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Mind the gap: An analysis of foregone health gains from unfunded cancer medicines in New Zealand

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ABSTRACT

Publicly funded cancer medicines listed on the New Zealand Pharmaceutical Schedule were compared with those listed on the Australian Pharmaceutical Benefits Scheme. To quantify the health gains offered by the cancer medicines funded in Australia but not in New Zealand, clinical trial data reporting median progression-free survival (PFS) and overall survival (OS) were sought. The differences in the median PFS and OS for the unfunded medicines, relative to the comparator medicine funded in NZ, were then assessed against the American Society of Clinical Oncology Cancer Research Committee (ASCO-CRC) recommended targets for clinically meaningful health gains. Our analysis confirms that, whilst New Zealand funds fewer cancer medicines than Australia, most of the additional medicines funded in Australia do not deliver clinically meaningful health gains as defined by the ASCO-CRC guidance. This suggests that New Zealand is not missing substantive opportunities for improvements to New Zealand's cancer survival rates through additional medicines funding. A policy of funding more new cancer medicines in order to achieve numerical parity with Australia or other countries would not result in substantive health improvement and would cost significantly more, and investing the millions of dollars needed to achieve funding parity with other countries would not represent good value for money in terms of delivering the best health outcomes for all New Zealanders, rather selective funding of new medicines that demonstrate clear clinical benefit and that are cost-effective and affordable is the sensible approach.

1. Introduction

The Pharmaceutical Management Agency, or PHARMAC, is the government agency that decides which medicines are publicly funded in New Zealand. PHARMAC is charged with ensuring that New Zealand obtains the best health outcomes from funded pharmaceuticals from within the amount of funding provided [1]. It is therefore interested in understanding whether its funding decisions enable access to the right mix of medicines to achieve that goal.

Pharmaceutical industry–funded reports frequently provide comparisons of medicines funded by various countries national healthcare systems [2–5], with some painting a picture of funded medicines access in New Zealand being low and slow. The authors of such reports usually draw their conclusions by counting the number of medicines funded in each country, or the time taken to fund them from regulatory approval, but rarely do they explore the value of the unfunded medicines in terms of their health benefits, risks, affordability, and likely impact on population health outcomes, including consideration of opportunity cost (alternative medicines or health services that the same funding could purchase). Some reports suggest that access to fewer cancer medicines in New Zealand results in worse population health outcomes. A recent example written by Medicines New Zealand [6], the New Zealand Pharmaceutical Industry association, argued that the observed lower cancer survival rate in New Zealand compared

A preliminary analysis comparing Australian and NZ cancer medicine funding at the cut-off date of 25 March 2015 was presented at the New Zealand Society of Oncology (NZSO) Meeting in October 2015, a report of these finding was also published on PHARMACs website http://www.pharmac.govt.nz/assets/cancer-comparisons-summary-2015-10-03.pdf. A short presentation of some of the analyses contained in this paper, cut-off date of 30 April 2016, was presented at the NZSO Meeting in October 2016.

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with Australia [7] was likely the result of differences in funding of cancer medicines between the two countries. We were interested in exploring this further by asking the question whether achieving numerical parity with Australia for funded cancer medicines would make a clinically meaningful impact on cancer outcomes for New Zealand.

Health benefits offered by new cancer medicines may range from marginal (progression-free survival [PFS] improvement of only a few weeks or less, with no effects on overall survival [OS]) to substantial and clinically meaningful (improved long-term OS of several months or more).

Most new cancer medicines are developed and marketed on the basis of clinical trial data showing *statistically* significant improvements in length of life or time to disease progression over placebo or a comparator treatment. However, in many cases, the *absolute* health gains for patients from these medicines are small, coupled with prices that are increasingly disproportionate to the small benefits provided [8–10]. A recent analysis by Howard and colleagues showed that the average launch price of new cancer medicines, adjusted for inflation and survival benefits, had increased 10% annually over the last decade, up US $8,500 each year [11]. This price inflation far outweighs the survival benefits offered by these new medicines with the estimated price per year of life in 1995 being $54,100, rising to $139,100 in 2005 and $207,000 by 2013. One example of disproportional pricing is in colorectal cancer; although new medicines have indeed improved outcomes for patients with metastatic disease, nearly doubling the median survival time from 12 to 21 months, this gain has come at a 340-fold increase in cost [12].

The rising cost of cancer medicines, and the impact on healthcare systems and patients, has been debated in many countries including the United States. Some US hematologists and oncologists have strongly asserted that the health gains offered for some new cancer medicines do not justify their premium costs, leading to decisions not to prescribe them [13–16] and recommendations to consider the so-called “financial toxicity” new medicines place on patients [17]. In countries with universal publicly funded healthcare the rising cost of medicines threatens the sustainability of these systems, risking budget overspend and diversion of funding away from other, more cost-effective health interventions [18,19].

In response to this increasing trend of higher pricing and more marginal health gains, the American Society of Clinical Oncology (ASCO) and the European Society for Medical Oncology (ESMO) have developed tools to help prescribers determine the value of the health benefits offered by new medicines [20,21]. The ASCO Cancer Research Committee (ASCO-CRC) also recently published recommended targets for clinically meaningful PFS and OS gains for new cancer treatments [22]. These targets were developed with broad input and diverse points of view by working groups comprising pancreas, breast, lung, and colon cancer experts including clinical investigators, biostatisticians, patient advocates, US Food and Drug Administration (FDA) oncologists, and industry oncologists.

PHARMAC uses its Factors for Consideration [23], previously Decision Criteria [24], which include, amongst other things, consideration of health need, benefits and risks, value for money and affordability to determine the relative importance (rank) of its various funding options and inform its funding decisions. Like many other public medicines funding bodies internationally, PHARMAC uses cost utility analyses (CUAs) to estimate the value-for-money, or cost effectiveness, of new medicines in terms of cost per quality-adjusted life-year (QALY). However, such analyses are complex to perform and can be highly imprecise, or biased, where the evidence base from clinical trials is limited or confounded, for example by cross-over of patients from the comparator arm to the intervention arm. Thus, relying on cost-effectiveness analyses alone to drive funding decisions through use of explicit cost-effectiveness thresholds as some public funding bodies do, is problematic. PHARMAC uses cost-effectiveness analyses to provide information on the relative value of one medicine funding choice compared with other funding choices. When used this way to deliver information regarding relative value, or rank, rather than trying to derive an absolute value, the impact of poor quality or biased clinical trial evidence is less critical. Using cost-effectiveness this way is also less resource intensive, in many cases simple models can be used with the impact of various inputs tested through sensitivity analyses, thus resource can be focussed on the few key inputs that impact the model outputs, and other inputs that don’t substantially change the output can be largely ignored.

However, when used in isolation cost-effectiveness analyses, whichever way they are used, do not address the issue of opportunity cost and affordability of new medicines. PHARMAC’s national fixed budget for medicines ensures that it fully considers the opportunity cost and affordability of new medicines when making its funding decisions. PHARMAC ranks new medicines as options for investment taking into account its Factors for Consideration, a process that ensures that funding for the most valuable and affordable medicines is progressed. However, having a fixed budget means that not all new medicines can be funded as health demands exceed ability to pay. Health gains may need to be foregone in some disease settings in order for PHARMAC to deliver on its objective of providing the best health outcomes from medicines for all New Zealanders from the available funding.

