Record of the Cancer Subcommittee of PTAC Meeting held on 9 July 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 an upcoming 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)
Allanah Kilfoyle
Anne O'Donnell
Chris Frampton
Lochie Teague
Matthew Strother
Peter Ganly
Richard Isaacs
Scott Babington
Tim Hawkins

Apologies:
Michelle Wilson

Item 13 – reviewed on 23 July 2021 (via Zoom)

Present

Marius Rademaker
Allanah Kilfoyle
Chris Frampton
Lochie Teague
Michelle Wilson
Matthew Strother
Richard Isaacs

Apologies:
Anne O'Donnell
Peter Ganly
Scott Babington

2. The role of PTAC Subcommittees and records of meetings

2.1. 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.

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

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

2.4. 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'.

2.5. 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.

3. Record of PTAC meeting held Monday, April 12, 2021

3.1. The Subcommittee reviewed the minutes of the PTAC meeting held on 12 April 2021 and agreed that the minutes be accepted.

4. Correspondence and Matters Arising

Lomustine

4.1. The Subcommittee noted that in April 2021 the supplier of lomustine (CeeNU) notified Pharmac of a discontinuation due to take effect from December 2022. The Subcommittee noted this was the only Medsafe approved lomustine product currently available in New Zealand.

4.2. The Subcommittee noted lomustine is a component of the PCV (procarbazine, lomustine and vincristine) chemotherapy regimen and considered that, whilst used in only a small number of people, this regimen nonetheless constitutes an important line of therapy in the treatment of certain brain tumours.

4.3. The Subcommittee considered relapsed high grade gliomas may utilise temozolomide as an alternative agent. The Subcommittee recommended seeking further input on this from neurooncologists regarding whether this would be an appropriate alternative treatment strategy for these patients in the absence of comparative evidence between temozolomide and lomustine, noting it would offer suitability benefits as an oral agent. The Subcommittee considered there to be little evidence regarding substitution of the PCV regimen with alternative agents for patients with low grade gliomas. The Subcommittee also considered that the non-availability of lomustine could result in the loss of a line of therapy for patients with low grade gliomas.

4.4. The Subcommittee considered bevacizumab may also be considered as a possible alternative line of therapy in some indications; however, the Subcommittee noted this had limited available evidence; in addition, it would require movement from an oral agent to an intravenous product.

4.5. The Subcommittee considered that due to declining demand, continuous future supply of lomustine could be difficult to procure; however, considered further investigation into potential alternative suppliers was important. The Subcommittee suggested that, as this is a global problem, communication with international

procurement agencies such as the PBS, SMC and NICE regarding the strategies they are pursuing would be of value.

4.6. The Subcommittee considered that clear communication with clinicians would be required regarding any discontinuation for this product.

Mitomycin

4.7. The Subcommittee noted recent changes in the availability of mitomycin and the associated concerns regarding long term stability of supply for this product.

4.8. The Subcommittee noted that mitomycin is the standard of care for the radical treatment of anal canal cancer. The Subcommittee noted that the overall incidence of this disease is increasing despite advances in preventative strategies against Human papillomavirus (HPV) transmission. The Subcommittee considered that mitomycin is also used also in metastatic breast cancer and, as part of chemoradiation or intravesical regimens in bladder cancer, and in ophthalmology.

4.9. The Subcommittee noted mitomycin is typically used short term and considered cisplatin could be an alternative agent for most indications; however the Subcommittee noted cisplatin has significant toxicity and may not be tolerated by some patients, particularly if used in a curative treatment setting where ototoxicity and nephrotoxicity can be debilitating.

4.10. The Subcommittee recommended engaging with the Urology Society regarding use in the intra-vesical setting to determine whether appropriate alternative agents if necessary could be used for Urological indications to potentially enable prioritisation of existing supplies of mitomycin across its other indications, if required.

4.11. The Subcommittee suggested investigation into international protocols and discussion with international agencies such as PBS, NICE and SMC regarding usage of mitomycin to understand what other jurisdictions were using or planning to do in light of potential supply issues.

5. Daratumumab in combination with bortezomib and dexamethasone for the treatment of patients with multiple myeloma who have received one prior line of myeloma therapy

Application

5.1. The Subcommittee considered a new application from Janssen for subcutaneous daratumumab (Darzalex SC) in combination with bortezomib and dexamethasone (DVd) for the treatment of patients with multiple myeloma who have received one prior line of myeloma therapy (1PL).

Recommendation

5.2. The Subcommittee **recommended** that subcutaneous daratumumab be funded with a **high priority**, within the context of treatment of malignancy, subject to the following Special Authority criteria:

> **DARATUMUMAB SUBCUTANEOUS**
> **Initial application – (relapsed/refractory multiple myeloma)** only from a relevant specialist or other medical practitioner on the recommendation of a relevant specialist. Approvals valid for 12 months for applications meeting the following criteria:

All of the following:

1. Patient has relapsed or refractory multiple myeloma with progressive disease; and
2. Patient has received one prior line of therapy for multiple myeloma; and
3. Either:
    3.1. Both:
        3.1.1. In patients who received first-line bortezomib, patient's disease was not refractory to bortezomib (ie received >6 months response to first-line bortezomib) nor were they intolerant to bortezomib; and
        3.1.2. Daratumumab subcutaneous to be administered in combination with bortezomib and dexamethasone for weeks 1 through 24 and as a monotherapy from week 25 until disease progression.
    3.2. Both:
        3.2.1. In patients who received first-line bortezomib, patients disease was refractory to bortezomib in first line or they were intolerant to bortezomib
        3.2.2. Daratumumab to be administered in combination with dexamethasone

Renewal application - (relapsed/refractory multiple myeloma) only from a relevant specialist or other 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 disease progression; and
2. The treatment remains appropriate and patient is benefitting from treatment.

In making this recommendation, the Subcommittee:

- noted the evidence of a substantial progression-free survival benefit and overall survival benefit from the addition of daratumumab, irrespective of its formulation, to second-line bortezomib and dexamethasone treatment for patients who received one prior line of therapy for multiple myeloma
- considered that there was no evidence to suggest a difference in efficacy between intravenous and subcutaneous daratumumab
- considered the subcutaneous formulation would substantially reduce the health system's infusion resource impact compared with the high impact of intravenous treatments for relapsed/refractory multiple myeloma
- noted the high cost of subcutaneous daratumumab for this patient population
- noted that funding daratumumab for only those patients who are not refractory to or intolerant of bortezomib would result in a need for bortezomib-refractory/intolerant patients. The Subcommittee considered it reasonable to enable access to those bortezomib-refractory/intolerant patients in the funded group based on the likely efficacy of daratumumab for this patient group and the unmet need that would arise of daratumumab were funded for only bortezomib responsive patients.

