5.02 DURVALUMAB

Solution concentrate for I.V. infusion 500 mg in 10 mL, Solution concentrate for I.V. infusion 120 mg in 2.4 mL, Imfinzi®

TREMELIMUMAB

Solution concentrate for I.V. infusion 300 mg in 15 mL, Imjudo®,

Astra Zeneca Pty Ltd

1 Purpose of submission

1.1 The Category 2 submission requested a Section 100 (Efficient Funding of Chemotherapy program), Authority Required (Streamlined) Pharmaceutical Benefits Scheme (PBS) listing for durvalumab in combination with tremelimumab for the first-line treatment of patients with advanced (unresectable) Barcelona Clinic Liver Cancer (BCLC) Stage B or Stage C hepatocellular carcinoma (HCC). The treatment course of 1,500 mg administered in combination with tremelimumab 300 mg as a single dose at Cycle 1, Day 1, followed by durvalumab 1,500 mg monotherapy every four weeks until disease progression is herein referred to as STRIDE (Single Tremelimumab Regular Interval Durvalumab).

1.2 Listing was requested on the basis of a cost-minimisation approach (CMA) versus atezolizumab plus bevacizumab (atezo + b), based on an anchored indirect treatment comparison (ITC). Key components of the submission are summarised in Table 1.

Table 1: Key components of the clinical issue addressed by the submission

Component	Description
Population	Patients with advanced (unresectable) BCLC Stage B or Stage C HCC
Intervention	Durvalumab 1,500 mg administered in combination with tremelimumab 300 mg as a single dose at Cycle 1/Day 1, followed by durvalumab 1,500 mg monotherapy Q4W until disease progression.
Comparator	Atezolizumab 1,200 mg in combination with bevacizumab 15 mg/kg Q3W until disease progression
Outcomes	OS, PFS, ORR, PROs, safety
Clinical claim	In patients with advanced (unresectable) BCLC Stage B or Stage C HCC, STRIDE is non-inferior in terms of efficacy and safety when compared to atezolizumab plus bevacizumab

Source: Table 1-1, pp 29-30 of the submission.
BCLC = Barcelona Clinic Liver Cancer; HCC = hepatocellular carcinoma; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PROs = patient reported outcomes; Q3W = every 3 weeks; Q4W = every four weeks; STRIDE = Single Tremelimumab Regular Interval Durvalumab.

2 Background

Registration status

2.1 Durvalumab in combination with tremelimumab was Therapeutic Goods Administration (TGA) registered in June 2023 for the treatment of adult patients with

unresectable HCC who have not received prior treatment with a human programmed death/-ligand 1 (PD-1/PD-L1) inhibitor.

For more detail on PBAC's view, see section 7 PBAC outcome.

3 Requested listing

3.1 Suggested additions are in italics and deletions are in strikethrough.

Tremelimumab – initial once-off treatment

MEDICINAL PRODUCT **Form**	**PBS item code**	**Max. Amount**	**№.of Rpts**
TREMELIMUMAB Injection	{NEW (Public)} {NEW (Private)}	300mg	0
Available brands			
Imjudo (300 mg/15mL injection, 15 mL vial)			
Restriction Summary [new1]/ Treatment of Concept: [new1A]			
Category / Program: Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals			
Prescriber type: ☒Medical Practitioners			
Restriction type: ☒Authority Required (STREAMLINED) [NEW]			
Administrative Advice: No increase in the maximum amount or number of units may be authorised.			
Administrative Advice: No increase in the maximum number of repeats may be authorised.			
Administrative Advice: Special Pricing Arrangements apply.			
Severity: Advanced (unresectable) Barcelona Clinic Liver Cancer Stage B or Stage C ~~hepatocellular carcinoma~~			
Condition: Hepatocellular carcinoma			
Indication: Advanced (unresectable) Barcelona Clinic Liver Cancer Stage B or Stage C hepatocellular carcinoma			
Treatment Phase: Initial *(once-off)* treatment			
Clinical criteria:			
Patient must be undergoing combination treatment with *PBS subsidised* durvalumab.			
AND			
Clinical criteria:			
Patient must have a WHO performance status of 0 or 1,			
AND			
Clinical criteria:			
Patient must not be suitable for transarterial chemoembolisation			
AND			
Clinical criteria:			
Patient must have Child Pugh class A			
AND			
Clinical criteria:			
The condition must be untreated with systemic therapy; **OR**			

Patient must have developed intolerance *of a severity necessitating permanent treatment withdrawal, in the absence of disease progression* to *any of the following: (i)* atezolizumab + *bevacizumab combination therapy;* ~~or~~ *(ii)* a vascular endothelial growth factor (VEGF) inhibitor *tyrosine kinase inhibitor (TKI)* ~~of a severity necessitating permanent treatment withdrawal.~~
AND
Treatment criteria:
Patient must not receive PBS-subsidised treatment with this drug for this indication more than once per lifetime

Durvalumab – initial and continuing treatment

MEDICINAL PRODUCT Form	**PBS item code**	**Max. Amount**	**№.of Rpts**
DURVALUMAB Injection	{NEW (Public)} {NEW (Private)}	1500mg	5
Available brands			
Imfinzi 500 mg/10 mL injection, 10 mL vial			
Imfinzi 120 mg/2.4 mL injection, 2.4 mL vial			
Restriction Summary [new2]/ Treatment of Concept: [new2A]			
Category / Program: Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals			
Prescriber type: ☒Medical Practitioners			
Restriction type: ☒Authority Required (STREAMLINED) [NEW]			
	Administrative Advice: No increase in the maximum amount or number of units may be authorised.		
	Administrative Advice: No increase in the maximum number of repeats may be authorised.		
	Administrative Advice: Special Pricing Arrangements apply.		
Severity: Advanced (unresectable) Barcelona Clinic Liver Cancer Stage B or Stage C hepatocellular carcinoma			
Condition: Hepatocellular carcinoma			
Indication: Advanced (unresectable) Barcelona Clinic Liver Cancer Stage B or Stage C hepatocellular carcinoma			
Treatment Phase: Initial treatment			
Clinical criteria:			
Patient must be undergoing combination treatment with tremelimumab for the first dose of treatment.			
AND			
Clinical criteria:			
Patient must have a WHO performance status of 0 or 1,			
AND			
Clinical criteria:			
Patient must not be suitable for transarterial chemoembolisation			
AND			
Clinical criteria:			
Patient must have Child Pugh class A			
AND			
Clinical criteria:			
The condition must be untreated with systemic therapy; **OR**			
Patient must have developed intolerance to atezolizumab or a vascular endothelial growth factor (VEGF) inhibitor of a severity necessitating permanent treatment withdrawal.			

Restriction Summary [new3]/ Treatment of Concept: [new3A]
Severity: Advanced (unresectable) Barcelona Clinic Liver Cancer Stage B or Stage C hepatocellular carcinoma
Condition: Hepatocellular carcinoma
Indication: Advanced (unresectable) Barcelona Clinic Liver Cancer Stage B or Stage C hepatocellular carcinoma
Treatment Phase: Continuing treatment
Clinical criteria:
Patient must have previously received PBS-subsidised treatment with this drug for this condition
AND
Clinical criteria:
Patient must not have developed disease progression while being treated with this drug for this condition.

3.2 Durvalumab is currently PBS listed for treatment of both small and non-small cell lung cancer, locally advanced, and metastatic or recurrent biliary tract cancer. The submission proposed a Special Pricing Arrangement (SPA) with the proposed effective AEMPs: $ per 15 mL vial for tremelimumab and $ per 500 mg/10 mL vial for durvalumab. The submission also proposed the 120 mg/2.4 mL vial for durvalumab at an equivalent price per mg.

3.3 The proposed restriction included a provision for commencing STRIDE treatment in patients who have developed intolerance to atezolizumab or a vascular endothelial growth factor (VEGF) inhibitor. The evaluation and ESC noted the proposed restriction was not consistent with the TGA product information (PI) for STRIDE, which states that tremelimumab in combination with durvalumab may be used only in adult patients with unresectable HCC who have not received prior treatment with a PD-1/PD-L1 inhibitor (and would therefore preclude prior treatment with atezolizumab). The Pre-Sub-Committee Response (PSCR) also stated a willingness from the Sponsor for the restriction to be based on PBAC's consideration of similar listings where switching due to intolerability is appropriate.

3.4 The criterion proposed for continuing treatment with STRIDE, 'Patient must not have developed disease progression while being treated with this drug for this condition' was not consistent with treatment provided in the pivotal trial, HIMALAYA. In HIMALAYA, patients who progressed on STRIDE were allowed to continue treatment. The potential applicability of this difference in the proposed listing and the trial evidence with regard to treatment beyond progression is discussed in paragraph 6.13.

3.5 In HIMALAYA patients were allowed to be rechallenged with a single dose of tremelimumab 300 mg and durvalumab 1,500 mg for one cycle, followed by durvalumab monotherapy 1,500 mg if they were deemed to be continuing to derive clinical benefit, but with evidence of progressed disease. This was inconsistent with the proposed PBS listing which provided for only a single dose of tremelimumab. This is discussed further in paragraph 6.13.

For more detail on PBAC's view, see section 7 PBAC outcome.

4 Population and disease

4.1 HCC is the most common form of primary liver cancer, accounting for approximately 90% of all liver cancer cases globally. In 2023, it was estimated 3,048 new cases of liver cancer were diagnosed, making liver cancer the twelfth most commonly diagnosed cancer and the sixth most common cause of cancer-related death in Australia[1]. Approximately 15-20% of patients present with advanced/unresectable HCC (aHCC), which limits the use of treatments with curative potential; for these patients, systemic therapy is considered the most appropriate treatment. The overall prognosis for patients with aHCC remains poor. Globally, the median overall survival (OS) for patients with intermediate- (BCLC Stage B) and for late-stage HCC (BCLC Stage Cor D) is 26 to 30 months and 8 to 19 months, respectively[2].

