Record of the Cancer Treatment Subcommittee of PTAC Meeting held on 12 April 2021

Cancer Treatment Subcommittee records are published in accordance with the Terms of Reference for the Pharmacology and Therapeutics Advisory Committee (PTAC) and PTAC Subcommittees 2016.

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

The Cancer Treatment Subcommittee may:

(a) recommend that a pharmaceutical be listed by Pharmac on the Pharmaceutical Schedule and the priority it gives to such a listing;

(b) defer a final recommendation, and give reasons for the deferral (such as the supply of further information) and what is required before further review; or

(c) recommend that Pharmac decline to list a pharmaceutical on the Pharmaceutical Schedule.

PTAC Subcommittees make recommendations, including priority, within their therapeutic groups of interest.

The record of this Subcommittee meeting will be reviewed by PTAC at its August 2021 meeting.

PTAC Subcommittees and PTAC may differ in the advice they provide to Pharmac, including recommendations' priority, due to the committees' different, if complementary, roles, expertise, experience, and perspectives.

Pharmac is not bound to follow the recommendations made below. Applications are prioritised by Pharmac against other funding options and progressed accordingly. The relative priority of any one funding choice is dependent on a number of factors, including (but not limited to) the recommendation of PTAC and/or PTAC Subcommittees, the mix of other applications being assessed, the amount of funding available, the success of commercial negotiations and/or the availability of clinical data.

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1. Attendance

Present

Marius Rademaker (Chair, PTAC member)
Allanah Kilfoyle
Anne O'Donnell
Chris Frampton
Lochie Teague
Matthew Strother (PTAC member)
Michelle Wilson
Tim Hawkins

Apologies:
Peter Ganly
Richard Isaacs
Scott Babington

Item 12 – reviewed on 30th April (via Zoom)

Present

Marius Rademaker (Chair, PTAC member)
Chris Frampton
Lochie Teague
Matthew Strother (PTAC member)
Michelle Wilson
Richard Isaacs
Scott Babington

Apologies:
Allanah Kilfoyle
Anne O'Donnell
Peter Ganly
Tim Hawkins

2. Summary of recommendations

2.1. The following recommendation summary is an order of the discussions held at the meeting.

Pharmaceutical and Indication	Recommendation
• 5.2 Venetoclax in combination with either azacitidine (based on the current eligibility criteria for azacitidine) or low dose cytarabine, for the treatment of newly diagnosed acute myeloid leukaemia ineligible for intensive induction chemotherapy	Medium Priority
• 5.3 Venetoclax in combination with either azacitidine (based on widened access to azacitidine) or low dose cytarabine, for the treatment of newly diagnosed acute myeloid leukaemia ineligible for intensive induction chemotherapy	High Priority
• 6.2 Widened access to peginterferon alfa-2a for the first-line treatment of myeloproliferative disorders	Declined
• 7.2 Osimertinib for the first-line treatment of locally advanced or metastatic epidermal growth factor receptor mutation (EGFRm) positive non-small cell lung cancer (NSCLC)	High Priority
• 8.4 Osimertinib for the second-line treatment of epidermal growth factor receptor mutation (EGFRm) T790M mutation-positive non-small cell lung cancer (NSCLC) after prior EGFR tyrosine kinase inhibitor (TKI) therapy	High Priority
• 8.5 Lenalidomide in combination with bortezomib and dexamethasone for the first-line treatment of transplant eligible patients with multiple myeloma	Low priority

• 8.6 Lenalidomide in combination with dexamethasone for the first-line treatment of transplant eligible patients with multiple myeloma	Declined
• 8.7 Lenalidomide in combination with bortezomib and dexamethasone for the first-line treatment of transplant ineligible patients with multiple myeloma	Low priority
• 9.7 Lenalidomide in combination with dexamethasone for the first-line treatment of transplant ineligible patients with multiple myeloma	Medium priority
• 9.2 Carfilzomib (once-weekly) for the second-line treatment of relapsed or refractory multiple myeloma	High priority
• 9.3 Carfilzomib (once-weekly) for the third-line treatment of relapsed or refractory multiple myeloma	Medium priority
• 9.4 Pomalidomide (in combination with bortezomib and dexamethasone) for the second-line treatment of relapsed or refractory multiple myeloma	High priority
• 9.5 Pomalidomide (in combination with bortezomib and dexamethasone) for the third-line treatment of relapsed or refractory multiple myeloma	High priority
• 9.6 Pomalidomide (in combination with dexamethasone) for the second-line treatment of relapsed or refractory multiple myeloma	Low priority
• 9.7 Pomalidomide (in combination with dexamethasone) for the third-line treatment of relapsed or refractory multiple myeloma	Low priority
• 10.2 Crizotinib for the treatment of ROS1 positive metastatic or locally advanced NSCLC	High Priority
• 10.3 Entrectinib for the treatment of ROS1 positive metastatic or locally advanced NSCLC	High Priority
• 11.2 Atezolizumab (Tecentriq) in combination with nab-paclitaxel for the treatment of advanced or metastatic triple-negative breast cancer (TNBC) with PDL1 expression ≥ 1%	Deferred

3. The role of PTAC Subcommittees and records of meetings

3.1. This meeting record of the Cancer Treatment Subcommittee of PTAC is published in accordance with the Terms of Reference for the Pharmacology and Therapeutics Advisory Committee (PTAC) and PTAC Subcommittees 2016, available on the Pharmac website at https://www.pharmac.govt.nz/assets/ptac-terms-of-reference.pdf.

3.2. The Terms of Reference describe, *inter alia*, the establishment, activities, considerations, advice, and the publication of such advice of PTAC Subcommittees and PTAC.

3.3. Conflicts of Interest are described and managed in accordance with section 7.2 of the PTAC Terms of Reference.

3.4. The Cancer Treatment Subcommittee is a Subcommittee of PTAC. The Cancer Treatment Subcommittee and PTAC and other PTAC Subcommittees have complementary roles, expertise, experience, and perspectives. The Cancer Treatment Subcommittee and other PTAC Subcommittees may therefore, at times, make recommendations for treatments for malignancy that differ from PTAC's, including the priority assigned to recommendations, when considering the same evidence. Likewise, PTAC may, at times, make recommendations for treatments for malignancy that differ from the Cancer Treatment Subcommittee's, or PTAC Subcommittees may make recommendations that differ from other PTAC Subcommittees'.

3.5. Pharmac considers the recommendations provided by both the Cancer Treatment Subcommittee and PTAC and any other relevant PTAC Subcommittees when assessing applications for treatments for malignancy.

4. Correspondence and Matters Arising

Obinutuzumab in combination with bendamustine followed by obinutuzumab maintenance monotherapy for the treatment of indolent non-Hodgkin lymphoma which has relapsed after, or is refractory to, a rituximab-containing regimen

4.1. The Subcommittee noted concerns raised by Pharmac staff when creating the model for obinutuzumab in combination with bendamustine followed by obinutuzumab maintenance monotherapy for the treatment of indolent non-Hodgkin lymphoma which has relapsed after, or is refractory to, a rituximab-containing regimen.

Discussion

4.2. The Subcommittee noted its previous recommendation to fund obinutuzumab in combination with bendamustine followed by obinutuzumab maintenance monotherapy for the treatment of indolent non-Hodgkin lymphoma (NHL) which has relapsed after, or is refractory to, a rituximab-containing regimen with a medium priority (October 2018). The Subcommittee, during its review recommended altering the Special Authority criteria to better align with the available evidence supporting the use of obinutuzumab in this patient population.

4.3. The Subcommittee noted that bendamustine may be contraindicated in patients who are heavily pre-treated, of advanced age, or have comorbidities. The Subcommittee noted that in New Zealand many patients with indolent NHL receive bendamustine in combination with rituximab as first line chemotherapy. The Subcommittee noted that the GADOLIN trial did not report how many patients had received bendamustine previously (Cheson et al. J Clin Oncol. 2018;36:2259-66).

4.4. The Subcommittee noted that most some patients would be re-exposed to bendamustine in combination with rituximab if a protracted initial response was achieved. The Subcommittee noted that some patients with relapsed low grade lymphomas may receive salvage chemotherapy and autologous transplant. The Subcommittee noted that if relapse was recent, retreatment with rituximab would not be allowed under access criteria and other patients might try alkylating agents with or without rituximab (eg. rituximab in combination with cyclophosphamide, vincristine and prednisolone). The Subcommittee considered that combination chemotherapy such as R-CHOP chemotherapy may be used in patients with a

short response to first line treatment with bendamustine in combination with rituximab.. The Subcommittee considered that the primary benefit of funding obinutuzumab would be in a patient group refractory to, or who relapse early after treatment with a rituximab containing treatment regimen.

4.5. The Subcommittee noted that patients with disease that is refractory to treatment or who progress early can be defined very specifically by Lugano criteria (van Heertum et al. Drug Des Devel Ther. 017;11:1719-28).In clinical practice however these specific criteria are not stringently applied outside of research studies, or as part of eligibility criteria specific to transplantation. The Subcommittee considered that the availability of obinutuzumab may result in additional testing to detect radiological relapse.

4.6. The Subcommittee noted that patient uptake is difficult to estimate. However, the Subcommittee considered that up to 20% of patients with follicular lymphoma would progress within 6 months of treatment commencement. Additional drivers may include: the potential low tolerability of obinutuzumab; that bendamustine is not the only initial treatment for patients with indolent NHL and may end up being intolerable for some patients; that some will have lymphoma transformation (10-20%) and not want to use bendamustine in combination with obinutuzumab; and that some patients would not want to be re-exposed to bendamustine. The Subcommittee considered that the percentage of patients with indolent NHL who would end up receiving obinutuzumab, if funded, would be no more than 10%. The Subcommittee estimated this based on an uptake rate of approximately 50% and the evidence indicating that 14% of (up taking) patients would be refractory to rituximab (Tarella C et al. PLoS One. 2014;9:e106745).

4.7. The Subcommittee noted that the GADOLIN trial did not include patients with mantle cell lymphoma and that only one patient with Waldenström macroglobulinaemia was included in the study, and noted that treatments such as ibrutinib may be appropriate for these patients. The Subcommittee considered that the criteria for access should therefore be limited to patients with follicular and marginal zone lymphoma. The Subcommittee considered that this criterion would limit access to approximately 75% of patients with indolent low-grade lymphomas.

4.8. The Subcommittee noted that the GADOLIN trial included patients who had refractory disease or had relapsed within 6 months of rituximab with/without chemotherapy. About half of the patients had refractory disease or had relapsed after induction rituximab/chemotherapy, the other half progressed in the 6 months after rituximab maintenance. The Subcommittee considered that it would be reasonable to limit access to only those patients who have relapsed within 6 months of receipt of rituximab to align with the intent of the patient population and the unmet need.

4.9. The Subcommittee therefore considered that it would be appropriate to amend the proposed Special Authority criteria for obinutuzumab as follows:

> Special Authority for Subsidy - PCT only – Specialist
> **Initial application** (follicular / marginal zone lymphoma) - only from a relevant specialist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 9 months for applications meeting the following criteria:
> All of the following:
> 1. Either:
> 1.1. Patient has follicular lymphoma; or
> 1.2. Patient has marginal zone lymphoma; and
> 2. Patient is refractory to any previous regimen containing rituximab within six months after treatment with rituximab; and

3. Patient has an ECOG performance status of 0-2; and
4. Patient has been previously treated with no more than four chemotherapy regimens; and
5. Obinutuzumab to be administered at a maximum dose of 1000 mg in combination with bendamustine at a maximum dose of 90 mg/m^2 for a maximum of 6 cycles; and

Renewal application (follicular / marginal zone lymphoma) - only from a relevant specialist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 24 months for applications meeting the following criteria:

1. Patient has no evidence of disease progression following obinutuzumab induction therapy; and
2. Obinutuzumab to be administered at a maximum of 1000 mg every 2 months for a maximum of 2 years; and
3. Obinutuzumab to be discontinued at disease progression.

New Zealand Society of Gastroenterology correspondence

4.10. The Subcommittee reviewed correspondence from the New Zealand Society of Gastroenterology (NZSG) regarding management of advanced hepatocellular carcinoma in New Zealand.

4.11. The Subcommittee took into account, where applicable, Pharmac's relevant decision-making framework when considering this agenda item.

Discussion

4.12. The Subcommittee noted that it had considered lenvatinib for the first-line treatment of hepatocellular carcinoma in October 2020, and recommended funding with a low priority. The Subcommittee noted that, in making its recommendation, the unmet need for a suitable treatment for hepatocellular carcinoma, and equity considerations due to high incidence of this this disease in Māori and Pacific people, had been considered.

4.13. The Subcommittee considered international treatments for hepatocellular carcinoma had progressed and there was a lack of available treatments in New Zealand to reflect new treatment standards and the significant unmet health need of this patient group.

4.14. The Subcommittee noted no new evidence to support lenvatinib had been presented so its recommendation to fund with a low priority remained appropriate. The Subcommittee noted the next step was for Pharmac to complete economic assessment of lenvatinib and rank this against other options for investment and considered an update on this process should be provided to Members at a future meeting.

5. Venetoclax in combination with either azacitidine or low dose cytarabine, for patients with newly diagnosed AML who are ineligible for intensive chemotherapy

Application

5.1. The Subcommittee noted an application from Abbvie for the use of venetoclax (Venclexta) in combination with azacitidine or low dose cytarabine for the first-line treatment of newly diagnosed acute myeloid leukaemia (AML) for patients who are ineligible for intensive induction chemotherapy.

Recommendation

5.2. The Subcommittee **recommended** that venetoclax in combination with either azacitidine (based on the current eligibility criteria for azacitidine) or low dose cytarabine, for the treatment of newly diagnosed acute myeloid leukaemia ineligible for intensive induction chemotherapy be listed with a **medium priority** within the context of treatment of malignancy, subject to the following Special Authority criteria:

> **VENETOCLAX**
> **INITIAL APPLICATION - previously untreated acute myeloid leukaemia**
> Applications only from a relevant specialist or any other medical practitioner on the recommendation of a relevant specialist. Approvals valid for 6 months.
> All of the following:
> 1. Patient has previously untreated acute myeloid leukaemia, according to World Health Organization (WHO) Classification; and
> 2. Patient must not be considered eligible for standard intensive remission induction chemotherapy; and
> 3. Venetoclax to be used in combination with azacitidine or low dose cytarabine
>
> **RENEWAL APPLICATION - previously untreated acute myeloid leukaemia**
> Applications only from a relevant specialist or any other medical practitioner on the recommendation of a relevant specialist. Approvals valid for 6 months.
> All of the following:
> 1. No evidence of disease progression; and
> 2. Treatment remains clinically appropriate and the patient is benefitting from and tolerating treatment.

5.2.1. In making this recommendation, the Subcommittee considered there to be good evidence of a survival advantage and clinically meaningful benefit for what is a patient group with a high unmet health need.

5.2.2. However, the Subcommittee considered that greater benefit could be expected for venetoclax in combination with azacitidine rather than low dose cytarabine, and noted that current access to azacitidine does not enable access for all patients ineligible for intensive chemotherapy.

5.2.3. The Subcommittee considered that, because of chemical instability following reconstitution of azacitidine, it would only be available in larger centres, and therefore, may increase inequities for patients who live rurally. The Subcommittee considered it would be very helpful if Te Aho o Te Kahu (the Cancer Control Agency) carefully evaluated administration and delivery of cancer medicines to rural patients.

5.3. The Subcommittee **recommended** that venetoclax in combination with either azacitidine (based on widened access to azacitidine) or low dose cytarabine, for the treatment of newly diagnosed acute myeloid leukaemia ineligible for intensive induction chemotherapy be listed with a **high priority** within the context of treatment of malignancy, subject to the following Special Authority criteria applying both to venetoclax and azacitidine (additions in bold, deletions in ~~strikethrough~~):

> **VENETOCLAX**
> **INITIAL APPLICATION - previously untreated acute myeloid leukaemia**
> Applications only from a relevant specialist or any other medical practitioner on the recommendation of a relevant specialist. Approvals valid for 6 months.
> All of the following:
> 1. Patient has previously untreated acute myeloid leukaemia, according to World Health Organization (WHO) Classification; and
> 2. Patient must not be considered eligible for standard intensive remission induction chemotherapy; and
> 3. Venetoclax to be used in combination with azacitidine or low dose cytarabine; and

RENEWAL APPLICATION - previously untreated acute myeloid leukaemia
Applications only from a relevant specialist or any other medical practitioner on the recommendation of a relevant specialist. Approvals valid for 6 months.
All of the following:

1. No evidence of disease progression; and
2. Treatment remains clinically appropriate and the patient is benefitting from and tolerating treatment.

AZACITIDINE
INITIAL APPLICATION - only from a haematologist or medical practitioner on the recommendation of a haematologist. Approvals valid for 12 months for applications meeting the following criteria:
All of the following:

1. Any of the following:
   1.1. The patient has International Prognostic Scoring System (IPSS) intermediate-2 or high-risk myelodysplastic syndrome; or
   1.2. The patient has chronic myelomonocytic leukaemia (10%-29% marrow blasts without myeloproliferative disorder); or
   1.3. The patient has Acute Myeloid Leukaemia ~~with 20-30% blasts and multi-lineage dysplasia, according to World Health Organisation Classification (WHO)~~; and
2. ~~The patient has performance status (WHO/ECOG) grade 0-2; and~~
3. ~~The patient does not have secondary myelodysplastic syndrome resulting from chemical injury or prior treatment with chemotherapy and/or radiation for other diseases; and~~
3. The patient has an estimated life expectancy of at least 3 months.

RENEWAL APPLICATION - previously untreated acute myeloid leukaemia
Applications only from a relevant specialist or any other medical practitioner on the recommendation of a relevant specialist. Approvals valid for 6 months.
All of the following:

1. No evidence of disease progression; and
2. Treatment remains clinically appropriate, and patient is benefitting from treatment

5.3.1. In making this recommendation, the Subcommittee considered there to be good quality evidence of a significant survival advantage and high clinical benefit for what is a patient group with a high unmet health need and potential access inequity.

5.3.2. The Subcommittee also noted its previous recommendation in July 2020 to widen access to azacitidine by removing the 20-30% blast count and therapy related myelodysplastic syndrome criteria (with a high and medium priority, respectively), which is reflected in the Special Authority criteria above.

Discussion

5.4. The Subcommittee noted that acute myeloid leukaemia (AML) is an aggressive heterogeneous haematologic malignancy characterised by the clonal expansion of myeloid precursors (blasts), resulting in their accumulation in the bone marrow, peripheral blood and other tissues including the spleen and liver, and that the underlying pathophysiology in AML consists of a maturational arrest of bone marrow cells in the earliest stages of development. The Subcommittee noted that the onset of AML is usually rapid, with presentation and diagnosis occurring within weeks of the onset of symptoms (Estey E & Döhner H. Lancet. 2006;368:1894-907)

5.5. The Subcommittee noted that AML is a relatively rare type of cancer but is the most common type of acute leukaemia diagnosed in New Zealand adults, and accounts for the largest number of deaths from leukaemia in New Zealand. The Subcommittee noted that the majority of patients present with complications of pancytopenia (low counts for all three types of blood cells: red blood cells, white blood cells, and platelets) and bone marrow failure such as anaemia (e.g. fatigue,

weakness, dizziness, headaches, pale skin, or shortness of breath), thrombocytopenia (e.g. bruising, excess bleeding such as bleeding gums or nosebleeds) and neutropenia (e.g. persistent and recurrent infections often accompanied with fever) or the clinical consequences of leukostasis due to an extremely high white blood cell count (e.g., difficulty breathing, confusion, and decreased consciousness).

