Australian Government
Department of Health and Aged Care
Therapeutic Goods Administration

# Australian Public Assessment Report for Tecentriq

## Active ingredient/s: Atezolizumab

## Sponsor: Roche Products Australia Pty Ltd

March 2023

# About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and Aged Care and is responsible for regulating therapeutic goods, including medicines, medical devices, and biologicals.
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- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to the Australian public outweigh any risks associated with the use of therapeutic goods.
- The TGA relies on the public, healthcare professionals and industry to report problems with therapeutic goods. The TGA investigates reports received to determine any necessary regulatory action.
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# About AusPARs

- The Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission. Further information can be found in Australian Public Assessment Report (AusPAR) guidance.
- AusPARs are prepared and published by the TGA.
- AusPARs are static documents that provide information that relates to a submission at a particular point in time. The publication of an AusPAR is an important part of the transparency of the TGA's decision-making process.
- A new AusPAR may be provided to reflect changes to indications or major variations to a prescription medicine subject to evaluation by the TGA.

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# Contents

# List of abbreviations

| Abbreviation | Meaning |
|---|---|
| ACM | Advisory Committee on Medicines |
| ADA | Anti-drug antibody |
| AE | Adverse event |
| ARTG | Australian Register of Therapeutic Goods |
| ASA | Australia specific annex |
| CMI | Consumer Medicines Information |
| DLP | Data lock point |
| EU | European Union |
| Fc | Fragment crystallisable |
| FDA | Food and Drug Administration (United States of America) |
| HER2 | Human epidermal growth factor 2 |
| IgG | Immunoglobulin G |
| ITT | Intent to treat |
| PD-1 | Programmed cell death protein 1 |
| PD-L1 | Programmed death-ligand 1 |
| PD-L2 | Programmed death-ligand 2 |
| PFS | Progression free survival |
| RMP | Risk management plan |
| TGA | Therapeutic Goods Administration |
| TNBC | Triple negative breast cancer |
| US(A) | United States (of America) |
| Wt | Wild type |

# Product submission

## Submission details

| | |
|---|---|
| *Type of submission:* | Provisional to full registration |
| *Product name(s):* | Tecentriq |
| *Active ingredient(s):* | Atezolizumab |
| *Decision:* | Sponsor withdrew on 21 March 2023 |
| *Date of decision:* | Not applicable |
| *Date of entry onto ARTG:* | Not applicable |
| *ARTG number(s):* | 277120 and 310681 |
| , *Black Triangle Scheme:* | Not applicable |
| *Sponsor's name and address:* | Roche Product Pty Limited<br>Level 8, 30 – 34 Hickson Road<br>Sydney NSW 2000 |
| *Dose form(s):* | Concentrated injection |
| *Strength(s):* | 840 mg/14 mL and 1200 mg/20 mL |
| *Container(s):* | Vial |
| *Pack size(s):* | One |
| *Approved therapeutic use:* | Not applicable |
| *Route(s) of administration:* | Intravenous infusion |
| *Dosage:* | Not applicable |
| *Pregnancy category:* | Category D<br>Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.<br>The use of any medicine during pregnancy requires careful consideration of both risks and benefits by the treating health professional. This must not be used as the sole basis of decision making in the use of medicines during pregnancy. The TGA does not provide advice on the use of medicines in pregnancy for specific cases. More information is available from obstetric drug information services in your State or Territory. |

## Product background

This AusPAR describes the submission by Roche Product Australia Pty Ltd (the sponsor) to register Tecentriq (atezolizumab) 840 mg/14 mL and 1200 mg/20 mL, concentrated injection to convert the registration of the following provisionally registered indication to a full registration:

*Triple-negative breast cancer*

*Tecentriq, in combination with nanoparticle albumin-bound paclitaxel, is indicated for the treatment of adult patients with unresectable locally advanced or metastatic triple-negative breast cancer (TNBC) whose tumours express PD-L1 (PD-L1 stained tumour-infiltrating immune cells [IC] of any intensity covering ≥ 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).*

## Triple negative breast cancer

Triple negative breast cancer (TNBC) accounts for approximately 12-17% of all breast cancers;[1] and is classically defined immunohistochemically as a tumour with less than 1% immunostaining for the estrogen receptor and progesterone receptor;[2] with no overexpression (0 or 1+ immunostaining on immunohistochemistry and/or no detectable amplification) of human epidermal growth factor 2 (HER2).[3]

The term TNBC was first used in 2005 to refer to a subset of breast cancer patients for whom chemotherapy was the only treatment available, as the lack of hormone receptor or HER2 biomarkers renders them ineligible to receive endocrine/hormonal therapy or anti-HER2 agents.[4]

Triple negative breast cancer is more common in patients of African or Hispanic descent than in other racial or ethnic groups.[1] Compared to other types of breast cancer, TNBC has a younger mean age of diagnosis, and is more likely to occur in premenopausal women.[5,6] TNBC is more likely to present as an interval tumour (cancers that develop between screening intervals) and tends to be diagnosed at a later stage with a larger primary tumour and with positive lymph node status, and tends to be higher grade.[5,6] Commensurate with these negative prognostic indicators, TNBC also has a higher likelihood of distant recurrence (with a median of recurrence at 2.6 years from diagnosis), shorter survival time after recurrence, and shorter median overall survival time (a median of 4.2 years).[6] The excess risk of distant recurrence appears to be attributable to development of visceral metastases within the first five years after diagnosis.[7] The rate of central nervous system involvement has been reported to be 36% amongst patients with recurrent disease.[8]

Being a 'catch-all' disease category defined by the lack of three biomarkers, it is perhaps unsurprising that TNBC is very heterogeneous, comprising a broad array of entities with distinct genomic, histological and clinical features.[9] Several classifications have been proposed in recent

1 Foulkes WD, et al. Triple-negative breast cancer. N Engl J Med. 2010 Nov 11;363(20):1938-48.

2 Hammond ME, et al. American Society of Clinical Oncology/College Of American Pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer. J Clin Oncol. 2010 Jun 1;28(16):2784-95.

3 Wolff AC, et al. American Society of Clinical Oncology; College of American Pathologists. Recommendations for human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists clinical practice guideline update. J Clin Oncol. 2013 Nov 1;31(31):3997-4013.

4 Brenton JD, Carey LA, Ahmed AA, Caldas C. Molecular classification and molecular forecasting of breast cancer: ready for clinical application? J Clin Oncol. 2005 Oct 10;23(29):7350-60

5 Alluri P, Newman LA. Basal-like and triple-negative breast cancers: searching for positives among many negatives. Surg Oncol Clin N Am. 2014 Jul;23(3):567-77.

6 Dent R, et al. Triple-Negative Breast Cancer: Clinical Features and Patterns of Recurrence. Clin. Cancer Res. 2007;13:4429–4434.

7 Dent R, et al. Pattern of metastatic spread in triple-negative breast cancer. Breast Cancer Res Treat. 2009 May;115(2):423-8.

8 Lin NU, et al. Clinicopathologic features, patterns of recurrence, and survival among women with triple-negative breast cancer in the National Comprehensive Cancer Network. Cancer. 2012 Nov 15;118(22):5463-72.

9 Pareja F, et al. Triple-negative breast cancer: the importance of molecular and histologic subtyping, and recognition of low-grade variants. NPJ Breast Cancer. 2016 Nov 16;2:16036.

decades based on histology or molecular characteristics. High-grade ductal invasive carcinoma is the most frequent histological type; other subtypes include medullary-like, apocrine, adenoid-cystic, and metaplastic carcinomas.[9]

From a molecular standpoint, the TNBC phenotype was initially noted to most commonly be 'basal-like', that is, expressing genes usually found in normal basal/myoepithelial cells of the breast and not expressing the estrogen receptor or HER2.[10] With further development of gene expression profiling, six different molecular subtypes have since been described: two subcategories of basal-like (basal-like 1 and basal-like 2), immunomodulatory, mesenchymal, mesenchymal stem-like, and luminal androgen receptor.[11]

Triple negative breast cancer also shows high clonal heterogeneity, and probably has a high likelihood of mosaicism at diagnosis.[12]

Recognition of the breast cancer susceptibility genes *BRCA1* and *BRCA2* emerged in the mid-1990s,[13] and an association with TNBC was soon drawn.[14] Whilst the prevalence of BRCA1 and/or BRCA2 (BRCA1/2) mutations are probably present in less than 5% of breast cancers overall, the rate is higher, maybe as high as 10-20% in TNBC.[15,16] There is a stronger association with *BRCA1* than *BRCA2*.[15] In selected patients with breast cancer (those referred for BRCA genetic testing) 57% of *BRCA1* carriers, 23% of *BRCA2* carriers, and 14% of patients found to not have a BRCA mutation had TNBC.[17] A schematic representation of the approximate prevalence and co-occurrence of hormone receptor, HER2 and BRCA abnormalities in breast cancer is illustrated in Figure 1 (below), incorporating estimates from multiple sources.[18,19,20]

10 Perou CM, et al. Molecular portraits of human breast tumours. Nature. 2000 Aug 17;406(6797):747-52

11 Lehmann BD, et al. Identification of human triple-negative breast cancer subtypes and preclinical models for selection of targeted therapies. J Clin Invest. 2011 Jul;121(7):2750-67.

12 Shah SPet al. The clonal and mutational evolution spectrum of primary triple-negative breast cancers. Nature. 2012 Apr 4;486(7403):395-9.

13 Evans DG, et al. Familial breast cancer. BMJ. 1994 Jan 15;308(6922):183-7.

14 Peshkin BN, et al. BRCA1/2 mutations and triple negative breast cancers. Breast Dis. 2010;32(1-2):25-33.

15 Armstrong N, et al. A systematic review of the international prevalence of BRCA mutation in breast cancer. Clin Epidemiol. 2019 Jul 11;11:543-561

16 Gonzalez-Angulo AM, et al. Incidence and outcome of BRCA mutations in unselected patients with triple receptor-negative breast cancer. Clin Cancer Res. 2011 Mar 1;17(5):1082-9.

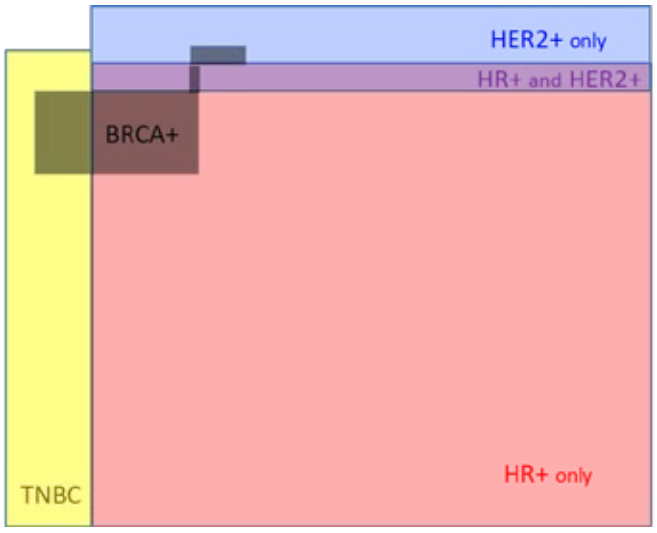
17 Atchley DP, et al. Clinical and pathologic characteristics of patients with BRCA-positive and BRCA-negative breast cancer. J Clin Oncol. 2008 Sep 10;26(26):4282-8.

18 Kohler BA, et al. Annual Report to the Nation on the Status of Cancer, 1975-2011, Featuring Incidence of Breast Cancer Subtypes by Race/Ethnicity, Poverty, and State. J Natl Cancer Inst. 2015 Mar 30;107(6):djv048..

19 Tomasello G, et al. Characterization of the HER2 status in BRCA-mutated breast cancer: a single institutional series and systematic review with pooled analysis. ESMO Open. 2022 Jul 7;7(4):100531

20 Gonzalez-Angulo AM, et al. Incidence and outcome of BRCA mutations in unselected patients with triple receptor-negative breast cancer. Clin Cancer Res. 2011 Mar 1;17(5):1082-9

**Figure 1: Schematic representation of the relative prevalence and co-occurrence of hormone receptor, HER2 and BRCA abnormalities in breast cancer, using estimates derived from rates reported in the literature**




| Category | Estimated % |
|---|---|
| HR+ only | 70 |
| HER2+ only | 3.75 |
| TNBC only | 11.5 |
| HR+ and HER2+ | 9.9 |
| HR+ and HER2+ and BRCA+ | 0.1 |
| TNBC and BRCA+ | 1.5 |
| HR+ and BRCA+ | 2.9 |
| HER2+ and BRCA+ | 0.35 |
| ***TOTAL*** | ***100*** |

Abbreviations: HER2 = Human epidermal growth factor 2, HR = hormone receptor, TNBA = triple negative breast cancer.

