

6.01 ATEZOLIZUMAB,
solution concentrate for I.V. infusion 1200 mg in
20 mL,
solution concentrate for I.V. infusion 840 mg in 14 mL,
Tecentriq[®]
plus
BEVACIZUMAB,
solution for I.V. infusion 100 mg in 4 mL,
solution for I.V. infusion 400 mg in 16 mL,
Avastin[®],
Roche Products Pty Ltd.

1 Purpose of submission

- 1.1 The submission requested a Section 100 listing (Efficient Funding of Chemotherapy) for atezolizumab 1,200 mg in combination with bevacizumab 15 mg/kg (Atezo+Bev) for use as an intravenous injection once every three weeks (Q3W) for the treatment of patients with unresectable locally advanced or metastatic Barcelona Clinic Liver Cancer (BCLC) stage B or stage C hepatocellular carcinoma (HCC) who have not received prior systemic treatment.
- 1.2 Listing was requested on the basis of a cost-effectiveness analysis versus sorafenib. The key components addressed by the submission are presented in Table 1.

Table 1: Key components of the clinical issue addressed by the submission (as presented in the submission)

Component	Description
Population	Patients with locally advanced or metastatic BCLC stage B or C HCC who have not received prior systemic treatment.
Intervention	Atezolizumab 1,200 mg and bevacizumab 15 mg/kg for intravenous infusion once every three weeks (Q3W).
Comparator	Tyrosine kinase inhibitors (TKIs) using sorafenib 400 mg tablet twice daily (BID) as the primary comparator.
Outcomes	Overall survival (OS), Progression-free survival (PFS), objective response rate (ORR), duration of response (DOR), time to progression (TTP), time to deterioration of patient-reported outcomes (PROs).
Clinical claim	Atezolizumab and bevacizumab (Atezo+Bev) is superior in efficacy to sorafenib as demonstrated by a statistically significant and clinically meaningful improvement in OS and PFS compared to sorafenib; and non-inferior in terms of safety (with respect to event rates) with a different adverse event profile. Treatment with Atezo+Bev is also associated with improvements in patient-reported outcomes, specifically a clinically meaningful delay in the deterioration of patient-reported physical functioning, role functioning, quality of life and symptoms compared to sorafenib.

Source: Table 1.1, p20 of the submission.

Abbreviations: Atezo+Bev = atezolizumab plus bevacizumab; DOR = duration of response; OS = overall survival; PFS = progression-free survival; PRO = patient-reported outcomes; q3w = once every 3 weeks; TKI = tyrosine kinase inhibitor; TTP = time to progression

2 Background

Registration status

- 2.1 The submission was lodged under the TGA/PBAC Parallel Process. A priority review for atezolizumab was granted by the TGA on 10th January 2020 for the indication of “Tecentriq, in combination with bevacizumab, is indicated for the treatment of patients with unresectable hepatocellular carcinoma (HCC) who have not received prior systemic therapy” and the sponsor submitted an application for marketing authorisation to the TGA on 24th January 2020. The application was identified for consideration under the United States Food and Drug Administration’s (FDA) Project Orbis and TGA Clinical Evaluation Reports were not available during evaluation.
- 2.2 The TGA Delegate’s Overview was received prior to PBAC consideration and the Delegate recommended approval of the proposed indication (see paragraph 2.1). Registration on the Australian Register of Therapeutic Goods (ARTG) is expected in early October 2020. The TGA Delegate considered that although the early data indicated a significant improvement in OS, the data remained immature and longer term follow up would be informative. The TGA Delegate considered the safety of Atezo+Bev had not been established in patients who had incompletely treated varices or who were at high risk of bleeding, and cannot be recommended for use in these patients (p6, Delegate’s Overview).
- 2.3 Atezo+Bev, in combination with platinum-doublet chemotherapy, is currently registered and reimbursed for the first-line treatment of adult patients with metastatic non-squamous non-small cell lung cancer (NSCLC).

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

(26.1% and 18.8% in the sorafenib and Atezo+Bev arms, respectively). Given the lack of specific second-line treatment options and the fact that the restrictions for sorafenib and lenvatinib do not specify the line of therapy (only that patients must not have received prior treatment with a VEGF TKI), these agents could likely be used following Atezo+Bev (i.e. second-line), which may have implications on the cost-effectiveness and financial estimates of the use of Atezo+Bev. The TGA indication for sorafenib does not specify treatment by line of therapy while lenvatinib is TGA-approved as a first-line treatment in HCC. The ESC considered that there is a high risk of post-progression TKI use without clarification, and there is no clinical evidence to support this use.

- 3.7 The submission proposed the following clinical criteria be included as part of the continuation restriction: “Patient must have stable or responding disease” for atezolizumab and “Patient must not develop disease progression while receiving treatment with this drug for this condition” for bevacizumab. Patients in the IMbrave150 trial were allowed to continue treatment with Atezo+Bev or sorafenib beyond disease progression until loss of clinical benefit or unacceptable toxicity. This is not reflected in the proposed listing for bevacizumab (restricted to non-progressing patients) or the current listing for sorafenib. It is unclear if the comparative efficacy of Atezo+Bev would be maintained if patients were to cease treatment with bevacizumab or sorafenib at progression. The Sponsor responded in the PSCR that similar proportions of patients received treatment beyond progression in both treatment arms in IMbrave150, and therefore comparative efficacy is likely to have been maintained and can be expected to hold in the Australian context. The Sponsor is amenable to the Secretariat’s amendments to the proposed continuation criteria for atezolizumab (i.e. patient must not have developed disease progression).

Atezolizumab

Name, Restriction, Manner of administration and form	PBS item code	Max. Amount	No. of Rpts	Manufacturer
ATEZOLIZUMAB Injection	11926Q (Public) 11927R (Private)	1200 mg	3	Roche Products Pty Ltd
Available brands				
Tecentriq (atezolizumab 1.2 g/20 mL injection, 20 mL vial)				

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Initial treatment Restriction summary [new]

Category / Program: Section 100 – Efficient Funding of Chemotherapy (Public/Private hospital)
Prescriber type: <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Restriction type/method: <input checked="" type="checkbox"/> Authority Required – Streamlined (new code)
Episodicity: [blank]
Severity: Advanced (unresectable) Barcelona Clinic Liver Cancer (BCLC) Stage B or Stage C
Condition: hepatocellular carcinoma (HCC)
PBS Indication [episodicity + severity + condition]: 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 bevacizumab
AND
Patient must have a WHO performance status of 0 or 1
AND
Patient must not be suitable for transarterial chemoembolization
AND
Patient must have Child Pugh class A
AND
Patient must not have received prior treatment with a vascular endothelial growth factor (VEGF) tyrosine kinase inhibitor (TKI) for this condition; OR
Patient must have developed intolerance to a VEGF TKI of a severity necessitating permanent treatment withdrawal
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
Administrative advice: In the first few months after start of immunotherapy, some patients can have a transient tumour flare with subsequent disease response. When progression is suspected, this should be confirmed through a confirmatory scan, taken at least four weeks later.

Continuing treatment (3-weekly regimen) Restriction summary [new]:

Name, Restriction, Manner of administration and form	PBS item code	Max. Amount	No. of Rpts	Manufacturer
ATEZOLIZUMAB Injection	NEW (Public) NEW (Private) 11802E (Public; if 7 repeats) 11801D (Private; if 7 repeats)	1200 mg	8	Roche Products Pty Ltd
Available brands				
Tecentriq (atezolizumab 1.2 g/20 mL injection, 20 mL vial)				

Category / Program: Section 100 – Efficient Funding of Chemotherapy (Public/Private hospital)
Prescriber type: <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Restriction type/ method: <input checked="" type="checkbox"/> Authority Required – Streamlined (new code)
PBS Indication: Advanced (unresectable) Barcelona Clinic Liver Cancer Stage B or Stage C hepatocellular carcinoma
Treatment phase: Continuing treatment – 3 weekly treatment regimen
Clinical criteria:
Patient must be undergoing combination treatment with bevacizumab until disease progression, unless not tolerated
AND
Patient must have previously received PBS-subsidised treatment with this drug for this condition
AND
Patient must have stable or responding disease. Patient must not have developed disease progression while being treated with this drug for this condition
Administrative advice: No increase in the maximum amount or number of units may be authorised

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Administrative advice: No increase in the maximum number of repeats may be authorised
Administrative advice: <i>Special Pricing Arrangements apply</i>

Bevacizumab

Name, Restriction, Manner of administration and form	PBS item code	Max. Amount	No. of Rpts	Manufacturer
BEVACIZUMAB Injection	NEW (Public) NEW (Private) 11803F (Public; if 7 repeats) 11811P (Private; if 7 repeats)	1800 mg	3 8	Roche Products Pty Ltd
Available brands				
Avastin (bevacizumab 400 mg/16 mL injection, 16 mL vial)				
Avastin (bevacizumab 100 mg/4 mL injection, 4 mL vial)				

Combined Initial & Continuing bevacizumab treatment Restriction summary [new]:

Category / Program: Section 100 – Efficient Funding of Chemotherapy (Public/Private hospital)
Prescriber type: <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Restriction type/method:- <input checked="" type="checkbox"/> Authority Required – Streamlined (new code)
Episodicity: [blank]
Severity: Advanced unresectable Barcelona Clinic Liver Cancer (BCLC) Stage B or Stage C
Condition: hepatocellular carcinoma (HCC)
PBS Indication [episodicity + severity + condition]: Advanced (unresectable) Barcelona Clinic Liver Cancer Stage B or Stage C hepatocellular carcinoma
Treatment phase: Initial Concurrent use with atezolizumab in this PBS indication
Clinical criteria:
Patient must be undergoing combination treatment with atezolizumab,
Treatment criteria:
Patient must be undergoing combination treatment with PBS-subsidised atezolizumab until disease progression, unless not tolerated, in this PBS indication
AND
Patient must have a WHO performance status of 0 or 1,
AND
Patient must not be suitable for transarterial chemoembolisation,
AND
Patient must have Child-Pugh class A,
AND
Patient must not have received prior treatment with a vascular endothelial growth factor (VEGF) tyrosine kinase inhibitor (TKI) for this condition, OR
Patient must have developed intolerance to a VEGF TKI of a severity necessitating permanent treatment withdrawal
Administrative Advice: No increase in the maximum number of repeats may be authorised

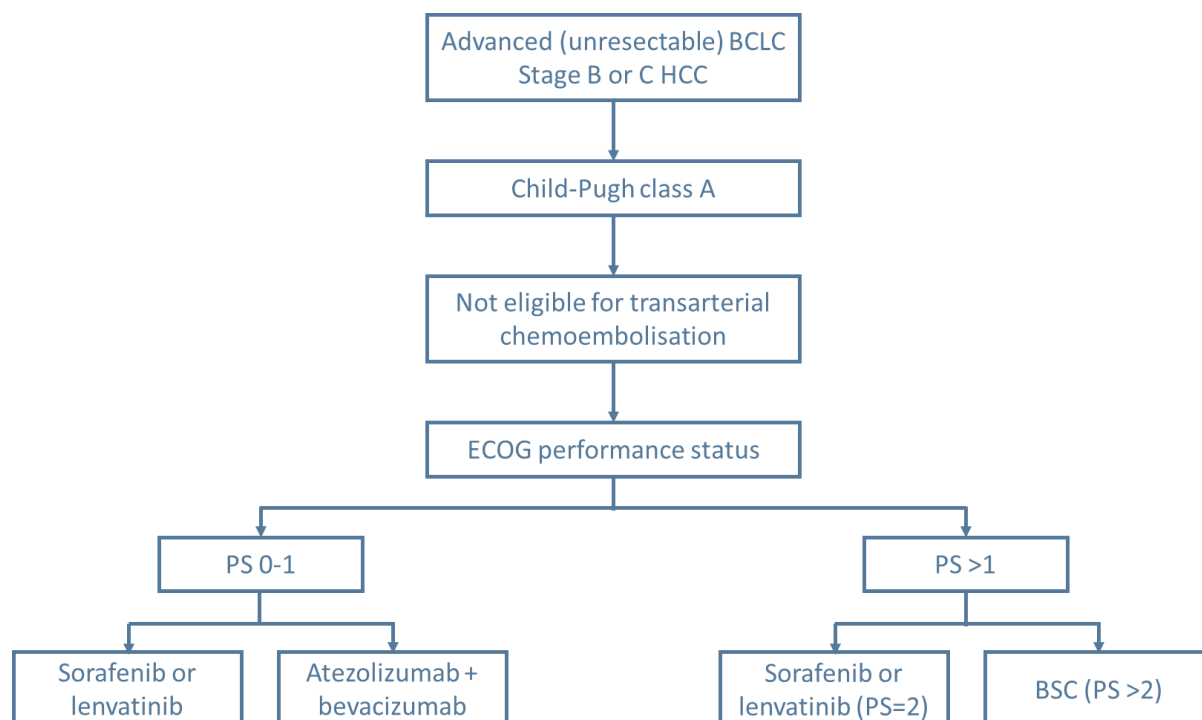
- 3.8 The PBAC considered that the listing for Atezo+Bev should (i) be restricted to patients with WHO PS 0 to 1, (ii) not allow use beyond disease progression and (iii) not allow use following a VEGF TKI unless intolerance to a TKI of a severity necessitating permanent treatment withdrawal occurred. The PBAC considered the restriction criteria for the VEGF TKIs should be amended to ensure use only after intolerance to a VEGF TKI or Atezo+Bev.