5.6. The Subcommittee noted evidence reporting that Māori have an increased risk of AML (risk ratio 1.5 in the age group 25-49 and risk ratio 1.3 in the age group 50-74), relative to New Zealand Caucasians (Tracey & Carter. Am J Haematol. 2005;79:114-8). The Subcommittee also noted that a recent study reported that Māori and Pacific people appeared to present with AML at a younger age than individuals of European descent (Chan et al. Blood. 2020;136:36-37. Abstract only) and that individuals of European descent were significantly older at diagnosis compared to other ethnicities (median of 70 years vs. 51 for Māori and 56 for Pacific peoples, and 58 for all other ethnicities, $p<0.001$). The Subcommittee noted that the age of a patient at diagnosis was an adverse prognostic factor for overall survival. Despite AML presenting at a younger age in Māori people, the higher incidence of comorbidities in the Māori population would result in Māori having a higher likelihood of being ineligible for intensive chemotherapy after diagnosis.

5.7. The Subcommittee noted that Chan et al. also reported that AML appears to disproportionately affect those who live in more socio-economically deprived areas (NZDep2013), with 23% of cases reported in the most deprived 20% of the population, compared with 16% of the cases in the least deprived 20%, and that socio-economic deprivation was also an adverse prognostic factor.

5.8. The Subcommittee considered that patients with newly diagnosed AML who are ineligible for intensive induction chemotherapy constitutes approximately 50% of newly diagnosed AML patients (approximately 60 - 70 patients per year). The Subcommittee noted that newly diagnosed AML patients currently undertake intensive induction chemotherapy , or low intensity therapy (azacitidine or low dose cytarabine (LoDAC)) if intensive chemotherapy is unsuitable.

5.9. The Subcommittee noted that the adverse features of AML in those patients ineligible for induction chemotherapy (including those with adverse cytogenetics and/or comorbidities) are particularly difficult to treat, with poor outcomes in patients receiving low-intensity therapies in terms of achieving remission, quality of life improvements and long-term survival, and that patients considered ineligible for intensive induction chemotherapy experience much lower rates of complete remission than patients eligible for induction chemotherapy.

5.10. The Subcommittee noted that venetoclax is an orally bioavailable, selective small molecule inhibitor of B-cell lymphoma-2 protein (BCL-2), an anti-apoptotic protein which is Medsafe approved for the treatment of adult patients with newly diagnosed AML who are ineligible for intensive chemotherapy.

5.11. The Subcommittee noted that azacitidine can be administered either subcutaneously or via an intravenous infusion for 7 consecutive days within a 28-day cycle for 6 cycles before a response is observed, and continued for longer if the patient responds. The Subcommittee considered that most patients who respond are likely to do so within 4-6 cycles. LoDAC can be self-administered (twice daily) by the patient/caregiver in the community, which minimises the burden of treatment delivery and need for repeated attendance at a hospital or

outpatient facility. The Subcommittee considered that because of its stability post constitution, it can be more readily administered by patient or carer in the community without regular day ward attendance.

5.12. The Subcommittee noted that azacitidine is funded for patients with AML, 20-30% blasts and multi-lineage dysplasia and that LoDAC is open listed on the Pharmaceutical Schedule. The Subcommittee considered that azacitidine and LoDAC monotherapies are associated with very poor survival rates in newly diagnosed patients with AML who are ineligible for induction chemotherapy.

5.13. The Subcommittee considered that the burden and manual dexterity needed to give (subcutaneous) azacitidine therapy, in combination with its instability once thawed (which necessitates that it be freshly made for each administration), may not be feasible for some patients, in particular those residing in rural and remote areas with greater limitations on accessing specialist treatment facilities. The Subcommittee noted that this may impact up to 15% of the AML population in New Zealand. The Subcommittee considered that it would be important to ensure that all patients eligible for azacitidine would be able to receive it.

5.14. The Subcommittee noted the pivotal evidence to support the proposed widening of access to venetoclax in this application from two phase III randomised trials:

5.14.1. DiNardo et al. N Engl J Med. 2020;383:617-29 (M15-656 (VIALE-A) trial): a phase III, double-blind, randomised controlled trial of 431 patients with newly diagnosed AML ineligible for standard induction chemotherapy (due to age or comorbidities) who received either venetoclax in combination with azacitidine) (azacitidine 75 mg per square metre of body-surface area subcutaneously or intravenously on days 1 to 7 every 28-day cycle; venetoclax 400 mg orally once daily in 28-day cycles; N=286) or azacitidine with matching placebo (N=145).

5.14.2. Venetoclax in combination with azacitidine, compared to azacitidine with placebo, resulted in a significantly improved: median overall survival (14.7 months vs 9.6 months, respectively; HR 0.66; 95% CI 0.52 to 0.85; P<0.001), composite complete remission rates (66.4% vs. 28.3%, respectively; P<0.001), transfusion independence for both red blood cells (59.8% vs 35.2%, respectively; P<0.001) and platelets (68.5% vs 49.7%, respectively; P<0.001), and median event-free survival (9.8 months vs 7.0 months, respectively; HR 0.63; 95% CI 0.50 to 0.80; P<0.001).

5.14.3. The venetoclax treated group experienced an increased incidence of ~~notable~~ serious adverse events, notably grade 3, or higher, febrile neutropenia (30% in the venetoclax group vs 10% in the control group) and grade 3, or higher, pneumonia (16% in the venetoclax group vs 22% in the control group), with 1% of patients in the venetoclax group experiencing tumour lysis syndrome. The mortality at 30 days was similar between the two groups (6% in the venetoclax group vs 7% in the control group).

5.14.4. Wei et al. Blood. 2020;135:2137-45 (M16-043 (VIALE-C) trial): a phase III double-blind randomised controlled trial of 211 patients with previously untreated AML who are ineligible for standard induction chemotherapy who received either venetoclax with LoDAC (venetoclax dosing began at 100 mg on day 1 and increased stepwise over 4 days to reach the target dose of 600 mg; LoDAC 20 mg/m^2 subcutaneous injection once daily on days 1 to 10 in all cycles; N=143) or LoDAC with matching placebo (N=68).

5.14.5. Venetoclax in combination with LoDAC, compared to LoDAC with placebo, resulted in a clinically meaningful improvement in median overall survival (8.4 months vs 4.1 months, respectively; HR 0.70; 95% CI 0.50 to 0.99; P=0.40), composite complete response rates (47.6% vs 13.2%, respectively; P<0.001), transfusion independence for both red blood cells (41% vs 18%, respectively; P=0.001) and platelets (48% vs 32%, respectively; P=0.40), and median event-free survival (4.7 months vs 2.0 months, respectively; HR 0.58; 95% CI 0.42 to 0.82; P=0.002).

5.14.6. The venetoclax treated group experienced a higher incidence of serious adverse events, such as febrile neutropenia (16% in the venetoclax group vs 18% in the placebo group) and pneumonia (13% in the venetoclax group vs 10% in the placebo group). There were also more serious bleeding events in patients receiving venetoclax (11%) compared to the placebo group (7%). There were 8 instances of tumour lysis syndrome, all in the venetoclax treated group.

5.15. The Subcommittee considered that the trials were of high strength and good quality and showed the benefit of venetoclax in combination with either azacitidine or LoDAC, compared to azacitidine or LoDAC monotherapy. The Subcommittee however noted that the survival outcomes in the VIALE-A trial were more compelling than those experienced in the VIALE-C trial. The Subcommittee considered that it would be important to widen access to azacitidine to afford the outcomes observed in the VIALE-A trial.

5.16. The Subcommittee noted that the VIALE-A and VIALE-C trials included patients with all subtypes of AML (including those with poor cytogenetic risk, secondary AML, and unfavourable blast counts) and indicated a benefit from treatment with venetoclax in combination with azacitidine or LoDAC, even for patients with p53 mutations which usually have a poorer outlook. The Subcommittee considered that the event-free and overall survival outcomes from VIALE-A and VIALE-C would be applicable to the New Zealand population.

5.17. The Subcommittee noted the Dombret et al. study in a patient population with AML with >30% blasts which indicated that the overall survival for azacitidine in this patient group was 10.4 months (95% CI, 8.0 to 12.7 months), and that outcomes with LoDAC are generally worse than with azacitidine (Dombret H, et al. Blood. 2015;126(3):291-9). The Subcommittee noted that the outcomes observed in this patient population were similar to that observed in the control arm of the VIALE-A trial.

5.18. The Subcommittee noted that. The Subcommittee noted that there is no direct comparison of venetoclax with azacitidine and venetoclax with LoDAC but considered that because the patient demographics of each trial were similar, comparison of outcomes between the trials would be reasonable. Hence, it was reasonable to deduce that venetoclax in combination with azacitidine was the most effective therapeutic approach for this population and that the lack of azacitidine resulted in inferior outcomes. The Subcommittee considered that the worse outcomes of venetoclax with LoDAC were considered attributable to the relative inefficacy of LoDAC compared to azacitidine.

5.19. The Subcommittee considered that there are likely to be significant quality-of-life benefits from not being dependent on red blood cell and/or platelet transfusions, and that these benefits should be included in subsequent cost-effectiveness

analyses for venetoclax in this context, if they are not already captured in clinical trial data on health-related quality of life.

5.20. The Subcommittee noted that the majority of AML patients will respond after the first cycle of treatment, but that perhaps an additional 20% will respond after one or more subsequent cycles. The Subcommittee considered that if a patient has not responded following 3 or 4 cycles, they are not likely to respond at all. The Subcommittee therefore considered it appropriate to require renewal/reassessment after 6 months.

5.21. The Subcommittee considered that, if venetoclax were to be funded in this context, there may be slightly elevated incidence of febrile neutropenia and pneumonia in venetoclax treated patients, but that it is unlikely to result in a significant impact on the health system. The Subcommittee noted that the VIALE A trial included patients with an ECOG performance status of 0-3. The Subcommittee considered that, given that it is expected that the patient's condition could improve with effective treatment, ECOG performance status would have little bearing on access to treatment if funded. The Subcommittee considered that given the likely lack of effect on access to treatment of an access criteria based on age and ECOG performance status, it was not necessary to include ECOG performance status in the venetoclax or azacitidine eligibility criteria.

5.22. The Subcommittee noted that venetoclax can cause rapid tumour reduction due to the initiation of apoptosis, and thus poses a risk of tumour lysis syndrome (TLS) at initiation and during the titration phase. Hence, hospital admission maybe required for several days depending on the combination agent used. The Subcommittee noted that CY3PA or P-glycoprotein inhibitors, which are commonly prescribed to patients with AML, can enhance the action and toxicity of venetoclax, which would require dosage modifications to reduce the risk of tumour lysis syndrome. The Subcommittee noted that tumour lysis syndrome is relatively uncommon (around 5% of patients, 1.4% of which would be considered serious) and that all patients are recommended to receive allopurinol to further alleviate the risk. The Subcommittee also noted that a small proportion of patients deemed to be at a higher risk of tumour lysis syndrome receive 3mg rasburicase, for the first 1-2 doses of Venetoclax (at most 3 doses).

5.23. The Subcommittee considered that currently about 80% of patients ineligible for intensive chemotherapy are receiving LoDAC monotherapy and 20% are receiving azacitidine. The Subcommittee considered that based on the current access criteria for azacitidine, it would be reasonable to assume that given the improved efficacy of venetoclax in combination with azacitidine, this would increase. The Subcommittee considered that if access were widened to azacitidine, approximately 85% of patients ineligible for intensive chemotherapy would receive venetoclax in combination with azacitidine.

5.24. The Subcommittee considered that because azacitidine in combination with venetoclax is significantly more effective than LoDAC in combination with venetoclax, all eligible patients should be prescribed the azacitidine combination where possible, but acknowledging the barriers to azacitidine use in rural communities and the stability advantage of LoDAC after reconstitution. The Subcommittee considered that access issues for treatments like azacitidine have the potential to create inequities in treatment options for rural patients and/or patient with difficulties in attending treatment centres . The Subcommittee considered it important to fund the better outcomes, where possible, like that observed in the VIALE-A trial. The Subcommittee considered that the provision of

cancer medicines closer to home for rural patients should be an important consideration for the work being undertaken by Te Aho o Te Kahu (the Cancer Control Agency).

6. Peginterferon alfa-2a for myeloproliferative neoplasms

Application

6.1. The Subcommittee noted a clinician application to widen access to peginterferon alfa-2a (Pegasys) for the treatment of myeloproliferative neoplasms.

Recommendation

6.2. The Subcommittee **recommended** that the application to widen access to peginterferon alfa-2a for the first-line treatment of myeloproliferative disorders be **declined.**

6.3. In making this recommendation, the Subcommittee considered that:

6.3.1. there is a lack of evidence supporting a benefit or reduced risk of peginterferon alfa-2a compared to hydroxyurea;

6.3.2. the current Special Authority criteria for peginterferon alfa-2a enables sufficient access for those patients with myeloproliferative neoplasms and a high health need (ie. patients who are intolerant or contraindicated to receive hydroxyurea); and

6.3.3. the suitability of the currently open listed oral treatment option was greater than that of the subcutaneous injection, noting the additional cost for this treatment.

Discussion

6.4. The Subcommittee noted the current Special Authority criteria for peginterferon alfa-2a. The Subcommittee noted that access to peginterferon alfa-2a was recently widened due to the discontinuation of interferon alfa-2a. The Subcommittee noted that this widening of access enabled access to peginterferon alfa-2a for people with:

- cutaneous T cell lymphoma; or
- myeloproliferative disorders:
    - if intolerant to hydroxyurea and treatment with anagrelide and busulfan is clinically inappropriate; or
    - if pregnant, planning to become pregnant, or lactating.

6.5. The Subcommittee noted that the applicant had requested that access for peginterferon alfa-2a be further widened, removing the requirement for patients to have trialled hydroxyurea or considered for busulfan or anagrelide. The applicant requested that access to peginterferon alfa-2a be made available for patients who require cytoreductive treatment and when hydroxyurea is unsuitable or contraindicated for them.

6.6. The Subcommittee noted that, usually, myeloproliferative neoplasms manifest in patients over the age of 50 or 60 years, and that patients with myeloproliferative

neoplasms commonly carry a mutation in the JAK2 tyrosine kinase, up-regulating cell growth and turnover. The Subcommittee noted that there is a background risk of myeloproliferative neoplasms developing into acute myeloid leukaemia (AML), where 10-year estimates of leukaemic transformation incidence range from 0.7 to 3% for essential thrombocythaemia (ET), 2.3-14.4% for polycythaemia vera (PV) and 10-20 % for primary myelofibrosis (PMF) (Vallapureddy et al. Blood Cancer J. 2019;9:12).

6.7. The Subcommittee noted a 2018 retrospective review of medical records by Hanna et al. of adult patients with polycythaemia vera in New Zealand (Hanna et al. (N Z Med J. 2018;131:38-45). The Subcommittee noted that 88 adult patients were identified during 1987 to 2007, 49 (55.7%) were Europeans and 36 (40.9%) Māori or Pacific peoples, and that although Māori or Pacific patients presented at an almost 14 years younger age than European patients (mean age of 54 years versus 68, respectively; P<.001), all population groups had the same prognosis. The Subcommittee considered that there is not enough data available to ascertain if Māori and Pacific patients have a different risk factor profile or a higher genetic susceptibility to myeloproliferative neoplasia.

6.8. The Subcommittee noted that there are no treatments for myeloproliferative neoplasms that are curative except for allogeneic stem cell transplant. The Subcommittee considered that, if access to peginterferon alfa-2a were to be widened to first line treatment for myeloproliferative neoplasms, that approximately 30 additional patients would be eligible for treatment.

6.9. The Subcommittee noted that many patients with myeloproliferative neoplasms are relatively asymptomatic, but that some patients experience lethargy, spleenic pain, and risk of thromboembolism. The Subcommittee noted that most patients are successfully treated with aspirin, venesection if necessary, and hydroxyurea if cytoreductive therapy is needed. The Subcommittee noted, however, that current treatments do not alter the progression of the disease but are administered to reduce constitutional symptoms and reduce complications such as thrombosis and bleeding.

6.10. The Subcommittee noted that although each type of myeloproliferative neoplasm has well defined diagnostic criteria, diagnosis of myeloproliferative neoplasms is complex due to shared similarities between the conditions, with and complex diagnostic process driven differentiation between the diseases based on blood counts, bone marrow, and specific mutation analysis. The Subcommittee noted that prognosis, likelihood of AML transformation, and disease progression are influenced by which driver mutation or mutations the patient has, and noted that the JAK2 mutation is the most common in patients with myeloproliferative neoplasms (Grinfeld et al. N Engl J Med. 2018;379:1416-30).

6.11. The Subcommittee noted that peginterferon alfa-2a is funded without restriction for myeloproliferative neoplasms in Australia, and that the FDA consider peginterferon-alfa-2a to be acceptable as a first line treatment for myeloproliferative neoplasms in young patients or patients considering pregnancy in the US.

6.12. The Subcommittee noted that ruxolitinib is funded for the treatment of intermediate to high-risk primary myelofibrosis, for which peginterferon alfa-2a provides limited or no benefit. The Subcommittee considered that patients eligible for ruxolitinib would not be part of the requested patient group for peginterferon alfa-2a.

6.13. The Subcommittee noted that the type of treatment for myeloproliferative neoplasms depends on a patient's risk factors (eg. age, history of thrombosis, JAK2 mutation status), and that patients with very low and low risk disease (ie no history of thrombosis, age 60 years or under) are usually treated with aspirin alone, either one or twice daily. The Subcommittee noted that patients with intermediate risk disease (ie no history of thrombosis, JAK2 un-mutated, over 60 years of age) are usually treated with hydroxyurea in combination with aspirin. The Subcommittee noted that patients with high-risk disease (ie a history of thrombosis or over 60 years of age with JAK2 mutation) are usually treated with hydroxyurea and either aspirin or systemic anticoagulation (Tefferi A. Barbui T. Am J Hematol. 92:94-108).

6.14. The Subcommittee noted that peginterferon alfa-2a is the preferred treatment for patients who are pregnant or planning to become pregnant, and potentially for younger patients due to the possible adverse effects from long term use of hydroxyurea. The Subcommittee noted that risk factors shift over time, and that essential thrombocythemia is the least likely to require systemic therapy and may remain stable for many years. The Subcommittee also noted that patients with polycythaemia vera would likely need more systemic cytoreductive treatment than patients with essential thrombocythemia.

6.15. The Subcommittee noted that patients with myeloproliferative neoplasms have a higher background risk of AML development due to clonal instability and the overall mutational landscape of myeloproliferative neoplasia. The Subcommittee noted that patients can be intolerant to hydroxyurea, and can experience skin reactions, ulceration, and non-melanoma skin cancers, tiredness, and muscle fatigue while on treatment.

6.16. The Subcommittee noted the following studies regarding the safety of hydroxyurea in the treatment of myeloproliferative neoplasms:

6.16.1. Cortelazzo et al. N Eng J Med. 1995;332:1132-6: a prospective, randomised trial of patients with essential thrombocythemia treated with hydroxyurea. No malignant transformations were observed.

6.16.2. Marchioli et al. J Clin Oncol. 2005;23:2224-32: a retrospective cohort study (ECLAP) of patients with polycythaemia vera treated with hydroxyurea. The rate of AML transformation for patients on hydroxyurea was 1.3 per 100 persons per year, which the Subcommittee considered could not be determined to be higher than the background risk of transformation with no treatment.

6.16.3. Marchetti et al. Am J Hematol. 2020;95;295-301: a nested case-controlled study of patients with myeloproliferative neoplasms subsequently diagnosed with a secondary cancer. Exposure to hydroxyurea since diagnosis was independently associated with a poorer outcome after secondary cancer diagnosis.

6.16.4. Birgegård et al. Leuk Res. 2018;74:105-9: a post-marketing observational study (EXELS) of patients with confirmed essential thrombocythemia treated with either hydroxyurea or anagrelide. Patients treated with hydroxyurea had an increased standardised incident ratio for AML and skin cancer than those who were never treated with hydroxyurea. However, the lack of statistically significant differences between hydroxyurea- and anagrelide-treated patients and the development of AML may have been either due to a true lack of

difference or that the study was insufficiently powered to demonstrate a difference.

6.17. The Subcommittee considered that the evidence listed above indicated that treatment with hydroxyurea may possibly additionally increase the known higher background risk of AML transformation in patients with myeloproliferative neoplasms. It was noted that there is not an increase in AMl when hydroxyurea is used in other haematological conditions, such as sickle-cell anaemia.

