

6.01 ATEZOLIZUMAB

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

1 Purpose of submission

- 1.1 The submission requested Section 100 – Efficient Funding of Chemotherapy (Streamlined) listing for atezolizumab in combination with taxane chemotherapy as first-line treatment for patients with unresectable locally advanced or metastatic triple-negative breast cancer (TNBC) whose condition expresses programmed death ligand 1 (PD-L1) of any intensity in tumour-infiltrating immune cells covering $\geq 1\%$ of the tumour area. Medicare Benefits Schedule (MBS) listing of immunohistochemistry (IHC) testing for evaluation of PD-L1 expression, to determine eligibility for treatment with atezolizumab was also requested.
- 1.2 Listing was requested on the basis of a cost-effectiveness analysis versus nanoparticle albumin-bound paclitaxel (nab-P).

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

Component	Description
Population	Patients with unresectable locally advanced or metastatic TNBC that has not been previously treated in the unresectable locally advanced or metastatic setting and who are PD-L1 positive on tumour-infiltrating immune cells ($\geq 1\%$ on IC)
Intervention	Test: IHC testing of PD-L1 on tumour-infiltrating immune cells Medicine: Atezolizumab in combination with taxane chemotherapy
Comparator	No test and treatment with nab-P
Outcomes	Overall survival Progression-free survival Safety Quality of life as measured by GHS/HRQoL, EQLQ-C30 and QLQ-BR23 breast module and EQ-5D-5L
Clinical claim	Atezolizumab in combination with taxane chemotherapy is superior in effectiveness and inferior, but clinically manageable, in safety compared with nab-paclitaxel alone in patients with unresectable locally advanced or metastatic TNBC 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)

TNBC = triple-negative breast cancer; PD-L1 = programmed death-ligand 1; IC = tumour-infiltrating immune cells; IHC = immunohistochemistry; nab-P = nanoparticle albumin bound paclitaxel; EQLQ-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; QLQ = quality of life questionnaire.

Source: Table 1.1.1, p 21 of the MSAC_PBAC Combined 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 paclitaxel protein-bound, 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 OS data) and data from the IMpassion131 trial.'
- 2.3 The provisional approval was based on IMpassion130 data from the 17 April 2018 data cut-off (while the current submission has provided data from the second interim analysis data cut-off of 2 January 2019). The Delegate's Overview stated 'there is a large amount of uncertainty in the evidence for this application. The main uncertainty relates to the limited supportive OS data in the ITT population, which impacts on the analysis of the PD-L1 subgroup, on which the proposed indication is based'. The Delegate noted that the available OS data were immature, and the PFS data were 'promising but not definitive'. In addition, the proportion of *de novo* metastatic TNBC in IMpassion130 was considered to be high compared with the expected Australian proportion of approximately 10%, which the Delegate considered to be relevant as patients who had prior (neo)adjuvant treatment may be less likely to respond to immune therapy than patients who have had no prior treatment. There was also uncertainty regarding the possible effect of anti-drug antibodies, and the safety profile, both of which the TGA will need additional data for analysis.
- 2.4 The atezolizumab TGA approval letter states that as part of the provisional registration, the following study reports should be submitted to the TGA:
 - IMpassion130 (expected to be available Q4 2020); and
 - IMpassion131 (expected to be available Q2 2020).
- 2.5 IMpassion131 is a phase 3, randomised controlled trial of atezolizumab plus paclitaxel compared with placebo plus paclitaxel for patients with previously untreated unresectable locally advanced or metastatic TNBC. The Delegate's Overview stated that the study design (including the inclusion criteria) appears similar to IMpassion130 overall but that paclitaxel will be used instead of nab-paclitaxel. The IMpassion131 clinical cut-off date for the final PFS analysis and interim OS analysis is estimated to be reached by Q1 2020 with results expected to be available in Q2 2020.

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

3 Requested listing

3.1 The requested listing is presented below. Suggestions and additions proposed by the Secretariat are added in italics and suggested deletions are crossed out with strikethrough.

Name, Restriction, Manner of administration and form	Max. Amt	No. of Rpts	Dispensed Price for 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 ^a \$5,318.47 (public) \$5,431.50 (private) Effective price ^a \$ [REDACTED] (public) \$ [REDACTED] (private)	TECENTRIQ® Roche Products Pty Ltd

Category / Program:	Section 100 – Efficient Funding of Chemotherapy (Private/Public Hospital code)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Restriction Level / Method:	<input type="checkbox"/> Unrestricted benefit <input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required – In Writing <input type="checkbox"/> Authority Required – Telephone/Electronic/Emergency <input checked="" type="checkbox"/> Authority Required - Streamlined
Severity:	Unresectable locally advanced or metastatic
Condition:	triple-negative breast cancer (<i>delete hyphen</i>)
Indication:	Unresectable locally advanced or metastatic triple-negative breast cancer
Treatment Phase:	Initial treatment
Clinical criteria:	The condition must be triple-negative breast cancer, The condition must be hormone receptor (estrogen 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 unresectable locally advanced or metastatic setting, AND Patient must have an Eastern Cooperative Oncology Group (ECOG) performance status of 1 or less, Patient must have a WHO performance status of 0 or 1. AND The treatment must only be initiated in combination with nanoparticle albumin-bound paclitaxel (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 therapy in the previous 12 months.
Caution:	<i>In the first few months after start of immunotherapy, some patients can have a transient tumour flare with subsequent disease response. When progression is suspected, this should be confirmed through a confirmatory scan, taken at least 4 weeks later.</i>
Administrative Advice:	Special Pricing Arrangements apply.

Category / Program:	Section 100 – Efficient Funding of Chemotherapy (Public/Private hospital codes)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Restriction Level / Method:	<input type="checkbox"/> Unrestricted benefit <input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required – In Writing

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	<input type="checkbox"/> Authority Required – Telephone/Electronic/Emergency <input checked="" type="checkbox"/> Authority Required - Streamlined
Severity:	Unresectable locally advanced or metastatic
Condition:	triple-negative breast cancer (<i>delete hyphen</i>)
Indication:	Unresectable locally advanced or metastatic triple-negative breast cancer
Treatment Phase:	Continuing treatment
Clinical criteria:	Patient must have previously been issued with an authority prescription for this drug for this condition, <i>Patient must have previously received PBS-subsidised treatment with this drug for this condition.</i> AND Patient must not have developed disease progression while being treated with this drug for this condition
Administrative Advice:	Special Pricing Arrangements apply.

Category / Program:	Section 100 – Efficient Funding of Chemotherapy (Private/Public hospital codes)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Restriction Level / Method:	<input type="checkbox"/> Unrestricted benefit <input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required – In Writing <input type="checkbox"/> Authority Required – Telephone/Electronic/Emergency <input checked="" type="checkbox"/> Authority Required - Streamlined
Severity:	Unresectable locally advanced or metastatic
Condition:	triple-negative breast cancer (<i>delete hyphen</i>)
Indication:	Unresectable locally advanced or metastatic triple-negative breast cancer
Treatment Phase:	Grandfathering treatment (<i>initial treatment of a patient commenced on non-PBS-subsidised treatment</i>)
Clinical criteria:	The condition must be triple negative breast cancer, <i>The condition must be hormone receptor (estrogen and progesterone receptor) negative</i> AND <i>The condition must be human epidermal growth factor receptor 2 (HER2) negative</i> AND Patient must have received treatment with this drug for this condition prior to the [PBS listing date] AND Patient must not receive more than 24 weeks of treatment under this restriction AND Patient must have had a WHO performance status of 0 or 1 prior to initiation of non-PBS subsidised treatment with this drug for this condition. AND The treatment must have been initiated in combination with nanoparticle albumin-bound paclitaxel (nab-paclitaxel) AND Patient must not have received taxane therapy in the 12 months prior to commencing non-PBS subsidised treatment with this drug for this condition 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 developed disease progression while being treated with this drug for this condition.
Administrative Advice:	Patients may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a 'Grandfathered' patient must qualify under the 'Continuing treatment' criteria. <i>This grandfathering restriction will cease to operate from [insert date 12 months from listing date here].</i> Special Pricing Arrangements apply.

^a Dispensed price for maximum amount (DPMA) includes Section 100 Highly Specialised Drugs fees and mark-ups of \$85.06 (public hospital), \$198 (private hospital – published price) and \$█ (private hospital – effective price).

3.2 The submission proposed a special pricing arrangement (SPA). The effective price for atezolizumab is based on a █% discount on the ex-manufacturer price. In the pre-PBAC response, the sponsor proposed an increased discount in the ex-

manufacturer price (■%) as a rebate based on an SPA reducing the effective ex-manufacturer price from \$■ to \$■.

- 3.3 The proposed intervention of “atezolizumab in combination with taxane chemotherapy” is broader than the intervention in the key IMpassion130 trial and that approved by the TGA for the proposed indication, which are atezolizumab in combination with one specific taxane, nab-P. The ESCs considered that the submission’s approach of broadening the restriction to include any taxane may be appropriate in order to provide greater flexibility for clinicians and because nab-P may be inferior to paclitaxel (see also paragraph 5.2). Further, the ESCs noted that nab-P is not PBS-listed for locally advanced TNBC (it is only approved for metastatic or HER2-positive breast cancer). The PBAC noted that no evidence for combination use with taxanes other than nab-P was presented in the submission and considered that the listing should be limited to treatment in combination with nab-P.
- 3.4 The ESCs noted that, while the currently available trial evidence is for use of atezolizumab in combination with nab-paclitaxel only, an upcoming trial is assessing atezolizumab in combination with paclitaxel in the target population (IMpassion131). The PBAC considered that data from the IMpassion131 trial may provide support for the broader listing requested.

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

4 Population and disease

- 4.1 TNBC (hormone 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, short progression-free survival (PFS) and short overall survival (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.
- 4.2 The target population includes unresectable locally advanced, recurrent and *de novo* metastatic TNBC. These patients present a heterogeneous group of malignancies that differ in natural history and response to treatment, and currently there is no one standard of care chemotherapy regimen. The ESCs noted that while it may have been better to consider each of these populations separately, the evidence available is limited and does not lend itself to further subgroup analysis.
- 4.3 Atezolizumab, a PD-L1 inhibitor, in combination with taxane chemotherapy, was proposed to be a first-line treatment of patients with unresectable locally advanced or metastatic TNBC whose tumours are PD-L1 positive.

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

5 Comparator

- 5.1 The submission nominated nab-P as the main comparator. The main argument provided in support of the nomination of nab-P as the main comparator was a sponsor-commissioned METIS survey¹ of 30 medical oncologists. The ESCs noted that the METIS data showed that the majority (58-65%) of Australian metastatic TNBC patients do not receive nab-P as first-line treatment for metastatic TNBC.

Choice of taxane

- 5.2 The ESCs noted the commentary stated that nab-P may be clinically preferable to other taxanes because it is solvent-free and does not require premedication with corticosteroids, making it more suitable for combination immunotherapy. However, the ESCs considered that while this is a theoretical advantage, other taxanes are recommended in practice instead of nab-P, largely because of concerns about toxicity (peripheral neuropathy) and higher cost. Furthermore, Rugo et al (2015)² suggests that nab-P (150 mg/m²) may be less effective than paclitaxel (90 mg/m²). The ESCs considered that Rugo et al provided more robust evidence than the retrospective observational analysis presented in the submission, and suggested that nab-P may be inferior to paclitaxel. The ESCs therefore considered that the nominated main comparator, nab-P, may not be representative of the effectiveness of treatment with any taxane as assumed in the submission.

Patients who have received prior taxane therapy

- 5.3 While the METIS data shows that nab-P was the most common first-line treatment for metastatic TNBC in patients regardless of whether they received prior anthracycline therapy, it may not be appropriate for those who had received prior taxane therapy. International guidelines (ASCO³, AGO⁴, NCCN⁵ and ESMO⁶) recommend avoiding re-challenging with a failed chemotherapy agent in the first-line metastatic TNBC setting. As such, patients who received previous taxane therapy in the (neo)adjuvant setting should not receive it again as first-line treatment in the metastatic setting. It should

¹ METIS Healthcare Research. Tecentriq in TNBC: Quantitative Marketing Research Report 2019.

² 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

³ Partridge AH, Rumble RB, Carey LA, Come SE, Davidson NE, Di Leo A, et al. Chemotherapy and targeted therapy for women with human epidermal growth factor receptor 2-negative (or unknown) advanced breast cancer: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol. 2014 Oct 10;32(29):3307-29.

⁴ Arbeitsgemeinschaft Gynäkologische Onkologie. Diagnosis and Treatment of Patients with early and advanced Breast Cancer 2019 (https://www.ago-online.de/fileadmin/downloads/leitlinien/mamma/2019-03/EN/Updated_Guidelines_2019.pdf).

⁵ National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Breast Cancer.2019 Contract No.: Version 3.2019 - September 6, 2019.

⁶ Cardoso F, Senkus E, Costa A, Papadopoulos E, Aapro M, Andre F, et al. 4th ESO-ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC 4)dagger. Ann Oncol. 2018 Aug 1;29(8):1634-57.

be noted that ESMO guidelines additionally state that, if given in the adjuvant setting, the preferred single-agent therapies are capecitabine or vinorelbine or eribulin, however a taxane and anthracycline may be re-used as first-line therapy in the advanced TNBC setting, particularly if there has been at least one year of disease-free survival. The ESCs noted that the majority of Australian TNBC patients who relapse will do so after receiving an anthracycline and taxane combination regimen. The ESCs reiterated that taxane therapy would not generally represent the preferred first-line therapy for patients who had progressed after prior taxane-based therapy⁷.