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

4 Population and disease

- 4.1 HCC is the 15th most commonly diagnosed cancer in Australia with an estimated 2,599 new cases in 2019 (Australian Institute of Health and Welfare; AIHW 2019). The incidence of HCC in Australia has increased from 1.8 to 8.6 per 100,000 head of population from 1982 to 2019 (AIHW 2019). The estimated mortality rate for HCC in Australia is 7.0 per 100,000, with an estimated 2,161 HCC-related deaths in 2019 (AIHW 2019). Up to 80% of patients first presenting with HCC have advanced, unresectable or metastatic disease with poor prognosis. The five-year survival rate of HCC in Australia in 2011-2015 was 19% (AIHW 2019). The ESC acknowledged that HCC survival is very poor in a real-world situation, and that treatment options for patients are limited given that performance status is often poor in advanced disease and few patients meet strict trial inclusion criteria.
- 4.2 Atezolizumab is a programmed death ligand 1 (PD-L1) inhibitor and bevacizumab is a VEGF inhibitor. The submission proposed that Atezo+Bev be listed for the treatment of patients with locally advanced or metastatic BCLC stage B or stage C HCC who have not received prior systemic treatment (first-line setting). The submission stated that Atezo+Bev is expected to replace use of TKI therapy (sorafenib or lenvatinib) for eligible patients in this setting.
- 4.3 The clinical management algorithm for the intended use of Atezo+Bev is presented in Figure 1. The submission stated that the algorithm was based on local and international clinical guidelines for patients with advanced HCC. The submission did not present the sources of the clinical guidelines and thus they could not be validated.

Figure 1: Proposed clinical management and treatment algorithm



Source: Figure 1.5, p 32 of the submission.

Abbreviations: BCLC = Barcelona Clinic Liver Cancer; BSC = best supportive case; HCC = hepatocellular carcinoma; PS = performance status

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

5 Comparator

5.1 The submission nominated sorafenib as the main comparator. The nomination of sorafenib as the comparator was appropriate and adequately justified, however, lenvatinib is also considered to be a relevant comparator as more recent PBS item reports show more prescriptions dispensed for lenvatinib than sorafenib. The Sponsor responded in the PSCR that lenvatinib was recommended by the PBAC using a cost minimisation analysis against sorafenib, based on non-inferior efficacy and safety and the same treatment cost per patient, and therefore sorafenib was an appropriate proxy for first-line TKI therapy in the target population. The ESC agreed with the Sponsor that sorafenib provided an acceptable comparison. The PBAC considered that an additional comparison against lenvatinib was unlikely to change the basis of listing for Atezo+Bev.

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 health care professionals (1) and organisations (4) via the Consumer Comments facility on the PBS website.
- 6.3 The comments from a healthcare professional described the unfavourable outcomes in HCC and estimated 5 year survival to be less than 20% of patients. The healthcare professional noted that Atezo+Bev is a major breakthrough in treatment and that it is superior to sorafenib in terms of extending life, having fewer side effects and offering patients better quality of life (QoL).
- 6.4 The PBAC noted the support for PBS listing of Atezo+Bev received from the Gastroenterological Society of Australia (GESA), Rare Cancers Australia, and Hepatitis Australia. GESA expressed strong support for listing based on unmet clinical need, poor efficacy and high toxicity of VEGF TKIs, and a substantial increase in survival and better QoL with Atezo+Bev. Rare Cancers Australia commented that the increase in survival seen with Atezo+Bev in this patient group has not been seen in over a decade of treatment. Hepatitis Australia also referred to increased survival and improved quality of life with Atezo+Bev.
- 6.5 The Medical Oncology Group of Australia (MOGA) expressed its strong support for the Atezo+Bev in HCC submission, categorising it as one of the therapies of “highest priority for PBS listing” on the basis of the IMbrave150 trial. The PBAC noted that the MOGA presented a European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for Atezo+Bev in HCC, which was limited to 4 (out of a maximum of 5, where 5 and 4 represent the grades with substantial improvement)¹, based on a comparison with sorafenib. MOGA stated that Atezo+Bev was scored based on progression free survival (PFS), as median overall survival (OS) of Atezo+Bev arm in the IMbrave150 trial was not yet reached. MOGA stated that the score is likely to increase to a 5 once OS is known (based on an OS hazard ratio [HR] of 0.58 which would result in an estimated median survival gain of > 5 months).

Clinical trials

- 6.6 The submission was based on one head-to-head trial comparing Atezo+Bev to sorafenib (N=501), IMbrave150.
- 6.7 The details of the trial presented in the submission are provided in Table 2.

¹ Cherny NI, Dafni U, Bogaerts J, et al: ESMO-Magnitude of Clinical Benefit Scale version 1.1. *Annals of Oncology* 28:2340-2366, 2017.

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Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
IMbrave150	A Phase III, Open-Label, Randomized Study of Atezolizumab in Combination With Bevacizumab Compared With Sorafenib in Patients With Untreated Locally Advanced or Metastatic Hepatocellular Carcinoma.	December 2019
	Ducieux MP et al. Atezolizumab 1 bevacizumab vs sorafenib in locally advanced or metastatic hepatocellular carcinoma: The randomised phase III study IMbrave150.	Annals of Oncology 2018; 29: viii267
	Finn RS et al. IMbrave150: A randomized phase III study of 1L atezolizumab plus bevacizumab vs sorafenib in locally advanced or metastatic hepatocellular carcinoma.	Journal of Clinical Oncology 2018; 36(15)
	Kim TY et al. IMbrave150: A randomized phase III study of 1L atezolizumab plus bevacizumab versus sorafenib in locally advanced or metastatic hepatocellular carcinoma.	Liver Cancer 2018; 7:170
	Lee KH et al. Atezolizumab + bevacizumab in hepatocellular carcinoma (HCC): Safety and clinical activity results from a phase Ib study.	Annals of Oncology 2018; 29
	Qin S et al. IMbrave150: A randomised phase III study of atezolizumab + bevacizumab vs sorafenib in locally advanced or metastatic hepatocellular carcinoma.	Annals of Oncology 2018; 29
	A Study of Atezolizumab in Combination With Bevacizumab Compared With Sorafenib in Patients With Untreated Locally Advanced or Metastatic Hepatocellular Carcinoma IMbrave150.	2020
	Cheng AL et al. IMbrave150: efficacy and safety results from a ph III study evaluating atezolizumab (atezo) 1 bevacizumab (bev) vs sorafenib (Sor) as first treatment (tx) for patients (pts) with unresectable hepatocellular carcinoma (HCC).	Annals of Oncology 2019; 30:ix186-ix187
	Galle PR et al. Patient-reported outcomes (PROs) from the Phase III IMbrave150 trial of atezolizumab (atezo) + bevacizumab (bev) vs sorafenib (sor) as first-line treatment (tx) for patients (pts) with unresectable hepatocellular carcinoma (HCC).	Journal of Clinical Oncology 2020; 38(4)

Source: Table 2.3, p47 of the submission.

Note: Cheng et al. (2019) and Galle et al. (2020) added during the evaluation

6.8 The key features of the direct randomised trial are summarised in Table 3. The primary outcomes in the trial were OS and PFS, with secondary outcomes of objective response rate (ORR), duration of response (DOR), time to progression (TTP), safety, and patient-reported outcomes (PROs) including European Organisation for the Research and Treatment of Cancer (EORTC) QLQ-C30 and QLQ-HCC18 questionnaires.

Table 3: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
Atezo+Bev vs. sorafenib						
IMbrave150	501	R, OL, MC 8.6 months	Low (overall); Moderate (PRO and safety)	Locally advanced or metastatic HCC who had not received prior systemic treatment	OS, PFS	OS, PFS

Source: compiled during the evaluation

Abbreviations: Atezo+Bev = atezolizumab plus bevacizumab; DB = double blind; HCC = hepatocellular carcinoma; MC = multicentre; OL = open-label; OS = overall survival; PFS = progression-free survival; PRO = patient-reported outcomes; R = randomised.

Note: The median duration of survival follow-up for all patients was 8.6 months (Atezo+Bev = 8.9 months, Sorafenib = 8.1 months)

- 6.9 Overall, IMbrave150 had a low risk of bias. While the trial was open-label, the key primary and secondary efficacy outcomes included independent review facility (IRF) assessment, which minimised the risk of bias since the IRF was blinded to treatment allocation. However, the assessment of patient-reported outcomes, such as QoL and subjective reporting of adverse events (AEs) may be affected by investigator, clinician and patient knowledge of treatment allocation. Withdrawal from the study by patients was higher in the sorafenib arm (11.5%) compared to the Atezo+Bev arm (3.5%); this may have potentially influenced the results of the survival analysis.
- 6.10 A higher proportion of patients received follow-up HCC systemic therapy in the sorafenib arm compared to the Atezo+Bev arm (44.2% vs 20.5%, respectively). The most common follow-up systemic therapy for patients was a TKI (26.1% and 18.8% in the sorafenib and Atezo+Bev arms, respectively). The submission noted that there are no second line systemic therapies currently reimbursed on the PBS for patients with HCC, based on the assumption that patients would receive either lenvatinib or sorafenib first-line and then be ineligible to receive the alternative agent (unless intolerant). However, the ESC clarified that the wording of the restrictions for sorafenib and lenvatinib are line agnostic, and it is likely that these agents could be used second-line following Atezo+Bev (paragraph 3.6). If the sorafenib and lenvatinib restrictions are updated to disallow second-line use, the outcomes in IMbrave150 may be artificially inflated relative to the Australian setting. The submission stated and the PSCR re-emphasised that the trial results are likely to be biased in favour of sorafenib given that more patients in the sorafenib arm received follow-up systemic therapy. However, the direction of bias is unclear as a higher proportion of patients in the Atezo+Bev arm (43.5%) were still on treatment compared to the sorafenib arm (14.5%) and the outcomes post-discontinuation in these patients are unknown in the longer term.
- 6.11 The ESC considered that the IMbrave150 trial had strict inclusion/exclusion criteria that are unlikely to reflect the circumstances of Australian patients with HCC. Trial patients were not permitted to receive non-steroidal anti-inflammatory drugs (NSAIDs) including aspirin, they must have had an endoscopy within 6 months of starting therapy due to bleeding risk, they must not have had a history of hepatic encephalopathy (even if Child-Pugh A), and those with active hepatitis B must have had suppressed viral load with antiviral medication. The PBAC it would be appropriate to include a 'Caution' in the restriction criteria that patients should be assessed for risk of variceal bleeding prior to treatment with Atezo+Bev as the safety of Atezo+Bev has not been established in patients who had incompletely treated varices, variceal bleeding within the previous 6 months or who were at high risk of bleeding.

Comparative effectiveness

- 6.12 A summary of the OS and PFS results is presented in Table 4, with the corresponding Kaplan-Meier curves in Figure 2 to Figure 4. The results demonstrated a statistically significant difference in OS and PFS, in favour of Atezo+Bev. The median duration of

follow-up for the trial was short (8.6 months) and the median OS in the Atezo+Bev arm was not reached, with only 28.6% (Atezo+Bev) and 39.4% (sorafenib) of patients having experienced an event. The Sponsor acknowledged the short follow-up and immature survival data in the PSCR; however they re-emphasised the significance of the magnitude of the benefit; i.e. the curves diverged from one month and continued to diverge until the end of the follow-up. The ESC considered that the improvement in OS (HR=0.58) is clinically significant despite the immaturity of the data, especially given the poor outcomes associated with HCC.

- 6.13 There was a high degree of censoring for survival and the number of patients remaining at risk after month 12 was low. Combined with the short duration of follow-up, this suggests the OS data were immature. The Sponsor stated in the PSCR that the high degree of censoring in the Atezo+Bev arm relative to the sorafenib arm occurred because more patients were alive in the Atezo+Bev arm at the time of the clinical cut-off date. The Sponsor also stated that, as the event rate is lower than expected, further data cuts are unlikely to be available in the near future. The ESC commented that given the aggressive tumour biology, it would be expected for events to occur relatively quickly.

Table 4: Summary of survival outcomes in IMbrave150

Outcome	Atezo+Bev		Sorafenib		Difference in median	P value	HR (95% CI)
	n/N (%)	Median time to event (95% CI)	n/N (%)	Median time to event (95% CI)			
OS (deaths)	96/336 (28.6)	NE	65/165 (39.4)	13.24 months (10.41, NE)	NE	0.0006	0.58 (0.42, 0.79)
PFS ^a (prog. event)	197/336 (58.6)	6.83 months (5.75, 8.28)	109/165 (66.1)	4.27 months (3.98, 5.55)	2.56 months	<0.0001	0.59 (0.47, 0.76)
PFS ^b (prog. event)	199/336 (59.2)	6.83 months (5.72, 7.69)	111/165 (67.3)	4.24 months (3.98, 5.45)	2.59 months	<0.0001	0.59 (0.46, 0.74)

Source: Table 2.13, p65 and Table 2.14, p67 of the submission.

