Application for changes to the Pharmaceutical Schedule

A guide to help people, clinicians, clinical groups and consumer groups prepare funding applications to PHARMAC

Foreword

PHARMAC is the government agency that decides, on the behalf of District Health Boards, which pharmaceuticals should be publicly fund in New Zealand. For more information on the process PHARMAC uses to make its funding decisions and how we determine if a proposal to fund a treatment would help us achieve our Statutory Objective, please visit the PHARMAC website.

PHARMAC's objective is "to secure, for eligible people in need of pharmaceuticals, the best health outcomes that are reasonably achievable from pharmaceutical treatment and from within the amount of funding provided".

Each year, PHARMAC receives a large number of applications that contain proposals either to fund new pharmaceuticals or to widen access to pharmaceuticals that we already fund. As PHARMAC must work within a fixed budget, we need to make difficult choices about which applications we should progress to a funding decision at any given time. This involves assessing large amounts of often complex information, to identify those proposals that would provide the best health outcomes.

We have written this funding application form for people, clinicians, clinical groups and consumer groups to use. We recognise that some individuals and groups won't have the same resource as pharmaceutical suppliers to prepare applications. This form is to help you provide the right information in order to progress the application.

This form is a guide – you don't have to follow it in detail, or at all, but it will make processing your application much easier and may reduce the time involved. If you don't know some information, please feel free to leave those sections blank; however the form does outline the general information that we need to assess a funding application. Having your application address these points may reduce follow-up questions to you, and could speed up how quickly we consider it.

The *Guidelines for Funding Applications to PHARMAC*, updated in 2015, set out the full information that we need to progress any funding application. We expect pharmaceutical suppliers to follow the full *Guidelines for Funding Applications to PHARMAC* when submitting a funding application. However, as an applicant, please feel free to view them should you wish to have more detailed information on submitting an application.

Send your applications to us at:

Email: **applications@pharmac.govt.nz**

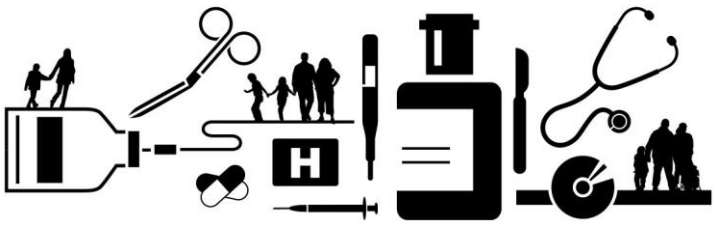
Post: **PO Box 10254**
The Terrace
Wellington 6143

You may also find it beneficial to talk to the relevant Therapeutic Group Manager at PHARMAC before you make a formal funding application. Please email us as above, and we will contact you.

We will keep you informed of progress. We publish and regularly update a record of all current funding applications via the Application Tracker on our website (**www.pharmac.govt.nz**), which details the current status of applications and relevant PTAC and subcommittee minutes.

Please note:

- We need you to supply copies of referenced articles that support the application, wherever possible. Have them referenced in the relevant section of the application form, and clearly say which (if any) cited publications you cannot provide.
- We prefer funding applications related to medicines that have been registered by Medsafe. While we can consider funding applications for unregistered medicines or unregistered indications, this is determined on a case–by-case basis.
- We may decide to defer our assessment of your application until we receive a full funding application from the supplier, which they would need to prepare in accordance with the full *Guidelines*.



PHARMAC
Pharmaceutical Management Agency

New Zealand Government

Applicant

Name

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Department & DHB, practice or organisation

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Are you making this application on behalf of a wider group (department, society, special interest group)? If so, who?

Breast Cancer Aotearoa Coalition (BCAC)

Is there anyone else that we should contact if we have questions about specific parts of this application?

No

Proposed pharmaceutical

Chemical

palbociclib

Presentations and strengths

Capsules 75mg, 100mg, 150mg

Brand name(s)

IBRANCE®

Suppliers (eg pharmaceutical companies, wholesalers)

Pfizer NZ Ltd

Price

Individual patients are currently paying around $6,000 per month for treatment in New Zealand (1-6). The annual cost of treatment with both palbociclib and fulvestrant in the private sector is $60,000-$80,000 per year. People accessing medication (Ibrance) from Malaysia are paying about $3,000 per month (7, 8).

Is it registered by Medsafe?

IBRANCE is indicated for the treatment of hormone receptor (HR) positive, human epidermal growth factor receptor 2 (HER2) negative locally advanced or metastatic breast cancer:
• in combination with an aromatase inhibitor;
• in combination with fulvestrant in women who have received prior endocrine therapy (9).

This submission is for the second indication listed above i.e. in combination with fulvestrant for those who have received prior endocrine therapy. It should be noted that fulvestrant is not currently subsidised in New Zealand. Listing of fulvestrant on the Pharmaceutical Schedule has been requested on a number of occasions, most recently in a submission by BCAC in May 2018. As indicated in the May 2018 submission, the registration for fulvestrant has lapsed.

Describe the indication(s) that funding is being sought for.

Treatment of people with hormone receptor positive advanced breast cancer who have failed prior endocrine therapy.

We understand that a submission was made in early 2018 by the sponsor, Pfizer, for the listing of palbociclib in combination with an aromatase inhibitor for first line treatment of advanced breast cancer.

