

Stakeholder meeting statement

Breast cancer treatment with anti-human epidermal growth factor receptor 2 (anti-HER2+) monoclonal antibody drugs

A stakeholder meeting was held on 28 May 2014 to discuss how the treatment of breast cancer in clinical practice will change with the availability of new anti-human epidermal growth factor receptor 2 (anti-HER2+) monoclonal antibody drugs (here on referred to as 'anti-HER2+ drugs') pertuzumab and trastuzumab emtansine, particularly in regards to the sequencing of therapies, partnering of therapy (i.e. understanding if drugs will be used in conjunction with other drugs/therapies) and the proportional use of these new drugs relative to existing drugs. An understanding of these issues is critical to the PBAC making informed judgements on submissions seeking to list new anti-HER2+ drugs and/or alter existing Pharmaceutical Benefits Scheme (PBS) listings as they have flow-on effects on considerations of the appropriate economic comparisons and expected financial budgetary impact for the Commonwealth.

Stakeholders including members of the Pharmaceutical Benefits Advisory Committee (PBAC), Medical Oncology Group Australia (MOGA), Cancer Australia, ANZ Breast Cancer Trials Group, Breast Cancer Network Australia, Roche Products Pty Ltd, GlaxoSmithKline Pty Ltd and the Department of Health participated in the meeting.

Background to this meeting

For greater context, this meeting statement should be read in conjunction with the March 2014 PBAC meeting Public Summary Documents relating to the considerations of pertuzumab and trastuzumab emtansine submissions. These are located through the following website link:

<http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2014-03>

At the March 2014 PBAC meeting, the PBAC deferred making a recommendation on listing pertuzumab and trastuzumab emtansine to enable it to first consider, establish and accept the cost-effectiveness of trastuzumab for the treatment of metastatic breast cancer (which is currently available via a Commonwealth funded program separate to the PBS), before making a judgement on the cost-effectiveness of all anti-HER2+ drugs in metastatic breast cancer, including trastuzumab emtansine and pertuzumab.

A positive PBAC recommendation to list pertuzumab and trastuzumab emtansine would depend on the PBAC being sufficiently satisfied that listing trastuzumab on the PBS for HER2-positive metastatic breast cancer is acceptably cost-effective. This is not yet the case. In view of the improved survival benefit that pertuzumab and trastuzumab emtansine have to offer, the PBAC considered it to be productive to engage with the sponsor, professional and patient advocacy groups and the sponsor of lapatinib outside of the formal PBAC submission process, in an endeavour to progress the potential updated PBS listings of all four anti-HER2+ drugs: trastuzumab, pertuzumab, trastuzumab emtansine and lapatinib.

Place in therapy of the new anti-HER2+ drugs

Current treatment practice of breast cancer as reflected through existing PBS restrictions divide breast cancer into 'early' disease and 'late/advanced' disease. For patients with early HER2+ breast cancer who have undergone surgery, PBS-subsidised trastuzumab with

adjuvant chemotherapy is available to patients. For patients with locally advanced HER2+ breast cancer, PBS-subsidised trastuzumab with neoadjuvant chemotherapy is available to patients. For patients with metastatic HER2+ breast cancer, trastuzumab in combination with taxanes (including docetaxel, paclitaxel or nab-paclitaxel) for patients who have not received chemotherapy for metastatic disease, or, trastuzumab as monotherapy for patients who have received one or more chemotherapy regimen(s) for metastatic disease, is available through the Late Stage Metastatic Breast Cancer program separate to the PBS (here on referred to as the 'Herceptin Program'). PBS subsidised lapatinib in combination with capecitabine, is available to patients where disease has progressed despite treatment with a taxane and trastuzumab for metastatic disease.

Based on drug-utilisation data presented at the meeting, it was noted that:

- The number of new patients on the Herceptin programme was stable at approximately 40 new patients per month;
- The cumulative number of registered patients on the programme was approximately 5,600 as of 28 February 2014;
- The number of active patients as of 28 February 2014 was approximately 1,600;
- Use of trastuzumab as monotherapy upon initiation was declining and trastuzumab monotherapy represented approximately one third of patients registered on the Herceptin Program;
- Available drug utilisation data does not differentiate between patients receiving combination therapy and those receiving trastuzumab monotherapy;
- Patients tend to remain on HER2 blockade (either trastuzumab or lapatinib) from the time of diagnosis to the end of their life unless placed on palliative care;
- Determining the length of time that patients receive trastuzumab treatment is difficult due to the lack of this data collection; and
- Determining the number of patients who receive one continuous course of treatment from those who remained on extended treatment or those who receive multiple courses and chemotherapy partners is difficult due to the absence of appropriate data collection.

