PTAC MEMORANDUM: Breast Cancer Review

From: Therapeutic Group Manager

Date: September 2018

QUESTIONS TO PTAC

1. Does the Subcommittee consider the current breast cancer treatment paradigm in New Zealand to be accurately represented? If not, how should it be amended?

2. Does the Subcommittee have any comments to make regarding the relative health need of breast cancer subpopulations?

3. Of the breast cancer treatments currently under assessment by PHARMAC, does the Subcommittee have any comments about the relative priority for funding taking into account all Factors for Consideration?

   3.1. Would the relative priority change if these treatments are considered on purely clinical grounds (i.e. not taking into account proposed price)?

4. Does the Subcommittee have any comments about pharmaceuticals for the treatment of breast cancer not yet considered by PHARMAC?

5. Does the Subcommittee have any other comments regarding breast cancer treatments?

PURPOSE OF THIS PAPER

There are a number of applications for breast cancer treatments on the agenda for consideration at this meeting. The purpose of this paper is to provide an overview of the breast cancer treatment landscape, including agents currently being considered by PHARMAC and agents that may be considered by PHARMAC in the future.

PHARMAC is also seeking advice from the Subcommittee regarding the breast cancer landscape in New Zealand, the potential place in therapy, and relative priorities for funding of the various treatments for breast cancer.

DISCUSSION

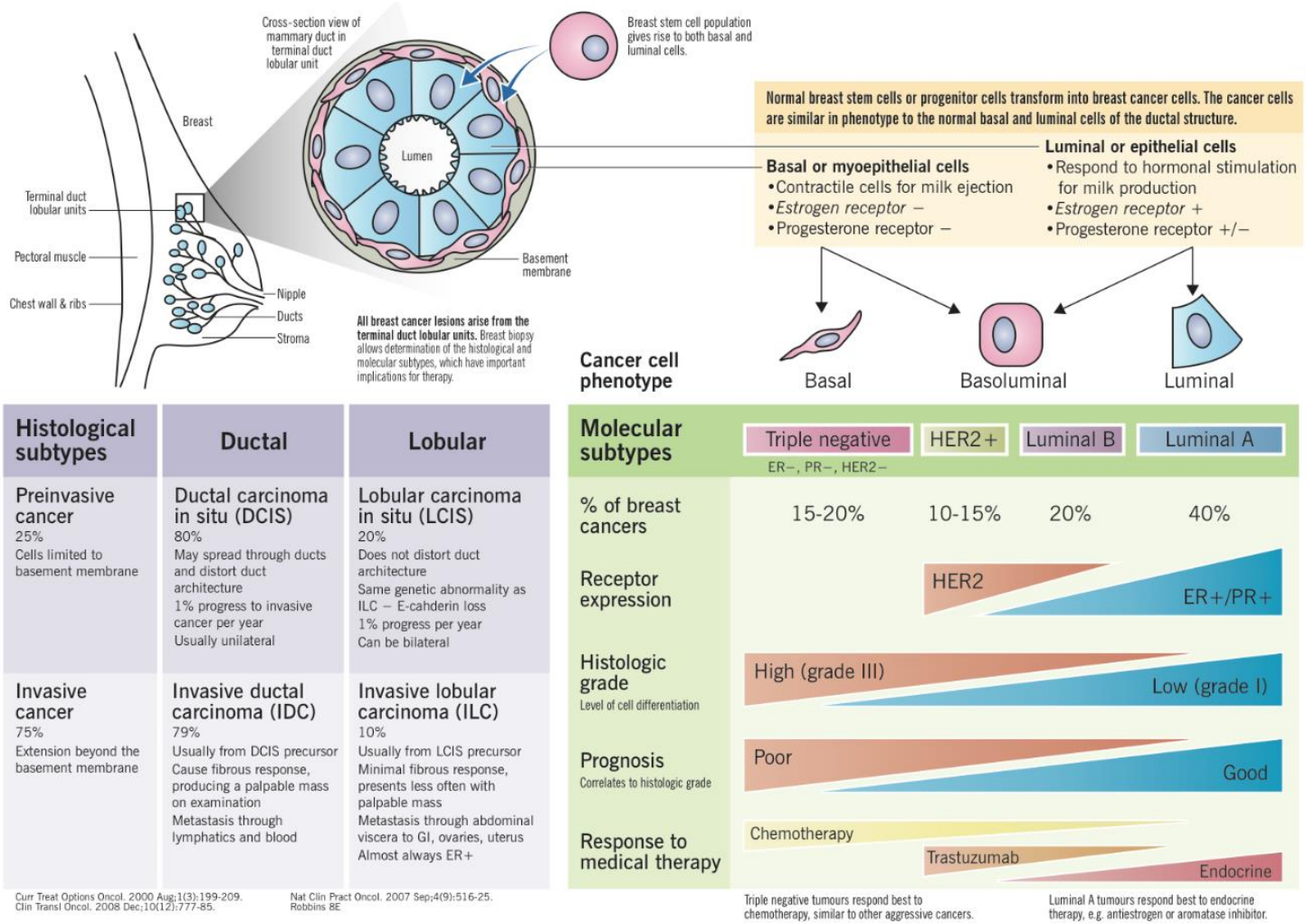
BACKGROUND

Breast cancer is the most commonly diagnosed cancer in women, and the leading cause of cancer-related death among women in New Zealand. More than 3,000 cases are diagnosed each year, and more than 600 women will die from the disease annually. The incidence is higher in Māori women than non-Māori (incidence rate 130.2 per 100,000 population vs 94.6 per 100,000 per population), and there are significant ethnic disparities in survival (Māori and Pacifica women having poorer outcomes than other ethnic groups).

Risk factors include age, increased breast density, alcohol intake, family history of breast cancer, nulliparity, use of combination hormone therapy, and postmenopausal obesity.

There are various histologic and molecular subtypes of breast cancer that differ in microscopic appearance and biologic behaviour (Figure 1). These factors are used to guide treatment decisions. The treatment landscape for breast cancer described below is based on European School of Oncology (ESO) and European Society for Medical Oncology (ESMO) guidelines (ESMO Clinical Practice Guidelines: Breast Cancer. Accessed 23 July 2018. Available at: https://www.esmo.org/Guidelines/Breast-Cancer).