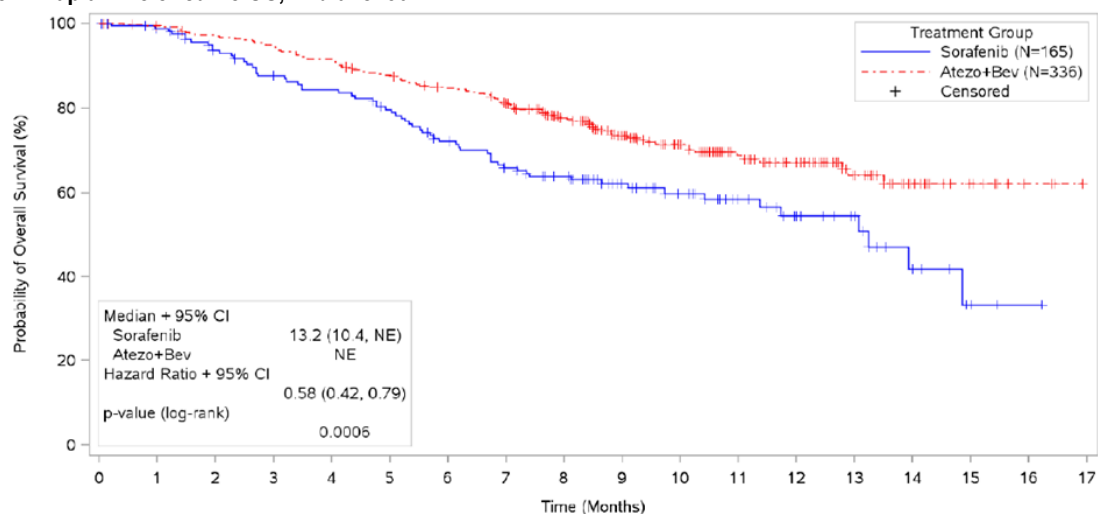
Abbreviations: Atezo+Bev = atezolizumab plus bevacizumab; CI = confidence intervals; HR = hazard ratio; n = number of participants reporting data; N = total participants in group; NE = not estimable; OS = overall survival; PFS = progression-free survival.

Note: Bold indicates statistically significant difference.

a Based on IRF-assessment per RECIST v1.1

b Based on IRF-assessment per HCC mRECIST

Figure 2: Kaplan-Meier curve OS, IMbrave150



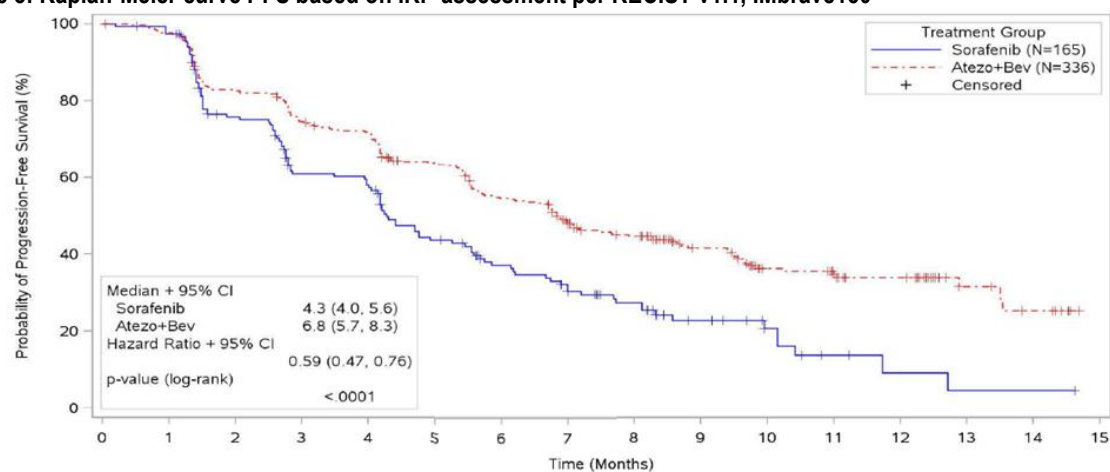
Patients remaining at risk

Sorafenib	165	157	143	132	127	118	105	94	86	60	45	33	24	16	7	3	1	NE
Atezo+Bev	336	329	320	312	302	288	275	255	222	165	118	87	64	40	20	11	3	NE

Source: Figure 2.3, p66 of the submission.

Abbreviations: Atezo+Bev = atezolizumab plus bevacizumab; CI = confidence interval; ITT = intention to treat; N = total participants in group; NE = not estimable

Figure 3: Kaplan-Meier curve PFS based on IRF-assessment per RECIST v1.1, IMbrave150



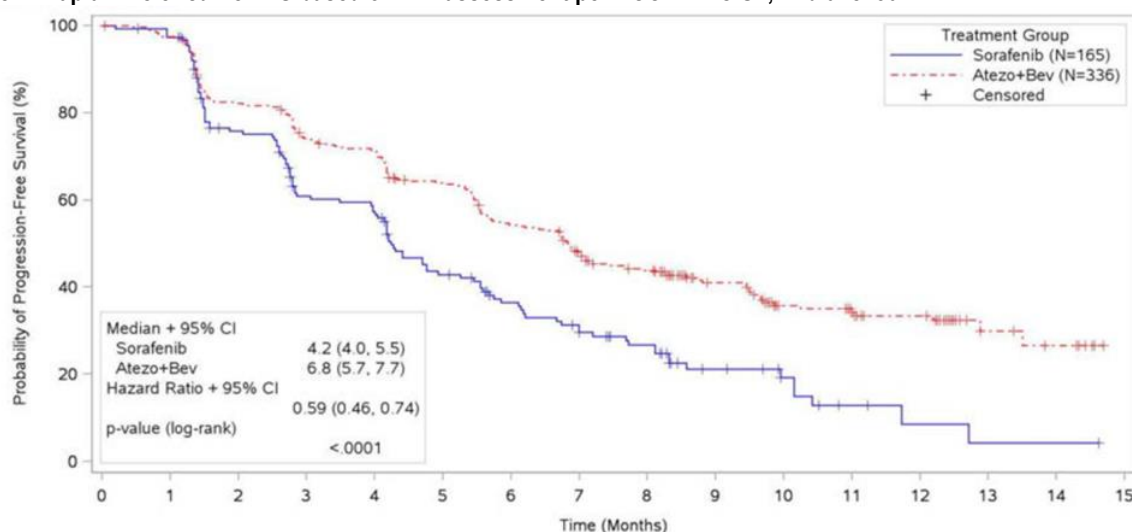
Patients remaining at risk

Sorafenib	165	148	109	84	80	57	44	34	27	15	9	4	2	1	1	NE
Atezo+Bev	336	322	270	243	232	201	169	137	120	74	50	46	34	11	7	NE

Source: Figure 2.4, p67 of the submission.

Abbreviations: Atezo+Bev = atezolizumab plus bevacizumab; CI = confidence interval; N = total participants in group

Figure 4: Kaplan-Meier curve PFS based on IRF-assessment per HCC mRECIST, IMbrave150



Patients remaining at risk		0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Sorafenib	165	148	109	84	79	56	43	33	27	14	9	4	2	1	1	NE	
Atezo+Bev	336	320	267	239	229	201	169	137	120	73	49	45	34	10	7	NE	

Source: Figure 2.5, p68 of the submission.

Abbreviations: Atezo+Bev = atezolizumab plus bevacizumab; CI = confidence interval; N = total participants in group

6.14 A summary of the ORR results based on IRF-assessment per RECIST v1.1 and IRF-assessment per HCC mRECIST is presented in Table 5. The results demonstrated a statistically significant difference in ORR, in favour of Atezo+Bev. A higher proportion of patients achieved confirmed complete response (CR) and partial response (PR) in the Atezo+Bev arm compared to the sorafenib arm based on RECIST v1.1 (CR: 5.5% vs. 0%; PR: 21.8% vs. 11.9%) and HCC mRECIST (CR: 10.2% vs. 1.9%; PR: 23.1% vs. 11.4%).

Table 5: Results of objective response rate, IMbrave150

Outcome	Atezo+Bev (N=326 ^c)	Sorafenib (N=159 ^c)	Odds ratio (95% CI)	Risk difference (95% CI)	P value
	n (%) (95% CI)	n (%) (95% CI)			
ORR ^a	89 (27.3) (22.54, 32.48)	19 (11.9) (7.35, 18.03)	2.90 (1.68, 5.01)	15.35 (7.90, 22.81)	<0.0001
ORR ^b	108 (33.2) (28.13, 38.64)	21 (13.3) (8.42, 19.60)	3.39 (2.02, 5.71)	19.94 (12.10, 27.78)	<0.0001

Source: Table 2.15, p69 of the submission.

Abbreviations: Atezo+Bev = atezolizumab plus bevacizumab; CI = confidence intervals; n = number of participants with event; N = total participants in group; ORR = objective response rate

Note: Bold indicates statistically significant difference

a Based on IRF-assessment per RECIST v1.1

b Based on IRF-assessment per HCC mRECIST

c ITT population with measurable disease at baseline

6.15 A summary of the DOR results based on IRF-assessment per RECIST v1.1 and IRF-assessment per HCC mRECIST is presented in Table 6. The results demonstrated a statistically significant difference in DOR, in favour of Atezo+Bev. The median DOR in the Atezo+Bev arm was not reached.

Table 6: Results of duration of response, IMbrave150

Outcome	Atezo+Bev (N=326 ^c)		Sorafenib (N=159 ^c)		Difference in median	P value	HR (95% CI)
	n/N (%)	Median time to event (95% CI)	n/N (%)	Median time to event (95% CI)			
DOR ^a (loss of resp.)	12/89 (13.5)	NE	6/19 (31.6)	6.28 months (4.67, NE)	NE	0.0051	0.23 (0.08, 0.70)
DOR ^b (loss of resp.)	24/108 (22.2)	NE	8/21 (38.1)	6.28 months (4.86, NE)	NE	0.0048	0.30 (0.12, 0.73)

Source: Table 2.16, p70 of the submission; Table 24 and Table 25, pp110-111 of the IMbrave150

Abbreviations: Atezo+Bev = atezolizumab plus bevacizumab; CI = confidence intervals; DOR = duration of response; HR = hazard ratio; n = number of participants reporting data; N = total participants in group; NE = not estimable

Note: Bold indicates statistically significant difference.

a Based on IRF-assessment per RECIST v1.1

b Based on IRF-assessment per HCC mRECIST

c Confirmed responders population include those in the ITT population who had an objective response

6.16 A summary of the TTP results based on IRF-assessment per RECIST v1.1 and IRF-assessment per HCC mRECIST is presented in Table 7. The results demonstrated a statistically significant difference in TTP, in favour of Atezo+Bev.

Table 7: Results of time to progression, IMbrave150

Outcome	Atezo+Bev (N=336)		Sorafenib (N=165)		Difference in median	P value	HR (95% CI)
	n/N (%)	Median time to event (95% CI)	n/N (%)	Median time to event (95% CI)			
TTP ^a	163/336 (48.5)	8.57 months (6.83, 9.86)	80/165 (48.5)	5.59 months (4.21, 7.72)	2.98 months	0.0105	0.70 (0.53, 0.92)
TTP ^b	164/336 (48.8)	8.28 months (6.80, 9.86)	82/165 (49.7)	5.55 months (4.21, 7.69)	2.73 months	0.0063	0.69 (0.52, 0.90)

Source: Table 2.17, p71 of the submission; pp1471-1472 of the IMbrave150 CSR

Abbreviations: Atezo+Bev = atezolizumab plus bevacizumab; CI = confidence intervals; HR = hazard ratio; n = number of participants reporting data; N = total participants in group; NE = not estimable; TTP = time to progression

Note: Bold indicates statistically significant difference.

a Based on IRF-assessment per RECIST v1.1

b Based on IRF-assessment per HCC mRECIST

6.17 A summary of the results for time to deterioration (TTD) of physical functioning, role functioning, global health status/quality of life (GHS/QoL) and patient-reported symptoms is presented in Table 8. The results demonstrated a statistically significant difference in TTD, in favour of Atezo+Bev, for all outcomes except jaundice. The median TTD of appetite loss, diarrhoea and pain (EORTC QLQ-HCC18) for Atezo+Bev was not reached. The ESC noted the statistically significant difference in TTD in favour of Atezo+Bev and considered this is likely to be clinically significant to patients with HCC in terms of improved quality of life.

Table 8: Results of time to deterioration, IMbrave150

Outcome	Atezo+Bev (N=336)		Sorafenib (N=165)		Difference in median	P value	HR (95% CI)
	n/N (%)	Median time to event (95% CI)	n/N (%)	Median time to event (95% CI)			
Physical functioning ^a	114/336 (33.9)	13.14 months (9.69, NE)	64/165 (38.8)	4.86 months (3.48, 6.24)	8.28 [^] months	<0.0001	0.53 (0.39, 0.73)
Role functioning ^a	136/336 (40.5)	9.13 months (6.51, NE)	69/165 (41.8)	3.58 months (2.20, 5.98)	5.55 months	0.002	0.62 (0.46, 0.84)
GHS/QoL ^a	132/336 (39.3)	11.24 months (5.98, NE)	66/165 (40.0)	3.58 months (3.02, 6.97)	7.66 months	0.003	0.63 (0.46, 0.85)
Appetite loss ^a	101/336 (30.1)	NE (4.14, NE)	54/165 (32.7)	7.62 (3.48, NE)	NE	0.0013	0.57 (0.40, 0.80)
Diarrhoea ^a	62/336 (18.5)	NE (9.69, NE)	63/165 (38.2)	4.44 (3.48, 5.59)	NE	<0.0001	0.23 (0.16, 0.34)
Fatigue ^a	164/336 (48.8)	5.68 (4.30, 7.10)	78/165 (47.3)	2.10 (1.45, 4.83)	3.58	0.0006	0.61 (0.46, 0.81)
Fatigue ^b	154/336 (45.8)	5.65 (4.30, 9.03)	79/165 (47.9)	2.14 (1.64, 2.83)	3.51	0.0004	0.60 (0.45, 0.80)
Pain ^a	131/336 (39.0)	9.72 (7.16, NE)	76/165 (46.1)	2.79 (2.14, 4.30)	6.93	<0.0001	0.46 (0.34, 0.62)
Pain ^b	101/336 (30.1)	NE (2.83, NE)	50/165 (30.3)	9.82 (4.27, NE)	NE	0.0147	0.65 (0.46, 0.92)
Jaundice ^b	128/336 (38.1)	10.55 (6.93, NE)	51/165 (30.9)	6.47 (5.55, NE)	4.08	0.1130	0.76 (0.55, 1.07)

Source: constructed during the evaluation; Table 2.18, p72 of the submission; Table 2.19, p74 of the submission; p1583, p1639, pp1647-1651 of the IMbrave150 CSR

Abbreviations: Atezo+Bev = atezolizumab plus bevacizumab; CI = confidence interval; EORTC QLQ-C30 = European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EORTC QLQ-HCC18 = European Organisation for the Research and Treatment of Hepatocellular Carcinoma Questionnaire 18 (HCC-specific 18-item); GHS/QoL= global health status/quality of life; HR = hazard ratio; n = number of participants reporting data; N = total participants in group; NE = not estimable; TTD = time to deterioration

Note: Bold indicates statistically significant difference.

a Based on EORTC QLQ-C30

b Based on EORTC QLQ-HCC18

[^] corrected error from submission during the evaluation

Comparative harms

6.18 A summary of the key AE data is presented in Table 9. Overall, the majority of the key AEs were not statistically significantly different between Atezo+Bev and sorafenib, with the exception of treatment-related AE (any grade) and treatment-related Grade 3/4 AE. A significantly higher proportion of patients in the sorafenib arm (94.2%) experienced at least one treatment-related AE (any grade) compared to patients in the Atezo+Bev arm (83.9%). In addition, sorafenib was associated with a significantly higher rate of treatment-related Grade 3/4 AE compared to Atezo+Bev (45.5% vs 35.6%, respectively).

