Cancer Treatment Subcommittee of PTAC
Meeting held 21 March 2014

(minutes for web publishing)

Cancer Treatment Subcommittee minutes are published in accordance with the *Terms of Reference for the Pharmacology and Therapeutics Advisory Committee (PTAC) and PTAC Subcommittees 2008*.

Note that this document is not necessarily a complete record of the Cancer Treatment Subcommittee meeting; only the relevant portions of the minutes relating to Cancer Treatment Subcommittee discussions about an Application or PHARMAC staff proposal that contain a recommendation are generally published.

The Cancer Treatment Subcommittee may:

(a) recommend that a pharmaceutical be listed by PHARMAC on the Pharmaceutical Schedule and the priority it gives to such a listing;
(b) defer a final recommendation, and give reasons for the deferral (such as the supply of further information) and what is required before further review; or
(c) recommend that PHARMAC decline to list a pharmaceutical on the Pharmaceutical Schedule.

These Subcommittee minutes were reviewed by PTAC at its meeting 14 &15 August 2014, the record of which will be available in October 2014.

Record of the Cancer Treatments Subcommittee of PTAC held at PHARMAC on 21 March 2014

1 Nab-paclitaxel correspondence

1.1 The Subcommittee noted correspondence from a clinician, in response to PTAC's May 2012 minute regarding nab-paclitaxel. Members noted the clinician had provided further information from the supplier regarding the use of nab-paclitaxel (Abraxane) in patients who had previously experienced hypersensitivity reactions (HSR) to paclitaxel or docetaxel. Members also noted that this correspondence had been reviewed by PTAC at its February 2014 meeting.

1.2 The Subcommittee noted that it had reviewed the funding of nab-paclitaxel at its September 2013 meeting. Members re-iterated their view that 3 weekly paclitaxel was rarely used and weekly paclitaxel was more efficacious and less toxic and rarely associated with hypersensitivity reactions.

1.3 The Subcommittee considered that it was difficult to determine if an HSR was to the paclitaxel molecule itself or the cremophor in the formulation, therefore, members considered that in patients who had experienced HSR to paclitaxel it would be more appropriate to use alternative treatment options rather than nab-paclitaxel. Members also noted that nab-paclitaxel was specifically contra-indicated in patients who had prior HSR to paclitaxel.

1.4 The Subcommittee reiterated its previous **recommendation** that nab-paclitaxel be funded only if cost neutral to weekly paclitaxel.

2 Plerixafor

2.1 The Subcommittee noted correspondence from a clinician, in response to its September 2013 minute regarding plerixafor.

2.2 The Subcommittee considered that the demand and potential use of plerixafor would be high if it were funded because increased stem cell yields or reduced failure of stem cell collection compared with chemotherapy/G-CSF or G-CSF alone stem cell mobilisation protocols, but it was significantly more expensive. Members considered that proposed Special Authority criteria were designed to limit use to those patients who had clearly failed a first attempt at stem cell mobilisation.

2.3 The Subcommittee considered that it would be reasonable to amend the proposed criteria as follows (changes in bold and strikethrough):

Plerixafor

Restricted
Autologous stem cell transplant – haematologist

All of the following:

1. Patient is to undergo an autologous stem cell transplant; and
2. A maximum of 4 doses of plerixafor would be used; and
3. Either:
    3.1. Efforts to collect >2×10^6 CD34 cells/kg **at first mobilisation attempt has failed** ~~have failed after 4 apheresis procedures~~; or
    3.2. Apheresis has not commenced or has been discontinued because of a suboptimal blood CD34 cell count including a CD34 cell count of ≤ 10/ µL as measured in peripheral blood on day 8 of G-CSF treatment if mobilisation by G-CSF alone; or
    3.3. Apheresis has not commenced or has been discontinued because of a suboptimal blood CD34 cell count including a CD34 cell count of ≤ 10/ µL as measured in peripheral blood on day 12 of chemotherapy with G-CSF mobilisation.