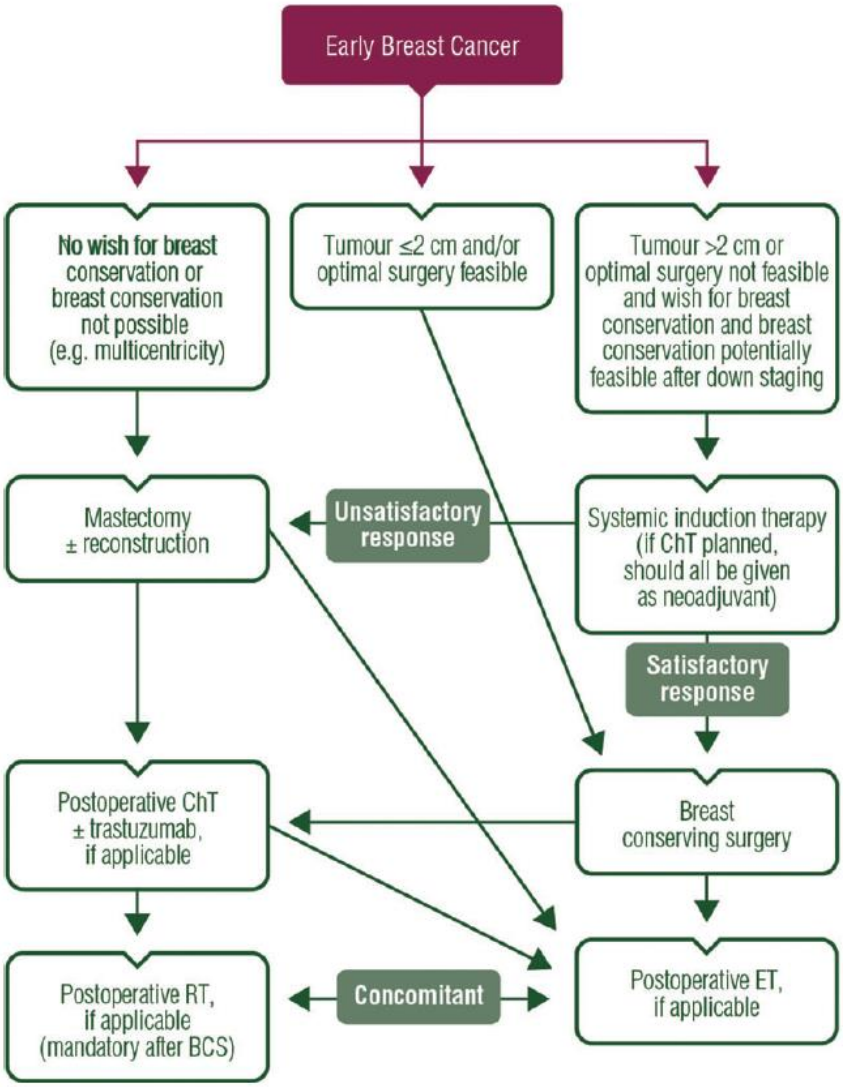
Figure 1: Histologic and molecular subtypes of breast cancer (McMaster Pathophysiology Review. Breast Cancer. Available at: http://www.pathophys.org/breast-cancer/. Accessed 16 July 2018)



EARLY BREAST CANCER

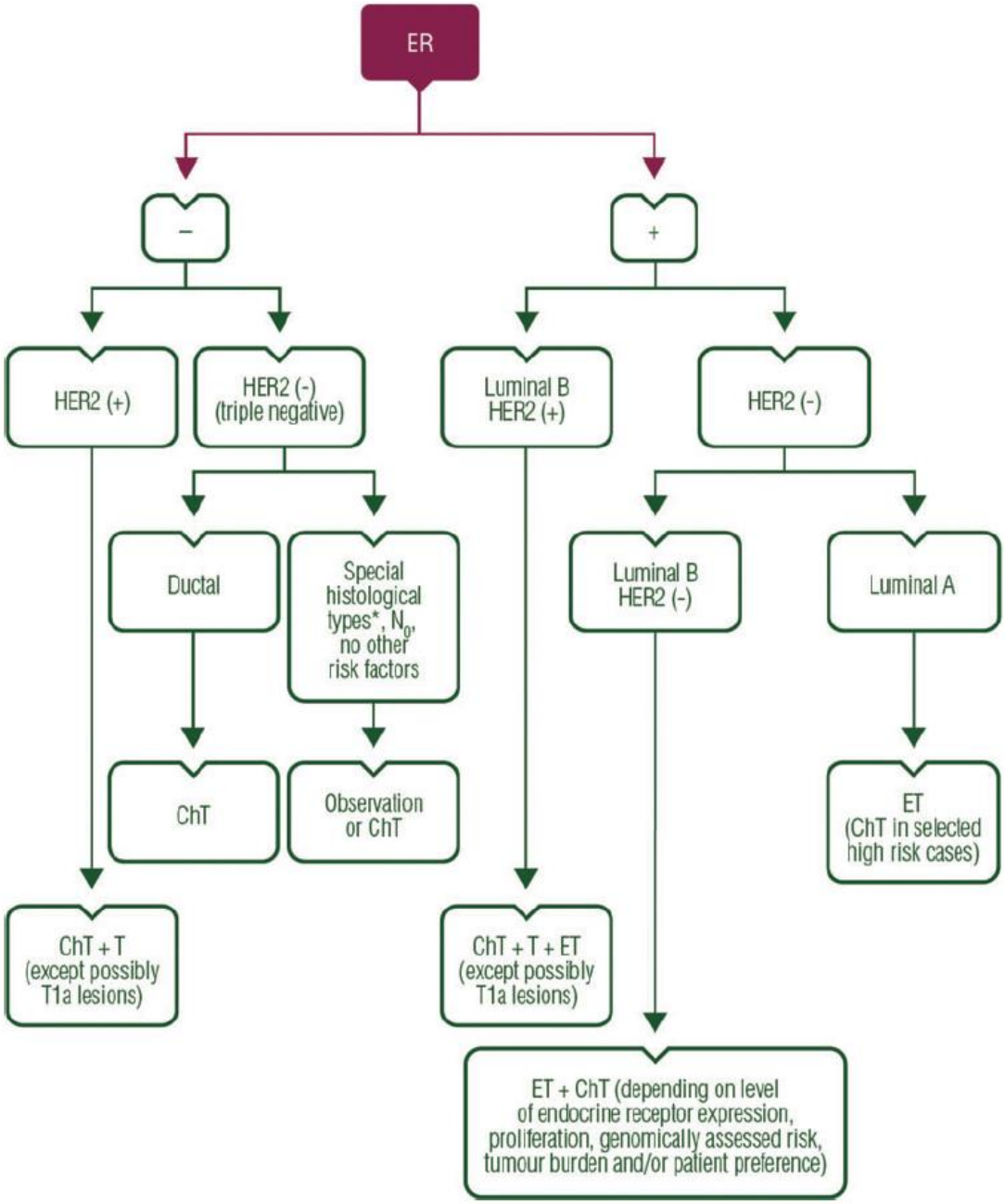
The most important prognostic factors in early breast cancer (eBC) are expression of hormone receptors, HER2, proliferation markers, the number of involved regional lymph nodes, tumour histology, and the size, grade, and presence of peri-tumoural vascular invasion. The treatment algorithm for eBC depends on factors including tumour burden, location, and biology, in addition to patient age and general health status. The primary treatment is surgery, with or without neodjuvant systemic therapy, post-operative radiation therapy, and/or adjuvant therapy (Figure 2). The choice of neoadjuvant or adjuvant systemic treatment is based on biomarker expression and intrinsic phenotype (Figure 3).

