or crossover, and the subjects are analysed according to the randomisation scheme

(data cut-off: 02 September 2019). The objective was to evaluate the efficacy of the T300+D and durvalumab arms in terms of objective response rate and duration of response.

- Interim Analysis 2: the second interim analysis was performed when 415 OS events had occurred in the T300+D and sorafenib arms combined (approximately 52% maturity) (data cut-off: 22 May 2020). The objective was to assess the primary objective of OS superiority for T300+D versus sorafenib in the full analysis set population. The threshold for data reporting was not met at Interim Analysis 2 (that is, the OS comparison for T300+D versus sorafenib was not statistically significant at a 2-sided alpha level of 0.0244) and the Independent Data Monitoring Committee recommended that the study continue to final analysis.

The final analysis was to be performed when there had been approximately 515 OS events in the T300+D and sorafenib arms combined (approximately 67% maturity), approximately 37.5 months after the first patient was randomised. The data cut-off date for the final analysis was 27 August 2021, 46 months after the first patient was randomised. At the data cut-off, there had been 555 OS events in the T300+D and sorafenib arms combined.

The formal statistical analysis of OS (primary endpoint) was performed for the following efficacy test hypotheses (alternative hypotheses):

- H_1 (primary): Difference between T300+D and sorafenib arms (for superiority).
- H_2 (key secondary): durvalumab is not inferior to sorafenib with non-inferiority margin of 1.08.
- H_3 (key secondary): Difference between durvalumab and sorafenib (for superiority).

Participant flow

A total of 1,324 patients were randomised:

- Durvalumab arm: 389 patients
- T300+D arm: 393 patients
- T75+D arm: 153 patients
- Sorafenib arm: 389 patients.

At the final data cut-off of 27 August 2021:

- A total of 91.2% of patients had discontinued study treatment with higher rate of discontinuation in the sorafenib treatment arm (94.4%, n = 353) compared to the durvalumab (88.6%, n = 342) and T300+D (88.7%, n = 345) treatment arms. The most frequent reasons for discontinuations were objective progressive disease with highest incidence in the durvalumab group (57.5%, 47% and 45.5% in the D, T300+D and sorafenib treatment groups, respectively). However, discontinuations due to AEs were higher in the T300+D and sorafenib treatment groups (7.8%, 13.4% and 16.8%, respectively).
- There were 339 patients (25.6%) still on study: 26.7% in the durvalumab arm, 31.8% in the T300+D arm and 20.6% in the sorafenib arm; a total of 114 patients (8.8%) were still receiving study treatment, with twice as many patients in the durvalumab and T300+D arms compared with the sorafenib arm still receiving study treatment.

Protocol violations or deviations

The clinical evaluation determined that the reported protocol deviations were unlikely to have affected the conduct/quality of study or the clinical interpretation of data.

Baseline characteristics

The baseline demographic and clinical characteristics of the patients were balanced in the treatment arms and were overall representative of the target population of patients with unresectable HCC.

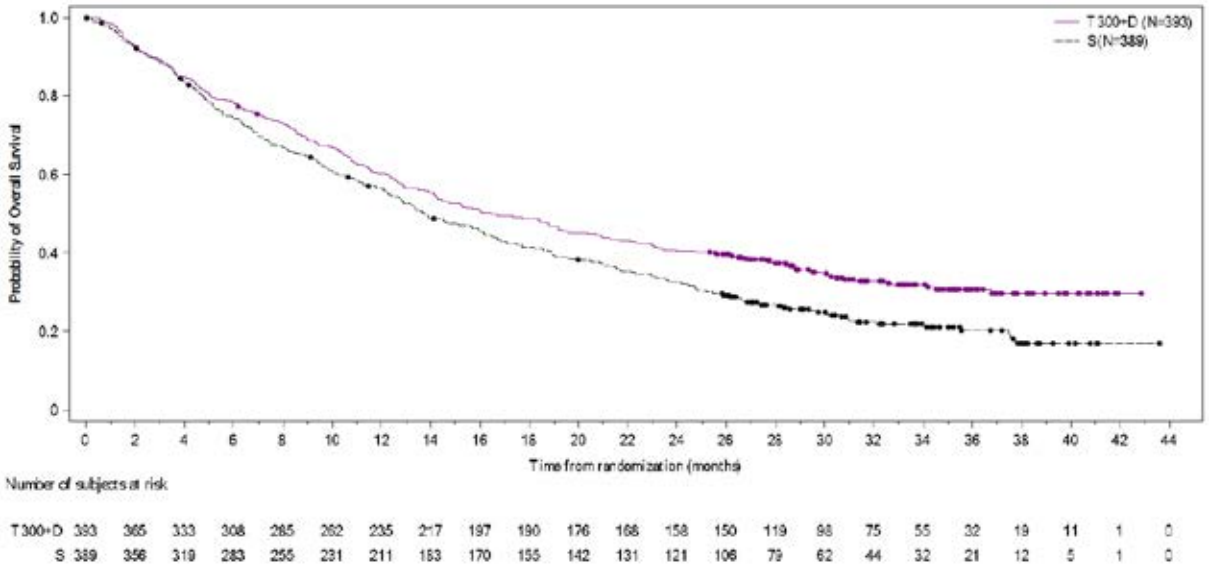
Results

Primary efficacy endpoint

Treatment with T300+D demonstrated a statistically significant and sustained improvement in OS compared with sorafenib. The hazard ratio (HR), adjusted for stratification factors, was 0.78 (96.02% CI: 0.65, 0.93; stratified log-rank two-sided p = 0.0035).

The Kaplan-Meier estimates for median OS were 16.4 months in the T300+D arm and 13.8 months in the sorafenib arm, an estimated 2.7-month difference in median values. The T300+D and sorafenib curves separated approximately 4 months after randomisation through the remainder of patient follow-up (see Figure 2 below):

Figure 2: Study D419CC00002 (HIMALAYA trial) Kaplan-Meier plot of overall survival in the T300+D versus sorafenib arms (full analysis set)



Abbreviations: FAS = Full Analysis Set; Q4W = every 4 weeks; S = sorafenib 400 mg twice daily; T300+D = tremelimumab 300 mg × 1 dose + durvalumab 1500 mg Q4W.

Survival rates at 18, 24 and 36 months are shown in Table 3 below.

Table 3: Overall survival (full analysis set)

	Number (%) of patients			
	D (N = 389)	T300+D (N = 393)	T75+D [a] (N = 153)	S (N = 389)
Median OS (months) [b]	16.56	16.43	16.36	13.77
95% CI for median OS [b]	14.06 - 19.12	14.16 - 19.58	12.39 - 19.65	12.25 - 16.13
Deaths, n (%)	280 (72.0)	262 (66.7)	123 (80.4)	293 (75.3)
Censored patients, n (%)	109 (28.0)	131 (33.3)	30 (19.6)	96 (24.7)
Still in survival follow-up [c]	0	0	0	0
Terminated prior to death [d]	109 (28.0)	131 (33.3)	30 (19.6)	96 (24.7)
Lost to follow-up	1 (0.3)	1 (0.3)	0	7 (1.8)
Withdrawn consent	4 (1.0)	5 (1.3)	0	10 (2.6)
Study completion[c]	104 (26.7)	125 (31.8)	30 (19.6)	79 (20.3)
OS rate at 12 months (%) [b]	59.3	60.2	59.5	56.2
95% CI for OS rate at 12 months [b]	54.2 - 64.0	55.2 - 64.9	51.3 - 66.8	51.0 - 61.0
OS rate at 18 months (%) [b]	47.4	48.7	46.4	41.5
95% CI for OS rate at 18 months [b]	42.4 - 52.3	43.6 - 53.5	38.4 - 54.1	36.5 - 46.4
OS rate at 24 months (%) [b]	39.6	40.5	37.3	32.6
95% CI for OS rate at 24 months [b]	34.8 - 44.5	35.6 - 45.3	29.6 - 44.9	27.9 - 37.4
OS rate at 36 months (%) [b]	24.7	30.7	22.9	20.2
95% CI for OS rate at 36 months [b]	20.0 - 29.8	25.8 - 35.7	16.6 - 29.8	15.8 - 25.1
HR [e]	0.86	0.78	-	-
95% CI for HR [e]	0.73 - 1.02	0.66 - 0.92	-	-
95.67% CI for HR [e, f]	0.73 - 1.03	-	-	-
96.02% CI for HR [e, f]	-	0.65 - 0.93	-	-
2-sided p-value [f, g]	0.0674	0.0035	-	-
Median (95% CI) duration of follow-up in all patients (months) [h]	32.56 (31.57 - 33.71)	33.18 (31.74 - 34.53)	37.82 (36.14 - 39.49)	32.23 (30.42 - 33.71)
Median (range) duration of follow-up in censored patients (months) [i]	31.61 (1.91 - 45.70)	32.36 (6.18 - 42.84)	37.06 (34.07 - 44.22)	30.36 (0.03 - 43.60)

CI, confidence interval; D, durvalumab monotherapy 1500 mg Q4W; DCO, data cut-off; ECOG, Eastern Cooperative Oncology Group; eCRF, electronic case report form; FAS, Full Analysis Set; HBV, hepatitis B virus; HCV, hepatitis C virus; HR, hazard ratio; IO, immuno-oncology; IWRS, Interactive Web Response System; KM, Kaplan-Meier; MVI, macrovascular invasion; N, total number of patients; n, number of patients included in analysis; OS, overall survival; Q4W, every 4 weeks; S, sorafenib 400 mg twice daily; T75+D, tremelimumab 75 mg × 4 doses + durvalumab 1500 mg Q4W; T300+D, tremelimumab 300 mg × 1 dose + durvalumab 1500 mg Q4W.

[a] Comparisons cannot be drawn between the T75+D arm and any other treatment arm as enrollment closure in the T75+D arm led to a difference in data maturity and duration of follow-up.
[b] Calculated using the KM technique.
[c] Patients confirmed alive in follow-up or on active study treatment at the time of final analysis reported 'study completion' on the disposition eCRF. Includes patients known to be alive at DCO.
[d] Includes patients with unknown survival status or patients who were lost to follow-up.
[e] Analysis performed using Cox proportional hazards model adjusting for treatment, etiology of liver disease (HBV vs HCV vs others), ECOG (0 vs 1), and MVI (yes vs no). Values of the variables used for adjustment were obtained from IVRS. A HR < 1 favors IO treatment arms to be associated with a longer OS than sorafenib.
[f] The adjusted alpha levels for the 2-sided superiority test of T300+D vs S and CI the for T300+D vs S and one-sided non-inferiority test of D vs S were derived based on the exact number of OS events for each comparison using the Lan and DeMets approach that approximates the O'Brien Fleming spending function.
[g] Analysis performed using stratified log-rank test adjusting for treatment, etiology of liver disease (HBV vs HCV vs others), ECOG (0 vs 1), and MVI (yes vs no). The values of the stratification factors were obtained from IWRS.
[h] Calculated using the reverse KM technique (with censor indicator reversed).
[i] Median for duration of follow-up is the arithmetic median.