4.2 The target population was defined as patients with advanced (unresectable) BCLC Stage B or Stage C HCC who are not eligible for locoregional therapy and had not received prior systemic therapy. The PBAC have previously considered this patient population (atezolizumab Public Summary Document (PSD), July 2020 PBAC meeting).

4.3 Durvalumab is a checkpoint inhibitor; a high-affinity, human, recombinant IgG1κ monoclonal antibody which acts as a potent inhibitor of PD-L1 receptors[1]. Tremelimumab is a fully human IgG2 monoclonal antibody targeting the cytotoxic T-lymphocyte associated protein 4 (CTLA-4) receptor known as an immune checkpoint. By blocking the interaction between CTLA-4 and CD80/CD86, tremelimumab enables binding of CD28 to CD80/CD86, which enhances CD8+ T cell activation and function, resulting in increased release of cytokines from T cells and peripheral blood mononuclear cells, enhancing the immune response.

4.4 The submission stated that the combination of tremelimumab and durvalumab (STRIDE) was developed on the theory that simultaneous blockade of PD-L1 and CTLA-4 pathways by durvalumab and tremelimumab may result in complementary, longer-lasting immune effects, enhanced anti-tumour activity and improved patient outcomes.[3]

For more detail on PBAC's view, see section 7 PBAC outcome.

5 Comparator

5.1 The submission nominated atezo + b as the main comparator. The nomination of atezo + b as the comparator for the treatment naive population was appropriate and adequately justified. Atezo + b (a PD-L1 inhibitor + VEGF inhibitor) was recommended

[1] Cancer Australia. Liver cancer in Australia statistics. Australian Government (2024). URL: https://www.canceraustralia.gov.au/cancer-types/liver-cancer/statistics

[2] Llovet JM et al. Hepatocellular carcinoma. *Nat Rev Dis Primers*. 2021 Jan 21;7(1):6.

[3] Grosso JF,. CTLA-4 blockade in tumor models: an overview of preclinical and translational research. Cancer Immun. 2013;13:5.

as one of the preferred option to treat first-line aHCC in the most recent National Comprehensive Cancer Network (NCCN Version 1.2025), American Society of Clinical Oncology (ASCO) and European Society for Medical Oncology (ESMO) guidelines and is now standard of care in Australia[4,5,6]. The PSCR noted that the European Society for Medical Oncology (ESMO) guidelines were updated post-submission, in February 2025, and now include STRIDE as an equally preferred option to atezo + b (Vogel et al 2025[7]).

5.2 Both durvalumab and atezolizumab work by binding to and blocking the PD-L1 protein. Tremelimumab primarily acts early in the T cell response, increasing activation to create a diverse T cell response (CTLA-4 inhibitor), and after approximately 4 weeks, most of the active compound has been eliminated from the body. This means that after the first month of treatment with STRIDE, PD-L1 inhibitor monotherapy (durvalumab) is being compared to the ongoing administration of two active treatments (the combination of a PD-L1 inhibitor [atezolizumab] and VEGF inhibitor [bevacizumab]).

5.3 The submission's requested listing was for STRIDE to be given to patients who were unable to tolerate atezolizumab or a VEGF inhibitor, however it did not provide evidence for efficacy and safety in this population.

5.4 In the context of the cost-minimisation approach taken by the submission, a further consideration for PBAC was that, under Section 101(3B) of the *National Health Act 1953*, when the proposed medicine is substantially more costly than an alternative therapy, the committee cannot make a positive recommendation unless it is satisfied that, for some patients, the proposed medicine provides a significant improvement in efficacy and/or reduction of toxicity over the alternative therapy. If the committee is so satisfied, it must make a statement to this effect.

5.5 Nivolumab (a PD-L1) plus ipilimumab (a CTLA-4) is a potential near market comparator and is currently being investigated in the CheckMate 9DW trial in the same patient population. Its submission to the TGA was accepted in September 2024 and a submission has been made to the July 2025 PBAC meeting.

For more detail on PBAC's view, see section 7 PBAC outcome.

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[4] NCCN Clinical Practice Guidelines in Oncology: Hepatocellular Carcinoma (Version 2.2024). NCCN; July 2, 2024.
[5] Rose MG et al. Systemic Therapy for Advanced Hepatocellular Carcinoma: ASCO Guideline Update Clinical Insights. *JCO Oncology Practice*. 2024;20(8):1035-9.
[6] Vogel A et al. Updated treatment recommendations for hepatocellular carcinoma (HCC) from the ESMO Clinical Practice Guidelines. *Annals of Oncology*. 2021;32(6):801-5.
[7] Vogel A, Chan SL, Dawson LA, Kelley RK, Llovet JM, Meyer T, Ricke J, Rimassa L, Sapisochin G, Vilgrain V, Zucman-Rossi J, Ducreux M; ESMO Guidelines Committee. Hepatocellular carcinoma: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann Oncol. 2025 Feb 20:S0923-7534(25)00073-0. Epub ahead of print.

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

6.2 The PBAC noted and welcomed the input from health professionals (3) as well as the Medical Oncology Group of Australia (MOGA) and two consumer organisations (Pancare; Rare Cancers Australia) via the Consumer Comments facility on the PBS website. Comments from health professionals described the poor prognosis of HCC, the lack of effective treatment and limited treatment options. They noted that some patients do not tolerate existing treatments and experience serious side effects and that additional options for therapy with proven benefit would enable some patients to have long term tumour control and maintain quality of life.

6.3 Pancare noted that liver cancer is one of Australia's deadliest cancers and that HCC is the most common type and highlighted the limited treatment options for patients if the cancer is advanced or has spread beyond the liver.

6.4 Both Pancare and Rare Cancers Australia highlighted the financial burden of treatment, the intersection of the costs of the treatment, inability to work and cost of living burden is a significant issue. Both organisations also noted that current treatments include surgery, immunotherapy, Selective Internal Radiation Treatment, neoadjuvant chemotherapy, and adjuvant chemotherapy. Pancare noted the superiority of STRIDE compared to sorafenib, however the PBAC noted Pancare may not have been aware that the main comparator in the submission was Atezo + b.

6.5 Rare Cancers Australia described how patients are often diagnosed at a later stage which worsens their prognosis and noted that many patients report experiencing both physical and financial toxicities from these treatments and that surgical treatment heavily affects quality of life and is associated with extensive recovery time.

6.6 The Medical Oncology Group of Australia (MOGA) expressed its strong support for the STRIDE submission, categorising it as one of the therapies of highest priority for PBS listing based on the results of the HIMALAYA trial. The PBAC noted that the MOGA presented a European Society for Medical Oncology Magnitude of Benefit Scale (ESMO-MCBS) score of 5 representing substantial improvement, based on a comparison with sorafenib, however the PBAC noted that MOGA may not have been aware that the main comparator in the submission was Atezo + b.

Clinical trials

6.7 The submission was based on one head-to-head trial comparing STRIDE (n=393) to sorafenib (n=389), HIMALAYA. For the anchored ITC, efficacy and safety data comparing atezo + b (n=336) to sorafenib (n=165) in the IMBRAVE150 trial were used.

An earlier data cut of IMBRAVE150 has previously been reviewed by the PBAC (atezolizumab PSD, July 2020 PBAC meeting).

6.8 Details of the trials presented in the submission are provided in

6.9 Table 2. For brevity, a complete list of publications is not presented in the Executive Summary.

Table 2: Master list of trials (and associated reports) presented in the submission

Study identifier (ID)	Reports/Protocol title/ Publication title	Publication citation
HIMALAYA (NCT03298451)	Clinical Study Report: Final analysis	August 2021
	LTFU1: Long-term follow-up analysis tables and figures	January 2023
	Rimassa et al., Five-year overall survival (OS) and OS by tumour response measures from the Phase 3 HIMALAYA study of tremelimumab plus durvalumab in unresectable hepatocellular carcinoma (uHCC).	ESMO. September 2024
	Clinical Study Protocol v7	September 2022
	Abou-Alfa, GK, Lau, G, Kudo, M, et al. (2022). Tremelimumab plus Durvalumab in Unresectable Hepatocellular Carcinoma.	NEJM Evid, 1(8). 2022.
	Sangro, B, Chan, SL, Kelley, RK, et al. Four-year overall survival update from the phase III HIMALAYA study of tremelimumab plus durvalumab in unresectable hepatocellular carcinoma	*Annals of oncology: official journal of the European Society for Medical Oncology*, 35(5), 448-457. 2024
	Sangro, B, Galle, PR, Kelley, RK, et al. Patient-Reported Outcomes From the Phase III HIMALAYA Study of Tremelimumab Plus Durvalumab in Unresectable Hepatocellular Carcinoma [Article in Press]	2024 *Journal of clinical oncology*.
IMBRAVE150 (NCT03434379)	Finn, RS, Qin, S, Ikeda, M, et al. Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma	2020 *N Engl J Med*, 382(20)., 1894-1905.
	Cheng, AL, Qin, S, Ikeda, M, et al. Updated efficacy and safety data from IMbrave150: Atezolizumab plus bevacizumab vs sorafenib for unresectable hepatocellular carcinoma	2022 *J Hepatol*, 76(4)., 862-873.
	Galle, PR, Finn, RS, Qin, S, et al. Patient-reported outcomes with atezolizumab plus bevacizumab versus sorafenib in patients with unresectable hepatocellular carcinoma (IMbrave150): an open-label, randomised, phase 3 trial	2021 *Lancet Oncol*, 22(7)., 991-1001.
	Kudo, M, Finn, RS, Galle, PR, et al. IMbrave150: Efficacy and Safety of Atezolizumab plus Bevacizumab versus Sorafenib in Patients with Barcelona Clinic Liver Cancer Stage B Unresectable Hepatocellular Carcinoma: An Exploratory Analysis of the Phase III Study	2023 *Liver Cancer*, 12(3)., 238-250.

