Australian Government

Medical Services Advisory Committee

Public Summary Document

Application No. 1570 – PD-L1 (Programmed Death Ligand 1) immunohistochemistry (IHC) testing for access to atezolizumab as first line therapy for patients with locally advanced or metastatic triple-negative breast cancer (TNBC)

Applicant: **Roche Products Pty Ltd**

Date of MSAC consideration: **MSAC 78th Meeting, 3 April 2020**

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, visit the MSAC website

1. Purpose of application

An application was received from Roche Products Pty Limited by the Department of Health. The integrated codependent submission requested:

- Medicare Benefits Schedule (MBS) listing of programmed death-ligand 1(PD-L1) immunohistochemical (IHC) testing for the evaluation of PD-L1 expression on tumour-infiltrating immune cells (IC) to determine eligibility for treatment with atezolizumab plus a taxane in patients with unresectable locally advanced or metastatic triple-negative breast cancer (TNBC); and
- Pharmaceutical Benefits Scheme (PBS) [Authority Required] listing for treatment with atezolizumab plus a taxane for the treatment of patients with unresectable locally advanced or metastatic TNBC who have evidence of PD-L1 expression on IC covering ≥1% of tumour area.

2. MSAC's advice to the Minister

After considering the strength of the available evidence in relation to the safety, clinical effectiveness and cost-effectiveness of programmed death-ligand 1(PD-L1) immunohistochemical (IHC) testing in some patients with unresectable locally advanced or metastatic triple-negative breast cancer (TNBC), MSAC deferred its advice on the creation of an MBS item for this purpose. Although inclined to support, MSAC will expeditiously reconsider this application at such time as the Pharmaceutical Benefits Advisory Committee (PBAC) recommends the codependent PBS listing of atezolizumab.

Consumer summary

Roche Products Pty Ltd applied for public funding through the Medicare Benefits Schedule (MBS) for a test called programmed death ligand 1 (PD-L1) immunohistochemistry (IHC). This test is used to help a person with triple-negative breast cancer (TNBC) know whether they can access a medicine called atezolizumab on the Pharmaceutical Benefits Scheme (PBS), in combination with chemotherapy.

TNBC is an aggressive type of cancer that is not easily treated using hormone therapy or other treatments that are commonly used for breast cancer. This application is for people who have TNBC that is advanced or has spread to other parts of the body.

Some TNBC cells (as well as cells from other types of cancer), and the immune cells inside the cancer, produce a protein called programmed death-ligand 1 (PD-L1). In healthy people, PD-L1 stops a person's immune system from attacking their normal cells. But if someone has cancer that expresses PD-L1, it stops the immune cells from attacking the cancer. Some medicines (called PD-L1 inhibitors or checkpoint inhibitors) can reduce this effect, which allows the person's immune system to recognise the cancer and attack it. If the person's PD-L1 IHC test shows that the immune cells inside the cancer are PD-L1 positive, this may mean that a PD-L1 inhibitor medicine such as atezolizumab will help them respond better to treatment. When combined with chemotherapy, this can help treat the cancer more effectively.

This application is for MBS funding of the PD-L1 test, and is linked to an application to the Pharmaceutical Benefits Advisory Committee (PBAC) for PBS listing of atezolizumab. The test and the medicine go hand in hand; this is called a codependent submission. The PBAC discussed the medicine at its meeting, but did not recommend its listing on the PBS because of concerns with the comparative effectiveness and cost-effectiveness of the medicine and how these are affected by the test results.

The PBAC therefore asked for MSAC's advice on which of the three commercially available PD-L1 test assays was the best one to use. MSAC noted that the three assays can give different results, and all three assays give the same result only about 60–70% of the time. MSAC advised that the reagent called SP142 was the most appropriate, as it was the assay used in the clinical studies of the medicine, and the other available assays are also not specifically approved by the Therapeutic Goods Administration (TGA) for TNBC.

The PBAC also asked MSAC whether a fresh biopsy (tissue sample) was needed for the test, or whether an old (archival) tissue sample could be used. MSAC advised that the most recent tissue sample (which could be archival) should be used.

MSAC's advice to the Commonwealth Minister for Health

MSAC was inclined to support the application to list programmed death ligand 1 (PD-L1) immunohistochemistry testing, but deferred its advice until the PBAC recommends that atezolizumab should be listed on the PBS. MSAC offered to reconsider this application at that time.

3. Summary of consideration and rationale for MSAC's advice

MSAC noted this codependent application for PD-L1 IHC testing for access to atezolizumab as first-line therapy for patients with locally advanced or metastatic TNBC. The PBAC deferred its recommendation to list atezolizumab on the PBS due to limited applicability of

clinical evidence in the relevant patient population, uncertainty in the claim of overall survival benefit and recognition that cost-effectiveness is likely to be affected by the choice of PD-L1 assay. The PBAC sought MSAC's advice on three points:

- concordance of the Ventana PD-L1 (SP142) assay with others and implications for incremental cost-effectiveness
- implications of possibly limiting testing to the SP142 assay, for this therapy and potential future therapies
- implications of possible variation between archival and recent biopsies with respect to PD-L1 expression, and whether a new biopsy would be required.

MSAC discussed the key trial (IMpassion 130), a double-blind, multicentre, randomised, placebo-controlled phase 3 trial of atezolizumab in combination with nab-paclitaxel compared with placebo with nab-paclitaxel as first-line treatment. The trial had 902 participants, including 42 Australians, who were stratified by PD-L1 status on enrolment (41% were PD-L1 positive according to the SP142 assay). MSAC noted the applicant's claim of benefit for overall survival in PD-L1 positive patients, but considered that the study design had statistical complications that introduced uncertainty in this claim. This was acknowledged in the applicant's pre-MSAC response.

In breast cancer, more cases show PD-L1 expression on tumour-infiltrating immune cells (ICs) than on tumour cells (TCs), with most TC-positive cases also being IC-positive (unlike other solid tumours). For this application, PD-L1 positivity was defined as PD-L1 expression on ICs covering ≥1% of the tumour area. MSAC noted the potential for confusion in the reporting and interpretation of PD-L1 testing across different cell types assessed using different assays and threshold of positivity across different cancers for different immunotherapy medicines. MSAC therefore emphasised the need for appropriate training and a satisfactory quality assurance program to be in place.

The Ventana SP142 PD-L1 IHC assay is listed by the Therapeutic Goods Administration (TGA) as a companion diagnostic test for TNBC. MSAC noted that other IHC assays for PD-L1 testing – Ventana SP263 and Agilent/Dako 22C3 – are available, however, SP263 and 22C3 are not TGA-approved for TNBC. SP263 is the most common PD-L1 IHC assay in use in Australia, primarily driven by its use in non-small cell lung cancer (NSCLC). MSAC noted that laboratories wishing to use an assay other than SP142 for TNBC would likely be required to perform a full in-house in vitro diagnostic validation to meet the TGA requirements (if the laboratories are aware of these implications of these TGA approvals), which would be a significant deterrent to using assays other than SP142 given the expected low volume of this testing in TNBC in individual laboratories. This would effectively limit the test to the SP142 assay, which MSAC considered to be appropriate. The applicant, in its pre-MSAC response, also agreed to limit testing to SP142. MSAC also noted the small patient population and suggested that inter-laboratory referrals would be required, as not all laboratories would be willing to set up the assay for the expected small number of cases per year.

MSAC discussed the concordance between the different PD-L1 assays. US Food and Drug Administration (FDA) criteria for concordant assays specify that overall per cent agreement (OPA) should be at least 90%. The IMpassion 130 trial undertook exploratory analysis of assay concordance on a subset of participants (n = 641). OPA was 69% between SP142 and SP263, and **redacted**% between SP142 and 22C3. The proportions of patients identified as PD-L1 positive in this subset were markedly different between assays: 46% using SP142, 75% using SP263 and **redacted**% using 22C3. Trends towards the greatest progression-free

survival and overall survival benefits were suggested in patients who were identified as positive using SP142.

MSAC also noted an Australian study (the SPRINT study) of assay concordance, which identified **redacted**.

Regarding potential variation between archival and recent biopsies of tissue samples, MSAC considered that genuine triple-negative breast cancers would not change in PD-L1 status over time to the same extent as in lung cancer, and the cut-off of 1% of the tumour area for PD-L1–expressing ICs was a low threshold. MSAC also considered that a repeat biopsy would be impractical for many patients. In its pre-MSAC response, the applicant also noted there was **redacted**. MSAC therefore considered that the most prudent and practical balance would be to specify the "most recent sample" for PD-L1 testing, which could be archival if necessary.