Figure 2: ESMO early breast cancer treatment algorithm (Senkus et al. Ann Oncol. 2015;26 Suppl 5; v8-30; *Appendix 1)*



Cht, chemotherapy; BCS, breast-conserving surgery; ET, endocrine therapy; RT, radiotherapy.

Figure 3: Early breast cancer systemic therapy choice (ESMO; Senkus et al. Ann Oncol. 2015;26 Suppl 5; v8-30; *Appendix 1)*

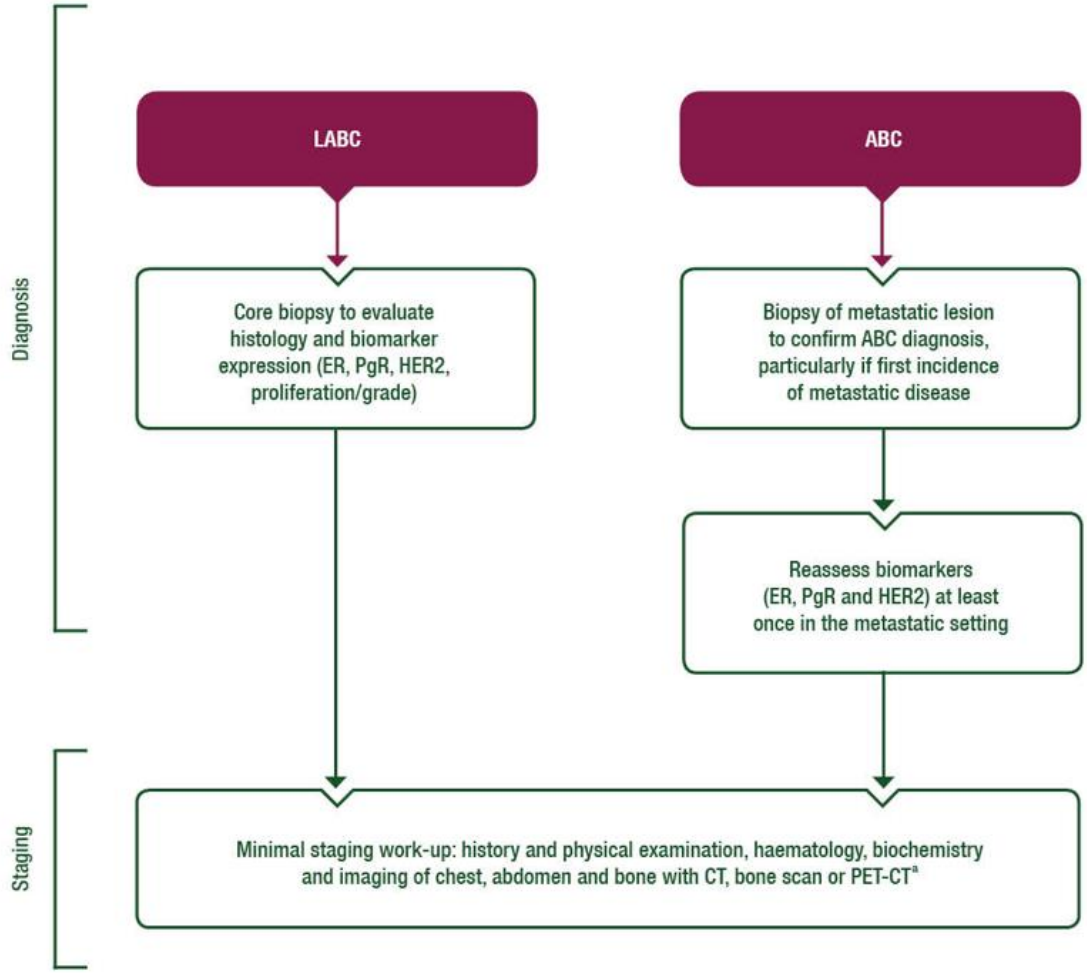


ER, oestrogen receptor; HER2, human epidermal growth factor 2 receptor; ChT, chemotherapy; ET, endocrine therapy; T, trastuzumab.

ADVANCED BREAST CANCER

Advanced breast cancer (ABC) comprises both locally advanced breast cancer (LABC) and metastatic breast cancer (mBC). In order to identify the most appropriate treatment, a biopsy should be carried out to confirm tumour histology and biomarker expression (Figure 4).