2.4 The Subcommittee **recommended** that it review the application again along with a cost utility analysis once plerixafor was registered.

3 Teniposide for CNS lymphoma

3.1 The Subcommittee considered an application from a clinician for the funding of teniposide for patients with primary central nervous system Lymphoma (PCNSL). Members noted that the application had been prompted by NPPA applications.

3.2 The Subcommittee noted that PCNSL is a variant of extranodal non-Hodgkin's Lymphoma (NHL) that involved the brain, leptomeniges, eyes or spinal cord. Members noted it is an uncommon disease affecting around 20-40 patients per year in New Zealand, mostly in patients aged 45-70 years. Members noted that the disease had poor prognosis.

3.3 The Subcommittee noted that immunodeficiency is a significant risk factor for PCNSL including HIV infection, iatrogenic immune suppression and congenital immune deficiencies. Members noted there had been an increase in the incidence of PCNSL with the HIV/AIDs epidemic that subsequently declined with the advent of highly active antiretroviral treatment (HAART).

3.4 The Subcommittee noted that historic treatment for PCNSL comprised whole brain radiation however this has considerable cognitive side effects (especially in the elderly) and responses were modest. Members noted that current treatment comprises systemic chemotherapy with high dose methotrexate combined with sequential radiation therapy in younger patients. Members noted that this approach resulted in amedian survival of about 30-50 months with approximately one third of patients surviving 5 years or more.

3.5 The Subcommittee noted that other combination chemotherapy regimens have also been studied including high dose cytosine arabinoside (cytarabine) in combination with high dose methotrexate which improved response and survival but had significantly increased toxicity and resulted in more deaths compared with high dose methotrexate alone (Ferreri AJ et al. Lancet. 2009;374(9700):1512-20). Members further noted other studies where high dose methotrexate had been combined with various agents including temozolomide, topoisomerase inhibitors,

vinca alkaloids, anthracyclines and more recently rituximab or peripheral blood stem cell transplantation.

3.6 The Subcommittee noted that with the exception of the Ferreri study there was no randomised study comparing treatment regimens. Members considered it was not possible to determine if the addition of any treatments to high dose methotrexate provided any benefits compared with high dose methotrexate alone.

3.7 The Subcommittee noted that in support of the application to fund teniposide for PCNSL the applicant had provided the clinical trial protocol for the HOVON 105 PCNSL/ALLG NHL 24 Phase III trial which was currently enrolling patients in Auckland, Australia and The Netherlands. Members noted that the study compared high dose methotrexate, carmustine ("BiCNU") teniposide ("Vumon"), and prednisolone (MBVP) chemotherapy with or without rituximab in newly diagnosed PCNSL patients. Members noted that the study planned to enrol 200 patients and had currently enrolled approximately 120 patients with an interim analysis planned for later in 2014.

3.8 The Subcommittee noted that the clinical trial protocol described the reason for the choice of MBVP which was that most centres in the Netherlands were accustomed to MBVP and referenced Poortmans et al (J Clin Oncol 2003;21:4483-4488), which was a single arm study of MBVP in 52 patients with non-AIDS related PCNSL that reported an overall response rate of 81%. Members noted that in turn Poortmans et al based their treatment schedule on the experience of the French GEOLAMS group (published in Desablens Ann Oncol 1996;7:216 (suppl 3)), which was a single arm study in 150 patients.

3.9 The Subcommittee noted that there was no other published study using the MBVP regimen and considered that studies of other regimens reported similar outcomes. Members considered MBVP did not constitute a standard regimen for PCNSL and that there were other funded treatment regimens that could be used. Members further noted that teniposide was not registered in New Zealand and is rarely used and where it is approved its licence is limited to treatment of relapsed acute lymphoblastic leukaemia.

3.10 The Subcommittee **recommended** that the application to list teniposide on the Pharmaceutical Schedule for the treatment of primary central nervous system Lymphoma (PCNSL) be declined. However, members recommended teniposide should be funded for individuals enrolled in the HOVON 105 PCNSL/ALLG NHL 24 study.

