Cancer Treatments Subcommittee of PTAC (CaTSoP) meeting held at PHARMAC on 13 April 2018 (minutes for web publishing)

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

The Cancer Treatments Subcommittee may:

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

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

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

These Subcommittee minutes will be reviewed by PTAC at its 9 & 10 August 2018 meeting.

1. Correspondence and Matters Arising

BRAF/MEK treatments

1.1. The Subcommittee noted that, in August 2017, PHARMAC had received a funding application for dabrafenib and trametinib for patients with advanced, BRAF mutant melanoma prepared by the clinicians comprising the Melanoma NZ clinical advisory group; and a letter in support of the funding application for vemurafenib and cobimetinib from Melanoma Network New Zealand.

1.2. The Subcommittee noted that in summary the submission communicated the authors opinion that there is value in these treatments as a first-line treatment for both inoperable advanced BRAF mutant melanoma and in a 'rapidly progressive' disease setting where there is insufficient time for funded immunotherapy to salvage patients with metastatic disease involving the brain, and for those with poor performance status excluded from funded PD1 inhibitor treatment.

1.3. The Subcommittee noted that all evidence referenced in the submission had been previously considered during PTAC and CaTSoP reviews of the funding applications from the suppliers for these combination regimens.

1.4. The Subcommittee noted that the funding of BRAF inhibitors had been considered by both PTAC and CaTSoP on a number of occasions, most recently by PTAC in August 2017 where it had reiterated the previous recommendation to decline funding for these treatments either as monotherapy or in combination.

1.5. The Subcommittee acknowledged there remains an unmet health need for patients with advanced melanoma and an ECOG score of >2, however, there is currently a lack of evidence to support the use of BRAF/MEK inhibitors in this setting.

1.6. The Subcommittee considered that questions remain regarding the appropriate use of these treatments which would likely be addressed as the evidence develops for their potential use such as in combination regimens or a second-line setting. The Subcommittee noted that it was interested to review new published evidence once it became available.

2. Myeloma Treatments Review

Application

2.1. The Subcommittee reviewed:

- A funding application from Janssen for daratumumab to be used in combination with bortezomib and dexamethasone for the treatment of patients with relapsed/refractory multiple myeloma (MM).

- A funding application from Celgene seeking to extend the current Special Authority criteria for lenalidomide to include patients with newly diagnosed MM who are ineligible for autologous stem cell transplant (ASCT) (first-line treatment, ASCT ineligible). In August 2017, this application was reviewed by PTAC who sought advice from CaTSoP on expected patient numbers, Special Authority criteria, the comparative health benefits and risks versus bortezomib-containing regimens, and the optimal place for lenalidomide in the therapeutic landscape.

- A funding application from a haematologist for lenalidomide as maintenance therapy following first-line ASCT in patients with MM.

- A funding application from a haematologist for lenalidomide for the treatment of patients with newly diagnosed MM who are eligible for ASCT (first-line treatment, ASCT-eligible).

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

Recommendation

2.3. The Subcommittee **recommended** that a decision regarding the funding of daratumumab for the treatment of patients with relapsed/refractory MM be deferred until longer-term follow-up data from the relevant clinical trials are made available.

2.4. The Subcommittee **recommended** that lenalidomide as first-line treatment for ASCT-ineligible patients with MM be listed only if cost-neutral to the health sector when compared with bortezomib containing regimens.

2.5. The Subcommittee **recommended** that lenalidomide as maintenance treatment for patients with MM following first-line ASCT be listed with a medium priority.

2.6. The Subcommittee **recommended** that a decision regarding the funding of lenalidomide as first-line treatment in ASCT-eligible patients with MM be deferred until additional data are available.

Discussion

General MM discussion

2.7. The Subcommittee noted that MM is a relatively rare haematological malignancy that predominantly affects older individuals. MM is not considered curable; treatment goals include delaying disease progression, extending duration of life, and improving quality of life.

2.8. The Subcommittee noted that the incidence of MM in New Zealand is similar to that of Australia, the UK, and the US. The Subcommittee noted the age-standardised incidence rate for Māori was 7.6 cases per 100,000; or approximately double that of the non-Māori populations (4.9 cases per 100,000), thought to be primarily due to a younger age at diagnosis.

2.9. The Subcommittee noted that the survival of patients with MM in New Zealand has steadily increased over the last two decades (1995-1998: median overall survival [OS] 19.4 months, 5-year OS 22%; 2011-2014: median OS 47.7 months, 5-year OS 45%), likely to be partly due to the introduction of improved targeted therapies.

2.10. The Subcommittee noted the increasing use of ASCT as a first-line treatment in eligible patients which is widely available in New Zealand at a cost of $30,000-60,000. The Subcommittee noted ASCT is effective following first relapse in those with a long remission duration. The Subcommittee noted survival in New Zealand is similar to Australia, the UK, and the US.

2.11. The Subcommittee noted that bortezomib-containing regimens are currently the most commonly used first-line treatment in New Zealand, with the combination of bortezomib, cyclophosphamide, and dexamethasone (CyBorD) favoured. Due to Special Authority restrictions on lenalidomide that limit its use to third line (or second line if peripheral neuropathy develops), thalidomide-containing regimens are the most commonly utilised second-line therapy.

2.12. The Subcommittee noted that, in addition to the new funding applications for MM to be considered at this meeting, bortezomib retreatment (considered prior to the funding of

lenalidomide) and pomalidomide have previously been considered by CaTSoP and/or PTAC and remain unfunded.

2.13. The Subcommittee noted that Medsafe registration for carfilzomib for the treatment of relapsed/refractory MM is underway, and that a funding application will likely be submitted in 2018. The Subcommittee noted other treatments including ixazomib and panobinostat, as well as an array of treatment combinations undergoing clinical trials, are likely to result in funding applications in the future. More effective combinations and treatment until progression are likely to result in high treatment costs, especially in the first line setting.

2.14. The Subcommittee considered that developing an optimal treatment pathway considering both costs and benefits in MM is complex. The Subcommittee considered that there is need for a wider consultation with relevant clinicians on a preferred national treatment algorithm but noted it would not be an easy task to get a consistent and objective New Zealand specific view, especially as net treatment costs would need to remain confidential.

Daratumumab for the treatment of patients with relapsed/refractory multiple myeloma

2.15. The Subcommittee noted that daratumumab (Darzalex) is a humanised monoclonal antibody that targets the CD38 protein on malignant plasma cells, causing cell death by antibody mediated cytotoxicity.

2.16. The Subcommittee noted that daratumumab has been approved for use in two indications in New Zealand: in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of patients with MM who have received at least one prior therapy; and as monotherapy for the treatment of patients with MM who have received at least three prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent or who are refractory to both a PI and an immunomodulatory agent. It was noted that the supplier has, at this stage, only submitted an application for daratumumab in combination with bortezomib and dexamethasone for patients with relapsed/refractory MM.

2.17. The Subcommittee noted that daratumumab in combination with bortezomib is administered as an intravenous infusion weekly from Week 1 to 9, every 2 weeks from Week 10 to 24, and every 4 weeks from Week 25 onwards until disease progression. The Subcommittee considered that the administration of daratumumab is relatively involved; a long infusion time is required, and the agent has been associated with infusion-related reactions.

