BCAC Submission to Pharmac for PEMBROLIZUMAB

Overview

Product Details

What is the registered name of the generic pharmaceutical?

pembrolizumab

What is the brand name of the pharmaceutical?

Keytruda®

Which therapeutic area does this pharmaceutical fall into?

Haem-Oncology

Please provide information on the various forms, strengths, and pack sizes of the pharmaceutical that you are seeking funding for.

100 mg/4 mL (25 mg/mL) concentrate for solution for infusion

Which companies produce and/or supply the pharmaceutical?

MSD

Proposed amendments

High-risk early-stage triple-negative breast cancer (TNBC) in combination with chemotherapy as neoadjuvant treatment, and then continued as monotherapy as adjuvant treatment after surgery.

In combination with chemotherapy, for the treatment of patients with locally recurrent unresectable or metastatic TNBC whose tumours express PD-L1 (CPS ≥10).

Disease and Current Treatment

Please provide an overview of the disease for which funded treatment is sought.

Breast cancer is diagnosed in about 3,500 people annually in New Zealand. The latest Ministry of Health mortality report shows nearly 700 deaths in 2019. It is therefore an important health issue in terms of physical and mental health and has a significant social and economic impact on society, families, and whānau. Despite the perception that cancer is an older person's disease, breast cancer is the number one cause of death for New Zealand women under 65. Having a relative living with or dying of breast cancer affects other family members significantly.

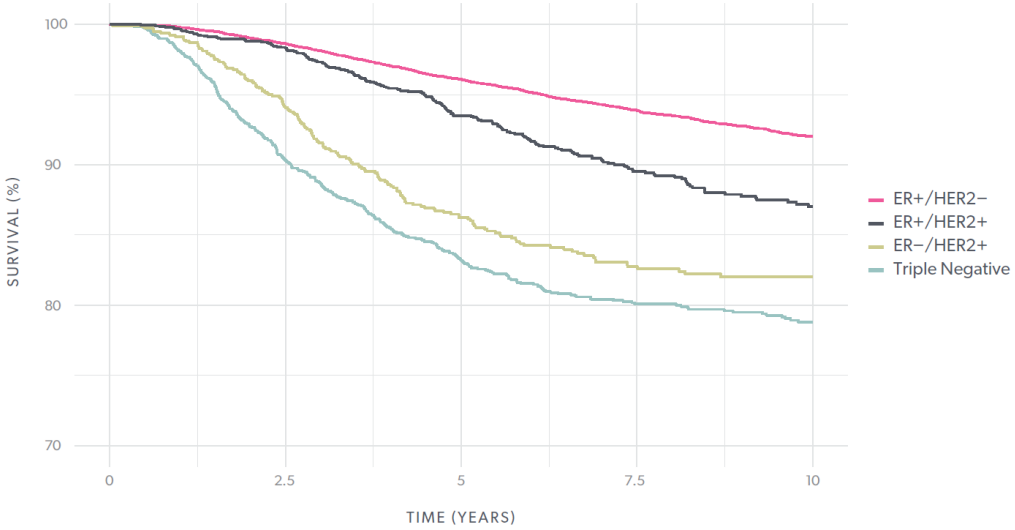
Triple-negative breast cancer is an aggressive breast cancer subtype that lacks expression of oestrogen and progesterone receptors and amplification or overexpression of human epidermal growth factor receptor 2 (HER2). The absence of these receptors renders endocrine and HER2-targeted therapies ineffective, leaving cytotoxic chemotherapy as the standard treatment option. Chemotherapy results in suboptimal antitumor response rates and short overall survival and response durations. There is a pressing need for better treatment options for New Zealand women with triple-negative breast cancer (TNBC), with both early and advanced disease. Pembrolizumab would be used to treat patients with triple negative breast cancer, both as neo-adjuvant and

adjuvant therapy in early high-risk breast cancer and in the treatment of advanced or metastatic breast cancer.

A report by the New Zealand Breast Cancer Foundation in 2018 found that median survival after a diagnosis of metastatic/advanced breast cancer in New Zealand is 16 months, considerably worse than overseas. For example, this compares with 29.4 months in the Netherlands, 36.8 months in Germany, 25 - 54 months in the USA, 23.1 months in France, and 33 months in Sweden. Therefore, although there have been improvements in rates of survival for breast cancer over the past decades, New Zealand still lags behind equivalent countries, for survival of people with metastatic breast cancer (Breast Cancer Foundation New Zealand 2018).

