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BCAC Response to Pharmac's Proposal to Decline Inactive Funding Applications
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Thank you for the opportunity to comment on Pharmac's proposal to decline inactive funding applications for a range of pharmaceuticals. In preparing our response we have sought advice from specialists in the field of breast cancer treatment, as well as our membership. We therefore hope Pharmac will carefully consider our comments on this proposal.

Fulvestrant -Breast cancer- locally advanced or metastatic breast cancer (1st line treatment)

BCAC objects strongly to the proposal to decline this application as it is out of step with current evidence and needs to be revisited. This is particularly concerning given the poor survival statistics for women in New Zealand with advanced breast cancer.

An application was made by BCAC in May 2018 for the listing of fulvestrant on the Pharmaceutical Schedule for treatment in accordance with internationally approved in indications for fulvestrant. At that time, the sponsor for this product (Astra Zeneca) had let registration lapse in New Zealand. It was subsequently re-registered in New Zealand with the following indications:

FASLODEX is indicated for the treatment of locally advanced or metastatic breast cancer in postmenopausal women of any age:

- not previously treated with endocrine therapy, or
- previously treated with endocrine therapy (antioestrogen or aromatase inhibitor) therapy, irrespective of whether their postmenopausal status occurred naturally or was artificially induced (1).

It was subsequently listed on the Pharmaceutical Schedule as follows:

FULVESTRANT – Retail pharmacy-Specialist – Special Authority see SA1895 below
Inj 50 mg per ml, 5 ml prefilled syringe.....1,068.00 2 ✔ **Faslodex**

➽SA1895 **Special Authority for Subsidy**
Initial application only from a medical oncologist or medical practitioner on the recommendation of a medical oncologist.
Approvals valid for 6 months for applications meeting the following criteria:
All of the following:

1 Patient has oestrogen-receptor positive locally advanced or metastatic breast cancer; and
2 Patient has disease progression following prior treatment with an aromatase inhibitor or tamoxifen for their locally advanced or metastatic disease; and
3 Treatment to be given at a dose of 500 mg monthly following loading doses; and
4 Treatment to be discontinued at disease progression.

Renewal only from a medical oncologist or medical practitioner on the recommendation of a medical oncologist. Approvals valid for 6 months for applications meeting the following criteria:
All of the following:

1 Treatment remains appropriate and patient is benefitting from treatment; and
2 Treatment to be given at a dose of 500 mg monthly; and
3 There is no evidence of disease progression.

Our previous application included first line evidence from the FIRST and FALCON trials, as well as a number of systematic reviews. As indicated below, the **FIRST trial reported results showing that overall survival is superior with fulvestrant in the first line setting.**

FIRST – fulvestrant 500mg versus anastrozole in ABC -with no prior endocrine therapy

The Fulvestrant fIRst-line (FIRST) Study was a phase II, randomised, open-label study comparing fulvestrant 500 mg with anastrozole 1 mg as first-line endocrine therapy for postmenopausal women with hormone receptor-positive (HR+) advanced breast cancer (ABC). FIRST compared fulvestrant high-dose (HD) regimen (500 mg/month plus 500 mg on day 14 of month 1) versus anastrozole (1 mg/d). Included were postmenopausal women with ER-positive and/or progesterone receptor-positive locally advanced or metastatic breast cancer and no prior endocrine therapy. Key exclusion criteria were presence of life-threatening metastases and prior treatment with a non-approved drug. The primary efficacy end point was clinical benefit rate (CBR), defined as the proportion of patients experiencing an objective response (OR) or stable disease for > or = 24 weeks.