5.3. The Subcommittee **recommended** that intravenous daratumumab be funded with a **high priority**, within the context of treatment of malignancy, subject to the following Special Authority criteria:

DARATUMUMAB INTRAVENOUS
Initial application – (relapsed/refractory multiple myeloma) only from a relevant specialist or other medical practitioner on the recommendation of a relevant specialist. Approvals valid for 12 months for applications meeting the following criteria:
All of the following:

1. Patient has relapsed or refractory multiple myeloma with progressive disease; and
2. Patient has received one prior line of therapy for multiple myeloma; and
3. Either:
    3.1. Both:

3.1.1. In patients who received first-line bortezomib, patient's disease was not refractory to bortezomib (ie received >6 months response to first-line bortezomib) nor were they intolerant to bortezomib; and
3.1.2. Daratumumab intravenous to be administered in combination with bortezomib and dexamethasone for weeks 1 through 24 and as a monotherapy from week 25 until disease progression.

3.2. Both:
3.2.1. In patients who received first-line bortezomib, patients disease was refractory to bortezomib in first line or they were intolerant to bortezomib
3.2.2. Daratumumab to be administered in combination with dexamethasone

Renewal application - (relapsed/refractory multiple myeloma) only from a relevant specialist or other 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 disease progression; and
2. The treatment remains appropriate and patient is benefitting from treatment.

In making this recommendation, the Subcommittee:

- noted the evidence of a substantial progression-free survival benefit and overall survival benefit from the addition of daratumumab, irrespective of its formulation, to second-line bortezomib and dexamethasone treatment for patients who received one prior line of therapy for multiple myeloma

- considered the suitability of intravenous daratumumab was substantially improved due to an accelerated 90-minute infusion protocol, which has been used anecdotally in New Zealand, and that use of this rapid treatment regimen would substantially reduce the health system's infusion resource impact compared with the high impact of intravenous treatments for relapsed/refractory multiple myeloma

- noted the high cost of intravenous daratumumab for this patient population

- noted that only funding daratumumab for patients who are not refractory to or intolerant of bortezomib would result in an unmet need for bortezomib-refractory/intolerant patients. The Subcommittee considered it reasonable to enable access to those bortezomib-refractory/intolerant patients in the funded group based on the likely efficacy of daratumumab for this patient group and the unmet need that would arise of daratumumab were funded for only bortezomib responsive patients

Discussion

5.4. The Subcommittee noted that an application for intravenous daratumumab in combination with bortezomib and dexamethasone was received in November 2017. The Subcommittee noted that in October 2019, CaTSoP recommended that daratumumab in combination with bortezomib & dexamethasone for relapsed/refractory multiple myeloma be listed within the context of treatment of malignancy, with a low priority. The Subcommittee noted that in October 2020, CaTSoP reiterated its previous recommendation following review of updated information from the CASTOR trial that was provided by the supplier, and at that time, the Subcommittee noted that intravenous daratumumab would be associated with a large, costly, infusion burden.

5.5. The Subcommittee noted that CaTSoP had considered several different medicines for the second-line treatment of relapsed/refractory multiple myeloma, including carfilzomib and pomalidomide, in April 2021.

5.6. The Subcommittee noted that Pharmac had received a new application for subcutaneous daratumumab in combination with bortezomib and dexamethasone (DVd) for the treatment of patients with multiple myeloma who have received one prior line of myeloma therapy in April 2021. The Subcommittee noted that the New Zealand Myeloma Interest Group (NZMIG) had expressed its preference for daratumumab to be funded as a subcutaneous formulation rather than intravenous.

5.7. The Subcommittee noted that daratumumab is an IgG1κ human monoclonal antibody that binds to the CD38 protein expressed at a high level on the surface of myeloma tumour cells and has been shown to inhibit the in vivo growth of CD38-expressing tumour cells.

5.8. The Subcommittee noted that the health need of this patient population has been previously described by CaTSoP at recent meetings, including its April 2021 meeting and by the NZMIG. In particular, the Subcommittee noted that patients with multiple myeloma that has relapsed after, or is refractory to, first-line therapy have an unmet health need because current second-line treatment options for this disease are unable to provide significant delays in disease progression and patients who are eligible for autologous stem cell transplant would receive all effective funded treatment options in their first treatment line, noting that this would leave them without any new, effective therapies available for treatment of relapsed/refractory disease and gaining minimal benefit (if any) from retreatment with previously used therapies or remaining options (eg thalidomide).

5.9. The Subcommittee noted that current standard of care treatment options in New Zealand are not aligned with international guidelines and that several additional options for use in second-line or later lines of treatment are available internationally (eg daratumumab, carfilzomib and pomalidomide, as well as other agents not previously considered by CaTSoP).

Intravenous daratumumab

5.10. The Subcommittee noted that intravenous daratumumab is given at a dose of 16 mg per kg, weekly for cycles one to three, then every three weeks for cycles four to eight, in combination with bortezomib and dexamethasone, then every four weeks until disease progression.

5.11. The Subcommittee noted that the supplier provided evidence that daratumumab infusion durations vary, with a patient's first infusion generally taking seven hours; the second infusion taking four hours and subsequent infusions being given over about three hours.

5.12. The Subcommittee noted that, as previously discussed, daratumumab infusion over a 90-minute period is feasible, according to a rapid infusion protocol (as described on the NSW Government's cancer treatment protocol website, eviQ.org.au) although this regimen is not present on the Medsafe data sheet. The Subcommittee considered that anecdotal reports of this rapid infusion protocol (used where daratumumab is made available for compassionate use in New Zealand) provided some evidence for its safety, efficacy and suitability. However, the Subcommittee considered that even if a rapid protocol were used, intravenous daratumumab would substantially impact infusion services.

5.13. The Subcommittee noted that in October 2020 CaTSoP reviewed updated, unpublished information from the phase III CASTOR trial that included 498 patients with multiple myeloma who had received at least one prior line of therapy and were not refractory to prior bortezomib. These patients were randomised (1:1) to receive intravenous daratumumab with bortezomib and dexamethasone (DVd) until disease progression (bortezomib and dexamethasone, Vd, for eight cycles) or Vd for eight cycles alone.

5.14. The Subcommittee noted that CASTOR reported PFS outcomes for the intention-to-treat population, which included patients who received one prior line, two to three prior lines and more than three prior lines of therapy (unpublished data) reporting PFS of 16.7 months DVd compared with 7.1 months Vd (HR 0.31; 95% CI 0.25 to 0.40; *p*<0.0001) and reported PFS for the subgroup who had received only one prior line of treatment, as above.

5.15. The Subcommittee considered that the one prior line subgroup aligned well with the New Zealand patient population who would be suitable candidates for DVd and who have a significant unmet need, of which about 70% or more would have had prior bortezomib exposure.

5.16. Overall, the Subcommittee considered that the supplier-provided evidence for intravenous daratumumab suggested that the greatest benefit from the addition of daratumumab occurs in patients who have received one prior line of treatment, rather than in later lines of treatment, and that this was likely due to earlier treatment when the disease is more chemotherapy-sensitive. However, the Subcommittee considered that the benefit of treatment would reduce if used in later lines of treatment, as has been seen for other novel agents.