Figure 1 based on data sources from the following publications:

Kohler BA, et al. Annual Report to the Nation on the Status of Cancer, 1975-2011, Featuring Incidence of Breast Cancer Subtypes by Race/Ethnicity, Poverty, and State. J Natl Cancer Inst. 2015 Mar 30;107(6):djv048

Tomasello G, et al. Characterization of the HER2 status in BRCA-mutated breast cancer: a single institutional series and systematic review with pooled analysis. ESMO Open. 2022 Jul 7;7(4):100531

Gonzalez-Angulo AM, et al. Incidence and outcome of BRCA mutations in unselected patients with triple receptor-negative breast cancer. Clin Cancer Res. 2011 Mar 1;17(5):1082-9

## Atezolizumab mechanism of action

Atezolizumab is fragment crystallisable (Fc)-engineered,[21,22] humanised, immunoglobulin G1 (IgG1) monoclonal antibody that binds to the programmed death-ligand 1 (PD-L1) molecule, interfering with its recognition by target receptors (PD-1 and B7.1) on T-cells.[23] Interaction between the ligand PD-L1 and its programmed cell death protein (PD-1) receptor is a negative regulatory mechanism of cytotoxic T-cell activity through the inhibition of T-cell proliferation and cytokine production.[23] PD-L1 may be expressed on tumour cells and tumour-infiltrating immune cells, and can contribute to the inhibition of an anti-tumour immune response in the microenvironment.[24]

Atezolizumab's blockade of PD-L1 binding to target receptors is believed to release PD-L1/PD-1 pathway mediated inhibition of the immune response, including reactivating the anti-tumour immune response. Atezolizumab does not bind to the programmed death-ligand 2 (PD-L2), so does not interfere with PD-L2/PD-1 mediated inhibitory signals.[23]

In syngeneic mouse tumour models, the blockade of PD-L1 activity resulted in decreased tumour growth.[23]

21 Fc engineering refers to modification of the fragment crystallisable (Fc) region of an antibody, aiming to increase tumour cytotoxicity through Fc-tail mediated effector functions such as antibody-dependent cellular cytotoxicity (ADCC), antibody-dependent cellular phagocytosis (ADCP), and complement-dependent cytotoxicity (CDC).

22 Horst HVD, Mutis T. Fc-Engineered Antibodies. Encyclopedia. Accessed 3 Aug 2022.

23 Approved Australian product information (PI) for atezolizumab. Accessed 3 Aug 2022.

24 Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. Nat Rev Cancer. 2012 Mar 22;12(4):252-64

## Current treatment options

When diagnosed at an early or locally advanced stage, treatment of TNBC is undertaken with curative intent and is usually multimodal; treatment may include chemotherapy, surgery and radiation therapy, where indicated.[25] Neoadjuvant (preoperative) chemotherapy allows assessment of pathological response (providing important prognostic information and guidance for adjuvant therapy decisions), and may downstage tumours to allow surgery in those with inoperable disease at presentation and/or facilitate breast-conserving surgery.[25] Rates of pathological complete response to neoadjuvant chemotherapy (defined as an absence of any invasive disease in the breast or resected nodes) are associated with an improvement in event free survival and overall survival in TNBC.[26] In Australia, in keeping with American guidelines,[25] sequential anthracycline and taxane-based regimens are commonly used, with or without carboplatin, either in the neoadjuvant or the adjuvant setting.

Despite treatment, metastatic recurrence develops in about 15% to 30% of patients.[6] In Australia and other high-income countries, most patients with metastatic TNBC present with recurrence following initial diagnosis of early-stage disease: a minority (perhaps 10% to 15%) present with *de novo* metastatic disease.

For patients with inoperable local relapse or distant metastases, TNBC is regarded as incurable and treatment intent becomes palliative. For patients with TNBC, median overall survival in the first line metastatic setting following relapse has been reported to be anywhere from 11 to 18 months, highlighting the variability inherent in this heterogeneous disease category.[27,28,29] For those who have received prior neoadjuvant or adjuvant therapies, survival rates are lower, particularly where relapse occurs within the first three years.[30]

Presence of a BRCA mutation in TNBC is associated with a better prognosis than for BRCA-wild type TNBC;[16] and PARP inhibitors (a group of pharmacological inhibitors of the enzyme poly (ADP-ribose) polymerase) exploiting the homologous repair deficiency associated with BRCA mutations have been developed and are approved in Australia for use in the metastatic setting.[31,32]

Identifying reliable biomarkers for efficacy of targeted agents in TNBC beyond BRCA has generally proven challenging, and chemotherapy remains the mainstay of treatment for BRCA wild-type TNBC. The only other treatment that has demonstrated a statistically significant survival advantage has been the addition of the PD-1 inhibitor pembrolizumab to standard-of-care first line chemotherapy in the metastatic setting (via the KEYNOTE-355 trial);[33] which recently demonstrated an overall survival benefit in patients with a combined positive score of at least

25 National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology. Breast Cancer Version 4.2022. 21 Jun 2022; National Comprehensive Cancer Network. Accessed 3 August 2022

26 Cortazar, P, et al Pathological complete response and long-term clinical benefit in breast cancer: pooled CTNeoBC pooled analysis Lancet 2014 (184): 164-172

27 Khosravi-Shahi P, et al. Metastatic triple negative breast cancer:optimizing treatment options, new and emerging targeted therapies. Asia-Pacific J Clin Oncol 2018; 14 (1):32-9.

28 Kassam F, et al. Survival outcomes for patients with metastatic triple-negative breast cancer: implications for clinical practice and trial design. Clin Breast Cancer. 2009 Feb;9(1):29-33

29 Miles DW, et al. First-line bevacizumab in combination with chemotherapy for HER2-negative metastatic breast cancer: pooled and subgroup analyses of data from 2447 patients. Ann Oncol. 2013 Nov;24(11):2773-80

30 Liedtke C, et al. Response to neoadjuvant therapy and long-term survival in patients with triple-negative breast cancer. J Clin Oncol. 2008 Mar 10;26(8):1275-81

31 Approved Australian product information (PI) for Lynparza (olaparib). Accessed August 2022.

32 AusPAR (initial registration) for Lynparza (olaparib) AstraZeneca Pty Ltd; PM-2014-04684-1-4. Published online February 2019. Available at: AusPAR: Olaparib | Therapeutic Goods Administration (TGA)

33 KeyNote 355 trial: A randomized, double-blind, phase III study of pembrolizumab (MK-3475) plus chemotherapy vs placebo plus chemotherapy for previously untreated locally recurrent inoperable or metastatic triple negative breast cancer. ClinicalTrials.gov Identifier: NCT02819518.

10%;[34] assessed at a central laboratory with the use of PD-L1 IHC 22C3 pharmDx (Agilent Technologies).[35]

Major international guideline treatment algorithms for unresectable locally advanced or metastatic TNBC (advanced/metastasised TNBC) hinge on whether the tumour harbours a BRCA mutation or is PD-L1 positive.[25,36] Selection of chemotherapy agent may also depend on what treatment was received in the neoadjuvant/adjuvant setting and the recurrence-free interval. Combination chemotherapy is not generally used, except for patients with visceral crisis, where the extra toxicity might be justified.[37]

For BRCA-mutated advanced TNBC, first-line preferred options include a PARP inhibitor, or platinum based chemotherapy.[25,36] The PARP inhibitors olaparib and talazoparib both have registered indications in Australia in line with such usage.[31,38,39]

For BRCA wild-type advanced TNBC, first line preferred options are limited to taxane- or anthracyclines-based chemotherapy, unless the tumour is PD-L1 positive, in which case a PD-1 inhibitor can be added to chemotherapy. [25, 36]

The choice of chemotherapy agent may be informed by a range of factors including socioeconomic. Docetaxel, paclitaxel, and nab-paclitaxel (protein-bound paclitaxel, or nanoparticle albumin–bound paclitaxel) are all taxanes that have demonstrated efficacy and are commonly used.[40,41]

In a sponsor-submitted document (Report 1107081), the following background regarding nab-paclitaxel and paclitaxel, as this is a key difference between two of the submitted randomised studies:

> 'Nab-paclitaxel, an albumin bound formulation of paclitaxel, was developed to address the toxicity issues related to the solvents used for both paclitaxel and docetaxel;[42] and to potentially improve the therapeutic index. Based on results from head-to-head Phase II and III trials, nab-paclitaxel received approval for treatment of HER2-negative metastatic breast cancer (mBC) in Europe and the USA;[40],[43]
>
> (Celgene Corporation, Summit. Abraxane (nab-paclitaxel) Package Insert, 2018).
>
> To date, however, few studies have directly compared the effectiveness of nab-paclitaxel and paclitaxel as monotherapies in the way they are used in routine clinical practice, which includes a broader patient population than what is included in clinical trials. Furthermore, the 1L-treated patients with mTNBC are rarely evaluated separately from the broader

34 Cortes J, et al. Pembrolizumab plus Chemotherapy in Advanced Triple-Negative Breast Cancer. N Engl J Med. 2022 Jul 21;387(3):217-226.

35 The PD-L1 IHC 22C3 pharmDx (by Agilent Technologies) is a qualitative immunohistochemical assay using monoclonal mouse anti-PD-L1, Clone 22C3, intended for use in the detection of PD-L1 protein in formalin-fixed, paraffin-embedded (FFPE) non-small cell lung cancer (NSCLC), urothelial carcinoma, esophageal cancer, head and neck squamous cell carcinoma (HNSCC), triple-negative breast cancer (TNBC), cervical cancer, and melanoma tissues using EnVision FLEX visualization system on Autostainer Link 48.

36 European Society for Medical Oncology (ESMO) Metastatic Breast Cancer Living Guidelines, v1.00 May 2022

37 Pauls M, et al. Current and New Novel Combination Treatments for Metastatic Triple-Negative Breast Cancer. Curr Oncol. 2022 Jul 7;29(7):4748-4767.

38 Australian Prescription Medicine Decision Summary for talazoparib. Accessed 3 Aug 2022

39 AusPAR for Talzenna (talazoparib tosilate), Pfizer Australia Pty Ltd; submission PM-2018-04458-1-4. Published online March 2020. Available at: AusPAR: Talazoparib (as tosilate) | Therapeutic Goods Administration (TGA)

40 Cardoso F, et al. 4th ESO-ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC 4)†. Ann Oncol. 2018 Aug 1;29(8):1634-1657.

41 Mahtani RL, et al. Comparative effectiveness of early-line nab-paclitaxel vs. paclitaxel in patients with metastatic breast cancer: a US community-based real-world analysis. Cancer Manag Res. 2018 Feb 8;10:249-256.

42 Gradishar WJ, et al. Phase III trial of nanoparticle albumin-bound paclitaxel compared with polyethylated castor oil-based paclitaxel in women with breast cancer. J Clin Oncol. 2005;23(31):7794-7803.

43 Gradishar WJ, et al. Significantly longer progression-free survival with nab-paclitaxel compared with docetaxel as first-line therapy for metastatic breast cancer [published correction appears in J Clin Oncol. 2011 Jul 1;29(19):2739]. J Clin Oncol. 2009;27(22):3611-3619.

HER2-negative population, and thus, information on the effectiveness of these two drugs in this specific population is largely lacking. In a recent study by Mahtani et al. 2018, patients with HER2-negative mBC treated with nabpaclitaxel in the first or second-line (2L) had significantly longer time to treatment discontinuation and time to next treatment (TTNT) than patients treated with paclitaxel. However, in a subgroup analysis among the mTNBC population, the clinical effectiveness of the two taxanes appeared similar (median 1L/2L TTNT, 6.2 vs 5.4 months, respectively; adjusted p = 0.7323).[39] Luhn et al. 2019,[42] further evaluated a cohort of mTNBC patients treated in routine US clinical practice, comparing the effectiveness of 1L nab-paclitaxel with paclitaxel monotherapy. In this observational comparative effectiveness study, overall survival and TTNT were similar in patients treated with nab-paclitaxel and those treated with paclitaxel. The similarity of efficacy results in clinical practice suggested that nab-paclitaxel and paclitaxel may be considered interchangeable as 1L treatments for patients with mTNBC.'

The real world study of nab-paclitaxel versus paclitaxel as first line therapy in metastatic TNBC setting noted in the above by the sponsor reported a median time to next therapy of 4.7 and 4.3 months, respectively, and median overall survival of 11.2 months and 10.8 months, respectively.[44]

# Regulatory status

Tecentriq (atezolizumab) was first registered on the Australian Register of Therapeutic Goods on 27 July 2017.[45] The indication approved at the time of initial ARTG registration is given as follows:

> *Tecentriq is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with progression on or after prior chemotherapy. In patients with tumour EGFR or ALK genomic aberrations, Tecentriq should be used after progression on or after targeted therapy.*

Over time, multiple submissions were made and approved to extend the indications of Tecentriq (atezolizumab) to include other forms of lung cancer, urothelial carcinoma, hepatocellular carcinoma and forms of breast cancer.

The indications given below are the complete indications (with either full or provisional approval) at the time that this submission was made.

