Advanced Breast Cancer Treatment in Aotearoa New Zealand

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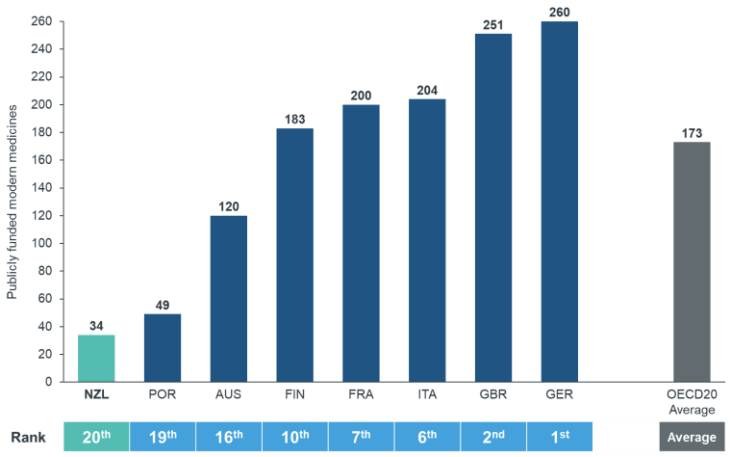
Introduction

Breast cancer (BC) is the most commonly diagnosed cancer in the world. In 2020, there were an estimated 2.3 million cases of female breast cancer globally, and about 685,000 women died from the disease [World Cancer Research Fund International; WCRF, 2022].

In 2020 in Aotearoa, 3,440 women were diagnosed with breast cancer (just over 27 percent of all female cancers), and 638 women died from it [Te Whatu Ora, 2023]. While Aotearoa has similar age-standardized rates of breast cancer as Australia (93 per 100,000 women for Aotearoa vs 96 per 100,000 for Australia) [WCRF], a recent study showed that in 2014–2018, our breast cancer death rates were 15.5% higher than Australia's [Aye et al., 2023]. Our death rates from breast cancer are even higher when compared with other countries such as Germany. While mortality rates are affected by various factors, it can be no coincidence that Aotearoa also has the lowest availability of publicly funded medicines of all OECD countries. Between 2011 and 2020, Aotearoa funded only 34 new medicines across all diseases, compared with the OECD average of 173 and Australia's 120 [IQVIA, 2021].



Source: (IQVIA, 2021)

New Zealand is also very slow to fund new medicines, with funding decisions taking on average 7.7 years [HealthiNZ, 2023], while by contrast, Germany funds medicines within days of their gaining regulatory approval and Japan within 90 days [Shawview, 2023].

Advanced breast cancer in Aotearoa

Survival after a diagnosis of metastatic, secondary or advanced breast cancer (referred to from now on as ABC) is usually either given as a median (the time from diagnosis to the point at which half of the patients are still living) or a percentage (percentage of people still alive after a certain time point). In New Zealand, median survival for all ethnicities combined was 18.8 months [Breast Cancer

Foundation NZ, 2018] compared with 24 months in Australia [Carson et al., 2019] and 38 months in Germany [Weide et al., 2019].

Our survival data in Aotearoa are even more shocking when viewed by ethnicity. Wāhine Māori have a higher rate of breast cancer diagnosis at any stage (121 per 100,000 for Māori, 89.6 per 100,000 for non-Māori for all breast cancer) and mortality (18.2 per 100,000 for Māori, 14.1 per 100,000 for non-Māori for all breast cancer). Median survival for wāhine Māori with ABC is 12.8 months [Breast Cancer Foundation NZ, 2018].

Advanced breast cancer survival rates by ethnicity in Aotearoa. (Figures in brackets are 95% confidence intervals.)

	NZ Māori	Pacific Island	Asian	European
Median survival (months)	12.8 (9.5, 18.6)	18.5 (12.1, 23.1)	26.8 (18.3, 36.4)	15.7 (13.7, 17.3)
One-year survival	50% (41, 59)	64% (52, 73)	82% (68, 90)	57% (53, 60)
Five-year survival	5% (2, 10)	21% (13, 31)	14% (5, 29)	15% (12, 18)

As mentioned previously, New Zealand has the slowest and lowest rates of approval of new medicines, and this includes medicines for ABC that deliver greater time before the cancer progresses and longer lives. This article provides a summary of access to treatments for ABC by sub-type in New Zealand and compares our situation with the accepted global recommendations from the Metastatic Breast Cancer Living Guideline published by the European Society of Medical Oncology (ESMO) [Gennari et al., 2021]. The Living Guideline is available from https://www.esmo.org/living-guidelines/esmo-metastatic-breast-cancer-living-guideline. We also compare our survival rates by sub-type [Breast Cancer Foundation NZ, 2018] with those of Germany from a recently presented study [Weide et al., 2019].