An application was also made to PHARMAC by BCAC for listing of fulvestrant in May 2018.

This current submission seeks that both palbociclib and fulvestrant be listed on the Pharmaceutical Schedule for people with advanced breast cancer who have failed previous endocrine therapy. BCAC believes this group is significantly disadvantaged and in critical need of further treatment options.

If this pharmaceutical has been registered by Medsafe, is it licenced for these indications? If not, is it licenced for these indications overseas? Please provide details.

Yes, palbociclib is registered by Medsafe as indicated above.

Fulvestrant registration has lapsed as indicated in our previous submission. In the EU, the approved indication for fulvestrant (Faslodex®) is

- as monotherapy for the treatment of oestrogen receptor positive, locally advanced or metastatic breast cancer in postmenopausal women: - not previously treated with endocrine therapy, or - with disease relapse on or after adjuvant antioestrogen therapy, or disease progression on antioestrogen therapy.
- in combination with palbociclib for the treatment of hormone receptor (HR) positive, human epidermal growth factor receptor 2 (HER2) negative locally advanced or metastatic breast cancer in women who have received prior endocrine therapy. In pre- or perimenopausal women, the combination treatment with palbociclib should be combined with a luteinizing hormone releasing hormone (LHRH) agonist (10).

How many people in New Zealand do you expect would receive the pharmaceutical?

We estimate that about 150 people would receive the pharmaceutical annually – however this is dependent on any restrictions (if any) that might be recommended for access to treatment. In addition, there might be more patients in the first year of listing, reflecting prevalence of patients with advanced breast cancer who currently have run out of treatment options.

What is the expected dosing?

The recommended dose is 125 mg of palbociclib once daily for 21 consecutive days followed by 7 days off treatment (Schedule 3/1) to comprise a complete cycle of 28 days. Treatment should be continued as long as the patient is deriving clinical benefit from therapy or until unacceptable toxicity occurs. When coadministered with palbociclib, the recommended dose of fulvestrant is 500 mg administered intramuscularly on Days 1, 15, 29, and once monthly thereafter.

Prior to the start of treatment with the combination of palbociclib plus fulvestrant, and throughout its duration, pre/perimenopausal women should be treated with an LHRH agonist according to local clinical practice.

Patients should be encouraged to take their dose at approximately the same time each day. If the patient vomits or misses a dose, an additional dose should not be taken that day. The next prescribed dose should be taken at the usual time.

Dose modification of IBRANCE is recommended based on individual safety and tolerability. Management of some adverse reactions may require temporary dose interruptions/delays, and/or dose reductions, or permanent discontinuation as per dose reduction schedules provided in the Datasheet.

IBRANCE is for oral use. It should be taken with food, preferably a meal to ensure consistent palbociclib exposure. Palbociclib should not be taken with grapefruit or grapefruit juice (see section 4.5). IBRANCE capsules should be swallowed whole (should not be chewed, crushed, or opened prior to swallowing). No capsule should be ingested if it is broken, cracked, or otherwise not intact (9).

What is the likely duration of treatment, if patients respond to treatment?

The median progression free survival in the group who received the combination of palbociclib and fulvestrant in the PALOMA-3 clinical trial was 9.2 months (95%CI 7.5-not estimable) (11). Duration of treatment will be dependent on stage of disease and other prognostic factors as well as response to treatment and adverse effects. In the PALOMA-3 trial, 4% of patients in the palbociclib/fulvestrant group discontinued treatment due to adverse effects of treatment (11).

Describe the setting that this pharmaceutical would be used in. Is the need for this this treatment limited to a hospital setting, or is it also required in the community? If in hospital, is it theatre only, on medical wards, or in outpatient clinics?

Administered orally therefore can be used in the outpatient setting. Fulvestrant is administered by intramuscular injection and would also be administered in the outpatient setting.

If this is a new pharmaceutical, are there likely to be other uses for it?

As already stated, use as first line treatment (in conjunction with letrozole), based on the PALOMA-2 trial (12) was the subject of an application to PHARMAC by the sponsor, Pfizer, in February 2018.

Treatment initiation

Is treatment with the pharmaceutical started empirically? If so, please describe the symptoms, signs or other features necessary to initiate therapy.

Diagnosis of HR positive advanced breast cancer (including locally advanced and metastatic disease) that has progressed after at least one line of therapy.

Are there any specific tests needed to confirm diagnosis? If so, please name these tests, and say whether these are currently performed routinely, where they take place, and whether they are funded.

Imaging, laboratory testing.

Should other therapies have been used prior to starting treatment with this pharmaceutical? If so, which?

First line endocrine therapies such as tamoxifen or an aromatase inhibitor would have been administered previously. This could be for early breast cancer or advanced disease. Patients who have had prior chemotherapy should not be excluded from treatment as patients who had previous chemotherapy in the PALOMA-3 clinical trial showed a statistically significant benefit with treatment (11).

Treatment initiation

Treatment continuation

How would treatment success be defined or measured?

Patients would be treated until disease progression or death.

What is the average length of treatment required before determining treatment response?

The median time to response in the PALOMA-3 trial for the palbociclib/fulvestrant treatment group was 112 days (11).

What other interventions would be needed in the event of treatment-related adverse events?