3.11 The Subcommittee noted that the applicant is a Principle Investigator for the HOVON 105 PCNSL/ALLG NHL 24 and strongly commended this initiative.

3.12 The Decision Criteria particularly relevant to this recommendation are: (i) The health needs of all eligible people within New Zealand; (iii) The availability and suitability of existing medicines, therapeutic medical devices and related products and related things; (iv) The clinical benefits and risks of pharmaceuticals; (v) The cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health and disability support services, (vi) The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule.

4 Temozolomide access widening

4.1 The Subcommittee considered an application from a clinician requesting that the funding for temozolomide be extended beyond the currently funded 6 cycles post radiation therapy for patients with high grade gliomas (anaplastic astrocytoma (AA) or glioblastoma multiforme (GBM)). The Subcommittee also noted letters from a number of other clinicians in support of the application.

4.2 The Subcommittee noted that it had previously considered an application for extended funding and at that time recommended the application be declined. Members noted that since that application was reviewed the price of temozolomide had decreased by approximately 80% with further price drops expected in the future.

4.3 The Subcommittee noted that approximately 260 patients are diagnosed with primary brain cancer each year in New Zealand, approximately 80% of which are gliomas (20% AA and 80% GBM). Members noted that PHARMAC data indicated that in the year ending June 2013, 125 patients with GBM and 20 patients with AA initiated treatment with funded temozolomide.

4.4 The Subcommittees noted that high grade gliomas were not curable with treatment aimed at reducing symptoms and prolonging disease free progression and survival times. Members noted that standard treatment in NZ comprises debulking surgery, where possible, combined with adjuvant radiation and chemotherapy. Members noted that due to the infiltrating nature of the disease complete surgical excision is not possible and it was difficult to determine treatment failure in the short term because approximately 20% of patients exhibit 'pseudo progression' which is associated with better overall survival.

4.5 The Subcommittee noted that the current funding of temozolomide is based on the Stupp study (Stupp et al N Engl J Med 2005;352:987-96; Stupp et al Lancet Oncol. 2009;10(5):459). Members considered that study remains the primary evidence for temozolomide in patients with GBM demonstrating that it significantly improved both progression-free survival and overall survival when added to adjuvant radiation therapy. Members noted that in this study patients were randomly assigned to receive radiotherapy alone (fractionated focal irradiation in daily fractions of 2 Gy given 5 days per week for 6 weeks, for a total of 60 Gy) or radiotherapy plus continuous daily temozolomide (75 mg per square meter of body-surface area per day, 7 days per week from the first to the last day of radiotherapy), followed by six cycles of adjuvant temozolomide (150 to 200 mg per square meter for 5 days during each 28-day cycle).

4.6 The Subcommittee noted that in the Stupp study 78% of patients started adjuvant temozolomide, median number of adjuvant cycles completed was 3 with 47% of patients completing the whole 6 cycles. Members noted that the majority of withdrawals were early, mainly due to disease progression or tolerability, but there is a tail of people who tolerate treatment well.

4.7 The Subcommittee considered that the application was well written. The Subcommittee noted that several guidelines recommended use of temozolomide beyond 6 cycles in patients responding to treatment, and that in some countries treatment to disease progression was standard therefore there was unlikely to ever be a randomised controlled study in this setting.

4.8 The Subcommittee noted that the applicant had provided a series of retrospective studies that examined the outcome for patients receiving adjuvant temozolomide for various durations. Members considered that whilst the evidence was of poor to moderate quality at best and likely subject to significant bias they did provide consistent results that more temozolomide was associated with longer progression free survival and overall survival.

4.9 The Subcommittee considered that in the absence of randomised controlled studies and taking into account the high health need of patients with high grade glioma it would be reasonable to extend temozolomide treatment for as long as the patient was benefitting. Members considered that approximately 50% of patients would likely be treated with more than 6 cycles for a median of 11-14 cycles.

