25 March 2019

Ms. Louisa Wall
Chairperson
Health Select Committee

By email: Dylan.Hanna@parliament.govt.nz

Dear Ms. Wall

Re: The Petition of Terre Maize "That the House of Representatives urge the Minister of Health and Pharmac to fund Kadcyla and Palbociclib for breast cancer sufferers"

It was a pleasure to meet you at the Cancer Care at a Crossroads conference during my recent visit to New Zealand; thank you for the opportunity to provide a submission on the important issue of the need for additional therapies for New Zealanders with advanced breast cancer (ABC).

I came to New Zealand after reading the *I'm Still Here* report published by Breast Cancer Foundation NZ. The survival data in this report, showing a median survival with ABC of only 16 months, was very disturbing. These days, we expect in developed countries to have a median survival nearer to three years. Even more disturbing, survival with a specific subtype, HER2+ ABC, in New Zealand is only 15.9 months (and only 13.3 months for patients whose cancer is also ER-negative), whereas advances in anti-HER2 medications have extended median survival to more than five years for this subtype in developed countries, as shown in cancer registries in Germany and France, for example.

I was very surprised to learn of the limited range of therapies publicly funded for ABC in New Zealand, and this is not just the new medications. New drugs are never the only reason for poor survival; however we do know that survival and quality of life are linked to available therapies. Most lines of therapy for ABC are not expensive, with the exception of HER2+ ABC and the new CDK 4/6 inhibitors for ER+ breast cancer. But New Zealanders are missing out across the spectrum, as I will discuss.

T-DM1 (Kadcyla) and other options for HER2+ ABC

HER2+ ABC represents about 20% of ABC patients. This subtype is the one that has seen the most significant overall survival benefit, thanks to a range of new anti-HER2 therapies. In HER2+ ABC, to keep blocking the HER2 pathway is **the** most crucial therapy, even if with trastuzumab (Herceptin or an approved biosimilar) alone. Yet I see that in New Zealand there is no possibility to block the HER2 pathway beyond the first line of treatment for ABC, not even continuing trastuzumab beyond 1st line.

It is most common these days for patients to have trastuzumab (Herceptin) and pertuzumab as a first-line treatment. Typically, when their cancer progresses on this treatment, they will be given **T-DM1 (Kadcyla, also known as trastuzumab emtansine) in the second line**. I am aware that PHARMAC has recommended T-DM1 with a medium priority as a second-line treatment for a "diminishing" pool of patients who were not given pertuzumab in the first line, but has deferred a

decision on T-DM1 as a second line for the majority of HER2+ patients "pending further evidence to support its use in this setting."

I am afraid this evidence will never arrive, because T-DM1 studies will not be repeated to prove its efficacy after pertuzumab. 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.

In the absence of T-DM1 (Kadcyla), what will be the options for these patients when their disease progresses? Internationally, the real-world standard of care is for patients to continue or re-try trastuzumab (Herceptin). However, in New Zealand this drug is not allowed to be used after progression on an earlier anti-HER2 therapy. 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).

