Cancer Treatments Subcommittee of PTAC meeting held 18

November 2011

(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.

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 16 & 17 February 2012, the record of which will be available in March 2012.

Contents

1 Matters Arising

1.1 Correspondence regarding lapatinib

1.1.1 The Subcommittee reviewed correspondence from GlaxoSmithKline (GSK) in which it requests re-consideration of its application for second line funding of lapatinib (Tykerb), taking into account a revised commercial proposal.

1.1.2 The Subcommittee noted the points made by GSK but did not consider the information provided changed its view. The Subcommittee reiterated its April 2011 view and **recommended** that the application to fund lapatinib as a second line treatment in patients with HER 2 positive metastatic breast cancer patients, following disease progression on trastuzumab, be declined.

2 Therapeutic group review including CaEC review

2.1 Erythropoietin for MDS

2.1.1 The Subcommittee noted that PHARMAC had received 5 HEC applications for erythropoietin in patients with refractory anaemia associated with myelodysplasia. Members considered that this treatment option may have some merit, however, it did not have sufficient information to make any recommendations regarding funding at this time.

2.1.2 The Subcommittee considered that it would be appropriate for PHARMAC to consider a Pharmaceutical Schedule funding application for erythropoietin for myelodysplastic syndrome. The Subcommittee **recommended** that PHARMAC staff request a funding application from the Haematology Society of Australia and New Zealand (HSANZ) for this indication.

2.2 Bortezomib

2.2.1 The Subcommittee noted that PHARMAC had received an application under CaEC for the funding of bortezomib for a patient with multiple myeloma (MM) who had received prior treatment with cyclophosphamide, dexamethasone and thalidomide (CTD). Members noted that the applicant had considered that the patient should receive funded bortezomib as they had only received 'one line of treatment' even though it had been delivered in two separate episodes (CTD from April 2008 -Feb 2009 and then restarted in April 2010).

2.2.2 The Subcommittee noted that PHARMAC staff had sought advice from the EC Panel and a Haematologist, some of whom considered that the patient had received "two lines" of therapy (and therefore the application should be declined since the funding of bortezomib in the 3rd line setting or beyond had been considered by PTAC/CaTSoP and PHARMAC and declined) whilst others considered that because the same treatment was used twice, the patient had only had received 'one line' of therapy and therefore would be eligible for funding under the current Special Authority.

2.2.3 The Subcommittee considered that this patient had clearly received two lines of therapy and therefore did not meet the Special Authority criteria for bortezomib. Members considered that the key determinant of determining the number of prior lines of treatment was whether or not the patient had a treatment free period between 2 periods of treatment, regardless of whether or not the same drug regimen was used.

2.2.4 The Subcommittee considered that there was no need to specifically include 'supportive treatments' in the definition of a line of therapy as such treatments would be included under the term 'known therapeutic chemotherapy regimen'.

2.2.5 The Subcommittee **recommended** that for clarity, the note applying to the bortezomib Special Authority be amended as follows (changes in bold and strikethrough):

> Note: A line of therapy is considered to comprise either: a) **treatment for a defined period of time with** a known therapeutic chemotherapy regimen ~~and supportive treatments~~; or b) a transplant induction chemotherapy regimen with stem cell transplantation ~~and supportive treatments~~.

2.3 Imatinib and Dasatinib for ALL

2.3.1 The Subcommittee noted that PHARMAC had recently received a CaEC application for dasatinib for a patient with Acute Lymphocytic Leukaemia (ALL). Members noted that during PHARMAC's consideration of funding of dasatinib for Chronic Myeloid Leukaemia (CML), some members of CaTSoP requested funding be extended to include 'BCR-ABL positive leukaemia', thus encompassing both CML and ALL. At that time some CaTSoP members considered that most BCR-ABL-positive ALL patients would be gaining access to imatinib by calling it CML, and that the two are clinically difficult to distinguish. Members noted that when notifying of its decision to fund dasatinib for CML only, PHARMAC stated that funding of dasatinib for all BCR-ABL positive leukaemias, including ALL, required further assessment by PHARMAC.

2.3.2 The Subcommittee considered Philadelphia Chromosome (Ph+)/ BCR-ABL positive ALL was quite a rare disease. Members considered that sometimes Ph+ ALL was clinically indistinguishable from blast crisis CML, but sometimes it was clearly a different disease. Members considered that currently most Ph+ ALL patients would be accessing funded imatinib or dasatinib as 'blast crisis CML' patients.

2.3.3 The Subcommittee considered it was standard practice to treat Ph+ ALL with imatinib or dasatinib and therefore it would be appropriate for PHARMAC to consider a Pharmaceutical Schedule funding application for both imatinib and dasatinib in this setting. The Subcommittee **recommended** that PHARMAC staff request a funding application from the Haematology Society of Australia and New Zealand (HSANZ).

3 Biosimilar filgrastim

3.1 The Subcommittee considered concerns around the use of biosimilar filgrastim use in HLA-matched unrelated (allogeneic) healthy stem cell donors, which was highlighted by a clinician. The Subcommittee also noted a response from Sandoz, the supplier of a biosimilar filgrastim (Zarzio), on the issue.

3.2 The Subcommittee noted that recently, the World Marrow Donor Association (Shaw et al. Haematologica 2011; 96(7): 942-947) considered that there was a potential risk of mutagenicity and immunogenicity with biosimilar filgrastim and that this risk was unacceptable in healthy stem cell donors. The Subcommittee noted that currently there were no data comparing the T and B-cell populations mobilised using biosimilar filgrastim compared with Neupogen.