Breast cancer treatment is individualised based on tumour characteristics, patient characteristics and treatment history. Survival with metastatic disease varies greatly by subtype, from 27.3 months for Luminal A patients down to 6.6 months for triple negative breast cancer. Five-year survival after metastatic diagnosis is only 5% in Māori populations, compared to 15% in non-Māori populations (Breast Cancer Foundation New Zealand 2018).

A recent report by BCFNZ from the Breast Cancer Register, Te Rēhita Mate Ūtaetae, reinforced that women with triple negative breast cancer (TNBC) have the poorest rates of 5-year and 10-year survival as shown below. Although the survival in TNBC has improved over time, this is likely to be due to earlier diagnosis, rather than any changes in treatment (Breast Cancer Foundation New Zealand 2022). Survival is still significantly worse than for other cancer sub-types.



SUBTYPE	5-YEAR SURVIVAL	10-YEAR SURVIVAL
ER+/HER2−	96% (96-96)	92% (91-93)
ER+/HER2+	94% (92-95)	87% (85-89)
ER−/HER2+	86% (84-88)	82% (80-85)
Triple Negative	83% (82-85)	79% (77-81)

Fig. 5.2-6. *Breast cancer-specific survival by receptor status of invasive tumours. Proportion of women surviving invasive breast cancer to 10 years by their tumour receptor status. Table: Proportion of women surviving to five and 10 years, (95% CI).*

Source: (Breast Cancer Foundation New Zealand 2022)

ESMO guidelines recommend the use of atezolizumab or pembrolizumab in triple negative metastatic breast cancer (mTNBC) where PD-L1 is expressed.

The treatment algorithm is shown in the graphic below (Figure 5 from the 2021 ESMO Guidelines).

