

**7.01 ATEZOLIZUMAB,
Solution concentrate for I.V. infusion,
840 mg in 14 mL,
Tecentriq[®],
Roche Products Pty Ltd.**

1 Purpose of submission

- 1.1 The resubmission requested Section 100 (Efficient Funding of Chemotherapy), Authority Required (Streamlined) listing for atezolizumab (ATZ), for use in combination with nanoparticle albumin-bound (nab)-paclitaxel (nab-P), for the first line treatment of patients with metastatic triple-negative breast cancer (mTNBC), whose tumours express programmed death ligand 1 (PD-L1) of any intensity in tumour-infiltrating immune cells covering $\geq 1\%$ of the tumour area, as determined by the companion diagnostic Ventana PD-L1 immunohistochemistry (IHC) SP142 assay.
- 1.2 Listing was requested on the basis of a cost-effectiveness analysis versus nab-paclitaxel. The key components of the clinical issue addressed by the resubmission are summarised in Table 1.

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

Component	Description
Population	Patients with <u>mTNBC</u> ^a who have not been previously treated for this condition in the metastatic setting.
Intervention	Test: IHC testing of PD-L1 on tumour infiltrating immune cells (<u>Ventana SP142 assay</u>) ^b Medicine: atezolizumab 840 mg IV infusion on days 1 and 15 of every 28 day cycle until disease progression, in combination with nab-paclitaxel ^c 100 mg/m ² IV infusion on days 1, 8, and 15 of each 28 day cycle until disease progression or unacceptable toxicity.
Comparator	Test: No test Medicine: nab-paclitaxel 100 mg/m ² IV infusion on days 1, 8, and 15 of each 28 day cycle until disease progression or unacceptable toxicity.
Outcomes	Overall survival Progression-free survival Safety Quality of life as measured by GHS/HRQoL, EORTC QLQ-C30 and QLQ-BR23 breast module and EQ-5D-5L.
Clinical claim	Atezolizumab <u>in combination with nab-paclitaxel</u> ^c is superior in effectiveness and inferior, but clinically manageable, in safety compared with nab-paclitaxel alone, in patients with <u>mTNBC</u> ^a who have not received prior treatment for metastatic disease and who are PD-L1-positive (PD-L1 stained IC covering $\geq 1\%$ of the tumour area).

Source: Table 1.1, p4 of the resubmission, Atezolizumab Product Information.

EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EQ-5D-5L = European Quality of Life 5 Dimension 5 Level; GHS/HRQoL = global health status/health related quality of life; IC = tumour-infiltrating immune cells; IHC = immunohistochemistry; IV = intravenous; mTNBC = metastatic triple-negative breast cancer; nab-P = nanoparticle albumin bound paclitaxel; PD-L1 = programmed cell death ligand-1; QLQ = quality of life questionnaire.

^a The proposed population in the March 2020 submission to PBAC included patients with unresectable locally advanced TNBC, as well as those with metastatic disease.

^b The March 2020 submission did not nominate any particular test for the evaluation of PD-L1 expression in tumour tissue.

^c The nominated medicinal intervention in the March 2020 submission was atezolizumab in combination with taxane chemotherapy.

Underlined text indicates changes compared with the previous submission.

2 Background

Registration status

- 2.1 Atezolizumab received a two-year provisional TGA registration in October 2019 for the following indication: ‘atezolizumab, in combination with nanoparticle albumin-bound paclitaxel, is indicated for the treatment of adult patients with unresectable locally advanced or metastatic TNBC whose tumours express PD-L1 (PD-L1 stained tumour-infiltrating immune cells [IC] of any intensity covering \geq 1% of the tumour), as determined by a validated test and who have not received prior chemotherapy for metastatic disease. This indication is approved under provisional approval based on progression free survival. Continued approval for this indication depends on verification and description of clinical benefit in a confirmatory trial(s).’
- 2.2 The TGA Delegate’s Overview stated: ‘The efficacy results are promising, but not definitive. They support provisional/accelerated approval, but not standard approval. The sponsor will be required to submit confirmatory data: more mature data from IMpassion130 (especially overall survival data) and data from the IMpassion131 trial.’ The provisional approval was based on IMpassion130 data from the April 2018 data cutoff. The current resubmission has provided data from the April 2020 data cutoff for IMpassion130.
- 2.3 IMpassion131, which compared ATZ+paclitaxel to placebo (PBO)+paclitaxel, failed to demonstrate that combining ATZ with paclitaxel resulted in any statistically significant improvement in progression free survival (PFS) or overall survival (OS) compared with paclitaxel alone in the PD-L1-positive population. While no formal statistical testing was performed, similar results were observed in the intention-to-treat (ITT) population (see below). The Pre-Sub-Committee response (PSCR) noted that the IMpassion131 trial results have not been formally submitted to TGA as this trial is no longer part of the strategy to convert from provisional to regular approval. The sponsor indicated that discussions with the TGA regarding the criteria for conversion to regular approval were continuing, given IMpassion 131 was no longer the confirmatory study. The PBAC therefore noted that the basis and timeline for conversion to regular approval is currently unclear. The PSCR also noted that based on the results of IMpassion131, the FDA has added a Limitation of Use statement to the USPI specifying that ATZ is not indicated for use in combination with paclitaxel in the mTNBC setting.
- 2.4 At the time of evaluation for PBAC consideration, the Clinical Evaluation Report, the TGA Delegate’s report, and the TGA provisional approval letter were available.

Previous PBAC consideration

- 2.5 The PBAC previously considered an integrated co-dependent submission for ATZ, in combination with taxane chemotherapy, as first line treatment for patients with

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unresectable locally advanced or metastatic TNBC whose tumours express PD-L1, at the March 2020 PBAC meeting. A concurrent application was made to MSAC requesting listing of PD-L1 IHC testing for the evaluation of PD-L1 expression on tumour infiltrating immune cells to determine eligibility for treatment with atezolizumab plus a taxane in the requested population.

2.6 The key matters of concern regarding the previous submission, and how the resubmission has addressed these concerns, are summarised in Table 2.

Table 2: Summary of key matters of concern

Component	Matter of concern	How the resubmission addresses it
Test assay used to determine PD-L1	The PBAC signalled a preference to limit testing to the Ventana PD-L1 (SP142) assay (para 7.2, March 2020 PSD).	Addressed. A minor submission has been submitted to MSAC, amending the proposed MBS item descriptor to specify that the Ventana SP142 assay must be used for IHC examination of PD-L1 expression for access to ATZ for mTNBC.
Proposed listing	The proposed listing for ATZ in combination with taxane chemotherapy was broader than the intervention in the IMpassion130 trial and the provisional TGA indication, which are for ATZ used only in combination with nab-P (para 7.4, March 2020 PSD).	Addressed. Restriction amended to specify that ATZ must be initiated in combination with nab-P.
	The restriction should require patients treated with taxanes in the (neo)adjuvant setting to have completed their treatment at least 12 months prior to initiation of ATZ, consistent with IMpassion130 (para 7.5, March 2020 PSD).	Addressed. Restriction amended to reflect PBAC comments.
Comparator	The nominated comparator, nab-P, may not represent optimal evidence-based treatment in the majority of the proposed population, including patients who have received previous taxane therapy, patients who are chemotherapy naïve, and patients with BRCA1/2 pathogenic variants. The most appropriate comparator in the heterogeneous population would be physician choice (para 5.0 and 7.6, March 2020 PSD).	Not adequately addressed. The restriction was amended to exclude patients with locally advanced TNBC, but this did not address the issue regarding the appropriate comparator in the mTNBC population.
Clinical place	The appropriate clinical place for ATZ is in addition to nab-P in patients who are PD-L1-positive, where a taxane would otherwise be used. The Australian population who would be appropriate for nab-P reflects approximately 10% of the IMpassion130 trial population, limiting the applicability of the trial data (para 7.7 and 7.12, March 202 PSD).	Not adequately addressed. While patients with locally advanced TNBC were excluded from the proposed Australian population, the PSCR for the previous submission stated that this patient group represented <10% of the total population (para 5.5, March 2020 PSD). The clinical place for ATZ+nab-P in the remaining patient subgroups was not adequately addressed.

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Component	Matter of concern	How the resubmission addresses it
Clinical effectiveness	As there was a non-statistically significant OS result in the ITT population, formal testing of OS in the PD-L1-positive subgroup could not be performed whilst controlling type I error. The magnitude of any OS gain was uncertain. More mature OS data may provide more confidence regarding the magnitude of any OS gain (para 7.10, March 2020 PSD).	Remains an issue. While updated OS data from the final OS analysis were provided, there was still no statistically significant difference between the treatment arms for the ITT population so formal testing of OS in the PD-L1 positive subgroup still could not be performed. The results for the PD-L1 subgroup were similar to those in the original submission.
	As nab-P is likely to be an inferior treatment for the majority of patients, the treatment effect of ATZ+nab-P is likely to be overestimated relative to current clinical practice (para 7.12, March 2020 PSD)	Not adequately addressed (see comments for comparator, above).
Economic model		
Extrapolation of OS	The use of different parametric functions to extrapolate OS in the proposed scenario versus the current scenario was not adequately justified and resulted in an extrapolated OS advantage that was not supported by the trial data (para 7.15, March 2020 PSD).	The gamma parametric function was used to extrapolate OS in both the proposed and the current scenario.
	In the absence of a statistically significant OS benefit, the economic model in any resubmission would need to be based on conservative assumptions regarding the magnitude of any modelled OS gains (para 7.22, March 2020 PSD)	Not adequately addressed. The use of the gamma function was less conservative than using either the log-logistic function or the Weibull function to extrapolate OS in both the proposed and current scenarios.
Utility values	The rationale for the approaches used to estimate the utility values were not adequately justified and the utility values were not conservative compared with those used in other economic evaluations of advanced breast cancer (para 7.17, March 2020 PSD).	Addressed. Utilities were mapped from the trial EQ-5D-5L data using an Australian scoring algorithm (Norman 2012) ^a . The utility applied in the progressive disease state was more consistent with those previously considered reasonable by the PBAC ^b and used in other economic evaluations of advanced breast cancer.
Doses of ATZ and nab-P (Section 3 and 4)	DUSC considered that number of doses of ATZ and nab-P were overestimated. The pre-PBAC response proposed a RSA with an episode cap of █ doses per patient treated with ATZ. 20 doses was considered more reasonable than the average of 27.4 administrations assumed in the submission (para 7.21, March 2020 PSD).	Addressed. Section 3 and 4 of the resubmission assumed a mean of █ doses of ATZ per patient and the number of doses of nab-P was limited to 10, as suggested by the DUSC. While this issue was addressed, the application of the proposed RSA in the economic evaluation was not appropriate.
Financial estimates		
Patient numbers	The DUSC considered the financial estimates in the submission to be considerably underestimated.	The resubmission attempted to address DUSC concerns by updating inputs for the estimate of the number of patients diagnosed at earlier stages of TNBC who then progress to mTNBC, and for the estimate of the proportion of patients who elect to have the PD-L1 tests. The updated estimate of the number of patients diagnosed at earlier stages of TNBC who then progress to mTNBC remains uncertain.

Source: Table 1.4, pp7-9 of the resubmission; Atezolizumab TNBC MSAC_PBAC Streamline Codependent Submission; 6.01, atezolizumab PSD, March 2020 PBAC meeting.

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ATZ = atezolizumab; EQ-5D-5L = European Quality of Life 5 dimensions 5 level questionnaire; IHC = immunohistochemistry; mTNBC = metastatic triple negative breast cancer; nab-P = nanoparticle albumin-bound paclitaxel; OS = overall survival; PD-L1 = programmed cell death ligand 1; PFS = progression free survival; PSCR = Pre-Sub-Committee Response; PSD = Public Summary Document; RSA = risk sharing arrangement.

^a Norman R, Cronin P, et al. Deriving utility weights for the EQ-5D-5L using a discrete choice experiment. Sydney: Centre for Health Economics Research and Evaluation (CHERE), University of Technology Sydney. 2012.

^b The resubmission applied a utility value of 0.583 in the progression state. This compares with a utility value of 0.555 used in the post-progression disease state in the November 2014 submission to PBAC for pertuzumab and trastuzumab (paragraph 6.50, pertuzumab and trastuzumab, PSD, November 2014 PBAC meeting).

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

3 Requested listing

Name, Restriction, Manner of administration and form	Max. Amt	No. of Rpts	Dispensed Price Max Amt	Proprietary Name and Manufacturer
ATEZOLIZUMAB Solution for IV infusion 840 mg in 14 mL vial	840 mg	5 (initial treatment) 11 (continuing treatment)	Published price \$5,057.52 ^a (public) \$5,167.75 ^b (private)	Tecentriq Roche Products Pty Ltd
			Effective price ^c \$ [REDACTED] ^a (public) \$ [REDACTED] ^d (private)	

Category/Program:	Section 100 – Efficient Funding of Chemotherapy
PBS indication:	Metastatic triple-negative breast cancer
Treatment phase:	Initial treatment
Restriction:	Authority Required - Streamlined
Clinical criteria:	<p>The condition must be hormone receptor (oestrogen and progesterone receptor) negative, AND The condition must be human epidermal growth factor receptor 2 (HER2) negative, AND The condition must be inoperable, AND Patient must not have been treated for this condition in the metastatic setting, AND Patient must have a WHO performance status of 0 or 1, AND The treatment must be initiated in combination with nab-paclitaxel, AND The condition must express programmed cell death ligand 1 (PD-L1) of any intensity in tumour-infiltrating immune cells covering ≥1% of the tumour area, AND Patient must not have received taxane (neo)adjuvant therapy in the previous 12 months.</p>
Treatment phase:	Continuing treatment
Clinical criteria:	<p>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.</p>

^a DPMA includes Section 100 Highly Specialised Drugs fees and mark-ups of \$85.78.

^b DPMA includes Section 100 Highly Specialised Drugs fees and mark-ups of \$196.01.

^c Includes a [REDACTED] % discount on the ex-manufacturer price as a rebate in the form of a special pricing arrangement; included in Sections 3 and 4 of the resubmission.

^d DPMA includes Section 100 Highly Specialised Drugs fees and mark-ups of \$ [REDACTED].

3.1 The PBAC previously considered that, given the current evidence, the appropriate clinical place for atezolizumab is in addition to nab-P, in patients who are PD-L1-positive, where a taxane would otherwise be used (para 7.7, atezolizumab Public Summary Document (PSD), March 2020 PBAC meeting). This is not explicitly specified in the proposed PBS restrictions; according to the resubmission's METIS data, only approximately one third of patients who have not received taxane (neo)adjuvant therapy in the previous 12 months would be treated with a taxane.