3.3 The Subcommittee noted that Sandoz is currently running a study of 200 unrelated, HLA-matched healthy donors mobilised with Zarzio with a planned safety follow-up of 10 years. The Subcommittee also noted that Zarzio is currently routinely being used for allogeneic stem cell mobilisation at St Bartholomew's Hospital, London and at 36 Parisian public hospitals.

3.4 The Subcommittee considered that there is currently no evidence that biosimilar filgrastim has a different safety profile in healthy donors when compared to patients groups requiring treatment for various indications, e.g neutropaenia or autologous stem cell mobilisation. The Subcommittee considered that there was no evidence of increased risk of immunogenicity and mutagenicity with biosimilar filgrastim compared with neupogen, and that at this time such a risk remained theoretical.

3.5 The Subcommittee considered that there are only approximately 100 allogeneic stem cell transplants performed per year in New Zealand, with each health donor receiving 5 doses of filgrastim, therefore, the usage of filgrastim in this indication would be very small compared with its usage in other indications like cancer treatment associated neutropaenia.

3.6 The Subcommittee noted that under the terms of the current Request for Proposals (RFP) for filgrastim, hospital sole supply (HSS) with a biosimilar could not commence prior to 1 January 2013. The Subcommittee also noted that under a Hospital Sole Supply agreement, hospitals would have a 1% discretionary variance to purchase an alternative brand of filgrastim for a small number of patients and this could include healthy stem cell donors, if they choose to.

3.7 The Subcommittee considered that it would be appropriate to award Hospital Sole Supply and community Sole Supply Status to a biosimilar brand of filgrastim provided that hospitals are able to continue to purchase an alternative brand of filgrastim for healthy stem cell donors if they choose.

4 Peglyated liposomal doxorubicin for ovarian cancer

4.1 The Subcommittee considered an application from a clinician on behalf of the NZ Gynaecologic Oncology Group (NZGOG) for the funding of pegylated liposomal doxorubicin hydrochloride (PLD, Caelyx, Janssen-Cilag Pty Limited) for patients with

advanced epithelial ovarian cancer whose disease has progressed following first line platinum based chemotherapy (i.e. second-line treatment).

4.2 The Subcommittee noted that in 2008, based on key evidence from study 30-49 reported by Gorden et al (Gynaecologic Oncology 2004), it had recommended PLD be funded, with medium priority, for the third-line treatment of advanced epithelial ovarian cancer in women who have failed a first-line and second-line chemotherapy regimen (including platinum). Members noted that despite receiving a positive recommendation for third line treatment, PLD remains unfunded because it is low on PHARMAC's priority list compared with other funding options, principally due to its relatively poor cost effectiveness and high budget impact in the third line setting.

4.3 The Subcommittee noted key new evidence provided by the applicant from a randomised phase III non-inferiority study, the CALYPSO study, in 976 women with platinum-sensitive relapsed/recurrent ovarian cancer after 1 or 2 lines of prior chemotherapy comparing combination carboplatin (AUC 5) plus PLD (30 mg/m2) every 28 days with standard combination carboplatin (AUC 5) plus paclitaxel (175 mg/m2) every 21 days for at least 6 weeks (Pujade-Lauraine et al J Clin Oncol 2010). Members noted evidence from two substudies of CALYPSO were also provided: one focusing on outcomes in elderly patients (>70 years) (Kurtz et al Ann Oncol 2011), the other focusing on hypersensitivity reactions (Joly et al Gynaecol Oncol 2011).

4.4 The Subcommittee noted that PLD/carboplatin significantly improved progression free survival compared with paclitaxel/carboplatin (HR 0.82, 95% CI 0.72-0.94, p=0.005), however, members noted that the absolute difference between the treatment groups was small at only 1.9 months (9.4 months vs 11.3). Members noted that overall survival data were immature and not reported.

4.5 The Subcommittee noted that patients treated with PLD/carboplatin experienced fewer grade 3 to 4 non-haematologic toxicities compared with patients treated with paclitaxel/carboplatin (28.4% v 36.8%, p<0.001). In particular, members noted that grade ≥ 2 sensory neuropathy, alopecia (and allergic/hypersensitivity reaction occurred more frequently in the paclitaxel/carboplatin treated patients, whereas, grade ≥2 nausea, vomiting, mucositis and hand foot syndrome occurred more frequently in PLD treated patients. Overall, members considered that the toxicity profile for PLD was favourable compared with paclitaxel.

4.6 The Subcommittee noted that in the CALYPSO study, patients were treated until disease progression with PLD/carboplatin treated patients receiving treatment every 4 weeks and paclitaxel/carboplatin treated patients receiving treatment every 3 weeks, with both treatment groups receiving a median of 6 treatment cycles (range 1–14). Members considered that in NZ patients would be treated for a maximum of 6 cycles rather than until disease progression, therefore, it was likely that in the NZ clinical setting patients would receive less PLD than was administered in the CALYPSO study. Members also noted that administration of PLD/carboplatin was less resource intensive compared with paclitaxel-carboplatin (1 hour infusion every 4 weeks compared with 5 hours every 3 weeks).