Dose interruption, cycle delay or dose reduction may be required for management of adverse events. In the PALOMA-3 trial, 54% of patients had dose interruption, 36% had cycle delay and 34% of patients had dose reduction while on combined treatment with palbociclib and fulvestrant.

Prescribing and dispensing

Should initiation of this therapy be limited to certain prescriber types? If so, please explain why.

Medical oncologist

If starting this therapy was limited to certain prescriber types, would it be appropriate for ongoing prescribing to be managed by a wider group of prescribers? If so, who?

There could be ongoing administration in the general practice setting with oversight by a medical oncologist.

Are there any other issues that PHARMAC should be aware of in relation to the administration of this pharmaceutical, such as infusion time, compounding requirements or safety issues?

No

Health need

Please include full citation details of supporting evidence (eg randomised controlled trials) and attach copies of any cited publications.

What is the health need of people with the indication(s) for which funding is sought? Please include details of whether reduced life expectancy could be expected or details of potential loss of quality of life including the cause of this loss.

Health need

Median survival after a diagnosis of metastatic / advanced breast cancer in New Zealand is 16 months, considerably worse than overseas (13). Survival varies greatly by subtype, from 27.3 months for Luminal A patients down to 6.6 months for triple negative breast cancer. One and five-year survival rates are also worse in New Zealand than overseas, with the gap widening in recent years (13). The 5 year survival rate is 15% for European women and only 5% for Māori women in New Zealand (13).

Perspectives provided by patients with advanced breast cancer (in italics) provide some insight into the health need for treatment in the New Zealand context (1-8, 14-21). A diagnosis of advanced breast cancer has a profound effect.

"Living with metastatic breast cancer is tough. I have tried to maintain a life as close to normal as possible. I work, I take my children to sports events, and encourage them with their homework. I catch up with friends, I try to be a positive partner to my loving husband, I push memories of the old me who used to be physically strong and adventurous to the back of my mind. Instead I set smaller goals and dream of all the places I want to travel to .... but because of this terrible disease my world is getting smaller now." (7)

"I still cry a little most days over my situation. I also laugh, find joy each day and try to stay in the moment. My oncologist said to me last time that to look at me you would never know! I said I hide it well! The ongoing cycle of scan, treat, repeat is emotionally and physically exhausting, but when I feel I can't do it anymore, I look at my husband and sons and suck it up." (17)

Is there an unmet health need in the populations that may potentially receive benefit from this treatment? If so, please explain.

Although there have been improvements in rates of survival over the past decades, New Zealand still lags behind equivalent countries (22). BCAC and its member groups are extremely concerned about the poor access to treatments in New Zealand for people with metastatic breast cancer.

Although the treatment goals in advanced breast cancer remain palliative in nature, access to a wider range of treatments, that are aimed at controlling symptoms, improving or maintaining quality of life and prolonging survival is needed in New Zealand.

New Zealand patients have access to limited therapies for advanced breast cancer compared with their international counterparts, which is thought to contribute to the poor duration of survival in New Zealanders with advanced breast cancer (13). For people who have metastatic breast cancer, extension of, and quality of, life are key priorities.

BCAC believes that there is a significant unmet health need in patients with metastatic breast cancer for a greater range of funded treatment options. The combination of palbociclib and fulvestrant would be a possible option for people who have already had treatment with first line endocrine therapies – these patients currently have limited options for treatment.

Are there sub-populations within these populations that have a higher health need?

Māori and Pacific women have poorer survival from breast cancer overall and are more likely to be diagnosed with metastatic disease as well as having more co-morbidities (23-25). A recent report from the University of Waikato and the Health Research Council of New Zealand paints a bleak picture of the health outcomes particularly in Māori and Pasifika women with breast cancer. Māori women have the highest breast cancer incidences in the world; 28% higher than NZ European women (117.2 vs 90.6 per 100,000). Māori women who are diagnosed with breast cancer are 76% more likely to die from their cancer than non-Māori women (26). Māori women are more likely to have metastatic breast cancer at diagnosis and are more likely to have oestrogen and progesterone receptor positive disease (13). Therefore, this treatment may be beneficial in improving survival statistics in Māori women.

Mode of detection, age and biological factors contribute to outcomes for Pasifika women with breast cancer (26).

Socioeconomic deprivation is associated with poorer outcomes in breast cancer and women treated publicly have poorer survival than those treated privately (26). Women from lower socioeconomic groups are also more likely to have co-morbid conditions, present with advanced disease and be treated in the public sector resulting in more serious disease, less optimal treatment and suboptimal outcomes (26).

Women who receive public care (versus private care) have a significantly higher risk of mortality from breast cancer (crude HR 1.95, 95%CI 1.75-2.17). After controlling for differences in demographic factors, the mortality risk is still 56% higher in women who receive public care versus private care (26).

