Australian Government
Department of Health and Aged Care
Therapeutic Goods Administration

Australian Public Assessment Report for Imfinzi

Active ingredient: Durvalumab

Sponsor: AstraZeneca Pty Ltd

December 2023

About the Therapeutic Goods Administration (TGA)

- 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.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety, and efficacy.
- 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.
- The TGA relies on the public, healthcare professionals and industry to report problems with therapeutic goods. The TGA investigates reports received to determine any necessary regulatory action.
- To report a problem with a therapeutic good, please see the information on the TGA website.

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
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ARTG	Australian Register of Therapeutic Goods
BCLC	Barcelona clinic liver cancer
CD	Cluster of differentiation
CI	Confidence interval
C_{max}	Maximum serum concentration
CMI	Consumer Medicines Information
CTLA	Cytotoxic T-lymphocyte-associated antigen
C_{trough}	Trough serum concentration
ECOG	Eastern Cooperative Oncology Group
ES	Extensive-stage
ESMO	European Society for Medical Oncology (
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
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
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
SCLC	Small cell lung cancer
TGA	Therapeutic Goods Administration
uHCC	Unresectable hepatocellular carcinoma
US(A)	United States of America
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:	Extension of indications
Product name:	Imfinzi
Active ingredient:	Durvalumab
Decision:	Approved
Date of decision:	19 June 2023
Date of entry onto ARTG:	20 June 2023
ARTG numbers:	283215 and 283216
, Black Triangle Scheme	No
for the current submission:	
Sponsor's name and address:	AstraZeneca Pty Ltd 66 Talavera Road Macquarie Park NSW 2113
Dose form:	Concentrated solution for infusion
Strengths:	120 mg and 500 mg
Container:	Vial
Pack size:	One
Approved therapeutic use for the current submission:	***Hepatocellular carcinoma (HCC)*** *Imfinzi in combination with tremelimumab 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
Dosage:	Imfinzi is for single use in one patient only. The recommended dose of Imfinzi depends on the indication as presented in Table 1 of the Product Information. Imfinzi is administered as an intravenous infusion over one hour. 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 Imfinzi (durvalumab) 120 mg and 500 mg, concentrated solution for infusion, vial for the following proposed extension of indications:[1]

> *Imfinzi in combination with tremelimumab is indicated for the treatment of patients with unresectable hepatocellular carcinoma (uHCC)*

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 represents about 90% of primary liver cancers.[2] The incidence of hepatocellular carcinoma (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]

The majority patients with HCC have underlying hepatitis B virus (HBV) and/or hepatitis C virus (HCV); 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 regions, 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]

The HCC prognosis and treatment depend on factors such as tumour burden, degree of liver dysfunction and clinical performance status. 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] The presence of underlying cirrhosis and other liver disease in majority of patients makes unresectable HCC a difficult-to-treat disease.

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[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)

[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.

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 variations in incidence with 2.4-fold higher rates of diagnosis and mortality in Indigenous Australians compared with non-Indigenous population.[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]

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 A[13] cirrhosis.[14]

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

Sorafenib, an oral tyrosine-kinase inhibitor targeting multiple kinases, was until recently 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, was approved as first-line treatment for advanced HCC in patients without main portal vein invasion and Eastern Cooperative Oncology Group

[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/

[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.

Performance Status (ECOG 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 European Society for Medical Oncology (ESMO) guidelines.[22,23,24]

In patients with HCC, second-line systemic therapy is recommended for suitable patients who have progressed on multi-kinase inhibitors and who have preserved liver function and good performance status. Second line treatments approved by the TGA include regorafenib, cabozantinib, and nivolumab. In addition, there is Phase III clinical trial evidence of improved survival to support the use of ramucirumab in patients who have progressed on (or are intolerant to) sorafenib (in those with α-fetoprotein level >400 ng/mL); ramucirumab is not approved in Australia for treatment of patients with HCC. Pembrolizumab (an anti-programmed cell death-1 (anti-PD-1) antibody) was granted accelerated approval by the United States (US) Food and Drug Administration (FDA) 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; pembrolizumab is not approved in Australia for the treatment of patients with HCC.