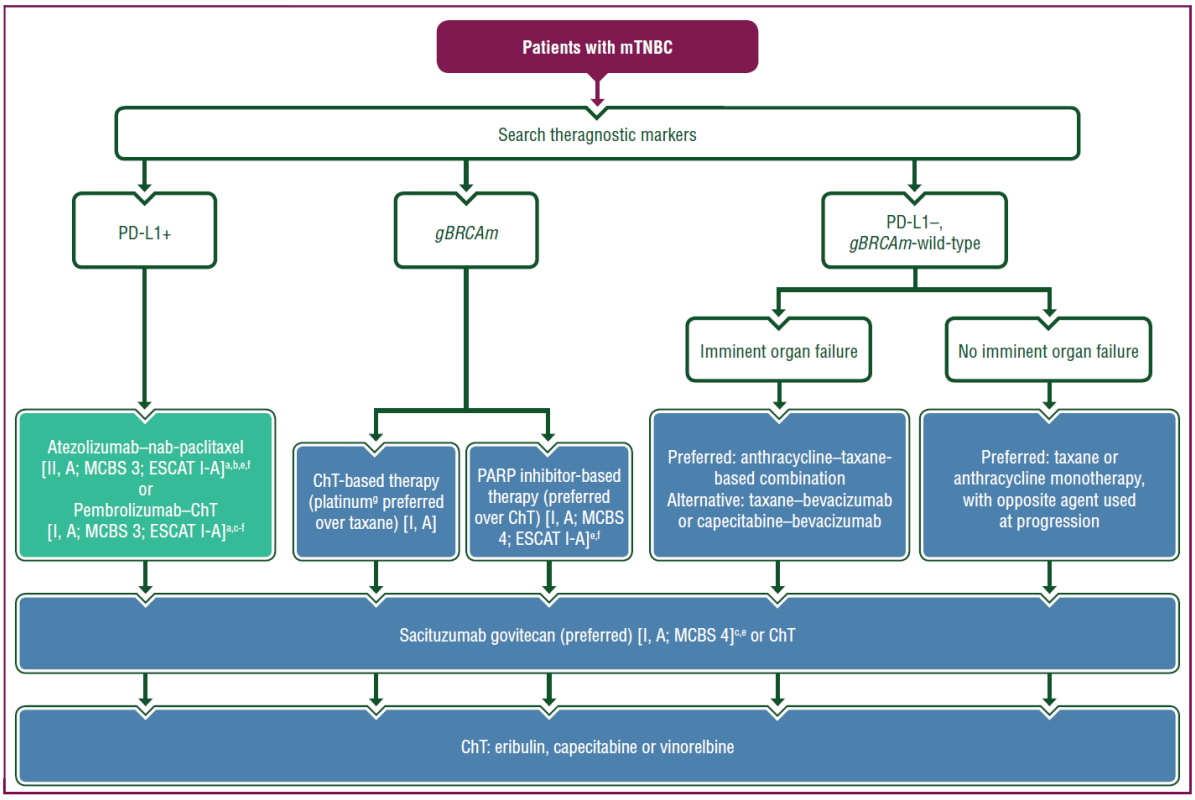


Figure 5. Treatment of mTNBC.
Purple: general categories or stratification; turquoise: combination of treatments or other systemic treatments; white: other aspects of management; blue: systemic anticancer therapy.
ChT, chemotherapy; EMA, European Medicines Agency; ESCAT, ESMO Scale for Clinical Actionability of Molecular Targets; FDA, Food and Drug Administration; *gBRCAm*, germline *BRCA1/2* mutation; ICI, immune checkpoint inhibitor; MCBS, ESMO-Magnitude of Clinical Benefit Scale; mTNBC, metastatic triple-negative breast cancer; PARP, poly (ADP-ribose) polymerase; PD-L1, programmed death-ligand 1.
[a] May be considered as monotherapy in further lines in case of high PD-L1 positivity and no previous exposure to ICI.
[b] EMA approved, not FDA approved.
[c] FDA approved, not EMA approved.
[d] ChT physician's choice of nab-paclitaxel, paclitaxel or gemcitabine/carboplatin.
[e] ESMO-MCBS v1.1[93] was used to calculate scores for new therapies/indications approved by the EMA or FDA. The scores have been calculated by the ESMO-MCBS Working Group and validated by the ESMO Guidelines Committee (https://www.esmo.org/guidelines/esmo-mcbs/scale-evaluation-forms-v1.0-v1.1/scale-evaluation-forms-v1.1).
[f] ESCAT scores apply to genomic alterations only. These scores have been defined by the guideline authors and validated by the ESMO Translational Research and Precision Medicine Working Group.[89]
[g] If not used previously.

Source:(Gennari, André et al. 2021)

It needs to be emphasised that most of the agents recommended for treatment of mTNBC such as PARP-inhibitors, atezolizumab, bevacizumab, pembrolizumab and sacituzumab govitecan) are not available (funded) for this population in New Zealand. Therefore, the options for New Zealand patients with this type of breast cancer are very limited indeed compared with their counterparts elsewhere.

The recently published New Zealand guidelines for Advanced Breast Cancer make the following recommendations for triple-negative advanced breast cancer.

Section VI. Triple Negative ABC

Guideline statement	LoE / GoR	NZ Consensus
In triple negative ABC patients (regardless of BRCA status), previously treated with anthracyclines with or without taxanes in the (neo)adjuvant setting, carboplatin demonstrated comparable efficacy and a more favorable toxicity profile, compared to docetaxel, and is therefore an important treatment option.	I/A	100%
For non-BRCA-associated triple negative ABC, there are no data supporting different or specific CT recommendations, besides platinum. Therefore, all CT recommendations for HER2 negative disease also apply for triple negative ABC.	I/A	100%
Immunotherapy for triple negative ABC Checkpoint inhibitors + chemotherapy (pembrolizumab + taxane or carboplatin/gemcitabine) is the preferred treatment option for 1st line therapy for most patients with PD-L1+* triple negative ABC, either de novo or diagnosed at least 6 months from (neo)adjuvant chemotherapy. *Pembrolizumab is Medsafe-approved but not Pharmac-funded (as of September 2022) for triple negative ABC.* *Nab-paclitaxel is Medsafe-approved but not Pharmac-funded (as of September 2022).* * CPS score ≥10	I/A	100%
Immunotherapy for triple negative ABC Atezolizumab in combination with nab-paclitaxel may be an option for 1st line therapy of patients with PD-L1+* triple negative ABC. *Atezoluzimab is Medsafe-approved but not Pharmac-funded (as of September 2022).* *Nab-paclitaxel is Medsafe-approved but not Pharmac-funded (as of September 2022).* * PD-L1 score ≥1% (SP142 PD-L1 IHC). ESMO-MCBS:3	II/B	85%
Checkpoint inhibitor monotherapy in later lines for triple negative ABC is not recommended, due to low response rates.	I/E	84%
Immunotherapy for other ABC subtypes Several ongoing trials are evaluating the role of this type of treatment in other ABC subtypes (non-TNBC) and, for the moment, it is not recommended outside clinical trials. * For PD-L1 testing, see Precision Medicine Statements.	NA/E	100%
Sacituzumab govitecan for triple negative ABC Sacituzumab govitecan is the preferred treatment option for patients with triple negative ABC, treated with ≥ 2 lines (at least one of them in the metastatic setting), since it demonstrated a 5.5 months benefit in OS and a 4 months benefit in PFS. Education, prophylaxis and early management of side effects, in particular diarrhea and nausea/vomiting, are important. *Sacituzumab govitecan is not Pharmac-funded or Medsafe-approved (as of September 2022).* ESMO-MCBS: 4	I/A	90%