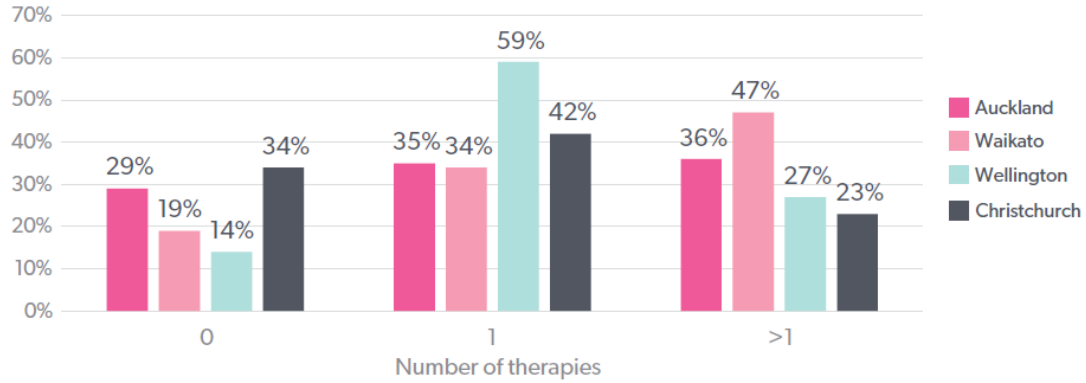
Health need

What are the treatments that patients with these indications currently receive, if any? Please describe the dose, duration of treatment, along with the risks and benefits associated with this treatment.

International recommendations for the treatment of advanced breast cancer indicate that the choice among different available agents as well as their sequence depends largely on which agents were previously administered and the response obtained, due to the link with endocrine resistance. For this reason, previous exposure, and not only line of treatment, should guide the recommendations (27). For example, ESMO guidelines include tamoxifen, aromatase inhibitors and fulvestrant as single therapy agents with the choice largely determined by previous exposure in the adjuvant setting. They also state that in the second-line setting, their use has been associated with a 6–7 months progression-free survival (PFS) benefit and an HRQoL improvement, and hence their ESMO-MCBS score is 4 (27).

Access to endocrine agents in New Zealand is limited, with only tamoxifen and aromatase inhibitors available. Analysis of hormone therapies received by patients with ER/PR + advanced breast cancer from the Breast Cancer Foundation NZ (BCFNZ) study found that 26% patients receive no hormone therapies at all, 37% receive 1 therapy and 37% receive >1 hormone therapy. Rates of treatment vary by region and are shown in the figure below (13). Therefore, because of the limited range of subsidised treatments, most patients are significantly disadvantaged in New Zealand compared with other equivalent countries.

Figure 41: Number of hormone therapies (ER+/PR+ patients)



Apart from hormone therapies, the other option available to New Zealand patients with advanced breast cancer is cytotoxic chemotherapy.

Are there any issues regarding the availability or suitability of existing treatments for this indication?

New drugs play a vital role in extending the lives of people with advanced breast cancer. Our healthcare professionals feel keenly the lack of publicly funded access to the latest medicines. There is also increasing emphasis overseas on continued therapy after disease progression, or re-trying a previously failed treatment, either after another treatment or in combination with another medicine. These options are often not available under NZ's current prescribing restrictions (28).

While there is limited international data about the number of lines of systemic therapy given to advanced breast cancer patients, studies suggest many patients can benefit from more than three lines of therapy. In New Zealand, only about 15% of patients have more than three systemic treatments. Few patients have metastatic biopsies that could suggest additional treatment options. Too many patients in New Zealand receive no systemic treatments at all (28).

Would the pharmaceutical replace or complement these existing treatments? Please explain.

Patients with advanced breast cancer in New Zealand receive fewer lines of therapy than do those in similar countries (13). Subsidised availability of palbociclib and fulvestrant would provide a further line of therapy to extend survival. As the PALOMA-3 study investigators point out, patients in this population might otherwise be given cytotoxic chemotherapy which may cause greater toxicity and reduced quality of life. Access to subsidised treatment with this combination could therefore delay or replace the need for cytotoxic chemotherapy.

Does this indication disproportionately affect any populations that may already be experiencing a health disparity?

Health need

Māori and Pasifika women have a higher risk of mortality from breast cancer compared to other ethnic groups. Late diagnosis, deprivation and differential access to cancer care services are key contributors to ethnic disparities (26). There are significant differences in the proportion of advanced and metastatic breast cancer cases at diagnosis by ethnicity, socioeconomic status and region.

"My mental battles are "if Ibrance was $70/month we could afford it. If it were $700/month perhaps my family could take turns helping, but at $7k/month who in my Pacific world would ever afford that?" (15)

There are also disparities in publically and privately treated patients, indicating that those in low socioeconomic groups, who already have poorer health outcomes, are more likely to die from advanced breast cancer. Rural Māori women also have poorer outcomes than their urban counterparts (26).

"I am immensely grateful and sheepishly aware of my privilege in that my mother has drawn on life savings and is paying for these drugs. It's an uncomfortable reality that the lack of funding for Ibrance puts a barrier between those of us with breast cancer who can access the outrageously expensive drugs and those who can't. It's demeaning to have to hustle and struggle for drugs such as Ibrance that promise precious time with loved ones." (7)

Is there an unmet health need in other people due to the indication, such as in people who care for or live with those with the indication, or from spread of disease?

Health need

Families and whānau are integral to the patient's life journey at this stage of disease and family members are affected negatively by the impact of a loved one having advanced breast cancer. This is manifested as increased stress and worry (5, 16, 29).