## Indications with full registration

At the time this submission was made, Tecentriq (azetolizumab) had received full registration for the following indications:

> ***Early-stage non-small cell lung cancer***
>
> *Tecentriq as monotherapy is indicated as adjuvant treatment following complete resection and no progression after platinum-based adjuvant chemotherapy for adult patients with stage II to IIIA (as per 7th edition of the UICC/AJCC staging system) NSCLC whose tumours have PD-L1 expression on ≥ 50% of tumour cells.*
>
> ***Metastatic non-small cell lung cancer***
>
> *Tecentriq, in combination with bevacizumab, paclitaxel and carboplatin, is indicated for the first-line treatment of adult patients with metastatic non-squamous non-small cell lung cancer (NSCLC). In patients with EGFR mutant or ALK-positive NSCLC, Tecentriq, in combination with bevacizumab, paclitaxel and carboplatin, is indicated only after failure of appropriate targeted therapies.*

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

45 AusPAR for Tecentriq (atezolizumab); Roche Products Pty Ltd PM-2016-02087-1-4. Published online September 2018. Available at: AusPAR: Atezolizumab | Therapeutic Goods Administration (TGA)

*Tecentriq, in combination with nanoparticle albumin-bound paclitaxel (nab-paclitaxel) and carboplatin, is indicated for first-line treatment of patients with metastatic non-squamous NSCLC who do not have tumour EGFR or ALK genomic aberrations.*

*Tecentriq as monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic NSCLC after prior chemotherapy. Patients with EGFR mutant or ALK-positive NSCLC should also have received targeted therapies before receiving Tecentriq.*

***Small cell lung cancer***

*Tecentriq, in combination with carboplatin and etoposide, is indicated for the first-line treatment of patients with extensive-stage small cell lung cancer (ES-SCLC).*

***Urothelial carcinoma***

*Tecentriq is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma who*

- are considered cisplatin ineligible and whose tumours express PD-L1 (PD-L1 stained tumour-infiltrating immune cells [IC] covering ≥ 5% of the tumour area), as determined by a validated test, or
- are considered ineligible for any other platinum-containing chemotherapy regardless of the level of tumour PD-L1 expression.

*This indication is approved based on overall response rate and duration of response in a single-arm study. Improvements in overall survival, progression-free survival, or health-related quality of life have not been established.*

***Hepatocellular carcinoma***

*Tecentriq, in combination with bevacizumab, is indicated for the treatment of patients with unresectable or metastatic hepatocellular carcinoma (HCC) who have not received prior systemic therapy.*

## Indications with provisional registration

At the time this submission was made, Tecentriq (azetolizumab) had provisional registration for the following indications:

***Triple-negative breast cancer***

*Tecentriq, in combination with nanoparticle albumin-bound paclitaxel, is indicated for the treatment of adult patients with unresectable locally advanced or metastatic triple-negative breast cancer (TNBC) whose tumours express PD-L1 (PD-L1 stained tumour-infiltrating immune cells [IC] of any intensity covering ≥ 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).*

## Current submission

This submission and its outcomes only concern the provisionally approved indication (treatment of PD-L1 positive triple-negative breast cancer (TNBC), as shown above). All other indications (shown above) have received full registration in Australia and are not part of this submission.

Tecentriq (atezolizumab) was provisionally registered on the ARTG for the specified indication on 24 October 2019.[46] The provisional approval was granted to provide early access to vital and life-saving medicines through time-limited registration.

Once a medicinal product receives provisional registration, that product enters a provisional registration period lasting for 2 years starting on the day registration commences (section 29(3) of the Therapeutic Goods Act 1989 (the Act)). After that time period, the sponsor must either apply for an extension to the provisional registration period, or, have submitted an application to transition from a provisional registration to a full registration.

With the submission described in this AusPAR, the sponsor sought to transition the provisional registration of Tecentriq (atezolizumab) for the indication of treatment of PD-L1 positive TNBC to full registration on the ARTG.

## Regulatory status in Australia and overseas

Guidelines internationally are consistent in recommending the addition of a PD-1 inhibitor to first line chemotherapy for patients with PD-L1 positive triple-negative breast cancer (TNBC), but regulatory approval and clinical guideline status of atezolizumab for this indication varies internationally.[47,48]

In Australia, atezolizumab was granted a limited-type approval for this indication through the TGA's provisional approval pathway. Similar limited-type approvals of atezolizumab for similar or equivalent indications (treatment of PD-L1 positive TNBC) were granted in the United States of America (USA) via the US Food and Drug Administration's (FDA) Accelerated Approval pathway; and in Canada where Health Canada granted a Notice of Compliance with conditions. Except for Australia and the TGA, the limited-type approvals are no longer in place. As the treatment landscape in the USA changed with full approval granted to pembrolizumab for the treatment of TNBC, the high unmet need condition required for the maintenance of the accelerated approval of Tecentriq in the USA was no longer met. As a result of this regulatory situation (not due to new safety or efficacy data), the Accelerated Approval granted for the TNBC indication in the USA was voluntarily withdrawn by the sponsor.[49] In Canada, initially granted approval with conditions (Notice of Compliance with Conditions) was converted to a full approval (Full Notice of Compliance) on 21 December 2022.

Currently, atezolizumab holds regular-type approvals for the treatment of PD-L1 positive TNBC in Europe (via the European Medicines Agency (EMA)), Switzerland (via Swissmedic), Japan (from the Pharmaceuticals and Medical Devices Agency (PMDA)), and Canada.[50] The primary population supporting all approvals was the subgroup of patients who had PD-L1 positive tumour samples: this was a stratification factor at randomisation of the pivotal trial.

In Australia, at time of provisional registration, the key aspects of the dataset (with clinical cut-off date 17 April 2018) that were considered to contribute significant uncertainty to the risk benefit assessment were as follows:

1. the small absolute size of the statistically significant increase in progression free survival (PFS) between arms (1.7 months in the intent to treat (ITT), 2.5 months in the PD-L1 positive group);

2. the immaturity of overall survival data;

46 Prescription medicines registration for Tecentriq (atezolizumab), submission PM-2019-02504-1-4. TECENTRIQ (Roche Products Pty Ltd) | Therapeutic Goods Administration (TGA)

47 National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology. Breast Cancer Version 4.2022. 21 Jun 2022; National Comprehensive Cancer Network (USA). Accessed 3 August 2022

48 European Society for Medical Oncology (ESMO) Metastatic Breast Cancer Living Guidelines, v1.00 May 2022

49 FDA letter: BLA 761034/S-044; Tecentriq (atezolizumab) injection. Tecentriq (atezolizumab) injection (fda.gov)

3. uncertainties about the reproducibility of PD-L1 testing using the SP142 clone;[51] in the TNBC setting, given concerns about inter-observer reliability in other cancer histologies, and uncertainty about the concordance between SP142-based and other PD-L1 tests in this setting;
4. the heterogeneous nature of the condition, and therefore unclear external validity of the trial data to patients in Australia with TNBC, in whom important characteristics may be different; and
5. the effect of immunogenicity on efficacy and safety, as anti-drug antibodies and neutralising antibodies occur in a notable proportion of atezolizumab-treated patients.

The Delegate for Submission PM-2019-02504-1-4 (PD-L1 positive TNBC indication);[46] concluded that:

> '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 the IMpassion130 trial;[52] (especially overall survival data) and data from the IMpassion131 trial.[53,]'

# Registration timeline

The following table captures the key steps and dates for this submission.

**Table 1: Timeline for Submission PM-2021-04838-1-4**

| Description | Date |
|---|---|
| Submission dossier accepted and first round evaluation commenced | 30 November 2021 |
| First round evaluation completed | 13 May 2022 |
| Sponsor provides responses on questions raised in first round evaluation | 19 July 2022 |
| Second round evaluation completed | 5 August 2022 |
| Delegate's Overall benefit-risk assessment and request for Advisory Committee advice | 1 September 2022 |
| Sponsor's pre-Advisory Committee response | 20 September 2022 |
| Advisory Committee meeting | 6 and 7 October 2022 |
| Registration decision (Outcome) | Sponsor withdrew submission on 21 March 2023 |
| Completion of administrative activities and registration on the ARTG | Not applicable |
| Number of working days from submission dossier acceptance to registration decision* | Not applicable |

* Statutory timeframe for standard submissions is 255 working days

# Submission overview and risk/benefit assessment

A summary of the TGA's assessment for this submission is provided below.

# Quality

A full quality evaluation was conducted at the time this product received initial registration.

See the related AusPAR describing the initial registration of Tecentriq (atezolizumab) for further information.[48]

# Nonclinical

A full nonclinical evaluation was conducted at the time this product received initial registration.

See the related AusPAR describing the initial registration of Tecentriq (atezolizumab) for further information.[48]

# Clinical

Three clinical study reports are referred to in this submission, as summarised below in Table 2. All three studies;[54,55,] were international, multicentre, randomised, placebo-controlled, double-blind studies, and atezolizumab was given at a dose of 840 mg every two weeks, in line with approved dosing. In the IMpassion031 trial;[55] which included both a neoadjuvant and an adjuvant component, the adjuvant component used different dosing and was unblinded.

## Efficacy

### *Summary of findings*

Brief summaries of the three submitted studies and the conclusions of the TGA evaluations regarding each are presented in Table 2, below.

**Table 1: Summary details and conclusion of the TGA evaluation of the three randomised studies with reports submitted to TGA through the three submissions described in this overview**

| Study/Report | IMpassion130 | Study/Report | IMpassion130 |
|---|---|---|---|
| **Data cut-off for clinical study report** | 14 April 2020 | 15 November 2019 (primary)<br>4 September 2020 (final overall survival) | 3 April 2020 |
| **Population** | Metastatic TNBC<br>(n = 902) | Metastatic TNBC<br>(n = 651) | TNM Stage T2 to T4d early or primary invasive TNBC<br>(n = 333) |
| **Intervention** | Atezolizumab plus nab-paclitaxel | Atezolizumab plus paclitaxel | Atezolizumab plus nab-paclitaxel followed by doxorubicin and cyclophosphamide |
| **Control** | Nab-paclitaxel | Paclitaxel | Placebo plus nab-paclitaxel followed by doxorubicin and cyclophosphamide (nab-pac-AC) |

| Study/Report | IMpassion130 | Study/Report | IMpassion130 |
|---|---|---|---|
| **Randomisation** | 1:1 | 2:1 | 1:1 |
| **Primary efficacy outcome measure** | Co-primary PFS and OS:<br>PFS is tested in ITT and PD-L1+ populations in parallel.<br>OS is tested hierarchically ITT then if significant in PD-L1 positive population | Primary: PFS (investigator-assessed), with hierarchical testing in PD-L1-positive then ITT population. | Co-primary: pathological complete response (pCR) (TNM stage ypT0/is ypN0) in ITT and PD-L1-positive populations.<br>pCR endpoints in ITT and PD-L1+ populations are tested in parallel |

Abbreviations: ADA = anti-drug antibodies; atezo = atezolizumab; atezolizumab+nab-pac-AC = neoadjuvant treatment with atezolizumab administered with nab-paclitaxel and followed by doxorubicin and cyclophosphamide; CCOD = clinical cut-off date; CI = confidence interval; CSR = clinical study report; DCO = data cut-off date; nab = nanoparticle albumin bound; HR = hazard ratio; ITT = intent to treat population; OS = overall survival; PD-L1-pos = PD-L1 positive defined as PD-L1 stained immune cells using the SP142 clone infiltrating at least 1% of the tumour area (also described as IC1/2/3); PFS = progression-free survival (RECIST v1.1 defined); placebo+nab-pac-AC = placebo in combination with nab-paclitaxel followed by doxorubicin and cyclophosphamide; TNBC = triple-negative breast cancer.

**Table 2 (continued)**

| Study/Report | IMpassion130 (Study WO29522) Report 1100481<br>See footnote;[54] | IMpassion131 (Study MO39196) Report 1100721<br>See footnote;[55] | IMpassion031 (Study WO39392) Report 1091712<br>See footnote;[56] |
|---|---|---|---|
| **Summary of main outcomes of interest relevant to this application**<br>(see Table 3) | PFS in PD-L1-positive population (co-primary)<br>*Previous (final) analysis (clinical cut-off date 17 April 2018):*<br>Median PFS was 2.5 months longer with atezolizumab. PFS HR (95% CI) 0.62 (0.49, 0.78), p < 0.0001.<br>*Follow up (14 April 2020):*<br>Descriptively, median PFS was 2.2 months longer with Atezolizumab | PFS in PD-L1-positive population (primary)<br>*Primary (clinical cut-off date 15 November 2019):*<br>No statistically significant difference was shown. Descriptively, median PFS was 0.2 months longer with atezolizumab. PFS HR (95% CI) 0.82 (0.60, 1.12), p = 0.2032.<br>*Follow up (clinical cut-off date 4 September 2020):*<br>Descriptively, median PFS was 0.8 months longer with atezolizumab | pCR in the ITT population (co-primary)<br>The pCR rate was 16.5% higher with atezolizumab (95% CI 5.9, 27.1), p = 0.0044 |

| Study/Report | IMpassion130 (Study WO29522) Report 1100481 See footnote;[54] | IMpassion131 (Study MO39196) Report 1100721 See footnote;[55] | IMpassion031 (Study WO39392) Report 1091712 See footnote;[56] |
|---|---|---|---|
| | OS in PD-L1-positive population (co-primary) immature at time of provisional approval.<br>*Final OS analysis at data cut-off 14 April 2020:*<br>Formal comparison couldn't be made, as a statistically significant difference was not shown in the ITT, and testing in the PD-L1-positive population was subsequent to the ITT in the testing hierarchy. Descriptively, difference in median OS between arms = 7.5 months (favouring atezolizumab). OS HR (95% CI) 0.67 (0.53, 0.86). | OS in PD-L1-positive population (secondary)<br>*Final (clinical cut-off date 4 September 2020):*<br>Descriptively, median OS was 6.2 months longer with placebo. OS HR (95% CI) 1.11 (0.76, 1.64).<br>The submitted report (Report 1100721) was final according to the initial dossier but the sponsor has stated subsequently that there will be a final CSR 'containing mostly disposition and safety updates.' | pCR in the PD-L1-positive population (co-primary)<br>No statistically significant difference was shown.<br>Descriptively, the pCR rate was 19.5% (95% CI 4.2, 34.8) higher in the atezolizumab arm.<br>The number of DFS, EFS and OS events were very small at this data cut-off (all below 20% incidence), precluding interpretation. |

Abbreviations: ADA = anti-drug antibodies; atezo = atezolizumab; atezolizumab+nab-pac-AC = neoadjuvant treatment with atezolizumab administered with nab-paclitaxel and followed by doxorubicin and cyclophosphamide; CCOD = clinical cut-off date; CI = confidence interval; CSR = clinical study report; DCO = data cut-off date; nab = nanoparticle albumin bound; HR = hazard ratio; ITT = intent to treat population; OS = overall survival; PD-L1-pos = PD-L1 positive defined as PD-L1 stained immune cells using the SP142 clone infiltrating at least 1% of the tumour area (also described as IC1/2/3); PFS = progression-free survival (RECIST v1.1 defined); placebo+nab-pac-AC = placebo in combination with nab-paclitaxel followed by doxorubicin and cyclophosphamide; TNBC = triple-negative breast cancer.