To describe the population health gains foregone from unfunded cancer medicines, PHARMAC commissioned research comparing funded cancer medicines in New Zealand and Australia. To understand whether any funding gap would likely be substantively contributing to New Zealanders’ poorer cancer outcomes compared with Australia, we considered whether the non-funded cancer medicines would deliver clinically meaningful health gains for patients or not. Australia was selected as the comparator because of cultural proximity, readily available medicines funding information, and its reportedly superior cancer survival rates compared with New Zealand [7]. For reasons of geographic proximity, along with population ties between the two countries, it is also often quoted in New Zealand as the most obvious comparator country.

2. Method

The Australian Pharmaceutical Benefits Scheme (PBS) [25] and the New Zealand Pharmaceutical Schedule [26] were queried to identify publicly funded cancer medicines as of April 30, 2016. Analyses were performed to identify the medicines and their funded indications in cancer that were the same in both countries as well as those funded in one country and not the other.

To describe the health gain expected from the medicines funded only in Australia and not in New Zealand, we sourced clinical trial data reporting PFS and OS for each of the Australian funded indications for these medicines from the Australian Product Information (PI) document. We selected PFS and OS as the most appropriate measure of health gain as these are standard, internationally recognised cancer endpoints widely used in comparative clinical trials to quantify health benefits.

PFS is defined as the time from randomisation (ie, when a patient is enrolled into a clinical trial) until cancer disease progression or death. OS is defined as the time from randomisation until death from any cause [27]. The Australian PI document was chosen as the primary source document for PFS and OS data.

Table 1
Summary of ASCO-CRC recommended targets for meaningful clinical trial goals.

Cancer type	Patient population	Improvement in PFS that would be considered clinically meaningful (mo)	Improvement in OS that would be considered clinically meaningful (mo)
Breast cancer	Metastatic triple negative, previously untreated for metastatic disease	4	4.5–6
Colon cancer	Disease progression with all prior therapies (or not a candidate for standard second or third-line options)	3–5	3–5
Lung cancer	Non-squamous cell carcinoma	4	3.25–4
	Squamous cell carcinoma	3	2.5–3
Pancreatic cancer	Fit patients (eligible for FOLFIRINOX)	4–5	4–5
	Less fit patients (eligible for Gemcitabine or gemcitabine / nab-paclitaxel)	3–4	3–4
Lower and Upper range across cancer types		**3–5**	**2.5–6**

Source: adapted from Ellis et al, 2014 [22]

The PI provides information about the quality, safety and effectiveness of the medicine and summarises the primary data used by the pharmaceutical company to gain regulatory approval. It contains information about the design and results of clinical trials as well as the indications for use of the medicine, and forms the basis of the therapeutic claims that can be made for the medicine by the pharmaceutical company. We searched the Australian Register of Therapeutic Goods [28] to identify relevant PI documents for each medicine. We also conducted an online search for relevant clinical trial data reported in peer-reviewed academic journals; where PI and journal articles reported different results for the same trial we used the PI as the primary data source.

We focused on comparative clinical trials that reported median PFS and OS gains for the new medicine compared with a New Zealand–funded alternative and calculated the median gain for each medicine. In some cases, the clinical trial data in the PI reported time to progression (TTP) data instead of PFS. In such cases, we used TTP as a substitute for PFS because both measures focus on time to disease progression, with TTP only differing from PFS in that it does not include deaths from non-cancer causes. Where multiple studies were reported with different indications or comparators, we selected the study that best reflected the Australian-funded indication and the relevant funded comparator in New Zealand. Where more than one such study was reported we used data from the study reporting the greatest gains for the Australian-funded treatment. Where no evidence was available from clinical trials with an appropriate New Zealand–funded comparator, we undertook an adjusted indirect comparison with common comparator using the Bucher method [29] to estimate the median gain relative to the New Zealand–funded comparator.

Our benchmarks for determining whether the medicines provided clinically meaningful health gains for patients were drawn from the recommendations of the ACSO-CRC [22]. Table 1 summarizes these recommendations. The recommended incremental gains defined as clinically meaningful across the cancer types considered ranged from the lowest to highest targets of 3.0 to 5.0 months, respectively, for PFS, and 2.5 to 6.0 months for OS.

We then assessed the PFS and OS gains for the cancer medicines we identified as being funded in Australia, but not New Zealand, against these targets to determine which would deliver clinically meaningful gains for patients.

3. Results

We identified 124 cancer medicines listed on the Australian PBS and 102 listed on New Zealand's Pharmaceutical Schedule at the analysis date of April 30, 2016. Eighty-nine were funded in both countries, with 35 funded exclusively in Australia and 13 funded exclusively in New Zealand, as shown in Fig. 1.

Fig. 2 outlines how the final set of cancer medicines for our analysis was derived. Clinical trial data reporting median PFS or OS gains relative to comparator treatments were available for 26 of the 35 cancer medicines funded in Australia but not in New Zealand. Nine medicines were excluded because no comparative clinical trial data reporting median PFS or OS gains were reported (fotemustine, combination goserelin with bicalutamide, nilutamide, degarelix, idarubicin capsules, ponatinib, brentuximab, trastuzumab subcutaneous, and rituximab subcutaneous).

Table 2 summarizes the final set of 26 cancer medicines analysed, their Australian-funded indication(s) and describes the source clinical trial for the PFS and OS data used and the New Zealand–funded comparator treatment. Nineteen medicines had a single indication funded in Australia and seven were funded for two indications each. For two medicines, OS data were available but PFS data were not reported, and for four medicines PFS was available but OS was not reported. For three medicines (axitinib, trametinib, and pembrolizumab), clinical trial data with a New Zealand–funded comparator were not available, necessitating adjusted indirect comparison analysis being performed (comparators being placebo for axitinib, dacarbazine for trametinib, and dacarbazine for pembrolizumab).

Table 3 presents the clinical trial PFS and OS outcome data reported for each of the 26 Australian-funded medicines, for each of their 33 funded indications, together with PFS and OS outcome data of their New Zealand–funded comparator treatments. Table 3 also shows the calculated PFS and OS gains relative to the comparator treatment for each medicine and the median PFS and OS gain across the group of medicines.

Fig. 3 presents the reported median PFS health gains for each of the Australian-funded cancer medicines relative to the New

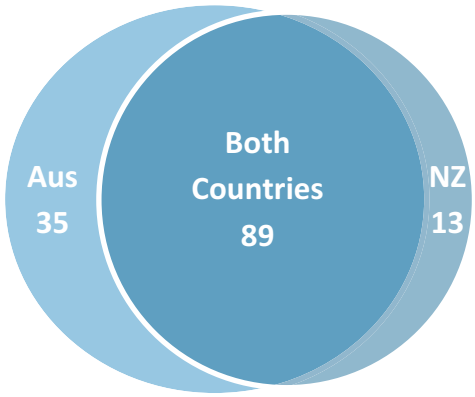


Fig. 1. Number of cancer medicines funded in Australia and New Zealand at April 30, 2016. Source: Australian Pharmaceutical Benefits Scheme and the New Zealand Pharmaceutical Schedule accessed April 30, 2016.

