# Memorandum

28 May 2015

To: Jackie Evans, Steffan Crausaz – PHARMAC

From: [redacted] – Sapere Research Group

## Re: PBAC cancer listings comparison – final result

This memo summarises our recent work for you with respect to:

- research and analysis of the progression free and overall survival gains associated with cancer medicines and indications that are funded in Australia but are not currently listed on the New Zealand Pharmaceutical Schedule[1]; and
- a comparison of those progression free and overall survival gains with recent research into defining "clinically meaningful" outcomes for participants in cancer clinical trials.

## Our approach

Our approach to undertaking this work can be summarised in the following steps.

1. PHARMAC provided us with a list of 22 cancer medicines that are publicly funded in Australia but not in New Zealand as at 25 March 2015. These products are outlined in **Appendix 1**.
2. We searched the Australian Register of Therapeutic Goods[2] and identified Product Information (PI) documents for each of these products. These documents typically contain information about the indications, design and results of one or more clinical cancer trials. In some cases, where the relevant PI document lacked relevant trial data (e.g. #6 idarubicin) we searched online for data in credible journals.
3. We focused on clinical trial data in the form of the median progression-free survival (PFS) and median overall survival (OS) gains for each trial for each product and its relevant comparator treatment. The results were entered into a spreadsheet in the workbook accompanying this memo. We then derived the 'marginal' median gain for the trial product for each endpoint (progression free and overall survival), relative to its reported relevant comparator treatment. In some cases, the marginal gain proved to be negative number.
4. The next step was to search the Australian Pharmaceutical Benefits Schedule (PBS) for all authorities granted to these 22 medicines, to determine which indications are funded.[3] We then filtered the clinical trial data so that only those trials with indications that are publicly funded in Australia are included in our comparative analysis. Trials for indications that do not have a PBS authority were filtered out at this point but remain in the underlying data set.

[1] The analysis does *not* include drugs which are funded both in Australia and New Zealand but where the funded indications differ. For example, Sunitinib is funded in Australia for renal cell carcinoma, GIST and pancreatic neuroendocrine tumour whereas in New Zealand, it is funded for renal cell carcinoma and GIST. A comparative analysis of *all* funded cancer drugs and indications could be undertaken but would require significant additional analysis and resources.

[2] See https://www.tga.gov.au/

[3] See http://www.pbs.gov.au/pbs/home

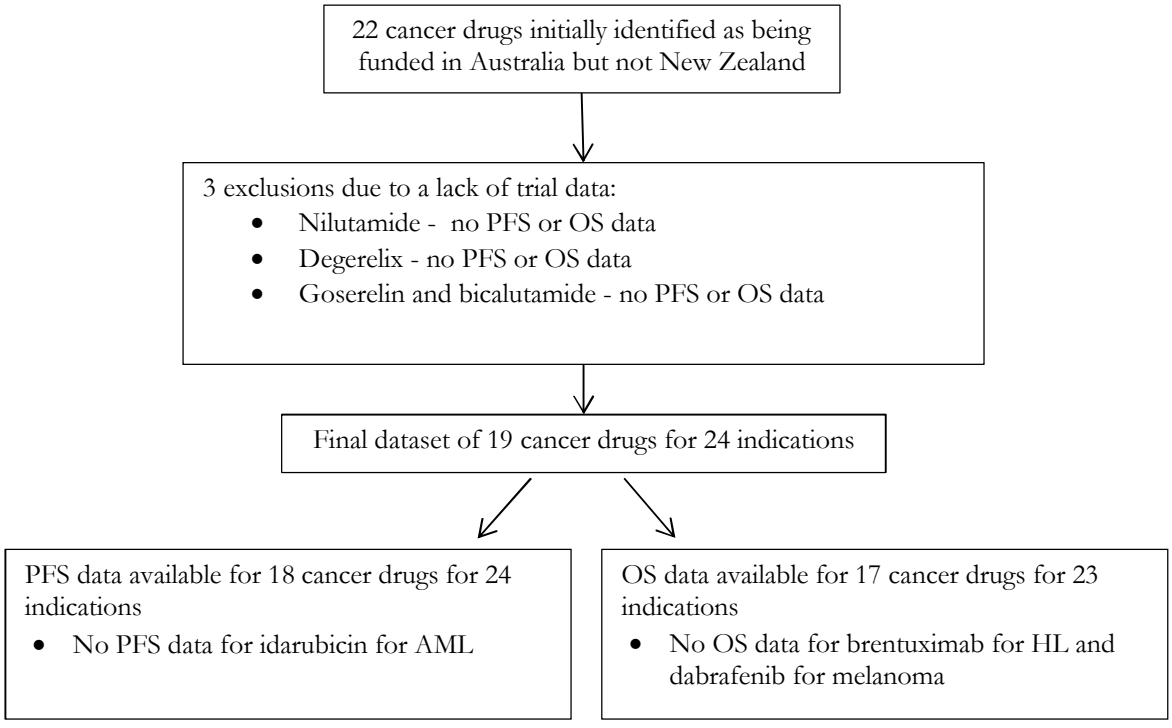
5. We also filtered some clinical data in response to feedback from PHARMACs Senior Therapeutic Group Manager for Oncology, Jackie Evans; for example, in cases where there are multiple trials with different comparator treatments she identified the appropriate comparator by examining the PBS funded population and/or consideration of current 'standard of care' or for other specific exclusions. These exclusions are documented in **Appendix 2**.