While sorafenib demonstrates a manageable tolerability profile in patients with advanced HCC, quality of life is often limited by certain adverse events (AEs) such as diarrhea, hand-foot skin reaction, and fatigue. First-line combination therapy with intravenous atezolizumab and bevacizumab 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 vascular endothelial growth factor receptor (VEGFR) tyrosine-kinase inhibitors) can exacerbate the pre-existing hepatopathy and increase the risk of liver-related AEs.

Hence, there is a need for other effective, safe and tolerable first-line systemic therapies in patients with uHCC.

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[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.

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 cluster of differentiation (CD)80 (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 antibody 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.

Tremelimumab is a human IgG2 monoclonal antibody directed against cytotoxic T-lymphocyte-associated antigen (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 CD80 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.

Targeting both the PD-1 and CTLA-4 pathways using dual checkpoint blockade could result in a potential additive anti-tumour 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.[25,26]

Regulatory status

The product received initial registration on the Australian Register of Therapeutic Goods (ARTG) on 2 October 2018. At the time that this submission was considered it was approved for the following indications:

Locally advanced non-small cell lung cancer (NSCLC)

Imfinzi is indicated for the treatment of patients with locally advanced, unresectable NSCLC whose disease has not progressed following platinum-based chemoradiation therapy.

Small cell lung cancer (SCLC)

Imfinzi in combination with etoposide and either carboplatin or cisplatin is indicated for the first-line treatment of patients with extensive-stage small cell lung cancer (ES-SCLC).

Malignant pleural mesothelioma (MPM)

Imfinzi in combination with pemetrexed and either cisplatin or carboplatin has provisional approval for the first-line treatment of patients with unresectable MPM with epithelioid histology.

The decision to approve this indication has been made on the basis of two phase 2 single arm studies. Continued approval of this indication depends on verification and description of clinical benefit in a confirmatory trial.

Biliary tract cancer (BTC)

[25] 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.

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

Imfinzi in combination with gemcitabine and cisplatin is indicated for the treatment of patients with locally advanced or metastatic biliary tract cancer (BTC).

At the time the TGA considered this submission, similar submissions had been approved in the European Union on 30 January 2023, United States of America on 21 October 2022, and Japan on 23 December 2022. A similar submission was under consideration in Singapore (submitted on 20 April 2022).

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

Table 1: International regulatory status

Region	Submission date	Status	Approved indications
European Union	6 April 2022	Approved on 30 January 2023	Imfinzi in combination with tremelimumab is indicated for the first line treatment of adults with advanced or unresectable hepatocellular carcinoma (HCC).
United States of America	22 April 2022	21 October 2022	Imfinzi is a programmed death-ligand 1 (PD-L1) blocking antibody indicated in combination with tremelimumab, for the treatment of adult patients with unresectable hepatocellular carcinoma (uHCC).
Japan	25 February 2022	23 December 2022	Unresectable hepatocellular carcinoma (uHCC)
Singapore	20 April 2022	Under consideration	Under consideration

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-2022-01573-1-4

Description	Date
Submission dossier accepted and first round evaluation commenced	31 May 2022
First round evaluation completed	1 November 2022
Sponsor provides responses on questions raised in first round evaluation	30 November 2022
Second round evaluation completed	16 January 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	20 June 2023
Number of working days from submission dossier acceptance to registration decision*	238

*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.

The following guideline was referred to by the Delegate as being relevant to this submission:

- 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):801-805.

Quality

Quality evaluation is not required for this submission as there are no proposed changes to the quality of the currently approved product in Australia. The quality of the currently approved product is suitable for the proposed changes in this submission. A full quality evaluation was conducted at the time this product received initial registration.