In the economic evaluation, MSAC considered the time horizon of 10 years to be long for patients with triple-negative breast cancer. The sensitivity analysis adjusting the overall positivity rate used in the economic evaluation for half the testing to be based on SP263 did not include an appropriate adjustment for the corresponding increase in false positive test results. If testing using only assay SP263 is not considered appropriate, the sensitivity analysis should be adjusted accordingly.

MSAC also noted the implications of the different rates of positive test results on the financial implications. Using SP142 only, an expected 41% of patients would test positive, resulting in a total net cost to the PBS/RPBS for atezolizumab of $**redacted**, and a total net cost to the PBS/RPBS of atezolizumab + nab-paclitaxel of $**redacted**. Using the SP263 or 22C3 assays, an expected 74% of patients would test positive, resulting in these estimates increasing to $**redacted** for atezolizumab, and to $**redacted** for atezolizumab + nab-paclitaxel.

Regarding the proposed item descriptor, MSAC considered that this should specify "tumour biopsy material" because IC infiltrate cannot be assessed from a cytology sample. MSAC also suggested that the explanatory notes to the item descriptor should clarify the definition of triple-negative breast cancer and define a positive PD-L1 result for PBS eligibility purposes. MSAC further suggested that, if a new MBS item is created, it not be subject to Rule 13 – otherwise it will be affected by other immunohistochemistry MBS items for breast cancer (if tested on a metastasis for instance). MSAC noted that, if testing is limited to patients with previously untreated patients with locally advanced or metastatic disease and an ECOG score of 0–1, this would require the test to be requested by the treating clinician (that is, it could not be pathologist determinable). MSAC also considered that, if the laboratory does not have access to a TGA-listed assay (that is, SP142), it should not undertake testing, so a limitation to the SP142 assay may not be needed in the item descriptor, and a note indicating that testing should be performed by a TGA-listed assay might suffice.

A foreshadowed MBS item reflecting the ESC and MSAC discussions is as follows.

Category 6 – PATHOLOGY SERVICES
MBS item number Immunohistochemical examination **by VENTANA SP142 Assay** of programmed death ligand 1 (PD-L1) **expression in tumour-infiltrating immune cells (IC) in** tumour **biopsy** material from a patient diagnosed with **unresectable** locally advanced or **metastatic** triple-negative breast cancer **and an ECOG score of 0–1, requested by, or on behalf of, a specialist or consultant physician,** to determine if the requirements relating to PD-L1 expression status for access to atezolizumab under the Pharmaceutical Benefits Scheme (PBS) are fulfilled. **This item must not be used more than once per patient.** **Explanatory Notes:** **Where available, the most recent tissue sample should be tested in preference to an archival tissue sample.** **Triple-negative breast cancer is defined as showing less than 1% positive nuclear staining for oestrogen receptor and for progesterone receptor, and negative overexpression/absence of gene amplification for human epidermal growth factor receptor 2 (HER2 or c-erb-B2).** **PD-L1 expression on ICs covering greater than or equal to 1% of the tumour area is considered a positive PD-L1 score for PBS eligibility purposes.** **A cytology sample is not an appropriate sample to test.** Fee: $74.50 Benefit: 75% = $55.90 85% = $63.35

Note: Text in **bold red font** indicates the ESCs or MSAC proposed amendments to the listing.

MSAC was inclined to support the application, but deferred its advice until such time as the PBAC recommends the codependent PBS listing of atezolizumab. Following a PBAC recommendation, MSAC will reconsider its advice based on a streamlined codependent submission.

4. Background

IHC testing for the evaluation of PD-L1 expression in patients diagnosed with unresectable locally advanced or metastatic TNBC has not been previously considered by MSAC.

PASC considered the PICO Confirmation for Application 1570 - PD-L1 testing for access to atezolizumab for the treatment of locally advanced or metastatic TNBC at its April 2019 meeting.

The concerns raised by PASC and how these have been addressed by the submission are listed in Table 1.

Table 1: PASC concerns and how these were addressed in the submission

PASC issue (1570 Ratified PASC Outcome, April 2019)	How it was addressed in the submission
PASC recommended that the TNBC population should include men.	*Men (n=4/902) were included in the key IMpassion130 trial and have not been excluded by the submission.*
PASC noted that the estimated population in the final PICO only included patients with metastatic and not locally advanced disease, so is likely to be an underestimate.	Unresectable locally advanced TNBC patients represented 9.8% of the total patient population in the IMpassion130 trial and the submission predicted there would be a similar proportion in the eligible Australian population. Khan et al (2019)[a] in South Western Sydney found that unresectable locally advanced TNBC represented 18% and metastatic TNBC 82% of a population-based cohort. *Thus, the addition of patients with unresectable locally advanced TNBC is likely to increase the population by 10-20%.*

PASC issue (1570 Ratified PASC Outcome, April 2019)	How it was addressed in the submission
PASC noted that ER-positive tumours are those with ER >1%, but expression of ER antigens can be dramatically affected by how tissue is fixed and processed, and the staining platform used. The true rate of ER-negative tumours may therefore be much lower than 20%.	*This was not addressed by the submission.*
PASC queried whether the *BRCA1/2* status of patients would affect outcomes. The applicant stated that about 15% of patients in the IMpassion130 trial were *BRCA1/2* positive and outcomes did not depend on *BRCA1/2* status. This data needed to be clarified.	This issue was addressed of the submission, which reported that patients with *BRCA1/2* deleterious mutations derived clinical benefit (PFS/OS) only if their tumours were also PD-L1 IC positive. *This contradicts the findings observed during the evaluation where the OS HR point estimates suggest that, irrespective of PD-L1 status, patients with* BRCA1/2 *deleterious mutations may have a poorer response to atezolizumab plus nanoparticle albumin-bound paclitaxel (nab-P) over nab-P alone than patients with wild type* BRCA1/2 *genes. This result is uncertain due to the small number of patients who had* BRCA1/2 *deleterious mutations.*
PASC noted that the available IHC assays differ in the cell types and thresholds used to define PD-L1 positivity. PASC expressed concern about the comparability of the different assays, noting that atezolizumab results had not been validated on other platforms.	This was addressed by the submission, which concluded that the patients assessed as being PD-L1 positive obtained clinical benefit from treatment with atezolizumab plus nab-P, whereas those who were PD-L1 negative did not, regardless of the PD-L1 assay used. *Although the HR data appears to support this, the median PFS/OS and the area between treatment arms of the Kaplan-Meier curves indicated a numerically larger incremental treatment effect in the biomarker evaluable population (BEP) SP142-IC and the ITT SP142-IC (evidentiary test) PD-L1-positive populations when compared to the larger PD-L1-positive populations identified by the three additional testing strategies (that included SP142-IC false-positive patients), which in turn was numerically larger than for the ITT unselected population (that included PD-L1-negative patients).*
PASC also considered that reproducibility of results with different assay kits and platforms may have an impact on treatment decisions.	The submission reported on the concordance between the three PD-L1 IHC assays commercially available in Australia. *There was low negative percent agreement between testing strategies (34% to 46%). This resulted in approximately 30% more patients being identified as PD-L1 positive by the other two assays, as compared with the evidentiary standard.*
PASC queried whether differences between tests would affect service provision by different laboratories/locations.	The submission indicated that pathologists should receive training for using the PD-L1 IC ≥1% scoring algorithm and the sponsor has implemented an extensive training program for oncologists and pathologists. This training should be suitable for use with all three commercially available PD-L1 IHC assays.
PASC suggested it may be appropriate to include a requester definition: 'requested by, or on behalf of, specialist or consultant physician'.	The submission agreed with this suggestion.
PASC advised that false-positive and false-negative rates must be considered, especially in terms of the consequences of a high false-positive rate on economic aspects for the PBAC.	*The submission did not adequately account for false-negative and false-positive results. All modelled outcomes were based on an analysis of survival data from patients identified as PD-L1 positive based on the SP142-IC assay. The economic model was not constructed to allow a sensitivity analysis of the impact of using different assays. The modelled outcomes may, therefore, not be applicable to the Australian PBS population if tests other than the SP142-IC assay are used to determine eligibility for atezolizumab.* *30% of patients in the BEP were PD-L1 negative according to the SP142-IC evidentiary standard and PD-L1 positive by SP263-IC,* ***redacted*** *and 22C3-CPS. An exploratory analysis of these patients found that they are likely to be "false positive". The HRs for OS and the median OS values all align more closely to the SP142-IC PD-*

PASC issue (1570 Ratified PASC Outcome, April 2019)	How it was addressed in the submission
	L1-negative population than the SP142-IC PD-L1-positive population. The Kaplan-Meier curves also show little or no true differences between treatment arms.