6. 3 drugs were excluded from the final analysis (excluded because no relevant PFS or OS data could be identified; nilutamide, degerelix and combination goserelin and bicalutamide (ZolaCos[4])) leaving a final analysis dataset of 19 drugs funded in Australia for 24 indications, of these PFS data were identified for 18 medicines for 24 of the indications and OS data for 17 medicines for 23 of the indications.

7. The marginal progression free and overall survival gains for each drug were then compared with the results of a study that surveyed four groups of experts in cancers of the pancreas, breast, lung, and colon that defined minimum "clinically meaningful" survival gains.[5] We drew upon the 'lowest' and 'highest' minimum thresholds reported in that study.

We checked with PHARMAC staff at several points in the process, to update on emerging results and to seek guidance on refining the research approach and analysis. Following a meeting on 23 April 2014, we incorporated PHARMAC's suggested changes; these changes are compiled in **Appendix 2** and annotated in a "comment" column [K] in the 'analysis' sheet of the accompanying workbook. Finally, we undertook a quality assurance on the identification and input of trial data from the PI documents to the spreadsheet.

**Figure 1: Flow chart of datasets for PFS and OS analysis**




[4] PHARMAC funds the individual components of goserelin and bicalutamide separately.

[5] Lee M. Ellis et al (2014) "American Society of Clinical Oncology Perspective: Raising the Bar for Clinical Trials by Defining Clinically Meaningful Outcomes" *Journal of Clinical Oncology* April 20, 2014 vol. 32 no. 12 1277-1280

We have structured the clinical trial database for PHARMAC's ongoing use; additional drugs and data for existing trials or new trials can be added and the results can be updated. Similarly, additional filtering of trial data can be undertaken. These steps could be undertaken by PHARMAC or, we are happy to assist. More detailed information about the structure of the workbook is attached as **Appendix 3** to this memo.