It is noted that during the course of evaluation, the TGA was notified (23 August 2022) of data discrepancies in survival data at study site 6208 (in Russia) which randomised 14 patients when site staff compared data to that reported in the local oncology registry which is only available to select medical personnel at the site. Although investigation is ongoing to evaluate the totality of the data at this site, the sponsor proactively performed an exploratory OS sensitivity analysis to assess the potential impact on the primary endpoint. Following a conservative approach (by removing all 14 patients randomised at this site), the stratified Cox model HRs for OS were 0.77 (95% CI: 0.65, 0.91) and 0.87 (95% CI: 0.73, 1.02) for T300+D versus sorafenib and durvalumab versus S, respectively, compared to the primary OS analysis results (T300+D versus sorafenib HR: 0.78 (95% CI: 0.66, 0.92) and durvalumab versus sorafenib HR 0.86 (95% CI: 0.73, 1.02).

A *post-hoc* analysis calculating piecewise constant treatment effects for the comparison of T300+D versus sorafenib did not show any evidence of initial detriment for T300+D prior to the separation of survival curve observed at 4 months.

Key secondary endpoints

The key secondary objective of non-inferiority between durvalumab monotherapy versus sorafenib was met as the upper bound of the HR (0.86; 95.67% CI: 0.73, 1.03) fell below the prespecified clinical non-inferiority margin of 1.08.

The Kaplan-Meier estimates for median OS were 16.6 and 13.8 months in the durvalumab and sorafenib arms, respectively. The estimate of the proportion of patients alive at 24 months was higher in the durvalumab versus sorafenib arm (39.6% versus 32.6%) with similar results observed at 36 months (24.7% versus 20.2%). The OS curves for durvalumab and sorafenib overlapped for approximately the first 9 months from randomisation, but after 9 months the OS separation was sustained over the long term follow up period.

A post-hoc analysis calculating piecewise constant treatment effects for the comparison of durvalumab versus sorafenib did not show any initial detriment in the treatment effect of durvalumab over the first 9 months.

However, treatment with durvalumab monotherapy did not meet the secondary objective of superiority versus sorafenib (HR was 0.86 (95.67% CI: 0.73, 1.03), p = 0.0674.

Sensitivity analysis

In the exploratory analysis, there was no significant difference in OS between T300+D versus durvalumab (HR was 0.90 (95% CI: 0.76, 1.07; stratified log-rank 2-sided nominal p = 0.2186). However, there was a trend for an increase in Kaplan-Meier estimates of OS rates over time in favour of T300+D compared with durvalumab especially at 36 months (30.7% versus 24.7%).

Subgroup analysis

Consistent with the overall OS analysis, HRs in all predefined subgroups were in favour of T300+D versus sorafenib (HR < 1) with the exception of females (HR 1.02; 95% CI: 0.67, 1.56) and HCV-positive patients (HR 1.06; 95% CI: 0.76, 1.49). For the durvalumab versus sorafenib comparison, HRs were < 1 for all predefined subgroups with the exception of HCV-positive patients (HR 1.05; 95% CI: 0.75, 1.48). However, interpretation was limited by lack of multiplicity adjustments and by small sample sizes in some subgroups.

Other secondary and exploratory endpoints

Results for confirmed objective response rate, best objective response and duration of response in the full analysis set at 32 weeks subset by Blinded Independent Central Review and investigator were consistent with results observed in the final analysis set suggesting lack of bias in investigator radiographic tumour assessment due to open-label study design. Approximately 4 times the number of patients who received T300+D experienced a best objective response (complete response or partial response) per the investigator using RECIST 1.1 when compared with patients who received sorafenib (23.9% versus 6.7%); 13 patients (3.3%) in the T300+D arm had a complete response compared with no patients with a best objective response of complete response in the sorafenib arm. In a post-hoc analysis, patients with a best objective response of complete response or partial response generally had similar OS benefit across both T300+D and sorafenib arms with the numerical increase in objective response rate favouring T300+D helping drive the observed overall OS benefit. Moreover, a differential effect in OS favouring T300+D was noted in patients with a best objective response of progressive disease.

The objective improvements in survival and tumour response endpoints were corroborated by improvements in patient reported outcomes. Treatment with T300+D resulted in a longer median time to deterioration of all scores compared with sorafenib with nominally significant differences reported for European Organisation for Research and Treatment of Cancer (EORTC) 30-item core quality of life questionnaire (QLQ-C30)[40] global health status/quality of life, physical functioning, fatigue, appetite loss, and nausea – EORTC 18-item hepatocellular cancer health-related quality of life questionnaire (QLQ-HCC18)[41] abdominal pain and abdominal swelling. Compared with sorafenib, durvalumab monotherapy resulted in a longer median time to deterioration of all scores and increased odds ratios of clinically meaningful improvement in disease-related symptoms, physical functioning, and global health status/quality of life. Overall, treatment with the T300+D and durvalumab regimens was well-tolerated from the patient perspective with no meaningful impact on health-related quality of life.

[40] **European Organisation for Research and Treatment of Cancer (EORTC) 30-item core quality of life questionnaire (QLQ-C30)** is a health-related quality of life questionnaires in cancer research, which assesses important functioning domains (including physical, emotional and role) and common cancer symptoms (for example, fatigue, pain, nausea, vomiting and appetite loss).

[41] **European Organisation for Research and Treatment of Cancer (EORTC) EORTC 18-item hepatocellular cancer health-related quality of life questionnaire (QLQ-HCC18)** is a health-related quality of life questionnaires in cancer research, which assesses hepatocellular carcinoma symptoms, and has been validated specifically for hepatocellular carcinoma.

Study D4190C00022 (Study 22)

Study D4190C00022 (also known as Study 22) was a Phase I/II multi-centre, international, open-label, multi-part study designed to evaluate the safety, tolerability, and clinical activity of durvalumab and tremelimumab administered as monotherapy, and durvalumab in combination with tremelimumab or bevacizumab, in patients with advanced HCC. Patients in this study were immunotherapy-naïve, but the majority had received prior first line treatment with sorafenib or other agents.

Overall, results from this open-label Phase I/II uncontrolled study suggest that CTL4-blockade by high-dose tremelimumab (as used in the T300+D and tremelimumab arms) followed by PD-L1 blockade with durvalumab has higher clinical activity in advanced HCC than durvalumab monotherapy (D arm) or the lower dose tremelimumab combination regimen (T75+D arm). Results from this study provided important evidence to determine the dose of tremelimumab and durvalumab that was used in the pivotal Phase III HIMALAYA trial.

Summary of clinical efficacy

The clinical evaluation's main findings on clinical efficacy are summarised as follows:

- The main evidence of efficacy of proposed T300+D regimen was provided by the Phase III pivotal multi-centre HIMALAYA trial conducted in 1,302 patients with unresectable HCC who had not received prior systemic therapy. The primary endpoint was OS; key secondary endpoints included PFS, investigator-assessed objective response rate and duration of response per RECIST v1.1. Blinded Independent Central Review analyses were also performed.
- The patient population recruited to the study comprised of a diverse, representative population of patients with unresectable HCC who had not received prior systemic therapy. Only patients with Child-Pugh class A disease were selected for this study.
- Majority of patients were male (83.7%), aged < 65 years (50.4%), Asian (50.7%) (white (44.6%), African American (1.7%), other (2.3%)), BCLC stage C (80.8%), ECOG PS 0 (62.6%); Child-Pugh class A (99.5%), macrovascular invasion (25.2%), extrahepatic spread (53.4%), viral etiology; hepatitis B (30.6%), hepatitis C (27.2%), and uninfected (42.2%).
- Baseline demographics and disease characteristics were generally balanced across treatment groups. Patients with esophageal varices were included except those with active or prior documented gastrointestinal bleeding within 12 months prior to study entry; a total of 93 patients (7%) with history of esophageal varices were included in the study with similar incidence across treatment groups.
- Supportive evidence of efficacy was provided by the uncontrolled, open-label, Phase I/II Study 22 which was also the first study conducted by sponsor to evaluate dual immune checkpoint blockade with durvalumab and tremelimumab in HCC. Primary outcome measures in Study 22 were related to safety, and OS was a secondary endpoint. Most patients in this study had received prior treatment with sorafenib/other VEGF inhibitors.
- The main efficacy results from HIMALAYA trial and Study 02 are summarised in Table 4 below.

Table 4: Study D419CC00002 (HIMALAYA trial) Summary of efficacy results for the proposed indication (full analysis set: final analysis)

	HIMALAYA		Study 22
	T300+D (N = 393)	S (N = 389)	T300+D (N = 75)
Follow-up duration (months)			
Median follow-up in all patients[a]	33.18	32.23	28.39
95% CI[a]	31.74, 34.53	30.42, 33.71	23.85, 31.54
OS			
Number of deaths (%)	262 (66.7)	293 (75.3)	49 (65.3)
Median OS (months) (95% CI)	16.43 (14.16, 19.58)	13.77 (12.25, 16.13)	17.05 (10.6, 22.8)
HR (95% CI)	0.78 (0.66, 0.92)		
HR (96.02% CI)	0.78 (0.65, 0.93)		–
p-value	0.0035		–
OS at 12 months (%) (95% CI)	60.2 (55.2, 64.9)	56.2 (51.0, 61.0)	57.6 (45.5, 68.0)
OS at 18 months (%) (95% CI)	48.7 (43.6, 53.5)	41.5 (36.5, 46.4)	47.8 (35.9, 58.7)
OS at 24 months (%) (95% CI)	40.5 (35.6, 45.3)	32.6 (27.9, 37.4)	38.3 (26.9, 42.2)
OS at 36 months (%) (95% CI)	30.7 (25.8, 35.7)	20.2 (15.8, 25.1)	–
p-value	0.0029[b]		–
Tumor response assessment	**Investigator assessment per RECIST 1.1**		**BICR per RECIST 1.1**
PFS			
Median PFS (months) (95% CI)	3.78 (3.68, 5.32)	4.07 (3.75, 5.49)	2.17 (1.91, 5.42)
HR (95% CI)	0.90 (0.77, 1.05)		–
p-value	0.1625		–
Progression-free at DCO n (%)	49 (12.5)	19 (4.9)	11 (14.7)
Treated with ≥ 1 cycle after PD n (%)	182 (46.9)	134 (35.8)	–
ORR[b]			
ORR n (%)	79 (20.1)	20 (5.1)	18 (24.0)
CR	12 (3.1)	0	1 (1.3)
PR	67 (17.0)	20 (5.1)	17 (22.7)
Odds ratio (95% CI)	4.69 (2.85, 8.04)		–
p-value	< 0.0001[c]		–
DoR[d]			
Median DoR (months)	22.34	18.43	18.43
TTR[d]			
Median TTR (months)	2.17	3.78	2.28

BICR, Blinded Independent Central Review; CI, confidence interval; CR, complete response; CSR, Clinical Study Report; D, durvalumab 1500 mg (20 mg/kg) Q4W; DCO, data cut-off; DoR, duration of response; FAS, full analysis set; HR, hazard ratio; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; Q4W, every 4 weeks; RECIST 1.1, Response Evaluation Criteria in Solid Tumors, version 1.1; S, sorafenib 400 mg twice daily; T300+D, tremelimumab 300 mg (4 mg/kg) for a single priming dose and durvalumab 1500 mg (20 mg/kg) Q4W; TTR, time to onset of objective response.

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

[b] Based on a Lan DeMets alpha spending function with O'Brien Fleming type boundary and the actual number of events observed, the boundary for declaring statistical significance for T300+D vs. S was 0.0398 (Lan and DeMets 1983).

