Access to oncology medicines in Australia

Roche response to Medicines Australia Oncology Industry Taskforce report

18 October 2013

Roche Products Pty Limited

Executive Summary

Roche welcomes the opportunity to comment on the July 2013 report, *Access to cancer medicines in Australia*, commissioned by the Medicines Australia Oncology Industry Taskforce (OIT). At Roche, we focus on developing medicines and diagnostics that will help patients live longer, better lives. We strive to address unmet medical needs through excellence in science – from early detection and prevention of disease to diagnosis, treatment and treatment monitoring. As both a diagnostics and a pharmaceuticals company, Roche is ideally placed to contribute to progress towards more personalised healthcare, opening up new ways to prevent, diagnose and treat illness.

Chapter 5 of the report includes data on the time and number of submissions required to achieve reimbursement in Australia. This data only includes submissions for which there was an eventual positive Pharmaceutical Benefits Advisory Committee (PBAC) recommendation, and hence do not fully reflect access issues in Australia. There are many medicines rejected by or never submitted to the PBAC, meaning these medicines (or indications) are not available on the Pharmaceutical Benefits Scheme (PBS) in Australia. Additionally, those medicines that successfully achieve PBS listing generally require more than one submission to the PBAC, thus increasing the time between Therapeutic Goods Administration (TGA) approval and listing. This is frustrating to the industry, since sponsors can only engage with the PBAC once a submission has been rejected, which lengthens the time from TGA approval to PBS listing and delays access to patients.

Chapter 5 also includes a table comparing access to a number of oncology medicines in Australia with key Organisation for Economic Cooperation and Development (OECD) countries. This table considers only initial indications. In Australia, every indication must undergo an assessment of cost-effectiveness by the PBAC prior to PBS listing. Each indication may require a number of submissions and take several years, leading to further gaps in access between Australia and other countries. When making comparisons between countries, it is also important to compare the extent of access, as the reimbursed population may be much narrower than that approved by the regulatory authority leading to significant access differences between countries. Data on the reimbursement status, time to reimbursement and extent of coverage for each of Roche's cancer medicines by indication is provided in Appendices to this response and show increasing separation in access with time.

Australia lags behind other OECD countries, where access to cancer treatments is enabled by one of the following mechanisms systematically employed for medicines:

- Formal assessments of cost effectiveness are not currently employed but coverage is based on assessments of effectiveness, cost and volume (United States Medicare, Medicaid and private health care plans).
- The health technology assessment (HTA) process is focused on incremental effectiveness and budget impact and may also take unmet need and level of innovation into consideration. External reference pricing is used to ensure pricing is consistent with economically comparable countries (France, Germany).
- A formal HTA process comparing both incremental effectiveness and cost is used, but a formal incremental cost-effectiveness ratio (ICER) threshold is not applied (The Netherlands, Sweden). This

leaves payers with the opportunity to value health gains differently in different therapeutic areas. At the same time, the existence of external reference pricing amongst Western European countries, enables payers in The Netherlands and Sweden to access prices that are no higher than those in other economically comparable European Union countries.

- A formal HTA process comparing both incremental effectiveness and cost is used, but solutions specifically designed to cope with oncology medicines have been introduced (United Kingdom, Canada).

More and more Australia stands alone, in continuing to apply a 'one-size-fits all' approach to cost-effectiveness thresholds and methodology, regardless of medicine or therapeutic area. Although there is no explicit cost-effectiveness threshold in Australia, experience suggests that the acceptable threshold is in the range of $45,000 - $60,000. The acceptable threshold declines when any form of clinical, economic and financial uncertainty exists in the economic evaluation. The World Health Organisation (WHO) has suggested an ICER range between 1 and 3 times gross domestic product (GDP) per capita as cost-effective. In 2012, the Australian GDP per capita was $64,321 and $44,598 adjusted for purchasing power parity. Using the criteria proposed by the WHO, ICERs in the range of $44,598 - $133,794 would be deemed cost-effective.

Additionally, while the PBAC Guidelines state that other factors (e.g. societal values) are taken into consideration, there is no transparency in how final decisions are made by the PBAC, and what weighting is given to these other factors. In contrast, other formal HTA systems have adapted to allow for decision making to consider criteria other than just economic efficiency.

The prices of Roche medicines reflect the value the innovation delivers to patients, their families and societies. When setting prices we consider clinical benefit relative to available alternatives, level of medical need addressed, the market situation and ability of healthcare systems and individuals to afford our medicines. Globally, Roche follows a "value based pricing" approach but does not target a specific cost-effectiveness threshold. A company operating globally must meet the expectations and value assessment criteria of a relevant large number of payers in order to be successful, but given the various different formal and informal value assessment criteria that payers apply, it is impossible to identify a single threshold that if met would satisfy all payers in all countries.

Prices requested for medicines in Australia are no higher than those requested and reimbursed in economically comparable countries. This means however, that at times prices requested in Australia are considerably higher than the price considered cost-effective under the Australian HTA system. As a result, several medicines and/or indications are not available to Australian patients but are available to patients in economically comparable countries.

It is important that the Australian community has a voice in determining what society believes is value for money in the determination of medicine reimbursement. These values can only be derived through a process that allows active participation by citizens and a clear set of decision-making principles reflecting formal evidence of society's preferences for funding healthcare. Societal preferences should be considered in determining whether factors such as burden of illness, unmet need and indirect costs such as productivity are relevant to willingness to pay thresholds.

It is also important to remember the value of a medicine continues beyond patent expiry, when generic and biosimilar competitors drive the price down markedly. In most cases, this occurs after 10 – 12 years on the market. When assessing the value of a medicine, it is therefore important to consider value over the entire lifetime of the medicine.

Stakeholders interviewed for the *Access to cancer medicines in Australia* Report acknowledged the challenges and risks facing the medicines industry in the development of new medicines. They also acknowledged the need to maintain a viable medicines industry by providing sufficient commercial incentives, so the industry can continue to introduce new medicines to benefit cancer patients. However, the application of an incremental cost-effectiveness framework and promotion of innovation are frequently not aligned.

An example of commercial disincentive is demonstrated when a new oncology medicine is added to the existing standard of care, and assessed for cost-effectiveness using the current methodology. The new medicine adds half a year of life to the standard of care, and also provides benefits in quality of life. By applying a hypothetical cost of only $4 (or the cost of a cup of coffee) per vial of this new medicine, the ICER associated with the new medicine + standard of care, when compared with standard of care alone, is $60,000-$70,000 per quality adjusted life-year (QALY) gained. This would likely be considered higher than the acceptable threshold for cost-effectiveness by the PBAC. In other words, the new medicine cannot be priced at the same price as a cup of coffee in order to be deemed cost-effective and meet the criteria for funding in Australia. An ICER-based system with an undifferentiated ICER threshold, by virtue of the mere methodology applied, will never show an acceptable outcome for combination treatments, given the increased cost associated with the extension of treatment duration and follow-up of patients.

In conclusion, Roche believes the reimbursement system in Australia needs review to consider the following aspects:

- Fit-for-purpose evaluation of medicines, taking into account budget impact, rarity of disease and clinical benefit.
- Incorporation of societal values and costs/benefits beyond the health system into the decision-making process.
- Earlier and increased engagement between industry and the PBAC to decide upon the scope of the decision problem.
- Increased citizens input into the decision-making process.
- Price benchmarking to economically comparable countries.
- Consideration of the value of a medicine over its entire lifecycle.

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Chapter 5 Issues on access to cancer medicines in Australia

5.1 Regulatory and reimbursement processes

Chart 5.1 (page 55) in the Report shows the average time from TGA approval to PBS listing has increased markedly since 2003. It is worth noting that this data only includes submissions for which there was an eventual positive recommendation, and hence do not fully capture access issues in Australia. There are many submissions initially or subsequently rejected, meaning that these medicines (or indications) are not available on the PBS in Australia. Additionally, there are medicines (or indications) never submitted to PBAC, either because it is not possible to meet the data requirements of the PBAC or to demonstrate cost-effectiveness at the price set by the global parent company. These medicines /indications are only available through private sales or compassionate access programs, leading to equity issues. Examples in the Roche portfolio are:

Initial or subsequent rejection, no further submissions made

- Bevacizumab (Avastin) non-small cell lung cancer
- Bevacizumab relapsed glioblastoma
- Vemurafenib (Zelboraf) for BRAF+ metastatic melanoma
- Trastuzumab (Herceptin) in HER2-positive advanced gastric cancer.

Decision made not to submit

- Bevacizumab metastatic breast cancer
- Bevacizumab renal cell carcinoma
- Bevacizumab relapsed, platinum sensitive ovarian cancer
- Erlotinib (Tarceva) pancreatic cancer
- Erlotinib non-small cell lung cancer first-line maintenance therapy
- Vismodegib (Erivedge) advanced basal cell carcinoma

Table 5.1 (page 56) in the Report shows that the overall success rate of major cost-effectiveness submissions between 2003 and 2012 was 36%. It is important to note that this success rate applies to all major, cost-effectiveness submissions regardless of whether they are a first-time or subsequent submission. The table below provides a further breakdown detailing the success rate according to whether the application was a first time or subsequent submission.

