Cancer Treatments Subcommittee of PTAC
Meeting held 5 October 2012

(minutes for web publishing)

Cancer Treatments 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 Treatments Subcommittee meeting; only the relevant portions of the minutes relating to Cancer Treatments Subcommittee discussions about an Application or PHARMAC staff proposal that contain a recommendation are generally published.
- that any part of the minutes relating to hospital pharmaceuticals and the establishment of a national Preferred Medicines List (PML) will be released, in a complete publication with the original Hospital Pharmaceuticals Subcommittee minutes and final recommendations made by PTAC, once PTAC have reviewed each therapeutic group.

The Cancer Treatments 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 on 14 & 15 February 2013, the record of which will be available in April 2013.

1. Previous Meeting

1.1. The Subcommittee reviewed the minutes of its previous meeting held on 2 March 2012.

1.2. The Subcommittee recommended that item 2.2.2 in relation to trastuzumab be amended as follows (changes in bold):

> 3.3.2. The Subcommittee noted that, although brain metastases are life limiting events, a small number of patients can survive 2-3 years with brain metastases **controlled with radiotherapy** and trastuzumab treatment. Members considered that trastuzumab treatment should be continued in patients with controlled brain metastases but treatment should be discontinued on evidence of systemic disease progression outside the brain. Members considered that only a small number of patients would present with intracranial progression without evidence of systemic progression.

1.3. The Subcommittee noted that its recommendation for mitotane, item 3.3.2, did not have a priority rating (changes in bold). Members recommended this item be amended as follows:

> 5.4.2 The Subcommittee recommended that mitotane should be listed on the Pharmaceutical Schedule for patients with adrenocortical carcinoma. **Members gave this recommendation a high priority.**

1.4. The remainder of the minute was accepted.

2. Matters Arising and Correspondence

2.1. ***Correspondence regarding Lapatinib***

2.1.1. The Subcommittee reviewed a letter from the Breast Cancer Special Interest Group of the NZ Association of Cancer Specialists (BSIG) requesting that lapatinib be funded in the second line setting for patients with HER 2 positive metastatic breast cancer (mBC) who have failed first line trastuzumab treatment. The Subcommittee also reviewed a revised commercial proposal from the supplier of lapatinib, GlaxoSmithKline NZ limited (GSK), for second line funding.

2.1.2. The Subcommittee noted that it had previously reviewed the funding of lapatinib as second line treatment of women with HER 2 positive mBC following trastuzumab failure on a number of occasions. Members noted that lapatinib was currently funded as an alternative option to trastuzumab for the first line treatment for HER 2 positive mBC.

2.1.3. The Subcommittee noted that no new evidence was provided, with the exception of one new unpublished study, comparing lapatinib with trastuzumab as first line treatment for HER 2 positive mBC (MA.31, Gelmon et al. presented at ASCO 2012) which demonstrated that progression free survival was inferior with

lapatinib compared to trastuzumab (PFS 8.8 months vs. 11.4 months, hazard ratio (HR) =1.33; 95% CI 1.06-1.67; p=0.01). Members considered that this evidence supported the use of trastuzumab as the preferred first line agent but that lapatinib remained a valid alternative funded treatment option for a small number of patients, for example those with early intolerance to trastuzumab, or those with brain metastases at presentation.

2.1.4. The Subcommittee considered that since all HER 2 positive mBC patients treated with first line trastuzumab would inevitably relapse, most would be treated with lapatinib if it were funded in the second line setting as requested. Members considered that, although the commercial proposal from GSK would limit the financial impact of funding lapatinib as a second line treatment option, the evidence for its use in this setting was unchanged.

2.1.5. The Subcommittee reiterated its view that the evidence in this setting demonstrated that lapatinib offered only modest benefits in terms of delaying disease progression, without any survival advantage. Therefore, the Subcommittee **recommended** that the application to fund lapatinib in the second line setting for patients with HER 2 positive metastatic breast cancer be declined.

2.1.6. The Subcommittee considered that BSIG may have a valid point in arguing inequity of access to lapatinib for patients with brain metastases, in that it is only funded for patients who have brain metastases at first presentation. However, members noted that this population was not the subject of the funding request.