6.18. The Subcommittee noted a summary and meta-analysis of clinical trials evaluating single-agent peginterferon alfa-2a for the treatment of myeloproliferative neoplasms, which did not report peginterferon to be superior to hydroxyurea in the treatment of myeloproliferative neoplasms (How J. Hobbs G. Cancers (Basel). 2020;12:1954). The Subcommittee noted that the phase III trials included in the analysis (Yacoub et al. Blood. 2019;134:1498-1509 (MPD-RC-111 trial), Knudsen et al. Blood. 2018;132(Supplement 1):580 (DLAHIA trial)) reported similar clinical response and remission rates between the two agents, and a higher rate of discontinuation for peginterferon alfa-2a. The Subcommittee considered the evidence supporting the use of pegylated interferon alfa-2a over hydroxyurea for the treatment of myeloproliferative neoplasms to be of weak strength and quality, with insufficient follow-up. The Subcommittee considered there was no current evidence to suggest peginterferon alfa-2a is associated with a delay in progression of disease (to primary myelofibrosis or AML) compared with hydroxyurea.

6.19. The Subcommittee noted that peginterferon alfa-2a is difficult to use compared with other available treatments, and many patients experience some adverse effects such as fatigue, myalgia, nausea, vomiting, or diarrhoea. The Subcommittee also noted that peginterferon alfa-2a can lead to neutropenia, anaemia, and thrombocytopenia, and late autoimmune toxicities such as hypothyroidism, vasculitis, or hepatitis. The Subcommittee noted that when peginterferon alfa-2a was compared with hydroxyurea in the Yacoub et al. and Knudsen et al. studies, grade 3 and 4 adverse events were significantly higher in the peginterferon groups compared with the hydroxyurea-treated patients. Knudsen et al. also reported that toxicity-related discontinuation was significantly increased in pegylated interferon (27%) compared to hydroxyurea (5%).

6.20. The Subcommittee noted that patients usually begin peginterferon alfa-2a with a starting dose of 45 µg/week with a gradual dose escalation in increments of 45 µg/week as tolerated. The Subcommittee noted that once target blood counts have been achieved, the dose of peginterferon alfa-2a may be tapered to the lowest dose that maintains normal blood counts. The Subcommittee noted that reducing the frequency of injections to fortnightly is achievable for many patients after 1–2 years of therapy. The Subcommittee considered that such dose modifications would result in significant wastage for patients who do not need the maximum dose. The Subcommittee considered that increased usage of peginterferon alfa-2a (and the likely long-term duration of therapy) presented challenges with teaching patients how to administer and store the solution, as well as presenting difficulties in transportation as the syringes need to be kept refrigerated.

7. Osimertinib for the treatment of EGFRm positive non-small cell lung cancer (NSCLC)

Application

7.1. The Subcommittee considered the following applications:

7.1.1. Osimertinib for the first-line treatment of locally advanced or metastatic Epidermal Growth Factor Receptor mutation (EGFRm) positive non-small cell lung cancer (NSCLC), following review of this application by PTAC; and

7.1.2. Osimertinib for the second-line treatment of EGFR T790M mutation-positive NSCLC after prior EGFR tyrosine kinase inhibitor (TKI) therapy, in light of updated evidence from the AURA-3 trial's final overall survival analysis.

Recommendation

7.2. The Subcommittee **recommended** that the application for osimertinib for the first-line treatment of locally advanced or metastatic epidermal growth factor receptor mutation (EGFRm) positive non-small cell lung cancer (NSCLC) be funded with a **high priority**, in the context of treatment of malignancy, subject to the following Special Authority criteria:

OSIMERTINIB
Special Authority for Subsidy – Retail Pharmacy - Specialist
Initial application – (NSCLC – first line) only from a relevant specialist or any other 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 locally advanced (Stage IIIb) or metastatic (Stage IV), non-squamous Non-Small Cell Lung Cancer (NSCLC); and
2. Either
   - 2.1 Patient is treatment naïve; or
   - 2.2 Both:
     - 2.2.1 The patient has discontinued gefitinib or erlotinib due to intolerance; and
     - 2.2.2 The cancer did not progress while on gefitinib or erlotinib; and
3. There is documentation confirming that the disease expresses activating mutations of EGFR tyrosine kinase; and
4. Treatment must be used as monotherapy; and
5. Patient has an ECOG performance status of 2 or less

Renewal - only from a relevant specialist or any other 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.

7.2.1. In making this recommendation, the Subcommittee considered the health need of patients with EGFRm positive NSCLC and the evidence supporting an overall survival (OS) benefit with osimertinib compared to first-generation tyrosine kinase inhibitors (TKIs) following long term follow-up, in a comparable patient population.

7.3. The Subcommittee **recommended** that the application for osimertinib for the second-line treatment of epidermal growth factor receptor mutation (EGFRm) T790M mutation-positive non-small cell lung cancer (NSCLC) after prior EGFR tyrosine kinase inhibitor (TKI) therapy be funded with a **high priority**, in the context of treatment of malignancy, subject to the following Special Authority criteria:

OSIMERTINIB
Special Authority for Subsidy – Retail Pharmacy - Specialist

Initial application - (NSCLC – second line) 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 locally advanced or metastatic non-small cell lung cancer; and
2. Patient has an ECOG 0-1; and
3. The patient must have received previous treatment with erlotinib or gefitinib; and
4. There is documentation confirming that the disease expresses T790M mutation of the EGFR gene following progression on or after erlotinib or gefitinib; and
5. The treatment must be given as monotherapy for a maximum of 3 months.

Renewal – (NSCLC) 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.

7.4. In making this recommendation, the Subcommittee considered: the health need of patients with EGFR T790M mutation-positive NSCLC; the evidence of a progression free survival (PFS) benefit with osimertinib in the second-line for EGFR T790M mutated NSCLC and supporting evidence of an OS benefit from osimertinib second-line in a comparable population, and the suitability of osimertinib compared with systemic chemotherapy.

Background

7.5. The Subcommittee noted that the application for osimertinib for the first-line treatment of locally advanced or metastatic EGFRm positive NSCLC was considered by PTAC in August 2020. At that time, PTAC recommended it be funded if cost-neutral to current first-line TKI's, erlotinib and/or gefitinib, due to:

- The high health need of people with lung cancer and the current availability of two effective agents in the same class funded for this indication; and
- The high quality, randomised-control trial evidence that reported benefit in progression free survival compared with the comparator (gefitinib or erlotinib); and
- The uncertain evidence regarding benefit in overall survival compared with the comparator (erlotinib or gefitinib); and
- The lack of evidence of superiority of osimertinib to the current two first-line pharmaceuticals for this indication.

7.5.1. At that time, PTAC considered that Pharmac could seek advice from CaTSoP regarding the sequence of treatments in this indication, and appropriate Special Authority criteria for osimertinib in the first-line setting.

7.6. The Subcommittee noted that the application for osimertinib for second-line treatment of EGFR T790M mutation-positive NSCLC after prior EGFR TKI therapy was received in November 2017 and was considered by CaTSoP in April 2018 with a recommendation to defer pending publication of longer-term follow-up data including mature survival data from the AURA-3 clinical trial.

7.6.1. The Subcommittee noted that Pharmac received correspondence from the supplier, AstraZeneca, and from clinicians regarding osimertinib, which was subsequently considered by CaTSoP in September 2018 and reiterated that publication of longer-term mature survival data (including AURA-3 trial data) was awaited.

7.6.2. The Subcommittee noted that updated AURA-3 study materials provided by the supplier in June 2020 were considered by PTAC in August 2020, where it was recommended that the application be deferred pending publication and peer-review of AURA-3 overall survival results.

7.6.3. The Subcommittee noted that in early 2021, a peer-reviewed publication of overall survival outcomes from the AURA-3 trial and two other publications from the trial were made available warranting further consideration of the application.

Discussion

7.7. PTAC and PTAC Subcommittees may differ in the advice they provide to Pharmac, including recommendations' priority, due to the committees' different, albeit complementary, roles, expertise, experience, and perspectives.

7.8. The Subcommittee noted that 90% of lung cancers diagnosed in New Zealand are non-small cell lung cancer (NSCLC) and that EGFRm positive disease has been estimated to occur in about 20% of NSCLC, equivalent to 91 new registrations in Māori and 337 in non-Māori based on 2018 data (Ministry of Health, 2018). The Subcommittee considered the health need of patients with NSCLC is well documented in previous CaTSoP and PTAC records and that the content of those records remains accurate in this regard.

7.9. The Subcommittee noted that international treatment guidelines recommend molecular testing for all patients with metastatic non-squamous lung cancer to identify potential therapeutic targets. The Subcommittee noted that approximately 65% of New Zealand patients with NSCLC received EGFR mutation testing in 2014 leading to an estimated prevalence of EGFRm positive disease of approximately 15.5% if all patients with NSCLC were tested (Tin Tin et al. Cancer Epidemiol. 2018;57:24-32).

7.10. The Subcommittee noted that mutation testing currently uses tumour tissue based samples, however, members considered that about 15-25% of patients may not be physically able to undergo the biopsy procedure required. The Subcommittee noted that liquid (blood) based testing is currently undertaken internationally and within some New Zealand centres, using circulating tumour DNA (ctDNA) typically via either private funding or as part of a clinical trial. The Subcommittee noted that some laboratories are developing their own assays, however, access to biopsies and testing is variable.

7.11. The Subcommittee considered the capability to undertake ctDNA testing consistently throughout New Zealand without the requirement for tissue biopsy would enable a greater number of patients to be tested for EGFR mutations. Members considered that ctDNA testing is likely to be introduced within the next five years and that there would be further evolution of mutation testing in New Zealand to track changes over time. The Subcommittee reiterated its suggestion for Pharmac to engage with laboratory representatives, noting the range of potential EGFR mutations and resistance mechanisms, with complexity and testing likely to increase over time.

7.12. The Subcommittee noted that people with EGFRm positive NSCLC currently receive first-line treatment with erlotinib or gefitinib, followed by second and third-line treatment with platinum-based chemotherapy and docetaxel, respectively. The Subcommittee considered that approximately 60-80% of patients with EGFRm

positive NSCLC respond to first-line treatment with erlotinib or gefitinib (time to progression of between 9.2 to 13.1 months based on Wang et al. Ther Adv Med Oncol. 2012;4:19-29), and approximately 40-60% of these patients will develop T790M mutation (based on Hata et al. Cancer. 2013;119:4325-32 and Chai et al. Cancer Manag Res. 2020;12:5439-50), signalling disease progression and acquired treatment resistance. The Subcommittee noted that there is currently no funded treatment to specifically target T790M mutation positive disease.

7.13. The Subcommittee considered the target EGFRm positive NSCLC population is mutually exclusive to the PD-L1 positive population with NSCLC and funding a new agent in this population would be unlikely to impact the broader funded treatment paradigm for NSCLC. The Subcommittee considered that there is evidence that immune checkpoint inhibitors are not as effective in patients with driver mutations, although the evidence for checkpoint inhibitors and driver mutation targeting agents is evolving.

7.14. The Subcommittee noted that osimertinib is a third-generation tyrosine kinase inhibitor (TKI) that has been investigated for EGFRm positive NSCLC in the phase III FLAURA (first-line osimertinib vs gefitinib or erlotinib) and AURA-3 (second-line osimertinib vs pemetrexed with carboplatin/cisplatin in T790M mutation positive disease) clinical trials. The Subcommittee noted that other third generation TKIs have been unsuccessful in trials therefore osimertinib was the only third generation TKI currently available.

7.15. The Subcommittee was made aware of evidence that, similar to first-generation TKIs, patients inevitably develop resistance to osimertinib either in the first- or second-line setting and considered that this may lead to resistance mechanisms that would either enable subsequent treatment options (eg first-generation TKIs, erlotinib and/or gefitinib) to be effective or render them ineffective (Leonetti et al. Br J Cancer. 2019; 121: 725–37). The Subcommittee considered it was unclear what the impact of these cross-resistant mechanisms would be on usage of erlotinib or gefitinib in the second line.

7.16. The Subcommittee noted that funding agencies in Australia (PBAC), England and Wales (NICE) and Canada (CADTH) have recommended osimertinib be funded in both the first- and second-line settings; however, osimertinib is recommended only as a second line treatment for patients with EGFRm T790M positive NSCLC by the Scottish Medicines Consortium (SMC). The Subcommittee also noted that osimertinib is recommended only as a first-line treatment for EGFRm positive NSCLC by the American Society of Clinical Oncology (ASCO) (Hanna et al. J Clin Oncol. 2021;39:1040-91).

Osimertinib in the first-line

7.17. The Subcommittee noted the application for osimertinib for the first-line treatment of locally advanced or metastatic EGFRm positive NSCLC targeted patients with stage IIIb or stage IV NSCLC who were treatment-naïve or had discontinued treatment with erlotinib/gefitinib due to intolerance (not progression), and who had WHO performance status of two or less.

7.18. The Subcommittee noted the key evidence for osimertinib in this setting comes from the phase III, double-blind, randomised (1:1) controlled FLAURA trial of osimertinib (80 mg once daily) compared with gefitinib (250 mg once daily) or erlotinib (150 mg once daily) in 556 treatment-naïve patients with locally advanced

or metastatic EGFRm positive NSCLC (Soria et al. N Engl J Med. 2018;372:113-25).

7.18.1. The Subcommittee noted that the FLAURA trial population was limited to only a few possible EGFR mutations, was generally well balanced between treatment groups and considered that, although there was a greater proportion of Asian participants than the New Zealand population, the population appeared relevant to the New Zealand context.

7.18.2. The Subcommittee noted that a greater proportion of patients received gefitinib in the comparator group (66%) compared to erlotinib, but considered the inverse to be true for New Zealand standard of care. Members considered, however, that the choice of first generation TKI was unlikely to make a difference in terms of subsequent eligible population, and considered the FLAURA trial comparators were comparable to standard of care.

7.18.3. The Subcommittee noted that the FLAURA trial reported an outcome of median PFS of 18.9 months with osimertinib compared to 10.2 months with the standard TKI comparator (hazard ratio [HR] for disease progression or death 0.46, 95%: CI 0.37-0.57, *P*<0.001) and noted that this PFS benefit of osimertinib compared to first-generation TKIs was statistically significant across all subgroups.

7.18.4. The Subcommittee noted that an updated publication of the FLAURA trial reported median overall survival (OS) of 38.6 months in the osimertinib group compared with 31.8 months in the comparator arm (HR 0.80, 95.05% CI: 0.64-1.00; *P*=0.046) (Ramalingam et al. N Engl J Med. 2020;382:41-50). The Subcommittee considered that the data for up to three years of follow-up indicated a significant benefit in OS from osimertinib compared to first-generation TKIs, noting that a number of patients remained on randomised first-line treatment at three years (78 [28%] in the osimertinib group and 26 [9%] in the comparator group).

7.18.5. The Subcommittee considered that the toxicities reported with osimertinib were as expected for a TKI treatment, and that the trial's secondary endpoints favoured osimertinib treatment.

7.18.6. The Subcommittee noted that 65% of the comparator group received subsequent treatment, with substantial crossover in 47% of these patients receiving osimertinib second line. The Subcommittee considered that the difference in OS seen with osimertinib in the context of this extent of crossover supports the survival benefit of this treatment.

7.19. The Subcommittee considered that first-line osimertinib uptake (compared to erlotinib or gefitinib) would be high and rapid among newly diagnosed EGFRm positive patients, in part due to the ASCO recommendation for its use as first-line treatment in this population. The Subcommittee considered that, based on current access to EGFR testing, approximately 200 patients per year might be eligible for first-line osimertinib treatment. The Subcommittee considered that, as testing becomes more accessible throughout New Zealand there is likely to be a gradual increase in the eligible patient numbers, with further increases once ctDNA testing becomes routinely available (potentially up to approximately 400 per year).

7.20. The Subcommittee considered that, if osimertinib were funded for first-line treatment of EGFRm positive NSCLC, current patients with stable disease on a

first-generation TKI who are not experiencing dose-limiting toxicities would be unlikely to switch to osimertinib. The Subcommittee noted that there was sparse evidence to inform what potential benefit patients who received first-line osimertinib might receive from second-line treatment with first-generation TKIs in the event of disease progression.

7.21. The Subcommittee considered that the Special Authority criteria proposed for first-line osimertinib in this setting, adjusted to align with currently funded TKI criteria and including ECOG rather than WHO performance status, would be appropriate to target funding.

Osimertinib in the second-line

7.22. The Subcommittee noted that the application for osimertinib for the second-line treatment of locally advanced or metastatic EGFRm T790M positive NSCLC targeted patients with stage IIIb or stage IV NSCLC who had progressed following treatment with an EGFR TKI.

7.23. The Subcommittee noted that the key clinical evidence for osimertinib in the second-line for EGFR T790M mutation positive NSCLC comes from the phase III, open-label, randomised (2:1) international, AURA-3 trial which recruited 419 patients with locally advanced or metastatic NSCLC whose disease has progressed with previous EGFR TKI therapy and whose tumours harbour a T790M mutation within the EGFR gene. The Subcommittee noted that overall survival was a secondary outcome in AURA-3 and that the final overall survival analysis had now been published (Papadimitrakopoulou et al. Ann Oncol. 2020;31:1536-44).

7.23.1. The Subcommittee noted that the cobas EGFR Mutation Test was used to confirm EGFRm and T790M mutation status after progression on a first-line EGFR TKI. The Subcommittee noted that participants were able to be enrolled if they had stable central nervous system metastasis and that there was a high proportion of Asian participants in the trial. Overall, the Subcommittee considered that the trial population and comparator treatments were comparable to the New Zealand setting.

7.23.2. The Subcommittee noted that AURA-3 participants were randomised to receive either 80 mg osimertinib orally once daily or intravenous pemetrexed 500 mg/m2 of body surface area plus either carboplatin (target area under the curve, 5) or 75 mg/m2 cisplatin every 3 weeks for up to six cycles, with or without pemetrexed maintenance, until disease progression or unacceptable toxicity. The Subcommittee noted that cross over to osimertinib was permitted at disease progression for participants in the comparator group.

7.23.3. The Subcommittee noted that the primary outcome of AURA-3 was progression free survival (PFS);;CaTSoP had previously reviewed a publication from AURA-3 with PFS outcomes in April 2018 which reported a benefit with osimertinib across all subgroups (Mok et al. N Engl J Med 2017; 376:629-640). The Subcommittee considered this was good quality evidence of a PFS benefit.

7.24. The Subcommittee noted that overall survival (OS) was a secondary endpoint and that the final OS analysis of AURA-3 after data cut-off (March 2019) reported a median OS of 26.8 months with osimertinib vs 22.5 months with platinum-pemetrexed which was not statistically significant (HR 0.87, 95% CI: 0.67 to 1.12,

P=0.277) (Papadimitrakopoulou et al. Ann Oncol. 2020;31:1536-44). The Subcommittee noted there was substantial crossover from platinum-pemetrexed to osimertinib (N=99; 73% of platinum-pemetrexed group) and considered that while this limited extrapolation of this data to the New Zealand setting, it suggests that osimertinib may be useful in either the second-line or third-line setting.

7.24.1. The Subcommittee noted that the AURA-3 final analysis used a rank preserving structural failure time model (RPSFTM) to report an exploratory crossover-adjusted median OS of 26.8 months with osimertinib vs 15.9 months with platinum-pemetrexed (HR 0.54, 95% CI: 0.18 to 1.60). The Subcommittee noted the wide confidence interval which crossed one, however, members considered that the statistical analysis with this model supports a survival benefit of osimertinib compared with platinum-pemetrexed chemotherapy and highlights the effect of treatment crossover on the results of the non-adjusted OS analysis.

7.24.2. The Subcommittee considered that the methods within the rank preserving structural failure time model (RPSFTM) crossover-adjusted analysis were reasonable and appropriate, and that the results were applicable to the New Zealand context as no third-line EGFR TKIs are available following progression on platinum-pemetrexed chemotherapy. However, the Subcommittee acknowledged that the confidence intervals were wide and that it was not possible to remove or account for all crossover effects. The Subcommittee considered that the evidence for OS was of moderate quality.