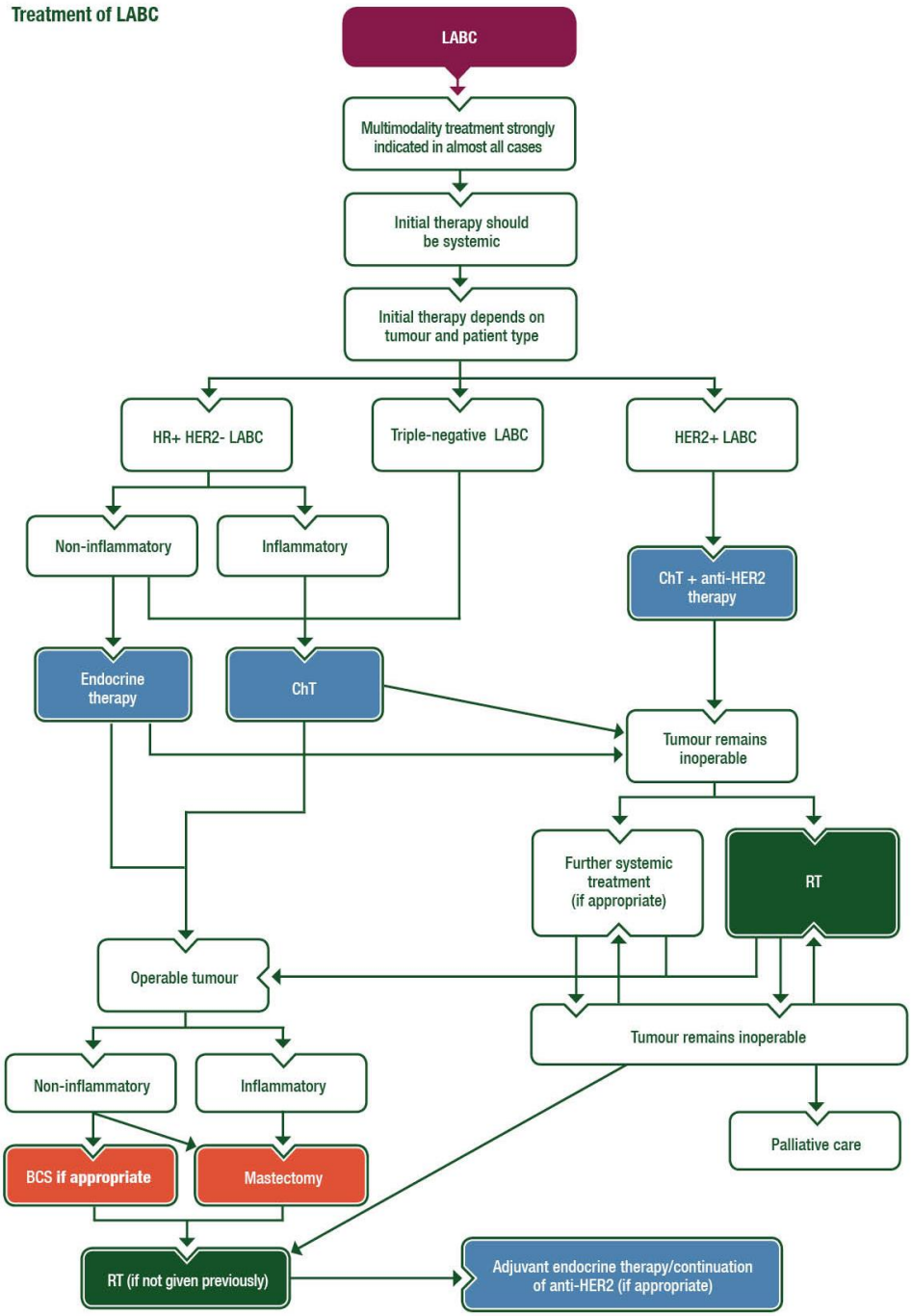
Figure 4: Diagnosis and staging of advanced breast cancer (Cardoso et al. Ann Oncol. 2018; doi: 10.1093/annonc/mdy192. [Epub ahead of print]; *Appendix 1*)



ABC, advanced breast cancer; CT, computed tomography; ER, oestrogen receptor; HER2, human epidermal growth factor receptor 2; LABC, locally advanced breast cancer; MRI, magnetic resonance imaging; PET-CT, positron emission tomography-computed tomography; PgR, progesterone receptor.

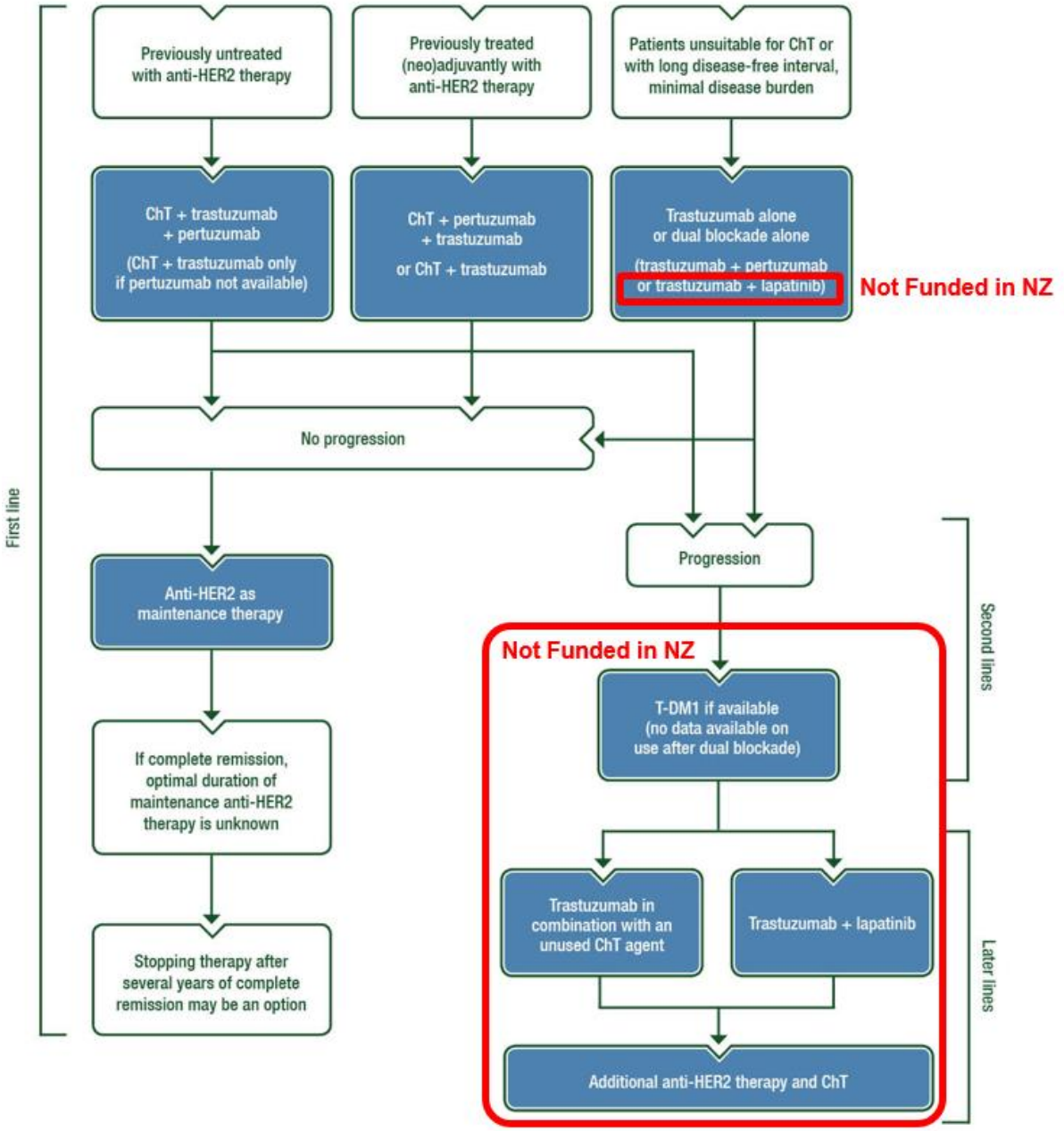
Patients who present with unresectable non-metastatic disease should first receive primary systemic therapy. If this renders the tumour(s) resectable, this should be followed by surgery and radiotherapy. If LABC remains inoperable after systemic therapy, radiotherapy should be considered. Patients with mBC should be treated with systemic therapy. The choice of systemic therapy will depend on biomarker expression (Figures 5-8)

