6.05 NIVOLUMAB

Injection concentrate for I.V. infusion 40 mg in 4 mL
Injection concentrate for I.V. infusion 100 mg in 10 mL
Opdivo®
IPILIMUMAB
Injection concentrate for I.V. infusion 50 mg in 10 mL
Yervoy®
Bristol-Myers Squibb Australia 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 nivolumab in combination with ipilimumab (NIVO+IPI) for the first-line treatment of patients with advanced (unresectable) Barcelona Clinic Liver Cancer (BCLC) Stage A, Stage B or Stage C hepatocellular carcinoma (HCC).

1.2 Listing was requested on the basis of a cost-minimisation approach (CMA) using an unmatched, unadjusted anchored indirect treatment comparison (ITC) versus atezolizumab plus bevacizumab (ATEZO+BEV) as the primary comparator. The Single Tremelimumab Regular Interval Durvalumab (STRIDE) treatment regimen was identified as a potential near market comparator; a secondary ITC comparing NIVO+IPI with STRIDE was also included in the submission. 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 A, B or C HCC who have not received prior systemic treatment
Intervention	Nivolumab plus ipilimumab (NIVO+IPI)
Comparators	Atezolizumab plus bevacizumab (ATEZO+BEV) Durvalumab plus tremelimumab (STRIDE)
Outcomes	Overall survival; progression free survival; objective response rate, duration of response.
Clinical claim	NIVO+IPI has non-inferior efficacy, and non-inferior but different safety compared to ATEZO+BEV NIVO+IPI has non-inferior efficacy, and non-inferior but different safety compared to STRIDE

Source: Table 1, p16 of the submission.
ATEZO+BEV = atezolizumab plus bevacizumab; BCLC = Barcelona Clinic Liver Cancer; HCC = hepatocellular carcinoma; NIVO+IPI = nivolumab plus ipilimumab; STRIDE = Single Tremelimumab Regular Interval Durvalumab.

2 Background

Registration status

2.1 **TGA status at time of PBAC consideration:** Not registered. The submission for NIVO+IPI for unresectable HCC was made under the Therapeutic Goods

Administration (TGA)/ Pharmaceutical Benefits Advisory Committee (PBAC) Parallel Process. A TGA Delegate's overview was provided on 17 June 2025. The Delegate noted there were no outstanding issues to address. The Delegate's decision is expected in September 2025.

2.2 The TGA Delegate proposed to approve registration of the products for the following indications:

- OPDIVO (NIVO), in combination with ipilimumab, is indicated for the first-line treatment of adult patients with unresectable or metastatic hepatocellular carcinoma.
- YERVOY (IPI), in combination with nivolumab, is indicated for the first-line treatment of adult patients with unresectable or metastatic hepatocellular carcinoma.

2.3 At the time of PBAC consideration, the Food and Drug Administration (FDA) and European Medicines Agency (EMA) granted approval to extend the therapeutic indications for NIVO and IPI for this indication. A regulatory submission to Health Canada was under evaluation for NIVO for HCC, with a separate submission for IPI planned.

Previous PBAC consideration

2.4 The PBAC has not previously considered NIVO+IPI for this indication.

2.5 NIVO in combination with IPI is currently PBS listed for the following indications:

- Stage IV clear cell variant renal cell carcinoma
- Stage IV (metastatic) non-small cell lung cancer
- Unresectable malignant mesothelioma

2.6 The PBAC recommended ATEZO+BEV (atezolizumab Public Summary Document (PSD), July 2020 PBAC meeting) and STRIDE (durvalumab plus tremelimumab, web outcome, May 2025 PBAC meeting) for the first-line treatment of patients with advanced (unresectable) BCLC Stage B or Stage C HCC. Systemic treatment for BCLC Stage A patients has not previously been considered by the PBAC.

3 Requested listing

3.1 Suggestions and additions proposed by the Secretariat are added in italics and suggested deletions are crossed out with strikethrough.

MEDICINAL PRODUCT Form	PBS item code	Dispensed Price Max. Amount	Max. Amount	№.of Rpts
Nivolumab Injection	NEW (HB) NEW (HS)	$2,535.34 [Published, Private Hospital] $2,457.52 [Published, Public Hospital] $[redacted] [a] [Effective, Private Hospital] $[redacted] [a] [Effective, Public Hospital]	120mg	3

Available brands	
OPDIVO (Nivolumab 40 mg/4 mL injection, 4 mL vial)	
OPDIVO (Nivolumab 100 mg/10 mL injection, 10 mL vial)	
Restriction Summary NEW1 / Treatment of Concept: NEW1A	
Concept ID (for internal Dept. use)	**Category / Program:** Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals
	Prescriber type: ☒Medical Practitioners
	Restriction type: ☒Authority Required (STREAMLINED) [NEW]
Prescribing rule level	***Administrative Advice:*** *No increase in the maximum number of repeats may be authorised.*
	Administrative Advice: *Special Pricing Arrangements apply.*
New I	**Indication:** Advanced (unresectable) Barcelona Clinic Liver Cancer Stage A, Stage B or Stage C hepatocellular carcinoma
	Treatment Phase: Induction therapy
	Clinical criteria: Patient must have a WHO performance status of 0 or 1
	AND
	Clinical criteria:
	Patient must not be suitable for curative surgical *therapies* ~~and/or locoregional therapies~~ *OR*
	Patient must not be suitable for locoregional therapies
	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* ~~of a severity necessitating permanent treatment~~ ~~withdrawal to any of the following: (i)~~ a vascular endothelial growth factor (VEGF) tyrosine kinase inhibitor (TKI), ~~(ii) atezolizumab/bevacizumab combination therapy~~ *of a severity necessitating permanent treatment withdrawal*.
	Treatment criteria:
	Patient ~~The treatment~~ must *receive this* drug in combination with PBS-subsidised treatment with ipilimumab as induction for this condition.
	Prescribing instructions: Induction treatment with nivolumab must not exceed a total of 4 doses at a maximum dose of 1 mg per kg every 3 weeks.
	Prescribing instructions: The patient's body weight must be documented in the patient's medical records at the time treatment is initiated.

[a] Effective prices are indicative as reported by the submission; based on the cost-minimised price calculated using an assumed effective price for atezolizumab.

MEDICINAL PRODUCT Form	PBS item code	Dispensed Price Max. Amount	Max. Amount	№.of Rpts
Nivolumab Injection	NEW (HB) NEW (HS)	$9,736.96 [Published, Private Hospital] $9,559.69 [Published, Public Hospital] $[redacted] [a] [Effective, Private Hospital] $[redacted] [a] [Effective, Public Hospital]	480mg	~~5~~*11*

Available brands	
OPDIVO (Nivolumab 40 mg/4 mL injection, 4 mL vial)	
OPDIVO (Nivolumab 100 mg/10 mL injection, 10 mL vial)	
Restriction Summary NEW2 / Treatment of Concept: NEW2A	
Concept ID (for internal Dept. use)	**Category / Program:** Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals
	Prescriber type: ☒Medical Practitioners
	Restriction type: ☒Authority Required (STREAMLINED) [NEW]
Prescribing rule level	***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.*
	Indication: Advanced (unresectable) Barcelona Clinic Liver Cancer Stage A, Stage B or Stage C hepatocellular carcinoma
	Treatment Phase: Maintenance therapy
	Clinical criteria: Patient must have previously received up to a maximum of 4 doses of PBS-subsidised combined therapy with nivolumab and ipilimumab as induction for this condition,
	AND
	Clinical criteria:
	Patient must not have developed disease progression while being treated with this drug for this condition.
	AND
	~~**Treatment**~~ ***Clinical*** **criteria:**
	The treatment must be *the only systemic anti-cancer therapy* ~~as monotherapy~~ for this condition
	~~**Prescribing instruction:**~~
	~~An increase in repeat prescriptions, up to a value of 11, may only be sought where the prescribed dosing is 240 mg administered fortnightly.~~
	Treatment criteria:
	Patient must be undergoing treatment with this drug administered once every 2 weeks - prescribe up to 11 repeat prescriptions; OR
	Patient must be undergoing treatment with this drug administered once every 4 weeks - prescribe up to 5 repeat prescriptions
	AND
	~~**Prescribing instruction:**~~ ***Treatment criteria:***
	Patient must not be undergoing continuing treatment beyond 24 cumulative months of nivolumab treatment from the first administered dose
	Prescribing instruction:
	Patients must only receive a maximum of 240 mg every two weeks or 480 mg every four weeks under a weight based or flat dosing regimen.

[a] Effective prices are indicative as reported by the submission; based on the cost-minimised price calculated using an assumed effective price for atezolizumab.

MEDICINAL PRODUCT Form	PBS item code	Dispensed Price Max. Amount	Max. Amount	№.of Rpts
Ipilimumab Injection	NEW (HB) NEW (HS)	$43,490.32 [Published, Private Hospital] $42,847.09 [Published, Public Hospital] $[redacted] [a] [Effective, Private Hospital] $[redacted] [a] [Effective, Public Hospital]	360mg	3

Available brands	
YERVOY (Ipilimumab 50 mg/10mL injection, 10 mL vial)	
YERVOY (Ipilimumab 200 mg/40 mL injection, 40 mL vial)	
Restriction Summary NEW3 / Treatment of Concept: NEW3A	
Concept ID (for internal Dept. use)	**Category / Program:** Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals
	Prescriber type: ☒Medical Practitioners
	Restriction type: ☒Authority Required (STREAMLINED) [NEW]
Prescribing rule	***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 A, Stage B or Stage C hepatocellular carcinoma
	Treatment Phase: Induction therapy
	Clinical criteria: Patient must have a WHO performance status of 0 or 1
	AND
	Clinical criteria:
	Patient must not be suitable for curative surgical ~~and/or locoregional therapies~~ *OR*
	Patient must not be suitable for locoregional therapies
	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* ~~of a severity necessitating permanent treatment withdrawal to any of the following: (i)~~ a vascular endothelial growth factor (VEGF) tyrosine kinase inhibitor (TKI)~~, (ii) atezolizumab/bevacizumab combination therapy~~ *of a severity necessitating permanent treatment withdrawal.*
	AND
	~~**Treatment**~~ ***Clinical*** **criteria:**
	Patient ~~The treatment~~ must *receive this drug* ~~be~~ in combination with PBS-subsidised ~~treatment with~~ nivolumab as induction therapy for this condition.
	Prescriber instruction:
	Induction treatment with ipilimumab must not exceed a total of 4 doses at a maximum dose of 3 mg per kg every 3 weeks.
	Prescriber instruction:
	The patient's body weight must be documented in the patient's medical records at the time treatment is initiated.

[a] Effective prices are indicative as reported by the submission; based on the cost-minimised price calculated using an assumed effective price for atezolizumab.

3.2 The submission proposed a Special Pricing Arrangement (SPA) with a proposed effective EMP for NIVO of $[redacted] per 100 mg/10 mL mg vial and for IPI of $[redacted] per 50 mg/10 mL vial. Effective prices are based on the cost-minimisation approach using an assumed effective price for atezolizumab.

3.3 The proposed restriction for NIVO+IPI was for use in patients with BCLC Stage A, Stage B or Stage C HCC who are not suitable for curative surgical and/or locoregional therapies. This is broader than the restriction for ATEZO+BEV, which is for BCLC Stage B and C HCC patients only.

3.4 The proposed restriction included a deviation from the current PBS restriction for atezolizumab in that the wording 'patients should be ineligible for TACE' was changed to 'the patient must not be suitable for curative surgical and/or locoregional therapies'. The submission stated that this was to ensure that the requested Stage A population is limited to the small number of patients who have no other effective treatment options. This was consistent with the eligibility criteria for the pivotal trial, CM-9DW.

3.5 The proposed restriction included a provision for commencing NIVO+IPI treatment in patients who have developed intolerance to atezolizumab or a vascular endothelial growth factor (VEGF) inhibitor. The Economic Sub-Committee (ESC) noted that this provision may allow sequential use of immunotherapy and advised that this was not appropriate without evidence to support such use.

3.6 The proposed criterion for continuing treatment with NIVO+IPI, 'Patient must not have developed disease progression while being treated with this drug for this condition' was not consistent with use in CM-9DW. In CM-9DW patients who progressed were allowed to continue treatment if they were deemed to be continuing to derive clinical benefit (see paragraph 6.12).