2.18. The Subcommittee noted that the key clinical evidence for the use of daratumumab in combination with bortezomib or lenalidomide based regimens in patients with relapsed/refractory MM comes from the CASTOR trial (Palumbo A, et al. N Engl J Med. 2016;375:754-66) and the POLLUX trial (Dimopoulos MA, et al. N Engl J Med. 2016;375:1319-31), respectively.

2.19. The Subcommittee noted that in the CASTOR trial, daratumumab in combination with bortezomib and dexamethasone was compared with bortezomib and dexamethasone alone. In the POLLUX trial, daratumumab in combination with lenalidomide and dexamethasone was compared with lenalidomide and dexamethasone alone.

2.20. The Subcommittee noted that in the CASTOR trial, 498 patients were randomly assigned 1:1 to receive daratumumab in combination with bortezomib and dexamethasone (n = 251) or bortezomib and dexamethasone alone (n = 247). The 12-month PFS rate was 60.7% in the daratumumab group and 26.9% in the control group. The Subcommittee considered that the PFS benefit was maintained across subgroups, although less reliably in patients who had received more than three lines of prior therapy. The overall response rate (ORR) was 82.9% in the daratumumab group and 63.2% in the control group (P<0.001). The ORR in patients with a very good partial

response or better was 59.2% in the daratumumab arm and 29.1% in the control arm (P<0.001).

2.21. The Subcommittee noted that in the POLLUX trial, 569 patients were randomly assigned 1:1 to receive daratumumab in combination with lenalidomide and dexamethasone (n = 286) or lenalidomide and dexamethasone alone (n = 283). The 12-month PFS rate was 83.2% in the daratumumab group and 60.1% in the control group. The Subcommittee considered that the PFS benefit was maintained across subgroups, although less reliably in patients who had received more than three lines of prior therapy. The ORR was 92.9% in the daratumumab group and 76.4% in the control group (P<0.001). The ORR in patients with a very good partial response or better was 75.8% in the daratumumab group and 44.2% in the control group (P<0.001).

2.22. The Subcommittee considered that the HR for the median PFS in the POLLUX trial was 0.37 which is substantially lower than that seen for other agents investigated in relapsed/refractory MM, including carfilzomib (HR 0.69; Stewart AK, et al. N Engl J Med. 2015;372:142-52), ixazomib (HR 0.74; Moreau P, et al. N Engl J Med. 2016;374:1621-34), and elotuzumab (HR 0.7; Lonial S, et al. N Engl J Med. 2015;373:621-31).

2.23. The Subcommittee noted that the patient populations in CASTOR and POLLUX were similar. Both included patients with relapsed or refractory MM who had received at least one previous line of therapy. Patients were excluded if they had relapsed while on the agent used as the control treatment in each trial respectively. The Subcommittee noted that the median follow-up period was 7.4 months in CASTOR and 13.5 months in POLLUX.

2.24. The Subcommittee considered that the 12-month PFS rate and response rates were higher in daratumumab-treated patients in POLLUX compared with CASTOR, but that the HRs were similar. It was also considered that the control arm of CASTOR had a worse outcome than the control arm of POLLUX. The Subcommittee considered that while this signals that daratumumab may be best used in combination with lenalidomide and dexamethasone, the result was complicated by prior treatment with the trial backbone therapy; in CASTOR, 66% of the patients had received previous treatment with bortezomib, whereas in POLLUX, only 18% of patients had received previous treatment with lenalidomide.

2.25. The Subcommittee considered that despite the prolongation of PFS in the daratumumab group, there were no observable difference in median OS between the daratumumab and control groups, but the Subcommittee acknowledged a significant difference in OS was unlikely to be observable in these interim results. The Subcommittee considered that PFS is regarded as a legitimate marker of benefit in MM.

2.26. The Subcommittee noted that bortezomib is only funded in New Zealand for patients with relapsed/refractory MM who have not received prior funded treatment with bortezomib. It was noted that if daratumumab was to be funded for use in combination with bortezomib and dexamethasone in the relapsed/refractory setting, the funding criteria for bortezomib may need to be changed.

2.27. The Subcommittee noted that both CASTOR (64% of the 295 planned events for the final analysis) and POLLUX (57% of the 295 planned events for the final analysis) had been published as interim analyses. The Subcommittee noted that the CASTOR and POLLUX trials are closed, but patient follow-up will continue and further data updates are expected. The Subcommittee was surprised that some of this data was not yet available for review given the publication dates of the interim analyses.

2.28. The Subcommittee considered that while the evidence regarding the efficacy of daratumumab in combination with bortezomib and dexamethasone (and lenalidomide and dexamethasone) for relapsed/refractory MM is promising, longer-term follow up data are required to confirm the significance of the results.

Lenalidomide for the treatment of patients with newly diagnosed, ASCT-ineligible multiple myeloma (first-line, ASCT-ineligible)

2.29. The Subcommittee noted that PTAC has previously considered a funding application for lenalidomide for newly diagnosed MM in ASCT-ineligible patients and agreed their minutes an accurate summary (PTAC minutes 2017-08). At the time, PTAC recommended that lenalidomide be funded for this indication only if cost-neutral to the health sector compared with bortezomib containing regimens in the first-line setting. PTAC also recommended that the funding application be referred to CaTSoP for further advice regarding patient numbers, the Special Authority criteria, the comparative health benefits and risks versus bortezomib-containing regimens, and the optimal place for lenalidomide in the therapeutic landscape.

2.30. The Subcommittee noted that lenalidomide is registered in New Zealand for the treatment of patients with newly diagnosed MM who are ineligible for ASCT and patients with previously treated MM, in combination with low-dose dexamethasone. Lenalidomide is initiated at a starting dose of 25 mg orally one daily on Days 1-21 of repeated 28-day cycles. It was noted that lenalidomide is only funded for use in combination with dexamethasone for MM in the third-line relapsed/refractory setting, and in the second-line for patients who develop severe, dose-limiting peripheral neuropathy with either bortezomib or thalidomide.

2.31. The Subcommittee noted that in New Zealand, approximately 80% of patients with newly diagnosed MM receive first-line treatment with subcutaneous bortezomib-based regimens. The Subcommittee noted that the standard of care in New Zealand for the majority of older non-transplantable patients includes treatment with CyBorD. If bortezomib is considered too difficult to manage (frequent visits to hospital and possibility of increased adverse reactions and lower efficacy in very old patients), a melphalan prednisone and thalidomide (MPT) combination tends to be used.

2.32. The Subcommittee considered that all patients eligible for ASCT in the first line setting are likely to receive one.

2.33. The Subcommittee considered the potential suitability benefit of the proposed lenalidomide treatment regimen that consists of oral tablets only. The Subcommittee noted that lenalidomide access was by restricted distribution program (i-access).

2.34. The Subcommittee noted that the key clinical evidence for the use of lenalidomide in patients with newly diagnosed ASCT-ineligible MM comes from the Phase 3 FIRST trial (primary analysis: Benboubker L, et al. N Engl J Med. 2014;371:906-17). The Subcommittee noted that since PTAC considered the application, the final analysis of survival outcomes in the FIRST trial have been published (Facon T, et al. Blood. 2018;131:301-10).