Source: Table 2-4, Table 2-6, pp 59-60 and pp 64-65 of the submission.
Blue shading indicates data previously seen by the PBAC.

6.10 The key features of the randomised trials are summarised in Table 3**.** The clinical claim was based on an anchored ITC of OS between HIMALAYA and IMBRAVE150.

6.11 Results from HIMALAYA were presented from 3 data cut-offs (DCOs):

- primary analysis (August 2021 DCO, median patient follow-up of 33.2 months for STRIDE).
- four-year long-term OS and safety follow-up (January 2023 DCO, median patient follow-up of 49.1 months for STRIDE).

- five-year long-term OS follow up (March 2024 DCO, median patient follow-up of 62.5 months for STRIDE).

6.12 Results from IMBRAVE150 were presented from 2 data cut-offs:

- primary analysis (August 2019 DCO, median patient follow-up of 8.6 months). Results from this data cut-off have previously been reviewed by the PBAC (atezolizumab PSD, July 2020 PBAC meeting).
- updated OS follow-up (August 2020 DCO, median patient follow-up of 15.6 months).

Table 3: Key features of the included evidence – indirect comparison

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
STRIDE vs sorafenib						
HIMALAYA	782 [a]	R, MC, OL 5 yrs	Low	Untreated advanced/unresectable HCC	OS, PFS, QoL, Safety	Median duration of treatment
Atezo + b vs sorafenib						
IMBRAVE150	501	R, MC, OL 15 mths	Low	Untreated advanced/unresectable HCC	OS, PFS, QoL, Safety	Median duration of treatment

Source: Table 2-12, p72 and Table 2-14, pp 75-76 of the submission.
Atezo + b = atezolizumab plus bevacizumab; HCC = hepatocellular carcinoma; MC = multi-centre; mths = months; OL = open label; OS = overall survival; PFS = progression-free survival; QoL = quality of life; R = randomised; STRIDE = Single Tremelimumab Regular Interval Durvalumab; yrs = years.
[a] Patients in HIMALAYA (N=1,324) were randomly assigned in a 1:1:1:1 ratio to 4 treatment arms. Out of the four 4 treatment arms, the submission appropriately included only the arms that provided direct comparative evidence of STRIDE with sorafenib (Arms C and D; n=782).
Blue shading indicates data previously seen by the PBAC.

6.13 Broadly, both the HIMALAYA and IMBRAVE150 trials had successful randomisation, with no substantial sources of bias in prognostic factors between treatment groups within each individual trial. Comparing the two trials, some differences were identified:

- Eligible patients in HIMALAYA were allowed to be rechallenged with a single dose of tremelimumab 300 mg and durvalumab 1,500 mg for one cycle, followed by durvalumab monotherapy 1,500 mg if they were deemed to be continuing to derive clinical benefit, but with evidence of progressed disease. The subgroup which received treatment rechallenge in the STRIDE arm (n=30, 7.6%) had approximately double the median OS compared to the STRIDE full analysis set (FAS) in HIMALAYA (30.42 months vs 16.43 months respectively). It is unclear what proportion of the longer median OS may be attributable to the treatment rechallenge or positive prognostic characteristics which made those patients eligible for rechallenge. Treatment rechallenge is inconsistent with the proposed PBS listing, which only allows for a single dose of tremelimumab and prohibits post-progression treatment. Efficacy data removing the rechallenge subgroup were requested but not available. The PSCR acknowledged the request but argued that the proposed analysis involved a small exploratory and highly selected

subgroup of patients and was inappropriate because these patients inherently had a different prognosis compared to the broader population in the HIMALAYA study. Further, the PSCR argued that censoring of the rechallenged patients would introduce bias as they had to be alive for at least 6 months to be considered for re-challenge and had to meet additional criteria.

- Both studies allowed retreatment beyond progression, and a greater proportion of patients in HIMALAYA continued treatment beyond progression (46.9% in the STRIDE arm and 35.8% of patients in the sorafenib arm) compared to patients treated with atezo + b in IMBRAVE150 (39.3%). There is potential for limited benefit with post-progression PD-L1 treatment[8], however it is unlikely to have a large effect on the OS results of HIMALAYA, and unlikely to bias the ITC as IMBRAVE150 also allowed for post-progression treatment.
- The proportion of patients with a non-viral cause of HCC was higher in HIMALAYA (41.8%) compared to IMBRAVE150 (30.5%). Patients with non-viral HCC present with more advanced disease, and have a worse prognosis compared to viral HCC aetiology[9]; this difference favours the prognosis of patients in IMBRAVE150 (atezo + b).
- Extra-hepatic spread at baseline was numerically lower in HIMALAYA compared to IMBRAVE150 (52.6% vs 60.8%); this difference favours the prognosis of patients in HIMALAYA (STRIDE).
- All the participants in HIMALAYA had a disease stage of BCLC B or C at baseline (as per the inclusion criteria), whereas in IMBRAVE150, a small proportion of patients (3.0%) had BCLC stage A disease. Patients with BCLC stage A have a better prognosis than patients with BCLC stage B or C, so this would favour the prognosis of patients in IMBRAVE150 (atezo + b), but the difference was likely small, given the small proportion of patients.

Comparative effectiveness

6.14 Results of OS at the five-year analysis (March 2024 DCO) and PFS at the August 2021 DCO are presented in Table 4. The corresponding Kaplan-Meier (KM) curves for OS are presented in Figure 1.

[8] Spagnolo, F., Boutros, A., Cecchi, F. *et al.* Treatment beyond progression with anti-PD-1/PD-L1 based regimens in advanced solid tumors: a systematic review. *BMC Cancer* **21**, 425 (2021). https://doi.org/10.1186/s12885-021-08165-0.

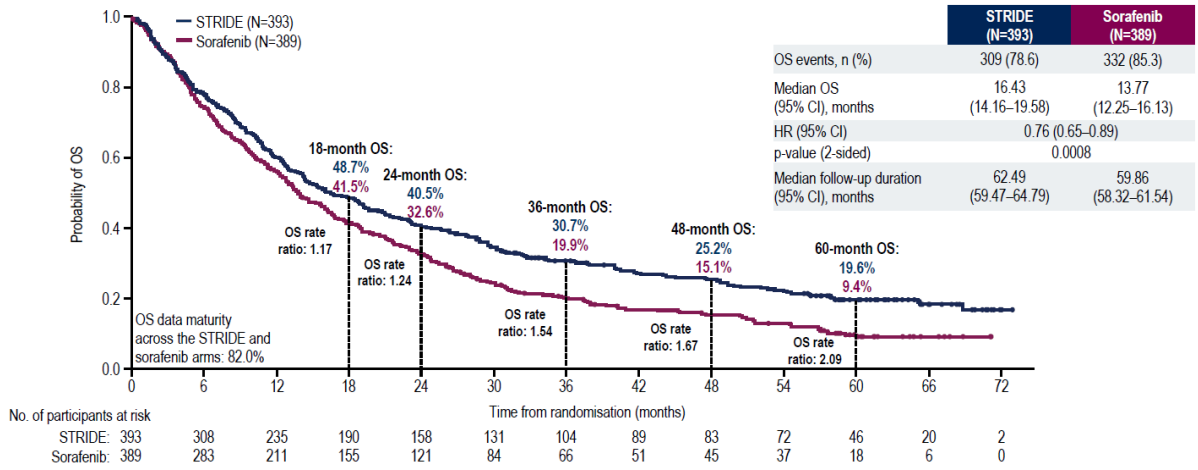
[9] El-Kassas M, et al. Characteristics and survival of patients with viral versus nonviral associated hepatocellular carcinoma: a multicenter cohort study. *Eur J Gastroenterol Hepatol*. 2025;37(1):83-93.

Table 4: Summary of HIMALAYA results, FAS

DCO	STRIDE (N=393)			Sorafenib (N=389)			Difference in median, months	HR (95% CI)
	Median follow-up (range), months	Events (%)	Median, months (95% CI)	Median follow-up (range), months	Events (%)	Median, months (95% CI)		
Overall Survival								
Five-year analysis *(1 March 2024)*	62.49 (59.47, 64.79)	309 (78.6)	16.43 (14.16, 19.58)	59.86 (58.32, 61.54)	332 (85.3)	13.77 (12.25, 16.13)	2.66	**0.76 (0.65, 0.89) p=0.0008**
Progression-Free Survival (RECIST 1.1)								
Final analysis *(27 August 2021)*	33.18 (31.74, 34.53)	335 (85.2)	3.78 (3.68, 5.32)	32.23 (30.42, 33.71)	327 (84.1)	4.07 (3.75, 5.49)	-0.29	0.90 (0.77, 1.05) p=0.1625

Source: Table 2-27, p105 of the submission; Table 2-28 p108 of the submission.
CI =confidence interval; DCO = data cut-off; FAS = full analysis set; HR =hazard ratio; N = number.
Dates incorrectly reported in the submission, corrected during the evaluation.
Bold indicates statistically significant results

Figure 1: Overall survival, HIMALAYA, FAS, five-year analysis, March 2024 DCO



Source: Figure 2-8, p106 of the submission.
CI = confidence interval; DCO = data cut-off; FAS = full analysis set; HR, hazard ratio; OS = overall survival.

6.15 STRIDE treatment demonstrated a statistically significant OS benefit over sorafenib, providing an additional median survival of 2.66 months. There were no statistically significant differences between STRIDE and sorafenib in the KM estimate for median PFS.

6.16 Updated results from IMBRAVE150 are presented (31 August 2020 DCO) in Table 5. There was a statistically significant OS benefit of atezo + b compared with sorafenib, with the magnitude of OS benefit being slightly diminished compared to the results from the primary analysis previously seen by the PBAC (atezolizumab PSD, July 2020 PBAC meeting).