5.17. The Subcommittee considered that similar outcomes to trial population would be expected in the corresponding New Zealand relapsed/refractory multiple myeloma population, although noted that the standard of care treatment for most of these patients would consist of bortezomib, dexamethasone and thalidomide which may provide slightly better outcomes than the bortezomib and dexamethasone trial comparator.

5.18. In relation to the cross-trial comparison of CASTOR (DVd) and ENDEAVOR (carfilzomib with dexamethasone, Kd) as previously discussed in October 2020 (para. 4.24), the Subcommittee reiterated that the trials appear to have similar patient populations with control arms receiving the same treatment regimen. However, the Subcommittee considered that these trials were not ideal for comparison of survival outcomes due to confounding effects (eg. uncertainty regarding subsequent treatment lines) and a non-significant reduction in risk of death from the ENDEAVOR trial. Overall, the Subcommittee considered that the supplier's cross-trial comparison provided low-quality evidence regarding the claim of improved survival with intravenous daratumumab compared with carfilzomib.

Subcutaneous daratumumab

5.19. The Subcommittee noted that subcutaneous daratumumab is available as a vial containing 1800 mg per 15 mL and once constituted, it can be kept refrigerated for 24 hours protected from light then for 15 hours at room temperature with ambient room light. Members considered that administration of the subcutaneous daratumumab in the community may be challenging due to its relatively short expiry time and large volume.

5.20. The Subcommittee noted that subcutaneous daratumumab is proposed to be administered as a flat dose of 1800 mg given over 3 to 5 minutes, administered in combination with bortezomib and dexamethasone weekly for weeks one to nine, then every three weeks for weeks ten to 24, and then as a monotherapy every four weeks until disease progression. The Subcommittee noted that bortezomib and dexamethasone are administered on a three-weekly cycle.

5.21. The Subcommittee noted that Medsafe approved subcutaneous daratumumab in May 2021 for the following indications:

Adult patients (18 years and over) with newly diagnosed multiple myeloma:

- Who are eligible for autologous stem cell transplant, for use in combination with bortezomib, thalidomide, and dexamethasone
- Who are ineligible for autologous stem cell transplant, for use in combination with bortezomib, melphalan and prednisone, or with lenalidomide and dexamethasone.

Adult patients (18 years and over) with multiple myeloma who have received:

- At least one prior therapy, for use in combination with bortezomib and dexamethasone, or with lenalidomide and dexamethasone
- 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, for use as monotherapy.

5.22. The Subcommittee noted that the evidence for the use of subcutaneous daratumumab comes from the COLUMBA monotherapy trial which used intravenous daratumumab as comparator and included 522 patients with relapsed/refractory multiple myeloma who had received at least three prior lines of therapy (Mateos et al. Lancet Haematol. 2020;7:e370-e380).

5.23. The Subcommittee noted that COLUMBA had coprimary endpoints of overall response rate (ORR) and maximum daratumumab C_{trough} (pre-dose concentration on cycle three day one). The Subcommittee noted that an overall response was reported in in 108/263 (41%) patients in the subcutaneous group and 96/259 (37%) in the intravenous group (relative risk 1.11, 95% CI 0.89 to 1.37), which met the specified non-inferiority criteria.

5.24. The Subcommittee noted that there was no difference in 12-month PFS or OS after a median of 13.7 months follow-up between the subcutaneous or intravenous formulations (PFS 27.2% vs 28.0% respectively; HR 1.00; 95% CI: 0.81 to 1.23; *p*=0.9710, and OS 73.5% vs 72.1%, respectively; HR 0.91; 95% CI: 0.66 to 1.25; *p*=0.5544) (Usmani et al. [Poster presentation]. American Society of Haematology conference; 2019: Abstract Nr. 1865).

5.25. The Subcommittee noted that fewer infusion-related reactions were reported with daratumumab subcutaneous (13%) compared with the intravenous formulation (35%) as would be expected with a subcutaneous formulation and considered that this was advantageous. The Subcommittee noted that similar rates of treatment-related adverse events were reported in the subcutaneous and intravenous groups and considered that no additional risks were identified with the subcutaneous formulation compared with intravenous daratumumab.

5.26. The Subcommittee also noted the following evidence from COLUMBA:

- Mateos et al. Blood. 2019; 134 (Supplement_1): 1906
- Usmani et al. J Cancer Res Clin Oncol. 2021;147:619-631
- Luo et al J Clin Pharmacol. 2021;61:614-627

General

5.27. The Subcommittee considered that the evidence suggests that daratumumab provides a PFS benefit compared with standard of care bortezomib retreatment with dexamethasone as Vd. The Subcommittee acknowledged that there is no direct evidence comparing subcutaneous daratumumab with Vd, however, the Subcommittee considered that there was no evidence to suggest that efficacy outcomes with subcutaneous daratumumab would be any different to those with intravenous daratumumab.

5.28. The Subcommittee noted that the CASTOR trial population, which excluded patients whose disease was refractory to bortezomib, was consistent with funding recommendations for IV and SC daratumumab in international jurisdictions. However, the Subcommittee considered that funding either formulation only for patients with prior bortezomib response may create an unmet need in patients with disease refractory to or intolerant of bortezomib. The Subcommittee considered that this would compound the inequity for those patients who have not previously benefitted from a bortezomib containing treatment regimen in first line. Members considered however that such patients could reasonably benefit from daratumumab without use in combination with bortezomib because daratumumab has a different mechanism of action to current first-line treatments. However, Members noted that the evidence of response with daratumumab in the absence of bortezomib was lower than in combination with bortezomib, but acknowledged that the evidence supporting this was from patient populations with varying degrees of pre-treatment. The Subcommittee considered it reasonable to enable access to daratumumab for those bortezomib-refractory/intolerant patients based on the likely efficacy of daratumumab in this patient group and the unmet need that would arise of daratumumab were funded for only bortezomib responsive patients.

5.29. The Subcommittee considered that some patient subgroups are unable to access effective treatment options such as the 10-20% of autologous stem cell transplant-eligible patients who did not receive a sufficient response to cyclophosphamide, bortezomib and dexamethasone (CyBorD), noting that at least a partial response is desirable before transplant. The Subcommittee further considered that approximately 5% of transplant-ineligible patients would not be fit enough to receive a bortezomib-containing regimen.

5.30. The Subcommittee considered that the relative efficacy of daratumumab (IV or SC, as DVd) was hard to establish relative to regimens used internationally for second-line treatment of relapsed/refractory multiple myeloma (ie carfilzomib/dexamethasone, carfilzomib/lenalidomide/dexamethasone, pomalidomide/bortezomib/dexamethasone and pomalidomide/dexamethasone). The Subcommittee noted that this is because not even published indirect comparisons such as network meta-analysis exist for these comparisons, let alone direct comparisons. The Subcommittee also noted that it is not feasible to accurately compare outcomes across their corresponding trials, which lack direct comparability (eg due to different trial designs and patient populations). The Subcommittee considered however, that all of these regimens are considerably more efficacious than currently funded second-line treatment options for relapsed/refractory multiple myeloma in New Zealand.