4 Population and disease

4.1 HCC is the most common primary liver cancer and a leading cause of cancer-related mortality globally. In Australia, the 5-year survival rate for HCC is approximately 18%, but for patients with advanced or metastatic disease, the estimated rate is below 5%.[1] The burden of HCC disproportionately impacts Aboriginal and Torres Strait Islander Australians, who have significantly higher incidence and mortality rates due to the disease. The median overall survival (OS) for patients with intermediate- (BCLC Stage B) and late-stage HCC (BCLC Stage C or D) is 26 to 30 months and 8 to 19 months, respectively.[2] Whilst the median OS for Stage A patients is typically much longer (> 6

[1] AIHW (2024). https://www.aihw.gov.au/getmedia/ea870f59-a9e4-4772-8fa8-e1206b56a552/cancer-data-in-australia.pdf?v=20250107162604&inline=true. Accessed February 25, 2025.

[2] Llovet JM, Kelley RK, Villanueva A, et al. Hepatocellular carcinoma. *Nature Reviews Disease Primers*. 2021/01/21 2021;7(1):6. doi:10.1038/s41572-020-00240-3

years) than what is seen in more advanced disease, patients who are deemed to have unresectable disease at Stage A have a much poorer prognosis.

4.2 The target population was defined as patients with advanced (unresectable) BCLC Stage A, B or Stage C HCC who are not suitable for curative surgical and/or locoregional therapies and had not received prior systemic therapy. Whilst the PBAC have previously considered listings for these patients with BCLC Stage B and C disease (atezolizumab PSD, July 2020 PBAC meeting), it has not previously considered these patients with BCLC Stage A disease. The proportion of BCLC Stage A patients who have unresectable disease that is not suitable for locoregional therapies is likely to be low. Stage A patients constituted 6% of patients in CM-9DW. An Australian study reporting real world data (N=220) on treatment choice for BCLC Stage 0 and Stage A whose disease was unresectable, reported that only 0.5% (n=1) of patients received systemic therapy with sorafenib (SORA).[3]

4.3 The Pre-Sub-Committee Response (PSCR) noted that since lodgement of the submission, NIVO+IPI had been included in recommendations for the first-line treatment of advanced HCC in the most recent National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology (ESMO) guidelines.[4,5] The ESC noted in the NCCN guidelines that ATEZO+BEV and STRIDE were listed as 'preferred regimens' and NIVO+IPI was listed as an 'other recommended regimen'. The ESC also noted in the ESMO guidelines that ATEZO+BEV and STRIDE were both allocated an A grade recommendation whereas NIVO+IPI was allocated a B grade recommendation.

4.4 NIVO is a fully human immunoglobulin G4 monoclonal antibody which binds to the programmed death-1 receptor and blocks its interaction with the ligands PD-L1 and PD-L2. Binding of PD-L1 to PD-1 results in inhibition of T-cells, which prevents overactivity of the immune system and autoimmune phenomena. IPI is a recombinant, fully human monoclonal antibody that binds to the cytotoxic T lymphocyte-associated antigen 4 (CTLA-4). Binding of IPI to CTLA-4 results in blockage of the inhibitory signal and therefore enhances T-cell response to tumour antigens. Combined with NIVO, this results in enhanced T-cell function.

5 Comparator

5.1 The submission nominated ATEZO+BEV (a PD-L1 inhibitor + VEGF inhibitor) as the main comparator. The selection of the comparator was appropriate for patients with BCLC Stage B and C advanced HCC, but not appropriate for Stage A patients. ATEZO+BEV is recommended as the preferred option to treat first-line advanced HCC in the NCCN

[3] https://onlinelibrary.wiley.com/doi/epdf/10.1002/jgh3.12793

[4] NCCN Clinical Practice Guidelines in Oncology: Hepatocellular Carcinoma (Version 1.2025). NCCN; March 20, 2025.

[5] Vogel A et al. Hepatocellular carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology. 2025;36(5):491-506.

(2024), American Society of Clinical Oncology (ASCO) and ESMO (2025) guidelines and is now standard of care in Australia[6,7,8]. For BCLC Stage A patients whose disease is not suitable for curative surgical and/or locoregional therapies, systemic therapies are recommended.[9] However, in Australia the systemic therapies, ATEZO+BEV, SORA and lenvatinib (LEN) are restricted to patients with BCLC Stage B and C patients only, meaning treatment options for these patients are limited (see paragraph 4.2).

5.2 Under the proposed restriction, patients who develop an intolerance to either a VEGF TKI or ATEZO+BEV may commence NIVO+IPI. The submission did not provide evidence for efficacy and safety in this population. For this subgroup of patients, best supportive care is the most appropriate comparator.

5.3 In the context of the cost-minimisation approach taken by the submission, a further consideration for PBAC is 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.

5.4 Durvalumab plus tremelimumab (a PD-L1 inhibitor + CTLA-4 inhibitor), STRIDE, was nominated as a near market comparator. The ESC considered that this was reasonable.

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

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 organisations (4) via the Consumer Comments facility on the PBS website. The PBAC noted the advice received from the Liver Foundation, Pancare Foundation and Rare Cancers Australia were supportive of listing NIVO+IPI on the PBS for HCC. The inputs described that HCC takes a physical and emotional toll on patients when dealing with the treatment burden which includes the side effects and financial implications of treatment. The inputs noted that carers are often left unsupported and overwhelmed, bearing emotional and financial burdens as well. The inputs noted that patients who live rurally or regionally have

[6] NCCN Clinical Practice Guidelines in Oncology: Hepatocellular Carcinoma (Version 2.2024). NCCN; July 2, 2024.
[7] Rose MG et al. Systemic Therapy for Advanced Hepatocellular Carcinoma: ASCO Guideline Update Clinical Insights. *JCO Oncology Practice*. 2024;20(8):1035-9.
[8] Vogel A et al. Hepatocellular carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology. 2025;36(5):491-506.
[9] https://www.mja.com.au/system/files/issues/214_10/mja250885.pdf

found it difficult to access timely specialist referrals and imaging due to travel. The input indicated the potential availability of NIVO+IPI offers new hope for patients and families. The inputs noted that like all treatments, there are a range of possible side effects with NIVO+IPI, however, the input indicated that this is equally true for other treatments for HCC. Side effects may include muscle cramps, weight gain, feeling cold, dry skin, and hair changes. However, the input indicated that patients generally report that these side effects are manageable and do not outweigh the potential benefits of the treatment.

6.3 The Medical Oncology Group of Australia (MOGA) expressed its strong support for the NIVO+IPI submission, categorising it as one of the therapies of "high priority for PBS listing" on the basis of the CheckMate-9DW trial. The PBAC noted that the MOGA presented a European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for NIVO+IPI, which was limited to 3 (out of a maximum of 5, where 5 and 4 represent the grades with substantial improvement)[10], based on a comparison with SORA/LEN. The PBAC noted however that the comparator in the submission was ATEZO+BEV.

Clinical trials

6.4 The submission was based on one head-to-head trial comparing NIVO+IPI (n=335) with investigators choice of SORA or LEN (n= 333), CM-9DW. For the unmatched, unadjusted, anchored ITC, efficacy and safety data comparing ATEZO+BEV (n=336) to SORA (n=165) in the IMBRAVE150 trial, and STRIDE (n = 393) to SORA (n = 389) in the HIMALAYA trial, were used. The PBAC has previously reviewed an earlier data cut of IMBRAVE150 with a median duration of follow up of 8.6 months (atezolizumab PSD, July 2020 PBAC meeting). This submission presents updated efficacy data from the IMBRAVE150 trial (median duration of follow up 15.6 months).

6.5 Details of the trials presented in the submission are provided in Table 2. For brevity, a complete list of publications is not presented.

[10] Cherny NI, Dafni U, Bogaerts J, et al: ESMO-Magnitude of Clinical Benefit Scale version 1.1. Annals of Oncology 28:2340-2366, 2017]

Table 2: Trials and associated reports presented in the submission

Study identifier (ID)	Report/ Protocol title/ Publication title	Publication citation
Checkmate 9DW (NCT04039607)	BMS (2024). A randomized, multi-center, phase 3 study of nivolumab in combination with ipilimumab compared to sorafenib or lenvatinib as first-line treatment in participants with advanced hepatocellular carcinoma (Check Mate 9DW: CHECKpoint pathway and nivoluMAb clinical Trial Evaluation 9DW). (Clinical Study Report).	BMS, 2024
IMBRAVE150 **(NCT03434379)**	Finn, R. S., et al. (2020). "Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma." New England Journal of Medicine 382(20): 1894-1905.	New England Journal of Medicine 382(20): 1894-1905.
	Galle, P. R., et al. (2021). "Patient-reported outcomes with atezolizumab plus bevacizumab versus sorafenib in patients with unresectable hepatocellular carcinoma (IMbrave150): an open-label, randomised, phase 3 trial."	The Lancet Oncology 22(7): 991-1001.
	Kudo, M., et al. (2023). "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."	Liver Cancer 12(3): 238-250
	Cheng, A. L., et al. (2022). "Updated efficacy and safety data from IMbrave150: Atezolizumab plus bevacizumab vs. sorafenib for unresectable hepatocellular carcinoma."	Journal of Hepatology 76(4): 862-873.
HIMALAYA (NCT03298451)	Abou-Alfa, G. K., et al. (2022). "Tremelimumab plus Durvalumab in Unresectable Hepatocellular Carcinoma."	NEJM evidence 1(8): EVIDoa2100070
	Sangro, B., et al. (2024). "Patient-Reported Outcomes from the Phase III HIMALAYA Study of Tremelimumab Plus Durvalumab in Unresectable Hepatocellular Carcinoma."	Journal of Clinical Oncology 42(23): 2790-2799.
	Sangro, B., et al. (2024). "Four-year overall survival update from the phase III HIMALAYA study of tremelimumab plus durvalumab in unresectable hepatocellular carcinoma."	Annals of Oncology 35(5): 448-457.

Source: Table 21, pp51-54 of the submission.
Blue shading indicates data previously seen by the PBAC.

6.6 The key features of the randomised trials are summarised in Table 3. The clinical claims were based on an unmatched, unadjusted, anchored ITC of OS between CM-9DW, IMBRAVE150 and HIMALAYA.

6.7 Results from CM-9DW were presented from 1 data cut-off (DCO; January 2024, median patient follow-up of 35.2 months) which reflected 1 formal interim analysis (IA) of OS planned for the study when at least 80% of the total number of OS events planned for the final analysis were observed.

6.8 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 DCO have previously been reviewed by the PBAC (atezolizumab PSD, July 2020 PBAC meeting) (Finn et. al, 2020).
- Updated OS follow-up (August 2020 DCO, median patient follow-up of 15.6 months) (Cheng et. al, 2022).

6.9 Results from HIMALAYA were presented from 2 data cut-offs:

- Primary analysis (August 2021 DCO, median patient follow-up of 33.2 months for STRIDE) (Abou-Alfa et. al, 2022).
- Four-year long-term OS and safety follow-up (January 2023 DCO, median patient follow-up of 49.1 months for STRIDE) (Sangro et. al, 2024).

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

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
NIVO+IPI vs SORA/LEN						
CM-9DW	668	R, MC, OL 35.2 months	Low	Untreated advanced/unresectable Stage A, B or C HCC	OS, ORR, DOR, QoL, Safety	Median duration of treatment
ATEZO+BEV vs SORA						
IMBRAVE150	501	R, MC, OL 15 months	Low	Untreated advanced/unresectable Stage A, B or C HCC	OS, ORR, DOR, PFS, QoL, Safety	Median duration of treatment
STRIDE vs SORA						
HIMALAYA	782 [a]	R, MC, OL 49.1 months (STRIDE) 47.3 months (SORA)	Low	Untreated advanced/unresectable Stage B or C HCC	OS, ORR, DOR, PFS, QoL, Safety	Median duration of treatment

Source: Table 28, p85 and Table30, pp 88 - 89 of the submission.
ATEZO+BEV = atezolizumab plus bevacizumab; DOR = duration of response; HCC = hepatocellular carcinoma; MC = multi-centre; NIVO+IPI =nivolumab plus ipilimumab; OL = open label; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; QoL = quality of life; R = randomised; STRIDE = Single Tremelimumab Regular Interval Durvalumab.
[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).

6.10 The median follow-up times across trials are notably higher in the CM-9DW (35.2 months) and HIMALAYA trials (49.1 months [STRIDE]; 47.3 months [SORA]) compared with IMBRAVE150 (15.6 months). The submission stated that interim data cuts of CM-9DW (to better match the follow-up duration of IMBRAVE150) were not available.