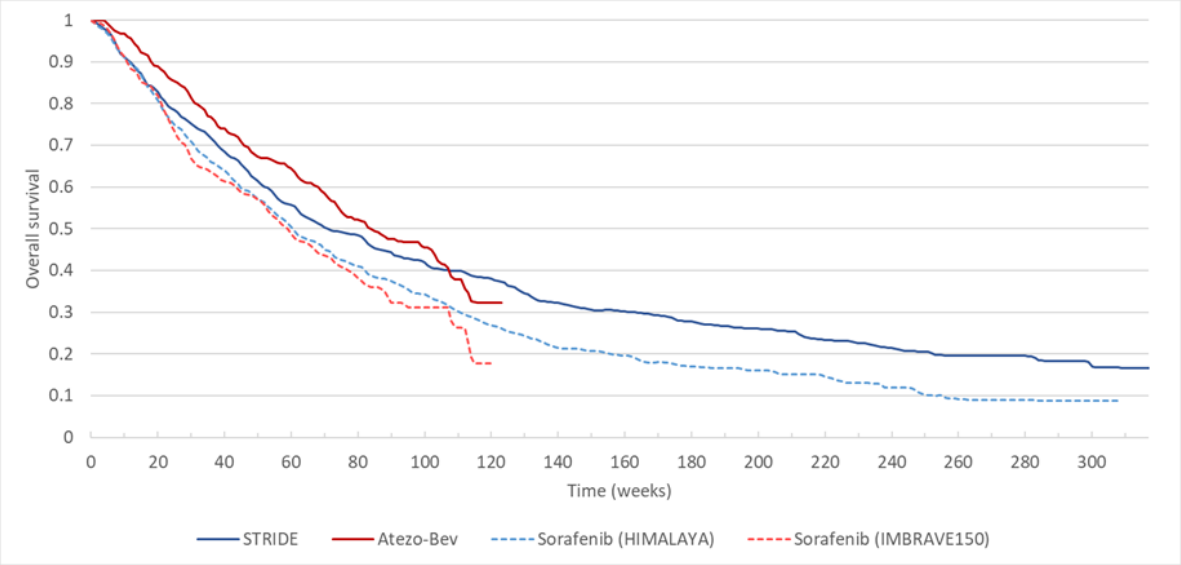
Table 5: Summary of IMBRAVE150 OS results (ITT)

DCO	Atezo + b (N=336)			Sorafenib (N=165)			HR (95% CI)
	Median follow-up (range), months	Events (%)	Median (range), months (95% CI)	Median follow-up (range), months	Events (%)	Median (range), months (95% CI)	
Primary analysis (DCO: 29 August 2019)	8.9	96 (28.6)	NE	8.1	65 (39.4)	13.2 (10.4, NE)	**0.58 (0.42, 0.79) p<0.001**
Updated analysis (DCO: 31 August 2020)	17.6 (0.1, 28.6)	291 (74.0)	19.2 (17.0, 23.7)	10.4 (0, 27.9)	134 (81.2)	13.4 (11.4, 16.9)	**0.66 (0.52, 0.85) p<0.001**

Source: Table 2-31, p112 of the submission.
Atezo + b = atezolizumab + bevacizumab; CI = confidence interval; DCO = data cut-off; HR = hazard ratio; ITT = intention to treat; NE = not estimable; OS = overall survival.
Bold indicates a statistically significant difference.
Blue shading indicates data previously seen by the PBAC.

6.17 The submission provided a naïve graphical comparison of the OS curves from the two key trials, presented in Figure 2. This comparison did not adjust for substantial differences in follow-up times and censoring between the two trials. The curves show patients treated with atezo + b had numerically better survival than patients treated with STRIDE, until the curves cross at around 110 weeks. However, data for atezo + b becomes uncertain and cannot be meaningfully interpreted beyond 96 weeks, at which point 120/336 patients had been censored and only 42/336 patients remained at risk.

Figure 2: Comparison of KM curves in the HIMALAYA and IMBRAVE150 trials



Source: Figure2-16, p 135 of the submission.
Atezo+Bev = atezolizumab plus bevacizumab; KM = Kaplan-Meier; STRIDE = Single Tremelimumab Regular Interval Durvalumab.
Note: Beyond week 96, heavy censoring makes the IMBRAVE150 data uncertain (atezo + bev and red sorafenib lines).

<u>Indirect treatment comparison (STRIDE versus atezo + b)</u>

6.18 The PSCR agreed with the evaluation that the OS curves cannot be meaningfully interpreted beyond 96 weeks, and argued that late separation and/or plateau of survival curves in the longer term, as seen in HIMALAYA, are often observed in immuno-oncology (IO) trials. The PSCR further argued that when survival curves show delayed separation, the HR changes over time, such that a single HR, as reported in the ITC (see below paragraphs) may be insufficient to fully capture survival benefits in the tail of the curve. From the overlay of the KM curves, the ESC considered that the two comparator arms for sorafenib were similar while the curves for STRIDE and atezo + b appeared to be different. However, the ESC also acknowledged that the lack of longer-term data and unreliability beyond 96 weeks for atezo + b complicates the ability to draw meaningful conclusions from the KM curves as presented in Figure 2. The pre-PBAC response stated that the difference in mode of action between STRIDE (IO+IO) and atezo + b (IO+VEGF) is a relevant consideration when comparing across the two trials because late separation and/or plateau of the survival curves are a particular feature of doublet IO therapy, such as STRIDE.

6.19 The submission presented an unmatched, unadjusted, anchored Bucher ITC between HIMALAYA and IMBRAVE150, to compare the efficacy (in terms of OS) and safety of STRIDE compared to atezo + b, using sorafenib as a common comparator. The PSCR acknowledged the Bucher ITC presented is oversimplistic and complicates interpretation of the clinical claim, however argued this was presented as the primary analysis as it is preferred in the PBAC Guidelines.

6.20 Minor differences in trial characteristics between HIMALAYA and IMBRAVE150 were noted in paragraph 6.13. These differences were unlikely to have had any material impact on the results of the ITC overall. The largest difference between the trials that is likely to have affected the ITC is the disparate follow-up times between HIMALAYA (median follow-up 62.5 months for STRIDE, 59.9 months for sorafenib) and IMBRAVE150 (median follow-up 17.6 months for atezo + b, 10.4 months for sorafenib). Despite these differences, the comparator (sorafenib) arms of the two trials performed similarly, with similar median OS and safety profiles, as described in Table 6 and Table 8.

6.21 The ITC for efficacy is presented in Table 6.

Table 6: ITC of OS for HIMALAYA vs IMBRAVE150

Trial	HIMALAYA		IMBRAVE150	
Treatment arm	**STRIDE (N = 393)**	**Sorafenib (N = 389)**	**Atezo + b (N = 336)**	**Sorafenib (N = 165)**
Median follow-up for OS, months	62.49 (59.47, 64.79)	59.86 (58.32, 61.54)	17.6 (0.1, 28.6)	10.4 (0, 27.9)
Events, n (%)	309 (78.6)	332 (85.3)	291 (74.0)	134 (81.2)
Median OS, months (95% CI)	16.43 (14.16, 19.58)	13.77 (12.25, 16.13)	19.2 (17.0, 23.7)	13.4 (11.4, 16.9)
HR (95% CI)	0.76 (0.65, 0.89) [a]		0.66 (0.52, 0.85) [a]	
ITC: STRIDE vs atezo + b, HR (95% CI), p-value	1.152 (0.86, 1.541), p=0.3431			

Source: Table 2-45, p 134 of the submission.
atezo + b = atezolizumab plus bevacizumab; CI = confidence interval; HR = hazard ratio; ITC = indirect treatment comparison; N = number; OS = overall survival; STRIDE = Single Tremelimumab Regular Interval Durvalumab.
[a] p<0.001
Note: HR values >1 indicate a greater risk of death associated with STRIDE treatment compared to atezo + b.

6.22 The submission argued that because the comparison failed to demonstrate a statistically significant difference, the efficacy of the two treatments may be considered similar. This is not a reasonable interpretation; the submission did not provide power calculations for the ITC. Further, the upper limit of the 95% CI suggested that patients treated with STRIDE may have up to 54% increased hazard of death compared to patients treated with atezo + b. Considering these results, the possibility that the effectiveness of STRIDE treatment is worse than atezo + b, cannot be ruled out, noting that the ITC lacked sufficient power to demonstrate statistical significance. The PSCR argued that wide CIs are more likely caused by heterogeneity between the trials as discussed above and are not reflective of the treatment effect. The pre-PBAC response argued that it was relevant to consider that the STRIDE regimen is the only therapy to have demonstrated a sustained survival benefit over the long term, that it eliminates the need for endoscopy and offers a less frequent and more convenient dosing schedule.

6.23 The PSCR reiterated the results of a matching-adjusted indirect comparison (MAIC) with a Cox proportional hazards model and piecewise analyses presented in the submission. The results are presented in the table below.

Table 7: OS results from Cox model and piecewise analyses for the MAIC between STRIDE and atezo + b

Study	Comparison	All period HR [95% CI]	Piecewise, HR [95% CI]	
			< 9 months	9 to 26.9 months
HIMALAYA*	STRIDE vs. sorafenib	0.72 [0.60, 0.87]	0.74 [0.55, 1.00]	0.69 [0.52, 0.92]
IMbrave150	Atezo+Bev vs. sorafenib	0.66 [0.52, 0.85]	0.62 [0.44, 0.87]	0.72 [0.51, 1.03]
MAIC	STRIDE vs. Atezo+Bev	1.09 [0.80,1.48]	1.19 [0.76, 1.87]	0.96 [0.61, 1.51]

Abbreviations: CI: Confidence interval, HR: Hazard ratio, MAIC: Matching-adjusted indirect comparison, OS: Overall survival.
*Reweighted
Source: Qin et al. (2023), Table 2-49, p147 of the submission.