[a] Khan, S, Kiely, B & Moylan, E 2019, 'Advanced Triple Negative Breast Cancer: Treatment Patterns and Outcomes in a Population-Based Cohort in South Western Sydney', Asia-Pacific Journal of Clinical Oncology, vol. 15, no. S5, pp. 80-81.
Source: Constructed during the evaluation

5. Prerequisites to implementation of any funding advice

Roche Diagnostics submitted a medical device in vitro diagnostic (IVD) Class 3 application in June 2019 for inclusion of the VENTANA PD-L1 (SP142) assay on the Australian Register of Therapeutic Goods (ARTG) as an abridgement to the current FDA approval specific to TNBC. Roche received inclusion in the ARTG for the VENTANA (SP142) PD-L1 assay, as a Companion Diagnostic test for TNBC on 2 September 2019 (ARTG 322582).

The VENTANA PD-L1 (SP263) assay and the Agilent/Dako PD-L1 (22C3) pharmDx assay are both TGA-approved as in vitro diagnostic (IVD) Class 3 medical devices for PD-L1 IHC testing in patients with NSCLC and urothelial carcinoma, but not TNBC. These tests are currently being used in clinical practice to identify PD-L1 positive (defined as ≥50% tumour proportion score) NSCLC for access to pembrolizumab.

The submission indicated that PD-L1 testing for the TNBC indication will be conducted in National Association of Testing Authorities (NATA) accredited Australian laboratories and that a request has been submitted for the implementation of a Quality Assurance Programme (QAP) by the Royal College of Pathologists of Australasia (RCPA).

National Pathology Accreditation Advisory Council (NPAAC) advice to MSAC
This testing is already being performed in some laboratories in Australia supported by Roche. The technical aspects of the staining are standard but the interpretation requires experience. Roche provide an on line module to train pathologists, and where the test is being performed, pathologists are double reading the stains to standardize the interpretation. The quality assurance programs for this marker are new. There is no Australian EQA program available at present, but RCPA QAP are running a pilot program for interpretation performance in 2020. There is an existing EQA for the technical performance of the stain offered by IQNPath[1] (a consortium which includes UK and major Euopean quality assurance programs). IQNPath will offer the interpretation module for the first time in 2020.

It is critical that biomarker testing is offered in a robust quality assurance framework to protect patients against false-positive or false-negative results.

6. Proposal for public funding

The applicant's initially requested MBS item is shown in Table 2.

[1] http://www.iqnpath.org/

Table 2: Applicant's initially proposed MBS listing

Category 6 – PATHOLOGY SERVICES
[MBS item number] Immunohistochemical examination by immunoperoxidase or other labelled antibody techniques using the programmed death ligand 1 (PD-L1) antibody of tumour material from a patient diagnosed with triple-negative breast cancer, to determine if the requirements relating to (PD-L1) expression status for access to atezolizumab under the Pharmaceutical Benefits Scheme (PBS) are fulfilled. Fee: $**redacted** Benefit: 75% = $**redacted** 85% = $**redacted**

Source: Table 1.8.1 of the MSAC_PBAC Combined Submission

The submission agreed with the suggestion by PASC that it may be appropriate to include a requester definition in the proposed MBS listing such as: 'requested by, or on behalf of, specialist or consultant physician' due to the differences in PD-L1 testing in TNBC compared with other tumour types. However, the Commentary noted the proposed MBS listing is not explicitly restricted to the particular antibody (SP142) used by the evidentiary standard test.

In its pre-MSAC response following the ESC discussion, the applicant provided an amended MBS item descriptor (Table 3). This was provided after consulting specialist breast cancer pathologists who supported the MBS item descriptor specifying the use of the SP142 assay as the descriptor is clearly linked to treatment with atezolizumab. Revised wording in Table 3 is in *italics*. However, the applicant considered that the MBS item descriptor (or PBS restriction) should not contain explicit wording with requirements for tissue samples, or any limitation to the number of times the MBS item could be billed for a patient.

Table 3: Applicant's amended MBS listing provided in pre-MSAC response

Category 6 – PATHOLOGY SERVICES
[MBS item number] Immunohistochemical examination by *VENTANA PD-L1 (SP142) Assay* using the programmed death ligand 1 (PD-L1) antibody of tumour material from a patient diagnosed with triple-negative breast cancer, to determine if the requirements relating to (PD-L1) expression status for access to atezolizumab under the Pharmaceutical Benefits Scheme (PBS) are fulfilled. Fee: $**redacted** Benefit: 75% = $**redacted** 85% = $**redacted**

Source: Table 1, p2 of the pre-MSAC response

7. Summary of public consultation feedback/consumer Issues

The Breast Cancer Network Australia (BCNA) supported MSAC consideration of the proposed service, particularly considering the limited treatment options for women with TNBC. BCNA indicated that patients who may benefit from treatment with atezolizumab should be able to access PD-L1 testing at an affordable price, and should not be excluded because of out-of-pocket expenses.

The Peter MacCallum Cancer Centre also supported the application, advising that PD-L1 testing allows targeted treatment in a patient population with a very strong clinical need, with cost savings for patients who otherwise may have to self-fund testing and therapy. However, it was noted that the addition of immunotherapy (atezolizumab) will increase the toxicity of patients' treatment.

8. Proposed intervention's place in clinical management

Description of the proposed intervention

The proposed medical service is an IHC test for evaluation of PD-L1 expression to determine eligibility for treatment with atezolizumab in patients with locally advanced or metastatic TNBC who are previously untreated in the advanced setting. The biopsy sample taken as part of a standard diagnostic process will be used for IHC testing with PD-L1. The testing would be done by a pathologist alongside other IHC tests which are done routinely.

The scoring threshold for TNBC is PD-L1 IHC staining of IC at any discernible intensity that covers ≥1% of the tumour area. The key IMpassion130 trial used the VENTANA PD-L1 (SP142) Assay to determine PD-L1 positivity. There are currently two other commercially available PD-L1 IHC assays that could also be used; the VENTANA PD-L1 (SP263) and Agilent/Dako PD-L1 (22C3) pharmDx assays.

Description of the medical condition(s)

TNBC accounts for approximately 15% of patients with breast cancer in Australia[2], and is defined as <1% IHC immunostaining for oestrogen and progesterone receptors, and HER2-negative by *in situ* hybridisation. TNBC tumours are generally larger in size and are more poorly differentiated compared to other breast cancers with an invasive phenotype. Therefore, patients have more extensive lymph node involvement and more advanced disease at diagnosis. Patients with TNBC are typically younger and have a poorer prognosis in the first 5 years after diagnosis than those with other breast cancer subtypes despite their good response rate to (neo)adjuvant chemotherapy[3].

Patients may be diagnosed with newly occurring (*de novo*) or recurrent unresectable locally advanced or mTNBC. Those with recurrent disease most likely had previous adjuvant treatment for early stage (I-III) breast cancer. The submission estimated that *de novo* TNBC is estimated to be approximately 25% of the proposed PBS population.

Place in clinical management

Currently, patients with unresectable locally advanced, recurrent or metastatic TNBC do not undergo PD-L1 IHC testing. They receive standard of care chemotherapy, including anthracyclines, taxanes and/or platinum-based chemotherapy (Figure 1). The regimen chosen depends on patient characteristics, previous treatment in the early breast cancer setting and clinician and/or patient choice. Typically, patients receive more than one line of chemotherapy.

It was proposed that patients diagnosed with unresectable locally advanced, recurrent or metastatic TNBC and with an ECOG of 0-1 would receive PD-L1 IHC testing (Figure 2). Those found to be PD-L1 IC positive would receive first-line treatment with atezolizumab in combination with taxane chemotherapy. Patients would continue to receive more than one line of treatment. The second-line chemotherapy regimen would vary and would be determined in the same way as for the current clinical algorithm.

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[2] Breast Cancer Network Australia: Triple negative breast cancer. Available from URL: https://www.bcna.org.au/understanding-breast-cancer/what-is-breast-cancer/triple-negative-breast-cancer/ [accessed 24 October 2019].

[3] Mehanna, J, Haddad, FG, Eid, R, Lambertini, M & Kourie, HR 2019, 'Triple-negative breast cancer: current perspective on the evolving therapeutic landscape', Int J Womens Health, vol. 11, pp. 431-437.