4.7 The Subcommittee also reviewed evidence from 2 randomised controlled studies of PLD monotherapy compared with gemcitabine monotherapy in patients with platinum resistant relapsed/recurrent ovarian cancer after prior chemotherapy (Ferrandina et al

J Clin Oncol 2008 and Mutch et al J Clin Oncol 2007). Members noted that the Ferrandina study also enrolled patients who were partially platinum sensitive. Members noted that in these two studies, and the Gordon study, where PLD was given as monotherapy, the dosing was higher (40-50 mg/m2 every 28 days) than in the CALYPSO study, where it was administered in combination with platinum. Members considered that in the New Zealand setting most second-line patients receiving PLD monotherapy would be started at a dose of 50 mg/m2 every 28 days.

4.8 The Subcommittee noted that in these studies there was no significant difference between PLD and gemcitabine in efficacy endpoints. However, members considered that the toxicity profile for PLD was more favourable than gemcitabine; PLD treated patients experienced less grade ≥ 3 neutropaenia but mucositis and hand foot syndrome occurred more frequently in PLD treated patients.

4.9 Overall, the subcommittee considered that PLD (plus or minus platinum) was as effective as other treatment options in patients with platinum sensitive, partially sensitive, or resistant relapsed/recurrent ovarian cancer. However, members considered that PLD had a better and more manageable toxicity profile. In particular members noted that paclitaxel associated sensory neuropathy was a particularly debilitating side effect, which may lead to treatment dose/reduction/discontinuation (with associated efficacy reduction) and in some cases was not reversible. Members also noted that the PLD would be simpler to administer than either paclitaxel or gemcitabine.

4.10 The Subcommittee noted that PLD was a relatively expensive treatment and although it had toxicity and administrative benefits, it would likely be poorly cost effective compared with currently funded treatment options, which were comparatively inexpensive. However, members noted there is a group of patients with relapsed/recurrent ovarian cancer whose disease remains stable for a significant period of time (2 years or more), therefore, the better side effect profile of PLD would likely improve the quality of life in these patients which would be beneficial.

4.11 The Subcommittee considered that it may be reasonable to limit the number of funded treatment cycles to a maximum of 6 for cost containment purposes, although, members noted this was not based on the dosing regimens used in the relevant clinical trials but rather a pragmatic approach.

4.12 The Subcommittee **recommended** that pegylated liposomal doxorubicin hydrochloride (PLD, Caelyx, Janssen-Cilag Pty Limited) be funded on the Pharmaceutical Schedule subject to Special Authority criteria for patients intolerant of platinum or those with platinum sensitive, partially sensitive, or platinum resistant advanced epithelial ovarian cancer whose disease has progressed following platinum based chemotherapy, as follows:

> **Pegylated liposomal doxorubicin hydrochloride - PCT Only – Specialist - Special Authority for Subsidy**
> **Initial application -** 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. Patient has advanced, epithelial ovarian cancer; and

2. Patient has documented disease progression following treatment with first line platinum based chemotherapy; and
3. Either:
   3.1 Both
      3.1.1 The patient has platinum sensitive or partially sensitive disease; and
      3.1.2 PLD to be administered in combination with a platinum drug at a maximum dose of 30 mg/m2 every 28 days for a maximum of 6 cycles; or
   3.2 Both
      3.2.1 Either:
         3.2.1.1.The patient has platinum resistant disease; or
         3.2.1.2 The patient is intolerant to platinum; and
      3.2.2 PLD to be administered as monotherapy at a maximum dose of 50 mg/m2 every 28 days for a maximum of 6 cycles.

4.13 The Subcommittee gave its recommendation for platinum resistant patients a low priority, and its recommendations for other populations (platinum intolerant, platinum sensitive or partially sensitive) medium priority. Members noted that its priority ratings would increase if the price of PLD was significantly reduced.

4.14 The Decision Criteria particularly relevant to these 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; (v) The cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health and disability support services. ,

5 Gefitinib for first line treatment of locally advanced or metastatic NSCLC in patients with EGFR activating mutations

5.1 The Subcommittee considered an application from AstraZeneca for the funding of gefitinib (Iressa) for the first-line treatment of patients with locally advanced or metastatic non-small cell lung cancer expressing epidermal growth factor receptor tyrosine kinase (EGFR) activating mutations.

5.2 The Subcommittee also considered a separate submission from a clinician requesting funding of EGFR tyrosine kinase inhibitors (erlotinib (Tarceva, Roche Products NZ Limited) and/or gefitinib (Iressa, Astra-Zeneca) for first-line use in advanced adenocarcinoma of the lung with activating mutations of the EGFR. In addition, the Committee considered information provided by the National Health Committee regarding EGFR testing.

5.3 The Subcommittee noted that it had previously twice considered the funding of gefitinib for third and second line treatment of advanced NSCLC and recommended it be declined because of insufficient evidence of efficacy. However, members considered that at that time gefitinib use was not being correctly targeted as the evidence was not limited to patients whose disease expressed EGFR activating mutations.

5.4 The Subcommittee considered that specific activating mutations in the tyrosine kinase domain of EGFR were associated with increased activity of the EGFR inhibitors gefitinib and erlotinib. Members considered that EGFR activating mutations were most common in adenocarcinomas which comprised approximately 50% of the NSCLC population; members considered that approximately half of adenocarcinomas would express EGFR activating mutations. Members considered that most squamous cell NSCLC would not express EGFR activating mutations and would therefore be unlikely to benefit from tyrosine kinase inhibitor treatment. Overall, members considered that approximately 40% of non-squamous cell NSCLC's would express EGFR activating mutations.