As for use of pembrolizumab in early breast cancer, there are no up to date New Zealand guidelines for recommended management of early breast cancer. The ESMO guidelines for early breast cancer are also out of date.

Recently the NCCN published their recommendation that “For patients with T1cN1-2 or T2-4N0 (stage II or III), early TNBC, the Panel recommends use of pembrolizumab (200 mg once every 3 weeks or 400 mg once every 6 weeks) in combination with neoadjuvant chemotherapy, followed by adjuvant pembrolizumab after surgery. Adjuvant pembrolizumab may be given either concurrent with or after completion of radiation therapy. Given that immune-mediated adverse events (irAEs) associated with pembrolizumab therapy can be severe and permanent, careful screening for and management of common toxicities are required. The ASCO guideline for management of irAEs in patients treated with immune checkpoint inhibitor therapy offers detailed practice

recommendations and should be consulted by clinicians who prescribe pembrolizumab for patients with early-stage TNBC."(Korde, Somerfield et al. 2022).

NICE in the United Kingdom also published their determination on the use of pembrolizumab as neoadjuvant/adjuvant therapy in November 2022. It states that

Pembrolizumab is recommended, within its marketing authorisation, as an option with chemotherapy for neoadjuvant treatment and alone as adjuvant treatment after surgery for adults with triple-negative:

• *early breast cancer at high risk of recurrence or*

• *locally advanced breast cancer.*

It is recommended only if the company provides pembrolizumab according to the commercial arrangement (NICE 2022).

BCAC and its member groups are justifiably concerned about the poor access to treatments in New Zealand for people with triple negative breast cancer. It is particularly important that treatments that are already recommended by clear-cut consensus within the breast cancer community are subsidised so that all those with breast cancer can access them, irrespective of their ability to pay.

Does the disease impact on the health of the patient's family, whānau or wider society? Please explain and provide sources of information.

Breast cancer is diagnosed in about 3,500 people annually in New Zealand. The latest Ministry of Health mortality report shows nearly 700 deaths in 2019. It is therefore an important health issue in terms of physical and mental health and has a significant social and economic impact on society, families, and whānau. Despite the perception that cancer is an older person's disease, breast cancer is the number one cause of death for New Zealand women under 65.

Receiving a diagnosis of advanced breast cancer is devastating for the patient and has deep impacts on colleagues, communities and whānau. Having a relative living with or dying of breast cancer affects other family members significantly both emotionally and financially. Women aged 44 years and younger have the highest rate of diagnosis of triple negative breast cancer (14.4%) (Breast Cancer Foundation NZ 2022). This group is most likely to contain young mothers whose time with dependent children is precious.

Women undertake many vital roles in our society, both professional and unpaid. These include caring for elderly parents, children and other family members, keeping households fed and running effectively and providing emotional support for friends and whānau. Keeping women alive with a good quality of life has huge benefits for families and society.

BCAC and its member groups are extremely concerned about the poor access to treatments in New Zealand for people with metastatic breast cancer. The group of women with triple negative breast cancer are of particular concern as they have few specific treatment options available.

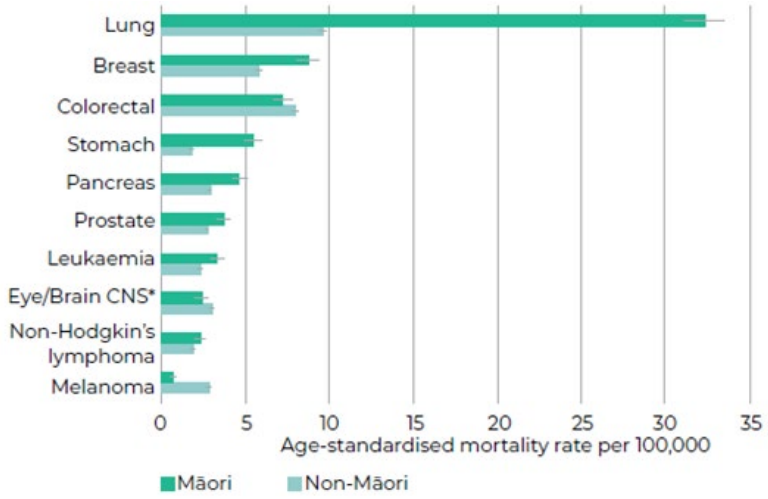
What is the impact of the disease on Māori health outcomes? Please explain and provide sources of information.