At 6 months CBR was similar for fulvestrant HD (n=102) and anastrozole (n=103), 72.5% v 67.0%, respectively (odds ratio, 1.30; 95% CI, 0.72 to 2.38; p=0.386). Objective response rate (ORR) was also similar between treatments: fulvestrant HD, 36.0%; anastrozole, 35.5%. Time to progression (TTP) was significantly longer for fulvestrant versus anastrozole (median TTP not reached for fulvestrant HD v 12.5 months for anastrozole; HR 0.63; 95% CI, 0.39 to 1.00; p=0.0496). Duration of OR and CB numerically favoured fulvestrant HD. Both treatments were well tolerated, with no significant differences in the incidence of prespecified AEs. It was concluded that first-line fulvestrant HD was at least as effective as anastrozole for CBR and ORR and was associated with significantly longer TTP. Fulvestrant HD was generally well tolerated, with a safety profile similar to that of anastrozole (2).

A subsequent publication reported follow-up data for TTP for the FIRST study. Follow-up analysis was performed when 79.5 % of patients had discontinued study treatment. Median TTP was 23.4 months for fulvestrant versus 13.1 months for anastrozole; a 34 % reduction in risk of progression (HR 0.66; 95 % CI 0.47 - 0.92; p=0.01). Best overall response to subsequent therapy and CBR for subsequent endocrine therapy was similar between the treatment groups. These longer-term, follow-up results confirmed efficacy benefit for fulvestrant 500 mg versus anastrozole as first-line endocrine therapy for HR+ advanced breast cancer in terms of TTP, and, importantly, show similar best overall response rates to subsequent endocrine therapy (3).

A further publication of the FIRST study reported OS for fulvestrant 500 mg versus anastrozole after approximately 65% of patients had died. Treatment effect on OS across several subgroups was examined. Tolerability was evaluated by adverse event monitoring. At data cut-off, 61.8% (fulvestrant 500 mg, n = 63) and 71.8% (anastrozole, n = 74) had died. The HR (95% CI) for OS with fulvestrant 500 mg versus anastrozole was 0.70 (0.50 to 0.98; p=0.04; median OS, 54.1 months vs 48.4 months). Treatment effects were generally consistent across the subgroups analysed. No new safety issues were observed. This analysis was unplanned, but instead was added after TTP results were analysed, and not all patients participated in additional OS follow-up. However, the results suggested that fulvestrant 500 mg extends OS versus anastrozole in patients with ABC (4).

FALCON – Fulvestrant 500mg versus Anastrozole in ABC with no prior endocrine therapy

The FALCON phase 3, randomised, double-blind trial investigated whether fulvestrant could improve PFS compared with anastrozole in postmenopausal patients who had not received previous endocrine therapy. Eligible patients had histologically confirmed ER-positive or progesterone receptor-positive, or both, locally advanced or metastatic breast cancer and were recruited from 113 academic hospitals and community centres in 20 countries. Patients were endocrine therapy-naive, with WHO performance status 0-2, and at least one measurable or non-measurable lesion. Patients

were randomised to fulvestrant (500 mg IM on Days 0, 14, 28, then every 28 days thereafter) or anastrozole (1 mg daily). The primary endpoint was PFS, determined by RECIST v1.1, intervention by surgery or radiotherapy because of disease deterioration, or death from any cause, assessed in the intention-to-treat (ITT) population. Safety outcomes were assessed in all patients who received at least one dose of randomised treatment (including placebo).

In total, 462 patients were randomised (fulvestrant=230 and anastrozole=232). PFS was significantly longer in the fulvestrant group than in the anastrozole group (HR 0.797, 95% CI 0.637-0.999, p=0.0486). Median PFS was 16.6 months (95% CI 13.83-20.99) in the fulvestrant group versus 13.8 months (11.99-16.59) in the anastrozole group.

The most common AEs were arthralgia (17% in the fulvestrant group vs 10% in the anastrozole group) and hot flushes (11% in the fulvestrant group vs 10% in the anastrozole group). Sixteen of 228 (7%) patients in the fulvestrant group, and 11 of 232 (5%) patients in the anastrozole group discontinued because of AEs. It was concluded that fulvestrant has superior efficacy for patients with hormone receptor-positive locally advanced or metastatic breast cancer who have not received previous endocrine therapy compared with a third-generation aromatase inhibitor, a standard of care for first-line treatment of such patients (5). OS data from this study are still awaited.