5.5 The Subcommittee reviewed evidence from 4 randomised controlled studies for gefitinib and two studies for erlotinib. Overall members considered that the evidence demonstrated that, compared with standard platinum based chemotherapy, tyrosine kinase inhibitor treatment significantly improved progression free survival by around 3-4 months and quality of life in patients with stage IIIB or IV NSCLC expressing EGFR activating mutations. However, members noted that because of cross-over in the relevant studies, no survival advantage had been demonstrated.

5.6 The Subcommittee noted that evidence from the IPASS study (Fukuoka et al J Clin Oncol 2011;29:2866-74) demonstrated that patients without EGFR activating mutations treated with gefitinib had a significantly shorter time to disease progression compared to those treated with standard platinum based chemotherapy, 1.5 months vs 5.8 months respectively, HR 2.98 (95% CI 2.048-3.975) p<0.0001). Members considered that on the basis of this evidence, patients without EGFR activating mutations should be treated with standard platinum based chemotherapy and not tyrosine kinase inhibitors.

5.7 The Subcommittee considered that clinically it was not possible, nor sensible, to distinguish between gefitinib or erlotinib. Members considered that the two had the same or similar efficacy and safety in NSCLC patients with EGFR activating mutations.

5.8 The Subcommittee noted that the current funding of erlotinib for second line treatment of patients with NSCLC regardless of EGFr status had been implemented prior to the clear understanding for the role of EGFR activating mutations in determining treatment response. Members considered that the funding criteria for erlotinib were no longer appropriate as they enabled erlotoinib to be used in some patients where we know it is very unlikely to be effective and for whom standard platinum based chemotherapy treatment would be more efficacious.

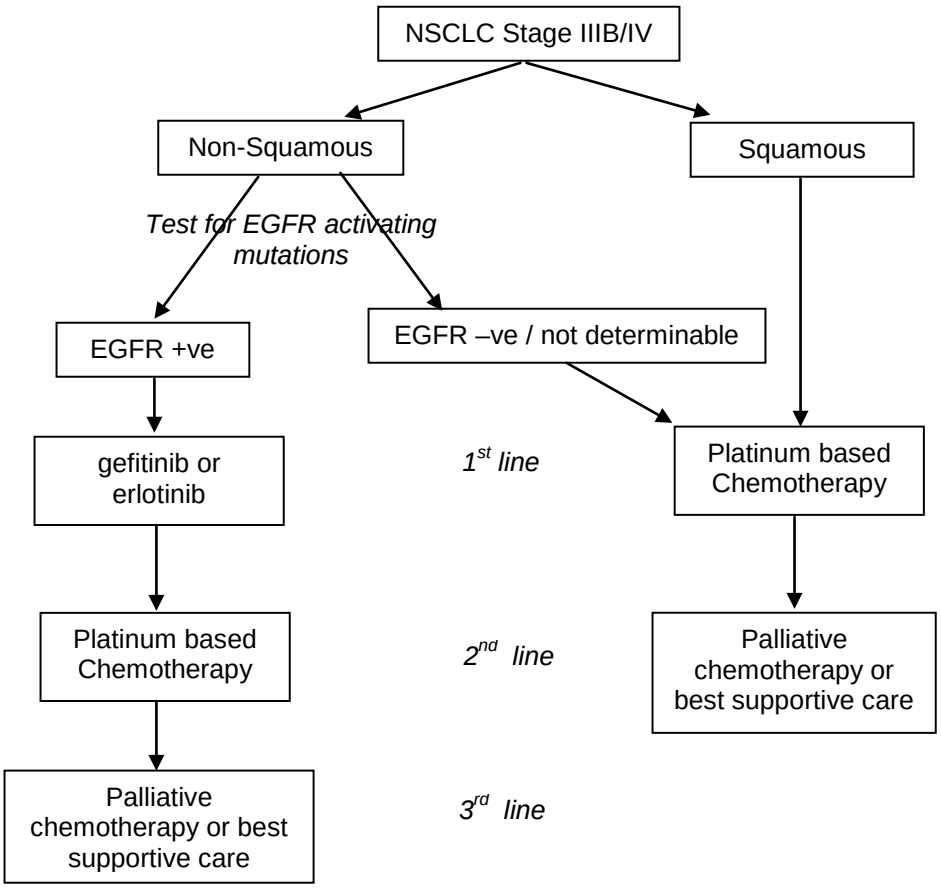
5.9 The Subcommittee considered that there was no evidence to support the use of a second tyrosine kinase inhibitor after failure of a prior tyrosine kinase inhibitor (erlotinib after gefitinib or vice versa), therefore members considered that if gefitinib were to be funded as a first line treatment option, funding for erlotinib in the second line setting should be amended to prevent its use after gefitinib.

5.10 The Subcommittee considered that all patients with non-squamous cell NSCLC should undergo testing for EGFR activating mutations in order to determine appropriate treatment. Members considered that, given the low likelihood of squamous cell NSCLC's expressing EGFR activating mutations, it was not

necessary, or sensible, to test squamous cell NSCLC patients. Members considered that tyrosine kinase inhibitors should only be funded for patients with EGFR activating mutations.