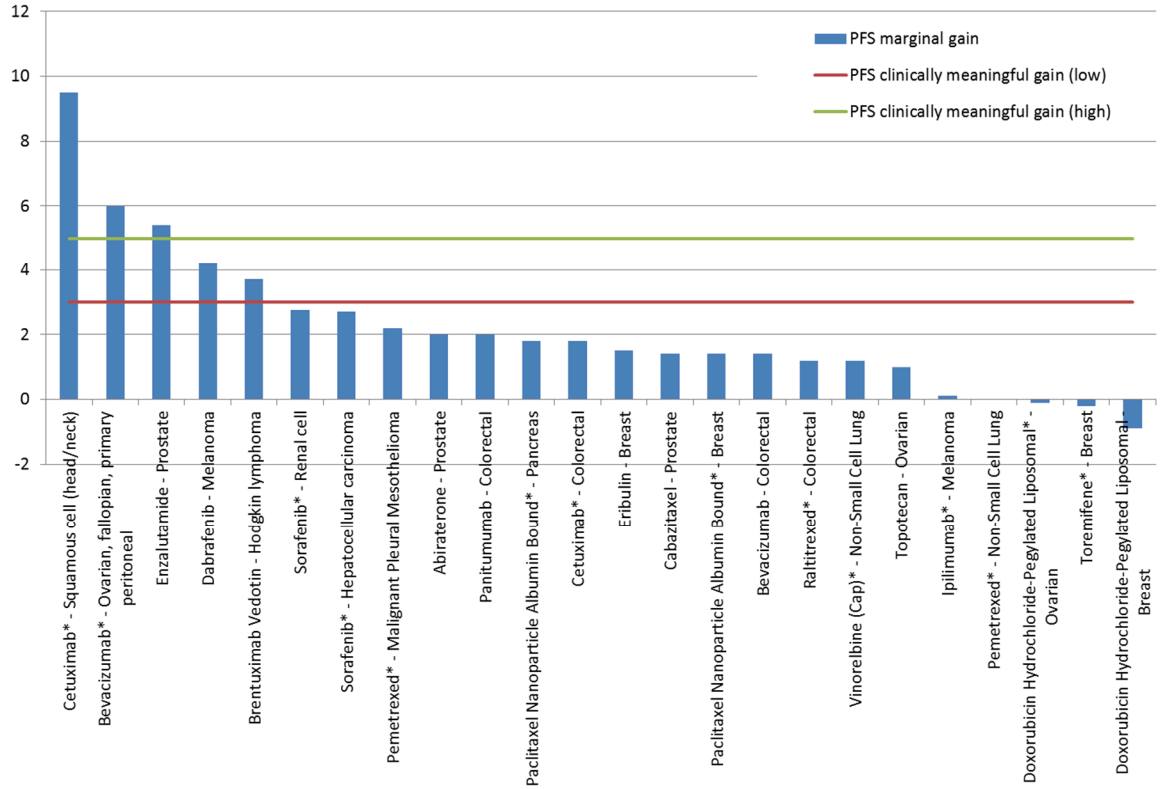
## Findings

We present our findings below in the form of charts for PFS and OS gains. These results are determined by the presence of PBS authorities and on the filtering of trial data. As this latter step involves a degree of judgment, it is possible that you might ultimately include a slightly different set of data. Nevertheless, in our view, the overall pattern is not likely to differ substantially from that presented here.

The charts present the marginal median PFS and OS gains ranked in order from the largest gains to those which appear to offer negative gains, relative to the comparator treatment. Some key points to note are:

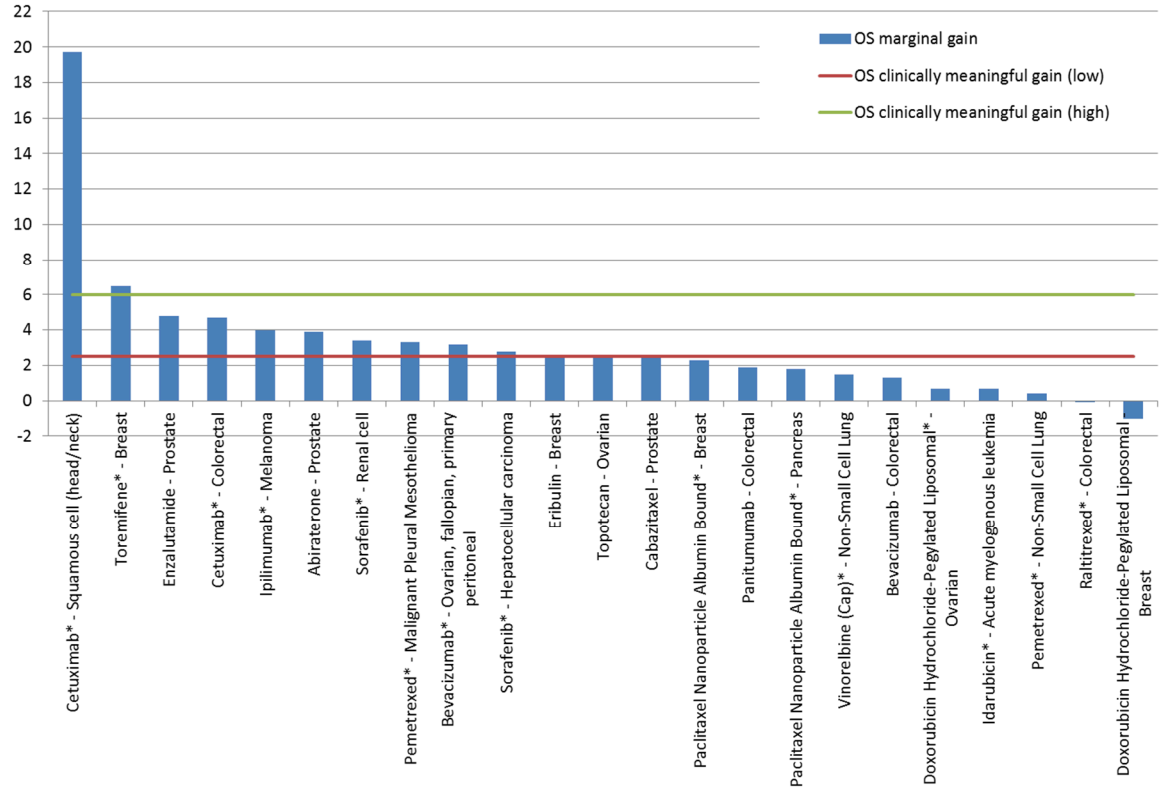
- Of the original list of 22 drugs, 19 drugs with 24 indications that are currently funded in Australia but not in New Zealand provided sufficient clinical trial data about PFS and/or OS gains to be included in the analysis;
- most of these medicines offer marginal median PFS or OS gains that are below even the lowest minimum threshold for clinically meaningful gains reported in Ellis et al (2014);
- the first item in each chart is an outlier and arises from a single trial for #9 Cetuximab in Head and Neck Cancer for patients unable to receive standard chemotherapy (therefore the comparator is radiotherapy alone). We understand that this treatment for this indication is currently on PHARMACs Priority List;
- We understand that most of the drugs/indications that are funded in Australia but not in New Zealand have been either assessed by PTAC and ranked, or a decision has made by the PHARMAC board not to fund them;
- Several of the drugs identified have alternative presentations that are funded in New Zealand (vinorelbine capsule, idarubicin capsule, combined goserelin with bicalutamide);
- Some of the drugs identified have been discontinued by the suppliers in New Zealand (idarubicin capsule, topotecan)