Treatment-naïve patients

- 5.4 The ESCs noted that *de novo* metastatic TNBC patients accounted for 25% of the ITT population in the key trial. These patients would be treatment naïve; patients who have not received prior anthracycline therapy are likely to receive an anthracycline-containing regimen in the first-line metastatic TNBC setting.
- 5.5 In patients who have *de novo* (treatment-naïve) locally advanced, non-inflammatory, unresectable TNBC, guidelines recommend neoadjuvant chemotherapy with a goal of rendering the tumour resectable and potentially achieving a pathological complete response⁸. Nab-P is not PBS listed for this population. The Pre-Sub-Committee Response (PSCR) stated this patient group is estimated to represent <10% of the total population.
- 5.6 The commentary considered that, for patients with advanced breast cancer who have had little or no previous exposure to chemotherapy and few comorbidities, Australian guidelines recommend combination chemotherapy, reserving sequential single-agent chemotherapy (such as nab-P alone) for patients with previous exposure to chemotherapy or significant co-morbidities (e.g. ECOG >1)⁹. As such, treating chemotherapy-naïve, ECOG <2 patients with nab-P monotherapy represents an inferior treatment strategy. The PSCR noted that, for metastatic disease, combination chemotherapy did not confer any survival benefit over single agent therapy¹⁰ and was not unequivocally recommended. The ESCs considered that combination chemotherapy may still be used in some circumstances, including in non-metastatic disease. As outlined above, the ESCs considered that anthracycline-based regimens are generally the preferred treatment for *de novo* metastatic disease.

⁷ Cardoso et al 2018. 4th ESO-ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC 4). Annals of Oncology 29: 1634-1657

⁸ National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Breast Cancer.2019 Contract No.: Version 3.2019 - September 6, 2019.

⁹ National Breast and Ovarian Cancer Centre. Recommendations For Use Of Chemotherapy for the treatment of advanced breast cancer, 2010.

¹⁰ Zeichner et al (2016), Zeichner SB, Terawaki H, Gogineni K. A review of systemic treatment in metastatic triple-negative breast cancer. Breast Cancer (Auckl) 2016;10:25–36.

Patients with BRCA1/2 deleterious mutations

- 5.7 For patients with BRCA1/2 deleterious mutations, all updated international guidelines (AGO, ESMO, NCCN) recommend platinum-containing chemotherapy regimens if not previously administered. As such, taxane monotherapy may represent an inappropriate comparator in this patient population. There is an ongoing phase III clinical trial, IMpassion132 [NCT03371017] exploring the role of atezolizumab in combination with platinum-containing regimens, with estimated primary completion date 1st January, 2023. The PSCR stated BRCA-mutated patients are expected to represent <10% of the proposed PBS population.

Overall

- 5.8 This heterogeneous population requires treatments tailored to patient characteristics and treatment history. The most appropriate comparator would be the therapy deemed most appropriate by physician choice. This would be consistent with the MSAC PICO Advisory Sub-Committee, which nominated the appropriate comparator as standard of care.
- 5.9 The ESCs agreed with the commentary that 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, including those with *de novo* metastatic disease or some patients with previously untreated locally advanced disease; and
 - patients with BRCA1/2 deleterious mutations.
- 5.10 As such, the ESCs agreed with the commentary that the most appropriate comparator for this heterogeneous population would be physician choice. The ESCs considered that nab-P is not the current choice of first-line treatment in up to 90% of the patients in the comparator arm of the IMpassion130 trial and is likely to be an inferior treatment for the majority of these patients and therefore the treatment effect of ATZ+nab-P is likely to be overestimated relative to current clinical practice.

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

6 Overview of the evidence base

Sponsor hearing

- 6.1 There was no hearing for this item.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from health care professionals (10) 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 and there are currently no other targeted treatments or immunotherapies available. 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 overall survival in patients with PD-L1-positive metastatic TNBC.

- 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. BCNA noted the results of the IMpassion130 trial and reported that additional months of PFS and OS are highly valued by patients and that patients are well-placed to weigh potential benefits of treatment against possible adverse events associated with treatment.
- 6.4 The Medical Oncology Group of Australia (MOGA) also expressed its strong support for the atezolizumab submission, categorising it as one of the therapies of “highest priority for PBS listing” on the basis of the IMpassion130 trial. The PBAC noted that the MOGA presented a European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for atezolizumab + nab-P compared to nab-P alone. MOGA claimed a score limited to 4 (out of a maximum of 5, where 5 and 4 represent the grades with substantial improvement)¹¹, however this score was based on a subgroup analysis of PD-L1 positive patients despite failure of the OS endpoint for the entire cohort to reach statistical significance.

Clinical trials

- 6.5 The approach taken in the submission was to present direct evidence of the effect of targeting the PD-L1-positive patients (IC \geq 1%) with atezolizumab in combination with nab-paclitaxel (ATZ+nab-P).

¹¹ Cherny NI, Dafni U, Bogaerts J, et al: ESMO-Magnitude of Clinical Benefit Scale version 1.1. *Annals of Oncology* 28:2340-2366, 2017

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Table 2: Direct evidence provided in the submission to support the use of the co-dependent technology

Study design	Extent of evidence supplied	Overall risk of bias in clinical trials
Prospective biomarker (PD-L1 expression) stratified randomised controlled trial of ATZ+nab-P versus nab-P ^a	☒ k=1 n=902	Low

^a Population with and without the biomarker randomised to medicine or usual care.

Source: Table .2.1, pp 59-60 of the submission

6.6 Details of the trial presented in the submission are provided in the table below. The ESCs and PBAC also noted the results of the Phase 3 IMpassion131 (scheduled primary completion date January 2020) which compares atezolizumab + paclitaxel to placebo + paclitaxel may also be informative in assessing the efficacy of atezolizumab in combination with a taxane.

Table 3: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
IMpassion130	Primary Clinical Study Report (CSR) – Study W029522, (IMpassion130). A phase III, multicenter, 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. 1085705, August 2018.	Primary and updated CSR for Study W029522, as presented with the submission.
	Updated CSR – Study W029522, (IMpassion130). A phase III, multicenter, 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. Second Interim Analysis of Overall Survival. Report No. 1092074, February 2019.	
	Schmid P, Adams S, et al. Atezolizumab and nab-paclitaxel in advanced triple-negative breast cancer.	New England Journal of Medicine. 2018; 379(22):2108-21.
	Emens L, Adams S, et al. IMpassion130: Phase III trial comparing 1L atezolizumab with nab-paclitaxel versus placebo with nab-paclitaxel in treatment-naïve patients with mTNBC.	Annals of Oncology. 2016;27:ix40
	Emens L, Adams S, et al. IMpassion130: A Phase III randomized trial of atezolizumab with nab-paclitaxel for first-line treatment of patients with metastatic triple-negative breast cancer (mTNBC).	Journal of Clinical Oncology. 2016;34, 15_suppl.
	Emens L, Adams S, et al. A phase III randomized trial of atezolizumab in combination with nab-paclitaxel as first line therapy for patients with metastatic triple-negative breast cancer (mTNBC).	Cancer Research. 2016;76(4 Supple): Abstract nr OT1-01-06.
	Schmid, Adams S, et al. IMpassion130: updated overall survival (OS) from a global, randomized, double-blind, placebo-controlled, Phase III study of atezolizumab (atezo) + nab-paclitaxel (nP) in previously untreated locally advanced or metastatic triple-negative breast cancer (mTNBC).	Journal of Clinical Oncology 37, 2019 (suppl; abstr 1003).
Schneeweiss A, Rugo HS, et al. IMpassion130: Expanded safety analysis from a P3 study of atezolizumab (A) + nab-paclitaxel (nP) in patients (pts) with treatment (tx)-naïve, locally advanced or metastatic triple-negative breast cancer (mTNBC).	Journal of Clinical Oncology 37, 2019 (suppl; abstr 1068).	

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Trial ID	Protocol title/ Publication title	Publication citation
	Adams S, Dieras V, et al. Patient-reported outcomes (PROs) from the phase III IMpassion130 trial of atezolizumab (atezo) plus nabpaclitaxel (nP) in metastatic triple-negative breast cancer (mTNBC). Clinical trial registry entry: NCT02425891 (Phase III)	Journal of Clinical Oncology 37, 2019 (suppl; abstr 1067). https://clinicaltrials.gov/show/nc t02425891 . 2015.

Source: Table .2.1, pp 59-60 of the submission.

6.7 The key features of the included evidence are summarised in the table below

Table 4: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
ATZ+nab-P versus PBO+nab-P						
IMpassion130	902 (ITT) 369 (PD-L1+ subgroup)	R, DB 18 mths ^a	Low	Unresectable locally advanced or metastatic TNBC	OS, PFS	Used

^a Median follow-up duration at second interim analysis (2 January 2019)

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.

Source: Sections 2.3 and 2.4 of the submission.

6.8 As nab-P monotherapy was the guideline-recommended first-line treatment in as few as 10.2% of the ITT population (prior anthracycline, taxane-naïve patients, as shown in Table 5 below) in the key trial means that the majority of the ITT comparator population may have received treatment inferior to standard of care. This limits the applicability of the trial to the Australian PBS population and over-estimates the likely treatment effect of ATZ+nab-P.

Table 5: Distribution of previous therapies in the key trial IMpassion130 ITT population

	Prior anthracycline therapy (%ITT)	No prior anthracycline therapy (%ITT)
Prior taxane therapy	393 (43.6%)	68 (7.5%)
No prior taxane therapy	92 (10.2%)	149 (16.5%)

ITT = Intention-to-treat population, N=902.

Source: Supplemental data provided by request from the sponsor.

6.9 Three stratification factors for randomisation were presence of liver metastases at baseline (yes versus no), prior taxane treatment (yes versus no), and PD-L1-positive status defined as PD-L1 stained tumour-infiltrating immune cells covering $\geq 1\%$ of the tumour area (yes versus no). Subgroup analyses by PD-L1 status were also prespecified.

6.10 The submission stated that treatment comparisons were based on the two-sided, stratified log-rank test at the 0.05 significance level split between progression-free survival (PFS) (0.01) and overall survival (OS) (0.04), with hierarchical testing to adjust for multiple statistical testing for PFS and OS, first in the intention-to-treat (ITT) and then in the PD-L1-positive populations. The OS results for the PD-L1-positive subgroups should therefore be interpreted with caution as the statistical analysis plan

specified that, in order to control for Type 1 error, this subgroup analysis would only be performed if the results in the ITT population were statistically significant.

- 6.11 The ESCs noted that there was a protocol amendment that doubled the allowable time for withholding treatment (from 42 days to 84 days) before discontinuation and noted that it was unclear how this may have impacted on the reported reasons for discontinuation and disease progression rates.

Comparative effectiveness

- 6.12 The PFS and OS observed from IMpassion130 (ITT population), at the most recent data cut-off (2 January 2019), are presented in the table below. ATZ+nab-P demonstrated a statistically significant benefit in prolonging PFS, compared with nab-P. However, the benefit is modest with a median PFS difference of less than 2 months. No statistically significant difference was observed in terms of OS between the comparative treatments.

Table 6: Summary of survival outcomes from IMpassion130 in the ITT population (data cut-off 2 January 2019)

	ATZ+nab-P	PBO+nab-P	Absolute difference	HR (95% CI)
Progression-free survival (PFS)*				
Progressed, n/N (%)	379/451 (84%)	404/451 (89.6%)		
Median PFS, months (95% CI)	7.16 (5.55, 7.43)	5.49 (5.32, 5.62)	1.67	0.80 (0.69, 0.92)
% not progressed at 12 months (95% CI)	24.73% (20.60, 28.86)	18.67% (14.97, 22.37)	6.06%	-
% not progressed at 24 months (95% CI)	10.22% (6.96, 13.48)	6.41% (3.79, 9.02)	3.81%	-
Overall survival (OS)				
Deaths, n/N (%)	255/451 (56.5%)	279/451 (61.9%)		
Median months OS (95% CI)	20.99 (19.02, 22.60)	18.73 (16.85, 20.30)	2.26	0.86 (0.72, 1.02)
% alive at 12 months (95% CI)	72.12% (67.91, 76.33)	68.05% (63.68, 72.43)	4.07%	-
% alive at 24 months (95% CI)	42.35% (37.29%, 47.42%)	38.67% (33.74%, 43.60%)	3.68%	-

Bold indicates statistically significant results.

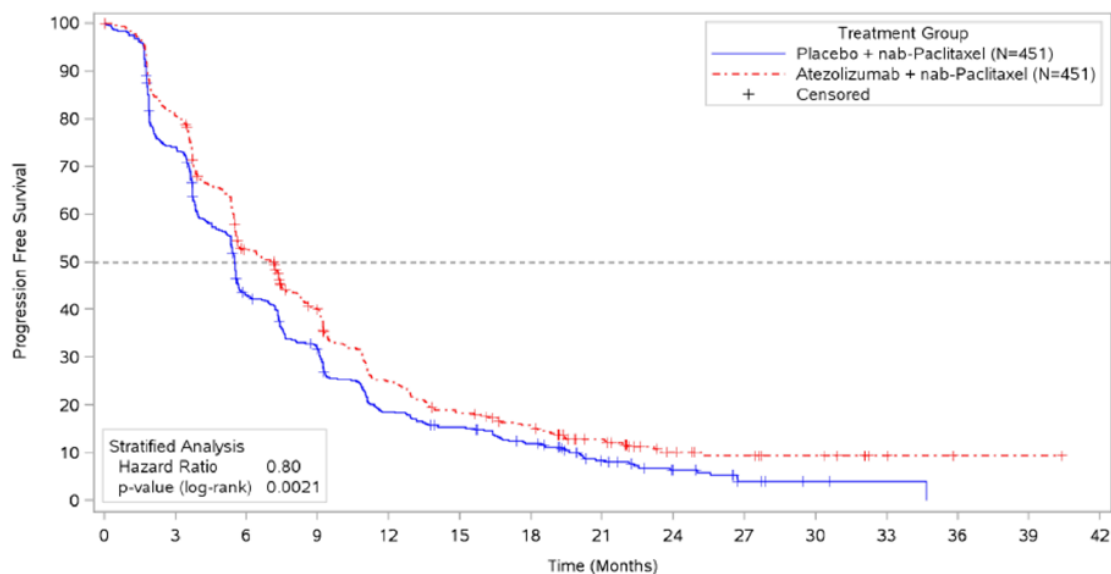
*investigator assessed progression-free survival

ATZ+nab-P = atezolizumab + nab-paclitaxel; INV = Investigator-assessed; ITT = Intention-to-treat population; PBO+nab-P = placebo + nab-paclitaxel; CI = confidence interval; N = total number of participants in the group; n = number of participants reporting data.