Table 1 Proportion of first-time and subsequent submissions that received a positive recommendation, major cost-effectiveness submissions, 2003-2012

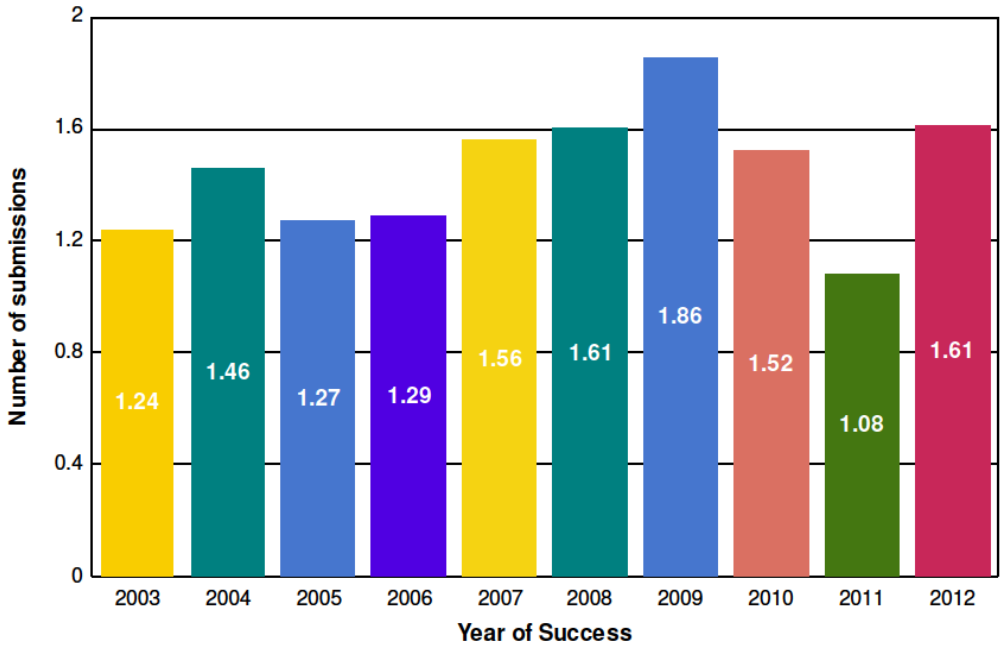
Submission number	Proportion of positive submissions (%), ATC category L	Proportion of positive submissions (%), All other ATC categories
1st time submission	38/109 (35%)	71/201 (35%)
2nd time submission	16/52 (31%)	30/79 (38%)
3rd time submission	11/22 (50%)	10/24 (42%)
4th time submission	3/5 (60%)	3/9 (33%)
5th time submission	0/1(0%)	2/4 (50%)
6th time submission	0/1 (0%)	1/1 (100%)
7th time submission	1/1 (100%)	0/0 (0%)
Total positive submissions	**69/191 (36%)**	**117/318 (37%)**

Source: Additional analysis provided by Pretium, September 2013

The data shows a low chance of success on first and second-time submissions, with the chance of success improving upon the third and subsequent submissions.

The chart below shows the average number of major submissions (cost-effectiveness and cost minimisation) required to achieve a positive recommendation grouped by year. The highest average number of submissions was in 2009 compared to the lowest in 2011. The decline in average number of PBAC submissions to success from 2009 to 2011 is driven by the success of major submissions based on cost-minimisation analyses. This trend was reversed in 2012 because of the higher proportion of submissions based on cost-effectiveness analyses during this period.

Figure 1 Average number of major PBAC submissions to success, ATC category L



Source: Pretium, May 2013

The 17-week review cycle from submission to review by the PBAC has been cited by the current and former PBAC Chairs as the fastest review process in the world. Whilst theoretically, this may be true, it must be remembered that very few medicines evaluated for cost-effectiveness receive a positive recommendation on their first submission. Additionally, post-PBAC processes (agreement on the wording of the PBS restriction, pricing negotiations, Department of Finance and Cabinet review) may take many months, meaning the time to access is much greater than 17 weeks.

The fact that most medicines/new indications require more than one submission to the PBAC to achieve PBS listing is a key factor in the lengthening time from TGA approval to listing. Perhaps the most frustrating element of this to industry sponsors is the inability to engage with the PBAC until a submission has been rejected. Prior to making a submission to the PBAC, the sponsor can meet with staff of the Pharmaceutical Benefits Division (PBD) of the Department of Health (DoH) to discuss the forthcoming application. However, PBD staff members are not the ultimate decision makers and as such, their advice may not reflect the opinions of the PBAC. Furthermore, evaluation of the submission is contracted out to external academic groups, who may also have differing opinions to the PBAC. Increasingly, sponsors are finding the PBAC to be raising new issues at their meeting. Since the last opportunity for the sponsor to provide a considered, written response to issues or comments made during the evaluation is one week prior to the PBAC meeting, there is no opportunity for the sponsor to address any concerns raised specifically by the PBAC prior to consideration. A 10 minute hearing at the PBAC meeting can be requested by the sponsor, however, this is not routine and would normally only be requested when issues have been raised by the evaluators.

Following a rejection, the sponsor can meet with the PBAC Chair to discuss a way forward. However, an entire 17 week-cycle is lost, since the earliest resubmission date is 17 weeks after the PBAC meeting. The resubmission will then be reconsidered a further 17 weeks after that, i.e. 8 months after the first meeting and rejection. The process is inherently inefficient in this regard. By contrast, the HTA system used by the National Institute of Clinical Excellence (NICE) in the United Kingdom involves a scoping meeting where the decision problem is discussed and agreed upon. This includes agreement on the comparator (a common reason for rejection in Australia), and the appropriate endpoints for determination of cost-effectiveness prior to the sponsor making their submission.

5.2 Evidentiary requirements to support access

Page 60 of the Report states, "*The ability to demonstrate differences in OS is also challenging for cancer medicines when cross-over is allowed. This masks (i.e. 'confounds') the ability to measure the OS from the experimental medicine because patients on both treatment arms receive the experimental medicine. For these reasons, the preference for evidence based on OS measures to support reimbursement decisions may not always be practicable*".

The following example demonstrates the challenges associated with performing cost-effectiveness analyses of oncology medicines when clinical trials of overall survival (OS) include crossover to the active medicine in the comparator arm. Crossover can under-estimate the OS benefit and subsequently the cost-effectiveness associated with the new treatment under evaluation.

A submission was recently made to PBAC for the use of bevacizumab in the first-line treatment of ovarian cancer. The primary sources of evidence used to estimate the effectiveness and safety of bevacizumab, in this setting, are the GOG-0218 and ICON-7 trials. In particular, the population of interest is patients at high-risk of relapse. These trials were not sponsored by Roche, the manufacturer of bevacizumab, but were performed by independent study groups.

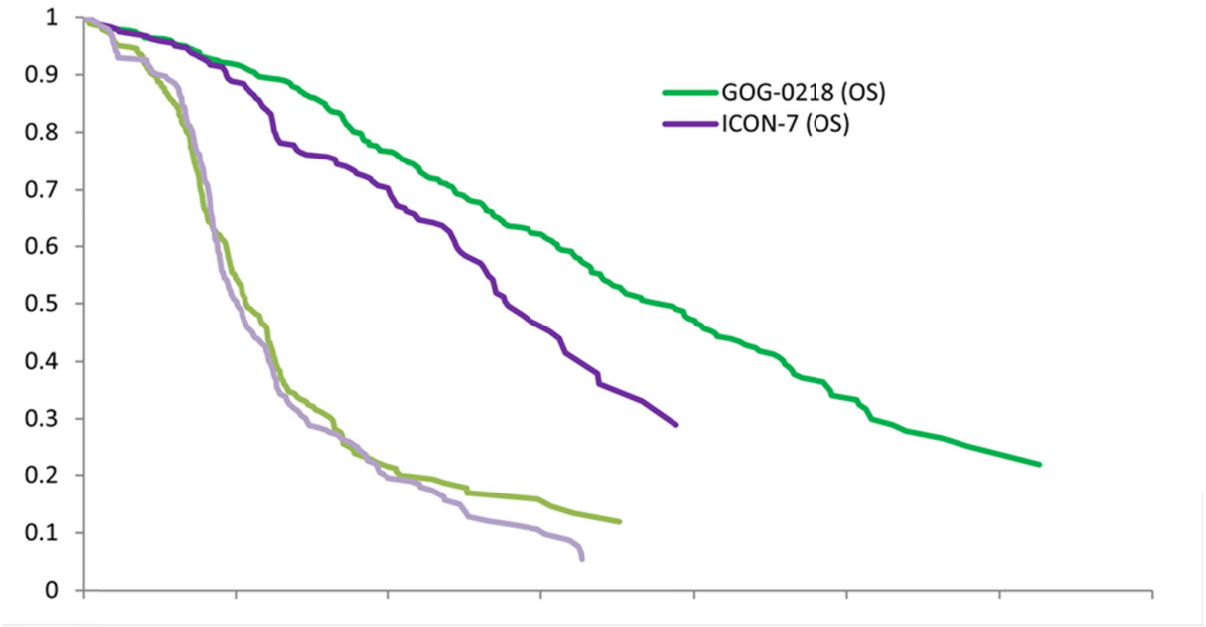
In the GOG-0218 trial, OS in the comparator chemotherapy arm (CP; carboplatin/paclitaxel) was significantly affected by the crossover use of bevacizumab. Following assessment of the primary endpoint at progression on first-line therapy, 27.7% of patients in the control arm received bevacizumab compared to only 15.1% from the active arm. Therefore, crossover to subsequent lines of bevacizumab therapy confounds the true estimate of OS between the active and comparator arms in GOG-0218.