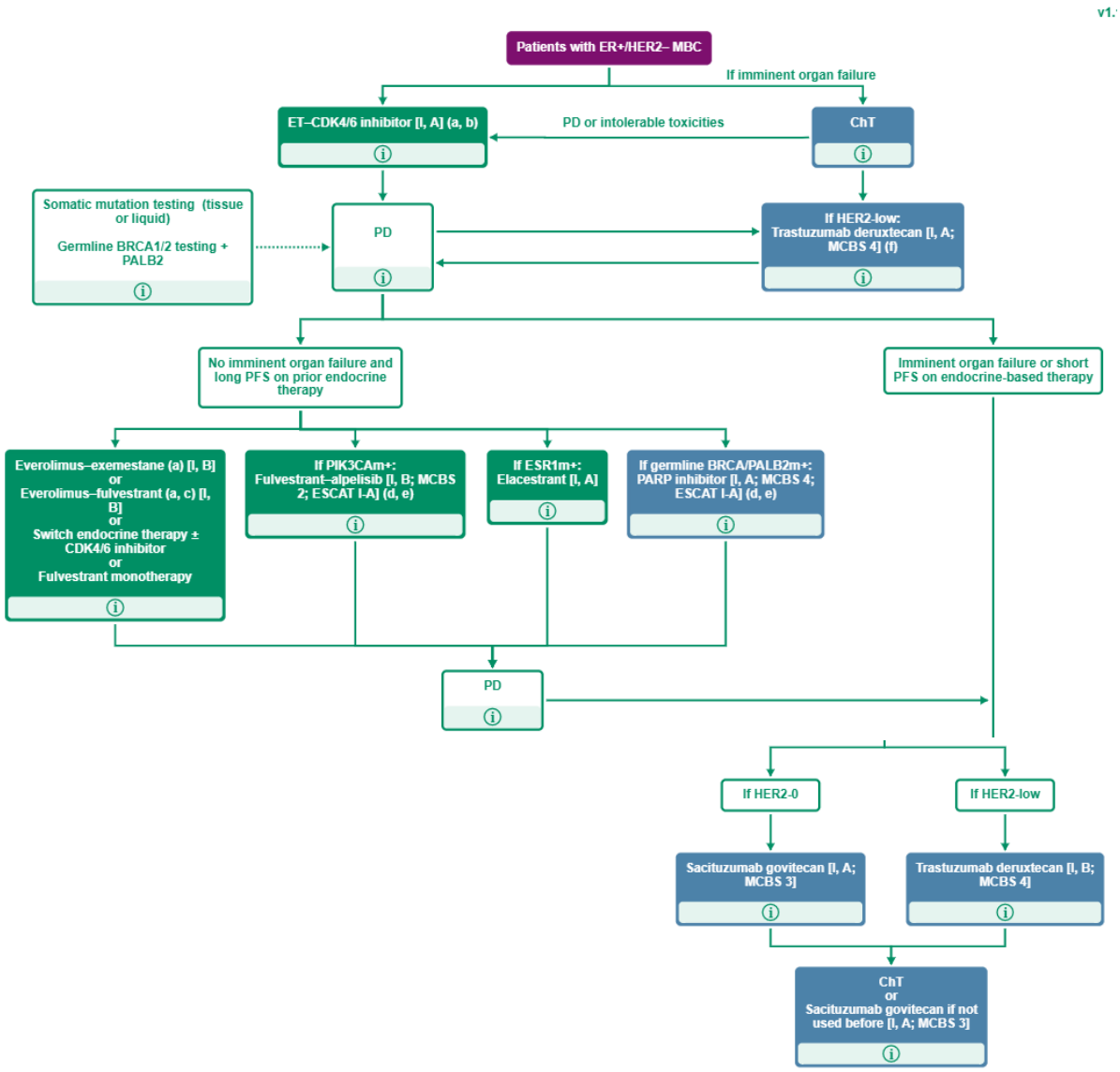
Recommended treatment of advanced breast cancer treatment by sub-type

Hormone receptor positive/HER2 negative ABC

Hormone receptor positive/HER2 negative (HR+/HER2-) is the most common type of BC in Aotearoa, at around 74% of all cases [Breast Cancer Foundation NZ, 2022].