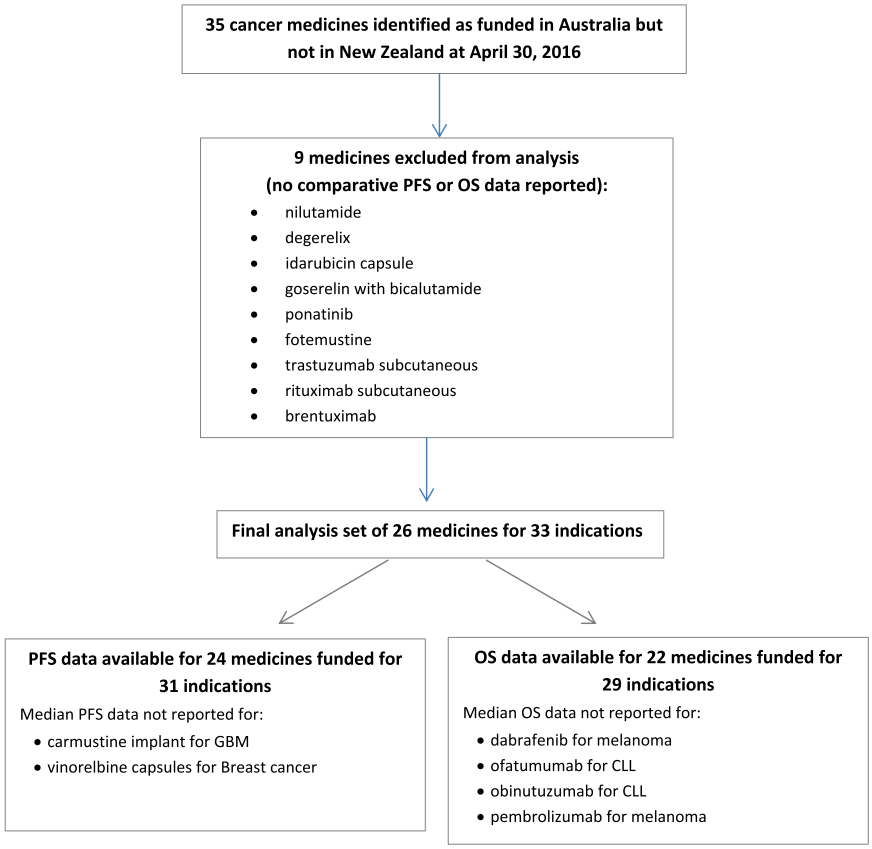


Fig. 2. Flow chart for deriving set of cancer medicines for foregone health gain analysis.

Zealand–funded comparator. These gains are ranked from the largest on the left to those that offer PFS losses on the right.

Fig. 3 also illustrates the relationship between the reported PFS gains and the ASCO-CRC working groups' clinically meaningful PFS targets. Green bars represent the gains that met or exceeded the ASCO-CRC upper target for clinically meaningful PFS health gain (PFS gain of 5 months or more), orange bars represent gains that fell below the upper target but met or exceeded the lower target ($\geq$3 months to $<$5 months), and red bars those that fell below the lower target ($<$3 months).The thresholds for clinically meaningful gains are also illustrated represented by horizontal lines.

Similarly, Fig. 4 presents the median OS gains relative to the New Zealand–funded comparator and their relationship with the ASCO-CRC targets for lower and upper clinically meaningful OS gain (green $\geq$6 months; orange $\geq$2.5 months to $<$6 months; red $<$2.5 months).

The median PFS and OS gains across all 26 cancer medicines were 2.2 and 2.6 months, respectively.

Three (12%) of the 26 cancer medicines reported both PFS and OS gains that would clearly be considered clinically meaningful, meeting the upper targets recommended by the ASCO-CRC (cetuximab for squamous cell head and neck cancer, pertuzumab for HER2-positive metastatic [stage IV] breast cancer in combination with trastuzumab, and trametinib for unresectable stage III or stage IV malignant melanoma in combination with dabrafenib). The majority of the medicines, 17 of 26 (65%), failed to meet the lowest clinically meaningful target for either PFS or OS gains, with seven medicines (27%) failing to meet the lowest target for both PFS and OS. Five (19%) of the 26 medicines provided either no health gain at all, or worse, health *losses* (a negative PFS or OS gain) when compared with the New Zealand–funded alternative.

Thirteen of the 26 medicines included in the final analysis set were funded for one of more of the specific cancer types considered by the ASCO-CRC working groups (breast, colon, lung, or pancreas). Figs. 5A and 5B outline the PFS and OS gains for these medicines relative to the specific targets recommended for each of the four cancer types (as outlined in Table 1). Only one of these 13 medicines (8%) exceeded the recommended upper target for clinically meaningful gains for both PFS and OS (pertuzumab for breast cancer), with the majority of the medicines, 10 of 13 (77%), failing to meet the lower minimum clinically meaningful targets for PFS or OS gains.

We also undertook an analysis of the correlation between PFS and OS gains for the 21 cancer medicines for 27 indications that had clinical trial data reported for both PFS and OS gains.

Fig. 6 plots the PFS and OS gains for the 27 indications (for 21 medicines) identified. Fig. 7 superimposes OS changes (gains or losses) beyond PFS gains. Linear correlation between PFS and OS gains was low, with a correlation coefficient of 43%, and many (15 of 27) medicine/indications had OS gains that were different from PFS gains by more than $\pm$1 month. This suggests, in this sample of 21 cancer medicines funded in one country and not another, that the extent of PFS gain is not a strong predictor of commensurate gain in OS.

4. Discussion

Our work describes the population health gains that may be foregone due to differences in public funding of cancer medicines between New Zealand and Australia. Such an analysis is possible within cancer, where the health benefits of new medicines are consistently supported by clinical trials that report standard progression-free survival and overall survival health outcome measures. Formal comparisons of the health benefits of treatments in or across other disease settings typically require more complex

Table 2
Cancer medicines identified for analysis.