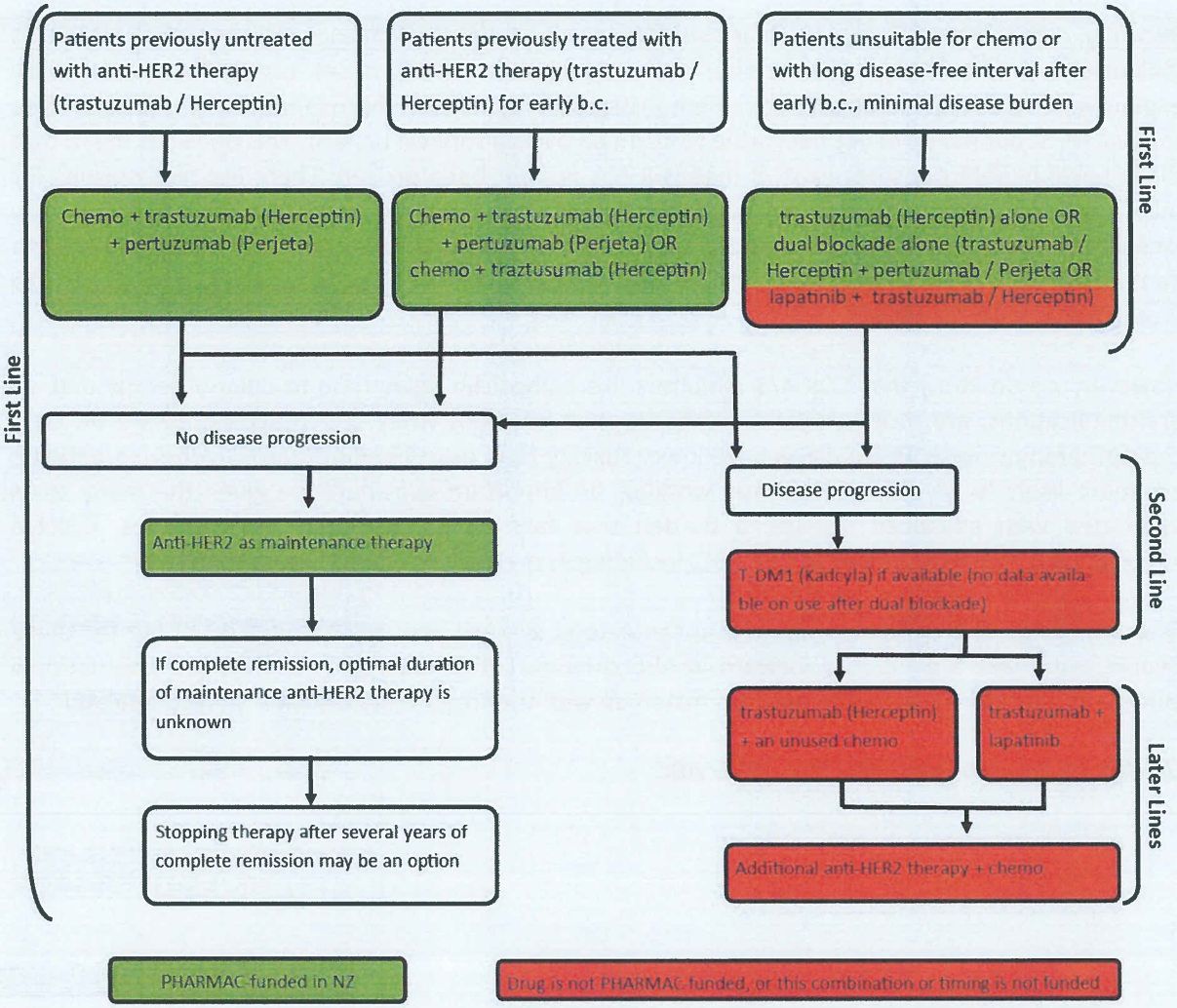
I suspect PHARMAC would argue that there is insufficient evidence in the form of randomised controlled trials for continuing with or returning to trastuzumab after disease progression. There are data, albeit limited, because the Phase 3 trials designed to answer this question were stopped early, due to major concerns that it was no longer ethical not to provide an anti-HER2 agent after progression on 1st line therapy. The reason is because disease progression and death are much faster, if we do not continue to block the HER2 pathway.

Clinical trials underway now have moved on from these questions; a very important proof of my statements is that the FDA and EMA now demand that the eligibility criteria for clinical trials for the next wave of anti-HER2 therapies specify that patients **must** have had both pertuzumab and T-DM1 (Kadcyla) in previous lines of treatment (so New Zealand patients would never be eligible to join these trials). In addition, the control arm of these new trials (which are for patients who have already had several lines of therapy) is trastuzumab (Herceptin) in combination with a chemotherapy agent, i.e. the control patients will be going **back** to trastuzumab, which they are not able to do in New Zealand. This reinforces that the **standard treatment is continuing trastuzumab for several lines of therapy, in combination with different chemo or endocrine therapy agents.**

These options (T-DM1 and continuing trastuzumab) are included in the international guidelines for treatment of HER2+ ABC, both the ASCO and NCCN (USA) guidelines and the ESO-ESMO ABC4 (European/International) guidelines.

Here is what those guidelines look like, and where the treatment options currently funded for New Zealanders with ABC sit within them.

Guidelines for people with HER2+ / ER- ABC



Note that all patients will eventually have disease progression; as I noted earlier, the median survival for these patients in NZ, without access to second and third line anti-HER2 treatment, is 13 months. The picture with regard to anti-HER2 therapy for patients with ABC that is HER2+ / ER+ is the same, but those patients do have hormone therapies as well, to target the ER+ aspects of their disease.