7.25. The Subcommittee noted the AURA-3 patient-reported outcomes which identified patients who received osimertinib had 15% better global health-related quality of life (QOL) (OR 2.11, CI 1.24 to 3.67, P=0.007) and increased time to deterioration for chest pain (HR, 0.52, 95% CI: 0.37 to 0.73, P<0.001) and dyspnoea (HR 0.66, 95% CI: 0.47 to 0.91, P=0.11) compared to the comparator (Lee et al. J Clin Oncol. 2018;36:1853-60). The Subcommittee noted that other metrics were not statistically significant but considered that there was a trend towards other improvements in QOL.

7.26. The Subcommittee also noted the following publications:

- Wu et al. J Clin Oncol. 2018;36:2702-9
- Yang et al. J Clin Oncol. 2020;38:538-47
- Akamatsu et al. Cancer Sci. 2018;109:1930-8
- Papadimitrakopoulou et al. Cancer. 2020;126:373-80

7.27. Overall, the Subcommittee considered that there is evidence of a PFS benefit with osimertinib second-line for EGFR T790M mutation-positive NSCLC, and that the post-hoc crossover-adjusted analysis supports an OS benefit in a comparable population.

7.28. The Subcommittee noted that osimertinib offers suitability over systemic chemotherapy due to easier administration and reduced toxicities.

7.29. The Subcommittee considered that most patients who discontinue first-line EGFR TKI treatment would be eligible for second-line treatment, therefore there would be a prevalent pool of patients with EGFR positive NSCLC that would be made up of

approximately 150 patients currently on a 1st generation TKI, and approximately 75 patients who have previously discontinued due to prior disease progression. The Subcommittee considered that uptake would likely be rapid.

7.30. The Subcommittee was made aware of a Canadian publication reporting participation in osimertinib clinical trials which reported that 97.5% of patients who progressed after first-line treatment with a first-generation EGFR TKI had a biopsy at disease progression, with patients typically requiring an average of two biopsies (Chu et al. Curr Oncol. 2020;27:27-33). The Subcommittee considered that in New Zealand, up to five biopsies may be attempted per patient and, based on the Canadian data, almost all of the approximately 150 New Zealand patients receiving an EGFR TKI per year would proceed to a biopsy post-disease progression, of which approximately 109 would have successful biopsies in the first instance.

7.31. The Subcommittee considered that, based on extrapolation of the Canadian trial data, approximately 40-60% of New Zealand patients would test positive for T790M mutation after progression on a TKI (approximately 62 of 109 successfully biopsied patients) which is slightly less than what may be estimated from the AURA-3 trial data alone (from Supplementary appendix S2). The Subcommittee reiterated that implementation of ctDNA testing would increase the number of T790M mutations identified.

7.32. The Subcommittee considered there was a long period of time between progression (occurring after about 10-12 months) and overall survival (about 20 to 30 months) in patients with EGFR positive NSCLC treated with EGFR TKIs or chemotherapy, providing ample opportunity for repeat biopsies if needed for T790M mutation testing (Wang et al. Ther Adv Med Oncol. 2012;4:19-29).

7.33. The Subcommittee noted that a validated, accredited T790M mutation test is not available in New Zealand although there is variable access to T790M testing which may be added into testing performed at some centres. The Subcommittee considered that Pharmac could seek further advice from professional pathology societies in New Zealand such as the Royal College of Pathologists of Australasia (RCPA) to understand testing in the New Zealand context independent of inter-centre variability. The Subcommittee considered that the number of patients who would seek access to funded treatments for T790M positive disease would increase if validated ctDNA testing were implemented and performed routinely in New Zealand.

7.34. The Subcommittee considered that funding of osimertinib in the second-line would have additional health system impact for 12- to 18-months due to on-treatment monitoring (monthly clinic visits, three-monthly CT scans, and blood tests), and a small number of patients (approximately <5%, or 3-4 patients per year) who would require hospital admission for management of grade 3-4 adverse events.

7.35. The Subcommittee considered that the proposed Special Authority criteria would appropriately target osimertinib treatment to the population with EGFR T790M mutation positive disease who would benefit in the second-line setting, including patients with central nervous system metastasis. The Subcommittee considered that further evaluation of these may be required if there were to be changes to the evidence regarding immune check point inhibitors in driver mutation NSCLC.

General

7.36. The Subcommittee considered that there was evidence to support benefit from osimertinib in each of the first-line and second-line treatment settings, and supported funding osimertinib for a treatment line, either within first-line or second-line. However, the Subcommittee considered that it was not clinically appropriate for a patient to receive osimertinib in more than one treatment line.

8. Lenalidomide for previously untreated newly diagnosed multiple myeloma

Application

8.1. The Subcommittee reviewed the application for lenalidomide for the first-line treatment of transplant eligible patients with multiple myeloma.

8.2. The Subcommittee reviewed the application for lenalidomide for the first-line treatment of transplant ineligible patients with multiple myeloma.

8.3. The Subcommittee took into account, where applicable, Pharmac's relevant decision-making framework when considering this agenda item.

Recommendation

8.4. The Subcommittee **recommended** that lenalidomide in combination with bortezomib and dexamethasone for the first-line treatment of transplant eligible patients with multiple myeloma be listed with a **low priority** within the context of treatment of malignancy, subject to the following Special Authority criteria:

> **Initial application – (Multiple myeloma – eligible for transplant)** 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 newly diagnosed multiple myeloma confirmed by histological diagnosis; and
> 2. Patient must be eligible for a primary stem cell transplantation; and
> 3. Patient requires first line treatment; and
> 4. Treatment is to be administered in combination with bortezomib and dexamethasone; and
> 5. Patient is to be treated for a maximum of 8 cycles.

8.4.1. In making this recommendation, the Subcommittee considered that:

8.4.1.1. the evidence supporting the benefit of this treatment regimen compared to standard of care was of weak strength, indicating improvements in rates of response and depth of response only;

8.4.1.2. the funding of lenalidomide in this setting and its current funding in the maintenance post- autologous stem cell transplant (ASCT) setting impairs the availability of 3rd line lenalidomide for this patient group;

8.4.1.3. the lenalidomide maintenance Special Authority criteria would need to be changed to allow continuation of access to lenalidomide;

8.4.1.4. access to treatment with lenalidomide in combination with bortezomib and dexamethasone (RVD) would not benefit infusional services in terms if decreased infusion load, given the frequent use of bortezomib as part of this regimen.

8.5. The Subcommittee **recommended** that lenalidomide in combination with dexamethasone for the first-line treatment of transplant eligible patients with multiple myeloma be **declined**.

8.5.1. In making this recommendation, the Subcommittee considered that:

8.5.1.1. lenalidomide in combination with dexamethasone (RD) is not an appropriate induction regimen for patients eligible for transplant and is not recommended in international guidelines,

8.5.1.2. meanwhile the data available indicates that RD is inferior to the current standard of care in this setting.

8.6. The Subcommittee **recommended** that lenalidomide in combination with bortezomib and dexamethasone for the first-line treatment of transplant ineligible patients with multiple myeloma be listed with a **low priority** within the context of treatment of malignancy, subject to the following Special Authority criteria:

Initial application – (Multiple myeloma – ineligible for transplant in combination with bortezomib and dexamethasone) only from a relevant specialist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 18 months for applications meeting the following criteria:
All of the following:

1. Patient has newly diagnosed multiple myeloma confirmed by histological diagnosis; and
2. Patient must be ineligible for a primary stem cell transplantation; and
3. Patient requires first line treatment; and
4. Treatment is to be administered in combination with bortezomib and dexamethasone; and
5. Lenalidomide is to be administered at a maximum dose of 25 mg per day

8.6.1. In making this recommendation, the Subcommittee considered that:

8.6.1.1. the evidence supporting a benefit of this treatment regimen compared with standard of care was of weak strength;

8.6.1.2. the evidence supporting the use of this regimen is from the SWOG S0777 trial, which did not include the current standard of care in New Zealand as a comparator, and that the population included in the trial was not representative of the population in New Zealand that would be ineligible for a transplant;

8.6.1.3. lenalidomide in combination with weekly bortezomib and dexamethasone (RVD-LITE) appears to have comparable efficacy with reduced toxicity and could be an option for this patient group, and where RVD-LITE had not been compared with lenalidomide in combination with dexamethasone;

8.6.1.4. the funding of lenalidomide in this setting would impact the availability of 3rd line lenalidomide for this patient group.

8.7. The Subcommittee **recommended** that lenalidomide in combination with dexamethasone for the first-line treatment of transplant ineligible patients with multiple myeloma be listed with a **medium priority** within the context of treatment of malignancy, subject to the following Special Authority criteria:

Initial application – (Multiple myeloma – ineligible for transplant in combination with dexamethasone) 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 newly diagnosed multiple myeloma confirmed by histological diagnosis; and
2. Patient must be ineligible for a primary stem cell transplantation; and
3. Patient requires first line treatment; and
4. Lenalidomide is to be administered at a maximum dose of 25 mg per day

Renewal application – (Multiple myeloma – ineligible for transplant in combination with dexamethasone) 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 must not have demonstrated progressive disease; and
2. Patient must not be receiving concomitant funded bortezomib; and
3. Treatment is to be administered at a maximum dose of 10 mg

8.7.1. In making this recommendation, the Subcommittee considered that:

8.7.1.1. there would be a considerable benefit from having an oral treatment regimen available for this patient group, which would reduce access barriers for this patient group;

8.7.1.2. evidence supporting the benefit of this treatment regimen compared to the current standard of care was of weak strength.

8.7.1.3. the guidelines for treatment of this patient group do not indicate the need for triple therapy;

8.7.1.4. that the funding of lenalidomide in this setting would impair the availability of 3rd line lenalidomide for this patient group, however it would mean that patients would be able to use a proteasome inhibitor (eg bortezomib) for the first time after relapse (see 9.47);

8.7.1.5. there would be considerable costs to the health sector for patients receiving treatment until progression. However, there would be savings associated with the lack of requirement for a bortezomib-containing regimen and the reduction in associated infusion costs and burden on healthcare resources.

Discussion

Multiple myeloma

8.8. The Subcommittee noted that there were approximately 400 incident cases of myeloma in New Zealand each year and that this was increasing. The Subcommittee considered that the incidence was greater in Māori and Pacific people. The Subcommittee noted that the median age for people with myeloma in New Zealand was approximately 70 years old and that this was lower for Māori and Pacific people (The Burden of Multiple Myeloma in New Zealand July 2019). The Subcommittee noted that the five year overall survival (OS) of a patient with myeloma was approximately 45%, with a median OS of 51.2 months (The Burden of Multiple Myeloma in New Zealand July 2019). The Subcommittee noted that the OS of Māori and Pacific people was poorer, but that cause-specific survival did not differ between populations. The Subcommittee considered that Māori and Pacific people were less likely to receive autologous stem cell transplant (ASCT).

8.9. The Subcommittee noted a recent registry study from the Australian and New Zealand Myeloma registry, which indicated that Māori and Pacific people presented with myeloma at younger age, were more likely to present with comorbidities, were more likely to present with an adverse karyotype, were less likely to commence 1st line therapy, and after adjusting for age their OS was less than other populations' (Blacklock et al. Clin Lymphoma Myeloma Leuk. 2019;19:10,sE213).

8.10. The Subcommittee noted that transplant eligibility was usually considered based on physiological fitness and that transplants are usually received by people under the age of 70. The Subcommittee considered that around half of all patients who present with myeloma would be eligible for transplant. However, the Subcommittee noted that the exact numbers of transplants could be obtained from the Australasian Bone Marrow Registry.

8.11. The Subcommittee noted correspondence from the New Zealand Myeloma Interest Group (NZMIG), which highlighted specific concerns regarding:

8.11.1.1. the lack of treatment options in the relapsed/refractory setting, in particular, those patients who progress on lenalidomide maintenance therapy;

8.11.1.2. the inequality in treatment access in the first line, given the requirement for regular day stay visits, presenting a barrier to treatment for many patients

8.11.1.3. access to lenalidomide in both transplant eligible and transplant ineligible patients.

8.12. The Subcommittee noted the potential toxicities of treatment with lenalidomide, principally, neutropoenia, infection and fatigue. The Subcommittee also noted the potential concern regarding an increase in second primary cancers associated with lenalidomide in combination with alkylators reported from surveillance of patient registry data (Costa et al. B J Haem. 2018;182:513-20).

8.13. The Subcommittee considered that it would be reasonable to assume that approximately 10-20% of patients currently do not respond to cyclophosphamide, bortezomib and dexamethasone (CyBorD) and that this estimate would be relevant to both transplant eligible and transplant ineligible patients. The Subcommittee considered that approximately 5% of transplant-ineligible patients would not be fit enough to receive a bortezomib containing regimen. The Subcommittee noted that the need to travel may also impact the use of bortezomib in this setting.

8.14. The Subcommittee considered that if lenalidomide were funded for the treatment of either transplant eligible or transplant ineligible patients with newly diagnosed multiple myeloma, it would be unlikely that first exposure to bortezomib would be reserved until a later line of therapy for most patients. The Subcommittee considered that the first remission is likely to be the most durable, and therefore reserving the first use of bortezomib until a later line of therapy would not occur unless the patient's circumstances were such that treatment with bortezomib posed significant difficulty or risk. The Subcommittee considered that if a patient progressed on a regimen in first line, clinicians would be likely to treat the patients with a different treatment in second line in order to offer the benefits of a different active agent.

8.15. The Subcommittee considered that it would be difficult to dictate or know exactly how lenalidomide would be used if it were funded for the first line treatment of newly diagnosed patients with multiple myeloma, however that it would be appropriate to impose some limitations on its usage to manage the fiscal risk regarding the use of lenalidomide for newly diagnosed patients.

8.16. The Subcommittee noted that currently transplant eligible patients are treated with induction therapy, which consists of 4-6 cycles of cyclophosphamide, bortezomib and dexamethasone (CyBorD) or 4-6 cycles of bortezomib, thalidomide and dexamethasone (BTD). The Subcommittee noted that post ASCT, these patients would be eligible for lenalidomide maintenance therapy. The Subcommittee considered that most patients would be treated with CyBorD and that this would be an appropriate comparator for new agents proposed for funding in this patient group.

8.17. The Subcommittee noted that currently transplant ineligible patients are treated with up to 9 cycles of a bortezomib based regimen (CyBorD, BTD or BMP) or thalidomide based regimens (CTD or MPT). The Subcommittee considered that most patients would be treated with CyBorD, however that there may be a group of patients who are treated with one of the thalidomide based regimens.

8.18. The Subcommittee considered that in the 2nd line setting patients would receive an alternative regimen to what was received in first line and that it would likely include bortezomib, unless not suitable or tolerated. The Subcommittee considered that these treatment options were suboptimal and noted the current applications for carfilzomib and daratumumab for patients with relapsed or refractory multiple myeloma for patients who had not previously received a transplant. The Subcommittee noted that only patients who had not had lenalidomide maintenance post ASCT would be eligible for lenalidomide in third line.

8.19. The Subcommittee noted that fluorescence in situ hybridisation test (FISH) is usually used to stratify transplant eligible patients based on risk status. The Subcommittee considered that if lenalidomide were funded for transplant ineligible patients, it might be used increasingly as a risk stratification method to aid with clinical decision making regarding the most appropriate treatment regimens for patients.

Lenalidomide for transplant eligible patients

8.20. The Subcommittee noted that in 2018, it had considered that there was insufficient evidence to support the application for lenalidomide for the treatment of patients with newly diagnosed multiple myeloma who are eligible for ASCT and thus deferred any recommendation until this became available (CaTSoP April 2018). The Subcommittee noted that since its last review, further evidence regarding the use of lenalidomide in combination with bortezomib and dexamethasone (RVD) as transplant induction therapy had been generated and that the use of RVD in this setting had become the standard of care in many countries.

8.21. The Subcommittee considered that there would be no concern with the use of lenalidomide in the absence of Medsafe approval, because it is used extensively in the first line setting in other countries.

8.22. The Subcommittee noted the importance of achieving at least a partial response prior to receiving an autologous stem cell transplant. The Subcommittee noted the results of the Pethema/GEM2012 trial, which included 458 patients aged less than

65 years. In this trial, patients received 6 cycles of RVD as induction therapy, followed by 2 cycles of RVD consolidation post ASCT (Rosinol et al. Blood. 2019;134:1337-45). The Subcommittee noted that response rates to RVD in this trial were similar to that of patients receiving VTD in the previous GEM2005 trial, but that the depth of response was greater for patients receiving RVD in the Pethema/GEM2012 trial and the proportion of patients with a very good partial response increased with each cycle of RVD, and considered this to be clinically relevant for this patient group.

8.23. The Subcommittee noted a retrospective review comparing RVD with CyBorD in the first line setting (Utervall et al. J. Haematology. 2019;103:247-54). The Subcommittee considered that the patient groups receiving RVD or CyBorD were similar in this retrospective review. The Subcommittee noted that the proportions of patients achieving a partial response with RVD compared to CyBorD were 98% and 88% respectively. The Subcommittee noted that the progression free survival (PFS) at 18 months (88% vs. 63%; p<0.001) was greater for patients receiving RVD compared to CyBorD. The Subcommittee noted that the OS at 18 months (95% vs. 89%; p=0.048) was greater for patients receiving RVD compared to CyBorD. The Subcommittee also noted that the outcomes were similar for patients regardless of whether they ended up receiving a transplant or not.

8.24. The Subcommittee noted a randomised, phase 2 trial (EVOLUTION) that compared RVD with CyBorD in patients with previously untreated multiple myeloma (Kumar et al. Blood. 2012;119(19):4375-82). The Subcommittee noted that this trial reported no difference in PFS, however the Subcommittee considered that the study was not sufficiently powered to be able to detect a difference due to the number of patients included in each treatment arm. The Subcommittee noted that the proportion of patients who obtained a partial response and very good partial response was numerically greater in patients receiving RVD compared with CyBorD, and considered that this trend aligned with the results of other trials in this patient population.

8.25. The Subcommittee noted the joint clinical practice guidelines from the American Society of Clinical Oncology and Cancer Care Ontario (Mickael et al. J Clin Oncol.2019;37:1228-63). These guidelines indicate that the optimal treatment regimen and cycle duration remain unproven, but that optimal treatment includes the combination of an immunomodulatory drug, a proteasome inhibitor and a corticosteroid.

8.26. The Subcommittee considered that there is limited evidence to support a benefit of RVD compared to the current standard of care (CyBorD). The Subcommittee however considered that the available evidence supports a benefit for RVD compared to current treatment options, and that this is primarily driven by the rates of response and depth of response, which is considered important for patients progressing to an ASCT.

8.27. The Subcommittee noted the results of the IFM2009 trial, in which patients were randomised to receive induction therapy with three cycles of RVD and then consolidation therapy with either five additional cycles of RVD or high-dose melphalan plus stem-cell transplantation followed by two additional cycles of RVD (Attal et al. N Engl J Med. 2017;376:1311-20). The Subcommittee noted that while the response rates differed significantly between the two treatment groups, there was no difference in OS between the two groups. The Subcommittee noted that the results of the long term follow up of this trial indicated no impact of delaying ASCT in this patient group (Perrot et al. ASH 2020:134538).

8.28. The Subcommittee considered that the most appropriate evidence to use to evaluate the OS and PFS for RVD in transplant eligible patients was from the Pethema/GEM2012 and IFM2009 trials.

8.29. The Subcommittee considered that funding RVD might result in a slight increase in the need to manage infections in patients receiving RVD, but that there would be no changes to the pharmacy, nursing, day stay requirement if funded, as such requirements primarily relate to the administration of bortezomib.

8.30. The Subcommittee considered that, if lenalidomide were funded for newly diagnosed, transplant ineligible multiple myeloma patients, uptake would be high, and RVD would be used by approximately 90% of incident newly diagnosed, transplant eligible multiple myeloma patients.

8.31. The Subcommittee considered that it would be appropriate to specify the maximum number of cycles, due to the potential otherwise for delayed transplant for this patient group as a means of managing the fiscal risk of funding lenalidomide in this setting. The Subcommittee considered that while it would be appropriate to limit the number of cycles to 8 cycles prior to transplant, specifying the funded regimen may not be appropriate, given the likely variation in use of lenalidomide in this setting.