Table 9: Summary of key adverse events in IMbrave150 (Safety Population)

n (%)	Safety Population			
	Atezo+Bev N = 329	Sorafenib N = 156	RR (95% CI)	RD (95% CI)
All causality				
At least one AE	323 (98.2)	154 (98.7)	0.99 (0.97, 1.02)	-0.01 (-0.03, 0.02)
Grade 3/4 AE	186 (56.5)	86 (55.1)	1.03 (0.86, 1.22)	0.01 (-0.08, 0.11)
Grade 5 AE	15 (4.6 [^])	9 (5.8)	0.79 (0.35, 1.77)	-0.01 (-0.06, 0.03)
Serious AE	125 (38.0)	48 (30.8)	1.23 (0.94, 1.62)	0.07 (-0.02, 0.16)
AE leading to treatment discontinuation from any study treatment	51 (15.5)	16 (10.3 [^])	1.51 (0.89, 2.56)	0.05 (-0.01, 0.11)
discontinuation from atezolizumab	28 (8.5)	-	-	-
discontinuation from bevacizumab	48 (14.6)	-	-	-
discontinuation from Atezo+Bev	23 (7.0)	-	-	-
AE leading to dose interruption of any study treatment	163 (49.5)	64 (41.0)	1.21 (0.97, 1.50)	0.09 (-0.01, 0.18)
Treatment-related				
At least one AE	276 (83.9)	147 (94.2)	0.89 (0.84, 0.95)	-0.10 (-0.16, -0.05)
related to atezolizumab	252 (76.6)	-	-	-
related to bevacizumab	241 (73.3)	-	-	-
Grade 3/4 AE	117 (35.6)	71 (45.5)	0.78 (0.62, 0.98)	-0.10 (-0.19, -0.01)
Grade 5 AE	6 (1.8)	1 (0.6)	2.84 (0.35, 23.43)	0.01 (-0.01, 0.03)
Serious AE	56 (17.0)	24 (15.4)	1.11 (0.71, 1.72)	0.02 (-0.05, 0.09)

Source: calculated during the evaluation based on Table 2.20, p75 of the submission.

Abbreviations: AE = adverse events; Atezo+Bev = atezolizumab plus bevacizumab; CI = confidence intervals; HR = hazard ratio; n = number of participants reporting data; N = total participants in group; RD = risk difference; RR = relative risk

Note: Bold indicates statistically significant difference.

[^] corrected error from submission during the evaluation

- 6.19 The treatment-related Grade 3/4 AEs reported with higher incidences ($\geq 2\%$ difference) in the sorafenib arm were palmar-plantar erythrodysesthesia syndrome (PPES), rash, blood bilirubin increased, diarrhoea, hypophosphataemia, and decreased appetite. The AEs reported with higher incidences ($\geq 2\%$ difference) in the Atezo+Bev arm were alanine aminotransferase increased, proteinuria, and infusion-related reaction (Table 10). The risk differences show that the Atezo+Bev arm had a significantly higher incidence of alanine aminotransferase increased and infusion-related reaction while the sorafenib arm had a significantly higher incidence of diarrhoea and PPES.

Table 10: Treatment-related Grade 3/4 adverse events (≥ 2% difference) in IMbrave150 (Safety Population)

n (%)	Safety Population			
	Atezo+Bev N = 329	Sorafenib N = 156	RR (95% CI)	RD (95% CI)
Alanine aminotransferase increased	7 (2.1)	0	NE	0.02 (0.01, 0.04)
Blood bilirubin increased	2 (0.6)	4 (2.6)	0.24 (0.04, 1.28)	-0.02 (-0.05, 0.01)
Diarrhoea	1 (0.3)	6 (3.8)	0.08 (0.01, 0.65)	-0.04 (-0.07, -0.01)
Palmar-plantar erythrodysesthesia syndrome	0	13 (8.3)	NE	-0.08 (-0.13, -0.04)
Rash	0	4 (2.6)	NE	-0.03 (-0.05, 0.00)
Decreased appetite	2 (0.6)	6 (3.8)	0.16 (0.03, 0.77)	-0.03 (-0.06, 0.00)
Hypophosphatemia	1 (0.3)	5 (3.2)	0.09 (0.01, 0.80)	-0.03 (-0.06, 0.00)
Proteinuria	9 (2.7)	1 (0.6)	4.27 (0.55, 33.39)	0.02 (0.00, 0.04)
Infusion-related reaction	7 (2.1)	0	NE	0.02 (0.01, 0.04)

Source: calculated during the evaluation based on Table 2.23, p78 of the submission.

Abbreviations: AE = adverse events; Atezo+Bev = atezolizumab plus bevacizumab; CI = confidence intervals; HR = hazard ratio; n = number of participants reporting data, N = total participants in group; NE = not estimable; RD = risk difference; RR = relative risk

Note: Bold indicates statistically significant difference; excluded pulmonary embolism (<2% difference) due to incorrect n (%) stated for sorafenib in the submission – should be 2 (1.3%) instead of 4 (2.6%)

6.20 A higher proportion of patients experienced treatment-related PPES in the sorafenib arm (48.1%, any grade; 8.3%, Grade 3/4) compared to the Atezo+Bev arm (0.6%, any grade; 0, Grade 3/4). The PBAC previously noted that the occurrence of PPES may have a significant impact on a patient’s quality of life (para 4.2, lenvatinib, Public Summary Document, November 2018 PBAC meeting).

Benefits/harms

6.21 A summary of the comparative benefits and harms for Atezo+Bev versus sorafenib is presented in Table 11.

Table 11: Summary of comparative benefits and harms for Atezo+Bev and sorafenib

Benefits						
Progression-free survival^a (median duration of follow-up 8.6 months)						
Event	Atezo+Bev	Sorafenib	Absolute Difference	HR (95% CI)		
Progressed/dead, n/N (%)	197/336 (58.6)	109/165 (66.1)	-	0.59 (0.47, 0.76) P <0.0001		
Median PFS, months (95% CI)	6.83 months (5.75, 8.28)	4.27 months (3.98, 5.55)	2.56 months			
% not progressed/dead at 6 months (95% CI)	54.51 (49.06, 59.96)	37.17 (29.00, 45.34)	17.34%			
% not progressed/dead at 12 months (95% CI)	34.00 (27.90, 40.10)	9.22 (0.00, 18.46)	24.78%			
Overall survival (median duration of follow-up 8.6 months)						
Deaths, n/N (%)	96/336 (28.6)	65/165 (39.4)	-	0.58 (0.42, 0.79) P=0.0006		
Median OS, months (95% CI)	NE	13.24 months (10.41, NE)	NE			
% Alive at 6 months (95% CI)	84.81 (80.93, 88.69)	72.25 (65.10, 79.40)	12.56%			
% Alive at 12 months (95% CI)	67.19 (61.26, 73.12)	54.60 (45.15, 64.04)	12.59%			
Harms						
	Atezo+Bev n/N	Sorafenib n/N	RR (95% CI)	Event rate/100 patients*		RD (95% CI)
				Atezo+Bev	Sorafenib	
Treatment-related Grade 3/4 adverse events (≥ 2% difference with a statistically significant RD)						
ALT increased	7/329	0/156	NE	2.1	0	0.02 (0.01, 0.04)
Diarrhoea	1/329	6/156	0.08 (0.01, 0.65)	0.3	3.8	-0.04 (-0.07, -0.01)
PPES	0/329	13/156	NE	0	8.3	-0.08 (-0.13, -0.04)
Infusion-related reaction	7/329	0/156	NE	2.1	0	0.02 (0.01, 0.04)

Source: constructed during the evaluation based on Table 2.13, p65, Table 2.14, p67 and Table 2.23, p78 of the submission; Table 20, p101 and Table 21, p104 of the IMbrave150 CSR

Abbreviations: ALT = alanine aminotransferase; Atezo+Bev = atezolizumab plus bevacizumab; CI = confidence intervals; HR = hazard ratio; n = number of participants reporting data; N = total participants in group; NE = not estimable; OS = overall survival; PFS = progression-free survival; PPES = palmar-plantar erythrodysesthesia syndrome; RD = risk difference; RR = relative risk

Note: Bold indicates statistically significant difference.

a Based on IRF-assessment per RECIST v1.1

* includes adverse events with onset date on or after the date of the first dose of study drug up to the data cut-off date

6.22 On the basis of direct evidence presented by the submission, for every 100 patients treated with Atezo+Bev in comparison with sorafenib:

- Approximately 25 additional patients will be alive or free from disease progression at 12 months,
- Approximately 13 additional patients will be alive at 12 months.

Over a median duration of follow-up of 8.6 months:

- Approximately 2 additional patients would experience an increase in alanine aminotransferase (a change in liver enzymes that can only be detected through blood tests and may/may not result in clinical symptoms),
- Approximately 2 additional patients would experience an infusion-related reaction (such as difficulty breathing and itching of the skin),
- Approximately 4 fewer patients would experience diarrhoea,

- Approximately 8 fewer patients would experience palmar-plantar erythrodysesthesia syndrome (hand-foot syndrome which causes redness, swelling and pain on the palms of the hands and/or the soles of the feet).

Clinical claim

- 6.23 The submission described Atezo+Bev as superior to sorafenib in terms of efficacy, as demonstrated by a statistically significant and clinically meaningful improvement in OS and PFS compared to sorafenib. The therapeutic conclusion of superior efficacy of Atezo+Bev over sorafenib was supported by the data, noting that the OS data were immature and may not accurately reflect the longer-term risks of death associated with Atezo+Bev, resulting in an uncertain magnitude in OS gain. The median duration of follow-up for the trial was short (8.6 months) and the median OS in the Atezo+Bev arm was not reached, with only 28.6% (Atezo+Bev) and 39.4% (sorafenib) of patients having experienced an event. In addition, there was a high degree of censoring for survival and the number of patients remaining at risk after month 12 was low. The ESC agreed with the Sponsor and the evaluation that despite the immaturity of the data, the early improvement in OS is statistically significant and clinically meaningful.
- 6.24 There is some question over the applicability of the data from IMbrave150 to the Australian setting, most notably due to the availability of follow-up HCC systemic therapies for use within the trial. Use of such therapies occurred in a higher proportion of sorafenib patients than Atezo+Bev patients; the impact of that difference on the comparative efficacy is unclear. There is the potential that the effect for Atezo+Bev compared with sorafenib in Australian practice may differ from IMbrave150 given that there are no therapies specifically PBS listed for use in the second-line setting.
- 6.25 The submission described Atezo+Bev as non-inferior to sorafenib in terms of safety (with respect to event rates) with a different AE profile. The therapeutic conclusion of non-inferiority in terms of safety was supported by the data, noting the different adverse event profile.
- 6.26 The PBAC considered the claims of superior comparative effectiveness and non-inferior safety were supported by the clinical evidence.

Economic analysis

- 6.27 The submission presented a stepped economic evaluation based on evidence from IMbrave150 and implemented a modelled cost-utility analysis for Atezo+Bev versus sorafenib. The model structure and rationale are summarised in Table 12.

Table 12: Summary of model structure, key inputs and rationale

Component	Summary
Treatments	Atezo+Bev vs sorafenib
Time horizon	10 years in the model base case versus 8.6 months median follow-up in IMbrave150 trial
Outcomes	Life-years gained (LYG) and quality-adjusted life-years (QALY) gained
Methods used to generate results	Partitioned-survival cohort analysis (area under the curve)
Health states	Three: progression-free disease, progressive disease and death.
Cycle length	1 week
Allocation to health states	Health state allocation over time determined by PFS and OS curves from IMbrave150 at the 29 August 2019 clinical cut-off. The OS data were used to estimate the life-years in each treatment arm.
Extrapolation method	Data were extrapolated using all available KM data, applied from median follow-up (8.6 months). The model was fitted to each treatment arm with an exponential distribution selected as base case for OS, log-normal selected for PFS, and gamma distribution selected for TTD. The selection of extrapolation curves for PFS and TTD was based on the best-fit validation for Atezo+Bev, with the same distributions applied to the sorafenib arm. The submission provided a test for convergence as part of the model but did not include convergence in the base case.
Health related quality of life	Calculated from EQ-5D data collected in the IMbrave150 trial. The utility data were based on the TTD by treatment status. The utility values applied: were on treatment Atezo+Bev = 0.769; on treatment sorafenib =0.724; off treatment (pooled) =0.627.
Post-progression cost included in a sensitivity analysis.	Costs for chemotherapy and TKI as subsequent therapies were calculated separately for each arm based on the reported utilisation of these therapies in IMbrave150 as they were considered to be lower in Atezo+Bev arm. However, there were 43.5% of patients on treatment in Atezo+Bev arm, while only 14.5% in sorafenib arm at the data cut off. This indicates that the TTD data for Atezo+Bev arm are immature and the proportion of use of post-discontinuation therapy after Atezo+Bev is underestimated. This proportion is expected to increase as more patients come off treatment.