**Table 2 (continued)**

| Study/Report | IMpassion130 (Study WO29522) Report 1100481 See footnote;[54] | IMpassion131 (Study MO39196) Report 1100721 See footnote;[55] | IMpassion031 (Study WO39392) Report 1091712 See footnote;[56] |
|---|---|---|---|
| **Relevant conclusions of TGA evaluations** | In the context of the submission to convert the provisional registration of the TNBC indication to full registration, the results of IMpassion130 remain the only clinical trial data evaluated by TGA that provide support for clinical benefit. | IMpassion131 is not supportive of the provisionally approved TNBC indication. | IMpassion031 is not supportive of the provisionally approved TNBC indication as the study setting is not adequately similar to confirm the clinical benefit of the metastatic usage. The early TNBC patient group may have different tumour immunology and has a different oncology treatment context. |

Abbreviations: ADA = anti-drug antibodies; atezo = atezolizumab; atezolizumab+nab-pac-AC = neoadjuvant treatment with atezolizumab administered with nab-paclitaxel and followed by doxorubicin

and cyclophosphamide; CCOD = clinical cut-off date; CI = confidence interval; CSR = clinical study report; DCO = data cut-off date; nab = nanoparticle albumin bound; HR = hazard ratio; ITT = intent to treat population; OS = overall survival; PD-L1-pos = PD-L1 positive defined as PD-L1 stained immune cells using the SP142 clone infiltrating at least 1% of the tumour area (also described as IC1/2/3); PFS = progression-free survival (RECIST v1.1 defined); placebo+nab-pac-AC = placebo in combination with nab-paclitaxel followed by doxorubicin and cyclophosphamide; TNBC = triple-negative breast cancer.

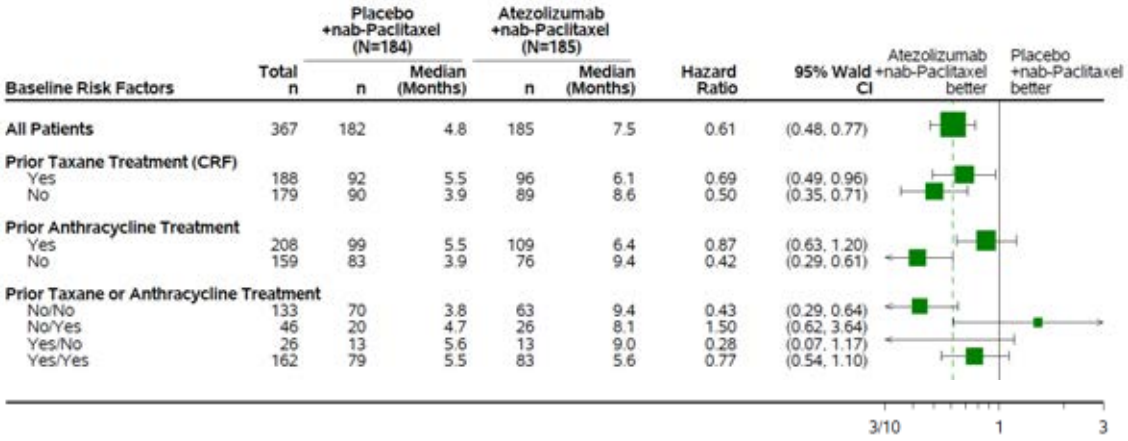
Investigator-assessed progression-free survival was the (co-)primary endpoint for both studies in the metastatic setting. Although they were double blinded, there is a possibility the well known toxicity profile of checkpoint inhibitors could have contributed to informal unblinding. However, sensitivity and concordance analyses were conducted using results according to blinded independent radiological review. These analyses were reassuring that investigator assessment was not significantly biased by informal unblinding, if it did occur.

## *Efficacy in patients who received prior anthracyclines or taxanes (IMpassion130 trial)*

A specific concern raised in the clinical evaluation (of the submission for the approval of the provisional registration of the PD-L1 positive TNBC indication for atezolizumab) was that the IMpassion130 trial;[54] patient population may not be adequately representative of Australian patients in terms of prior therapies.

An exploratory subgroup analysis of efficacy in patients enrolled in the IMpassion130 trial who had previously received (neo)adjuvant chemotherapy (see Figures 2 and 3) raised questions about whether there was an efficacy benefit with addition of atezolizumab to first line treatment with nab-paclitaxel for patients with metastatic PD-L1 positive TNBC who have received (neo)adjuvant anthracycline or taxane treatment. In the previous TGA clinical evaluation, it was estimated that this would be the majority of Australian patients up to 90%.

**Figure 2: Impassion 130 trial; Forest plots of hazard ratios for progression-free survival in subgroups based on prior receipt of (neo)adjuvant taxane and/or anthracycline, within the PD-L1 positive patient population (data cut-off date: 17 April 2018)**



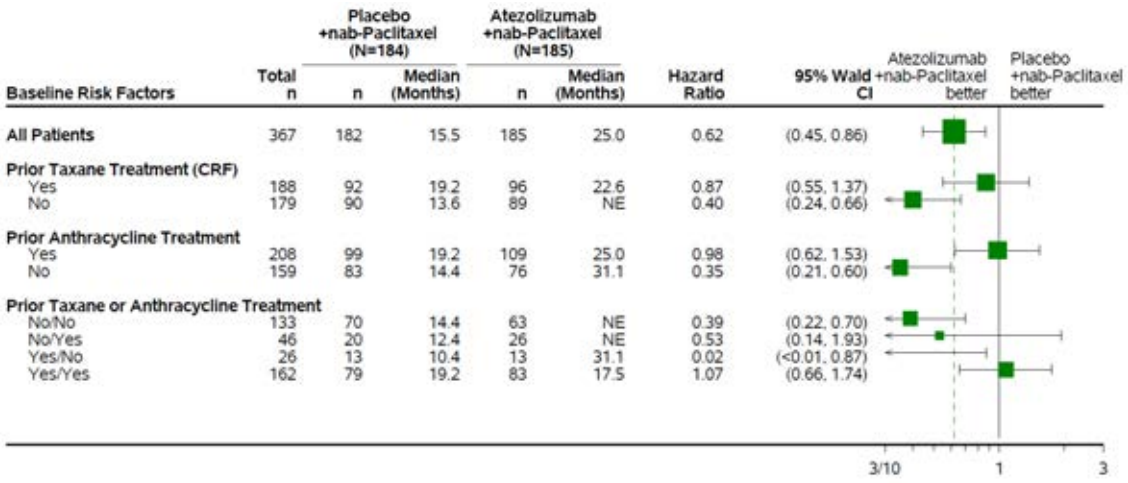

Abbreviations: CI = confidence interval; CRF = case report form; N = number of participants in randomised control group; n = number of participants with baseline risk factor.

Hazard ratios and the associated Wald confidence intervals were estimated using unstratified Cox regression adjusted for log sum of diameters at Baseline presence of liver metastases, age, ECOG performance status, race group, number of sites and time from initial diagnosis to Metast/LA diagnosis (years).

The vertical dashed line indicates the hazard ratio for all patients.

The size of the symbol is proportional to the size of the population in the subgroup.

**Figure 3: Impassion130 trial; Forest plots of hazard ratios for overall survival in subgroups based on prior receipt of (neo)adjuvant taxane and/or anthracycline, within the PD-L1 positive patient population (data cut-off date: 17 April 2018)**




Abbreviations: CI = confidence interval; CRF = case report form; N = number of participants in randomised control group; n = number of participants with baseline risk factor.

Hazard ratios and the associated Wald confidence intervals were estimated using unstratified Cox regression adjusted for log sum of diameters at Baseline presence of liver metastases, age, ECOG performance status, race group, number of sites and time from initial diagnosis to Metast/LA diagnosis (years).

The vertical dashed line indicates the hazard ratio for all patients. The size of the symbol is proportional to the size of the population in the subgroup.

## *Discordant findings between the IMpassion130 and IMpassion131 trials*

Efficacy findings from IMpassion130 and IMpassion131 trials are compared in Table 3, below. Because the results were discordant, the sponsor conducted extensive *post-hoc* exploratory analyses in Report 1107081, which was provided to TGA by the sponsor with this Type S submission (a submission to the TGA to convert the registration of this indication from a provisionally approved to a fully approved one). A summary of these analyses is presented in Table 4 and Table 5.

**Table 2: Report 1107081; Summary of IMpassion130 and IMpassion131 trials as summarised and supplied by sponsor**

| | IMpassion130[a] | | IMpassion131[c] | |
|---|---|---|---|---|
| | PI+nP N=184 | Atezo+nP N=185 | PI+P N=101 | Atezo+P N=191 |
| **Primary Analysis Investigator-Assessed PFS (Co-Primary for IMpassion130, Primary Endpoint for IMpassion131)** | | | | |
| No. (%) of patients with events | 157 (85.3%) | 138 (74.6%) | 64 (63.4%) | 115 (60.2%) |
| Median, months | 5.0 | 7.5 | 5.72 | 5.95 |
| Stratified hazard ratio (95% CI)<br>p-value (log-rank) | 0.62 (0.49–0.78)<br>< 0.0001 | | 0.82 (0.60, 1.12)<br>0.2032 | |
| **Median Duration of Survival Follow-Up at Primary Analysis** | | | | |
| Median, months (min-max) | 11.83 (0.1–29.5) | 13.11 (0.0–32.3) | 8.64 (0.0–26.1) | 9.03 (0.5–25.4) |
| **Final Overall Survival Analysis (Co-Primary Endpoint for IMpassion130 [b], Secondary Endpoint for IMpassion131 [d])** | | | | |
| No. (%) of patients with events | 139 (75.5%) | 120 (64.9%) | 39 (38.6%) | 84 (44.0%) |
| Median, months | 17.91 | 25.43 | 28.29 | 22.05 |
| Stratified hazard ratio (95% CI)<br>p-value (log-rank) | 0.67 (0.53, 0.86)<br>0.0016 [e] | | 1.11 (0.76, 1.64)<br>0.5798 [f] | |
| **Median Duration of Survival Follow-Up at Final Analysis** | | | | |
| Median, months (min-max) | 16.26 (0.1–53.0) | 23.43 (0.0–55.8) | 15.80 (0.0–35.3) | 15.24 (0.5–35.0) |

Abbreviations: atezo + nP = atezolizumab plus nab-paclitaxel; atezo + P = atezolizumab plus paclitaxel; pI + nP = placebo plus nab-paclitaxel; pI + P = placebo plus paclitaxel.

a Clinical cut-off date for the IMpassion130 trial = 17 April 2018 (except see b, below)

b Final overall survival analysis clinical cut-off date = 14 April 2020

c Clinical cut-off date for the IMpassion131 trial = 15 November 2019, (except see d, below)

d Final overall survival analysis clinical cut-off date = 4 September 2020

e Not formally tested

f The IMpassion131 trial was not designed or powered for determining survival benefit in the atezolizumab plus nab-paclitaxel versus placebo plus paclitaxel arms.