Nonclinical

No new nonclinical data or further nonclinical evaluation were required for this submission. The TGA considers that previously submitted and evaluated data satisfactorily address nonclinical aspects of safety/efficacy relating to this submission.

Clinical

Summary of clinical studies

The clinical dossier consisted of:

- One Phase I/II supportive study: Study D4190C00022 (also known as Study 22)
- One Phase III pivotal study: Study D419CC00002 (also known as the HIMALAYA trial)

Since Imfinzi and Imjudo are proposed to be used in combination for the proposed uHCC indication, the two Submissions PM-2022-01573-1-4 and PM-2022-01514-1-4 are related and share the same clinical supporting data. For further details regarding the HIMALAYA trial and Study 22, please refer to AusPAR for Submission PM-2022-01514-1-4.

Pharmacology

Durvalumab is a fully human, high affinity, IgG1 kappa monoclonal antibody that blocks the interaction of PD-L1 with PD-1 and CD80.

Pharmacokinetics

Absorption, distribution, metabolism and excretion

- Imfinzi (50 mg/mL) aqueous solution is to be administered via intravenous infusion.
- In patients with advanced HCC, following intravenous infusion of 20 mg/kg durvalumab once every 4 weeks, no durvalumab accumulation, in terms of maximum serum concentration (C_{max}) and trough serum concentration (C_{trough}), was observed. By contrast, following 1500 mg once every 4 weeks, durvalumab accumulation was identified and the accumulation ratios for C_{max} and C_{trough} were 1.42 and 1.54, respectively.
- Central volume of distribution (V1) and peripheral volume of distribution (V2) for durvalumab were 3.45 L and 2.13 L, respectively.
- Durvalumab is not primarily cleared via hepatic or renal pathways; instead, the primary elimination pathways of durvalumab are protein catabolism via reticuloendothelial system or target mediated disposition.
- Durvalumab clearance is estimated to be low (0.277 L/day).

Inter-subject variability

The inter-subject variability on durvalumab clearance and V1 were 0.09 L/day and 0.052 L, respectively. The proportional and additive components of the associated residual variability were 0.25 and 4.28, respectively.

Special populations

Population pharmacokinetic (PK) analysis indicated that tumour type, gender, body weight, serum albumin, creatinine clearance, lactate dehydrogenase, age (<65 years, between 65 and 75 years, >75 years), renal and hepatic function (normal, mild, moderate), race, region, anti-drug antibody (ADA) and ECOG PS are unlikely to affect durvalumab exposure to any clinically significant extent.

Population pharmacokinetics

The updated analysis indicated that durvalumab PK data could be described by a 2-compartment model with time-dependent elimination.

Drug-drug interactions

No formal drug-drug interaction studies have been conducted with durvalumab. However, adverse drug-drug interactions between durvalumab and other therapeutics is not anticipated given its clearance pathways. In addition, no interactions between durvalumab and etoposide and carboplatin, cisplatin or tremelimumab has been identified.

Although the PK data provided is limited, the proposed PI generally appears to accurately reflect this information.

Pharmacodynamics

Primary pharmacodynamics

Substantial and consistent increases in CD4+Ki67+T-cells were observed following treatment with T75+D, T300+D[27] or tremelimumab 750 mg once every 4 weeks monotherapy that were associated with increasing tremelimumab dose.

Patients receiving T300+D or tremelimumab monotherapy exhibited the highest elevations in CD8+Ki67+T-cells that correspond with complete response or partial response.

Secondary pharmacodynamics

Following durvalumab administration to patients with uHCC, the number of treatment-emergent ADA-positive patients was low; ADA titres were also low as was the number of patients developing neutralising antibodies for durvalumab.

Exposure-response

There were no relationships between simulated durvalumab exposure metrics and OS or PFS.

There were no relationships between simulated durvalumab exposure and >Grade 3 drug-related AEs, >Grade 3 drug-related adverse events of special interest (AESIs) or AEs leading to durvalumab discontinuation.