2.2. ***Correspondence regarding gemcitabine***

2.2.1. The Subcommittee reviewed a letter from the Breast Cancer Special Interest Group of the NZ Association of Cancer Specialists (BSIG) in response to PTAC's May 2012 minute relating to its application for the funding of gemcitabine for the treatment of patients with metastatic breast cancer (mBC) with gemcitabine to be used at the treating clinician's discretion.

2.2.2. The Subcommittee noted that it had not reviewed the application for gemcitabine and considered that they did not agree with some of the points made by PTAC. In particular, members considered that gemcitabine would primarily be used as a single agent as fourth or fifth line treatment, few patients would be treated, approximately 20-25% of all mBC patients, and that duration of treatment in these patients would be short.

2.2.3. The Subcommittee considered there to be little financial risk of funding gemcitabine in this setting and reiterated its previous **recommendation** to remove the Special Authority criteria from gemcitabine, with high priority.

3. Ipilimumab for metastatic melanoma

3.1. The Subcommittee considered an application from Bristol-Myers Squibb (NZ) Limited for the funding of ipilimumab (Yervoy) on the Pharmaceutical Schedule for the treatment of patients with previously systemically treated, unresectable, stage IIIc or IV melanoma.

3.2. The Subcommittee noted that the application had been reviewed by PTAC at its August 2012 meeting where it recommended that the application be declined.

3.3. The Subcommittee noted that melanoma was common in NZ and patients presented with a wide spectrum of disease behaviour from aggressive disease that progress rapidly, to indolent disease, with patients living for several years. Members noted however that it was not possible at present to identify the factors that predicted the likely clinical course.

3.4. The Subcommittee considered that the standard current treatment option for advanced melanoma patients was dacarbazine (DTIC). Members considered that this treatment was well tolerated but provided modest benefit in a small number of patients only. Members noted that clinical evidence demonstrated that dacarbazine was associated with 5-15% overall response rate, with approximately 5% of patients experiencing long term survival. Members also noted that temozolomide was recently approved for use in metastatic melanoma. However, members considered it offered similar benefits to dacarbazine and noted that it was not funded in this setting. Members further noted that it had recently recommended funding for vemurafenib (Roche) with low priority, but that PTAC had subsequently recommended it be declined principally because of its high cost and its apparent modest, and only short-term, effect. The Subcommittee considered that there was an unmet health need for more effective treatment options for patients with advanced melanoma.

3.5. The Subcommittee noted that ipilimumab is a new class of treatment for advanced melanoma that worked by stimulating the body's own immune response. Members noted that ipilimumab is a monoclonal antibody which blocks the T-cell CTLA-4 receptor and stimulates non-specific T-cell activation. Members noted that, unlike most treatments for advanced cancers, ipilimumab was given for a defined treatment duration (3 mg/kg for 4 doses) in patients with unresectable or metastatic melanoma who have failed or are intolerant to prior therapy (i.e. second line treatment). Members noted that studies of ipilimumab were on going in the first line settings using a higher dose (10 mg/kg)

3.6. The Subcommittee considered that the key evidence for ipilimumab was a study published by Hodi et al (2010). Members noted that this was a randomised, double blind, trial comparing ipilimumab (3 mg/kg) with gp100 peptide (a tumour vaccine) (n=403), ipilimumab alone (n=137) or gp100 peptide alone (n=136) in HLA-A*0201 positive patients with unresectable stage III or IV melanoma whose disease had progressed after either chemotherapy or IL-2. Members noted that patients received treatment once every 3 weeks for 4 treatments and patients could be retreated on disease progression if they had experienced a previous treatment response or had stable disease.

3.7. The Subcommittee considered that although there was no placebo group in this study, it was reasonable to consider the gp100 arm as the control group, since it appeared to provide no added advantage, and there was no reason to think that the gp100 would have been worse than placebo.

3.8. The Subcommittee noted an imbalance in the presence of central nervous system (CNS) metastases at baseline (15% in the gp100 peptide arm compared with

approximately 11% in the other treatment arms). However, the Subcommittee considered that the absolute difference was small and, although it would tend to favour ipilimumab, members considered that this imbalance would not have altered the main conclusions about the relative magnitude of effect or the strength of the evidence.