6.11 A key difference between CM-9DW, IMBRAVE150 and HIMALAYA that may affect the transitivity of the trials was that the latter two studies only included SORA in the comparator arm, while CM-9DW included an investigator's choice of LEN or SORA. The submission claimed that there is evidence to support the claim that LEN has superior efficacy versus SORA and as a result comparisons of NIVO+IPI to its comparators (STRIDE and HIMALAYA) may be potentially biased against NIVO+IPI. The submission therefore conducted supplementary ITCs based on the SORA subgroup of CM-9DW, however only 15% of patients in the comparator arm received SORA with the remaining 85% receiving LEN. The PBAC have previously considered LEN to be non-inferior in terms of effectiveness compared with SORA (para. 11.2, lenvatinib PSD, July 2018 PBAC Meeting).

6.12 Broadly, the CM-9DW, HIMALAYA and IMBRAVE150 trials had successful randomisation, with no substantial sources of bias in prognostic factors. Comparing the trials, the ESC noted some differences in patient characteristics that may impact the transitivity of the trials were identified:

- There was no restriction in the CM-9DW or IMBRAVE150 trials regarding disease severity according to BCLC stage, however, the HIMALAYA trial was restricted to patients with BCLC Stage B or C disease. The CM-9DW trial has a smaller proportion of patients with BCLC Stage C versus HIMALAYA and IMBRAVE150 (73% vs 82% vs 82%). This difference favours the prognosis of patients in CM-9DW.
- The CM-9DW trial reported a higher proportion of patients with an Eastern Cooperative Oncology Group performance score (ECOG PS) of 0 (71.3%), compared to the IMBRAVE150 (62.3%) and HIMALAYA (62.0%) trials. This difference favours the prognosis of patients in CM-9DW.
- The CM-9DW trial and HIMALAYA enrolled a smaller proportion of patients with macrovascular invasion (MVI) (25.3% and 26.0% respectively) compared with IMBRAVE150 (39.9%) indicating that patients enrolled in the IMBRAVE150 trial may have had more advanced disease at baseline. Extra-hepatic spread at baseline was numerically lower in HIMALAYA (52%) and CM-9DW (54%) compared to IMBRAVE150 (61%); this difference favours the prognosis of patients in HIMALAYA and CM-9DW compared with IMBRAVE150.
- The proportion of non-viral cases of HCC was higher in HIMALAYA (42%) and CM-9DW (36%), compared to IMBRAVE150 (31%). The rate of HBV aetiology HCC was 31% in HIMALAYA, 34% in CM-9DW, both lower than in IMBRAVE150 (48%). Patients with non-viral HCC present with more advanced disease, and have a worse prognosis compared to viral HCC aetiology[11]; this difference favours the prognosis of patients in IMBRAVE150 compared with HIMALAYA and CM-9DW.
- In CM-9DW, 18.5% patients in the NIVO+IPI arm (13.7% on NIVO monotherapy), and 47.1% in the SORA/LEN arm continued treatment beyond progression. The duration of treatment beyond progression was 2.64 months in the NIVO+IPI arm (1.92 months in the NIVO monotherapy) and 0.66 months in the SORA/LEN arm. This difference represents an imbalance in the amount of treatment received by each arm, with more patients in the SORA/LEN arm receiving treatment beyond progression compared to the NIVO+IPI arm, however noting that the duration of treatment beyond progression was less in the SORA/LEN arm than in the NIVO+IPI arm. Similarly, in the IMBRAVE150 trial

[11] 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.

132 (39%) patients in the ATEZO+BEV cohort continued to receive treatment beyond progression. The number of patients in the SORA cohort who were treated beyond progression was not reported. In HIMALAYA, 184 (47.3%) patients receiving STRIDE and 192 (51.3%) patients in the SORA arm continued treatment beyond disease progression. The proportion of patients receiving treatment beyond progression was higher in HIMALAYA and IMBRAVE150 than the NIVO+IPI cohort in CM-9DW. Treatment beyond disease progression is of uncertain clinical benefit.

6.13 Overall, comparison of event rates across common reference groups in the 3 trials showed that the median OS (months) in the CM-9DW trial (SORA/LEN = 20.6; SORA = 20.8) was longer than for the IMBRAVE150 (SORA = 13.4) and the HIMALAYA trial (SORA = 13.8 months). Similarly, median PFS (months) in the CM-9DW trial (SORA/LEN = 9.2; SORA = 11.1) was longer than for the IMBRAVE150 trial (SORA = 4.3) and the HIMALAYA trial (SORA = 4.1). The PSCR acknowledged this exchangeability issue but stated that the direction of any resulting bias was unclear. The ESC considered these differences imply that CM-9DW enrolled patients may have had more favourable prognostic factors and/or had disease which responded better to SORA/LEN compared to patients in HIMALAYA and IMBRAVE150.

Comparative effectiveness

Direct comparison: NIVO+IPI versus SORA/LEN

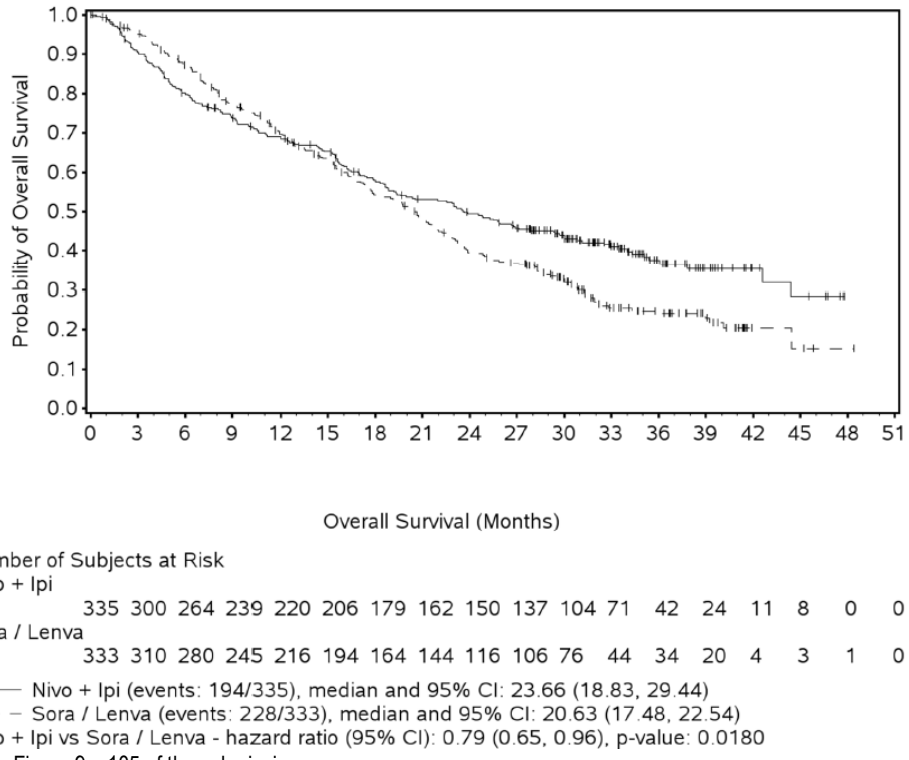
6.14 The OS results of the direct comparison in CM-9DW are presented in Table 4 and the corresponding Kaplan-Meier (KM) curves are presented in Figure 1 (January 2024 DCO; median patient follow-up of 35.20 months).

Table 4: Overall survival in the CM-9DW trial: median follow-up of 35.2 months (ITT)

	NIVO+IPI (N=335)	SORA/LEN (N=333)
Events, n/N (%)	194/335 (57.9)	228/333 (68.5)
Median OS (95% CI), months [a]	23.66 (18.82, 29.44)	20.63 (17.48, 22.54)
Overall survival rate (95% CI)		
3-month	90.4 (86.7, 93.1)	95.1 (92.2, 97.0)
6-month	80.1 (75.4, 84.0)	87.1 (83.0, 90.3)
9-month	73.7 (68.6, 78.1)	77.4 (72.4, 81.6)
12-month	68.4 (63.1, 73.2)	69.7 (64.4, 74.5)
18-month	57.9 (52.3, 63.1)	54.3 (48.6, 59.7)
24-month	49.4 (43.8, 54.8)	39.2 (33.7, 44.7)
36-month	37.5 (31.6, 43.4)	24.1 (19.0, 29.6)
HR (95% CI; p-value)[b, c]	**0.79 (0.65, 0.96; p=0.0180)**	

Source: Table 35, p104 of the submission, Table 7.2-1, p72 of the submission.
CI = confidence interval; HR = hazard ratio; IPI = ipilimumab; ITT = intention to treat; LEN = lenvatinib; NIVO = nivolumab; OS = overall survival; SORA = sorafenib.
[a] Based on Kaplan Meier estimate.
[b] Stratified Cox proportional hazard model.
[c] Two-sided p-value from stratified log-rank test.
Boundary for statistical significance p-value <= 0.0257.
Bold text indicates a statistically significant result.

Figure 1: Kaplan Meier curves of overall survival in the CM-9DW trial (NIVO+IPI vs SORA/LEN) (ITT)



Source: Figure 9, p105 of the submission.
CI = confidence interval; Ipi/IPI = ipilimumab; ITT = intention to treat; Lenva/LEN = lenvatinib; Nivo/NIVO = nivolumab; Sora/SORA = sorafenib.

6.15 The median OS for NIVO+IPI and SORA/LEN was 23.66 months and 20.63 months, respectively. There was statistically significant improvement in OS for NIVO+IPI over

SORA/LEN (HR: 0.79; 95%CI: 0.65, 0.96; p=0.0180). The KM curves show an initial separation from approximately 3 months favouring SORA/LEN. This trend continued until the curves crossed at approximately 12 months, suggesting that the proportional hazards assumption was violated. Given the violation of the proportional hazards assumption, the evaluation considered the HR, CIs and p-values for this analysis should be interpreted with caution. There were 12 deaths in the NIVO+IPI arm due to study drug toxicity with 11 of these occurring within the first 6 months of treatment. By comparison, 6 deaths attributable to study drug toxicity occurred in the SORA/LEN arm, with 2 of these occurring in the first 12 months. The PSCR noted this pattern of survival has been observed in other indications for NIVO+IPI and that this combination is known to result in early treatment-related toxicity (largely due to the IPI component); however, this is balanced over time by the long-term survival of a proportion of patients (Schadendorf, 2017). The PSCR suggested that this risk may be mitigated through careful selection of patients by clinicians although notes that no specific guidelines on the topic exist to identify these types of patients. The ESC noted the requested restrictions do not account for this particular patient population and that no clinical evidence was provided to inform which patients would be less likely to experience early toxicity. The pre-PBAC response suggested that patients with extrahepatic spread (EHS) or macrovascular invasion (MVI), alpha fetoprotein (AFP) levels ≥400 ng/mL, larger tumours and higher number of liver nodules (>3), poorer liver function, and worse performance status, may not be considered the most appropriate candidates for NIVO+IPI based on an early death analysis using a multivariate logistic model.

6.16 During the evaluation results for restricted mean survival time (RMST) were extracted from the CM-9DW Clinical Study Report (CSR). The results are presented in Table 5.

Table 5: Restricted mean survival time of overall survival in the CM-9DW trial (ITT)

	NIVO+IPI N=335	SORA/LEN N=333	Difference months (95% CI)
6-month	5.45 (5.31, 5.59)	5.68 (5.56, 5.79)	-0.22 (-0.40, -0.05)
12-month	9.88 (9.49, 10.27)	10.37 (10.03, 10.70)	-0.49 (-1.00, 0.02)
18-month	13.72 (13.06, 14.37)	14.12 (13.53, 14.71)	-0.40 (-1.28, 0.48)
24-month	16.92 (16.00, 17.85)	17.00 (16.15, 17.85)	-0.08 (-1.33, 1.18)
30-month	19.71 (18.51, 20.90)	19.19 (18.09, 20.28)	0.52 (-1.10, 2.14)
36-month	22.16 (20.70, 23.62)	20.80 (19.49,22.11)	1.36 (-0.61, 3.32)

Source: Table 14.2.1.14, p 483 of Attachment ca2099dw-primary-csr-14-tables, of the submission.
CI = confidence interval; IPI = ipilimumab; LEN = lenvatinib; NIVO = nivolumab; OS = overall survival; SORA = sorafenib.

6.17 RMST is recommended for use to estimate treatment effect when the proportional hazards assumption has been violated. The analysis demonstrated that for the first 24 months SORA/LEN had numerically longer median OS compared to NIVO+IPI. At 36 months NIVO+IPI had a longer median OS than SORA/LEN, but this difference was not statistically significant, noting that RMST analyses were post-hoc and not powered to achieve statistical significance.