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 HCC.

The Delegate also notes the publication by Abou-Alfa et al. (2022).[28]

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 in combination with tremelimumab or bevacizumab in subjects with advanced HCC.

[27] 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.

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

Summary of clinical efficacy

The clinical evaluation's main findings 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 (ORR) and duration of response per Response Evaluation Criteria In Solid Tumours (RECIST) version 1.1[29] blinded independent central review (BICR) 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 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%), Barcelona clinic liver cancer (BCLC)[30] Stage C (80.8%), ECOG PS 0 (62.6%); Child-Pugh Class score A (99.5%), macrovascular invasion (25.2%), extrahepatic spread (53.4%), viral etiology; hepatitis B (30.6%), hepatitis C (27.2%), uninfected (42.2%).
- Baseline demographics and disease characteristics were generally balanced across treatment groups. Patients with oesophageal varices were included except those with active or prior documented GI bleeding within 12 months prior to study entry; a total of 93 patients (7%) with history of oesophageal 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 or other vascular endothelial growth factor (VEGF) inhibitors.
- The main efficacy results from HIMALAYA trial and Study 22 are summarised in Table 3 below.

[29] 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.

[30] The **Barcelona Clinic Liver Cancer (BCLC) staging system** looks at the number and size of tumours in the patient's liver, Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) and the liver function using Child-Pugh score. There are 5 stages to the BCLC staging system.
Stage 0 (very early stage): tumour is less than 2 cm, ECOG PS 0 and Child-Pugh A.
Stage A (early stage): a single tumour of any size, or up to 3 tumours all less than 3 cm, ECOG PS 0, and Child-Pugh A or B.
Stage B (intermediate stage): many tumours in the liver, ECOG PS 0 and Child-Pugh A or B.
Stage C (advanced stage): cancer has spread into the blood vessels, lymph nodes or other body organs or ECOG PS 1 or 2, Child-Pugh A or B.
Stage D: Child-Pugh C, or ECOG PS 3 or 4.

Table 3: 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.

- 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 (hazard ratio (HR) = 0.78; 96.02% confidence interval (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 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 ORR 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 were 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 (ORR 24.0% and best objective response of complete response 1.3% or partial response 22.7%).
- Median time to onset of objective response 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 (time to onset of objective response: 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 trial 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 demonstrated 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 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 durvalumab) 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 durvalumab, 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 durvalumab, 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 (in 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 ORR 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.[31] 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.

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.

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 were similar for T330+D (97.4%) and sorafenib (95.5%).
- The commonest AEs in the sorafenib arm were palmar-plantar erythrodysesthesia, 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%), aspartate aminotransferase (AST) increased (14.4%), decreased appetite (13.7%), asthenia 12.6%) and alanine aminotransferase (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 treatment-related AEs 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.

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

- 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%). Seven 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 immune-related adverse events (irAEs) was low (≤5.7% patients per arm).
  - There were 1.5% of patients in the T300+D arm died due to irAEs (pneumonitis, hepatic events, myocarditis, and myasthenia gravis).
  - Diarrhoea or 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 or rash irAEs were uncommon (T330+D 4.9% versus durvalumab alone 0.8% versus sorafenib 3.5%).
- Hepatic AEs and hepatic treatment-related AEs were comparable across all treatment arms. The addition of tremelimumab did not significantly increase hepatotoxicity and the majority of treatment-related AEs were low overall and were predominantly Grade 1 or 2 events.
- Haemorrhagic events were low across all treatment arms: treatment related hemorrhage 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 adverse drug reactions 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.

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 + ipilimumab) was also observed following tremelimumab and durvalumab treatment in this submission.