Based on the limited GOG-0218 trial data available to the sponsor from the independent study group, it was not possible to adjust for crossover using statistical methods (e.g. rank preserving structural failure time model etc.) as part of the PBAC submission for bevacizumab in the first-line treatment of ovarian cancer.

In the ICON-7 trial, only 1% of patients received bevacizumab following disease progression. Unlike the GOG-0218 trial whereby crossover and subsequent lines of therapy confound the true estimate of OS, the OS result determined from the ICON-7 trial is likely to more accurately reflect a true estimate of the OS benefit attributable to bevacizumab when used in the first line setting.

For both the GOG-0218 and ICON-7 trials, the median progression-free survival (PFS) results for high-risk patients across comparator (carboplatin/paclitaxel) arms are similar, as would be expected (Figure 2). It is not unexpected that the comparator chemotherapy arms for PFS in both trials mirror one another as shown. However, the results when comparing OS show an almost 11-month difference between these same populations, with clear separation between the Kaplan Meier curves for OS in the chemotherapy arms of GOG-0218 and ICON-7 (Figure 2). Given that there is no difference in the PFS curves for the time that patients are responding to treatment, this is highly suggestive of the separation being due to something occurring after progression and subsequent to completion of first-line bevacizumab therapy. It is argued that this difference is primarily driven by the significant magnitude of crossover to bevacizumab and other antineoplastic therapies allowed in the GOG-0218 trial which was not apparent in the ICON-7 trial.

Figure 2 Comparator carboplatin/paclitaxel PFS and OS curves from GOG-0218 and ICON-7 for the high-risk subgroup



5.3 International comparisons

Australia lags behind other OECD countries, where access to oncology medicines is enabled by one of the following mechanisms systematically employed for medicines:

1. Formal assessments of cost effectiveness are not currently employed but coverage is based on assessments of effectiveness, cost and volume (US Medicare, Medicaid and private health care plans).[1]
2. The HTA process is focused on incremental effectiveness and budget impact and may also take unmet need and level of innovation into consideration. External reference pricing is used to ensure pricing is consistent with economically comparable countries (France, Germany).
3. A formal HTA process comparing both incremental effectiveness and cost is used, but a formal ICER threshold is not applied (The Netherlands, Sweden). This leaves payers with the opportunity to value health gains differently in different therapeutic areas. At the same time, the existence of external reference pricing amongst Western European countries, enables payers in The Netherlands and Sweden to access prices that are no higher than those in other economically comparable EU countries.
4. A formal HTA process comparing both incremental effectiveness and cost is used, but solutions specifically designed to cope with oncology medicines have been introduced (UK, Canada).

Table 5.3 (page 65) of the Report compared the reimbursement status for a number of medicines in Australia with that in other OECD jurisdictions, however only the initial indication is included in the table. In Australia, every indication must undergo an assessment of cost-effectiveness by the PBAC prior to inclusion on the PBS. For each indication, this may require a number of submissions and take several years, leading to further gaps in access between Australia and other countries. The time to reimbursement in key

[1] Coverage in the US does not necessarily equate to access, as patient co-payments vary between plans and may be a barrier to access

OECD markets, including those employing formal HTA processes, for all Roche cancer medicines and indications is summarised in Appendix A. While the time to access in Australia was comparable with that in other countries in the late 1990s and early 2000s, the data show an increasing delay in access in the past decade.

It is also important to note when making comparisons between countries that the level of access may not be equivalent. In Australia, it is now commonplace for medicines to be approved with lengthy PBS restrictions detailing patients' eligibility for initial and ongoing treatment, in order to ensure treatment is directed to patients in whom it will be most cost-effective. This means the population that can be treated may be much narrower than that approved by the TGA. Since the criteria for determining which patients can and cannot be treated are based on the results of diagnostic tests or clinical assessments, inevitably some patients will miss out on treatment because they fail to meet the criteria for access. The implementation of such detailed eligibility criteria also requires significant resources from clinicians, pharmacists, sponsors and government staff to maintain. A comparison of the extent of reimbursement coverage in key OECD markets for all Roche cancer medicines and indications is summarised in Appendix B.

Germany has recently implemented a system where all new medicines and indications are automatically reimbursed at the price set by the sponsor company, with a review of comparative effectiveness conducted during the first 6-months after launch and pricing negotiations completed 12-months after launch.

In France, the HTA agency follows a two-step process involving a technical assessment of comparative effectiveness and a pricing negotiation. The technical assessment includes an appraisal of 'Medical Benefit' which determines whether a medicine should be reimbursed and the reimbursement rate, a grading of the 'Improvement of Medical Benefit' which provides a basis for price fixing in comparison with alternatives, and an opinion on the target population eligible for treatment in the reimbursement scheme. In some cases, the committee recommends reimbursement be restricted for a selection of indications, certain groups of patients or granted only when prescribed by a specialist physician or when the patient meets diagnostic criteria. The committee may also require a commitment from the company to perform studies to assess real-life effectiveness or drug utilisation after reimbursement. The agency reassesses comparative efficacy and safety and may restrict access at a later date.

In jurisdictions that formally assess the incremental cost-effectiveness ratio (ICER), systems have evolved to make allowances for oncology medicines. In the UK, NICE applies a threshold of £30,000/QALY (Quality Adjusted Life Year). However, special guidance applies in circumstances where the following criteria apply:

- the treatment is indicated for patients with a short life expectancy, normally less than 24 months
- there is sufficient evidence to indicate that the treatment offers an extension of life, normally of at least an additional three months, and
- the treatment is licensed, or otherwise indicated, for small patient populations.

If these conditions are met, NICE may take into account an extra QALY weight for the end-of-life health state, thus raising the cost-effectiveness threshold (e.g. to £60,000/QALY if the committee agrees that the QALYs experienced by the patients concerned are worth twice the norm). Vemurafenib was approved by NICE in the UK for metastatic melanoma, with the appraisal report stating, *"The Committee was satisfied*

that vemurafenib met all the criteria for being a life-extending, end-of-life treatment and that the trial evidence presented for this was robust". By contrast, vemurafenib was rejected by the PBAC in Australia at a price no higher than that used in the UK economic evaluation.

Additionally, as discussed in Section 4.5 (page 49) of the Report, the British government established the Cancer Drugs Fund in 2010 to provide an alternate funding mechanism for oncology medicines in England (the fund does not cover Scotland, Wales and Northern Ireland). The fund was established to address differences in observed drug utilisation differences between the UK and other countries, which were particularly pronounced in oncology. The poor access and utilisation of cancer medicines led to pressure to find alternative solutions, and demonstrates the limitations of an ICER-based HTA approach. It was recently announced that the Fund will continue to 2016, beyond the introduction of the Value Based Pricing (VBP) system in 2014. Prime Minister David Cameron said the Cancer Drugs Fund had been a "*massive success*" and added that should he be re-elected he would recommend that it be continued beyond 2016. Health Secretary Jeremy Hunt said the Government had made an exception for cancer because they considered it "*the number one killer and we do think that we had a particular problem with a lack of access to these drugs*." (BBC News, 26 September 2013).

Canada undertakes a Common Drug Review (CDR) to assess new medicines and provide formulary listing recommendations to all publicly funded drug plans (except Québec). In spite of the CDR, significant variability was evident in the availability of cancer medicines between the different provinces. In 2011, a separate approval pathway specifically for oncology medicines was introduced and applies nationally to all provinces (except Québec). The oncology specific pathway is headed by the pan-Canadian Oncology Drug Review (pCODR). Submissions for cancer medicines that may potentially be funded by the participating provincial and territorial drug plans are directed to pCODR who will make a listing recommendation.

While cost effectiveness is an important part of the review, other criteria are also considered with the aim of understanding a broader societal perspective by examining burden of illness, unmet need and, notably, patient values.