6.18 Median PFS by blinded independent clinical review (BICR) was 9.07 months for the NIVO+IPI treatment arm which was numerically shorter than the 9.20 months for the SORA/LEN treatment arm. The HR for PFS (BICR) was numerically in favour of NIVO+IPI (HR: 0.87; 95% CI: 0.72,1.06), however was not statistically significant.

Direct comparison: ATEZO+BEV versus SORA

6.19 Updated results from IMBRAVE150 are presented (31 August 2020 DCO) in Table 6.

Table 6: Summary of IMBRAVE150 overall survival results (ITT)

	ATEZO+BEV N=336	SORA N=165
Primary analysis (DCO: 29 August 2019)		
Events n/N (%)	96/336 (28.6)	65/165 (39.4)
Median OS (95% CI), months	NE	13.2 (10.4, NE)
HR (95% CI; p-value)	**0.58 (0.42, 0.79; p<0.001)**	
Updated analysis (DCO: 31 August 2020)		
Events n/N (%)	291/336 (74.0)	134/165 (81.2)
Median OS (95% CI), months	19.2 (17.0, 23.7)	13.4 (11.4, 16.9)
HR (95% CI; p-value)	**0.66 (0.52, 0.85; p<0.001)**	

Source: Table 40, p111 of the submission.
ATEZO+BEV = atezolizumab + bevacizumab; CI = confidence interval; DCO = data cut-off; HR = hazard ratio; ITT = intention to treat; NE = not estimable; OS = overall survival; SORA = sorafenib.
Blue shading indicates data previously seen by the PBAC.

6.20 A statistically significant OS benefit for ATEZO+BEV compared with SORA was observed at the updated analysis.

Direct comparison: STRIDE versus SORA

6.21 OS analysis for the HIMALAYA trial from the January 2023 data cut-off is reported in Table 7.

Table 7: Overall survival in the HIMALAYA trial: median follow-up of 48 months (ITT)

	STRIDE N=393	SORA N=389
Events, n/N (%)	291/393 (74.0%)	316/389 (81.2%)
Median OS (95% CI), months	16.4 (14.2, 19.6)	13.8 (12.3, 16.1)
HR (95% CI; p-value)	**0.78 (0.67, 0.92; p=0.0037)**	

Source: Table 44, p117 of the submission.
CI = confidence intervals; HR = hazard ratios; ITT = intention-to-treat; OS = overall survival; SORA = sorafenib; STRIDE = Single Tremelimumab Regular Interval Durvalumab.
Bold text indicates a statistically significant result.

6.22 The median OS was longer in the STRIDE arm (16.4 months) compared with the SORA arm (13.8 months). Overall, a statistically significant treatment benefit with regards to OS was observed in the STRIDE cohort relative to the SORA cohort (HR=0.78; 95% CI: 0.67, 0.92; p=0.0037).

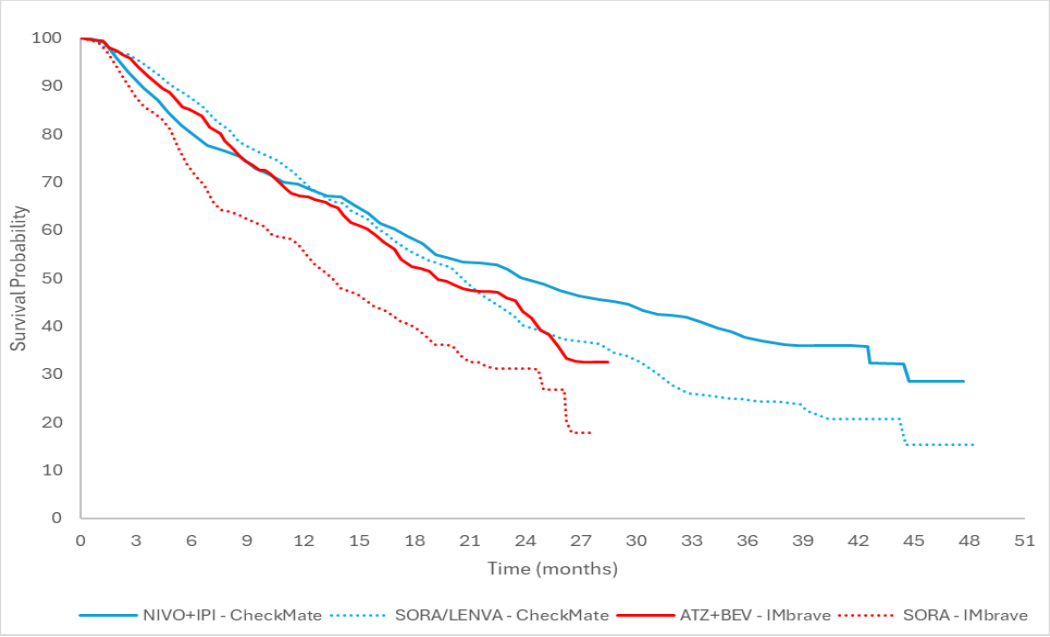
Indirect treatment comparisons

6.23 The submission presented unmatched, unadjusted, anchored Bucher ITCs to compare efficacy and safety of NIVO+IPI compared to STRIDE and ATEZO+BEV, using the common (anchor) SORA and SORA/LEN arms of the included trials. Given the violation of the proportional hazards assumption observed for OS in CM-9DW the use of OS as

the common outcome of interest is likely inappropriate as the treatment effect of NIVO+IPI appears to change over time and the ITC may produce inaccurate estimates of effect.

Indirect treatment comparison (NIVO+IPI versus ATEZO+BEV)

6.24 The NIVO+IPI versus ATEZO+BEV ITC analyses for the ITT (SORA/LEN) population and the SORA subgroup of CM-9DW are presented in Table 8, with corresponding KM curves of the OS analysis, presented in Figure 2: **Kaplan Meier curves of overall survival in the CM-9DW (NIVO+IPI vs SORA/LEN) and IMBRAVE150 (ATEZO+BEV vs SORA) trials**



Source: Figure 31, p171 of the submission. ATEZO+BEV = atezolizumab plus bevacizumab; LENVA = lenvatinib; NIVO+IPI = nivolumab plus ipilimumab; SORA = sorafenib.

6.25 Figure 3 and Figure 2 respectively.

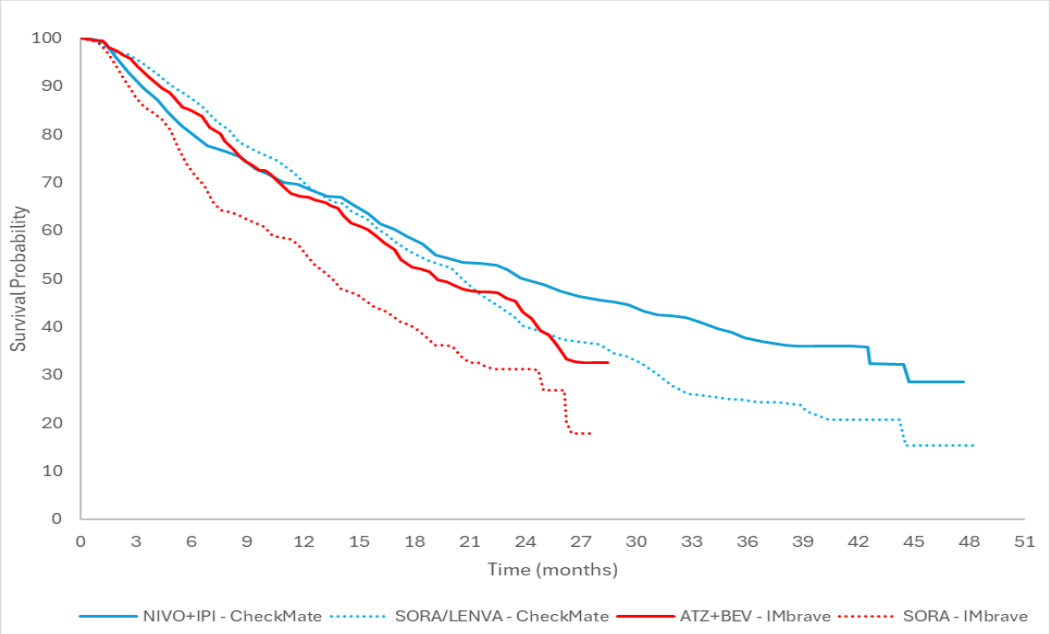
Table 8: Overall survival: NIVO+IPI versus ATEZO+BEV

	Direct Estimate HR [95% CI]		Indirect Estimate HR [95% CI] p-value
Analysis	**NIVO+IPI (N=335) vs. SORA/LEN (N=333)**	**ATEZO+BEV (N=336) vs. SORA (N=165)**	**NIVO+IPI vs. ATEZO+BEV**
CM-9DW vs IMBRAVE150	0.79 [0.65, 0.96]	0.66 [0.52, 0.85]	1.197 [0.875, 1.638] (p = 0.2612)
Analysis	**NIVO+IPI (N=335) vs. SORA (N=50)**	**ATEZO+BEV (N=336) vs. SORA (N=165)**	**NIVO+IPI vs. ATEZO+BEV**
CM-9DW (SORA subgroup) vs IMBRAVE150	0.70 [0.49, 0.98]	0.66 [0.52, 0.85]	1.061 [0.694, 1.622] (p = 0.7860)

Source: Table 67, p169 of the submission

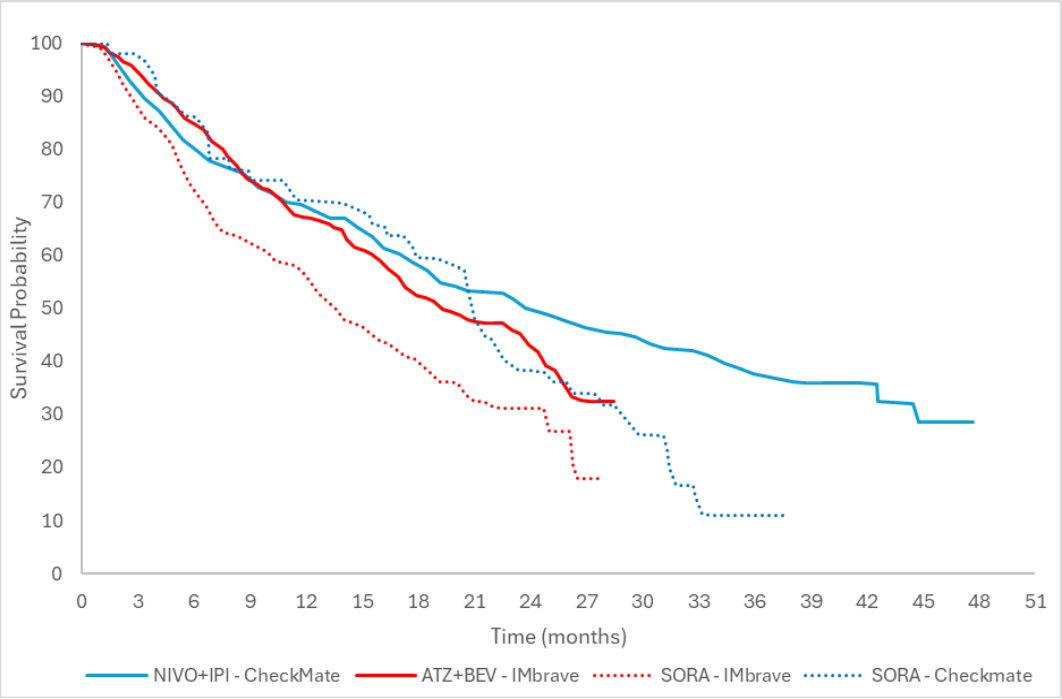
ATEZO+BEV = atezolizumab plus bevacizumab; CI = confidence interval; HR = hazard ratio; LEN = lenvatinib; NIVO+IPI = nivolumab plus ipilimumab; SORA = sorafenib.

Figure 2: Kaplan Meier curves of overall survival in the CM-9DW (NIVO+IPI vs SORA/LEN) and IMBRAVE150 (ATEZO+BEV vs SORA) trials



Source: Figure 31, p171 of the submission. ATEZO+BEV = atezolizumab plus bevacizumab; LENVA = lenvatinib; NIVO+IPI = nivolumab plus ipilimumab; SORA = sorafenib.

Figure 3: Kaplan Meier curves of overall survival in the CM-9DW (NIVO+IPI vs SORA subgroup) and IMBRAVE150 (ATEZO+BEV vs SORA) trials



Source: Figure 30, p170 of the submission.
ATZ+BEV = atezolizumab plus bevacizumab; NIVO+IPI = nivolumab plus ipilimumab; SORA = sorafenib.