"My family are all affected by this. The stress and anxiety felt by them has a big impact on their ability to function normally so it is not just the patient who needs medical intervention, but the whole family."(16)

"The family are affected and upset as they see a loved one in pain, and knowing there is nothing they can do to help." (19)

"Having metastatic breast cancer has affected my health and quality of life significantly by limiting my lifespan and influencing my decisions regarding many aspects of my life, including ongoing employment. Members of my family are also affected by their concern for me, and by their awareness that I may not live long enough to participate in significant milestones in their lives."(5)

"Despite being in relatively good shape, the cancer affects every decision we make. It's always there, hanging over us. My husband suffers from chronic depression, a condition which has worsened since my diagnosis. My friends and family worry about me; if I am unwell, everyone panics. It does affect the whole family, as well as my friends and coworkers."(20)

"My parents, who are in their 80s, have been devastated by my diagnosis, just as I am devastated at the thought of the pain that it inflicts on them, and on my husband and children." (3)

"My elderly parents don't want to bury their own daughter, and are quite traumatised by what I am going through, and I am still very involved in their care. That's the thing about a woman my age, we are so valuable, and at the crux of family life at both ends of the spectrum. We are the lynchpins of families, and all the while still productive members of society." (6)

The emotional health and development of children and adolescents in the family are negatively affected. Extension of a parent's life and better symptom control during that period can all contribute to a child's ability to cope with their parent's situation.

"Cancer changed our status overnight from being a partner/wife to patient/carer. For the most part of the last 2 years, we struggled as the shared responsibilities for kids and household became his solely. It was and still is a big adjustment for him mentally, emotionally and physically having to care for 3 people in every way." (15)

The stresses of living with terminal disease and struggling to manage symptoms are compounded by financial difficulties, which in turn limit patients' ability to manage symptoms. The cost of GP visits becomes a major financial burden when patients no longer have regular hospital appointments; inability to afford appointments means patients don't get the symptom relief they need. People with advanced breast cancer and their families face a huge financial burden, which is with them for the rest of their lives. Three-quarters of people with advanced breast cancer have had a decline in household finances; nearly half say their situation is "a lot worse" (13).

"The mental pain & suffering – the financial & emotional stress. The constant worrying about can I afford to not keep working, can I afford to live like I used too? What happens when my funded options no longer work – should I be trying to save for that day? How can I save for that day when I no longer can work? Do I re mortgage the house so I can afford a drug that will give me more time with my children, my husband? Do I use the life savings to live another year or 2 or 3? How will my family survive after I die? Is the question their life or mine? The family should not have to ask that either, the pressure is immense to all." (19)

Health benefits and risks in the indication(s) for which funding is sought

Please include full citation details of supporting evidence (eg randomised controlled trials) and attach copies of any cited publications.

Discuss the potential benefits from treatment with the pharmaceutical compared with current treatment options (if any).

As indicated earlier, many patients in New Zealand with advanced ER+/PR+ breast cancer do not have access to further lines of hormonal therapy because of the limited range of treatment classes being funded currently. Funded options currently include aromatase inhibitors and tamoxifen or non-specific treatment such as cytotoxic chemotherapy.
"I am currently trying to balance parenting and full time work with all the side effects that come with surgery and chemo. These are not just the physical changes, nausea and fatigue, but the mental struggles that come with a stage 4 diagnosis, particularly at my stage in life. This has had a massive impact on both me and my children." (2)

Only patients able to self-fund have access to fulvestrant or other treatments. Access to further lines of therapy is important as these can be utilised to extend survival. The BCFNZ study showed that the number of lines of therapy correlates with survival as shown in the table below.

Table 10: Survival by number of hormone therapies (ER+/PR+ patients)

	0	1	>1
Median survival	10.4 (6.8, 13.9)	17.3 (14.1, 21.3)	36.4 (30.2, 40)
One-year survival	45% (37, 53)	61% (54, 67)	85% (80, 89)
Five-year survival	10% (6, 16)	17% (12, 23)	29% (23, 35)

The main clinical evidence for the use of palbociclib in the treatment of patients with advanced breast cancer comes from the PALOMA-3 clinical trial. In this Phase III trial, the combination of palbociclib and fulvestrant was compared in a double-blind randomised controlled trial with fulvestrant and placebo. It is important to note when considering the clinical significance of these results that fulvestrant is not the current standard of care in New Zealand. As BCAC's submission in May 2018 requesting the funding of fulvestrant on the Pharmaceutical Schedule, the availability of fulvestrant would represent an improved standard of care to that currently available in New Zealand, particularly for people who have failed existing therapies.

PALOMA-3 (NCT01942135) evaluated the palbociclib and fulvestrant versus placebo and fulvestrant in 521 patients >18 years of age with advanced hormone receptor (HR) positive, HER 2 negative breast cancer that had relapsed or progressed during prior endocrine therapy. The study was conducted at 144 sites in 17 countries (Australia, Belgium, Canada, Germany, Ireland, Italy, Japan, Korea, Netherlands, Portugal, Romania, Russia, Taiwan, Turkey, UK, Ukraine and USA). Patients were randomly assigned in a 2:1 ratio to receive palbociclib and fulvestrant or placebo and fulvestrant. Premenopausal or perimenopausal women also received goserelin. The primary end point was investigator-assessed progression-free survival. Secondary end points included overall survival, objective response, rate of clinical benefit, patient-reported outcomes, and safety (11, 30-35).