Fulvestrant Plus Anastrozole in ABC as First Line Therapy

Mehta et al. (2012) reported that the combination of fulvestrant and anastrozole prolonged progression-free survival and marginally prolonged overall survival among postmenopausal patients with hormone receptor–positive metastatic breast cancer who had been randomly assigned to receive the aromatase inhibitor anastrozole plus fulvestrant, as compared with anastrozole alone, as first-line therapy (6). Note that this study used a dose of 250mg, which is lower than the current standard dose and was therefore not included in our previous submission. Overall survival for this trial was reported in 2019 by the same authors (7).

In this trial, patients were randomly assigned patients to receive either anastrozole or fulvestrant plus anastrozole. Randomisation was stratified according to adjuvant tamoxifen use. Analysis of survival was performed by means of two-sided stratified log-rank tests and Cox regression. Efficacy and safety were compared between the two groups, both overall and in subgroups.

Of 707 patients who had undergone randomisation, 694 had data available for analysis. The combination-therapy group had 247 deaths among 349 women (71%) and a median overall survival of 49.8 months, as compared with 261 deaths among 345 women (76%) and a median overall survival of 42.0 months in the anastrozole-alone group, a significant difference (hazard ratio for death, 0.82; 95% confidence interval [CI], 0.69 to 0.98; P = 0.03 by the log-rank test). In a subgroup analysis of the two strata, overall survival among women who had not received tamoxifen previously was longer with the combination therapy than with anastrozole alone (median, 52.2 months and 40.3 months, respectively; hazard ratio, 0.73; 95% CI, 0.58 to 0.92); among women who had received tamoxifen previously, overall survival was similar in the two groups (median, 48.2 months and 43.5 months, respectively; hazard ratio, 0.97; 95% CI, 0.74 to 1.27) (p=0.09 for interaction). The incidence of long-term toxic effects of grade 3 to 5 was similar in the two groups. Approximately 45% of the patients in the anastrozole-alone group crossed over to receive fulvestrant.

It was concluded that the addition of fulvestrant to anastrozole was associated with increased long-term survival compared with anastrozole alone, despite substantial crossover to fulvestrant after progression during therapy with anastrozole alone. The results suggest that the benefit was particularly notable in patients without previous exposure to adjuvant endocrine therapy (7).

We therefore propose that Pharmac reconsiders this proposal and lists fulvestrant for first line use in people with locally advanced or metastatic disease, on the basis that they already have advanced disease and are therefore demonstrably in need of this treatment. Many of these patients will have already received tamoxifen or aromatase inhibitors in the early breast cancer setting and they have therefore already effectively failed on these treatments.

Pertuzumab - Breast cancer, HER2-positive, locally advanced, inflammatory or early-stage, neoadjuvant treatment

BCAC objects strongly to the proposal to decline this application as it is out of step with current evidence and needs to be revisited. We note that the recommendation to decline this treatment was based on evidence reviewed by CaTSoP at a 2018 meeting.

At that time, CaTSoP considered evidence from the CTNeoBC, NeoSPHERE and TRYPHAENA studies. Since then,

- the PEONY trial has been published, which supports the NeoSPHERE study results (8).
- the 3-year results from the KRISTINE study (comparing neoadjuvant trastuzumab emtansine plus pertuzumab (T-DM1+P) with docetaxel, carboplatin, trastuzumab plus P (TCH+P) for HER-2+ stage II to III breast cancer showed that T-DM1+P led to a lower pathologic complete response rate (44.4% v 55.7%; p=0.016), but fewer grade 3 or greater and serious adverse events (AEs) (9) .