Recommendation following the clinical evaluation

In summary, the Clinical Evaluator's overall assessment included the following:

> 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/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 PS 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 (400mg twice daily orally) as the comparator in the pivotal Phase III study was appropriate. Evidence of efficacy/safety 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 PS 0).
>
> Durvalumab demonstrated an acceptable safety profile consistent with that known for durvalumab and a better safety profile when compared to sorafenib. 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 manageable according to toxicity management guidelines. Although more toxicity was observed with the T300+D compared to durvalumab, T300+D did not significantly increase treatment related hepatotoxicity, as evidenced by the incidence of hepatic disorder. Treatment-related AEs associated with VEGF inhibitors, such as hypertension, proteinuria and bleeding events,[32] were rare or not observed in the HIMALAYA trial with T300+D. The T300+D regimen was not associated with increased bleeding risk in the HIMALAYA trial suggesting that T300+D may be administered without the requirement for recent endoscopy although this was not specifically addressed in the submitted studies.
>
> There was lack of adequate evidence of efficacy/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.

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

> Hence, the benefit-risk profile is not favourable for proposed indication but can become favourable if [the specific comments raised by clinical evaluation][33] 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's recommendation was that Imfinzi 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:

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

The sponsor's response 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 durvalumab (Imfinzi) is favourable for the following proposed indication:
>
> > *Imfinzi in combination with tremelimumab is indicated for the treatment of patients with unresectable hepatocellular carcinoma (uHCC).*

[33] Inclusion of this information is beyond the scope of this AusPAR.

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

> Despite limitations regarding submitted evidence of efficacy/safety as second-line of systemic treatment for adults 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 Imfinzi be approved for the following indication:
>
> > *Imfinzi in combination with tremelimumab is indicated for the treatment of patients with unresectable hepatocellular carcinoma (uHCC).*

Risk management plan

The sponsor is required to comply with product vigilance and risk minimisation requirements.

The TGA decided a RMP was not required (see TGA's guidance on 'when an RMP is required')

The TGA may request an updated RMP at any stage of a product's life-cycle, during both the pre-approval and post-approval phases. Further information regarding the TGA's risk management approach can be found in risk management plans for medicines and biologicals and the TGA's risk management approach. Information on the Australia specific annex (ASA) can be found on the TGA website.

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 HCC, with an incidence of 8.9 per 100,000 and an associated 2,424 deaths. 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.[34] 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 HBV and HCV, cirrhosis secondary to alcohol or non-alcoholic fatty liver disease, and other rarer conditions such as hereditary 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.[35] At present, molecular profiling may be considered in patients

[34] Australian Institute of Health and Welfare (AIHW) Cancer in Australia 2021, last updated 15 August 2023. Available at: https://www.aihw.gov.au/reports/cancer/cancer-in-australia-2021/summary.
[35] Zehir A et al. Mutational landscape of metastatic cancer revealed from prospective clinical sequencing of 10,000 patients. Nat Med, 2017;23:703-13.

with advanced disease in order to determine eligibility into clinical trials of new molecular targeted agents such as IDH1, IDH2, FGF and KRAS.[36] 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.[37]

Current treatment options

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

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 (single tremelimumab regular interval 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 3 HIMALAYA trial which forms the basis of this submission.

Proposed indication

The sponsor is seeking registration for the use of Imfinzi in combination with tremelimumab, with the proposed indication as follows:

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

The proposed recommended Imfinzi dose is 1500 mg at Cycle 1 Day 1, in combination with a single 300 mg tremelimumab priming dose, followed by Imfinzi as monotherapy every 4 weeks. (Patients with a body weight of 30 kg or less must receive weight-based dosing, equivalent to Imfinzi 20 mg/kg and tremelimumab 4 mg/kg until weight is greater than 30 kg. Tremelimumab should be administered prior to Imfinzi on the same day.)

Benefits and uncertainties of benefit

Pivotal study: HIMALAYA trial, a phase III, open-label, randomised study

[36] 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.
[37] Sia D et al. Identification of an immune-specific class of hepatocellular carcinoma, based on molecular features. *Gastroenterology*, 2017;153:812-26.