5.31. The Subcommittee considered that daratumumab (as DVd) was a generally well-tolerated regimen with tolerability similar to that of pomalidomide (PVd), both of which were considered to be less toxic than carfilzomib, but overall considered that less toxicity occurs with daratumumab. As recorded in October 2020, the Subcommittee considered that daratumumab may be a more suitable option for treatment of elderly or frail patients who might otherwise not be able to receive a

more toxic therapy such as carfilzomib which is associated with cardiac toxicity. The Subcommittee considered that the reduced infusion risk with daratumumab SC alleviates a substantial treatment-related risk in this patient population.

5.32. The Subcommittee noted that treatment with daratumumab requires pan-antigen matched blood in case blood transfusion is needed, although members considered that not all patients require a transfusion during second-line treatment and that this is likely manageable by blood banks.

5.33. The Subcommittee noted that many patients would have second-line treatment with bortezomib as a SC injection administered at an infusion service, and noted that self administration and community administration of bortezomib is possible for some, but not all, patients. The Subcommittee noted that current standard of care is administered until maximum response and is then discontinued. The Subcommittee noted that daratumumab SC would require additional infusional resources. The Subcommittee considered that the short expiry would also reduce the feasibility of self-administration and community administration, and therefore administration of daratumumab SC may require ongoing treatment in hospital. The Subcommittee considered that daratumumab SC may be challenging to self administer because of the 15 ml volume of the subcutaneous injection, possibly requiring multiple injections per dose. The Subcommittee considered that the short expiry would also reduce feasibility of self administration in the community. The Subcommittee considered that ongoing use of daratumumab until disease progression would lead to an ongoing infusion requirement, in comparison to current standard of care, which is discontinued once maximum response is obtained. The Subcommittee considered that the subcutaneous formulation would reduce access inequities, based on chair time, however, it may not fully address inequities as patient travel is still required for access to treatment even if onsite treatment time is shorter.

5.34. The Subcommittee noted that the treatment time, infusion burden and infusion administration costs of daratumumab SC are minimal (three to five minutes per injection) compared with the significant IV infusion requirements for carfilzomib (about 20 hours per year if using ARROW protocol dosing 70 mg/m^2 once weekly, for three out of every four weeks per cycle) or monoclonal antibody treatment (eg daratumumab IV, three to seven hours depending on cycle [approximately 70 hours in year one and 40 hours each subsequent year], or 90 minutes per infusion if using the rapid treatment protocol [approximately 40 hours in year one and 20 hours each subsequent year]).

5.35. The Subcommittee considered that the option to use the 90-minute rapid protocol could substantially reduce the infusion impact of daratumumab IV, but that this would remain a substantial impact on the infusion service resource. The Subcommittee considered that cannulation required for IV treatment takes time and can become more difficult over time. The Subcommittee considered that the health system impact for daratumumab SC as DVd would be slightly more than that of PVd, given pomalidomide is an oral therapy that doesn't have the same infusion impact, noting that daratumumab SC would still require infusion day resource for maintenance dosing.

5.36. The Subcommittee noted that there is individual variation in treatment response with this disease. Members considered that, if daratumumab (IV or SC) were funded for second-line treatment, that transplant-ineligible patients would likely be offered lenalidomide third-line, and transplant-eligible patients (who would have previously received lenalidomide maintenance and have received bortezomib first- and second-line) may be offered either carfilzomib (Kd) or pomalidomide (PVd), if

funded, as lenalidomide is no longer accessible in the relapsed/refractory setting since its funding as first line maintenance therapy. The Subcommittee considered that reserving daratumumab for use in a later line would mean missing out on its expected benefit in the second line setting. However, members noted that the NZMIG may have a different view of treatment sequencing.

5.37. The Subcommittee noted the high cost of daratumumab SC and IV, with the high additional cost to health system for infusion of the IV treatment. The Subcommittee considered that biosimilar competition was an important factor when considering the funding of either formulation. The Subcommittee considered that in the absence of biosimilar competition the preferred treatment out of the two daratumumab formulations would be daratumumab SC. The Subcommittee considered that if the SC formulation were funded there would be a greater benefit to the health system from the lower infusion resource requirements. Members considered that subsequently changing a funded product from an SC formulation to an IV formulation would be challenging given the substantial resource impact and patient preference/expectation.

5.38. The Subcommittee considered that if daratumumab were funded in the relapsed/refractory setting, reconsideration regarding access to other treatments (eg. lenalidomide) would be required. The Subcommittee noted that evidence was emerging regarding the use of novel agents in combination with funded and unfunded treatments and that it would be important to ensure that new treatments were funded in combination with only those treatments where a positive recommendation had been obtained.

5.39. The Subcommittee considered that the below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for daratumumab if it were to be funded in New Zealand for second-line treatment of relapsed/refractory multiple myeloma. This PICO captures key clinical aspects of the proposal and may be used to frame any future economic assessment by Pharmac staff. This PICO is based on the Subcommittee's assessment at this time and may differ from that requested by the applicant. The PICO may change based on new information, additional clinical advice, or further analysis by Pharmac staff.

Population	Relapsed/refractory multiple myeloma (second-line treatment).
Intervention	Daratumumab, 1800mg subcutaneous injection, or 16 mg per kilogram administered intravenously, until disease progression.
Comparator(s)	Bortezomib retreatment (CyBorD or BTD).
Outcome(s)	Patients treated with daratumumab IV treatment with dexamethasone were reported to have a longer PFS and OS to patients treated with bortezomib with dexamethasone. Daratumumab sub-cutaneous injection has been reported to be non-inferior to daratumumab IV.
Table definitions: Population, the target population for the pharmaceutical; Intervention, details of the intervention pharmaceutical; Comparator, details the therapy(s) that the patient population would receive currently (status quo – including best supportive care); Outcomes, details the key therapeutic outcome(s) and source of outcome data.	

6. Pembrolizumab for relapsed/refractory Hodgkin lymphoma

Application

6.1. The Subcommittee considered an application from Merck, Sharp and Dome (MSD) for the funding of Pembrolizumab (Keytruda) for the treatment of relapsed/refractory Hodgkin lymphoma (HL) after two or more lines of chemotherapy for patients who are either ineligible for, or relapsed following, an autologous stem cell transplant.

Recommendation

6.2. The Subcommittee **recommended** that pembrolizumab for the treatment of relapsed/refractory Hodgkin lymphoma post autologous stem-cell transplant be listed with a **high priority** within the context of treatment for malignancy subject to the following Special Authority criteria:

Initial application (relapsed/refractory Hodgkin lymphoma – eligible for autologous stem cell 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:

Both:

1. Both:
    - 1.1. Patient has relapsed/refractory Hodgkin lymphoma after two or more lines of chemotherapy; and
    - 1.2. Patient has previously undergone autologous stem cell transplant; and
2. Patient has not previously received funded pembrolizumab for Hodgkin lymphoma

Renewal application (relapsed/refractory Hodgkin lymphoma– eligible for autologous stem cell transplant) - 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. Patient has achieved a partial or complete response to pembrolizumab after 6 treatment cycles; and
2. Treatment remains clinically appropriate, and the patient is benefitting from and tolerating treatment; and
3. Patient is to receive a maximum of 35 total cycles of pembrolizumab treatment.