**Table 3: Report 1107081; Sponsor's summary of factors considered by exploratory *-hoc* analysis with comparison focused on the PD-L1 positive population using the final overall survival clinical cut off dates for both the IMpassion130 (14 April 2020) and IMpassion131 (4 September 2020) trials**

| Category (factors considered) | Notable findings | IMpassion130 trial | IMpassion131 trial |
|---|---|---|---|
| **Study design** (Stratification factors, inclusion/ exclusion criteria, statistical considerations (sample size, statistical power, efficacy endpoints) | Timing of final OS analysis | OS event driven | PFS event driven |
| | Median follow up at final OS analysis | 23.4 months | 15.2 months |
| | PD-L1-positive sample size | 369 | 292 |
| | Randomisation ratio | 1:1 | 2:1 |
| | Power (final OS analysis) | 88% for ITT | 70% for PD-L1 positive |
| | Target HR for OS | 0.78 in ITT | 0.62 in PD-L1 positive |
| | Mandatory steroid co-medication | No | Steroid pre-medication* |
| **Study conduct** | No notable differences in major procedural or medical procotol deviations. No meaningful impact of the COVID-19 pandemic. | | |
| **Study population** (Baseline patient characteristics, including demographics, disease characteristics, and pre-baseline treatment received; regions; real world prognostic score (ROPRO); Baseline characteristics between control arms, including | Ethnicity | White 69%<br>Asian 18% | White 58%<br>Asian 30% |
| | Diagnosed at Stage IV | 21% | 30% |
| | Prior cancer medical therapy | 66% | 58% |
| | Prior taxane (IxRS) | 52% | 49% |
| | Prior anthracyclines | 57% | 51% |
| | Previous surgical and medical procedures (not active at Baseline) | 30% | 16% |

| Category (factors considered) | Notable findings | IMpassion130 trial | IMpassion131 trial |
|---|---|---|---|
| propensity score analysis) | Current medical conditions (ongoing at Baseline) | 89% | 77% |
| | Prior curative-intent surgery | 74% | 60% |
| | Prior radiation therapy | 63% | 50% |
| | Regional subgroup analyses did not explain the discrepancy between trials, but was subject to limited interpretability due to subgroup size. | | |
| | IMpassion130 controls had a higher average baseline ROPRO, i.e. worse ROPRO prognosis, than IMpassion131 controls. The difference was not specific to the PD-L1-positive subpopulation. The ROPRO difference between the control arms did not translate into an actual OS difference between the control arms: no statistical difference between the control arms was observed on propensity scoring analysis on propensity scoring analysis. Adjusting for differences in baseline characteristics using the IPTW approach accounted for some of the difference in OS between the IMpassion130 and IMpassion131 control arms, and only for a small proportion of the observed risk difference in PFS. | | |
| **Study treatment** (Chemotherapy partner (nab-paclitaxel versus paclitaxel); exposure to concomitant medications unrelated to breast cancer, (corticosteroids, antibiotics, and proton pump inhibitors); anti-cancer therapies following progressive disease) | Chemotherapy partner medicine | nab-paclitaxel | paclitaxel |
| | Non-anticancer concomitant medications at study entry were similar across the two studies. | | |
| | Non-anticancer concomitant medications post-baseline | Different between the trials. | |
| | Concomitant antibiotics or PPIs | Insufficient patients received concomitant antibiotics or PPIs to interpret comparative survival. | |
| | Concomitant steroids | Subgroup results by receipt of systemic steroids was not suggestive of worse efficacy | All received steroids at similar rates, so couldn't be analysed. |
| | Treatment after progression (medical and surgical) and receipt of on-study radiation therapy was similar across the two studies. | | |

| Category (factors considered) | Notable findings | IMpassion130 trial | IMpassion131 trial |
|---|---|---|---|
| **Additional efficacy analyses** (Landmark subgroup analysis; Tumor Growth Inhibition Overall Survival (TGIOS) analysis, biomarker analyses) | Subgroup analysis based on a 6-month landmark (PFS and OS) in subgroups based on whether patients survived to 6 months prior to a PFS event or censoring, or not. | The sponsor concludes that the OS KM curves for the placebo and atezo arms appear to diverge more for patients who reached the 6m landmark than for the subgroup who progressed or were censored previous to 6m, and that therefore there could be a delayed treatment effect of atezolizumab. | |
| | 'Tumor Growth Inhibition Overall Survival' modelling (based on change in sum of the longest diameter [SLD] of target lesions, incorporating prognostic factors) | 'A decrease in tumor growth rate was observed in both IMpassion130 (Roche Report No. 1090201, January 2019) and IMpassion131. This decrease in growth rate translated to a survival benefit in IMpassion130, but not in IMpassion131.'<br>'There appears to be some evidence that the effect of atezolizumab on the tumor growth rate is also delayed as the tumor profiles in both arms of IMpassion131 follow overlapping trajectories until approximately 12.5 to 25 weeks, after which point they separate.' | |
| | Subgroup analysis based on whether PD-L1 positive status was based on a sample from the primary tumour, versus from a metastasis | 'While it might be hypothesised that tumor tissue collected in the metastatic setting would be better associated with improved clinical outcome compared to the primary tissue collected in the early disease setting in both IMpassion130 and IMpassion131, this result was not observed.' | |
| | Gene expression profiling (GEP) at C1D1 versus C2D1 of cryopreserved PBMCs from randomly selected responders to investigate the differential impact of steroids. | Analyses included PD-L1 positive responders in IMpassion130 (n=29) and IMpassion131 (n=26).<br>'Signaling pathways associated with proliferation and activation of CD4 and CD8 T-cells are comparatively enriched in atezo+nP versus atezo+P exposed cells, suggesting that corticosteroids may reduce systemic atezolizumab-mediated T-cell activation...' | |
| **PK and immunogenicity** (Pharmacokinetic profiles of atezolizumab in combination with nab-paclitaxel or paclitaxel; prevalence of ADA) | PK | PK across the two studies was very similar. | |
| | Immunogenicity | 'The atezolizumab immunogenicity rates of IMpassion130 and IMpassion131 were also comparable and relatively low (11.8% and 16.8%, respectively in the PD-L1-positive populations.' Report 1107081 contains very little consideration of immunogenicity. This topic is discussed further under a dedicated heading (see *Immunogenicity* below ). | |

| Category (factors considered) | Notable findings | IMpassion130 trial | IMpassion131 trial |
|---|---|---|---|
| **Additional safety analyses** (Deaths due to PD occurring within 30 days of study treatment discontinuation; subgroup analysis by age, race and region, common taxane-related toxicity assessment (myelo-suppression, infections, peripheral neuropathies)) | IMpassion131 deaths within 30 days of treatment discontinuation | - | This analysis did not reveal a toxicity-based reason for the discrepant survival findings in IMpassion131 trial compared to IMpassion130 trial. |
| | Subgroup analysis of safety: age (< 65 years versus 65 and older) | Toxicity was generally worse in older patients (65 years or older) than younger patients, in both studies. 'this may be partially explained by increased exposure (higher median treatment duration) to atezolizumab and/or taxanes in the older subgroups.' | |
| | Subgroup analysis of safety: race | There were numerical differences but no unifying trend of note or specific safety signals. | |
| | Subgroup analysis of safety: region (Asia, Europe and Middle East, Central America, North America) | There were numerical differences but no unifying trend of note or specific safety signals. | |
| | Taxane-related toxicities: myelosuppression, infections, peripheral neuropathy, | Comparable across studies. Infections were 10% higher in the atezo arm of IMPassion130 than any of the other three arms. There was no evidence of a safety benefit of nab-paclitaxel over paclitaxel. | |

Abbreviations: ADA = anti-drug antibodies; C1D1 = cycle 1, day 1; C2D1 = cycle 2, day 1; HR = hazard ratio; ITT = intent-to-treat population; OS = overall survival; PBMC = peripheral blood mononuclear cells; PD = progressive disease; PFS = progression-free survival; PK = pharmacokinetics; PPI = proton pump inhibitor.
*8-10 mg dexamethasone or equivalent administered for at least first 2 infusions, and permitted for subsequent infusions.

### Table 4: IMpassion130 and IMpassion131 trials; Control arm comparison of outcomes in trials

| IMpassion131 vs. Impassion130 (reference) | PFS - INV HR (CI95%) | | OS HR (CI95%) | |
|---|---|---|---|---|
| | Unadjusted | IPTW adjusted | Unadjusted | IPTW adjusted |
| Control arm comparison | 0.85 (0.66 – 1.11) | 0.96 (0.75 – 1.24) | 0.64 (0.45 – 0.93) | 0.72 (0.49 – 1.05) |

Abbreviations: HR = hazard ratio; IPTW = inverse probability of treatment weighting; INV = investigator; OS = overall survival; PFS = progression-free survival.

IMpassion130 trial clinical cut-off date = 14 April 2020;

IMpassion131 trial clinical cut-off date = 4 September 2020.

# Safety

Safety findings from the three submitted studies are in keeping with the known toxicity profile of this drug, which is notable for immune related adverse reactions. Whilst the toxicities are now well-described and usually manageable, they are not trivial and can have permanent and sometimes fatal consequences.

# Immunogenicity

## *Immunogenicity of atezolizumab across studies*

Anti-drug antibodies (ADA) and neutralising antibodies occur in a notable proportion of atezolizumab-treated patients across settings.[23] At time of provisional approval, it was unclear what the implications of this might be for efficacy and safety across indications. Since that time, the sponsor has conducted an extensive exploratory analysis across randomised studies of atezolizumab, to analyse the effect of ADAs and neutralising antibodies on clinical outcomes. This analysis formed the basis of a regulatory submission that was received by TGA (PM-2020-01859-1-4);[50] and a sponsor authored literature publication with the following abstract:[51]

> 'Antibody therapeutics can be associated with unwanted immune responses resulting in the development of anti-drug antibodies. Optimal methods to evaluate the potential effects of ADA on clinical outcomes in oncology are not well established. In this study, we assessed efficacy and safety, based on ADA status, in patients from over 10 clinical trials that evaluated the immune checkpoint inhibitor atezolizumab as a single agent or as combination therapy for several types of advanced cancers. ADA can only be observed post randomisation, and imbalances in baseline prognostic factors can confound the interpretation of ADA impact. We applied methodology to account for the confounding effects of baseline clinical characteristics and survivorship bias on efficacy. Adjusted meta-analyses revealed that despite numerical differences in overall survival and progression-free survival between ADA-positive and ADA-negative patients from some studies, ADA-positive patients from studies with an overall treatment effect derived benefit from atezolizumab, compared with their adjusted controls. Based on large, pooled populations from atezolizumab monotherapy or combination studies, unadjusted descriptive analyses did not identify a clear relationship between ADA status and frequency or severity of adverse events. Data also suggested that any ADA impact is not driven by neutralising activity. Collectively, this exploratory analysis suggests that the potential for ADA development should not impact treatment decisions with atezolizumab.'

The following changes to the content of the Australian PI was as a result of the related anti-drug antibody/neutralising antibody update submitted to the TGA:[57]

> 'Across multiple Phase II and III studies, 13.1% to 54.1% of patients developed treatment-emergent anti-drug antibodies and 4.3% to 27.5% of patients developed neutralising antibodies. The median time to ADA onset ranged from 3 weeks to 5 weeks.
>
> A decrease in exposure (9% increase in clearance) was observed in ADA-positive patients compared to ADA-negative patients; however, this effect on exposure is not expected to be

50 Submission PM-2020-01859-1-4 was a submission to make changes to the product information (PI) to amend the immunogenicity sections and to include updated paediatric information. The purpose of this submission was is to fulfil a commitment to the TGA to submit cross-indication analyses of atezolizumab anti-drug antibodies (ADA) and neutralising antibodies. In addition, the sponsor proposed an update to paediatric information in the PI based on a pharmacokinetic and safety Study GO29664. Changes to the Australian Product Information were approved by the TGA on 17 September 2021.
51 Peters S, et al. Evaluation of atezolizumab immunogenicity: Efficacy and safety (Part 2). Clin Transl Sci. 2022 Jan;15(1):141-157.

clinically meaningful given the flat exposure-response relationship and adequate target exposure achieved regardless of ADA status.

Patients who developed treatment emergent ADAs tended to have overall poorer health and disease characteristics at Baseline. Exploratory analyses adjusting for imbalances in baseline health and disease characteristics were conducted to assess the effect of ADA on efficacy. These analyses did not exclude possible attenuation of efficacy benefit in patients who develop ADA compared to patients who did not develop ADA.

Across pooled datasets for patients treated with atezolizumab monotherapy and with combination therapies, the rates of adverse events (AEs) which have been observed for the ADA-positive population compared to the ADA-negative population is presented [see Table 6]. Available data do not allow conclusions to be drawn on possible patterns of adverse drug reactions or their causal relationship with ADAs.'

### *Immunogenicity in triple negative breast cancer*

The formation and clinical relevance of ADAs in the TNBC setting was assessed in all the IMpassion trials. The extent of observed immunogenicity, the rate of potential false negatives due to assay drug tolerance, and notable imbalances in baseline characteristics between ADA subgroups are outlined in Table 6 below. The imbalances complicate interpretation of the exploratory efficacy analyses by ADA subgroup (see Table 7).