2.35. The Subcommittee noted that in the FIRST trial, 1623 patients with previously untreated, symptomatic, and measurable MM who were ineligible for stem-cell transplantation were randomly assigned 1:1:1 to treatment with lenalidomide plus dexamethasone (Rd) until disease progression (28-day cycles; n = 535), Rd for 72 weeks (18 cycles; n = 541), or MPT for 72 weeks (n = 547). The Subcommittee noted that at the time of the primary analysis, the median duration of follow-up among surviving patients was 37.0 months. The median PFS was 25.5 months for continuous Rd, 20.7 months for 18 cycles of Rd, and 21.2 months for MPT.

2.36. The Subcommittee noted that at the time of the final analysis, the median duration of follow-up for surviving patients was 67 months. The Subcommittee considered that the PFS results were consistent with those of the primary analysis. The median PFS was 26.0 months for continuous Rd, 21.0 months for 18 cycles of Rd, and 21.9 months for MPT (continuous Rd vs MPT: HR 0.69, 95% CI 0.59-0.79, P<0.00001; continuous Rd vs 18 cycles of Rd: HR 0.70, 95% CI, 0.60-0.81). The median OS was 59.1 months for continuous Rd, 62.3 months for 18 cycles of Rd, and 49.1 months for MPT (continuous

Rd vs MPT: HR 0.78, 95% CI 0.67-0.92, P=0.0023: continuous Rd vs 18 cycles of Rd: HR 1.02, 95% CI 0.86-1.20).

2.37. The Subcommittee noted that the median PFS for patients with partial response or better was 33.2 months for continuous Rd, 23.1 months for 18 cycles of Rd, and 25.8 months for MPT. The median PFS for patients with very-good partial response or better was 52.5 months for continuous Rd, 30.0 months for 18 cycles of Rd, and 31.8 months for MPT. The Subcommittee considered that this indicates that patients should receive lenalidomide continuously until relapse.

2.38. The Subcommittee considered that at the time of the final analysis, continuous Rd was favoured over MPT for PFS and OS for the majority of subgroups analysed. Patients with high-risk cytogenetics possibly benefited less, but patient numbers were small.

2.39. The Subcommittee noted that at the time of the final analysis, the incidence of second primary malignancies was 7% in the continuous Rd group, 7% in the 18 cycles of Rd group, and 9% in the MPT group.

2.40. The Subcommittee noted that at the time of the final analysis, the median time to next antimyeloma treatment was 36.7 month in the continuous Rd group, 28.5 months in the 18 cycles of Rd group, and 26.7 months in the MPT group.

2.41. The Subcommittee noted that an analysis of health-related quality of life of patients in the FIRST trial demonstrated that treatment with Rd was associated with superior quality of life compared with MPT (Delforge M, et al. Haematologica. 2015;100:826-33).

2.42. The Subcommittee also reviewed the results of a related trial which investigated the combination of bortezomib with lenalidomide and dexamethasone in patients with newly diagnosed MM (Durie et al. Lancet 2017; 389: 519–27). Within this trial, 525 patients with newly diagnosed MM who were not planned for immediate ASCT were randomly assigned 1:1 to treatment with Rd or bortezomib plus Rd (VRd). The Subcommittee noted that compared with the FIRST trial, the participants were younger and many (69%) were considered transplant eligible. Median follow-up was 55 months. Median PFS was 43 months in the VRd group and 30 months in the Rd group (stratified HR 0.712; 96% Wald CI 0.56-0.906; one-sided P-value 0.0018). The median OS was 75 months in the VRd group and 64 months in the Rd group (HR 0.709; 95% Wald CI 0.524-0.959; two-sided P value 0.0250). All participants received thromboembolic prophylaxis.

2.43. The Subcommittee considered that there is high quality evidence demonstrating that lenalidomide provides a health benefit in patients with newly diagnosed ASCT-ineligible MM. The Subcommittee considered that there are no additional risks compared to non-bortezomib–based regimens.

2.44. The Subcommittee considered that the subsets of ASCT-ineligible patients that would benefit most from the funding of lenalidomide would include those with standard risk cytogenetics, those for whom travel is an issue (bortezomib requires outpatient subcutaneous administration; lenalidomide is oral), patients with neuropathy, and elderly patients.

2.45. The Subcommittee considered that, with the evidence available, it is difficult to compare the health benefits and risks of lenalidomide and bortezomib-containing regimens, but it was reasonable at this stage to consider they have the same or similar benefits.

2.46. The Subcommittee considered that the uptake of lenalidomide would be rapid.

Lenalidomide for maintenance treatment following frontline ASCT in patients with multiple myeloma (second-line)

2.47. The Subcommittee noted that there are a number of agents either already in use internationally or under development for post-transplant maintenance therapy in MM, including ixazomib, carfilzomib, elotuzumab, vorinostat, and panobinostat (Sengsayadeth S, et al. Blood Cancer J. 2017;7:e545).

2.48. The Subcommittee considered that most drugs for maintenance therapy are now used in triplet combinations, often including a proteasome inhibitor and/or an immunomodulatory drug.

2.49. The Subcommittee noted that the key clinical evidence for the use of lenalidomide as maintenance therapy after ASCT comes from three clinical trials (CALGB, McCarthy PL, et al. N Engl J Med. 2012;366:1770-81; GEMIMA, Palumbo A, et al. N Engl J Med, 2014;371:895-905; IFM, Attal M, et al N Engl J Med. 2012;366:1782-91). The results of these trials were pooled in a meta-analysis conducted at the request of the US Food and Drug Administration to evaluate the efficacy and safety of post-ASCT lenalidomide maintenance in patients with newly diagnosed MM (McCarthy PL, et al. J Clin Oncol. 2017;35:3279-89).

2.50. The Subcommittee noted that patients enrolled in the CALGB and IFM trials could have received any induction regimen, whereas patients enrolled in the GIMEMA trial received lenalidomide-based induction therapy.

2.51. The Subcommittee noted that patients enrolled in the CALGB and IFM trials were randomly assigned to maintenance therapy with lenalidomide 10 mg per day increasing to 15 mg per day after 3 months, or placebo. The patients in the GIMEMA trial were randomly assigned to maintenance therapy with lenalidomide 10 mg or no maintenance therapy (observation).

2.52. The Subcommittee noted that data from 1208 patients were pooled in the meta-analysis (lenalidomide maintenance, n = 605; placebo/observation, n = 603). The median follow-up was 79.5 months. The median PFS was 52.8 months with lenalidomide maintenance and 23.5 months with placebo/observation (HR 0.48; 95% CI, 0.41-0.55). The Subcommittee considered that lenalidomide maintenance improved PFS in all subgroups, including patients with high-risk cytogenetics (t[4;14] or del17p); however, it was noted that cytogenetic data was not available for the majority of patients (missing data, n = 641).