6.24 The PSCR noted that the results of the MAIC with piecewise HRs highlighted numeric differences between 0-9 months and 9-26.9 months that suggested an improved HR

in HIMALAYA and a sustained effect of STRIDE versus atezo + b in the long term. Over the common follow-up period of approximately 2 years, the HR point estimate was 1.09 (95% CI: 0.80, 1.48).

6.25 The ESC considered the results of the MAIC appeared to be similar to the unadjusted ITC and provide some limited additional support for the claim of non-inferior comparative effectiveness, but that overall the evidence remained uncertain.

Comparative harms

6.26 Both trials collected adverse event (AE) data, however the longer follow-up in HIMALAYA compared to IMBRAVE150 may have biased the safety comparison in favour of atezo + b. The submission compared only overall rates of AEs, which showed no substantial differences as described in Table 8. Considering these data, the claim of non-inferior safety appears reasonable.

6.27 The PSCR noted that unlike for patients undergoing treatment with STRIDE, patients undergoing treatment with atezo + b may require an endoscopic assessment and oesophageal banding procedures, if varices are present, to minimise the risk of adverse events. The PSCR also acknowledged that these procedures are considered safe but noted they can be more challenging in patients with aHCC, increase the risk of complication and can delay initiation of treatment.

Table 8: Overview of AEs in HIMALAYA and IMBRAVE150

AE category	HIMALAYA		IMBRAVE150		RR (95% CI)	RD (95% CI)
	STRIDE (N=388)	Sorafenib (N=374)	Atezo + b (N=329)	Sorafenib (N=156)		
Median duration of treatment (months)	5.5	4.1	8.4/7	4		
Median duration of follow-up (months)	33.18	32.23	17.6	10.4		
Any AE, n (%)	378 (97.4)	357 (95.5)	322 (98)	154 (99)	1.001 (0.961, 1.043)	0.001 (-0.039, 0.04)
Treatment-related AEs, n (%)	294 (75.8)	317 (84.8)	284 (86)	148 (95)	0.955 (0.871, 1.048)	-0.03 (-0.108, 0.047)
Any grade ≥ 3, n (%)	196 (50.5)	196 (52.4)	207 (63)	89 (57)	0.85 (0.688, 1.05)	-0.094 (-0.211, 0.023)
Any grade ≥ 3 related to study drug, n (%)	100 (25.8)	138 (36.9)	143 (43)	72 (46)	**0.721 (0.534, 0.974)**	-0.097 (-0.212, 0.018)
SAE, n (%)	160 (41.2)	111 (29.7)	160 (49)	51 (33)	0.908 (0.66, 1.249)	-0.054 (-0.167, 0.059)
Serious TRAE, n (%)	68 (17.5)	36 (9.6)	76 (23)	25 (16)	1.228 (0.703, 2.145)	0.003 (-0.084, 0.09)
Deaths due to an AE, n (%)	30 (7.7)	27 (7.2)	23 (7)	9 (6)	0.859 (0.35, 2.111)	-0.009 (-0.068, 0.05)

Source: Table 2-46, p 136 of the submission.
AE = adverse event; atezo + b = atezolizumab plus bevacizumab; CI = confidence interval; RD = risk difference; RR = relative risk; SAE = serious adverse event; STRIDE = Single Tremelimumab Regular Interval Durvalumab; TRAE = treatment-related adverse event.
Bold indicates a statistically significant difference.

Benefits/harms

6.28 A benefits and harms table was not presented as the submission made a claim of non-inferiority.

Clinical claim

6.29 The submission described STRIDE as non-inferior in terms of effectiveness compared with atezo + b and non-inferior in terms of safety compared to atezo + b.

6.30 The therapeutic conclusion of non-inferior effectiveness may not be supported by the evidence. Whilst results from the key HIMALAYA trial suggested that STRIDE treatment led to a significant benefit in terms of OS compared to sorafenib (despite not demonstrating a PFS benefit), the submission's anchored, unmatched and unadjusted ITC did not demonstrate non-inferiority of STRIDE compared to atezo + b. A principal issue for consideration was that the point estimate for the HR was > 1 with a wide 95% CI and upper bound of 1.541, suggesting that STRIDE treatment may confer an increased risk of death compared to atezo + b, noting that the ITC lacked the power to demonstrate statistical significance. The submission did not nominate a non-

inferiority margin, and the upper limit of the 95% CI suggested patients could be at 54% increased risk of death with STRIDE treatment compared to atezo + b.

The submission's claim of non-inferior safety of STRIDE compared to atezo + b was supported by the evidence in the ITC, which showed numerically similar adverse event rates between the HIMALAYA and IMBRAVE150 trials. There was a general trend for numerically fewer AEs associated with STRIDE compared to atezo + b (apart from serious treatment related adverse events), which was consistent with the differences in treatment protocols: after the first 4 weeks, the only active treatment in STRIDE was a PD-L1 inhibitor (durvalumab) monotherapy compared to ongoing regular doses of both a PD-L1 inhibitor (atezolizumab) combined with a VEGF inhibitor (bevacizumab).

6.31 The PBAC considered that the claim of non-inferior comparative effectiveness based on the comparisons presented in the submission were uncertain; however, taking into account the matching-adjusted comparison presented in the PSCR and totality of the available evidence, the PBAC considered the claim was, on balance, likely to be reasonable.

6.32 The PBAC considered that the claim of non-inferior comparative safety was reasonable and adequately supported by the data.

Economic analysis

6.33 The submission presented a CMA comparing STRIDE to atezo + b based on the HIMALAYA and IMBRAVE150 trials. The reasonableness of this approach is contingent on the assumption that STRIDE is at least as effective and safe as atezo + b.

6.34 The components and assumptions for the CMA are summarised in Table 9.

Table 9: Key components and assumptions of the cost-minimisation approach

Component	Claim or assumption
Therapeutic claim: effectiveness	Based on evidence presented, effectiveness is assumed to be non-inferior.
Therapeutic claim: safety	Based on evidence presented, safety is assumed to be non-inferior.
Evidence base	Indirect comparison of randomised trials. The indirect comparison is based on the HIMALAYA trial, which compared tremelimumab in combination with durvalumab (STRIDE) to sorafenib, and the IMBRAVE150 trial, which compared atezo + b to sorafenib.
Equi-effective doses	Single dose tremelimumab (300 mg) with durvalumab (1,500 mg) at Cycle 1, Day 1 and durvalumab (1,500 mg) every 4 weeks for a total of 5.5 months (STRIDE) is equi-effective to atezolizumab (1,200 mg) every 3 weeks for a total of 8.4 months with bevacizumab 15 mg/kg every 3 weeks for a total of 7.0 months. 8,938 mg durvalumab + 300 mg tremelimumab = 14,560 mg atezolizumab + 10,880 mg bevacizumab
Direct medicine costs	The cost of STRIDE per treatment course was $[redacted], $[redacted], higher than the cost of atezo + b per treatment course which was $[redacted] (based on the assumed effective prices of atezo + b)
Other costs or cost offsets	MBS cost, item 13950 for the administration of the intravenous infusion ($123.05), applied to both STRIDE and atezo + b.

Source: Table 3-1 p 151 of the submission.
atezo + b = atezolizumab plus bevacizumab; MBS = Medicare Benefits Schedule; mg = milligram; STRIDE = Single Tremelimumab Regular Interval Durvalumab.

6.35 The estimation of equi-effective doses was based on the dosage regimens in HIMALAYA and IMBRAVE150. The submission sourced the dose per infusion of bevacizumab from the atezolizumab PSD, which applied a mean dose per infusion of 1,076 mg in the economic model (para 6.46, atezolizumab PSD, July 2020 PBAC Meeting). This was reasonable. The dosage regimens used in the trials were consistent with each medicine's TGA approved PI. The equi-effective dose assumed 100% dose intensity. The relative dose intensity (RDI) in HIMALAYA was 100% for tremelimumab and 97.6% for durvalumab. The results of the CMA applying the RDI for STRIDE in HIMALAYA and atezo + b in IMBRAVE150 are presented in the CIC section of the Commentary.

6.36 The submission acknowledged that an alternative dosing regimen for atezolizumab was available on the PBS to allow patients to continue to receive atezolizumab where bevacizumab is discontinued. This alternative dose was 1,680 mg (given as two 840 mg vials) every 4 weeks. The four weekly regimen was not included in the CMA presented by the submission because of low utilisation of the atezolizumab monotherapy continuing regimen (2.1% of the total atezolizumab HCC utilisation based on PBS Statistics, November 2020 to July 2024). This was reasonable given that patients in IMBRAVE150 received atezo + b every 3 weeks only.

6.37 The equi-effective doses for STRIDE and atezolizumab were based on the median treatment duration reported in HIMALAYA and IMBRAVE150. The median duration of follow-up in IMBRAVE150 (August 2020 DCO) was 15.6 months, and the median duration of treatment was 8.4 months with atezolizumab and 7.0 months with bevacizumab. The median duration of treatment with durvalumab was 5.5 months and 1 month with tremelimumab based on the four-year HIMALAYA analysis

(January 2023 DCO) with a median follow-up of 49.1 months. The submission argued that given the difference in duration of follow-up between the two trials, using the median treatment duration reported in HIMALAYA and IMBRAVE150 was appropriate. The pre-PBAC response stated that applying mean duration of treatment as reported for both primary analyses in the CMA is inappropriate and disproportionately biases the results against durvalumab due to the trial's longer-term follow-up.

6.38 The submission concluded that 8,938 mg durvalumab Q4W + 300 mg tremelimumab single dose was equi-effective to 14,560 mg atezolizumab Q3W+ 10,880 mg bevacizumab QW3.