#	Medicine name	Summary of indication(s) funded in Australia	Clinical trial name [source] - trial description	Comparator treatment
1	Raltitrexed	Advanced colorectal cancer	Trial 003 [30] - randomized, open label, phase 3	Fluorouracil and leucovorin
2	Pemetrexed	Mesothelioma in combination with cisplatin	EMPHACIS [31]- randomized, single-blind, phase 3	Cisplatin
		Locally advanced or metastatic non-small cell lung cancer (NSCLC) following prior platinum based chemotherapy	Hanna et al [32]- randomized, open label, phase 3	Docetaxel
3	Vinorelbine (capsule)	Locally advanced or metastatic non-small cell lung cancer (NSCLC)	Trial 97 CA 205 [33] - randomized, open label, phase 2	IV vinorelbine
		Advanced breast cancer following failure of standard prior therapy including an anthracycline	Trial CA221 [34] - randomized, open label, phase 2	IV vinorelbine
4	Nano-particle albumin–bound paclitaxel	Metastatic breast cancer	Trial CA012-0 [35]- randomized, open label, phase 3	Paclitaxel
		Stage IV (metastatic) adenocarcinoma of the pancreas in combination with gemcitabine	MPACT [36] – randomized open label, phase 3	Gemcitabine
5	Cabazitaxel	Castration-resistant metastatic prostate cancer; previously failed treatment with docetaxel due to resistance or intolerance	TROPIC [37] – randomized, open label, phase 3	Mitoxantrone
6	Pegylated liposomal doxorubicin hydrochlorided	Metastatic breast cancer; previously failed treatment which included capecitabine and a taxane due to resistance or intolerance	Study I97-328 [38] – randomized, open label, phase 3	Doxorubicin
		Advanced epithelial ovarian cancer after a failed first-line platinum-based chemotherapy regimen	Gordon et al [39] - randomized, open label, phase 3	Topotecan
7	Panitumumab	RAS wild-type metastatic colorectal cancer in combination with first line chemotherapy, or after having failed to respond to first-line chemotherapy	PRIME study 20050203 [40] – randomized, open label, phase 3	FOLFOX
8	Cetuximab	RAS wild-type metastatic colorectal cancer in combination with first line chemotherapy, or after having failed to respond to first-line chemotherapy	CRYSTAL study (EMR 62 202-013) [41]- randomized, open label, phase 3	FOLFIRI
		Stage III, Iva, or IVb squamous cell cancer of the larynx, oropharynx or hypopharynx intolerant or contraindicated to cisplatin, in combination with radiation therapy	EMR 62 202-006 [42] - randomized, open label, phase 3	Radiation therapy
9	Ipilimumab	Unresectable stage III or stage IV malignant melanoma	CA184-024 [43]- randomized, double-blind placebo-controlled, phase 3	Dacarbazine
10	Bevacizumab	Metastatic colorectal cancer in combination with first-line chemotherapy	NO16966 [44] - randomized, double-blind placebo-controlled, phase 3	FOLFOX-4 or XELOX
		Stage IIIB, IIIC, or stage IV epithelial ovarian, fallopian tube or primary peritoneal cancer in combination with platinum-based chemotherapy	GOG-0218 [45] - randomized, double-blind placebo-controlled, phase 3	Carboplatin with paclitaxel
11	Dabrafenib	BRAFV600 mutation positive unresectable stage III or stage IV malignant melanoma	BREAK-3 [46]- randomized, open label, phase 3	Dacarbazine
12	Sorafenib	Advanced hepatocellular carcinoma	SHARP Study 100554 [47] - randomized, double-blind placebo-controlled , phase 3	Placebo
		Stage IV clear cell variant renal cell carcinoma with progressive disease following first-line treatment with a tyrosine kinase inhibitor	TARGET Study 11213 [48]- randomized, double-blind placebo-controlled , phase 3	Placebo
13	Eribulin	Locally advanced or metastatic breast cancer following failure of at least 2 prior chemotherapeutic regimens	EMBRACE study 305 [49] - randomized, open label, phase 3	Treatment of physician's choice
14	Topotecan	Advanced metastatic ovarian cancer after failure of prior therapy that includes a platinum compound	Randomised, open label, phase 3 [50]	Paclitaxel
15	Toremifene	No restriction on funding—indicated for hormone-dependent metastatic breast cancer in postmenopausal patients	Study 5/044 [51] - randomized, open label, phase 2	Tamoxifen
16	Enzalutamide	Castration-resistant metastatic carcinoma of the prostate unsuitable for, or having failed treatment with, docetaxel due to resistance or intolerance	CRPC2 (AFFIRM) study [52] - randomized, double-blind placebo-controlled , phase 3	Placebo

Table 2 (*continued*)

#	Medicine name	Summary of indication(s) funded in Australia	Clinical trial name [source] - trial description	Comparator treatment
17	Pertuzumab	Metastatic (stage IV) HER2-positive breast cancer in combination with trastuzumab and a taxane	CLEOPATRA [53]- randomized, open label, phase 3	Trastuzumab plus placebo
18	Trastuzumab emtansine	Metastatic (stage IV) HER2-positive breast cancer following pertuzumab and/or trastuzumab treatment failure	EMILIA [54] - randomized, open label, phase 3	Lapatinib plus capecitabine
19	Crizotinib	ALK-mutation positive stage IIIB (locally advanced) or stage IV (metastatic) non-small cell lung cancer	Study 1007 [55] - randomized, open label, phase 3	Pemetrexed or docetaxel
20	Pomalidomide	Multiple myeloma ineligible for stem cell transplant and having failed prior lenalidomide and bortezomib	Study CC-4047-MM-003 [56]- randomized, open label, phase 3	High dose dexamethasone
21	Ofatumumab	$CD20^+$ chronic lymphocytic leukemia in combination with chlorambucil in patients who have non-progressed disease and are inappropriate for fludarabine-based chemotherapy	COMPLEMENT 1 Study OMB110911 [57] - randomized, open label, phase 3	Chlorambucil
22	Obinutuzumab	$CD20^+$ chronic lymphocytic leukemia together with chlorambucil, previously untreated and inappropriate for fludarabine-based chemotherapy	BO21004/CLL11 [58] - randomized, open label, phase 3	Chlorambucil
23	Carmustine implant	Suspected or confirmed glioblastoma multiforme at time of surgery	Westphal et al [59] - randomized, double-blind placebo-controlled , phase 3	Placebo implant
24	Trametinib	Unresectable stage III or stage IV malignant melanoma in combination with dabrafenib	MEK115306 (COMBI-d) [60]- randomized, double-blind placebo-controlled , phase 3	Dabrafenib (indirect comparison with dacarbazine undertaken using BREAK-3 [46])
25	Pembrolizumab	Unresectable stage III or stage IV malignant melanoma negative for a BRAF V600 mutation, or positive for a BRAF V600 mutation and must have progressed following treatment with a BRAF inhibitor unless contraindicated or not tolerated	KEYNOTE 006 [61] - randomized, open label, phase 3	Ipilimumab (indirect comparison with dacarbazine undertaken using CA184-024 [43])
26	Axitinib	Stage IV clear cell variant renal cell carcinoma following first-line treatment with a tyrosine kinase inhibitor	AXIS [62]- randomized, open label, phase 3	Sorafenib (indirect comparison with placebo undertaken using SHARP Study 100554 [47])

measures, such as modelling predicted quality-adjusted life years (QALYs) extrapolated from surrogate outcomes over shorter timeframes.

We used the ASCO-CRC recommendations for this analysis as these offer internationally authoritative targets for clinically meaningful health gain developed with input from a wide range of stakeholders, including oncologists and patients. The ASCO-CRC approach is easy to understand and technically simple, without the requirement to model assumptions in the absence of direct evidence of survival gains. Other cancer specific health benefit scales are available such as the recently published ASCO Value Framework (ASCO-VF) [20] and European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) [21]. Both have similarities to the ASCO-CRC targets, the main difference being that the ASCO-VF and the ESMO-MCBS derive a score that can be used to consider the relative magnitude of health benefit that can be anticipated from new cancer medicines, whereas the ASCO-CRC work derived absolute targets for defining what would, or would not, be considered a clinically meaningful benefit. Given that both the ASCO-CRC targets and the ACSO-VF and ESMO-MCBS use the progression-free survival and overall survival gains reported from clinical trials, we expect that the conclusions reached using the different methodologies would be similar. Indeed the ESMO-MCBS publication [21] notes that the ASCO-CRC recommended targets for overall survival benefits correlate very closely with the thresholds for ESMO-MCBS score of 4–5, and the recommended targets for PFS correlate closely with the thresholds for ESMO-MCBS score of 3–4, the highest attainable when the primary outcome is PFS. We further note there have been recent concerns published regarding the ASCO-VF [63-66], culminating in recent changes to it [67].

While this analysis shows that, as at April 30, 2016, New Zealand funded fewer cancer medicines than Australia (102 *v* 124), it also shows that New Zealand has avoided funding a large number of cancer medicines that offer little or no clinically meaningful benefit for patients relative to currently funded options in New Zealand, and in some cases it has avoided funding medicines that deliver health losses.