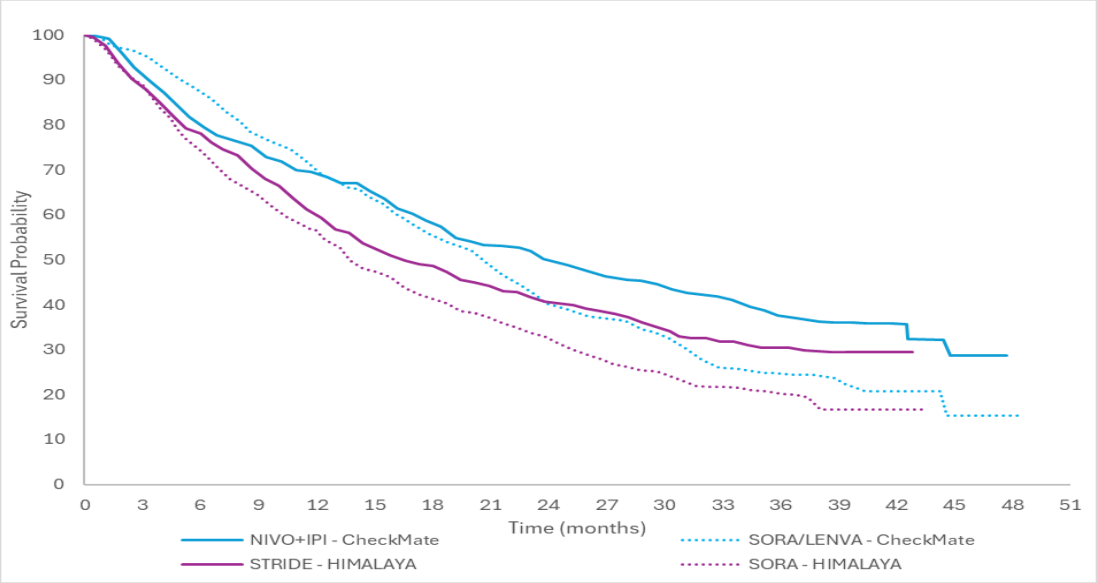
6.26 The ESC noted that based on the SORA/LEN arm of CM-9DW, the results produced a point estimate which suggested NIVO+IPI conferred a 20% increased hazard of death compared to ATEZO+BEV (HR=1.197; 95% CI: 0.875, 1.638). Based on the results for the SORA subgroup of the SORA/LEN arm in the CM-9DW trial, the ITC yielded a point estimate of 1.061 (95% CI: 0.649, 1.622). The ESC noted that the results for the SORA subgroup of the SORA/LEN arm in the CM-9DW trial were associated with a wide confidence interval and were based on a post-hoc analysis of a subgroup with a small sample size (N=50) that represented only 15% of the comparator arm which makes these results less robust and vulnerable to confounding, noting this is a non-stratified subgroup.

6.27 The submission did not present a non-inferiority margin (NIM) and instead stated that non-inferiority could be argued if the comparison failed to demonstrate a statistically significant difference, resulting in the two treatments being considered similar. The evaluation considered this was not a reasonable interpretation; the submission did not provide calculations of the power required to achieve statistical significance in the ITC. Further, both the point estimate and most of the 95% CI for the HR are > 1, suggesting patients treated with NIVO+IPI may have an increased hazard of death compared to patients treated with ATEZO+BEV. Considering the point estimate results, the ESC advised that the possibility that NIVO+IPI treatment is significantly worse than ATEZO+BEV cannot be ruled out, noting that the ITC lacks sufficient power to demonstrate statistical significance.

6.28 The ESC also agreed with the evaluation that the comparability of the KM curves is limited by the observed difference in OS between the comparator (SORA and SORA/LEN) arms of the two trials, indicating there may be differences between the study populations which may have biased the results.

<u>Indirect treatment comparison (NIVO+IPI versus STRIDE)</u>

The NIVO+IPI versus STRIDE ITC for efficacy analysis for the ITT (SORA/LEN) population and SORA subgroup is presented in Table 9, with corresponding KM curves, presented in Figure 4: Kaplan Meier curves of overall survival in the CM-9DW (NIVO+IPI vs SORA/LEN) and HIMALAYA (STRIDE vs SORA) trials



Source: Figure 33, p 174 of the submission.
LENVA = lenvatinib; NIVO+IPI = nivolumab plus ipilimumab; SORA = sorafenib; STRIDE = Single Tremelimumab Regular Interval Durvalumab.

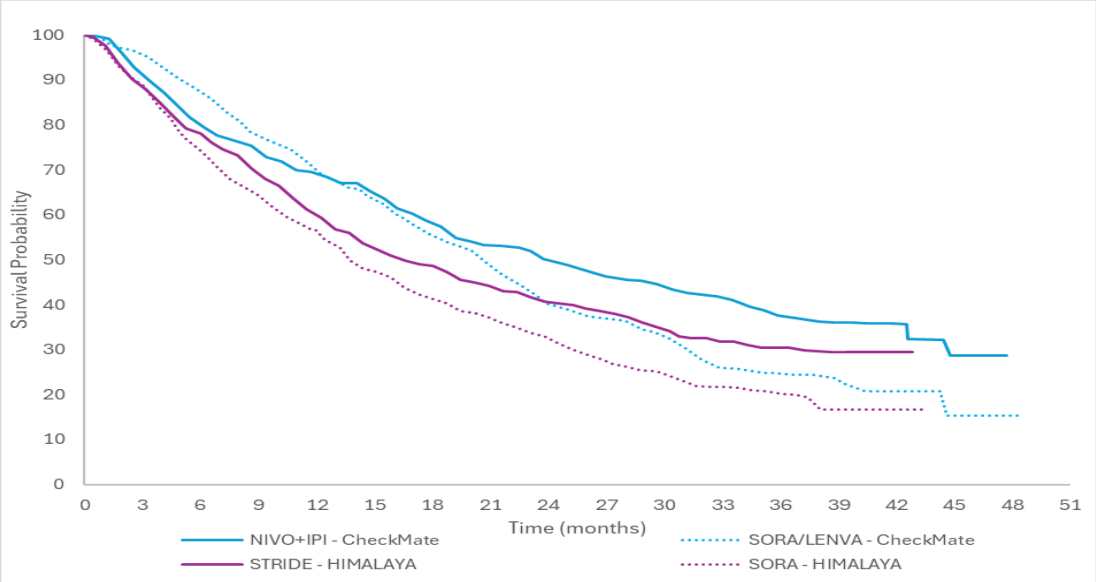
6.29 Figure 5 and Figure 4, respectively.

Table 9: Overall survival: NIVO+IPI versus STRIDE

	Direct Estimate HR [95% CI]		Indirect Estimate HR [95% CI] p-value
Analysis	**NIVO+IPI (N=335) vs. SORA/LEN (N=333)**	**STRIDE (N=393) vs. SORA (N=389)**	**NIVO+IPI vs. STRIDE**
CM-9DW vs HIMALAYA	0.79 [0.65, 0.96]	0.78 [0.67, 0.92]	1.013 [0.788, 1.302] (p = 0.9209)
Analysis	**NIVO+IPI (N=335) vs. SORA (N=50)**	**STRIDE (N= 393) vs. SORA (N=389)**	**NIVO+IPI vs. STRIDE**
CM-9DW (SORA subgroup) vs HIMALAYA	0.70 [0.49, 0.98]	0.78 [0.67, 0.92]	0.897 [0.613, 1.314] (p = 0.5779)

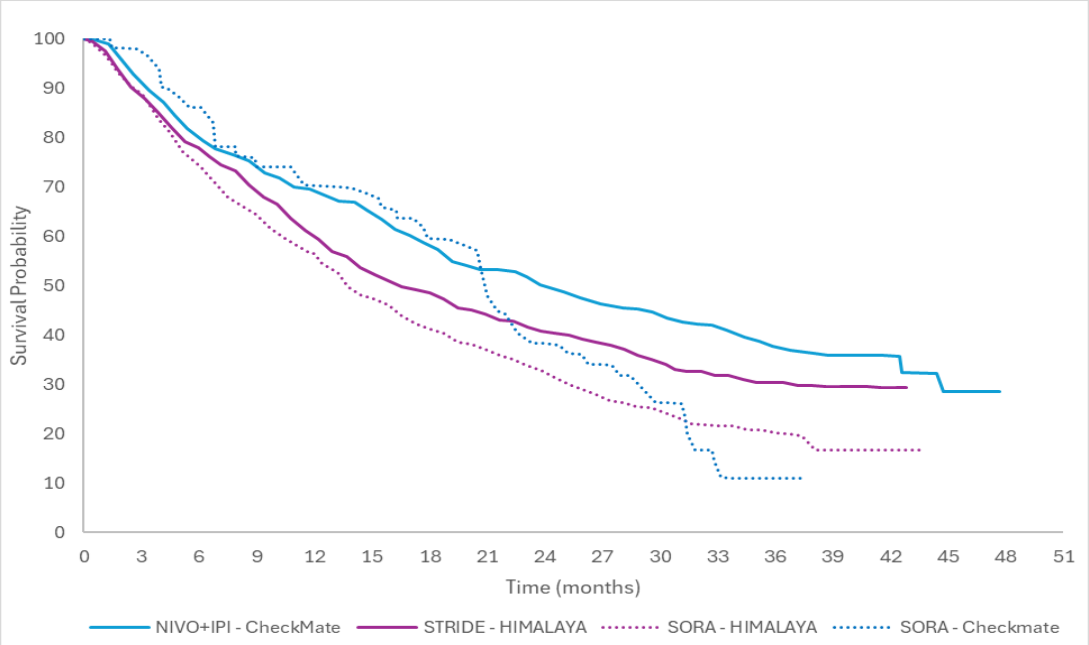
Source: Table 67, p172 of the submission
CI = confidence interval; HR = hazard ratio; LEN = lenvatinib; NIVO+IPI = nivolumab plus ipilimumab; SORA = sorafenib; STRIDE = Single Tremelimumab Regular Interval Durvalumab.

Figure 4: Kaplan Meier curves of overall survival in the CM-9DW (NIVO+IPI vs SORA/LEN) and HIMALAYA (STRIDE vs SORA) trials



Source: Figure 33, p 174 of the submission.
LENVA = lenvatinib; NIVO+IPI = nivolumab plus ipilimumab; SORA = sorafenib; STRIDE = Single Tremelimumab Regular Interval Durvalumab.

Figure 5: Kaplan Meier curves of overall survival in the CM-9DW (NIVO+IPI vs SORA) and HIMALAYA (STRIDE vs SORA subgroup) trials



Source: Figure 32, p173 of the submission.
NIVO+IPI = nivolumab plus ipilimumab; SORA = sorafenib; STRIDE = Single Tremelimumab Regular Interval Durvalumab.

6.30 The submission reported that using the SORA/LEN cohort of the CM-9DW trial, the results showed comparable OS for patients treated with NIVO+IPI versus STRIDE (HR=1.013; 95% CI: 0.788, 1.302). The ESC noted that the point estimate was smaller

than reported for the ATEZO+BEV comparison. However, the ESC considered that the observed differences in the KM curves between the comparator arms of the two trials indicated there were likely differences between the study populations which may bias the results.

6.31 The submission noted the SORA subgroup of the SORA/LEN arm in the CM-9DW trial results demonstrated a numerically favourable OS benefit in favour of treatment with NIVO+IPI relative to STRIDE (HR=0.897; 95% CI: 0.613, 1.314). However, the ESC noted that the results were associated with a wide confidence interval and were based on a post-hoc analysis of a subgroup with a small sample size (N=50) that represented only 15% of the comparator arm.

6.32 The submission did not elect an NIM, the consequences of which have been discussed at paragraph 6.27 and apply equally to comparison of NIVO+IPI with STRIDE.

Matched adjusted indirect comparison

6.33 The submission referred in its discussion of the interpretation of the evidence, to a matched adjusted indirect comparison (MAIC) that was conducted to compare NIVO+IPI to ATEZO+BEV and STRIDE. These data were not presented as ITC evidence to inform the submission's conclusion but instead results were provided in a submission attachment.

6.34 The PSCR stated that the detailed methodology of the MAIC was unavailable at the time of the submission. The PSCR provided a supporting document for the ITC (STC and MAIC) detailing methods and results of the analyses. The ESC noted that the results of the MAIC suggested non-inferiority of NIVO+IPI with ATEZO+BEV and STRIDE but noted that these were not evaluated.