6.3. The Subcommittee **recommended** that pembrolizumab for the treatment of relapsed/refractory Hodgkin lymphoma for patients ineligible for autologous stem-cell transplant be listed with a **high priority** within the context of treatment for malignancy subject to the following Special Authority criteria:

Initial application (relapsed/refractory Hodgkin lymphoma - ineligible for autologous stem cell 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:

Both:

1. Both
    - 1.1. Patient has relapsed/refractory Hodgkin lymphoma after two or more lines of chemotherapy; and
    - 1.2. Patient is ineligible for autologous stem cell transplant; or
2. Patient has not previously received funded pembrolizumab for Hodgkin lymphoma

Renewal application (relapsed/refractory Hodgkin lymphoma- ineligible for autologous stem cell transplant) - 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. Patient has achieved a partial or complete response to pembrolizumab after 6 treatment cycles; and
2. Treatment remains clinically appropriate, and the patient is benefitting from and tolerating treatment; and
3. Patient is to receive a maximum of 35 total cycles of pembrolizumab treatment.

6.4. In making these recommendations, the Subcommittee noted:

- the very high health need of these patients
- the lack of effective alternative funded therapies
- the improved response rate and progression-free survival compared to funded and unfunded treatments (eg. brentuximab vedotin), noting that the overall survival data was immature, but that progression free survival was a reasonable surrogate for overall survival in this patient group
- the reduced toxicity profile and improved convenience of pembrolizumab in comparison to currently funded treatments
- its previous recommendations and considerations regarding the funding of brentuximab vedotin for relapsed/refractory Hodgkin lymphoma.

Discussion

6.5. The Subcommittee noted that brentuximab vedotin for relapsed/refractory HL was reviewed by PTAC in August 2018, where it was recommended for decline due to incomplete evidence, lack of overall survival data, and uncertainty around durability of response and level of benefit. The Subcommittee noted that CaTSoP then reviewed the proposal in September 2018. At this meeting it was recommended for funding with a high priority for relapsed/refractory HL following two or more lines of chemotherapy for patients who are ineligible for autologous stem cell transplant or have already had an autologous stem cell transplant.

6.6. The Subcommittee noted that pembrolizumab as a 'bridge to transplant' for the treatment for relapsed/refractory HL for individuals eligible for autologous or allogeneic stem cell transplantation, had been previously considered by CaTSoP 2019. The Subcommittee noted that this application for patients with relapsed/refractory Hodgkin's lymphoma after two or more lines of chemotherapy for patients who are either ineligible for, or relapsed following, an autologous stem cell transplant had been previously considered by PTAC at its May 2018 meeting. PTAC deferred making a recommendation at that time pending updated evidence from KEYNOTE-204 trial and referred the application to CaTSoP, seeking the Subcommittee's view on the health benefits of pembrolizumab and brentuximab vedotin in this setting. The Subcommittee noted that it had reviewed this application in September 2018 where it also deferred making a recommendation, pending a comparison of brentuximab with pembrolizumab in this setting. The Subcommittee noted that the KEYNOTE-204 trial comparing brentuximab vedotin and pembrolizumab in the patient group for whom funding was requested has since been published (Kuruvilla et al. Lancet Oncol. 2021;22:512-24).

6.7. The Subcommittee considered that the prognosis for people with relapsed/refractory HL depends on multiple factors, including; time to relapse, stage of disease at time of relapse, and performance status. The Subcommittee noted that patients with refractory disease, including those who relapse less than three months after completion of treatment, have significantly worse outcomes than those who relapse having previously been in remission for longer periods.

6.8. The Subcommittee noted that currently the first line treatment for people with HL is chemotherapy which has a response rate of approximately 80%. The Subcommittee noted that the 20% of patients who are refractory or relapse following first line chemotherapy will go on to received second-line high dose

salvage chemotherapy, which may be followed by autologous-SCT if patients are eligible. The Subcommittee considered patients who had received second line salvage chemotherapy and relapsed after autologous stem cell transplant (auto-SCT) or are not eligible for auto-SCT had a severe health need as they would not be expected to live beyond 12 months. The Subcommittee considered that approximately 10-15 patients per year would be eligible for pembrolizumab in this setting. The Subcommittee noted that there is no evidence that HL disproportionately affects Māori, Pacific people, or those experiencing socioeconomic deprivation.

6.9. The Subcommittee noted the KEYNOTE-204 trial (Kuruvilla et al. Lancet Oncol. 2021;22:512-24), comparing pembrolizumab (n=151) and brentuximab vedotin (n=153) for the treatment of patients with relapsed/refractory HL post autologous-SCT (approximately a third of participants) or if ineligible for auto-SCT (two thirds of participants). The Subcommittee noted that ineligibility for auto-SCT could depend on chemotherapy-refractory disease, advanced age or the presence of comorbidities. The Subcommittee noted that over 80% of patients included in the trial were under the age of 65 and had received two or more previous lines of therapy. The Subcommittee considered that the patient population that was included in this trial was largely representative of the patient population that would access pembrolizumab if funded in New Zealand, although noted that there was a small proportion of patients included in the trial that had previously received brentuximab vedotin.

6.10. The Subcommittee noted that in the KEYNOTE-204 trial, the proportion of patients with an objective response was 65.6% in the pembrolizumab treatment group (95% CI 57.4 to 73.1) compared to 54.2% in the brentuximab vedotin treatment group (95% CI 46.0 to 62.3). The Subcommittee noted that median progression-free survival was 13.2 months (95% CI 10.9 to19.4) for the pembrolizumab treatment group versus 8.3 months (95% CI 5.7 to 8.8) for the brentuximab vedotin treatment group (hazard ratio (HR): 0.65 [95% CI 0·48 to 0·88]; p=0·0027). The Subcommittee noted that for many subgroups, the hazard ratio for progression-free survival was in favour of pembrolizumab compared to brentuximab vedotin, including those who had received ≥2 prior lines of treatment (HR: 0.67; [0.49 to 0.92]) and those without prior exposure to brentuximab vedotin (HR: 0.65; [0.48 to 0.88]).

6.11. The Subcommittee noted that overall survival from this trial was not reported because this endpoint had not been reached. However, the Subcommittee considered that the use of progression-free survival as a surrogate for overall survival was reasonable in this patient group given the late stage of the disease and the lack of effective treatments, which indicates that PFS translates quickly into survival status.

6.12. The Subcommittee noted that in this trial, treatment was to continue for up to two years or 35 cycles in the absence of disease progression or unacceptable adverse events for both treatment arms. The Subcommittee considered that this duration was longer than what would be expected for the usual duration of treatment with brentuximab vedotin and noted that only a small portion of patients were still receiving brentuximab vedotin after two years, although acknowledged that and noted that the majority of discontinuations in this treatment arm were due to progression. The Subcommittee noted that a greater proportion of patients in the pembrolizumab treatment arm remained on treatment at the two-year mark. The Subcommittee noted that similar results to that observed for pembrolizumab in the KEYNOTE 204 trial, using larger doses for shorter periods, have been reported

elsewhere (PFS 69% at 24 weeks and 46% at 52 weeks; Armand et al. J Clin Oncol. 2016;34:3733-39).