[c] Nominal p-value. ORR and PFS were not included in the multiple testing procedure.

[d] Confirmed complete response.

- The HIMALAYA trial met its primary objective as treatment with T300+D resulted in a statistically significant and clinically meaningful 22% improvement in OS compared to sorafenib (HR = 0.78; 96.02% CI: 0.65, 0.93; p = 0.0035). The Kaplan-Meier estimate of median OS was 16.43 months in the T300+D arm, which was approximately 2.7 months longer than the median OS in the sorafenib arm (13.77 months).
- The OS benefit in the T300+D arm was sustained over time supported by the greater proportion of patients treated with T300+D that were alive at 12, 18, 24, and 36 months compared to patients treated with sorafenib.
- The HIMALAYA trial met its key secondary objective: durvalumab monotherapy was noninferior to sorafenib (S) in terms of OS (HR = 0.86; 95.67% CI: 0.73, 1.03; p < 0.0674), as the upper limit of the 95.67% CI for the HR was lower than the 1.08 non-inferiority margin. However, OS superiority for durvalumab versus sorafenib was not achieved.
- Results of the sensitivity analyses and subgroup analyses of OS for T300+D versus sorafenib and durvalumab versus sorafenib comparisons were consistent with those of the primary OS analyses with the exception of reduced efficacy in the female and HCV-positive subgroups for both comparisons. However, the study was not sized for individual subgroup evaluation and no adjustments were made for multiple testing subgroup analyses, thus limiting confirmatory evidence for any of the subgroup analyses.
- The objective response rate based on investigator assessment was approximately 4 times higher in the T300+D arm (20.1%) compared with the sorafenib arm (5.1%) (odds ratio = 4.69; 95% CI: 2.85, 8.04; nominal p < 0.0001). Best objective response was mainly driven by partial response (17.0% versus 5.1%) with very few complete response (3.1% versus 0). Similar results were observed in the T300+D arm in Study 22 (objective response rate 24.0% and best objective response of complete response 1.3% or partial response 22.7%).
- Median TTR was shorter in the T300+D compared with the sorafenib arm (2.17 versus 3.78 months) and duration of response was longer in the T300+D compared with the sorafenib arm (22.34 versus 18.43 months). Similar results were observed with T300+D in Study 22 (TTR: 2.28 months; duration of response: 18.43 months).
- The Kaplan-Meier estimates for median PFS in the HIMALAYA trial were similar in the T300+D (3.78 months) and sorafenib (4.07 months) arms (HR = 0.90 (95% CI: 0.77, 1.05)) with the curves separating in favour of T300+D.
- Improvement in patient reported outcomes were assessed only in the pivotal Phase III study. Treatment with T300+D demonstrated a clinically meaningful delay in time to deterioration in a broad range of patient-reported symptoms, function, and global health status/quality of life compared with sorafenib.

Evidence of contribution of durvalumab to the proposed T300+D regimen was demonstrated by the following results observed in the HIMALAYA and Study 22:

- Non-inferiority between durvalumab and the standard of care sorafenib treatment in terms of OS
- Overall survival estimates following durvalumab monotherapy were similar in the HIMALAYA trial and Study 22.

However, superiority of durvalumab over sorafenib was not shown in the pivotal HIMALAYA trial.

The following results support the contribution of tremelimumab to the proposed combination in the pivotal HIMALAYA trial:

- A 10% reduction in average risk of death observed with T300+D versus D

- A clear and sustained separation of the T300+D and durvalumab OS curves occurs at 24 months with a large proportion of patients (approximately 40% for T300+D and D) still at risk for an event at this time
- Prespecified OS rates of 18, 24, and 36 months in HIMALAYA numerically favoured
- T300+D over D, with OS rate at 36 months of 30.7% with T300+D versus 24.7% for D
- The T300+D curve separated from sorafenib at 4 months compared to a separation at 9 months for durvalumab versus sorafenib.
- Objective response rates were 20.1% and 17% with T300+D and D, respectively.
- Best objective response of complete response was higher with T300+D (3.1%, 12/393) compared to durvalumab (1.5%, 6/389).
- Disease control rates were higher in the T300+D compared to durvalumab arm (60.1% versus 54.8%)
- Median duration of response was longer with T300+D compared to durvalumab (22.34 versus 16.82 months)

Supportive evidence for contribution of tremelimumab to the proposed T300+D regimen was also provided by results observed in the Phase I/II Study 22.

Conclusions on clinical efficacy

The clinical evaluation concluded the following:

- Overall, evidence of efficacy of the proposed T300+D regimen as first-line systemic therapy in patients with unresectable HCC was mainly provided by results from the pivotal Phase III HIMALAYA trial with supportive evidence provided by the uncontrolled, open label Phase I/II Study 22.
- Evidence to support use of proposed combination (T300+D) regimen as second line therapy in patients with uHCC was limited. The pivotal HIMALAYA trial only evaluated patients who had not received prior systemic therapy. Limited evidence of efficacy of proposed combination (T300+D) regimen as second line therapy was only provided by the Phase I/II Study 22 which evaluated the safety/tolerability, efficacy, PKs and immunogenicity of durvalumab and tremelimumab as monotherapy, and durvalumab in combination with tremelimumab or bevacizumab in 433 patients with unresectable HCC. Patients in this study were immunotherapy-naïve, but most had received prior first line treatment with sorafenib or other agents. Enrolment in the T300+D safety run-in arm (Part 2B) began approximately 8 months after the start of the other 3 treatment arms (in Part 2A) leading to differences in treatment exposure and follow-up times between treatment arms at the final data cut-off confounding interpretation of results. Confirmed objective response rate was higher in the first-line patients in the T300+D arm in the second-line subgroup (35% versus 20%). Subgroup analysis of PFS showed that median PFS was longer for the T300+D arm than for the other three treatment arms in the 'first-line' subgroup but it was similar across all four treatment arms in the 'second line' subgroup. However, small patient numbers and imbalances in baseline patient characteristics between subgroups limit interpretation of subgroup analyses

Safety

Safety data was provided in the pivotal HIMALAYA trial and the supportive Study 22. The pivotal safety dataset used to characterise the safety profile of durvalumab in combination with tremelimumab in the proposed indication was derived from the HCC T300+D pool which

included 462 patients with unresectable HCC from the HIMALAYA trial and Study 22 who received T300+D.

Supportive assessments of the safety and tolerability of tremelimumab and durvalumab were provided in the pan-tumour pools.[42] The pan-tumour pools provided the safety profile of tremelimumab and durvalumab in a much larger patient population in 18 studies that included patients with a variety of cancer types (including HCC but predominantly lung and head and neck cancers. It is noted that the pan-tumour pools did not assess safety of the proposed T300+D dosing regimen. Furthermore, there were some differences in how safety variables were collected in individual non-HCC studies, and these only provided supportive safety data in this submission.

Patient exposure

In the pivotal HIMALAYA trial, the median total treatment duration was the same for the durvalumab component of the durvalumab (5.5 months) and T300+D (5.5 months) arms. In the sorafenib arm, the median total treatment duration was 4.1 months.

Adverse events

An overview of AEs reported in the HCC-tumour and pan-tumour safety pools is provided in Table 5 below.

[42] A pan-tumour pool involves patients across a variety of tumour types.

Table 5: Overview of adverse events (safety analysis set)

AE category	Number (%) of patients [a]				
	HCC-tumor pool		Pan-tumor pool		
	T300+D (N = 462)	D (N = 492)	D (N = 4045)	T75+D (N = 3319)	T750 (N = 643)
Any AE	451 (97.6)	443 (90.0)	3825 (94.6)	3151 (94.9)	609 (94.7)
Any AE possibly related to any study treatment [b]	355 (76.8)	267 (54.3)	2339 (57.8)	2253 (67.9)	460 (71.5)
Any AE possibly related to durvalumab [b]	349 (75.5)	267 (54.3)	2332 (57.7)	2215 (66.7)	1 (0.2) [b]
Any AE possibly related to tremelimumab [b]	224 (48.5)	0	0	2088 (62.9)	452 (70.3)
Any AE of CTCAE Grade 3 or 4 [c]	240 (51.9)	204 (41.5)	1754 (43.4)	1773 (53.4)	383 (59.6)
Any AE with outcome of death	34 (7.4)	30 (6.1)	231 (5.7)	229 (6.9)	44 (6.8)
Any SAE (including events with outcome of death) [d]	189 (40.9)	161 (32.7)	1446 (35.7)	1493 (45.0)	338 (52.6)
Any AE leading to discontinuation of any study treatment	63 (13.6)	47 (9.6)	397 (9.8)	550 (16.6)	155 (24.1)
Any AE leading to discontinuation of durvalumab	63 (13.6)	47 (9.6)	387 (9.6)	501 (15.1)	0
Any AE leading to discontinuation of any study treatment, possibly related to any study treatment [b]	41 (8.9)	26 (5.3)	183 (4.5)	332 (10.0)	125 (19.4)
Any AE leading to discontinuation of durvalumab, possibly related to durvalumab [b]	41 (8.9)	26 (5.3)	179 (4.4)	292 (8.8)	0
Any AE leading to discontinuation of tremelimumab, possibly related to tremelimumab [b]	3 (0.6)	0	0	232 (7.0)	125 (19.4)
Any AE leading to dose modification of study treatment [e]	149 (32.3)	112 (22.8)	1129 (27.9)	953 (28.7)	146 (22.7)
Any AE leading to dose delay or interruption of any study treatment [f]	149 (32.3)	112 (22.8)	1120 (27.7)	945 (28.5)	144 (22.4)
Any AE leading to dose delay or interruption of durvalumab [f]	148 (32.0)	112 (22.8)	1103 (27.3)	915 (27.6)	1 (0.2)

Abbreviations: AE = adverse event; CRF = case report form; CTCAE = Common Terminology Criteria for Adverse Events (version 4.03); D = durvalumab 1500 mg (or equivalent); HCC = hepatocellular carcinoma; IV = intravenous; SAE = serious adverse event; T300+D = tremelimumab 300 mg for a single dose in combination with durvalumab 1500 mg every 4 weeks; T75+D = durvalumab given at a dose of 20 mg/kg every 4 weeks (or equivalent) IV in combination with tremelimumab 1 mg/kg every 4 weeks (or equivalent), for any line of therapy (across tumour types); T750, tremelimumab monotherapy 10 mg/kg every 4 weeks (or equivalent) for any line of therapy (across tumour types).

a Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories.

b As assessed by the investigator. Missing responses are counted as related.

c All CTCAE grades per patient, not just the maximum, are considered when identifying whether there is a Grade 3 or 4.

d Seriousness, as assessed by the investigator. An AE with missing seriousness is considered serious.

e Includes AEs on the AE CRF form with action taken indicating dose reduction, dose increase, dose delay or dose interruption, and AEs meeting study level dose delay definitions, where applicable.

f Includes AEs on the AE CRF form with action taken indicating dose delay or dose interruption, and AEs meeting study level dose delay definitions, where applicable.

Includes AEs with an onset date on or after the date of first dose or pre-treatment AEs that increase in severity on or after the date of first dose up to and including 90 days following the date of last dose of study medication or up to and including the date of initiation of the first subsequent therapy (whichever occurs first).