Source: 3.1, p90 of the submission and data compiled during evaluation.

Abbreviations: Atezo+Bev = atezolizumab + bevacizumab; HCC = hepatocellular carcinoma; KM = Kaplan-Meier; LYG = Life-years gained; OS = overall survival; PFS = progression-free survival; QALY= quality-adjusted life-years; TKI = tyrosine kinase inhibitor; TTD = time to treatment discontinuation.

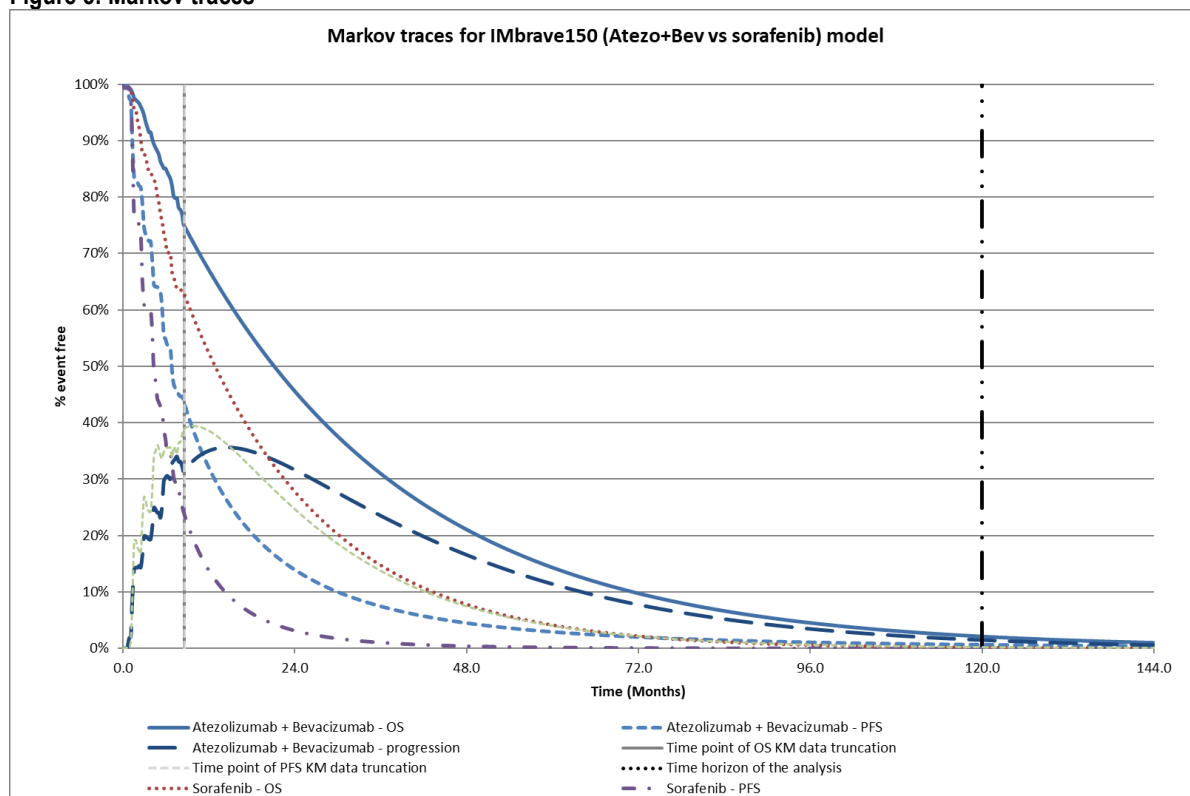
6.28 The submission presented a partitioned-survival analysis of Atezo+Bev compared to sorafenib. The OS data were extrapolated using an exponential function. The choice of parametric function was tested in sensitivity analyses; the results of the economic model were somewhat sensitive to the choice of extrapolation function (Table 13 and Table 15).

6.29 The model assumed that costs and utilities were driven by treatment status rather than by disease status. Thus, costs and QALY estimates were based on TTD rather than time in progressed/non-progressed health states. The submission stated that due to the difference between TTD and PFS for both treatment arms in IMbrave150, it was assumed that TTD better reflects patients' 'on treatment' status than their disease status (as captured by PFS). The use of TTD will capture the costs of continuing treatment beyond progression. While this is consistent with treatment in IMbrave150, it does not reflect the proposed use of bevacizumab or the current use of sorafenib in HCC on the PBS which are both limited to patients who are not progressed. Additionally, a post-hoc analysis provided by the sponsor during the evaluation demonstrated that 34.8% of patients in the Atezo+Bev arm and 32.7% of patients in

the sorafenib arm continued to receive treatment beyond disease progression, noting that ongoing treatment status beyond disease progression was unknown for 27.1% and 23% of patients in the Atezo+Bev and sorafenib arm, respectively. The Sponsor responded in the PSCR that the impact for costs and QALYs in using disease status rather than treatment status is marginal.

- 6.30 The submission included post-discontinuation treatment costs as a sensitivity analysis based on the observed treatments in IMbrave150. In estimating the costs of subsequent therapy, the submission assumed that in the absence of any PBAC accepted superiority claims between immunotherapy monotherapy and TKI treatment in this setting, the later-line TKI treatments and immunotherapy could be pooled, with the costs considered equivalent. The assumptions for the cost of post-discontinuation included use of cabozantinib as a proxy cost for TKI therapies and oxaliplatin for chemotherapies, although these drugs are not PBS listed for HCC. The cost estimates were based on the cabozantinib published price.
- 6.31 However, in estimating the proportion of patients treated post-discontinuation the submission applied the sum of the lines of therapy as the numerator over all randomised patients. The appropriate calculation would have been to estimate the proportion of those who received at least one post-discontinuation therapy out of all those who had progressed. A sensitivity analysis was conducted during the evaluation, estimating the proportion of patients receiving post-discontinuation treatment based on number of patients that discontinued in both arms. Correcting the calculation increased the ICER by 5%.
- 6.32 The base case model did not incorporate convergence of the extrapolated curves and assumed that the treatment effect for Atezo+Bev relative to sorafenib was ongoing. A subsequent sensitivity analysis conducted during the evaluation applied convergence to OS from 8.6 months (median follow-up) to 10 years (120 months). The ESC considered that convergence of the extrapolated curves was a key driver of the economic model (see paragraph 6.35). The ESC agreed with the PSCR that convergence from 8.6 months was likely to be too conservative but considered it represented a reasonable lower bound.
- 6.33 Traces for the model results are presented in Figure 5. According to the traces, approximately half of the patients in the Atezo+Bev treatment arm will have progressed by the first 7 months compared with 4.5 months for the sorafenib arm. This was similar to the difference in median PFS in IMbrave150. The proportion of OS that came from the KM data compared to the extrapolation period for Atezo+Bev was 25.8% and 37.6% in the sorafenib arm.

Figure 5: Markov traces



Source: Figure 3.8 and Figure 2.9, p120 of the submission. Combined during evaluation using workbook 'Economic evaluation'. Abbreviations: KM = Kaplan-Meier; OS = overall survival; PFS = progression-free survival

- 6.34 For each treatment arm, OS, PFS and TTD were extrapolated out to 20 years, with the submission reporting all outcomes at 10 years (base case time horizon). The submission justified the 10-year time horizon for the base case on the basis that the OS curves separated 1 month after treatment initiation, and that a 10-year time horizon was previously accepted by the PBAC for sorafenib and has been used in other HTA submissions overseas. Overall, the extrapolation relied on immature data for Atezo+Bev arm, as the median OS was not reached.
- 6.35 A summary of key drivers of the economic model is shown in Table 13. The key relevant drivers with an impact on the ICER of more than 10% included the time horizon, the extrapolation method for the OS curve, the assumed cost of the comparator (sorafenib), convergence of OS curve and discount rate. These results are based on the effective price of Atezo+Bev.

Table 13: Key drivers of the model

Description	Method/Value	Impact Base case: \$45,000 to < \$55,000/QALY gained
Time horizon	IMbrave150 data extrapolated from 8.6 median follow-up to 10 years	Medium, favours Atezo+Bev (ICER = \$55,000 < \$75,000/QALY for 5 years)
Extrapolation	Selection of exponential function for OS for both treatment arms. The chosen function was not best fit (based on AIC/BIC) for either of the arms.	High, ICER varies from \$25,000 to < \$35,000/QALY (Gompertz) to \$75,000 to < \$95,000/QALY (log normal for sorafenib)
Convergence of OS curve	No convergence in the base case. Convergence applied from 8.6 months (median follow-up)	High, favours Atezo+Bev (ICER = \$135,000 to < \$155,000/QALY)

Source: developed during the evaluation based on the excel model 'Economic Evaluation'

Abbreviations: AIC = Akaike Information Criterion; Atezo = atezolizumab; Bev = bevacizumab; BIC = Bayesian Information Criterion; ICER = incremental cost effectiveness ratio; OS = overall survival; PFS = progression-free survival; QALY = quality adjusted life years; TTD = time to treatment discontinuation.

6.36 The stepped economic evaluation is summarised in Table 14 and outlined as follows: Step 1 was based on the IMbrave150 time horizon (limiting the trial data to the 8.6 months of median follow-up) to estimate life-year gained (LYG) and incorporating utility values to estimate QALYs; Step 2 applied a 10-year time horizon with the chosen extrapolation curves for OS, PFS; and Step 3 and beyond included subsequent various costs for medical resource use, treatments for adverse events and end of life (each in a separate step). The cost per QALY using the effective price of the comparator is presented in paragraph 6.43 (Committee-in-Confidence).

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Table 14: Results of the stepped economic evaluation

Step and component	Atezo+Bev	Sorafenib	Increment
Step 1: Trial setting IMbrave150, trial time horizon up to 8.6 months (median follow-up)			
Costs	\$ [redacted]	\$ [redacted]	\$ [redacted]
Life -years	LY: [redacted]	LY: [redacted]	LY: [redacted]
QALYs	QALY: [redacted]	QALY: [redacted]	QALY: [redacted]
Incremental cost/extra LY and QALYs gained			\$ [redacted] /LY gained; \$ [redacted] /QALY gained
Step 2: Time horizon 10 years, extrapolation of OS, PFS, TTD			
Costs	\$ [redacted]	\$ [redacted]	\$ [redacted]
Life -years	LY: [redacted]	LY: [redacted]	LY: [redacted]
QALYs	QALY: [redacted]	QALY: [redacted]	QALY: [redacted]
Incremental cost/extra LY and QALYs gained			\$ [redacted] /LY gained; \$ [redacted] /QALY gained
Step 3: Inclusion of medical resource use costs			
Costs	\$ [redacted]	\$ [redacted]	\$ [redacted]
Life -years	LY: [redacted]	LY: [redacted]	LY: [redacted]
QALYs	QALY: [redacted]	QALY: [redacted]	QALY: [redacted]
Incremental cost/extra LY and QALYs gained			\$ [redacted] /LY gained; \$ [redacted] /QALY gained
Step 4: Inclusion of adverse events related cost			
Costs	\$ [redacted]	\$ [redacted]	\$ [redacted]
Life -years	LY: [redacted]	LY: [redacted]	LY: [redacted]
QALYs	QALY: [redacted]	QALY: [redacted]	QALY: [redacted]
Incremental cost/extra LY and QALYs gained			\$ [redacted] /LY gained; \$ [redacted] /QALY gained
Step 5: utility values applied to life-years, estimation of QALY			
The weighting of life-years to determine QALYs was introduced and applied from Step 1			
Step 6: Inclusion of end of life cost			
Costs	\$ [redacted]	\$ [redacted]	\$ [redacted]
Life -years	LY: [redacted]	LY: [redacted]	LY: [redacted]
QALYs	QALY: [redacted]	QALY: [redacted]	QALY: [redacted]
Incremental cost/extra LY and QALYs gained			\$ [redacted] /LY gained; \$ [redacted] /QALY gained
Step 7: base case (summary)			
Costs	\$ [redacted]	\$ [redacted]	\$ [redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER			\$ [redacted] /QALY gained

Source: Table 3.22 to Table 3.26, pp1221-123 of the submission.

Abbreviations: ICER = incremental cost-effectiveness ratio; LY = life-years; OS = overall survival; PFS = progression-free survival; QALY = quality-adjusted life-years; TTD = time to treatment discontinuation.

The redacted table shows the base case ICER in the range of \$45,000 to < \$55,000 per QALY.

6.37 The results of key univariate sensitivity analyses are summarised in Table 15. The results from these analyses show that the ICER was most sensitive to variations in the time horizon (paragraph 6.38), the inclusion of post-discontinuation therapy costs (paragraph 6.41), the assumption of the effective price of sorafenib, and the assumed extrapolation function applied to OS for sorafenib (paragraph 6.40). Additional sensitivity analyses were conducted during the evaluation including the convergence of OS for Atezo+Bev (paragraph 6.39), using different functional forms for the extrapolation of OS, and applying PFS (disease status) to costs and QALYs to both arms

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in the model. The ICER was highly sensitive to the convergence of OS, and sensitive to the choice of extrapolation function.