CDK4/6 inhibitors [e.g. palbociclib (Ibrance®), ribociclib (Kisqali®), abemaciclib (Verzenio®)], combined with endocrine therapy [e.g., tamoxifen, anastrozole (Anatrole®), letrozole (Letrole®), exemestane, fulvestrant (Faslodex®)] have become the standard for first-line treatment (the first treatment offered after diagnosis of ABC) of HR+/HER2- ABC. This combined treatment is based on data from several trials that showed clinically meaningful improvements in progression-free survival (time until the disease progresses) and overall survival (length of life following treatment) compared with endocrine therapy alone [Mavratzas and Marmé, 2021]. More specifically, as the ESMO guideline shows, first-line treatment for ER+/HER2- ABC should consist of endocrine therapy + a CDK4/6 inhibitor, except in cases of imminent organ failure where chemotherapy is indicated. Second-line treatment (the next treatment after the cancer progresses) should be based on the results of testing for somatic mutations and germline BRCA and PALB testing; depending on the outcome, second-line treatment should include various combinations of: everolimus (Afinitor®), exemestane, fulvestrant (Faslodex®) in combination or as monotherapy; alpelisib (Piqray®) (PIK3CAm+); a PARP inhibitor such as olaparib (Lynparza®) (BRCA or PALB2m+); elacestrant (Orserdu®) (ESR1m+); the antibody drug conjugate (ADC) sacituzumab govitecan (Trodelvy®) (HER2 0)

then chemotherapy; or another ADC, trastuzumab deruxtecan (Enhertu®) (HER2 low), followed by sacituzumab govitecan then chemotherapy.



Source: (Gennari, André et al. 2021)

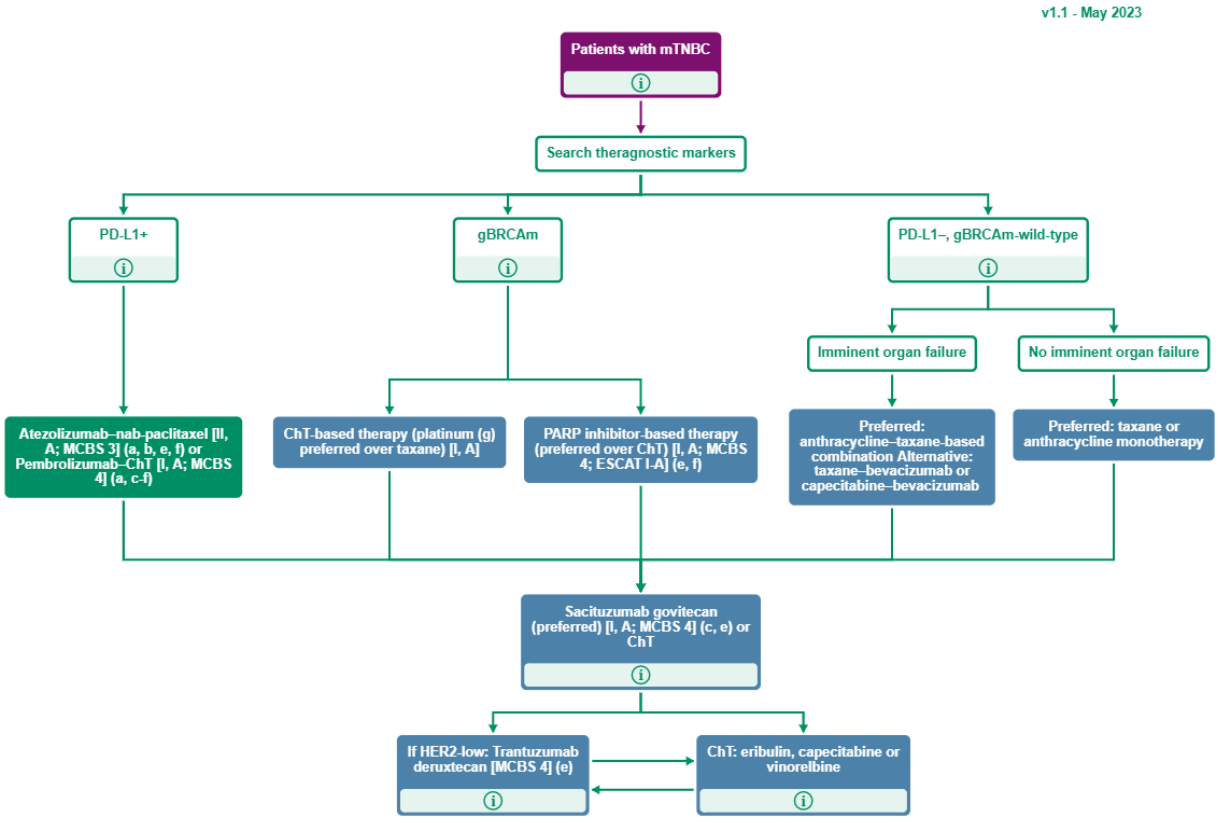
Triple negative ABC

Triple negative BC (TNBC) comprises around 10% of breast cancers [Breast Cancer Foundation NZ, 2022] and is the most challenging type of BC to treat, particularly at the advanced stage.