8.32. The Subcommittee considered that lenalidomide in combination with dexamethasone (RD) was not an appropriate induction regimen for patients eligible for transplant and is not recommended in international guidelines (Mickael et al. J Clin Oncol.2019;37:1228-63). The Subcommittee considered that while there is no direct comparative data, it noted a review, which included a cross trial comparison, which indicated that RD is inferior to the current standard of care (CyBorD and BTD) when considering the treatment response rates achieved with commonly used induction regimens in patients with multiple myeloma (Kumar. Med Oncol. 2010;27(Suppl 1):S14-24).

Lenalidomide for transplant ineligible patients

8.33. The Subcommittee noted that in 2018 it was difficult to compare the health benefits and risks of lenalidomide and bortezomib containing regimens, but it was reasonable to consider at that stage that they had the same or similar benefits (CaTSoP April 2018).

8.34. The Subcommittee noted that there were no comparative trials between RVD and RD and the standard of care treatment for this population. However, the Subcommittee considered that the benefit of lenalidomide could be reasonably extrapolated from the indirect evidence available.

8.35. The Subcommittee noted the final analysis of the phase 3 FIRST trial of upfront treatment for multiple myeloma (Facon et al. 2018;131:301-10). The Subcommittee noted that this trial included 1623 patients, randomised to receive RD continuously, RD for 18 cycles or MPT for 72 weeks. The Subcommittee noted that PFS was significantly longer with RD continuous vs. MPT (hazard ratio [HR], 0.69; 95% confidence interval [CI], 0.59-0.79; P < .00001). The Subcommittee also noted that the median OS was 10 months longer with RD continuous vs MPT (59.1 vs 49.1 months; HR, 0.78; 95% CI, 0.67-0.92; P = .0023). The Subcommittee noted that there was a similar PFS benefit for RD continuous compared with RD for 18 cycles, however that there was no OS benefit for RD continuous vs RD for 18 cycles. The Subcommittee noted that continuous RD was

associated with fewer haematologic and neurologic adverse effects, a moderate increase in infections and fewer second primary haematologic cancers compared with MPT. The Subcommittee considered that this highlighted a potential discrepancy with the with increased risk of second primary malignancy reported from surveillance of patient registry data (Costa et al. 2018).

8.36. The Subcommittee noted a network meta-analysis indirect comparison of first line treatments for newly diagnosed transplant ineligible patients (Gil-Sierra et al. Eur J. Haematol. 2020;105(1):56-65). The Subcommittee noted that the hazard ratio in PFS was statistically significantly better for RVD compared to CTD (0.454; 95% Credibility Intervals (CrI) 0.23, 0.891) and MPT (0.511; 95% CrI 0.384, 0.682), with a numerically better difference than BMP (0.775; 95% CrI 0.43, 1.402). The Subcommittee noted that the hazard ratio in PFS was statistically significantly better for RD compared to MPT (0.719; 95% CrI 0.612, 0.849), however the difference was not numerically better than CTD (0.639; 95% CrI 0.34, 1.199), and was numerically worse than that of BMP (1.091; 95% CrI 0.638, 1.887). The Subcommittee reiterated the inherent limitations of such indirect comparison methods.

8.37. The Subcommittee noted the results of the randomised, phase 3 trial (SWOG S0777) comparing RVD and RD in patients with previously untreated multiple myeloma, without an intent for immediate transplant (Durie et al. Blood Cancer J. 2020;10:53). The Subcommittee noted that 43% of the 525 patients included in the trial were aged 65 years and over and 69% of all patients were intended for transplant. The Subcommittee considered that the most appropriate evidence to evaluate the OS and PFS of RVD and RD in the transplant ineligible patient population was from this trial. However, the Subcommittee considered that although similar, this trial included a younger, fitter population than the average New Zealand transplant ineligible population.

8.37.1. The Subcommittee noted that the median PFS for RVD in SWOG S0777 was greater than that of RD (41 months vs 29 months; p=0.003). The Subcommittee noted that the median OS for RVD was greater than that of RD (NR vs. 69 months; p=0.0114) and that when adjusting for age, RVD was better than RD for both PFS and OS. The Subcommittee noted that the subgroup and multivariate analyses reported that all age groups randomised to RVD had greater PFS and OS. However, in patients aged less than 65 years, the differences were statistically significant for PFS only, and the OS difference was only statistically significant in patients aged greater than 75 years. The Subcommittee noted that the proportion of patients with grade 3 toxicity and those who discontinued treatment because of toxicity was greater for those patients who received RVD than RD.

8.38. The Subcommittee noted a phase 2 trial of modified lenalidomide in combination with VD (RVD-lite) in transplant ineligible patients with multiple myeloma (O'Donnell et al. Br J Haematol. 2018;182:222-30; O'Donnell et al. Blood 2019;134 (Supplement_1):3178). The Subcommittee noted that this trial included 53 patients with a median age of 72 years and that patients received bortezomib 1.3 mg/m2 weekly. After a median follow up of 61 months the median PFS was 41.9 months and the OS was not reached (5 year OS of 61.3%). The Subcommittee considered that given the reported 5 year OS in New Zealand (The Burden of Multiple Myeloma in New Zealand July 2019), there may be a benefit of this regimen compared to the current status quo for patients in New Zealand. The Subcommittee noted the concern regarding the requirement for twice weekly

bortezomib, and considered that although this trial was not randomised the results regarding this regimen are promising.

8.39. The Subcommittee considered that if funded, this would result in a slight increase in the need to manage infections in patients receiving RVD, as per the SWOG S0777 trial protocol, but that there would be no changes to the pharmacy, nursing, day stay requirement if funded, as such requirements primarily relate to the administration of bortezomib.

8.40. The Subcommittee considered that, if lenalidomide were funded for newly diagnosed, transplant ineligible multiple myeloma patients, the uptake of RVD or RVD-LITE would be high and be used in approximately 75% of patients with transplant ineligible multiple myeloma compared with RD.

8.41. The Subcommittee considered that it would be important to specify the maximum number of cycles of RVD for transplant ineligible patients. The Subcommittee considered that there was data to support varying cycle numbers, and therefore it was not appropriate to limit the cycle numbers for lenalidomide in this setting. The Subcommittee noted that RVD-LITE had not been trialled against RD in this patient group. The Subcommittee considered that clinicians may elect between the use of the RVD-LITE and full dose RVD regimen depending on patient performance status.

8.42. The Subcommittee noted the results of a randomised phase 3 trial that investigated the efficacy of RD followed by maintenance 10 mg/day without dexamethasone (RD-R) (Larocca et al. Blood. blood.2020009507). The Subcommittee noted that the event free survival (EFS) was 10.4 with RD-R vs. 6.9 months with continuous RD (HR 0.70, 95% CI 0.51-0.95, p=0.02). Median PFS was 20.2 vs 18.3 months (HR 0.78, 95% CI 0.55-1.10, p=0.16), 3-year OS was 74% vs 63% (HR 0.62, 95% CI 0.37-1.03, p=0.06). The Subcommittee considered that on this basis, it would be possible that a proportion of patients would cease treatment with dexamethasone after 9 cycles and receive a lower maintenance dose of lenalidomide. The Subcommittee considered that it would be difficult to estimate the uptake of this therapy, but that it would be driven by a combination of patient fitness and disease risk.

8.43. The Subcommittee noted the joint clinical practice guidelines from the American Society of Clinical Oncology and Cancer Care Ontario (Mickael et al. J Clin Oncol.2019;37:1228-63). These guidelines indicate that optimal treatment includes the combination of a corticosteroid in combination with either an immunomodulatory drug or a proteasome inhibitor. The Subcommittee considered that in the future, there may be a desire to use one of the novel proteasome inhibitors.

8.44. The Subcommittee considered that it remains difficult to compare bortezomib based regimens with RD in transplant ineligible patients. However, the Subcommittee considered that there was a benefit of providing an option of an entirely oral regimen (RD) compared to the weekly SC injection. The Subcommittee considered that this would reduce the burden for patients, who require multiple visits to the day stay to receive the current standard of care. The Subcommittee considered that the added convenience and suitability of this as an option would be particularly beneficial.

8.45. The Subcommittee considered that for patients receiving RD, it would be important to factor in the cost of continuous therapy vs. the current standard of

care, which is administered for a fixed duration. However, the Subcommittee noted that there would be a significant reduction in the infusion costs and treatment visits for patients compared with the current standard of care.

8.46. The Subcommittee considered that it would be necessary to allow sufficient flexibility for patients receiving RD to reduce the dose of lenalidomide and stop dexamethasone if deemed necessary by the treating clinician.

8.47. The Subcommittee considered that if RD were funded in this setting, this may provide an indirect benefit of delaying treatment with bortezomib, resulting in the patient being exposed to bortezomib for the first time in a later line of therapy.

9. Carfilzomib and pomalidomide for relapsed/refractory multiple myeloma

Application

9.1. The Subcommittee noted that Pharmac sought further advice from the Subcommittee regarding pomalidomide and carfilzomib in the relapsed/refractory setting for multiple myeloma, and that this advice was requested in the context of:

9.1.1. A supplier submission received in February 2021 from Celgene for pomalidomide for relapsed/refractory multiple myeloma (second-line and third-line);

9.1.2. Correspondence from members of the New Zealand Myeloma Interest Group [NZMIG]).

Recommendation

9.2. The Subcommittee **recommended** that carfilzomib (once-weekly) for the second-line treatment of relapsed or refractory multiple myeloma be funded with a **high priority**, in the context of treatment for malignancy, subject to the following Special Authority criteria:

> **CARFILZOMIB**
> **Initial application** – (relapsed/refractory multiple myeloma) only from a haematologist or medical practitioner on the recommendation of a haematologist. Approvals valid for 6 months for applications meeting the following criteria:
> All of the following:
> 1. Patient has relapsed or refractory multiple myeloma with progressive disease; and
> 2. Patient has received one prior line of treatment ; and
> 3. Treatment to be administered in combination with dexamethasone.
>
> **Renewal** - (relapsed/refractory multiple myeloma) only from a haematologist or any other medical practitioner on the recommendation of a haematologist. Approvals valid for 6 months for applications meeting the following criteria:
> Both:
> 1. No evidence of disease progression; and
> 2. The treatment remains appropriate and patient is benefitting from treatment.

9.2.1. In making this recommendation, the Subcommittee considered

- The high health need of patients with relapsed/refractory multiple myeloma (including lenalidomide-refractory disease) requiring second-line treatment; and

- The evidence for a PFS benefit with carfilzomib compared with bortezomib in this setting, and the evidence of an OS benefit in this setting from the ENDEAVOR trial; and

- That it was reasonable to extrapolate the benefits observed in the ENDEAVOR trial to the ARROW trial noting the different levels of prior treatment in these populations.

9.3. The Subcommittee **recommended** that carfilzomib (once-weekly) for the third-line treatment of relapsed or refractory multiple myeloma be funded with a **medium priority**, in the context of treatment of malignancy, subject to the following Special Authority criteria:

CARFILZOMIB
Initial application – (relapsed/refractory multiple myeloma) only from a haematologist or medical practitioner on the recommendation of a haematologist. Approvals valid for 6 months for applications meeting the following criteria:
All of the following:
1. Patient has relapsed or refractory multiple myeloma with progressive disease; and
2. Patient has received two prior lines of treatment; and
3. Treatment to be administered in combination with dexamethasone.

Renewal - (relapsed/refractory multiple myeloma) only from a haematologist or any other medical practitioner on the recommendation of a haematologist. Approvals valid for 6 months for applications meeting the following criteria:
Both:
1. No evidence of disease progression; and
2. The treatment remains appropriate and patient is benefitting from treatment.

9.3.1. In making this recommendation, the Subcommittee considered

- The high health need of patients with relapsed/refractory multiple myeloma (including lenalidomide-refractory disease) requiring third-line treatment, however that the need for treatment in this setting was less than that in first relapse; and

- The evidence for a PFS benefit with carfilzomib compared with bortezomib in this setting, and the evidence of an OS benefit in this setting from the ENDEAVOR trial; and

- That it was reasonable to extrapolate the benefits observed in the ENDEAVOR trail to the ARROW trial noting the different levels of prior treatment in these populations.

9.4. The Subcommittee **recommended** that pomalidomide (in combination with bortezomib and dexamethasone, as PVd) for the second-line treatment of relapsed or refractory multiple myeloma be funded with a **high priority**, in the context of treatment of malignancy, subject to the following Special Authority criteria:

POMALIDOMIDE
Initial application – (relapsed/refractory multiple myeloma) only from a haematologist or medical practitioner on the recommendation of a haematologist. Approvals valid for 6 months for applications meeting the following criteria:
All of the following:
1. Patient has relapsed or refractory multiple myeloma with progressive disease; and

2. Patient has received one prior line of treatment; and
3. Treatment to be administered in combination with dexamethasone and bortezomib (PVd).

Renewal - (relapsed/refractory multiple myeloma) only from a haematologist or any other medical practitioner on the recommendation of a haematologist. Approvals valid for 6 months for applications meeting the following criteria:
Both:
1. No evidence of disease progression; and
2. The treatment remains appropriate and patient is benefitting from treatment.

9.4.1. In making this recommendation, the Subcommittee considered:

- The high health need of patients with relapsed/refractory multiple myeloma (including lenalidomide-refractory disease) requiring second-line treatment; and

- The evidence for a PFS benefit with pomalidomide with bortezomib and dexamethasone in this setting; and

9.5. The Subcommittee **recommended** that pomalidomide (in combination with bortezomib and dexamethasone, as PVd) for the third-line treatment of relapsed or refractory multiple myeloma be funded with a **high priority**, in the context of treatment of malignancy, subject to the following Special Authority criteria:

POMALIDOMIDE
Initial application – (relapsed/refractory multiple myeloma) only from a haematologist or medical practitioner on the recommendation of a haematologist. Approvals valid for 6 months for applications meeting the following criteria:
All of the following:
1. Patient has relapsed or refractory multiple myeloma with progressive disease; and
2. Patient has received two prior lines of treatment; and
3. Treatment to be administered in combination with dexamethasone with bortezomib (PVd).

Renewal - (relapsed/refractory multiple myeloma) only from a haematologist or any other medical practitioner on the recommendation of a haematologist. Approvals valid for 6 months for applications meeting the following criteria:
Both:
1. No evidence of disease progression; and
2. The treatment remains appropriate and patient is benefitting from treatment.

9.5.1. In making this recommendation, the Subcommittee considered:

- The high health need of patients with multiply relapsed/refractory multiple myeloma (including lenalidomide-refractory disease) requiring third-line treatment; and

- The evidence for a PFS benefit with pomalidomide with bortezomib and dexamethasone in this setting.

9.6. The Subcommittee **recommended** that pomalidomide (in combination with dexamethasone, as Pd) for the second-line treatment of relapsed or refractory multiple myeloma be funded with a **low priority**, in the context of treatment for malignancy, subject to the following Special Authority criteria:

POMALIDOMIDE
Initial application – (relapsed/refractory multiple myeloma) only from a haematologist or medical practitioner on the recommendation of a haematologist. Approvals valid for 6 months for applications meeting the following criteria:
All of the following:
1. Patient has relapsed or refractory multiple myeloma with progressive disease; and
2. Patient has received one prior line of treatment ; and
3. Treatment to be administered in combination with dexamethasone (Pd).

Renewal - (relapsed/refractory multiple myeloma) only from a haematologist or any other medical practitioner on the recommendation of a haematologist. Approvals valid for 6 months for applications meeting the following criteria:
Both:
1. No evidence of disease progression; and
2. The treatment remains appropriate and patient is benefitting from treatment.

9.6.1. In making this recommendation, the Subcommittee considered:

- The high health need of patients with relapsed/refractory multiple myeloma requiring additional effective second-line treatment options; and

- The suitability or an oral regimen for this population; and

- That it was reasonable to assume that the benefit of this agent for this patient group would be better in this setting, in the absence of comparative trial data, based on evidence of benefit from this treatment in the second line.

9.7. The Subcommittee **recommended** that pomalidomide (in combination with dexamethasone, as Pd) for the third-line treatment of relapsed or refractory multiple myeloma be funded with a **low priority**, in the context of treatment for malignancy, subject to the following Special Authority criteria:

POMALIDOMIDE
Initial application – (relapsed/refractory multiple myeloma) only from a haematologist or medical practitioner on the recommendation of a haematologist. Approvals valid for 6 months for applications meeting the following criteria:
All of the following:
1. Patient has relapsed or refractory multiple myeloma with progressive disease; and
2. Patient has received two prior lines of treatment ; and
3. Treatment to be administered in combination with dexamethasone (Pd).

Renewal - (relapsed/refractory multiple myeloma) only from a haematologist or any other medical practitioner on the recommendation of a haematologist. Approvals valid for 6 months for applications meeting the following criteria:
Both:
1. No evidence of disease progression; and
2. The treatment remains appropriate and patient is benefitting from treatment.

9.7.1. In making this recommendation, the Subcommittee considered:

- The high health need of patients with relapsed/refractory multiple myeloma requiring third-line treatment; and

- The suitability or an oral regimen for this population; and

- The evidence for a PFS benefit with pomalidomide with dexamethasone in patients with multiply relapsed disease.

Discussion

9.8. The Subcommittee considered that, based on real-world clinical practice, almost all patients with multiple myeloma will receive first-line treatment although only about 61% and 38% of patients will receive second- and third-line treatments, respectively.

9.9. The Subcommittee considered that the possible second-line treatment options consisted of bortezomib retreatment (as CyBorD/BTD) or bortezomib in

combination with melphalan and prednisone (BMP) and that it was preferable to expose patients to new agents than retreating with bortezomib. Alternatively, patients would receive a thalidomide-based regimen, which would consist of cyclophosphamide, thalidomide and dexamethasone (CTD) or melphalan, prednisone and thalidomide (MPT), all for approximately six to 12 cycles. The Subcommittee noted that patients could be eligible for lenalidomide in combination with dexamethasone until progression if neuropathy prevents use of bortezomib and thalidomide-based regimens. The Subcommittee noted that in patients with relapsed/refractory multiple myeloma, if remission was for greater than two to three years, and the patient was transplant eligible, a second autologous stem cell transplant would be offered.

9.10. The Subcommittee considered that the choice of second-line regimen would be determined by the duration of response to first-line treatment, toxicities experienced in the first-line, and patient-specific factors including the desire for oral therapy.

9.11. The Subcommittee noted that once a patient progresses after second line therapy, if they had received an autologous stem cell transplant with lenalidomide maintenance there are no further options for this patient group. The Subcommittee noted that lenalidomide with dexamethasone with or without bortezomib was a third-line treatment option, only for transplant-ineligible patients who had not received lenalidomide maintenance post autologous stem cell transplant.

9.12. The Subcommittee was made aware of data reporting progression-free survival (PFS) of around eight months with bortezomib retreatment in relapsed multiple myeloma, from two clinical trials, and considered the efficacy of bortezomib retreatment after first-line bortezomib to be limited:

- A 6.5-month duration of response was reported in 130 patients who received bortezomib with or without dexamethasone after median two prior lines of therapy (Petrucci et al. Br J Haematol. 2013;160:649-59); and

- In the CASTOR trial control arm of bortezomib and dexamethasone (N = 113), median PFS was 7.1 months and median PFS in patients who had received one prior line of therapy was 7.9 months. About 45% of patients had received one prior line, and about 70% of patients had prior bortezomib exposure (Spencer et al. Haematologica. 2018;103:2079-87).

9.13. The Subcommittee considered that the duration of benefit from thalidomide in the second-line setting was hard to estimate, as clinical trials generally allow use of agents at relapse that are less comparable to the New Zealand setting, however, noted that thalidomide is associated with relatively short PFS and toxicities including neuropathy which limit its use. The Subcommittee considered it reasonable to assume that outcomes would be similar to that observed in patients retreated with bortezomib.