Of the cancer medicines funded in Australia but not in New Zealand, only three medicines clearly exceed ASCO-CRC's recommended upper target for clinically meaningful gains in both PFS and OS. PHARMAC continues to assess all three of these medicines for funding, relative to other medicines for other diseases that also wait funding. At the time of writing, these medicines are a considered by PHARMAC to be lower priority for funding relative to other medicines for other diseases also waiting for funding, and thus no positive funding decision has been made for them. PHARMAC has no definitive timeframe for when its funding decisions must be made; this is because the relative priority of the various medicine funding options may change over time. The relative priority of any one medicine is dependent on the mix of other medicines being assessed at any one time; details like the amount of funding available, success of negotiations with suppliers or new clinical data can also change the relative priorities of one

Table 3
Clinical trial reported outcomes and calculated PFS and OS gains, relative to the New Zealand–funded comparator.

#	Medicine name	Abbreviated indication funded in Australia	Reported PFS (mo)			Reported OS (mo)		
			Trial subject	Comparator	Marginal gain	Trial subject	Comparator	Marginal gain
1	Raltitrexed	Colorectal*	4.8	3.6	1.2	10.1	10.2	-0.1
2	Pemetrexed	Mesothelioma*	6.1	3.9	2.2	13.3	10.0	3.3
		NSCLC	2.9	2.9	0.0	8.3	7.9	0.4
3	Vinorelbine (cap)	NSCLC	3.3	2.1	1.2	9.4	7.9	1.5
		Breast	n.r.	n.r.	n.r.	9.4	10.2	-0.8
4	Nanoparticle albumin bound paclitaxel	Breast	5.2	3.8	1.4	15.0	12.7	2.3
		Pancreatic	5.5	3.7	1.8	8.5	6.7	1.8
5	Cabazitaxel	Prostate	2.8	1.4	1.4	15.1	12.7	2.4
6	Pegylated liposomal doxorubicin hydrochloride	Breast	6.9	7.8	-0.9	21.0	22.0	-1.0
		Ovarian	4.1	4.2	-0.1	14.5	13.8	0.7
7	Panitumumab	Colorectal	10.8	7.9	2.9	27.4	20.7	6.7
8	Cetuximab	Colorectal	11.4	8.4	3.0	28.4	20.2	8.2
		Head and neck*	24.4	14.9	9.5	49.0	29.3	19.7
9	Ipilimumab	Melanoma	2.7	2.5	0.2	11.2	9.1	2.1
10	Bevacizumab	Colorectal	9.4	8.0	1.4	21.2	19.9	1.3
		Ovarian	19.1	13.1	6.0	43.8	40.6	3.2
11	Dabrafenib	Melanoma	6.9	2.7	4.2	n.r	n.r	n.r
12	Sorafenib	Hepatocellular	5.5	2.8	2.7	10.7	7.9	2.8
		Renal	5.6	2.8	2.8	19.3	15.9	3.4
13	Eribulin	Breast	3.7	2.2	1.5	13.2	10.6	2.6
14	Topotecan	Ovarian*	6.5	5.5	1.0	15.8	13.3	2.5
15	Toremifene	Breast*	5.6	5.8	-0.2	38.2	31.7	6.5
16	Enzalutamide	Prostate	8.3	2.9	5.4	18.4	13.6	4.8
17	Pertuzumab	Breast	18.5	12.4	6.1	56.5	40.8	15.7
18	Trastuzumab emtansine	Breast	9.6	6.4	3.2	30.9	25.2	5.8
19	Crizotinib	NSCLC	7.7	3.0	4.7	20.3	22.8	-2.5
20	Pomalidomide	Multiple myeloma	3.7	1.9	1.8	12.8	8.1	4.7
21	Ofatumumab	CLL	22.4	13.1	9.3	n.r	n.r	n.r
22	Obinutuzumab	CLL	27.2	11.1	16.1	n.r	n.r	n.r
23	Carmustine implant	Glioblastoma	n.r	n.r	n.r	13.9	11.6	2.3
24	Trametinib	Melanoma	*10.9*	*3.0*	*7.9*	*16.6*	*9.0*	*7.6*
25	Pembrolizumab	Melanoma	*4.1*	*2.8*	*1.3*	*n.r*	*n.r*	*n.r*
26	Axitinib	Renal	*9.5*	*2.8*	*6.7*	*19.5*	*15.9*	*3.6*
				Median gain	**2.2**			**2.6**

n.r. = data not reported; data displayed in *italics* has been derived from indirect comparison analysis using Bucher method.

* Indications that had clinical trial data that presented time-to-progression instead of PFS gains.

funding choice over the others. While no positive finding decision has yet been made for these medicines, if in the future they do become prioritised above other medicines for other diseases and funding is available they would be funded. Most of the other cancer medicines identified in this analysis are also under active consideration by PHARMAC [68].

We undertook this work in response to reports ascribing international differences in population health outcomes to simple counts of absolute numbers of publicly funded medicines [2-5]. We have found that simply having more funded medicines numerically does not necessarily lead to meaningful health gains. One limitation of our work, however, is that we excluded medicines that have at least one funded indication in New Zealand. The funded indications for these medicines may not be identical across Australia and New Zealand. There remains scope for further research to explore the health consequences of these differences. We note that in general New Zealand has fewer funding restrictions on its cancer medicines than Australia (in New Zealand, about 80% of publicly-funded cancer medicines are open listed (ie, funded for any use) compared with 10% in Australia).

It is also noteworthy that three of the medicines included in the analysis identified as not being funded in New Zealand do have alternative presentations of the active ingredient(s) that *are* funded; New Zealand funds an injectable formulation of vinorelbine, whereas Australia funds both injectable and capsule formulations. Similarly, while New Zealand funds both paclitaxel and doxorubicin, Australia funds paclitaxel and nano-particle–bound paclitaxel (nab-paclitaxel) and doxorubicin and pegylated liposomal doxorubicin (PLDH). In addition, one of the medicines included in the analysis (topotecan), has been previously funded in New Zealand but was subsequently discontinued by the pharmaceutical suppliers in New Zealand for commercial reasons unrelated to PHARMAC's activities.

Where there is some evidence of clinically meaningful benefit for a new medicine, PHARMAC must deploy its funding resources across all diseases to obtain the best health outcomes for the population, guided by its Factors for Consideration. We estimate the cost to the Australian government of funding all of the 26 cancer medicines for the 33 indications identified in this analysis to be approximately AUD $600 million per annum [69]. In New Zealand terms, funding all of these medicines to achieve funding parity with Australia would cost approximately NZD $130 million per annum (using 0.9145 as the average AUD/NZD exchange rate over past 12 months and NZ's population being 19.3% that of Australia's) [70]. This is more than New Zealand currently spends on all of its 102 funded cancer medicines for its population of around 4.7 million people.