3.9. The Subcommittee noted that that evidence from the Hodi study indicated a modest improvement in a median overall survival of 3.7 months in the ipilimumab arms compared with the gp100 alone arm (10.1 months vs. 6.4 months). However, members noted that the 95% confidence intervals overlapped, although the hazard ratio for death reached statistical significance (HR 0.66, p=0.003). The Subcommittee noted that ipilimumab provided no progression free survival benefit and the Kaplan-Meier curves for progression free survival was very similar in all three treatment groups. The Subcommittee noted that the Kaplan-Meier curve for overall survival appeared to show a tail of long term survivors for patients who received ipilimumab (approximately 10%). However, members noted that the number of patients contributing to this tail was tiny (42 patients at 36 months and 8 at 48 months) and, therefore, considered the evidence, at this time, for any additional long term benefit of ipilimumab was very weak, given the wide underlying variation in the natural history of the disease.

3.10. The Subcommittee noted that, consistent with its indiscriminate T-cell activating mode of action, a high proportion (60%) of patients treated with ipilimumab experienced significant autoimmune toxicities affecting the gastrointestinal tract, joints, skin, liver and endocrine system. Members considered that severe (grade 3 or 4) gastrointestinal toxicity was of most concern, affecting 5% of patients and linked with 5 of 14 deaths in the Hodi trial. Members noted that severe diarrhoea should be treated early with high dose oral corticosteroids and may lead to several weeks hospitalisation and use of other immunosuppressants such as infliximab. The Subcommittee noted that overall ipilimumab-related mortality was 2%.

3.11. The Subcommittee also considered evidence from an uncontrolled trial (Prieto 2012) which reported long term outcomes from 177 patients who received ipilimumab with various other drugs. Members considered that, although the study demonstrated 5 year survival of 13-25%, because this disease could have an indolent disease course in some patients, without a control arm, it was difficult to draw any conclusion about the benefit of ipilimumab.

3.12. The Subcommittee also considered evidence from a third trial (Robert 2011) comparing ipilimumab (10 mg/kg) in combination dacarbazine with dacarbazine and placebo in 502 previously untreated metastatic melanoma patients (first line treatment). Members noted that this study demonstrated a similar magnitude of benefit to the Hodi study with a 3.1 month difference in overall survival between the treatment groups (11.2 months ipilimumab plus dacarbazine vs. 9.1 months dacarbazine plus placebo) and approximately an 8% difference in 3 year overall survival rate from a population of 67 survivors. Members noted that the Kaplan-Meyer survival estimate at 4 years in both treatment groups was approximately 10%.

3.13. The Subcommittee considered the cost-effectiveness analysis conducted by the supplier, which resulted in a CUA of approximately $100,000 per QALY. However, members considered that, based on the evidence, the supplier's analysis

overestimated the benefits and it was likely that the cost per QALY was considerably higher.

3.14. The Subcommittee considered that overall the evidence was relatively strong for ipilimumab providing a small increase in median overall survival. However, the evidence was very weak for any long term benefit. Members considered that the evidence at this time indicated that the autoimmune effects of ipilimumab were too hazardous to justify the small, and uncertain, benefit at the price being offered. Therefore, the subcommittee **recommended** that the application be declined.

3.15. 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; (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. Nilotinib for Chronic Myeloid Leukaemia (CML)

4.1. The Subcommittee reviewed an application from the Haematology Society of Australia and New Zealand (HSANZ) for the listing of nilotinib (Tasigna) on the Pharmaceutical Schedule for the treatment of 3 groups of patients with Chronic Myeloid Leukaemia (CML):

4.1.1. patients who have failed, or are intolerant to both imatinib and dasatinib treatment; and

4.1.2. patients with high risk disease who have failed first line dasatinib; and

4.1.3. patients who have failed first line imatinib treatment with mutations that predict better response to nilotinib rather than dasatinib.

4.2. The Subcommittee noted that they had previously considered the funding of nilotinib on several occasions and had recommended that it be funded for patients who are intolerant to, or have CML disease resistance to, both imatinib and dasatinib or with known mutations predicting inferior response to both imatinib and dasatinib, i.e. 3rd line treatment. Members noted that this new application from HSANZ requested similar funding, however, it also requested second line funding for a small number patients under certain circumstances.

4.3. The Subcommittee considered that the currently funded treatment choices (imatinib and dasatinib) were appropriate for the vast majority of CML patients. Members considered that, given its well-known long term safety and efficacy profile, and the expected price drops following patent expiry next year, imatinib remained the preferred first line treatment option for the vast majority of patients with CML and that treatment with dasatinib was an appropriate second line treatment option. However, the Subcommittee considered there was an unmet medical need for a third funded treatment option for patients unable to be treated with currently funded treatment options or where there was good evidence that treatment with imatinib or dasatinib was suboptimal.