Source: Table 2.5.1, p80 and Table 2.5.3, p84 of the submission.

- 6.13 The Kaplan-Meier plots of PFS and OS in the ITT population are presented below.

Figure 1: Kaplan-Meier plot of investigator-assessed progression-free survival in the ITT population in IMpassion130 (data cut-off 2 January 2019)



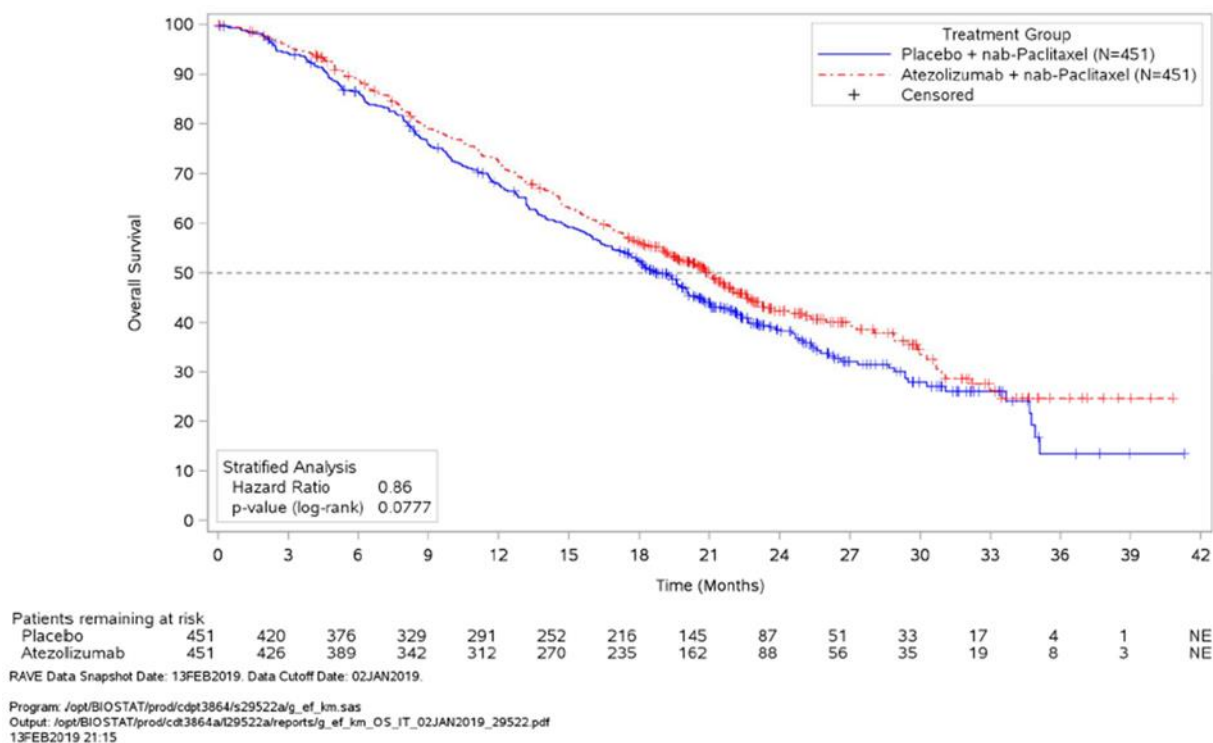
Patients remaining at risk		0	3	6	9	12	15	18	21	24	27	30	33	36	39	42
Placebo	451	329	186	134	78	62	46	24	13	5	2	1	NE	NE	NE	
Atezolizumab	451	361	227	165	100	73	58	37	17	11	8	3	1	1	1	NE

RAVE Data Snapshot Date: 13FEB2019. Data Cutoff Date: 02JAN2019.

Program: /opt/BIOSTAT/prod/cdpt3864/s29522a/g_ef_km.sas
Output: /opt/BIOSTAT/prod/cdpt3864a/l29522a/reports/g_ef_km_PFS_INV_IT_02JAN2019_29522.pdf
13FEB2019 21:13

ITT = intention-to-treat; N = total participants in group.
Source: Figure 2.5.1, p 81 of the submission.

Figure 2: Kaplan-Meier plot of overall survival in the ITT population in Impassion130 (data cut-off 2 January 2019)



ITT = intention-to-treat; NE = not evaluable.

Source: Figure 2.5.3, p85 of the submission.

6.14 The summary of survival outcomes from the PD-L1-positive and PD-L1-negative subgroups is presented below.

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Table 7: Summary of survival outcomes from IMpassion130 in the PD-L1-positive or PD-L1-negative population (data cut-off 2 January 2019)

	ATZ+nab-P	PBO+nab-P	Absolute difference	HR (95% CI)
PD-L1-positive population				
Progression-free survival (PFS)^a				
Progressed, n/N (%)	149/185 (80.5%)	163/184 (88.6%)		
Median PFS, months (95% CI)	7.46 (6.70, 9.23)	5.29 (3.81, 5.55)	2.17	0.63 (0.50, 0.80)
% not progressed at 12 months (95% CI) ^b	30.31% (23.47%, 37.15%)	17.32% (11.71%, 22.93%)	12.99%	
Overall survival (OS)				
Deaths, n/N (%)	94 (50.8%)	110 (59.8%)		
Median months OS (95% CI)	25.03 (19.55, 30.65)	17.97 (13.63, 20.07)	7.06	0.71 (0.54, 0.93) ^e
% alive at 24 months (95% CI) ^c	50.70% (42.89, 58.52)	36.90% (28.96, 44.85)	13.8%	
PD-L1-negative population^d				
Progression-free survival (PFS)^f				
Progressed, n/N (%)	241/266 (90.3%)	230/267 (86.5%)		
Median PFS, months (95% CI)	5.59 (5.39, 7.26)	5.59 (5.45, 7.26)	0	0.93 (0.77, 1.11)
% not progressed at 12 months (95% CI)	19.55% (14.65%, 24.45%)	20.82% (15.74%, 25.91%)	-1.17%	
Overall survival (OS)				
Deaths, n/N (%)	161 (60.5%)	169 (63.3%)		
Median months OS (95% CI)	19.65 (16.26, 21.62)	19.61 (16.85, 22.18)	0.04	0.97 (0.78, 1.20)

^a Investigator-assessed PFS

^b Two-year duration not provided by the CSR or submission.

^c One-year duration not provided by the CSR or submission.

^d No landmark analyses were provided for the PD-L1-negative population. Some raw PFS data was presented in the 'Economic Evaluation.xlsx' file with the submission, but was inadequate in this form, and did not specify which clinical cut-off date it represented.

^e 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.

^f Provided in the PSCR.

Statistically significant relative risks are bolded.

ATZ+nab-P = atezolizumab + nab-paclitaxel; PBO+nab-P = placebo + nab-paclitaxel

Source: Table 11, p 23 + Table 12, p 25 of the CSR for IMpassion130Feb2019 and Table 23, p 114 + Table 25, p 117 of the CSR for IMpassion130Aug2018, Table 7 of the PSCR.

6.15 ATZ+nab-P demonstrated a statistically significant benefit in prolonging PFS, compared with nab-P, in the PD-L1-positive subgroup. However, the benefit is modest with a median PFS difference of a little over 2 months. The ESCs considered that the difference in PFS was small and may not be clinically meaningful, particularly in the absence of any statistically significant difference in OS in the ITT population.

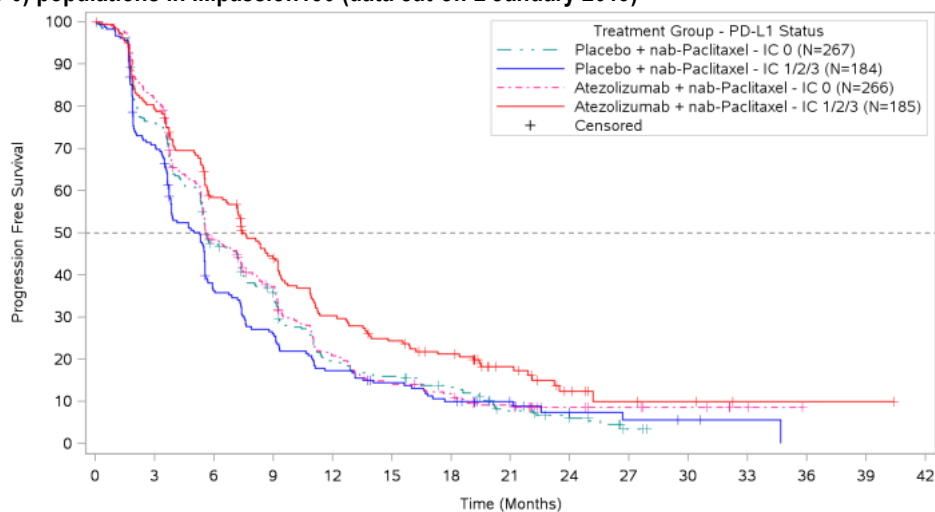
6.16 The submission claimed that a clinically meaningful improvement in OS was observed in the PD-L1-positive population. The commentary considered that differences in OS data in the PD-L1-positive subgroup should be interpreted with caution as the statistical analysis plan specified that in order to control for type 1 error, this subgroup analysis would only be performed if the results of the ITT population were statistically significant. The ESCs considered that it was not appropriate to conduct statistical analyses on this endpoint, as there was no difference in OS demonstrated for the ITT population (per the statistical analysis plan). As such, the ESCs considered that the OS

results for the PD-L1-positive subgroup should be interpreted with caution and should not be used to support any superiority claim.

6.17 The ESCs noted that, in the PBO+nab-P arms, PD-L1-negative patients had better PFS and OS than patients in the PD-L1-positive groups (19.6 versus 18.0 months median OS, respectively). The ESCs noted that this was in contrast to other studies which have found PD-L1 positivity to be a positive prognostic biomarker. As noted in the ‘Claim of co-dependence’, it is possible that the PD-L1-positive patients enrolled in the IMpassion130 trial have an unfavourable prognosis compared to those who are PD-L1 negative. However this may also indicate a difference in the response to nab-P (with PD-L1-positive patients having a worse response to nab-P compared with PD-L1-negative patients). There is no biologically plausible rationale to suggest that PD-L1 status predicts treatment effect variation with nab-P, but this difference contributes to the variation in hazard ratios across the two arms in the IMpassion130 trial, and thus to the related tests for interaction.

6.18 The Kaplan-Meier plots of PFS and OS in the PD-L1-positive population, and OS in the PD-L1-negative population are presented below.

Figure 3: Kaplan-Meier plot of investigator-assessed progression-free survival in the PD-L1-positive (IC 1/2/3) and PD-L1-negative (IC 0) populations in IMpassion130 (data cut-off 2 January 2019)

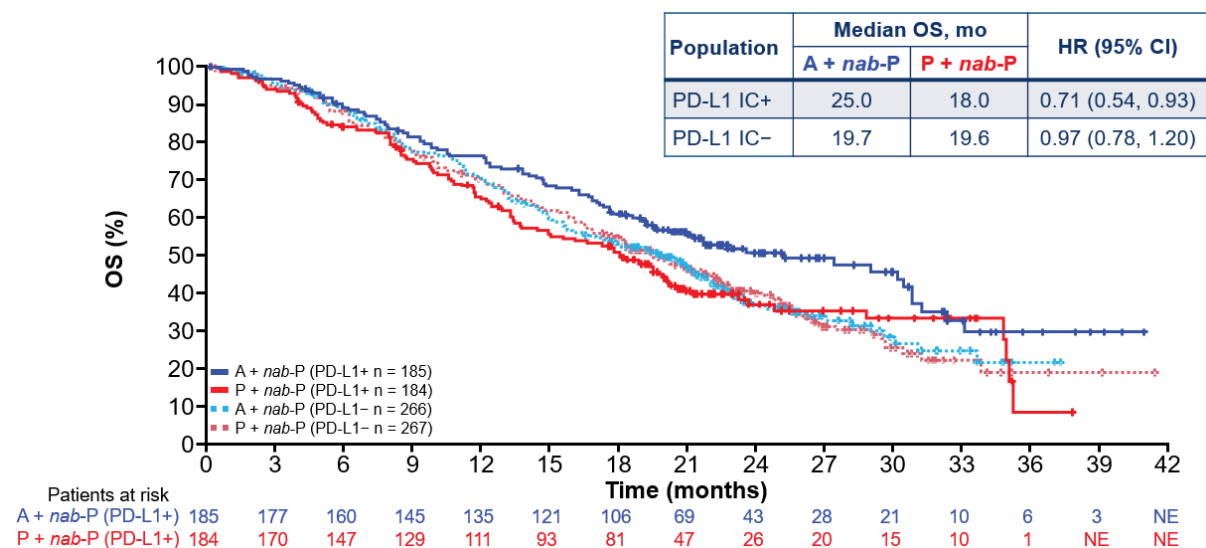


Placebo - IC 0	267	201	123	89	48	39	30	15	9	2	NE	NE	NE	NE	NE
Placebo - IC 1/2/3	184	128	63	45	30	23	16	9	4	3	2	1	NE	NE	NE
Atezolizumab - IC 0	266	215	123	90	49	33	26	18	9	7	5	2	NE	NE	NE
Atezolizumab - IC 1/2/3	185	146	104	75	51	40	32	19	8	4	3	1	1	1	NE

N = total participants in group; PD-L1 = programmed death-ligand 1.

Source: Figure 2 of the PSCR.

Figure 4: Kaplan-Meier plot of overall survival in the PD-L1-positive and PD-L1-negative populations in IMpassion130 (data cut-off 2 January 2019)



Note: patient at risk data for the A + nab-P and P + nab-P in the PD-L1- groups were not provided.

A = atezolizumab; CI = confidence interval; HR = hazard ratio; mo = months; N = total participants in group; nab-P = nab-paclitaxel; OS = overall survival; P = placebo; PD-L1 IC+ = programmed death-ligand 1 immune cell positive; PD-L1 IC- = programmed death-ligand 1 immune cell negative

Source: Slides 8 and 9 from Schmid (2019)¹² Two quality of life (QoL) measures (European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 + European Quality of Life 5 Dimensions, 5 Level) were recorded throughout the key trial but failed to demonstrate a significant difference in QoL between patients in the ATZ+nab-P arm compared to the PBO+nab-P arm.