Figure 5: ESMO locally advanced breast cancer treatment algorithm (Cardoso et al. Ann Oncol. 2018; doi: 10.1093/annonc/mdy192. [Epub ahead of print]; *Appendix 1*)



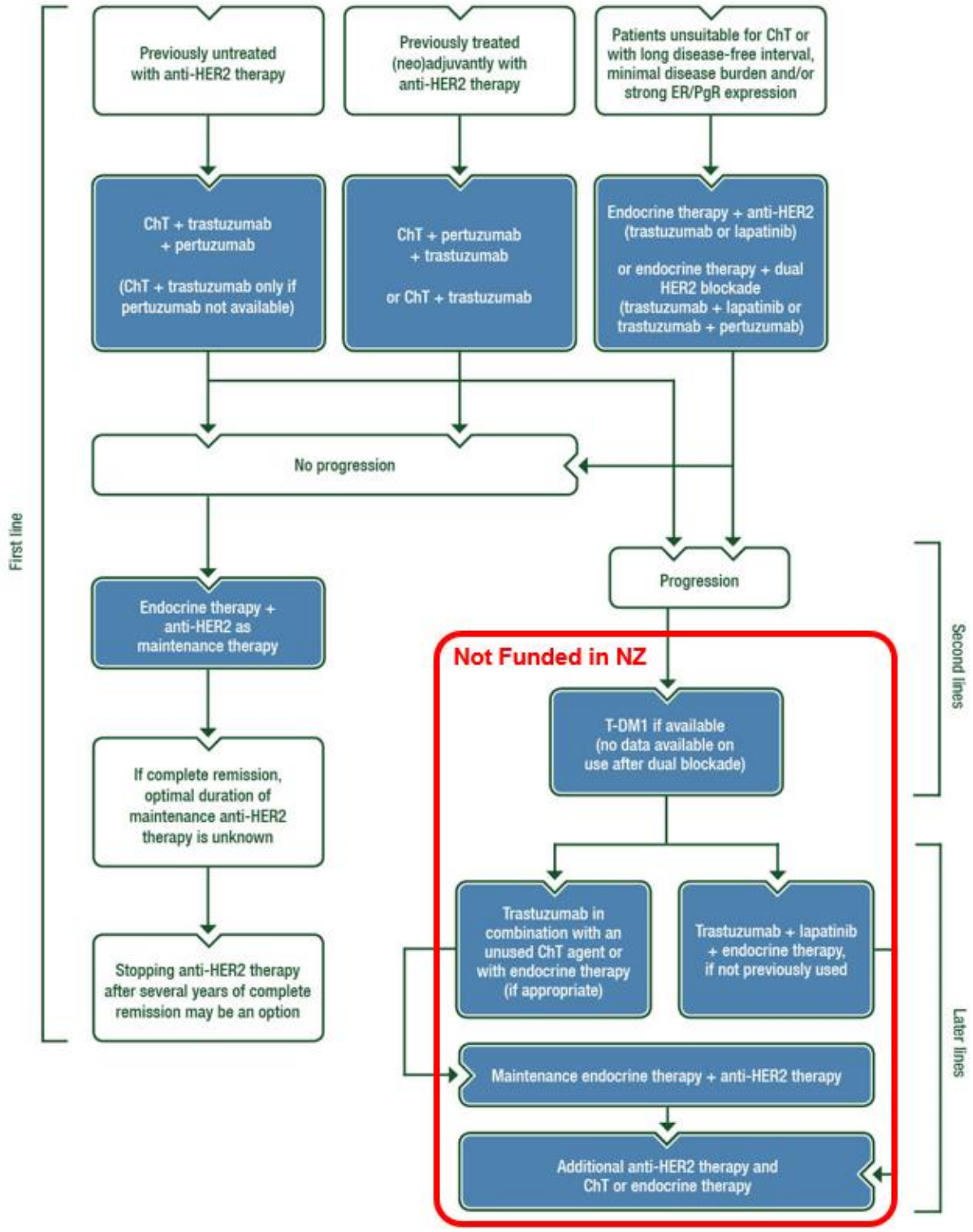
BCS, breast conserving surgery; ChT, chemotherapy; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; LABC, locally advanced breast cancer; RT, radiotherapy.