4.4. The Subcommittee considered that approximately 20% of patients would develop CML resistant to imatinib in the first year with a further 20% experiencing intolerance to imatinib. Members considered that the resistance rate for dasatinib was lower than imatinib but intolerance was slightly higher at approximately 10%.

4.5. The Subcommittee considered that approximately 10-20% of patients would present with high risk CML disease, members considered that it was appropriate that such patients be treated with dasatinib first line, followed by nilotinib on disease progression or intolerance.

4.6. The Subcommittee considered that although, in general, they considered dasatinib and nilotinib to be similar, some specific mutations predicted a better response to one or the other drug. Members noted there were currently at least 90 known different mutations in the BCR-Abl gene associated with CML and that at present approximately 3 of these mutations appeared to predict improved response to nilotinib compared with dasatinib. Members considered that in such patients following imatinib treatment failure, it was appropriate that nilotinib be used as second line treatment rather than dasatinib. Members considered that more mutations are likely to be discovered in the future and therefore, considered that any Special Authority criteria for nilotinib should not specify exact mutations as they would likely be superceded in a short period of time and require constant updating. Members further noted that there are differences in the side effect profile of dasatinib and nilotinib which may make one or the other contraindicated in a patient with particular comorbidities.

4.7. The Subcommittee agreed with the recommended treatment alogorithm suggested by the HSANZ and considered that under this algorithm approximately 10% of CML patients would access funded nilotinib. The Subcommittee considered that most patients who received nilotinib treatment under these criteria were unlikely to have a sustained response greater than 2 years.

4.8. The Committee **recommended**, with a high priority, that nilotinib be listed in the Pharmaceutical Schedule, subject to the following Special Authority:

Nilotinib - Special Authority for Subsidy
Initial Application only from a relevant specialist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 6 months for applications meeting the following criteria
All of the following:

1. Patient has a diagnosis (confirmed by a haematologist) of chronic myeloid leukaemia (CML) in blast crisis, accelerated phase, or in chronic phase; and
2. Any of the following:
    - 2.1. Patient has documented CML disease progression or treatment failure* with both of imatinib and dasatinib; or
    - 2.2. Patient has documented CML disease progression or treatment failure* with imatinib and is intolerant of dasatinib; or
    - 2.3. Patient has documented CML disease progression or treatment failure* with dasatinib and is intolerant of imatinib; or
    - 2.4. Patient is intolerant of both imatinib and dasatinib; or
    - 2.5. Patient had high risk disease** at diagnosis and has documented disease progression or treatment failure with dasatinib; or

2.6. Patient has documented CML disease progression or treatment failure* with imatinib and has a BCR--ABL kinase domain mutation that predicts greater sensitivity to nilotinib than dasatinib; and
3. Maximum nilotinib dose of 800 mg/day; and
4. Subsidised for use as monotherapy only.

Notes: *treatment failure as defined by Leukaemia Net Guidelines or TIDEL strategy. ** High risk disease at diagnosis as defined by EUTOS/SOKAL score

Renewal Application only from a relevant specialist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 6 months for applications meeting the following criteria
All of the following:
1. Lack of treatment failure while on nilotinib as defined by Leukaemia Net Guidelines; and
2. Nilotinib treatment remains appropriate and the patient is benefiting from treatment; and
3. Maximum nilotinib dose of 800 mg/day; and
4. Subsidised for use as monotherapy only.

4.9. The Subcommittee considered the risk of slippage under the proposed criteria would be low but **recommended** that, if funded, the uptake rates of nilotinib should be reviewed over time and clinicians audited if it obtained greater than 10% market share.

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

5. Peg-asparaginase for adult Acute lymphoblastic leukaemia

5.1. The Subcommittee reviewed an application from a clinician on behalf of the NZ Leukaemia Study Group for the funding of pegylated asparaginase (pegasparaginase) for adult patients with Acute Lymphoblastic Leukaemia (ALL). The Subcommittee noted that in ALL the leukemic cells are unable to synthesize the essential amino acid asparagine, whereas normal cells are able to make their own asparagine; thus leukemic cells require high amount of extra cellular circulating asparagine for their survival and growth. Members noted that asparaginase catalyses the conversion of L-asparagine to aspartic acid and ammonia thus depriving leukemic cells of circulating asparagine and inhibiting their growth.