TNBC is now known to be a diverse disease more accurately categorized according to the immune status of the tumour, rather than simply an absence of hormone and HER2 receptors [Leon-Ferre and Goetz, 2023]. Firstly, it is now known that TNBC tumours may be either ‘immune-enriched’, or ‘hot’, meaning they exhibit a higher level of tumour-infiltrating lymphocytes (TILs), or ‘cold’, meaning they are low in TILs. The hot tumours have a more favourable prognosis than the cold tumours. Second, TNBC may exhibit high or low levels of the biomarker PD-L1. Finally, TNBC tumours may be positive

or negative for BRCA mutations. Importantly, better understanding of TNBC in terms of TIL, PD-L1 and BRCA status have all led to more targeted treatment of TNBC, which is much needed.

According to current guidelines, first-line treatment of advanced TNBC should ideally consist of atezolizumab (Tecentriq®) + nab-paclitaxel (Abraxane®) or pembrolizumab (Keytruda®) + chemotherapy for PD-L1-positive TNBC, and a PARP inhibitor (e.g., olaparib) or platinum-based chemotherapy (e.g., cisplatin) for TNBC with germline BRCA mutations. In TNBC that is PD-L1-negative and gBRCA-negative (or wild type), a combination of an anthracycline (e.g., doxorubicin) + a taxane (e.g., docetaxel or paclitaxel) combination or bevacizumab (Avastin®) + chemotherapy is recommended for cases with imminent organ failure and either a taxane or anthracycline monotherapy otherwise. Second line, sacituzumab govitecan is recommended by all guidelines. Later-line treatments include trastuzumab deruxtecan, for patients with HER2-low breast cancer, and a PARP inhibitor for patients with gBRCA associated TNBC, but only if they have not received one first line. The European guidelines (ESMO) recommend eribulin, capecitabine, or vinorelbine chemotherapy for the third line setting and beyond, while American guidelines do not make any specific recommendations on chemotherapy.



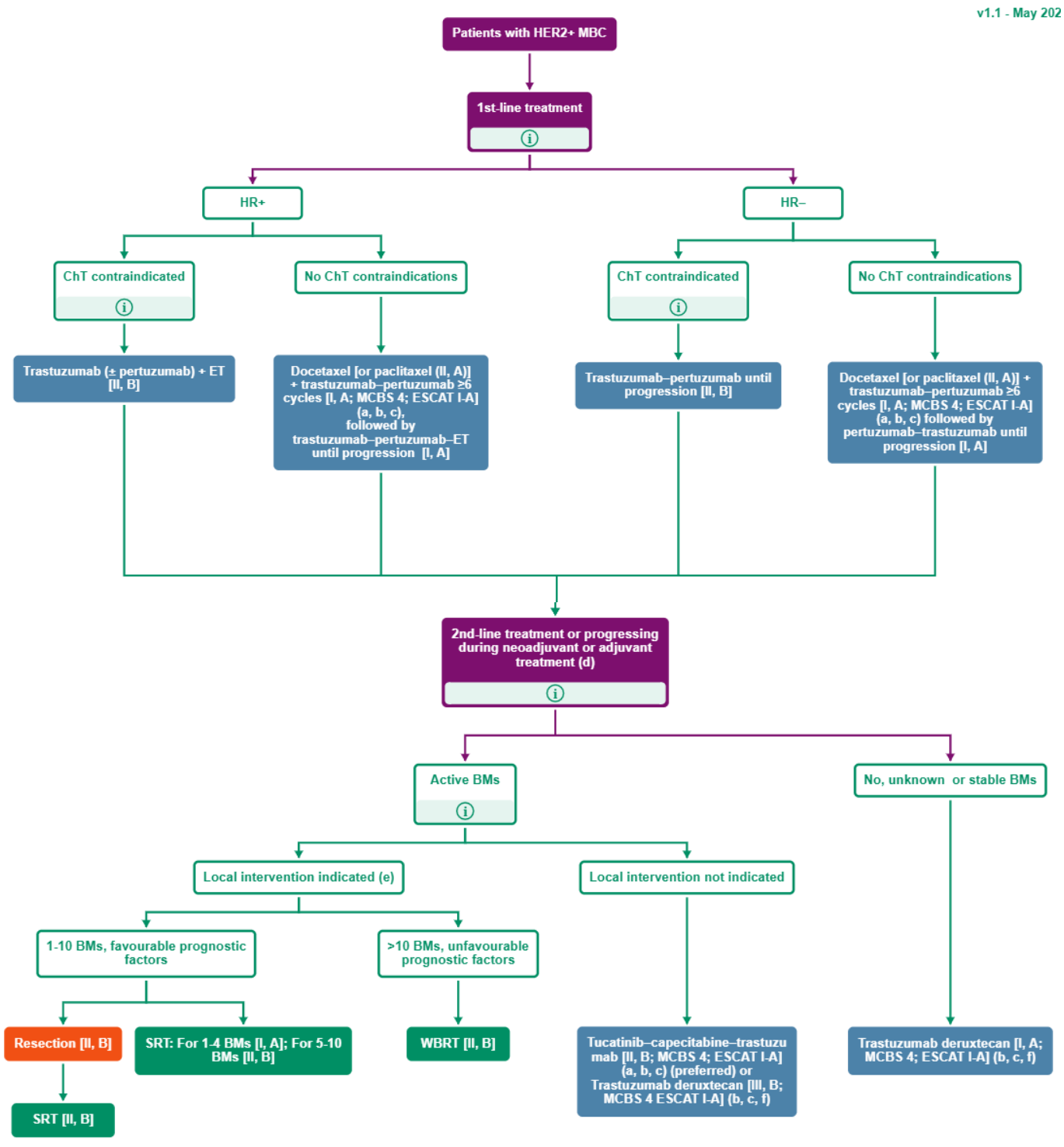
Source: (Gennari, André et al. 2021)