In 2019, NICE recommended pertuzumab, in combination with trastuzumab and chemotherapy as an option for the neoadjuvant treatment of adults with human epidermal growth factor receptor 2 (HER2)-positive breast cancer; that is, in patients with HER2-positive, locally advanced, inflammatory or early-stage breast cancer at high risk of recurrence. This was based on the benefits seen in NeoSPHERE and TRYPHAENA, but also the benefits of the combination in the adjuvant therapy setting. We consider that PHARMAC should consider the inequity associated with denying people with breast cancer who need this combination in the neoadjuvant setting, when this treatment is available, subsidised, in the metastatic disease setting.

The recently published 17th St. Gallen International Breast Cancer Consensus Conference included 3,300 participants who took part in this important annual critical review of the "state of the art" in the multidisciplinary care of early-stage breast cancer. Seventy-four expert panellists from all continents discussed and commented on previously elaborated consensus questions as well as many key questions on early breast cancer diagnosis and treatment asked by the audience (10).

The panel considered that, for women with stage 2 or 3 tumours, preoperative or neoadjuvant systemic therapy offers clinical advantages, including tumour downstaging which may affect surgical options in the breast or axilla. Additionally, the use of preoperative treatment invites customisation of therapy based on the extent of treatment response, which serves as a prognostic marker and can identify women with residual cancer who may require additional adjuvant systemic therapy. The 2019 panel had endorsed preoperative systemic therapy as the preferred approach for women with

stage 2 or 3, HER2 positive or triple negative cancers as shown in the table (Table 3 from the publication) below. This was endorsed again in 2021 (10).

Table 3. Systemic Therapy for HER2-positive or triple-negative breast cancers

Anatomic Stage		Tumor Subtype	
		HER2+	TNBC
Stage 1 *Typically as adjuvant therapy*	T1a	TH – case by case	Chemo – case by case
	T1b	TH	TC chemo
	T1c	TH	AC/T chemo
Stage 2 *Neoadjuvant therapy preferred*		AC/TH or TCH, with addition of P if neoadj and/or node-positive	AC/T chemo**
Stage 3 *Neoadjuvant therapy preferred*		AC/THP or TCHP*	AC/T chemo**
Residual invasive cancer after neoadjuvant therapy		trastuzumab emtansine	capecitabine

T = taxane

H = trastuzumab

P = pertuzumab

C = cyclophosphamide

A = anthracycline such as doxorubicin or epirubicin

*consider addition of adjuvant neratinib after trastuzumab if tumor is ER positive and 4 or more positive LN though panel noted there are no data for use in patients also receiving pertuzumab or trastuzumab emtansine

**some panelists favor inclusion of carboplatin in neoadjuvant therapy for TNBC

Source: Burstein et al. 2021 (10)

Based on the totality of evidence (and rational basis for) this combination, a patient who requires neo-adjuvant therapy to shrink their tumour prior to surgery should logically be treated with the internationally endorsed combination including pertuzumab.

This option is supported by various guidelines as well as a number of recently published “real world” studies that collated data from patient cohorts being treated with the combination and compared results with those from randomised clinical trials (11-13).

- Murthy et al. (2018) reported on a retrospective study to determine the pathologic complete response (pCR) rate for trastuzumab and pertuzumab (HP)-containing regimens compared with trastuzumab (H)-containing regimens for stage II to III HER2(+) BC. The study included 977 patients with stage II to III HER2(+) BC who received neoadjuvant HER2-targeted therapy from 2005 to 2016 and underwent definitive breast and axillary lymph node surgery. Univariate/multivariate logistic regression and the χ(2) test for comparing proportions was used for the statistical analysis. The pCR rate was higher for the HP group (n = 170) compared with the H group (n = 807): 59% versus 46% (odds ratio, 1.7; 95% CI, 1.21-2.37; p= 0.0021). After adjustment for clinically important factors (age, date of diagnosis, stage, tumour grade, nodal status, hormone receptor [HR] status, menopausal status, and chemotherapy backbone) the adjusted odds ratio was 2.25 (95% CI, 1.08-4.73; p=0.032). In multivariate analysis, a significant predictor of pCR in both groups included HR status (HR-negative > HR-positive). It was concluded that HP-containing regimens yield higher pCR rates compared with H-containing regimens in patients with stage II to III HER2(+) BC in clinical practice regardless of chemotherapy backbone (11).