5.2. The Subcommittee noted that ALL is most common in childhood and is curable in about 85% of paediatric cases, whereas, the cure rate in adolescent or adult onset ALL is much lower, at around 45%. Members considered that this difference may be due to differences in biology of the disease and possibly the routine use of pegasparaginase. However, members noted that there had been many other changes over time, including use of other drugs and regimens, therefore, there was not a clear link between increased use of pegasparaginase and improved cure rates in children. Members noted that in general adult ALL was more challenging to treat

than paediatric ALL due to increased toxicity and prevalence of unfavourable cytogenetics.

5.3. The Subcommittee noted that the aim of treatment for ALL is to induce a lasting remission/cure, and treatment generally comprises induction chemotherapy followed by further consolidation and maintenance chemotherapy. Members noted that multiple regimens had been developed for adult ALL, most often based upon paediatric ALL regimens, but as there were few comparative prospective randomized controlled trials, at present there is no known single best regimen for ALL and patients are routinely enrolled into clinical trials. Members considered that treatment with asparaginase, as part of combination chemotherapy, was a critical element for successful treatment of ALL.

5.4. The Subcommittee noted that there are three kinds of asparaginase available, erwina asparaginase, native *e.coli* L-asparaginase and pegasparaginase. Members noted that pegasparaginase was routinely used in the treatment of paediatric patients with ALL but it was currently unfunded for adults which members considered was inequitable.

5.5. The Subcommittee considered that erwina asparaginase was the least used asparaginase as it is more expensive and less efficacious than either L-asparaginase or pegasparaginase. Members considered it would only be used in patients with allergy to both L-asparaginase and pegasparaginase.

5.6. The Subcommittee noted there was a clear link between asparagine levels and ALL disease outcomes as demonstrated by an adult ALL study, CALGB 9511, in patients receiving pegasparaginase as part of an ALL protocol (Wetzler 2007). Members noted that compared with those patients who did achieve asparagine depletion those who did not achieve asparagine depletion had inferior OS (P = .002; hazard ratio [HR]= 2.37; 95% CI = 1.38-4.09) and DFS (P = .012; HR = 2.21; 95% CI = 1.19-4.13).

5.7. The Subcommittee noted that, whilst there were no randomised controlled studies comparing L-asparaginase with pegasparaginase in adults, a study in 118 children (Avramis 2002) had demonstrated that treatment with pegasparaginase resulted in a more rapid clearance of lymphoblasts and a more prolonged asparaginase activity compared with L-asparaginase. Members noted that 26% of L-asparaginase patients had high-titre antibodies, whereas 2% of pegasparaginase patients had those levels and that these antibodies were associated with low asparaginase activity in the native arm, but not in the pegasparaginase arm. Adverse events, infections, and hospitalization were similar between arms.

5.8. The Subcommittee considered that overall there was good evidence in children that pegasparaginase was more efficacious than L-asparginase, had a longer half-life and was less antigenic. Members considered that it was reasonable to extrapolate this to the adult setting.

5.9. The Subcommittee noted that the improved half-life of pegasparaginase meant fewer injections were needed compared with L-asparaginase with dose equivalence being 1 injection of 2,500 units/m2 of pegasparaginase to 6-9 injections of 2,500 units/m2 of L-asparinginase. Members noted that as well as the increased resources needed

to administer L-asparinginase, it was a particularly painful injection for patients to receive.

5.10. The Subcommittee **recommended**, with high priority, that pegasparaginase should be funded for the treatment of adult and adolescent patients with ALL when administered as part of a multi-agent chemotherapy regimen given with curative intent. Members considered that under these criteria approximately 12-20 patients per annum would access funding.

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

6. Rituximab for 17p del CLL

6.1. The Subcommittee considered an application from two clinicians on behalf of the Haematology Society of Australia and New Zealand (HSANZ) requesting funding of rituximab (MabThera, Roche) for transplant-ineligible patients with Chronic Lymphocytic Leukaemia (CLL) 17p deletion or mutations of TP53 in combination with high-dose corticosteroids.