- 3.2 The resubmission proposed a special pricing arrangement (SPA). The requested effective price for ATZ was based on a [REDACTED] % discount on the proposed ex-manufacturer price (AEMP). The requested effective price in the March 2020 submission was based on a [REDACTED] % discount on the AEMP.
- 3.3 Both the requested published AEMP (\$4,971.74) and the requested effective AEMP (\$[REDACTED]) for the maximum amount of 840 mg were lower than in the previous submission (published AEMP \$5,233.41, effective AEMP \$[REDACTED]). The requested effective AEMP in the resubmission represents a [REDACTED] % decrease from the previous submission.
- 3.4 The requested listing differed from the previous submission in regards to the following key criteria:
- Patients are required to have inoperable metastatic disease, while in the previous submission patients with either unresectable locally advanced or metastatic disease were eligible;
 - The restriction specifies that ATZ must be initiated in combination with nab-P, while, previously, ATZ was required to be used in combination with taxane chemotherapy; and
 - The criterion that patients must not have received taxane (neo)adjuvant therapy in the previous 12 months was not included in the previous submission.
- 3.5 The requested restriction for initial treatment incorporated the suggestions and additions previously proposed by the Secretariat (para 3.1, atezolizumab PSD, March 2020 PBAC meeting).
- 3.6 The resubmission also proposed a listing for transitioning arrangements (from non-PBS to PBS-subsidised supply – ‘grandfather’ arrangements), and estimated that 93 patients from a patient access program for ATZ would be eligible to receive PBS subsidised treatment should PBAC recommend ATZ for listing on the PBS in August 2021. The proposed restriction was consistent with that previously suggested by the Secretariat (para 3.1, atezolizumab PSD, March 2020 PBAC meeting).
- 3.7 The resubmission stated that a minor submission has been submitted to MSAC, amending the proposed MBS item for the companion diagnostic descriptor to specify that the Ventana SP142 assay must be used for IHC examination of PD-L1 expression for access to PBS-subsidised ATZ for mTNBC.

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

4 Population and disease

- 4.1 TNBC (progesterone and oestrogen receptor-negative and human epidermal growth factor receptor 2 (HER2)-negative breast cancer) is an aggressive disease associated with poor prognosis; with high risk of relapse, and a short PFS and OS. Patients with TNBC are typically younger and at a more advanced stage at diagnosis than in other

breast cancers, and do not respond to hormone therapy or HER2 targeted agents. TNBC makes up approximately 16% of all locally advanced and metastatic breast cancer in Australia, according to the submission’s METIS market research data (2020).

4.2 The target population includes patients with previously untreated:

- Recurrent mTNBC, the largest subgroup of the target population, estimated to be approximately 20% of the proportion of prevalent patients with early TNBC.
- *de novo* mTNBC, estimated to represent approximately 10% of the target population.
- mTNBC containing Breast Cancer gene 1/2 (BRCA1/2) pathogenic variants, estimated to represent approximately 17% of the target population. These patients form part of the recurrent and *de novo* mTNBC groups as described above.

4.3 In contrast, the previous submission also included patients with unresectable locally advanced TNBC.

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

5 Comparator

5.1 The resubmission nominated nab-P as the main comparator. The sponsor argued that there is a large range of currently used chemotherapies to treat mTNBC (e.g. carboplatin, anthracyclines and taxanes), and no individual chemotherapy regime has demonstrated clear superiority. The choice of chemotherapy depends on the individual patient’s circumstance, such as previous treatments, cumulative toxicity, and the presence of pathogenic gene variants. The resubmission claimed the majority of patients receive a taxane in the first-line (1L) setting, referring to updated METIS market research conducted in 2020. These data show that the majority of Australian mTNBC patients do not receive taxanes as 1L treatment, as summarised in Table 3 below.

Table 3: Estimated taxane use in the three subgroups of the proposed target population, based on market research of 30 Australian oncologists

First-line treatment of mTNBC (%)	De novo metastatic	Relapsed after 12+ months following completion of (neo) adjuvant taxane	BRCA mutation positive & relapsed after 12+ months following completion of (neo) adjuvant taxane
Nab-P	25%	26%	12%
Paclitaxel	20%	6%	6%
Docetaxel	2%	2%	2%
Total	47%	34%	20%

Source: Data extracted from slide 19, METIS quantitative marketing research report, August 2020. Totals calculated during the evaluation. mTNBC = metastatic triple-negative breast cancer; Nab-P = nanoparticle albumin-bound paclitaxel.

5.2 The greatest taxane use was in *de novo* mTNBC, where 47% of patients were expected to receive a taxane; these patients represent less than 10% of the target population (patients with BRCA1/2 pathogenic variants, who form part of the *de novo* mTNBC

group, are treated differently). According to the original submission's METIS market research, conducted in 2019, approximately 95% of relapsed mTNBC patients would have received a prior taxane in the (neo)adjuvant setting.

- 5.3 Nab-P likely represents sub-optimal treatment for patients with BRCA1/2 pathogenic variants who have relapsed after 12+ months following completion of (neo)adjuvant taxane therapy; international guidelines (the Arbeitsgemeinschaft Gynäkologische Onkologie (AGO)¹, the European Society for Medical Oncology (ESMO)²) recommend platinum-containing chemotherapy regimens if not previously administered, or a poly-ADP ribose polymerase (PARP) inhibitor (NCCN³). This is consistent with the resubmission's METIS market research, which showed that, in Australia, carboplatin is the most commonly prescribed treatment in this population (43% of patients), with nab-P only being used in approximately 12% of patients.
- 5.4 The ESC agreed with the commentary that the resubmission's argument does not justify the selection of nab-P as the primary comparator. To ensure each patient receives optimal therapy, this heterogeneous population requires tailored treatment. The PBAC previously considered that the most appropriate comparator would be physician choice (para 7.6, atezolizumab PSD, March 2020 PBAC meeting). This is not an unusual comparator in this population, and has been used in other clinical trials for this disease⁴. The PSCR argued that no individual chemotherapy regime has demonstrated clear superiority in this setting and given that nab-P is prescribed for the largest number of patients in the target population, it is appropriate for the main comparator in this resubmission to be nab-P. The ESC noted that platinum-based chemotherapy has demonstrated superiority to other treatments in patients with BRCA1/2 pathological variants, which make up approximately 17% of the target population. Furthermore, the fact that METIS survey data show oncologists only selected taxane therapy in approximately one third of the target population suggests that the other therapies may confer a benefit not offered by taxane therapy, be it improved safety profiles or consideration of prior therapies (e.g. anthracycline-naïve). Overall the ESC considered that the evidence presented supported physician choice as the most appropriate comparator as previously advised by the PBAC. The ESC considered that the impact on translation of effect estimates for the comparison

¹ AGO: Diagnosis and Treatment of Patients with early and advanced Breast Cancer Version 2020.1; URL: https://www.ago-online.de/fileadmin/ago-online/downloads/leitlinien/kommission_mamma/2020/Updated_Guidelines_2020.pdf

² Cardoso, F *et al.* 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). *Annals of Oncology*, Volume 31, Issue 12, 2020; 1623-1649.

³ National Comprehensive Cancer Network Guidelines Version 5.2020 - Breast Cancer; as provided with the resubmission.

⁴ Li, C.H., Karantza, V., Aktan, G. *et al.* Current treatment landscape for patients with locally recurrent inoperable or metastatic triple-negative breast cancer: a systematic literature review. *Breast Cancer Res* 2019; 21, 143.

presented (ATZ versus nab-P) to Australian clinical practice (ATZ versus physician choice) was unclear.

- 5.5 The resubmission acknowledged that the PARP inhibitor talazoparib may be a near market comparator, however it did not consider it relevant for the target Australian population, as talazoparib was rejected at the November 2019 PBAC meeting. Also, in November 2020, the FDA granted accelerated approval for pembrolizumab plus chemotherapy for use in the untreated mTNBC population, based on recently published early efficacy data⁵; this trial allowed physician's choice of three comparator chemotherapies (nab-paclitaxel; paclitaxel; or gemcitabine plus carboplatin).

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 individuals (1), health care professionals (7) and organisations (2) via the Consumer Comments facility on the PBS website. The health care professional comments outlined the clinical need for access to effective medicines for patients with TNBC as it is an aggressive form of breast cancer resulting in short life expectancy and there are currently no other targeted treatments or immunotherapies available. Health care professionals also noted that TNBC disproportionately affects younger patients and that the majority of patients cannot afford to self-fund treatment with atezolizumab. The comments described the trial evidence for atezolizumab, which health care professionals considered showed that atezolizumab has the potential to improve patient quality of life, and for a subset of patients, to markedly improve overall survival, with minimal treatment related side effects.
- 6.3 The PBAC noted the advice received from Breast Cancer Network Australia (BCNA) in support of listing atezolizumab on the PBS for treatment of patients with TNBC. BCNA noted that people with TNBC have poorer clinical outcomes than other subtypes of breast cancer and that chemotherapy has been the only systemic treatment available for these patients with atezolizumab being a new option for this group of patients. BCNA noted the results of the IMpassion130 trial and reported that additional months of both PFS and OS are highly valued by patients and that patients are well-placed to

⁵ Cortes, JavierLuis, Fein *et al.* Pembrolizumab plus chemotherapy versus placebo plus chemotherapy for previously untreated locally recurrent inoperable or metastatic triple-negative breast cancer (KEYNOTE-355): a randomised, placebo-controlled, double-blind, phase 3 clinical trial. *The Lancet*, Volume 396, Issue 10265, 1817 - 1828

weigh potential benefits of treatment against possible adverse events associated with treatment.

- 6.4 The Medical Oncology Group of Australia (MOGA) also expressed its support for the atezolizumab submission. The PBAC noted that the MOGA presented a European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for atezolizumab + nab-P, which was limited to 4 (out of a maximum of 5, where 5 and 4 represent the grades with substantial improvement)⁶, based on a comparison with nab-P alone in the pre-planned PD-L1 positive subgroup of the IMpassion130 trial. MOGA noted the difference in OS was not tested for significance due to a pre-specified testing hierarchy (so it was not technically eligible for an ESMO MCBS score based on OS), and atezolizumab + nab-P would score a 3 if PFS was used instead.

Clinical trial

- 6.5 The resubmission was based on one head-to-head trial comparing ATZ+nab-P to PBO+nab-P (N=902), IMpassion130. This is the same trial considered in the previous submission, although updated data from the final analysis (clinical cut-off date 14 April 2020) were presented.
- 6.6 The resubmission did not present full details of IMpassion131, which was similar in design to IMpassion130, but compared ATZ+paclitaxel (ATZ-P) with PBO+paclitaxel (PBO+P). The trial was excluded on the basis that the primary end point was not met; there was no statistically significant difference in PFS between the two treatment arms in the PD-L1-positive population. The requested listing for ATZ was amended to stipulate that ATZ must be administered in combination with nab-P. The resubmission claimed that the benefit-risk assessment of ATZ+nab-P has not changed in light of the IMpassion131 results, which it proposed may be related to the pairing of ATZ and paclitaxel. The IMpassion131 results are likely relevant to the interpretation of IMpassion130 results, and are further discussed below.
- 6.7 Details of the trial presented in the resubmission are provided in the table below.

⁶ Cherny NI, Dafni U, Bogaerts J, et al: ESMO-Magnitude of Clinical Benefit Scale version 1.1. *Annals of Oncology* 28:2340-2366, 2017]

Table 4: Trials and associated reports presented in the resubmission

Trial ID	Protocol title/ Publication title	Publication citation
IMpassion130 (NCT02425891) (WO29522)	Update CSR Study: A phase III, multicentre, randomized, placebo-controlled study of atezolizumab (anti-PD-L1 antibody) in combination with nab-paclitaxel compared with placebo with nab-paclitaxel for patients with previously untreated metastatic triple-negative breast cancer. Report No. 1100481. August, 2020.	Updated primary CSR Study: Report No. 1100481, August 2020.
	Schmid P, Rugo HS, Adams S, et al. Atezolizumab plus nab-paclitaxel as first-line treatment for unresectable, locally advanced or metastatic triple-negative breast cancer (IMpassion130): updated efficacy results from a randomised, double-blind, placebo-controlled, phase 3 trial.	<i>The Lancet Oncology</i> . 2020;21(1):44-59.
	Adams S, Diéras V, Barrios CH, et al. Patient-reported outcomes from the phase III IMpassion130 trial of atezolizumab plus nab-paclitaxel in metastatic triple-negative breast cancer.	<i>Annals of Oncology</i> 2020;31(5):582-89.
	Iwata H, Inoue K, Kaneko K, et al. Subgroup analysis of Japanese patients in a Phase 3 study of atezolizumab in advanced triple-negative breast cancer (IMpassion130).	<i>Japanese Journal of Clinical Oncology</i> 2019;49(12):1083-91.

Source: Table 2.3, p 27 of the resubmission.

6.8 The key features of the direct randomised trial, IMpassion130, are summarised in the table below.

Table 5: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
ATZ+nab-P vs. PBO+nab-P						
IMpassion130	902 (ITT) 369 (PD-L1+ subgroup)	R, DB 19 months ^a	Low	Unresectable locally advanced or metastatic TNBC	OS, PFS	Used

Source: Sections 2.3 and 2.4 of the original submission.

ATZ = atezolizumab; nab-P = nab-paclitaxel; PBO = placebo; ITT = intention to treat; DB = double blind; OS = overall survival; PFS = progression-free survival; R = randomised; TNBC = triple negative breast cancer.

^a Median follow-up duration at final data cut-off date, 14 April 2020.

Comparative effectiveness

6.9 Updated results from the final analysis (14 April 2020) for IMpassion130 were provided in the resubmission. These were consistent with the results previously considered by the PBAC, from the 2 January 2019 clinical cut-off date. The OS results remained non-significant in the ITT population (hazard ratio (HR) 0.87; 95% confidence interval (CI) 0.75, 1.02), with the hierarchical study design precluding formal statistical testing of the PD-L1 subgroup. The results in the PD-L1-positive subgroup are summarised in Table 6 and Figure 1, below. It is unusual that median OS exceeds the median duration of follow-up; this phenomenon may be suggestive of instability in the Kaplan-Meier estimates, and outliers in the data⁷.

⁷ Abbott, D *et al.* How Median Follow-up Time Informs Survival Outcomes: Lessons from a Trial of Acute Myeloid Patients Treated with Venetoclax and Azacitidine. *Blood* 2019; 134 (Supplement_1): 5897.