Disease progression AEs reported in Study 1108, Study 6, Study 10, and Study 11 are not included in this summary.

Overall, no new or unexpected safety findings were identified upon comparison of the HCC T300+D pool or HCC durvalumab pool with the pan-tumour pools.

Study D419CC00002 (HIMALAYA trial)

The safety analyses in the HIMALAYA trial included 1,302 patients who received at least one dose of: STRIDE (n = 388), durvalumab (n = 388), sorafenib (n = 374), or T75+D (n = 152).

Any AE regardless of attribution occurred in 97.4%, 88.9%, 95.5% and 95.4% of patients receiving STRIDE, durvalumab, sorafenib and T75+D respectively (for AEs by Preferred Term occurring in ≥10% of patients in any treatment arm).

The most frequently reported AE Preferred Terms in the T300+D arm were diarrhoea (26.5%), pruritus (22.9%), rash (22.4%), decreased appetite and fatigue (17.0% each) and pyrexia (12.9%). The majority of the events that were reported at a ≥5% greater frequency in the T300+D arm compared with those reported in the sorafenib arm are known adverse drug reactions (ADRs) for durvalumab or tremelimumab (pruritus, rash, aspartate aminotransferase (AST) increased, and hypothyroidism). Diarrhoea, palmar-plantar erythrodysaesthesia syndrome, alopecia and hypertension were all reported at a higher frequency (≥5% greater frequency) in the sorafenib arm than the T300+D arm and these are all known ADRs for sorafenib. Asthenia occurred at a similar frequency in the D, T300+D, and sorafenib arms.

Serious adverse events (SAEs), AEs leading to discontinuation of study treatment, AEs leading to dose delay, immune-related adverse events (irAEs) and infusion reaction AE are shown in the Table 6 below.

Table 6: Study D419CC00002 (HIMALAYA trial) Adverse events in any category (safety analysis set)

	Number (%) of patients			
AE category [a]	D (N = 388)	T300+D (N = 388)	T75+D (N = 152)	S (N = 374)
Any SAE (including events with outcome of death), possibly related to treatment [b]	32 (8.2)	68 (17.5)	28 (18.4)	35 (9.4)
Any AE leading to discontinuation of study treatment	32 (8.2)	53 (13.7)	23 (15.1)	63 (16.8)
Any AE leading to discontinuation of study treatment, possibly related to treatment [b]	16 (4.1)	32 (8.2)	13 (8.6)	41 (11.0)
Any AE leading to dose delay [c]	95 (24.5)	134 (34.5)	58 (38.2)	178 (47.6)
Any AE leading to dose delay, possibly related to treatment [b, c]	54 (13.9)	83 (21.4)	42 (27.6)	144 (38.5)
Any immune mediated AE [d]	64 (16.5)	139 (35.8)	53 (34.9)	30 (8.0)
Any infusion reaction AE [e]	11 (2.8)	20 (5.2)	9 (5.9)	2 (0.5)

AE, adverse event; AEPI, adverse event of possible interest; AESI, adverse event of special interest; CTCAE, Common Terminology Criteria for Adverse Events; D, durvalumab monotherapy 1500 mg Q4W; DCO, data cut-off; imAE, immune-mediated adverse event; IP, investigational product; MedDRA, Medical Dictionary for Regulatory Activities; Q4W, every 4 weeks; S, sorafenib 400 mg twice daily; SAE, serious adverse event; T75+D, tremelimumab 75 mg × 4 doses + durvalumab 1500 mg Q4W; T300+D, tremelimumab 300 mg × 1 dose + durvalumab 1500 mg Q4W.

[a] Patients with multiple events in the same category are counted only once in that category. Patients with events in more than 1 category are counted once in each of those categories.

[b] As assessed by the Investigator. Missing responses were counted as treatment-related.

[c] AEs on the AE case report form with Action taken = Drug interrupted.

[d] ImAEs are identified from AESIs and AEPIs using a programmatic approach.

[e] As assessed by the Investigator.

Includes AEs with an onset date on or after the date of first dose or pre-treatment AEs that increase in severity on or after the date of first dose up to and including 90 days following the date of last dose of study medication or up to and including the date of initiation of the first subsequent therapy (whichever occurred first).

Patients with an AE of maximum CTCAE Grade 5 after the DCO have been reset to 'unknown' at the DCO. This affected 0 patients in the D arm, 0 patients in the T300+D arm, 0 patients in the T75+D arm, and 0 patients in the S arm.

MedDRA version 23.1. CTCAE version 4.03.

Treatment-related adverse events

In the HIMALAYA trial, treatment-related adverse events (TRAEs) occurred in 75.8%, 51.2%, 84.8% and 69.7% of patients receiving STRIDE, durvalumab, sorafenib and T75+D respectively.

In the STRIDE arm, the commonest drug related AEs of any grade included:

- Rash 19.6% (versus sorafenib 12.3%)
- Pruritus 17.0% (versus sorafenib 5.6%)
- Diarrhoea 16.5% (versus sorafenib 38.8%)
- Hypothyroidism 10.8% (versus sorafenib 2.1%)

In the STRIDE arm, the commonest drug related AEs of grade 3 or 4 included:

- Increased lipase 4.4% (versus sorafenib 2.1%)
- Diarrhoea 3.4% (versus sorafenib 4.0%)
- Increased amylase 2.6% (versus sorafenib 0.3%)
- Increased AST 2.3% (versus sorafenib 1.6%)

Deaths

In the HIMALAYA trial, AEs with outcome of death occurred in 7.7%, 6.7%, 7.2% and 7.9% of patients receiving STRIDE, durvalumab, sorafenib and T75+D respectively. TRAEs with outcome of death occurred in 2.3%, 0%, 0.8% and 1.3% of patients receiving STRIDE, durvalumab, sorafenib and T75+D respectively.

Grade 3 to 4 adverse events

In the HIMALAYA trial, Grade 3 or 4 AEs occurred in 50.5%, 37.1%, 52.4% and 39.5% of patients receiving STRIDE, durvalumab, sorafenib and T75+D respectively. The two most frequent Grade 3 to 4 AE (≥5% patients in any treatment arm) in the STRIDE arm were lipase increased and AST increased. Palmar-plantar erythrodysaesthesia syndrome (9.1%) and hypertension (6.1%) were the two most frequent Grade 3 to 4 AEs (≥ 5% patients in any treatment arm) for patients in the sorafenib arm.

Serious adverse events

In the HIMALAYA trial, SAEs occurred in 40.5%, 29.6%, 29.7% and 34.2% of patients receiving STRIDE, durvalumab, sorafenib and T75+D respectively.

Treatment-related SAEs were also reported more frequently in the T300+D group: 17.5%, 8.2%, 9.4% and 18.4% of patients receiving STRIDE, durvalumab, sorafenib and T75+D respectively.

Discontinuation due to adverse event

In the HIMALAYA trial, AEs leading to discontinuation occurred in 13.7%, 8.2%, 16.8%, and 15.1% of patients receiving STRIDE, durvalumab, sorafenib and T75+D respectively. Treatment-related AEs leading to discontinuation showed similar trends (8.2%, 4.1% and 11% in the T300+D, durvalumab and sorafenib groups, respectively) with these AEs generally occurring in only single patients in any treatment group. However, events occurring in 2 or more patients included diarrhoea, colitis, hepatitis, immune-mediated hepatitis, rash, alanine aminotransferase increased, and aspartate aminotransferase increased; these events were uncommon, and incidence was similar across treatment groups and were consistent with the known ADRs of study treatments or of HCC.

Dose interruption due to adverse event

In the HIMALAYA trial, AEs leading to dose delay on occurred in 34.5%, 24.5%, 47.6%, and 38.2% of patients receiving STRIDE, durvalumab, sorafenib and T75+D respectively. TRAEs leading to dose delay on occurred in 21.4, 13.9%, 38.5%, and 27.6% of patients receiving STRIDE, durvalumab, sorafenib and T75+D respectively.

Liver toxicity

Integrated safety analyses showed that overall, the addition of tremelimumab (HCC T300+D pool) did not increase liver toxicity compared with durvalumab alone. In general, the frequency, severity, relatedness, and incidence of discontinuations were similar for hepatic Standardised Medical Dictionary for Regulatory Activities (MedDRA)[43] Queries SMQ[44] AEs/SAEs (including deaths) in the HCC T300+D and HCC durvalumab pools. Reported events, including alanine aminotransferase (ALT) increased, AST increased, hepatic function abnormal, hepatitis, and hepatic failure, were consistent with the disease under study. The incidence of drug induced liver injury[45] events was very low within the HCC-tumour pools (one patient each in the HCC T300+D and HCC durvalumab pools, 0.2%) and pan-tumour pools (D pool: 4 patients < 0.1%; T75+D pool: 12 patients, 0.4%). Fewer than 2% of patients in the HCC T300+D and HCC durvalumab pools had fatal hepatic SMQ AEs (1.3% and 1.4%, respectively). In total, 3.9% of patients in the HCC T300+D pool and 3.5% of patients in the HCC durvalumab pool had

[43] The **Medical Dictionary for Regulatory Activities (MedDRA)** is a single standardised international medical terminology, developed as a project of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) which can be used for regulatory communication and evaluation of data pertaining to medicinal products for human use. As a result, MedDRA is designed for use in the registration, documentation and safety monitoring of medicinal products through all phases of the development cycle (that is, from clinical trials to post-marketing surveillance). Furthermore, MedDRA supports ICH electronic communication within the ICH's Electronic Common Technical Document (eCTD) and the E2B Individual Case Safety Report.

[44] **Standardised MedDRA Queries (SMQs)** are groupings of terms from one or more MedDRA System Organ Classes (SOCs) that relate to a defined medical condition or area of interest. They are intended to aid in case identification.

[45] **Drug induced liver injury (DILI)** also known as drug-induced hepatoxicity, is acute or chronic liver damage caused by a prescription, over the counter (OTC) or complementary medicine. Hepatoxicity due to type A reactions, or intrinsic DILI is typically dose-related and occurs in a large proportion of individuals exposed to the drug, (predictable) and onset is within a short time span (hours to days). Idiosyncratic DILI is not closely dose-related, and occurs in only a small proportion of exposed susceptible individuals (unpredictable) and exhibits a variable latency to onset of days to weeks.

durvalumab-related hepatic SMQ AEs leading to discontinuation; 0.4% of patients had tremelimumab-related hepatic SMQ AEs leading to Discontinuation. Hepatic event immune-mediated adverse events (imAEs) were infrequent and occurred at similar frequencies between the HCC T300+D and HCC durvalumab pools.

In the HIMALAYA trial, the overall frequency of hepatic AEs per Hepatic Disorder SMQs was consistent across all treatment arms (37.1%, 33.2% and 32.4% in the T300+D, durvalumab and sorafenib groups, respectively, see table 8.4.5a in clinical evaluation report).