PALOMA-3 – Publication of Interim Analysis – Data cutoff 5 Dec 2014- Turner et al. 2015
As reported in the first publication by Turner et al. in the NEJM in 2015, the pre-planned interim analysis was performed by an independent data and safety monitoring committee after 195 events of disease progression or death had occurred. The median progression-free survival was 9.2 months (95% CI 7.5 to not estimable) with palbociclib-fulvestrant and 3.8 months (95% CI, 3.5 to 5.5) with placebo-fulvestrant (HR for disease progression or death, 0.42; 95% CI, 0.32 to 0.56; $p<0.001$).

The most common grade 3 or 4 adverse events in the palbociclib-fulvestrant group were neutropenia (62.0%, vs. 0.6% in the placebo-fulvestrant group), leukopenia (25.2% vs. 0.6%), anaemia (2.6% vs. 1.7%), thrombocytopenia (2.3% vs. 0%), and fatigue (2.0% vs. 1.2%). Febrile neutropenia was reported in 0.6% of palbociclib-treated patients and 0.6% of placebo-treated patients. The rate of discontinuation due to adverse events was 2.6% with palbociclib and 1.7% with placebo.

It was concluded that, among patients with hormone-receptor positive metastatic breast cancer who had progression of disease during prior endocrine therapy, palbociclib combined with fulvestrant resulted in longer progression-free survival than fulvestrant alone (33).

PALOMA-3 – Final Analysis – Data cutoff 16 March 2015- Cristofanilli et al. 2016

By March 16, 2015, 259 progression-free-survival events had occurred (145 in the fulvestrant plus palbociclib group and 114 in the fulvestrant plus placebo group); median follow-up was 8.9 months (IQR 8.7-9.2). Median progression-free survival was 9.5 months (95% CI 9.2-11.0) in the fulvestrant plus palbociclib group and 4.6 months (3.5-5.6) in the fulvestrant plus placebo group (HR 0.46, 95% CI 0.36-0.59, p<0.0001).

Grade 3 or 4 adverse events occurred in 251 (73%) of 345 patients in the fulvestrant plus palbociclib group and 38 (22%) of 172 patients in the fulvestrant plus placebo group. The most common grade 3 or 4 adverse events were neutropenia (223 [65%] in the fulvestrant plus palbociclib group and one [1%] in the fulvestrant plus placebo group), anaemia (ten [3%] and three [2%]), and leukopenia (95 [28%] and two [1%]). Serious adverse events (all causalities) occurred in 44 patients (13%) of 345 in the fulvestrant plus palbociclib group and 30 (17%) of 172 patients in the fulvestrant plus placebo group.

PIK3CA mutation was detected in the plasma DNA of 129 (33%) of 395 patients for whom these data were available. Neither PIK3CA status nor hormone-receptor expression level significantly affected treatment response. It was concluded that fulvestrant plus palbociclib was associated with significant and consistent improvement in progression-free survival compared with fulvestrant plus placebo, irrespective of the degree of endocrine resistance, hormone-receptor expression level, and PIK3CA mutational status.

The authors stated that the combination could be considered as a therapeutic option for patients with recurrent hormone-receptor positive, HER2 negative metastatic breast cancer that has progressed on previous endocrine therapy (11).

PALOMA-3 – Analysis of Safety – Verma et al. 2016

With palbociclib, neutropenia was the most common grade 3 (55%) and 4 (10%) adverse event; median times to onset and duration of grade >3 episodes were 16 and 7 days, respectively. Asian ethnicity and below-median neutrophil counts at baseline were significantly associated with an increased chance of developing grade 3–4 neutropenia with palbociclib/fulvestrant. Dose modifications for grade 3–4 neutropenia had no adverse effect on progression-free survival. In the palbociclib/fulvestrant arm, febrile neutropenia occurred in 3 (<1%) patients. The percentage of grade 1–2 infections was higher than in the fulvestrant/placebo arm. Grade 1 stomatitis occurred in 8% of patients. It was concluded that palbociclib plus fulvestrant treatment was well tolerated, and the primary toxicity of asymptomatic neutropenia was effectively managed by dose modification without apparent loss of efficacy (35).

PALOMA-3 – Overall Survival Analysis – Turner et al. 2018

Among 521 patients who underwent randomization, the median overall survival was 34.9 months (95% CI, 28.8 to 40.0) in the palbociclib–fulvestrant group and 28.0 months (95% CI, 23.6 to 34.6) in the placebo–fulvestrant group (HR for death, 0.81; 95% CI, 0.64 to 1.03; p=0.09; absolute difference, 6.9 months). CDK4/6 inhibitor treatment after the completion of the trial regimen occurred in 16% of the patients in the placebo–fulvestrant group. Among 410 patients with sensitivity to previous endocrine therapy, the median overall survival was 39.7 months (95% CI, 34.8 to 45.7) in the palbociclib–fulvestrant group and 29.7 months (95% CI, 23.8 to 37.9) in the placebo–fulvestrant group (HR 0.72; 95% CI, 0.55 to 0.94; absolute difference, 10.0 months). The median duration of subsequent therapy was similar in the two groups, and the median time to the receipt of chemotherapy was 17.6 months in the palbociclib–fulvestrant group, as compared with 8.8 months in the placebo–fulvestrant group (HR 0.58; 95% CI, 0.47 to 0.73; p<0.001). No new safety signals were observed with 44.8 months of follow-up. Among patients with hormone-receptor positive, HER2 negative advanced breast cancer who had sensitivity to previous endocrine therapy, treatment with palbociclib–fulvestrant resulted in significantly longer overall survival than treatment with placebo–fulvestrant. The differences in overall survival in the entire trial group were not significant (30, 34).