9.14. The Subcommittee was made aware of evidence that a significant number of patients (about 50%) progress on lenalidomide maintenance and have few subsequent treatment options, as they are unlikely to receive a response from thalidomide and early relapse after prior bortezomib treatment makes its use in retreatment less likely to be successful (Sanchez et al. Blood. 2019;134(Suppl_1):1779).

9.15. The Subcommittee considered that in New Zealand the second-line treatment options provide suboptimal benefits and that there is a definite need for more effective second-line treatment for multiple myeloma including lenalidomide-refractory patients. The Subcommittee considered the unmet need for treatments in later lines of therapy was also high, but that the number of patients requiring treatment in this context was less, and that there would be a proportion of patients who would remain eligible for lenalidomide-based treatment in this setting.

9.16. The Subcommittee noted that multiple myeloma treatment is evolving internationally with use of other combinations and other treatments, and was made aware of international clinical guidelines that recommend second-line treatments or combinations that are not funded in New Zealand (Kumar et al. J Natl Compr Canc Netw. 2018;16:11-20; Moreau et al. Ann Oncol. 2017;28(suppl_4):iv52-iv61). The Subcommittee noted that some of the potential treatments that could be used by patients with relapsed/refractory multiple myeloma include, but are not limited to carfilzomib, ixazomib, pomalidomide, daratumumab and elotuzumab.

9.17. The Subcommittee noted that the New Zealand Myeloma Interest Group (NZMIG) has expressed its preference for daratumumab (especially if subcutaneous) and carfilzomib, which the NZMIG consider very effective, to be funded for the treatment of relapsed/refractory multiple myeloma. However, the Subcommittee noted that Pharmac sought advice at this time regarding carfilzomib and pomalidomide in the context of currently funded treatments (ie without consideration of unfunded treatments such as daratumumab).

Carfilzomib

9.18. The Subcommittee noted that it had previously reviewed an application for carfilzomib in the relapsed/refractory setting in October 2019 following PTAC's review of the application in February 2019. The Subcommittee noted that carfilzomib is an intravenously-administered proteasome inhibitor and that Medsafe has approved carfilzomib (Kyprolis) in combination with either lenalidomide and dexamethasone, or dexamethasone alone, for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least one prior therapy. The Subcommittee noted that the Medsafe data sheet lists the following recommended dosing regimens for carfilzomib in this setting:

9.18.1. Carfilzomib (with dexamethasone) administered as a 20 mg/m^2 starting dose, then on cycle 1 day 8, if tolerated, carfilzomib dose increased to 70 mg/m^2 once weekly (30-minute infusion); and

9.18.2. Carfilzomib (with dexamethasone and lenalidomide) administered as a 20 mg/m^2 starting dose, then on cycle 1 day 8, if tolerated, carfilzomib dose increased to 27 mg/m^2 twice weekly (10-minute infusion) or 56 mg/m^2 twice weekly (30-minute infusion).

9.19. The Subcommittee noted that international funding bodies in Australia, Canada, England and Wales, and Scotland have recommended carfilzomib in combination with dexamethasone be funded for second-line use (and for third-line use in Canada). The Subcommittee noted that the once-weekly regimen is funded in Australia for patients with relapsed/refractory multiple myeloma.

Evidence for carfilzomib with dexamethasone (second-line and third-line)

9.20. The Subcommittee noted that evidence for twice-weekly carfilzomib comes from the randomised (1:1), phase III, open-label, multicentre ENDEAVOR trial of 929 patients with relapsed or refractory multiple myeloma (Dimopoulos et al. Lancet Oncol. 2016;17:27-38). The Subcommittee noted that the median age of ENDEAVOR participants was 65 years and considered this group was slightly younger than New Zealand patient population who are about 70 years at diagnosis. The Subcommittee noted that participants had one to three (median two) prior lines of therapy, with half of participants in each group having received two or three prior lines, and 54% of participants having previously received bortezomib.

9.20.1. The Subcommittee noted that participants received carfilzomib 56 mg/m^2 twice weekly (20 mg/m^2 on days one and two of cycle one; 56 mg/m^2 thereafter) with dexamethasone (20 mg oral or intravenous [IV] infusion) or bortezomib (1.3 mg/m^2; IV bolus or subcutaneous [SC] injection) with dexamethasone as 28-day cycles continued until disease progression. The Subcommittee noted that this dosing was one of the Medsafe-approval regimens and considered that the bortezomib comparator treatment was a relevant treatment option in the New Zealand setting, although triple therapy may also be used.

9.20.2. The Subcommittee noted that the primary endpoint was progression-free survival (PFS) in the intention-to-treat population, which was a median 18.7 months (95% CI 15.6–not estimable) with carfilzomib versus 9.4 months (8.4–10.4) with bortezomib (hazard ratio, HR 0.53; 95% CI: 0.44 to 0.65; P<0.0001). The Subcommittee noted that PFS in patients previously exposed to bortezomib was 15.6 months (12.9 to not evaluable) with carfilzomib vs 8.1 months (6.6 to 9.5) with bortezomib. The Subcommittee considered that the outcomes in the control arm of this trial were indicative of the outcomes that could be expected with bortezomib retreatment.

9.20.3. The Subcommittee noted that carfilzomib was favoured over bortezomib retreatment in all patient subgroups except patients with disease refractory to prior bortezomib or lenalidomide, although there were small patient numbers in those groups.

9.20.4. The Subcommittee noted the pre-planned interim overall survival (OS) analysis was performed at cut-off date Jan 3, 2017, at which time the median OS was 47.6 months (95% CI 42.5-not evaluable) with carfilzomib versus 40.0 months (32.6-42.3) in the bortezomib group (HR 0.791 [95% CI 0.648-0.964], one-sided *P*=0.010) (Dimopoulos et al. Lancet Oncol. 2017;18:1327-37). The Subcommittee noted that there was less OS benefit in patients over 75 years of age, those with renal impairment (creatine clearance <30 mL/min) and those with high-risk cytogenetics.

9.21. The Subcommittee noted that evidence for once-weekly carfilzomib comes from the randomised (1:1), open-label, phase III ARROW trial of 578 patients with relapsed and refractory multiple myeloma with measurable disease who had received two or three prior treatments (including a proteasome inhibitor and immunomodulatory imide drug ie lenalidomide or thalidomide) (Moreau et al. Lancet Oncol. 2018;19:953-64). The Subcommittee noted that the ARROW population were more heavily pre-treated and disease-refractory than the ENDEAVOR population.

9.21.1. The Subcommittee noted that participants received carfilzomib 70 mg/m^2 once weekly (20 mg/m^2 day 1 cycle 1; 70 mg/m^2 thereafter) or carfilzomib 27 mg/m^2 twice weekly (20 mg/m^2 days 1 and 2 during cycle 1; 27 mg/m^2 thereafter). The Subcommittee noted that all patients received dexamethasone 40 mg on days 1, 8, 15 (all cycles) and 22 (cycles 1–9 only) and that the 28-day treatment cycles continued until disease progression or unacceptable toxicity.

9.21.2. The Subcommittee considered that the lower dose carfilzomib comparator was less relevant and that a twice weekly standard dose (ie 56 mg/m^2 twice weekly as per ENDEAVOR and Medsafe approved dose) would have been more relevant to the New Zealand population.

9.21.3. The Subcommittee noted that the primary endpoint was PFS in the intention-to-treat population, which was median 11.2 months (95% CI 8.6 to 13.0) with 70 mg/m^2 once weekly vs 7.6 months (95% CI: 5.8 to 9.2) with 27 mg/m^2 twice weekly (HR 0.69, 95% CI: 0.54 to 0.83; *P*=0.0029).

9.21.4. The Subcommittee noted that median PFS was greater with 56 mg/m^2 twice-weekly in ENDEAVOR (18.7 months) than with 70 mg/m^2 once-weekly in ARROW (11.3 months), however, data with propensity score adjustment suggested there was more benefit with the ARROW regimen (median PFS 21.0 months) compared with ENDEAVOR (14.9 months). The Subcommittee noted that, due to the lack of non-inferiority or superiority testing, CaTSoP previously considered in October 2019 that these high-dose once-weekly and twice-weekly regimens likely provided comparable PFS benefits.

9.21.5. The Subcommittee considered it likely that a population with fewer prior lines of treatment (eg more akin to the ENDEAVOR population) would receive a greater PFS benefit than that reported for ARROW participants from the once-weekly 70 mg/m^2 ARROW regimen.

9.22. The Subcommittee noted further evidence of once-weekly carfilzomib dosing comes from the abstract of a phase II trial (GEM-KyCyDex) presented at the December 2020 ASH conference (Mateos et al. 415 Paper presented at: American Society of Haematology Annual Meeting; December 2020). The Subcommittee noted that 198 participants received carfilzomib 70mg/m^2 (days 1,8,15) and dexamethasone 20mg (days 1,8,15) with or without cyclophosphamide IV 300mg/m2 (days 1,8, 15).

9.22.1. The Subcommittee noted that the median age was 70 years and that 61% of participants received one prior line of treatment. The Subcommittee noted that all patients had previously been treated with bortezomib, that about 90% responded to bortezomib treatment and approximately 70% had been previously treated with lenalidomide, half of who had refractory disease.

9.22.2. The Subcommittee noted the reporting that after median follow-up of 15.6 months, median PFS was 20.7 months with carfilzomib, dexamethasone and cyclophosphamide vs 15.2 months carfilzomib and dexamethasone (*P*=0.2). The Subcommittee considered that it was expected that cyclophosphamide would add benefit, especially in immunomodulatory imide drug-refractory patients where there was a significant benefit in PFS (26.2 months vs 7.7 months; *P*=0.01). The Subcommittee considered that this supported the evidence of effect from once-weekly carfilzomib in the ARROW trial.

Evidence for carfilzomib with dexamethasone and lenalidomide (second-line)

9.23. The Subcommittee noted evidence from the randomised (1:1), open-label, multicentre, phase III ASPIRE study, which included 792 patients with relapsed multiple myeloma with measurable disease (Stewart et al. N Engl J Med. 2015;372:142-52; Dimopoulos et al. J Hematol Oncol. 2018;11:49). The Subcommittee noted that 43% of participants had received one prior line of therapy and 65% had two to three prior lines. The Subcommittee noted that 65% of participants had received prior bortezomib and 20% prior lenalidomide, although the trial did not include patients who were refractory to these agents.

9.23.1. The Subcommittee noted that participants received carfilzomib twice weekly (20 mg/m^2 days 1 and 2 of cycle 1; 27 mg/m^2 thereafter until progression or unacceptable toxicity; omitted on D8 and D9 during cycles 13 to 18; and discontinued after 18 cycles) with lenalidomide (25 mg days 1-21) and dexamethasone (40 mg days 1, 8, 15 and 22) or lenalidomide with dexamethasone (control group) according to the same dosing.

9.23.2. The Subcommittee noted that the primary endpoint was PFS in the intention-to-treat population, which was median 26.3 months (95% CI: 23.3 to 30.5) with carfilzomib vs 17.6 months (95% CI: 15.0 to 20.6) in the control group (HR for progression or death, 0.69; 95% CI, 0.57 to 0.83; *P*=0.0001).

9.23.3. The Subcommittee considered that this evidence indicates a benefit from carfilzomib in the carfilzomib group with lenalidomide and that hazard ratios for PFS in subgroups suggest most subgroups appear to benefit from treatment (eg according to number of prior lines, prior bortezomib use or not). The Subcommittee considered that this data suggests the carfilzomib regimen could be considered effective in the second-line or third-line setting.

Summary

9.24. The Subcommittee considered that the evidence supporting a benefit of carfilzomib for patients with relapsed/refractory multiple myeloma was stronger for patients who had received only one prior line of treatment, compared with patients with multiply relapsed disease. The Subcommittee also considered that the unmet need for patients at initial relapse was greater, given the current treatment options available, than the unmet need in multiply relapsed patients.

9.25. The Subcommittee noted that quality of life (QOL) from the addition of carfilzomib in ENDEAVOR treatment was similar to QOL with bortezomib and dexamethasone (Ludwig et al. Blood Cancer J. 2019;9:23); that QOL data in ARROW indicated a preference for once-weekly treatment (Moreau et al. Leukemia. 2019;33:2934-46); and that ASPIRE suggested that QOL with carfilzomib, lenalidomide and dexamethasone was as good or better than QOL with lenalidomide and dexamethasone alone (Stewart et al. J Clin Oncol. 2016;34:3921-30). The Subcommittee considered all carfilzomib QOL outcomes were similar, indicating that carfilzomib is well tolerated, that it does not negatively impact quality of life, and that weekly dosing is preferred.

9.26. The Subcommittee noted that there was no direct comparative evidence for carfilzomib 70 mg/m^2 once weekly vs 56 mg/m^2 twice weekly, and that it was reasonable to assume that the differences between ENDEAVOR and ARROW patients reflect the extent of pre-treatment in these groups. The Subcommittee considered that the evidence for carfilzomib once-weekly and twice-weekly dosing

was of good strength and quality. Overall, the Subcommittee considered this evidence suggests carfilzomib once weekly would provide benefits in the second-line and in the third-line setting, and that the evidence from ENDEAVOR and ASPIRE suggests the benefit would be across all subgroups with relapsed/refractory MM (although there would be smaller benefit in lenalidomide-refractory disease).

9.27. The Subcommittee noted that the higher carfilzomib doses given once weekly were equivalent to dosing of 70 mg/m2 and 112 mg/m2 per week and that these regimens are used in some jurisdictions (registered in USA and Switzerland; being considered by TGA and Canada). The Subcommittee considered it reasonable to infer that efficacy is probably similar between these two dosing regimens and that risks may be similar, although weekly treatment may be slightly better tolerated.

9.28. The Subcommittee considered that, if funded as a second-line or third-line treatment, carfilzomib and dexamethasone could be administered either according to the ENDEAVOR trial dosing (56 mg/m^2 twice weekly) or the ARROW trial dosing (70 mg/m^2 once weekly) until disease progression. The Subcommittee noted that in October 2019 CaTSoP had thought that the uptake of 70 mg/m^2 once weekly would be low, given uncertainty of benefit. The Subcommittee considered that the updated publication with evidence of impact from once-weekly dosing, along with the submission from the NZMIG indicating that this dosing regimen would be preferred by New Zealand clinicians, suggests that once-weekly may be preferred due to its lesser impact on infusion resources. The Subcommittee considered that the higher weekly dosing may be used in patients who find the twice-weekly treatment challenging eg due to travel requirements and infusion burden.

9.29. The Subcommittee considered that it would be reasonable to assume that the outcomes observed with twice-weekly carfilzomib in the ENDEAVOR trial would be similar if these patients had received the once-weekly dosing regimen used in the ARROW trial. The Subcommittee therefore considered that it would be reasonable to use the outcomes from each trial as a surrogate for the benefit of carfilzomib-based therapy at initial relapse or in multiply relapsed patients.

Pomalidomide

9.30. The Subcommittee noted that CaTSoP had previously reviewed in April 2016 an application for pomalidomide in combination with dexamethasone in the relapsed/refractory (fourth-line) setting and had recommended it be funded with a low priority (refer to the Application Tracker for full history). The Subcommittee noted that pomalidomide is an immunomodulatory agent that is an analogue of thalidomide, and that it is administered as an oral treatment.

9.31. The Subcommittee noted that Medsafe has approved pomalidomide in combination with dexamethasone for the treatment of patients with relapsed and refractory multiple myeloma who have received at least two prior treatment regimens, including both lenalidomide and bortezomib, and have experienced disease progression on the last therapy. The Subcommittee noted that the Medsafe-approved dosing regimen is pomalidomide 4 mg per day taken orally on days 1-21 of repeated 28-day cycles (21/28 days), in combination with dexamethasone, until disease progression.

9.32. The Subcommittee noted that the New Zealand Myeloma Interest Group considers that pomalidomide is less burdensome for patients than carfilzomib but

prefers to reserve pomalidomide for use in later lines. However, the Subcommittee noted that the impact of pomalidomide on reducing the infusion burden would only be relevant if it were not used in combination with bortezomib, which is administered subcutaneously.

9.33. The Subcommittee noted that international funding bodies in Australia and Canada have recommended pomalidomide be funded for second-line or third-line use; in Scotland is pomalidomide is recommended for third-line use; and in England and Wales it is recommended for fourth-line or later use, in combination with dexamethasone.

9.34. The Subcommittee noted that the evidence supporting the use of pomalidomide in earlier lines of therapy is in combination with bortezomib and dexamethasone, while the evidence supporting the use of pomalidomide in later lines is in combination with dexamethasone.

Evidence for pomalidomide in combination with bortezomib and dexamethasone

9.35. The Subcommittee noted evidence from the randomised (1:1), open-label, phase III MM-007 (OPTIMISMM) study, which included 559 patients with relapsed or refractory multiple myeloma with measurable disease Richardson et al. Lancet Oncol. 2019;20:781-94). The Subcommittee noted that participants had received one to three prior lines of therapy (median one) including a lenalidomide-containing regimen; that 50-72% had prior exposure to bortezomib; and that 40-64% had a prior transplant.

9.35.1. The Subcommittee noted that participants received oral pomalidomide (4 mg/day on days 1-14) with bortezomib (1.3 mg/m2) and low-dose dexamethasone (20 mg if aged ≤75 years, otherwise 10 mg) (PVd regimen) or bortezomib with low-dose dexamethasone (Vd regimen), and that 21-day treatment cycles continued until progressive disease or unacceptable toxicity.

9.35.2. The Subcommittee noted that the primary endpoint was PFS, which was median 11.2 months (95% CI 9.7 to 13.7) with pomalidomide, bortezomib and dexamethasone vs 7.1 months (5.9 to 8.5) with bortezomib and dexamethasone (HR 0.61, 95% CI 0.49 to 0.77; *P*<0.0001).

9.35.3. The Subcommittee noted the overall response rate in patients who had once prior line and whose disease was refractory to lenalidomide was 85.0% with pomalidomide, bortezomib and dexamethasone vs 50.8% with bortezomib and dexamethasone; overall response rates were 95% vs 60%, respectively, in patients who had one prior line and were lenalidomide sensitive. The Subcommittee noted that median PFS in lenalidomide refractory patients was 12.84 months with pomalidomide, bortezomib and dexamethasone vs 9.49 months with bortezomib and dexamethasone (*P*=0.028) and median PFS in lenalidomide sensitive patients was 20.01 months with pomalidomide, bortezomib and dexamethasone vs 11.96 months with bortezomib and dexamethasone (*P*=0.049).

9.35.4. The Subcommittee considered that the evidence indicated a clear benefit in multiple myeloma including those with refractory disease, and provided a benefit whether or not a patient has previously received bortezomib and whether or not a patient has had a transplant. The Subcommittee considered that if use of pomalidomide were restricted to patients with lenalidomide refractory disease, this would mean that only patients who had previously

received an autologous stem cell transplant would be eligible based on the current Special Authority criteria for lenalidomide.

9.35.5. The Subcommittee noted that health-related quality of life (QOL) was maintained in MM-007 despite the addition of pomalidomide, although some patients in both groups had a clinically meaningful worsening of QOL (Weisel et al. Leuk Lymphoma. 2020;61:1850-9).

Evidence for pomalidomide in combination with dexamethasone

9.36. The Subcommittee noted evidence from the phase III, multicentre, randomised (2:1), open-label MM-003 (NIMBUS) study, which included 455 patients with refractory or relapsed and refractory multiple myeloma following two previous treatments of bortezomib and lenalidomide (San Miguel et. al. Lancet Oncology. 2013; 14:1055-66). The Subcommittee noted that this was a heavily pre-treated and disease-refractory population with about 95% of participants having received more than two prior lines of treatment (median 5 previous treatments); more than 90% of patients were refractory to lenalidomide; and about 80% of patients were refractory to bortezomib.

9.36.1. The Subcommittee noted that participants received oral pomalidomide (4 mg/day on days 1, 8, 15 and 22) with low-dose dexamethasone (40 mg/day on days 1, 8, 15 and 22) (Pd regimen) or high-dose dexamethasone (40 mg/day on days 1-4, 9-12, and 17-20), and that 28-day treatment cycles continued until progressive disease or unacceptable toxicity.