**Table 5: IMpassion 130/IMpassion 131 trials; Selected metrics regarding the anti-drug antibody rates in clinical trials and known differences in baseline characteristics of those subgroups that could have impacted outcomes**

| | | | IMpassion130 trial | IMpassion131 trial |
|---|---|---|---|---|
| Baseline rate of ADA-positivity | | | 1.6% (ITT) | 1.3% |
| Post-baseline rate of ADA-positivity | | | 13.1% (ITT)<br>11.8% (PD-L1 positive) | 14.7% (ITT)<br>16.8% (PD-L1 positive) |
| Proportion of post-baseline samples that had atezolizumab concentrations that were at or below the estimated drug tolerance limit of the ADA assay (were unlikely to be false negatives) | | | 53% (ITT) | 60% (ITT) |
| Baseline differences between ADA-positive and ADA-negative subgroups ... | ... that could be expected to predict worse prognosis for ADA-positive patients | baseline tumour burden | ADA-positive:<br>40% higher median baseline SLD (ITT)<br>50% higher median number of metastatic sites at enrolment (ITT) | ADA-positive:<br>19%/54% higher median baseline SLD (ITT/PD-L1-positive) |
| | | baseline inflammation | ADA-positive:<br>22% higher median baseline CRP (ITT) | ADA-positive:<br>96%/184% higher median baseline CRP (ITT/PD-L1 positive) |
| | ... that could be expected to predict better prognosis for ADA-positive patients | baseline age or performance status | ADA-positive: 8% lower proportion of patients aged 65 years or older (ITT) | ADA-positive:<br>16% less ECOG PS 1 (PD-L1-positive) |
| | | incidence of prior taxane | ADA-positive:<br>27% less incidence of prior taxane (ITT) | ADA-positive:<br>25%/23% less incidence of prior taxane (ITT/PD-L1-positive) |

Abbreviations: ADA = anti-drug antibodies; CRP = C-reactive protein; ECOG PS = Eastern Cooperative Oncology Group performance status score; ITT = intention to treat; PD-L1 = programmed death-ligand 1; SLD = sum of longest diameters of target lesions per RECIST v1.1

### *Efficacy by anti-drug antibody status in triple negative breast cancer*

Results in the IMpassion130 and IMpassion131 trials in the ITT and PD-L1-positive populations, by subgroups based on ADA status, are summarised in Table 6. In the IMpassion031 trial, the incidence of treatment-emergent ADAs was 13% (21 out of 157) in the ITT (see Table 7). Exploratory subgroup analysis in the ITT showed a pathological complete response rate of 67% for the ADA-positive subgroup (n = 21) and 58% for the ADA-negative subgroup (n = 136).

**Table 6: IMpassion130/IMpassion131 trials; Efficacy results across trials by anti-drug antibody status**

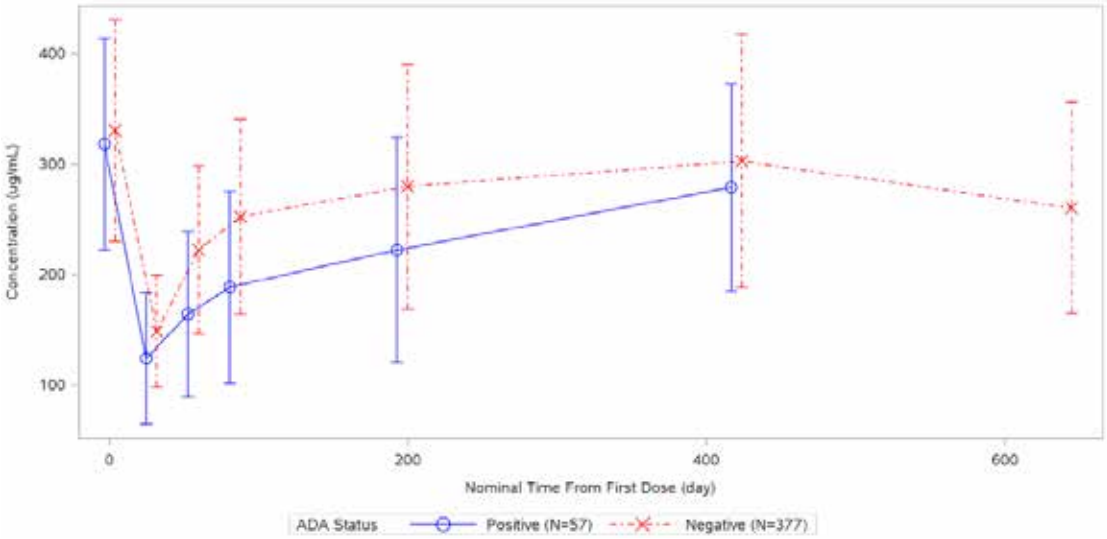
| | **IMpassion130 trial atezolizumab + nanoparticle albumin-bound (nab)-paclitaxel** | | | | **IMpassion131 trial atezolizumab plus paclitaxel** | | | |
|---|---|---|---|---|---|---|---|---|
| | **Intent to treat** | | **PD-L1 positive** | | **Intent to treat** | | **PD-L1 positive** | |
| **ADA status** | **ADA-** | **ADA+** | **ADA-** | **ADA+** | **ADA-** | **ADA+** | **ADA-** | **ADA+** |
| N | 377 | 57 | 157 | 21 | 284 | 51 | 125 | 25 |
| **Progression-free survival per investigator assessment** | | | | | | | | |
| % with event | 88 | 84 | 83 | 81 | 82 | 82 | 78 | 80 |
| Median PFS (95% CI), in months | 7.4 [6, 8] | 5.5 [4, 8] | 8.1 [7, 9] | 8.3 [5, 11] | 5.9 [5, 7] | 5.4 [4, 7] | 7.2 [6, 9] | 5.4 [4, 8] |
| **Overall survival** | | | | | | | | |
| % with event | 72 | 65 | 66 | 57 | 52 | 59 | 47 | 52 |
| Median OS (95% CI), in months | 21.9 [20, 31] | 21.3 [15, 34] | 27.0 [20, 31] | 31.1 [17, NE] | 19.7 [17, 22] | 14.0 [12, 27] | 22.1 [19, 31] | 14.0 [12, NE] |

Abbreviations: ADA = anti-drug antibody; atezo+P = atezolizumab plus paclitaxel; atezo+nP = atezolizumab plus nanoparticle albumin-bound (nab)-paclitaxel; ITT = intent-to-treat population; NE = not estimable; OS = overall survival; PFS = progression-free survival per investigator assessment; PD-L1 = programmed death-ligand 1; PD-L1-pos = the PD-L1 positive sub-population of the ITT.

### *Pharmacokinetics by anti-drug antibody status in triple negative breast cancer*

There was a general trend of lower exposure in the ADA positive subgroup compared with the ADA negative subgroup in both IMpassion130 (see Figure 4) and IMpassion131 trials (see Figure 5), but the distributions can be seen to be overlapping. The independent impact of ADA on atezolizumab clearance was previously reported based on time varying population pharmacokinetics modelling to be approximately 9%. This is a magnitude of difference that is unlikely to be clinically relevant.

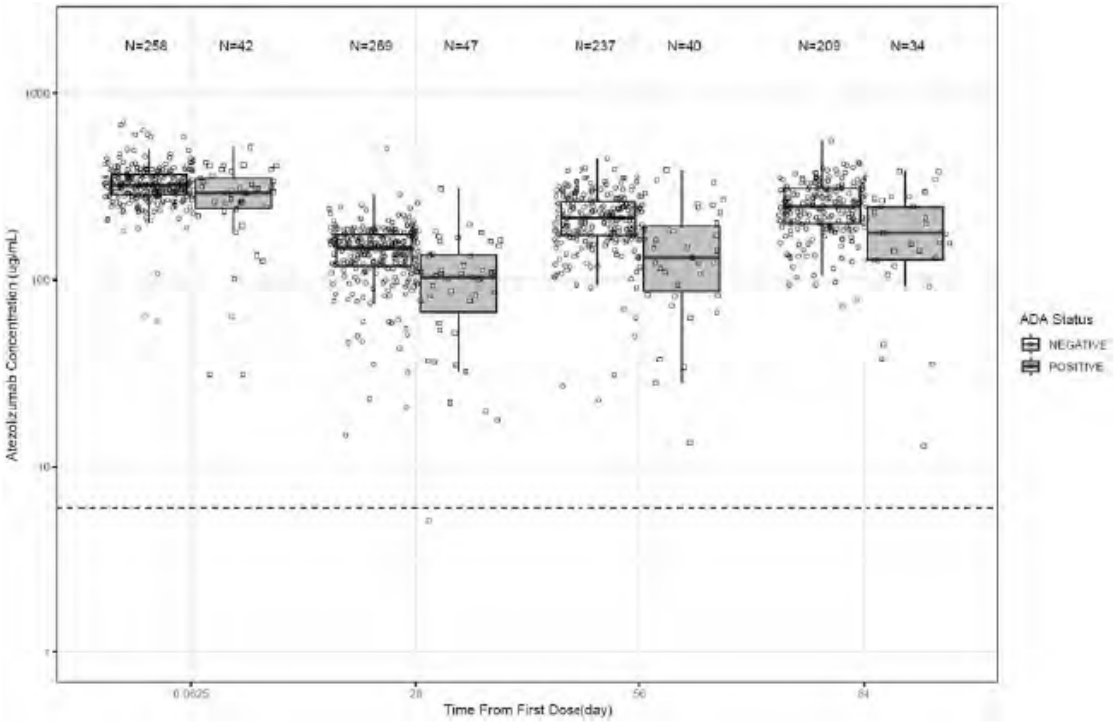
**Figure 4: IMpassion130 trial; Plot of mean serum atezolizumab concentration versus time by treatment-emergent antidrug antibody status**




Abbreviations: ADA = anti-drug antibodies

A drug concentration was deemed to be an artifact and omitted from group descriptive statistics if the concentration is (1) > 0 at pre-dose of Cycle 1 Day 1, (2) below limit of quantification (BLQ) at Cmax or (3) unidentifiable due to more than one result at a given planned time, (4) Atezolizumab post-infusion sample under 70 µg/mL.

**Figure 5: IMpassion131 trial; Box plots of serum atezolizumab concentration versus time by treatment-emergent anti-drug antibody status**




Abbreviations: ADA = anti-drug antibodies; IV = intravenous

Note: Time 0.0625 corresponds to Cycle 1 maximum concentration ($C_{max}$), and all other timepoints correspond to minimum concentrations $C_{min}$.

Data cut-off: 15 November 2019

## Companion diagnostic considerations

In all three submitted studies, randomisation was stratified based on PD-L1 status of the tumour. Tumour samples were stained using Ventana's SP142 PD-L1 antibody clone;[53] and scored centrally based on how much of the sample tumour area contained immune cells bound to the SP142 antibody (PD-L1 staining immune cells).[52] The randomisation strata were defined as PD-L1 positive (where at least 1% of the tumour sample area contained PD-L1 staining ICs) or PD-L1 negative (where less than 1% of the tumour sample area contained PD-L1 staining immune cells).[45]

# Risk management plan

The sponsor has made a submission to transition atezolizumab (Tecentriq) from a provisional registration to full registration (known as a Type S submission) for the following indication:

> *Tecentriq, in combination with nanoparticle albumin-bound paclitaxel, is indicated for the treatment of adult patients with unresectable locally advanced or metastatic TNBC whose tumours express PD-L1 (PD-L1 stained tumour-infiltrating immune cells of any intensity covering greater or equal to 1% of the tumour), as determined by a validated test and who have not received prior chemotherapy for metastatic disease.*

Tecentriq is currently registered for the following indications: non-urothelial cancer; small cell lung cancer; urothelial cancer and hepatocellular cancer.

52 Herbst RS, et al. Predictive correlates of response to the anti-PD-L1 antibody MPDL3280A in cancer patients. Nature. 2014 Nov 27;515(7528):563-7.

The dosing regimen for Tecentriq for the TNBC indication is 840 mg administered by intravenous infusion, followed by 100 mg/m$^2$ nab-paclitaxel. For each 28 day cycle Tecentriq is administered on Day 1 and 15, and nab-paclitaxel is administered on Day 1, 8 and 15.

The sponsor has submitted European Union (EU)-risk management plan (RMP) version 22.0 (dated 24 August 2021; data lock point (DLP) 2 June 2021) and Australia specific annex (ASA) version 14.0 (dated 2 March 2022) in support of this application. The documents were submitted on 2 March 2022 and are updates (reviewed by the TGA on 7 April 2022) to replace the RMP/ASA submitted with the Type S application (EU-RMP version 20.1 (dated 15 July 2021; DLP 7 April 2021) and ASA version 13.0 (dated 20 October 2021)).

In response to TGA questions, the sponsor has submitted ASA version 14.1 (dated 19 August 2022) in support of its application.

The most recently evaluated EU-RMP for the TNBC indication was EU-RMP version 7.1 (dated 15 July 2019; DLP 26 February 2019) and ASA version 8.1 (dated August 2019).

The summary of safety concerns and their associated risk monitoring and mitigation strategies are summarised in Table 8. Further information regarding the TGA's risk management approach can be found in risk management plans for medicines and biologicals and the TGA's risk management approach.