Clinicians advised that treatment practice in Australia would likely follow updated treatment guidelines as suggested by the American Society of Clinical Oncology. Although these are not yet available, clinicians considered that for a majority of patients not already on trastuzumab treatment, the following drug treatment regimens setting aside individual patient circumstances, in order of line of treatment, are likely to be prescribed:

1 st line treatment:	Pertuzumab (+ trastuzumab + taxane)
2 nd line treatment:	Trastuzumab emtansine monotherapy
3 rd line treatment and later: chemotherapy	Lapatinib + capecitabine or trastuzumab +

Patients who relapse within 12 months of treatment with trastuzumab in the adjuvant setting would usually receive trastuzumab emtansine rather than pertuzumab + trastuzumab + taxane. These treatment algorithms concurred with the PBAC's March 2014 understanding of how drug therapies are likely to be prescribed in practice.

With regards to pertuzumab being given in conjunction with trastuzumab and a taxane, the PBAC noted in March 2014 that the current TGA registered indication for pertuzumab requires use with specifically docetaxel. The PBAC considered that other taxane partners (paclitaxel and nab-paclitaxel) are clinically equivalent to docetaxel and it is likely that other taxanes (and possibly other cytotoxic partners) would be used instead of docetaxel to some extent despite the TGA registered indication. The consensus on the question of ‘when would it be reasonable to remove the requirement that pertuzumab be given in combination with a taxane?’ was that it would be reasonable when new, supportive clinical data on such use is available.

Lapatinib is expected to be prescribed as third line therapy with the exception of patients with brain metastases. In recognition of the lack of data on the effectiveness of new anti-HER2+ drugs in the brain, there was an expectation from clinicians that lapatinib would be used earlier in patients with brain metastases in an effort to delay radiotherapy. A barrier to optimal use of lapatinib is the current PBS requirement for treatment with taxane prior to lapatinib.

With pertuzumab and trastuzumab emtansine likely to push use of trastuzumab to later lines of therapy together with the likelihood that trastuzumab has a diminishing marginal clinical benefit with increasing length of exposure, the PBAC noted that the extent of the incremental benefit of anti-HER2+ drug therapy over no anti-HER2+ drug therapy, is not known in this context. Sponsors and clinicians noted the results from a published study (Olson et al. 2013) suggesting that patients demonstrate clinical benefit from multiple-lines of anti-HER2+ drug therapy and therefore considered that trastuzumab in the third-line setting and beyond would provide patients with some clinical benefit.

Projected PBS drug usage

Estimating drug utilisation of new and existing drug treatments is complicated by factoring in an initial uptake period for the new anti-HER2+ drugs which would be different to drug-utilisation when the new anti-HER2+ drugs are established in clinical practice.

Based on the likely clinical treatment pathways with the introduction of the new anti-HER2+ drugs and existing drug-utilisation data, clinicians estimated that initially, the number of patients likely to be on pertuzumab treatment may reasonably be equal to the prevalent patient population with metastatic breast cancer yet to have received anti-HER2+ drug therapy combined with approximately 80% of the incident patient population with metastatic breast cancer (as up to 20% of patients may not be suited to pertuzumab as first line treatment).

With regards to trastuzumab emtansine usage, clinicians predicted a large initial uptake in the first couple of years of listing trastuzumab emtansine as one third of the patients currently on the Herceptin Program may be switched to trastuzumab emtansine because of disease progression. At the time point when the new anti-HER2+ drugs are established in clinical practice clinicians considered that trastuzumab emtansine use would predominantly occur in the second and third line treatment settings for the patient population diagnosed with metastatic HER2+ breast cancer and naïve to anti-HER2+ drug therapy. A table summarising the likely breakdown of trastuzumab emtansine use is shown below:

Line of therapy	Trastuzumab emtansine use in patients with metastatic HER2+ breast cancer and naïve to anti-HER2+ drug therapy
1 st line	Approximately up to 20%
2 nd line	Approximately 60%
3 rd line and later	Approximately 20%

The difficulty and confounding effect of estimating the number of patients on the Herceptin Program who are likely to switch over to trastuzumab emtansine and the number of patients prescribed trastuzumab emtansine after use of pertuzumab, were noted.