- The frequency of AEs of maximum Common Terminology Criteria for Adverse Events (CTCAE)[46] Grade 3 or 4 in the System Organ Class of hepatobiliary disorders was low (D, 2.3%; T300+D, 4.4%; T75+D, 3.9%; S, 2.7% patients).
- The frequency of treatment-related events in the System Organ Class of hepatobiliary disorders was low (D, 4.6%; T300+D, 7.0%; T75+D, 7.2%; S, 4.3% patients)
- Treatment-related AEs of drug induced liver injury were very infrequent and there was only one report of treatment-related esophageal varices haemorrhage, which occurred in the T75+D arm
- There were 6 deaths due to hepatic AEs in the T300+D arm (Preferred Terms: oesophageal varices haemorrhage, hepatitis, 2 events of immune-mediated hepatitis, 2 events of hepatic failure), 4 in the durvalumab arm (Preferred Terms: hepatic cirrhosis, oesophageal varices haemorrhage, 2 events of hepatic failure), 2 in the T75+D arm (Preferred Terms: hepatitis, hepatic failure), and 8 in the sorafenib arm (Preferred Terms: hepatic encephalopathy, hepatorenal syndrome, oesophageal varices haemorrhage, liver abscess, 4 events of hepatic failure).
- In the T300+D treatment arm, deaths due to one event of hepatic failure, one event of hepatitis, and 2 events of immune-mediated hepatitis were considered treatment-related. One death due to hepatic failure in each of arms T75+D and sorafenib were considered treatment-related. No deaths due to AEs in the Hepatic Disorder SMQ were treatment-related in the durvalumab arm.
- The incidence of AESIs/adverse events of potential interest (AEPIs) of hepatic events (grouped term) were similar in all treatment arms: 24.5%. 24.7%, 21.7% and 21.1% in the D, T300+D, T75+D and sorafenib treatment arms, respectively. Hepatic events determined as immune AEs were reported in 6.7%, 7.5%, 9.2% and 0.3%, respectively.

Renal toxicity

No clinically significant changes were observed in the renal function parameters.

Other clinical chemistry

In the HIMALAYA trial, findings relating to clinical chemistry parameters were as expected for this patient population with HCC-related liver disease. There were no obvious patterns or imbalances in clinical chemistry abnormalities, and any shifts were generally comparable across treatment arms.

Haematology

In the HIMALAYA trial, there were no clinically significant changes in haematology parameters between treatment groups.

[46] **The Common Terminology Criteria (CTC)** is a standardised classification of side effects used in assessing drugs for cancer therapy, in particular. Specific conditions and symptoms may have values or descriptive comment for each level, but the general guideline is 1 – Mild, 2 – Moderate, 3 – Severe, 4 - Life threatening, 5 - Death.

Cardiovascular safety

Neither the HIMALAYA trial nor Study 22 were designed to formally assess electrocardiogram interval, rhythm, rate, or morphology.

Immunogenicity

Tremelimumab:

- In the integrated safety analyses, the incidence of treatment-emergent ADA to tremelimumab positivity was similar in the HCC T300+D (10.1%), pan-tumour T75+D (12.1%) and pan-tumour T750 (8.0%) pool patients. The types and frequency of AEs reported in treatment-emergent ADA positive patients were similar to those reported in patients who were ADA negative.
- In the HIMALAYA trial, treatment induced anti-tremelimumab antibodies were detected in 11.0% of patients receiving STRIDE and 21.6% receiving T75+D at any visit; neutralising antibodies were detected in 4.4% and 15.7% of patients respectively.

Durvalumab:

- In the integrated safety analyses, the incidence of treatment-emergent ADA to durvalumab positivity was similar in the HCC T300+D (2.8%), HCC durvalumab (2.4%) and pan-tumour durvalumab (2.7%) pool patients. The types and frequency of AEs reported in treatment-emergent ADA positive patients were similar to those reported in patients who were ADA negative.
- In the HIMALAYA trial, treatment induced anti-durvalumab antibodies were detected in 3.1%, 2.5% and 4.6% of patients receiving STRIDE, durvalumab and T75+D respectively; neutralising antibodies were detected in 1.7%, 0.7% and 0 patients respectively.

There were no new types of events or events clearly suggestive or indicative of infusion reactions or immune complex disease. For patients who were ADA-positive, the AEs with Grade ≥3 observed were consistent with what has been observed in patients treated with durvalumab or tremelimumab. There was no marked impact of positive ADA to durvalumab or tremelimumab on categorical AE data. In the HIMALAYA trial, immune mediated AEs were reported at a higher frequency in the tremelimumab-containing treatment arms (T300+D, 35.8%; T75+D, 34.9% patients) compared with those reported in the durvalumab arm (16.5% patients). The frequency of immune mediated AEs that led to discontinuation of study treatment was low (≤5.7% patients per arm). Six patients (1.5%) in the T300+D arm died due to immune mediated AEs (pneumonitis, myocarditis, myasthenia gravis and 3 hepatic events (one hepatitis, 2 immune mediated hepatitis)). There were no fatal immune mediated AEs in the other treatment arms.

In the HIMALAYA trial, AESIs of hypersensitivity/anaphylactic reactions (grouped term) were uncommon (D, 3 patients (0.8%); T300+D, 5 patients (1.3%); T75+D, no patients; S, 2 patients (0.5%)). The incidence of infusion reactions was low, but numerically higher in the T300+D (5.2%) compared to the durvalumab (2.8%) and sorafenib (0.5%) groups.

In the HCC and pan-tumour safety pools: AESIs of infusion-related reactions (grouped term) were reported at a low frequency in both the HCC-tumour pools (1.5% and 0.8% in the T300+D and durvalumab pools, respectively) and the pan-tumour pools (1.4% and 1.7% in the durvalumab and T75+D pools, respectively). The AESIs of hypersensitivity/anaphylactic reactions (grouped term) were reported at a low frequency in the HCC-tumour pools (1.3% and 0.6% in the T300+D and durvalumab pools, respectively) and the pan-tumour pools (0.8% and 0.7% in the durvalumab and T75+D pools, respectively).

Adverse events of special interest, adverse events of potential interest and immune mediated adverse events

The discussion on immune mediated AEs (including hepatic, colitis, rash, endocrinopathies, thyroid, renal, pancreatic, myocarditis, myasthenia gravies, Guillain-Barré syndrome, myositis, and other) is noted.

Regarding AESIs AEPIs and immune mediated AEs reported in the HIMALAYA trial, the following is notable:

- Immune mediated AEs requiring treatment with high-dose corticosteroids occurred in 20.1%, 9.5%, 1.9% and 19.1% of patients receiving STRIDE, durvalumab, sorafenib and T75+D respectively.
- Immune mediated events leading to discontinuation of study treatment occurred in 5.7%, 2.6%, 1.6% and 5.3% of patients receiving STRIDE, durvalumab, sorafenib and T75+D respectively.

In addition, the clinical evaluation highlighted the following:

Haemorrhage:

- The addition of tremelimumab (HCC T300+D pool) did not lead to an increase in haemorrhagic events compared with durvalumab alone. The HCC T300+D and HCC durvalumab pools showed similar frequency (T300+D versus durvalumab: 12.1% versus 12.4%), severity (CTCAE grade 3 or 4: 4.3% versus 4.3%), relatedness (1.9% versus 1.0%) and incidence of discontinuations (1.7% versus 0.8%) for haemorrhagic SMQ AEs/SAEs including deaths (1.7% versus 1.2%).
- The incidence and severity of haemorrhagic events in the pan-tumour durvalumab pool was similar to that observed in the HCC T300+D and HCC durvalumab pools.
- In the HIMALAYA trial, overall, haemorrhage AEs and haemorrhage TRAEs, as captured by haemorrhage SMQs, were similar and low across all treatment arms; there was no observed increase in the tremelimumab-containing arms compared with the durvalumab arm. Sorafenib had the highest frequency of haemorrhage TRAEs (4.8%) compared with <2% in the immuno-oncology-containing treatment arms. Grade 3 or 4 treatment-related haemorrhage events occurred in 0.5%, 0%, 1.1% and 2% of patients receiving STRIDE, durvalumab, sorafenib and T75+D respectively. There were no reported treatment-related oesophageal varices haemorrhage in arms D, T300+D, or S, and one event reported for arm T75+D.
- The frequencies of fatal haemorrhage s were also similar across treatment arms (D, 1.5%; T300+D, 2.1%; T75+D, 0.7%; S, 1.3%). There were 8 deaths due to AEs in the haemorrhage SMQ in arm T300+D, 6 in arm D, one in arm T75+D and 5 in the sorafenib arm. Although there were some deaths due to haemorrhage, none were reported to be treatment-related in the immuno-oncology arms. T300+D was also not associated with increased bleeding risk, despite no requirement for recent endoscopy for study entry.

Immune mediated adverse events:

- In the HIMALAYA trial, the most common immune-mediated events were hepatic events, diarrhoea/colitis, and dermatitis/rash.
- Diarrhoea/colitis:
  - AESIs/AEPIs of diarrhoea/colitis (grouped term) were reported most frequently in the sorafenib arm (15.5%, 27.8%, 22.4% and 44.9% in the D, T300+D, T75+D and sorafenib treatment arms, respectively).

- Diarrhoea/colitis imAEs were uncommon (0.8%, 5.9%, 5.9% and 0.3%, respectively). However, serious imAEs of diarrhoea/colitis were reported at a higher frequency in the tremelimumab-containing treatment arms (T300+D, 3.4%; T75+D, 3.3%) compared with the durvalumab (0.5%) and sorafenib (0%) arms.
- Discontinuations due to imAEs of diarrhea/colitis only occurred in the durvalumab (0.3%) and T300+D (1.3%) arms. There were no deaths due to imAEs of diarrhoea or colitis.

Dermatitis/rash:

- AESIs/AEPIs of dermatitis/rash (grouped term) were reported at a higher frequency in the tremelimumab-containing treatment arms (28.6%, 46.1%, 38.8% and 30.2% in the D, T300+D, T75+D and sorafenib treatment arms, respectively).
- However, incidence of dermatitis/rash imAEs was low (0.8%, 4.9%, 3.9% and 3.5%, respectively).
- Serious imAEs of dermatitis/rash and discontinuations were infrequent.
- Dermatitis/rash is a known ADR for durvalumab monotherapy and durvalumab in combination with tremelimumab therapy.

Pneumonitis:

- The incidence of AESIs/AEPIs of pneumonitis (grouped term) was infrequent but was reported at a higher frequency in the T300+D (2.8%) and T75+D (5.9%) compared with the durvalumab (1.8%) and sorafenib (0.5%) treatment groups.
- Pneumonitis immune mediated AEs were also reported at a higher frequency in the T300+D (1.3%) and T75+D (4.6%) groups compared with durvalumab (0.8%) and sorafenib (0%) groups.
- Grade 3 or 4 imAEs of pneumonitis were reported by one patient in the durvalumab arm and 4 patients in the T75+D arm; all events were considered treatment-related. There were no Grade 3 or 4 imAEs of pneumonitis in the T300+D arm.
- Serious imAEs of pneumonitis were reported at a higher frequency in the T75+D (3.3%) compared with the durvalumab (0.8%) and T300+D (0.8%) arms, but discontinuations due to imAEs of pneumonitis were low (durvalumab: 0.5%; T300+D: 0.3%; T75+D: 2.6%).
- The majority of pneumonitis event imAEs required high-dose corticosteroids and one patient in the T300+D arm had a fatal imAE of pneumonitis.