Table 15: Key results of sensitivity analyses (effective price Atezo+Bev)

Variable or assumption	Base case value	Atezolizumab + bevacizumab versus sorafenib		
		Incremental cost	Incremental effectiveness (QALY)	ICER (per QALY)
Base case – assumed discount on list price sorafenib: █%		\$ █	█	\$ █
Costs				
Inclusion of post-discontinuation therapy costs (cabozantinib cost applied)	Post-discontinuation therapy costs are excluded	\$ █	█	\$ █
Inclusion of post-discontinuation therapy costs (sorafenib cost applied)	Post-discontinuation therapy costs are excluded	\$ █	█	\$ █
Cost of sorafenib with █% discount on published price	Assumed █% discount on published price of sorafenib	\$ █	█	\$ █
Cost of sorafenib at published price	Assumed █% discount on published price of sorafenib	\$ █	█	\$ █
Outcomes				
Convergence				
Convergence of OS of Atezo+Bev treatment arm from 8.6 months (median follow-up)	No convergence applied	\$ █	█	\$ █
Convergence of OS from 36 months (#1)	No convergence applied	\$ █	█	\$ █
Extrapolation				
OS extrapolation follows Gamma distribution in Atezo+Bev arm and log-normal in sorafenib arm. Based on best statistical fit as per AIC and BIC (#2)	OS extrapolation follows exponential distribution in both arms	\$ █	█	\$ █
Extrapolation for OS, PFS, TTD based on best fit for both treatment arms. Atezo+Bev: gamma distributions; sorafenib: log-normal	Same distributions functions were applied to both treatment arms. OS: exponential; PFS: log-normal; TTD: gamma	\$ █	█	\$ █
Time horizon				
5 years	10 years	\$ █	█	\$ █
7.5 years (#3)	10 years	\$ █	█	\$ █
Multivariate analysis				
Using disease status (PFS) for costs and QALYs in both treatment arms. And using 'progression free' utility values for Atezo+Bev (0.749) and sorafenib (0.744), and 'progresses' utility value for both arms (0.698) ^a	Used treatment status (TTD) for cost and QALYs in both treatment arms. With utility values based on 'on treatment' Atezo+Bev (0.769) and sorafenib (0.724); and 'off treatment' for both arms (0.627).	\$ █	█	\$ █
#1 + #2 + #3 ^b		\$ █	█	\$ █

Source: Table 3.28, p127, Table 3.29, p129, Table 3.30, p131 of the submission.

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Abbreviations: AIC = Akaike Information Criteria; BIC = Bayesian Information Criteria; OS = overall survival; PD = progressed disease; PFS = progression-free survival; TTD = time to treatment discontinuation.

Note:

a The value was estimated by changing the formula in the excel workbook 'Economic Evaluation', sheet 'Atezo+Bev' cells [AR7:AR1051] and [BC7:BC1051] to corresponding rows in column [M] (PFS values); in sheet 'Sorafenib' cells [AP7:AP1051] to corresponding rows in column [M] (PFS values).

b Multivariate sensitivity analysis added for ESC ADV with convergence from 36 months, best fit extrapolation and 7.5 year time horizon.

The redacted table shows ICERs in the range of \$15,000 to < \$25,000 per QALY, to \$135,000 to < \$155,000 per QALY.

- 6.38 The ESC considered that extrapolation of the 8.6 months follow-up to a time horizon of 10 years was not supported. The ESC noted that advanced HCC patients in a lenvatinib vs. sorafenib study (Kudo et al) had 3 year survival of 15%, and sorafenib patients in the SEER database had 2 year survival of <10%, making a 10-year time horizon unrealistic. The ESC considered that a time horizon of 5 or 7.5 years would be reasonable, despite the possibility of a small percentage of patients having a durable response. If the time horizon is decreased to 7.5 years, the ICER increased to \$45,000 to < \$55,000 per QALY; if it is decreased to 5 years, the ICER increased to \$55,000 to < \$75,000 per QALY (Table 15). The ESC noted that while sorafenib was recommended in 2008 using a 10 year time horizon, it considered a 5 or 7.5 year time horizon would be more appropriate for Atezo+Bev given the immature clinical data and the extent of extrapolation. The pre-PBAC response stated that a 5-year time horizon is overly conservative, especially in the context that the median survival improvement with Atezo+Bev over sorafenib is expected to exceed the survival improvement observed with sorafenib over best supportive care.
- 6.39 Regarding OS curve convergence, the Sponsor stated in the PSCR that the convergence commencing from 8.6 months (median follow-up) to 10 years (time horizon), generating an ICER of \$135,000 to < \$155,000 per QALY, was improbable, since the life-years gained was [REDACTED] (i.e. an average survival improvement of [REDACTED] months). The Sponsor noted the 25th percentile OS improvement was 3 months, with survival curves continuing to diverge with longer follow-up. The ESC considered that the Sponsor's base case with no curve convergence was not appropriate; however, the ESC agreed with the PSCR that convergence from 8.6 months may be overly conservative, although noted it provided a reasonable lower bound. If convergence is applied from 36 months, the ICER increased to \$55,000 to < \$75,000 per QALY gained (Table 15), compared to \$45,000 to < \$55,000 per QALY gained in the base case (which assumed no convergence of the OS curves).
- 6.40 The submission applied an exponential distribution to the extrapolation of OS curves which may have favoured Atezo+Bev. The choice of extrapolation function was based on the OS data for Atezo+Bev, that were immature at the data cut-off, and the chosen function was not the best fit based on AIC and BIC. The AIC and BIC results indicate that the log-normal function has the best fit for sorafenib. The Sponsor responded in the PSCR that best statistical fit does not always result in clinically plausible estimates, and further noted that the best statistical fit for both intervention and comparator

arms (not just the sorafenib arm) was a log-normal function that generated an ICER of \$55,000 to < \$75,000 per QALY gained, which was similar to the base case. The ESC noted that the extrapolation function was a key driver of the model. The AIC and BIC results indicate that the gamma function has the best fit for Atezo+Bev and the log-normal function has the best fit for sorafenib. If these functions are applied, the ICER is \$55,000 to < \$75,000 per QALY gained (Table 15).

- 6.41 The base case analysis did not include the costs of post-discontinuation therapy even though the clinical impact of those therapies as experienced in IMbrave150 on OS is included. The impact of including post-discontinuation costs was tested in a sensitivity analysis and decreased the ICER to \$15,000 to < \$25,000 per QALY using cabozantinib as the post-discontinuation therapy. However, the proportions of patients assumed to be using post-discontinuation therapies for the Atezo+Bev arm are likely to be underestimated (since 43.5% of patients were on treatment in Atezo+Bev arm and 14.5% in sorafenib arm, at the data cut-off) and are expected to increase as more patients come off treatment. An additional sensitivity analysis using sorafenib as the post-discontinuation therapy increased the ICER from \$15,000 to < \$25,000 per QALY (using cabozantinib costs) to \$45,000 to < \$55,000 per QALY gained (Table 15).
- 6.42 The PBAC considered a multivariate analysis incorporating a best fit extrapolation (gamma function for Atezo+Bev and log-normal function for sorafenib), convergence of survival from 36 months and a 7.5 year time horizon generating an ICER of \$75,000 to < \$95,000 per QALY (Table 15) provided a reasonable upper bound estimate of the cost effectiveness of Atezo+Bev. The cost per QALY using the effective price of the comparator is presented in paragraph 6.43 (Committee-in-Confidence).

Committee-In-Confidence information

- 6.43 The ICER using the effective price for sorafenib (█ for 60 x 200 mg tablets) was █ for the base case analysis and █ for the multivariate analysis (discussed in paragraph 6.42).

End Committee-In-Confidence information

Drug cost/patient

- 6.44 The cost per patient is presented in Table 16. Based on the mean duration of treatment as reported in IMbrave150 (█ months for atezolizumab, and █ months for bevacizumab) the cost of the Atezo+Bev regimen per patient per course of treatment was \$█. This was based on the effective price of \$█ for atezolizumab and \$█ for bevacizumab, for a total of █ cycles and █ cycles, respectively. Applying the proportion of use in public (34.55%) and private (65.45%) hospitals and mean duration of treatment from the economic model resulted in a higher cost per patient for Atezo+Bev of \$█.
- 6.45 The financial estimates used a treatment cost per patient of \$█.
- 6.46 The estimated cost of the comparator, sorafenib based on the mean duration in the IMbrave150 was \$█ and based on the estimations in the economic model

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\$ [REDACTED]. Due to the use of a market share approach in the financial implications, it was not possible to extract a treatment cost per patient for sorafenib.

Table 16: Drug cost per patient for proposed drug

	Trial dose and duration Atezo+Bev	Model	Financial estimates	Sorafenib Trial dose and duration	Sorafenib Model	Sorafenib Financial estimates
Mean dose	Atezo: [REDACTED] ^a mg per dose Bev: [REDACTED] ^a mg per dose	Atezo: 1,200 mg per dose Bev: 1,076 mg per dose	Atezo: 1,200 mg per dose Bev: 1,100 mg per dose	[REDACTED] ^a mg per dose	400 mg per dose	400 mg per dose
Mean duration/Mean number of doses received	Duration: Atezo: [REDACTED] months Bev: [REDACTED] months Doses received: Atezo: [REDACTED] (SD [REDACTED]) Bev: [REDACTED] (SD [REDACTED])	Atezo: [REDACTED] months Bev: [REDACTED] months	Atezo: [REDACTED] months Bev: [REDACTED] months	Duration: [REDACTED] months Doses received: [REDACTED] (SD [REDACTED])	[REDACTED] months	Based on number of scripts in market estimates
Cost/patient/cycle (DPMQ/DPMA)	Atezo: \$ [REDACTED] ^b Bev: \$ [REDACTED] (per 21 days cycle)	Atezo: \$ [REDACTED] Bev: \$ [REDACTED] (per 21 days cycle)	Atezo: \$ [REDACTED] Bev: \$ [REDACTED]	\$ [REDACTED] ^b per 30 days cycle (assumed effective price)	\$ [REDACTED] (assumed effective price) per 30 days cycle	\$5,547.79 (published)
Cost/patient (DPMQ/DPMA)	Based on mean number of doses: Atezo: \$ [REDACTED] ^c Bev: \$ [REDACTED] ^c	Atezo: \$ [REDACTED] Bev: \$ [REDACTED] ^d	\$ [REDACTED] ^e	Based on mean number of doses: \$ [REDACTED] ^f	\$ [REDACTED] ^g	NE

Source: Table 26, pp 156-157 of the trial report, Section 3 workbook, sheet 3a of the utilisation-and-cost-model.

Abbreviations: Atezo = atezolizumab; Bev = bevacizumab; DPMA = dispensed price for maximum amount; DPMQ = dispensed price for maximum quantity; NE = not estimable; SD = standard deviation.

Note:

a Calculated based on mean total cumulative dose divided by the mean number of doses received (= [REDACTED]) for Atezo, and (= [REDACTED]) for Bev, and (= [REDACTED]) for sorafenib;

b Based on the mean dose and the ex-man price for Atezo, Bev and sorafenib, ([REDACTED]);

c The cost per patient per cycle multiplied by the mean number of doses received;

d Estimated in the submission, based on the modelled duration of treatment, undiscounted cost, in excel workbook "Economic evaluation, sheet "ATEZO+BEV", column BG (Atezo) and column BH (Bev) by amending the formula and removing the discount multiplier;

e Based on the estimated net cost to PBS/RPBS over estimated number of treated patients in Year 1 in Section 4 (= \$ [REDACTED] / [REDACTED] patients), this population excluded [REDACTED] grandfathered patients to align with the economic model;

f The cost per patient per cycles divided by 60 doses (2 doses per day) and multiplied by the mean number of doses received (= (\$ [REDACTED] / 60) * [REDACTED]);

g Estimated in the submission, based on the modelled duration of treatment, undiscounted cost, in excel workbook "Economic evaluation, sheet "Sorafenib", column AS by amending the formula and removing the discount multiplier.

Estimated PBS usage & financial implications

6.47 This submission was not considered by DUSC.

- 6.48 The submission used a mixed epidemiological and market share approach to estimate the expected financial impact associated with the listing of Atezo+Bev. The submission stated that since the proposed PBS restriction for Atezo+Bev was narrower (WHO PS 0-1) than the current PBS restriction for sorafenib and lenvatinib (WHO PS 0-2), an epidemiological approach was used to estimate the number of patients eligible for Atezo+Bev. The cost of the drugs that were assumed to be replaced, sorafenib and lenvatinib, were based on published prices. The economic evaluation assumed that a ■% discount applied to the published price of sorafenib; this assumption was not carried through into the financial estimates provided in the submission. The submission did not estimate the utilisation of atezolizumab monotherapy 1,680 mg Q4W, which was requested as a separate listing (paragraph 3.1). The key inputs used by the submission in forming the financial estimates are summarised in Table 17.