- Gonzalez- Santiago et al. (2020) investigated whether the benefit on pCR seen in clinical trials was confirmed in a real-world setting in a multicentre, retrospective study in patients with HER2-positive early BC receiving neoadjuvant treatment with pertuzumab and trastuzumab in routine clinical practice (n = 243). The primary endpoint was total pCR (tpCR) (ypT0/is ypN0). Pertuzumab and trastuzumab were combined with anthracyclines and taxanes in 74.1% of patients, with single-agent taxane in 11.1% of patients and with platinum-based chemotherapy (CT) in 14.4% of patients. The tpCR rate was 66.4%:71% with anthracyclines and taxanes, 59.3% with single-agent taxane, and 48.6% with platinum-based combinations. The tpCR rate was higher among patients with hormone receptor (HR)-negative tumours (80.9%) vs HR-positive tumours (55.4%) ($p < 0.001$). A pCR in the breast (ypT0/is) was achieved in 67.6% of patients. Of 143 patients who showed radiological complete response (rCR) (62%), 112 (78.3%) patients also achieved tpCR. Assessment of rCR by magnetic resonance imaging (MRI) showed the highest negative predictive value (NPV) for predicting tpCR (83.5%). Breast-conserving surgery was performed in 58.7% of patients. Grade 3 and grade 4 toxicities were reported in 33 (18.2%) and 12 (6.6%) patients, respectively. No toxicity leading to death was reported. This real-world analysis showed that neoadjuvant pertuzumab, trastuzumab, and chemotherapy achieve comparable or even higher rates of tpCR than those seen in clinical trials. The pCR benefit is higher in HR-negative tumors. The assessment of rCR by MRI showed the highest ability for predicting pCR. In addition, this neoadjuvant strategy confers an acceptable safety profile (12).

- Boer et al. (2021) determined the pCR rate obtained with dual HER2 blockade with trastuzumab and pertuzumab in routine clinical practice. They also investigated the impact of neoadjuvant systemic therapy (NST) on performing breast-conserving surgery and survival. This was a multicentre, retrospective, observational study in patients with stage II and III HER2+ early breast cancer who received pertuzumab and trastuzumab-based NST. Data were collected from patients' medical records. There were 82 patients included in the study treated in 8 cancer centres in Hungary between March 2015 and January 2020. The study included women with a median age of 50.3 years. The majority of the patients (95%) received a sequence of anthracycline-based chemotherapy followed by docetaxel. pCR was

achieved in 54% of the cases. As a result of NST a significant increase of conservative breast surgeries (33% vs. 3.6% planned, p = 0.0001) was observed. Ki67 expression and neutrophil-to-lymphocyte ratio (NLR) significantly predicted pCR. None of the variables were independent predictors of DFS. It was concluded that the pCR rate achieved demonstrated the reproducibility of trial data in a real-world population. The rate of breast-conserving surgery was significantly increased (13).

Based on our conversations with various specialists in the field of breast cancer, this treatment should not be restricted to people as adjuvant therapy, but should also be available as neoadjuvant therapy in suitably selected patients who need this treatment. These patients are, because of their tumour size, and possibly other risk factors in particular need of combination therapy with pertuzumab in combination with trastuzumab and other agents, to enable the best possible outcome.

Lapatinib and other tyrosine kinase inhibitors

BCAC doesn't have any particular comments to make on the proposal to decline lapatinib as a second line treatment. The availability of TDM-I provides an option for these patients. Some of the newer targeted tyrosine kinase inhibitors (TKIs) such as neratinib and tucatinib, should be made available for New Zealand patients in the near future.

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