**Table 7: Summary of safety concerns**

| Summary of safety concerns | | Pharmacovigilance | | Risk Minimisation | |
|---|---|---|---|---|---|
| | | Routine | Additional | Routine | Additional |
| **Important identified risks** | Immune-mediated hepatitis | ✔ | – | ✔ | ✔† |
| | Immune-mediated pneumonitis | ✔ | – | ✔ | ✔† |
| | Immune-mediated colitis | ✔ | – | ✔ | ✔† |
| | Immune-mediated pancreatitis | ✔ | – | ✔ | ✔† |
| | Immune-mediated endocrinopathies (diabetes mellitus, hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis) | ✔ | – | ✔ | ✔† |
| | Immune-mediated neuropathies (Guillain-Barré syndrome and myasthenia gravis) | ✔ | – | ✔ | ✔† |
| | Immune mediated meningoencephalitis | ✔ | – | ✔ | ✔† |
| | Infusion-mediated reactions | ✔ | – | ✔ | ✔† |

| Summary of safety concerns | | Pharmacovigilance | | Risk Minimisation | |
|---|---|---|---|---|---|
| | | Routine | Additional | Routine | Additional |
| | Immune-mediated myocarditis | ✔ | – | ✔ | ✔† |
| | Immune-mediated nephritis | ✔ | – | ✔ | ✔† |
| | Immune-mediated myositis | ✔ | – | ✔ | ✔† |
| | Immune-mediated severe cutaneous adverse reactions | ✔ | – | ✔ | ✔‡ |
| **Important potential risks** | Anti-drug antibodies | ✔ | – | ✔ | – |
| | Embryofetal toxicity | ✔ | – | ✔ | – |
| **Missing information** | Long term use | ✔ | ✔* | – | – |

* Ongoing Study MO39171 (TAIL trial) and Study MO29983 (SAUL trial)

† Patient Alert Card

‡ Dear Health Care Professional Letter (One time dissemination distributed November 2020)

The summary of safety concerns has previously been considered to be acceptable by the TGA. Unless there are further issues identified in the current clinical evaluation, the safety concerns are acceptable

Routine and additional pharmacovigilance activities have been proposed. There are two additional pharmacovigilance studies (the TAIL and SAUL trials);[53,54] to study long term safety. The pharmacovigilance plan is acceptable.

Routine and additional risk minimisation activities have been proposed. Additional risk minimisation consists of a Patient Card which has been previously considered to be acceptable.

The Delegate will provide advice on the acceptability of the removal of the provisional registration wording from the Product Information/Consumer Medicines Information (CMI) when considering whether to approve the Type S application (see *Advice to the Delegate*).

53 TAIL trial: A Phase III/IV, single arm, multicenter study of atezolizumab (Tecentriq) to investigate long-term safety and efficacy in previously-treated patients with locally advanced or metastatic non-small cell lung cancer. ClinicalTrials.gov Identifier: NCT03285763

54 SAUL trial: An open label, single arm, multicenter, safety study of atezolizumab in locally advanced or metastatic urothelial or non-urothelial carcinoma of the urinary tract. ClinicalTrials.gov Identifier: NCT02928406

# Risk-benefit analysis

## Delegate's considerations

### *Provisional registration pathway*

The TGA provisional registration process provides a pathway through which therapeutic goods can be registered in Australia even though there may be meaningful uncertainties that remain to be addressed. This allows for time limited registration of a therapeutic good based on early promising data, to provide a mechanism of early access despite residual uncertainties, for patients unable to access the confirmatory study, during the time that confirmatory data is being generated. As intended, it is a temporising measure limited in duration to two years, and automatically lapses at the end of that period. Two-year extension periods can be applied for twice, such that the total duration of provisional registration can be up to six years.

The criteria used by TGA to judge eligibility for provisional determination (to enter the provisional registration pathway) are based on assessing whether the circumstances are clinically appropriate to justify early access. This assessment depends on whether the condition is life threatening or seriously debilitating; whether the preliminary evidence is so strongly suggestive of a therapeutic advance that making it available based on earlier evidence is justifiable despite the uncertainty; and whether there is an adequate plan to collect data to address the residual uncertainties whilst provisional registration is in place.

### *Key uncertainties for this submission and scope of the submitted data*

The main uncertainties that remained regarding atezolizumab plus nab-paclitaxel for PD-L1 positive triple negative breast cancer (TNBC) at time of provisional registration are listed above in *Summary of findings,* above. The contribution of the submitted data to reducing each uncertainty is addressed under the subheadings below.

### *Progression-free survival*

A statistically significant increase in progression-free survival (PFS) was seen in the IMpassion130 trial with the addition of atezolizumab to first line nab-paclitaxel. The absolute size of the statistically significant increase between arms in the IMpassion130 trial was marginal: 2.5 months in the PD-L1 positive population. In context of this heterogeneous disease, there is uncertainty about the clinical meaningfulness of this endpoint in isolation. It is clinically rational therefore that PFS was made a co-primary endpoint alongside overall survival, meaning both endpoints much reach statistical significance for a population benefit to be concluded.

*IMpassion130 trial*

With further follow up (repeated PFS analysis at time of final overall survival analysis), the difference in PFS between arms remained marginal (2.2 months in the PD-L1 positive population) (see Table 3, above).

*IMpassion131 trial*

This study did not demonstrate a difference in PFS between patients with metastatic TNBC who received atezolizumab in addition to first-line paclitaxel, and those who received placebo plus paclitaxel (see Table 3, above).

*IMpassion031 trial*

No data regarding PFS benefit for patients with metastatic TNBC was available from this study, as it is a study in the early breast cancer setting.

*Progression free survival summary*

No data has been submitted that reduces the uncertainty with regard to the marginal size and clinical meaningfulness of PFS benefit for patients with metastatic TNBC who receive atezolizumab in addition to first line nab-paclitaxel chemotherapy.

## Overall survival

At time of the first pre-specified interim analysis of overall survival in the IMpassion130 trial, survival data from were immature, with an information fraction of 59%. In the intent to treat (ITT) population, no statistically significant difference between arms was demonstrated. Due to the testing hierarchy, which prioritised the ITT population, overall survival in the PD-L1-positive population could not be formally tested. Descriptive analysis showed a median of 25 months in the atezolizumab arm and 18 months in the placebo arm.

*IMpassion130 trial*

With additional follow up, a final overall survival analysis has been performed. At this final overall survival analysis, the overall survival data are now mature. The conclusion remains unchanged: whilst strongly suggestive of a clinically meaningful benefit due to magnitude, a statistically significant difference in overall survival was not demonstrated in this study with the addition of atezolizumab to first line nab-paclitaxel for patients with metastatic TNBC. Descriptive analysis of overall survival in the PD-L1 positive subgroup at the time of final overall survival analysis showed a median of 25 months in the atezolizumab arm and 18 months in the placebo arm. See Table 3, above.

*IMpassion131 trial*

A statistically significant difference in overall survival was not demonstrated in this study with the addition of atezolizumab to first-line paclitaxel for patients with metastatic TNBC. Descriptive analysis of overall survival in the PD-L1 positive subgroup showed a median of 22 months in the atezolizumab arm and 28 months in the placebo arm. See Table 3, above.

*IMpassion031 trial*

No data on overall survival benefit for patients with metastatic TNBC was available from this study, as it is a study in the early breast cancer setting.

*Overall survival summary*

The submitted data reduces the uncertainty presented by immaturity of survival data. However, there remains no statistically significant demonstration of a survival benefit with the use of atezolizumab in the first-line treatment of metastatic TNBC. As statistically significant findings were not demonstrated for both co-primary endpoints of IMpassion130, it is not possible to make a statistically valid conclusion of benefit.

## Reliability and concordance of the SP142 clone

The Delegate at time of provisional approval noted concerns about the SP142 antibody;[53] regarding concordance with other PD-L1 antibodies, and regarding reproducibility of PD-L1 scoring. All three submitted studies used SP-142 testing, and none of the submitted data directly addressed these concerns, however they are addressed in published peer-reviewed medical literature, as below.

*Concordance with other antibodies*

In the lung cancer setting, the SP142 clone has been demonstrated to be less sensitive than other commonly used PD-L1 clones such as 22C3;[35] 28-8 and SP263 for the detection of PD-L1 on tumour cells and immune cells.[55,56,57] It is possible that in the TNBC setting, too, SP142 may not identify the

55 Hirsch, F. R., et al. PD-L1 Immunohistochemistry Assays for Lung Cancer: Results from Phase 1 of the Blueprint PD-L1 IHC Assay Comparison Project. J Thorac Oncol 12, 208–222 (2017).

56 Xu, H., et al. Assessment of Concordance between 22C3 and SP142 Immunohistochemistry Assays regarding PD-L1 Expression in Non-Small Cell Lung Cancer. Sci Rep 7, 16956 (2017)

57 Torlakovic, E., et al. 'Interchangeability' of PD-L1 immunohistochemistry assays: a meta-analysis of diagnostic accuracy. Mod Pathol 33, 4–17 (2020).

same patients as would be identified using a different PD-L1 antibody clone. A published *post-hoc* analysis of the IMpassion130 trial, made the following conclusions on this topic:[58]

> 'Whether classification of PD-L1 status by the different assays results in equivalent clinical outcomes is unknown as there is a paucity of clinical trials to specifically address this question. Nevertheless, there is evidence from IMpassion130 that using the different clones 22C3 and SP263 stratified by combined positive score of 1 and IC staining at the 1% cutpoint respectively, that patients show similar differences in outcome when treated with atezolizumab, although they are not precisely the same patients.'

*Inter-observer reliability*

There have previously been significant concerns about poor reliability in immune cells PD-L1 scoring, with the Blueprint 2 academic study demonstrating an overall intraclass correlation coefficient of 0.18 to 0.19.[59] High inter-observer variability has therefore been of concern in other applications: for example, with use of the SP142 PD-L1 antibody in the non-small cell lung cancer setting to differentiate between patients with an immune cells score (IC);[60] of less or equal to IC2 or IC3 (< 50% versus ≥ 50% tumour area containing PD-L1 staining immune cells).[61]

With regard to this issue in the TNBC setting, two publications relating to a single, Roche-sponsored study were identified in the literature that appear to have been designed to directly address this concern.[62,63] The latter of these states the following conclusion:[55]

> '...this study demonstrates the Ventana PD-L1 (SP142) Assay to have excellent intraobserver and interobserver reproducibility among pathologists with specific, detailed training in SP142 PD-L1 assessment in TNBC, but lower agreement among pathologists untrained or with minimal training in SP142 PD-L1 assessment in TNBC.'

Whilst these publications were authored by the sponsor, so is the submitted dossier.

*SP142 test summary*

If patients were to be selected for treatment with atezolizumab, other tests for PD-L1 status using other PD-L1 antibodies may not identify the same patients with TNBC as SP142.

If the SP142 test was to be used to determine PD-L1 status of TNBC for the purpose of identifying patients who could expect to benefit from atezolizumab treatment, it would not be acceptably reliable in clinical practice unless specific training in SP142 PD-L1 assessment in TNBC was provided.

## *External validity of IMpassion130 trial to Australians with triple negative breast cancer*

Generally, the heterogeneous nature of TNBC poses a challenge to the external validity of using a single randomised study to predict outcomes for the broader TNBC population. This is discussed further below under '*Synthesis of data'.*

As noted in *Summary of findings* (above), specific concerns were raised during clinical evaluation of the initial TNBC submission that the proportion of patients in IMpassion130 trial who had not

58 Rugo HS Loi S Adams S, et al. Performance of PD-L1 immunohistochemistry (IHC) assays in unresectable locally advanced or metastatic triple-negative breast cancer (MTNBC): post-hoc analysis of IMpassion130. ESMO 2019 Congress. Barcelona, Spain: Annals of Oncology; 2019:v851–v934.

59 Tsao MS, et al. PD-L1 Immunohistochemistry Comparability Study in Real-Life Clinical Samples: Results of Blueprint Phase 2 Project. J Thorac Oncol. 2018 Sep;13(9):1302-1311

60 The IC scoring system is based on the proportion of the tumour area occupied by PD-L1 expressing tumour-infiltrating immune cells (IC cells) (as a percentage of total tumour area).

61 File for Advisory Committee on Medicines (ACM) meeting number 27 (June 2021).

62 Pang JM, et al. 297P SP142 immunohistochemistry (IHC) PD-L1 inter- and intra-pathologist agreement in triple negative breast carcinoma (TNBC). Ann Oncol. 2020 Sep;31(S4):S361.

63 Pang JB, et al. SP142 PD-L1 Scoring Shows High Interobserver and Intraobserver Agreement in Triple-negative Breast Carcinoma But Overall Low Percentage Agreement With Other PD-L1 Clones SP263 and 22C3. Am J Surg Pathol. 2021 Aug 1;45(8):1108-1117

received prior neoadjuvant or adjuvant treatment for their TNBC (37%) was much higher than the proportion that would be expected in Australian clinical practice (5 to 10%). Prior receipt of neoadjuvant or adjuvant treatment predicts poorer survival in the metastatic setting,[64] and may impact the effectiveness and/or safety of combination treatment with immune checkpoint inhibition and chemotherapy. Therefore, the results seen in the IMpassion130 trial might not predict the efficacy and safety of this combination for an Australian population with TNBC. Subgroup results according to prior receipt of taxane or anthracycline lent weight to this concern (see Figure 2 and Figure 3).

During the discussion of the Advisory Committee on Medicines ACM, it was noted by breast oncology experts that the proportion of patients presenting with *de novo* metastatic disease in Australia may actually be increasing over time, as earlier treatments become more and more successful at preventing development of metastatic disease.

### *Effect of immunogenicity*

Since the provisional approval, immunogenicity data from the IMpassion131 trial has become available in addition to what was already known from the IMpassion130 trial. Similar rates of ADAs were seen in the two studies, though there was a numerically lower rate in the IMpassion130 trial (12% versus 17% in the PD-L1 positive populations). Numerically higher median survival was seen in the ADA negative compared to the ADA positive subgroup in the IMpassion131 trial (median overall survival 22 months versus 14 months, respectively, in the PD-L1 positive population) but this finding was not consistent with the IMpassion130 trial (see Table 6). Differences in baseline characteristics of these populations (see Table 7) confounds interpretation of the ADA based subgroup analyses.
Safety was similar regardless of ADA status, though analysis is again difficult to interpret due to the small subgroup sizes and *post hoc* nature of the analysis, with possible confounders at Baseline. Whilst some events appeared to be higher in the ADA positive subgroup compared to the ADA-negative subgroup, others ('drug hypersensitivity' and 'anaphylactic reaction') did not.