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Table 17: Key inputs for financial estimates

Parameter	Value applied and source	Comment
Incidence population	HCC representing 82% of all liver cancer, and growth rate for liver cancer of 3.67%	This represents total HCC incidence in Australia
Proportion of all liver cancer diagnoses (ICD-10 code C22) that are HCC	82%	Australian specific prospective population-based study of newly diagnosed HCC patients which is not treatment specific.
Proportion of patients diagnosed at BCLC stage A/B/C HCC in Australia	A=26% B=22% C=37%	Hong 2018. Australian population-based cohort study of newly diagnosed HCC patients
Proportion of patients with liver cancer in Child-Pugh A	56%	Hong 2018. Australian population-based cohort study of newly diagnosed HCC patients
Proportion of BCLC stage B HCC patients who receive TACE	45.7%	Included assumption that all who did not receive TACE were eligible for Atezo+Bev. This may be an overestimation.
Proportion of patients with HCC who have WHO PS 0 or 1	87.4%	Assumption that PS is not correlated with BCLC stage at diagnosis, likely underestimates eligibility in early stage diagnosis and overestimates eligibility in later stage diagnosis. The submission proposed that this would balance out when applied to the whole population. Impact of this variable is tested in a sensitivity analysis.
Uptake rate	█%	Assumption. Based on IMbrave150 “superior OS and quality of life benefit compared to comparators”. The submission tested a lower uptake rate of █% in the first year in the sensitivity analysis.
Proportion of sorafenib and lenvatinib in HCC setting replaced with Atezo+Bev after listing	88% ^a	This may be an overestimate since it assumes that all patients for whom it is eligible (WHO PS 0-1) will be treated with Atezo+Bev rather than sorafenib and lenvatinib.
Grandfathered patients	< 500	The evaluation considered this is most likely an overestimate.
Comparators	Sorafenib and lenvatinib	Sorafenib is the comparator used in Section 1, Section 2 and Section 3 of the submission. However, lenvatinib was not presented as comparator.
MBS item	MBS item number 13918: \$99.50 (reflecting IV infusion >1 hour duration)	Appropriate

Source: Table 4.2, pp136-137, Table 4.12, 144, Table 4.34, p161, of the submission.

Abbreviations: AIHW = Australian Institute of Health and Welfare; Atezo = atezolizumab; BCLC = Barcelona Clinic Liver Cancer; Bev = bevacizumab; HCC = hepatocellular carcinoma; ICD-10 code = International Classification of Disease version 10; MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefit Scheme; TACE = transarterial chemoembolisation; WHO PS = World Health Organisation performance status.

Note:

a The submission assumed that of the total sorafenib and lenvatinib HCC market that includes patients with WHO PS 0-2, 88% are patients with WHO PS 0-1. The submission assumed that 100% of patients with WHO PS 0-1 will be replaced by Atezo+Bev.

- 6.49 The submission estimated the number of eligible HCC patients to receive Atezo+Bev based on five subgroups:
- Subgroup 1: BCLC stage A who experience recurrence and are ineligible for TACE
 - Subgroup 2: BCLC stage B1 patients who experience recurrence and are ineligible for TACE
 - Subgroup 3: BCLC stage B2-B4 and ineligible for TACE
 - Subgroup 4: BCLC stage C disease who are Child-Pugh A, WHO PS 0 or 1
 - Subgroup 5: Stage B patients who received TACE but overtime become too weak to continue receiving TACE ('unTACEable').
- 6.50 The evaluation considered the estimates provided by the submission were reasonable and consistent with the proposed TGA registration and requested PBS listing. However, the extent to which patients described by groups 1, 2 and 5 are captured in current sorafenib/lenvatinib use is unknown.
- 6.51 The submission did not estimate prevalent patients due to the average duration of treatment being less than 1 year. Therefore, the evaluation considered the inclusion of grandfathered patients was appropriate. The submission included < 500 grandfathered patients. The submission did not provide justification for the high number of grandfathered patients.
- 6.52 The submission assumed an uptake rate of █% of Atezo+Bev from Year 1 onward, which represents 100% of the sorafenib and lenvatinib (WHO PS 0-1) use. A sensitivity analysis showed that the estimates were sensitive to this assumption. The Sponsor stated in the PSCR that given the demonstrated health outcomes in IMbrave150, unanimous feedback from the members of Roche's Hepatocellular Cancer Advisory Board was that Atezo+Bev is the first-line treatment of choice for every patient who satisfies PBS eligibility criteria. Therefore, it is reasonable to assume that all patients eligible for Atezo+Bev would have otherwise initiated on a first-line TKI. The PBAC agreed with the ESC that the uptake rate was overestimated as some patients may have contra-indications to Atezo+Bev (e.g., autoimmune disease), be unwilling to receive intravenous therapy, and/or not be able to access multi-disciplinary care (i.e. remote location, low socio-economic status and poor health literacy as may occur with HCC patients).
- 6.53 The market share estimates for sorafenib and lenvatinib informed the estimates of replacement and were based on a combination of PBS item reports and PBS 10% sample market data.
- 6.54 The submission estimated that 87.4% of patients with HCC have WHO PS 0 or 1. The evaluation considered that this figure likely underestimated eligibility in early stage diagnosis and overestimated eligibility in later stage diagnosis, which accounts for 65% of patient numbers (Subgroup 4). The PBAC agreed with the ESC that this figure of

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87.4% was a significant overestimate, as patients with BCLC B or C are often frail and do not have WHO PS 0 or 1.

- 6.55 The submission assumed that upon listing of Atezo+Bev all HCC patient with WHO PS 0 or 1 would be treated with Atezo+Bev, which constituted 88% of all sorafenib and lenvatinib patients. The PBAC considered that this assumption was not well justified and is most likely an overestimate. A sensitivity analysis indicated that the financial estimates were sensitive to the assumed extent of substitution for sorafenib and lenvatinib.
- 6.56 The PBAC considered there may be risk of use outside the Atezo+Bev restriction after progression on (not intolerance to) sorafenib and lenvatinib.
- 6.57 The effective price of bevacizumab reflects the [REDACTED] rebate proposed in the SPA (which does not apply to the mark-ups and dispensing fees that would be associated with dispensing of bevacizumab).
- 6.58 The financial estimates for the use of Atezo+Bev are presented in Table 18.

Table 18: Estimated use and financial implications (effective price for Atezo+Bev; published price for sorafenib and lenvatinib)

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of patients treated	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Grandfathered patients	[REDACTED]					
Number of scripts dispensed ^a	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Estimated financial implications of Atezo+Bev						
Atezo	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Bev	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Total cost to PBS/RPBS less copayments	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Estimated financial implications for sorafenib and lenvatinib (published prices)						
Saving to PBS/RPBS less copayments	-\$15,645,943	-\$16,001,957	-\$16,371,028	-\$16,753,647	-\$17,150,289	-\$17,561,480
Net financial implications						
Net cost to PBS/RPBS	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Net cost to MBS	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Net cost to PBS/RPBS/MBS	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]

Source: Table 4.12, p144; Table 4.13, p145; Table 4.26, p155; Prepared during the evaluation from Table 4.28, p156, Table 4.29, p157, Table 4.30, p 158; Table 4.32, p159; Table 4.36, p161; Table 4.36, p161 and ATEZO_BEVA_utilisation-and-cost-model.xlsm, '5. Impact – net' of the submission.

Abbreviations: MBS=Medicare Benefits Schedule; PBS=Pharmaceutical Benefits Scheme; RPBS=Repatriation Pharmaceutical Benefits
 Note: a Assuming [REDACTED] scripts (atezolizumab) and [REDACTED] scripts (bevacizumab) per year as estimated by the submission.

The redacted table shows that at Year 6, the estimated number of patients treated was 500 < 5,000; the estimated number of scripts dispensed was 20,000 < 30,000; and the net cost to the PBS would be \$10 million to < \$20 million.

- 6.59 The ESC noted that utilisation data for sorafenib and lenvatinib provided by the DUSC Secretariat indicated that there were 718 patients treated with a TKI for advanced HCC

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in 2019². The ESC noted that this is more than the number of patients estimated to be treated with Atezo+Bev in Year 1 (500 to < 5,000), although it may be consistent with the use of Atezo+Bev only in patients with a WHO PS of 0 and 1. The ESC considered that a Risk Sharing Arrangement may be appropriate to manage the risk of the financial implications substantially exceeding those presented in the submission. The pre-PBAC response stated that triangulation using an alternative approach informed by DUSC and published Australian literature infers that 632 of the 718 patients treated with a TKI would meet ECOG PS 0-1 criteria, given that 88% of patients treated with sorafenib have an ECOG PS of 0-1 (Table 1, Doyle 2016).

6.60 Key results of univariate sensitivity analyses presented in the submission are provided in Table 19. The results showed that the estimates were most sensitive in Year 1 to the change in the assumed uptake rate, to the assumed proportion of patients with WHO PS 0-1 and to the assumed proportion of patients who received TACE. An additional sensitivity analysis was conducted as part of the evaluation by estimating the impact of a lower replacement rate for sorafenib and lenvatinib scripts (from 88% to 50%), resulting in an increase in the estimated net cost to the PBS/RPBS.

Table 19: Key univariate sensitivity analysis for estimated cost to PBS/RPBS (Atezo+Bev effective prices)

Year		2020	2021	2022	2023	2024	2025
Base case		\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
<i>Variable or assumption</i>	<i>Base case value</i>						
Patients receiving TACE Hong 2018 (24.0%)	45.7%	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Patients with ECOG PS 0 or 1 Hsu 2013 (77%)	87.4%	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
First year uptake rate ([REDACTED]%)	[REDACTED]%	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Replacement of sorafenib and lenvatinib scripts at 50% of the total market	88% ^a	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]

Source: Table 4.38, p162 and Table 2.40, p163 of the submission.

Abbreviations: ECOG PS=Eastern Cooperative Oncology Group performance status; PBS=Pharmaceutical Benefits Scheme; RPBS=Repatriation Pharmaceutical Benefits Scheme; TACE = transarterial chemoembolisation.

Note:

a The submission assumed that of the total sorafenib and lenvatinib HCC market that includes patients with WHO PS 0-2, 88% are patients with WHO PS 0-1. The submission assumed that 100% of patients with WHO PS 0-1 will be replaced by Atezo+Bev.

The redacted table shows that at Year 6, with a lower replacement rate for sorafenib and lenvatinib scripts (from 88% to 50%), the estimated net cost to the PBS would be \$20 million to < \$30 million.

² Services Australia Supplied Prescription database, extracted 25 May 2020.

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

Quality use of medicines

- 6.61 No information was provided in the submission on quality use of medicines; however, the PBAC noted that HCC patients may be treated by hepatologists who may not be familiar with immunotherapy and management of the associated AEs. The PBAC considered this group of specialists may require additional support to ensure appropriate use of Atezo + Bev in clinical practice.
- 6.62 The PBAC noted that the safety of Atezo+Bev has not been established in patients who had incompletely treated varices, variceal bleeding within the previous 6 months or who were at high risk of bleeding and considered it would be appropriate to include a 'Caution' in the restriction criteria that patients should be assessed for risk of variceal bleeding prior to treatment with Atezo+Bev.

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 - Public and Private Hospital) Authority Required (STREAMLINED) listing of atezolizumab in combination with bevacizumab (Atezo+Bev) for the treatment of patients with advanced unresectable BCLC stage B or stage C HCC who have not received prior systemic treatment. The PBAC considered there was a high clinical need in this patient population and recognised the substantial clinical benefit provided by Atezo+Bev, despite the immaturity of the overall survival data. The PBAC's recommendation for listing was based on, among other matters, its assessment that the cost-effectiveness of Atezo+Bev would be acceptable at the price proposed in the submission, with an appropriate risk sharing arrangement to manage the risk of use outside the restriction.
- 7.2 The PBAC was satisfied that Atezo+Bev provides, for some patients, a significant improvement in efficacy over sorafenib. The PBAC noted that lenvatinib was also PBS listed for HCC but, as lenvatinib was recommended on the basis of non-inferior efficacy and safety to sorafenib, considered sorafenib was an appropriate proxy for first-line TKI therapy in the target population.
- 7.3 The PBAC noted that there is a high clinical need for effective treatments in advanced HCC, given the poor prognosis for patients and the poor efficacy and high toxicity of current treatments. The PBAC noted this was supported by the consumer comments received for this submission.
- 7.4 The PBAC noted the Sponsor sought the PBAC's consideration for an 'alternative' PBS restriction that would extend use to patients with a WHO PS of 2. The PBAC noted that patients with a WHO PS of 2 were not included in the trial population and the PBAC advised that the requested restriction criterion was not supported. The PBAC agreed with the Secretariat that the proposed continuation criteria for Atezo+Bev should not allow treatment after disease progression, and noted that the Sponsor indicated in its

pre-PBAC response that it is amenable to this restriction amendment. The PBAC considered that Atezo+Bev should not be used following a VEGF TKI unless intolerance of a severity necessitating permanent treatment withdrawal occurred.