6.2. The Subcommittee noted that it had previously considered an application from Roche in 2010 and 2011 for the funding of rituximab for CLL. Members noted that it had considered that evidence from the key study (CLL-8 study, Hallek 2008 and 2009) demonstrated that patients with chromosome 17p deletion CLL did not appear to respond to the addition of rituximab to fludarabine and cyclophosphamide (FC) and, therefore, it recommended the Special Authority criteria specifically exclude funding for patients with 17p deletion CLL. Members noted that rituximab was funded from 1 August 2011 for patients without chromosome 17p deletion CLL.

6.3. The Subcommittee noted that it had previously recommended that alemtuzumab (MabCampath, Sanofi) should be funded, with medium priority, for CLL patients with 17p53 deletion who are refractory to fludarabine and where an allogeneic transplant is planned. However, members noted that Sanofi had recently withdrawn alemtuzumab from commercial sale for CLL patients so PHARMAC has been unable to progress this funding proposal. However, members noted that Sanofi would provide alemtuzumab free of charge to patients with CLL through a compassionate access program.

6.4. The Subcommittee noted that the application comprised subgroup analyses of patients with 17p deletion from the two main randomised trials of rituximab for CLL it had previously considered; CLL8 (Hallek 2010) and REACH (Robak 2010).

6.5. The Subcommittee noted that in the CLL8 study 51 of 817 patients had 17p deletion CLL. Members further noted the overall response rate was significantly improved in patients receiving rituximab (68% vs. 34% (p=0.025) and median progression-free survival (PFS) was also improved (11.3 months vs. 6.5 months, p=0.019). Members noted that overall PFS and overall survival (OS) were both significantly shorter in

CLL patients that had 17p deletion compared with those that didn't and there was no significant improvement in OS in patients with 17p del CLL receiving rituximab compared with those that did not. The Subcommittee noted that 42 of 552 patients in the REACH study had 17p deletion. The risk ratio (RR) for PFS was 0.75 (95% CI 0.38-1.49) for patients with 17p deletion compared with 0.63 (95% CI 0.49-0.81) for patients without 17p deletion.

6.6. The Subcommittee also noted a recently published trial of rituximab in combination with high-dose dexamethasone in 54 patients with relapsed/refractory CLL (19% of patients had 17p deletion) (Smolej 2012). Members noted that two schedules of rituximab were used: group 1, rituximab 500 mg/m^2 day 1, 8, 15, 22 (375 mg/m^2 in 1st dose) every 4 weeks; group 2, 500 mg/m^2 day 1 (375 mg/m^2 in 1st cycle) repeated every 3 weeks. Members noted that after a median follow-up of approximately 10 months, median PFS was 6 months in Group 1 and 6.9 months in Group 2; median overall survival was 14.1 months in Group 1 vs. not reached in Group 2. The Subcommittee noted that the trial publication did not report the results for subgroups of patients, including those with 17p deletion.

6.7. The Subcommittee also noted a study of high dose methylprednisolone (HDMP) in 25 patients with advanced refractory CLL of whom 45% had p53 abnormalities (Thornton 2003) in which overall response rate was 77% with a median duration of 12 months.

6.8. The Subcommittee noted that in general patients with 17p deletion CLL have poorer prognosis, with relatively short PFS and OS regardless of treatment used compared with non-17 p del CLL. Members considered that the benefits of rituximab treatment in 17p deletion CLL were relatively small. Members noted that patients with 17p deletion CLL who were not eligible for transplant were likely to do poorly regardless of treatments used.

6.9. The Subcommittee noted the cost of rituximab, and considered that it was likely to be poorly cost-effective in patients with 17p deletion CLL given the small incremental benefits and likely treatment related adverse events. Members recognised the health need in this patient group but considered that rituximab would likely not offer significant benefits compared with other treatment options, in particular high dose methylprednisolone.

6.10. The Subcommittee **recommended** that the application to be declined.

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

7. Irinotecan and oxaliplatin for pancreatic cancer

7.1. The Subcommittee considered an application from clinicians on behalf of the Gastrointestinal Special Interest Group (GI-SIG) of the New Zealand Association of Cancer Specialists (NZACS), requesting the funding of irinotecan and oxaliplatin

when used in combination with infusional 5-fluorouracil (FOLFIRINOX) for the treatment of ECOG performance status 0-1 patients with metastatic pancreas adenocarcinoma. The Subcommittee considered the application to be succinct and of good quality.