In The Netherlands, a new reimbursement system for specialist in-hospital medicines was introduced in January 2012 to facilitate faster market access to new innovative medicines. At the time of market authorisation the drug is conditionally included in the standard insurance package (i.e. drug is reimbursed). Within one year, the value of the drug is assessed, after which reimbursement may be continued, restricted to certain subpopulations or stopped. The comprehensiveness of this evaluation depends on the budget impact and therapeutic value of the drug. Medicines with a low budget impact (<€2.5 million) are not extensively assessed. Full assessments (including therapeutic value, cost-effectiveness and outcomes research proposal) are only performed for medicines with a budget impact of >€2.5 million. However, there is no formal threshold for cost-effectiveness currently since criteria other than efficiency are also important and to date access has not been denied to "essential" medicines that are available in neighbouring countries at the same price. A proposal for outcomes research is required for medicines with a high budget impact, therapeutic added value and where there is limited data at the time of marketing approval. For these medicines it is obligatory to develop further outcomes research. To gather this real-life data, indication-based registries are being developed, in order to gather data not only on the active drug, but on the

comparator as well. Finally, after a predefined period (currently four years), the medicines are re-assessed in terms of effectiveness, cost-effectiveness, budget impact and real-world use. Dependent on (cost-) effectiveness of the drug a final conclusion will be drawn, with funding either continued, restricted to certain subpopulations or withdrawn. To date, no drugs have been withdrawn because of unacceptable cost-effectiveness with the Minister for Health having the final decision making authority.

More and more Australia stands alone, in continuing to apply a 'one-size-fits all' approach to cost-effectiveness thresholds and methodology, regardless of drug or therapeutic area. Although there is no explicit cost-effectiveness threshold in Australia and there is said to be 'wriggle room' (Dr Suzanne Hill, 31 July 2013, Launch of OIT Report), experience suggests that the acceptable threshold is in the range of $45,000 - $60,000. The acceptable threshold declines when any form of clinical, economic and financial uncertainty exists in the economic evaluation. Of note, the World Health Organisation has suggested an ICER range between 1 and 3 times gross domestic product (GDP) per capita as cost-effective (Deloitte Access Economics 2012). In 2012, the Australian GDP per capita was $64,321 and $44,598 adjusted for purchasing power parity (Australian Bureau of Statistics). Using the criteria proposed by the WHO, ICERs in the range of $44,598 - $133,794 would be deemed cost-effective.

In contrast to Australia, other formal HTA systems have adapted to allow for decision making to consider other criteria other than just economic efficiency (e.g. unmet need or rarity of disease). These countries demonstrate a willingness to accept higher ICER thresholds in certain situations or do not impose an ICER threshold. In addition, the process used for evaluation of medicines that claim no additional clinical benefit or have a low budget impact may be bypassed or substantially simplified in other countries. The HTA systems employed by France, Germany, UK, The Netherlands, Sweden and Canada cannot be dismissed as being less sophisticated, given they are invited to participate and recognised in international HTA collaborations.

Chapter 6 Stakeholder views

6.2 Regulatory and reimbursement approval

Co-dependent PBS and MBS process

As mentioned in the Report, the co-dependent process is complex and adds significant time to the review. There are a number of detailed steps that must be undertaken to determine the protocol for review of the diagnostic before the joint drug-diagnostic application can be submitted. This adds approximately 10 months review time to the normal process, and often considerable complexity, with the Protocol Advisory Subcommittee (PASC) requesting information beyond that necessary for the assessment of the drug-diagnostic pair. Additionally, whilst the notion of a single process for the review of technologies is desirable, the process is yet to achieve this. Decisions are made by two separate committees who meet at different times. This necessitates multiple meetings to reach a decision due to the interdependence of their decision-making, adding further time to the review process. Once decisions are made, there are no clear timelines for listing of the diagnostic on the Medicare Benefits Schedule, nor clear guidance on whether PBS listing of a drug can proceed without Medicare Benefits Schedule (MBS) listing.

This means that drug-diagnostic pairings are being penalised by greater complexity and a longer timeframe to patient access than their non-codependent counterparts. Even when the sponsor is willing to fund the cost of diagnostic tests, it is not possible to bypass this complex system. Furthermore, there can be difficulties meeting the evidentiary requirements given Australia is the only country in the world to have implemented health technology assessment for co-dependent technologies

6.3 Value of cancer medicines

Roche position on how the price of a medicine is decided

Stakeholders interviewed for the Report commented that the prices of some cancer medicines are not justified, and that the medicines industry often has unrealistic price expectations. Many stakeholders urged sponsors to provide greater transparency regarding how medicine prices are set in Australia and globally (page 76).

At Roche, our primary contribution is to invent and develop medicines and diagnostics that significantly improve people's lives. We work with many different partners to continuously and sustainably reduce the barriers that prevent people from having access to our products. Our aim is for every person who needs our products to be able to access and benefit from them.

Patients and health consumer organisations, healthcare providers, governments and payers, non-government organisations (NGOs), shareholders, as well as Roche employees are demanding transparency and social responsibility in how we determine our price expectations, resulting in fast access for patients as well as a predictable and sustainable financial performance of both Roche and healthcare systems around the world.

Globally, Roche follows a "value based pricing" approach but does not target a specific cost-effectiveness threshold. Given the various different formal and informal value assessment criteria that payers apply it

would simply be impossible to identify a single threshold that if met would satisfy all payers in all countries. A company operating globally must meet the expectations and value assessment criteria of a relevant large number of payers in order to be successful.

The prices of Roche products (medicines and diagnostics) reflect the value the innovation delivers to patients, their families and societies. When setting prices we consider the clinical benefit relative to available alternatives, the level of medical need addressed, the market situation and the ability of healthcare systems and individuals to afford our products. Based on the many successfully concluded pricing and reimbursement negotiations for our products, it follows that the prices established in these negotiations reflect the value that these products deliver to patients, their families and societies.

When developing pricing assumptions, Roche believes that value has many components in line with the value assessment criteria applied by our customers. In addition to patient outcomes (mortality, morbidity and quality of life) this includes improvements in efficiency of healthcare delivery, avoiding unnecessary treatments and procedures, and improving drug administration and compliance in treatment.

When deciding on the Australian price, as with every country, Roche assesses the viability of a price that is fully aligned with the anticipated willingness to pay of the Australian payer for a specific medicine. Of major concern in this viability assessment is the comparability of the optimal price for Australia with prices in economically comparable countries. On one hand, this ensures that prices requested for Australia are no higher than those requested in economically comparable countries. On the other hand, this may mean in some cases that prices requested in Australia are considerably higher than the price that would be considered cost-effective under the Australian HTA system.

If a medicine was only to be sold in Australia, it would be possible to reach a price agreement in line with the local buyers' willingness to pay for most medicines. However, since Roche sells products globally, the company must anticipate the interdependencies of prices that could potentially be achieved in various markets. While a pharmaceutical payer in one country may be willing to tolerate price differences aimed at addressing a substantially different ability to pay between payers (e.g. between Germany and Romania), such differential treatment will certainly be less tolerated when it is simply due to a different HTA methodology applied rather than ability to pay. Payers are not concerned with the details of different HTA methodologies applied by payers abroad. Rather, they simply demand the same low prices found abroad. This restricts the ability of a company like Roche to grant price concessions exclusively to payers that apply different HTA methodologies but are otherwise economically comparable.

The prices requested for the Australian market are no higher than those implemented in economically comparable countries such as those in Western Europe. As a reflection of the international price dependencies (external reference pricing and parallel trade), Roche Australia operates within a global pricing band set by the parent company and cannot price below this band.

This global pricing band is set after consideration of a number of factors including payer research. This payer research is typically conducted for the largest markets (France, Germany, UK, Spain, Italy and US) and seeks to understand the value a payer subscribes to the outcomes provided by the new medicine. The payers' willingness to pay in these economically comparable countries takes into consideration the unmet

need, clinical benefit, budget impact and degree of innovation. Access is granted in most of these markets because Roche requests prices for its medicines in line with willingness and ability to pay. Roche simply cannot afford to ignore the expectations of these markets, since commercial success relies on reimbursement in the largest markets.

Markets of similar wealth to Australia (i.e. similar proportion of GDP spent on health) are willing and able to pay the global price. Australia is ranked by the International Monetary Fund as the 5th wealthiest country in the world based on GDP per capita (using current prices and USD). This means that as a country Australia has an ability to pay comparable to countries in Western Europe.

However, access is frequently denied as Australia's decision to fund is made on the basis of allocative efficiency that considers only the opportunity cost to the health system using a threshold for cost-effectiveness lacking empirical foundation, instead of society's willingness and ability to pay. Although there is no explicit cost-effectiveness threshold in Australia, and the PBAC Guidelines state that other factors (e.g. societal values) are taken into consideration, there is no transparency in how final decisions are made by the PBAC, and what weighting is given to these other factors.

Page 77 of the Report states, "*Various stakeholders noted that pricing of medicines should be considered in light of the value the Australian community places on the benefits of these medicines. Various stakeholders noted that the Australian community has limited input into the current decision-making processes of Government, and there is little provision within the decision-making framework for considering the value these new medicines provide to the broader community*".