6.39 The submission included cost offsets associated with differences in the frequency of administering STRIDE and atezo + b in the CMA. There were fewer infusions with STRIDE than with atezo + b due to the differences in frequency of administration (4-weekly versus 3-weekly, respectively) and in treatment durations (5.5 months for durvalumab, 8.4 months for atezolizumab and 7.0 months for bevacizumab). The submission estimated that this reduction in infusions was expected to reduce the cost to the MBS by $759.83 per patient treated.

6.40 The results of the CMA based on the assumed effective prices are presented in Table 10. The submission applied an assumed effective ex-manufacturer price for atezolizumab ($) based on an assumed % rebate to the published ex-manufacturer price.

Table 10: Results of the cost-minimisation approach based on assumed effective prices of atezolizumab

	Atezolizumab	Bevacizumab	Tremelimumab	Durvalumab
Vial strength (mg)	1,200	100	300	500
AEMP per vial	$ [a]	$61.77	$	$
AEMP per mg	$	$0.62	$	$
Cumulative mg per treatment course	14,560	10,880	300	8,938
Total treatment costs per patient per course by drug	$	$6,720	$	$
Total treatment costs per patient per course	$		$	
MBS costs administration of the intravenous infusion	$1,493.01		$733.17	
Total treatment costs including administration	$			

Source: Table 3-6 p157 of the submission
AEMP = approved ex-manufacturer price; MBS = Medicare Benefits Schedule.
[a] assumed a % rebate on the published AEMP
Italicised were incorrectly reported in the submission (AEMP per vial of durvalumab: $, AEMP per mg: $), correctly calculated in Attachment 3.1 CMA.xls

6.41 The results of a sensitivity analysis accounting for the proportion of rechallenged patients (7.6%) who received two doses of tremelimumab in HIMALAYA resulted in an estimated cost per vial of durvalumab of $ (based on the assumed effective price of atezolizumab).

6.42 The PSCR acknowledged the preference for using mean duration of treatment in CMAs but argued that this approach may not be suitable given the significant difference in follow-up durations between the trials. The PSCR noted that it was unclear whether the actual trial data (with a median follow-up of 8.6 months) or the modelled treatment duration (based on a 7.5-year time horizon with convergence of OS applied from 36 months) had been used. Further, the PSCR argued that the estimate from either approach may not be appropriate for comparison with STRIDE, for which the mean duration of treatment is derived from the four-year analysis with a median follow-up of 49.12 months. The PSCR stated it is difficult to comment on a proposed CMA based on mean treatment durations, when the mean treatment duration for the comparator is not available.

6.43 The ESC considered the rationale to rely on median treatment durations rather than mean treatment durations was not strong and therefore considered it was appropriate for the CMA to be based on mean treatment durations, consistent with standard practice. The ESC also considered it may be reasonable for STRIDE rechallenge patients to be included in the CMA inputs.

6.44 Based on the advice of the ESC, the Department obtained additional information on the utilisation of atezolizumab for BCLC/HCC (listed on 1 November 2020), which may provide an alternative (and more balanced) duration of follow-up to inform a mean treatment duration input for atezo + b. An analysis for the period since listing to 28 February 2025 (4 years 4 months) found a mean treatment duration with atezolizumab of 307 days. The PBAC considered the duration of utilisation data for atezolizumab was much closer to the duration of follow-up available for STRIDE from the HIMALAYA trial (~ 5 years) and may represent a more balanced alternative input for the CMA.

6.45 Should the PBAC accept the clinical claim of overall non-inferior effectiveness and safety, the cost-minimisation approach must establish that the cost per patient for treatment with STRIDE would be no more than the cost per patient of atezo + b. When these cost per patient calculations are uncertain, the guiding principle is that the Australian Government should not bear the financial risk of this uncertainty because the Australian population already has access to therapy that is at least as effective and safe.

Drug/ cost/patient/year

6.46 The drug cost per patient per year using the assumed effective prices of STRIDE and atezo + b is presented in Table 11.

Table 11: Drug cost per patient for proposed and comparator drugs

	STRIDE Trial dose and duration	STRIDE CMA	STRIDE Financial estimates	Atezo + bev Trial dose and duration	Atezo + bev Model	Atezo + bev Financial estimates
Mean dose	Durva: 1,500 mg per dose Trem: 300 mg per dose	Durva: 1,500 mg per dose Trem: 300 mg per dose	Durva: 1,500 mg per dose Trem: 300 mg per dose	NR	Atezo: 1,200 mg per dose Bev: 1,076 mg per dose	Atezo: 1,200 mg per dose Bev: 1,076 mg per dose
Median DoT/number of cycles received	5.5 months[a] Durva: *5.96* Trem: *1.00*	5.5 months[a] Durva: 5.96 Trem: 1.00	5.5 months[a] Durva: 5.96 Trem: 1.00	NR	Atezo[b] : 8.4 months; 12.13 Bev[b]: 7 months; 10.11	Atezo[b]: 8.4 months Bev[b]: 7 months
Cost per vial	Trem: $[redacted] Durva: $[redacted]			Atezo: $[redacted] (assumed effective price) Bev: $61.77		
Cost per cycle	Trem: $[redacted] Durva: $[redacted]	Trem: $[redacted] Durva: $[redacted]		NE	Atezo: $[redacted] Bev: $665	
Cost/patient/course [c]	Trem: $[redacted] Durva: $[redacted]	Trem: $[redacted] Durva: $[redacted]		NE	Atezo: $[redacted] Bev: $6,720	

Source: Table 3-4 p155 table 4-5 p163 of the submission, Section 4 Workbook of the submission, Table 14.3.1.7 durvalumab and tremelimumab CSR.

atezo = atezolizumab; bev = bevacizumab; CMA = cost-minimisation analysis; durva = durvalumab; DoT = duration of treatment; NE = not estimable; NR = not reported; trem = tremelimumab, STRIDE = Single Tremelimumab Regular Interval Durvalumab.

[a] median treatment duration as reported in HIMALAYA January 2023 data cut-off.

[b] median treatment duration as reported in IMBRAVE150 August 2020 data cut-off.

[c] the cost per patient per cycle multiplied by the median number of doses received.

Estimated PBS usage & financial implications

6.47 This submission was not considered by DUSC. The submission used a market share approach to estimate the extent of use and financial impact of listing STRIDE on the PBS. The financial estimates presented in the submission were based on both published and assumed effective prices. The sources of data utilised are shown in Table 12.

Table 12: Key inputs for financial estimates

Parameter	Value applied and source	Comment
Market for HCC without listing of STRIDE		
Estimated HCC market (scripts) in 2024: atezolizumab	Initial: [redacted] [1] Continuing: [redacted] [1]	Medicare statistics. Estimated the number of scripts for atezolizumab during the most recent financial year, 2023/2024. This was reasonable
Annual market growth	Initial: 5.96% in Yr 1 to 3.43% in Yr 6 Continuing: 14.58% in Yr 1 to 7.73% in Yr 6	Linear forecast based on PBS/RPBS atezolizumab script numbers for July 2022 to July 2024. The annual growth rate was calculated based on service volumes in financial years rather than calendar years.
Projected size of the current anti- HCC treatments: atezolizumab	Initial: [redacted] [1] in Yr 1 to [redacted] [1] in Yr 6 Continuing: [redacted] [1] in Yr 1 to [redacted] [2] in Yr 6	Calculated 2023/24 atezolizumab scripts and the estimated annual growth of HCC market. This was appropriate
Projected size of the current anti- HCC treatments: bevacizumab	[redacted] [2] in Yr 1 to [redacted] [2] in Yr 6	As bevacizumab is unrestricted, the number of scripts for HCC was assumed to be equal to atezolizumab scripts, initial and continuing combined. This was appropriate.
Market for HCC with listing of STRIDE		
Uptake rate (rate of substitution) for atezo + b	From [redacted]% in Yr 1 to [redacted]% in Yr 6	Assumption; applied to atezolizumab initial scripts. This was uncertain.
Proportion of atezolizumab continuation scripts displaced	From [redacted]% in Yr 1 to [redacted]% in Yr 6	The ratio of continuing script volumes relative to initial script volumes was based on the duration of therapy in IMBRAVE150. This was reasonable
Proportion of bevacizumab scripts displaced	From [redacted]% in Yr 1 to [redacted]% in Yr 6	
MBS costs	$123.05	MBS item number 13950. This was appropriate.

Source: Table 4-1 p 159, Table 4-3, Table 4-4 of the submission, Section 4 Workbook of the submission; 4.
atezo + b = atezolizumab plus bevacizumab; HCC = hepatocellular carcinoma; MBS = Medicare Benefit Schedule; PBS = Pharmaceutical Benefits Scheme; PSD = Public Summary Document; RPBS = Repatriation Pharmaceutical Benefit Scheme; STRIDE = Single Tremelimumab Regular Interval Durvalumab.
The redacted values correspond to the following ranges:
[1] *500 to < 5,000*
[2] *5,000 to < 10,000*

6.48 There may be a small proportion of patients who develop intolerance to atezolizumab and under the proposed restriction would subsequently be eligible to commence STRIDE. This was not accounted for in the financial estimates.

6.49 The annual growth rate was calculated based on service volumes in financial years rather than calendar years. Summing the monthly volumes by calendar year to calculate the annual growth rate would have been more appropriate.

6.50 The submission assumed that [redacted]% (Year 1) to [redacted]% (Year 6) of aHCC patients treated with atezo + b would initiate treatment with STRIDE. The proportion of atezolizumab continuing scripts and bevacizumab scripts displaced were calculated based on the median duration of therapy for atezolizumab in IMBRAVE150.