The Commentary stated that both algorithms assume predominantly taxane-based chemotherapy is used in the metastatic TNBC setting. However, treatment guidelines and recent Australian data have shown that this may not be the case. In addition, the algorithm failed to accommodate the varied treatment approaches in patient subpopulations with either *BRCA1/2* deleterious mutations (usually receive platinum-based chemotherapy) or unresectable locally advanced TNBC (receive chemoradiotherapy with a goal of rendering the tumour operable), as delineated by international guidelines.

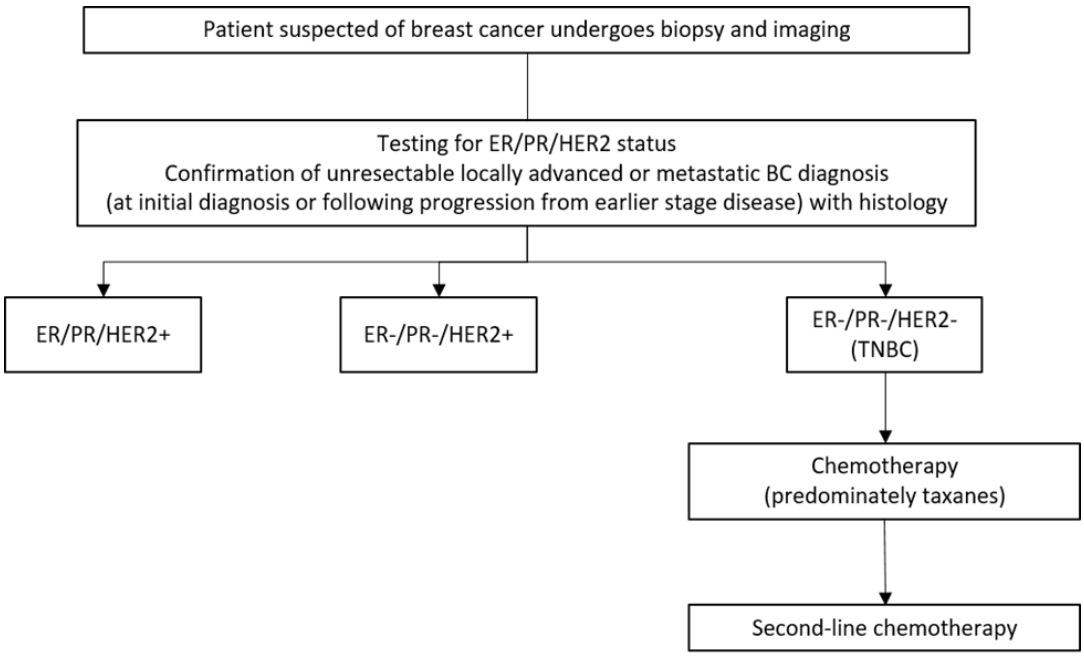

Figure 1: Current clinical management algorithm
BC = breast cancer; ER = oestrogen; HER2 = human epidermal growth factor receptor; PR = progesterone; TNBC = triple-negative breast cancer
Source: Figure 1.5.1 from the MSAC_PBAC Combined Submission

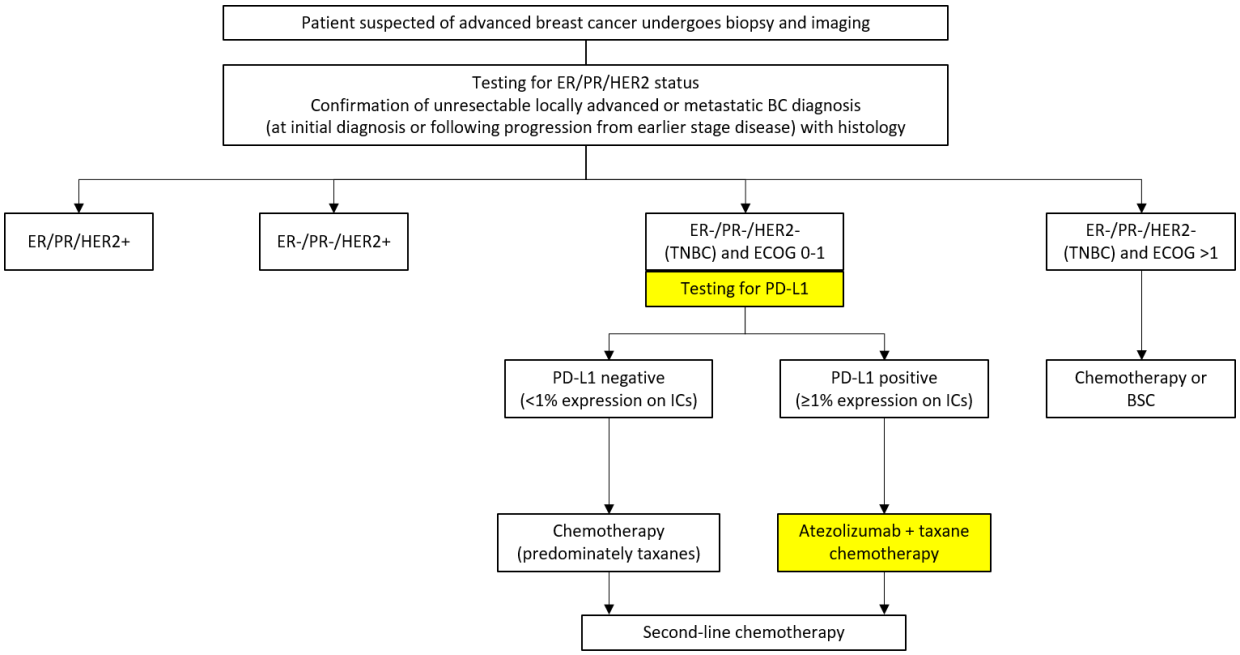

Figure 2: Proposed clinical management algorithm
BC = breast cancer; BSC = best supportive care; ECOG = Eastern Cooperative Oncology Group; ER = oestrogen; HER2 = human epidermal growth factor receptor; PR = progesterone; TNBC = triple-negative breast cancer
Source: Figure 1.5.2 from the MSAC_PBAC Combined Submission

9. Comparator

The appropriate comparator to PD-L1 IHC testing is no testing.

The PD-L1 testing strategy (SP142-IC) used to stratify patients according to their PD-L1 IC positivity in the IMpassion130 trial was considered the evidentiary standard against which the percent agreement and comparative health outcomes for the other three testing strategies were measured.

The submission nominated nab-P as the main comparator for the proposed medicine. However, the Commentary stated that this is much narrower than the "standard of care" nominated as the comparator in the PASC-ratified PICO Confirmation. Additionally, nab-P is only PBS funded for 'metastatic breast cancer', not for unresectable locally advanced disease and so is not a suitable comparator for the Australian setting for this subpopulation.

Furthermore, the selected comparator was not appropriate for first-line use in up to 90% of the ITT population in the IMpassion130 trial. Therefore, the Commentary considered the applicability of the treatment received (nab-P) by patients in the key IMpassion130 trial is concerning.

10. Comparative safety

The approach taken in the submission was to present direct evidence of the effect of targeting patients with PD-L1-positive TNBC with atezolizumab and nanoparticle albumin-bound paclitaxel (ATZ+nab-P) to improve their PFS and OS (Table 4).

Table 4: Evidence provided in the submission to support the use of the codependent technology

Study design	Extent of evidence supplied	Overall risk of bias in clinical trials
Double-randomised controlled trial[a]	☐ k= n=	
Single-randomised (3-arm) controlled trial[b]	☐ k= n=	
Prospective biomarker stratified randomised controlled trial of medicine[c]	☒ k=1 ITT: n=902 BEP: n=614	ITT population: low risk of bias ITT PD-L1-positive population: medium risk of attrition bias BEP population: high risk of attrition bias
Retrospective biomarker stratified randomised controlled trial of medicine[d]	☐ k= n=	

[a] randomised to test versus no (or alternative) test, with each component subsequently randomised to the proposed medicine or comparator medicine; [b] randomised to ARM 1: test + medicine in test-positive patients or usual care in test-negative patients vs ARM 2: no test + usual care vs ARM 3: no test + medicine; [c] population with and without the biomarker randomised to medicine or usual care; [d] randomised to medicine or usual care and then biomarker status determined.
BEP = biomarker evaluable population; ITT = intention-to-treat; k = number of studies; n = number of patients; PD-L1 = programmed death ligand 1

Adverse events from testing

The PD-L1 IHC test is performed on the same tumour specimen used for the histological assessment and standard diagnostic work-up of patients suspected of having breast cancer, and there is likely no requirement for most patients to undergo any additional procedures associated with the collection of tumour tissue in order to perform PD-L1 IHC testing. For those with recurrent disease, PD-L1 IHC testing could be performed on archival tumour tissue.