**Figure 2: Median Progression-Free Survival - marginal gains relative to comparator treatment**




**Source**: clinical trial data from Product Information documents; meaningful gains from Ellis et al (2014)

**Figure 3: Median Overall Survival - marginal gains relative to comparator treatment**




**Source**: clinical trial data from Product Information documents; meaningful gains from Ellis et al (2014)

## Comment

This analysis is one perspective on the trial data and the recent research into clinically meaningful gains. In looking at the charts included here, several observations are worth noting

- the clinical trial data (blue bars) are ranked by size of marginal gain, but could instead be grouped by the medicine so that products with more than one trial are side by side. We have produced this chart in the accompanying workbook;
- the clinical trial data (blue bars) are factual data, in the form of marginal gains derived from a comparison of the median PFS and OS gains reported in clinical trials for a given product the trial's comparator treatment;
- the thresholds of "clinically meaningful" gains (green line and red line) are one view, based on expert opinion. We have used the range of views reported in the study by Ellis et al (2014), taking a 'low' and a 'high' for the minimum thresholds considered to be meaningful. Other approaches are possible, for example, using an average of the reported thresholds, or using cancer-specific thresholds for relevant medicines being considered in this work (i.e. pancreas, breast, lung, and colon). It is possible to include other thresholds that you may view as being appropriate.

Overall, the main contribution of this work has been in identifying, collating and presenting the clinical trial data in a framework that allows future analysis and scenarios to be undertaken. We are open to feedback if you would like to discuss the filtering of the trial data or any other refinements.

## Appendix 1: List of products

The table below sets out the cancer medicines identified by PHARMAC for the purposes of this analysis, together with the respective indications and basic information about the clinical trials from which the data were sourced. A sequential number was assigned to each medicine for ease of identification. Exclusions from this initial list are set out in Appendix 2 below.