6.51 The estimated utilisation and financial impact of listing STRIDE on the PBS using the assumed effective prices are presented in Table 13. The total saving to the PBS/RPBS of listing STRIDE was estimated to be net cost saving in Year 1 increasing to net cost saving in Year 6, and a total net cost saving in the first 6 years of listing based on

assumed effective prices. The pre-PBAC response argued that the CMA presented did not include costs associated with oesophageal banding procedures, ongoing endoscopic surveillance for high-risk patients or management costs of high-grade oesophageal variceal bleeding, associated with treatment with atezo + b and omits potential cost-savings to the health budget beyond the PBS.

Table 13: Estimated use and financial implications of STRIDE, assumed effective prices

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use of STRIDE						
Number of scripts dispensed	[redacted][1]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
Estimated financial implications of STRIDE						
Cost to PBS/RPBS less copayments	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]
Estimated financial implications for atezo + b						
Cost to PBS/RPBS less copayments	-$[redacted][4]	-$[redacted][4]	-$[redacted][4]	-$[redacted][4]	-$[redacted][4]	-$[redacted][4]
Net financial implications						
Net cost to PBS/RPBS	-$[redacted][4]	-$[redacted][4]	-$[redacted][4]	-$[redacted][4]	-$[redacted][4]	-$[redacted][4]
Net cost to MBS	-$[redacted][4]	-$[redacted][4]	-$[redacted][4]	-$[redacted][4]	-$[redacted][4]	-$[redacted][4]
Net cost to Government	-$[redacted][4]	-$[redacted][4]	-$[redacted][4]	-$[redacted][4]	-$[redacted][4]	-$[redacted][4]

Source: Table 4-10 p166, Table 4-18 p172, Table 4-22 p175 of the submission.
atezo + b = atezolizumab + bevacizumab; MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme; STRIDE = Single Tremelimumab Regular Interval Durvalumab.
The redacted values correspond to the following ranges:
[1] *< 500*
[2] *500 to < 5,000*
[3] *$0 to < $10 million*
[4] *net cost saving*

For more detail on PBAC's view, see section 7 PBAC outcome.

7 PBAC Outcome

7.1 The PBAC recommended the Section 100 (Efficient Funding of Chemotherapy), Authority Required (Streamlined) listing of durvalumab and single dose tremelimumab (a.k.a. STRIDE) for the treatment of patients with advanced (unresectable) Barcelona Clinic Liver Cancer (BCLC) Stage B or Stage C hepatocellular carcinoma (HCC). The PBAC's recommendation for listing was based on, among other matters, its assessment that the cost effectiveness of STRIDE would be acceptable if it were cost minimised to atezolizumab + bevacizumab for this indication.

7.2 The PBAC considered the equi-effective doses were:

- A single dose of tremelimumab 300 mg + durvalumab 1,500 mg given at the start of Cycle 1 + ongoing durvalumab at a dose of 1,500 mg once every four weeks for a duration of 11.6 months (based on the mean treatment duration in HIMALAYA over 5 years' follow-up); and
- Ongoing atezolizumab at a dose of 1,200 mg + bevacizumab 15 mg/kg once every 3 weeks for a duration of 10.2 months (based on PBS utilisation data for

atezolizumab over approximately 4 years and 4 months years' follow-up (paragraph 6.44).

The PBAC acknowledged it is standard practice for treatment durations for equi-effective doses and cost minimisation approaches for chemotherapy and/or immunotherapy treatments to be based on the mean treatment durations from the clinical trials. However, in this case the Committee considered an alternative approach was justified due to the substantial imbalance in available follow-up duration between STRIDE and atezolizumab + bevacizumab and considered that given the availability of PBS utilisation data beyond 4 years, relying on this data resulted in a more balanced approach for determining the equi-effective doses.

7.3 The PBAC considered there was a place in therapy for STRIDE as an alternative to atezolizumab + bevacizumab and that STRIDE represented a useful therapy for patients with risk of bleeding and thrombosis where a VEGF inhibitor containing regimen may carry additional patient risks. The PBAC also acknowledged the input from consumer organisations and health professionals that described the poor prognosis of HCC and the limited treatment options with reports of many patients experiencing serious side effects. The Committee further noted that STRIDE may offer improved treatment access to patients living in rural areas because it eliminates the need for endoscopic screening to assess risk of bleeding and a less frequent dosing schedule. In addition, the PBAC noted the strong support from MOGA which categorised STRIDE as a therapy of highest priority for PBS listing based on the results of the HIMALAYA trial.

7.4 With respect to the requested listing and restriction the PBAC noted the request for use in patients naïve to systemic treatment or with intolerance to atezolizumab or VEGF inhibitor but considered that this was inappropriate and inconsistent with the TGA indication which states the patient must not have received prior treatment with a PD-1/PD-L1 inhibitor. The PBAC further noted the pivotal trial allowed for patients to be rechallenged with STRIDE after progression, however considered it was appropriate for the listing to be consistent with the existing listing of atezolizumab + bevacizumab and not permit further treatment after disease progression.

7.5 The PBAC considered that the nominated comparator of atezolizumab + bevacizumab was reasonable, however noted the tyrosine kinase inhibitors sorafenib and lenvatinib are also listed for this indication, and that a submission for nivolumab + ipilimumab had also been submitted for consideration to the July 2025 meeting.

7.6 The PBAC noted the submission was supported by the pivotal HIMALAYA trial (N = 782), a randomised controlled trial comparing STRIDE to sorafenib, and the comparator of atezolizumab + bevacizumab was informed by the IMBRAVE150 trial (N = 501), which it had previously considered in the original atezolizumab + bevacizumab submission. The Committee noted the clinical claims were supported primarily by an anchored indirect treatment comparison (ITC) of these two trials (including a matching-adjusted comparison presented in the PSCR) with sorafenib as the common

comparator. The PBAC further considered that while there were some differences between the trials (as described in paragraph 6.9), the trials were likely sufficiently similar for this purpose in terms of design and the populations recruited, but agreed that the substantial difference in available follow up (~5 years for STRIDE compared to ~15 months for atezolizumab + bevacizumab) created challenges for interpreting the comparisons.

7.7 In addition to these issues, the PBAC noted the HIMALAYA trial allowed for treatment rechallenge for eligible patients at the time of disease progression and that this subgroup (n=30, 7.6%) had approximately double the median overall survival (OS) compared to the full analysis population (30.42 months vs 16.43 months respectively). The PBAC further noted that efficacy data for the treatment arm of HIMALAYA excluding the rechallenge subgroup were not provided, so the impact of this could not be further explored.

7.8 The PBAC noted the results of the pivotal HIMALAYA trial of STRIDE versus sorafenib found a statistically significant benefit in terms of overall survival (HR 0.76, 95% CI 0.65, 0.89) and the Kaplan-Meier curves favoured STRIDE over the duration of follow-up from approximately 6 months onwards. Whilst there was no statistically significant difference observed in terms of progression free survival, the PBAC was satisfied that STRIDE provides, for some patients, a significant improvement in effectiveness over sorafenib, and by extension, is also likely to be superior to lenvatinib, based on the previously established non-inferiority of these agents (paragraph 11.2, lenvatinib PSD, July 2018 PBAC meeting).

7.9 The PBAC noted that the claim of non-inferior comparative effectiveness was based on a single-step ITC of STRIDE and atezolizumab + bevacizumab based on the HIMALAYA and IMBRAVE150 trials, with sorafenib as the common comparator. The PBAC noted the claim of non-inferiority in the submission was based on a lack of a statistically significant difference in OS outcomes and no non-inferiority margin was nominated; and further noted there did not appear to be a margin established in the literature for ITCs in BCLC/HCC. The PBAC considered that despite the difference in follow up, the comparator arm in the two trials performed similarly, providing some additional confidence that populations in the trials were likely to be comparable. The PBAC noted the results of the ITC for OS did not find a statistically significant difference between STRIDE and atezolizumab + bevacizumab (HR 1.152, 95% CI 0.86, 1.541) and expressed concern that the upper limit of the 95% CI exceeded 1.5 and raised the possibility that treatment outcome with STRIDE could be worse than for atezolizumab + bevacizumab. However, the Committee considered the substantial difference in follow-up between the trials complicated interpretation of the results of the anchored ITC and considered the matching-adjusted indirect comparison (MAIC) presented in the PSCR was informative and additionally supportive.

7.10 The PBAC noted the results of the MAIC, which used a Cox proportional hazards model and piecewise analyses to stratify groups by treatment duration of less than 9 months or 9 to26.9 months (Table 8), suggested an improvement in the HR of OS in the longer

term (MAIC <9 mths, HR 1.19, 95% CI 0.76, 1.87; versus 9 to 26.9 mths, HR 0.96, 95% CI 0.61, 1.51). Overall, the PBAC agreed with the ESC and considered the results of the MAIC were generally similar to the unadjusted ITC and provided some additional support for the claim of non-inferior comparative effectiveness, and considered that whilst some uncertainty remained, the claim was likely to be reasonable.

7.11 With regards to comparative safety, the PBAC noted the results of the ITC did not suggest any major differences in safety and considered the claim of non-inferiority was overall supported. Furthermore, the PBAC acknowledged the longer follow-up for STRIDE and noted that safety profile appeared to be consistent over the longer term.

7.12 The PBAC noted the submission requested the listing of STRIDE on a cost minimisation basis with atezolizumab with bevacizumab and considered this was reasonable. The Committee considered it was inappropriate for the median treatment duration (durvalumab = 5.5 mths, atezolizumab = 8.4 mths, bevacizumab = 7.0 mths) to be used for determining the treatment durations and equi-effective doses for the cost minimisation approach (CMA), but considered other aspects of the approach, including the use of direct medicine costs (albeit based on assumed effective prices in the submission), dose intensity and MBS costs/offsets were reasonable. The PBAC also considered that it was reasonable to include STRIDE rechallenge patient data in the CMA, as the impact of excluding these patients from the clinical comparison was unable to be assessed.