Figure 5: ESMO ER-negative, HER2-positive ABC (Cardoso et al. Ann Oncol. 2018; doi: 10.1093/annonc/mdy192. [Epub ahead of print]; *Appendix 1*)



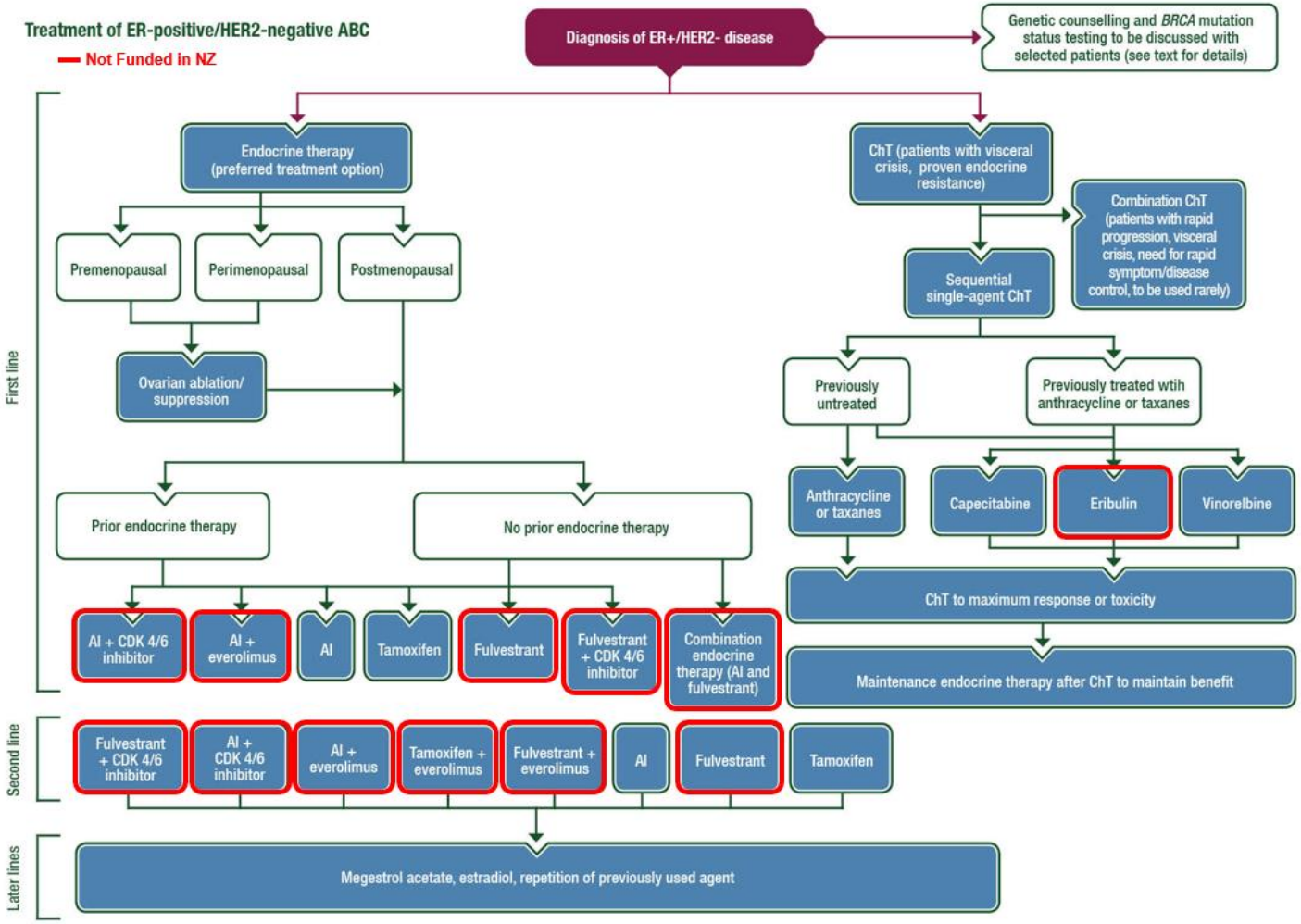
ABC, advanced breast cancer; ChT, chemotherapy; ER, oestrogen receptor; HER2, human epidermal growth factor receptor 2; T-DM1, trastuzumab emtansine.

Figure 6: ESMO ER-positive, HER2-positive ABC (Cardoso et al. Ann Oncol. 2018; doi: 10.1093/annonc/mdy192. [Epub ahead of print]; *Appendix 1*)