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Table 6: Comparison of updated efficacy data, PD-L1-positive population, IMpassion130

	CCOD: 2 Jan 2019			CCOD: 14 April 2020		
	ATZ+nab-P n/N (%)	PBO+nab-P n/N (%)	HR (95% CI)	ATZ+nab-P n/N (%)	PBO+nab-P n/N (%)	HR (95% CI)
Median duration of follow-up, months	19.42	15.74	-	23.43	16.26	-
Remain on treatment (n/N)^a			-			-
ATZ	39/451	0/451		26/451	5/451 ^b	
Nab-P	19/451	13/451		7/451	6/451	
Investigator-assessed PFS						
Progressed, n/N (%)	149/185 (80.5%)	163/184 (88.6%)	0.63 (0.50, 0.80)	154/185 (83.2%)	167/184 (90.8%)	0.63 (0.50, 0.79)
Median PFS, months (95% CI)	7.46 (6.7, 9.2)	5.29 (3.8, 5.6)		7.46 (6.7, 9.2)	5.29 (3.8, 5.6)	
% not progressed at 12 months (95% CI)	30.31% (23.5, 37.2)	17.32% (11.7, 22.9)		30.77% (24.0, 37.6)	17.72% (12.1, 23.4)	
OS						
Deaths, n/N (%)	94/185 (50.8%)	110/184 (59.8%)	0.71 (0.54, 0.93) ^c	120/185 (64.9%)	139/184 (75.5%)	0.67 (0.53, 0.86) ^c
Median OS, months (95% CI)	25.03 (19.6, 30.7)	17.97 (13.6, 20.1)		25.43 (19.6, 30.7)	17.91 (13.6, 20.3)	
% alive at 24 months (95% CI)	50.70% (42.9, 58.5)	36.90% (29.0, 44.9)		35.84% (28.8, 42.9) ^d	22.17% (15.9, 28.5) ^d	

Source: Data extracted from Table 28, PBAC 6.01.COM.101 and Table PBAC.7, PBAC 6.01.COM.39 from original submission commentary, Tables 1 and 2, p 12 of the IMpassion130 Feb2019 CSR; Table 2.4, p 30 of the resubmission and Figure 1, p 36 and unlabelled table, p 1176 of the IMpassion130 Aug2020 CSR.

ATZ+nab-P = atezolizumab + nanoparticle albumin-bound paclitaxel; CCOD = Clinical cut-off date; CI = confidence interval; HR = stratified hazard ratio; OS = overall survival; PBO+nab-P = placebo + nanoparticle albumin-bound paclitaxel; PFS = progression-free survival.

^a Data from the ITT population; data for the PD-L1-positive population could not be located in the resubmission.

^b These patients crossed over to active ATZ treatment.

^c No formal testing of OS was performed in the PD-L1-positive population because study design dictated formal testing could only occur if OS was first statistically significant in the ITT population – which it was not.

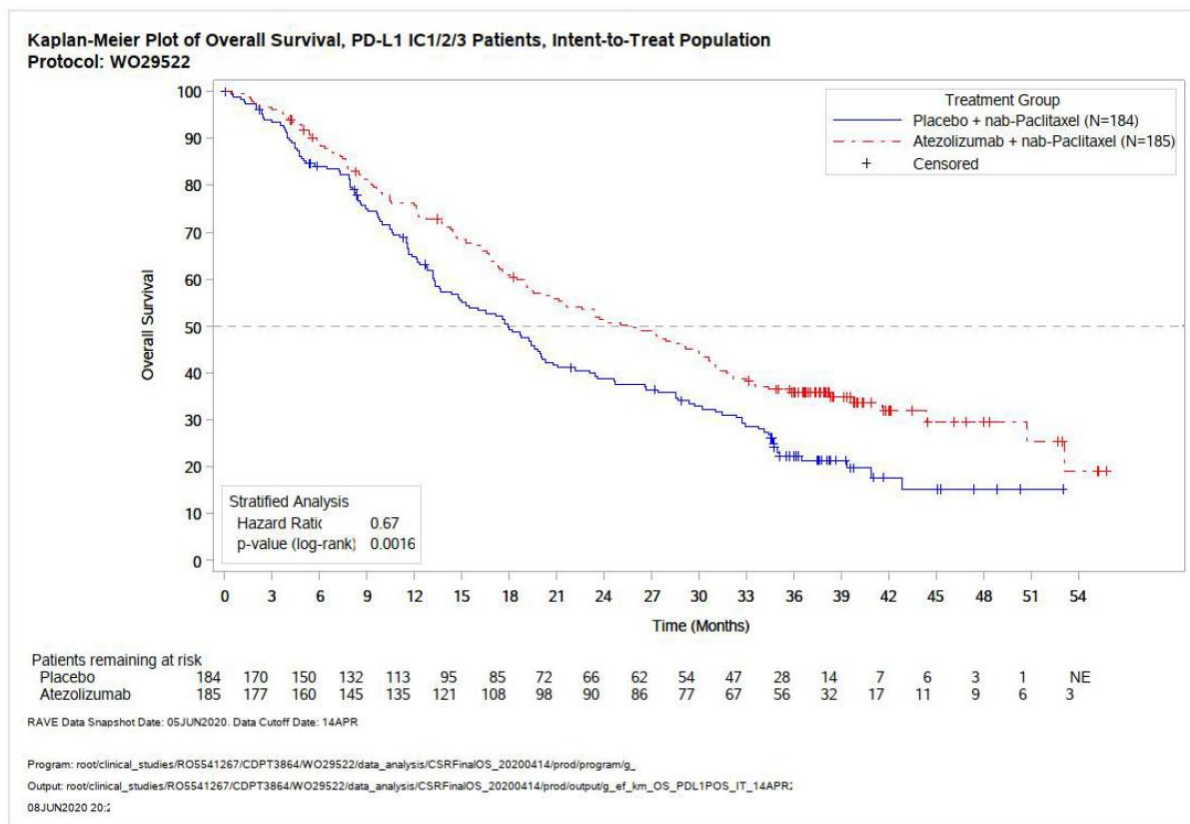
^d Updated data only provided 36 months' duration, not 24 months, which makes comparison difficult.

Statistically significant relative risks are bolded.

Blue shading indicates data previously seen by the PBAC.

6.10 As reported in the interim analysis of IMpassion130, in the final cut off no treatment effect was seen in PD-L1-negative patients (OS unstratified HR=1.05; 95% CI: 0.87, 1.28 and stratified HR= 1.02; 95% CI: 0.84, 1.24).

Figure 1: Kaplan-Meier Plot of Overall Survival in the PD-L1-positive population, IMpassion130, CCOD 14 April 2020



Source: Figure 2.4, p 32 of the resubmission.

CCOD = clinical cut-off date; IC 1/2/3 = PD-L1-positive patients; PD-L1 = programmed cell death-ligand 1.

- 6.11 Patients in the ATZ+nab-P arm of IMpassion130 demonstrated an approximate PFS benefit of 2 months, and OS benefit of 7.5 months compared to the PBO+nab-P arm. Approximately 13% of the PD-L1-positive population (n/N = 47/369) in IMpassion130 had locally advanced, unresectable disease; these patients are no longer part of the target Australian population, and have a favourable prognosis compared to mTNBC. The mTNBC PD-L1-positive subgroup (n/N = 321/369) of IMpassion130 generated an unstratified HR of 0.69 (95% CI 0.53, 0.89) at the 14 April 2020 clinical cut-off date. The PSCR noted that this was unchanged compared with the unstratified HR of 0.69 (95%CI 0.54, 0.88) for the full PD-L1 population including patients with locally advanced disease. The pre-PBAC response noted from the most recent data cut, the updated PFS data shows 13% of patients in the IMpassion130 trial are still responding and have not progressed after nearly 5 years (54 months), supporting the claim that there are long term responders to this therapy.
- 6.12 The study design of IMpassion131 was modelled on IMpassion130; they shared the same patient population/line of therapy, eligibility criteria and stratification factors. Patients in IMpassion131 had reasonably similar baseline characteristics and prognostic factors compared with those in IMpassion130. As such, based on the limited IMpassion131 data provided with the resubmission, transitivity issues for

inter-trial comparisons appear minimal. The main difference between the trials was the selection of nab-P vs paclitaxel as the chemotherapy backbone. A comparison of key efficacy outcomes of the two trials is provided in Table 7 below.

Table 7: Comparison of overall survival between IMpassion130 and IMpassion131

IMpassion130 median OS (months) at final analysis (14 April 2020)	ATZ+nab-P (95% CI)	PBO+nab-P (95% CI)	Stratified HR (95% CI)
ITT Population (N=902)	21.0 (19.0, 23.4)	18.7 (16.9, 20.8)	0.87 (0.75, 1.02)
PD-L1-positive Population (N=369)	25.4 (19.6, 30.7)	17.9 (13.6, 20.3)	0.67 (0.53, 0.86)
PD-L1-negative Population	NR	NR	1.02 (0.84, 1.24)
IMpassion131 median OS (months) at updated interim OS analysis (19 August 2020)	ATZ+P (95% CI)	PBO+P (95% CI)	Stratified HR (95% CI)
ITT Population (N=651)	19.2 (16.8, 22.5)	22.8 (17.1, 28.3)	1.11 (0.87, 1.42)
PD-L1-positive Population (N=292)	22.1 (19.2, 30.5)	28.3 (19.1, NE)	1.12 (0.76, 1.65)
PD-L1-negative Population	NR	NR	NR

Source: Constructed during the evaluation from data in Table 2.4, p 30 of the resubmission, and p 12 of Miles 2020⁸.

ATZ+nab-P = atezolizumab + nanoparticle albumin-bound paclitaxel; ATZ+P = atezolizumab + paclitaxel; CI = confidence interval; HR = hazard ratio; NE = not evaluable; OS = overall survival; PBO+nab-P = placebo + nanoparticle albumin-bound paclitaxel; PBO+P = placebo + paclitaxel; PD-L1 = programmed death-ligand 1.

6.13 In the IMpassion131 trial the PBO+P arm demonstrated greater median OS than the ATZ+P arm (28.3 vs 22.1 months respectively) in the PD-L1-positive subgroup. In addition, the PD-L1-positive subgroups in both arms had greater survival than the ITT population, consistent with other studies suggesting that PD-L1 positivity is a positive prognostic marker (para 6.17, atezolizumab PSD, March 2020 PBAC meeting). In contrast, the PBO + nab-P PD-L1-positive group in IMpassion130 had lower survival than the PBO + nab-P PD-L1-negative group. Given the similarity between IMpassion130 and IMpassion131 cohorts, the ESC considered this inconsistency raises internal validity concerns and increases uncertainty of the replicability of OS results observed in the PD-L1 subgroup in IMpassion130. The pre-PBAC response argued that the IMpassion131 trial results do not discredit the IMpassion130 results as they were designed to answer two distinct questions.

6.14 The resubmission stated that a review of the trial data is ongoing. Hypotheses, suggested by the sponsor, for the difference in the outcomes between the two trials include: a different synergy between ATZ and nab-P compared to paclitaxel; steroid premedication administered with paclitaxel hampered efficacy of ATZ; and direct differences in the efficacy of nab-P and paclitaxel. However, the most striking difference between the two trials was the results in the comparator arms of the PD-

⁸ Miles D, *et. al.* Primary results from IMpassion131, a double blind placebo controlled randomised phase 3 trial of first line paclitaxel ± atezolizumab for unresectable locally advanced/metastatic triple negative breast cancer. Presented at the ESMO 2020 Virtual Congress, online: <https://oncologypro.esmo.org/meeting-resources/esmo-virtual-congress-2020/primary-results-from-impassion131-a-double-blind-placebo-controlled-randomised-phase-iii-trial-of-first-line-paclitaxel-pac-atezolizumab-atez>

L1-positive subgroups, with a median OS of 17.9 months in the PBO+nab-P arm of IMpassion130 compared with 28.3 months in the PBO+P arm of IMpassion131. In contrast, the outcomes in the ATZ+nab-P and ATZ+P arms were similar in the PD-L1-positive subgroups of both trials (median OS 25.4 and 22.1 months, respectively).

- 6.15 It is unlikely that differences in the direct effects of nab-P and paclitaxel monotherapies would account for the increase in median OS observed between the PBO+nab-P and PBO+P arms. A recent observational study of 200 patients which compared first-line nab-P with paclitaxel in mTNBC found similar efficacy, concluding the two agents could be used interchangeably (HR 0.98; 95%CI: 0.67–1.44)⁹. This is consistent with head-to-head RCTs of nab-P and paclitaxel, considered in the nab-P PSD (Nov 2008), which found no significant difference in efficacy in the advanced breast cancer population. The ESC agreed with the commentary that the TNBC subgroup analysis of PFS and OS results for the ITT population in Rugo et. al. (2015)¹⁰ did not, in fact, support the conclusion that nab-P is less effective than paclitaxel. The ESC also noted that in contrast to this submission the previous submission for atezolizumab argued that nab-P and paclitaxel may be considered interchangeable as 1L treatments for patients with mTNBC.
- 6.16 The fact that PD-L1 expression appears to be a positive prognostic factor, which was not observed in IMpassion130, was previously noted (paragraph 6.17, atezolizumab PSD, March 2020 PBAC meeting). The results from IMpassion131 amplify this concern; of the four treatment arms across the two trials, as described in Table 7 above, only the PBO+nab-P arm of IMpassion130 recorded a decrease in median survival from the ITT to the PD-L1-positive population. The available data cannot preclude the possibility that the performance of this control arm was aberrant, which increases uncertainty about the benefit of ATZ+nab-P described by IMpassion130. The resubmission did not address this concern, and data for the PD-L1-negative subgroup in IMpassion131 were not provided. To reduce this uncertainty, the performance of the PBO+P arm of IMpassion131 needs to be reconciled with the performance of the PBO+nab-P arm of IMpassion130. The PBAC considered this issue would need to be addressed to provide confidence in the replicability of OS results observed in the PD-L1 subgroup in IMpassion130.

Comparative harms

- 6.17 The updated safety data from the final data cut-off for IMpassion130 were consistent with the safety profile for ATZ+nab-P presented in the previous submission. A summary of the comparative safety data is presented in Table 8 below. Patients in the

⁹ Luhn P, et. al.. Comparative effectiveness of first-line nab-paclitaxel versus paclitaxel monotherapy in triple-negative breast cancer. *J Comp Eff Res* 2019 Oct;8(14):1173-1185.