7.13 The PBAC considered it was established practice for CMAs for therapies of this type to use mean treatment durations from the clinical trials to determine equi-effective doses. However, the Committee also acknowledged the substantial difference in follow-up duration between the STRIDE and atezolizumab + bevacizumab trials has a substantial impact on the CMA results, and the mean treatment duration from IMBRAVE150 for atezolizumab (6.8 mths) + bevacizumab (6.5 mths) is likely to be artificially low due to the substantially shorter duration of follow-up, which would disadvantage STRIDE. The PBAC noted atezolizumab + bevacizumab has been listed on the PBS for BCLC/HCC for more than 4 years, and considered the mean treatment duration on the PBS may provide an alternative source to inform the CMA, that would be more comparable to the duration of follow-up available for STRIDE from the HIMALAYA trial. The PBAC noted an analysis undertaken by the Department, based on approximately 4 years and 4 months years of PBS listing data, found a mean treatment duration of 307 days for atezolizumab (not reported for bevacizumab) and considered this was a more reasonable treatment duration input for determining the equi-effective doses of STRIDE and atezolizumab + bevacizumab, and also considered the input for STRIDE should remain based on the HIMALAYA trial (durvalumab = 11.6 mths).

7.14 The PBAC noted the submission estimated the listing of STRIDE would result in a net saving to the PBS over 6 years, however noted these analyses were based on assumed effective prices. However, the PBAC noted the inputs to the estimates (outlined in Table 12) were generally reasonable (but would need to be updated to align with the

equi-effective doses and treatment durations described in paragraph 7.2) and considered that, if listed on a cost minimisation basis with atezolizumab + bevacizumab, that the listing would likely be cost neutral to the PBS. The PBAC considered it was appropriate for STRIDE to join the existing Risk Sharing Arrangement for atezolizumab for this indication with no increase to existing caps.

7.15 The PBAC advised that, under Section 101(3BA) of the *National Health Act 1953*, that tremelimumab should not be treated as interchangeable with any other drugs.

7.16 The PBAC advised that STRIDE is not suitable for prescribing by nurse practitioners.

7.17 The PBAC recommended that the Early Supply Rule should not apply as it currently cannot be applied to Section 100 - Efficient Funding of Chemotherapy listings.

7.18 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because durvalumab + tremelimumab (a.k.a STRIDE) is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over atezolizumab + bevacizumab, the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were not met.

7.19 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

Outcome:
Recommended

8 Recommended listing

8.1 Add new item:

Tremelimumab – initial once-off treatment

MEDICINAL PRODUCT **Form**	**PBS item code**	**Max. Amount**	**№.of Rpts**
TREMELIMUMAB Injection	{NEW (Public)} {NEW (Private)}	300mg	0
Available brands			
Imjudo (300 mg/15mL injection, 15 mL vial)			
Restriction Summary [new1]/ Treatment of Concept: [new1A]			
Category / Program: Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals			
Prescriber type: ☒Medical Practitioners			
Restriction type: ☒Authority Required (STREAMLINED) [NEW]			
Administrative Advice: No increase in the maximum amount or number of units may be authorised.			
Administrative Advice: No increase in the maximum number of repeats may be authorised.			
Administrative Advice: Special Pricing Arrangements apply.			

Severity: Advanced (unresectable) Barcelona Clinic Liver Cancer Stage B or Stage C ~~hepatocellular carcinoma~~
Condition: Hepatocellular carcinoma
Indication: Advanced (unresectable) Barcelona Clinic Liver Cancer Stage B or Stage C hepatocellular carcinoma
Treatment Phase: Initial *(once-off)* treatment
Clinical criteria:
Patient must be undergoing combination treatment with *PBS subsidised* durvalumab.
AND
Clinical criteria:
Patient must have a WHO performance status of 0 or 1,
AND
Clinical criteria:
Patient must not be suitable for transarterial chemoembolisation
AND
Clinical criteria:
Patient must have Child Pugh class A
AND
Clinical criteria:
The condition must be untreated with systemic therapy; **OR**
Patient must have developed intolerance *of a severity necessitating permanent treatment withdrawal, in the absence of disease progression* to a vascular endothelial growth factor (VEGF) *tyrosine kinase inhibitor (TKI)* ~~of a severity necessitating permanent treatment withdrawal.~~
AND
Treatment criteria:
Patient must not receive PBS-subsidised treatment with this drug for this indication more than once per lifetime

Durvalumab – initial and continuing treatment

MEDICINAL PRODUCT **Form**	**PBS item code**	**Max. Amount**	**№.of Rpts**
DURVALUMAB Injection	{NEW (Public)} {NEW (Private)}	1500mg	5
Available brands			
Imfinzi 500 mg/10 mL injection, 10 mL vial			
Imfinzi 120 mg/2.4 mL injection, 2.4 mL vial			
Restriction Summary [new2]/ Treatment of Concept: [new2A]			
Category / Program: Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals			
Prescriber type: ☒Medical Practitioners			
Restriction type: ☒Authority Required (STREAMLINED) [NEW]			
Administrative Advice: No increase in the maximum amount or number of units may be authorised.			
Administrative Advice: No increase in the maximum number of repeats may be authorised.			
Administrative Advice: Special Pricing Arrangements apply.			
Severity: Advanced (unresectable) Barcelona Clinic Liver Cancer Stage B or Stage C hepatocellular carcinoma			
Condition: Hepatocellular carcinoma			
Indication: Advanced (unresectable) Barcelona Clinic Liver Cancer Stage B or Stage C hepatocellular carcinoma			

Treatment Phase: Initial treatment
Clinical criteria:
Patient must be undergoing combination treatment with tremelimumab for the first dose of treatment.
AND
Clinical criteria:
Patient must have a WHO performance status of 0 or 1,
AND
Clinical criteria:
Patient must not be suitable for transarterial chemoembolisation
AND
Clinical criteria:
Patient must have Child Pugh class A
AND
Clinical criteria:
The condition must be untreated with systemic therapy; **OR**
Patient must have developed intolerance of a severity necessitating permanent treatment withdrawal, in the absence of disease progression to a vascular endothelial growth factor (VEGF) tyrosine kinase inhibitor (TKI) .
Restriction Summary [new3]/ Treatment of Concept: [new3A]
Severity: Advanced (unresectable) Barcelona Clinic Liver Cancer Stage B or Stage C hepatocellular carcinoma
Condition: Hepatocellular carcinoma
Indication: Advanced (unresectable) Barcelona Clinic Liver Cancer Stage B or Stage C hepatocellular carcinoma
Treatment Phase: Continuing treatment
Clinical criteria:
Patient must have previously received PBS-subsidised treatment with this drug for this condition
AND
Clinical criteria:
Patient must not have developed disease progression while being treated with this drug for this condition.

Flow-on changes

Lenvatinib

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
LENVATINIB					
lenvatinib 4 mg capsule, 30	11638M	3	90	2	lenvima
Restriction Summary [11167] / Treatment of Concept: [11168]					
Category / Program: GENERAL – General Schedule (Code GE)					
Prescriber type: ☒Medical Practitioners					
Restriction type: ☒Authority Required (Streamlined) [11168]					
Administrative Advice: No increase in the maximum number of repeats may be authorised.					
Administrative Advice: Special Pricing Arrangements apply.					
Indication: Advanced (unresectable) Barcelona Clinic Liver Cancer Stage B or Stage C hepatocellular carcinoma					
Treatment Phase: Initial treatment					
Clinical criteria:					
The treatment must be the sole PBS-subsidised therapy for this condition					

AND
Clinical criteria:
Patient must not be suitable for transarterial chemoembolisation
AND
Clinical criteria:
Patient must have a WHO performance status of 2 or less
AND
Clinical criteria:
Patient must have Child Pugh class A
AND
Clinical criteria:
The condition must be untreated with systemic therapy; or
Patient must have developed intolerance of a severity necessitating permanent treatment withdrawal, in the absence of disease progression, to any of the following: (i) a vascular endothelial growth factor (VEGF) tyrosine kinase inhibitor (TKI), (ii) atezolizumab/bevacizumab combination therapy, *(iii) durvalumab/tremelimumab combination therapy*.

Sorafenib

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
SORAFENIB					
sorafenib 200 mg tablet, 60	9380Q	2	120	2	Nexavar

Restriction Summary [11167] / Treatment of Concept: [11168]
Category / Program: GENERAL – General Schedule (Code GE)
Prescriber type: ☒Medical Practitioners
Restriction type: ☒Authority Required (Streamlined) [11160]
Administrative Advice: No increase in the maximum quantity or number of units may be authorised.
Administrative Advice: No increase in the maximum number of repeats may be authorised.
Administrative Advice: Special Pricing Arrangements apply.
Administrative Advice: Sorafenib is not PBS-subsidised for adjunctive treatment after resection, ablation or chemoembolization. Sorafenib is not PBS-subsidised for maintenance therapy after disease progression.
Indication: Advanced Barcelona Clinic Liver Cancer Stage B or Stage C hepatocellular carcinoma
Treatment Phase: Initial treatment
Clinical criteria:
The treatment must be the sole PBS-subsidised therapy for this condition
AND
Clinical criteria:
Patient must have a WHO performance status of 2 or less
AND
Clinical criteria:
Patient must have Child Pugh class A
AND
Clinical criteria:
The condition must be untreated with systemic therapy; or

Patient must have developed intolerance of a severity necessitating permanent treatment withdrawal, in the absence of disease progression, to any of the following: (i) a vascular endothelial growth factor (VEGF) tyrosine kinase inhibitor (TKI), (ii) atezolizumab/bevacizumab combination therapy, *(iii) durvalumab/tremelimumab combination therapy.*

This restriction may be subject to further review. Should there be any changes made to the restriction the sponsor will be informed.

9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

9 Sponsor's Comment

The sponsor has no comment.