However, the Commentary stated that PD-L1 status will differ between the primary tumour and metastases for some patients. Thus, PD-L1 IHC testing should be conducted using new

biopsies or surgical tumour samples, rather than archival material, if possible. A new biopsy may be taken to determine that the hormone receptor status of the recurrent or metastatic tumours has not altered. An additional biopsy for the purposes of PD-L1 IHC testing would only be required if adequate tumour tissue for PD-L1 IHC testing was not available. Re-biopsy rates have previously been considered by MSAC to be around 8–10%, although MSAC noted that these rates included other types of cancer such as lung cancer involving smaller samples than is usually the case with breast cancer, and thus likely higher re-biopsy rates.

Adverse events from atezolizumab plus nab-paclitaxel
A higher incidence of grade 3-4 adverse events (AEs), serious AEs and AEs leading to dose modification/interruption or discontinuation was observed in the ATZ+nab-P arm compared to the placebo plus nab-paclitaxel (PBO+nab-P) arm in both the ITT and PD-L1-positive populations (see Table 5).

The Commentary stated that patients with:

- false-positive PD-L1 results who receive atezolizumab plus taxane chemotherapy will experience more harms (adverse events), and require more treatment discontinuations or interruptions than with chemotherapy alone. These patients may or may not obtain some additional benefit from treatment with atezolizumab
- false-negative PD-L1 results who forgo treatment with atezolizumab plus taxane chemotherapy may have a shorter time before progression and/or death than if they had received the targeted treatment.

However, the Commentary stated that, given there is no reference standard for PD-L1 IHC testing on IC, the proportion of patients likely to have false-positive or false-negative PD-L1 results could not be determined.

Table 5: Overview of adverse events and deaths in the safety-evaluable population in IMpassion130 (data cut off 17 April 2018)

Adverse event	ITT safety-evaluable population (%)		RR (95% CI) (ATZ+nab-P vs. PBO+nab-P)	PD-L1-positive safety-evaluable population (%)		RR (95% CI) (ATZ+nab-P vs. PBO+nab-P)
	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)**
Number 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)
Number 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)**
Atezolizumab/placebo	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 atezolizumab/placebo	139 (30.8)	103 (23.5)	**1.31 (1.05, 1.63)**	60 (32.4)	38 (21.0)	**1.54 (1.09, 2.19)**

AE = adverse event; ATZ+nab-P = atezolizumab + nab-paclitaxel; CI = confidence interval; N = total participants in group; NC = not calculable; PD-L1=programmed death-ligand 1; PBO+nab-P = placebo + nab-paclitaxel; SAE = serious adverse event; 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.
Source: data combined from Table 2.5.12, p 101 and Table 2.5.13, p 102 of the MSAC_PBAC Combined Submission.

11. Comparative effectiveness

Prognostic evidence
PD-L1 expression was identified as a prognostic factor for Stage I-III TNBC. Higher levels of PD-L1 expression in either tumour or immune cells associated with the tumour predicted longer survival (DFS and OS) than lower or no PD-L1 expression in Stage I-III TNBC patients. There were no studies identified to determine if PD-L1 expression is also a prognostic factor in Stage IV TNBC. The Commentary stated that two studies reported that patients receiving (neo)adjuvant chemotherapy were 3–4 times more likely to have a complete response if they had upregulated PD-L1 mRNA expression on IC compared to patients with no upregulation of PD-L1 mRNA.

The Commentary stated that this contradicts the predicted effect of PD-L1 in dampening the immune response, which would lead to a worse prognosis. This may be the case in the IMpassion130 trial; in the comparator arm, there appeared to be a non-significant decrease in PFS and OS among patients with PD-L1 IC-positive TNBC compared with those who were PD-L1 IC negative.

Thus, the Commentary stated that PD-L1-positive patients enrolled in the IMpassion130 trial did not have a prognostic benefit (and may have a poorer prognosis) compared to those who are PD-L1 negative.

Concordance of PD-L1 IHC tests
The overall percent agreement (OPA) between the other PD-L1 assays and the evidentiary standard SP142-IC assay was between 64% and 69%, with a high degree of positive percent agreement (PPA) between tests (95% to 98%). The Commentary stated this indicates that almost all patients assessed as being PD-L1 positive using the SP142-IC strategy were also assessed as being PD-L1 positive when tested using the SP263-IC, **redacted** and 22C3-CPS strategies.

However, the Commentary stated that the low negative percent agreement (NPA) between tests (34% to 46%) suggests that a large number of patient tumour specimens in the biomarker evaluable population (BEP) assessed as being PD-L1 negative using the SP142-IC strategy were assessed as being PD-L1 positive by other strategies. This was reflected in the variability of the prevalence of PD-L1 positivity identified by the four testing strategies (Table 6).

Table 6: Prevalence of PD-L1 positives and negatives in the BEP population (n=614)

Testing strategy	Prevalence of PD-L1 positive	Prevalence of PD-L1 negative
SP142-IC	46% (n=285)	54% (n=329)
SP263-IC	75% (n=460)	25% (n=154)
redacted	redacted% (n=redacted)	redacted% (n=redacted)
22C3-CPS	81% (n=497)	19% (n=117)

CPS = combined positive score; IC = tumour-infiltrating immune cells
Source: Table 2(T).4.9 of the Section 2 – Test submission document

The Commentary stated that the **redacted**% difference between the PD-L1-positive populations for the evidentiary standard compared to the additional testing strategies indicates that the three additional testing strategies cannot be considered concordant with the evidentiary standard.

In its pre-ESCs response, the applicant provided results from the Australian SPRINT study:

- **redacted**
- **redacted**.

From these results, the applicant noted:

- **redacted**
- **redacted**
- **redacted**
- **redacted**
- **redacted**

Table 7: redacted
Source: Table 3, p9 of the applicant's pre-ESCs response (from the SPRINT study)

Tissue sample
In its pre-MSAC response, the applicant provided new unpublished data currently being reviewed by JAMA Oncology (under embargo; strictly academic in confidence), which evaluated the impact of atezolizumab on survival (both PFS and OS) in PD-L1-positive samples determined from archival versus fresh tissue in IMpassion130. **Redacted**.

Figure 1: Redacted
Source: Figure 3, p5 of the pre-MSAC response

Figure 2: Redacted
Source: Figure 4, p5 of the pre-MSAC response

Effectiveness (based on direct evidence only)
The submission concluded from the data presented for PFS (Table 8) and OS (Table 9) from the BEP showing that patients assessed as being PD-L1 positive obtained a clinical benefit from treatment with ATZ+nab-P whereas those who were PD-L1 negative did not, regardless of the PD-L1 assay used.

However, the Commentary stated this claim could not be substantiated for several reasons.

- The BEP (n=614) was subject to attrition bias and may not be representative of the ITT population (n=902). No reasons for exclusion of patients from the BEP were reported, e.g. availability of biopsy tissue, testing country, etc.
- The HRs for the PD-L1-positive patients as determined by the four testing strategies appear to support the conclusion reached by the submission. However, the median PFS/OS values and the areas between the intervention and control arms in the Kaplan-Meier curves do not appear to support the same conclusion:
    - the difference in median OS showed numerically longer survival after receiving the intervention in the BEP and ITT SP142-IC PD-L1-positive populations compared to the other three BEP PD-L1-positive populations; and
    - the areas between the intervention and control Kaplan-Meier OS curves for the four BEP and the ITT PD-L1-positive populations are suggestive of a stronger treatment effect in the BEP SP142-IC and the ITT SP142-IC populations when compared to the other testing strategies, which are in turn stronger than for the ITT unselected population.
- The 30% of patients who were PD-L1 negative according to the evidentiary standard and PD-L1 positive by SP263-IC, **redacted** and 22C3-CPS were more likely to be "false positive" than "false negative" according to an exploratory *post hoc* analysis:
    - the HRs for OS and the median OS values all align numerically more closely to the SP142-IC PD-L1-negative population than the SP142-IC PD-L1-positive

population. The Kaplan-Meier curves also show little or no true differences between treatment arms; and

- given that these "false positive" patients do not appear to derive any additional benefit from atezolizumab, MSAC should consider limiting PD-L1 IHC testing to determine PD-L1 positivity in TNBC to the evidentiary standard, the VENTANA PD-L1 SP142 assay.