PBS restrictions for anti-HER2+ drugs

Various aspects of the current PBS restrictions and potential new PBS restrictions for the new anti-HER2+ drugs were discussed particularly, restrictions relating to partner therapy, sequencing of therapy and frequency of use. It was noted that the overall aim of PBS-restrictions was not to provide treatment guidelines but to achieve the greatest balance between restricting use of a drug to circumstances considered to be cost-effective based on available evidence and how clinicians would like to prescribe the drug in practice. In summary, the following comments were made regarding possible PBS restrictions likely to apply to anti-HER2+ drugs:

Pertuzumab

- It is reasonable to expect that pertuzumab is given in combination with trastuzumab and a taxane;
- The need for pertuzumab to be given in combination with a taxane could be reviewed in future pending the development of further clinical trial evidence that would support such a change. It would be helpful for the PBAC to be provided with a list of upcoming trials that study pertuzumab given without a taxane, to assist any future review;
- There are other taxanes that clinicians considered may be reasonable to prescribe in place of docetaxel despite pertuzumab's current TGA registration;
- It may be reasonable to limit pertuzumab PBS subsidy to one continuous treatment course only. PBS subsidy would not be available for patients to stop and start pertuzumab treatment or for use in patients following disease progression; and
- A patient's HER2 status must be demonstrated and confirmed in lesions by in situ hybridisation (ISH testing) where possible.

Trastuzumab emtansine

- It would be reasonable to expect that an initial PBS listing would limit use to 2nd or 3rd line treatment due to the currently available evidence;
- Ideally, the restriction will not limit use to just 2nd line use as some patients may not be suitable candidates for taxane chemotherapy or may not want to undergo chemotherapy initially (to avoid the unpleasant side-effects of chemotherapy) and may want to undergo trastuzumab emtansine. It was noted that evidence of trastuzumab emtansine in first-line use may potentially be available in approximately 12 months from a forthcoming clinical trial;
- It may be reasonable to limit trastuzumab emtansine PBS subsidy to one continuous course only. PBS subsidy would not be available for patients to stop and start trastuzumab emtansine or for use in patients where disease progression occurs;

- Patients who relapse during or within 12 months of completing adjuvant treatment with trastuzumab should have the option of 1st line trastuzumab emtansine; and
- A patient's HER2 mutation status must be demonstrated and confirmed in lesions where possible by in situ hybridisation (ISH testing).

Lapatinib

- The introduction of trastuzumab emtansine is likely to position lapatinib as 3rd line treatment;
- PBS subsidised lapatinib would not be available for combination use with other anti-HER2+ drugs due to the current absence of evidence;
- A requirement for lapatinib to be used in combination with capecitabine is currently supported by the available clinical data;
- It may be reasonable to limit lapatinib PBS-subsidy to one continuous course only. PBS subsidy would not be available for patients to stop and start lapatinib or for patients where disease progression occurs; and
- A patient's HER2 mutation status must be demonstrated and confirmed in lesions where possible by in situ hybridisation (ISH testing).

Trastuzumab

- It was noted that trastuzumab will need to be accepted as cost-effective for listing on the PBS; and
- Clinicians considered it appropriate for trastuzumab to be available to patients on the PBS at any stage of a patient's treatment for breast cancer.

Data collection

It was considered that capturing data on the following would aid the assessment of any cost-effectiveness consideration by the PBAC:

- Drug therapy selection;
- Sequencing of drug therapy;
- Selection of partner chemotherapies and/or other therapies;
- The date of therapy commencement, disease relapse and switching or ceasing of therapy,
- Number of patients currently receiving drug treatment;
- The duration of treatment;

The difficulty in readily collecting the above data from the Herceptin Program was noted due to the program remaining outside of the PBS. A central data collection point similar to that administered by Cambridge University was suggested. Participants noted the National Health and Medical Research Council (NHMRC) is considering a project on post-market utilisation and surveillance in cancer drugs.

It was agreed that it may be valuable to reconvene in the future to review if the PBS restrictions were still 'fit for purpose' in the context of new or developing clinical evidence. A restriction review would not necessarily need to be undertaken through a stakeholder meeting forum.

It was also suggested that it may be useful to have a data working group, informed by lists of current and upcoming clinical trial results, to discuss if the desired data could be captured.

The working group could include representatives from key stakeholders including the Cancer Council Australia and the NHMRC.

Concluding remarks

Stakeholders agreed on how the new drugs for metastatic breast cancer could be used in accord with best clinical practice and evolving clinical evidence, subject to the demonstration of their cost-effectiveness to support subsidisation under the PBS. Stakeholders agreed it was important to allow shared decision making on choice of treatment between clinicians and patients. The discussion arising from this meeting will be considered by the PBAC as part of any future considerations of submissions from sponsors. The Breast Cancer Network Australia emphasised the importance of access to PBS subsidisation of the new anti-HER2+ drugs as soon as possible. Roche indicated an intention to continue to pursue listing trastuzumab emtansine and pertuzumab on the PBS in a timely manner by undertaking further discussion with the Department (and relevant stakeholders with access to breast cancer registries) to progress drug price considerations and drug utilisation estimates.