CDK 4/6 inhibitors (palbociclib / ribociclib / abemaciclib) and other options for ER+ ABC

Patients with oestrogen receptor positive (ER+) breast cancer (about 70% of ABC patients in NZ) have three kinds of treatment available to them. Endocrine therapies (e.g. tamoxifen, aromatase inhibitors and fulvestrant) are not expensive and are the treatment of choice for this subtype of breast cancer. The recommendation is that several lines of endocrine-based therapy are given before going to chemotherapy. Chemotherapy is also cheap (with only a few exceptions) and is reserved for patients with extensive symptomatic disease or rapid progression, or when all endocrine therapies have been used.

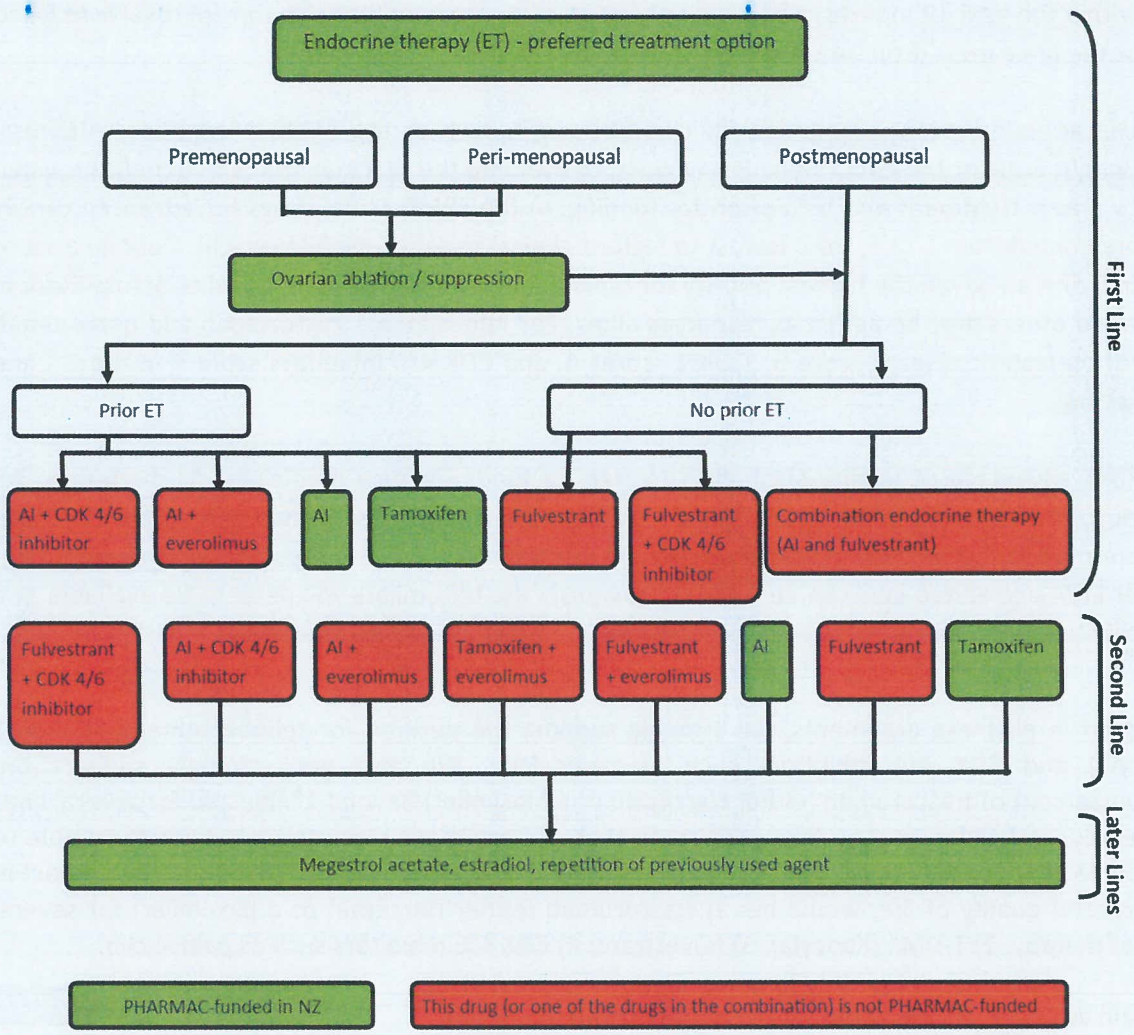
I was very surprised to learn that fulvestrant, which has been around for a long time, is very efficacious and is not very expensive, is not funded in New Zealand. This is a very valuable therapy in the oncologist's toolkit. It delays the use of chemotherapy and is very well tolerated, with only minor side effects.