6.19 The ESCs noted that subgroup analyses by prior treatment found that ATZ+nab-P did not demonstrate a statistically significant benefit in OS compared with nab-P in those patients who had received prior anthracycline/taxane combination therapy in both the ITT and PD-L1-positive subgroups.

6.20 The ESCs also noted that the PSCR provided a likelihood-ratio test for interaction with treatment effect for prior taxane treatment on the OS endpoint, with no interaction found ($p=0.3254$) for the ITT population. The ESCs noted that, when this was performed on the PD-L1-positive population, it yielded a statistically significant result (ratio of hazard ratios 1.92, 95% CI 1.095, 3.368, $p=0.03$). This suggests that, in PD-L1-positive patients, the treatment effect (in terms of HR) of ATZ+nab-P compared with nab-P for those who had not received prior taxane treatment was greater than the treatment effect for those who had received prior taxane therapy.

6.21 Although these subgroup analyses are only exploratory (noting these were not appropriately powered and patients were not randomised into these subgroups), they

¹² Schmid P, Adams S, Rugo HS, et al. IMpassion130: updated overall survival (OS) from a global, randomized, double-blind, placebo-controlled, Phase III study of atezolizumab (atezo) + nab-paclitaxel (nP) in previously untreated locally advanced or metastatic triple-negative breast cancer (mTNBC). *Journal of Clinical Oncology*. 2019;37(15_suppl):1003-03.

suggest that there is no evidence of OS benefit for ATZ+nab-P in the majority of the target PBS population in current clinical practice (65–79%, depending on the true *de novo* metastatic TNBC incidence), even compared with a potentially inferior treatment for these patients.

Comparative harms

6.22 Safety data were collected up until the first data cut-off for IMpassion130 (17 April 2018); no safety data were assessed at the updated data cut-off of 2 January 2019. A higher incidence of grade 3-4 adverse events (AEs), serious AEs and AEs leading to dose modification/interruption was observed in the ATZ+nab-P arm compared to the PBO+nab-P arm. These data are summarised in the table below.

Table 8: Overview of adverse events and deaths in IMpassion130 (data cut-off 17 April 2018)

Adverse event	ITT safety evaluable population, n (%)		RR (95% CI)	PD-L1-positive population, n (%)		RR (95% CI)
	ATZ+nab-P (N=452)	PBO+nab-P (N=438)		ATZ+nab-P (N=185)	PBO+nab-P (N=181)	
Any AE	449 (99.3)	429 (97.9)	1.01 (1.00, 1.03)	185 (100)	177 (97.8)	1.02 (1.00, 1.05)
No. of deaths	181 (40.0)	203 (46.3)	0.86 (0.74, 1.01)	63 (34.1)	88 (48.6)	0.70 (0.55, 0.90)
No. of patients with at least one:						
Grade 5 AE	6 (1.3)	3 (0.7)	1.94 (0.49, 7.70)	2 (1.1)	1 (0.6)	1.96 (0.18, 21.39)
Related Grade 5 AE	3 (0.7)	1 (0.2)	2.91 (0.30, 27.84)			
Grade 3-4 AE	220 (48.7)	185 (42.2)	1.15 (1.00, 1.33)	1 (0.5)	0	NC
Related Grade 3-4 AE	179 (39.6)	132 (30.1)	1.31 (1.09, 1.58)	95 (51.4)	72 (39.8)	1.29 (1.03, 1.62)
SAE	103 (22.8)	80 (18.3)	1.25 (0.96, 1.62)	76 (41.1)	49 (27.1)	1.52 (1.13, 2.04)
Related SAE	56 (12.4)	32 (7.3)	1.70 (1.12, 2.57)	42 (22.7)	31 (17.1)	1.33 (0.87, 2.01)
AE leading to discontinuation of any study treatment	72 (15.9)	36 (8.2)	1.94 (1.33, 2.83)	37 (20.0)	14 (7.7)	2.59 (1.45, 4.62)
ATZ/PBO	29 (6.4)	6 (1.4)	4.68 (1.96, 11.17)	12 (6.5)	4 (2.2)	2.94 (0.96, 8.93)
Nab-paclitaxel	72 (15.9)	36 (8.2)	1.94 (1.33, 2.83)	37 (20.0)	14 (7.7)	2.59 (1.45, 4.62)
AE leading to any dose interruption of ATZ/PBO	139 (30.8)	103 (23.5)	1.31 (1.05, 1.63)	60 (32.4)	38 (21.0)	1.54 (1.09, 2.19)
AESI						
Any grade	259 (57.3)	183 (41.8)	1.37 (1.20, 1.57)	66 (36.5)	105 (56.8)	0.61 (0.49, 0.77)
Grade 3-4	34 (7.5)	19 (4.3)	1.73 (1.00, 2.99)	7 (3.9)	10 (5.4)	0.68 (0.27, 1.76)
Serious AESIs	19 (4.2)	6 (1.4)	3.07 (1.24, 7.61)	-	-	-

Notes: Relative risks and 95% confidence intervals for relative risks were calculated using the Normal approximation to the binomial distribution. **Statistically significant relative risks are bolded.** All patients were divided according to the VENTANA SP142-IC assay.

AE = adverse event; AESI = adverse event of special interest; ATZ+nab-P = atezolizumab + nab-paclitaxel; CI = confidence interval; N = total participants in group; NC = not calculable; No. = number; PD-L1=programmed death-ligand 1; PBO+nab-P = placebo + nab-paclitaxel; SAE = serious adverse event; vs = versus

Source: Data combined from Table 2.5.12, p 101 and Table 2.5.13, p 102 of the submission and Table 42, p. 145, and Table 67, p. 169 of the CSR IMpassion130 Aug2018.

- 6.23 In the safety-evaluable population, a higher proportion of ATZ+nab-P compared to PBO+nab-P patients also had adverse events of special interest (AESIs) (57.3% versus 41.8%) and Grade 3-4 AESIs (7.5% versus 4.3%). The most common AESIs were immune-related rash, hepatitis, hypothyroidism and hyperthyroidism.
- 6.24 In the safety-evaluable population at the data cut-off of 17 April 2018, more patients in the ATZ+nab-P arm compared to the PBO+nab-P arm had died due to AEs. A summary of these deaths is in Table 9.

Table 9: Summary of deaths in the safety-evaluable population in IMpassion130 (data cut-off 17 April 2018)

	Number of patients (%)		Relative risk (95% CI) (ATZ+nab-P vs. PBO+nab-P)
	ATZ+nab-P (N=452)	PBO+nab-P (N=438)	
Deaths	181 (40.0)	203 (46.3)	0.86 (0.74, 1.01)
Cause of death			
Adverse event	6 (1.3)	3 (0.7)	1.94 (0.49, 7.70)
Progressive disease	157 (34.7)	186 (42.5)	0.82 (0.69, 0.97)
Other ^a	18 (4.0)	14 (3.2)	1.25 (0.63, 2.47)

ATZ+nab-P = atezolizumab + nab-paclitaxel; CI = confidence interval; MedDRA = Medical Dictionary for Regulatory Activities; N = total participants in group; PBO+nab-P = placebo + nab-paclitaxel; vs = versus.

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

^a Includes deaths due to AEs, unrelated, and those outside of the 30-day reporting period from the last dose.

Source: Table 2.5.19, p 106 of the submission with 'other' definition taken from Table 38, p 138 of the CSR for IMpassion130Aug2018.

- 6.25 The CSR defined 'other' as including deaths due to AEs. The PSCR clarified that deaths due to progression of metastatic breast cancer were captured as progressive disease, not as adverse events. All other deaths, irrespective of the relationship to study drug, which occurred during the safety follow up period (30 days after the last dose of study drug or until initiation of another anti-cancer therapy, whichever occurs first) were captured as "death due to AE". Once the safety follow-up period had ended any deaths that were considered related to study treatment were also captured as "death due to AE". The ESCs considered this issue was appropriately addressed.
- 6.26 The submission provided updated Periodic Benefit-Risk Evaluation Report/Periodic Safety Update Report (PBRER/PSUR) for atezolizumab covering the interval 18 November 2018 to 17 May 2019 (inclusive). This update has identified a risk of immune-related myositis associated with the use of atezolizumab, based on 4 cases of myositis with a fatal outcome in 3 cases suggestive of cardiac involvement. Atezolizumab is recommended to be withheld for moderate or severe (grade 2 or 3) immune-related myositis and to be permanently discontinued for recurrent severe or life-threatening myositis (recurrent grade 3 and grade 4).

Benefits/harms

6.27 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

Event	ATZ+nab-P	PBO+nab-P	Absolute difference	HR (95% CI) ^d		
Progression free survival (median duration of follow up 18 months)						
ITT population						
Progressed, n/N (%)	379/451 (84%)	404/451 (89.6%)		0.80 (0.69, 0.92) P=0.0025		
Median PFS, months (95% CI)	7.16 (5.55, 7.43)	5.49 (5.32, 5.62)	1.67			
% not progressed at 12 months (95% CI)	24.73% (20.60, 28.86)	18.67% (14.97, 22.37)	6.06%			
% not progressed at 24 months (95% CI)	10.2% (6.96, 13.48)	6.4% (3.79, 9.02)	3.8%			
PD-L1-positive population						
Progressed, n/N (%)	149/185 (80.5%)	163/184 (88.6%)		0.63 (0.50, 0.80) 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	30.31% (23.47, 37.15)	17.32% (11.71, 22.93)	12.99%			
Overall survival (median duration of follow up 18 months)						
ITT population						
Deaths, n/N (%)	255/451 (56.5%)	279/451 (61.9%)		0.86 (0.72, 1.02) P=0.0777		
Median OS, months (95% CI)	20.99 (19.02, 22.60)	18.73 (16.85, 20.30)	2.26			
% alive at 12 months (95% CI)	72.12% (67.91, 76.33)	68.05% (63.68, 72.43)	4.07%			
% alive at 24 months (95% CI)	42.35% (37.29, 47.42)	38.67% (33.74, 43.60)	3.68%			
PD-L1-positive population						
Deaths, n/N (%)	94/185 (50.8%)	110/184 (59.8%)		0.71 (0.54, 0.93) P=0.0133 ^c		
Median OS, months (95% CI)	25.03 (19.55, 30.65)	17.97 (13.63, 20.07)	7.06			
% alive at 24 months (95% CI) ^b	50.70% (42.89, 58.52)	36.90% (28.96, 44.85)	13.8%			
Harms (median duration of treatment 22 weeks)						
	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	179/452	132/438	1.31 (1.09, 1.58)	39.6	30.1	0.09 (0.03, 0.16)
Treatment-related SAE	56/452	32/438	1.70 (1.12, 2.57)	12.4	7.3	0.05 (0.01, 0.09)
AEs leading to treatment discontinuation	139/452	103/438	1.31 (1.05, 1.63)	30.8	23.5	0.07 (0.01, 0.13)

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

^b One-year duration not provided by the CSR or submission.

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

^d Data cut-off: 2 January 2019

Statistically significant relative risks and risk differences are bolded.

ATZ = atezolizumab; ITT = intention-to-treat; 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.

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 submission.

6.28 On the basis of direct IMpassion130 trial presented in the submission, for every 100 patients treated with ATZ+nab-P in comparison with nab-P:

- In the unselected ITT population treated with ATZ+nab-P: at 12 months, approximately 6 additional patients would remain progression-free. The median increase in PFS would be 1.7 months, and there is no statistically significant benefit in OS.
- In PD-L1-positive patients treated with ATZ+nab-P: at 12 months, approximately 13 additional patients will remain progression-free. The median increase in PFS would be 2.2 months, and it was not appropriate to conduct a formal statistical test for OS.
- Adverse events experienced by PD-L1-positive patients treated with ATZ+nab-P over the median duration of treatment of 22 weeks:
 - 9 additional patients will experience a treatment-related Grade 3-4 AE
 - 5 additional patients will experience a treatment-related SAE
 - 7 additional patients will experience an AE leading to treatment discontinuation.

Clinical claim

6.29 The submission described ATZ+nab-P as superior in terms of effectiveness compared with nab-P alone in the first-line treatment of patients with unresectable locally advanced or metastatic TNBC 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.

6.30 The ESCs agreed with the commentary that the therapeutic conclusion presented in the submission was not adequately supported by the evidence presented. Whilst statistical significance was demonstrated favouring ATZ+nab-P for PFS in both the ITT and PD-L1-positive subgroup, the benefit was small and may not be clinically meaningful. There was no statistically significant difference in OS in the ITT population and it was not appropriate to conduct a formal statistical test for OS in the PD-L1-positive subgroup.

6.31 The key trial also enrolled a relatively high proportion of patients with chemotherapy-naïve TNBC (37% of the ITT), who may be more likely to respond to chemo/immunotherapy compared to patients who have had previous chemotherapy

exposure. In addition, as few as 10.2% of the ITT population in the key trial may have received an optimal comparator (taxane-naïve, anthracycline-pretreated patients). The majority of the target Australian population will have received prior taxane- and anthracycline-based (neo)adjuvant chemotherapy for which there is some uncertainty as to whether ATZ+nab-P is clinically beneficial. The ESCs considered that the IMpassion130 trial had internal validity concerns (including the protocol amendment to the time between withholding treatment and discontinuation) and substantial external validity concerns (including the use of a comparator that was not standard clinical practice, which likely led to an overestimation of the treatment effect of ATZ+nab-P relative to current clinical practice, the inclusion of a heterogeneous population, and the reliance on PFS from the prespecified analyses where an OS difference would be a more clinically meaningful outcome).