¹⁰ Rugo HS et al, Randomized Phase III Trial of Paclitaxel Once Per Week Compared With Nanoparticle Albumin-Bound Nab-Paclitaxel Once Per Week or Ixabepilone With Bevacizumab As First-Line Chemotherapy for Locally Recurrent or Metastatic Breast Cancer: CALGB 40502/NCCTG N063H (Alliance) *J Clin Oncol* 2015 Jul 20;33(21):2361-9

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ATZ+nab-P arm continued to experience more grade 3-4 adverse events (AEs), serious adverse events (SAEs), adverse events of special interest (AESIs) and discontinuations than those in the PBO+nab-P arm. The ESC noted that some of point estimates of relative risk had increased slightly but noting the confidence intervals, considered that the changes were not substantial.

Table 8: Comparison of key adverse events, IMpassion130, safety evaluable population, CCOD 17 April 2018 vs 14 April 2020

Adverse event	CCOD: 17 April 2018			CCOD: 14 April 2020		
	ATZ+nab-P (N=452) n (%)	PBO+nab-P (N=438) n (%)	RR (95% CI)	ATZ+nab-P (N=460) ^a n (%)	PBO+nab-P (N=430) ^a n (%)	RR (95% CI)
Any AE	449 (99.3)	429 (97.9)	1.01 (1.00, 1.03)	457 (99.3)	421 (97.9)	1.01 (1.00, 1.03)
No. of patients with at least one:						
Grade 5 AE	6 (1.3)	3 (0.7)	1.94 (0.49, 7.70)	6 (1.3)	3 (0.7)	1.87 (0.47, 7.43)
Related Grade 5 AE	3 (0.7)	1 (0.2)	2.91 (0.30, 27.84)	2 (0.4)	1 (0.2)	1.87 (0.17, 20.54)
Grade 3-4 AE	220 (48.7)	185 (42.2)	1.15 (1.00, 1.33)	233 (50.7)	183 (42.6)	1.19 (1.03, 1.37)
Related Grade 3-4 AE	179 (39.6)	132 (30.1)	1.31 (1.09, 1.58)	191 (41.5)	129 (30.0)	1.38 (1.16, 1.66)
SAE	103 (22.8)	80 (18.3)	1.25 (0.96, 1.62)	110 (23.9)	80 (18.6)	1.29 (0.99, 1.66)
Related SAE	56 (12.4)	32 (7.3)	1.70 (1.12, 2.57)	58 (12.6)	31 (7.2)	1.75 (1.15, 2.65)
AE leading to discontinuation of any study treatment	72 (15.9)	36 (8.2)	1.94 (1.33, 2.83)	88 (19.1)	36 (8.4)	2.29 (1.59, 3.29)
ATZ/PBO	29 (6.4)	6 (1.4)	4.68 (1.96, 11.17)	37 (8.0)	4 (0.9)	8.65 (3.12, 24.06)
Nab-paclitaxel	72 (15.9)	36 (8.2)	1.94 (1.33, 2.83)	85 (18.5)	36 (8.4)	2.21 (1.53, 3.19)
AE leading to any dose interruption of ATZ/PBO	139 (30.8)	103 (23.5)	1.31 (1.05, 1.63)	160 (34.8)	102 (23.7)	1.47 (1.19, 1.81)
AESI						
Any grade	259 (57.3)	183 (41.8)	1.37 (1.20, 1.57)	270 (58.7)	179 (41.6)	1.41 (1.23, 1.61)
Grade 3-4	34 (7.5)	19 (4.3)	1.73 (1.00, 2.99)	39 (8.5)	20 (4.7)	1.82 (1.08, 3.07)
Serious AESIs	19 (4.2)	6 (1.4)	3.07 (1.24, 7.61)	19 (4.1)	7 (1.6)	2.54 (1.08, 5.98)

Source: Constructed during the evaluation, from data in Table 2.6, p 37 of the resubmission and Table 27, p 85 of the IMpassion130 Aug2020 CSR.

AE = adverse event; AESI = adverse event of special interest; ATZ = atezolizumab; CCOD = clinical cut-off date; CI = confidence interval; N = total participants in group; nab-P = nanoparticle albumin-bound paclitaxel; No. = number; PBO = placebo; RR = relative risk; SAE = serious adverse event.

^a Eight patients switched from the PBO+nab-P arm into the ATZ+nab-P arm at the 14 April 2020 CCOD.

Notes: Relative risks and 95% confidence intervals for relative risks were calculated during the evaluation using the Normal approximation to the binomial distribution. Nominally statistically significant relative risks are bolded.

Blue shading indicates data previously seen by the PBAC.

6.18 There were no changes in the number of deaths due to AEs in the ATZ+nab-P and PBO+nab-P arms at the updated clinical cut-off date 14 April 2020 (6 vs 3).

6.19 The safety profile of ATZ+nab-P in the PD-L1-positive population is compared in Table 9 below. Generally, the risk of high-grade AEs and discontinuations was higher in patients who received ATZ+nab-P compared to PBO+nab-P.

Table 9: Comparison of key adverse events, IMpassion130, safety evaluable PD-L1-positive population, CCOD 17 April 2018 vs 14 April 2020

Adverse event	CCOD: 17 April 2018			CCOD: 14 April 2020		
	ATZ+nab-P (N=185) n (%)	PBO+nab-P (N=181) n (%)	RR (95% CI)	ATZ+nab-P (N=190) ^a n (%)	PBO+nab-P (N=176) ^a n (%)	RR (95% CI)
No. of patients with at least one:						
Grade 5 AE	2 (1.1)	1 (0.6)	1.96 (0.18, 21.39)	2 (1.1)	1 (0.6)	1.85 (0.17, 20.25)
Related Grade 5 AE	1 (0.5)	0	NC	1 (0.5)	0	NC
Grade 3-4 AE	95 (51.4)	72 (39.8)	1.29 (1.03, 1.62)	102 (53.7)	70 (39.8)	1.35 (1.08, 1.69)
Related Grade 3-4 AE	76 (41.1)	49 (27.1)	1.52 (1.13, 2.04)	82 (43.2)	47 (26.7)	1.62 (1.20, 2.17)
SAE	42 (22.7)	31 (17.1)	1.33 (0.87, 2.01)	47 (24.7)	29 (16.5)	1.50 (0.99, 2.27)
Related SAE	21 (11.4)	14 (7.7)	1.47 (0.77, 2.80)	23 (12.1)	13 (7.4)	1.64 (0.86, 3.13)
AE leading to discontinuation of any study treatment	37 (20.0)	14 (7.7)	2.59 (1.45, 4.62)	46 (24.2)	12 (6.8)	3.55 (1.95, 6.48)
ATZ/PBO	12 (6.5)	4 (2.2)	2.94 (0.96, 8.93)	18 (9.5)	2 (1.1)	8.34 (1.96, 35.41)
Nab-paclitaxel	37 (20.0)	14 (7.7)	2.59 (1.45, 4.62)	44 (23.2)	12 (6.8)	3.40 (1.86, 6.22)
AE leading to any dose interruption of ATZ/PBO	60 (32.4)	38 (21.0)	1.54 (1.09, 2.19)	73 (38.4)	38 (21.6)	1.78 (1.27, 2.49)
AESI						
Any grade	105 (56.8)	66 (36.5)	1.56 (1.24, 1.96)	112 (58.9)	62 (35.2)	1.67 (1.33, 2.11)
Grade 3-4	10 (5.4)	7 (3.9)	1.40 (0.54, 3.59)	13 (6.8)	7 (4.0)	1.72 (0.70, 4.21)
Serious AESIs	NR	NR	NR	NR	NR	-

Source: Constructed during the evaluation, from data in Table 35, pp 102-104 and Table 36, p 105 of the IMpassion130 Aug2020 CSR. AE = adverse event; AESI = adverse event of special interest; ATZ = atezolizumab; CCOD = clinical cut-off date; CI = confidence interval; N = total participants in group; nab-P = nanoparticle albumin-bound paclitaxel; No. = number; NR = not reported; PD-L1=programmed death-ligand 1; PBO = placebo; RR = relative risk; SAE = serious adverse event.

^a Five patients switched from the PBO+nab-P arm into the ATZ+nab-P arm at the 14 April 2020 CCOD.

Notes: The safety evaluable PD-L1-positive patients represent the subset of the safety evaluable population who were PD-L1-positive. Relative risks and 95% confidence intervals for relative risks were calculated during the evaluation using the Normal approximation to the binomial distribution. Nominally statistically significant relative risks are bolded. Blue shading indicates data previously seen by the PBAC.

Benefits/harms

6.20 A summary of the comparative benefits and harms for ATZ+nab-P versus PBO+nab-P is presented in the table below.

Table 10: Summary of comparative benefits and harms for ATZ+nab-P and PBO+nab-P, IMpassion130 at final analysis (CCOD 14 April 2020)

Event	ATZ+nab-P	PBO+nab-P	Absolute difference	HR (95% CI)		
Progression free survival, PD-L1-positive population (median duration of follow up 21.9 months)						
Progressed, n (%)	154/185 (83.2%)	167/184 (90.8%)		0.63 (0.50, 0.79) P=<0.0001		
Median PFS, months (95% CI)	7.46 (6.70, 9.23)	5.29 (3.81, 5.55)	2.17			
% not progressed at 12 months (95% CI) ^a	30.77% (23.95, 37.59)	17.72% (12.08, 23.36)	13.05%			
Overall survival, PD-L1-positive population (median duration of follow up 21.9 months)						
Death, n(%)	120/185 (64.9%)	139/184 (75.5%)		0.67 (0.53, 0.86) P=0.0016 ^d		
Median OS, months (95% CI)	25.43 (19.55, 30.69)	17.91 (13.63, 20.30)	7.52			
% alive at 24 months (95% CI) ^b	42.35% (37.29%, 47.42%)	38.67% (33.74%, 43.60%)	3.68%			
% alive at 36 months (95% CI) ^c	35.84% (28.75, 42.92)	22.17% (15.86, 28.47)	13.67%			
Harms, safety evaluable population (median duration of treatment 22.3 weeks for ATZ+nab-P, 21.1 weeks for PBO+nab-P)						
	ATZ+nab-P n/N	PBO+nab-P n/N	RR (95% CI)	Event rate/100 patients	RD (95% CI)	
				ATZ+nab-P	PBO+nab-P	
Treatment related grade 3-4 AEs	191/460	129/430	1.38 (1.16, 1.66)	41.5	30.0	0.11 (0.05, 0.18)
Treatment related SAE	58/460	31/430	1.75 (1.15, 2.65)	12.6	7.2	0.05 (0.02, 0.09)
AEs leading to treatment discontinuation	88/460	36/430	2.29 (1.59, 3.29)	19.1	8.4	0.11 (0.06, 0.15)

Source: Tables 2.5.1-2.5.4, pp80-85 and Table 2.5.12, p 101 and Table 2.5.13, p 102 of the resubmission, and Table 6, p 16 of the Feb 2019 IMpassion130 CSR.

ATZ = atezolizumab; CCOD = clinical cut-off date; CI = confidence interval; nab-P = nanoparticle albumin-bound paclitaxel; OS = overall survival; PBO = placebo; PD-L1 = programmed death ligand-1; PFS = progression free survival; RD = risk difference; RR = risk ratio.

^a Two-year duration not provided by the CSR or resubmission.

^b Data from 2 January 2019 CCOD.

^c Updated data only provided OS at 36 months.

^d No formal testing of OS was performed in the PD-L1-positive population because hierarchy of testing indicated formal testing could only occur if OS was first statistically significant in the ITT population.

Statistically significant relative risks are bolded.

6.21 On the basis of direct evidence presented by the resubmission, for every 100 PD-L1-positive patients treated with ATZ+nab-P in comparison with PBO+nab-P:

- Approximately 13 additional patients will remain progression-free after 12 months, and approximately 14 additional patients will remain alive at 36 months compared with nab-P monotherapy. These results are highly uncertain given the statistical analysis was inconsistent with the pre-specified statistical analysis plan, and the results are also inconsistent with the findings from the similar IMpassion131 trial. Further, this benefit may be overestimated because the nab-P may be an inferior treatment choice for some patients in the comparator arm

and is additionally uncertain because the median OS was longer than the median follow-up.

- Adverse events experienced by PD-L1-positive patients treated with ATZ+nab-P over the median duration of treatment of 29 weeks:
 - 12 additional patients will experience a grade 3-4 AE.
 - 5 additional patients will experience a treatment related SAE.
 - 11 additional patients will experience an AE leading to treatment discontinuation.

Clinical claim

- 6.22 The resubmission described ATZ+nab-P as superior in terms of effectiveness compared with nab-P alone in the first-line treatment of patients with mTNBC whose tumours are PD-L1-positive (PD-L1 stained IC covering $\geq 1\%$ of the tumour area), and inferior but clinically manageable in terms of safety compared to nab-paclitaxel alone. The PBAC previously considered that the claim of superior effectiveness was not adequately supported (para 7.13, atezolizumab PSD, March 2020 PBAC meeting).
- 6.23 The resubmission modified the proposed PBS population to more closely align with the patients of IMpassion130, which addressed some of the concerns raised in the previous consideration of ATZ (March 2020). However, the ESC agreed that the selection of nab-P as the comparator was not adequately justified and that it may represent an inferior comparator therapy for the majority of patients in IMpassion130 and the target Australian population. These concerns have been compounded by the recent results of IMpassion131, where the PBO+P arm demonstrated greater median OS, compared to the ATZ+P arm. This increases the uncertainty about the reliability and replicability of the benefit demonstrated for ATZ+nab-P in IMpassion130. For these reasons, the PBAC considered that the claim of superior effectiveness remained not adequately supported by the data.
- 6.24 The ESC considered that the claim of inferior safety was reasonable, but that it is unclear whether it is clinically manageable compared with nab-P alone. The PBAC considered that the claim of inferior safety was reasonable.

Economic analysis

- 6.25 The resubmission presented a modelled evaluation based on the IMpassion130 trial data. The types of economic evaluation presented were a cost-effectiveness (cost-per-life-year-gained (LYG)) and a cost-utility analysis (cost-per-quality-adjusted life-year (QALY)-gained). This was unchanged from the previous submission. The ESC previously considered that the clinical claim was not supported by the evidence, as the difference in PFS was small and may not be clinically meaningful, and no statistically significant difference in OS was established for the PD-L1-positive population. In addition, benefits are likely to be overestimated given the potentially inferior comparator used

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in IMpassion130. As such, the ESC considered that modelling a non-significant treatment benefit was not appropriate and resulted in a high level of uncertainty in the model results (para 6.42, atezolizumab PSD, March 2020 PBAC meeting). The PBAC agreed with the ESC that these concerns remain outstanding.