2.53. The Subcommittee noted that in the meta-analysis, median PFS after next therapy was 73.3 months with lenalidomide maintenance compared with 56.7 months with placebo/observation (HR 0.72; 95% CI 0.62-0.84). The Subcommittee considered that this indicates that lenalidomide maintenance therapy does not induce resistance to salvage treatments.

2.54. The Subcommittee considered that in the meta-analysis, when OS was analysed by induction regimen, the most favourable OS benefit with lenalidomide maintenance was observed in patients who had received lenalidomide-based induction.

2.55. The Subcommittee considered that the primary safety issue in the CALGB and IFM trials was the higher incidence of second primary malignancies in patients receiving lenalidomide maintenance compared with those receiving placebo (data not available from the GIMEMA). The Subcommittee noted that the increased incidence of second primary malignancy observed in the lenalidomide maintenance group led to the IFM trial stopping treatment in January 2011 (recruitment was initiated in July 2006). The Subcommittee considered that melphalan, which is used in conjunction with ASCT, may contribute to the high incidence of second primary malignancy observed in the trials.

2.56. The Subcommittee considered that there is strong evidence that lenalidomide as maintenance therapy following ASCT in patients with newly diagnosed MM provides a survival benefit, but there is a clear risk of second primary malignancy.

2.57. The Subcommittee considered that funding lenalidomide as maintenance therapy would require more frequent clinic visits than the current treatment regimen.

2.58. The Subcommittee considered that the population who would receive lenalidomide maintenance therapy would be approximately 120 patients per year.

Lenalidomide for the treatment of patients with newly diagnosed, ASCT-eligible multiple myeloma (first-line)

2.59. The Subcommittee noted that standard of care in New Zealand for the majority of younger transplantable patients, includes induction treatment with 3-6 cycles of CyBorD, then high dose melphalan, and a limited period of consolidation with thalidomide (instead of cyclophosphamide), bortezomib, and dexamethasone.

2.60. The Subcommittee noted the applicant has suggested that lenalidomide would be given in place of cyclophosphamide as a triplet regimen for induction (i.e. RVD - lenalidomide, bortezomib and dexamethasone). Patients would receive four cycles of RVD prior to ASCT with the remainder as consolidation following transplant. Including consolidation, a total of nine cycles would be expected.

2.61. The Subcommittee noted that no published trials were provided that directly compare bortezomib-based regimens to lenalidomide-based regimens for ASCT induction and consolidation, nor any evidence that adding lenalidomide to bortezomib-based regimens would provide improved efficacy.

2.62. The Subcommittee considered there was insufficient evidence to support the application for lenalidomide for the treatment of patients with newly diagnosed MM who are eligible for ASCT, and thus deferred the application for future consideration when additional evidence is available.

3. Hexylaminolevulinate hydrochloride for detection of bladder cancer

Application

3.1. The Subcommittee reviewed the application from Juno Pharmaceuticals NZ limited for hexylaminolevulinate hydrochloride for the diagnostic detection of non-invasive bladder cancer under blue fluorescent light.

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

Recommendation

3.3. The Subcommittee **deferred** making a recommendation regarding the funding of hexylaminolevulinate hydrochloride for the detection of bladder cancer.

Discussion

3.4. The Subcommittee noted that bladder cancer is half as common in women compared to men; and while it can occur at any age, even in children, it is rare under the age of 50 years. The Subcommittee considered that rates of bladder cancer appear to be decreasing in both Māori and non-Māori.

3.5. Around 75% of bladder cancers are superficial (non-muscle invasive bladder cancer, NIMBC) being confined to the inner lining of the bladder which is typically treated with surgical and/or topical treatments. However, in 25% of cases the cancer has invaded the bladder wall (muscle invasive bladder cancer, MIBC) and partial or complete removal of the bladder is necessary, or alternatively radiation therapy with or without chemotherapy.

3.6. The Subcommittee noted that after resection alone, early stage NMIBC has a recurrence risk of up to 61% within 1 year and 78% within 5 years, the majority as further NMIBC. The Subcommittee noted that a patients' risk of recurrence following resection is based on tumour characteristics.

3.7. The Subcommittee noted that hexaminolevulinate hydrochloride is a blue light cystoscopy agent which is administered as a solution directly into the bladder via catheter one hour prior to cytoscopic examination. The Subcommittee noted the mechanism of action is that photoactive porphyrins accumulate intracellularly in bladder wall lesions which fluoresce red under blue light. The Subcommittee noted that fluorescence may also be seen as a result of inflammation.

3.8. The Subcommittee considered that while most urology units have a cystoscope it is unclear whether all have the capability to use a blue light source or what the costs involved for DHBs to upgrade to a cystoscope that has blue light capability would be.

3.9. The Subcommittee noted that hexaminolevulinate hydrochloride (Hexvix) is Medsafe registered for diagnostic use only; to contribute to the diagnosis and management of bladder cancer in patients with known or high suspicion of bladder cancer. The Subcommittee noted that the supplier's application states that the product is used during transurethral resection of bladder tumour (TURBT) although the registration is for diagnostic use only.

3.10. The Subcommittee noted evidence for the use of hexaminolevulinate including from the following studies:

- Schmidbauer et al 2004, J Urol;171:135-8
- Jocham et al 2005, J Urol;174:862-6
- Grossman et al 2007, J Urol;178: 62-7
- Stenzl et al 2010, J Urol;184:1907-14
- Hermann et al 2011, BJUI; 108: E297-303
- Grossman et al 2012, J Urol;188:58-62
- Malmström et al. 2009 Eur Urol ;56: 247-56
- O'Brien T et al 2013 BJU Int.; 112: 1096-104
- Zlatev DV et al 2015 Urol Clin North Am.;42: 147-57
- Von Runstedt FC and Lerner SP 2014 Curr Opin Urol.; 24:532-9

3.11. The Subcommittee considered that studies report increased rates of detection of NMIBC with hexaminolevulinate vs white light cystoscopy (WLC) and a longer time to recurrence (16 vs 9 months) of NMIBC at 4 years median follow-up, but a small increase in false positive rates (17.3.vs 21.9%).

3.12. The Subcommittee considered from the information provided it was highly uncertain whether there would be either a reduction in bladder resections or any impact on MIBC rates from the use of hexaminolevulinate. The Subcommittee considered an advantage from hexaminolevulinate with regard to a reduction in progression or survival probability in bladder cancer patients has not been demonstrated to date, with no difference in intra-vesical therapy rates (Von Runstedt et al. 2014, Curr Opin Urol; 24:532-9).

3.13. The Subcommittee considered that bladder cancer patients typically undergo cystoscopy every three months in the first two years after initial diagnosis followed by

every six months for the subsequent two to three years, and then annually thereafter. The Subcommittee considered the majority of the costs associated with management of bladder cancer were from repeated cystoscopy. The Subcommittee considered that use of hexaminolevulinate would likely have no impact on the rate of cystoscopy, but would increase the time required for a procedure.