5.11 The Subcommittee considered that, if funded, gefitinib would replace platinum based doublet chemotherapy as standard first line treatment in patients with locally advanced/metastatic non-squamous NSCLC expressing EGFR activating mutations. Members considered that such patients would then be treated with platinum based doublet chemotherapy, single agent chemotherapy or best supportive care on disease progression. Members considered that in this patient group first line treatment with gefitinib would replace second line treatment with erlotinib,.

5.12 The subcommittee **recommended** the following testing and treatment algorithm for stage IIIB or IV NSCLC patients.



5.13 The Subcommittee noted that currently there is limited access in DHB hospitals to EGFR activating mutation testing. Members considered that DHBs should, at minimum, provide access to EGFR activating mutation testing for patients with advanced/metastatic non-squamous cell NSCLC to determine appropriate treatment for these patients. Members noted and supported, the National Health Committee's development of national consensus guidelines for EGFR activating mutation testing

protocols. Members considered that testing should be done using PCR methodology .

5.14 The Subcommittee noted that currently some NSCLC patients were diagnosed through Fine Needle Aspirate (FNA), which may not provide sufficient material for EGFR mutation testing. Members considered that current testing methodology required paraffin block samples obtained during surgery or via core needle biopsy sampling but this is not always possible. Members considered that, where appropriate, a culture shift in some DHB hospitals may be needed to implement core needle biopsy sampling as standard. Members noted that core needle biopsy carried an increased risk of pneumothorax and was more invasive and time consuming compared with FNA. Members recommended that the costs of funding EGFR activating mutation testing for all non-squamous NSCLC patients including the cost associated with biopsy practices changes should be included in the budget impact and cost-utility analyses of the funding recommendations made.

5.15 The Subcommittee noted that following implementation of EGFR activating mutation testing there may be a small group of patients diagnosed with NSCLC who may have started treatment with erlotinib but have insufficient archived sample to retrospectively determine EGFR activating mutation status. Members considered that such patients should be able to continue to receive funded erlotinib whilst they continued to respond to treatment.

5.16 The Subcommittee **recommended** that gefitinib be listed on the Pharmaceutical Schedule with a high priority subject to the following Special Authority:

> **Gefitinib - Retail Pharmacy – Specialist - Special Authority for Subsidy**
> **Initial application** only from a relevant specialist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 4 months for applications meeting the following criteria:
> All of the following:
> 1. Patient has treatment naïve locally advanced, or metastatic, unresectable, non-squamous Non Small Cell Lung Cancer (NSCLC); and
> 2. Documentation confirming that disease expresses activating mutations of EGFR tyrosine kinase; and
> 3. Gefitinib is to be given for a maximum of 3 months.
>
> **Renewal application** only from a relevant specialist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 6 months where radiological assessment (preferably including CT scan) indicates NSCLC has not progressed.

5.17 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.

5.18 The Subcommittee further **recommended** that the Special Authority criteria for current funding of erlotinib be amended, with high priority, as follows (changes in bold and strikethrough).

Erlotinib - Retail Pharmacy – Specialist - Special Authority for Subsidy
Initial application only from a relevant specialist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 4 months for applications meeting the following criteria:
All of the following:
1 Patient has advanced, unresectable, Non Small Cell Lung Cancer (NSCLC); and
2 Patient has documented disease progression following treatment with first line platinum based chemotherapy; and
3. Either:
3.1 All of the following
3.1.1 The patient has non-squamous NSCLC; and
3.1.2 Documentation confirming that disease expresses activating mutations of EGFR tyrosine kinase; and
3.1.3 The patient has not received prior treatment with gefitinib; or
3.2 Insufficient biopsy sample available to determine EGFR mutation status or precise histological type; and
4. Erlotinib is to be given for a maximum of 3 months.

Renewal application only from a relevant specialist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 6 months where radiological assessment (preferably including CT scan) indicates NSCLC has not progressed.

5.19 The Decision Criteria particularly relevant to these recommendations 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,

6 Sorafenib for advanced HCC and second line treatment of advanced RCC

6.1 The Subcommittee considered an application from Bayer New Zealand Ltd for the listing of sorafenib tosylate (Nexavar) on the Pharmaceutical Schedule for the treatment of patients with inoperable advanced hepatocellular carcinoma (HCC) with preserved liver function (Child Pugh score 5-7) and second line treatment of patients with advanced renal cell carcinoma (RCC) following treatment failure on, or intolerance to, sunitinib or other targeted treatments.

6.2 The Subcommittee noted that it and PTAC had previously reviewed the funding of sorafenib for patients with advanced, inoperable, hepatocellular carcinoma (HCC) and PTAC had also reviewed its funding as first line treatment of patients with advanced renal cell carcinoma (RCC). Members noted that both applications were recommended for decline.

6.3 The two indications (HCC and RCC) were discussed separately.

Hepatocellular Carcinoma

6.4 The Subcommittee noted that the high incidence of HCC in New Zealand compared with other Western countries was a public health concern especially in Maori, Pacific Island and Chinese New Zealander populations consistent with the higher incidences of Hepatitis B and C infection in these populations.

6.5 The Subcommittee considered that the supplier's claim that sorafenib was reimbursed in the USA was misleading, noting that around 50 million people in the USA are not covered by private or government funded insurance schemes and therefore do not receive funding for medicines or other healthcare costs.

6.6 The Subcommittee noted that it had previously reviewed the key evidence provided in the application (SHARP, Llovet et al NEJM 2008;359:378-90 and an Asia-pacific Study, Chen et al Lancet Oncology 2009;10:25-34). Members considered that the new evidence provided in the submission was of moderate strength and quality comprising mainly partially reported, unpublished, small, single arm prospective or retrospective observational studies.