- 6.32 The PBAC considered that the clinical claim of superior effectiveness compared with nab-P alone in the first-line treatment of patients with unresectable locally advanced or metastatic TNBC whose tumours are PD-L1-positive (PD-L1 stained IC covering $\geq 1\%$ of the tumour area) was not adequately supported by the clinical evidence as the difference in PFS may not be clinically meaningful, the OS benefit was not robust as formal statistical testing could not be conducted, there was uncertainty regarding the test for interaction with PD-L1, nab-P was a potentially inferior comparator in many patients in IMpassion130 and the applicability of the trial to current Australian clinical practice was limited.
- 6.33 The PBAC considered that the claim of inferior but clinically manageable safety compared to nab-paclitaxel alone was reasonable.

Claim of co-dependence

- 6.34 In TNBC, the PD-L1 biomarker is often associated with tumour-infiltrating immune cells. PD-L1 binds to one of two inhibitory receptor proteins, programmed death protein-1 (PD-1) and B7.1 found on the surface of T-cells, activating a checkpoint inhibitor pathway that dampens the immune response. Its biological purpose is to prevent auto-immunity. Blockade of the binding between PD-L1 and PD-1/B7.1 with monoclonal antibodies directed to either PD-1 or PD-L1 restores T-cell mediated tumour cell killing and has been shown to be effective in treating patients with various cancer types.
- 6.35 Thus, the expectation of a greater effect from atezolizumab in patients with greater PD-L1 expression, supporting the need for IHC testing for PD-L1 expression on IC to determine eligibility for treatment with atezolizumab, is biologically plausible.
- 6.36 Chemotherapy can induce multiple immunomodulatory changes leading to an increased immune response to the tumour. However, chemotherapy can also lead to PD-L1 upregulation in tumour cells, which dampens the immune response. This leads to the rationale for combining atezolizumab with chemotherapy in TNBC. Thus, the

submission concluded that the addition of atezolizumab to chemotherapy treatment aims to prevent the dampening of the immune response, allowing the immune cells to respond to the increased immunogenicity of the tumour and increase the likelihood that the infiltrating immune cells can kill tumour cells.

- 6.37 However, chemotherapy with taxanes causes leukocytopenia, diminishing the ability to have an immune response at all. The effects of this leukocytopenia on checkpoint inhibitor immunotherapy is not known. Thus, there is some uncertainty about the rationale for using background (taxane) chemotherapy.
- 6.38 Additionally, TNBC patients with upregulated IC PD-L1 expression were 3–4 times more likely to have a complete response to (neo)adjuvant chemotherapy. The mechanism for the counterintuitive correlation between increased IC PD-L1 expression and increased response to chemotherapy (given its role in dampening the immune response) is poorly understood. This may be related to the known favourable prognostic value of CD8+ tumour-infiltrating lymphocytes in breast cancer and may also explain the favourable prognostic value of PD-L1 expression on IC in TNBC. However, there are limited data available on this relationship in unresectable locally advanced or metastatic TNBC in the published literature.
- 6.39 The ESCs questioned whether the biological plausibility for the use of atezolizumab in patients with increased PD-L1 expression was reasonable given that other trials of immunotherapy in TNBC, including in PD-L1-positive populations, have failed to show convincing clinical benefit, with or without combination chemotherapy.¹³
- 6.40 In the IMpassion130 trial, there was evidence of a difference in OS between PD-L1-positive and PD-L1-negative patients receiving the comparator (nab-P monotherapy), favouring patients with no PD-L1 expression on IC. Thus, it is possible that the PD-L1-positive patients enrolled in the IMpassion130 trial have an unfavourable prognosis compared to those who are PD-L1 negative. The ESCs considered that this effect may indicate a difference in the response to nab-P, with PD-L1-positive patients having a worse response to nab-P compared with PD-L1-negative patients. There is no biologically plausible rationale to suggest that PD-L1 status predicts treatment effect variation with nab-P, but this difference contributes to the variation in hazard ratios across the two arms in the IMpassion130 trial, and thus to the related tests for interaction.
- 6.41 The ESCs also noted that interaction tests for an OS treatment effect by PD-L1 status had p-values of 0.02 for the 17 April 2018 data cut-off and 0.06 for the 2 January 2019 data cut-off (as provided in the PSCR). Overall the ESCs considered that this suggests

¹³ Marra, A., Viale, G., Curigliano, G. (2019) Recent advances in triple negative breast cancer: the immunotherapy era. *BMC Med* 17, 90 (2019) <https://doi.org/10.1186/s12916-019-1326-5>

there is some evidence that PD-L1 status may predict variation in the treatment effect of atezolizumab, but the evidence for this is uncertain.

Economic analysis

6.42 The submission presented a modelled evaluation based on the direct trial IMpassion130. The types of economic evaluation presented were a cost-effectiveness (cost-per-life-year-gained) and a cost-utility analysis (cost-per-QALY-gained). The commentary considered this was appropriate and consistent with the submission’s clinical claim that PD-L1 testing and ATZ+nab-P treatment in patients whose tumours express PD-L1 IC $\geq 1\%$ (the proposed scenario) has superior effectiveness and inferior (but clinically manageable) safety profile compared with no testing and treatment with nab-paclitaxel (the current scenario). The ESCs 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 due to external validity concerns. As such, the ESCs considered that modelling a non-significant treatment benefit was not appropriate and resulted in a high level of uncertainty in the model results.

6.43 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
Treatments	PD-L1 testing and treatment with atezolizumab plus nab-P (as a proxy for a taxane) for patients whose tumours express PD-L1 using the VENTANA SP142-IC $\geq 1\%$ compared with no PD-L1 testing and treatment with nab-P
Time horizon	10 years compared with a median follow up of 18 months in IMpassion130
Outcomes	Life-years gained (LYG) and quality-adjusted life-years gained (QALYG)
Methods used to generate results	Partitioned survival (area under the curve) analysis
Health states	Three: Progression-free survival (PFS), Progression, and Death
Cycle length	1 week
Allocation to health states	Health state allocation over time determined by PFS and overall survival (OS) curves from IMpassion130 at the 2 January 2019 data cut-off, extrapolated using standard parametric functions over the time horizon of the model.
Extrapolation method in the submission base case ^a	The submission extrapolated the KM curves of OS, PFS and time to off treatment (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 selection of a different parametric function for OS in the comparative scenario was unjustified, and the model is sensitive to the parametric functions used. The survival curves of the two comparative scenarios did not converge within the modelled time horizon in the submission base case.
Health related quality of life in the submission base case ^a	EQ-5D-5L results from IMpassion130, converted into utilities using the UK scoring algorithm.

Source: Sections 3.1 to 3.5 of the submission.

nab-P = nanoparticle albumin-bound paclitaxel; PD-L1 = programmed death ligand 1.

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^a Changes were made to the extrapolation methods and utility values in the pre-PBAC response's revised base case.

6.44 The submission's approach to modelling the current scenario (i.e. no-test and treatment with nab-paclitaxel) was the extrapolation of single PFS, OS and time-to-off-treatment (TToT) curves from the IMpassion130 ITT patient population treated with nab-P. While this approach may be appropriate in the base case when assuming the prevalence of PD-L1-positive patients in current clinical practice was consistent with that in the trial, it was difficult to carry out sensitivity analyses that varied the prevalence of PD-L1 expression without modifying the model structure presented by the submission. The clinical management inputs are presented below.

Table 12: Clinical management inputs

Scenario	Testing	Predictive value	IMpassion130 modelled outcomes
Proposed: Test and drug	PD-L1 test positive (40.91%)	True positive: 93.2%	PD-L1-positive patients that received ATZ+nab-P
		False positive: 6.8%	PD-L1-negative patients that received ATZ+nab-P
	PD-L1 test negative (59.09%)	True negative: 96.6%	PD-L1-negative patients that received nab-P
		False negative: 3.4%	PD-L1-positive patients that received nab-P
Current: No test, no drug	N/A	N/A	ITT patients that received nab-P

Source: Table 3.4.1, Section 3 of the submission

ATZ = atezolizumab; ITT = intention-to-treat; N/A = not applicable; nab-P = nanoparticle albumin-bound paclitaxel; PD-L1 = programmed death ligand-1

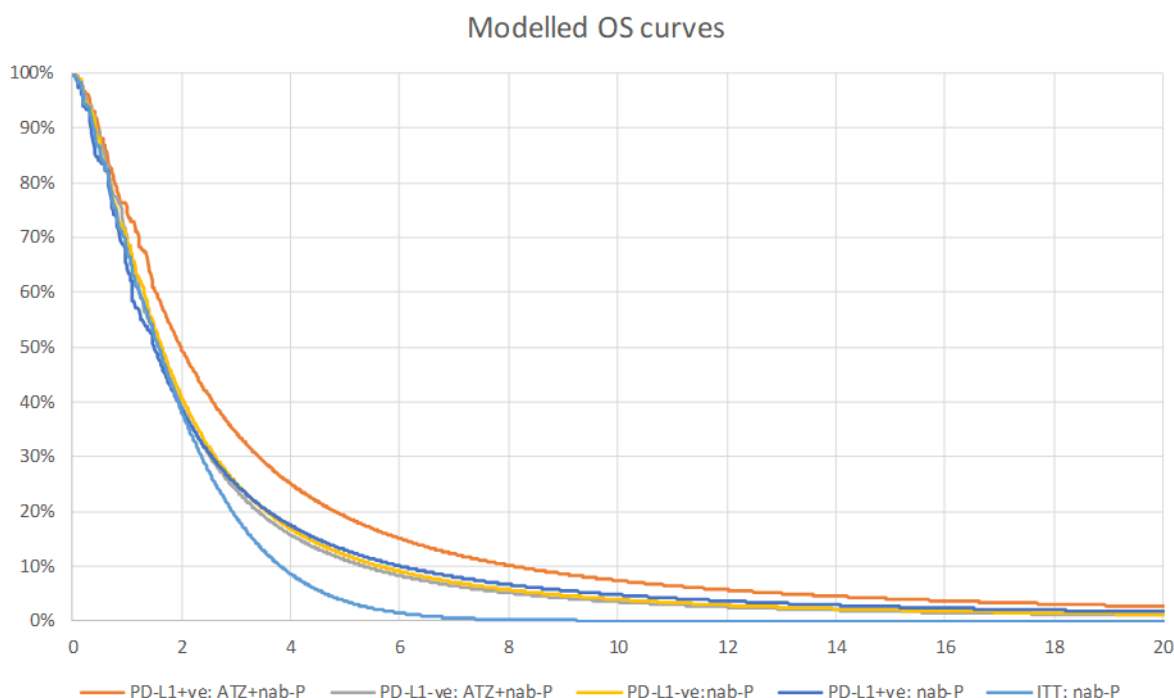
6.45 The submission selected the log-logistic function to extrapolate OS beyond the median follow up for all sub-populations in the proposed scenario (i.e. regardless of treatment received and PD-L1 status), and the Weibull function for the current scenario. The submission claimed that the parametric distributions were evaluated for their goodness of fit against the clinical trial data using the Akaike information criterion (AIC) and Bayesian information criterion (BIC) statistics, graphical inspection of fit and assessment of clinical plausibility. The AIC and BIC statistics did not justify the use of the log-logistic function to extrapolate OS for all patient populations in the proposed scenario. The ESCs noted that the PSCR maintained that this approach was appropriate in the context of a codependent model. The ESCs agreed with the commentary that the use of different functions for the proposed and current scenarios was not adequately justified and that this approach resulted in an implausible OS advantage for the proposed scenario.

6.46 Furthermore, using different parametric functions to extrapolate OS for PD-L1-negative patients in the proposed scenario and those in the current scenario is implausible. Approximately 60% of the patient population in the proposed scenario did not change their treatment as a result of PD-L1 testing (as they were PD-L1 negative). Given that PD-L1 testing, without a change in management, is unlikely to result in a change in survival, the use of different parametric functions for this patient population is inappropriate and resulted in modelling of a treatment benefit for patients after receiving a PD-L1 test and no change in management. The model is

sensitive to this assumption. As discussed further below, this issue was addressed in the pre-PBAC response as the same parametric function (Weibull) was applied for PD-L1-negative patients in the proposed and current scenarios.

6.47 The modelled OS curves in the submission base case for each subpopulation in the proposed scenario and the population in the current scenario are presented below.

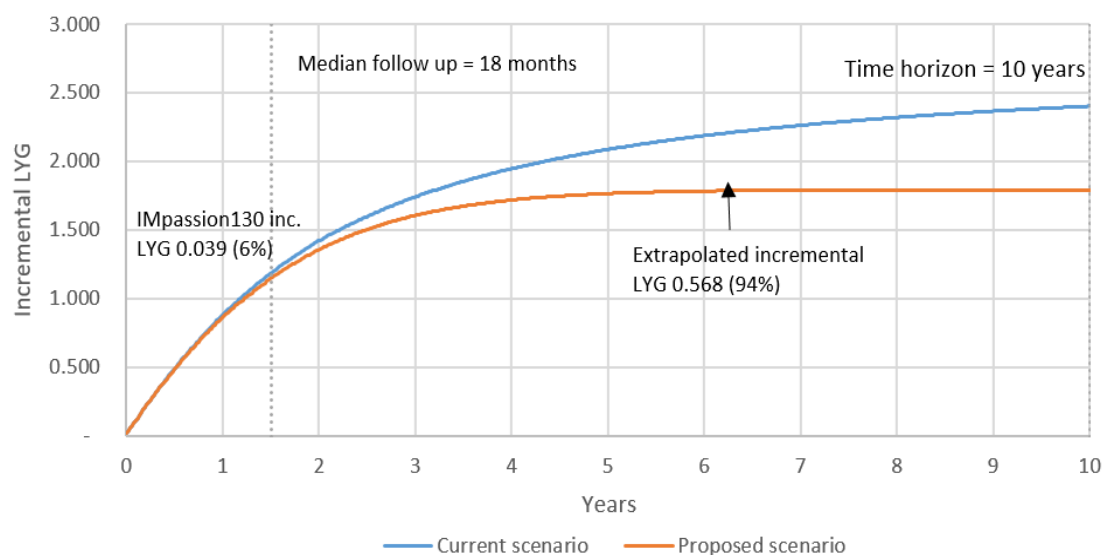
Figure 5: Modelled overall survival curves used in the base case of the economic model (submission base case)



Source: Compiled during the evaluation based on information presented in 'Economic Evaluation.xlsx' of the submission
 ATZ = atezolizumab; ITT = intention-to-treat; nab-P = nanoparticle albumin-bound paclitaxel; PD-L1 = programmed death ligand-1.
 PD-L1+ve:ATZ+nab-P (38%), PD-L1-ve:ATZ+nab+P (3%), PD-L1-ve: nab-P (57%); PD-L1+ve: nab-P (2%) make up the proposed scenario.
 The ITT: nab-P arm was used to model the current scenario.