3.14. The Subcommittee noted that currently mitomycin C is given as a single dose perioperatively for localised low grade tumours, which reduces recurrence by 17%, and BCG is given for multifocal and/or large volume, histologically confirmed new or recurrent low grade bladder cancers and reduces recurrence by 24%. The Subcommittee noted that both agents also reduce rates of stage progression (progression rate estimate in all patient risk groups was 8% (95% CI: 0, 15) with TURBT and BCG maintenance and 4% (95% CI: -26, 32) with TURBT and Mitomycin C maintenance) (Diagnosis and Treatment of Non-Muscle Invasive Bladder Cancer: AUA/SUO Joint Guideline: 2016).

3.15. The Subcommittee noted that the effect of hexaminolevulinate on recurrence rate in patients with TURBT and early intravesical instillation of chemotherapy was not confirmed by a prospective randomized trial, and considered that this likely indicated that chemotherapy compensates for any increased detection from hexaminolevulinate. (O'Brien et al., 2013, BJU Int; 112:1096-104).

3.16. The Subcommittee noted that the supplier had not presented any comparison with other bladder cancer detection methods currently used in DHB hospitals. The Subcommittee noted that current detection methods include mRNA urinary analysis or narrow band imaging (NBI).

3.17. The Subcommittee noted that mRNA RT-qPCR urinary analysis of genetic biomarkers previously validated for initial diagnosis of urothelial carcinoma appeared to have a 93% sensitivity and a 97% NPV in patients with haematuria (Lotan et al, J Urol 2016; 35:531.e15-22) and reduced cystoscopy by around 20% (Darling et al. 2017, Adv Ther; 34:1087-96).

3.18. The Subcommittee noted that narrow band imaging is a technology that filters out the red light spectrum of white light enhancing the mucosal and submucosal vasculature, and has a higher sensitivity that white light (Li et al. 2013, Int J Urol; 20:602-9), with a very high levels of sensitivity and specificity, 94% and 85% respectively (Zheng et al. 2012, J Thorac Dis;8:3205-16), and reduced recurrence rates of low grade tumours (Naito et al. 2016, Eur Urol; 70:506-15). The Subcommittee considered narrow band imaging is currently widely used during existing white light cystoscopy procedures without additional time of cost involved.

3.19. The Subcommittee noted a meta-analysis of 7 studies comparing hexaminolevulinate and NBI (Lee et al. 2015, BMC Cancer; 15:566) which reported that recurrence rate of cancers resected using hexaminolevulinate compared with NBI did not differ significantly (OR=1.11, 95% CI 0.55-2.1); and that no difference was observed in progression rate between cancers resected by all methods.

3.20. The Subcommittee considered that from the currently available evidence it was highly uncertain what the benefit from use of hexaminolevulinate for bladder cancer patients over standard practice would be, if any, as the presented evidence did not indicate improvements in major outcomes.

3.21. Members considered that use of hexaminlevulinate should be considered as a device rather than a therapeutic treatment as there was a lack of evidence for its use in the treatment of cancer. As such, members question whether this would fall within the scope of PHARMAC's current activities with regards to hospital devices.

3.22. The Subcommittee considered that hexaminolevulinate would likely reduce recurrence of NIMBC if topical therapy were not used but would likely not be superior to currently widely used NBI.

3.23. The Subcommittee considered that no evidence had been presented to indicate that hexaminolevulinate has an impact on invasive bladder cancer.

3.24. The Subcommittee considered that for any further assessment of this product that specialist advice from the Urology Society be sought regarding the current preferred diagnostic procedures, rates of invasive bladder cancer, the potential impact of hexaminolevulinate on the frequency of TURBT, prognosis and on survival.

3.25. The Subcommittee considered that the supplier's application did not use consistent language and was selective and incomplete in terms of the information presented.

4. Olaparib for the treatment of BRCA-mutated relapsed ovarian cancer

Application

4.1. The Subcommittee considered a funding application from AstraZeneca for the use of olaparib for the treatment of BRCA-mutated platinum-sensitive relapsed ovarian, fallopian tube, or primary peritoneal cancer with high-grade serous features or a high-grade serous component.

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

Recommendation

4.3. The Subcommittee **recommended** that olaparib be funded with a high priority for the treatment of BRCA-mutated platinum-sensitive relapsed ovarian, fallopian tube, or primary peritoneal cancer with high grade serous features or a high-grade serous component, subject to the following Special Authority criteria:

> Special Authority for Subsidy – Retail Pharmacy – Specialist
> Initial – only from a medical oncologist or relevant specialist on the recommendation of a medical oncologist. Approvals valid for 12 months.
> All of the following:
> 1. Patient has high-grade serous* epithelial ovarian, fallopian tube, or primary peritoneal cancer; and
> 2. There is documentation confirming germline *BRCA1* or *BRCA2* gene mutation; and
> 3. Patient has received at least two lines of previous treatment with platinum-based chemotherapy; and
> 4. Patient has platinum sensitive disease defined as disease progression occurring at least 6 months after the last dose of the penultimate line of platinum-based chemotherapy; and
> 5. Patient's disease must have achieved partial or complete response to treatment with the immediately preceding platinum-based regimen; and
> 6. Patient's disease has not progressed following prior treatment with olaparib; and
> 7. Treatment will be commenced within 8 weeks of the patient's last dose of immediately preceding platinum-based regimen; and
> 8. Treatment to be administered as maintenance treatment; and
> 9. Treatment not to be administered in combination with other chemotherapy.
>
> Renewal – only from a medical oncologist or relevant specialist on the recommendation of a medical oncologist. Approvals valid for 12 months.
> All of the following:
> 1. Treatment remains clinically appropriate and patient is benefitting from treatment; and
> 2. No evidence of progressive disease; and
> 3. Treatment to be administered as maintenance treatment; and
> 4. Treatment not to be administered in combination with other chemotherapy.

Note: *high grade serous includes tumours with high-grade serous features or a high-grade serous component

Discussion

4.4. The Subcommittee noted that the application for olaparib for ovarian cancer had been considered by PTAC at its meeting in May 2017 which deferred making a recommendation pending publication of the results of the SOLO2 study. The Subcommittee noted PTAC had also referred the application to CaTSoP for advice regarding BRCA testing and appropriate Special Authority criteria.

4.5. The Subcommittee noted that subsequently the supplier of olaparib had provided additional evidence to support their application, including the published results of the SOLO2 trial, along with comment on the May 2017 PTAC minutes.

4.6. The Subcommittee noted that 95% of ovarian malignancies are derived from epithelial cells, of which 75% are serous carcinoma. The Subcommittee noted that serous ovarian, fallopian tube, and peritoneal cancers are similar in histology and clinical behaviour.

4.7. The Subcommittee noted that ovarian cancers in BRCA mutation carriers are more likely to be of higher grade than ovarian cancers in age-matched controls, and that women with BRCA gene mutations have an increased risk of ovarian and breast cancer.

4.8. The Subcommittee noted that approximately 70% of ovarian cancer patients present with stage III or IV disease, as early stage disease is often asymptomatic and the symptoms associated with ovarian cancer are nonspecific.

4.9. The Subcommittee noted that Pacifika and Māori women experience a higher incidence of ovarian cancer and have a higher mortality rate compared with non-Māori, non-Pacifika women.