9.36.2. The Subcommittee noted that the primary endpoint was PFS in the intention-to-treat population, and that updated PFS at the time of interim OS analysis was median 4.0 months (95% CI 3.6 to 4.7) pomalidomide plus low-dose dexamethasone vs 1.9 months (1.9 to 2.2) high-dose dexamethasone (HR 0.48; 95% CI: 0.39 to 0.60; *P*<0.0001).

9.36.3. The Subcommittee noted that the median PFS in lenalidomide resistant patients was 3.9 months (95% CI: 3.5 to 4.6) vs 1.9 months (1.9 to 2.2); *P*<0.0001).

9.36.4. The Subcommittee considered that, while a small improvement in PFS, these results favoured low dose dexamethasone over high dose dexamethasone in this heavily pre-treated patient population with resistant disease.

9.37. The Subcommittee also noted the following evidence for pomalidomide in relapsed and/or refractory multiple myeloma:

- Weisel et al. Clin Lymphoma Myeloma Leuk. 2015;15:519-30
- Dimopoulos et al. Leukemia. 2020. doi: 10.1038/s41375-020-01021-3. Online ahead of print
- San Miguel et al. Haematologica. 2015;100:1334-9
- Dimopoulos, et al. Haematologica. 2015;100:1327-33
- Morgan et al. Br J Haematol. 2015;168:820-3

Summary

9.38. The Subcommittee considered that the evidence supporting the use of pomalidomide in combination with bortezomib and dexamethasone in the second- and third-line setting was of good quality and high strength. The Subcommittee considered that the evidence supporting the use of pomalidomide in combination with dexamethasone in the relapsed/refractory setting was of reasonable quality.

9.39. The Subcommittee considered that the evidence indicates that pomalidomide is well tolerated with minimal risks. The Subcommittee considered that it was difficult to compare pomalidomide with other novel agents in the early relapsed setting (eg. carfilzomib and daratumumab).

9.40. The Subcommittee considered that there would be a limited benefit of funding pomalidomide in combination with dexamethasone in earlier lines of therapy (ie second-line), because the benefit in second line therapy is difficult to ascertain, having been studied only in later lines of therapy. However, the Subcommittee considered that it would be reasonable to assume that there would be improved survival from pomalidomide in combination with dexamethasone when used in earlier lines of treatment compared with that observed in the heavily pre-treated population in the MM-003 (NIMBUS) study.

9.41. The Subcommittee noted that pomalidomide appears to be effective regardless of prior therapy, and considered that use of this agent would be preferred for patients with multiply relapsed disease (who have progressed on other lines of treatment). The Subcommittee noted that there was no evidence to inform efficacy of other treatments (eg lenalidomide) subsequently used in patients whose disease has become resistant to pomalidomide. The Subcommittee considered that pomalidomide represents an additional line of treatment that may be reserved for use as a third- or later line and considered these patients would benefit most as they have few other options available.

9.42. The Subcommittee noted that the use of pomalidomide in combination with bortezomib is outside the Medsafe-approved pomalidomide indications but considered this use would be reasonable given that its use is informed by a body of clinical trial evidence and it is routine internationally.

9.43. The Subcommittee noted that pomalidomide with dexamethasone is an oral therapy, whilst pomalidomide with bortezomib would require infusion resources.

9.44. The Subcommittee noted that the supplier-proposed Special Authority criteria for pomalidomide considered whether or not a patient had received a prior autologous stem cell transplant, however, the Subcommittee considered that progression on a lenalidomide-containing prior treatment regimen was a more meaningful distinction.

General

9.45. The Subcommittee noted that there was no randomised controlled trial evidence comparing second-line treatment options against each other (ie carfilzomib vs pomalidomide) therefore evidence was lacking to inform preferred treatment sequencing. However, the Subcommittee considered that there would be a preference for carfilzomib to be used second-line, with pomalidomide reserved for third-line or later use. The Subcommittee noted that it will consider an application for subcutaneous daratumumab at a future meeting and that the Subcommittee could again indicate the preferred treatment options for this population at that time.

9.46. The Subcommittee considered that it would be reasonable to target funding via Special Authority criteria to enable carfilzomib and pomalidomide each to be used once per patient lifetime, or to be used in pre-specified treatment lines, as supported by evidence.

9.47. The Subcommittee noted the estimate that 50% of patients with multiple myeloma may be eligible for transplant. However, the Subcommittee considered this estimate was likely too high for second- or third-line patients, as transplant eligibility decreases over time given the age of patients at initial diagnosis. The Subcommittee considered that in time, the funded use of lenalidomide in the relapsed/refractory setting would be indicative of the proportion of patients who are ineligible for transplant in third-line setting. The Subcommittee noted that there are approximately 400 patients diagnosed with multiple myeloma each year and considered that approximately 50% would initially be eligible for transplant. The Subcommittee considered that on this basis there would be approximately 130 patients who would relapse post-transplant each year; that there would be approximately 150 patients who would relapse after first line treatment if ineligible for transplant each year; and there would be approximately 170 patients who would require treatment in the third line setting each year.

9.48. The Subcommittee considered that the number of cycles received will depend on PFS which is influenced by prior lines of therapy and the proportion of patients whose disease was refractory, therefore the treatment cost per cycle would be most useful for cost-effectiveness assessment, as opposed to cost per treatment, given the variable extent of pre-treatment in the clinical trials.

9.49. The Subcommittee considered that for second-line treatment, comparators could be bortezomib retreatment as CyBorD/BTD, or MPT and CTD. The Subcommittee considered that the key outcome of interest in this setting was improved PFS (above that gained from bortezomib retreatment). The Subcommittee considered the most appropriate comparator for use in the second-line would be BTD, unless the patient could not tolerate bortezomib, in which case regimens without bortezomib would be used. The Subcommittee considered that the efficacy of thalidomide in this setting is limited by the development of neuropathy, and efficacy difficult to establish from the scientific evidence base as most studies use more novel agents at relapse. The Subcommittee considered that outcomes would be expected to be worse without bortezomib.

9.50. The Subcommittee considered that for third-line treatment, standard therapy is lenalidomide and dexamethasone with or without bortezomib, although patients who had a prior autologous stem cell transplant with lenalidomide maintenance could be considered for third-line treatment with a bortezomib and/or thalidomide-based regimen. The Subcommittee considered that the key outcomes of interest in this setting were improved PFS and OS.

10. Crizotinib and entrectinib for the treatment of ROS1 positive NSCLC

Application

10.1. The Subcommittee considered the following applications for the treatment of ROS1 positive non-small cell lung cancer (NSCLC);

10.1.1. A clinician application for crizotinib for the treatment of metastatic or locally advanced NSCLC with ROS1 gene rearrangement not amenable to curative intent treatment; and

10.1.2. An application from Roche Products (New Zealand) for entrectinib for the treatment of adult patients with ROS-1 positive, locally advanced or metastatic NSCLC.

Recommendation

10.2. The Subcommittee **recommended** that crizotinib for the treatment of ROS1 positive metastatic or locally advanced NSCLC be funded with a **high priority** within the context of treatments for malignancy.

10.3. The Subcommittee **recommended** that entrectinib for the treatment of ROS1 positive metastatic or locally advanced NSCLC be funded with a **high priority** within the context of treatments for malignancy.

10.4. The Subcommittee considered the following Special Authority criteria to be appropriate for funding a ROS1 targeted treatment for ROS1 positive metastatic or locally advanced NSCLC:

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 locally advanced or metastatic, unresectable, non-squamous non-small cell lung cancer; and
2 There is documentation confirming that the patient has a ROS1 tyrosine kinase gene rearrangement using an appropriate ROS1 test; and
3 Patient has an ECOG performance score of 0-2.

Renewal 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:
Both:
1 No evidence of progressive disease according to RECIST criteria; and
2 The patient is benefitting from and tolerating treatment.

10.5. In making this recommendation, the Subcommittee considered the high health need of patients with ROS1 positive NSCLC, health needs for Māori patients and whanau, and those patients and families from areas of high social deprivation index, the lack of alternative funded targeted treatment options, and the evidence of crizotinib or entrectinib treatment in this patient group. The Subcommittee noted that whilst this was of low quality and strength by standard trial design definitions, the biological rationale is compelling and the specialist clinical opinion of these results supports a very strong benefit from treatment in this patient group.

Background

10.6. The Subcommittee noted that, in August 2020, PTAC reviewed the application for crizotinib for the treatment of locally advanced or metastatic, ROS1 gene translocation positive non-small cell lung cancer (NSCLC) and recommended it be listed with a low priority due to the high health need of patients with ROS1 NSCLC, a lack of funded targeted treatments for this patient group, the low quality evidence of moderate benefit, and the uncertain impact on the health system.

10.7. The Subcommittee noted that PTAC considered advice from CaTSoP and specialists involved in the treatment of lung cancer in New Zealand could be sought regarding: appropriate Special Authority criteria; clarification on the proportion of people with ROS1 NSCLC expected to be unfit for funded platinum-based chemotherapy; the proportion of people expected to be tested for the ROS1 gene mutation if a tyrosine kinase inhibitor (TKI) for ROS1 NSCLC were funded; the sequence of wider NSCLC mutation testing if a ROS1 targeted treatment were funded; and the incremental cost of adding ROS1 to a concurrent panel of tests when compared with a separate, subsequent ROS1 test.

10.8. The Subcommittee noted that entrectinib has not been previously considered by PTAC or CaTSoP.

Discussion

10.9. PTAC and PTAC Subcommittees may differ in the advice they provide to Pharmac, including recommendations' priority, due to the committees' different, albeit complementary, roles, expertise, experience, and perspectives.

10.10. The Subcommittee noted that c-ros oncogene 1 (ROS1) gene rearrangement is a rare driver mutation observed in approximately 1–2% of NSCLC patients and is mutually exclusive to other driver mutations more commonly seen in NSCLC such as those affecting the epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) (Davies et al. Clin Cancer Res. 2013;19:4040-5). The Subcommittee noted that ROS1 NSCLC appears to affect younger patients without a history of smoking, with between 10% and 25% of patients presenting with CNS metastases at the time of diagnosis and up to 50% developing CNS metastases at some point during the course of their disease (Chi et al. Cancers (Basel). 2010;2:2100-37).

10.11. The Subcommittee noted that lung cancer is the largest contributor to ethnic inequities in cancer mortality (Teng et al. BMC Cancer. 2016;16:755) and that lung cancer disproportionately affects Māori compared with non-Māori (MoH. 2019). The Subcommittee noted that the proportion of Māori patients with ROS1 NSCLS is unknown; however, it has previously been considered reasonable to assume a similar rate of 1-2%, noting no elevated risk for Māori to account for the increased prevalence of ROS1 NSCLC amongst non-smokers. Furthermore international studies have to date failed to identify any ethnically driven differences in incidence.

10.12. The Subcommittee noted that while patients with ROS1 NSCLC have an enhanced sensitivity to standard chemotherapy, the durability of response to chemotherapy was considered poor, and the toxicity significant. The Subcommittee noted evidence indicating improved response to pemetrexed-based chemotherapies in ROS1 NSCLC patients with evidence of progression free survival (PFS) of approximately 8 months (range 6.4-11 months), however they also noted this evidence involved small patient numbers and was unlikely to be duplicated in the future given the international availability of tyrosine kinase inhibitors for this patient group (Park et al. J Thorac Oncol. 2018;13:1373-82).

10.13. The Subcommittee noted that, unlike EGFR and ALK positive NSCLC's, there are currently no funded treatments In New Zealand that target the ROS1 gene rearrangement; First line treatment for patients with ROS1-positive NSCLC remains platinum-based doublet chemotherapy involving 4 cycles of 3 weekly platinum/pemetrexed, followed by 3 weekly pemetrexed single agent maintenance

in patients who have not progressed on initial treatment. The Subcommittee noted this may be followed with second line chemotherapy with 3 weekly docetaxel, for up to 6 cycles, in patients who remain well enough to receive treatment at disease progression. The Subcommittee noted that patients with a poor performance status, which can result from the symptom burden of advanced lung cancer, would be unlikely to tolerate systemic chemotherapy and this is generally not recommended in these patients.

10.14. The Subcommittee noted that chemotherapy has high toxicity. Patients currently experience Grade III toxicity events at a rate of 43% to 65% (Gandhi et al. N Engl J Med. 2018;378:2078-92). The Subcommittee consider that the proportion of patients who are unfit for standard platinum-based chemotherapy is unknown, as NSCLC is usually diagnosed with late-stage disease, and many patients are not even considered for chemotherapy. The Subcommittee considered that a conservative estimate of the proportion of ROS1 positive NSCLC patients who would be unfit for currently funded treatments to be approximately 20%.

10.15. The Subcommittee considered that, based on ROS1 driver mutations estimated to occur in 1-2% of NSCLC patients, there is likely to be between 10 and 17 patients who may be eligible for ROS1 targeted therapy per year.

10.16. The Subcommittee noted that access to funded biomarker testing differs regionally. This may be due to availability of the tissue as the biopsy sample is used hierarchically for mutation testing after the histology is confirmed, or patient suitability to undergo a tissue biopsy, and that ROS1 tissue-based testing at diagnosis is not currently part of the standard testing panel. The Subcommittee considered that biomarker testing for ROS1 would likely be sequential following testing for ALK and EGFR, and considered that, as testing for ROS1 becomes more prevalent and/or ctDNA blood testing becomes available, the number of patients tested may increase, and that given the low prevalence of disease a small increase in patient numbers eligible for ROS1 targeted therapy may be seen.

10.17. The Subcommittee noted that crizotinib and entrectinib are both multi-targeted inhibitors with different targets and mechanisms of action: crizotinib is an inhibitor of ALK and c-MET as well as ROS1, which acts as a target for p-Glycoprotein; entrectinib is an inhibitor of receptor tyrosine kinases (encoded by the NTRK genes NTRK1, NTRK2 and NTRK3, respectively), ROS1 and ALK. The Subcommittee noted that preclinical studies have indicated the ability of entrectinib to pass through the blood-brain barrier (de la Cruz et al. Cancer Res. 2019;79:3894[Abstract only]) but that here is very little published data regarding the central nervous system (CNS) activity of crizotinib. The subcommittee noted that patients with brain metastases were able to be included in the PROFILE 1001 study and durable responses were seen for patients with ROS1-positive NSCLC with CNS metastases.

10.18. The Subcommittee noted that crizotinib and entrectinib are Medsafe approved for the treatment of patients with ROS1-positive advanced NSCLC with recommended doses of 250 mg orally twice daily and 600 mg orally once daily respectively, continued for as long as the patient is deriving clinical benefit.

Crizotinib

10.19. The Subcommittee noted a Phase I dose-expansion cohort study (PROFILE 1001). This involved 50 patients with ROS1 mutated NSCLC (identified by break-apart FISH and RT-PCR), who had an ECOG score of 0-2, and who had received

crizotinib 250 mg twice daily until disease progression (Shaw et al. N Engl J Med. 2014;371:1963-71).

10.19.1. The Subcommittee noted the median age of participants was 53. 78% were non-smokers and approximately 85% (43/50) had undergone prior treatment, with crizotinib therefore used as first-, second-, and third-line treatment.

10.19.2. The Subcommittee noted that, among the 50 participants, three (6%) had a complete response, 33 (66%) had a partial response and 9 (18%) had stable disease. The Subcommittee noted three patients (6%) experienced progressive disease however considered only one true incidence of disease progression occurred in this cohort noting one tested negative for ROS1 on a follow up scan and the other discontinued treatment due to adverse events within two weeks; however, achieved disease response following subsequent treatment.

10.19.3. The Subcommittee noted the median time to response of 1.7 months with the objective response rate (ORR) of 72% (95% CI 58% to 83%), and the median duration of response of 17.6 months (95% CI, 14.5 to not reached [NR]). The Subcommittee considered that crizotinib was a well-tolerated therapy, with the most common adverse event being slight visual impairment.

10.20. The Subcommittee noted a 2019 update of the PROFILE 1001 trial (Shaw et al. Ann Oncol. 2019;30:1121-26), which included an additional 46 months of follow-up data. The Subcommittee noted that the ORR was 72% (95% CI 58% to 83%), with a median duration of response of 24.7 months and a median overall survival of 51.4 months: representing 79% survival at 12 months, and 51% at 48 months. The Subcommittee considered that, whilst this was non-randomised evidence, it presented a significant difference in durability of response when compared to standard chemotherapy – which resulted in a median progression free survival of five months and median overall survival of approximately 7-13 months.

10.21. The Subcommittee noted a phase II open-label multi-centre study of crizotinib in the treatment of patient with ROS1-positive NSCLC who had received 0-3 previous lines of prior therapy, with or without brain metastases (Wu et al. J Clin Oncol. 2018;36:1405-11). The Subcommittee noted that the median duration of follow-up was 21.4 months with an ORR of 71.7% (95% CI 63.0% to 79.3%) and with 17 (13%) complete responses and 74 (58%) partial responses, and that the median overall survival was reported as 32.5 months, however 59.8% of patients were still in follow-up at the data cut-off, so the Subcommittee considered that this data is immature. The Subcommittee noted that the median time to response was 1.9 months, and that the median progression-free survival was 15.9 months (95% CI 12.9 to 24.0).

10.21.1. The Subcommittee considered HRQoL data collected from the trial using the EORTC quality of life questionnaire to report patient outcomes. and reported a 12% improvement in health-related quality-of-life in cycles 3 to 5, 7, and 10 of the trial, which continued to improve or remain stable through treatment.

10.22. The Subcommittee noted a 2014 study by Solomon et al., which examined the efficacy of crizotinib versus chemotherapy for the treatment of ALK-positive NSCLC (Solomon et al. N Engl J Med. 2014;371:2167-77). The Subcommittee noted that while overall survival was not statistically significantly different, progression free survival was appreciably longer with crizotinib than with chemotherapy (HR 0.45; 95% CI 0.35 to 0.60; P<0.001). The Subcommittee also

noted that quality of life improved with crizotinib compared to chemotherapy, and symptom burden was reduced.

10.23. The Subcommittee also noted the following trials and studies regarding the efficacy of crizotinib in the treatment of NSCLC:

- Shen et al. Cancer Med. 2020;9:3310-18)
- Xu et al. Cancer Med. 2020;9:3328-36
- Zheng et al. Lung Cancer. 2020;147:130-6
- Vuong et al. Target Oncol. 2020;15:589-98

Entrectinib

10.24. The Subcommittee noted an integrated analysis of two phase I studies (ALKA-372-001 open-label, multicentre, dose escalation trial and STARTRK-1 open-label, multicentre safety evaluation) and one phase II study (global basket study STARTRK-2 open-label, multicentre) on the treatment of patients with ROS1 positive NSCLC with entrectinib at a dose of at least 600 mg orally once per day until progression (Dziadziuszko et al. J Clin Oncol. 2021;JCO2003025).

10.25. The Subcommittee noted that 161 patients were included in the trials, with 62% never-smokers, 95% had an ECOG of 0-1 and 62.7% of patients having received more than one prior line of therapy, with up to two prior lines of therapy permitted for trial inclusion. The Subcommittee noted that 56 (34.8%) patients had brain metastases and 46% of patients had received prior radiation, 61% of which were within 2 months of starting entrectinib and considered this complicated the assessment of the impact of entrectinib in treating CNS metastases in ROS-1 NSCLC.

10.25.1. The Subcommittee noted that the median follow-up was 15.8 months (95% CI 10.4 to 22.9) with an ORR of 67.1%, with a median time to response of 4 weeks and a median progression-free survival of 15.7 months (95% CI 11.0 to 21.1).

10.25.2. The Subcommittee noted that patients with brain metastases who had received no prior irradiation, or who had received radiation therapy more than six months prior to trial enrolment, had an ORR of 46% in the brain. However, the Subcommittee considered that patients with previous radiation therapy complicated the assessment of the effect of entrectinib on brain metastases and that more data was needed to ascertain the longer-term effect of entrectinib on brain metastases.

10.25.3. The Subcommittee noted the adverse events reported for entrectinib, with seven patients reporting grade IV toxicity. However, members considered the adverse events reported were easily treated and of low clinical impact.