| # | Product name | Indication | Clinical Trial Code | Clinical Trial Type | Comparator Treatment |
|---|---|---|---|---|---|
| 1 | Raltitrexed | Palliative treatment of advanced colorectal cancer | Trial 003 | Controlled Phase 3 | Combination of fluorouracil and calcium |
| 2 | Pemetrexed | Malignant Pleural Mesothelioma; Non-Small Cell Lung Cancer | EMPHACIS | Multicentre, randomised, single-blind Phase 3 (with vitamin supplement to reduce toxicity) | Cisplatin |
| 3 | Vinorelbine (Cap) | First line treatment of advanced non-small cell lung cancer; advanced breast cancer | 97 CA 205 | Randomised Phase 2 | IV vinorelbine |
| 4 | Paclitaxel Nanoparticle Albumin Bound | Breast, Non-Small Cell Lung, Pancreas | CA012-0 | Multi-centre trial | Solvent-based paclitaxel; Gemcitabine |
| 5 | Cabazitaxel | Hormone refractory metastatic prostate cancer previously treated with a docetaxel containing regimen | TROPIC | Randomised, open-label, international, multi-centre, phase III study | Mitoxantrone + prednisone |
| 6 | Idarubicin | Acute myelogenous leukemia | JOC, 1992 | Randomised phase III study | Daunorubicin w cytarabine |
| 7 | Pegylated Liposomal Doxorubicin Hydrochloride-PLDH | Metastatic Breast Cancer | Study I97-328 | Phase III randomised study | Doxorubicin |
| | Pegylated Liposomal Doxorubicin Hydrochloride-PLDH | Ovarian Cancer | Study I96-352 | Randomised, open-label trial | Topotecan |

| # | Product name | Indication | Clinical Trial Code | Clinical Trial Type | Comparator Treatment |
|---|---|---|---|---|---|
| 8 | Panitumumab | wild-type RAS metastatic colorectal cancer | Study 20050181 | Phase 3 randomised, controlled trial - ECOG 0/1 status | Folfiri |
| 9 | Cetuximab | RAS* wild-type metastatic colorectal cancer | Study CA225025 | Randomised, open-label study | Best supportive care (BSC) |
| | Cetuximab | squamous cell cancer of the head and neck | Study EMR 62 202-006 | Randomised study | Radiation therapy |
| 10 | Ipilimumab | Unresectable or metastatic melanoma | Study MDX010-20 | Phase 3, double-blind study | gp100 peptide vaccine |
| 11 | Bevacizumab | Metastatic Colorectal Cancer | NO16966 | Phase III randomised, double-blind (for bevacizumab), clinical trial | FOLFOX-4 or XELOX + Placebo |
| | Bevacizumab | Ovarian, Fallopian Tube or Primary Peritoneal Cancer | GOG-0218 | Phase III multicentre, randomised, double-blind, placebo controlled, three arm study | Carboplatin/Paclitaxel/Placebo |
| 12 | Brentuximab Vedotin | Hodgkin lymphoma | SG035-0003 | Open-label, single-arm, multicenter study | Most recent prior systemic therapy |
| 13 | Dabrafenib | BRAFV600 mutation positive unrespectable Stage III or metastatic (Stage IV) melanoma | BREAK-3 | Phase III randomised, open-label study | Dacarbazine |
| 14 | Sorafenib | Advanced hepatocellular carcinoma; | Study 100554 | Phase III, international, multi-centre, randomised, double blind, placebo-controlled | Placebo |
| | Sorafenib | advanced renal cell carcinoma | Study 11213, TARGET | Phase III multi-centre, randomised, double blind, placebo-controlled trial | Placebo |
| 15 | Eribulin | Locally recurrent or metastatic breast cancer | EMBRACE | Randomized Phase 3 comparative study | Treatment of physician's choice (TPC) |
| 16 | Topotecan | Ovarian carcinoma | | no info | Paclitaxel |
| 17 | Goserelin (&) Bicalutamide | Advanced prostate cancer | | Randomised, multicentre, controlled clinical trial | Flutamide w goserelin acetate implant or leuprorelin acetate depot |
| 18 | Toremifene | Hormone-dependent metastatic breast cancer in postmenopausal patients | North American 5/044 | Prospective, randomised, controlled clinical | Tamoxifen 20mg |

| # | Product name | Indication | Clinical Trial Code | Clinical Trial Type | Comparator Treatment |
|---|---|---|---|---|---|
| 19 | Enzalutamide | Metastatic castration-resistant prostate cancer who have previously received docetaxel. | AFFIRM | Randomised, placebo-controlled, multicentre phase 3 clinical trial | Placebo |
| 20 | Nilutamide | Previously untreated metastatic prostatic carcinoma | various trials | | |
| 21 | Abiraterone | Metastatic advanced prostate cancer | Study 301 | Randomized placebo controlled multicenter phase 3 clinical study | Placebo in in combination with prednisone or prednisolone |
| 22 | Degarelix | Prostate cancer | | Open-label, multi-centre, randomised, active comparator, parallel-group study | Leuprorelin |