Table 8: Summary results for PFS by PD-L1 assay (data cut off 2 January 2019): BEP

PFS		SP142-IC	SP263-IC	redacted	22C3-CPS	ITT-PD-L1 (SP142-IC)
PD-L1 positive		46% BEP (n=285)	75% BEP (n=460)	redacted (n=redacted)	81% BEP (n=497)	41% ITT (n=369)
Median PFS (months)	Intervention	8.3	7.5	redacted	7.5	7.5
	Control	4.1	5.3	redacted	5.4	5.3
Difference in median PFS (months)		4.2	2.2	redacted	2.1	2.2
HR (95% CI)		0.60 (0.47, 0.78)	0.64 (0.53, 0.79)	redacted (redacted)	0.68 (0.56, 0.82)	0.63 (0.50, 0.80)
PD-L1 negative		54% BEP (n=329)	25% BEP (n=154)	redacted (n=redacted)	19% BEP (n=117)	59% ITT (n=533)
Median PFS (months)	Intervention	5.7	5.5	redacted	5.5	5.6
	Control	5.6	6.9	redacted	5.5	5.6
Difference in median PFS (months)		0.1	-1.4	redacted	0.0	0.0
HR (95% CI)		0.86 (0.68, 1.09)	1.08 (0.77, 1.51)	redacted (redacted)	1.0 (0.68, 1.49)	0.90 (0.75, 1.08)

BEP = biomarker evaluable population; CI = confidence interval; Control = placebo + nab-paclitaxel; CPS = combined positive score; HR = hazard ratio; IC = tumour-infiltrating immune cells; Intervention = atezolizumab plus nab-paclitaxel; ITT = intention-to-treat; PFS = progression-free survival
Source: Table 2(T).4.10 and Table 2(T).4.11 of the Section 2 – Test submission document

Table 9: Summary results for OS by PD-L1 assay (data cut off 2 January 2019): BEP

OS		SP142-IC	SP263-IC	redacted	22C3-CPS	ITT-PD-L1 (SP142-IC)
PD-L1 positive		46% BEP (n=285)	75% BEP (n=460)	redacted (n=redacted)	81% BEP (n=497)	41% ITT (n=369)
Median OS (months)	Intervention	27.3	22.0	redacted	21.6	25.0
	Control	17.9	18.7	redacted	19.2	18.0
Difference in median OS (months)		9.4	3.3	redacted	2.4	7
HR (95% CI)		0.74 (0.54, 1.01)	0.75 (0.59, 0.96)	redacted (redacted)	0.78 (0.62, 0.99)	0.69 (0.52, 0.91)
PD-L1 negative		54% BEP (n=329)	25% BEP (n=154)	redacted (n=redacted)	19% BEP (n=117)	59% ITT (n=533)
Median OS (months)	Intervention	20.8	17.9	redacted	14.7	19.7
	Control	20.7	20.5	redacted	19.6	19.6
Difference in median OS (months)		0.1	-2.6	redacted	-4.9	0.1
HR (95% CI)		0.95 (0.72, 1.27)	1.15 (0.76, 1.74)	redacted (redacted)	1.12 (0.70, 1.77)	0.94 (0.75, 1.17)

BEP = biomarker evaluable population; CI = confidence interval; CPS = combined positive score; HR = hazard ratio; IC = tumour-infiltrating immune cells; ITT = intention-to-treat; OS = overall survival
Source: Table 2(T).4.10 and Table 2(T).4.11 of the Section 2 – Test submission document

Clinical effectiveness of atezolizumab

Results from the 2 January 2019 cut-off are presented for the ITT unselected and PD-L1-positive populations (Table 10), and for the PD-L1-negative population (Table 11). The Commentary stated that, for every 100 PD-L1-positive patients treated with ATZ+nab-P, an additional 13 patients would remain progression-free at 1 year and an additional 14 patients would be alive after 2 years compared with nab-P monotherapy. In comparison, for every 100 unselected patients treated with ATZ+nab-P, only half as many additional patients (6) would remain progression-free at 1 year compared with nab-P monotherapy, but there would be no significant difference in the number of ITT unselected and PD-L1-negative patients remaining alive after 2 years (3–4 additional patients).

Table 10: Summary of PFS and OS comparing the ITT unselected and PD-L1-positive populations in the IMpassion130 trial (data cut off 2 January 2019)

	ITT PD-L1-positive population		Unselected ITT population	
	ATZ+nab-P	PBO+nab-P	ATZ+nab-P	PBO+nab-P
PFS				
Events/N (%) **Median (95% CI)**	149/185 (80.5%) 7.46 (6.70, 9.23)	163/184 (88.6%) 5.29 (3.81, 5,55)	379/451 (84.0%) 7.16 (5.55, 7.43)	404/451 (89.6%) 5.49 (5.32, 5.62)
Absolute difference RD (95% CI) at 1 year	RD = –12.99 (–21.84, –4.14)		RD = –6.06 (–11.61, –0.52)	
HR (95% CI), p-value	HR = 0.63 (0.50, 0.80), p < 0.0001		HR = 0.80 (0.69, 0.92), p = 0.0021	
OS				
Events/N (%) **Median (95% CI)**	94/185 (50.8%) 25.03 (19.55, 30.65)	110/184 (59.8%) 17.97 (13.63, 20.07)	255/451 (56.5%) 20.99 (19.02, 22.60)	279/451 (61.9%) 18.73 (16.85, 20.30)
Absolute difference RD (95% CI) at 2 years	RD = –13.80 (–24.94, –2.66)		RD = –3.69 (–10.75, 3.38)	
HR (95% CI), p-value	HR = 0.71 (0.54, 0.93), p = 0.0133[a]		HR = 0.86 (0.72, 1.02), p = 0.0777	

ATZ+nab-P = atezolizumab + nab-paclitaxel; CI = confidence interval; HR = hazard ratio; ITT = intention-to-treat; N = total participants in group; OS = overall survival; PBO+nab-P = placebo + nab-paclitaxel; PD-L1 = programmed death ligand 1; PFS = progression-free survival; RD = risk difference

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

Source: Table 2.5.1, Table 2.5.2, Table 2.5.3 and Table 2.5.4 of the MSAC_PBAC Combined Submission

Table 11: Summary of OS for the PD-L1-negative treatment arms in the IMpassion130 trial (data cut off 2 January 2019)

OS	ITT PD-L1 negative population	
	ATZ+nab-P	PBO+nab-P
Events/N (%) **Median (95% CI)**	161/266 (60.5%) 19.65 (16.26, 21.62)	169/267 (63.3%) 19.61 (16.85, 22.18)
Absolute difference - RD (95% CI) at 2 years	RD = 3.18 (–5.89, 12.24)	
HR (95% CI)	HR = 0.97 (0.78, 1.20), p = 0.7635	

ATZ+nab-P = atezolizumab + nab-paclitaxel; CI = confidence interval; HR = hazard ratio; N = total participants in group; NNT = number needed to treat; PBO+nab-P = placebo + nab-paclitaxel; RD = risk difference

Source: Table OS_PDL1NEG_IT_02JAN2019_29522 Time to event Summary for overall survival provided by the applicant on request

Clinical claim

On the basis of the benefits and harms reported in the evidence base (summarised above), the applicant claimed that, relative to nab-P, ATZ+nab-P has inferior safety and superior effectiveness.

The Commentary considered that the claim of inferior safety was reasonable, but the claim of superior effectiveness was uncertain. Although the results of the IMpassion130 trial are suggestive of treatment effect modification with ATZ+nab-P by PD-L1 status, the OS results were exploratory and the prespecified statistical testing procedure was not followed. 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. In addition, the target Australian population was not well represented in the key trial, which was comprised of nearly 40% taxane- and anthracycline-naïve patients. The majority of unresectable locally advanced and metastatic TNBC patients in Australia will have received prior anthracycline/taxane combination therapy but ATZ+nab-P failed to demonstrate a survival benefit in these patients (in both the ITT and PD-L1-positive subgroup). Although these subgroup data were exploratory, the results suggest caution is needed when considering the clinical claim.

12. Economic evaluation

The submission presented a modelled evaluation based on the direct trial IMpassion130. The types of economic evaluation presented were a cost-effectiveness analysis (cost-per-life-year-gained) and a cost-utility analysis (cost-per- quality-adjusted life year [QALY]-gained).