PALOMA-3 – Patient Reported Outcomes

This analysis compared patient-reported outcomes (PROs) between the two treatment groups. PROs were assessed on day 1 of cycles 1-4 and of every other subsequent cycle starting with cycle 6 using the EORTC QLQ-C30 and its breast cancer module, QLQ-BR23. High scores (range 0-100) could indicate better functioning/quality of life (QoL) or worse symptom severity. Repeated-measures mixed-effect analyses were carried out to compare on-treatment overall scores and changes from baseline between treatment groups while controlling for baseline. Between-group

comparisons of time to deterioration in global QoL and pain were made using an unstratified log-rank test and Cox proportional hazards model.

Questionnaire completion rates were high at baseline and during treatment (from baseline to cycle 14, >/=95.8% in each group completed >/=1 question on the EORTC QLQ-C30). On treatment, estimated overall global QoL scores significantly favoured the palbociclib plus fulvestrant group [66.1, 95% CI 64.5-67.7 versus 63.0, 95% CI 60.6-65.3; p=0.0313]. Significantly greater improvement from baseline in pain was also observed in this group (-3.3, 95% CI -5.1 to -1.5 versus 2.0, 95% CI -0.6 to 4.6; p=0.0011). No significant differences were observed for other QLQ-BR23 functioning domains, breast or arm symptoms. Treatment with palbociclib plus fulvestrant significantly delayed deterioration in global QoL (p<0.025) and pain (p<0.001) compared with fulvestrant alone.

It was concluded that palbociclib plus fulvestrant allowed patients to maintain good QoL in the endocrine resistance setting while experiencing substantially delayed disease progression (31).

Relevance of PALOMA-3 Clinical Trial Results to the NZ Context

As earlier stated, it is important to note that fulvestrant is not subsidised in New Zealand and therefore is only available to self-funding patients. BCAC's May 2018 submission requesting the listing of fulvestrant on the Pharmaceutical Schedule sought to have this option available to NZ patients. As far as BCAC is aware no decision has been made to list fulvestrant. The incremental benefit of palbociclib and fulvestrant in the New Zealand context may therefore be more substantial that demonstrated in the PALOMA-3 study. In New Zealand, advanced breast cancer patients who have failed on currently available endocrine therapies will include those who have not had access to fulvestrant (the control comparator treatment in PALOMA-3). If treated with any therapy, these patients may well be treated with cytotoxic chemotherapy which is likely to be more toxic than the combination of palbociclib and fulvestrant.

Some New Zealand Patient Perspectives

"I have been taking palbociclib and fulvestrant for the last 8 months and this has meant I have been able to delay chemotherapy enabling me to continue working as nurse specialist and continue to pay taxes. I experience minimal side effects on this treatment. The alternative for me if I wasn't on Palbociclib would be chemotherapy which would almost certainly cause debilitating side effects resulting in my having to take frequent sick leave and certainly impacting negatively on my quality of life and my ability to work as nurse specialist. I may even have had to quit my job. In the 3 years since my diagnosis I have only taken 5 days off work due to sickness." (1)

"I am now on my third cycle of Ibrance or to put it in perspective $ 17,400. I think the effect of this drug was summed up by my Oncologist after the last examination of my liver JESUS, the results have been dramatic, no side effects, I have more energy, my liver is significantly less swollen I can breathe easier and I can again feel positive, useful and independent." (4)

"Treatment with palbociclib (in combination with fulvestrant) has been effective in keeping my cancer stable, which has delayed the onset of chemotherapy treatment. Generally, I have felt well during this treatment and able to participate normally in family and community life." (5)

"My quality of life with Ibrance is fantastic- side effects are minimal and nothing given the alternative. It's worth every cent to buy me the wellness time that it is." (6)

"While on Ibrance, I was able to carry on more or less normally for that time. I had to let some commitments lapse, but was still able to carry on as a very active member of my community and be fully present in my children's lives and see two of them through high school and into university."(8)

"This drug is the one shining light that we have in getting me to see out my parents' final years, spending time with my family making memories and continuing to work and contribute as a tax payer to the community." (21)

Discuss the potential risks from treatment with the pharmaceutical compared with current treatment options (if any).

Risks associated with palbociclib and fulvestrant

As reported by Verma et al. (2016) in their detailed safety analysis of the PALOMA-3 clinical trial, the adverse effects that were commonly associated with the palbociclib and fulvestrant combination included haematological adverse effects such as neutropenia, leucopoenia, thrombocytopenia and anaemia. These were observed at significantly higher rates with palbociclib/fulvestrant than with fulvestrant/placebo. Although grade 3–4

neutropenia occurred in 221 (65%) of 340 patients in the palbociclib arm, febrile neutropenia was reported in only 3 (0.9%) patients in the palbociclib/fulvestrant arm and 2 (0.6%) of 172 patients in the placebo/fulvestrant arm. During study treatment, 39 (11%) patients in the palbociclib arm received G-CSF on the basis of the investigator's judgment. Palbociclib-induced neutropenia was reversible and can be readily managed by dose delay, dose interruption, or dose modification without affecting efficacy. With close monitoring of the complete blood count, particularly early on during treatment, dosing can be optimised and ongoing treatment can be administered while minimising the risk for clinically significant AEs (35).