4.10. The Subcommittee noted that the current first-line treatment for ovarian cancer is usually surgery, with or without radiotherapy, followed by platinum-based chemotherapy (carboplatin or cisplatin with or without paclitaxel). The Subcommittee considered that the majority of patients relapse following platinum-based chemotherapy (around 70% at 2 years after first-line treatment), and therefore subsequent lines of therapy are usually required.

4.11. The Subcommittee noted that olaparib is an inhibitor of human Poly-(ADP-ribose) polymerase (PARP) enzymes, which are required for the effective repair of DNA. The Subcommittee noted that in the BRCA mutated setting, inhibition of PARP leaves cells with DNA breaks that cannot be repaired, leading to genomic instability and ultimately cell death.

4.12. The Subcommittee noted that olaparaib (Lynparza) is indicated as monotherapy for the maintenance treatment of patients with platinum-sensitive relapsed BRCA-mutated (germline or somatic) high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial response) after platinum-based chemotherapy.

4.13. The Subcommittee noted that there are at least five PARP inhibitors in clinical development for the treatment of ovarian cancer; olaparib is the first to be approved for use in New Zealand.

4.14. The Subcommittee noted that the key clinical evidence for the use of olaparib in the supplier's requested population comes from the international, multi-centre, double-blind, randomised, placebo-controlled, Phase 3 SOLO-2 trial (Pujade-Lauraine E, et al. Lancet Oncol. 2017;18:1274-84).

4.15. The Subcommittee noted that the SOLO2 trial included 295 patients with histologically confirmed, relapsed, high-grade serous ovarian cancer or high-grade endometrioid cancer, including primary peritoneal or fallopian tube cancers, who had a predicted deleterious or suspected deleterious BRCA1/2 mutation.

4.16. The Subcommittee noted that germline BRCA1/2 mutation was confirmed in 97% of patients in both treatment arms; no patients had a confirmed somatic BRCA1/2 mutation.

4.17. The Subcommittee noted that additional eligibility criteria for SOLO2 included an age of 18 years or older, an ECOG performance status of 0-1, at least two prior lines of platinum-based chemotherapy, either complete or partial response to the most recent regimen, and platinum-sensitive disease (disease progression occurring at least 6 months after the last dose of platinum therapy was given) following their penultimate line of chemotherapy before enrolment.

4.18. The Subcommittee noted that 43% of the olaparib arm and 37% of the placebo arm had received three or more lines of prior platinum-based therapy.

4.19. The Subcommittee noted that patients were randomly assigned 2:1 to olaparib 300 mg (two 150 mg tablets) twice daily or matching placebo until disease progression or investigator decision to stop treatment.

4.20. The Subcommittee noted that after a median follow-up of 22 months, the primary endpoint of investigator-assessed progression-free survival (PFS) defined as the time until objective radiological disease progression or death, was 19.1 months in the olaparib arm compared with 5.5 months in the placebo arm (HR 0.30; 95% CI 0.22-0.41; P<0.0001).

4.21. The Subcommittee considered that radiological monitoring of patients with ovarian cancer was not currently standard of care in New Zealand, with clinical progression, not RECIST, used to determine management. The Subcommittee considered that access criteria which required radiologically measured response would have a significant impact on the DHB radiology services. The Subcommittee considered that access criteria should balance the increased pharmaceutical costs for a longer duration of therapy from use of clinically determined progression with the overall costs to and impact on the health system for radiological monitoring.

4.22. The Subcommittee noted that the 12-month PFS was 65% in the olaparib arm compared with 21% in the placebo arm; the 24-month PFS was 43% in the olaparib arm compared with 15% in the placebo arm.

4.23. The Subcommittee noted that time to first subsequent therapy was 27.9 months in the olaparib arm compared with 7.1 months in the placebo arm (HR 0.28; 95% CI 0.21-0.38; P<0.0001). The time to second subsequent progression was not reached in the olaparib arm compared with 18.4 months in the placebo arm (HR 0.50; 95% CI 0.34-0.72; P<0.0002). The time to second subsequent therapy was not reached in the olaparib arm compared with 18.2 months in the placebo arm (HR 0.37; 95% CI 0.26-0.53; P<0.0001).

4.24. The Subcommittee noted that median OS was not reached in either group and considered that the OS data was immature.

4.25. The Subcommittee noted that the most common grade 1-2 adverse events in both treatment arms were nausea, fatigue or asthenia, vomiting, abdominal pain, and diarrhoea; and that these occurred at approximately double the rate in patients receiving olaparib compared with placebo. Grade 1-2 dysgeusia occurred in 27% of patients in the olaparib arm. The most common AE of grade 3 or worse in the olaparib arm was anaemia (18% of patients). The incidence of myelodysplasia and secondary leukaemia was 2% in the olaparib arm and 4% in the placebo arm. The incidence of all secondary

malignancies was equivalent between the treatment arms. Overall, 11% of patients in the olaparib arm and 2% of patients in the placebo arm discontinued treatment.

4.26. The Subcommittee considered that SOLO-2 was a well-designed trial, and that the improvement in PFS was clinically meaningful and significant in a group of patients who had already achieved complete or partial response with multiple lines of prior treatment at the time of enrolment.

4.27. The Subcommittee considered that there was no appreciable difference in quality of life outcomes for patients receiving olaparib or placebo in SOLO-2, and that maintaining quality of life is important in a population with minimal cancer burden.

4.28. The Subcommittee noted that additional clinical evidence comes from Study 19 – a randomised, double-blind, placebo-controlled Phase 2 trial of an olaparib capsule presentation conducted prior to SOLO2 (Ledermann J, et al. New Engl J Med. 2012;366:1382-92).

General comments

4.29. The Subcommittee considered that based on currently available evidence olaparib would provide a health benefit to patients with BRCA-mutated platinum-sensitive relapsed ovarian, fallopian tube, or primary peritoneal cancer with high-grade serous features or a high-grade serous component.

4.30. The Subcommittee considered that the inclusion of olaparib in the treatment paradigm would delay time to subsequent therapy but would not reduce the lines of therapy received. The Subcommittee considered that due to the use of subsequent lines of treatment OS data would be difficult to appropriately interpret.

4.31. The Subcommittee noted that there were two other PARP inhibitors in late stage development in similar populations and considered that there was likely a class-effect of PARP inhibitors in this indication.

BRCA testing

4.32. The Subcommittee noted that the application was for patients with germline or somatic BRCA-mutated disease. The Subcommittee considered that we would expect 15-17% of patients with high-grade serous ovarian cancer to have germline BRCA mutations, and 4-7% of patients in this population to have somatic BRCA mutations.

4.33. The Subcommittee considered that in New Zealand testing for germline BRCA mutation is based on EVIQ guidelines (https://www.eviq.org.au/) and is available to all patients with high-grade serous cancer, patients aged ≤70 years, or patients with a personal or family history of breast or other BRCA-related cancer.

4.34. The Subcommittee considered that testing for somatic BRCA mutations was not currently available in the publicly funded service. The Subcommittee considered that if eligibility criteria for olaparib where to include somatic mutation, this would likely result in re-biopsy and retesting for BRCA status after each round of chemotherapy to determine eligibility; particularly noting enrichment of this mutation in later lines of treatment.

4.35. The Subcommittee noted that Australian olaparib eligibility was in part defined by germline class 4 or 5 BRCA1 or BRCA2 mutation.