6.7 The Subcommittee reviewed evidence, in the form of a slide presentation and abstract from the 2011 American Society of Clinical Oncology meeting, from a randomised controlled study comparing the safety and efficacy of sorafenib with sunitinib in 1,074 patients with advanced HCC, with preserved liver function (Child-Pugh A (score 5-6)) (Cheng et al, J Clin Oncol 29: 2011 (suppl; abstr 4000)). Members noted an Independent Data Monitoring Committee stopped the study early for futility and safety concerns with sunitinib. Members noted that results for sorafenib in this study were similar to those seen in the SHARP study: Median overall survival was 7.9 months for sunitinib and 10.2 months for sorafenib (HR 1.30 [1.13–1.50], P=0.0010); PFS was 3.6 and 3.0 months respectively (HR 1.13 [0.99–1.30], P=0.1215) and TTP was 4.1 and 3.8 months respectively (HR 1.13 [0.98–1.31], P=0.1688). Members noted that and exploratory analysis suggested improved survival in patients with Hepatitis C compared with Hepatitis B.

6.8 The Subcommittee considered that evidence, in the form of slide presentations and abstracts, from observational studies indicated that degree of cirrhosis was an important predictor of outcome in patients with advanced HCC treated with sorafenib. Members noted that in the GIDEON study (Marrero et al J Clin Oncol 29: 2011 (suppl; abstr 4001)), a prospective observational study of 1571 patients treated with sorafenib for advanced HCC, median time to progression was 4.2 months in Child Pugh Score A patients, 3.6 months in Child Pugh Score B patients and 2.1 months in Child Pugh Score C patients, overall survival was 10.3 months, 4.8 months and 2 months respectively.

6.9 The Subcommittee considered that, overall, the evidence demonstrated that sorefanib did provide a small overall and progression free survival gain for patients. However, members considered that sorafenib was associated with clinically significant toxicity such as hand foot syndrome in approximately 9% of patients. Members considered that the toxicity profile of sorafenib likely explained the lack of

any apparent improvement in quality of life in patients treated with sorafenib compared with best supportive care.

6.10 The Subcommittee considered that there was a high unmet medical need for effective treatments in patients with advanced HCC, however, members considered that sorafenib was a relatively ineffective treatment that would be unlikely to meaningfully meet that health need. Members considered that although sorafenib has a small, but measurable, effect on length of life it did not improve quality of life for patients and, even taking into account the revised commercial proposal provided by the supplier, it remained a relatively expensive treatment. Members considered that funding aimed at preventing disease in these populations would provide better health outcomes than funding sorafenib.

6.11 The Subcommittee considered that sorafenib was a very expensive treatment given the limited benefit demonstrated; therefore, members **recommended** that the application for sorafenib for the treatment of patients with inoperable advanced HCC with preserved liver function (Child Pugh score 5-7) be declined.

6.12 The Decision Criteria particularly relevant to these recommendations 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,*

Renal Cell Carcinoma

6.13 The Subcommittee considered that the evidence provided for sorafenib as a second line treatment of patients with advanced RCC was weak, comprising mainly small, unpublished, prospective and retrospective single arm studies and expanded access programmes.

6.14 The Subcommittee considered that overall these studies demonstrated that median progression free survival of approximately 4 months for patients treated with sorafenib as a second line treatment for RCC. However, members noted that because these were no randomised controlled studies it was not possible to determine if sorafenib provided any benefit compared with best supportive care in the this setting.

6.15 The Subcommittee noted evidence from a randomised Phase II/III study in 723 patients which showed that treatment with axitinib (Pfizer) significantly improved PFS compared with sorafenib, median PFS 6.7 months vs 4.7 months (HR=0.665, 95% CI; P<0.0001) in patients with previously treated advanced RCC (Rini et al J Clin Oncol 29: 2011 (suppl; abstr 4503)).

6.16 The Subcommittee considered that overall sorafenib would likely have little positive benefit on overall survival or quality of life in patients with advanced renal cell carcinoma (RCC) following treatment failure on sunitinib or other targeted

treatments. Members considered that it may be reasonable to offer sorafenib as a second line treatment option for patients intolerant of sunitinib whose disease had not progressed while on sunitinib.

6.17 The Subcommittee considered that sorafenib was a very expensive treatment with no demonstrable benefit; therefore, members **recommended** that the application for sorafenib for the second line treatment of patients with advanced renal cell carcinoma (RCC) following treatment failure on, or intolerance to, sunitinib or other targeted treatments be declined.

6.18 The Decision Criteria particularly relevant to these 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; (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,

7 Everolimus for RCC

7.1 The Subcommittee considered an application from Novartis NZ Ltd for the funding of everolimus (Afinitor) on the Pharmaceutical Schedule for the treatment of patients with advanced Renal Cell Carcinoma (RCC) in patients who have received prior VEGF-targeted therapy (i.e. second line therapy).

7.2 The Subcommittee also considered a separate submission from a clinician on behalf of the Genito-Urinary Special Interest Group of the NZ Association of Cancer Specialists (GU SIG). Members noted that GU-SIG had requested funding of everolimus as a first line treatment for certain patients with advanced RCC in addition to second line funding in patients who have received prior treatment (as per the supplier's submission).