The base case economic evaluation used the prevalence of PD-L1 IC ≥1% expression identified in the IMpassion130 trial (40.91%) using the Ventana SP142-IC assay. Two scenarios were provided in the model: current (no-test and treatment with nab-P) and proposed (Ventana SP142-IC assay + treatment with ATZ+nab-P or nab-P alone stratified by PD-L1-IC status). The health outcomes (OS and PFS) modelled in the submission were based on the results of the Ventana SP142 assay. 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 was low.

The Commentary stated that, given the variation in the proportion of patients testing positive with each of the commercially available 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, if test assays other than Ventana SP142 are used. This uncertainty was not considered by the submission, and cannot be reliably assessed given the information provided. However, if MSAC and the PBAC accept that the Weibull parametric function is the most appropriate method for extrapolating the OS curves in both the proposed scenario and the current scenario, this ICER is likely to lie between $**redacted**/QALY and $**redacted**/QALY, or between $**redacted**/QALY and $**redacted**/QALY when using the submission's extrapolation functions (Table 12).

Table 12: ICERs and considerations of various PD-L1-positive funding scenarios

	PBAC funded medicine: restricted to PD-L1 ≥1% (VENTANA SP-142)	PBAC funded medicine: not restricted by a PD-L1-based eligibility criterion
Submission base case	Applicant estimated ICER in this setting: $redacted/QALY Assuming Weibull parametric function was the most appropriate for both the proposed and current scenarios: $redacted/QALY	NR
No MSAC funded test	NR	Assuming extrapolation functions the same as the submission's base case: $redacted/QALY Assuming Weibull parametric function was the most appropriate for both the proposed and current scenarios: $redacted/QALY

See Section 6 of the PBAC Public Summary Document for a detailed description of the economic evaluation.
NR = not reported
Source: Compiled during the evaluation based on information presented in 'Economic Evaluation.xlsx' with the submission

In its pre-PBAC and pre-MSAC responses, the applicant revised its base case economic model resulting in an ICER of $**redacted** per QALY gained (Table 13). These results were not independently verified.

Table 13: Revised base case economic evaluation

Parameter		Inc. costs	Inc. QALYs	ICER ($/QALY)
Submission base case		$redacted	0.406	$redacted
Revised base case addressing ESCs Advice ǂ				
1	Australian-specific utilities applied (Progression-free: 0.734, Progression: 0.684)	$redacted	0.424	$redacted
2	1 + limit the cost of nab-P to 10 administrations due to toxicity for all nab-P arms	$redacted	0.424	$redacted
3	2 + add disease management costs post treatment discontinuation	$redacted	0.424	$redacted
4	3 + amend overall survival parametric extrapolation to Weibull for all nab-P arms	$redacted	0.250	$redacted
5	4 + converge atezolizumab + nab-P overall survival curve to comparator overall survival curve (no test + nab-P), starting from 90 months until 120 months	$redacted	0.218	$redacted
6	Revised base case in pre-PBAC response redacted	$redacted	redacted	$redacted

ǂ The proportion of treatment settings between Public/Private has been amended from 33%/67% in the initial model to 31.4%/68.6% in the updated model (consistent with the revised financial estimates)
Source: Table 1, p4 of pre-PBAC and pre-MSAC response

13. Financial/budgetary impacts

The submission used an epidemiological approach to estimate the expected cost to the MBS of listing the test and the associated medicine on the PBS (Table 14).

Table 14: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use of the PD-L1 test						
Number of patients tested	redacted	redacted	redacted	redacted	redacted	redacted
Revised[a]	redacted					
Number of patients likely to receive a positive test result	redacted	redacted	redacted	redacted	redacted	redacted
Estimated financial implications of the PD-L1 test to the MBS						
Cost to MBS (100% schedule fee)[b]	$redacted	$redacted	$redacted	$redacted	$redacted	$redacted
Revised (85% schedule fee)[c]	$redacted	$redacted	$redacted	$redacted	$redacted	$redacted
Copayments[c]	$redacted	$redacted	$redacted	$redacted	$redacted	$redacted
Estimated financial implications for other MBS Items, including administration and on-treatment monitoring						
Cost to MBS (100% schedule fee)	$redacted	$redacted	$redacted	$redacted	$redacted	$redacted
Revised (85% schedule fee)[c]	$redacted	$redacted	$redacted	$redacted	$redacted	$redacted
Copayments[c]	$redacted	$redacted	$redacted	$redacted	$redacted	$redacted
Net financial implications						
Net cost to MBS	$redacted	$redacted	$redacted	$redacted	$redacted	$redacted
Revised (85% schedule fee)[c]	$redacted	$redacted	$redacted	$redacted	$redacted	$redacted
Copayments[c]	$redacted	$redacted	$redacted	$redacted	$redacted	$redacted

[a] The submission inappropriately included the cost of the MBS test to grandfathered patients in the first year.
[b] These values could not be verified based on information presented in the submission's Excel workbook, although they appeared similar to values calculated during the evaluation.
[c] Assuming all patients receive the test in an outpatient setting, and therefore pay a 15% co-payment. Submission base case used the 100% schedule fee, which is inappropriate.
Source: Table 4.3.2, Table 4.6.3, Table 4.6.9 of the MSAC_PBAC Combined Submission

The Commentary stated that it is uncertain whether the estimated cost of listing the PD-L1 test on the MBS is an underestimate or overestimate given that:

- the number of patients receiving the PD-L1 test to determine eligibility to ATZ+nab-P is uncertain. The number of patients with inoperable locally advanced or metastatic TNBC and an ECOG score of 0-1 is uncertain given that:
  - it is possible the proportion of patients diagnosed with de novo metastatic TNBC is overestimated by the submission, although there is a paucity of Australian data to inform this parameter; and
  - the proportion of patients diagnosed with earlier stages of TNBC that progress to Stage III inoperable or Stage IV is likely to be underestimated by the submission
- the number of patients that are likely to test positive may be different from that estimated in IMpassion130. As noted above, tests other than the evidentiary standard may be used in clinical practice if the MBS item is not restricted to the use of VENTANA SP142. These testing strategies resulted in **redacted**% of patients being identified as PD-L1 positive, compared to 46% in the BEP of the key trial based on the evidentiary standard (VENTANA SP142).

In its pre-PBAC and pre-MSAC responses, the applicant revised its base case financial model (Table 15). Related to the MBS impact of PD-L1 testing, the applicant updated the PD-L1 testing rate to 95% (from 82% in original application) as recommended by DUSC, and included a retesting rate of 4%. These results were not independently verified.

Table 15: Revised financial implications for the Australian Government

	Year of PBS listing					
	2020	**2021**	**2022**	**2023**	**2024**	**2025**
Number of PD-L1 tests	redacted	redacted	redacted	redacted	redacted	redacted
Number of patients treated with atezolizumab + nab-P	redacted	redacted	redacted	redacted	redacted	redacted
Overall net cost to PBS/ RPBS (with proposed atezolizumab effective price and expenditure cap)	$redacted	$redacted	$redacted	$redacted	$redacted	$redacted
Cost to MBS	$redacted	$redacted	$redacted	$redacted	$redacted	$redacted
Overall effective net cost to government health budgets	$redacted	$redacted	$redacted	$redacted	$redacted	$redacted

Source: Table 2, p6 of the pre-PBAC & pre-MSAC response

14. Key issues from ESCs of both PBAC and MSAC for MSAC

Table 16: Summary of key issues from ESCs for MSAC

ESCs key issue	ESCs advice to MSAC
Rationale for codependence	The rationale for codependency is 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 to determine eligibility for treatment with atezolizumab. However, other trials of immunotherapy in TNBC, including in PD-L1-positive populations, have failed to show convincing clinical benefit, with or without combination chemotherapy.
Clinical utility of PD-L1 testing (predictive role of test)	The ESCs considered the predictive and prognostic capability of the PD-L1 biomarker to be highly uncertain on the basis of the evidence presented from the IMpassion130 trial. The prespecified analysis plan required the OS treatment effect to be statistically significant in the ITT population before proceeding to assess the OS treatment effect for the PD-L1-positive subgroup. This prerequisite was not met. Exploratory tests for an OS treatment effect by PD-L1 status interaction had p-values of 0.02 for the April 2018 data cut-off and 0.06 for the Jan 2019 data cut-off (from the pre-ESCs response). This suggests there is some evidence that PD-L1 status may predict variation in the treatment effect of atezolizumab, but the evidence for this is uncertain.
Analytical validity of PD-L1 testing for available assays	There was low concordance in the relevant subgroup from the IMpassion130 trial between the VENTANA PD-L1 SP142 assay with IC assessment (the evidentiary standard) and the two other commercially available assays that might be used in clinical practice (VENTANA PD-L1 SP263 and Agilent/Dako PD-L1 22C3 pharmDx) with **redacted** or CPS assessment. The lack of concordance was mainly driven by the large number of SP142-IC-negative patients that were assessed as being PD-L1 positive by the other test options. These options may be identifying additional patients less likely to benefit from atezolizumab.
Item descriptor	The ESCs suggested that it would be appropriate to specify the VENTANA SP142 Assay and IC assessment approach in the item descriptor to limit testing to the evidentiary standard due to the poor analytical concordance with alternative test options. The ESCs suggested that the item descriptor should specify that the patient has unresectable locally advanced or metastatic cancer. The ESCs suggested that the item descriptor should specify the requester is a specialist or consultant physician. The ESCs suggested that, where available, the most recent tissue sample should be tested in preference to archival tissue samples. The ESCs suggested that it may be appropriate to limit testing to once per patient, in order to limit unnecessary repeated re-testing of samples initially considered PD-L1 negative.