6.26 The key components of the economic evaluation are summarised in the table below.

Table 11: Summary of model structure, key inputs and rationale

Component	Summary	Comparison with previous submission
Treatments	PD-L1 testing using the Ventana SP142 and treatment with ATZ plus nab-P for patients whose tumours express PD-L1 IC $\geq 1\%$, and nab-P alone for those whose tumours do not express PD-L1 (the proposed scenario), compared with no PD-L1 testing and treatment with nab-P for all patients (the current scenario).	Unchanged
Time horizon	10 years compared with a median follow up of 18.8 months in IMpassion130	Unchanged
Outcomes	Life-years gained (LYG) and quality-adjusted life-years gained (QALYG)	Unchanged
Methods used to generate results	Partitioned survival (area under the curve) analysis	Unchanged
Health states	Three: Progression-free survival (PFS), Progression, and Death	Unchanged
Cycle length	1 week	Unchanged
Allocation to health states	Health state allocation over time determined by PFS and overall survival (OS) curves from IMpassion130 at the 14 April 2020 clinical data cut-off, extrapolated using standard parametric functions over the time horizon of the model.	OS and PFS data have been updated compared with the previous submission, in which data were based on IMpassion130 at the 2 January 2019 data cut-off.
Extrapolation method in the submission base case	The resubmission extrapolated the KM curves of OS, PFS and time to off treatment (TTOT) from median duration of follow-up of 18.8 months in IMpassion130. Log-logistic distributions were chosen to extrapolate the PFS and TTOT curves for all patient populations in both comparative scenarios. Gamma distributions were chosen to extrapolate OS curves for all patients in both scenarios. The model is sensitive to the parametric functions used for OS extrapolation. The survival curves of the two comparative scenarios did not converge within the modelled time horizon in the resubmission base case, but was allowed given the model structure.	Updated. The previous submission extrapolated the KM curves of OS, PFS and TTOT from median duration of follow-up of 18 months in IMpassion130. Log-logistic distributions were chosen to extrapolate the PFS, OS and TTOT curves for patient populations in the proposed scenario (regardless of treatment received or PD-L1 status). In contrast, in the current scenario where there was no test and all patients received nab-P, log-logistic distributions were used to extrapolate PFS and TTOT and Weibull was chosen for OS extrapolation. The PBAC previously considered that the selection of a different parametric function for OS extrapolation in the comparative scenario was unjustified (para 7.15, atezolizumab PSD, March 2020 PBAC meeting).
Health related quality of life in the submission base case	EQ-5D-5L results from IMpassion130, converted into utilities using the Australian scoring algorithm.	Updated. The previous submission converted the EQ-5D-5L data from IMpassion130 using the UK scoring algorithm. The PBAC previously considered that the rationale for the approaches used to estimate utility values in the submission

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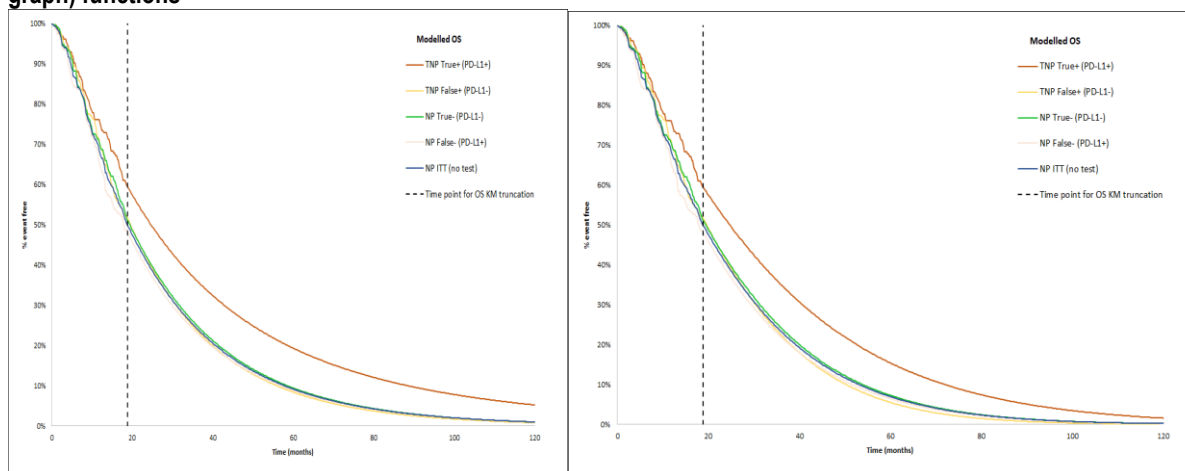
Component	Summary	Comparison with previous submission
		and also in the pre-PBAC response were not adequately justified. Further, the utility values were not conservative compared with values that have been used in other economic evaluations of advanced breast cancer (para 7.17, atezolizumab PSD, March 2020 PBAC meeting).
Duration of treatment – both nab-P and ATZ	The resubmission limited the costs of ATZ and nab-P by applying a cap on the average number of ATZ administrations to ■ and a cap on the number of nab-P to 10.	New to the revised model. The previous model did not apply caps to the duration of treatments, which were based on trial-observed and extrapolated TTOT. The pre-PBAC response to the previous submission proposed caps to the ATZ duration of treatment and presented a revised model.

Source: Sections 3.1 to 3.5 of the resubmission.

ATZ = Atezolizumab; IC = immune cells; nab-P = nanoparticle albumin-bound paclitaxel; PD-L1 = programmed death ligand 1; PSD = Public Summary Document.

- 6.27 Compared with the previous submission, the key changes in the revised economic model presented in the resubmission were the parametric functions for extrapolation of OS, caps on ATZ and nab-P administrations and application of the Australian algorithm for utility values.
- 6.28 The resubmission chose Gamma functions to extrapolate the OS curves from the median follow-up of 18.8 months, and stated that the Gamma function was more clinically plausible (than the Weibull functions) and the best fit upon visual inspection and Akaike information criterion (AIC) statistics. Gamma, Log-logistic and Weibull functions had a similar goodness of fit to within-trial OS data, based on AIC and Bayesian information criterion (BIC) statistics and visual inspection. However, the application of these different extrapolation methods resulted in noticeably different extent of separation of OS curves beyond the point of extrapolation of the trial data, particularly within the later part of the modelled time horizon (Figure 2 below), which has no robust clinical data to support it. The ESC noted that all functions presented fit the KM data reasonably well but selection of the Gamma extrapolation lead to a significant plateau in the curve for the true positive population. The ESC considered that although there is some evidence of ongoing treatment effect for PD-L1 inhibitors in some indications, in this indication it may not be clinically plausible to assume ongoing benefit and survival for some patients up to 10 years, as TNBC is an aggressive disease and median survival is typically only 15-16 months. The ESC considered that assuming ongoing survival benefit was not consistent with the broader evidence for PD-L1 inhibitors in this population, where trials have not demonstrated substantial OS benefit. The pre-PBAC response reiterated that the sponsor considered gamma extrapolation the most clinically plausible based on advice from clinicians at the Roche Advisory board meeting where attendees agreed they would expect to see some flattening of the curve.
- 6.29 The figure below presents the modelled overall survival curves using Gamma (base case of the resubmission’s model) and Weibull functions respectively.

Figure 2: Kaplan-Meier OS and extrapolations from median follow up using Gamma (left graph) and Weibull (right graph) functions



Source: Figure 3.6, p58 of the resubmission for the Gamma extrapolation and constructed during the evaluation using “Revised Economic Evaluation.xlsx” for the Weibull extrapolation.

OS = overall survival; PD-L1 = programmed cell death ligand 1; TNP = Tecentriq (atezolizumab) + nanoparticle albumin-bound paclitaxel; NP = nanoparticle albumin-bound paclitaxel; ITT = intention to treat; KM = Kaplan-Meier.

- 6.30 The key concern over the previous submission was the use of different extrapolation methods for the comparative scenarios. Using the optimistic log-logistic extrapolation for the proposed scenario and the pessimistic Weibull extrapolation for the current scenario in the previous submission overestimated the incremental OS benefit of proposed scenario compared with current scenario. The PBAC previously advised that, “in the absence of a statistically significant OS benefit (when adjusted for multiplicity), the economic model would need to be based on conservative assumptions regarding the magnitude of any modelled OS gains” (para 7.22, atezolizumab PSD, March 2020 PBAC meeting). In the revised economic model presented with the resubmission, when using the same parametric functions for OS extrapolation in both scenarios, regardless whether it is log-logistic or Weibull, the incremental OS benefit is similar, and both result in a smaller OS benefit than from extrapolation using the Gamma function. Therefore the application of the Gamma function to extrapolate OS curves did not result in a conservative estimate of the OS benefit from treatment with ATZ+nab-P. The PBAC previously considered that using the Weibull function (in all arms) resulted in OS estimates that were more clinically plausible (para 7.15, atezolizumab PSD, March 2020 PBAC meeting). The model was sensitive to the parametric functions used for OS extrapolation.
- 6.31 The revised model presented in the resubmission allowed the OS curve for PD-L1 true positive patients treated with ATZ+nab-P in the proposed scenario to converge with the OS curve for the patients in the current scenario (starting from 90 months and converging at the end of time horizon of 10 years), although neither the base case nor sensitivity analyses presented in the resubmission incorporated the factor of convergence. The revised base case in the pre-PBAC response to the previous submission applied convergence of the ATZ+nab-P OS curve to the current scenario curve; commencing from 90 months with convergence occurring at the end of the

time horizon (120 months). The PBAC noted that no justification was provided for the point at which convergence was commenced (para 6.50, atezolizumab PSD, March 2020 PBAC meeting). The resubmission did not provide a justification for the selection of time point for commencing convergence, and the model was sensitive to the time points assumed for OS convergence.

- 6.32 The resubmission applied a cap of [REDACTED] on the accumulated average number of administrations of ATZ, based on the time to off treatment (TTOT) data, which resulted in an average of [REDACTED] ATZ administrations being costed in the base case for PD-L1 true positive patients treated with ATZ+nab-P. The most recent data from IMpassion130 indicated that the mean number of treatments with ATZ was 23 administrations for PD-L1-positive patients (Table 35, p102 of final updated IMpassion130 Clinical Study Report (CSR)). At this data cut off, 26 patients in the ITT population remained on treatment with ATZ alone or ATZ+nab-P (Table 6 above). The extrapolated TTOT from trial median follow-up of 18.8 months indicated that true positive patients would receive an average of 28.25 administrations of ATZ during the full treatment course (Table 15 below). The application of a cap on the average number of ATZ administrations considerably reduced the cost of the proposed scenario and, consequently, the incremental cost between the two comparative scenarios.
- 6.33 The resubmission claimed that an episode of care (EoC) cap for ATZ at [REDACTED] would be implemented in the form of subsidisation caps. These annual subsidisation caps would be calculated by multiplying the predicted number of patients treated by the effective price of [REDACTED] ATZ doses. It was proposed that the sponsor would rebate [REDACTED]% of expenditure above the agreed subsidisation caps. Whether the total cost of ATZ reaches the annual subsidisation cap would depend on the accuracy of the resubmission's estimation of the number of patients likely to be treated each year and the duration of treatment. If the number of patients per year is overestimated, the cost per patient for ATZ in clinical practice may exceed the cost per patient applied in the model. The ESC noted that reliance on subsidisation caps to achieve a cost-effective price introduced substantial additional uncertainty in the ICERs derived and the PBAC agreed with the ESC that the ICERs without application of the proposed caps were the appropriate base case for decision-making.
- 6.34 The resubmission also applied a cap of 10 treatments on the number of nab-P administrations for all patients in both scenarios, based on their respective TTOT curves. This resulted in an average of approximately 8 or 9 administrations being costed depending on PD-L1 status and comparative scenarios. This is compared with an average of 30.20 administrations for true positive patients and 21.77 for true negative patients in the proposed scenario, and 20.07 for patients in the current scenario, when treatment durations were based on TTOT curves.
- 6.35 The resubmission justified the application of a cap of 10 administrations for nab-P based on dose-limiting toxicity, as suggested by DUSC (para 6.75, atezolizumab PSD, March 2020 PBAC meeting). However, the health outcomes observed from

IMpassion130 and those extrapolated over 10-year time horizon were based on a much longer average nab-P treatment duration. The most recent data from IMpassion130 indicated that, PD-L1-positive patients received nab-P (when used in combination with ATZ) for an average of approximately 28.2 administrations, while patients (both PD-L1-positive and negative) in the control arm received nab-P for an average of 19.8 administrations (Table 35, p102 of final updated IMpassion130 CSR), when most patients had discontinued nab-P (Table 6, above). Reducing the cost of nab-P due to potentially intolerable toxicity without adjusting corresponding health outcomes was not appropriate. The application of the cap on the number of nab-P administrations substantially reduced the incremental cost between the two comparative scenarios and favoured the proposed scenario. The PSCR and pre-PBAC response argued that reducing the number of nab-P doses followed the recommendation by DUSC. While the number of doses of nab-P may be limited in clinical practice due to cumulative toxicity, (especially where patients have previously been treated with taxanes) the ESC considered it is not reasonable to adjust the duration (cost) of the treatment, but not the outcomes in the model; these should reflect treatment and outcomes received in IMpassion130. As advised by DUSC, it may be appropriate to limit the number of nab-P doses in the financial estimates, which should reflect the expected use in Australian practice.

- 6.36 The resubmission revised the utility estimates by applying the EQ-5D-5L data derived from IMpassion130 with preference weights from Norman (2012), based on an Australian population, in the base-case of the revised economic model. The progression-free and progressive disease health state utility values were 0.695 and 0.583, respectively. The revised utility estimates appeared reasonable. The utility estimate for progressive disease was generally consistent with the utility value that was previously considered reasonable by the PBAC for advanced breast cancer (0.555 for progressive disease, para 6.50, Pertuzumab and trastuzumab, PSD, November 2014 PBAC meeting). The resubmission presented sensitivity analyses using utility values sourced from literature. The utility values used have a modest impact on the model results. A higher utility value for either the progression-free or the progressive disease health state will favour the proposed scenario over the current scenario given a modelled prolonged PFS and OS from treatment with ATZ+nab-P.
- 6.37 The key drivers of the model are summarised below.