6.48 The incremental life years gained (discounted) in the submission's base case over the modelled time horizon are summarised in the figure below. The incremental life years gained at median follow up (18 months) in the IMpassion130 trial was 0.039 (approximately two weeks). Beyond the median follow up, in the extrapolated portion of the OS curves, patients in the proposed scenario accrued an additional 6.8 months of survival compared to those in the current scenario (approximately 7.3 months overall). Approximately 94% of the incremental benefit in terms of life-years gained in the submission's base case was therefore derived from the extrapolated portion of the OS curves.

Figure 6: Incremental life-years gained in the submission’s base case



Parametric function used to extrapolate OS

	True-positive	False-positive	True-negative	False-negative
Proposed scenario	log-logistic	log-logistic	log-logistic	log-logistic
Current scenario	Weibull			

Source: Compiled during the evaluation based on information presented in ‘Economic Evaluation.xlsx’ of the submission. ATZ = atezolizumab; LYG = life year gained; nab-P = nanoparticle albumin-bound paclitaxel; PD-L1 = programmed death ligand-1.

6.49 In the National Institute for Health and Care Excellence (NICE) consideration of ATZ+nab-P, long-term OS was estimated to be 4% at 6 years and 0.2% at 10 years for PD-L1-positive patients treated with ATZ+nab-P based on sponsor provided clinical expert opinion¹⁴. This was significantly lower than estimated in the submission’s base case, which estimated OS to be 15% at year 6 and 7.5% at year 10 for PD-L1-positive patients treated with ATZ+nab-P (using a log-logistic parametric function). The Weibull parametric function (OS rate of 5.2% at 6 years and 0.3% at 10 years) may reflect the OS of patients treated with ATZ+nab-P more accurately. Further, a Weibull distribution was used in the Sponsor’s submission to NICE, and in the NICE technology assessment prepared by the evidence review group. The ESCs noted that the PSCR disagreed with the use of Weibull distributions to extrapolate OS in all comparative scenarios, arguing that the modelled OS benefit was supported by efficacy data from the IMpassion130 trial. The ESCs noted that, for both AIC and BIC, Weibull was the best fit for all

¹⁴ Table 37, p180 of the NICE Committee Papers for Atezolizumab with nab-paclitaxel for treating PD L1-positive, triple-negative, advanced breast cancer [ID1522] available from: <https://www.nice.org.uk/guidance/GID-TA10433/documents/committee-papers>

treatment arms except the PD-L1-positive population treated with nab-P (false negatives, approximately 2% of the modelled population).

- 6.50 The pre-PBAC response presented a revised base case which applied the log-logistic function only for the OS extrapolation of true PD-L1-positive patients treated with ATZ+nab-P. The Weibull function was used for extrapolation of OS for all other populations in the model. In addition, the revised base case in the pre-PBAC response converged the ATZ+nab-P OS curve to the current scenario curve; with convergence applied from 90 months to the end of the time horizon (120 months). The PBAC noted that no justification was provided for the point at which convergence was commenced.
- 6.51 The pre-PBAC response's approach, which continued to apply the log-logistic function for extrapolation of OS in true PD-L1-positive patients treated with ATZ+nab-P, estimated an average of 0.31 incremental life years gained (3.7 months) in the proposed scenario compared with the current scenario, versus 0.039 incremental life years gained at median follow up (18 months) in the IMpassion130 trial with the OS gains not being statistically significant when adjusted for multiplicity.
- 6.52 The PBAC acknowledged that there was little difference in the AIC and BIC statistics between the Weibull and log-logistic distributions in the proposed scenarios, but noted that Weibull was the best fitting function for the proposed scenario for true PD-L1-positive patients using AIC and BIC. The PBAC noted that the sponsor argued that the log-logistic function is appropriate to extrapolate OS for the PD-L1-true-positive population that receive ATZ+nab-P and "the potential for ongoing and durable response is further supported by clinical data from other immunotherapy trials and is consistent with expectations of clinicians who are experts in this field". However, the PBAC considered that the use of different parametric functions for the proposed scenario for true PD-L1-positive patients (treated with ATZ+nab-P) and the current scenario was not adequately justified and (even with convergence to the comparator curve from 90 to 120 months) resulted in an OS advantage that was not adequately supported by the clinical trial data. The PBAC considered that the Weibull function resulted in OS estimates that were more clinically plausible (as outlined in Paragraph 6.49). As such, the PBAC considered that the Weibull parametric function is the most appropriate method for extrapolating the OS curves in both the proposed scenario and the current scenario, based on the clinical data currently available.
- 6.53 The submission did not account for disutilities associated with treatment. The ESCs agreed with the commentary that this was not reasonable, as there was an inferior safety profile with combination treatment (ATZ+nab-P) compared to monotherapy (nab-P). In addition, the submission failed to consider the likelihood of re-biopsy or re-testing, and any adverse events relating to the conduct of either the original or subsequent tests. The ESCs considered that disutility from these events should have been included. The pre-PBAC response maintained that it is not appropriate to apply disutilities associated with treatment in the economic evaluation because the impact

of adverse events on patient quality of life is captured within the EQ-5D data from the IMpassion130 trial, which is used in the model.

- 6.54 The base case economic evaluation used the prevalence of PD-L1 IC $\geq 1\%$ expression identified in the IMpassion130 trial (40.91%) using the Ventana SP142-IC assays. The health outcomes (OS and PFS) modelled in the submission were based on the results of the Ventana SP142 test. There are currently two other commercially available PD-L1 IHC assays that can be used to determine PD-L1 status in TNBC; the VENTANA PD-L1 (SP263) and Agilent/Dako PD-L1 (22C3) pharmDx assays. The concordance between these tests is poor. No evidence of the prevalence of PD-L1 expression in the patient population was provided by the submission.
- 6.55 Given the variation in the proportion of patients testing positive with each of the assays and the variation of ATZ+nab-P treatment effect between these patient populations, it is likely that the cost-effectiveness of the proposed scenario in the Australian population will differ (likely worsen), if test assays other than Ventana SP142 are used. This uncertainty was not considered by the submission, and cannot be reliably tested given the information provided by the submission. However, if tests other than the Ventana SP142 are used in clinical practice, it is likely that the ICER will increase. Using the more appropriate Weibull parametric function for extrapolation of the OS curves in both the proposed scenario and the current scenario, the ICER (based on the submission's base case) is likely to lie between \$155,000 to < \$255,000/QALY and \$355,000 to < \$455,000/QALY¹⁵ (or \$55,000 to < \$75,000/QALY and \$115,000 to < \$135,000/QALY when using the submission's extrapolation functions). The ESCs noted that it is likely that the cost-effectiveness of ATZ+nab-P in the Australian population would differ depending on the assays used and considered that this could be addressed by limiting testing to the VENTANA SP142.
- 6.56 The submission stated that the Australian-mapped utilities were considerably lower than expected (0.665 for progression-free survival; and 0.554 for progressive disease), therefore the preference weights from the EQ-5D-5L mapped using a UK scoring algorithm (van Hout, 2012) were used. This resulted in PFS and progressive disease utilities of 0.723 and 0.649, respectively. The utility value used in the post-progressive disease health state appeared higher than others previously considered reasonable by the PBAC (0.555; paragraph 6.50, Pertuzumab and trastuzumab, Public Summary Document (PSD), November 2014 PBAC meeting), and used in other economic evaluations of advanced breast cancer. The ESCs considered that use of utility values from a UK scoring algorithm was not adequately justified in the submission and noted that use of the Australian scoring algorithm (using Viney et al (2014), which applied tariffs derived through discrete choice experiments) increased the ICER from \$55,000

¹⁵ This ICER corresponds to a 'no-test' scenario, where no patients are tested for PD-L1 expression, and all patients are treated with ATZ+nab-P.

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to < \$75,000 to \$55,000 to < \$75,000 per QALY. The pre-PBAC response presented an alternative analysis of the EQ-5D data, applying Australian tariffs using the crosswalk algorithm from van Hout et al (2012), returning a set of 3L values from the original 5L EQ-5D questionnaire, and then applying time trade-off derived tariffs in EQ-5D from Viney et al (2011). The pre-PBAC response stated that this approach gave utility values of 0.734 for PFS and 0.684 for progressive disease, however these values could not be verified and the rationale for the approach was not adequately justified.

6.57 The ESCs also noted that the submission inappropriately excluded costs of management of the disease, which favoured the proposed scenario as patients remain alive longer in the modelled proposed scenario. The revised base case in the pre-PBAC response attempted to address this issue.

6.58 The key drivers of the model are summarised below.

Table 13: Key drivers of the model (submission base case)

Description	Method/Value	Impact
		Submission base case: \$55,000 to < \$75,000/QALY
Modelling OS	Use of OS data from IMpassion130 trial, where no statistically significant benefit in OS was demonstrated.	High, likely to favour the proposed scenario
Extrapolation	Log-logistic distribution was used to extrapolate OS curves in the proposed scenario and Weibull distribution in the current scenario.	High, favours the proposed scenario. When using Weibull distribution for OS extrapolation in both scenarios, the ICER increased to \$155,000 to < \$255,000/QALY
Utilities	Higher values for model health states based on EQ-5D data from IMpassion130, translated into utilities based on a UK scoring algorithm, and no disutility for AEs.	Moderate, favours proposed scenario. Using an Australian scoring algorithm (Viney 2014) increased the ICER to \$55,000 to < \$75,000/QALY
Testing assay	The modelled outcomes were based on VENTANA SP142 (the evidentiary standard), however, other assays are commercially available in Australia.	Unclear, likely to favour proposed scenario

Source: Compiled during the evaluation based on information presented in 'Economic Evaluation.xlsx' of the submission.
 AE = adverse event; ICER = incremental cost-effectiveness ratio; EQ-5D = EuroQoL five dimension; OS = overall survival; QALY = quality-adjusted life year.

6.59 The results of stepped economic evaluation are presented below.

Table 14: Results of the stepped economic evaluation (submission base case)

Step and component	Proposed scenario (test/ATZ+nab-P)	Current scenario (no test/nab-P)	Increment
Step 1: trial-based costs and outcomes			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Life years gained	1.66	1.60	0.06
Incremental cost/extra life year gained			\$ [REDACTED]
Step 2: parametric extrapolation from 18 months to a 10 year time horizon			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Life years gained	2.40	1.80	0.61
Incremental cost/extra life year gained			\$ [REDACTED]
Step 3: inclusion of MRU costs			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Life years gained	2.40	1.80	0.61
Incremental cost/extra life year gained			\$ [REDACTED]
Step 4: inclusion of AE costs			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Life year gained	2.40	1.80	0.61
Incremental cost/extra life year gained			\$ [REDACTED]
Step 5: inclusion of utilities to determine QALYs			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
QALYs	1.63	1.22	0.406
Incremental cost/extra QALY gained			\$ [REDACTED]
Step 6: inclusion of post progression treatment costs			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
QALYs	1.63	1.22	0.406
Incremental cost/extra QALY gained			\$ [REDACTED]
Step 7: inclusion of end of life costs			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
QALYs	1.63	1.22	0.406
Incremental cost/extra QALY gained			\$ [REDACTED]

Source: Compiled during the evaluation based on information presented in Table 3.8.1, Section 3 of the main body and 'Economic Evaluation.xlsx' included in the submission.

AE = adverse event; ATZ = atezolizumab; MRU = medical resource use; nab-P = nanoparticle albumin-bound paclitaxel; QALY = quality-adjusted life year.

6.60 The model is most sensitive to the extrapolation of OS of the two comparative scenarios from the median follow-up in IMpassion130 to the modelled time horizon. As noted above, the selection of parametric functions for the extrapolation of OS in the base case was not adequately justified and did not appear reasonable. When Weibull distributions were used to extrapolate OS in both comparative scenarios, the incremental cost effectiveness ratio increased to \$155,000 to < \$255,000/QALY from the submission base case of \$55,000 to < \$75,000/QALY.

6.61 The pre-PBAC response provided a revised base case that resulted in an ICER of \$55,000 to < \$75,000 per QALY which included changes to: the way the utilities were calculated; the duration of nab-P therapy; disease management costs post treatment discontinuation; extrapolation of OS; the price of atezolizumab; and the inclusion of a risk sharing arrangement (RSA) with caps that are based on an average of [REDACTED] administrations of atezolizumab per patient. The PBAC noted this represented

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significant changes to the economic model, which could not be evaluated in the context of a pre-PBAC response.