In a two-stage survey, a cross-section of Australians was questioned about the importance of costs in setting priorities in health care. The results suggest that allocation of resources based only on opportunity cost (allocative efficiency) is not shared by the general public since they feel it is unfair to discriminate against patients with a high-cost illness. Hence, the cost-effectiveness approach to assigning priorities in health-care may be imposing an excessively simple value system upon resource allocation decision making (Nord et al, 1995).

It is important that the Australian community has a voice in determining what society believes is value for money in the determination of drug reimbursement and in determining equity principles. In valuing a medicine, it is important to consider: health benefits to patients; non-health benefits to patients such as productivity; benefits to carers and family; and benefits to society, the healthcare system and the social system (Lloyd Sansom, former Chair of the PBAC; 13 September 2013; personal communication at Roche Town Hall meeting). These values can only be derived through:

- Systematic research to determine a cost-effectiveness threshold that reflects modern Australia's preferences for healthcare.
- Citizen and ethicist involvement to develop a clear set of decision-making principles that reflect society's views as to whether factors such as burden of illness, unmet need and indirect costs such as productivity, should be considered in the process.
- Routine consumer, patient and ethicist input into the funding decision for each medicine.

These decision-making frameworks have been implemented in other HTA markets (e.g. the UK, Scotland, Canada and The Netherlands). Whilst these countries follow a similar assessment process based on cost-effectiveness, societal considerations are also taken into consideration when making access decisions.

The goals of the Australian National Medicines Policy are: healthy consumers; quality use of medicines; equity of access; quality, safety and efficacy; and a viable and responsible pharmaceutical industry. All of these components need to be co-ordinated to ensure the ultimate goal of healthy consumers is achieved.

Considering the value of a medicine over its lifetime

It is also important to remember the value of a medicine continues beyond patent expiry, when generic and biosimilar competitors drive the price down markedly. In most cases, this occurs after 10 – 12 years on the market. When assessing the value of a medicine, it is therefore important to consider value over the entire lifetime of the medicine.

Two examples are provided to illustrate the value of a medicine before and after patent expiry.

Cost-effectiveness of mycophenolic acid before and after patent expiry

An analysis was performed changing the price of the originator brand of mycophenolic acid (CELLCEPT®) from that accepted in the original PBAC submission to the current price which has significantly decreased since the availability of generic competition, the move to Formulary 2 (F2) and the introduction of price disclosure.

Results showed that with patent expiry and the introduction of generics, mycophenolic acid became cost saving in renal transplantation per additional patient free of rejection and per additional patient with a functioning graft (Table 2). The ICER for cardiac transplantation reduced by 2.6-fold. This analysis comes with the caveats around use of models from 13-16 years ago, without reviewing the need for evolution of model structure.

Table 2 ICERS (LYS) over the lifecycle of mycophenolic acid

PBS Indication	Year	ICER in PBAC Submission	ICER using PBS pricing for mycophenolic acid Dec 2013 (implementation of next price reduction)
Renal transplant	1997	$11,010 / extra patient free of rejection $46,421 / extra patient with functioning graft	Cost saving / extra patient free of rejection Cost saving / extra patient with functioning graft
Cardiac transplant	2000	$74,540/ LYS $65,770 / extra patient free of rejection	$29,203/ LYS $25,767 / extra patient free of rejection

Abbreviations: LYS=life-year saved

Although mycophenolic acid is not an oncology therapy, this example demonstrates the importance of assessing the value of any medicine over its entire lifecycle, not just at the time of PBS listing.

Cost-effectiveness of paclitaxel across indications before and after patent expiry

An analysis was performed changing the price of the originator brand of paclitaxel (TAXOL) from that accepted in the original PBAC submission to the current price with the availability of generic competition, the move to F2 and the introduction of price disclosure.

Results showed that with patent expiry and the introduction of generics, the ICER for paclitaxel reduced four-fold for the ovarian cancer restriction and 12-fold for the breast cancer restriction. For the adjuvant breast cancer restriction, paclitaxel became cost saving with the introduction of generics. This analysis comes with the caveats around use of models from 13-19 years ago, without reviewing the need for evolution of model structure.

Table 3 ICERS (LYS) over the lifecycle of paclitaxel

PBS Indication	Year	ICER in PBAC Submission	ICER using PBS pricing for paclitaxel September 2013
Ovarian cancer	1994	$22,486/ LYS	$5,846/ LYS
Breast cancer	1997	$14,462/ LYS	$1,182/ LYS
Adjuvant breast cancer	2000	$16,991/ LYS	Dominant (cost-saving)

Source: Provided to Roche Products by Bristol-Myers Squibb
Abbreviations: LYS=life-year saved

Without the initial introduction of the originator brand of medicines, this additional long-term value with the introduction of generic medicines would never be realised. These analyses highlight the importance of looking at value of a medicine over its entire lifecycle.

Incentives for R&D

Stakeholders interviewed for the Report acknowledged the challenges and risks facing the medicines industry in the development of new medicines (page 76). They also acknowledged the need to maintain a viable medicines industry by providing sufficient commercial incentives, so that the industry can continue to introduce new medicines to benefit cancer patients (page 76). Many countries now utilise cost effectiveness methods to inform the pricing of health care technologies. In parallel, several countries' industrial policy and reimbursement mechanisms aim to reward innovation of pharmaceuticals. Therefore, understanding scenarios where the application of incremental cost-effectiveness analysis and promotion of innovation are not aligned is of importance to healthcare policy makers and decision makers.

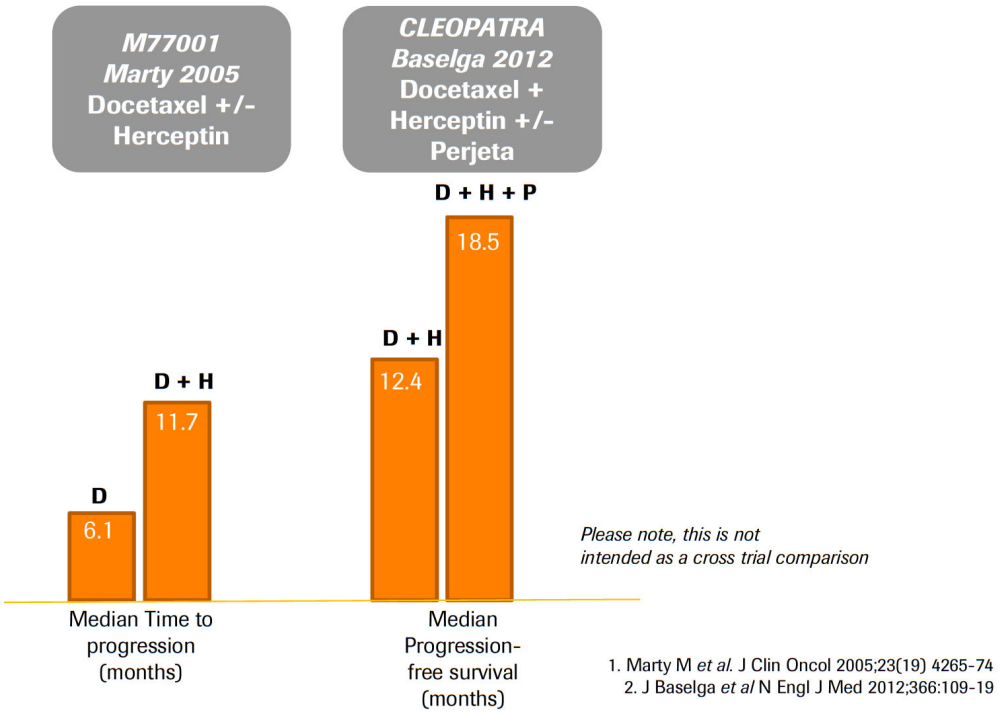
This example shows the disincentives associated with the development of a new biological medicine for advanced breast cancer, which is add-on therapy to the existing standard of care.

"Zero price medicines" analysis

A cost-utility model for a metastatic oncology therapy from a UK perspective (pertuzumab (Perjeta) for the first-line treatment of metastatic breast cancer (mBC)) was used to demonstrate this issue. The model evaluates pertuzumab used in combination with trastuzumab (Herceptin) plus docetaxel (an existing standard of care therapy). Adding pertuzumab to trastuzumab plus docetaxel extends median PFS by approximately 6 months, or a 50% improvement (Figure 3). An increase in OS is also predicted – the median OS was 37.6 months in the trastuzumab plus docetaxel arm, and has not been met in the

pertuzumab, trastuzumab plus docetaxel arm (lower 95% CI: 42 months). Within the modelled economic evaluation, the mean overall quality-adjusted survival gain is > 6 months.