Infections, fatigue, stomatitis, rash, decreased appetite, pyrexia, nausea, diarrhoea and vomiting were observed in >10% of the study population in the palbociclib/fulvestrant treatment arm. There was a higher incidence of all-grade infections in the palbociclib/fulvestrant arm (42%) than in the fulvestrant/placebo arm (30%); however, infections were mainly grade 1–2 in severity. The frequency of grade 3–4 events was similar between treatment arms (2% and 3%, respectively) (35).

It should be noted that the improved efficacy, coupled with the favourable safety profile of palbociclib plus fulvestrant, was also reflected in patient-reported outcome data, which demonstrate that patients were able to maintain quality of life during treatment, whereas patients treated with placebo plus fulvestrant experienced a deterioration of their quality of life (31).

Risks associated with Current Treatments

There are a range of other treatment options including "no treatment", other hormone therapies and cytotoxic chemotherapy. Obviously, treatment with palbociclib/fulvestrant would have treatment-related adverse effects that would not be experienced by people having no treatment. Compared with current hormone therapies, which are monotherapies, there would be a higher rate of haematological adverse effects with palbociclib/fulvestrant treatment. Compared with cytotoxic chemotherapy, the consequences of myelosuppression experienced during palbociclib treatment are different from those associated with chemotherapy-induced myelo-ablation, which is characterised by a more acute onset of neutropenia and a prolonged suppression of all cell lines. Chemotherapy-induced neutropenia is a well-known cause of complications, such as febrile neutropenia and infections, which may be life-threatening. Febrile neutropenia is not commonly associated with palbociclib, likely owing to the shorter duration and lesser severity of neutropenia compared with chemotherapy (35).

"I am now in need of palbociclib (Ibrance) which I expect would give me another 2 years of normal life and will allow me to continue working. If I don't have access to Ibrance, I will be forced to have chemotherapy and will have to stop working. I will have to spend time in hospital receiving treatment, will lose my hair, be exhausted for months and likely spend further time in hospital due to infections."(16)

"Since I stopped taking Ibrance, I have now moved onto capecitabine. It has had much harder side effects, but mostly a fatigue that has meant that I can only operate out and about for a couple of hours at a time. Instead of the cancer being there mostly in the background while I get on with life, as it was for the past two years, I feel like it is now the centre of everything. I can't make plans, I let people down, I miss my children's events and from one day to the next I don't know what, if anything, I'll be able to manage. The contrast with Ibrance couldn't be more profound and I am very grateful that I had that good two years on Ibrance, when my children were younger." (8)

Are there sub-populations that have higher potential benefits or risks? If so, please describe.

Univariate analysis of PALOMA-3 showed that Asian ethnicity and below median absolute neutrophil count conferred a significantly greater risk for developing Grade 3-4 neutropenia in the palbociclib arm

Would this treatment provide any health benefits or risks to any people beyond the individual who was receiving treatment? If so, what benefits or risks would result?

Benefits to others include improved quality of life for the patient being reflected in less stress and worry for family and whanau who are the primary carers. Extended life and manageable quality of life in the patient with advanced breast cancer help eliminate the stress and worry in family and whānau members. Public provision of the treatment will lessen the financial burden and stress for those families who currently must decide whether, and how, to raise funds to cover the cost of treatment. There are no additional risks for family and whānau.

"Being able to take Palbociclib, gives me hope of continuing to raise my children, enjoy life with my husband, and hopefully even return, in some way to my work." (3)

"The longer I can stay alive and feel well, without serious treatment side effects, the longer I can participate in family life and contribute as a mother, grandmother, sister, aunt, mother-in-law. And the less worry and disruption I will cause to family members." (5)

"I am the Mum who with Pharmac's help can be a Mum to my children for longer. I can continue to be here to read, cook, cuddle, protect and love for longer. I can have more time to prepare my babies to face the world without their Mum." (14)

How would funding the pharmaceutical result in other measurable benefits or risks to the health sector, eg changes in number of surgeries, hospitalisations, nursing time, diagnostic tests?

Compared with cytotoxic chemotherapy, this treatment is far less likely to result in use of outpatient facilities such as chemotherapy outpatient clinics and in hospital admissions.

Suitability

Please include full citation details of supporting evidence (eg randomised controlled trials) and attach copies of any cited publications

Are there any features of the treatment that may impact on its use (eg method of delivery, size, shape, taste)? If so, please explain.

This is an oral treatment, therefore suitable for use on an outpatient basis. An injection of fulvestrant must be administered monthly by the intramuscular route.

Costs and savings

Please include full citation details of supporting evidence (e.g. randomised controlled trials) and attach copies of any cited publications

Would the funding of this treatment create any costs or savings to the health system (eg would treatment require increased monitoring, or would it free up clinician time)?

Compared with chemotherapy, this treatment would free up time in outpatient hospital facilities as cancer centres, and this would result in savings in oncologists, nurses, allied health workers and others' time.

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