Myocarditis:

- AESIs/AEPIs of myocarditis events (grouped term) were uncommon and reported for only one patient in the durvalumab arm and 2 patients in the T300+D arm; all myocarditis events were imAEs.
- The myocarditis event in the durvalumab arm was Grade 3 or 4 and led to treatment discontinuation. One event in the T300+D arm led to treatment discontinuation, and there was one fatal event.
- High-dose systemic corticosteroids were required for one myocarditis imAE in the T300+D arm and one myocarditis imAE in the durvalumab arm.

Endocrinopathies, myasthenia gravis, renal events, pancreatic events, interstitial lung disease and myositis:

- Noted.

Other safety issues and safety in special populations

Summary of clinical safety from the HIMALAYA trial

The clinical evaluation's main safety findings in the pivotal HIMALAYA trial are summarised as follows:

- Overall incidence of AEs was similar for T330+D (97.4%) and sorafenib (95.5%).
- The commonest AEs in the sorafenib arm were palmar-plantar erythrodysaesthesia, diarrhoea, fatigue and hypertension.
- The commonest AEs in the T300+D arm were diarrhoea (26.5%), pruritus (22.9%), rash (22.4%), decreased appetite (17.0%), fatigue (17.0%) and pyrexia (12.9%).
- The commonest AEs in the durvalumab alone arm were diarrhoea (14.9%), pruritus (14.4%), AST increased (14.4%), decreased appetite (13.7%), asthenia 12.6%) and ALT increased (11.2%).
- The incidence of Grade ≥3 AEs was similar in the T300+D (50.5%) and sorafenib arms (52.4%), and lower in the durvalumab arm (37.1%); the commonest of these in the T300+D arm were increased AST and increased lipase.
- The incidence of TRAE was higher in the Sorafenib arm (84.8%) than the T300+D arm (75.8%) and durvalumab arm (52.1%). The commonest treatment related Grade ≥3 AEs in the immuno-oncology-containing regimen were increased AST, ALT and amylase/lipase.
- Treatment discontinuation due to AEs were similar for T330+D (13.7%) and sorafenib (16.8%), and lower in the durvalumab arm (8.2%), most commonly due to diarrhoea, colitis, hepatitis, rash and increased ALT/AST.
- The frequency of treatment-related fatal AEs was slightly higher in the T300+D arm (2.3%; 9 of 388 patients) than the sorafenib arm (0.8%) and durvalumab arm (0%). 7 of the 9 treatment-related fatal events in the T300+D arm were attributed to disease progression, metastases or viral etiology and the role of study treatment could not be excluded.
- Immune mediated AEs were more frequent in the T300+D arm (35.8%) than the durvalumab monotherapy arm (16.5%).
  - Discontinuation of study treatment due to irAEs was low (≤ 5.7% patients per arm).
  - 1.5% of patients in the T300+D arm died due to irAEs (pneumonitis, hepatic events, myocarditis, and myasthenia gravis).
  - Diarrhoea/colitis irAEs were uncommon (T300+D 5.9% versus durvalumab alone 0.8% versus sorafenib 0.3%). Serious irAEs of diarrhoea/colitis more common in the T300+D arm (3.4%) than the sorafenib arm (0%) and durvalumab alone arm (0.5%). Discontinuation due to irAEs of diarrhea/colitis in the T300+D arm was 1.3% and 0.3% in the durvalumab alone arm.
  - Dermatitis/rash irAEs were uncommon (T330+D 4.9% versus durvalumab alone 0.8% versus sorafenib 3.5%).
- Hepatic AEs and hepatic TRAEs were comparable across all treatment arms. The addition of tremelimumab did not significantly increase hepatotoxicity and the majority of TRAEs were low overall and were predominantly Grade 1 or 2 events.

- Haemorrhagic events were low across all treatment arms: treatment related haemorrhage AEs were higher for those in the sorafenib arm (4.8%) compared with the immuno-oncology-containing treatment arms (<2%). No treatment-related esophageal variceal hemorrhagic events were reported in the T300+D or sorafenib arms. T300+D was also not associated with increased bleeding risk, despite no requirement for recent endoscopy for study entry.
- Clinically important changes in hematology and clinical chemistry parameters were as expected for this patient population with HCC-related liver disease. There were transient elevations in liver function tests and predominantly asymptomatic elevations in amylase and lipase. In cases where amylase and lipase laboratory values elevated beyond low grade, there was no associated increase in diagnoses of pancreatitis.

Summary of safety comparison between unresectable hepatocellular carcinoma population and pan-tumour pools

- Commonly reported AEs that were reported at a ≥ 5% higher incidence in the HCC T300+D pool compared with the pan-tumour T75+D pool were pruritus, rash and AST increased, all of which are known ADRs for tremelimumab; the higher incidence of AST increased may also be attributed to underlying liver disease.
- The only commonly reported AE that was reported at a ≥5% higher incidence in the HCC durvalumab pool compared with the pan-tumour durvalumab pool was AST increased which was likely due to underlying liver disease.
- Overall, no new or unexpected safety findings were identified upon comparison of the HCC T300+D pool or HCC durvalumab pool with the pan-tumour pools.

Additional comments on safety:

- In general, the identified risks associated with durvalumab monotherapy are consistent with those of other anti-PD-1/PD-L1 agents such as atezolizumab, nivolumab and pembrolizumab. The identified risks for tremelimumab are also considered identified risks for the durvalumab and tremelimumab combination (for example, lipase increased, amylase increased, intestinal perforation and large intestine perforation). These risks are consistent with those associated with other marketed anti PD-1/PD-L1/CTLA agents such as pembrolizumab, and the combination of nivolumab and ipilimumab.

The clinical evaluation's conclusion on post-marketing data on durvalumab is as follows:

- The cumulative global post-marketing patient exposure to durvalumab (10 mg/kg) since launch to 30 June 2021 has been estimated to be 52,006 patient-years.
- No new safety concern was identified based on the post-marketing safety reports.
- No new periodic safety update reports were provided in current submission.

Conclusions on clinical safety

The clinical evaluation concluded that overall, the safety and tolerability of tremelimumab administered in combination with durvalumab was generally consistent with the known safety profile for each agent, and AEs were well tolerated and manageable according to toxicity management guidelines. Of note, the increased risk of irAEs observed following treatment with dual checkpoint inhibition (for example, nivolumab and ipilimumab combination) was also observed following tremelimumab and durvalumab treatment in this submission.

Recommendation following the clinical evaluation

Overall, the results from the pivotal Phase III HIMALAYA trial in patients with unresectable HCC provided evidence that a single priming dose of tremelimumab combined with durvalumab improves efficacy and has a clinically meaningful improvement over the standard of care (at time of this study) sorafenib monotherapy. Evidence of efficacy and safety was established in patients with uHCC who have not received prior systemic therapy and have Child Pugh class A liver function and good performance status (ECOG of 0). In Australia, sorafenib or lenvatinib is currently recommended as initial systemic therapy in patients with advanced (BCLC stage C) or multifocal HCC that is not amenable to curative or locoregional therapy (BCLC stage B) and who have preserved liver function and good performance status. Lenvatinib (a multiple kinase inhibitor against VEGFR-1, -2, and -3 and fibroblast growth factor receptor (FGFR)-1, -2, -3, and -4) is also approved as first-line treatment for advanced HCC in patients without main portal vein invasion and a Performance Status of 0 to 1. The use of sorafenib (400 mg twice a day orally) as the comparator in the pivotal Phase III study was appropriate. However, the TGA has also approved first-line combination therapy atezolizumab (a PD-L1 inhibitor) and bevacizumab (an angiogenesis inhibitor targeting vascular endothelial growth factor A) in patients with unresectable HCC which is also the preferred option to treat first-line HCC.[22,23,24]

It is noted that nivolumab is approved by TGA as monotherapy for the treatment of patients with hepatocellular carcinoma after prior sorafenib therapy. This indication is approved based on objective response rate and duration of response in a single arm study. An improvement in survival or disease-related symptoms has not been established. However, in April 2021, the United States Food and Drug Administration (FDA)'s Oncological Drug Advisory Committee voted against maintaining the accelerated approval of nivolumab for second-line treatment following progression on sorafenib following negative results of the CheckMate 459 trial and low objective response rate. Based on the results of nivolumab monotherapy in the CheckMate 040 trial, its efficacy in combination with the CTLA-4 inhibitor ipilimumab was further investigated in another arm of the study and the combination of nivolumab and ipilimumab was approved by the FDA in March 2020 for patients with HCC who were previously treated with sorafenib. However, the CTL4-inhibitor ipilimumab (Yervoy) is not approved in Australia for use in HCC. It is only approved as monotherapy for treatment of unresectable or metastatic melanoma; it is approved in combination with nivolumab (opdivo) for treatment of renal cell carcinoma, non-small cell lung cancer and malignant pleural mesothelioma.

There was lack of adequate evidence of efficacy or safety of proposed combination (T300+D) as second line systemic therapy for patients with uHCC. All of the patients in the pivotal Phase III HIMALAYA trial and 27% to 35% of patients in the Phase I/II supportive Study 22 received proposed combination treatment as first line systemic therapy. Results observed in the uncontrolled Phase I/II Study 22 did not provide conclusive evidence of efficacy/safety of proposed combination (T300+D) as second line treatment.

Hence, the benefit-risk profile is not favourable for proposed indication but can become favourable if comments below are addressed specifically related to proposed wording reflecting the patient population evaluated in the pivotal efficacy/safety study (as first line systemic therapy for uHCC).

The first round of clinical evaluation recommendation was that Imjudo could not be approved for patients who had previously received systemic therapy, with the recommendation that approval could potentially be granted for the following indication:

> *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 sponsor's response to this included the following:

- Data from two independent studies supporting the proposed indication of uHCC have been provided with this application. The HIMALAYA trial enrolled a first line patient population, and Study 22 enrolled a predominately second line patient population, with roughly two-thirds (n = 223 (33.2%)) of the subjects enrolled in Parts 2 and 3 receiving treatment with sorafenib prior to enrolment. In the T300+D arm, 73.3% (n = 55) of subjects were previously treated with sorafenib prior to study entry.
- Importantly, both studies include both T300+D and durvalumab arms. In this way, patients receiving durvalumab act as a control across both studies and the overall results can be interpreted together to ascertain the value of T300+D independent of line of therapy.
- Consistency of improved benefit of the T300+D over durvalumab was observed across all prespecified endpoints from the HIMALAYA trial and Study 22.
- The HIMALAYA trial demonstrates that T300+D was superior to sorafenib with a tolerable and manageable safety profile. Two independent well-conducted studies support a clear evaluation of the contribution of each component of the proposed T300+D regimen in first- and second-line unresectable HCC. Overall, the results support that a single priming dose of tremelimumab combined with durvalumab improves efficacy and has a clinically meaningful improvement over durvalumab monotherapy, with benefit of the tremelimumab priming dose observed across both studies.

Following review of the sponsor's response, the clinical evaluation modified their assessment of benefit-risk balance, with the following conclusion:

- All of the patients in the pivotal Phase III HIMALAYA trial and 27% to 35% of patients in the Phase I/II supportive Study 22 received proposed combination treatment as first line systemic therapy. Results observed in the uncontrolled Phase I/II Study 22 only provided supportive evidence of efficacy/safety of proposed combination (T300+D) as second line treatment. There is no data on efficacy/safety of the proposed T300+D combination treatment for patients who have failed first line treatment with other agents such as combination of atezolizumab and bevacizumab.[22] However, it is acknowledged that proposed combination (T300+D) could provide a potential therapeutic option for patients who have failed first line of treatment with sorafenib after individual benefit-risk assessment by treating physicians.