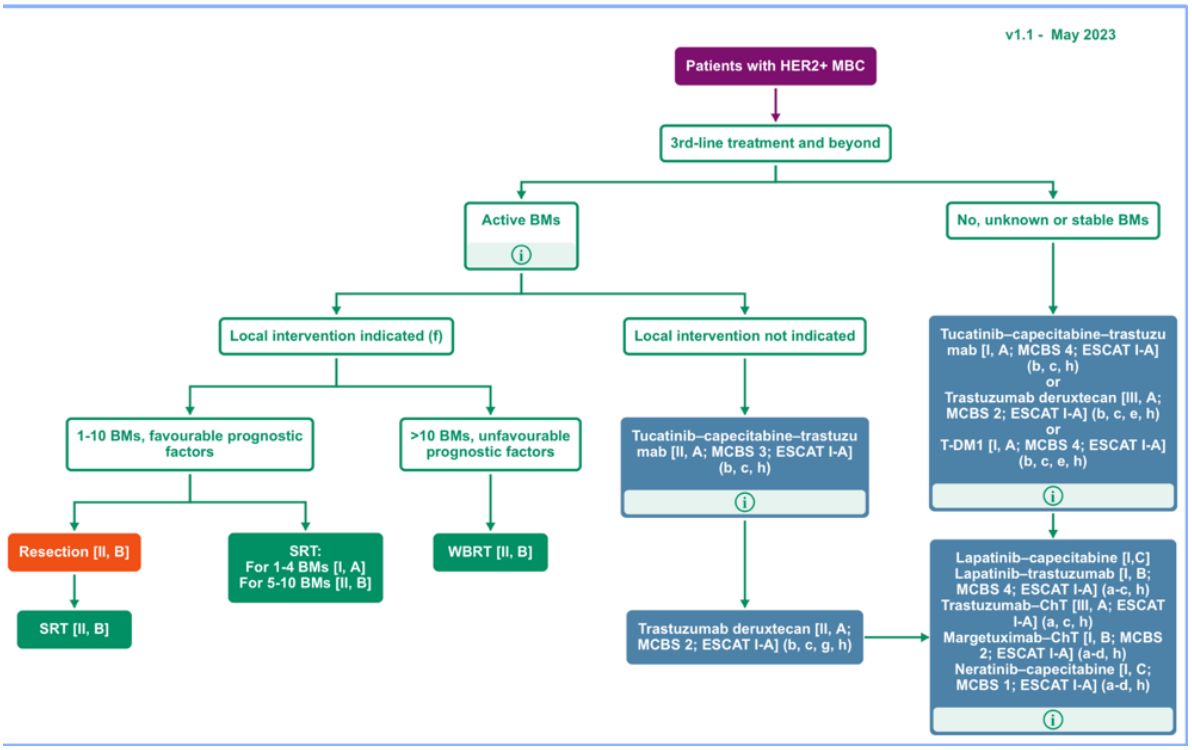
HER2-positive ABC (either HR+ or HR-)

HER2+ breast cancers make up 15–16% of breast cancers (HR+/HER2+: 10.6%; HR-/HER2+: 5.2%) [Breast Cancer Foundation NZ, 2022].