In recent years, approximately 3,500 have been diagnosed with breast cancer annually in Aotearoa New Zealand; this number has steadily increased over time in line with our growing and aging population. The actual rate of diagnoses (per 100,000 women) has increased slightly over the past 20 years for both wāhine Māori and non-Māori women (Te Aho o Te Kahu Cancer Control Agency He

Pūrongo Mate Pukupuku o Aotearoa 2021). In 2018, the incidence of breast cancer per 100,000 women was 124.9 for Māori and 97.4 for non-Māori (Ministry of Health 2020). It is therefore of significant concern that Māori health outcomes, particularly for wāhine Māori are being impacted by poor access to treatments for breast cancer.

Wāhine Māori are more likely to be diagnosed with advanced disease and are more likely to die from breast cancer than non-Māori/non-Pacific women. Pacific women are also more likely to be diagnosed with advanced disease and more likely to die of breast cancer than non-Māori/non-Pacific women.

Age- and sex-standardised cancer-related mortality 2007–2017



* CNS = central nervous system

Source: (Te Aho o Te Kahu Cancer Control Agency He Pūrongo Mate Pukupuku o Aotearoa 2021)

Does the disease fall into one of the categories of PHARMAC's Māori health areas of focus?

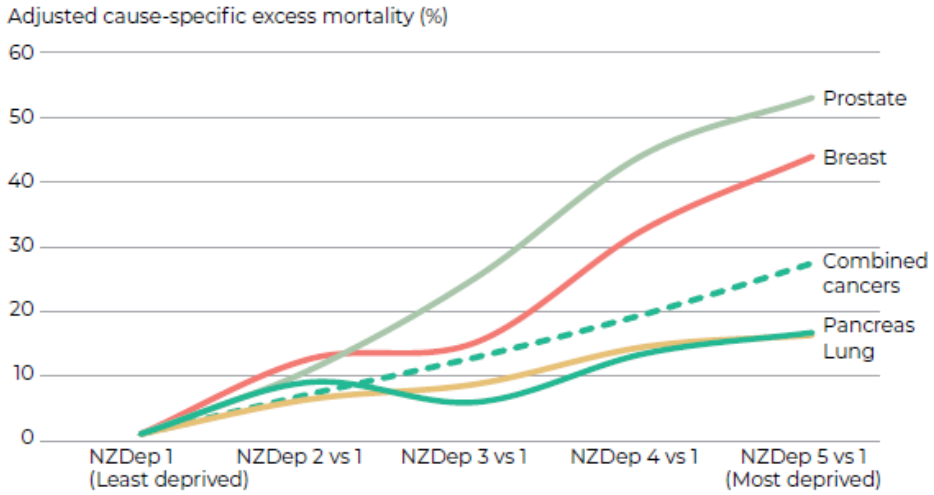
Yes

Does the disease disproportionately affect population groups that may already be experiencing a health disparity?

People who are economically deprived are already in poorer health in New Zealand. Overall, cancer incidence is higher among those living in the more deprived areas – although this varies depending on the type of cancer. Poverty is a barrier to accessing early diagnosis and best-practice treatment for cancers, leading to inequities in cancer survival between the poor and the affluent. This is particularly important for highly treatable cancers, where finding a cancer early and treating it quickly can significantly improve survival outcomes (Te Aho o Te Kahu Cancer Control Agency He Pūrongo Mate Pukupuku o Aotearoa 2021).

The figure below (from Te Aho), shows the impact of economic deprivation on survival

Impact of deprivation on cancer survival, 2007–2016



Source: (Te Aho o Te Kahu Cancer Control Agency He Pūrongo Mate Pukupuku o Aotearoa 2021)

The fact that many New Zealanders must personally pay to gain access to cancer medicines that are evidence-based and recommended by their oncologists is creating a two-tiered health system in which those who can pay will live longer. Families are being forced to cash in retirement savings, sell properties, set up 'Give a Little' pages and fundraise to gain benefits in quality of life, progression free survival and overall survival. This situation is lamentable and does not contribute to the notion of equity within health care. The Ministry of Health's definition of equity is: "In Aotearoa New Zealand, people have differences in health that are not only avoidable but unfair and unjust. Equity recognises different people with different levels of advantage require different approaches and resources to get equitable health outcomes."