- 7.5 The PBAC considered that VEGF TKIs (sorafenib and lenvatinib) should remain as first-line treatments for HCC in line with clinical evidence, and second-line use should not occur following disease progression after patients have been treated with Atezo+Bev. The PBAC noted there will be flow-on restriction changes to sorafenib and lenvatinib regarding their line of therapy (item numbers 9380Q and 11638M, respectively).
- 7.6 The submission was based on one head-to-head randomised, Phase III, open-label multi-centre trial (IMbrave150; N=501) comparing Atezo+Bev to sorafenib in patients with previously untreated advanced HCC. The PBAC noted that the median duration of follow-up for the trial was short (8.6 months) and the median OS in the Atezo+Bev arm was not reached, with only 28.6% (Atezo+Bev) and 39.4% (sorafenib) of patients having experienced an event. The PBAC considered that the improvement in OS (HR=0.58) represents a substantial clinical benefit, despite the immaturity of the data, given the poor outcomes associated with HCC.
- 7.7 The PBAC noted that the statistical difference in time to deterioration (TTD) in favour of Atezo+Bev is likely to be clinically significant to patients in terms of improved QoL. While the submission described Atezo+Bev as non-inferior to sorafenib in terms of safety, the PBAC noted it had a different AE profile. The PBAC noted Atezo+Bev was associated with significantly less diarrhoea and palmar-plantar erythrodysesthesia syndrome compared with sorafenib, but more cases of increased alanine aminotransferase and infusion-related reactions.
- 7.8 The PBAC noted the strict inclusion and exclusion criteria of IMbrave 150 and considered this may limit the generalisability of the trial results to Australian clinical practice (paragraph 6.11). The PBAC considered that, in clinical practice, the benefit of Atezo+Bev may be smaller and the safety worse than observed in IMbrave 150. In particular, the PBAC noted patients with incompletely treated oesophageal and/ or gastric varices or at high risk of bleeding were excluded from IMbrave 150. The PBAC considered that the PBS restriction should include a caution for patients to be assessed for risk of variceal bleeding before treatment with Atezo+Bev.
- 7.9 The PBAC noted the base case ICER presented in the submission was \$45,000 to < \$55,000 per quality adjusted life year (QALY) gained (assuming an effective sorafenib price at ■■■% of the published price). The PBAC noted the economic model did not assume convergence of the OS curves and inclusion of convergence was a key driver of the result (paragraph 6.35). The PBAC considered the 10 year time horizon applied in the model was unreasonable, given the life expectancy of HCC patients and the extent of extrapolation required with only 8.6 months of follow-up in IMbrave150. The PBAC considered a 7.5 year time horizon with convergence of OS curves from 36 months was more reasonable. The PBAC noted the multivariate analysis incorporating these changes (and using the best fit extrapolation for OS in both treatment arms)

resulted in an ICER of \$75,000 to < \$95,000 per QALY gained (paragraph 6.42). The PBAC noted the ICERs using the effective price of sorafenib (paragraph 6.43). The PBAC considered the cost effectiveness of Atezo+Bev was likely to be within the range previously considered reasonable for this condition.

- 7.10 The PBAC considered that the number of patients expected to be treated with Atezo+Bev (500 to < 5,000 in Year 1, increasing to 500 to < 5,000 in Year 6) was likely overestimated. The PBAC considered it is unlikely 87.4% of patients with Stage C disease (Subgroup 4, as defined in paragraph 6.49) would have a WHO PS of 0 or 1. The PBAC considered 77% would be a more reasonable estimate in this population, consistent with the rate applied in the sensitivity analysis. The PBAC also considered the estimated uptake of Atezo+Bev in each of the eligible subgroups of patients (■%) may be overestimated as some patients may have contra-indications to Atezo+Bev (e.g., autoimmune disease), be unwilling to receive intravenous therapy, and/or not be able to access multidisciplinary care, and the applicability of the clinical data to the Australian population (paragraph 7.8) may limit uptake. The PBAC considered an 80% uptake per year in eligible incident patients would be more reasonable. The PBAC noted the number of patients expected to be treated with Atezo+Bev with these revisions is < 500 in Year 1 and 500 to < 5,000 in Year 6. The PBAC noted that not all patients treated in Year 1 would receive a full treatment course (as patients commence treatment throughout the year) and a lower uptake rate should be applied in Year 1 to account for a lower number of prescriptions per patient.
- 7.11 The PBAC noted the submission indicated < 500 patients would require grandfathering onto PBS-subsidised treatment and these patients are appropriately included in the financial estimates with a reduced treatment cost applied to account for treatment already received. The PBAC recommended that the grandfathering listing could be removed after 12 months.
- 7.12 The PBAC advised that a risk sharing arrangement with expenditure caps based on the cost of atezolizumab as defined by the patient numbers in paragraph 7.10 would be required to manage the risk of Atezo+Bev use outside the restriction criteria; in particular, use in patients with a WHO PS of 2 and as a second-line treatment after progression on (not intolerance to) sorafenib/ lenvatinib. Acknowledging the high clinical need in patients with HCC, the PBAC considered that while a rebate of less than ■ above the expenditure caps may be appropriate, any rebate would need to require the sponsor to rebate ■ of the cost of atezolizumab use outside the defined RSA cap, noting that the cost effectiveness of such use would be unknown.
- 7.13 The PBAC found that the criteria prescribed by the National Health (Pharmaceutical and Vaccines – Cost Recovery) Regulations 2009 for Pricing Pathway A were met. Specifically, the PBAC found that in the circumstances of its recommendation for Atezo+Bev:

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- a) The treatment is expected to provide a substantial and clinically relevant improvement in efficacy over the nominated comparator in terms of overall survival in the advanced HCC patient population;
- b) The treatment is expected to address a high and urgent unmet clinical need as the current medicines available for the treatment of patients with advanced HCC have limited efficacy and high toxicity;
- c) It would be in the public interest for the subsequent pricing application to be progressed under Pricing Pathway A on the basis of the preceding findings.

7.14 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 Amend existing listings for atezolizumab and bevacizumab as follows:

Name, Restriction, Manner of administration and form	PBS item code	Max. Amount	No. of Rpts	Manufacturer
ATEZOLIZUMAB Injection	11926Q (Public) 11927R (Private)	1200 mg	3	Roche Products Pty Ltd
Available brands				
Tecentriq (atezolizumab 1.2 g/20 mL injection, 20 mL vial)				

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Initial treatment Restriction summary [new]:

Category / Program: Section 100 – Efficient Funding of Chemotherapy (Public/Private hospital)
Prescriber type: <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Restriction type/method: <input checked="" type="checkbox"/> Authority Required – Streamlined [new code]
Episodicity: [blank]
Severity: Advanced (unresectable) Barcelona Clinic Liver Cancer Stage B or Stage C
Condition: hepatocellular carcinoma
PBS 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 bevacizumab and atezolizumab until disease progression, unless not tolerated
AND Patient must have a WHO performance status of 0 or 1
AND Patient must not be suitable for transarterial chemoembolisation
AND Patient must have Child Pugh class A
AND The condition must be untreated with systemic therapy
OR Patient must have developed intolerance to a vascular endothelial growth factor (VEGF) tyrosine kinase inhibitor (TKI) of a severity necessitating permanent treatment withdrawal
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
Administrative advice: In the first few months after start of immunotherapy, some patients can have a transient tumour flare with subsequent disease response. When progression is suspected, this should be confirmed through a confirmatory scan, taken at least four weeks later.
Caution: The safety of atezolizumab in combination with bevacizumab has not been established in patients who have incompletely treated varices, variceal bleeding within the previous 6 months or who are at high risk of bleeding. Patients should be assessed for risk of variceal bleeding prior to treatment with this combination.

Name, Restriction, Manner of administration and form	PBS item code	Max. Amount	No. of Rpts	Manufacturer
ATEZOLIZUMAB Injection	NEW (Public) NEW (Private)	1200 mg	8	Roche Products Pty Ltd
Available brands				
Tecentriq (atezolizumab 1.2 g/20 mL injection, 20 mL vial)				

Continuing treatment (3-weekly regimen) Restriction summary [new]:

Category / Program: Section 100 – Efficient Funding of Chemotherapy (Public/Private hospital)
Prescriber type: <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Restriction type / method: <input checked="" type="checkbox"/> Authority Required – Streamlined (new code)
PBS Indication: Advanced (unresectable) Barcelona Clinic Liver Cancer Stage B or Stage C hepatocellular carcinoma
Treatment phase: Continuing treatment of hepatocellular carcinoma – 3 weekly treatment regimen
Clinical criteria: Patient must be undergoing combination treatment with bevacizumab and atezolizumab until disease progression, unless not tolerated
AND Clinical criteria:

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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
Prescriber instructions:
PBS supply of this drug must be through only one of the two continuing treatment regimens at any given time
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

Grandfather treatment Restriction summary [new]:

Category / Program: Section 100 – Efficient Funding of Chemotherapy (Public/Public hospital)
Prescriber type: <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Restriction type / method: <input checked="" type="checkbox"/> Authority Required – Streamlined (new code)
PBS Indication: Advanced (unresectable) Barcelona Clinic Liver Cancer Stage B or Stage C hepatocellular carcinoma
Treatment phase: Transitioning from non-PBS subsidised to PBS-subsidised supply – Grandfather treatment
Clinical criteria
Patient must have commenced non-PBS subsidised treatment with this drug for this PBS indication prior to [insert listing date here]
AND
Clinical criteria
Patient must have met all the PBS eligibility criteria applying to a non-grandfather patient under the Initial treatment restriction for this PBS indication prior to having commenced non-PBS subsidised treatment with this drug
AND
Clinical criteria
Patient must have not developed disease progression while receiving treatment with this drug for this condition
Prescribing instructions:
A Grandfathered patient may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a Grandfathered patient must qualify under the continuing treatment criteria.
Administrative advice:
This grandfather restriction will cease to operate from 12 months after the date specified in the Clinical criteria

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Name, Restriction, Manner of administration and form	PBS item code	Max. Amount	No. of Rpts	Manufacturer
ATEZOLIZUMAB Injection	NEW (Public) NEW (Private)	1680 mg	5	Roche Products Pty Ltd
Available brands				
Tecentriq (atezolizumab 840 mg/14 mL injection, 14 mL vial)				

Continuing treatment (4-weekly regimen) Restriction summary [new]:

Category / Program: Section 100 – Efficient Funding of Chemotherapy (Public/Private)
Prescriber type: <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Restriction level/method: <input checked="" type="checkbox"/> Authority Required – Streamlined (new code)
Severity: Advanced unresectable Barcelona Clinic Liver Cancer (BCLC) Stage B or Stage C
Condition: Hepatocellular carcinoma
PBS Indication: Advanced (unresectable) Barcelona Clinic Liver Cancer Stage B or Stage C hepatocellular carcinoma
Treatment phase: Continuing treatment – 4 weekly treatment regimen
Clinical criteria:
Patient must be undergoing combination treatment with bevacizumab until disease progression, unless not tolerated
AND
Patient must have previously received PBS-subsidised treatment with this drug for this condition
AND
Patient must not have developed disease progression while being treated with this drug for this condition
Prescriber instructions: PBS supply of this drug must be through only one of the two continuing treatment regimens at any given time
Administrative Advice: No increase in the maximum amount or number of units may be authorised.
Administrative Advice: Special Pricing Arrangements apply

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Name, Restriction, Manner of administration and form	PBS item code	Max. Amount	Nº. of Rpts	Manufacturer
BEVACIZUMAB Injection	NEW (Public) NEW (Private)	1800 mg	8	Roche Products Pty Ltd
Available brands				
Avastin (bevacizumab 400 mg/16 mL injection, 16 mL vial)				
Avastin (bevacizumab 100 mg/4 mL injection, 4 mL vial)				

Combined Initial & Continuing bevacizumab treatment Restriction summary [new]:
Category / Program: Section 100 – Efficient Funding of Chemotherapy (Public/Private hospital)
Prescriber type: <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Restriction type / method: <input checked="" type="checkbox"/> Authority Required – Streamlined (new code)
PBS Indication: Advanced (unresectable) Barcelona Clinic Liver Cancer Stage B or Stage C hepatocellular carcinoma
Treatment phase: Concurrent use with atezolizumab in hepatocellular carcinoma
Treatment criteria:
Patient must be undergoing combination treatment with PBS-subsidised atezolizumab for this PBS indication
Administrative Advice: No increase in the maximum number of repeats may be authorised
Caution:
The safety of atezolizumab in combination with bevacizumab has not been established in patients who have incompletely treated varices, variceal bleeding within the previous 6 months or who are at high risk of bleeding. Patients should be assessed for risk of variceal bleeding prior to treatment with this combination.

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Flow on changes to existing first line VEGF TKI inhibitors:

9380Q sorafenib

Restriction Summary 8540 / ToC: 8616: Authority Required: Streamlined

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.
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
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 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 tyrosine kinase inhibitor, (ii) atezolizumab/bevacizumab combination therapy.

Restriction Summary 8615 / ToC: 8617: Authority Required: Streamlined

No changes

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.
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.
Indication: Advanced Barcelona Clinic Liver Cancer Stage B or Stage C hepatocellular carcinoma
Treatment Phase: Continuing treatment
Clinical criteria: The treatment must be the sole PBS-subsidised therapy for this condition
AND
Clinical criteria: Patient must have previously received PBS-subsidised treatment with this drug for this condition
AND
Clinical criteria: Patient must not develop disease progression while receiving treatment with this drug for this condition

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11638M lenvatinib:

Restriction Summary 8593 / ToC: 8593: Authority Required: Streamlined

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 tyrosine kinase inhibitor, (ii) atezolizumab/bevacizumab combination therapy.

Delete the following Grandfather listing that is now more than 12 months old:

Restriction Summary 8618 / ToC: 8618: Authority Required: Streamlined

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 – grandfathered patients
Clinical criteria:
Patient must have received non-PBS subsidised treatment with this drug for this condition prior to 1 March 2019
AND
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
Prescribing Instructions:
A patient may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a Grandfathered patient must qualify under the Continuing treatment criteria.

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Restriction Summary 8619 / ToC: 8584: Authority Required: Streamlined

No changes

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: Continuing treatment
Clinical criteria:
The treatment must be the sole PBS-subsidised therapy for this condition
AND
Clinical criteria:
Patient must have previously received PBS-subsidised treatment with this drug for this condition
AND
Clinical criteria:
Patient must not develop disease progression while receiving treatment with this drug for this condition

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.

10 Sponsor's Comment

Roche welcomes the PBAC's decision to recommend atezolizumab and bevacizumab, for the treatment of patients with unresectable locally advanced or metastatic Barcelona Clinic Liver Cancer (BCLC) stage B or stage C hepatocellular carcinoma (HCC) who have not received prior systemic treatment.

Roche are working with the Department of Health towards a PBS listing at the earliest opportunity.