Figure 3 Results associated with adding pertuzumab to standard of care in first-line metastatic breast cancer



Abbreviations: D=docetaxel; H=Herceptin (trastuzumab); P=Perjeta (pertuzumab)

At an incremental cost-effectiveness ratio (ICER) threshold of £20,000/QALY gained, total background costs exceeded the acceptable incremental cost, despite clinically significant QALY gains exceeding 6 months (Figure 4). The total cost of pertuzumab, trastuzumab and taxane would need to be lower than the cost of trastuzumab plus taxane (without pertuzumab) in order to achieve the ICER threshold. Pertuzumab would need to be priced at –£198 for an 18.5 month course to achieve this ICER threshold. Or in other words, no positive price is permissible for this ICER. At an ICER threshold of £30,000/QALY gained, the acceptable incremental cost which can be attributed to pertuzumab is £306 per month for an 18.5 month course (Figure 5).

Figure 4 Acceptable incremental cost at £20,000/QALY threshold

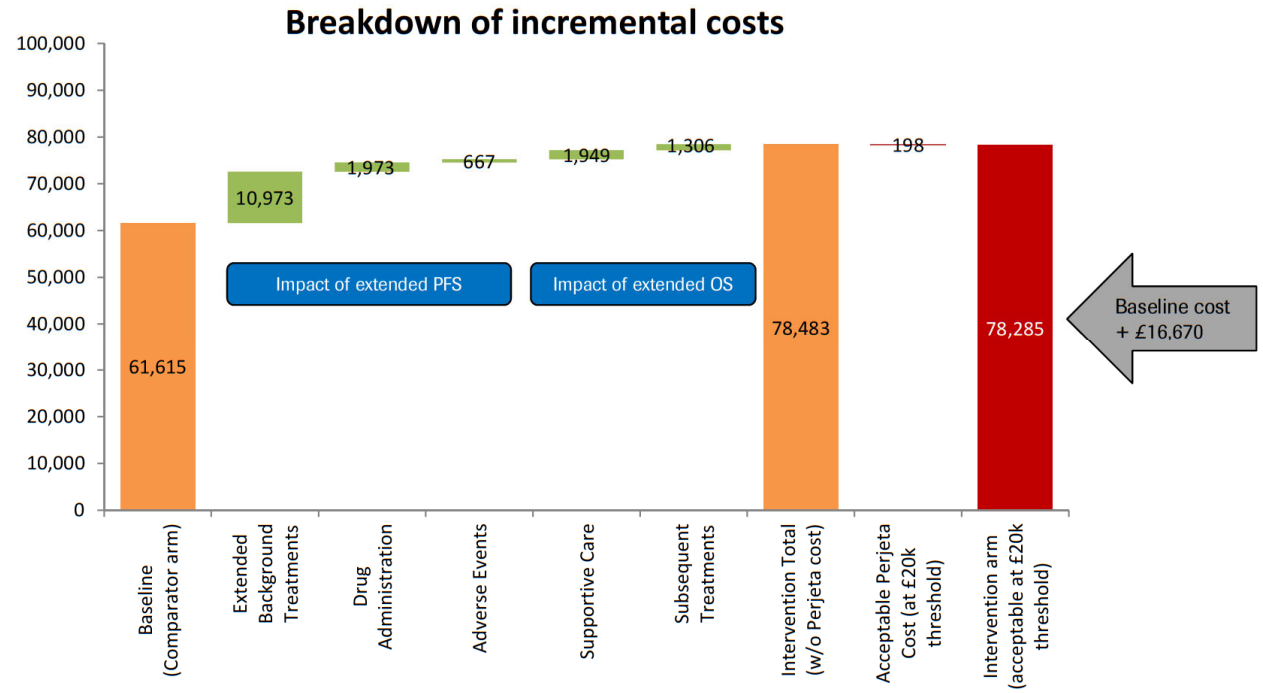
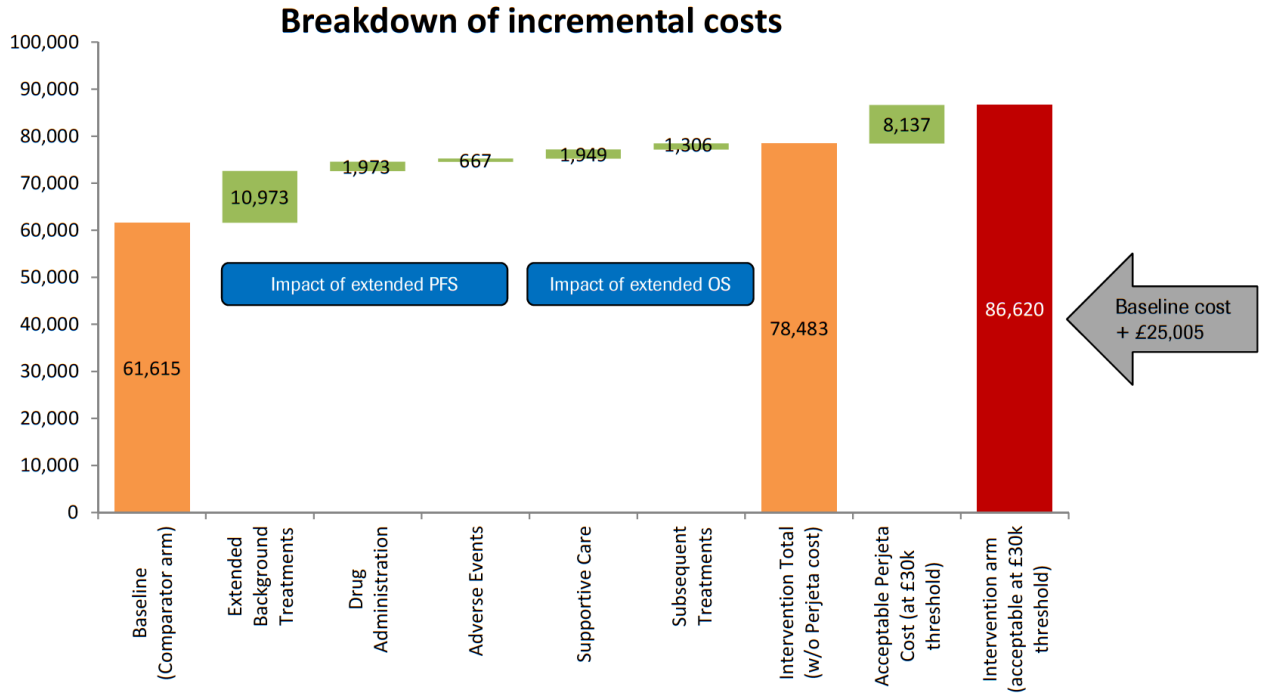
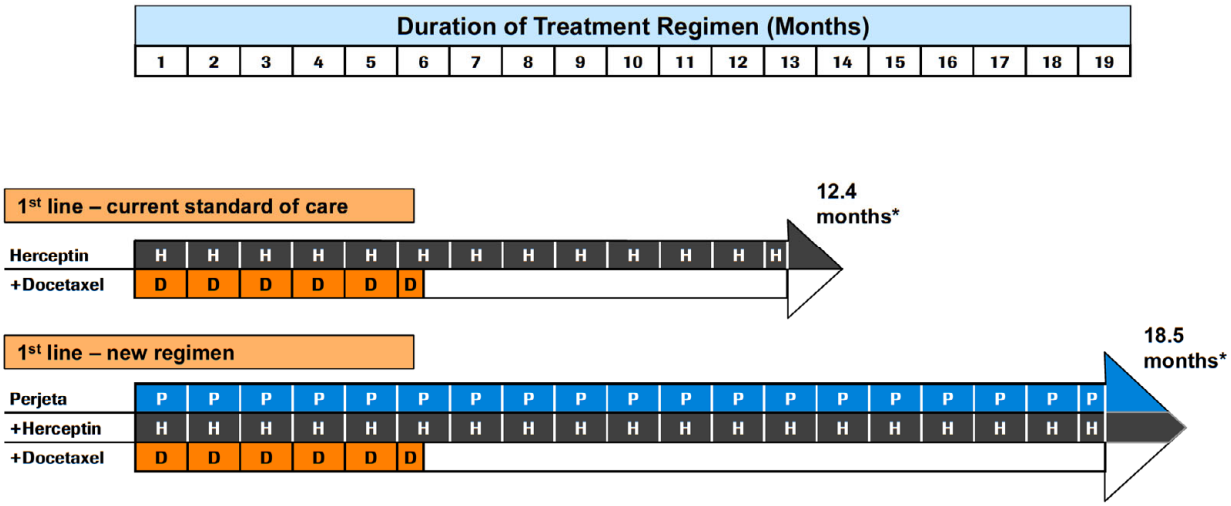


Figure 5 Acceptable incremental cost at £30,000/QALY threshold



This outcome is largely explained by the combination therapy being administered until tumour progression which extends the duration and cost of the existing standard of care (Figure 6).

Figure 6 Increased effectiveness of combination therapy increases cost of standard of care



For every month of progression-free survival gained, the cost of background therapy is also increased. Therefore, incremental costs are generated by the background therapy, including administration and monitoring costs, to a level where no or limited "headroom" is left for the new medicine to generate costs and remain below the threshold. It is common for clinical trials of new oncology medicines to add the investigational agent to background therapy, rather than replace the existing therapy (as done in other therapeutic areas) because of the risk to the patient if the new medicine is not effective.