## Appendix 2: Record of exclusions and changes

As agreed 23 April 2015

| # | Product | Comments |
|---|---|---|
| 1 | Raltitrexed | Three trials with different durations; use trial #003 because it has the longest follow-up period (and appears to offer the best results in terms of survival gains). |
| 2 | Pemetrexed | There are two PBS authorities: (1) Locally advanced or metastatic non-small cell lung cancer; and (2) Mesothelioma.<br>• Non-small cell lung cancer - exclude trial with comparator of Gemcitabine + Cisplatin as focus is on first-line treatment, whereas PBS authority is for second-line treatment; retain other study (comparator is Docetaxel);<br>• Mesothelioma - use EMPHACIS trial, selecting arm that includes vitamin supplements to manage side effects, as the results appear better. Filter out non-supplement arm from this trial. |
| 3 | Vinorelbine (Cap) | Use the trial that compares Vinorelbine capsules with IV vinorelbine presentation - is the appropriate comparator; exclude use of trial CA222 (vinorelbine capsules vs. Docetaxel). |
| 4 | Paclitaxel Nanoparticle Albumin Bound | PBS authorities include: (1) Stage IV (metastatic) adenocarcinoma of the pancreas; (2) need to also add in metastatic breast cancer and HER2 positive breast cancer.<br>• Breast trial CA012-0 - include as metastatic breast cancer has PBS authority<br>• Non-Small Cell Lung - exclude as no PBS authority.<br>• Pancreas trial - retain as first line and uses comparator in PBS authority. |
| 5 | Cabazitaxel | One study in the PI document; accepted for inclusion |
| 6 | Idarubicin (capsule) | Could exclude as trial data is IV form; whereas PBS authority is capsule; for time being just note (IV) next to trial. Note that according to Pfizer, the capsule form is discontinued. |
| 7 | Pegylated Liposomal Doxorubicin (PLDH) | • Use the full name or abbreviated to PLDH<br>• Use Study I97-328 as the appropriate comparator is used (i.e. Doxorubicin) |
| 8 | Panitumumab | • Exclude Study 20050203 as focus is first-line treatment, whereas the PBS authority is for second-line treatment; the comparator is Folfox<br>• Include Study 20050181 as the focus is second-line treatment; the comparator is Folfiri with irinotecan (as required by the PBS authority); use arm ECOG 0/1 as it has better results; consistent with taking the 'most generous' interpretation of the marginal gains. |
| 9 | Cetuximab | There are two PBS authorities: (1) Stage III, IVa or IVb squamous cell cancer of the larynx, oropharynx or hypopharynx; (2) metastatic colorectal cancer.<br>• Squamous cell head and neck cancer - use trial EMR 62 202-006 - comparator is radiotherapy, which is appropriate for some patients if they're not well enough for Cisplatin; the PBS authority notes that for patients to Cetuximab, they must have a contraindication to Cisplatin; therefore we can filter out trial EMR 62 202-002, which uses Cisplatin as the comparator.<br>• Colorectal cancer - include trial CA225025 as focus is on second-line treatment (comparator BSC) as per PBS authority; exclude trials EMR 62 202-013 (comparator Folfiri) and Study EMR 62 202-047 (comparator Folfox) as focus is on first-line treatment. |
| 10 | Ipilimumab | One study in the PI document; accepted for inclusion |