7.2. The Subcommittee noted that pancreatic cancer was the fifth most common cause of cancer death in 2009, accounting for 5% of all deaths and that Māori generally show higher registration and mortality rates than non-Māori. Members noted that current standard treatment for advanced pancreatic cancer in New Zealand comprised single agent gemcitabine, which had been shown to provide 1 year survival rates of 18% and median overall survival of 5.6 months (Burris 1997). The Subcommittee considered that there was a significant unmet health need for better treatments for advanced pancreatic cancer.

7.3. The Subcommittee reviewed evidence from one randomised trial that evaluated the efficacy of FOLFIRINOX compared with gemcitabine in 342 patients (ECOG 0-1) with metastatic pancreatic cancer who had not previously been treated with chemotherapy (Conroy 2011). The Subcommittee considered that the trial was well conducted. Members noted that patients were randomised to receive FOLFIRINOX or gemcitabine. FOLFIRINOX treatment comprised oxaliplatin 85 mg/m^2, leucovorin 400 mg/m^2, irinotecan 180 mg/m^2, IV bolus 5-FU 400 mg/m^2, followed by continuous IV infusion of 5-FU 2,400 mg/m^2 over 46 hours. Treatment was repeated every 2 weeks for up to 6 cycles. Gemcitabine was administered at a dose of 1,000 mg/m^2 weekly for 7 weeks followed by 1 week of rest, then weekly for 3 out of every 4 weeks thereafter.

7.4. The Subcommittee noted that after a median follow-up of 26.6 months, patients administered FOLFIRINOX had a significant improvement in median overall survival (11.1 months vs. 6.8 months, hazard ratio (HR) for death, 0.57; 95% confidence interval [CI] 0.45 to 0.73; P<0.001) and median progression-free survival was also significantly improved by 3.1 months (6.4 months vs. 3.3 months, HR for disease progression, 0.47; 95% CI 0.37 to 0.59; P<0.001). Members noted that patients administered FOLFIRINOX had improved quality of life. The Subcommittee considered the regimen to be highly efficacious in the treatment of pancreatic cancer, with a substantial improvement in length of remission and overall survival in an area of large unmet need.

7.5. The Subcommittee noted that the combination treatment was associated with higher rates of grade 3 and 4 toxicities including neutropenia, febrile neutropenia, thrombocytopenia, diarrhoea, and sensory neuropathy compared with gemcitabine. Members noted that filgrastim was administered to 42.5% of patients in the clinical trial who received FOLFIRINOX and 5.3% of patients who received gemcitabine (p<0.001).

7.6. The Subcommittee noted that the FOLFIRINOX treatment regimen requires more frequent infusions and longer infusion times that gemcitabine and that this would impact on costs to the health sector. Members considered that the impact on use of anti-diarrhoeal and anti-emetics would be relatively small, but there may be some impact on the use of filgrastim for treatment, or prevention of neutropenia.

7.7. The Subcommittee noted that the trial had tight exclusion criteria and considered that in practice, due to its significant toxicity, that clinicians would likely use FOLFORINOX sparingly, targeting it to younger healthier patients and therefore, members considered that only a small number of patients would receive this treatment if it was funded.

7.8. The Subcommittee **recommended** that irinotecan and oxaliplatin should be funded, when used in combination with infusional 5-fluorouracil (FOLFIRINOX), for the treatment of ECOG performance status 0-1 patients with metastatic pancreas adenocarcinoma. Members gave this recommendation a high priority

7.9. The Subcommittee noted that it had previously reviewed the current Special Authority restrictions applying to irinotecan and oxaliplatin in August 2011 and recommended that the Special Authority restriction applying to oxaliplatin should not be removed at that time and that PHARMAC staff seek further information from disease specialists regarding potential market changes prior to removing the Special Authority on irinotecan. Members noted that subsequent to these recommendations, the prices of oxaliplatin and irinotecan had reduced substantially following the award of new tenders. The Subcommittee considered that the increased uptake from removing the Special Authority on irinotecan was likely to be low and that although oxaliplatin would be more widely used if the Special Authority was removed, the financial risk was limited given the recent price reduction.

7.10. The Subcommittee **recommended** that the Special Authority applying to both oxaliplatin and irinotecan be removed with high priority, therefore allowing these agents to be funded for the treatment of metastatic pancreas adenocarcinoma and other indications.