If cost utility threshold-based decision rules are used to directly calculate price, under plausible scenarios for many oncology medicines, the innovation that generates additional patient benefit cannot be awarded a price. Instead the permissible incremental cost is captured by the cost of the existing standard of care. Consequently, there is no incentive or reward for the development of such a medicine, which may represent a significant breakthrough in a therapeutic area.

The required reduction in price would remove commercial viability to develop new treatments. The only other alternative would be to wait for background therapies to lose patent prior to approval in ICER threshold countries; which is associated with inequality of patient access. It is clear that, without changes to the current Australian HTA approach, it will not be possible to make many new technologies available to Australian patients. This is particularly true for combination treatments which are commonplace in oncology. An ICER-based system with an undifferentiated ICER threshold, by virtue of the mere methodology applied, will never show an acceptable outcome for such combination treatments, given the extension of treatment duration and follow-up of patients.

"Cost of a cup of coffee" analysis

An alternative analysis was performed using the same oncology combination therapy. By applying a hypothetical cost of AUD$4 (or the cost of a cup of coffee) per vial of pertuzumab, the ICER associated with pertuzumab plus trastuzumab plus docetaxel compared with trastuzumab plus docetaxel is $60,000-$70,000 per QALY gained. This would likely be considered higher than the acceptable threshold for cost-effectiveness by the PBAC.

In other words, an innovative medicine adding half a year of life to the standard of care, as well as benefits in quality of life, cannot be priced at the same price as a cup of coffee in order to be deemed cost-effective and meet the criteria for funding in Australia.

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About Roche

Headquartered in Basel, Switzerland, Roche is a leader in research-focused healthcare with combined strengths in pharmaceuticals and diagnostics. Roche is the world's largest biotech company with truly differentiated medicines in oncology, infectious diseases, inflammation, metabolism and neuroscience. Roche is also the world leader in in-vitro diagnostics and tissue-based cancer diagnostics and a frontrunner in diabetes management. Roche's personalised healthcare strategy aims at providing medicines and diagnostic tools that enable tangible improvements in the health, quality of life and survival of patients.

Roche's anti-cancer medicines include nine products approved for use in Australia: Avastin (bevacizumab) in advanced breast cancer, advanced colorectal (bowel) cancer, advanced non-small cell lung cancer, advanced renal cell (kidney) cancer, advanced ovarian cancer and advanced brain (glioma) cancer; Erivedge (vismodegib) in advanced basal cell carcinoma; Herceptin (trastuzumab) in early and advanced breast cancer, and advanced gastric (stomach) cancer; Kadcyla (trastuzumab emtansine) in advanced breast cancer; MabThera (rituximab) in non-Hodgkin's lymphoma (NHL) and chronic lymphocytic leukaemia (CLL); Perjeta (pertuzumab) in advanced breast cancer; Tarceva (erlotinib) in advanced non-small cell lung cancer and advanced pancreatic cancer; Xeloda (capecitabine) in advanced breast cancer, early colon cancer, advanced colorectal cancer and advanced oesophagogastric cancer; and Zelboraf (vemurafenib) in advanced melanoma.

In addition to medicines, Roche is developing new diagnostic tests that may have a significant impact on disease management for cancer patients in the future. With a broad portfolio of tumour markers as well as a range of molecular oncology tests, Roche will continue to be one of the leaders in providing cancer-focused treatments and diagnostics.

In 2012, Roche invested over 8 billion Swiss francs in research and development worldwide, including approximately $36 million (AUD) in pharmaceuticals in Australia. Genentech, in the United States, is a wholly owned member of the Roche Group. Roche is the majority shareholder in Chugai Pharmaceutical, Japan. For more information: www.roche-australia.com.

Appendix A Comparison of reimbursement and time to reimbursement by indication for Roche products across key OECD markets

Product and Indication	Australia			US[b]			France			Germany[c]			The Netherlands			UK			Canada		
	Reimbursed	Date of Access	Time to Access[a]	Reimbursed	Date of Access	Time to Access[a]	Reimbursed	Date of Access	Time to Access[a]	Reimbursed	Date of Access	Time to Access[a]	Reimbursed	Date of Access	Time to Access[a]	Reimbursed	Date of Access	Time to Access[a]	Reimbursed	Date of Access[f]	Time to Access[a]
Bevacizumab																					
1L mCRC	Yes	07/09	**50**	Yes	02/04	**0**	Yes	09/05	**8**	Yes	01/05	**0**	Yes	01/05	**0**	CDF	10/10	**70**	Yes	06-09	**4+**
mBC	No	-	**-**	Not indicated			Yes	12/07	**7**	Yes	03/09	**0**	Yes	04/07	**1**	CDF	10/10	**44**	Not indicated		
RCC	No	-	**-**	Yes	07/09	**0**	Yes	09/08	**9**	Yes	12/07	**0**	Yes	01/08	**1**	No	-	**-**	Not indicated		
NSCLC	No	-	**-**	Yes	10/06	**0**	Yes	05/08	**9**	Yes	08/07	**0**	Yes	09/07	**1**	No	-	**-**	No	-	-
Relapsed GBM	No	-	**-**	Yes	05/09	**0**	Not indicated			Not indicated			Not indicated			Not indicated			Yes	11-13	**9+**
1L OC	UE	-	**18+**	Not indicated			Yes	12/12	**12**	Yes	12/11	**0**	Yes	09/12	**9**	CDF	12/11	**0**	Not indicated		
Recurrent OC	No	-	**-**	Not indicated			Yes	09/12	**0**	Yes	09/12	**0**	Yes	04/13	**7**	CDF	09/12	**0**	Not indicated		
Capecitabine																					
mBC (monoTx)	Yes	11/99	**18**	Yes	04/98	**0**	Yes	03/02	**0**	Yes	03/02	**0**	Yes	03/02	**0**	Yes	05/03	**15**	Yes	07/99	**11**
1L mCRC	Yes	05/01	**4**	Yes	04/01	**0**	Yes	07/01	**5**	Yes	01/01	**0**	Yes	01/01	**0**	Yes	05/03	**29**	Yes	02-06	**24+**
mBC (+ taxane)	Yes	11/02	**3**	Yes	09/01	**0**	Yes	03/02	**0**	Yes	03/02	**0**	Yes	03/02	**0**	Yes	03/02	**0**	Yes	06/02	**0**
Adjuvant CRC	Yes	4/06	**7**	Yes	6/05	**0**	Yes	12/06	**21**	Yes	3/05	**0**	Yes	3/02	**0**	Yes	04/06	**14**	Yes	09/06	**9**
GC	Yes	8/10	**37**	Not indicated			Yes	8/08	**17**	Yes	3/07	**0**	Yes	3/07	**0**	Yes	07/10	**41**	Not indicated		
XELOX mCRC	Yes	8/10	**28**	Not indicated			Yes	8/09	**18**	Yes	2/08	**0**	Yes	2/08	**0**	Yes	02/08	**0**	Not indicated		
Oesophagogastric	Yes	8/10	**18**	Not indicated			Not indicated			Not indicated			Not indicated			Not indicated			Yes	08-12	**0+**
Erlotinib																					
2/3L NSCLC	Yes	8/08	**31**	Yes	11/04	**0**	Yes	8/06	**11**	Yes	9/05	**0**	Yes	5/06	**8**	Yes	11/08	**31**	Yes	05-07	**5+**
Pancreatic	No	-	**-**	Yes	11/05	**0**	No	-	**-**	Yes	1/07	**0**	Yes	1/07	**0**	No	-	-	Not indicated		
1L maintenance NSCLC	No	-	**-**	Yes	4/10	**0**	No	-	**-**	Yes	4/10	**0**	Yes	6/10	**2**	No	-	-	No	-	**-**
1L EGFR+ NSCLC	UE	-	**36+**	Yes	5/13	**0**	Yes	6/12	**10**	Yes	8/11	**0**	Yes	9/11	**1**	Yes	06/12	**11**	No	-	**-**
Pertuzumab																					
1L mBC	TBS	-	-	Yes	6/12	**0**	Yes[g]	01/14	**10**	Yes[c]	3/13	**0**	Yes	3/13	**0**	CDF	3/13	**0**	Yes[g]	01/14	14+
Rituximab																					
Relapsed & iNHL	Yes	2/99	**6**	Yes	11/97	**0**	Yes	12/98	**6**	Yes	6/98	**0**	Yes	6/98	**0**	Yes	6/98	**0**	Yes	01-03	**9+**
DLBCL	Yes	07/03	**15**	Yes	02/06	**0**	Yes	10/03	**19**	Yes	03/02	**0**	Yes	03/02	**0**	Yes	09/03	**19**	Yes	02-04	**0+**
1L iNHL + CVP	Yes	08/06	**15**	Yes	09/06	**0**	Yes	06/05	**10**	Yes	08/04	**0**	Yes	08/04	**0**	Yes	08/04	**0**	Yes	05-07	**0+**