Comparative harms

Direct comparison: NIVO+IPI versus SORA/LEN

6.35 The results of NIVO+IPI versus SORA/LEN for safety are presented in Table 10. Based on the increased proportion of serious treatment-related adverse events (28.3% vs 14.5%), Grade 3-4 treatment related serious adverse events (25.0% vs 12.9%), treatment-related AEs leading to discontinuation (17.8% vs 10.5%) and numerically more deaths due to study drug toxicity (n=12 [3.6%] vs n=3 [0.9%]), NIVO+IPI demonstrated an inferior safety profile compared to SORA/LEN.

Table 10: Overview of safety profile of NIVO/IPI versus SORA/LEN in the CM-9DW trial

	NIVO+IPI N=332	SORA/LEN N=325
	n (%)	n (%)
All-casualty AEs	331 (99.7)	320 (98.5)
Treatment-related AEs	278 (83.7)	297 (91.4)
Grade 3-4 treatment-related AEs	137 (41.3)	138 (42.5)
All-causality SAEs	176 (53.0)	143 (44.0)
Treatment-related SAEs	94 (28.3)	47 (14.5)
Grade 3-4 treatment-related SAEs	83 (25.0)	42 (12.9)
AEs leading to discontinuation	88 (26.5)	75 (23.1)
Treatment-related AEs leading to discontinuation	59 (17.8)	34 (10.5)
Deaths	192 (57.8)	224 (68.9)
Deaths due to study drug toxicity	12 (3.6)	3 (0.9)

Source: Table 48, p126 of the submission, Table 8.2-2, p118, Table 8.4-2, p133 of the CSR.
AE = adverse event; SAE = serious adverse event.

Indirect treatment comparison (NIVO+IPI versus ATEZO+BEV)

6.36 No safety data were available for the post-hoc SORA subgroup in the CM-9DW trial, and as a result the submission presented results for the overall SORA/LEN cohort only (Table 11). Median duration of treatments was lower in the NIVO+IPI arm compared to ATEZO+BEV (4.7 vs 8.4/7 months).

Table 11: Overview of safety profile: NIVO+IPI versus ATEZO+BEV

	Direct Estimate OR [95% CI]		Indirect Estimate OR [95% CI]
	NIVO+IPI vs. SORA/LEN	ATEZO+BEV vs. SORA	NIVO+IPI vs. ATEZO+BEV
All-cause AEs	5.17 [0.6, 44.51]	0.6 [0.12, 2.91]	8.617 [0.591, 125.573]
Treatment-related AEs	0.49 [0.3, 0.79]	0.34 [0.16, 0.74]	1.441 [0.582, 3.566]
All-cause SAEs	1.44 [1.06, 1.95]	1.95 [1.31, 2.9]	0.738 [0.448, 1.218]
Treatment-related SAEs	2.34 [1.58, 3.45]	1.57 [0.96, 2.59]	1.49 [0.793, 2.803]
AEs leading to discontinuation	1.2 [0.84, 1.71]	2.15 [1.23, 3.75]	0.558 [0.288, 1.081]
Treatment-related AEs leading to discontinuation	1.85 [1.16, 2.91]	NR	NA
Deaths	0.62 [0.45, 0.85]	0.69 [0.46, 1.02]	0.899 [0.54, 1.496]

Source: Table 70, p177 of the submission.
AE = adverse event; ATEZO+BEV = atezolizumab plus bevacizumab; CI = confidence interval; LEN = lenvatinib; NA = not applicable; NIVO+IPI = nivolumab plus ipilimumab; NR = not reported; OR = odd ratio; SAE = serious adverse event; SORA = sorafenib.

6.37 The submission also conducted indirect comparisons for frequently occurring Grade 3-4 treatment-related adverse events between NIVO+IPI and ATEZO+BEV with comparable rates occurring between the respective CM-9DW and IMBRAVE150 trials in the intervention arms (41.3% versus 43.5%). The submission reported that there was a reduction in the risk of hypertension and proteinuria for NIVO+IPI relative to ATEZO+BEV (OR=0.008; 95% CI: 0.000, 0.143; and OR=0.004; 95% CI 0.000, 0.134, respectively). Conversely, a reduction in the risk of rash and aspartate aminotransferase (AST) increase was detected for ATEZO+BEV relative to NIVO+IPI (OR=38.521; 95% CI: 1.516, 978.933; and OR=6.273; 95% CI 1.060, 37.117, respectively).

Indirect treatment comparison (NIVO+IPI versus STRIDE): Safety

6.38 The results of the ITC for NIVO+IPI versus STRIDE for safety are presented in Table 12.

Table 12: Overview of safety profile: NIVO+IPI versus STRIDE

	Direct Estimate OR [95% CI]		Indirect Estimate OR [95% CI]
	NIVO IPI vs. SORA/LEN	**STRIDE vs. SORA**	**NIVO IPI vs. STRIDE**
All-cause AEs	5.17 [0.6, 44.51]	1.8 [0.81, 3.98]	2.872 [0.289, 28.525]
Treatment-related AEs	0.49 [0.3, 0.79]	0.56 [0.39, 0.81]	0.875 [0.477, 1.605]
All-cause SAEs	1.44 [1.06, 1.95]	1.61 [1.19, 2.17]	0.894 [0.583, 1.372]
Treatment-related SAEs	2.34 [1.58, 3.45]	2.06 [1.33, 3.18]	1.136 [0.633, 2.039]
AEs leading to discontinuation	1.2 [0.84, 1.71]	0.78 [0.53, 1.16]	1.538 [0.907, 2.611]
Treatment-related AEs leading to discontinuation	1.85 [1.16, 2.91]	0.73 [0.45, 1.19]	2.534 [1.298, 4.949]
Deaths	0.62 [0.45, 0.85]	1.08 [0.63, 1.85]	0.574 [0.307, 1.073]

Source: Table 71, p178 of the submission.
AE = adverse event; CI = confidence interval; LEN = lenvatinib; NIVO+IPI = nivolumab plus ipilimumab; OR = odd ratio; SAE = serious adverse event; SORA = sorafenib; STRIDE = Single Tremelimumab Regular Interval Durvalumab.

6.39 A difference favouring STRIDE for treatment related AEs leading to discontinuation was observed (OR=2.534; 95%CI: 1.298, 4.949).

6.40 Review of Grade 3-4 treatment-related AEs in patients treated with NIVO+IPI versus STRIDE showed that there was no difference between NIVO+IPI versus STRIDE with regards to individual Grade 3-4 treatment-related AEs, except for AST increase whereby there was a greater risk in the NIVO+IPI arm compared to the STRIDE arm (OR=7.089; 95% CI: 1.175, 42.774).

Benefits/harms

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

Clinical claim

6.42 The submission described NIVO+IPI as:

- Non-inferior to the primary comparator ATEZO+BEV in terms of comparative effectiveness and safety (noting different AE profiles) in patients with unresectable HCC.
- Non-inferior to STRIDE in terms of comparative effectiveness and safety (noting different AE profiles) in patients with unresectable HCC.

6.43 The evaluation considered the therapeutic conclusion presented in the submission was not adequately supported by the evidence presented in the submission in terms of effectiveness.

6.44 Whilst the direct results from the CM-9DW trial showed that NIVO+IPI led to a statistically significant improvement in OS relative to SORA/LEN (HR=0.79; 95% CI: 0.65, 0.96, p=0.0180), the corresponding KM curves cross suggesting a violation of the

proportional hazards assumption. Given the violation of the proportional hazards assumption the HR, CIs and p-values for this analysis should be interpreted with caution. RMST analysis of OS for NIVO+IPI vs SORA/LEN showed that OS numerically favoured SORA/LEN up until 24 months. From 24 months OS numerically favoured NIVO+IPI, however results were not statistically significant. The PSCR acknowledged that this combination is known to result in early treatment-related toxicity (largely due to the IPI component) and suggested that this risk may be mitigated through careful selection of patients by clinicians. The ESC noted the requested restrictions do not account for this particular patient population and no clinical evidence was provided to inform which patients would be less likely to experience early toxicity.

6.45 The submission's anchored ITC did not adequately demonstrate non-inferiority in terms of efficacy or safety of NIVO+IPI compared to the primary comparator ATEZO+BEV or the near market comparator, STRIDE. Given the violation of the proportional hazards assumption observed for OS in CM-9DW, the use of OS as the common outcome of interest is likely inappropriate as the treatment effect of NIVO+IPI appears to change over time.

6.46 For both the NIVO+IPI ITT (SORA/LEN) versus ATEZO+BEV and STRIDE ITC analyses, there were a number of transitivity issues between the trials, including differences in the comparator treatment regimen (15% SORA; 85% LEN in CM-9DW; SORA in IMBRAVE150 and HIMALAYA), differences in patient baseline characteristics and differences in the duration of follow-up. Most notably, event rates differed across common reference groups; the median OS (months) in the CM-9DW trial (SORA/LEN = 20.63; SORA = 20.76) was longer than for IMBRAVE150 (SORA = 13.4) and HIMALAYA (SORA=13.8). The ESC considered these differences meant it was difficult to discern how much of the median OS benefit described in the NIVO+IPI arm of the CM-9DW trial is attributable to treatment benefit, and how much may be due to favourable prognostic factors of the trial population compared to the trial populations of IMBRAVE150 and HIMALAYA.

6.47 For the NIVO+IPI ITT (SORA/LEN) versus ATEZO+BEV ITC analysis the point estimate and most of the 95% CI for the HR for the comparison against the primary comparator ATEZO+BEV are > 1, suggesting patients treated with NIVO+IPI may have up to a 64% increased hazard of death compared to patients treated with ATEZO+BEV (HR=1.197; 95% CI 0.875, 1.638). The absence of a statistically significant difference in OS between NIVO+ IPI and ATEZO+BEV does not necessarily establish non-inferiority; this would have required that the confidence limits of the difference in treatment effect did not include an a priori stated clinically meaningful difference favouring the comparator (PBAC Guidelines, v5.0, 2016).

6.48 Analysis of the NIVO+IPI SORA subgroup versus ATEZO+BEV yielded a HR of 1.061 (95% CI: 0.649, 1.622). The result was associated with a wide confidence interval with a large proportion > 1. Additionally, the small sample size of the SORA subgroup (approximately 15%) potentially limits the interpretability of the results, with an

increased risk of variability of results and a higher risk of Type II errors, reducing the ability to confidently generalise findings from these analyses to a broader population.

6.49 The NIVO+IPI ITT (SORA/LEN) versus STRIDE ITC analysis yielded a HR=1.013 (95% CI: 0.788, 1.302), the SORA subgroup analysis reported a HR=0.897 (95% CI: 0.613, 1.314). Given the transitivity issues noted above, and the absence of a stated non-inferiority margin the claim of non-inferior efficacy was not supported.

6.50 The ESC acknowledged the concerns with the evidence presented raised by the evaluation and noted that the point estimates of the ITCs tended to numerically favour the comparator. Overall, the ESC agreed with the evaluation that the claim of non-inferior efficacy was not adequately supported by the evidence provided in the submission.

6.51 The submission reported that the NIVO+IPI ITT (SORA/LEN) versus ATEZO+BEV ITC safety analysis showed no substantial differences between treatments based on all-cause and treatment-related AEs, all-cause and treatment-related SAEs, AEs leading to discontinuation and deaths. The submission additionally noted that the NIVO+IPI ITT (SORA/LEN) versus STRIDE ITC safety analysis identified no substantial differences between cohorts based on all-cause and treatment-related AEs, all-cause and treatment-related SAEs, and AEs leading to discontinuation and death. A difference favouring STRIDE for treatment related AEs leading to discontinuation (OR=2.534; 95%CI: 1.298, 4.949) was however found. Overall, the ESC considered the submission's claim of non-inferior safety of NIVO+IPI compared to both ATEZO+BEV and STRIDE was uncertain given the transitivity concerns identified, but likely reasonable (noting different AE profiles).

6.52 The PBAC considered that the claim of non-inferior comparative effectiveness was not adequately supported by the data.

6.53 The PBAC considered that the claim of non-inferior comparative safety was uncertain given the transitivity concerns identified.

Economic analysis

6.54 The submission presented a CMA comparing NIVO+IPI to ATEZO+BEV for the treatment of first-line HCC. The reasonableness of the approach is contingent upon accepting the claim of non-inferior comparative effectiveness and safety, which the ESC considered was not adequately supported by the available data. The submission did not present a CMA comparing NIVO+IPI to STRIDE. The evaluation considered this was reasonable given STRIDE was nominated as a near-market comparator.