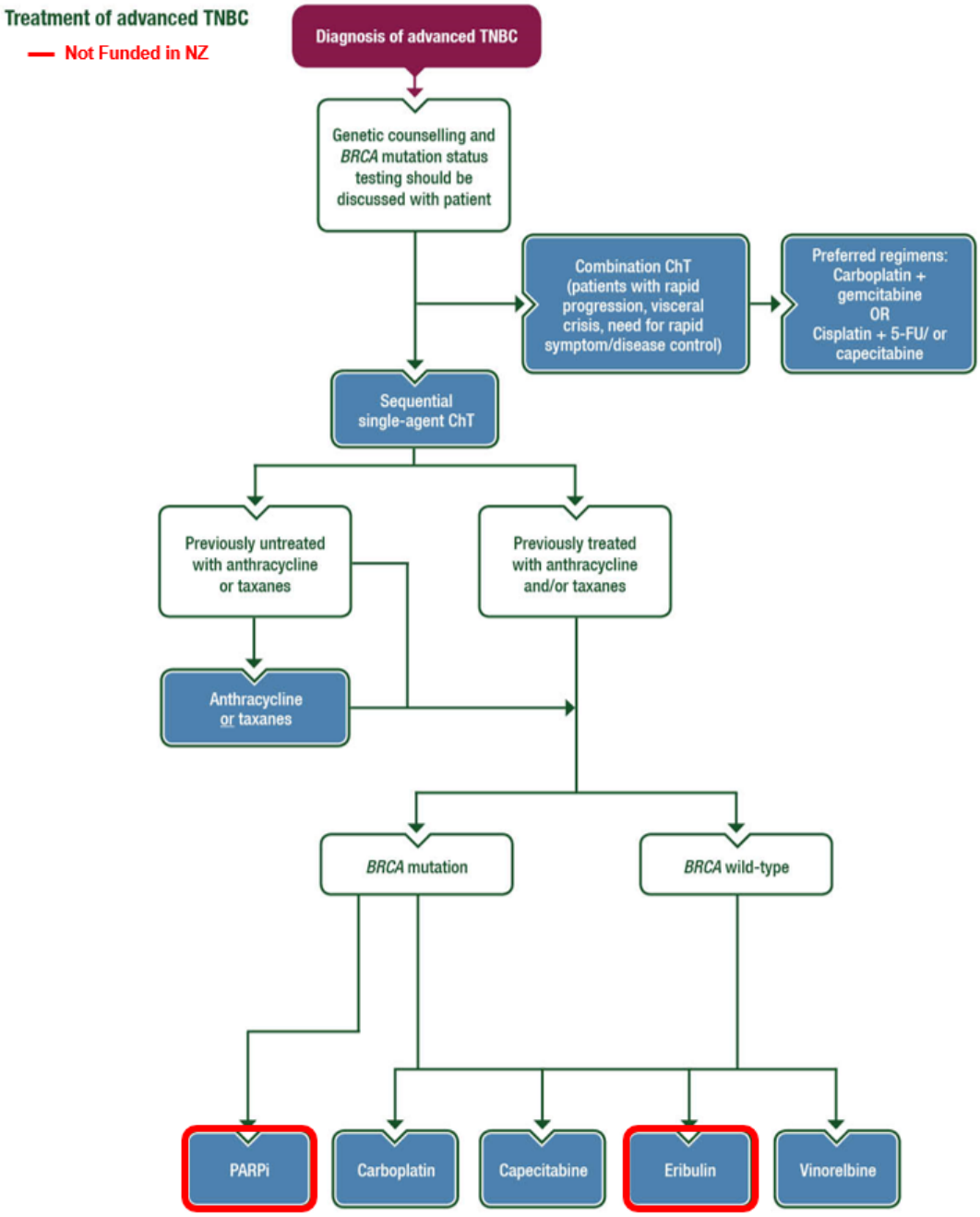
ABC, advanced breast cancer; ChT, chemotherapy; ER, oestrogen receptor; HER2, human epidermal growth factor receptor 2; PgR, progesterone receptor; T-DM1, trastuzumab emtansine.

Figure 7: ESMO ER-positive, HER2-negative ABC (Cardoso et al. Ann Oncol. 2018; doi: 10.1093/annonc/mdy192. [Epub ahead of print]; *Appendix 1*)



ABC, advanced breast cancer; AI, aromatase inhibitor; ChT, chemotherapy; ER, oestrogen receptor; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2.

Figure 8: ESMO ER-negative, HER2-negative ABC (Cardoso et al. Ann Oncol. 2018; doi: 10.1093/annonc/mdy192. [Epub ahead of print]; *Appendix 1*)



5-FU, fluorouracil; ChT, chemotherapy; PARPI, poly adenosine diphosphate ribose polymerase inhibitor; TNBC, triple-negative breast cancer.

SYSTEMIC TREATMENTS

Table 1 details non-chemotherapy systemic treatments currently recommended for the treatment of breast cancer can be broadly categorized into hormonal therapies and targeted therapies (Please note that Table 1 has been compiled by PHARMAC staff with reference to various international guidelines and a view of products on the horizon but is not intended to be exhaustive).

Table 2 presents all currently unfunded agents previously considered by PTAC or CaTSoP for the treatment of breast cancer.

Table 1: Targeted and hormonal therapies included in ESMO guidelines and the funding status in New Zealand

Therapy Type	Agent	Brand	MOA	Patient Group	Registered for BC in NZ	Currently funded by PHARMAC	To be reviewed at current meeting (indication)
Hormonal Therapy	Anastrozole	Rolin	Aromatase inhibitor	ER+	✓	✓ *	-
	Exemestane	Pfizer exemestane	Aromatase inhibitor	ER+	✓	✓ *	-
	Letrozole	Letrole	Aromatase inhibitor	ER+	✓	✓ *	-
	Tamoxifen	Genox	Selective oestrogen receptor modulator (SERM)	ER+	✓	✓ *	-
	Fulvestrant	Faslodex	Selective oestrogen receptor degrader (SERD)	ER+ HER2-	✗	✗	Yes (ER+ advanced BC)
Targeted Therapy	Eribulin‡	Halaven	Microtubule dynamics inhibitor	HER2-	✗	✗	-
	Everolimus‡	Afinitor	mTOR inhibitor	ER+ HER2-	✗	✗	-

Therapy Type	Agent	Brand	MOA	Patient Group	Registered for BC in NZ	Currently funded by PHARMAC	To be reviewed at current meeting (indication)
	Palbociclib	Ibrance	CDK 4/6 inhibitor	ER+ HER2-	✓	✗	Yes (ER+ HER2- advanced BC)
	Ribociclib‡	Kisqali	CDK 4/6 inhibitor	ER+ HER2-	✗	✗	-
	Lapatinib	Tykerb	Tyrosine kinase inhibitor	HER2+	✓	✓ †	-
	Neratinib	Nerlynx	Tyrosine kinase inhibitor	HER2+	✗	✗	-
	Pertuzumab	Perjeta	Anti-HER2 mAb	HER2+	✓	✓ †	Yes (early BC & previously treated HER2+ mBC)
	Trastuzumab	Herceptin	Anti-HER2 mAb	HER2+	✓	✓ †	-
	Trastuzumab-emtansine (TDM-1)	Kadcyla	Anti-HER2 mAb conjugated to cytotoxic DM1	HER2+	✓	✗	Yes (HER2+ mBC)
	Bevacizumab	Avastin	Anti-VEGF mAb	Any mBC	✓	✗	-
	Olaparib	Lynparza	PARP inhibitor	*BRCA*-mutated HER2-	✗	✗	-
	Talazoparib	BMN-673	PARP inhibitor	*BRCA*-mutated HER2-	✗	✗	-

Therapy Type	Agent	Brand	MOA	Patient Group	Registered for BC in NZ	Currently funded by PHARMAC	To be reviewed at current meeting (indication)
Checkpoint Inhibitors‡	Pembrolizumab/ Nivolumab/ Atezolizumab/ Durvalumab/ Avelumab	Keytruda/ Opdivo/ Tecentriq/ Imfinzi/ Bavencio	Anti-PD1/PD-L1 mAb	HER2- ER-	✗	✗	-
	Ipilimumab	Yervoy	Anti-CTLA4 mAb	HER2- ER-	✗	✗	-

*Open listed.