  Overall, the benefit-risk profile of tremelimumab (Imjudo) is favourable for the following proposed indication:

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

The second round of clinical evaluation recommendation was amended to the following:

- Despite limitations regarding submitted evidence of efficacy/safety as second line of systemic treatment for adult patients with uHCC, it is acknowledged that the proposed combination (T300+D) could provide a potential therapeutic option for patients who have failed first line of treatment with sorafenib after individual benefit-risk assessment by treating physicians.

  It is recommended that the marketing application for Imjudo be approved for the following indication:

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

Risk management plan

The sponsor has submitted EU- risk management plan (RMP) version 2.0 succession 1.0 (dated 17 February 2022; data lock point (DLP) 27 August 2021) and Australia-specific annex (ASA) version 1.0 succession 1.0 (dated 6 April 2022) in support of this application. In its response to a TGA request for information, the sponsor has submitted EU-RMP version 2.0 succession 3.0 (dated 10 November 2022; DLP 27 August 2021) and ASA version 1.0 succession 2.0 (dated 25 November 2022) in support of its application. The sponsor has submitted EU-RMP version 2.0 succession 4.0 (dated 27 December 2022; DLP 27 August 2021) and ASA version 1.0 succession 3.0 (dated 16 March 2023) on 24 March 2023.

Initially, there were no proposed safety concerns for tremelimumab in the EU-RMP and ASA. There are no safety concerns for durvalumab in the most recently evaluated EU-RMP (version 4.1, dated 17 August 2020, DLP 26 April 2019), and ASA (version 11.2, dated 7 April 2022) for Submission PM-2021-03648-1-4 on unresectable malignant pleural mesothelioma. EU-RMP version 2.0 succession 4.0 (dated 27 December 2022; DLP 27 August 2021) for tremelimumab includes 'immune-mediated adverse reactions' as an important identified risk. The sponsor has not included this safety concern in ASA version 1.0 succession 3.0 (dated 16 March 2023). The sponsor has provided adequate justification for not including it.

Routine pharmacovigilance only is proposed. This is acceptable considering there are no safety concerns to date in the ASA.

No routine risk minimisation was proposed at the first round of evaluation as there were no safety concerns. However, EU-RMP version 2.0 succession 3.0 submitted with the sponsor's response to a TGA request for information includes a Patient Alert Card as additional risk minimisation to address the important identified risk 'immune-mediated adverse reactions' which is not included as a safety concern in the ASA. The sponsor's justification for not implementing a Patient Card is acceptable. The sponsor has included information in the PI that the CMI should be provided to the patient to inform them of the risk of immune-mediated adverse reactions when the first dose of tremelimumab is administered.

The sponsor has adequately addressed the recommendations regarding the CMI.

Risk-benefit analysis

Delegate's considerations

Condition

The incidence rate of hepatocellular cancer in Australia has continued to increase over the past decade, despite a reduction in the overall cancer incidence rate. In 2021, 2,832 Australians were diagnosed with hepatocellular carcinoma (HCC), with an incidence of 8.9 per 100,000 and an associated 2,424 deaths.[47] HCC is seventh commonest cause of cancer related death in Australia; the age standardised mortality rate of 7.0 per 100,000 has increased by more than 200% from 1982 to 2019, more than for any other cancer.[47] On the basis of annual projections, it is estimated by the World Health Organisation that worldwide, more than one million patients will die from liver cancer in 2030.[9]

Risk factors for HCC are well known, including Hepatitis B and C virus, cirrhosis secondary to alcohol or non-alcoholic fatty liver disease, and other rarer conditions such as hereditary

[47] https://www.aihw.gov.au/reports/cancer/cancer-in-australia-2021/summary

haemochromatosis, alpha-1 antitrypsin deficiency and primary biliary cirrhosis.[9] The underlying aetiology is an important consideration due to its association with differential mechanisms leading to the development of HCC as well as possible relationship with response to treatment.

Hepatocellular carcinoma is among the group of solid cancers with the fewest somatic mutations that can be targeted with molecular therapies, and no mutations are used in clinical practice to predict therapeutic response.[48] At present, molecular profiling may be considered in patients with advanced disease in order to determine eligibility into clinical trials of new molecular targeted agents such as IDH1, IDH2, FGF and KRAS.[49] genomic evidence for immune activation is seen in about a third of early stage hepatocellular carcinomas, whereas 25% have no immune infiltrate; understanding the interaction between cancer cells and the tumour microenvironment will be important in developing new therapy and identifying useful biomarkers.[50]

Current treatment options

Recent advances have seen the approval for use of a number of systemic therapies for advanced disease in Australia, including first line therapies lenvatinib, atezolizumab plus bevacizumab; and second line therapies regorafenib, cabozantinib, and nivolumab.

Until recently, sorafenib was the standard of care in the upfront treatment of patients with advanced HCC, with an increase in median survival to 10.7 months from 7.9 months with placebo. Since 2020, the updated recommended treatment of advanced HCC in the first line setting is now the combination of atezolizumab and bevacizumab, having shown an OS benefit over sorafenib (IMbrave150 trial). Sorafenib and lenvatinib remain first-line treatment alternatives. It remains unclear what the benefits of second line and subsequent systemic therapy options are for patients who have received atezolizumab and bevacizumab as first-line treatment.

Despite therapeutic advances in unresectable HCC, additional treatments for this population are needed. The sponsor has highlighted the increased bleeding risk in patients with HCC and the need for adequate endoscopic evaluation and management of oesophageal varices within 6 months prior to treatment with front-line atezolizumab plus bevacizumab combination.

Targeting both the PD-1 and CTLA-4 pathways using dual checkpoint blockade could result in a potential additive tumour effect with a longer duration of immune activation. Tremelimumab in combination with durvalumab (STRIDE and durvalumab monotherapy) versus sorafenib in the treatment of patients with unresectable HCC not previously treated with systemic therapy was evaluated in the Phase III HIMALAYA trial which forms the basis of this submission.

Proposed indication

The sponsor proposes to register tremelimumab (Imjudo), a new therapeutic entity, as a combination therapy with durvalumab for the following indication:

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

The proposed recommended tremelimumab (Imjudo) dose is as follows:

[48] Zehir A, Benayed R, Shah RH, et al. Mutational landscape of metastatic cancer revealed from prospective clinical sequencing of 10,000 patients. Nat Med 2017;23:703-13.
[49] National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: Hepatobiliary Cancers. Version 2.2022 – July 15, 2022. Fort Washington (PA): National Comprehensive Cancer Network (NCCN); 2022.
[50] Sia D, Jiao Y, Martinez-Quetglas I, et al. Identification of an immune-specific class of hepatocellular carcinoma, based on molecular features. Gastroenterology 2017;153:812-26.

Single tremelimumab regular interval durvalumab (STRIDE): 300 mg* Imjudo as a single priming dose in combination with durvalumab (Imfenzi) 1500 mg at Cycle 1 Day 1, followed by durvalumab monotherapy every 4 weeks. (*4mg/kg weight based dosing for patients ≤30kg)

Benefits and uncertainties of benefit

The pivotal study (HIMALAYA trial) is a phase III, open-label, randomised study.

- Tremelimumab and durvalumab combination (T300+D) arm: n = 393
- Durvalumab arm: n = 389
- Sorafenib arm: n = 389

Patients were required to have uHCC who were not eligible for locoregional therapy and have not received prior systemic therapy for HCC.

Primary endpoint: OS comparing T300+D to sorafenib:

- 16.4 versus 13.8 months in the T300+D and sorafenib arms, respectively
- HR = 0.78 (96.02% CI: 0.65, 0.93), p = 0.0035

The study met its primary objective. In addition, the OS benefit in the T300+D arm was sustained over time with a trend showing greater proportion of patients treated with T300+D that were alive at 18, 24, and 36 months (48.7%, 40.5%, and 30.7%, respectively) compared with patients treated with sorafenib (41.5%, 32.6%, and 20.2%, respectively).

Secondary endpoints were supportive and included OS comparing durvalumab versus sorafenib for non-inferiority; OS at 18, 24 and 36 months, PFS, time to progression, objective response rate and disease control rate.

Supportive evidence of efficacy in immunotherapy-naïve patients with uHCC shown by Phase I/II Study 22.

Results of the sensitivity analyses and subgroup analyses of OS for T300+D versus sorafenib and durvalumab versus sorafenib comparisons were consistent with those of the primary OS analyses with the exception of reduced efficacy in the female and HCV-positive subgroups for both comparisons. However, the study was not sized for individual subgroup evaluation and no adjustments were made for multiple testing subgroup analyses, thus limiting confirmatory evidence for any of the subgroup analyses.

The HIMALAYA trial was not designed to compare T300+D versus durvalumab monotherapy, however, the following results provide some evidence of contribution of tremelimumab to the proposed T300+D regimen:

- A 10% reduction in average risk of death observed with T300+D versus durvalumab
- A clear and sustained separation of the T300+D and durvalumab OS curves occurs at 24 months with a large proportion of patients (approximately 40% for T300+D and D) still at risk for an event at this time.
- Prespecified OS rates of 18, 24, and 36 months in the HIMALAYA trial numerically favoured.
- T300+D over D, with OS rate at 36 months of 30.7% with T300+D versus 24.7% for durvalumab
- The T300+D curve separated from sorafenib at 4 months compared to a separation at 9 months for durvalumab versus sorafenib.

- Objective response rates were 20.1% and 17% with T300+D and D, respectively, and median duration of response was longer with T300+D compared to durvalumab (22.34 versus 16.82 months).

The contribution of durvalumab to the efficacy of the proposed T300+D regimen was demonstrated by non-inferiority between durvalumab and sorafenib in terms of OS in the HIMALAYA trial. Durvalumab failed to achieve OS superiority relative to sorafenib (p = 0.0674); this provides supportive evidence that both components of the T300+D combination regimen are needed to achieve a statistically significant OS effect compared to sorafenib.

Uncertainties

As highlighted by the clinical evaluation, evidence for efficacy of the proposed T300+D regimen in the second line setting is limited. The pivotal Phase III HIMALAYA trial only evaluated patients with unresectable HCC who had not received prior systemic therapy. The Phase I/II Study 22 evaluated the safety/tolerability, efficacy, PKs and immunogenicity of durvalumab and tremelimumab as monotherapy, and durvalumab in combination with tremelimumab or bevacizumab in 433 patients with unresectable HCC. In this study, most patients had received prior first line treatment (sorafenib or other agents) and were immunotherapy-naïve. In the subgroup of patients in the T300+D arm receiving second line therapy, the objective response rate was 20% (compared to 35% for those in the first-line setting). Subgroup analysis of PFS showed that median PFS was longer for the T300+D arm than for the other three treatment arms in the 'first-line' subgroup but it was similar across all four treatment arms in the 'second line' subgroup. The interpretation of these results is confounded by differences in treatment exposure and follow-up times between the T300+D and the three other treatment arms at the final data cut-off; in addition, small patient numbers and imbalances in baseline patient characteristics between subgroups limit the interpretation of subgroup analyses. Study 22 should be interpreted with caution given that it pooled efficacy results from the multi-part of the study, containing both randomised and non-randomised patients, did not include formal testing of efficacy endpoints (secondary endpoints) and enrolled a study population that differed from the proposed indication for this submission (that is, first line unresectable HCC).