Based on health gains alone, a case for funding most of medicines we identified (17 of 26) cannot be made. These medicines failed to meet even the lowest clinically meaningful target for either PFS or OS gains, compared with currently funded medicines in New Zealand; five provide worse health outcomes, with their clinical trials evidence showing accelerated time to disease progression or death. The estimated cost of funding these five medicines in New Zealand would be approximately $10 million per year based on current Australian prices

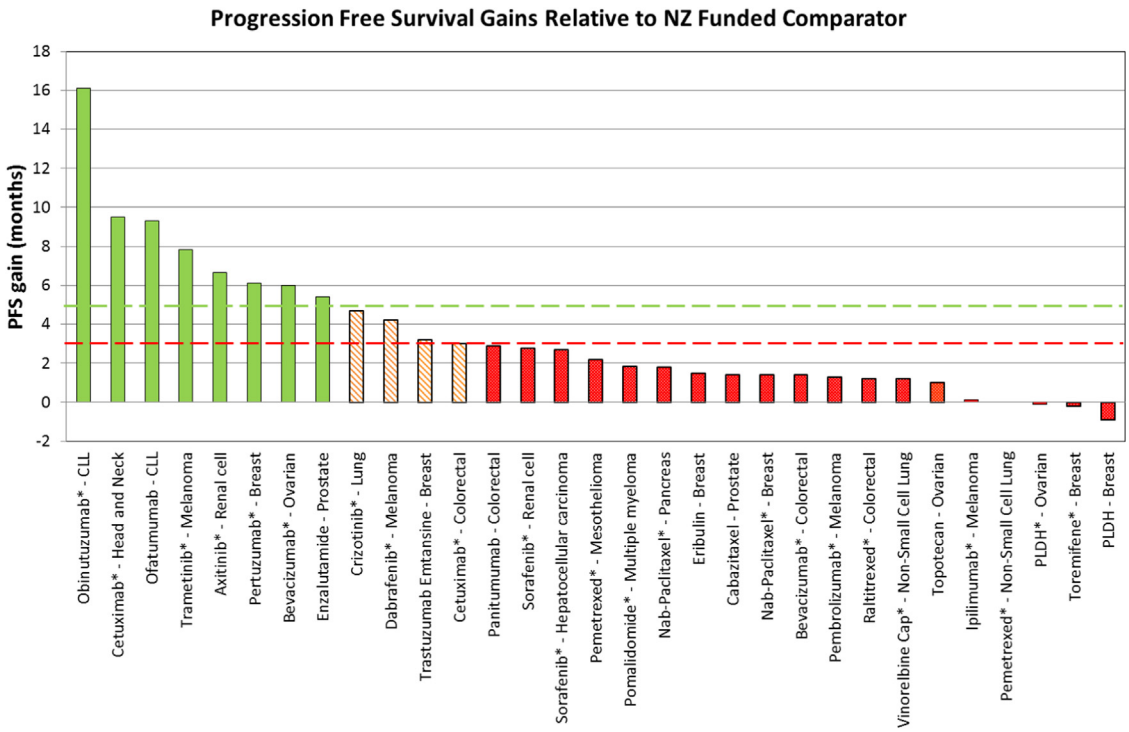


Fig. 3. PFS gains foregone for medicines funded in Australia but not in New Zealand. Medicines marked with an asterisk (*) have been assessed by PHARMAC and either remain under assessment for funding or have been declined by PHARMAC, http://www.pharmac.govt.nz/patients/ApplicationTracker. Green bars represent the gains that met or exceeded the ASCO-CRC overall upper target for clinically meaningful PFS health gain (PFS gain of 5 months or more), orange striped bars represent gains that fell below the upper target but met or exceeded the lower target ($\geq$ 3 months to $<$ 5 months), and red spotted bars those that fell below the lower target ($<$ 3 months). Horizontal dashed lines represent the thresholds for the upper and lower targets of 5 months and 3 months, respectively.

and volumes, and the clinical trial evidence shows that they would have a negative impact on New Zealand's overall cancer survival and disease progression outcomes compared with the status quo.

Although many new cancer treatments may meet the regulatory standards for marketing approval, ie, show statistically significant health gains in a clinical trial setting, the magnitude of these gains are often small and in many cases cannot be

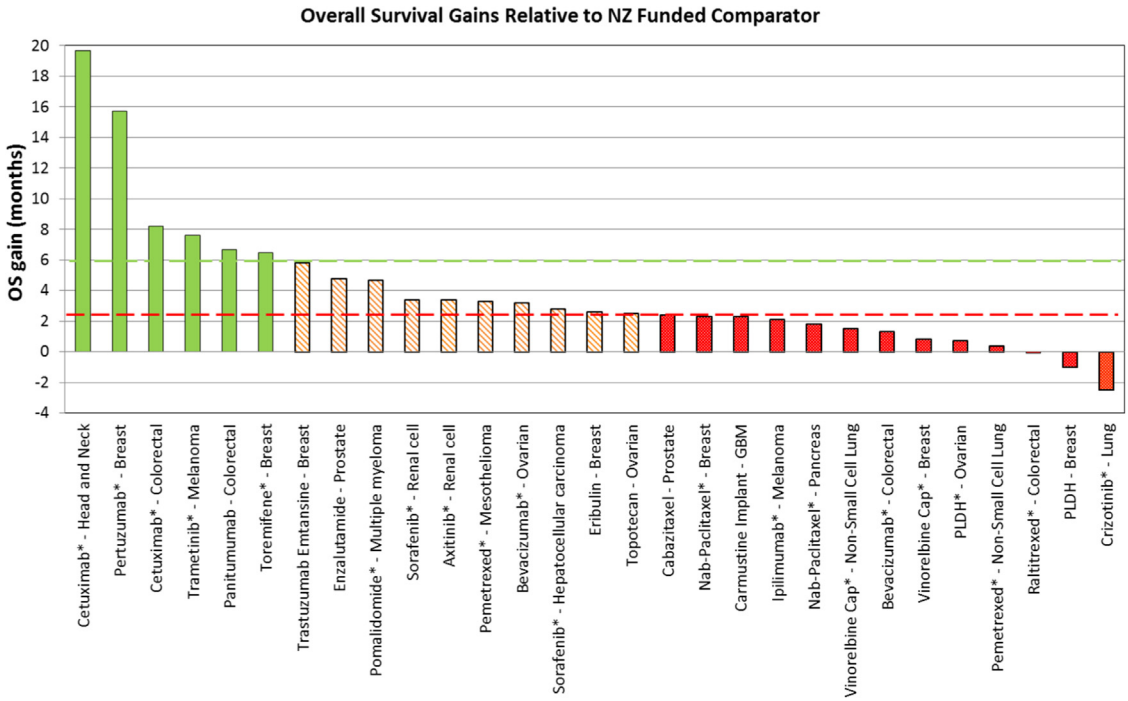


Fig. 4. OS gains foregone for medicines funded in Australia but not in New Zealand. Medicines marked with an asterisk (*) have been assessed by PHARMAC and either remain under assessment for funding or have been declined by PHARMAC, http://www.pharmac.govt.nz/patients/ApplicationTracker. Green bars represent the gains that met or exceeded the ASCO-CRC overall upper target for clinically meaningful OS health gain (OS gain of 6 months or more), orange striped bars represent gains that fell below the upper target but met or exceeded the lower target ($\geq$ 2.5 months to $<$ 6 months), and red spotted bars those that fell below the lower target ($<$ 2.5 months).