7.11. The Decision Criteria particularly relevant to the recommendations 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; (vi) The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule.*

8. Oxaliplatin for oesophageal and gastric cancer

8.1. The Subcommittee considered an application from a clinician on behalf of a group of clinicians including the chair of the Gastrointestinal Special Interest Group (GI-SIG) of the New Zealand Association of Cancer Specialists (NZACS), for the funding of oxaliplatin in combination with epirubicin and capecitabine (EOX) or 5-FU (EOF) for patients with advanced oesophagogastric cancer.

8.2. The Subcommittee noted that most patients with gastric or oesophageal cancers present with locally advanced (inoperable) or metastatic disease and 5 year survival rates are currently poor at around 10-15%. Members noted that current standard treatment comprises a triplet regimen of either ECX (epirubicin, cisplatin, and capecitabine) or ECF (epirubicin, cisplatin, and 5-FU) both of which due to the cisplatin component required pre and post administration hydration protocols and duration at a day unit of 8 hours.

8.3. The Subcommittee reviewed key evidence from a randomised trial (Cunningham 2008) in which 1,002 patients with locally advanced (inoperable) or metastatic oesophageal, stomach or gastro-oesophageal junction cancer were randomised to receive one of four triplet therapies: epirubicin and cisplatin plus either fluorouracil (ECF) or capecitabine (ECX) or epirubicin and oxaliplatin plus either fluorouracil (EOF) or capecitabine (EOX). The Subcommittee considered that the study was of good quality

8.4. The Subcommittee noted that after a median follow-up of 17.1 months, the unadjusted hazard ratio for death for the non-inferiority comparisons of capacitabine vs. fluorouracil was 0.86 (95% confidence interval [CI], 0.80 to 0.99) and for the comparison of oxaliplatin vs. cisplatin, the hazard ratio was 0.92 (95% CI, 0.80 to 1.10). Members noted that overall survival did not differ significantly between the fluorouracil groups or between the oxaliplatin and cisplatin groups with median overall survival of 9.9 months (ECF), 9.9 months (ECX), 9.3 months (EOF) and 11.2 months (EOX) respectively. Median progression free survival was 6.2 months (ECF), 6.7 months (ECX), 6.5 months (EOF) and 7.0 months (EOX) respectively.

8.5. The Subcommittee noted that cisplatin treatment, as compared with oxaliplatin, was associated with significantly higher rates of grade 3 or 4 neutropenia and alopecia but significantly less grade 3 or 4 diarrhoea and peripheral neuropathy although members noted that rates of peripheral neuropathy were low in both treatment groups (≤5%).

8.6. The Subcommittee considered that, overall, the evidence demonstrated that oxaliplatin was at least as good as cisplatin and it may have a slight benefit in terms of overall survival and toxicity profile.

8.7. The Subcommittee considered that if oxaliplatin was funded as requested, it would displace a significant proportion of cisplatin use and it would likely be used in 300-350 patients per annum. Overall they considered that oxaliplatin would provide significant benefits to the health system from reduced day unit time and reduce used of hydration protocols, renal assessment and audiometry testing associated with cisplatin use.

8.8. The Subcommittee considered that the evidence demonstrated no difference in the efficacy between flouropyrimidine choice (Oral capecitabine vs. infusional 5-FU). Members considered that the choice of flouropyrimidine would likely not change compared to current usage. Therefore in some cases patients would receive EOX and some EOF if oxaliplatin were funded.

8.9. The Subcommittee **recommended** that oxaliplatin should be funded, when used in combination with epirubicin and a flouropyrimidine (EOX/EOF) for the treatment of patients with for patients with advanced oesophagogastric cancer. Members gave this recommendation a high priority

8.10. The Subcommittee noted that it had previously reviewed the current Special Authority restrictions applying to oxaliplatin in August 2011 and recommended that the Special Authority restriction applying to oxaliplatin should not be removed. Members noted that subsequent to these recommendations the prices of oxaliplatin had reduced substantially following the award of new tenders. The Subcommittee

considered that oxaliplatin would be more widely used if the Special Authority was removed, principally in small bowel and gastric cancers, but considered that financial risk was limited, given the recent price reduction.

8.11. The Subcommittee **recommended** that the Special Authority applying to oxaliplatin be removed with high priority, therefore allowing it to be funded for the treatment of advanced oesophagogastric cancer and other indications.

8.12. The Decision Criteria particularly relevant to the recommendations 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; (vi) The budgetary impact (in terms of the pharmaceutical budget and the Government's*