4.36. The Subcommittee considered that the funding of olaparib, or another treatment where eligibility was determined by germline BRCA mutation status, would have an impact on genetic testing and counselling services to appropriately support patients and downstream affected families.

4.37. The Subcommittee considered that there are currently no international guidelines to confirm the timing of somatic tumour testing. The Subcommittee considered that while it was difficult to determine the impact on ancillary health services, including genetic testing services and radiology, if eligibility where to include somatic BRCA mutation status this would likely be significant.

4.38. The Subcommittee considered that, based on biological plausibility, while it was likely that the clinical utility of PARP inhibitor treatment in ovarian cancer patients with somatic BRCA mutation would be similar to those with a germline BRCA mutation, there was currently limited evidence for the magnitude and durability of a treatment effect in this patient cohort. The Subcommittee considered that there was currently insufficient evidence to support the use of olaparib for ovarian cancer patients with somatic BRCA mutation.

5. Rituximab maintenance for CD20+ low grade or follicular B-cell Non-Hodgkin's Lymphoma

Application

5.1. The Subcommittee a funding application from Roche for the widening of access to rituximab for maintenance in CD20+ low grade or follicular B-cell Non-Hodgkin's Lymphoma (NHL) following initial treatment induction.

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

Recommendation

5.3. The Subcommittee **recommended** that rituximab for maintenance in CD20+ low grade or follicular B-cell Non-Hodgkin's Lymphoma (NHL) following initial treatment induction be listed with a medium priority.

Information Reviewed

5.4. The application with all documentation provided by the applicant

Discussion

5.5. The Subcommittee noted that an original application had been received in February 2011 for maintenance treatment in patients with relapsed/refractory follicular NHL and CaTSoP had in August 2011 recommended for decline. CaTSoP noted in that meeting that it would welcome a submission from the supplier for the use of rituximab maintenance following induction therapy for previously untreated follicular NHL, including longer term data from PRIMA. The Committee noted this submission is in response to that consideration and includes data from PRIMA.

5.6. The Subcommittee noted the need in these patient's post-induction therapy relates primarily to the possibility of relapse. Most patients continue to be productive and enjoy a reasonably good quality of life until relapse when further chemotherapy is required (occasionally ASCT used at relapse). The Subcommittee noted most patients are currently discharged to primary care after induction. The Subcommittee noted the goal of maintenance treatment would be to prolong remission for as long as possible.

5.7. The Subcommittee considered estimates of 120 eligible patients per annum appeared reasonable given PHARMACs Special Authority data. The Subcommittee noted that uptake if funded may not be universal (perhaps 20-30% would not use) given the good quality of life most patients would have at the time of treatment. If eligible some may choose to have a period of maintenance treatment at a later stage.

5.8. The Subcommittee noted the Primary Rituximab Maintenance (PRIMA) study included in the supplier's submission with a recent abstract outlining 10 years of follow up (Salles et al. Lancet.2011;377:42-51; Salles et al. Blood.2013;122:509; Salles et al. Blood.2017;130:486). The Subcommittee noted PRIMA is the primary evidence for the effectiveness of rituximab maintenance after first-line induction therapy with the regimens most commonly used in NZ (R-CHOP, R-CVP), although the Subcommittee noted the R-CVP does not tend to be used as much now and there has been increasing use of bendamustine/rituximab since the funding of bendamustine in 2017.

5.9. The Subcommittee noted the PRIMA study was an open-label, randomised, phase III trial that was conducted between December 2004 and April 2007 at 223 study sites across 25 countries. The trial had two phases (induction and maintenance). All patients received induction therapy and were then randomised in a 1:1 ratio to receive either rituximab therapy or no further treatment (observation) at the end of induction chemotherapy. The rituximab maintenance phase continued for 2 years, or until disease progression. Ninety percent of patients in the rituximab maintenance group received >90% of their projected rituximab dose, which the Subcommittee would be consistent with what would occur if funded in New Zealand.

5.10. The Subcommittee considered PFS was the main indicator of benefit. At the 10 year follow up PFS was 51% in the rituximab maintenance arm versus 35% in the observation arm. The Subcommittee noted time to next treatment was prolonged in the rituximab maintenance arm (not yet reached) versus 6.1 years in the observation arm giving a 38% reduction in risk of disease progression requiring treatment during the 10 years of follow-up. The Subcommittee noted only 607 entered the extended follow-up period with six countries not participating. The Subcommittee noted the patient numbers did wane over the long follow-up period, with 172 deaths occurring during the observation period and an unclear number lost-to-follow up. The Subcommittee noted that some data was presented to show that the arms remained balanced despite the losses.

5.11. The Subcommittee noted the infusion burden given the number of additional infusions despite infusion times being able to be reduced as per protocols if tolerated. The Subcommittee noted the potential risk around increased infections caused by neutropenia, but the Subcommittee considered this risk was small given the rates of grade 3 or 4 adverse events were low in both arms of the PRIMA trial (3-4%).

5.12. The Subcommittee considered the PRIMA trial provided good-quality evidence and is relevant to the New Zealand population. but the original publication lacked strength given the short duration of follow-up. The Subcommittee considered the 6 and 10 year follow-ups which have been presented at conferences and published as abstracts do address this issue satisfactorily.

6. Osimertinib for locally advanced or metastatic EGFR T790M mutation-positive non-small cell lung cancer (NSCLC) second-line after prior EGFR TKI therapy

Application

6.1. The Subcommittee reviewed a funding application from AstraZeneca for the use of osimertinib for the treatment of adult patients with locally advanced or metastatic EGFR T790M mutation-positive non-small cell lung cancer (NSCLC) who have progressed on or after prior treatment with an EGFR tyrosine-kinase inhibitor (TKI).

6.2. The Subcommittee took into account, where applicable, PHARMAC's relevant decision-making framework

Recommendation

6.3. The Subcommittee **deferred** making a recommendation regarding the funding of osimertinib for the treatment of adult patients with locally advanced or metastatic *EGFR*

T790M mutation-positive NSCLC pending publication of longer follow-up including mature survival data from the AURA3 trial.

Discussion

6.4. The Subcommittee noted that funding applications for nivolumab (Opdivo, Bristol Myers-Squibb), pembrolizumab (Keytruda, Merck Sharpe & Dohme), and atezolizumab (Tacentriq, Roche) for the second-line treatment of advanced NSCLC patients have previously been considered by PTAC and CaTSoP.

- Nivolumab: CaTSoP April 2016, PTAC May 2016.
- Pembrolizumab: PTAC November 2016, CaTSoP March 2017, PTAC May 2017, PTAC November 2017.
- Atezolizumab: PTAC August 2017, CaTSoP August 2017.

6.5. The Subcommittee noted that osimertinib is an orally administered third-generation TKI and is a selective and irreversible inhibitor of EGFR harbouring single (L858R or del746-750) or double (L858R/T790M or del746-750/T790M) mutations (Wu et al. Molecular Cancer, 2018;17:38).

6.6. The Subcommittee noted that a number of third generation EGFR TKIs are under development for the treatment of NSCLC, the majority of which target the T790M mutation.