Traditionally one of the harder sub-types to treat at the advanced stage, this is now associated with longer survival times because of modern HER2-targeted treatments. Initial treatment of HER2+ ABC depends on presence or absence of HR positivity, but all options involve anti-HER2 treatment,

whether or not chemotherapy or endocrine therapy are indicated. Second line treatments after trastuzumab (Herceptin ®, Herzuma® and various other brand names)/pertuzumab (Perjeta®) include trastuzumab emtansine (Kadcyla®), tucatinib (Tukysa®), and trastuzumab deruxtecan (Enhertu®).





Source: (Gennari, André et al. 2021)

At third line, the ESMO treatment algorithm includes tucatinib in cases of brain metastasis, trastuzumab deruxtecan, margetuximab (Margenza®) and lapatinib (Tykerb®) in combination with trastuzumab.

It is now generally accepted that some form of HER2 suppression should be included at all treatment lines even if it involves retreatment with a drug already used previously, usually trastuzumab. In fact, multiple guidelines including those issued by ESMO, the American National Comprehensive Cancer Network and New Zealand's own Advanced Breast Cancer Guidelines [Breast Cancer Special Interest Group (Breast SIG) New Zealand, 2022] recommend retreatment with trastuzumab in a range of combinations to fourth-line and beyond.

The situation in Aotearoa

Hormone receptor positive/HER2 negative ABC

Median survival in Aotearoa is 27.3 months for ER+/PR+/HER2- ABC and 15.9 months for luminal B1 (ER+ only) ABC compared with 39 months for HR+/HER2- ABC in Germany.

Of the first-line agents listed in the ESMO guideline, palbociclib is funded by PHARMAC for use with an aromatase inhibitor such as exemestane, or with fulvestrant (Faslodex®) for those who have previously received an aromatase inhibitor. Regarding the other two CDK4/6 inhibitors, abemaciclib (Verzenio®), is being considered by Medsafe but has not yet been approved for use in New Zealand, while ribociclib (Kisqali®) is Medsafe-approved but not funded. By comparison, Australia funds all three CDK4/6 inhibitors.

For later lines, alpelisib is not funded in Aotearoa or Australia. Elacestrant was only recently approved in the USA (January 2023) for second-line treatment of advanced HR+/HER- BC [Hoy SM, 2023], so it will be some time before any potential application is made in Aotearoa. Trastuzumab deruxtecan (for HER2-low cancers) is under consideration by Medsafe, and sacituzumab govitecan is

publicly funded in Australia (March 2022) and England (July 2022), but is not approved by Medsafe or funded by PHARMAC in New Zealand.

Triple negative ABC

Median survival for triple negative ABC is 6.6 months in New Zealand compared with 20 months in Germany.

Chemotherapy is the standard treatment for triple negative ABC in Aotearoa. However, the targeted treatments so desperately needed for this BC sub-type are missing as is nab-paclitaxel, recommended first-line in PD-L1-positive cases. For gBRCA-mutated triple negative ABC, the PARP inhibitors talazoparib (Talzenna®) and olaparib are Medsafe-registered, but not funded for this purpose in New Zealand. Pembrolizumab combined with chemotherapy is also Medsafe registered for triple negative ABC where tumours express PD-L1, but while this is now considered the gold standard for this type of triple negative ABC in guidelines, it is not yet funded in New Zealand. Atezolizumab and nab-paclitaxel are also Medsafe-approved but not funded in New Zealand.

In summary, **New Zealand does not currently fund any of the recommended treatments for triple negative ABC,** with the exception of chemotherapy.

HER2-positive ABC (either HR+ or HR-)

Median survival for HER2+ ABC in Aotearoa ranges from 13.3 months (HR- disease) to 24 months (HR+ disease). Median survival in Germany is 45 months (the specific data used do not indicate HR status).