7.3 The Subcommittee noted that everolimus was an orally administered mTOR inhibitor indicated for the treatment of patients with advanced renal cell carcinoma (RCC) who have received prior VEGF-Targeted therapy such as currently funded sunitinib (Sutent, Pfizer). Members noted that the majority of patients have predominantly clear cell histology RCC and 25-30% present with advanced disease. Members noted there were well validated prognostic risk factors important for predicting outcomes in patients with RCC. Members noted that prior to the funding of sunitinib most patients were treated with interferon which was not considered optimal treatment.

7.4 The Subcommittee considered key evidence from a randomised, Phase III, double-blind, placebo-controlled study in 416 predominant clear cell advanced RCC patients who had received prior treatment with sunitinib, sorafenib or both (RECORD-1, Motzer et al. Lancet 2008;372:449–56 and Motzer et al. Cancer 2010;116:4256–65). Members noted that patients were randomised 2:1 to receive everolimus 10 mg/day (n=277) or placebo (n=139) both in addition to best supportive care. The Subcommittee considered that the RECORD-1 study population was representative of the patient population in New Zealand.

7.5 The Subcommittee noted that patients were continued on their randomised treatment until disease progression following which they were unblinded and those initially randomised to placebo were permitted to receive open-label everolimus. Members further noted that following a pre-planned interim analysis, the study population was unblinded and the remaining patients on placebo were permitted to receive open label everolimus. Members noted that in total 80% of patients initially randomised to placebo crossed over to everolimus. Members considered that, although the study was of good strength and quality for the primary endpoint, progression free survival (PFS), because of the unblinding and significant cross-over, it was weak for clinically important secondary endpoints including overall survival and quality of life.

7.6 The Subcommittee noted that everolimus increased median PFS by 3 months compared with placebo (4.9 months everolimus vs 1.9 months placebo HR, 0.33; 95% CI, 0.25-0.43; P <0.001). However, members noted that there was no difference in quality of life or overall survival between the two treatment groups. Members noted that no patients reported complete response to treatment, only one reported a partial response, with the majority having stable disease.

7.7 The Subcommittee noted that adverse events were more frequently reported within the everolimus treatment group than in the placebo group, with patients receiving everolimus had higher rates of grade 3 or 4 stomatitis, infections, non-infectious pneumonitis, lymphopenia, hyperglycaemia, hypophosphataemia, and hypercholesterolaemia. Members considered that overall everolimus was well tolerated with only 7% of patients requiring dose reduction.

7.8 The Subcommittee noted the supplier had undertaken analyses of overall survival from RECORD-1 using three different methods to adjust for cross over in the placebo treatment group, the first a comparison against a UK cohort the second and third calculated using different statistical estimation approaches (Inverse Probability-of-Censoring Weighting model (IPCW) and Rank Preserving Structural Failure Time model (RPSFT)). Members considered that the UK cohort was a poor proxy for the placebo treated patient group, noting that the median overall survival in this group appeared worse than interferon treated patient groups in randomised controlled trials in similar RCC populations (e.g Hudes et al N Engl J Med 2007;356:2271-81). Members considered that the IPCW and RPSFT methods were subject to bias and should only be considered exploratory.

7.9 The Subcommittee considered that although the effect of everolimus on overall survival could not be determined from the evidence provided, it was possible that the improvement demonstrated for disease free progression translated to some overall survival benefit. Members noted that a review article examining results of 30 studies in advanced RCC patients demonstrated that treatment effects on disease progression endpoints were associated with treatment effects on overall survival (Delea et al J Clin Oncol 27:15s, 2009 (suppl; abstr 5105)).

7.10 The Subcommittee considered there was no evidence to support the use of everolimus in the first line treatment of patients with advanced RCC at this time. However, members noted that a phase III study of everolimus in this setting was ongoing (RECORD-3).

7.11 The Subcommittee **recommended** that the applications from the supplier and GU-SIG for second line funding of everolimus for patients with advanced RCC who have received prior VEGF-targeted therapy be declined.

7.12 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.

7.13 The Subcommittee further **recommended** that the application from GU-SIG for first line funding of everolimus for patients with advanced RCC be declined.

7.14 The Decision Criteria particularly relevant to these recommendations 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.

8 Sunitinib for imatinib refractory GIST

8.1 The Subcommittee considered an application from Pfizer NZ Ltd to widen funded access to sunitinib (Sutent) on the Pharmaceutical Schedule for the treatment of patients with gastrointestinal stromal tumours (GIST) refractory to imatinib due to treatment failure or intolerance.

8.2 The Subcommittee considered that the molecular pathways of disease in GIST were well understood and the use of tyrosine kinase inhibitors, such as imatinib and sunitinib, made biological sense.

8.3 The Subcommittee considered that many patients with GIST who show disease progression on funded imatinib 400 mg daily are currently receiving additional 'top up' imatinib, to 800 mg daily, from its supplier (Novartis).

8.4 The Subcommittee noted PTAC had previously reviewed the funding of suntinib for imatinib refractory GIST patients in 2006 and recommended the application be declined. The Subcommittee noted that, at its August 2011 meeting, following receipt of Cancer Exceptional Circumstances applications, it had considered that in the absence of new evidence for sunitinib PTAC's 2006 recommendation remained valid.

8.5 The Subcommittee noted that in its resubmission, the supplier now provides further evidence in the form of a slide presentation by Schoffski et al. from the European

Society of Medical Oncology (ESMO) 2008 meeting, and a clinical study report, of the final analysis of the pivotal Phase III study A6181004.