10.25.4. The Subcommittee also noted the following trials and studies regarding the efficacy of entrectinib in the treatment of NSCLC:

- Drilon et al. Lancet Oncol. 2020;21:261-70
- Barlesi et al. Ann Oncol. 2020;31:s1391-2 (Abstract only)

General

10.26. The Subcommittee considered the evidence available to support ROS1 specific TKI treatment with crizotinib in ROS1 NSCLC to be of moderate strength and quality, and for entrectinib in ROS1 NSCLC to be of moderate quality. The Subcommittee considered that the biological rationale is robust, the parallel data with ALK inhibitors and the clinical interpretation of this data supports the conclusion that ROS1 targeted treatments in ROS1 NSCLC provide a durable response and progression-free survival, substantively superior to chemotherapy, with favourable toxicity. The Subcommittee considered the evidence was compelling and consistent in the context of this disease with low patient numbers meaning that only phase I or II or retrospective cohort studies were viable, without randomised data available. The Subcommittee considered that it is very unlikely that there will be further phase III randomised trials for either of these agents against a chemotherapy comparator, as ROS1 targeted therapies have been approved in other jurisdictions for some time. The Subcommittee noted that crizotinib has been approved by both the PBAC and Scottish Medicines Consortium in July 2018, and in Canada in May 2019, and that entrectinib was approved by the PBAC in March 2020, NICE (UK and Wales) August 2020, Scotland December 2020, and Canada in January 2021.

10.27. The Subcommittee noted that the European Society of Medical Oncology (ESMO) guidelines recommend single agent crizotinib or entrectinib in the first line or second line in patients with stage IV NSCLC with ROS1 rearrangement, and considered this would be the likely treatment paradigm should these agents be funded in New Zealand (ESMO 2020. Accessed March 2021).

10.28. The Subcommittee considered that there is a degree of class-effect for TKIs that target ROS1 in the treatment of ROS1 NSCLC. However, they considered that while the applicant has proposed there is a potential difference between crizotinib and entrectinib due to different effects on brain metastases relating to CNS penetration. The Subcommittee considered that a therapeutic agent that can cross the blood-brain barrier is an attractive option in NSCLC, but that there was currently insufficient evidence that entrectinib is more effective than crizotinib in this setting.

10.29. The Subcommittee considered both crizotinib and entrectinib have suitability advantages over current chemotherapy treatment and may provide health system advantages due to reduced infusion requirements when compared to chemotherapy. The Subcommittee considered the impact of these advantages was difficult to predict, as numbers are very small, and as there may be some patients who progress to chemotherapy following TKI treatment who may have been considered unsuitable for this in the first line. The Subcommittee considered that both crizotinib and entrectinib are well tolerated and are likely to improve progression-free survival, patient quality of life, and median overall survival if they were to be funded for this patient group.

10.30. The Subcommittee considered that ROS1 specific TKIs would best be placed as first-line treatments, and that a ROS1 targeted TKI should be funded with a high priority.

11. Atezolizumab in combination with nab-paclitaxel for triple-negative breast cancer

Application

11.1. The Subcommittee considered the application from Roche for the use of atezolizumab (Tecentriq) in combination with nab-paclitaxel for the treatment of advanced or metastatic triple-negative breast cancer (TNBC) with programmed death-ligand 1 (PD-L1) expression ≥ 1%, following PTAC's review of this application in November 2020.

Recommendation

11.2. The Subcommittee **recommended** that the application for atezolizumab (Tecentriq) in combination with nab-paclitaxel for the treatment of advanced or metastatic triple-negative breast cancer (TNBC) with PDL1 expression ≥ 1% be **deferred**, pending further published data of long-term follow-up from the IMpassion131 and IMpassion132 trials.

11.2.1. In making this recommendation, the Subcommittee considered that the data available, with up to 18-month median follow-up from a single clinical trial, suggested there was activity in this combination but that the benefits were modest. The Subcommittee considered that more mature, published data from the IMpassion131 and IMpassion132 trials after longer durations of follow-up may strengthen the evidence that demonstrates potential survival benefit of atezolizumab in this combination regimen for triple-negative breast cancer, however members acknowledged that this data may not be forthcoming.

11.3. In making this recommendation, the Subcommittee also considered the high health need of this patient population with limited suitable treatment options; the limitations and uncertainty of the trial data available; the evidence for use of this regimen in the first line setting with nab-paclitaxel only; and the potential high cost of this combination regimen which is not funded in New Zealand.

Background

11.4. PTAC and PTAC Subcommittees may differ in the advice they provide to Pharmac, including recommendations' priority, due to the committees' different, albeit complementary, roles, expertise, experience, and perspectives.

11.5. The Subcommittee noted that, in November 2020, PTAC reviewed the application for atezolizumab in combination with nab-paclitaxel for the treatment of unresectable locally-advanced or metastatic triple-negative breast cancer, and recommended it be declined due to evidence of a lack of overall survival benefit (compared with placebo plus nab-paclitaxel) in a key clinical trial (IMpassion130) and limitations of the PD-L1 positive subgroup analysis of that trial.

11.6. The Subcommittee noted that, in making its recommendation, PTAC considered the high unmet health need of patients with triple-negative breast cancer including the lack of effective funded treatment options for triple-negative breast cancer; the novel approach of immune checkpoint inhibitor treatment in combination with chemotherapy for triple-negative breast cancer; the challenges associated with PD-L1 testing in New Zealand; the limited relevance of the treatment regimen (including nab-paclitaxel) to the New Zealand patient population; and the lack of quality of life data, which affected the ability of PTAC to assess of the supplier's therapeutic claims.

11.7. The Subcommittee noted that PTAC had suggested that CaTSoP's advice be sought, including advice on; the use of paclitaxel instead of nab-paclitaxel with atezolizumab in this indication, the treatment paradigm for patients with triple-negative breast cancer in New Zealand, the impact paclitaxel and corticosteroid premedication may have on immunotherapy activity, the results of the IMpassion131 trial, and patient number estimates for atezolizumab in this setting.

Discussion

11.8. The Subcommittee noted that more than 3,000 people are diagnosed with breast cancer each year, with approximately 25% diagnosed with metastatic disease and more than 600 women die from breast cancer annually. The Subcommittee noted that there is higher incidence in Māori women than non-Māori women (age-standardised incidence rate for females ≥25 years 175.1 per 100,000 population vs 134.8 per 100,000 per population in 2013-15) and that Māori have worse survival with advanced breast cancer compared to other ethnic groups (Wai 2575 Māori Health Trends Report. Ministry of Health, 2019).

11.9. The Subcommittee noted that triple-negative breast cancer accounts for 15-20% of all breast cancer but has the worst prognosis out of all breast cancer subtypes. The Subcommittee was made aware of New Zealand data that indicates the median overall survival for patients with triple-negative breast cancer is estimated to be 6.6 months (Insights into living – and dying – with advanced breast cancer in New Zealand. New Zealand Breast Cancer Foundation, 2018).

11.10. The Committee was made aware of international data that as reported a variable median overall survival of breast cancer (any subtype) of up to 18 months (Gobbini et al. Eur J Cancer. 2018;96:17-24; Yardley et al. Ann Oncol. 2018;29:1763-70; Miles et al. Ann Oncol. 2013;24:2773-80) and data reporting median progression-free survival of patients with metastatic triple-negative breast cancer from 2.9 months to 7.7 months with median overall survival ranging from 11.0 months to 12.6 months (Khosravi-Shahi et al. Asia Pac J Clin Oncol. 2018;14:32-9).

11.11. The Subcommittee considered that people with triple-negative breast cancer have a very high health need due to the rapid progression of this disease and lack of effective treatment options.

11.12. The Subcommittee considered that approximately 40% of patients with triple-negative breast cancer will have PD-L1 expression of 1% or greater, equivalent to 6.6 to 8% of all breast cancers in New Zealand (180-240 patients/year).). The Subcommittee considered that genetic counselling may be undertaken for patients under 50 years of age or those with a family history of breast cancer; however, considered that not all patients would be tested for BRCA mutation status and PD-L1 testing would not be routinely undertaken, as these currently do not influence the choice of funded treatment options.

11.13. The Subcommittee considered that patients whose disease is not rapidly progressive receive sequential single-agent chemotherapy, generally followed by an anthracycline (ie doxorubicin or epirubicin), taxane (ie paclitaxel or docetaxel) or vinorelbine if there was no prior exposure to these agents. The Subcommittee noted there is no preferred chemotherapy regimen for this disease and regimens can differ between treating clinicians and treating centres, although paclitaxel with gemcitabine is used less commonly in this population in New Zealand.

11.14. The Subcommittee noted that the key evidence for atezolizumab in combination with nab-paclitaxel was from the multi-centre, phase III, randomised (1:1), placebo controlled, double-blind IMpassion130 trial of 902 patients from 246 centres excluding New Zealand with untreated locally advanced or metastatic triple-negative breast cancer, in which patients received atezolizumab with nab-paclitaxel or placebo with nab-paclitaxel until disease progression or intolerable toxicity (Schmid et al. N Engl J Med. 2018;379:2108-21; Schmid et al. Lancet Oncol. 2020;21:44-59). The Subcommittee noted that the initial results were reported after median follow-up of 12.9 months, with updated results reported after median follow-up of 18.5 months in the atezolizumab group and 17.5 months in the placebo group.

11.14.1. The Subcommittee noted that co-primary endpoints in the trial's whole intention-to-treat (ITT) population (n = 902) and the PD-L1 positive ≥1% retrospectively-identified subgroup (N = 369) were progression-free survival (PFS) and overall survival (OS), tested hierarchically, and that the trial included secondary endpoints as expected. The Subcommittee noted that the initial sample size was extended to the 902 patients to enable overall survival assessment with the type 1 error (0.05) split between analyses of PFS (0.01) and OS (0.04).

11.14.2. The Subcommittee noted that IMpassion130 used the Ventana SP142 assay for PD-L1 status, which is different to the assays and scoring methods used in clinical trials for other immunotherapy agents (eg the combined positive score [CPS] used with pembrolizumab). The Subcommittee considered that PD-L1 assays and scoring methods may not be directly interchangeable, presenting challenges in their use and interpretation alongside potential treatment options, as discussed in previous CaTSoP meeting records. The Subcommittee considered that the patient groups were similar between trial treatment arms and that the proportion of PD-L1 positive cases was similar to that reported in the literature.

11.14.3. The Subcommittee noted statistically significant differences in PFS in both the whole trial's ITT population (7.2 months atezolizumab + nab-paclitaxel vs 5.5 months placebo + nab-paclitaxel, hazard ratio (HR) 0.80, 95% confidence interval (CI) 0.69 to 0.92, P=0.002) and PD-L1 positive subgroup (7.5 months atezolizumab + nab-paclitaxel vs 5.0 months placebo + nab-paclitaxel, HR 0.62, 95% CI 0.49 to 0.78, P<0.001) (Schmid et al. N Engl J Med. 2018;379:2108-21). The Subcommittee noted that these results reported absolute differences that were small, with gains of about two months even in the PD-L1 positive subgroup (who received greater benefit than the whole ITT population), but considered these results could be considered clinically important given the poor prognosis otherwise, and considered this probably precipitated the accelerated approval of this regimen in other jurisdictions.

11.14.4. The Subcommittee noted that the updated IMpassion130 results reported 24-month PFS in the whole ITT population of 10% (95% CI 7 to 13) with atezolizumab + nab-paclitaxel vs 6% (95% CI 4 to 9) with placebo + nab-paclitaxel. The Subcommittee noted that 24-month PFS in the PD-L1 subgroup was 12.4% (95% CI 6.5 to 18.3) with atezolizumab + nab-paclitaxel vs 7.4% (95% CI 2.8 to 12.0) with placebo + nab-paclitaxel (Schmid et al. Lancet Oncol. 2020;21:44-59). The Subcommittee considered that the PFS benefit was predominantly seen in the PD-L1 positive group and it was unclear whether other subgroups (including some groups with small patient numbers) had a difference in benefit.

11.14.5. The Subcommittee noted that the difference in OS in the whole ITT population was not statistically significant (21.0 months atezolizumab + nab-paclitaxel vs 18.7 months placebo + nab-paclitaxel, stratified HR 0.86, 95% CI 0.72 to 1.02, P=0.0777) and therefore the OS in the PD-L1 subgroup was not formally testable nor tested, although a difference of 7 months was reported for the PD-L1 positive subgroup (25.0 months atezolizumab + nab-paclitaxel vs 18.0 months placebo + nab-paclitaxel, stratified HR 0.71, 95% CI 0.54 to 0.93). Members considered that the 7-month difference in OS for PD-L1 positivity may be clinically meaningful, although they noted that the benefit from this regimen was only reported in a single trial.

11.14.6. The Subcommittee noted that crossover in IMpassion130 was not substantial (4-6%), especially considering the few other available treatment options and rapidly progressive disease often seen in this patient group.

11.14.7. The Subcommittee noted that response rates were slightly higher in the PD-L1 positive subgroup (58.9% atezolizumab + nab-paclitaxel vs 42.6% placebo + nab-paclitaxel, P=0.002) than in the whole ITT population (56.0% atezolizumab + nab-paclitaxel vs 45.9% placebo + nab-paclitaxel, P=0.002), but no evidence of statistical heterogeneity between the PD-L1 positive and residual PD-L1 negative subgroups had been presented.

11.14.8. The Subcommittee noted that adverse events led to discontinuation in 15.9% of patients who received atezolizumab + nab-paclitaxel (of which 6.4% led to discontinuation of atezolizumab) and in 8.2% of patients who received placebo + nab-paclitaxel (of which 1.4% led to discontinuation of placebo) (Table S3; Supplementary Appendix). The Subcommittee considered that the adverse events initially reported in IMpassion130 and in the updated publication were as expected for this regimen, with no additional safety signals identified.

11.14.9. The Subcommittee noted that IMpassion130 reported no significant difference in the time to deterioration of health-related quality of life and functioning with the addition of atezolizumab to nab-paclitaxel, suggesting that atezolizumab did not detrimentally impact quality of life in this population (Adams et al. Ann Oncol. 2020;31:582-9).

11.15. The Subcommittee noted that Pharmac had received correspondence in February 2021 from Roche in response to the November 2020 PTAC record, which noted the non-significant OS result in the IMpassion130 whole ITT population. The Subcommittee noted that Roche had included a published meta-analysis that reported PFS to be a surrogate for OS in advanced or metastatic triple-negative breast cancer, mainly concentrating on benefits in the PD-L1 positive population who received a longer duration of response than patients with PD-L1 negative disease (Hirai et al. Breast Cancer Res Treat. 2020;181:189-98). However, the Subcommittee considered there were difficulties using progression free survival as a surrogate for overall survival when statistical significance was not demonstrated in the updated data and considered that the information did not materially change the view that the lack of significant OS in the IMpassion130 overall ITT population was disappointing.

11.16. The Subcommittee noted that the IMpasson131 trial investigating the combination of atezolizumab with paclitaxel in triple-negative breast cancer reported a small difference in PFS that was not statistically significant, and did not report a difference in overall survival (Miles et al. Ann Oncol. 2020;31 Suppl_4:S1147-8). The Subcommittee noted that the United States (US) Food and Drug

Administration (FDA) made a public alert notification based on the results of this trial in August 2020 and subsequently updated the US Prescribing Information with a warning that paclitaxel should not be used instead of nab-paclitaxel with atezolizumab in this setting as the same benefit cannot be assumed.

11.17. The Subcommittee noted that the US FDA Oncologic Drugs Advisory Committee (ODAC) is reviewing the accelerated approval status of atezolizumab with nab-paclitaxel for this indication and voted in April 2021 to maintain approval due to the health need of this population. The Subcommittee noted that this consideration was ongoing and there was a concern about the lack of further studies to confirm benefit. The Subcommittee was made aware of a recent publication describing accelerated approvals where long-term outcomes are uncertain, including atezolizumab with nab-paclitaxel, which are currently under review (Beaver et al. N Engl J Med. 2021;384:e68. doi: 10.1056/NEJMp2104846. Epub 2021 Apr 21).

11.18. The Subcommittee noted that nab-paclitaxel has been discussed by CaTSoP on previous occasions including in the context of metastatic breast cancer (refer to the Pharmac Application Tracker). The Subcommittee considered that there is a theoretical potential effect of paclitaxel and corticosteroid premedication on immunotherapy activity, although the reasons for the difference in outcomes with paclitaxel and atezolizumab compared with nab-paclitaxel and atezolizumab remain unclear. Based on the totality of evidence available, the Subcommittee considered there was no role for paclitaxel with atezolizumab in this setting. The Subcommittee considered that Pharmac could seek further clinical advice regarding nab-paclitaxel with input from breast cancer and gastrointestinal cancer special interest groups.

11.19. The Subcommittee noted that the proposed addition of atezolizumab with nab-paclitaxel into the treatment paradigm for patients whose triple-negative breast cancer has PD-L1 expression of 1% or greater would require the addition of PD-L1 testing for all patients with metastatic TNBC. The Subcommittee considered that, if atezolizumab and nab-paclitaxel were funded in this setting, patients with PD-L1 positive disease would likely use this combination therapy in the first line, and patients with PD-L1 negative disease would be offered sequential single-agent chemotherapy, and subsequent combination treatment with carboplatin and gemcitabine may be considered.

11.20. The Subcommittee considered that, if funded, atezolizumab would need to be used in combination with nab-paclitaxel (not paclitaxel) for triple-negative breast cancer and that it would be used as a first-line therapy for metastatic disease, as evidence for its use is only in this setting. The Subcommittee considered treatment would be until disease progression, after which patients would be expected to receive taxanes/vinorelbine therapy; however members noted there to be limited treatment options for aggressive and progressed disease.

11.21. The Subcommittee considered that the biology of this disease requires treatment to commence within weeks, therefore there would not be a ready group of untreated prevalent patients awaiting treatment. The Subcommittee considered that the supplier estimate of eligible patients, based on epidemiological data that assumed 40% of incident patients with a metastatic TNBC diagnosis will have positive PD-L1 expression, was too high. Based on extrapolation from current regional data of metastatic TNBC diagnoses, the Subcommittee considered 30-35 patients per year nationwide would be a more appropriate estimate.

11.22. The Subcommittee noted the potential high cost of this combination regimen, which includes nab-paclitaxel as another treatment that is not funded in New Zealand. The Subcommittee also noted that immunotherapy toxicities occur in a small number of patients but require significant and intensive health system resource for their management. The Subcommittee noted that adding immunotherapy treatment would increase infusion service resource for treatment administration, although noted that nab-paclitaxel has a shorter infusion duration than paclitaxel.

11.23. The Subcommittee noted that the PD-L1 threshold for positivity (1%) may be affected by inter-laboratory variability and therefore this threshold may be less meaningful and considered that this is not an optimal target for identifying patients who will benefit. The Subcommittee considered that Pharmac staff could engage with representatives of laboratories in New Zealand for advice regarding complex and/or variable testing requirements.

Summary

11.24. Overall, the Subcommittee noted that the body of evidence for atezolizumab and nab-paclitaxel in triple-negative breast cancer is contradictory and considered that although the IMpassion130 data suggests there is activity in this combination, it provided only modest benefits. The Subcommittee considered that the pending FDA ODAC decision on approval of this regimen was concerning and considered that longer-term, published, follow-up data of the IMpassion131 and IMpassion132 trials would help inform its assessment of this regimen in addressing the health need of people with triple-negative breast cancer.

11.25. The Subcommittee noted that Pharmac had also received correspondence from Merck Sharpe and Dohme in response to the November 2020 PTAC record, highlighting the Keynote-355 trial of pembrolizumab in combination with the trial investigators' choice of chemotherapy (paclitaxel, nab-paclitaxel or gemcitabine with carboplatin) in the same population with TNBC, although Keynote-355 used a different PD-L1 assay (using CPS score) compared with IMpassion130. The Subcommittee noted that data from Keynote-355 suggested that both paclitaxel and nab-paclitaxel were able to be used in combination with pembrolizumab (Cortes et al. Lancet. 2020;396:1817-28).