4.10 The Subcommittee **recommended** that the Special Authority criteria for temozolomide be amended as follows with medium priority (changes in bold and strikethrough):

Temozolomide – Special Authority – Retail pharmacy
Special Authority for subsidy
Initial application only from a relevant specialist. Approvals valid for 12 months for applications meeting the following criteria:
All of the following:

1. Either:
    1.1. Patient has newly diagnosed glioblastoma multiforme; or
    1.2. Patient has newly diagnosed anaplastic astrocytoma*; and
2. Temozolomide is to be (or has been) given concomitantly with radiotherapy; and
3. Following concomitant treatment adjuvant temozolomide is to be used **in 5 day treatment cycles** ~~for a maximum of six cycles of 5 days treatment~~ at a maximum dose of 200 mg/m^2 **per day**.

Renewal application only from a relevant specialist. Approvals valid for 12 months for applications meeting the following criteria:
All of the following:

1. Either:
    1.1. Both:
        1.1.1. Patient has glioblastoma multiforme; and
        1.1.2. The treatment remains appropriate and the patient is benefitting from treatment; or
    1.2. All of the following
        1.2.1. Patient has anaplastic astrocytoma*; and
        1.2.2. The treatment remains appropriate and the patient is benefitting from treatment ; and
        1.2.3. Adjuvant temozolomide is to be used for a maximum of 24 months.

Notes: Indication marked with a * is an Unapproved Indication. Temozolomide is not subsidised for the treatment of relapsed glioblastoma multiforme.

~~Reapplications will not be approved.~~ Studies of temozolomide show that its benefit is predominantly in those patients with a good performance status (WHO grade 0 or 1 or Karnofsky score >80), and in patients who have had at least a partial resection of the tumour.

4.11 The Decision Criteria particularly relevant to this recommendation are: (i) The health needs of all eligible people within New Zealand; (iii) The availability and suitability of existing medicines, therapeutic medical devices and related products and related things; (iv) The clinical benefits and risks of pharmaceutical.

5 Pertuzumab

5.1 The Subcommittee considered an application from Roche Products (New Zealand) Ltd for funding of pertuzumab (Perjeta) for the first-line treatment of patients with HER2-positive metastatic breast cancer in combination with trastuzumab and docetaxel. The Subcommittee also noted a letter from the New Zealand Breast Cancer Special Interest Group in support of the application.

5.2 The Subcommittee noted that the application was considered by PTAC at its February 2014 meeting where it recommended funding of pertuzumab with low priority and recommended the application be reviewed by CaTSoP. Members also noted additional papers provided by PTAC for consideration.

5.3 The Subcommittee noted that pertuzumab is a recombinant humanized monoclonal antibody that binds to subdomain 2, the extracellular dimerization domain, of the human epidermal growth factor receptor 2 protein (HER2) preventing dimerization and blocking signalling pathways. Members noted that pertuzumab is relatively inactive on its own but its activity increases significantly when combined with trastuzumab.

5.4 The Subcommittee noted key evidence from the CLEOPATRA study which was a randomized, phase III study comparing trastuzumab plus docetaxel with pertuzumab plus trastuzumab plus docetaxel as first line treatment for patients with HER2-positive locally recurrent, unresectable or metastatic breast cancer (Baselga et al. NEJM. 2012;366:109-19; Swain et al. Lancet Oncology 2013;14:461-71). Members noted that in this study patients could have had prior neoadjuvant or adjuvant treatment, with treatment having been completed at least 12 months prior, with 11% of patients having received prior adjuvant trastuzumab treatment and 50% having had prior adjuvant chemotherapy.

5.5 The Subcommittee noted that patients were randomly assigned to placebo plus trastuzumab plus docetaxel (control group n=406) or pertuzumab plus trastuzumab plus docetaxel (pertuzumab group n=402). Members noted pertuzumab or placebo was given at a fixed loading dose of 840 mg, followed by 420 mg every 3 weeks until disease progression or the development of toxic effects that could not be effectively managed.