6.55 The components and assumptions for the CMA are summarised in Table 13.

Table 13: 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 treatment comparison (ITC) of NIVO+IPI and ATEZO+BEV based on the CM-9DW trial, which compared NIVO+IPI to SORA/LEN, and the IMBRAVE150 trial, which compared ATEZO+BEV to SORA.
Equi-effective doses	A dose of nivolumab (1 mg/kg) every 3 weeks for a maximum of 4 doses with ipilimumab (3 mg/kg) every three weeks for a maximum of 4 doses, followed by nivolumab monotherapy (480 mg) every 4 weeks for a total duration of 4.68 months 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. 1,656 mg nivolumab + 881 mg ipilimumab = 14,610 mg atezolizumab + 11,174 mg bevacizumab The estimated doses and duration of treatment were based on median values from CM-9DW and IMBRAVE150.
Direct medicine costs	The cost of NIVO+IPI per treatment course was $[redacted], which is $[redacted] higher than the cost ATEZO+BEV per treatment course which was $[redacted] (based on the assumed effective prices of ATEZO+BEV).
Other costs or cost offsets	MBS cost, item 13950 for the administration of the intravenous infusion ($123.05), applied to both NIVO+IPI and ATEZO+BEV.

Source: Table 81, pp197-198 of the submission; Attachment 11 NIVO IPI 1L HCC Cost-Minimisation Analysis, worksheets: CMA, Dosing and Assumptions, Admin Costs, Comparator drug cost per course.
ATEZO+BEV = atezolizumab plus bevacizumab; ITC = indirect treatment comparison; kg = kilogram; MBS = Medicare Benefits Schedule; mg = milligram; NIVO+IPI = nivolumab plus ipilimumab.

6.56 The submission estimated the equi-effective doses of NIVO+IPI and ATEZO+BEV based on the median treatment duration in CM-9DW and IMBRAVE150 (Cheng 2022). The ESC agreed with the evaluation that this was inappropriate as it underestimated the treatment exposure required to achieve the assumed equi-effective outcomes. The dosage regimens used in the trials were consistent with each medicine's TGA approved Product Information.

6.57 The submission acknowledged that alternative dosing regimens (either 2 weekly or 4 weekly) for ATEZO were available on the PBS to allow patients to continue to receive ATEZO where BEV is discontinued. These dosing regimens were not included in the CMA presented by the submission. This was based on low utilisation of ATEZO 2 weekly or 4 weekly regimens (3.6% of the total ATEZO HCC utilisation based on PBS Statistics, December 2023 to November 2024). The evaluation considered that this was reasonable given that patients in IMBRAVE150 received ATEZO+BEV every 3 weeks only.

6.58 The submission stated that the CMA was based on 4-weekly dosing for the NIVO monotherapy treatment phase (rather than 240 mg every 2 weeks). The evaluation considered this was reasonable; patients in CM-9DW were administered 480 mg every 4 weeks of NIVO monotherapy.

6.59 Dosage of NIVO+IPI in the induction phase and BEVA are weight based, the submission used the average patient weight in the CM-9DW trial of 73.42 kg to estimate total average dose per patient. The evaluation considered this was reasonable.

6.60 The proposed equi-effective doses for NIVO+IPI and ATEZO+BEV were based on the median duration of therapy (DOT) reported in CM-9DW and IMBRAVE150. The submission stated that in CM-9DW, 100% of patients who received treatment (N=332) in the NIVO+IPI arm had discontinued treatment at the time of analysis, and the median follow-up was 35.2 months. Relative dose intensity was not reported in CM-9DW and therefore was not included in the CMA. The median DOT in CM-9DW was 4.68 months. The number of days of NIVO monotherapy was calculated as the difference between the total DOT (4.68 months, 142 days) and the DOT for the NIVO+IPI combination (63 days, based on 4 doses every 3 weeks), resulting in 79 days of NIVO monotherapy equivalent to 2.84 doses every four weeks. There was a difference between the median (4.68 months) and mean duration of treatment (8.73 months) for NIVO+IPI.

6.61 In IMBRAVE150 17.9% (60/336) of patients were still on therapy at the time of the updated analysis of efficacy and safety data (Cheng 2022), with a median duration of follow-up of 15.6 months. The submission stated that the ongoing treatment of patients in IMBRAVE150 potentially underestimated the DOT of ATEZO+BEV and was biased against NIVO+IPI. The median duration of treatment applied in the CMA was 8.4 months for ATEZO and 7.0 months for BEV. The evaluation considered that the difference in the applied treatment duration for NIVO+IPI and ATEZO+BEV may not be justified (noting the non-inferiority claim).

6.62 The equi-effective doses were estimated in the submission as 1,656 mg NIVO (Q3W initial and Q4W continuing) + 881 mg IPI Q3W was equi-effective to 14,610 mg ATEZO Q3W + 11,174 mg BEVA Q3W.

6.63 The CMA results using an assumed effective AEMP ([redacted]% rebate to the published ex-manufacturer price) for ATEZO ($[redacted]), the current BEV price of $53.82 and a proposed effective EMP for NIVO ($[redacted] per vial) are presented in Table 14. The submission derived an effective EMP for IPI for a 50 mg vial of $[redacted], based on the total treatment cost of $[redacted], inclusive of administration costs. Thus, cost-minimisation in the submission was achieved through varying the price of IPI only and not through changes to the price of NIVO which was assumed 'fixed' in this analysis. The ESC did not accept the CMA proposed in the submission as the use of the median treatment duration in CM-9DW and IMBRAVE150 underestimated the treatment exposure required to achieve the assumed equi-effective outcomes.

Table 14: Results of the cost-minimisation approach based on assumed effective prices

	Atezolizumab	Bevacizumab	Nivolumab	Ipilimumab
Vial strength (mg)	1,200	100	100	50
AEMP per vial	$[redacted] [a]	$53.82	$[redacted] [b]	$[redacted]
AEMP per mg	$[redacted]	$0.54	$[redacted]	$[redacted]
DOT (doses)	12.2	10.1	6.8	4.0
Cumulative mg per treatment course	14,610	11,174	1,656	881
Total treatment costs per patient per course by drug	$[redacted]	$6,013.63	$[redacted]	$[redacted]
Total treatment costs per patient per course	$[redacted]		$[redacted]	
MBS costs administration of the intravenous infusion	$1,493.13		$841.34	
Total treatment costs including administration	$[redacted]			

Source: Table 84 and Table 85, p204 and Table 86, p205 of the submission. Attachment 11_NIVO IPI 1L HCC Cost-Minimisation Analysis, Sheet "Comparator drug cost per course", cells E9 and E10.
AEMP = approved ex-manufacturer price; MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme.
[a] assumed effective price for atezolizumab per vial.
[b] proposed effective price for nivolumab per 100 mg vial.

6.64 The PSCR stated the median for both trials was used in the CMA as the mean DOT for ATEZO+BEV was not published. In addition, the PSCR reiterated arguments made in the submission that the use of the mean DOT from the IMBRAVE150 was not appropriate given 17.9% of patients were still on therapy at the time of the updated analysis, whereas in CM-9DW all patients had finished therapy. The PSCR agreed with the evaluator that a difference in DOT for NIVO+IPI and ATEZO+BEV may not be justified (see paragraph 6.61) and proposed an alternative methodology for calculating equi-effective doses. The alternative methodology was to equate the mean DOT of NIVO+IPI from CM-9DW in months (8.73 months) to represent completed mean treatment exposure. The PSCR did not provide new calculations or analyses with this assumption.

6.65 The ESC acknowledged the alternative methodology proposed by the PSCR for calculating equi-effective doses. The ESC also noted that PBS utilisation data for ATEZO were proposed as a methodology to determine equi-effective doses during considerations of the STRIDE submission at the May 2025 PBAC meeting (durvalumab plus tremelimumab, web outcome, May 2025 PBAC meeting). The ESC noted the CMA results based on mean treatment duration reported in CM-9DW and the assumed effective price for ATEZO are presented in Table 15. The ESC agreed with the PSCR that, with only a truncated mean duration available for IMBRAVE150, it would be appropriate to apply the mean treatment duration reported in CM-9DW to both the NIVO+IPI and ATEZO+BEV arms to determine equi-effective doses for the CMA. The ESC advised that with the methodology proposed in the PSCR incorporated, and the inclusion of the effective price for ATEZO, the remaining inputs of the CMA were reasonable.

Table 15: Results of the cost-minimisation approach proposed by the PSCR based on assumed effective prices

	Atezolizumab	Bevacizumab	Nivolumab	Ipilimumab
Vial strength (mg)	1,200	100	100	50
AEMP per vial	$[redacted] [a]	$53.82	$[redacted] [b]	$[redacted]
AEMP per mg	$[redacted]	$0.54	$[redacted]	$[redacted]
DOT (doses)	12.7[c]	12.7[d]	11.24[e]	4.0
Cumulative mg per treatment course	15,240	13,987	3,769	881
Total treatment costs per patient per course by drug	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Total treatment costs per patient per course	$[redacted]		$[redacted]	
MBS costs administration of the intravenous infusion	$1,556.99		$1,383.08	
Total treatment costs including administration	$[redacted]			

Source: Calculated during the preparation of the ESC advice

AEMP = approved ex-manufacturer price; MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme.

[a] assumed effective price for atezolizumab per vial.

[b] proposed effective price for nivolumab per 100 mg vial.

[c] Mean duration of treatment for atezolizumab of 8.73 months as per nivolumab + ipilimumab Table 6.1-2 of the ca2099dw CSR.

[d] Mean duration of treatment for bevacizumab of 8.73 months as per nivolumab + ipilimumab Table 6.1-2 of the ca2099dw CSR.

[e] Mean duration of treatment for nivolumab + ipilimumab 8.73 months, Table 6.1-2 of the ca2099dw CSR

NIVO+IPI cost/patient/course

6.66 The drug cost per patient per year using the assumed effective prices of atezolizumab is presented in Table 16Table 16.

Table 16: Drug cost per patient for proposed and comparator drugs

	NIVO+IPI Trial dose and duration	NIVO+IPI CMA	NIVO+IPI Financial estimates	ATEZO+BEV Trial dose and duration	ATEZO+BEV CMA	ATEZO+BEV Financial estimates
Mean dose	IPI: 220 mg [a] NIVO initial: 73 mg [a] NIVO continuing:480 mg	IPI: 220 mg [a] NIVO initial: 73 mg [a] NIVO continuing:480 mg	IPI: 250 mg [b] NIVO initial: 80mg [b] NIVO continuing:480 mg	ATEZO: 1,200mg BEV: NR	ATEZO: 1,200mg BEV: 1,101mg [a]	ATEZO: 1,200mg BEV: 1,200mg [b]
Median DOT/number of cycles received	DOT: 4.68 months Cycles: IPI: 4 NIVO initial: 4 NIVO continuing: 2.84	DOT: 4.68 months Cycles: IPI: 4 NIVO initial: 4 NIVO continuing: 2.84	DoT: 4.68 months Cycles: IPI: 4 NIVO initial: 4 NIVO continuing: 2.84	ATEZO DOT: 8.4 months Cycles: 12.2 BEV DoT: 7 months Cycles: 10.1	ATEZO DOT: 8.4 months Cycles: 12.2 BEV DoT: 7 months Cycles: 10.1	ATEZO DOT: 8.4 months Cycles: 12.2 BEV DoT: 7 months Cycles: 10.1
Number of vials per cycle	IPI: 4.4 NIVO initial: 0.73 NIVO continuing: 4.8 cycle		IPI: 5 NIVO initial: 0.8 NIVO continuing: 4.8	ATEZO: 1 BEV: N/A	ATEZO: 1 BEV: 11.01	ATEZO: 1 BEV: 12
Cost per vial	AEMP IPI: $[redacted] (50 mg /10mL) NIVO: $[redacted] (100 mg / 10mL)			AEMP ATEZO: $[redacted] (assumed effective price) (1.2g / 20 mL) BEV: $53.82 [a] (100mg / 4mL)		
Cost/patient/ course	IPI: $[redacted] NIVO: $[redacted]	IPI: $[redacted] NIVO: $[redacted]	IPI: $[redacted] NIVO: $[redacted]	ATEZO: $[redacted] BEV: NA	ATEZO: $[redacted] BEV: $6,013.63	ATEZO: $[redacted] BEV: $6,522.98

Source: Table 81, pp197-198, Table 82, p200, Table 84, p204, Table 86, p205, Table 96, pp213-214, Table 100, p017 of the submission.
AEMP = approved ex-manufacturer price; ATEZO = atezolizumab; BEV = bevacizumab; DOT = duration of treatment; DPMA = dispensed price per maximum amount; IPI = ipilimumab; N/A = not applicable; NIVO = nivolumab; NR = not reported.
[a] Weight-based dosing using the average weight from CM-9DW was applied to calculate the dose of NIVO (initial), IPI (initial) and bevacizumab.
[b] In the financial estimates whole vials were applied for NIVO (initial), IPI (initial) and bevacizumab
[c] Financial estimates recalculated during the evaluation using bevacizumab (100mg) price of $53.82 (April 2025 AEMP, price disclosure reductions).