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Table 12: Key drivers of the model

Description		Method/Value	Impact#
Modelling OS		Use of OS data from IMpassion130 trial, where no statistically significant benefit in OS was demonstrated.	Resubmission base case: \$██████ ¹ /QALY*
Extrapolation of OS	Parametric functions	Gamma distribution was used to extrapolate OS curves for all patients in both comparative scenarios from median duration of follow-up 18.8 months	High, favours the proposed scenario. When using either the Weibull distribution or the Log-logistic distribution for OS extrapolation in both scenarios, the ICER increased to approximately \$██████ ² /QALY.
	Convergence of OS curves	The base case did not model a convergence of OS curves of PD-L1-positive patients treated with ATZ+nab-P in the proposed scenario and those treated with nab-P in the current scenario	High, favours the proposed scenario. When assuming convergence commencing from 90 or 60 months, the ICER increased to \$██████ ² /QALY and \$██████ ² /QALY respectively.
Duration of ATZ treatment		A cap of average ██████ administrations was applied to TTOT curves	High, favours the proposed scenario. Excluding the cap, the ICER increased to \$██████ ² /QALY.
Duration of nab-P treatment		A cap of 10 administrations was applied to TTOT curves	High, favours the proposed scenario. Excluding the cap, the ICER increased to \$██████ ² /QALY

Source: Compiled during the evaluation based on information presented in 'Revised Economic Evaluation.xlsx' of the resubmission. OS = overall survival; PD-L1 = programmed death ligand 1; ICER = incremental cost effectiveness ratio; QALY = quality-adjusted life year; ATZ = atezolizumab; nab-P = nanoparticle albumin-bound paclitaxel; TTOT = time to off treatment.

*The results of ICER were updated during the evaluation using the MBS item 13950 for chemotherapy drug administration.

Values include reduction in ATZ cost due to proposed treatment cap implemented via RSA caps

The redacted values correspond to the following ranges:

¹\$55,000 to <\$75,000/QALY gained

²\$75,000 to <\$95,000/QALY gained

6.38 The results of the stepped economic evaluation are presented below.

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Table 13: Results of the stepped economic evaluation

Step and component	Proposed scenario	Current scenario	Increment
Step 1: trial-based costs and outcomes (PFS KM truncated at 41.89 months, OS KM 53.03 months and TTOT KM 37.49 months)			
Costs	\$ [redacted]	\$7,938	\$ [redacted]
LYG	2.03	1.87	0.16
Incremental cost/extra LYG gained			\$ [redacted] ¹
Step 2: time horizon extended to 10 years (PFS, OS and TTOT KM curves in IMpassion130 extrapolated from 18.83 months)			
Costs	\$ [redacted]	\$7,938	\$ [redacted]
LYG	2.32	2.04	0.28
Incremental cost/extra LYG gained			\$ [redacted] ²
Step 3: Inclusion of MRU cost			
Costs	\$ [redacted]	\$9,967	\$ [redacted]
LYG	2.32	2.04	0.28
Incremental cost/extra LYG gained			\$ [redacted] ²
Step 4: Inclusion of AE cost			
Costs	\$ [redacted]	\$10,089	\$ [redacted]
LYG	2.32	2.04	0.28
Incremental cost/extra LYG gained			\$ [redacted] ²
Step 5: utility weights applied			
Costs	\$ [redacted]	\$10,089	\$ [redacted]
QALYs	1.45	1.27	0.18
Incremental cost/extra QALY gained			\$ [redacted] ³
Step 6: Inclusion of progression treatment cost			
Costs	\$ [redacted]	\$14,152	\$ [redacted]
QALYs	1.45	1.27	0.18
Incremental cost/extra QALY gained			\$ [redacted] ³
Step 7: Inclusion of end of life cost			
Costs	\$ [redacted]	\$16,592	\$ [redacted]
QALYs	1.45	1.27	0.18
Incremental cost/extra QALY gained			\$ [redacted] ³
Step 8: Inclusion of episode of care cap			
Costs	\$ [redacted]	\$16,592	\$ [redacted]
QALYs	1.45	1.27	0.18
Incremental cost/extra QALY gained (resubmission's base case)			\$ [redacted] ²

Source: Compiled during the evaluation using "Results" worksheet of "Revised Economic Evaluation.xlsx".

PFS = progression-free survival; KM = Kaplan-Meier; OS = overall survival; TTOT = time to off treatment; LYG = life years gained; MRU = medical resources use for disease monitoring and management; AE = adverse events; QALY = quality-adjusted life year.

Note that the results presented above are slightly different from those presented in the resubmission, due to the updated cost of drug administration (MBS item 13950 \$111.40 replacing both Items 13915 and 13918) used in the "Treatment and MRU costs" worksheet of "Revised Economic Evaluation.xlsx".

Note that the numbers may not add up due to rounding.

The redacted values correspond to the following ranges:

¹\$95,000 to <\$115,000/QALY gained

²\$55,000 to <\$75,000/QALY gained

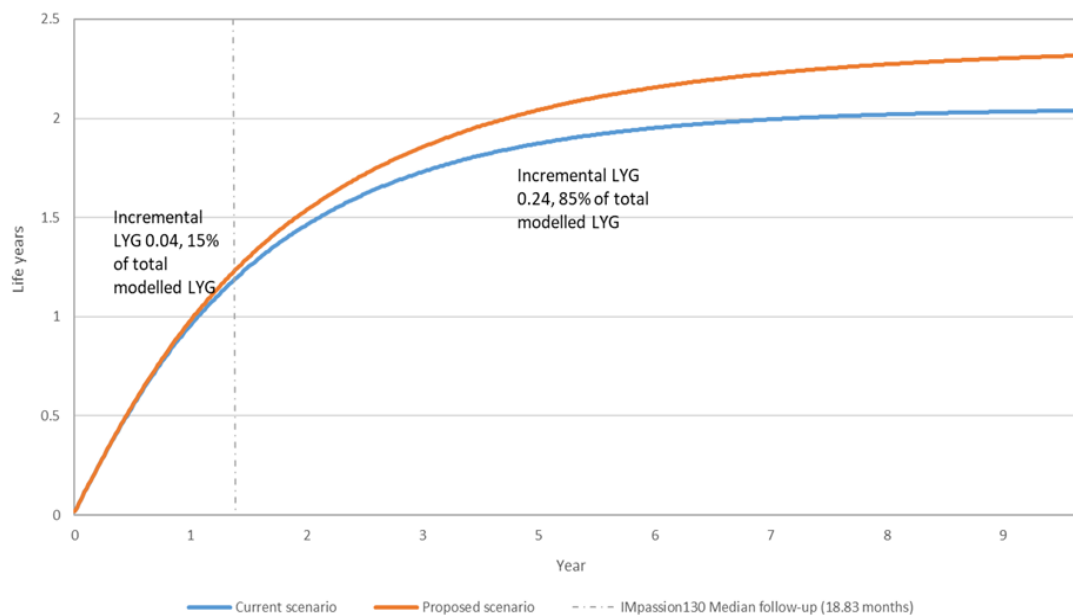
³\$75,000 to <\$95,000/QALY gained

6.39 The above table indicates that extrapolation of health outcomes from trial-based data to 10 years increases the incremental LYG considerably, which results in a substantial decrease in the incremental cost-effectiveness ratio (ICER) from \$95,000 to <\$115,000/LYG to \$55,000 to <\$75,000/LYG. Extrapolation to 10 years had a minor impact on the cost of the proposed scenario, which also marginally favoured treatment with ATZ+nab-P, due to the very similar, but slightly favourable

extrapolated TTOT curve for ATZ compared to the Kaplan-Meier (KM) TTOT curve for ATZ used in Step 1 (truncated at 37.49 months).

- 6.40 The vast majority (85%) of the incremental life years gained were accrued during the extrapolated period of the model. The figure below presents the life years gained within the trial period and within the extrapolation period.

Figure 3: Life years gained during IMpassion130 and during the extrapolated modelled time horizon in both the proposed and current scenarios (resubmission's base case)



Source: Constructed during the evaluation using data presented in "Revised Economic Evaluation.xlsx".

LYG = life-years gained

- 6.41 The other step that had a large impact on the result of economic evaluation was the inclusion of an episode of care cap of an average of █ doses of ATZ, which resulted in a decrease of almost \$15,000 to <\$25,000/QALY gained (from \$75,000 to <\$95,000/QALY to the base case of \$55,000 to <\$75,000/QALY).
- 6.42 The estimated cost of nab-P in Step 1 of the economic evaluation presented in the resubmission was not trial-based; the number of nab-P administrations was limited to 10 treatments. The inclusion of the cap on the number of nab-P treatments had a significant impact on the result of economic evaluation reducing the ICER from \$75,000 to <\$95,000/QALY to the submission's base case of \$55,000 to <\$75,000/QALY.
- 6.43 The results of key sensitivity analyses presented in the resubmission and performed during the evaluation are summarised below. Given that the EoC cap for ATZ appeared to be based on a proposed utilisation subsidisation cap, which would depend on the estimated total number of patients treated, it is uncertain whether the actual truncated cost, based on an average █ doses of ATZ, will be realised in clinical practice. As such, the results of sensitivity analyses are presented with and without the EoC cap for ATZ applied.

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Table 14: Results of key sensitivity analyses

Analyses	With EoC cap for ATZ			Without EoC cap for ATZ		
	Incremental cost	Incremental QALY	ICER	Incremental cost	Incremental QALY	ICER
Base case	\$ [redacted]	0.18	\$ [redacted] ¹	N/A		
All else equal to base case but the application of EoC cap	N/A			\$ [redacted]	0.18	\$ [redacted] ²
No cap on the number of nab-P treatments (base case assumed maximum 10 treatments)	\$ [redacted]	0.18	\$ [redacted] ²	\$ [redacted]	0.18	\$ [redacted] ³
Extrapolation of OS (base case Gamma extrapolation) <ul style="list-style-type: none"> Weibull function Log-logistic function 	\$ [redacted] \$ [redacted]	0.16 0.16	\$ [redacted] ² \$ [redacted] ²	\$ [redacted] \$ [redacted]	0.16 0.16	\$ [redacted] ³ \$ [redacted] ³
OS curves of two comparative scenarios converge at 10 years (no convergence in base case) <ul style="list-style-type: none"> From 90 months From 60 months 	\$ [redacted] \$ [redacted]	0.17 0.15	\$ [redacted] ² \$ [redacted] ²	\$ [redacted] \$ [redacted]	0.17 0.15	\$ [redacted] ³ \$ [redacted] ³
Time horizon (base case 10 years) <ul style="list-style-type: none"> 5 year 7.5 years 15 years 	\$ [redacted] \$ [redacted] \$ [redacted]	0.12 0.16 0.20	\$ [redacted] ³ \$ [redacted] ² \$ [redacted] ⁴	\$ [redacted] \$ [redacted] \$ [redacted]	0.12 0.16 0.20	\$ [redacted] ⁵ \$ [redacted] ³ \$ [redacted] ²
Utilities for PF and PD states (base case PF 0.695, PD 0.583) <ul style="list-style-type: none"> PF 0.760; PD 0.550 PF 0.730; PD 0.450 	\$ [redacted] \$ [redacted]	0.19 0.17	\$ [redacted] ⁴ \$ [redacted] ²	\$ [redacted] \$ [redacted]	0.19 0.17	\$ [redacted] ² \$ [redacted] ³
Multivariate analyses						
#1: No cap on nab-P treatments and Weibull extrapolation for OS	\$ [redacted]	0.16	\$ [redacted] ³	\$ [redacted]	0.16	\$ [redacted] ⁵
#2: No cap on nab-P treatments and log-logistic extrapolation for OS	\$ [redacted]	0.16	\$ [redacted] ³	\$ [redacted]	0.16	\$ [redacted] ⁵
#3: No cap on nab-P treatments and OS curves converge from 90 months	\$ [redacted]	0.17	\$ [redacted] ³	\$ [redacted]	0.17	\$ [redacted] ⁵
#4: No cap on nab-P treatments and OS curves converge from 60 months	\$ [redacted]	0.15	\$ [redacted] ³	\$ [redacted]	0.15	\$ [redacted] ⁶
#1 + #3	\$ [redacted]	0.15	\$ [redacted] ³	\$ [redacted]	0.15	\$ [redacted] ⁵
#1 + #4	\$ [redacted]	0.13	\$ [redacted] ⁵	\$ [redacted]	0.13	\$ [redacted] ⁶
#2 + #3	\$ [redacted]	0.15	\$ [redacted] ³	\$ [redacted]	0.15	\$ [redacted] ⁶
#2 + #4	\$ [redacted]	0.14	\$ [redacted] ⁵	\$ [redacted]	0.14	\$ [redacted] ⁶

Source: Compiled during the evaluation using "Revised Economic Evaluation.xlsx".

EoC = episode of care; ATZ = atezolizumab; QALY = quality-adjusted life years; ICER = incremental cost effectiveness ratio; N/A = not applicable; nab-P = nanoparticle albumin-bound paclitaxel; OS = overall survival; PF = progression-free; PD = progressive disease; Note that the numbers may not add up due to rounding.

The redacted values correspond to the following ranges:

¹\$55,000 to <\$75,000/QALY gained

²\$75,000 to <\$95,000/QALY gained

³\$95,000 to <\$115,000/QALY gained

⁴\$55,000 to <\$75,000/QALY gained

⁵\$115,000 to <\$135,000/QALY gained

⁶\$135,000 to <\$155,000/QALY gained

- 6.44 As noted earlier, it is inappropriate to limit the number of treatments with nab-P in terms of costs without adjusting the corresponding health outcomes. It is also highly uncertain whether the average cost of ATZ per patient would be able to be limited to [REDACTED] administrations in practice, through the use of RSA caps. When excluding the caps on the number of treatments of both nab-P and ATZ, the ICER would increase to \$95,000 to <\$115,000/QALY from the base case that included caps on both nab-P and ATZ (\$55,000 to <\$75,000/QALY).
- 6.45 The model was sensitive to the parametric functions used for OS extrapolation. Compared with Gamma function used in the base case, both Weibull and log-logistic functions had similar fits to the observed Kaplan-Meier OS curves, but would produce a more conservative estimate of OS benefit. Including treatment caps, the ICER was \$75,000 to <\$95,000/QALY and \$75,000 to <\$95,000/QALY when using Weibull and Log-logistic functions, respectively.
- 6.46 Multivariate sensitivity analyses indicated that excluding the caps on the number of treatments for both ATZ and nab-P and applying Weibull functions for OS extrapolation would increase the ICER to \$115,000 to <\$135,000/QALY. Similarly, excluding the treatment caps and using Log-logistic functions to extrapolate OS would increase the ICER to \$115,000 to <\$135,000/QALY.