- Tremelimumab + durvalumab (T300+D): n = 393
- Durvalumab: n = 389
- Sorafenib: 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: overall survival 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, TTP, ORR 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 durvalumab) 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 durvalumab, 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 durvalumab, 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 overall survival 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 ORR 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 or limitations include the following:

- Subgroup analyses did not show improvements in overall survival 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 + 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%). Adverse event 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 adverse drug reactions for durvalumab or tremelimumab (pruritus, rash, aspartate aminotransferase increased, and hypothyroidism).

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

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

Treatment-related AEs: 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 SAEs: T300+D = 17.5% versus 9.4% in sorafenib arm and 8.2% in durvalumab arm.

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

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

- Incidence of fatal hemorrhages similar across treatment arms (durvalumab 1.5%; T300+D, 2.1%; T75+D, 0.7%; sorafenib, 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 AEs:

- The incidence of AESIs / adverse events of potential interest of hepatic events (grouped term) were similar in all treatment arms: 24.5%. 24.7%, 21.7% and 21.1% in the durvalumab, 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 AEs: T300+D = 35.8% versus 16.5% in durvalumab monotherapy arm.

- There were 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/colitis imAEs were uncommon (T300+D = 5.9% versus durvalumab = 0.8% versus sorafenib = 0.3%). 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/colitis.
- Incidence of dermatitis/rash imAEs was low (T300+D = 4.9% versus durvalumab = 0.8% versus sorafenib = 3.5%). Serious imAEs of dermatitis/rash and discontinuations were infrequent.

The risk of myasthenia gravis, pancreatic events, hypersensitivity/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 unresectable hepatocellular carcinoma is considered to be positive. The improvement in median overall survival 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, ORR, 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 adverse events were overall manageable. The safety profile demonstrated is acceptable when considered in the context of a serious and life-threatening condition such as unresectable hepatocellular carcinoma.

Proposed action

The benefit risk assessment for tremelimumab in combination with durvalumab is considered to be favourable in adult patients with unresectable hepatocellular carcinoma. The delegate therefore supports the registration of durvalumab for the following indication:

> *Imfinzi in combination with tremelimumab 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 unresectable hepatocellular carcinoma) 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 PD-1 or a 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 US 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.

Conclusion

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

> *Imfinzi in combination with tremelimumab 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.*

Outcome

Based on a review of quality, safety, and efficacy, the TGA approved the registration of Imfinzi (durvalumab) 120 mg and 500 mg, concentrated solution for infusion, vial, for the following extension of indications:

> ***Hepatocellular carcinoma (HCC)***
>
> *Imfinzi in combination with tremelimumab 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.*

As such, the full indications at this time were:

> ***Locally advanced non-small cell lung cancer (NSCLC)***
>
> *Imfinzi is indicated for the treatment of patients with locally advanced, unresectable NSCLC whose disease has not progressed following platinum-based chemoradiation therapy.*
>
> ***Small cell lung cancer (SCLC)***
>
> *Imfinzi in combination with etoposide and either carboplatin or cisplatin is indicated for the first-line treatment of patients with extensive-stage small cell lung cancer (ES-SCLC).*
>
> ***Malignant pleural mesothelioma (MPM)***
>
> *Imfinzi in combination with pemetrexed and either cisplatin or carboplatin has provisional approval for the first-line treatment of patients with unresectable MPM with epithelioid histology.*

The decision to approve this indication has been made on the basis of two phase 2 single arm studies. Continued approval of this indication depends on verification and description of clinical benefit in a confirmatory trial.

Biliary tract cancer (BTC)

Imfinzi in combination with gemcitabine and cisplatin is indicated for the treatment of patients with locally advanced or metastatic biliary tract cancer (BTC).

Hepatocellular carcinoma (HCC)

Imfinzi in combination with tremelimumab 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.

Attachment 1. Product Information

The PI for Imfinzi 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.

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Reference/Publication #