People living with mental health and addiction issues have significantly reduced life expectancy compared with the general population, mainly due to dying early from physical illnesses, such as heart disease and cancers. Access to and quality of health care are major contributors, including access to cancer screening, timely diagnosis, and treatment. Research in Aotearoa has found that, among people diagnosed with breast or colorectal cancers, survival is much poorer for those with a history of recent contact with specialist mental health services (Te Aho o Te Kahu Cancer Control Agency He Pūrongo Mate Pukupuku o Aotearoa 2021).

Who is the target population?

The target population is women with triple-negative breast cancer (TNBC). The indications for pembrolizumab target treatment to two subgroups of women. Breast Cancer Aotearoa Coalition proposes that pembrolizumab be listed on the Pharmaceutical Schedule, consistent with both clinical evidence and MEDSAFE approval (MSD 2022), for

- High-risk early-stage triple-negative breast cancer (TNBC) in combination with chemotherapy as neoadjuvant treatment, and then continued as monotherapy as adjuvant treatment after surgery.
- In combination with chemotherapy, for the treatment of patients with locally recurrent unresectable or metastatic TNBC whose tumours express PD-L1 CPS ≥10.

Costs

Please detail whether there are any additional health-related costs or savings to the person receiving treatment that are likely to be incurred if the pharmaceutical is funded.

Should this treatment be listed on the Pharmaceutical Schedule, patients would receive treatment in conjunction with chemotherapy, therefore the incremental costs to the person receiving treatment would be quite small, in terms of travel and administration costs. As it would be administered in the hospital outpatient setting, there would be no co-payment.

Contrast this with the current situation where patients and their families are having to mortgage homes, borrow money and undertake fund raising to obtain access to this treatment. The list price (ex-manufacturer excluding GST) of this pharmaceutical on the Pharmaceutical Schedule (for other indications) is $4680 per vial, with an ECP price of $49.14 per mg. There is a confidential rebate that presumably reduces the cost of treatment considerably.

For breast cancer patients currently receiving treatment in New Zealand, the per patient cost for drug alone in the private sector is approximately $8000 per cycle including GST. The patient is also charged consultation and administration fees of about $1300 per cycle (including GST). There is a cap on treatment costs per patient of $60,000 or $69,000 including GST for drug cost (provided by MSD - the manufacturer). After this cap is reached, drug costs are not charged to the patient, but they continue to pay for administration.

(Note: These figures were obtained from Metavivors currently undertaking treatment at various centres throughout New Zealand. They may vary across the country, especially administration costs).

Please detail whether there are any health-related costs or savings that may be experienced by the family, whānau and wider society of the person receiving the treatment, if the pharmaceutical is funded.

The treatment related costs to family/whanau are reductions in expenditure compared with the current situation.

The list price (ex-manufacturer excluding GST) of this pharmaceutical is $4680 per vial, with an ECP price of $49.14 per mg. The per patient cost for drug alone (MSD price cap per patient) in the private sector is approximately $8000 per cycle including GST. The patient is also charged consultation and administration fees of about $1300 per cycle (including GST). There is a cap on treatment costs per patient of $60,000 or $69,000 including GST (provided by MSD - the manufacturer). These figures were obtained from Metavivors currently undertaking treatment at various centres throughout New Zealand.

For society as a whole, access will be available to more individuals - including those who are currently more economically disadvantaged, therefore there will be an incremental cost associated with making this treatment available on the Pharmaceutical Schedule. From a societal perspective, the cost per patient will be considerably less as Pharmac should be able to achieve a more favourable (rebated) price than patients are currently paying. Plus, the additional costs associated with treatment such as GST, administration costs (which are at a premium in the private sector) and costs to attend private clinics will be shifted from being a patient responsibility, to being borne by the public health system.

Suitability

Are there any features of the pharmaceutical that may impact use by the person receiving the treatment? If so, please explain.

The treatment is administered in the hospital outpatient setting as an infusion, therefore this requires the patient to attend such a clinic to receive treatment – concurrently with the chemotherapy they would otherwise be receiving. When given as neo-adjuvant therapy, the patient's surgery will be delayed to enable administration prior to surgery.

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