6.7. The Subcommittee noted that osimertinib is indicated for the treatment of adult patients with locally advanced or metastatic EGFR T790M mutation-positive NSCLC at a dosage of 80 mg once daily.

6.8. The Subcommittee noted that the health need of New Zealand patients with advanced lung cancer has recently been considered by both PTAC and CaTSoP. A detailed description is available in previous minutes regarding applications for nivolumab, pembrolizumab, and atezolizumab for advanced NSCLC.

6.9. The Subcommittee considered that in published trials investigating first- and second-generation EGFR TKIs for the treatment of EGFR mutation-positive NSCLC, median progression-free survival (PFS) is approximately 9 months with all patients eventually progressing (Gonzalez-Larriba et al. Transl Lung Cancer Res, 2017; doi: 10.21037/tlcr.2017.10.03).

6.10. The Subcommittee considered that three patterns of disease progression are seen in patients with EGFR mutation-positive NSCLC: rapid, gradual, and local only. It was noted that patients with the T790M mutation tend to experience gradual progression with maintained ECOG performance status, and therefore often receive second-line therapy.

Evidence

6.11. The Subcommittee noted that the key clinical evidence for osimertinib for the treatment of adult patients with locally advanced or metastatic EGFR T790M mutation-positive NSCLC who have progressed on or after prior treatment with an EGFR TKI comes from the open-label, randomised, international, Phase 3 AURA3 trial (Mok TS, et al. N Engl J Med. 2017;376:629-40).

6.12. The Subcommittee noted that approximately 50% of individuals screened for inclusion in AURA3 were excluded because their T790 mutation status was not confirmed. Members considered that this may indicate there is some uncertainty regarding the accuracy of testing for the T790 mutation. Members considered that this may result in a higher number patients than estimated receiving osimertinib, especially where a less specific test be implemented in New Zealand.

6.13. The Subcommittee considered it was unclear whether T790M testing was routine or widely available in all New Zealand centres; and that plasma circulating tumour DNA testing, as was used in AURA3, was not widely available in New Zealand.

6.14. The Subcommittee considered that New Zealand patients currently undergo biopsy to determine mutation status. Members considered that if funding eligibility were to be determined by mutation status, patients would likely undergo re-biopsy at relapse which would mean additional costs for DHBs and could result in health equity issues.

6.15. The Subcommittee noted that there was significant crossover in AURA3 from the platinum plus pemetrexed arm to osimertinib, and that a significant number of patients in the osimertinib arm received subsequent treatment with chemotherapy or radiotherapy after discontinuing osimertinib. The Subcommittee considered that these factors would confound the analysis of overall survival (OS).

6.16. The Subcommittee noted that in AURA3, the original sample size estimate was 610 patients, which, at 400 progression events, would have provided >95% power to detect a difference in PFS assuming the true hazard ratio (HR) is 0.67 at a 5% 2-sided significance level. The Subcommittee considered that the language used in the protocol would allow the sponsor to abandon the OS analysis.

6.17. The Subcommittee noted that in AURA3, a total of 419 patients were randomly assigned 2:1 to osimertinib or platinum plus pemetrexed. At the time of the analysis at 26% maturity, progression events had occurred in 250 patients. The Subcommittee considered that the reduced enrolment number could indicate that final OS data would never be published.

6.18. The Subcommittee considered that, in general, there is evidence demonstrating interim analyses overestimate efficacy by approximately 60% when compared with analyses conducted at full maturity (Counsell N, et al. Clin Trials. 2017;14:67-77).

6.19. The Subcommittee noted that at a median follow-up of 8.3 months the median PFS was 10.1 months in the osimertinib arm vs 4.4 months in the platinum-pemetrexed arm (HR after adjustment for Asian and non-Asian race 0.30; 95% CI 0.23-0.41; P<0.001).

6.20. The Subcommittee considered that the response seen in patients with CNS metastases who received osimertinib in AURA3 indicated there was CNS penetration. The Subcommittee considered that a good outcome in this patient population is unusual, and that there is an unmet need for an effective agent for patients with EGFR mutation-positive NSCLC with CNS metastases.

6.21. The Subcommittee considered that the safety and quality of life data provided were limited but did indicate that patients in the osimertinib arm likely had clinically significant improvements in some measures and the safety profile of osimertinib appeared consistent with previous reports.

General comments

6.22. The Subcommittee considered that while the results of AURA3 are promising, the data are currently immature and may overstate the likely benefit of the agent. The Subcommittee considered that the magnitude of benefit osimertinib may provide was highly uncertain based on the data provided.

6.23. The Subcommittee considered that it was unclear whether the profile of patients included in the AURA3 trial is relevant to the New Zealand population, as the mutation profile of the New Zealand non-Asian population is not yet known.

6.24. The Subcommittee considered there is some published evidence to support patients with EGFR mutation-positive NSCLC being less responsive to anti–PD-1/PD-L1

therapies and that if osimertinib were funded consideration should be given to the lung cancer treatment paradigm and appropriate sequencing of these agents.

6.25. The Subcommittee noted that in November 2017 the PBAC did not recommend osimertinib for use in the requested population in part because, although it was accepted that osimertinib is more effective than standard chemotherapy, the magnitude of incremental OS benefit was difficult to determine on the evidence presented.

7. Calcium phosphate (Caphosol Dispersible) for oral mucositis

Application

7.1. The Subcommittee reviewed updated information from the supplier of calcium phosphate oral rinse for its use to prevent and minimise the effects of oral mucositis.

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

Recommendation

7.3. The Subcommittee reiterated its March 2013 **recommendation** that funding of calcium phosphate mouthwash be declined.

Discussion

7.4. The Subcommittee noted that it had previously considered an application for calcium phosphate oral rinse (vial presentation) for oral mucositis following chemotherapy or radiation therapy in March 2013. The Subcommittee noted that CaTSoP had recommended that application be declined based primarily on poor quality evidence.

7.5. The Subcommittee noted that in 2013 it was also noted that benzydamine was currently used for the treatment of oral mucositis however a part-charge applied to benzydamine solution that may be limiting its use and recommended that benzydamine be fully subsidised. The Subcommittee noted that since August 2014 benzydamine had been fully funded.

7.6. The Subcommittee noted that the current submission was for funding of Caphasol Dispersible, an effervescent tablet formulation.

7.7. The Subcommittee noted that the primary randomised trial provided was considered by CaTSoP in 2013, however a number of publications not previously considered had also been provided including:

- Treister et al., BJC, 2017; 116:21-7
- Wong et al., Radiotherapy Onc, 2017;122:207-11
- Raphael et al., Supportive Care in Cancer, 2014;22:3-6
- McGuire et al., Supportive Care in Cancer, 2013;21:3165-77

7.8. The Subcommittee considered that overall the level of evidence of calcium phosphate mouthwash remained poor and did not show a benefit from the use of calcium phosphate mouthwash over standard care such that its use in the treatment of oral mucositis could not be supported.

7.9. The Subcommittee considered that the suppliers submission was incomplete in that it did not include a number of unsupportive trials regarding the use of calcium phosphate mouthwash that had been published since 2013.