Product and Indication	Australia			US[b]			France			Germany[c]			The Netherlands			UK			Canada		
	Reimbursed	Date of Access	Time to Access[a]	Reimbursed	Date of Access	Time to Access[a]	Reimbursed	Date of Access	Time to Access[a]	Reimbursed	Date of Access	Time to Access[a]	Reimbursed	Date of Access	Time to Access[a]	Reimbursed	Date of Access	Time to Access[a]	Reimbursed	Date of Access[f]	Time to Access[a]
1L follicular NHL	Yes	08/06	**0**	Yes	09/06	**0**	Yes	10/08	**9**	Yes	01/08	**0**	Yes	01/08	**0**	Yes	02/08	**1**	Yes	05-07	**0+**
1L CLL	Yes	12/11	**28**	Yes	02/10	**0**	Yes	01/10	**11**	Yes	02/09	**0**	Yes	01/09	**-1**	Yes	07/09	**5**	Yes	09-11	**0+**
Relapsed CLL	Yes	12/11	**23**	Yes	02/10	**0**	Yes	07/12	**23**	Yes	08/09	**0**	Yes	01/09	**-7**	Yes	07/10	**18**	Yes	16/11	**8-11**
Trastuzumab																					
mBC	No[d]	12/01	**17**	Yes	09/98	**0**	Yes	05/01	**8**	Yes	08/00	**0**	Yes	08/00	**0**	Yes	03/02	**20**	Yes	00-02	**8+**
Adjuvant eBC	Yes	10/06	**6**	Yes	11/06	**0**	Yes	10/06	**5**	Yes	05/06	**0**	Yes	01/06	**-3**	Yes	08/06	**4**	Yes	05-07	**-6+**
1L GC	No	-	**-**	Yes	01/12	**0**	Yes	02/11	**23**	Yes	1/10	**0**	Yes	01/10	**0**	Yes	11/10	**11**	Yes	10-12	**-6+**
Neoadjuvant eBC	Yes	12/12	**6**	Not indicated			Yes	01/13	**13**	Yes	12/11	**0**	Yes	12/11	**0**	Yes	12/11	**0**	Not indicated		
Trastuzumab emtansine																					
2/3L mBC	UE[e]	-	**-**	Yes	2/13	**0**	Not yet approved			Not yet approved			Not yet approved			Not yet approved			UE		
Vemurafenib																					
mM	No	-	**-**	Yes	8/11	**0**	Yes	2/13	**12**	Yes[c]	2/12	**0**	Yes/UE	9/12	**7**	Yes	12/12	**0**	Yes	12/13	4+
Vismodegib																					
Advanced BCC	No	-	**-**	Yes	1/12	**0**	UE			Yes[c]	7/13	**0**	Yes	8/13	**1**	CDF	7/13	**0**	UE		

Notes:

a Time from regulatory approval to reimbursement in months. In The Netherlands, this may be negative due to retrospective effect of funding decisions.

b Coverage effective from regulatory approval. However, Medicare systems may take 30 days to update; States may take up to 6 months to update Medicaid systems

c Coverage effective from regulatory approval. Since 2011, a dossier is submitted outlining clinical benefit to inform pricing negotiations conducted 12-months after launch. Reimbursement can be withdrawn if an agreement on price is not reached. Pertuzumab and vismodegib are awaiting review. Vemurafenib is subject to further review.

d Not listed on PBS; funded via a separate Government fund

e Initial submission rejected; a resubmission is planned

f Reimbursement is granted at the provincial level and therefore dates vary across provinces.

g Positive recommendation, reimbursement not yet effective.

h Yes if reimbursed under National Health Scheme after review by NICE. CDF if funded in England only, via the Cancer Drugs Fund.

Abbreviations: 1L=first line, mCRC=metastatic colorectal cancer, mBC=metastatic breast cancer; RCC=renal cell carcinoma; NSCLC=non-small cell lung cancer; GBM=glioblastoma, OC=ovarian cancer, monoTx=monotherapy, CRC=colorectal cancer, GC=gastric cancer, XELOX=Xeloda + oxaliplatin, 2/3L=second/third line, EGFR+=Epithelial growth factor receptor positive, iNHL=indolent non-Hodgkin's Lymphoma, DLBCL=Diffuse large B-cell lymphoma, CLL=Chronic Lymphocytic Leukaemia, eBC=early breast cancer, mM=metastatic melanoma; BCC=basal cell carcinoma, UE=under evaluation, TBS=to be submitted

Appendix B Comparison of breadth of reimbursement by indication for Roche products across key OECD markets

Product and Indication	Restrictions to Reimbursed Patient Population						
	Australia	**US**	**France**	**Germany**	**The Netherlands**	**UK**	**Canada**
Bevacizumab							
1L mCRC	1L only. WHO PS 0 & 1. Dosage restricted.	Per label	Per label	Per label	Per label	Induction only	Restricted
mBC	-	Not indicated	Per label	Per label	1L HER2– + paclitaxel, when anthracycline contraindicated	Triple (oestrogen & progesterone receptor, HER2) negative only	-
RCC	-	Per label	Per label	Per label	1L + interferon alfa-2a. Patients with good or intermediate prognosis	-	-
NSCLC	-	Per label	Per label	Per label	1L + carboplatin + paclitaxel. Excludes squamous cell	-	-
Relapsed GBM	-	Per label	Not indicated	Not indicated	Not indicated	Not indicated	Restricted
1L OC	Subgroup with high risk of relapse requested	Not indicated	Per label	Per label	Per label	7.5 mg/kg only. High risk population.	-
Recurrent OC	-	Not indicated	Per label	Per label	Per label	Per label	-
Multiple lines mCRC	-	Per label	Per label	Per label		-	-
Capecitabine							
mBC (monoTx)	Per label	Per label	Per label	Per label	Per label	Per label	Per label
1L mCRC	Per label	Per label	Per label	Per label	Per label	Per label	Per label
mBC (+ taxane)	Per label (docetaxel)	Per label	Per label	Per label	Per label	Per label	Per label
Adjuvant CRC	Stage III (Duke's C) only	Per label	Per label	Per label	Per label	Per label	Restricted
Gastric cancer	Stage III/IV oesophagogastric cancer only.	Not indicated	Per label	Per label	Per label	Per label	Not indicated
Oesophagogastric cancer	Stage III/IV. Cisplatin only.	Not indicated	Not indicated	Not indicated	Not indicated	Not indicated	Not indicated

Product and Indication	Restrictions to Reimbursed Patient Population						
	Australia	**US**	**France**	**Germany**	**The Netherlands**	**UK**	**Canada**
	WHO PS <2						
XELOX mCRC	Per label	Not indicated	Per label	Per label	Per label	Per label	Per label
Erlotinib							
2/3L NSCLC	Stage IIIB, IV. WHO PS <3 3L or 2L where docetaxel/pemetrexed not indicated[a]	Per label	Per label	Per label	Per label	2L only	Per label
Pancreatic	-	Per label	-	Per label	Per label	-	-
1L maintenance NSCLC	-	Per label	-	Per label	Per label	-	-
1L EGFR+ NSCLC	UE	Per label	Per label	Per label	Per label	Per label	-
Pertuzumab							
1L mBC	Per label	Per label	Per label	Per label	Per label	Per label	-
Rituximab							
Relapsed & iNHL	Per label	Per label	Per label	Per label	Per label	Per label	Per label
DLBCL	1L only	Per label	Per label	Per label	Per label	Per label	Per label
1L iNHL	With chemo only	Per label	Per label	Per label	Per label	Per label	Per label
1L CLL/relapsed CLL	With fludarabine & CYP only.	Per label	Per label	Per label	Per label	Per label	Per label
Trastuzumab							
mBC	HER2+ (ISH+, IHC 3+, IHC2+ & ISH+) Monotherapy or with taxanes.	Per label	Per label	Per label	Per label	IHC3+ only	Restricted
Adjuvant eBC	HER2 positivity by ISH 52 weeks only	Per label	Per label	Per label	Per label	Per label	Restricted
1L GC	-	Per label	Per label	Per label	HER2+ (IHC 3+, IHC2+ & ISH+)	IHC3+ only	Restricted
Neoadjuvant eBC	Locally advanced only HER2 positivity by ISH 52 weeks only	Not indicated	Per label	Per label	Per label	Per label	Not indicated
Trastuzumab emtansine							
2/3L mBC	UE	Per label	Not yet approved	Not yet approved	Not yet approved	Not yet approved	-

Product and Indication	Restrictions to Reimbursed Patient Population						
	Australia	**US**	**France**	**Germany**	**The Netherlands**	**UK**	**Canada**
Vemurafenib							
mMelanoma	-	Per label	Per label	Per label	Per label	Per label	Patients with ECOG>1 &/or brain mets excluded in some provinces. 1L only in Quebec
Vismodegib							
Advanced BCC	-	Per label	Pending	Per label	Per label	Per label	-

Notes:

a Under review.

Abbreviations: CYP=cyclophosphamide; WHO PS=World Health Organization Performance Status; UE=Under evaluation