†Special authority criteria apply.

‡Has not previously been considered by PHARMAC for the treatment of breast cancer.

Table 2: Unfunded agents previously considered by PTAC and/or CaTSoP for the treatment of breast cancer

Agent	Indication	PTAC priority (date)	CaTSoP priority (date)	Approval
Anastrozole	Widening of access for second line treatment of advanced breast cancer	List (Feb 2002)	-	Sep 2002
Anastrozole	Third line treatment of advanced breast cancer	List (May 1997)	-	Dec 1998
Anastrozole	Early breast cancer after two years of tamoxifen treatment	Medium (May 2006)	Medium (Apr 2006)	Dec 2008
Anastrozole	Widening of access for first line treatment of advanced breast cancer	Medium (Aug 2003)	Medium (Apr 2003)	Jun 2005
Aromatase inhibitors	Breast cancer (removal of special authority)	Recommended alteration to access criteria (Nov 2007)	-	Nov 2008
Aromatase Inhibitors	Include stage IIIc for breast cancer	List (Nov 2007)	-	Aug 2008
Capecitabine	Locally advanced or metastatic breast cancer after failure of two prior chemotherapeutic regimes	Decline (Mar 2000) Decline (Nov 2000)	-	Nov 2002
Docetaxel	Early breast cancer	High (Nov 2010)	High (Aug 2010)	Jun 2011
Docetaxel	Early breast cancer- contraindicated to anthracycline treatment	High (Nov 2010)	High (Aug 2010)	Jun 2011
Docetaxel	Adjuvant treatment in breast cancer	Deferred (Feb 2005) Cost neutral (Nov 2006)	Cost neutral (Oct 2006)	May 2007

Agent	Indication	PTAC priority (date)	CaTSoP priority (date)	Approval
Exemestane	Widening of access for breast cancer	Low (May 2004)	Low (Mar 2004)	Jun 2007
Fulvestrant	Breast cancer - locally advanced or metastatic breast cancer (3rd line treatment)	Decline (Jul 2008)	-	-
Gemcitabine	Metastatic breast cancer	Decline (May 2012)	-	Nov 2012
Lapatinib	Breast cancer - Second line metastatic HER2 positive breast cancer	Decline (Nov 2007) Decline (Nov 2010) Decline (Feb 2011) Decline (Feb 2012) Decline (Feb 2013) Decline (Aug 2013)	Low (Nov 2010) Decline (Apr 2011) Decline (Nov 2011) Decline (Oct 2012) Decline (Mar 2013)	-
Lapatinib	Breast cancer - first line metastatic HER2 positive breast cancer	Medium (Feb 2011)	Cost neutral (Apr 2011)	Feb 2012
Letrozole	Breast cancer in post-menopausal women	List (Feb 2002) Medium (Nov 2003)	Medium (Apr 2003)	Jun 2005
Letrozole	First line treatment for new patients with early breast cancer	Medium (May 2006)	Medium (Apr 2006)	Aug 2008
Letrozole	Third line treatment of advanced, tamoxifen refractory, breast cancer	List (May 1998)	-	Dec 1998
Letrozole	First line treatment of advanced breast cancer	Deferred (Feb 2002)		

Agent	Indication	PTAC priority (date)	CaTSoP priority (date)	Approval
		Low (Nov 2003)	Deferred (Apr 2003)	Sep 2009
Nab-paclitaxel	Metastatic breast cancer	Cost neutral (Nov 2010) Cost neutral (Feb 2011) Low (Aug 2013) Cost neutral (Feb 2014) Cost neutral (Aug 2014)	Cost neutral (Nov 2010) Cost neutral (Sep 2013) Cost neutral (Mar 2014)	-
Palbociclib	Breast cancer, locally advanced/metatastic, HER2 negative, HR positive, first-line endocrine treatment	-	To be reviewed (Aug 2018)	-
Pertuzumab	breast cancer, HER2-positive, locally advanced, inflammatory or early-stage, neoadjuvant treatment	-	To be reviewed (Aug 2018)	-
Pertuzumab	Breast cancer; HER2 positive, metastatic, previously-treated	Deferred (Feb 2017)	-	-
Pertuzumab	Breast cancer; HER2 positive, metastatic, treatment naive	Low (Feb 2014) Low (Aug 2014) Low (May 2015)	Low (Mar 2014) Low (Mar 2015)	Dec 2016
Trastuzumab	early HER2-positive breast cancer - 12-month regimen	Decline (Aug 2006) Decline (Jul 2008) Decline (May 2009)	-	Jun 2010
Trastuzumab	early HER2-positive breast cancer – 9-week regimen	High (Nov 2006) High (Feb 2007)	High (Oct 2006)	May 2007

Agent	Indication	PTAC priority (date)	CaTSoP priority (date)	Approval
Trastuzumab	Breast cancer-treatment beyond disease progression	Decline (Feb 2011)	Decline (Nov 2010)	-
Trastuzumab	Breast cancer-Metastatic. Retreatment following previous trastuzumab adjuvant treatment	Recommended alteration to access criteria (Feb 2011)	High (Nov 2010)	Sep 2011
Trastuzumab emtansine	HER2-positive metastatic breast cancer after prior trastuzumab and a taxane	Low (Nov 2017)	-	*Option for investment*
Trastuzumab, subcutaneous	Breast cancer, same indication as IV trastuzumab	Decline (Nov 2014) Cost neutral (Nov 2015)	Low (Mar 2015)	*Prioritized*
Zoledronic acid	Bone metastases associated with prostate cancer, breast cancer and multiple myeloma	Decline (Aug 2003)	Decline (Apr 2003)	Oct 2014
Zoledronic acid	Breast cancer, early, in postmenopausal women	Decline (Feb 2015) Low (Nov 2015) Medium (Aug 2017)	Low (Mar 2015) Medium (Mar 2017)	Dec 2017

APPENDICES

Appendix 1: Senkus et al. Ann Oncol. 2015;26 Suppl 5; v8-30.

Cardoso et al. Ann Oncol. 2018; doi: 10.1093/annonc/mdy192. [Epub ahead of print].