8.6 The Subcommittee noted that this was a randomised, double blind, placebo controlled study in which 312 imatinib refractory GIST patients were randomised 2:1 to receive sunitinib 50 mg once daily or placebo until disease progression. Members noted that following disease progression patients were unblinded and permitted to receive open label sunitinib and that, following a planned interim analysis, the study population was unblinded and all remaining patients still on placebo were permitted to receive open label sunitinib. Members noted that 83% of placebo patients received sunitinib. Members considered that although the study was of good strength and quality for the primary endpoint of progression free survival (PFS), because of the unblinding and significant cross-over, it was weak for overall survival and quality of life.

8.7 The Subcommittee noted that results of the planned interim analysis (Demitri et al Lancet 2006;368:1329) demonstrated that sunitinib significantly improved median time to tumour progression by 4.8 months compared with placebo (27.3 vs 6.4 weeks, HR 0.33, 95% CI 0.23-0.47, p<0.0001). However, members noted there was no difference in overall survival in the final analysis between the 2 treatment arms. Members considered that this result was likely due to the large number of patients randomised to the placebo group who received sunitinib.

8.8 The Subcommittee noted that the supplier conducted a post-hoc analyses of overall survival using a rank-preserved structural failure time method (RPSFT). Members considered that this post-hoc analysis was exploratory and subject to bias and it was not possible to say with certainty if sunitinib had any positive effect on overall survival.

8.9 The Subcommittee considered that GIST was a complex disease and differentiation between stable (cystic) disease and disease progression was difficult. Members noted that in some instances the lesions appear to get larger following initial treatment. Members considered that maintaining stable disease was an important treatment goal in GIST and a clinically relevant 'response to treatment' included both patients with stable disease and those in remission. Members noted that imatinib dose increases, or surgery to remove the primary lesion followed by further treatment with imatinib, may be valid alternative treatment options in the patient group being sought for sunitinib funding.

8.10 The Subcommittee **recommended** that Special Authority criteria for the funding of sunitinib on the Pharmaceutical Schedule be amended, with low priority, to include funding for patients with GIST after failure of imatinib treatment, due to resistance or intolerance as follows (changes in bold and strikethrough).

Sunitinib - Retail Pharmacy – Specialist - Special Authority for Subsidy
Initial application **- (RCC) -** only from a relevant specialist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 3 months for applications meeting the following criteria:
All of the following:

1 The patient has metastatic renal cell carcinoma; and

2 Either

2.1 The patient is sunitinib treatment naive; or

2.2 The patient received sunitinib prior to 1 November 2010 and disease has not progressed; and

3 The patient has good performance status (WHO/ECOG grade 0-~~1~~2); and

4 The disease is of predominant clear cell histology; and

5 The patient has intermediate or poor prognosis defined as:

Any of the following:

5.1 Lactate dehydrogenase level > 1.5 times upper limit of normal; or
5.2 Haemoglobin level < lower limit of normal; or
5.3 Corrected serum calcium level > 10 mg/dL (2.5 mmol/L) ; or
5.4 Interval of < 1 year from original diagnosis to the start of systemic therapy; or
5.5 Karnofsky performance score of ≤ 70; or
5.6 ≥ 2 sites of organ metastasis; and

6 Sunitinib to be used for a maximum of 2 cycles.

Initial application - (GIST) - only from a relevant specialist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 3 months for applications meeting the following criteria:

All of the following:

1 The patient has unresectable or metastatic malignant gastrointestinal stromal tumour (GIST); and

2 Either

2.1 The patient's disease has progressed following treatment with imatinib; or
2.2 The patient has documented treatment-limiting intolerance, toxicity to, imatinib

Renewal **– (RCC) -** only from a relevant specialist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 3 months for applications meeting the following criteria:

Both:

1 No evidence of disease progression; and

2 The treatment remains appropriate and the patient is benefiting from treatment.

Renewal – (GIST) - only from a relevant specialist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 3 months for applications meeting the following criteria:

Both:

1 The patient has responded to treatment or has stable disease as determined by Choi's modified CT response evaluation criteria as follows:

Any of the following:

1.1 The patient has had a complete response (disappearance of all lesions and no new lesions) , or
1.2 The patient has had a partial response (a decrease in size of >/= 10% or decrease in tumour density in Hounsfield Units (HU) of >/= 15% on CT and no new lesions and no obvious progression of non measurable disease), or
1.3 The patient has stable disease (does not meet criteria 1.1. or 1.2 and does not have progressive disease and no symptomatic deterioration attributed to tumour progression; and

2 The treatment remains appropriate and the patient is benefiting from treatment.

Notes:
RCC - Sunitinib treatment should be stopped if disease progresses.
Poor prognosis patients are defined as having at least 3 of criteria 5.1-5.6. Intermediate prognosis patients are defined as having 1 or 2 of criteria 5.1-5.6.
GIST - It is recommended that response to treatment be assessed using Choi's modified CT response evaluation criteria (J Clin Oncol, 2007, 25:1753-1759). Progressive disease is defined as either: an increase in tumour size of >/= 10% and not meeting criteria of partial response (PR) by tumour density (HU) on CT; or: new lesions, or new intratumoral nodules, or increase in the size of the existing intratumoral nodules.

1.1. The Decision Criteria particularly relevant to these recommendations 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,*