6.13. The Subcommittee noted that the safety profile of pembrolizumab was similar to that of brentuximab vedotin, with slightly more patients discontinuing treatment in the brentuximab vedotin arm (25/152 [16%]) compared to the pembrolizumab arm (19/148 [13%]).

6.14. The Subcommittee considered that the evidence supporting the use of pembrolizumab in relapsed/refractory HL was of moderate strength and quality, derived from a single trial comparing two currently unfunded agents in New Zealand. The Subcommittee considered it reasonable to consider this evidence as relevant to New Zealand, as it had previously recommended funding brentuximab with a high priority.

6.15. The Subcommittee noted that there is no direct evidence comparing pembrolizumab or brentuximab vedotin with conventional treatment (standard of care in New Zealand), but that there is non-experimental uncontrolled observational evidence suggesting that novel agents such as pembrolizumab and brentuximab vedotin have significant improvement in median overall survival compared to patients who did not receive novel agents (85.6 vs 17.1 months; p<0.001; Bair et al. AM J Haematol. 2017;92:879-84).

6.16. The Subcommittee also noted two studies regarding pembrolizumab in the treatment of HL previously considered by CaTSoP:

- Chen et al. J Clin Oncol. 2017;35:2125-2132.
- Armand et al. J Clin Oncol. 2016;34:3733-3799.

6.17. The Subcommittee noted four additional studies regarding pembrolizumab in the treatment of HL:

- Chen et al. Blood. 2019;134:1144-53
- Armand et al. Blood. 2019;134:22-9
- Armand et al. Blood Adv. 2020;4:2617-22
- Kuruvilla et al. Lancet Oncol. 2021;22:512-24

6.18. The Subcommittee considered that if pembrolizumab were to be funded for relapsed/refractory HL that some patients ineligible for transplant because of disease refractory to salvage chemotherapy may respond to treatment and become eligible. The Subcommittee considered, however, that the primary reasons for ineligibility for transplant were comorbidities and fitness, therefore, the expected increase in the number of auto-SCTs would be modest if pembrolizumab were funded for this patient group. The Subcommittee considered that it would be reasonable to assume that there would be no change in the number of allo-SCTs given the uncertainty regarding the impact of funding pembrolizumab on this outcome. The Subcommittee considered that funding of pembrolizumab may incur some additional cost to the health system if more patients become eligible for auto- SCT, but that because pembrolizumab was considerably less toxic than currently funded treatments, there might be decreased cost to the health system associated with the reduced need for supportive care.

6.19. The Subcommittee noted two trials comparing brentuximab vedotin to salvage chemotherapies (single arm trials) that reported longer progression-free survival

and overall survival with brentuximab vedotin vs standard chemotherapies for transplant ineligible patients (Brockelmann et al. Eur J Haematol. 2017;99:553-8) and patients post auto-SCT (Chen et al. Blood. 2016;128:1562-6). The Subcommittee noted that in the Chen et al 2016 trial, some patients were in remission after 5 years, and considered that this was indicative of a potentially curative effect of brentuximab vedotin for some patients in this group. The Subcommittee considered that the outcomes and patient population for brentuximab vedotin in the KEYNOTE 204 trial to be similar to that observed in the Chen et al. 2016 and Brockelmann et al. trials; the progression-free survival with brentuximab vedotin was 8.3 months in KEYNOTE-204, compared with 9.3 months in those patients who had relapsed post autologous SCT (Chen et al. Blood. 2016) and 15.1 months in those ineligible for auto-SCT the (Brockelmann et al. Eur J Haematol. 2017).

6.20. The Subcommittee noted the significantly different progression free survival observed for pembrolizumab compared to brentuximab in KEYNOTE 204 trial and considered that it would be reasonable to assume that the benefit of pembrolizumab extends beyond that observed for brentuximab (Chen et al. Blood. 2016; Brockelmann et al. Eur J Haematol. 2017). The Subcommittee considered that in the Chen et al. 2016 and Brockelmann et al. trials, progression free survival aligned closely to overall survival. The Subcommittee considered that a similar relationship could reasonably be inferred for the use of pembrolizumab in this setting.

6.21. The Subcommittee considered that the table below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for pembrolizumab if it were to be funded in New Zealand for relapsed/refractory HL. This PICO captures key clinical aspects of the proposal and may be used to frame any future economic assessment by PHARMAC staff. This PICO is based on the Subcommittee's assessment at this time and may differ from that requested by the applicant. The PICO may change based on new information, additional clinical advice, or further analysis by PHARMAC staff.

Population	Patient has relapsed/refractory Hodgkin's lymphoma after two or more lines of chemotherapy; and Patient is ineligible for autologous stem cell transplant; or Patient has previously undergone autologous stem cell transplant
Intervention	Pembrolizumab, 200mg fixed dose administered as an IV infusion over 30 minutes every three weeks. In the trial patients were treated until disease progression, with a maximum of 35 cycles.
Comparator(s) (NZ context)	Post-transplant: salvage chemotherapy (eg gemcitabine, dexamethasone and cisplatin [GDP]) Ineligible for transplant: palliative care
Outcome(s)	Longer PFS. While there is no direct comparison between pembrolizumab and current NZ chemotherapy treatments, brentuximab vedotin has a longer PFS and OS with compared to standard chemotherapies for transplant ineligible patients (Brockelmann et al) and patients post autologous stem cell transplant (Chen et al. 2016). KEYNOTE 204 provides evidence of a longer PFS in patients treated with pembrolizumab vs brentuximab vedotin.

Table definitions: Population, the target population for the pharmaceutical; Intervention, details of the intervention pharmaceutical; Comparator, details the therapy(s) that the patient population would receive currently (status quo – including best supportive care); Outcomes, details the key therapeutic outcome(s) and source of outcome data.

7. Pembrolizumab for the first-line treatment of microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) unresectable or metastatic colorectal cancer treatment, and the treatment unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) cancers that have progressed following prior treatment.

Application

7.1. The Subcommittee considered two applications;

- An application from Merck Sharpe and Dohme (MSD) for the use of pembrolizumab for the first-line treatment of unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer; and

- A consumer application for the use of pembrolizumab in adult and paediatric patients for the treatment of unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) cancers that have progressed following prior treatment.

Recommendation

7.2. The Subcommittee **recommended** that pembrolizumab for the first-line treatment of microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer be listed with a **high priority** within the context of treatments for malignancy subject to the following Special Authority criteria:

INITIAL APPLICATION – MSI-H/dMMR advanced colorectal cancer

Only from a medical oncologist; approvals valid for four months.

1. Patient has deficient mismatch repair (dMMR); or microsatellite instability-high (MSI-H) metastatic colorectal cancer; and
2. The patient has not received prior systemic therapy administered in the metastatic setting; and
3. The patient must have an ECOG performance score of 0-1; and
4. Baseline measurement of overall tumour burden is documented; and

RENEWAL-

Only from a medical oncologist; approvals valid for four months.