| # | Product | Comments |
|---|---|---|
| 11 | Bevacizumab | There are two PBS authorities: (1) Stage IIIB, IIIC or Stage IV epithelial ovarian, fallopian tube or primary peritoneal cancer; (2) metastatic colorectal cancer (first-line treatment).<br>• Epithelial ovarian, fallopian tube or primary peritoneal cancer - exclude trial AVF4095g as it focuses on relapsed patients whereas the PBS authority is for previously untreated patients. Include trial GOG-0218 as focus is first-line.<br>• Trial MO22224 is for ovarian cancer specifically; exclude as it is covered under the broader authority of epithelial ovarian, fallopian tube or primary peritoneal.<br>• Colorectal - there are two first-line treatment trials: exclude trial AVF2107g as the IFL regimen used is no longer recommended as standard treatment; include NO16966 study (comparator is FOLFOX-4 or XELOX). |
| 12 | Brentuximab Vedotin | One study in the PI document; accepted for inclusion |
| 13 | Dabrafenib | One study in the PI document; accepted for inclusion |
| 14 | Sorafenib | There are two PBS authorities: (1) renal cell; (2) hepatocellular carcinoma. Include the sole trial included in the Product Information sheet for each authority; exclude the thyroid trial results as no PBS authority. |
| 15 | Eribulin | One study in the PI document; accepted for inclusion |
| 16 | Topotecan | One study in the PI document; accepted for inclusion |
| 17 | Goserelin (&) Bicalutamide | PHARMAC Board declined commercial proposal for Zolacos in 2010 (combination not specifically reviewed by PTAC) – individual are components fully funded in NZ. Excluded from analysis as no trial data available. |
| 18 | Toremifene | Three arms of the study; the standard dosing of tamoxifen (comparator) is 20 mg/day, so use the north American study results. |
| 19 | Enzalutamide | One study in the PI document; accepted for inclusion |
| 20 | Nilutamide | • Product Information sheet did not report trial data on a survival gain basis. Trials reported in literature seem to focus on other measures of their performance with respect to prostate cancer; unable to find survival gain data.<br>• nilutamide is another anti-androgen (similar to bicalutamide, and flutamide; flutamide is fully funded in NZ without restriction, bicalutamide is funded under Special Authority for patients with advanced prostate cancer.<br>• Exclude from charts as no PFS or PS gains reported |
| 21 | Abiraterone | Two trials on PI, one treatment naïve one treatment experience: use trial #301 because it reflects Australian funding; accepted for inclusion. |
| 22 | Degarelix | • Product Information sheet did not report trial data on a survival gain basis. Trials reported in literature seem to focus on other measures of their performance with respect to prostate cancer; unable to find survival gain data.<br>• Jackie ordered a recent article (Klotz et al, 2014) reporting trial results; it did not include PFS/OS data compared with leuprorelin and/or Goserelin (both fully funded in NZ without restriction).<br>• Exclude from charts as no PFS or PS gains reported |

## Appendix 3: Structure of the workbook

The accompanying work is labeled: "PBS vs Pharmac Schedule B comparison for cancer drugs - 28 April 2015.xls" The table below outlines the name and purpose of the each worksheet. These sheets can be grouped into three broad categories:

- data input and analysis worksheets (sheets numbered 1-5);
- output sheets in the form of charts (PFS and OS charts); and
- product-specific worksheets for the 22 medicines of focus, with pasted information showing clinical trial data and PBS authorities. These sheets are included to enable checking and ease of future reference.

**Filtering the results** – refer to the sheet "5.analysis". Column J has a Yes/No filter for each trial in the form of a drop-down box. An exclusion or inclusion of a row will flow through to the ranking and charts. For additions, the charts may need to be reset be reselecting the enlarged data matrix (right click on the chart and choose 'select data'). The reason for any exclusion is noted in Column K.

**Adding new data** – new lines for additional clinical trials can be added to the sheet "2.trial data". A corresponding line should be added to the "5.analysis" sheet.

| Worksheet name | Description |
|---|---|
| Notes | Outlines the purpose of the workbook, date of completion and authors. Describes the structure of the workbook and the purpose of each spreadsheet. |
| 1. listing comparison | The spreadsheet supplied by PHARMAC; it lists the cancer medicines that are publicly funded in Australia and New Zealand. It also identifies the medicines of focus for this study - those products that are funded in Australia but not New Zealand. |
| 2. trial data | Contains all potentially relevant trial results; this includes information about the type of trial, indication and the comparator treatment; the trial results are focused on the median PFS and OS gains; a marginal gain relative to the comparator treatment is derived. Results for TTP (Time to Progression) are also included, where available, for completeness. |
| 3. PBS authorities | A list of the authorities on PBS for each of the cancer medicines. |
| 4. meaningful gains | A summary of results from Ellis et al (2014). |
| 5. analysis | Summarises the trial data alongside the PBS authorities. Contains a filter column that includes a drop-down filter Yes/No box for each trial for each medicine. The results are automatically ranked into two summary tables that underpin the output charts. |
| Chart PFS | Output chart showing ranked marginal median PFS gains |
| Chart OS | Output chart showing ranked marginal median OS gains |
| Product-specific worksheets | Contains pasted summaries of clinical trial data and PBS authorities. These are included to enable checking and ease of future reference. |