Overall, the Delegate agrees with the clinical evaluation that despite limitations regarding efficacy/safety of T300+D in the second line setting, this combination remains a potential therapeutic option for patients who have progressed on (or no longer be suitable for) sorafenib after individual benefit-risk assessment by the treating clinician. The Delegate will seek the opinion of Advisory Committee on Medicines (ACM) regarding whether the available evidence from Study 22 is adequate to support use of T300+D in the second line setting.

Other uncertainties and limitations include the following:

- Subgroup analyses did not show improvements in OS with T300+D compared with sorafenib in the female and HCV-positive subgroups. However, the study was not sized for individual subgroup evaluation and no adjustments were made for multiple testing subgroup analyses, thus limiting confirmatory evidence for any of the subgroup analyses.
- The pivotal HIMALAYA trial was an open-label design; however the sponsor was blinded to treatment assignment and did not have access to any aggregate summaries by treatment arm during the study.
- Only patients with preserved liver function (Child-Pugh class A) were studied in the HIMALAYA trial. The trial also excluded patients with thrombosis in the main trunk of the portal vein.

Risks and uncertainties of risk

In general, the safety and tolerability of tremelimumab administered in combination with durvalumab was consistent with the known safety profile for each agent, and the safety profile observed was expected in a population who may also have underling liver disease. The T300+D regimen has an acceptable tolerability compared to sorafenib, and AEs were manageable per toxicity management guidelines. No unexpected safety events were noted with T300+D. Notably, as expected, there is an increased risk of immune-mediated AEs (imAEs) observed following tremelimumab and durvalumab treatment, as observed for other dual checkpoint inhibitor (for example, PD-L1 inhibitor plus CTLA4 inhibitor) regimen.

In the HIMALAYA trial:

Overall incidence of AEs was similar in the T300+D (97.4%) and sorafenib (95.5%) arms; AE profile differed as expected:

- Most frequent AEs in the T300+D arm were diarrhoea (26.5%), pruritus (22.9%), rash (22.4%), decreased appetite and fatigue (17.0% each) and pyrexia (12.9%). AE profile for sorafenib as established, including palmar-plantar erythrodysaesthesia syndrome (46.5%), fatigue (19.0%), hypertension (18.2%) and abdominal pain (16.8%).
- Most events that were reported at a ≥5% greater frequency in the T300+D arm compared with those reported in the sorafenib arm are known ADRs for durvalumab or tremelimumab (pruritus, rash, aspartate aminotransferase increased, and hypothyroidism).

Grade 3 or 4 adverse events: 50.5% in the T300+D arm versus 52.4% in the sorafenib arm; lower in the durvalumab treatment arm (37.1%).

- two most frequent Grade 3 or 4 AEs (≥ 5% patients) in the T300+D arm were AST increased and lipase increased.

Treatment-related adverse events: higher in the T300+D and sorafenib arms

- approximately 25% Grade 3 or 4, driven by transient elevations in liver transaminases and symptomatic increases in amylase/lipase.

Treatment-related serious adverse events: 17.5% in the T300+D arm versus 9.4% in the sorafenib arm and 8.2% in the durvalumab arm.

Frequencies of AEs resulting in treatment discontinuation: 13.7% in the T300+D arm versus 16.8% in the sorafenib arm; lowest in the durvalumab monotherapy arm (8.2%).

Frequency of treatment-related haemorrhage was highest in the sorafenib arm (4.8%) compared to T300+D (1.8%) and durvalumab (0.8%).

- Incidence of fatal haemorrhage is similar across treatment arms (D, 1.5%; T300+D, 2.1%; T75+D, 0.7%; S, 1.3%)

Treatment-related fatal haemorrhages were not reported in the immuno-oncology-containing treatment arms, with only two identified in the sorafenib arm (0.5%). No treatment-related oesophageal variceal haemorrhagic events were reported in the T300+D or sorafenib arms. T300+D was also not associated with increased bleeding risk, despite no requirement for recent endoscopy for study entry.

Hepatic adverse events:

- The incidence of AESIs/AEPIs of hepatic events (grouped term) were similar in all treatment arms: 24.5%. 24.7%, 21.7% and 21.1% in the D, T300+D, T75+D and sorafenib treatment arms, respectively.

- Hepatic events determined as immune mediated AEs were reported in 6.7%, 7.5%, 9.2% and 0.3%, respectively.

Immune mediated adverse events: 35.8% in the T300+D arm versus 16.5% in the durvalumab monotherapy arm

- 1.5% of patients (n = 6) in the T300+D arm died due to imAEs (pneumonitis, 3 hepatic events, myocarditis, and myasthenia gravis); there were no fatal imAEs in the other treatment arms.
- Diarrhoea or colitis imAEs were uncommon (5.9% in the T300+D arm versus 0.8% in the durvalumab arm versus 0.3% in the sorafenib arm). However, serious imAEs of diarrhoea/colitis were reported at a higher frequency in the tremelimumab-containing treatment arms (T300+D, 3.4%; T75+D, 3.3%) compared with the durvalumab (0.5%) and sorafenib (0%) arms. Discontinuations due to imAEs of diarrhea/colitis only occurred in the durvalumab (0.3%) and T300+D (1.3%) arms. There were no deaths due to imAEs of diarrhoea or colitis.
- Incidence of dermatitis or rash imAEs was low (4.9% in the T300+D arm versus 0.8% in the durvalumab arm versus 3.5% in the sorafenib arm). Serious imAEs of dermatitis or rash and discontinuations were infrequent.

The risk of myasthenia gravis, pancreatic events, hypersensitivity or anaphylactic reactions, infusion reaction AEs is noted; the risk of immunogenicity is also noted. Across the AE profile, there was no marked difference in categorical AE data for patients positive for either durvalumab or tremelimumab ADA compared with ADA-negative patients.

Benefit-risk balance

Overall, the benefit-risk assessment for tremelimumab in combination with durvalumab for the treatment of patients with uHCC is considered to be positive. The improvement in median OS was 2.7 months in the pivotal HIMALAYA trial (16.43 months for T300+D versus 13.77 months for sorafenib; HR = 0.78) with a sustained OS benefit over time; this improvement in OS is considered to be statistically significant and clinically meaningful. Evidence of contribution of tremelimumab to the proposed T300+D regimen was provided by numerically better outcomes for OS, objective response rate, best objective response, disease control rate and duration of response in the T300+D compared to durvalumab monotherapy in the HIMALAYA trial.

The safety and tolerability of tremelimumab in combination with durvalumab was consistent with the known safety profile for each agent and AEs were overall manageable. The safety profile demonstrated is acceptable when considered in the context of a serious and life-threatening condition such as uHCC.

Proposed action

The benefit risk assessment for tremelimumab in combination with durvalumab is considered to be favourable; the Delegate therefore supports the registration of tremelimumab for the following indication:

> *Imjudo in combination with durvalumab is indicated for the treatment of adult patients with unresectable hepatocellular carcinoma*

The Delegate will seek the opinion of ACM regarding whether the available evidence from Study 22 is adequate to support use of T300+D in the second line setting.

Advisory Committee considerations

The Advisory Committee on Medicines (ACM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following.

Specific advice to the Delegate

1. ***Does the available data support the use of tremelimumab in combination with durvalumab in the proposed population, including its use in the second line/subsequent setting?***

The ACM noted that the provided randomised data is for the first line treatment setting only. In Study 22 (a single arm study), tremelimumab in combination with durvalumab did appear to have similar activity in the second line setting. However, this statement is based on a small subset (patients who had uHCC) within Study 22.

With regards to the proposed wording for the indication, the ACM recommended specifying use only in patients without prior treatment with a programmed cell death protein 1 (PD-1) or a programmed death-ligand 1 (PD-L1) inhibitor, as this aligns with the clinical data provided.

The ACM discussed the efficacy of combination therapy compared to monotherapy within this setting. It was noted that tremelimumab has a similar mechanism of action to ipilimumab and combination data for ipilimumab with nivolumab post-sorafenib received accelerated approval by the United States Food and Drug Administration (FDA). However, this was a single arm study with no control arm. The ACM noted that it seems likely the CTLA4 combination may be more useful than the single agent and this is supported for tremelimumab/durvalumab by post sorafenib data in a single arm study. However, due to limitations of the study design, the ACM was of the view that the submitted studies could lead to conclusions regarding toxicity difference, but not compare the efficacy outcomes between the proposed dosing regimen to the monotherapy.

2. ***Any other advice?***

[The ACM has no further advice.]

Conclusion

The ACM considered this product to have an overall positive benefit-risk profile for the indication:

> *Imjudo in combination with durvalumab is indicated for the treatment of adult patients with unresectable hepatocellular carcinoma who have not received prior treatment with a PD-1/PD-L1 inhibitor.*

Outcome

Based on a review of quality, safety, and efficacy, the TGA approved the registration of Imjudo (tremelimumab) 25 mg/1.25 mL and 300 mg/15 mL, concentrated solution for injection, vial:

> ***Hepatocellular carcinoma (HCC)***
>
> *Imjudo in combination with durvalumab is indicated for the treatment of adult patients with unresectable hepatocellular carcinoma (uHCC) who have not received prior treatment with a PD-1/PD-L1 inhibitor.*

Specific conditions of registration applying to these goods

- Imjudo (tremelimumab) is to be included in the Black Triangle Scheme. The PI and CMI for Imjudo must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date that the sponsor notifies the TGA of supply of the product.
- The Imjudo EU-risk management plan (RMP) (version 2.0 succession 4.0, dated 27 December 2022, data lock point 27 August 2021), with Australian specific annex (version 1.0 succession 3.0, dated 16 March 2023), included with Submission PM-2022-01514-1-4, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

  An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).

  Unless agreed separately between the supplier who is the recipient of the approval and the TGA, the first report must be submitted to TGA no later than 15 calendar months after the date of the approval letter. The subsequent reports must be submitted no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of the approval letter. The annual submission may be made up of two PSURs each covering six months. If the sponsor wishes, the six monthly reports may be submitted separately as they become available.

  If the product is approved in the EU during the three years period, reports can be provided in line with the published list of EU reference dates no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of the approval letter.

  The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on Good Pharmacovigilance Practices (GVP) Module VII- periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration. Each report must have been prepared within ninety calendar days of the data lock point for that report.
- It is a condition of registration that all batches of Imjudo tremelimumab imported into/manufactured in Australia must comply with the product details and specifications approved during evaluation and detailed in the Certified Product Details (CPD).

  Laboratory testing & compliance with Certified Product Details (CPD)

  – All batches of Imjudo tremelimumab supplied in Australia must comply with the product details and specifications approved during evaluation and detailed in the Certified Product Details (CPD).

  – When requested by the TGA, the sponsor should be prepared to provide product samples, specified reference materials and documentary evidence to enable the TGA to conduct laboratory testing on the Product. Outcomes of laboratory testing are published biannually in the TGA Database of Laboratory Testing Results http://www.tga.gov.au/ws-labs-index and periodically in testing reports on the TGA website.

Attachment 1. Product Information

The PI for Imjudo approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA PI/CMI search facility.

Therapeutic Goods Administration

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Reference/Publication #