1. No evidence of disease progression; and
2. The total treatment received must not exceed 24 months

8.2.1 In making this recommendation the Subcommittee considered the high health need of patients with metastatic or unresectable MSI-H/dMMR colorectal cancer and the evidence supporting durability of response and suitability compared to currently available treatments.

7.3. The Subcommittee **deferred** making a recommendation on pembrolizumab for the treatment of microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) cancers that have progressed following prior treatment pending the publication of the KEYNOTE 158 trial.

8.3.1. In making this recommendation, the Subcommittee considered that the evidence available was of low quality with uncertainty in the validity of pembrolizumab as a tumour agnostic treatment. The Subcommittee considered there was variable positive data within individual tumour entities however this was not consistent enough between tumours to make generalisations about treatment.

8.3.2. The Subcommittee considered that whilst there was insufficient mature data for pembrolizumab as a tumour agnostic treatment, further assessment could be considered for individual tumour entities based on the availability of evidence demonstrating benefit from pembrolizumab treatment noting the available evidence for treatment of MSI-H/dMMR endometrial cancer appeared promising.

Discussion

7.4. The Subcommittee noted that DNA mismatch repair (MMR) is a key process in maintaining genomic stability and is facilitated by MMR proteins which are responsible for the control and coordination of repair of spontaneous point mutations within cellular proliferation. The Subcommittee noted that defects in the MMR process, leading from deficient MMR (ie dMMR) due to the loss or absence of activity of MMR proteins, are associated with genome-wide instability and the progressive accumulation of mutations especially within regions of simple repetitive DNA sequences known as microsatellites which result in a high microsatellite instability (MSI-H) phenotype, allowing mutations to be accumulated rapidly, resulting in tumour development.

7.5. The Subcommittee noted that dMMR is characterised by immunohistochemically determined loss of one or more MMR proteins (MSH2, MLH1, MSH6, PMS2), and confirmation of MLH1 promoter methylation is used to determine a cohort of patients who should proceed to genetic testing. The Subcommittee noted that MSI-H is determined by PCR assessment and characterised by 3 to 5 tumour microsatellite loci deleted if using a standard 5-panel profile, or >30% if a larger panel is used. The Subcommittee noted that in New Zealand immunohistochemistry is routinely performed for colorectal and endometrial cancers to confirm MSI and MMR status but is typically only performed for other tumour types on request. This would be for patients with a personal or family history suggestive of Lynch Syndrome (a cancer syndrome associated with inherited mutational changes in MMR resulting in genetic predisposition to different cancer types).

7.6. The Subcommittee noted a study of dMMR prevalence across a variety of tumour types (Le et al. Science. 2017;357:409-13) which reported, from a survey of 12,000 tumours, the most common cancers with dMMR were endometrial, gastric adenocarcinoma, small intestinal malignancies, and colorectal adenocarcinomas, with the proportion of dMMR higher in early stage tumours rather than late stage tumours, though this was not seen in all cancer types. The Subcommittee noted that due to their high mutation burden, dMMR cancers present significantly higher levels of neoantigens, which can provide a preclinical rational for the efficacy of immunotherapy in treating these cancers.

7.7. The Subcommittee noted that prognosis and treatments are variable for MSI-H/dMMR tumour types;

8.7.1 The Subcommittee noted that 90% of metastatic colon cancer is incurable, and that patients often have a poor prognosis of approximately

24-26 months regardless of chemo-sensitivity with the most aggressive current funded chemotherapy options in New Zealand. The Subcommittee noted that the prevalent patient population in New Zealand is younger than the worldwide average and considered that this attributes to the severe health need of colorectal cancer in New Zealand.

8.7.2 The Subcommittee noted endometrial cancer MSI is a negative prognostic feature, especially as there is no effective standard of care for metastatic disease and durability of response to current treatments is poor. The Subcommittee noted MSI-H/dMMR status in ovarian cancer is usually associated as being chemo-sensitive, with lower grade disease and longer overall survival.

8.7.3 The Subcommittee considered that patients with MSI-H/dMMR tumours have different health needs based on response rates to current treatments, durability of response, and the general prognosis associated with each malignancy and the tumour origin. The Subcommittee considered that there is insufficient evidence published to adequately analyse the competing prognostic risks of MSI-H/dMMR tumour subtypes and overall prognosis appears to be less dependent on dMMR status and more on stage of disease when comparing early vs. late-stage disease. The Subcommittee noted that within some tumour types, dMMR cohorts perform better than others especially if compared to BRAF mutational prognosis.

8.8 The Subcommittee also noted that the proportion of patients expected to be dMMR in the metastatic setting differs across tumour types and considered that approximately 5% of stage IV cancers of any type will be MSI-H/dMMR.

8.8.1 The Subcommittee noted that 15% of colorectal cancers are considered to be dMMR, with approximately 20% of colorectal cancers in the New Zealand patient population metastatic at diagnosis (Sharples et al. N Z Med J. 2018;131:24-39). The Subcommittee considered it more appropriate to use cancer registrations to estimate patient numbers, since these were associated with histology information. In their estimate of patient numbers, the Subcommittee assumed that 20% of cancer registrations in colorectal cancer (3,189) were metastatic, approximately 5% (based on 4% in the submission) were MSI-H/dMMR and 90% had an ECOG status of 0-1. The Subcommittee considered that this would equate to around 32 patients per year with MSI-H/dMMR solid tumours in New Zealand, among whom 95% could be expected to take up pembrolizumab, with a small a prevalent pool of patients in the first year.

8.9 The Subcommittee noted that there is no evidence that MSI-H/dMMR solid tumours disproportionately affect Māori, Pacific or other groups in the community who are socially or economically disadvantaged.

Colorectal cancer

8.10 The Subcommittee noted four phase II trials investigating immune checkpoint inhibitors (including pembrolizumab) in the treatment of colorectal cancer:

- Overman et al. Lancet Oncol. 2017;18:1182-91
- Le et al. Science. 2017;357:409-13

- Le et al. J Clin Oncol. 2020;38:11-9
- Andre et al. ASCO 2020. Gastrointestinal Cancers Symposium. Abstract 218

8.10.1 The Subcommittee noted that these were all small phase II studies of less than 450 people, with only three published studies despite a number of reports. The Subcommittee noted that FDA approval was granted to these treatments for colorectal cancer on the basis of this phase II data and biological plausibility. The Subcommittee noted that most of the Phase II studies were uncontrolled platform trials that merged selected arms in order to generate data and considered that randomised controlled trials of immunotherapy compared to placebo will likely never be undertaken, based on the evidence of response to immunotherapy treatment.

8.11 The Subcommittee noted a number of immunotherapy studies investigating treatment with dual immune checkpoint inhibitors as opposed to single agent therapy in MSI-H/dMMR metastatic colorectal cancer:

- Overman et al. J Cin Oncol. 2018;36:773-79
- Cohen et al. ASCO 2020. Gastrointestinal Cancers Symposium. Abstract 101

8.12 The Subcommittee considered that the PFS results from single and dual immunotherapy agent studies to be promising, demonstrating durable response with over 70% of PFS maintained at 12 months.