Estimated PBS usage & financial implications

6.67 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 NIVO+IPI on the PBS. The financial estimates were based on both published and assumed effective prices. The sources of data utilised are shown in Table 17Table 17.

Table 17: Key inputs for financial estimates

Parameter	Value applied and source	Comment
Estimated current market for advanced (unresectable) HCC (scripts) for atezolizumab	7,063 total ATEZO scrips Jan- Dec 2024	Medicare statistics. The source of the data was appropriate. These data are for the use of ATEZO+BEV in patients with 1L HCC with BCLC Stage B and C and does not account for patients with Stage A as proposed by the requested listing.
Growth rate for ATEZO	Year 1 and Year 2: 12.8% - Average growth rate from November 2022 to October 2024 based on Medicare PBS Item Statistics data. Year 3 and Year 4: 10.0% - Assumed. Year 5 and Year 6: 8.0% - Assumed.	The growth rate in 2022-2023 was 9.8%, while in 2023-2024 it was 15.8%. The assumptions for Year 3 to Year 6 are uncertain.
Uptake rate (market share) of NIVO+IPI	[redacted]%	Source: Clinical survey (N=9). The uptake rate was uncertain
Script equivalence between NIVO+IPI and ATEZO+BEV	NIVO initial: 1 IPI initial: 1 Continuing NIVO (ATEZO Q3W): 0.35 Continuing NIVO (ATEZO Q4W): 0.41	Based on the median duration of treatment for each regimen in CM-9DW and IMBRAVE150 and the relevant PIs. The ESC agreed with the PSCR that, consistent with the changes in the CMA, the DOT should be updated to reflect the proposed application of the mean DOT of CM-9DW being applied to both treatment arms.
MBS	$123.05	MBS item number 13950. This was appropriate.

Source: Table 93, p210 and Table 100, p217 of the submission; and NIVO IPI 1L HCC Utilisation and Cost Model, worksheet 7.Net changes -MBS, cell O63.
1L = first line; ATEZO = atezolizumab; BCLC = Barcelona Clinic Liver Cancer; BEV = bevacizumab; HCC = hepatocellular carcinoma; IPI= ipilimumab; MBS = Medicare Benefits Schedule; NIVO= nivolumab; PBS= Pharmaceutical Benefits Scheme; Q3W = every 3 weeks, Q4W = every 4 weeks.

6.68 The requested listing of NIVO+IPI included patients with BCLC Stage A HCC. The PBS restriction for ATEZO+BEV for this population specifies BCLC Stage B and C patients. Therefore, the financial estimates do not account for patients with BCLC Stage A. The number of eligible BCLC Stage A patients is likely to be small; in IMBRAVE150 Stage A patients represented 6% of patients. The evaluation considered this approach underestimated the cost to Government of listing NIVO+IPI.

6.69 The submission assumed that [redacted]% of advanced (unresectable) BCLC Stage B or C HCC patients, with WHO performance status of 0 or 1 patients treated with ATEZO+BEV would initiate treatment with NIVO+IPI. The proportion of ATEZO continuing scripts and BEVA scripts replaced were calculated based on the median DOT for ATEZO. The ESC agreed with the PSCR that, consistent with the changes in the CMA, the DOT should be updated to reflect the proposed application of the mean DOT of CM-9DW being applied to both treatment arms.

6.70 The estimated utilisation and financial impact of listing NIVO+IPI on the PBS using the assumed effective prices are presented in Table 18.

Table 18: Estimated use and financial implications

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

Source: Table 95, p212, Table 102, p218, Table 103, p219, Table 106, p 221 of the submission, and NIVO IPI 1L HCC Utilisation and Cost Model, worksheet 4c. Impact – affected (eff) and worksheet 5. Impact – net.

ATEZO = atezolizumab; BEV = bevacizumab; IPI= ipilimumab; MBS= Medicare Benefits Schedule; NIVO= nivolumab; PBS= Pharmaceutical Benefits Scheme; RPBS= Repatriation Pharmaceutical Benefits Scheme.

[a] Values were recalculated during evaluation using bevacizumab (100mg) AEMP of $53.82 (April 2025 AEMP, price disclosure reductions).

The redacted values correspond to the following ranges:

[1] *500 to < 5,000*

[2] *$0 to < $10 million*

[3] *$10 million to < $20 million*

6.71 The total cost to the PBS/RPBS of listing NIVO+IPI was estimated to be $0 to < $10 million in Year 6, and a total of $0 to < $10 million in the first 6 years of listing. The net cost to the PBS/RPBS in each year is due to the inclusion of wastage in the financial estimates, whereby no vial sharing was assumed. The PSCR noted that the financial estimates will need to be updated to reflect the proposed application of the mean DOT of CM-9DW being applied to both treatment arms.

Quality Use of Medicines

6.72 The submission stated that that given the adverse effect profile of immuno-oncology agents, the Sponsor has established an extensive quality use of medicine approach to optimise the potential benefits of treatment with NIVO+IPI, while minimising the potential risks of these medicine for Australian patients. The submission provided an overview of the QUM initiatives that includes physician education, nursing and pharmacy educational services, patient education, educational materials for awareness and management of immune related adverse reactions including a sponsor run platform and a Risk Management Plan for NIVO+IPI.

Financial Management – Risk Sharing Arrangements

6.73 The submission stated that the sponsor was willing to work with the Department to determine the appropriate arrangement if NIVO+IPI is recommended by the PBAC, acknowledging the current risk-sharing arrangements related to ATEZO.

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

7 PBAC Outcome

7.1 The PBAC did not recommend the listing of nivolumab in combination with ipilimumab (NIVO+IPI) for the first-line treatment of patients with advanced (unresectable) Barcelona Clinic Liver Cancer (BCLC) Stage A, Stage B or Stage C hepatocellular carcinoma (HCC). The PBAC considered the magnitude of benefit in overall survival (OS) of NIVO+IPI over sorafenib (SORA)/lenvatinib (LEN) in the CM-9DW trial was uncertain. The PBAC considered the claim of non-inferior effectiveness of NIVO+IPI versus atezolizumab plus bevacizumab (ATEZO+BEV) was not adequately supported by the evidence presented due to wide confidence intervals for OS hazard ratios (HR) in the indirect treatment comparisons (ITCs), with point estimate results that favour the comparator. The PBAC considered that these results did not sufficiently rule out the possibility of a conclusion of inferiority. The PBAC also considered this was in the context of limited clinical need for additional treatment options in HCC with the availability of ATEZO+BEV and the recent recommendation of Single Tremelimumab Regular Interval Durvalumab (STRIDE) in May 2025.

7.2 The primary reason for this outcome was due to the comparative clinical evidence.

7.3 The PBAC noted input from the Liver Foundation, Pancare Foundation, Rare Cancers Australia and the Medical Oncology Group of Australia (MOGA) which was supportive of listing NIVO+IPI on the PBS for HCC. The PBAC acknowledged the impact of HCC on those with this condition and their families. However, the PBAC considered there was a low clinical need for NIVO+IPI as first-line treatment for HCC given it is not recommended as a preferred regimen for HCC in current treatment guidelines (see paragraph 4.3) and there are alternatives on the PBS (ATEZO+BEV) or recommended to be listed on the PBS (STRIDE).

7.4 The PBAC noted the submission nominated ATEZO+BEV as the main comparator and STRIDE as a near market comparator. The PBAC considered the comparators nominated by the submission were appropriate.

7.5 The PBAC noted the evidence for NIVO+IPI was based on one head-to-head trial, CM-9DW, in which the combination was compared with investigators choice of SORA or LEN. The PBAC noted that whilst the results from the CM-9DW trial showed that NIVO+IPI led to a statistically significant improvement in OS over SORA/LEN (HR=0.79; 95% CI: 0.65, 0.96), the corresponding Kaplan Meier (KM) curves cross suggesting a violation of the proportional hazards assumption. Given the violation of the proportional hazards assumption the PBAC agreed with the evaluation that the HR, CIs and p-values for this analysis should be interpreted with caution. The PBAC noted

that restricted mean survival time (RMST) analysis of OS for NIVO+IPI vs SORA/LEN showed that OS numerically favoured SORA/LEN up until 24 months, with results after 24 months numerically favouring NIVO+IPI. Overall, the PBAC considered the magnitude of benefit in OS of NIVO+IPI over SORA/LEN in the CM-9DW trial was uncertain.

7.6 The clinical claim was based on ITCs between NIVO+IPI (informed by CM-9DW) and ATEZO+BEV (informed by IMBRAVE150) using the SORA/LEN and SORA arms as the common comparator. The PBAC noted there were transitivity issues between the trials including differences in the comparator treatment regimen, in patient baseline characteristics, duration of follow-up and also in event rates across the common reference groups (see paragraph 6.46). The PBAC agreed with the ESC that the differences indicated that patients in CM-9DW were likely to have a better prognosis than patients in IMBRAVE150. The Bucher indirect comparison based on the SORA/LEN arm of the CM-9DW trial reported an OS HR of 1.197 (95% CI: 0.875, 1.638) with the Committee noting that the confidence intervals were wide with point estimate results that favour the comparator. The PBAC noted similar results were reported for the ITC based on the SORA subgroup of the SORA/LEN arm of the CM-9DW trial with an OS HR of 1.061 (95% CI: 0.649, 1.622). The PBAC agreed with the ESC that the small sample size and post-hoc nature of the SORA subgroup ITC further increased the uncertainty. The PBAC considered that the wide confidence intervals, with point estimates generally favouring the comparators, did not sufficiently rule out the possibility of a conclusion of inferiority. Overall, the PBAC considered that the clinical claim of non-inferior efficacy versus ATEZ+BEV was not adequately supported by the evidence provided in the submission.

7.7 The PBAC noted that a claim of non-inferior efficacy was also made against the near market comparator, with a secondary ITC comparing NIVO+IPI (informed by CM-9DW) with STRIDE (informed by HIMALAYA) also included in the submission. The PBAC noted the ITC based on the SORA/LEN arm of the CM-9DW trial reported a HR of 1.013 (95% CI: 0.788, 1.302), and the SORA subgroup analysis reported a HR=0.897 (95% CI: 0.613, 1.314). In addition to the concerns outlined in paragraph 7.5 regarding the OS results of the CM-9DW trial, the PBAC noted there were transitivity issues between the trials in this comparison (see paragraph 6.46 and 6.30). The PBAC agreed with the ESC that, although the point estimate in the SORA subgroup analysis was numerically favourable it was based on a post-hoc analysis of a subgroup with a small sample size. Overall, agreed with the ESC that the point estimates were smaller than for the ATEZO+BEV comparison but the confidence intervals remained wide, and considered that a claim of non-inferior efficacy versus STRIDE was not adequately supported by the evidence provided in the submission.

7.8 The PBAC noted the increased proportion of serious treatment-related adverse events (28.3% versus 14.5%) and deaths due to study drug toxicity (3.6% versus 0.9%) in the NIVO+IPI arm compared to the SORA/LEN arm of the CM-9DW trial. The PBAC noted the NIVO+IPI versus ATEZO+BEV ITC safety analysis showed no substantial differences between treatments based on all-cause and treatment-related AEs, all-cause and

treatment-related SAEs, AEs leading to discontinuation and deaths. The PBAC noted a difference favouring STRIDE was noted for treatment-related adverse events leading to discontinuation, but a review of Grade 3-4 treatment-related adverse events showed no difference for NIVO+IPI versus STRIDE, except for AST increase where there was a greater risk in the NIVO+IPI arm. The PBAC considered the submission's claims of non-inferior safety of NIVO+IPI compared to either ATEZO+BEV or STRIDE were uncertain given the transitivity concerns identified.

7.9 The PBAC considered the cost-minimisation approach and financial estimates were not relevant as the clinical claim was not accepted.

7.10 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:
Not recommended

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.

10 Sponsor's Comment

Bristol Myers Squibb Australia is committed to working with the Department of Health, Disability and Ageing and the PBAC to bring this important treatment option to Australian patients with advanced (unresectable) Barcelona Clinic Liver Cancer (BCLC) Stage A, Stage B or Stage C hepatocellular carcinoma (HCC).