## *Synthesis of data*

This submission proposes conversion of the existing indication for atezolizumab plus nab-paclitaxel for the treatment of metastatic TNBC from provisional to full registration.

As discussed under *Current treatment options* in the *Product background* (above), there are very limited options for the treatment of advanced TNBC, particularly for BRCA wild type disease. In context of the lack of non-chemotherapy options for this population with generally aggressive disease and encouraged by the success of checkpoint inhibition in other tumour settings, regulatory approvals were made worldwide on the basis of the data from IMpassion130 trial, despite its limitations. In Canada, the USA and Australia, the uncertainties were formally recognised through the use of limited-type approval mechanisms, with the assumption that the uncertainties would decrease with further data. Specifically, it was expected that a similar result would be seen in the very similar IMpassion131 trial. Unfortunately, repetition of the study question, using atezolizumab partnered with paclitaxel rather than nab-paclitaxel, failed to replicate the results seen in the IMpassion130 trial.

There are multiple, in depth analyses of putative reasons for the divergent findings to be found amongst the medical literature and online medical community;[65] [66] [67] and the sponsor has submitted an in-depth report analysing differences between the two trials (see Table 4

64 Liedtke C, et al. Response to neoadjuvant therapy and long-term survival in patients with triple-negative breast cancer. J Clin Oncol. 2008 Mar 10;26(8):1275-81.

65 Franzoi MA, and de Azambuja E. Atezolizumab in metastatic triple-negative breast cancer: IMpassion130 and 131 trials - how to explain different results? ESMO Open. 2020 Nov;5(6):e001112.

66 https://www.vumedi.com/video/2020-esmo-updates-on-1l-io-in-advanced-tnbc-is-nab-paclitaxel-a-preferred-partner-for-atezo-what-are/

67 https://www.vumedi.com/video/2020-esmo-update-on-io-strategies-in-mtnbc-how-does-atezolizumab-fit-into-current-soc-can-we-transit/

One hypothesis is that the difference in chemotherapy partner agent between trials (nab-paclitaxel in the IMpassion130 trial and solvent-based paclitaxel in the IMpassion131 trial) is responsible for the different outcomes. Whilst paclitaxel is the cheaper and more widely available of the two compounds, the solvent in which it is based causes significant hypersensitivity,[68] necessitating the use of glucocorticoid/corticosteroid premedication.[69] Development of nab-paclitaxel was initially undertaken to eliminate the solvent associated toxicity, however, preclinical and clinical data have variably suggested improvements in efficacy and safety endpoints for nab-paclitaxel over solvent-based paclitaxel.[70] Whether paclitaxel and nab-paclitaxel differ in safety and efficacy in the treatment of breast cancer remains controversial, particularly in the TNBC setting. In pancreatic cancer, nab-paclitaxel has been shown to promote macrophage activation and immunostimulatory cytokine expression, providing a possible point of difference that could favour immune priming.[71]

Another suggestion is that the corticosteroids that are required as pre-medication with solvent-based paclitaxel may have affected efficacy of the combination, *per se*. Nab-paclitaxel was selected as the treatment partner for atezolizumab in the IMpassion130 trial to eliminate this as a possible confounder. Associations between survival after checkpoint inhibitor treatment have been observed with some reasons for usage (supportive care/treatment of brain metastases) yet not others (treatment of immune-related adverse events),[72] and similarly with timing of administration (corticosteroid treatment commenced two months after starting the checkpoint inhibitor, versus earlier).[73] However, it is ultimately not possible to tell whether the association between administration of corticosteroids and poorer outcomes is prognostic or predictive.[74,75] That is, the association between poorer survival and steroids may be confounded by indication: patients who receive steroids for brain metastases or supportive treatment are sick enough to require steroids; and patients who receive steroids for immune-related adverse events may be experiencing more efficacy alongside more toxicity.

Differences between the IMpassion130 and IMpassion131 trial populations could also have contributed. Despite the extensive analyses conducted by the sponsor, no single factor to explain the discordant outcomes was identified. Possible sources of heterogeneity that were not reported (presumably not measured) and for which there are literature supporting possible relevance include claudin-low molecular subtype,[76] level of immunohistochemistry staining for HER2 (0

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71 Cullis J, et al. Macropinocytosis of Nab-paclitaxel Drives Macrophage Activation in Pancreatic Cancer. Cancer Immunol Res. 2017 Mar;5(3):182-190

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74 Jove M, et al. Impact of baseline steroids on efficacy of programmed cell death-1 (PD-1) and programmed death-ligand 1 (PD-L1) blockade in patients with advanced non-small cell lung cancer. Transl Lung Cancer Res. 2019 Dec;8(Suppl 4):S364-S368

75 Jessurun CAC, et al. The combined use of steroids and immune checkpoint inhibitors in brain metastasis patients: a systematic review and meta-analysis. Neuro Oncol. 2021 Aug 2;23(8):1261-1272.

76 Taylor NA, et al. Treg depletion potentiates checkpoint inhibition in claudin-low breast cancer. J Clin Invest. 2017 Sep 1;127(9):3472-3483

versus 1+; both considered negative),[77,78] tumour mutational burden (TMB), immune infiltration and tumour microenvironment.[79 80 81 82 83]

Whether, and to what extent any of the above factors contributed to the discordant findings between the IMpassion130 and IMpassion131 trials is ultimately unknown. Chance may have played a role. Broadly, the discordant findings emphasise the challenges of extrapolating isolated TNBC trial outcomes to external TNBC populations. The difference of 10 months between the median overall survival in each of the placebo arms of the IMpassion130 and IMpassion131 trials (see Table 3) highlights the variability that can be seen in this clinical setting.

The conclusion of the sponsor-submitted document, Report 1107081, is as follows:

> 'The mature and consistent data from IMpassion130 trial continue to support the use of atezolizumab plus nab-paclitaxel as treatment for patients with PD-L1 positive mTNBC. Acknowledging cross-trial differences between IMpassion130 and IMpassion131 trials, the sponsor is of the opinion that the results of IMpassion131 trial do not refute the clinically meaningful and durable benefit observed in IMpassion130 trial.
>
> Overall, the favorable benefit-risk assessment for atezolizumab combined with nab-paclitaxel in patients with PD-L1 positive mTNBC remains unchanged. This conclusion is further supported by the more mature data from IMpassion130 trial, the current therapeutic landscape, and the continued high unmet need in mTNBC.'

The Delegate agrees with the sponsor that the IMpassion130 trial data are now mature, and that the level of evidentiary support for the TNBC indication is essentially unchanged.

The Delegate notes that the US Food and Drug Administration (FDA) oncology specific advisory expert committee, Oncologic Drugs Advisory Committee, voted in April 2021 to maintain the FDA Accelerated Approval of the analogous US indication.[84] The split vote is in keeping with the persisting uncertainties but the overall opinion that a limited type approval was warranted due to ongoing unmet need. In July 2021, however, the treatment landscape in the USA changed with full approval granted to pembrolizumab for the treatment of TNBC, and the high unmet need condition required for the maintenance of the accelerated approval of Tecentriq in the USA was no longer met. As a result of this regulatory situation (not due to new safety or efficacy data), the Accelerated Approval indication in the USA was withdrawn voluntarily by the sponsor.

The Delegate is now faced with a different question to the one that was posed to the ACM. The Delegate needs to decide not whether the provisional registration in Australia should be maintained, but whether it should be converted to full registration. Thus, the question that the Delegate must answer in coming to a decision on this Type S submission is whether the uncertainties that were present at time of provisional registration have been adequately reduced by the submitted data to justify conversion to full registration. As the submitted data has not meaningfully changed the persisting uncertainty, the Delegate must conclude that the answer is no.

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83 Bianchini G, et al. Treatment landscape of triple-negative breast cancer - expanded options, evolving needs. Nat Rev Clin Oncol. 2022 Feb;19(2):91-113.

84 https://www.onclive.com/view/biomarkers-for-selection-of-extended-endocrine-therapy-in-hr-breast-cancer

# Proposed action

The sponsor proposes to convert the *provisionally registered* triple negative breast cancer indication to *full registration*.

After review of the submitted data, the level of evidentiary support for the TNBC indication is essentially unchanged.

The increase in PFS with additional of atezolizumab to nab-paclitaxel remains marginal, and its clinical significant unclear.

With further data maturity, an overall survival benefit remains suggested by the magnitude of descriptive difference between arms in the PD-L1 positive population but is still not statistically interpretable due to hierarchical testing of endpoints in the study design.

Whilst it was anticipated the results of the IMpassion131 trial would reduce the uncertainty about the external validity of the IMpassion130 trial to Australian patients with TNBC, they have not done so.

Significant uncertainties remain about the repeatability and external validity of the finding of the IMpassion130 trial, given the heterogeneity of TNBC as a condition, and subgroup findings indicating results were driven by efficacy in patients who hadn't received prior treatment with (neo) adjuvant taxanes or anthracyclines

Conversion of the TNBC indication to full registration is not adequately supported by the submitted data.

# Advisory Committee considerations

The Advisory Committee on Medicines (ACM) having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following.

## *Specific advice to the Delegate*

1. ***The Delegate's conclusion is that the submitted data do not support conversion of the existing provisionally registered indication to a full registration.***

   ***The opinion of the committee is sought regarding this conclusion.***

The ACM noted that this is a complex and challenging decision and discussed the atezolizumab efficacy data and TNBC treatment access at length.

The ACM was of the view that the totality of evidence suggests that adding immunotherapy results in clinically meaningful improvement in overall survival for metastatic PD-L1 positive TNBC however the efficacy data provided by IMpassion130 and IMpassion 131 trials in support of atezolizumab remain significantly problematic.

The ACM questioned the statistical design of the IMpassion 130 trial and stated that it could have been designed to test outcomes in the PD-L1 subgroup prior to the ITT in the testing hierarchy. The ACM noted that the exploratory analysis indicated a median overall survival advantage of over seven months for atezolizumab and nab-paclitaxel in the PD-L1 positive TNBC group compared to placebo and nab-paclitaxel. The ACM noted that this is a clinically significant difference.

The ACM also discussed the discordant results from IMpassion131 trial which showed no improvement in overall survival for atezolizumab and paclitaxel versus paclitaxel alone. The ACM noted some hypotheses for these results including a chance occurrence, issues with the PD-L1 assessment, and differences in the study populations relating to pre-treatment. Overall, the ACM noted that the reasons for the differences in outcome between the IMpassion130 and IMpassion131 trials are not clearly understood and reiterated that the clinically meaningful overall survival results from the IMpassion130 trial are from the exploratory analysis only. The ACM agreed that a statistically significant benefit in survival was not demonstrated in either study.

The ACM noted that access and time from diagnosis to treatment is important. Considering this, the ACM discussed the potential for unmet clinical need should atezolizumab not obtain full registration (noting that provisional registration would lapse). The ACM noted that another immunotherapy of the same class with similar mechanism of action is now registered for PD-L1 positive TNBC and as such there are no longer clear grounds to state atezolizumab is addressing an unmet clinical need. The ACM also noted that mechanisms such as the Special Access Scheme (SAS) and Authorised Prescribers Scheme may be used to allow supply of therapeutic goods that are not included in the Australian Register of Therapeutic Goods.

While the ACM acknowledged a trend towards a positive benefit-risk profile, on balance, the ACM agreed with the Delegate's conclusion that the submitted data do not support conversion of the existing provisional indication to full registration. In drawing this conclusion the ACM reiterated the challenges and uncertainty with the provided studies and a lack of unmet clinical need.

Given the design of the IMpassion130 trial, accrual of additional observations is unlikely to strengthen the available evidence.

### *Conclusion*

The ACM agreed that Tecentriq (atezolizumab) had an overall negative benefit-risk profile for the proposed indication for full registration as the evidence submitted did not satisfactorily establish the efficacy of the product. The ACM noted that while the exploratory analysis demonstrated a clinically meaningful improvement in overall survival for PD-L1 positive metastatic TNBC patients, neither the IMpassion130 trial nor the IMpassion131 trial demonstrated statistically significant improvements in survival. Furthermore, the registration of another same-class immunotherapy for PD-L1 positive TNBC means there is not clear unmet clinical need for this population.

## Conclusion following the Advisory Committee advice

The Delegate believed that provisional registration of the TNBC indication was appropriate given the specific and different question posed at that time and in that situation. However, confirmatory data has not become available, as had been hoped. Conversion of the atezolizumab TNBC indication from a provisional registration to a full registration is therefore, not adequately supported by the submitted data.

# Outcome

The sponsor withdrew their submission on 21 March 2023 before a decision had been made by the TGA.

## Specific conditions of registration applying to these goods

The sponsor withdrew their submission on 21 March 2023 before a decision had been made by the TGA

**Therapeutic Goods Administration**

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Reference/Publication #