The picture is more optimistic for first- and second-line treatment of HER2-positive BC. PHARMAC currently funds the first-line treatment options of trastuzumab and pertuzumab and trastuzumab emtansine second line (but only if it hasn't already been used as a post-neoadjuvant treatment in early breast cancer). However, for later lines this picture changes. Amongst the options for later line treatment, the following are not funded in New Zealand: trastuzumab deruxtecan; tucatinib; lapatinib; neratinib; margetuximab; and retreatment with trastuzumab. Indeed, trastuzumab deruxtecan is now the preferred option for second-line treatment in guidelines, not trastuzumab emtansine. The lack of available, funded options is therefore a concern at second, third and fourth lines of treatment.

The lack of funding for trastuzumab at later lines of treatment leaves very few options for New Zealand patients with recurrent metastatic HER2+ breast cancer. However, the recent funding approval for the trastuzumab biosimilar Herzuma®, presumably at a lower cost than Herceptin®, may encourage PHARMAC to consider funding trastuzumab re-treatment at later lines and the lower cost may make self-funding a possibility for some patients.

Summary of drug availability in Aotearoa by ABC sub-type*

The tables below summarise the internationally recommended treatments discussed in this article, grouped according to ABC sub-type, with information on which are funded for ABC in Aotearoa compared with Australia. Trade names have been included for reference; however, some treatments are available under various trade names or only as generic versions if they have been available for many years.

HR+/HER2- ABC

Drug	Type/mode of action	Earliest treatment line recommendation	Funded in Australia	Funded in NZ
Abemaciclib (Verzenio®)	CDK4/6 inhibitor	First	Yes	No
Alpelisib (Piqray®) if PIK3CA-mutated	PI3K inhibitor	Second	No	No
Anastrozole (Anatrole®/Arimidex®)	Endocrine therapy	First	Yes	Yes
Elacestrant (Orserdu®) if ESR1-mutated	Estrogen receptor degrader	Second	No	No
Eribulin (Halaven®)	Chemotherapy	First	Yes	No
Everolimus (Afinitor®)	mTOR inhibitor	Second	Yes	No
Exemestane (Aromasin®/generic)	Endocrine therapy	First	Yes	Yes
Fulvestrant (Faslodex®)	Endocrine therapy	First	Yes	Yes
Letrozole (Letrole®)	Endocrine therapy	First	Yes	Yes
Olaparib (Lynparza®) if gBRCA-mutated	PARP inhibitor	Second	No	No
Palbociclib (Ibrance®)	CDK4/6 inhibitor	First	Yes	Yes
Ribociclib (Kisqali®)	CDK4/6 inhibitor	First	Yes	No
Sacitizumab govitecan (Trodelvy®)	Antibody drug conjugate	Second	No	No
Talazoparib (Talzenna®) if gBRCA	PARP inhibitor	Second	No	No
Tamoxifen (Nolvadex®/ Soltamox®)	Endocrine therapy	First	Yes	Yes
Trastuzumab deruxtecan (Enhertu®) for HR+/HER2 low ABC	Antibody drug conjugate	Second	No	No

Triple negative ABC

Drug	Type/mode of action	Earliest treatment line recommendation	Funded in Australia	Funded in NZ
Atezolizumab (Tecentriq®) if PDL-1-mutated	Immunotherapy	First	Yes	No
Bevacizumab (Avastin®)	Antiangiogenic	Second	Yes	No
Capecitabine (Xeloda®/generic versions)	Chemotherapy	First	Yes	Yes
Cisplatin (generic versions)	Chemotherapy	First	Yes	Yes
Docetaxel (Taxotere®)	Chemotherapy	First	Yes	Yes

Doxorubicin (Adriamycin®/Rubex®)	Chemotherapy	First	Yes	Yes
Eribulin (Halaven®)	Chemotherapy	Third	Yes	No
Nab-paclitaxel (Abraxane®)	Chemotherapy	First	Yes	No
Olaparib (Lynparza®) if gBRCA-mutated	PARP inhibitor	First	No	No
Paclitaxel (Taxol®)	Chemotherapy	First	Yes	Yes
Pembrolizumab (Keytruda®) if PDL-1-mutated	Immunotherapy	First	Yes	No
Sacitizumab govitecan (Trodelvy®)	Antibody drug conjugate	Second	Yes	No
Talazoparib (Talzenna®) if gBRCA-mutated	PARP inhibitor	First	No	No
Trastuzumab deruxtecan (Enhertu®) for HER2 low ABC	Antibody drug conjugate	Third	No	No
Vinorelbine (Navelbine®)	Chemotherapy	Third	Yes	Yes