5.6 The Subcommittee noted that pertuzumab treatment improved progression-free survival by 6 months compared with the control group (hazard ratio for progression

or death, 0.62 (95% confidence interval [CI] 0.51 to 0.75; P<0.001). Members further noted median overall survival in the control arm was 37.6 months but had not been reached in the pertuzumab arm and after a median follow-up of 30 months 38% of control group had died compared to 28% of patients treated with pertuzumab (HR for death 0.66 (95% CI 0.52 to 0.84; P<0.001).

5.7 The Subcommittee noted that the benefit of pertuzumab was maintained with or without prior adjuvant chemotherapy treatment, therefore, whilst more patients in New Zealand were likely to have had prior adjuvant chemotherapy with trastuzumab than the CLEOPATRA study population members considered this would not negatively impact the expected efficacy of subsequent pertuzumab plus trastuzumab treatment in the NZ population.

5.8 The Subcommittee noted that there was no evidence that pertuzumab worsened the known cardiac toxicity of trastuzumab, however, members noted higher rates of diarrhoea and rash in the pertuzumab group compared with the control group.

5.9 The Subcommittee noted that treatment of HER 2 breast cancer was rapidly evolving. Members noted that neoadjuvant and adjuvant studies of pertuzumab were ongoing and considered that the benefits of pertuzumab may be greater in these earlier settings. Members also noted that other HER 2 blockade treatments and combinations of treatments had been studied, or were in development. Members considered that while combination treatment with lapatinib and trastuzumab was cheaper than pertuzumab and trastuzumab, it was more toxic with only around 70% of patients able to tolerate treatment, and was less effective.

5.10 Overall, the Subcommittee considered that the evidence was of good quality and demonstrated that pertuzumab improved progression free survival by around 6 months and added little toxicity to trastuzumab treatment. Whilst members considered that these benefits were impressive for the HER-2 positive metastatic breast cancer setting members considered that pertuzumab was extremely expensive and the cost was vastly disproportionate to the benefits provided.

5.11 The Subcommittee **recommended** that pertuzumab should be funded on the Pharmaceutical Schedule for the first-line treatment of patients with HER2-positive metastatic breast cancer in combination with trastuzumab and docetaxel with low priority. The Subcommittee recommended that Special Authority criteria be based on the eligibility criteria for the CLEOPATRA study as follows:

> Pertuzumab – PCT only – Specialist – Special Authority
> Special Authority for Subsidy
> Initial application — (metastatic breast cancer) only from a relevant specialist or medical practitioner on the recommendation of a relevant specialist.
> Approvals valid for 12 months for applications meeting the following criteria:
> All of the following:
>
> 1. The patient has metastatic breast cancer expressing HER-2 IHC 3+ or ISH+ (including FISH or other current technology); and
> 2. Either:
>   2.1. Patient is chemotherapy treatment naïve; or
>   2.2. Patient has not received prior treatment for their metastatic disease and has had a treatment free interval of at least 12 months between prior (neo)adjuvant chemotherapy treatment and diagnosis of metastatic breast cancer; and

3. The patient has good performance status (ECOG grade 0-1);
4. Pertuzumab to be administered in combination with trastuzumab;
5. Pertuzumab maximum first dose of 840 mg, followed by maximum of 420 mg every 3 weeks; and
6. Pertuzumab to be discontinued at disease progression.

Renewal — (metastatic breast cancer) only from a relevant specialist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 12 months for applications meeting the following criteria:
Both:

1. The patient has metastatic breast cancer expressing HER-2 IHC 3+ or ISH+ (including ISH or other current technology); and
2. The cancer has not progressed at any time point during the previous 12 months whilst on pertuzumab and trastuzumab.

5.12 The Decision Criteria particularly relevant to this recommendation are: (i) The health needs of all eligible people within New Zealand; (ii) The particular health needs of Maori and Pacific peoples; (iii) The availability and suitability of existing medicines, therapeutic medical devices and related products and related things; (iv) The clinical benefits and risks of pharmaceuticals; (v) The cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health and disability support services, (vi) The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule.