Cancer Treatments Subcommittee of PTAC
Meeting held 18 September 2015

(minutes for web publishing)

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Note that this document is not necessarily a complete record of the Cancer Treatments Subcommittee meeting; only the relevant portions of the minutes relating to Cancer Treatments Subcommittee discussions about an application or PHARMAC staff proposal that contains 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 5 & 6 November 2015.

Record of the Cancer Treatments Subcommittee of the Pharmacology and Therapeutics Committee (PTAC) meeting held at PHARMAC on 18 September 2015

1 Matters Arising and Correspondence

Plerixafor

1.1 The Subcommittee noted that PHARMAC sought advice on the proposed restrictions for plerixafor prior to initiating commercial negotiations with the supplier, subject to sufficient budget headroom.

1.2 The Subcommittee recommended the below alteration to the restrictions below as recommended by PTAC in May 2015, with subsequent changes following advice from CaTSoP members in bold (new change marked in bold and strikethrough):

PLERIXAFOR - Restricted
Autologous stem cell transplant – haematologist
Limited to one dose daily for a maximum of three days
All:
1. Patient is undergoing stem cell transplantation;
2. **Patient has not had a previous unsuccessful mobilisation attempt with plerixafor; and**
3. **Any of the following:**
    2.1 Patient is undergoing G-CSF mobilisation; and
        2.1.1 Either:
            2.1.1.1 Has a suboptimal peripheral blood CD34 count of ≤ 10 x 10^6 / L on day 5 after 4 days of G-CSF treatment; or
            2.1.1.2 Efforts to collect >1×10^6 CD34 cells/ kg have failed after one apheresis procedure; or
    2.2 Patient is undergoing chemotherapy and G-CSF mobilisation; and
        2.2.1 One of the following:
            2.2.1.1 Has rising white blood cell counts of > 5 ~~10~~ x 10^9 / L and a suboptimal peripheral blood CD34 count of ≤ 10 x 10^6 / L; or
            2.2.1.2 Efforts to collect >1×10^6 CD34 cells/ kg have failed after one apheresis procedure; or
            2.2.1.3 The peripheral blood CD34 cell counts are decreasing before the target has been received; or
    2.3 A previous mobilisation attempt with G-CSF or G-CSF plus chemotherapy has failed.

1.3 The Subcommittee recommended that PHARMAC review the wording of restriction criterion 2 to ensure the intent of the restriction is as clear as possible.

1.4 The Subcommittee noted a considerable number of patients will likely meet this proposed criteria and PHARMAC could expect the uptake of plerixafor to be rapid.

Gefitinib and Erlotinib Special Authority review

1.5 The Subcommittee noted that PHARMAC staff sought advice on amending the current time period permitted for switching between gefitinib and erlotinib for the first line treatment of non-small cell lung cancer. Members noted that the current criteria allowed for switching between the two treatments for intolerance within the first 6 weeks of treatment commencing, provided that the patient's disease has not progressed

1.6 The Subcommittee considered that for some patients 6 weeks was too short a timeframe to recognise genuine treatment intolerance as the focus would likely be more on early treatment response during this timeframe.

1.7 The Subcommittee **recommended** amending the gefitinib and erlotinib Special Authority/Restriction criteria to increase the permitted timeframe for switching due for intolerance from the current 6 weeks to 12 weeks.

2 Pembrolizumab for metastatic melanoma

Application

2.1 The Subcommittee considered an application from Merck Sharpe and Dohme (MSD) for the funding of pembrolizumab (Keytruda) for the treatment of patients with metastatic or unresectable melanoma stage III or IV.

Recommendation

2.2 The Subcommittee **recommended** that pembrolizumab should be funded for the treatment of metastatic or unresectable melanoma stage III or IV with low priority. The Subcommittee noted that its low priority rating was influenced by the early evidence base, and consequent uncertainty about pembrolizumab's longer term benefits and potential risks, as well as its very high cost.

2.3 The Decision Criteria particularly relevant to this recommendation are *(i) The health needs of all eligible people in 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; and (vi) The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule.*

Discussion

2.4 The Subcommittee considered that New Zealand had a very high incidence of advanced melanoma and considered that there was an unmet health need for new treatments. The Subcommittee noted that three other treatments for melanoma had been considered by it and/or PTAC in recent years, namely, ipilimumab (Yervoy) for previously treated unresectable (stage IIIC or stage IV) melanoma and vemurafenib (Zelboraf) and dabrafenib (Tafinlar) for BRAF V600

mutation positive unresectable (stage IIIC or stage IV) melanoma. Members noted that to date PTAC had recommended all be declined primarily due to their very poor cost effectiveness at the proposed prices. Members also noted a number of other new treatments were in development for the treatment of advanced melanoma which would likely be submitted to PHARMAC in coming months.

2.5 The Subcommittee noted that pembrolizumab was the first in a new class of monoclonal antibody programmed cell death (PD-1) inhibitors in development for treatment of a range of cancers. Members noted that PD-1 down-regulates the immune system, therefore PD-1 inhibitors work by activating the patient's own immune system to attack the cancer cells. Members noted that as well as MSD's pembrolizumab, Bristol-Myers Squibb recently had its PD-1 inhibitor (nivolumab) approved by regulators overseas for the treatment of advanced melanoma. Members noted that both nivolumab and pembrolizumab were administered intravenously.

2.6 The Subcommittee noted that the evidence base for pembrolizumab in melanoma comprised 3 studies; a phase I/II study Keynote-001, a randomised phase II study Keynote-002 and a randomised phase III study Keynote-006. Members noted that there are no studies comparing pembrolizumab with dacarbazine, the currently funded melanoma treatment in New Zealand. Members noted that Keynote-001 had only been partly published and that Keynote-002 was not included in the supplier's submission.

2.7 The Subcommittee noted that Keynote-001 (which has been part published in Hamid, O et al Engl J Med 2013; 369:134-144 and Robert, C et al. Lancet. 2014; 384: 1109–1117) was an open-label, multicentre, Phase I study in patients with locally advanced or metastatic melanoma or non-small cell lung cancer. Members noted that this was a complex study which was initially designed as a dose escalation study and was then amended to enrol several cohorts of patients examining various dosing regimens including 2 mg/kg every 3 weeks, 10 mg/kg every 2 weeks and 10 mg/kg every 3 weeks in various populations. Members noted that published data was limited to ipilimumab-refractory melanoma patients and a cohort of treatment naïve patients, however, the supplier also provided unpublished evidence from all of the ipilimumab treatment naïve patients enrolled in this study. Members noted that various cohort and pooled analyses of patients from different cohorts were undertaken.

2.8 The Subcommittee noted that results of the primary efficacy measure in Keynote-001 of overall response rate (ORR) varied across the dosing cohorts and patient populations examined, with ORR of 26% reported by Robert et al in a pooled analysis of ipilimumab-refractory advanced melanoma patients treated with pembrolizumab at doses of 2 mg/kg or 10 mg/kg every 3 weeks compared with the unpublished evidence provided by the supplier of 31-44% ORR in ipilimumab naïve patients across the dosing cohorts. The Subcommittee noted that the 10 mg/kg Q2W dosing regimen appeared to produce numerically higher response rates as compared to the other two dosing regimens examined (2 mg/kg Q3W or 10 mg/kg Q3W). Members noted that median progression free (PFS) survival ranged from 3.3 months for ipilimumab refractory patients treated pembrolizumab

at 2 mg/kg Q3W to 8.7 months for ipilimumab naive patients treated pembrolizumab at 10 mg/kg Q2W.

2.9 The Subcommittee noted that pembrolizumab treatment was associated with fatigue, pruritus, and rash as well as a number of immune mediated side effects. Members noted that whilst the majority of adverse events were grade 1 or 2 around 3% of patients reported grade 3 fatigue which would impact on patients activities of daily living.

2.10 The Subcommittee noted that Keynote-002 (Ribas, A et al. Lancet Oncol August 2015; 16: 908–18.) was a randomised phase 2 trial of patients with unresectable stage III or stage IV melanoma with ECOG performance status 0-1 and confirmed progressive disease within 24 weeks after two or more ipilimumab doses and, if BRAFV600 mutant-positive, previous treatment with a BRAF or MEK inhibitor or both. Members noted that this study was not provided by the supplier but considered this was a reasonable omission given the funding application was primarily for funding of pembrolizumab for ipilimumab treatment naïve patients. Members noted that in this study 540 patients were randomly assigned (1:1:1) to pembrolizumab 2 mg/kg (n=180) or pembrolizumab 10 mg/kg (n=181) given intravenously every 3 weeks or investigator-choice chemotherapy (n=179) (paclitaxel plus carboplatin, paclitaxel, carboplatin [eliminated with protocol amendment one], dacarbazine, or oral temozolomide). Members noted that 86 (48%) of patients randomised to chemotherapy crossed over to pembrolizumab treatment, with 46 randomly assigned to receive 2 mg/kg and 40 to receive 10 mg/kg.

2.11 The Subcommittee noted that the primary endpoint was progression-free survival by independent central review, with secondary endpoints including objective response rate, complete or partial response rates by central review, response duration, the time from best overall response of complete or partial response until disease progression; and safety. Members noted that the median PFS as assessed by central review was 2.9 months in both of the pembrolizumab groups compared with 2.7 months in the chemotherapy treatment group. Members noted that pembrolizumab did show significant improvement in PFS, with hazard ratios of 0.57 (95% CI 0.45–0.73) for pembrolizumab 2 mg/kg and 0.50 (95% CI 0.39–0.64) for 10 mg/kg compared with chemotherapy ($p<0.0001$ for both). Members further noted that pembrolizumab significantly improved PFS when assessed by investigator review and agreed with the author's view that possible investigator bias in this partly open-label trial might explain the greater effect size as compared with central review results. Overall, members considered that the median progression free survival results from this study were unreliable.

2.12 The Subcommittee noted that Keynote-006 (Robert, C et al. N Engl J Med. 2015 Jun 25;372(26):2521-32) was a randomized, controlled, phase III study that enrolled patients with unresectable stage III or IV melanoma with ECOG performance status 0-1 who had received no more than one previous systemic therapy for advanced disease (approximately 65% of patients were treatment naïve). Members noted that 834 patients were randomised in a 1:1:1 ratio to receive pembrolizumab 10 mg/kg every 2 weeks (n=279) or every 3 weeks (n=277) or four doses of ipilimumab (at 3 mg per kilogram) every 3 weeks (n=278) with pembrolizumab administered intravenously over a 30-minute period

and continued until disease progression, the onset of unacceptable side effects, an investigator's decision to discontinue treatment, withdrawal of patient consent, or 24 months of therapy. Members noted that the pembrolizumab doses used in this study were higher than the 2 mg/kg Q3W dosing recommended on the Medsafe approved datasheet and being sought by the supplier for funding.

2.13 The Subcommittee noted that median progression free survival (PFS) the primary endpoint of the study, was 5.5 months (pembrolizumab 10 mg/kg Q2W), 4.1 months (pembrolizumab 10 mg/kg Q3W) and 2.8 months (ipilimumab) with hazard ratios for disease progression for pembrolizumab versus ipilimumab of 0.58 (95% CI, 0.46 to 0.72; P<0.001) for the 2-week regimen and 0.58 (95% CI, 0.47 to 0.72; P<0.001) for the 3-week regimen. Median overall survival (OS) was not reached in any of the arms, but 1 year survival rates were 74.1% ,68.4% and 58.2 % respectively, with hazard ratios for death for the two pembrolizumab regimens of 0.63 (95% CI, 0.47 to 0.83; P<0.0005) and 0.69 (95% CI, 0.52 to 0.90; P = 0.0036) versus ipilimumab. Members noted that grade 3 to 5 severe adverse events occurred in 13% and 10% of patients in the pembrolizumab groups compared with 20% in the ipilimumab group.

2.14 The Subcommittee noted that the efficacy results reported for the ipilimumab arm of Keynote-006 were somewhat better than reported in the ipilimumab Phase 3 study (Hodi et al N Engl J Med 2010; 363:711-23), but considered that this may be due to Keynote-006 including pre-treated and treatment naïve patients, whereas in Hodi et al all patents were pre-treated.

2.15 The Subcommittee considered that overall there was good evidence that pembrolizumab had some efficacy; however, members considered it was a very difficult application to consider as the clinical trials presented and analyses undertaken all had limitations. Members considered that at this time there was only weak evidence to inform an estimate of the magnitude and duration of benefit of pembrolizumab compared with currently funded treatment. Members considered that the evidence was complex and rapidly evolving and that longer term evidence was needed to be more certain of the benefits and harms of this new class of treatment. Members noted that whilst the current adverse event profile of pembrolizumab appeared manageable the potential for longer term immune-mediated toxicities needed to be considered. Members expressed some doubt about the supplier's conclusions regarding dose equivalence across the range of doses examined in the various clinical trials, with some members considering that there may be a dose effect favouring higher and more frequent dosing regimens.

2.16 The Subcommittee considered that there was a significant discrepancy in the consumer and media-reported view of the benefit of pembrolizumab and the available evidence. Members considered that whilst there was a high unmet need for new treatment options for melanoma patients the pricing being sought was excessive given the current early, and evolving, nature of the evidence and lack of certainty for its longer term benefit and potential risks. Members noted that the public pricing being sought by MSD was higher than it is currently receiving for pembrolizumab through its private cost share programme.

2.17 The Subcommittee noted that the application for pembrolizumab would likely be reviewed by PTAC at its November 2015 meeting.

3 Leuprorelin and Goserelin

Application

3.1 The Subcommittee noted a paper from PHARMAC staff regarding potential future funding arrangements for the gonadotropin-releasing hormone (GnRH) analogues leuprorelin and goserelin.

Recommendation

3.2 The Subcommittee **recommended** that PHARMAC issue a Request for Proposals (RFP) for the supply of a single gonadotropin-releasing hormone (GnRH) analogue. The Subcommittee noted that it would like to be advised of the potential outcome of the RFP prior to any decision being made.

3.3 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; and (vi) The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule.*

Discussion

3.4 The Subcommittee noted key questions of the paper were regarding 1) the therapeutic equivalence of different brands of the same strengths of leuprorelin used to treat prostate cancer and breast cancer and 2) the therapeutic equivalence of leuprorelin and goserelin to treat prostate cancer and breast cancer.

3.5 The Subcommittee noted the studies comparing goserelin acetate with leuprorelin in the treatment of patients with prostate cancer. The Subcommittee considered that most of the studies seem to indicate bioequivalence of the two chemicals and there were no studies indicating they weren't equivalent. The Subcommittee noted the Sarosdy et al study (Urology 1998;52:82-88) which compared 1-monthly goserelin (3.6 mg) plus antiandrogen therapy (bicalutamide or flutamide) with 1-monthly leuprolide (7.5 mg) plus antiandrogen therapy in 1,800 patients with Stage D2 prostate cancer, in which there were no significant differences in outcomes (time to progression and survival) between the groups with the exception of the patient group receiving leuprolide and flutamide which had a significantly poorer outcome than the other three groups.

3.6 The Subcommittee considered that, overall, goserelin and leuprorelin produce the same therapeutic effect in the treatment of prostate cancer and that for the

treatment of prostate cancer there was no evidence that the chemicals when given at the same dosing frequencies weren't equivalent.

3.7 The Subcommittee noted there was one study presented comparing the efficacy of 3-monthly leuprolide (11.25 mg, n=41) with 1-monthly goserelin (3.6 mg, n=38) in the treatment of patients with breast cancer (Aydiner et al. Med Oncol 2013; 30:354 doi 10.1007). The Subcommittee noted that the study found that at the one-month assessment there were no significant differences in mean follicle stimulating hormone or oestradiol levels between the two groups ($p = 0.143$ and $p = 0.683$, respectively), but the median of mean luteinising hormone level was higher in the leuprolide group ($p = 0.025$).

3.8 The Subcommittee noted that the reduction in oestradiol levels at one month compared to baseline revealed no statistically significant difference it appeared that there was a favourable effect in the monthly goserelin group ($p=0.08$) compared with the 3-monthly leuprolide group ($p=0.544$). The Subcommittee considered that for the treatment of breast cancer, monthly goserelin (3.6 mg) may be more efficacious than three monthly doses of leuprorelin (11.25 mg for Lucrin Depot PDS and 22.5 mg for Eligard). However, members noted that most patients would be treated with monthly doses of leuprorelin and with the exception of a few patients the chemicals could be considered equivalent.

3.9 The Subcommittee considered that it would be reasonable for PHARMAC to run a competitive process which would result in only one funded brand of leuprorelin. The Subcommittee noted that whilst the excipients of the different brands of GnRH analogues were different the different brands of leuprorelin could be considered therapeutically equivalent across the same dosing frequencies (e.g. 1 monthly Lucrin Depot PDS could be considered equivalent to 1 monthly Eligard).

3.10 The Subcommittee considered that it would be clinically reasonable to reference price goserelin to leuprorelin (or vice versa), or to run a competitive process that would result in only one of goserelin or leuprorelin being funded. The Subcommittee considered that there would be few clinical issues if patients needed to switch from goserelin to leuprorelin (or vice versa) to access a fully funded GnRH treatment. The Subcommittee noted that there may be a small group of patients for whom the difficulty with a switch may relate more to the administering device i.e. needle type, as opposed to the change in pharmaceutical.

3.11 The Subcommittee considered that the standard treatment for patients receiving adjuvant breast cancer therapy is goserelin. The Subcommittee could not foresee any problem with this group of patients switching chemicals if necessary and considered this was unlikely to have an impact on long term outcomes for them but noted there was insufficient evidence to support this view.

3.12 The Subcommittee considered a competitive process could be initiated for the supply of a single GnRH analogue (ie one of either goserelin or leuprorelin). The Subcommittee further considered that ideally the current range of dosing options (1-month, 3-month and 6-month) should be maintained but at minimum 1 and 3 month dosing options should be funded. Members considered that a long

transition period, 6 months, would be preferable for managing funding changes (brand and/or chemical) in this patient population.

4 Bendamustine for CLL and iNHL

Application

4.1 The Subcommittee reviewed an application from Janssen for the funding of bendamustine (Ribomustin) for first-line treatment of chronic lymphocytic leukaemia (CLL) and first-line and relapsed refractory indolent non-Hodgkin's lymphoma (iNHL).

Recommendation

4.2 The Subcommittee **recommended** that bendamustine should be funded for first-line treatment of chronic lymphocytic leukaemia (CLL) in combination with rituximab, with medium priority.

4.3 The Subcommittee **recommended** that bendamustine should be funded for first-line treatment of indolent non-Hodgkin's lymphoma (NHL), with medium priority.

4.4 The Subcommittee deferred making a **recommendation** on the funding of bendamustine for relapsed refractory indolent non Hodgkin's lymphoma (NHL) pending publication of the NHL 2-2003 study.

4.5 The Decision Criteria particularly relevant to this recommendation are: *(i) The health needs of all eligible people in 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; (vii) The direct cost to health service users; and (viii) The Government's priorities for health funding, as set out in any objectives notified by the Crown to PHARMAC, or in PHARMAC's Funding Agreement, or elsewhere.*

Discussion

4.6 The Subcommittee noted that this application from Janssen had been reviewed by PTAC at their August 2015 meeting the draft minute of which was considered at this meeting.

4.7 The Subcommittee noted that the applicant was seeking funding for bendamustine as:

- monotherapy for the first-line treatment of CLL for patients unable to tolerate treatment with FCR (fludarabine, cyclophosphamide and rituximab); and
- in combination with rituximab for the first-line treatment of patients with indolent NHL, including mantel call lymphoma (MCL); and
- for the treatment of patients with relapsed or refractory indolent NHL with or without rituximab.

4.8 The Subcommittee also noted an application, first received in July 2013, from Lymphoma New Zealand (a special interest group with representation from NZ specialist haematologists, oncologists, radiation oncologists) for the funding of bendamustine for treatment naive or relapsed refractory follicular and mantle cell lymphoma.

4.9 The Subcommittee noted that bendamustine was not a new drug being a derivative of nitrogen mustard, members noted it has been licensed and subsequently marketed by a number of suppliers for a variety of cancer indications globally.

4.10 The Subcommittee noted that CLL was a disease with highly variable clinical course, members noted that a portion of patients need no treatment but in some it was a highly active disease. Members noted that some of this variation was driven by demographic and patient variables and that some specific genetic mutations were associated with poorer prognosis notably p53 mutations/deletions, occurring in 5-10% of patients and without somatic IgG variable gene hypermutation. Members noted that treatment choices were generally driven by patient's CLL disease activity and need for treatment and their medical fitness and comorbidities. Members noted that currently in New Zealand fit patients requiring first-line systemic treatment received rituximab in combination with fludarabine and cyclophosphamide (FC-R) whilst older patients who were less fit with comorbidities receive chlorambucil monotherapy. Members noted that around 50% of patients receiving FCR would have an extremely good, durable response, compared a response rate of around 30-50% with chlorambucil which is not durable.

4.11 The Subcommittee noted that key evidence for the use of bendamustine in CLL comprised a randomised, open-label, Phase III study of bendamustine compared with chlorambucil in 319 previously untreated patients with advanced (Binet stage B or C) CLL (Knauf et al. J Clin Oncol. 2009; 27: 4378-84 and Knauf et al., Br J Haematol. 2012; 159: 67-77). Members noted that the patients enrolled in this study were relatively young (median age 63) compared with the average age of diagnosis in New Zealand (72 years) and were fairly fit, therefore were more representative of the patient group currently likely receiving FCR in New Zealand rather than chlorambucil.

4.12 The Subcommittee noted that median PFS was improved by 12.4 months in the bendamustine treated group (median PFS 21.2 months) compared with chlorambucil (median PFS 8.8 months, $p< 0.0001$; hazard ratio 2.83). Members noted that complete response rate was higher for bendamustine (31%) compared with 2% complete response for chlorambucil-treated patients. Members noted

that median OS was not reached in the bendamustine group and was 78.8 months for the chlorambucil group.

4.13 The Subcommittee noted unpublished evidence from a study of bendamustine plus rituximab (BR) compared with fludarabine, cyclophosphamide rituximab (FCR) in treatment naïve physically fit patients without del(17p) CLL (presented at ASH 2013 and ASH 2014 by Eichhorst et al available http://www.bloodjournal.org/content/122/21/526 and https://ash.confex.com/ash/2014/webprogram/Paper69485.html). Members noted that the overall response rate was identical in both arms with 97.8% (p=1.0) whilst complete response rate (CR) (confirmed by central immunohistology) with FCR was 47.4% as compared to 38.1% with BR (p=0.031). PFS was 85% at 2 years in the FCR arm and 78.2% in the BR arm (p=0.041) and there was no difference in OS rate for the FCR vs BR arm (94.2% vs 95.8% at 2 years p=0.593). Members noted that in younger patients FCR appears to be better than BR but in older patients both treatments appeared to provide similar efficacy, members considered that this was likely due to dose modification of FCR in older patients.

4.14 The Subcommittee considered that currently in New Zealand quite a lot of older, less fit patients with CLL were being treated with low intensity FCR regimens. Members considered that if funded bendamustine would likely reduce use of low intensity FCR as well as chlorambucil but that these treatments would likely be used after bendamustine on relapse. Members considered that the supplier's estimate of the number of patients treated were a little low, members estimated that approximately 35 new patients would initiate treatment each year, with treatment continuing for approximately 2 years.

4.15 The Subcommittee considered that it was difficult to set criteria for the appropriate CLL patient population to be treated with bendamustine but considered that in general it would be most beneficial for older and frailer patients in particular patients with a Cumulative Illness Rating Scale (CIRS) score of 6 or more or a GFR <50 mL/min. Members also considered that bendamustine would provide better efficacy if it was administered in combination with rituximab rather than as monotherapy as requested by the supplier.

4.16 The Subcommittee noted that the current standard chemotherapy regimens used for symptomatic- low grade NHL in New Zealand include 6-8 cycles of R-CHOP (rituximab, cyclophosphamide, vincristine, doxorubicin and prednisone) or R-CVP (rituximab, cyclophosphamide, vincristine and prednisone). Members noted that best evidence for use of bendamustine in this patient population was from a randomised, open-label, non-inferiority phase III trial comparing treatment with bendamustine plus rituximab (BR n=274) or rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP n=275) for a maximum of 6 cycles in treatment naïve patients with indolent or mantle-cell lymphomas (NHL1-2003 (StiL study): Rummel et al. Lancet. 2013; 381: 1203-10). Members noted that progression-free survival was 38 months (> 3 years) longer in the BR group compared with the R-CHOP group (BR median PFS 69.5 months [vs R-CHOP median PFS 31.2 months; HR 0.58, 95% CI 0.44–0.74; p<0.0001). Complete response rate was also significantly higher in BR treated patients (104 [40%] vs 76 [30%]; p=0·021) and it was also better tolerated than R-CHOP.

4.17 The Subcommittee also noted evidence from a randomised, open label, non-inferiority phase III trial comparing bendamustine plus rituximab vs R-CHOP/R-CVP in for treatment naïve patients with indolent non-Hodgkin's lymphoma or mantle cell lymphoma (BRIGHT study, Flinn et al Blood 2014 123: 2944-2952). Patients were randomized to receive BR (n=224) or standard therapy (R-CHOP or R-CVP) (n=223) for 6 cycles with 2 additional cycles of treatment were permitted at investigator discretion. Investigators pre-assigned patients to the most appropriate standard treatment (R-CHOP/R-CVP) during screening based on patients' performance status, comorbidities, and general health. Among patients receiving standard therapy, 104 were treated with R-CHOP and 119 with R-CVP. Members noted that CR rate, the primary endpoint of the study, was 31% in the BR treatment group and 25% in the standard-therapy treatment group (CR-rate ratio 1.26; P= .0225 for NI); the CR rate for BR was greater than the 22% threshold for NI (ie, .88% of the CR rate for standard therapy), but,he higher CR rate with BR treatment was not statistically superior to standard therapy (P = .1269). Members noted that overall response rates were 97% BR vs. 91% for the standard-therapy treatment group, which was statistically superior for the BR treatment group (HR 1.04; 95% confidence interval [CI]: 0.99-1.09; P = .0102).

4.18 The Subcommittee considered that if funded bendamustine in combination with rituximab would likely defer, rather than replace, treatment with R-CHOP/R-CVP. Members agreed with PTACs estimated patient numbers of 225 per year. Members considered that patients with Mantle Cell lymphoma had a higher health need for bendamustine than other patients with indolent NHL as it sometimes demonstrated a more aggressive disease course.

4.19 The Subcommittee considered that the evidence for use of bendamustine in relapsed/refractory NHL was weak, with key evidence comprising one unpublished randomised controlled study comparing bendamustine plus rituximab (BR) versus fludarabine rituximab (FR) in patients with relapsed follicular, indolent or mantle cell lymphoma, study NHL 2-2003. Members considered that publication of this study was required before any meaningful conclusions about the use of bendamustine in this setting could be drawn.

4.20 Overall the Subcommittee considered that the evidence supported the funding of bendamustine for first line CLL and indolent NHL, however, members considered that the evidence for its use in relapsed/refractory NHL was weaker and insufficient to make a recommendation for funding in this setting at this time.

5 Bevacizumab for Ovarian Cancer

Application

5.1 The Subcommittee considered a further application from Roche Products NZ Limited for the funding of bevacizumab (Avastin) for the first line treatment of patients with untreated advanced (FIGO Stage IIIB or IIIC, sub-optimally debulked (maximum diameter of any gross residual disease > 1cm)), or

metastatic (FIGO stage IV), epithelial ovarian, fallopian tube, or primary peritoneal cancer.

Recommendation

5.2 The Subcommittee **recommended** that the application for the funding of bevacizumab on the Pharmaceutical Schedule be declined.

5.3 The Decision Criteria particularly relevant to this recommendation are: *(i) The health needs of all eligible people in 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; and (vi) The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule.*

Discussion

5.4 The Subcommittee noted that this application was reviewed by PTAC at its February 2014 meeting where it recommended funding be declined and that the application should be reviewed by Cancer Treatments Subcommittee of PTAC (CaTSoP) when final data from the ICON7 study had been published. Members further noted that further correspondence from Roche Products, including final unpublished data from the ICON7 study, was reviewed by PTAC at its November 2014 meeting where it reiterated its recommendation that the application be declined.

5.5 The Subcommittee reviewed a further submission from Roche Products NZ limited including final publication of the ICON-7 trial (Oza AM et al. The Lancet Oncology. 2015;16(8):928-36). The Subcommittee noted that ICON-7 was a phase III, randomised, open-label, multicentre study of first line bevacizumab, carboplatin and paclitaxel (CPB) vs. carboplatin and paclitaxel alone (CP) in 1,528 patients with high risk early, or advanced, ovarian cancer who had undergone debulking surgery. Members noted that in this study bevacizumab was administered at 7.5mg/kg, given concurrently with chemotherapy every 3 weeks for 5 or 6 cycles and then continued as monotherapy for up to a further 12 additional cycles or until disease progression whichever occurred earlier. Members noted that this dosing was inconsistent with the product's Medsafe approved datasheet.

5.6 The Subcommittee noted that results of the final analysis demonstrated that median progression free survival (the primary endpoint of the study) was 17.5 months in the CP arm compared with 19.9 months in the CPB arm (HR=0.93, 95% CI 0.83-1.05; P=0.25), members noted that this result was non-significant, however, members noted that in a pre-planned analysis of high-risk patients bevacizumab treatment increased median PFS by 5.5 months (CP 10.5 months CP vs. 16 months CPB, (HR=0.73, 95% CI 0.61-0.88; P=0.001). Members further noted that there was no difference in overall survival between the two randomised groups (58.6 months in the CP compared with 58 months in the CPB

arms respectively (HR=0.99, 95% CI 0.85-1.14; P=0.85), however, in the high-risk group bevacizumab treatment improved median OS (30.2 months in the CP arm and 39.7 months in CPB arm, HR=0.78, 95% CI 0.63-0.97; P=0.03).

5.7 The Subcommittee considered that whilst the data was encouraging the evidence for the high risk group was of limited strength as the study was underpowered for this population. The Subcommittee considered that issue, along with its high cost and the unapproved dosing regimen proposed by the supplier made it difficult to recommend funding.

5.8 The Subcommittee noted evidence from a study of dose dense paclitaxel and carboplatin compared with conventional paclitaxel and carboplatin in 637 Japanese patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer (JGOG 3016, Katsumata N et al Lancet Oncol. 2013 Sep;14(10):1020-6). Members noted that in this study median progression-free survival was significantly longer in the dose-dense treatment group than in the conventional treatment group (28.2 months vs 17.5 months hazard ratio 0·76, 95% CI 0·62-0·91; p=0·0037) as was median overall survival 100.5 months vs. 62.2 months (HR 0·79, 95% CI 0·63-0·99; p=0·039). Members considered that if these promising results were confirmed in the ongoing study ICON-8 in non-Japanese patients, due to report in the next 2-3 years, then dose dense paclitaxel and carboplatin would likely become the standard of care for treating patients with advanced ovarian cancer. Members also noted that metronomic paclitaxel as delivered in dose dense chemotherapy may potentially also working as an anti-angiogenic therapy.