HER2+ ABC ***

Drug	**Type/mode of action**	**Earliest treatment line recommendation**	**Funded in Australia**	**Funded in NZ**
Capecitabine (Xeloda®/ generic versions)	Chemotherapy	Second	Yes	Yes
Docetaxel (Taxotere®)	Chemotherapy	First	Yes	Yes
Lapatinib (Tykerb®)	Tyrosine kinase inhibitor	Third	Yes	No
Margetuximab (Margenza®)	Monoclonal antibody	Third	No	No
Neratinib (Nerlynx®)	Tyrosine kinase inhibitor	Second	No	No
Paclitaxel (Taxol®)	Chemotherapy	First	Yes	Yes
Pertuzumab (Perjeta®)	Monoclonal antibody	First	Yes	Yes
Trastuzumab (Herceptin®, Herzuma®, others)	Monoclonal antibody	First	Yes	Yes
Trastuzumab deruxtecan (Enhertu®)	Antibody drug conjugate	Second	Recommended for funding on PBS**	No
Trastuzumab emtansine (Kadcyla®)	Antibody drug conjugate	Second	Yes	Yes (if not previously used in early BC)
Trastuzumab retreatment (Herceptin®, Herzuma®, others)	Monoclonal antibody	Second	Yes	No
Tucatinib (Tukysa®)	Tyrosine kinase inhibitor	Second	No	No

*For a more detailed description of drugs available and funded in Aotearoa vs Australia, see https://www.breastcancer.org.nz/content/striving-better-care

**Trastuzumab deruxtecan for HER2+ ABC was recommended for funding on Australia's Pharmaceutical Benefits Scheme (PBS) by the Australian Pharmaceutical Benefits Advisory Committee (PBAC) at their March 2023 meeting. Funding announcements are expected within a few months of this meeting. Pembrolizumab for mTNBC was recommended at the March meeting and funded on the PBS as of 1st September 2023.

***Some HER2+ cancers are also HR+; for the purposes of this table we have focused on anti-HER2 therapies.

Other treatments commonly used outside Aotearoa

There are a number of other medicines not specifically mentioned in guidelines that are widely used elsewhere but not yet funded for breast cancer indications in Aotearoa, for example osteoporosis treatments used to treat or prevent bone metastases. Some examples are listed below.

- **Ibandronate (Bondronat®)** is a bisphosphonate used to reduce bone loss and help prevent fractures in those whose metastatic cancer has moved to their bones. In Aotearoa, **zoledronic acid (Zometa®)** is funded for this purpose.
- **Denosumab (Xgeva® or Prolia®)** is a monoclonal antibody that is registered and funded in Aotearoa for treating osteoporosis. It is also known to reduce tumour formation and growth in people whose cancer has spread to the bones, and may also prevent breast cancer in people with a BRCA gene mutation. It is more effective than a bisphosphonate such as ibandronate in preventing fractures in women with bone metastases [Gennari, André et al., 2021].
- **Pegylated liposomal doxorubicin (Caelyx®)**. This is a cytotoxic chemotherapy agent that has been formulated in liposomes so that it is less likely to cause side effects than doxorubicin. In New Zealand, doxorubicin is funded but not Caelyx®.
- **Sub-cutaneous trastuzumab** and **sub-cutaneous trastuzumab + pertuzumab (brand name Phesgo®)** are alternative formulations that can be given by injection rather than by intravenous infusion. This has huge benefits in terms of convenience and efficiency as they can be administered without a lengthy visit to an infusion centre at a hospital.

Conclusion

As a 'first-world' country, Aotearoa should and could have among the best ABC survival rates in the world. Important advances were made with the funding approvals in 2020 for palbociclib (HR+/HER2-) and trastuzumab emtansine (HER2+). However, this article shows that large gaps in our arsenal of treatments remain for all ABC sub-types and our survival times are shortened. To improve the situation for those with ABC in Aotearoa there will need to be ongoing concerted efforts from healthcare professionals, patient advocates and patients, with better engagement from government and PHARMAC. To bring us up to global standards, politicians and policy makers will need to commit to reform, along with ongoing increases in the medicines budget to bring us closer to the OECD average. Other countries such as Germany, Japan and the UK operate successful systems for evaluating and providing modern medicines rapidly to those who need them, delivering benefits to individuals, society and health systems [Shawview 2023]. Aotearoa should evaluate these systems and urgently implement reform of the 30-year-old PHARMAC model, replacing the narrow focus on limiting spending and rationing medicines with investing in innovation to improve our health outcomes. There is a vast body of evidence supporting the use of newer and more effective treatments for ABC and it is long overdue for Aotearoa to follow the evidence and provide the

effective modern treatments that will give all New Zealanders with advanced breast cancer longer healthier lives.

Updated

4th September 2023

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