Recently, other targeted drugs, such as everolimus and a new class of drugs called CDK 4/6 inhibitors (palbociclib / ribociclib / abemaciclib) were developed. These drugs are unfortunately very expensive. The CDK4/6 inhibitors have demonstrated a significant improvement in progression-free survival (PFS) but have not yet been able to claim an overall survival benefit. This does not mean that the survival benefit does not exist, it means it has not yet been proven. There are two reasons for this: it is much harder to prove a statistically significant OS benefit for such a large and generally longer-surviving patient group. Secondly, the trials of these drugs were not sufficiently powered to demonstrate overall survival benefit. It will most probably take a future meta-analysis of all trials to prove this survival benefit.

However, we do know that CDK 4/6 inhibitors like palbociclib delay time to chemotherapy and, as oral medications, are much easier for patients than infusions (they also reduce pressure on busy chemotherapy suites). These drugs have lower toxicity than most chemotherapy agents, so patients are more likely to be able to continue working, an important consideration given the many costs associated with advanced disease, a burden that falls on patients and their families. CDK4/6 inhibitors are now widely used in ER+ ABC, including in my own clinic.

Given the large ER+ patient group, if you can extend survival and improve quality of life for these people, you make a giant step forward in ABC survival. Let us look again at how the international guidelines for patients with ER+ patients match up with the treatments available in New Zealand.

Guidelines for Treatment of ER+ / HER2- ABC



Prioritising drugs for funding in the absence of Level 1 randomised clinical trial evidence

As I have explained, 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.

So, how can you make a decision as to how to prioritise limited resources? This problem is not unique to New Zealand. Here are some things you could consider.

1. Accept international guidelines such as ABC4, which reflect real-world clinical practice, as evidence of efficacy of a new medicine or of different applications for a medicine in the cancer treatment pathway. After all, patients in routine clinical practice are often very different from a clinical trial population, and measuring real-world results will increasingly become how we quantify the ongoing benefits of therapies.

2. Consider more creative ways to provide early access to medications, while penalising the pharmaceutical companies if their products do not live up to the hype. For example, in Germany they have a system where new drugs are made temporarily available based on PFS benefit, but

within the next 12 months, a survival benefit must be proven otherwise the approval is revoked or the price must drop substantially.

3. Use an independent assessment of clinical benefit, such as the ESMO Magnitude of Clinical Benefit Scale or the ASCO Value Framework, to evaluate the real magnitude of benefit provided by a new treatment and help prioritize funding. In the ESMO scale, drugs for advanced cancer are graded from 1 to 5, from lowest to highest clinical benefits. Medicines which obtain a score of 5 or 4 are given the highest priority for rapid endorsement by national bodies across Europe, while others may be added as resources allow. For information, trastuzumab and pertuzumab for metastatic disease score 5, T-DM1 scores 4, and CDK 4/6 inhibitors score 4 in the 2nd line setting.

4. Take advantage of quality biosimilars to free up funds for new medicines. As medicines like Herceptin have come off patent, biosimilars have been developed, tested and approved. These are more complex than a simple generic like paracetamol, but the ones that are made in FDA- or EMA-accredited labs can be trusted. Obviously the biosimilars will need to be available at a substantially lower price to bring an advantage to health funding authorities.

Based on in all these arguments, we strongly support the petition for reimbursement of T-DM1 (Kadcyla) and CDK 4/6 inhibitors such as palbociclib. We also very strongly support the reimbursement of trastuzumab (either Herceptin or a biosimilar) beyond 1st line and for several lines of therapy, and of fulvestrant. We understand that, for economic reasons, you may not be able to reimburse all these agents at once. For that reason, my suggested priority, based on their impact in survival and quality of life, would be: 1) trastuzumab (either Herceptin or a biosimilar) for several lines of therapy; 2) T-DM1 (Kadcyla); 3) fulvestrant; 4) CDK 4/6 inhibitors such as palbociclib.

I remain available for any additional information you may need.

Yours sincerely

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Chair, ABC Global Alliance and ABC Guidelines
ESMO Board of Directors & Director of Membership
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