**Written submission to the Health Select Committee**
**concerning**
**Petition of Emma Crowley**

**"That the House of Representatives urge the Minister of Health to provide sufficient funding to PHARMAC to subsidise all of the drugs listed in the European ESMO guidelines for the treatment of advanced breast cancer."**

---

Breast Cancer Foundation NZ supports the petition of Emma Crowley and would like to comment on several aspects of the petition request.

## 1. PHARMAC's increasingly outdated paradigm for funding decisions

We note that PHARMAC currently relies almost exclusively on evidence from clinical studies and trials when making cancer drug funding decisions, as can be seen in the minutes of CaTSoP and PTAC meetings.

This has been a justifiable, if far-from-perfect, strategy, given that unbiased, well-randomised control trials (RCTs) with sufficient statistical power are considered the gold standard for demonstrating the efficacy of a new medicine. However, in healthcare terminology, ***efficacy*** is not the same as ***effectiveness***. ***Efficacy*** is the extent to which an intervention (e.g. a medicine) does more good than harm under *ideal circumstances* (i.e., a carefully selected group of patients in a clinical trial), while ***effectiveness*** assesses whether an intervention does more good than harm when provided under *usual circumstances* of healthcare practice[1] (i.e. in real-world patients of varying ethnicities with multiple health problems, treated by clinicians with varying treatment styles and preferences).

PHARMAC committee meeting minutes reveal a strong focus on efficacy, and very little on effectiveness. Little mention or weight is given to real-world evidence and none to internationally accepted best practice ("standard of care"), yet these are in themselves evidence and play a significant role (along with clinical trial evidence) in the development of international clinical guidelines, such as the ESO-ESMO guidelines featured in Emma Crowley's petition request.

At this point in time, the PHARMAC-preferred randomised clinical trial evidence of survival benefits for new drugs is becoming harder and more expensive to attain. This is partly because the advent of precision medicine means new drugs tend to target much smaller patient groups (for example, breast cancers with high levels of the PD-L1 protein), so their clinical trials will be correspondingly small and not statistically strong, even for highly efficacious medicines.

Another (rather ironic) reason is that some highly effective new drugs (e.g. palbociclib / Ibrance, the subject of another petition considered recently by the Health Committee) benefit such a large group of patients and achieve such long survival in trials that it is much harder to prove a statistically significant survival benefit. This does not mean the benefit doesn't exist, but it hasn't yet been proven. This isn't helped by the fact that some of the trials are statistically under-powered to demonstrate overall survival benefit. This is the fault of pharmaceutical companies; not something

[1] B Haynes, "Can it work? Does it work? Is it worth it? The testing of healthcare interventions is evolving." *BMJ.* 1999;319:652–653

for which patients should be penalised.

It is important to recognise that there will be no new trial evidence for most, if not all, the breast cancer drugs currently awaiting funding by PHARMAC. As Dr Fatima Cardoso, arguably the world's leading oncologist in advanced breast cancer (ABC), wrote in her letter to the Health Committee after she visited New Zealand in January,

> *"many of the areas in which PHARMAC is waiting for more evidence, or has chosen not to fund on the basis of lack of Level 1 evidence, do not have that evidence forthcoming. The world has accepted these as standard therapies and is now moving on to testing the next generation of new drugs or combination therapies."*

***The decreasing availability of definitive overall survival benefit data from randomised trials of highly targeted new drugs, plus the "no new evidence" status of drugs awaiting PHARMAC funding, are factors of great concern for future PHARMAC decisions. A new paradigm for funding decisions, intentionally incorporating and placing greater weight on real-world studies and standard of care evidence is needed urgently.***

## 2. Should clinical guidelines direct PHARMAC funding decisions (as requested in this petition)?

Clinical guidelines for the management of cancer identify, evaluate and summarise the highest quality evidence and most current data about treatments, their risks and benefits, and their cost-effectiveness. They synthesise available evidence from both **efficacy and effectiveness** research to compare outcomes of different healthcare interventions[2]. Such guidelines present a clinical consensus for doctors and patients to use in making decisions about appropriate care in varying real-world clinical circumstances.

However, guidelines today also play an increasing role in higher-level policy decisions. "The methods and information generated from evidence-based guidelines efforts are critical inputs into health policy analysis and decision-making"[2]. This includes funding decisions: "Although CPGs [Clinical Practice Guidelines] were originally targeted exclusively to clinicians to help in decision-making, their target audience has grown. Because CPGs explicitly identify tests and treatments that are recommended (or not recommended), other groups, including health system administrators, disease advocates, litigators, **and payers**, are now using CPGs to define the standards of care. For example, insurers may **base coverage decisions for patients being treated…on which therapies are recommended in CPGs for this illness**."[3]

***Clinical guidelines are acceptable as a basis for pharmaceutical funding decisions.***

## 3. Why the ESO-ESMO guidelines?

The ESO-ESMO ABC (Advanced Breast Cancer) guidelines are "consensus guidelines", meaning they're a statement of evidence-based, state-of-the-art knowledge, written by a representative group of experts in a particular area[4]. In the case of ESO-ESMO ABC, an independent panel of 44

---

[2] K.N. Lohr et al. "Health policy issues and applications for evidence-based medicine and clinical practice guidelines", *Health Policy* 46 (1998) 1–19

[3] C R Cooke and M K Gould, Advancing clinical practice and policy through guidelines;" *Am J Respir Crit Care Med*. 2013 May 1;187(9):910-4.

[4] Council of Europe, "Developing a methodology for drawing up guidelines on best medical practice" Recommendation Rec(2001)13 and explanatory memorandum (2002)

medical specialists in advanced breast cancer from the UK, Europe, USA / Canada, Asia and Australia, meets every two years in Lisbon, Portugal to review the most up-to-date clinical trial and real-world evidence, and to update the guidelines accordingly.

It is hard to see how this level of attention, care and expertise in evaluating the evidence for ABC medicines can be matched by PHARMAC staff and committee members, who have responsibility for thousands of medicines in the Combined Pharmaceutical Budget along with, as of March 2019, 87,000 medical devices. The ESO-ESMO ABC panel reviews the evidence every two years, a frequency that PHARMAC cannot hope to match.

***The ESO-ESMO ABC guidelines encapsulate a high-quality, robust body of evidence endorsed by clinical leaders worldwide.***

## 4. Should "standard of care" drive PHARMAC funding decisions?

While clinical guidelines systematically integrate clinical trial evidence and real-world studies to define best treatment, they are not prescriptive, meaning that doctors usually have a range of options to choose from within the guidelines, or indeed can choose not to follow them at all.

This means there is another layer of evidence to draw on, namely, "standard of care" – current best practice as implemented in the clinical environment to treat a particular medical condition – which we believe should be considered by PHARMAC in its funding decisions.

This evidence is especially important when PHARMAC is considering medicines that are no longer included in clinical trials, or when trials take many years to produce survival data. For example, palbociclib / Ibrance (recently considered by PHARMAC), is now standard of care in other countries, as evidenced by these casual statements made in the course of presentations by experts at the recent St Gallen Breast Cancer Conference:

**Professor Dr. Sibylle Loibl, Head of the German Breast Group, Germany**
*"CDK 4/6 inhibitors [like palboclib] are well-established as a standard treatment for ER+/HER2- advanced breast cancer for both pre- and post-menopausal patients."*

**Professor Nicholas Turner, consultant medical oncologist, Royal Marsden NHS Trust, UK**
*''CDK 4/6 inhibitors in combination with endocrine therapy are now the standard of care for treating advanced ER+ breast cancer. They substantially defer chemotherapy.''*

**Professor Christoph Zielenski, Medical Oncologist, Vienna Cancer Centre, Austria:**
*"It is rapidly changing, the treatment paradigm for ER+/HER2- advanced breast cancer. We cannot imagine living without [CDK 4/6 inhibitors such as palbociclib] these days."*

Breast Cancer Foundation NZ believes that this standard-of-care evidence should be considered by PHARMAC in its funding decisions.

***"Standard of care" provides valuable data about a medicine's effectiveness and sets a real-world benchmark for treatment funding that must not be ignored. We do not believe there is clinical justification for New Zealand to sit below the standard of care delivered in Australia, UK and other comparable countries.***

## 5. Equity and ethics

PHARMAC has a stated goal of eliminating inequities in access to medicines by 2025. It identifies Medicine Availability as one of the primary drivers of inequity, and also acknowledges that it controls that driver.

| Primary drivers | Secondary drivers | PHARMAC's role |
|---|---|---|
| **Medicine availability** | PHARMAC's decision making processes for investment in medicines | Control |
| | Funding restrictions and schedule rules | Control |
| | Prescriber awareness of funded medicine(s) available | Role |

Source: https://www.pharmac.govt.nz/medicines/equity/

In addition to the lack of clinical justification mentioned above, Breast Cancer Foundation NZ does not believe it is equitable or, indeed, ethical for New Zealand to sit below the standard of care delivered in Australia, UK and other comparable countries.

Here are just two examples of inequities that dictate much poorer outcomes for Kiwis with ABC.

I. Clinical Trials

Depriving Kiwi patients of standard-of-care treatment serves them a double whammy of inequity by rendering them ineligible for clinical trials of newer medicines. For example, the criteria for the HER2CLIMB clinical trial, currently testing a new drug called tucatinib for people with advanced HER2+ breast cancer, state that patients must have "received previous treatment with trastuzumab (Herceptin), pertuzumab (Perjeta), ***and*** T-DM1 (Kadcyla)".

Those three drugs – Trastuzumab and Perjeta in the first line, and Kadcyla in the second line – are clearly considered the standard of care that all patients with HER2+ ABC will have received. However, Kadcyla isn't funded in NZ; PHARMAC has deferred a decision on Kadcyla as a second line for HER2+ patients on the grounds it needs further evidence to justify Kadcyla's use after Perjeta.

As Dr Fatima Cardoso said,

> *"I am afraid this evidence will never arrive, because [Kadcyla] studies will not be repeated to prove its efficacy after [Perjeta]. As is frequently the case in a field of constant development such as oncology, treatment standards change over time and clinical trial data may become outdated. A fair amount of common sense must exist to allow adaptation of standards and available therapies. This is not done randomly, but under the guidance of regulators (the FDA and European Medicines Agency / EMA) and of the world's experts in the field through international guidelines.*
>
> *"So, if PHARMAC wishes to wait for this evidence, New Zealanders will never receive the treatment that is standard elsewhere."*

***It is inequitable and unethical to force the exclusion of Kiwi women from clinical trials for new medicines.***

II. Continuing Herceptin after disease progression

Internationally, the real-world standard of care in ABC is for patients to continue or re-try Herceptin after their disease progresses. However, in New Zealand, PHARMAC restrictions mean Herceptin cannot be used after progression. As Dr Cardoso said,

> *"So, in other words, there is a dead-end for patients who need anti-HER2 therapy beyond the first line. And this is the reason for such an appalling survival for HER2+ advanced breast cancer patients in New Zealand (about 1 year, when they live consistently over 5 years in other developed countries)."*

This is not just a question of **equity** but also of **ethics**. Dr Cardoso noted,

> *"I suspect PHARMAC would argue that there is insufficient evidence in the form of randomised controlled trials for continuing with or returning to [Herceptin] after disease progression. There are data, albeit limited, because the Phase 3 trials designed to answer this question were stopped early,* ***due to major concerns that it was no longer ethical not to provide an anti-HER2 agent after progression on 1st line therapy.****"*

***PHARMAC's refusal to allow more flexible prescribing of already-approved medicines is inequitable and unethical.***

People with ABC also face employment and financial inequities when non-availability of new medicines forces them to rely on last-resort chemotherapy to control the spread of disease. Chemo's toxicity often forces patients to give up work before they want to and when they can't afford to, forcing further inequities onto their families. Newer medicines typically delay time to chemotherapy and, for oral medications, are much easier for patients than infusions (they also reduce pressure on busy chemotherapy suites). Patients taking these new drugs are thus more likely to be able to continue working if they wish to.

***Rather than "eliminating inequities in access to medicines by 2025", as PHARMAC states its intention, the current mechanism and criteria for funding new medicines exacerbate inequities.***

New Zealand's median survival after a diagnosis of ABC is 16 months, compared with around three years elsewhere. The ABC Global Alliance has a goal of doubling median survival by 2025, which will likely make median survival at least three times that of New Zealand: the gap will widen.

Not all of that survival improvement will come from new medicines, but a significant proportion of it is now coming from new medicines and will continue to do so. Looking at the new drug pipeline for ABC, talazoparib and atezolizumab are already FDA-approved and being prescribed internationally. Then there is a cluster of drugs still under investigation, such as tucatinib. How long before those medicines will considered, prioritised and funded by PHARMAC?

We know this is daunting, to say the least. A funding agency in a small country with limited resources to investigate new therapies – and reluctant to consider the budget increase required to raise our standard of care to international levels – must feel considerable trepidation. If it doesn't, perhaps it has underestimated the challenge.

Because the end-game here is not just a couple more years of life for people with terminal breast cancer (though that in itself more than justifies the changes we have talked about in this submission). The end-game is ABC becoming a chronic condition, one that people live with rather than die of – similar to diabetes, or HIV. Think back to the 1980s and 1990s, when HIV infection

inevitably led to death from AIDS. Researchers and clinicians refused to allow the belief that "HIV is a death sentence" to prevail and – eventually – governments and other health funders rose to the challenge, with amazing results.

New Zealand can and must rise to the same challenge for people with ABC. Already, doctors believe that a very small percentage of patients can be cured of this "incurable" condition. This percentage will increase over time, gains that will be almost entirely due to new medicines.

***If New Zealand truly wants equity for ABC patients, now is the time for PHARMAC to acknowledge the expertise of leading ABC clinicians around the world, to embrace clinical guidelines as a basis for funding decisions, and to give due consideration to real-world evidence and international standard of care.***

***Now is the time to do much, much better.***

---

**Breast Cancer Foundation NZ thanks members of the Health Select Committee for their consideration of Emma Crowley's petition and the associated evidence.**

**For further information on this submission, please contact research manager Adèle Gautier adeleg@bcf.org.nz / 021 423 353, or chief executive Evangelia Henderson evangeliah@bcf.org.nz / 021 357 900.**