Drug cost/patient/course

- 6.47 Taking into account the [REDACTED] % discount on the AEMP proposed in the resubmission, and applying caps on the number of administrations for both ATZ and nab-P as presented in the base case of the model, the average dispensed drug cost per patient per course of ATZ for PD-L1-positive patients was \$ [REDACTED], based on an average treatment duration of 9.19 months and a cost per dose of \$ [REDACTED] (an average dose of 840 mg every two weeks; 31.4% public hospital use). The average cost per patient per course for nab-P, when used in combination with ATZ, is \$ [REDACTED], based on an average treatment duration of 2.76 months and a cost per dose of \$ [REDACTED] (dose of 100 mg/m²; body surface area (BSA) = 1.78; 2x100 mg vials; 31.4% public hospital use). This equalled a total cost of \$ [REDACTED] per patient. If treatment durations were based on KM and extrapolated TTOT curves (12.99 months of ATZ and 9.26 months of nab-P), the total cost per patient per course was \$ [REDACTED] (cost for ATZ \$ [REDACTED] and cost for nab-P \$ [REDACTED]).

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6.48 In the current scenario (as represented by false negative patients treated with nab-P¹¹), the expected cost per patient per course of nab-P for PD-L1-positive patients, with the application of a cap of 10 doses, is \$ [REDACTED], based on an average duration of 2.58 months and a cost per dose of \$ [REDACTED] (dose of 100 mg/m²; BSA = 1.78; 2x100 mg vials; 31.4% public hospital use). Without the cap, the cost per patient is \$ [REDACTED], based on an average treatment duration of 5.39 months (derived from KM and extrapolated TTOT curves).

6.49 The average duration of therapy and average medicine costs per patient for each of the test/treatment pathways are provided in the table below.

Table 15: Calculation of the cost per patient per course for each of the included medicines (undiscounted)

	Proposed scenario								Current scenario	
	Test positive: ATZ+nab-P				Test negative: nab-P				ITT	
	True-positive ^a		False-positive		True-negative ^a		False-negative			
% patients (weight)	38.1%		2.8%		57.1%		2.0%		100%	
Average duration of therapy										
	Base case	TTOT	Base case	TTOT	Base case	TTOT	Base case	TTOT	Base case	TTOT
ATZ	[REDACTED] mths ([REDACTED] doses)	12.99 mths (28.25 doses)	[REDACTED] mths ([REDACTED] doses)	9.03 mths (19.63 doses)	N/A				N/A	
Nab-P	2.76 mths (9.01 doses)	9.26 mths (30.20 doses)	2.81 mths (9.16 doses)	7.40 mths (24.14 doses)	2.70 mths (8.81 doses)	6.68 mths (21.77 doses)	2.58 mths (8.41 doses)	5.39 mths (17.56 doses)	2.65 mths (8.65 doses)	6.16 mths (20.07 doses)
Weighted ATZ	[REDACTED] mths ([REDACTED] doses) in the base case versus 12.72 mths (27.66 doses) based on modelled TTOT				N/A				N/A	
Total weighted ATZ	[REDACTED] mths ([REDACTED] doses) in the base case versus 5.21 mths (11.32 doses) based on modelled TTOT								N/A	
Total weighted nab-P	2.72 mths (8.88 doses) in the base case versus 7.66 mths (24.97 doses) based on modelled TTOT								2.65 mths (8.65 doses) in the base case versus 6.16 mths (20.07 doses)	
Average medicine costs per patient (undiscounted)										
	Base	TTOT	Base	TTOT	Base	TTOT	Base	TTOT	Base	TTOT

¹¹ The economic model included a single arm to model both the PD-L1-positive and PD-L1-negative patients in the resubmission base case. However, the financial estimates only considered the difference in treatment costs for the PD-L1-positive population. Therefore, the implied per-treatment cost of PD-L1-positive patients treated with nab-P was taken from the ‘false-negative’ sub-population in the economic model. This treatment pathway in the economic model was based on PD-L1-positive patients treated with nab-P, and is therefore suitable for comparison.

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	Proposed scenario								Current scenario	
	Test positive: ATZ+nab-P				Test negative: nab-P				ITT	
	True-positive ^a		False-positive		True-negative ^a		False-negative			
case		case		case		case		case		
ATZ cost per dose	\$ [REDACTED]				N/A				N/A	
Nab-P cost per dose	\$ [REDACTED]				\$ [REDACTED]				\$ [REDACTED]	
ATZ	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	N/A				N/A	
Nab-P	\$7,265	\$24,365	\$7,386	\$19,474	\$7,105	\$17,567	\$6,786	\$14,169	\$6,975	\$16,196
Weighted ATZ	\$ [REDACTED] in the base case versus \$ [REDACTED] based on TTOT				N/A				N/A	
Total weighted ATZ	\$ [REDACTED] in the base case versus \$ [REDACTED] based on TTOT								N/A	
Total weighted nab-P	\$ [REDACTED] in the base case versus \$ [REDACTED] based on TTOT								\$ [REDACTED] in the base case versus \$ [REDACTED] based on TTOT	
Total cost per patient	\$ [REDACTED] in the base case versus \$ [REDACTED] based on TTOT								\$ [REDACTED] in the base case versus \$ [REDACTED] based on TTOT	

Source: Compiled during evaluation based on Revised Economic Evaluation.xlsx.

ATZ = atezolizumab; nab-P = nanoparticle albumin-bound paclitaxel; ITT = intention to treat; TTOT = time to off treatment, mths = months; N/A = not applicable.

Note that the numbers may not add up due to rounding.

6.50 The average cost per patient per course for ATZ+nab-P and nab-P alone differed between the submission’s economic model and financial analysis due to differences in the estimated number of doses. The economic model set a cap on the accumulated average number of doses of ATZ based on TTOT, and a cap on the maximum number of doses of nab-P based on TTOT, which resulted in an average of [REDACTED] doses of ATZ and 9.01 doses of nab-P for PD-L1-positive patients, and 8.41 doses of nab-P for PD-L1 false-negative patients who were treated with nab-P monotherapy. In contrast, the financial analysis simply assumed [REDACTED] doses for ATZ and 10 doses for nab-P (irrespective of whether it was used in combination with ATZ or alone).

Estimated PBS usage & financial implications

6.51 This resubmission was not considered by DUSC.

6.52 The resubmission used an epidemiological approach to determine the number of patients likely to be treated with ATZ+nab-P and the expected financial impact of listing ATZ+nab-P on the PBS and Government health budget. The approach was unchanged from the previous submission, although with updated inputs.

6.53 Key input parameters used in the resubmission’s approach are provided in the table below.

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Table 16: Key inputs for financial estimates

Parameter	Value applied and source	Comment
Estimation of incident breast cancer patients	AIHW Cancer in Australia report, extrapolated using a linear function	The approach was unchanged from the previous submission and considered reasonable by DUSC and PBAC previously.
Proportion of patients with TNBC	15%, Cancer Council Australia (2019)	Unchanged from the previous submission, and considered reasonable by DUSC previously.
Proportion of incident patients diagnosed with <i>de novo</i> mTNBC	25%, IMpassion130 CSR, p1470 (25% <i>de novo</i> metastatic TNBC)	34.8% in the previous submission to include both unresectable locally advanced (9.8%) and <i>de novo</i> mTNBC (25%). DUSC previously considered the estimate was reasonable.
Population diagnosed with early TNBC who progress to mTNBC	20% over 10 years, 6.01 atezolizumab DUSC Advice March 2020	DUSC considered that 20% is a more reasonable estimate of 10 year distant recurrence for TNBC. The resubmission applied this 10-year distant recurrence rate constantly to the patients diagnosed each year in the previous 10 years.
10 year TNBC survival rate	44%, Lin (2012)*	New to the resubmission to estimate the number of patients who remain alive among those who diagnosed with early stage TNBC each year in the past 10 years. The previous submission did not apply survival rate, and the distant recurrence was only estimated for the past 40 months. The estimate appeared reasonable, but the application of a constant survival rate to all the patients diagnosed each year in the previous 10 years may not be inappropriate.
% of recurrent mTNBC patients who had no taxane therapy in the previous 12 months	64%, METIS Healthcare Research, 2020	New to the resubmission, given the revised requested listing.
ECOG status of 0 or 1.	78%, METIS Healthcare Research (2019)	Unchanged from the previous submission. DUSC previously considered the estimate was reasonable.
% patients who elect to have the PD-L1 test	95%, 6.01 atezolizumab DUSC Advice March 2020	82% was used in the previous submission. DUSC previously considered that 95% was more reasonable.
Estimate of proportion of patients who are PD-L1-positive	41%, as reported in IMpassion130 trial	Unchanged from the previous submission.
# of ATZ administrations	█ administrations, 6.01 atezolizumab DUSC Advice March 2020	DUSC previously considered this was reasonable.
Split of patients receiving substituted taxane regimens	62% nab-P 29% paclitaxel 9% docetaxel METIS Healthcare Research, 2020	The estimates were uncertain. However, the impact on the total cost to PBS and/or Government is likely to be minimal.
# of nab-P administrations (in combination with ATZ or used alone)	10 administrations, DUSC advice	DUSC previously considered 10 doses of nab-P was a reasonable estimate.
# of administrations of paclitaxel	13.33, Source not reported	The inclusion of paclitaxel and docetaxel as substituted medicines was new to the
# of administrations of docetaxel	4.44, Source not reported	

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		resubmission. The resubmission did not provide the source for the estimated duration of treatment with paclitaxel and docetaxel.
MBS Items		
MBS Items 13918 and MBS Item 13915 - administration of ATZ+nab-P	\$101.00 \$67.10 10 administrations for ATZ+nab-P and 10 for ATZ alone.	These MBS items were appropriate; Although MBS items 13918 and 13915 have been replaced by 13950, this will not have a major impact on the total cost to the Government budget.
MBS Item 13915 - administration of taxane alone	\$67.10 10.4 weighted average number of administrations across all taxane regimens	
MBS item 56807- CT scan of chest, abdomen and pelvis	\$568.4, one CT scan every 3 cycles (12 weeks)	
MBS item 105- subsequent specialist visit	\$45, once per treatment cycle	
MBS item 65070- blood tests	\$16.95, once per treatment cycle	
MBS item 66512- blood tests	\$17.70, once per treatment cycle	
MBS item 31548 – breast biopsy	\$206.25, 0.26 per treated patient	
MBS item TBC – PD-L1 test	\$74.50, 2.57 per treated patient (to account for the test in the broader population for selecting eligible patients)	

Source: Compiled during the evaluation based on "Revised Section 4 Workbook.xlsx"

AIHW = Australian Institute of Health and Welfare; ATZ = atezolizumab; CSR = clinical study report; CT = computed tomography; MBS = Medical Benefits Schedule; mTNBC = metastatic triple negative breast cancer; ECOG = Eastern Cooperative Oncology Group; PD-L1 = programmed death-ligand 1; nab-P= nanoparticle albumin-bound paclitaxel; CT = computerized tomography; TBC = to be confirmed.

*Lin NU et al. Clinicopathologic features, patterns of recurrence, and survival among women with triple-negative breast cancer in the national comprehensive cancer network. *Cancer*, 2012; 118: 5463-72.

6.54 The resubmission estimated the number of incident *de novo* mTNBC and the number of patients who were diagnosed at early stage TNBC and then progress to mTNBC, respectively. The number of incident *de novo* mTNBC was based on data from IMpassion130 trial in which 25% of incident TNBC patients were diagnosed at the metastatic stage. DUSC previously considered that this estimate was reasonable (p4, 6.01. atezolizumab DUSC ADV, March 2020).

6.55 The number of recurrent mTNBC patients was estimated from the number of incident TNBC patients diagnosed at an early stage in the previous 10 years and those who developed distant recurrence over 10 years. A distant recurrence rate of 20% over 10 years was assumed in the resubmission, as suggested by DUSC (6.01 atezolizumab DUSC Advice March 2020), based on published literature (Early Breast Cancer Trialists' Collaborative 2019, Radosa 2017 and Lin 2012)¹². The 10-year survival rate of 44% for

¹² Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Increasing the dose intensity of chemotherapy by more frequent administration or sequential scheduling: a patient-level meta-analysis of 37 298 women with early breast cancer in 26 randomised trials. *Lancet* 2019; 393: 1440–52

Radosa JC et al. Evaluation of Local and Distant Recurrence Patterns in Patients with Triple-Negative Breast Cancer According to Age. *Ann Surg Oncol*. 2017; 24(3): 698–704.

TNBC patients was based on Lin 2012. Although these estimates may be reasonable, the application of these estimates in the resubmission did not appear appropriate.

- 6.56 The resubmission applied a constant distant recurrence rate (20%) and a constant survival rate (44%) to the patients diagnosed with early stage TNBC each year in the past 10 years to estimate the number of recurrent mTNBC patients in each year of the first 6 years of listing. The ESC agreed with the commentary that patients diagnosed with early stage TNBC in year 1 are unlikely to have the same distant recurrence rate or survival rate as those diagnosed in year 10 which is not captured when applying cumulative incidence data. However, the ESC considered that application of a constant distant recurrence rate and a constant survival rate was unlikely to have a major impact on the patient estimates.
- 6.57 The proposed PBS restriction for initial treatment in the resubmission included the criterion that a patient must not have received taxane (neo)adjuvant therapy in the previous 12 months to be eligible for treatment with ATZ+nab-P. To estimate the proportion of incident recurrent mTNBC patients who would meet this criterion, the resubmission conducted an online quantitative survey of 30 medical oncologists (METIS 2020). It was estimated that 64% of recurrent mTNBC patients would meet the prior taxane criterion. This value was calculated using the following inputs:
- Percentage mTNBC patients diagnosed with early stage TNBC treated with a non-taxane regimen: 16%
 - Percentage mTNBC patients diagnosed with early stage TNBC treated with a taxane-containing regimen: 84%
 - Percentage mTNBC patients treated with a taxane-containing regimen that relapse after 12 months: 57%
- 6.58 The resubmission considered that the use of all taxanes currently listed on the PBS are likely to be affected with the PBS listing of ATZ, specifically nab-P monotherapy (comparator), paclitaxel and docetaxel. The economic model presented in the resubmission did not consider paclitaxel or docetaxel as potential comparators. The previous submission only considered cost offsets resulting from substitution of nab-P in the financial estimates. DUSC previously considered a proportion of people would receive other, less costly taxanes, so the cost of substituted medicines was likely overestimated (6.01 atezolizumab DUSC Advice March 2020).
- 6.59 The resubmission assumed that patients would receive 10 doses of nab-P, 13.3 doses of paclitaxel or 4.4 doses of docetaxel. The resubmission did not provide sources for the estimated duration of treatment with paclitaxel or docetaxel (13.3 weeks). It appeared that the duration of treatment were matched to the assumed duration of

Lin NU et al. Clinicopathologic features, patterns of recurrence, and survival among women with triple-negative breast cancer in the national comprehensive cancer network. *Cancer*, 2012; 118: 5463-72.