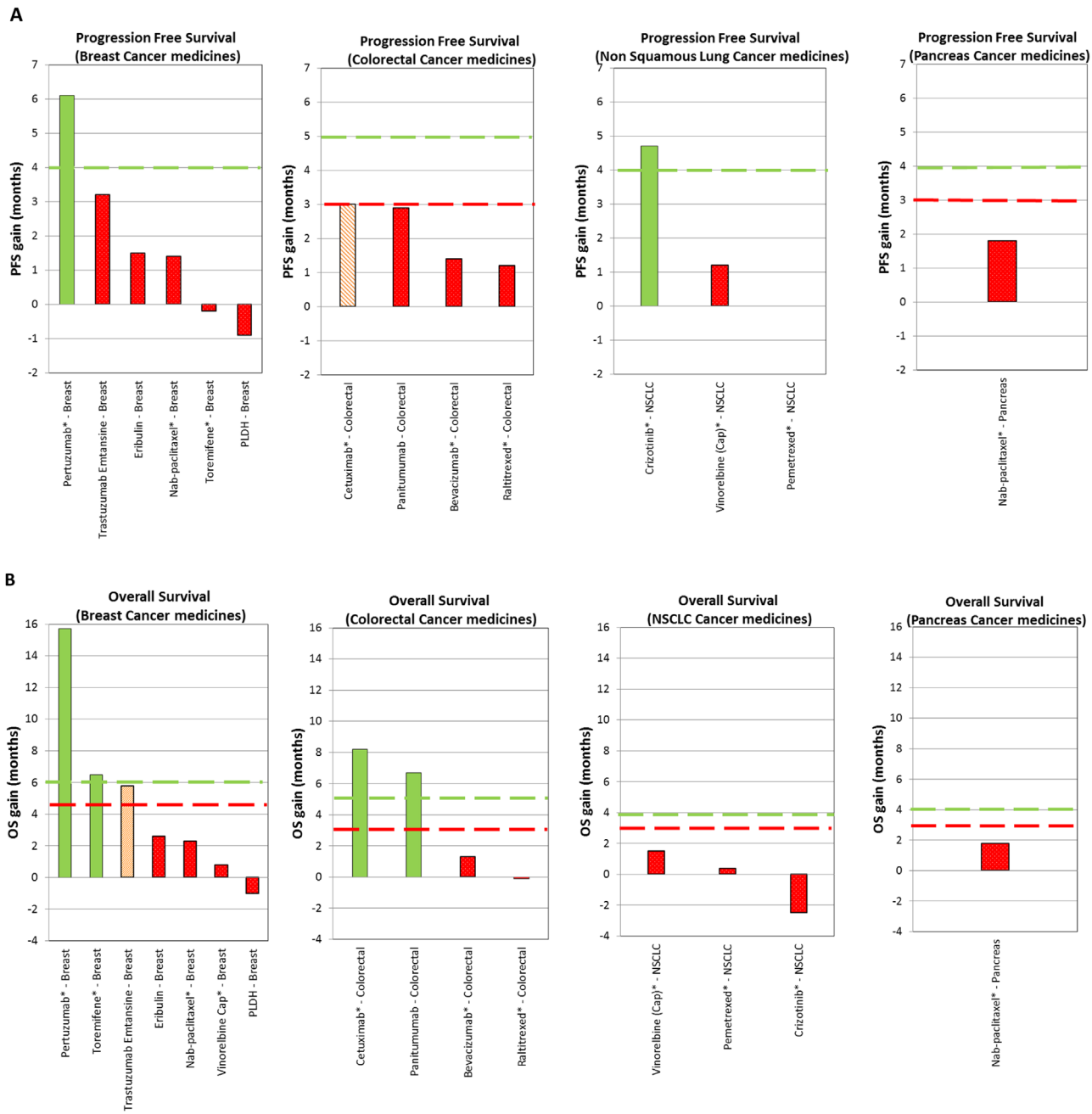
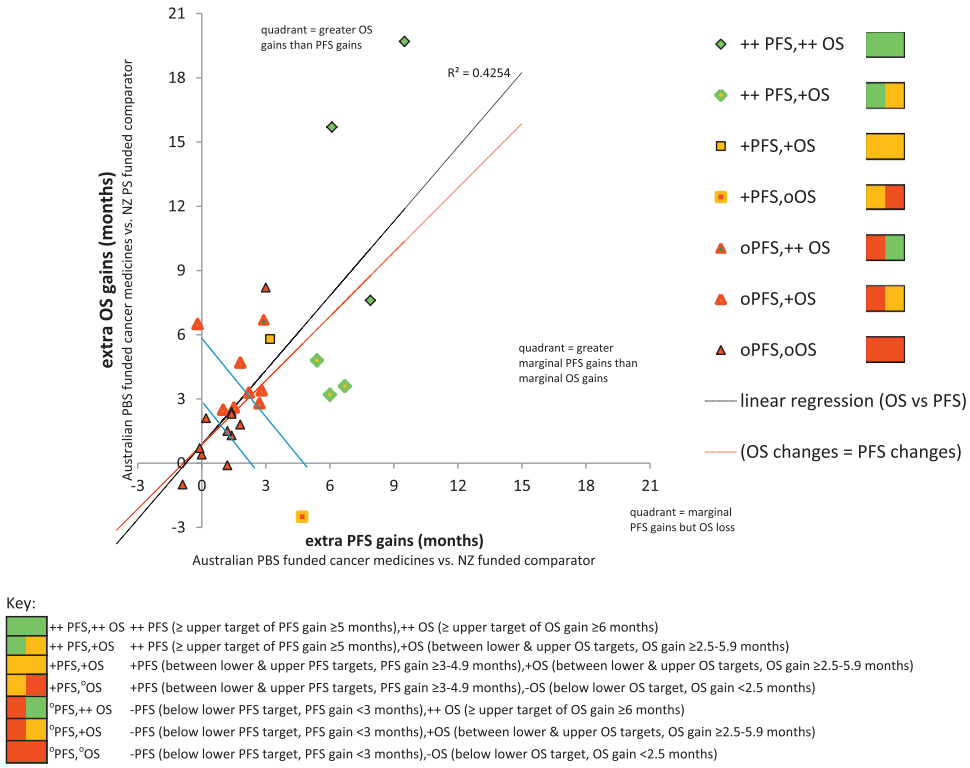


Fig. 5. (A) PFS gains and (B) OS gains foregone for breast, colon, lung, and pancreas medicines funded in Australia but not in New Zealand. Medicines marked with an asterisk (*) have been assessed by PHARMAC and either remain under assessment for funding or have been declined by PHARMAC, http://www.pharmac.govt.nz/patients/ApplicationTracker. Green bars represent the gains that met or exceeded the ASCO-CRC overall upper target for clinically meaningful PFS health gain, orange striped bars represent gains that fell below the upper target but met or exceeded the lower target, and red spotted bars those that fell below the lower target. Horizontal dashed lines represent the thresholds for the upper and lower targets for each cancer disease type—refer to Table 1 for details regarding PFS gain targets for individual cancer disease types (breast, lung, colon, and pancreas).

considered clinically meaningful for patients in terms of improving the length or quality of life. Our work supports the findings of a review of the 71 cancer medicines for solid cancers approved by the US FDA in the 12 years between 2002 to 2014, which showed overall progression-free and overall survival gains of only 2.5 and 2.1 months respectively, with only 42% meeting the targets set by the ASCO-CRC for clinically meaningful gains [9].