6.62 The results of key sensitivity analyses (using the submission base case) are summarised below.

Table 15: Results of key sensitivity analyses conducted during the evaluation (using the submission base case)

#	Parameter (base case)	Value tested	Inc. costs	Inc. QALYs	ICER (\$/QALY)
	Base case		\$ [REDACTED]	0.406	\$ [REDACTED]
Extrapolation: overall survival					
1	PD-L1 test/ ATZ+nab-P: KM with log-logistic tail, irrespective of treatment assignment	Proposed: PD-L1 true positive: KM with log-logistic tail PD-L1 false positive and PD-L1 (true and false) negative: KM with Weibull tail	\$ [REDACTED]	0.241	\$ [REDACTED]
2	No test/nab-P arm: KM with Weibull tail	No test/nab-P arm: KM with Weibull tail	\$ [REDACTED]	0.125	\$ [REDACTED]
3		All arms: KM with Weibull tail	\$ [REDACTED]	0.137	\$ [REDACTED]
Utilities					
	Utilities from IMpassion130, using UK scoring algorithm: PFS: 0.723 PD: 0.649	Utilities from IMpassion130, using an Australian scoring algorithm (Viney et al 2014): PFS: 0.665 PD: 0.554	\$ [REDACTED]	0.355	\$ [REDACTED]
		Utilities from IMpassion130, using Australian scoring algorithm + OS extrapolation as per #2 above	\$ [REDACTED]	0.113	\$ [REDACTED]
		Utilities from IMpassion130, as presented in the pre-PBAC response. PFS: 0.734, progression: 0.684 (not verified)	\$ [REDACTED]	0.424	\$ [REDACTED]
Testing parameters^a					
	Include estimates of inter-laboratory reproducibility to estimate the false-positive and false-negative rate of the evidentiary standard	Assume 0% false positive and false negative ^b	\$ [REDACTED]	0.417	\$ [REDACTED]
		Assume 0% false positive and false negative ^b + #1 above	\$ [REDACTED]	0.259	\$ [REDACTED]
		Assume 0% false positive and false negative + #2 above	\$ [REDACTED]	0.134	\$ [REDACTED]
	PD-L1 test and PD-L1 IC ≥ 1% treated with ATZ+nab-P	Assume no testing (all patients treated with ATZ+nab-P irrespective of PD-L1 status)	\$ [REDACTED]	0.39	\$ [REDACTED]
	PD-L1 test and PD-L1 IC ≥ 1% treated with ATZ+nab-P	Assume no testing (all patients treated with ATZ+nab-P irrespective of PD-L1 status) + #2 above	\$ [REDACTED]	0.12	\$ [REDACTED]

Source: Compiled during the evaluation based on information presented in Section 3.5 and 'Economic Evaluation.xlsx' of the submission. ATZ = atezolizumab; ICER = incremental cost-effectiveness ratio; KM = Kaplan Meier; nab-P = nab-paclitaxel; OS = overall survival; PD = progressive disease; PD-L1 = programmed death ligand-1; PFS = progression-free survival; QALY = quality adjusted life year.

^a Insufficient information was provided in the submission to determine that the impact of different assays would have on the cost-effectiveness of ATZ+nab-P for PD-L1-positive patients. The effectiveness of ATZ+nab-P compared to nab-P alone appeared to differ between the evidentiary standard (VENTANA SP142) and the other commercially available PD-L1 assays.

^b The submission did not model the survival outcomes of patients identified as 'false positive' and 'false negative'. Instead, the submission used the estimates of inter-laboratory reproducibility to estimate the proportion of patients who would be considered 'false-positive' and

'false-negative', and used the survival outcomes of those who tested positive (as false negatives) and those who tested negative (as false positives).

The redacted table shows ICERs in the range of \$55,000 to < \$455,000/QALY.

Drug cost/patient/course: \$ [REDACTED] (based on the price proposed in the submission)

- 6.63 Taking into account the [REDACTED] % discount on the ex-manufacturer price proposed in the submission, the dispensed drug cost per treatment course of atezolizumab for PD-L1-positive patients is \$ [REDACTED] based on an average treatment duration of 12.47 months, and an average dose of 840 mg every two weeks. The cost per treatment course for nab-paclitaxel, when in combination with atezolizumab is \$ [REDACTED] based on an average duration of [REDACTED] months and cost per dose of \$805 (dose of 100 mg/m²; BSA = 1.78; 2x100 mg vials; 33% public hospital use). This equalled a total cost of \$ [REDACTED] per patient. The pre-PBAC response proposed a reduction in the effective ex-manufacturer price for atezolizumab from \$ [REDACTED] to \$ [REDACTED] per 840 mg vial, in combination with an RSA with caps that are based on an average of [REDACTED] administrations of atezolizumab per patient. The pre-PBAC response estimated that this would equate to a reduction in the assumed treatment duration from 12.47 months to [REDACTED] months, and a reduction in the cost per treatment course of atezolizumab for PD-L1-positive patients from \$ [REDACTED] to \$ [REDACTED] (atezolizumab drug cost only, as stated in the pre-PBAC response).
- 6.64 In the current scenario (as represented by false negative patients treated with nab-P¹⁶), the expected cost of nab-paclitaxel for PD-L1-positive patients is \$ [REDACTED] based on an average duration of [REDACTED] months and a cost per dose of \$805 (dose of 100 mg/m²; BSA = 1.78; 2x100 mg vials; 33% public hospital use), based on the estimates provided in the submission.
- 6.65 The average duration of therapy and average medicine costs per patients for each of the test/treatment pathways are provided in Table 16 (based on the values provided in the submission).

¹⁶ The economic model included a single arm to model both the PD-L1 positive and PD-L1 negative patients in the submission 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.

Table 16: Calculation of the cost per patient per course for each of the included medicines (undiscounted), based on the submission

	Proposed scenario				Current scenario
	Test positive: ATZ+nab-P		Test negative: nab-P		ITT
	True positive	False positive ^a	True negative	False negative ^a	
% patients (weight)	38.1%	2.8%	57.1%	2.0%	100%
Average duration of therapy (months)					
Atezolizumab	12.47	8.91			
Nab-P					
Weighted ATZ	12.23		N/A		
Total weighted ATZ per patient	5.0				N/A
Total weighted nab-P per patient					
Average medicine costs per patient (undiscounted)					
Atezolizumab	\$	\$	N/A		N/A
Nab-P	\$	\$	\$	\$	\$
Weighted ATZ	\$		N/A		N/A
Total weighted ATZ per patient	\$				N/A
Total weighted nab-P per patient	\$				\$

Source: Compiled during the evaluation based on information presented in 'Economic Evaluation.xlsx' of the submission.

ATZ = atezolizumab; ICER = incremental cost-effectiveness ratio; ITT = intention to treat; N/A = not applicable; nab-P = nab-paclitaxel.

^a The submission did not model the survival outcomes of 'false-positive' and 'false-negative' patients. Instead, the submission used the estimates of inter-laboratory reproducibility to estimate the proportion of patients who would be considered 'false-positive' and 'false-negative', and used the survival outcomes of those who tested positive and treated with nab-P (as false negatives) and those who tested negative and treated with ATZ+nab-P (as false positives). Therefore, the duration of therapy for the false-positive population is the duration of therapy in PD-L1-negative patients treated with ATZ+nab-P. Similarly, the duration of therapy for the false-negative population is actually the duration of therapy in PD-L1-positive patients treated with nab-P.

6.66 The per-administration cost of nab-P is significantly higher than the per-administration cost of other taxanes available on the PBS, such as paclitaxel. Nab-P (and by extension, other taxanes) will be used in both arms and the duration of nab-P when in combination with ATZ is longer than the duration of therapy in patients treated with nab-P alone. If the listing of atezolizumab results in a change to the background therapy (i.e. a substitution away from other, cheaper therapies to nab-P), this is likely to result in a higher incremental cost per patient.

6.67 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 duration of nab-P treatment. A comparison of the estimated cost per patient in the financial implications (PD-L1 positive only, Section 4), compared to the implied¹⁶ average cost of therapy for PD-L1-positive patients in the economic model are summarised in the table below (based on the values provided in the submission).

Table 17: Comparison of intervention costs between the economic model and financial analysis for the PD-L1-positive population (based on the submission)

	Proposed scenario		Current scenario	
	Economic model	Financial analysis	Economic model	Financial analysis
Cost of atezolizumab				
Average duration of therapy	12.47 months		N/A	N/A
Number of administrations*	27.4	27.4	N/A	N/A
Cost per administration		\$ [REDACTED]	N/A	N/A
Average cost per patient		\$ [REDACTED]	N/A	N/A
Cost of nab-paclitaxel				
Average duration of therapy	[REDACTED] months	[REDACTED] months	[REDACTED] months	[REDACTED] months
Number of administrations*	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Cost per administration		\$804.68		\$804.68
Average cost per patient	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]

Source: Compiled during the evaluation based on information presented in 'Economic evaluation.xlsx' and 'Section 4 Workbook.xlsx'.

N/A = not applicable.

* The submission appeared to make an error in the derivation of the number of administrations of nab-P in its financial analysis. The number of administrations of nab-P that is associated with the average duration of therapy was actually double that estimated by the submission. For example, the number of administrations of nab-P associated with an average treatment duration of [REDACTED] months is actually double that estimated by the submission - [REDACTED] administrations.

Note: There is likely to be a small difference in the average number of administrations between Section 3 and Section 4 due to the method of calculation. In Section 3, the actual number of doses required (on days 1, 8, and 15 of a 28-day cycle) were determined based on the time to treatment discontinuation (TTOT) curves at weekly intervals. In Section 4, this estimate was based on the average duration of therapy (in months, derived from the TTOT curves), multiplied by the expected number of administrations required per month (i.e. 3 treatments per 28 day period, multiplied by the average number of days per month (365.25/12))

Estimated PBS & financial implications

- 6.68 This submission was considered by DUSC. The submission used an epidemiological approach to determine the number of patients likely to receive PD-L1 testing for the purposes of determining eligibility for use with ATZ+nab-P and the expected financial impact of listing ATZ+nab-P on the PBS.
- 6.69 Key input parameters used in the submission's approach are provided in the table below.

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Table 18: Key inputs for financial estimates (based on the submission's estimates)

Parameter	Value applied and source	Comment
Estimation of incident breast cancer patients	AIHW Cancer in Australia extrapolated using a linear function	This was reasonable.
Proportion of patients with TNBC	15% based on the Cancer Council Australia ¹⁷	This value appeared reasonable, and consistent with previous PBAC decision making. However, it is slightly lower than that considered in the Ratified PICO (17%).
Incident % of patients diagnosed with unresectable locally advanced or <i>de novo</i> metastatic TNBC	34.8%, IMpassion130 CSR (25% <i>de novo</i> metastatic TNBC and 9.8% with unresectable locally advanced TNBC)	The commentary considered this value from the trial evidence (% patients with locally advanced or metastatic TNBC with an ECOG of 0-1 and receiving 1L treatment) was not appropriate to apply to the population of patients with TNBC, however DUSC considered the submission's estimate was reasonable.
Prevalent population diagnosed with early TNBC who progress to metastatic TNBC	Evidence from Naher (2018) that 8% (11/173) of early TNBC patients had a distant recurrence, over 40-months	The commentary considered this is likely to be an underestimate, and does not include those who progress to unresectable Stage III disease. PBAC previously considered that around 21% over 10 years was a more likely estimate (paragraph 6.41, Palbociclib PSD, November 2017 PBAC meeting). This value was also applied to the entire patient population with TNBC (not just those diagnosed with earlier stages of disease). DUSC agreed this was underestimated.
% ECOG status of 0 or 1	78% METIS Healthcare Research Data (2019) ³	The commentary considered that the representativeness of this survey to TNBC patients in Australia is unclear, however DUSC considered the submission's estimate was reasonable.
% patients who elect to have the PD-L1 test	82% based on test uptake from the United States	DUSC considered a testing uptake of 95% would be appropriate for the Australian population. DUSC considered that if the PD-L1 test was available on the MBS there would be no impediment to patients having the test.
% PD-L1 positive	41%, as reported in IMpassion130	The proportion of patients testing positive in the trial as per the VENTANA SP142 test, and therefore eligible for treatment with ATZ+nab-P. This proportion may differ in Australian practice where different tests are available in clinical practice with higher test-positive rates.
# grandfathered patients	< 500, Assumption	The commentary considered this appeared reasonable.

¹⁷ Cancer Council. Breast cancer. 2019; <https://www.cancer.org.au/about-cancer/types-of-cancer/breast-cancer/>. Accessed 28/10/2019.

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Parameter	Value applied and source	Comment
# administrations of ATZ+nab-P per patient (proposed scenario)	ATZ: 27.37 doses Nab-P: 14.02 administrations	The average number of administrations of nab-P was incorrect (approximately half the expected number). In the economic model, the submission assumed an average of 28.12 administrations per patient was applicable for nab-P. DUSC considered the number of doses of ATZ and nab-P were overestimated.
# administrations of nab-P per patient (current scenario)	10.6 administrations	The number of administrations was incorrect (approximately half) and compared to 19.73 in the economic model. DUSC considered the number of doses of nab-P was overestimated.
MBS items		
MBS items: administration of ATZ+nab-P (per-patient-per-course; proposed scenario)	MBS Item 13918: 27.37 administrations MBS Item 13915: 9.35 administrations	The commentary considered this appeared reasonable.
MBS items: administration of nab-P alone (per-patient-per-course; current scenario)	MBS Item 13915: 21.19 administrations	
On treatment monitoring costs: ATZ+nab-P (per-patient-per-course proposed scenario)	MBS Item 56807 (every 12 weeks): 4.56 MBS Items 105, 65070 and 66512 (every 4 weeks):13.68	
On treatment monitoring costs: nab-P (per-patient-per-course proposed scenario)	MBS Item 56807 (every 12 weeks): 2.35 MBS Items 105, 65070 and 66512 (every 4 weeks):7.06	

Source: Compiled during the evaluation based on information provided in 'Section 4 Workbook.xlsx'.
AIHW = Australian Institute of Health and Welfare.

6.70 The estimated extent of use and financial implications, as estimated in the submission, are provided in Table 19 below.

Table 19: Estimated use and financial implications (submission's estimates)

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use and cost of the test						
Total patients tested	■	■	■	■	■	■
Total cost to MBS	\$■	\$■	\$■	\$■	\$■	\$■
Total cost to MBS (85% schedule fee)	\$■	\$■	\$■	\$■	\$■	\$■
Copayments	\$■	\$■	\$■	\$■	\$■	\$■
Estimated extent of use of atezolizumab						
Number of patients treated	■	■	■	■	■	■
Number of scripts dispensed	■	■	■	■	■	■

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	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated financial implications of atezolizumab						
Cost to PBS/RPBS less copayments	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Estimated financial implications for nab-P						
Cost to PBS/RPBS less copayments	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Net financial implications						
Net cost to PBS/RPBS	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Net cost to MBS ⁱ	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Net cost to PBS/RPBS/MBS	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]

Source: Table 4.3.2, Table 4.6.3, Table 4.3.10, Table 4.3.13, Table 4.4.3, Table 4.6.2, Table 4.6.9, and Table 4.7.8 of the submission.