ESCs key issue	ESCs advice to MSAC
Economic	The modelled outcomes were based on VENTANA SP142 (the evidentiary standard), however, other assays are commercially available in Australia. The ESCs noted that it is likely that the cost-effectiveness of atezolizumab in combination with taxane chemotherapy (ATZ+nab-P) in the Australian population would likely reduce if other test options were used. The economic evaluation modelled an implausible OS advantage on the basis of testing only, without a change in treatment. This favoured atezolizumab.
Financial estimates	The financial estimates were considered by DUSC. The ESCs considered that use of other test options may increase the number of TNBC patients eligible for atezolizumab.

ESCs discussion

The ESCs suggested that the proposed item descriptor should be amended to explicitly state that testing is for patients with unresectable locally advanced or metastatic disease. The ESCs considered that, due to instability in test results for a patient over time, it would not be appropriate for patients with early stage disease to access PD-L1 testing to determine access to atezolizumab in the event that their disease later progresses.

The ESCs suggested that it would be appropriate for the item descriptor to specify the VENTANA SP142 IHC assay and IC assessment are used for determining PD-L1 status for the purpose of helping determine eligibility for atezolizumab. The ESCs noted that the BEP analysis showed there was relatively poor analytical concordance across the alternative PD-L1 IHC assays (VENTANA SP263 and Agilent/Dako 22C3) and assessment approaches compared with the evidentiary standard (VENTANA SP142 IC) used in the IMpassion130 trial. The ESCs considered that the BEP-based concordance analysis from this trial indicated a substantial number of false positives were detected with the alternative test options, suggesting that these alternatives may identify additional patients who are less likely to benefit from treatment with atezolizumab. The ESCs noted that the pre-ESCs response (p1) indicated the applicant was amenable to limiting testing to the VENTANA SP142 assay and IC assessment approach. The ESCs acknowledged that this may present some practical impositions on pathology laboratories currently using other test platforms.

The ESCs suggested that the item descriptor should specify the requester is a specialist or consultant physician. The ESCs noted that the existing item descriptor for PD-L1 IHC testing in NSCLC does not have this restriction, however most other P7 Genetics MBS items do specify the type of requester. The ESCs considered that PD-L1 testing in NSCLC for access to first-line pembrolizumab monotherapy had different clinical implications compared with PD-L1 testing in TNBC for access to atezolizumab in terms of subsequent access to alternative immunotherapies.

The ESCs suggested that the item descriptor should specify that the most recent available tissue sample should be tested. The ESCs noted there is some evidence of up-regulation or down-regulation of PD-L1 expression with chemotherapy or progression to metastatic disease. The ESCs considered that some patients will require re-biopsy to confirm metastatic disease and suggested that, where available, the most recent tissue sample should be tested in preference to archival tissue samples.

Given the potential for intra- and inter-observer disagreement on the PD-L1 positivity score at the ≥1% IC threshold, the ESCs considered that it may be appropriate to limit testing to once per patient, in order to prevent unnecessary re-testing of samples initially considered PD-L1 negative, and unnecessary procedures to obtain new samples.

The ESCs noted that the submission claimed that "direct evidence from the IMpassion130 trial showed that patients assessed as being PD-L1 positive obtained clinical benefit from treatment with atezolizumab plus nab-paclitaxel (ATZ+nab-P) whereas those who were PD-L1-negative did not". The ESCs considered that this claim of clinical utility was not supported by the evidence as whilst statistical significance was demonstrated favouring ATZ+nab-P for greater PFS in both the ITT and PD-L1-positive subgroup, the benefit was small and may not be clinically meaningful. In addition, there was no statistically significant difference in OS in the ITT population and therefore no formal statistical test for OS in the PD-L1-positive patients was possible according to the prespecified analytical protocol.

The ESCs also noted that interaction tests for an OS treatment effect by PD-L1 status had p-values of 0.02 for the April 2018 data cut-off and 0.06 for the January 2019 data cut-off (as provided in the pre-ESCs response). The ESCs considered that this suggests there is some evidence that PD-L1 status may predict variation in the treatment effect of atezolizumab, but the evidence for this is uncertain.

The ESCs noted that the primary evidence for the analytical concordance of the proposed test against other test options was from an exploratory post-hoc analysis of the BEP in the IMpassion130 trial. The ESCs noted that the OPA for these alternatives compared to the evidentiary standard (SP142-IC assay and IC assessment approach) was between 64% and 69% and this poor concordance was mainly driven by the large number of SP142-IC-negative patients that were assessed as being PD-L1 positive by the other assays and assessment approaches (IC or CPS). The ESCs also noted that, for the patients who were assessed as SP142-IC negative and positive according to the other options, the OS HRs and the median OS values aligned more closely to the SP142-IC PD-L1-negative population than the SP142-IC-positive population. The ESCs considered that this indicated that the alternative options may be identifying additional patients who are less likely to benefit from treatment with atezolizumab.

The ESCs noted that the draft study report of the Australian SPRINT study was provided with the pre-ESCs response as additional supportive evidence for intra- and inter- observer reproducibility of pathologists' assessments of PD-L1 IC staining using the VENTANA SP142 assay. The ESCs also noted that the **redacted.** The ESCs also noted that the risk of bias was not assessed for this study, but considered that it appears to be at least as high risk of bias as the BEP (post-hoc) analysis from the IMpassion130 trial, where there was some uncertainty about how the comparisons were conducted, the timing between assessing the samples from different assays and the blinding of results. Further, the ESCs noted the applicant's acknowledgement that the SPRINT study **redacted**.

The ESCs noted that the main economic issue specific to MSAC was that testing with alternative PD-L1 assays available in Australian may result in some patients' PD-L1 status being determined by an assay/scoring algorithm different than the evidentiary standard (VENTANA SP142-IC). The ESCs noted that it is likely that the cost-effectiveness of atezolizumab in combination with taxane chemotherapy (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-IC.

The ESCs also noted that the use of different parametric functions across the model arms to extrapolate OS for patients in the proposed scenario compared with the current scenario resulted in an OS benefit associated with PD-L1 testing alone (that is, for patients who test negative for PD-L1 and so do not receive a change in treatment). The ESCs considered that

this modelled OS benefit in these patients was not plausible, and the consequence is that this resulted in an ICER that favoured atezolizumab.

The ESCs noted that the estimated extent of use and financial implications are discussed in the DUSC advice on this item. The ESCs considered that use of other test options may increase the number of TNBC patients eligible for atezolizumab.

The ESCs noted advice from the Royal College of Pathologists of Australasia noting the ambiguity in the current PD-L1 testing program in Australia and the need for high quality training and quality assurance to ensure that testing is consistent. The ESCs noted the applicant's Pre-ESCs Response (p3) described the pathologist training program on PD-L1 IC assessment using SP142, including online and face to face training, and the improvements made to this training and certification in response to the SPRINT study.

15. Other significant factors

Nil.

16. Applicant comments on MSAC's Public Summary Document

Roche welcomes MSAC's inclination to support PD-L1 IHC testing in Australian patients with unresectable locally advanced or metastatic triple-negative breast cancer. Roche is committed to working with MSAC and the Department of Health to ensure that eligible patients who are PD-L1-positive can receive PD-L1 testing.

17. Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website: visit the MSAC website