Our analysis also demonstrates that gains in PFS do not confer a commensurate gain in overall survival, with poor correlation between the two outcomes (see Appendix B). As an example, in our analysis, the median PFS gain for crizotinib for ALK-positive non-small cell lung cancer was 4.7 months, yet the median OS gain was 2.5 months worse than the comparator. Our findings support the work of others confirming that caution is needed when interpreting the health benefits for cancer treatments on the basis of PFS gains alone [71,72]. There is also an increasing trend towards using even earlier surrogate endpoints in cancer [10], such as tumor response rates. Such endpoints enable companies to bring their medicines to market sooner, often using accelerated approval pathways; however, the evidence supporting the validity of early endpoints as surrogates for cancer survival is limited [73]. A recent analysis of cancer medicines granted FDA approval on the basis of surrogate endpoints between 2008 and 2012 showed that of the 36 approved, only five were subsequently shown to improve



Key:

++ PFS,++ OS	++ PFS (≥ upper target of PFS gain ≥5 months),++ OS (≥ upper target of OS gain ≥6 months)
++ PFS,+OS	++ PFS (≥ upper target of PFS gain ≥5 months),+OS (between lower & upper OS targets, OS gain ≥2.5-5.9 months)
+PFS,+OS	+PFS (between lower & upper PFS targets, PFS gain ≥3-4.9 months),+OS (between lower & upper OS targets, OS gain ≥2.5-5.9 months)
+PFS,°OS	+PFS (between lower & upper PFS targets, PFS gain ≥3-4.9 months),-OS (below lower OS target, OS gain <2.5 months)
°PFS,++ OS	-PFS (below lower PFS target, PFS gain <3 months),++ OS (≥ upper target of OS gain ≥6 months)
°PFS,+OS	-PFS (below lower PFS target, PFS gain <3 months),+OS (between lower & upper OS targets, OS gain ≥2.5-5.9 months)
°PFS,°OS	-PFS (below lower PFS target, PFS gain <3 months),-OS (below lower OS target, OS gain <2.5 months)

Fig. 6. Cancer medicines funded in Australia but not in New Zealand—correlation between gains for PFS and OS. Blue downward-sloping lines represent the lower and upper targets for clinically-meaningful PFS and OS gains. The closer a medicine/indication's result lies to the linear regression line, the closer is the medicine/indication's OS gain to its PFS gain. The further away from the vertical and horizontal axes, the greater the difference.

OS, with the majority either failing to improve survival or having an unknown effect [74]. Others have argued that cancer medicines in particular get an "easy ride" from regulators, through a mix of methodological weaknesses in clinical trials, accelerated approval pathways and reliance on early surrogate outcomes that are highly variable in their ability to predict survival outcomes [10,75].

Health benefits, in terms of PFS and OS gains, are only part of the information taken into account by PHARMAC when making its cancer

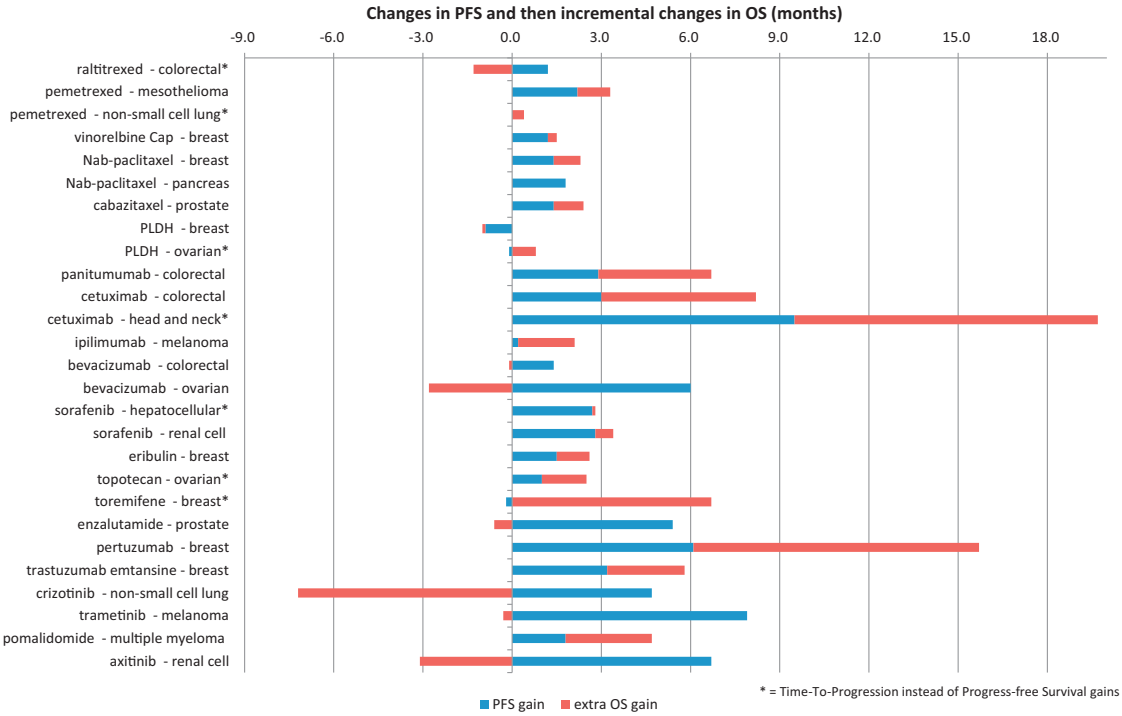


Fig. 7. Cancer medicines funded in Australia but not in New Zealand—gains in PFS, and then extra (incremental) gains in OS (beyond the PFS changes). Notes: Close correlation between PFS and OS gains would cause the gaps between PFS and OS to be uniform, ie, the red bars would be roughly equal. The longer the red bar, the greater the difference between the OS and PFS gains (ie, the extra OS gain, beyond PFS gain). Negative extra OS gains (ie, red bars to the left of the vertical axis) denote the OS gain being less than the PFS gain. Asterisks (*) denote clinical trial data that presented time-to-progression instead of PFS gains.

medicine funding decisions [76]. While our analysis here focusses on PFS and OS gains, some medicines may provide other benefits not captured using these endpoints. For example, new treatments may be better tolerated, easier to administer or free up health sector resources. PHARMAC makes its decisions taking into account its Factors for Consideration, which capture all such benefits [23]. Notably, PHARMAC must make its decisions within the funding available. This means that all new funding applications are assessed relative to each other, so that the value of investing in new cancer medicines can be compared with possible investment in new medicines for other conditions such as diabetes, asthma and infections.

5. Conclusions

Our analysis shows that, while New Zealand funds fewer cancer medicines than Australia, most of these additional medicines do not deliver clinically meaningful health gains in terms of extending time to disease progression or death for cancer patients. This suggests that simply funding more cancer medicines to achieve funding parity with Australia would likely not represent good value for money in terms of delivering the best health outcomes for New Zealanders. PHARMAC's method for selective funding of new medicines that demonstrate clear clinical benefit and that are cost-effective and affordable is a sensible approach, ensuring that scarce health dollars are not directed towards medicines that are unlikely to deliver clinically meaningful health gains to patients.

Conflicts of interest

R. Pauls and G. Blick were contracted by PHARMAC to undertake initial analysis work. J. Evans, T. Wang, R.S. Metcalfe, and S. Crausaz are employees of PHARMAC. G. Laking is a former member of PHARMAC's Pharmacology and Therapeutics Advisory Committee (PTAC) and its Cancer Treatments Subcommittee of PTAC, and remains an independent expert on PHARMAC's Named Patient Pharmaceutical Assessment panel. R.M. Strother is a member of PHARMAC's Pharmaceutical and Therapeutics Advisory Committee (PTAC) and its Cancer Treatments Subcommittee of PTAC. R. Pauls is a former employee of PHARMAC.

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