Revisions to the financial estimates applied during the evaluation included:

- The submission inappropriately included the cost of the MBS test to grandfathered patients in the first year.
- Assuming all patients receive the test and treatment monitoring in an outpatient setting, and therefore pay a 15% co-payment.
- Assuming 41% of patients test positive for PD-L1.
- Assuming 27.37 scripts per patient per course of atezolizumab as estimated by the submission.
- Assuming [REDACTED] scripts of nab-P in the current scenario would be replaced by [REDACTED] scripts in the proposed scenario.
- The submission inappropriately halved the number of administrations required per treatment course for patients in both arms.

The redacted table shows that at Year 6, the estimated number of patients tested was 500 to < 5000; the estimated number of patients treated with atezolizumab was < 500; and the estimated number of scripts for atezolizumab was 10,000 to < 20,000.

- 6.71 The total cost to the PBS/RPBS of listing atezolizumab in combination with nab-paclitaxel was estimated (in the submission) to be \$20 to < \$30 million in Year 6, and a total of \$100 to < \$200 million in the first 6 years of listing. This included the increased usage of nab-paclitaxel in the proposed test/treatment scenario.
- 6.72 The submission assumed that < 500 patients will be grandfathered. The submission stated that a patient access program for atezolizumab is planned for commencement in November 2019, immediately following TGA approval, for the first-line treatment of patients with unresectable locally advanced or metastatic TNBC. The submission stated that eligibility for the access program will be aligned with the proposed initial treatment restriction for PBS listing. As no actual patient numbers were provided by the sponsor, DUSC questioned whether uptake to the access program would be this high.
- 6.73 DUSC considered the estimates presented in the submission to be significantly underestimated. The main issues identified were:
- The submission substantially underestimated the number of patients diagnosed at earlier stages of TNBC who then progress to advanced disease, and there were methodological concerns regarding the base population used to calculate the number of patients with recurrent disease. The pre-PBAC response revised this by applying a recurrence rate of 10% to the cumulative incident population from the

five years preceding listing. An estimate of 5-year survival of TNBC of 77% was also applied to account for mortality over the same 5-year period.

- The proportion of patients who elect to have the PD-L1 test was underestimated based on US data which were not applicable to the Australian setting. The pre-PBAC response revised this estimate from 82% to 95% as recommended by DUSC.
- The number of PD-L1 tests was underestimated as the submission did not account for retesting. The pre-PBAC response assumed a 4% re-testing rate.
- The number of patients eligible for treatment may differ in Australian practice given that testing strategies, other than the evidentiary standard, are available in Australian clinical practice. The performance of these testing strategies was not concordant and so the number of test-positive results will differ depending on the test used. The submission applied the lowest test-positive rate, so the test-positive rate in practice may be higher.

6.74 DUSC considered that the average number of atezolizumab doses used in the financial estimates (27.37 doses, 12.6 month duration) was an overestimate, and that it would be reasonable to assume ■ doses of atezolizumab per patient. As noted above, the pre-PBAC response proposed an episode of care cap of ■ doses per patient treated with atezolizumab, beyond which it would fully rebate the cost of atezolizumab in its proposed RSA. The calculations provided with the pre-PBAC response applied an average of ■ doses, rather than a cap of ■ doses.

6.75 DUSC also noted that the typical maximum duration of nab-P in the metastatic setting is 10-12 treatments, limited by neuropathy. In patients who had prior taxane (51% in the trial population), dose-limiting toxicity would occur much earlier. DUSC considered 28 doses of nab-P (as assumed in the economic model and the commentary-corrected financial estimates) was an overestimate and that an average of 10 doses would be a more reasonable estimate. This was corrected in the pre-PBAC response, which assumed an average of 10 doses of nab-P per patient in the economic model and financial estimates.

6.76 The revised financial estimates presented in the pre-PBAC response estimated a net cost to the PBS/RPBS for listing of atezolizumab of \$20 to < \$30 million in year 6 of listing and \$100 to < \$200 million over the first 6 years of listing, however these estimates have not been independently verified.

Quality use of medicines

6.77 TNBC patients have a high risk of recurrent disease and may have received a taxane in the early breast cancer setting. Requiring these patients to retreat a taxane after treatment failure would not be clinically appropriate due to a low response rate. The PBAC considered that the listing should require that patients treated with taxanes in

the neoadjuvant or adjuvant setting must have completed taxane treatment at least 12 months prior to relapse.

Financial management – risk sharing arrangements

6.78 No subsidisation cap has been proposed. However, the sponsor indicated that it is willing to work with the PBAC and the Department to explore risk sharing arrangements (RSAs) in order to reduce sources of uncertainty to Government and expedite patient access in this area of high unmet need.

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

7 PBAC outcome

7.1 The PBAC did not recommend atezolizumab for the first line treatment of patients with unresectable locally advanced or metastatic triple-negative breast cancer who are PD-L1 positive. The PBAC considered that there was a high clinical need for effective treatments for these patients, but considered that the applicability of the clinical evidence to the relevant patient population was limited and the magnitude of the overall survival benefit claimed was uncertain. The PBAC also noted that the incremental cost-effectiveness ratio was high and likely to be underestimated due to reliance on optimistic assumptions regarding overall survival, which were not sufficiently supported by the clinical evidence. The PBAC also noted that the cost-effectiveness of atezolizumab was likely to be affected by the choice of PD-L1 assay used to determine eligibility to treatment.

7.2 The PBAC noted that the submission was an integrated co-dependent submission and sought advice from MSAC on the following issues relevant to IHC testing for PD-L1 expression on IC:

- The concordance of the Ventana PD-L1 IHC (SP142) assay with other available tests and advice on the implications of this to estimates of the incremental effectiveness of atezolizumab.
- Given the impact of different test assays on (likely higher) PD-L1-positive rates and consequent higher ICERs, the PBAC signalled a preference to limit testing to the Ventana PD-L1 IHC (SP142) assay. What would be the consequences, including for rates of false positives, of limiting to this assay versus being agnostic to the choice of assay for the purpose of helping determine eligibility for atezolizumab? How should this issue best be addressed in the MBS item descriptor and/or PBS restriction?
- In the context of potential future applications for targeted treatments for PD-L1-positive TNBC, what are the potential consequences for these treatments of limiting testing to the Ventana PD-L1 IHC (SP142) assay?

- Given the differences between archival and recent biopsies with respect to positive PD-L1 expression, should recent biopsies be required when available and should this be included in the MBS item descriptor and/or PBS restriction?
- 7.3 The PBAC acknowledged the high clinical need for effective therapies for patients with TNBC, who have higher rates of disease recurrence and poorer survival outcomes than other breast cancer subtypes.
- 7.4 The PBAC noted that the proposed listing for atezolizumab in combination with taxane chemotherapy is broader than the intervention in the IMpassion130 trial and that approved by the TGA, which have atezolizumab used only in combination with nab-P. The PBAC considered that, given the absence of clinical data in combination with other taxanes, the listing should be limited to treatment in combination with nab-P. The PBAC noted the pre-PBAC response requested that concomitant therapy should only be required at initiation of treatment and considered this was appropriate (i.e. a requirement for on-going use of concomitant nab-P may not be appropriate in the event of dose-limiting toxicities). The PBAC considered that the IMpassion131 trial of atezolizumab in combination with paclitaxel may provide support for a broader listing once its results become available.
- 7.5 The inclusion criteria in the IMpassion130 trial required that patients who received taxanes in the neoadjuvant or adjuvant setting must have completed treatment at least 12 months prior to randomization. The PBAC considered that a corresponding requirement should be included in the restriction, i.e. to require patients treated with taxanes to have completed their taxane treatment at least 12 months prior to initiation of atezolizumab.
- 7.6 The PBAC noted that the submission nominated nab-P as the comparator. Although nab-P + placebo was the comparator in the key trial, the PBAC agreed with the ESCs and the commentary that 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, including those with *de novo* metastatic disease or some patients with previously untreated locally advanced disease; and patients with BRCA1/2 deleterious mutations. The PBAC considered the most appropriate comparator for this heterogeneous population would be physician choice, but noted that there are various treatment pathways and the available evidence was limited to the comparison with nab-P.
- 7.7 The PBAC considered that, given the current evidence, the appropriate clinical place for atezolizumab is in addition to a nab-P, in patients who are PD-L1 positive, where a taxane would otherwise be used.
- 7.8 The PBAC noted that the main evidence for atezolizumab was based on the second interim analysis (January 2019 cut-off) of the IMpassion130 trial, where the median duration of follow-up was 18 months in the ITT population and 15.5 months in the PD-

L1-positive population. The PBAC noted that results from the next data cut-off, with more mature OS data (final OS analysis) are expected to be available later in 2020.

- 7.9 The PBAC noted that ATZ+nab-P demonstrated a statistically significant benefit in prolonging PFS, compared with nab-P. However, the PBAC considered that the small difference in median PFS of 2.2 months for the PD-L1 population was of unclear clinical significance.
- 7.10 The hierarchical design of the key trial meant that, because there was a non-statistically significant OS result in the ITT population, formal testing of OS for the PD-L1-positive subgroup could not be performed whilst controlling type I error (α) at the nominal level. The PBAC considered that, as a result, the claim of a survival benefit for ATZ+nab-P compared with nab-P was plausible, but not robust, and consequently the magnitude of any OS gain was uncertain. The PBAC considered that more mature OS data may provide more confidence regarding the magnitude of any OS benefit.
- 7.11 The PBAC noted that there was evidence suggesting a difference in OS between PD-L1-positive and PD-L1-negative patients receiving nab-P monotherapy, favouring patients with no PD-L1 expression on IC. The PBAC agreed with the ESCs that this difference contributes to the variation in hazard ratios across the two arms in the IMpassion130 trial, and thus to the related tests for interaction. The PBAC considered there is some evidence that PD-L1 status may predict variation in the treatment effect of atezolizumab, but the evidence for this is uncertain.
- 7.12 The PBAC noted that the Australian population who would be appropriate for nab-P under the current guidelines reflects approximately 10% of the IMpassion130 trial population. The PBAC considered that the limited applicability of the IMpassion130 trial data to the Australian population made the comparison difficult to interpret. The PBAC also considered that, as nab-P monotherapy is likely to be an inferior treatment for the majority of patients in the comparator arm of the key trial, the treatment effect of ATZ+nab-P is likely to be overestimated relative to current clinical practice.
- 7.13 The PBAC considered that the clinical claim of superior effectiveness compared with nab-P alone in the requested population was not adequately supported by the clinical evidence as the difference in PFS may not be clinically meaningful, the OS benefit was not robust as formal statistical testing could not be conducted, there was uncertainty regarding the test for interaction with PD-L1 status, nab-P was a potentially inferior comparator in many patients in IMpassion130 and the applicability of the trial to Australian current clinical practice was limited.
- 7.14 The PBAC considered that the claim of inferior but clinically manageable safety compared to nab-paclitaxel alone was reasonable.
- 7.15 The submission used different parametric functions to extrapolate OS in the proposed scenario (log-logistic function) versus the current scenario (Weibull function). The pre-PBAC response acknowledged that it was inappropriate to use a different parametric

function for PD-L1 negative patients who do not receive ATZ+nab-P in the proposed scenario. The pre-PBAC response also argued that the log-logistic function is appropriate to extrapolate OS for true PD-L1-positive patients who do receive ATZ+nab-P and “the potential for ongoing and durable response is further supported by clinical data from other immunotherapy trials and is consistent with expectations of clinicians who are experts in this field”. However, the PBAC considered that the use of different parametric functions between arms to extrapolate OS was not adequately justified and resulted in an extrapolated OS advantage that was not supported by the clinical trial data (noting the magnitude of any OS gains were uncertain given the OS gain observed in the trial was not statistically significant when adjusted for multiplicity and was likely overestimated due to the use of a sub-optimal comparator). The PBAC considered that using the Weibull function (in all arms) resulted in OS estimates that were more clinically plausible. The PBAC noted this would increase the ICER from \$55,000 to < \$75,000/QALY to \$155,000 < \$255,000/QALY (using the submission’s base case).

- 7.16 The PBAC noted that it is likely that the cost-effectiveness of ATZ+nab-P in the Australian population would differ depending on the assays used and considered that this would be a significant issue in terms of assessing the cost-effectiveness of atezolizumab. The PBAC requested that the MSAC consider the issues relevant to testing as outlined in paragraph 7.2.
- 7.17 The PBAC considered that the the rationale for the approaches used to estimate utility values in the 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.
- 7.18 The pre-PBAC response provided a revised base case that attempted to address many of the issues raised by the ESCs, however a significant number of changes were made to the economic model which could not be independently verified or evaluated in the context of a pre-PBAC response.
- 7.19 The PBAC noted that DUSC considered the financial estimates to be significantly underestimated. The PBAC noted that any underestimation of the number of treated patients would be conservative in the context of an RSA with a [REDACTED] % rebate above the caps. The PBAC considered that the patient numbers estimated in the pre-PBAC response were more reasonable than those estimated in the submission.
- 7.20 DUSC noted that the number of patients identified as eligible for treatment would depend on the PD-L1 testing assay and would be higher if alternative tests become available. The PBAC also noted that the proportion of PD-L1-positive patients in current Australian clinical practice may differ from the trial and this would impact on the number of eligible patients.
- 7.21 DUSC considered that the number of doses of atezolizumab and nab-P were overestimated. The pre-PBAC response proposed an episode of care cap of [REDACTED] doses

per patient treated with atezolizumab, beyond which it would fully rebate the cost of atezolizumab in its proposed RSA. The calculations provided with the pre-PBAC response applied an average of ■ doses, rather than a cap of ■ doses. The PBAC considered ■ doses to be more reasonable than the average of 27.4 administrations assumed in the submission.

7.22 The PBAC considered that any resubmission would need to be a major submission and would need to be based on updated clinical trial data. 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. The PBAC advised that an RSA with a ■% rebate above the expenditure caps would be required, and that this would need to be based on utilisation assumptions which did not result in overestimates.

7.23 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 given the genuine unmet need for a new treatment option in patients with unresectable locally advanced or metastatic triple-negative breast cancer. Roche is committed to working with the PBAC and the Department of Health to ensure that Australian patients with unresectable locally advanced or metastatic triple-negative breast cancer who are PD-L1-positive can access atezolizumab.