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treatment with nab-P (10 doses, with doses administered on days 1, 8 and 15 of each 28 day cycle).

6.60 The resubmission also included the cost of re-biopsy procedures associated with the collection of tumour tissue, should adequate tissue (fresh or archival) not be available to conduct PD-L1 testing. This addressed the comment made by MSAC as part of its assessment of the original submission, that re-biopsy rates have previously been considered by MSAC to be around 8-10% (PD-L1 IHC testing, PSD April 2020 MSAC meeting). DUSC also considered that diagnostic biopsy may be repeated in 10% of patients (6.01 atezolizumab DUSC Advice March 2020). The resubmission included the costs of re-biopsy, which is reasonable. However, retesting of PD-L1 status was not considered. DUSC previously considered that the number of PD-L1 tests was underestimated as the submission did not account for retesting (6.01 atezolizumab DUSC Advice March 2020). The PSQR stated that retesting of PD-L1 status would not be clinically appropriate and retesting of the same specimen would not be eligible to attract a Medicare benefit.

6.61 The estimated use and financial implications are presented below.

Table 17: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of patients treated	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
Number of scripts dispensed - ATZ ^a	█ ²	█ ²	█ ²	█ ²	█ ²	█ ²
Number of scripts dispensed –nab-P ^b	█ ²	█ ²	█ ²	█ ²	█ ²	█ ²
Estimated financial implications of ATZ+nab-P						
Cost to PBS/RPBS less copayments	\$█ ³	\$█ ³	\$█ ⁴	\$█ ⁴	\$█ ⁴	\$█ ⁴
Estimated financial implications for taxanes						
Cost to PBS/RPBS less copayments	-\$█ ⁵	-\$█ ⁵	-\$█ ⁵	-\$█ ⁵	-\$█ ⁵	-\$█ ⁵
Net financial implications						
Net cost to PBS/RPBS	\$█ ³	\$█ ³	\$█ ³	\$█ ³	\$█ ³	\$█ ³
Net cost to MBS	\$█ ⁵	\$█ ⁵	\$█ ⁵	\$█ ⁵	\$█ ⁵	\$█ ⁵
Net cost to PBS/RPBS/MBS	\$█ ³	\$█ ³	\$█ ³	\$█ ³	\$█ ⁴	\$█ ⁴
Previous submission March 2020						
Net cost to PBS/RPBS	\$█ ³	\$█ ⁴	\$█ ⁴	\$█ ⁴	\$█ ⁴	\$█ ⁴

Source: Table 4.6, p87, Table 4.7, p88, Table 4.9, p89, Table4.15, p92, Table 4.17, p93, Table4.24, p98, Table 4.32, p105 of the resubmission and Table 19, pp39-40 of atezolizumab, Ratified PBAC PSD, March 2020 PBAC meeting.

ATZ = atezolizumab; nab-P= nanoparticle albumin–bound paclitaxel

^a Assuming █ doses per treatment course as estimated by the resubmission.

^b Assuming 10 doses per treatment course as estimated by the resubmission.

Blue shading indicates data previously seen by the PBAC.

The redacted values correspond to the following ranges:

¹500 to <5,000

²5,000 to <\$15,000

³\$10 million to <\$20 million

⁴\$20 million to <\$30 million

⁵\$0 to <\$10 million

- 6.62 The estimated net financial implications to the PBS/RPBS were \$10 million to <\$20 million in Year 1, increasing to \$10 million to <\$20 million in Year 6. The estimated overall net financial implications to the PBS/RPBS over the first 6 years of listing was \$100 million to <\$200 million.
- 6.63 The net impact on the estimated number of patients with recurrent mTNBC who were diagnosed with early stage TNBC but developed distant recurrence in the first 6 years of listing was uncertain. Therefore, the number of eligible patients may be either over- or under-estimated. Any over-estimate of the number of patients likely to be treated has implications for the proposed risk sharing arrangement, in the form of annual subsidisation caps, as discussed above.

Financial Management – Risk Sharing Arrangements

- 6.64 The resubmission stated that an EoC cap was proposed in order to achieve an ICER within the willingness to pay range for the PBS/RPBS listing of ATZ in combination with nab-P.
- 6.65 The resubmission further stated that the EoC cap was proposed to be implemented in the form of subsidisation caps. These annual subsidisation caps would be calculated by multiplying the predicted number of patients treated by the effective price of ■ ATZ doses. Any expenditure above the agreed subsidisation caps was proposed to be rebated by the sponsor at ■%. The resubmission stated that the sponsor will be willing to discuss alternate means of operationalising this risk sharing arrangement at the appropriate time.

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

7 PBAC Outcome

- 7.1 The PBAC did not recommend atezolizumab (ATZ) for the first line treatment of patients with metastatic triple-negative breast cancer (TNBC) who are PD-L1 positive. The PBAC considered that there was a high clinical need for effective treatments for these patients, but previously considered that the clinical evidence in the relevant patient population was limited and the survival benefit claimed was uncertain. The PBAC noted that the resubmission provided updated trial data, but considered the additional data did not provide confidence that atezolizumab provided the claimed overall survival benefit and use of nab-P as the comparator further added uncertainty in the claimed benefit. In addition, the PBAC noted that a confirmatory trial in a similar patient group had reported contradictory results. The PBAC noted that the incremental cost-effectiveness ratio remained high and modelled assumptions regarding overall survival were not sufficiently supported by the clinical evidence.
- 7.2 The PBAC noted that there is a high clinical need for effective treatments for patients with TNBC, where outcomes are poor and there are currently no other targeted treatments or immunotherapies available. The PBAC also noted the consumer

comments from clinicians that stated that for a subset of patients, atezolizumab has the potential to markedly improve overall survival.

- 7.3 The PBAC noted that the restriction was revised in the resubmission to specify patients must have PD-L1 of any intensity in tumour-infiltrating immune cells covering $\geq 1\%$ of the tumour area as determined by the companion diagnostic Ventana PD-L1 immunohistochemistry (IHC) SP142 assay. The PBAC considered this was appropriate and consistent with the MSAC's previous consideration of the PD-L1 testing for access to atezolizumab.
- 7.4 The PBAC previously considered that, given the current evidence, the appropriate clinical place for atezolizumab is in addition to nab-P, in patients who are PD-L1-positive, where a taxane would otherwise be used (para 7.7, atezolizumab PSD, March 2020 PBAC meeting). The PBAC acknowledged that some guidelines recommend use of ATZ+nab-P in this population. The PBAC noted that the proposed use of ATZ was revised in the resubmission to be in combination with nab-P (rather than any taxane). The PBAC considered this was appropriate given the negative outcomes of the IMpassion131 trial in which ATZ was used in combination with paclitaxel. The PBAC also considered that it was appropriate that the resubmission had revised the target population to exclude patients with locally advanced TNBC, who are not currently eligible for PBS funded treatment with nab-P. The PBAC also noted the revised restrictions specify that patients must not have received taxane (neo)adjuvant therapy in the previous 12 months. The PBAC considered that these changes were reasonable but that the resubmission did not adequately identify and define the patient population who would otherwise receive a taxane.
- 7.5 The PBAC previously considered the most appropriate comparator for this heterogeneous population (patients who have received previous taxane therapy; patients who are chemotherapy naïve, including those with *de novo* metastatic disease and patients with BRCA1/2 deleterious mutations) would be physician choice (para 7.6, atezolizumab PSD, March 2020 PBAC meeting). However, the PBAC considered that the resubmission did not adequately address the fact that nab-P is not the only treatment pathway for this population and in some patients, may be an inferior treatment choice. The PBAC noted that the submission did not present a robust analysis of the relative efficacy of nab-P versus other treatment options in this population. The PBAC noted that the evidence for ATZ was based on the IMpassion130 trial, where the comparator was nab-P. The PBAC considered that as nab-P may not be representative of physician choice in the PBS population, the extent of clinical benefit compared with physician choice is not informed by this trial.
- 7.6 The PBAC noted that the resubmission provided updated data from the final analysis (clinical cut-off date 14 April 2020) of the head-to-head trial comparing ATZ+nab-P to PBO+nab-P, IMpassion130. The PBAC noted that results were consistent with those previously considered by the PBAC, from the 2 January 2019 clinical cut-off date. The PBAC noted that ATZ+nab-P demonstrated a statistically significant benefit in prolonging PFS, compared with nab-P. However, the PBAC recalled it previously

considered that the small difference in median PFS of 2 months for the PD-L1 population was of unclear clinical significance. The OS results also remained non-significant in the ITT population (hazard ratio (HR) 0.87; 95% confidence interval (CI) 0.75, 1.02), with the hierarchical study design precluding formal statistical testing of the PD-L1 subgroup. The PD-L1-positive subgroup of IMpassion130 generated an unstratified HR of 0.69 (95% CI 0.54, 0.88) at the 14 April 2020 clinical cut-off date, with a median OS benefit of 7.5 months. These results were similar to that noted in the original submission, and while clinically relevant, were similarly uncertain. As such, the PBAC considered that the updated data did not provide additional confidence that ATZ would provide the claimed OS benefit.

- 7.7 The PBAC also noted that results were available for the head-to-head trial comparing ATZ+P to PBO+P, IMpassion131. IMpassion131 was intended to be a confirmatory trial for conversion of the provisional listing for atezolizumab and was similar in design to IMpassion130. The PBAC considered that the IMpassion131 results were relevant to the interpretation of IMpassion130 results. The PBAC noted that in the IMpassion131 trial the PBO+P demonstrated greater median OS than the ATZ+P arm (28.3 vs 22.1 months respectively) in the PD-L1-positive subgroup. The PBAC also noted that results in the comparator arms of the PD-L1-positive subgroups in IMpassion130 and IMpassion131 were not consistent, with a median OS of 17.9 months in the PBO+nab-P arm of IMpassion130 compared with 28.3 months in the PBO+P arm of IMpassion131. In contrast, the outcomes in the ATZ+nab-P and ATZ+P arms were similar in the PD-L1-positive subgroups of both trials (median OS 25.4 and 22.1 months, respectively). Further, PD-L1 expression was not observed as a positive prognostic factor in IMpassion130. Given the similarity between IMpassion130 and IMpassion131 cohorts, the PBAC considered this inconsistency raises internal validity concerns and suggests that the performance of the control arm in IMpassion130 cannot be excluded as aberrant, which increases uncertainty about the benefit of ATZ+nab-P described by IMpassion130.
- 7.8 The PBAC recalled that it had previously considered that the claim of inferior safety compared with nab-P alone was reasonable and noted that the updated IMpassion130 trial data did not change its conclusions regarding safety.
- 7.9 The PBAC noted that the model presented in the resubmission was largely unchanged compared with the previous submission, with the exception of the extrapolation of OS, the utilities applied and the assumed duration of treatment for ATZ and nab-P.
- 7.10 The PBAC noted the same parametric functions (Gamma distributions) were used for all patients in both the proposed scenario and the current scenario. The PBAC noted that gamma distributions included some flattening of the OS curve, which assumed an ongoing, durable response for some patients. However, the PBAC considered this has not been adequately demonstrated for this population. The PBAC recalled it had previously considered the Weibull function resulted in OS estimates that were more clinically plausible (para 7.15, atezolizumab PSD, March 2020 PBAC meeting). The PBAC also recalled that it had previously recommended “in the absence of a

statistically significant OS benefit (when adjusted for multiplicity), the economic model would need to be based on conservative assumptions including regarding the magnitude of any modelled OS gains” (para 7.22 atezolizumab PSD, March 2020 PBAC meeting). The PBAC noted that the updated IMpassion130 data had not provided additional confidence in the OS benefit and additionally, in the context of the IMpassion131 trial results, uncertainty regarding the treatment effect remains. The PBAC considered that the OS extrapolation functions applied in the resubmission did not adequately address the PBAC’s previous concerns and were not appropriately conservative. Further, the model relied on the majority (85%) of overall survival benefit (LYG) accrued in the extrapolated period, with substantial additional survival beyond the point of median follow-up. The PBAC noted that the model was also sensitive to convergence of the survival curves, though the choice of the timepoint for commencement of convergence (applied in sensitivity analyses) was not justified.

- 7.11 The PBAC noted that the resubmission introduced caps on the number of administrations for both ATZ and nab-P applied in the model. The PBAC noted that realisation of the ICER relied on only reimbursing ■ doses of ATZ and so cost effectiveness would only delivered through the RSA, and only where financial estimates are accurate. In the context of other concerns about the ICER resulting from the uncertain modelled OS benefit, this approach added to the uncertainty that the proposed ICER would be achieved.
- 7.12 The PBAC noted that in resubmission model the Australian-specific algorithm (Norman 2012¹³) was applied to the final EuroQol- 5 Dimension (EQ-5D) data from IMpassion130 (PFS: 0.695, Progression: 0.583). The PBAC considered that this was appropriate.
- 7.13 The PBAC noted that multivariate sensitivity analyses excluding caps on nab-P, using Weibull functions for OS extrapolations and converging the OS curves from 60 months increased the ICER to \$115,000 to <\$135,000/QALY gained where caps on ATZ were modelled and that the ICER increased to \$135,000 to <\$155,000/QALY gained without caps on the number of ATZ doses. Thus, the PBAC considered that not only was the ICER uncertain due to the OS uncertainty, it was also sensitive to alternative and realistic assumptions regarding its extrapolation.
- 7.14 The PBAC noted that the resubmission’s approach to the financial estimates was largely unchanged from the previous submission, although with updated inputs that were consistent with DUSC’s and PBAC’s previous recommendations. The PBAC considered that the financial estimates remained somewhat uncertain as the estimated number of patients with recurrent mTNBC who were diagnosed with early stage TNBC but developed distant recurrence in the first 6 years of listing was

¹³ Norman R et al. Deriving utility weights for the EQ-5D-5L using a discrete choice experiment. Working paper 2012/01. Centre for Health Economics Research and Evaluation (CHERE), University of Technology Sydney. 2012.

uncertain. Any over-estimate of the number of patients likely to be treated has implications for the proposed risk sharing arrangement.

7.15 The PBAC considered that it would be preferable that a decision is made regarding the provisional registration status prior to any resubmission and considered that any resubmission would need to address the comparator issue, the uncertainty in the OS benefit, revise the economic model as outlined in paragraph 7.10 and 7.11 without reliance on the RSA for cost-effectiveness.

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

Outcome:

Rejected

8 Context for Decision

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

9 Sponsor's Comment

Roche is disappointed with the outcome of this submission. We remain committed to Australian triple negative breast cancer patients and will continue to seek innovative therapeutic developments in this area of clinically unmet need.