8.13 The Subcommittee noted the phase III, randomised, open-label trial (KEYNOTE-177; N=307) of pembrolizumab (200 mg 3-weekly) versus standard of care/investigators choice of chemotherapy for the first-line treatment of patients with MSI-H or dMMR metastatic colorectal cancer (Andre et al. N Engl J Med. 2020;383:2207-18). The Subcommittee noted pembrolizumab was given for a maximum of 35 cycles (equivalent to approximately 2 years), or until there was unacceptable toxicity or disease progression, with chemotherapy given until evidence of disease progression or toxicity.

8.13.1 The Subcommittee noted the concept of ‘sided-ness’ in the management of colorectal cancer was an important consideration in treatment choice and noted that the performance of patients in the control arm accounted for this with respect to enabling investigators choice for exposure to biologic therapies in the control arm. The Subcommittee considered this was appropriate and resulted in a pragmatic appropriate control arm.

8.13.2 The Subcommittee noted that colorectal patients with *BRAF* mutations typically have worse outcomes due to the inherently chemo-resistant nature of the mutation and can be over-represented in the dMMR patient population. The Subcommittee considered that patients with *BRAF* mutations were evenly distributed between the control and treatment arms in KEYNOTE-177.

8.13.3 The Subcommittee noted that the primary endpoints were progression free survival and overall survival, with secondary endpoints of response rate, safety, duration of response, and quality of life. The Subcommittee noted that crossover was permitted upon progression and considered that this may create challenges for analysis of overall survival, noting approximately 60% of patients accessed immunotherapy second line.

8.13.4 The Subcommittee noted that the PFS was reported to be 16.5 months compared to 8.2 months after the median follow up of 32.4 months (24.0-48.3). The Subcommittee noted the hazard ratio for death was reported to be 0.60 (95% CI 0.45 to 0.80; p=0.0002). The authors of the study considered that this hazard ratio was not valid, due to the progression-free survival curves for the two treatment groups crossing and not being parallel, indicating that the proportional hazards assumption was violated. Thus, the authors had considered that the hazard ratio should have been estimated from 8 months onwards or a restricted means analysis used to calculate an overall hazard ratio over the whole period without making the proportional hazards assumption. The Subcommittee agreed with this statistical approach. The Subcommittee considered the estimated restricted means for progression free survival over 24 months to be a more appropriate summary of the treatment effects, at 13.7 months for the pembrolizumab group (95% CI 12 to 15.4 months) versus 10.8 months for chemotherapy (95% CI 9.0 to 12.2 months).

8.13.5 The Subcommittee noted that 9.2% of participants in KEYNOTE-177 who received pembrolizumab were assumed to undergo surgery with curative intent as a consequence of a response to treatment, while 8.4% were assumed to undergo surgery with chemotherapy.

8.13.6 The Subcommittee noted grade ≥3 treatment related events differed between arms, occurring in 56% of pembrolizumab treatment patients compared to 78% of the chemotherapy treatment arm indicating pembrolizumab was better tolerated than chemotherapy. The Subcommittee considered that this difference would have significant resource implications however noted that pembrolizumab was associated with greater immune-mediated side effects which typically required more costly treatment interventions.

8.14 The Subcommittee noted an abstract from the 2021 ASCO Gastrointestinal Cancers Symposium (abstract 6) which presented the updated and now final progression free survival analysis for KEYNOTE-177. The Subcommittee noted that pembrolizumab was superior to chemotherapy for progression free survival (median 16.5 months versus 8.2 months, respectively; HR 0.60; 95% CI 0.45 to 0.80; p= 0.0002) and that the 12- and 24-month progression free survival rates were 55.3% and 48.3% with pembrolizumab vs 37.3% and 18.6% with chemotherapy.

8.14.1 The Subcommittee noted this data indicated some patients do poorly in the initial months of treatment due to a lack of early treatment efficacy and time until treatment effect, depending on the speed of disease progression.

8.14.2 The Subcommittee noted that overall, all subgroups analysed appear to favour pembrolizumab, including the *BRAF* mutation subgroup, and that there were no new safety signals identified.

7.15. The Subcommittee noted the health-related quality of life results from KEYNOTE-177 reported improvements in global health score, physical functioning, social functioning, and fatigue in the pembrolizumab treated group compared to the control group (Andre et al. Lancet Oncol. 2021;22:665-77). The Subcommittee considered that the differences in scores between the two treatment groups were clinically

significant, and that the quality-of-life improvements presented are very important to patients.

MSI-H/dMMR cancers (non-colorectal)

7.16. The Subcommittee noted a phase II observational cohort study investigating the use of pembrolizumab for the second- or subsequent line of treatment for 12 different MSI-H/dMMR tumour types, 55% of which were non-colorectal cancers (Le et al. Science. 2017;357:409-13). The Subcommittee noted that objective responses were similar between colorectal cancer and other cancer subtypes; 52% (95% CI, 36 to 68%) of patients with colorectal cancers versus 54% (95% CI, 39 to 69%) of the patients with cancers originating in other organs. The Subcommittee noted, however, that the patient numbers in each cohort were very small for groups other than colorectal and endometrial cancers and considered this made comparison of results between subgroups difficult.

7.17. The Subcommittee noted the phase II observational, open-label, non-randomised KEYNOTE-158 study (N=233) of pembrolizumab (200 mg for a maximum of 35 cycles) for the treatment of non-colorectal MSI-H/dMMR malignancy with advanced/metastatic disease who had progressed or had intolerance to standard therapy (Marabelle et al. J Clin Oncol. 2020;38:1-10). The Subcommittee noted that 27 individual tumour types were assessed, as well as one basket 'other' group.

8.17.1 The Subcommittee noted that the overall progression free survival was 4.1 months across all tumour types (95% CI 2.4 to 4.9) and that the median overall survival was 23.5 months (95% CI 13.5 to 'not reached'), with no new safety signals reported.

8.17.2 The Subcommittee noted that the greatest anti-tumour activity was observed in the endometrial and gastric cancer subgroups, with median progression free survival of 25.7 months (95% CI 4.9 to 'not reached') and 11.0 months (95% CI 2.1 to 'not reached'), respectively.

8.18 The Subcommittee noted updated, unpublished data from KEYNOTE-158 presented at ASCO 2021, which reported that 16% of patients were still on treatment at 37 months follow-up. The Subcommittee also noted that 73% of patients with endometrial cancer were still alive at 12 months, with an objective response rate of 30.8%, and a median duration of response of 47.5 months.

8.19 The Subcommittee also noted the following studies providing evidence for pembrolizumab for the treatment of MSI-H/dMMR solid tumours:

- Marabelle et al. J Clin Oncol. 2020;38:1-10
- Le et al. N Engl J Med. 2015;372:2509-20
- Zhao et al J Hematol Oncol. 2019;12:54

General

8.20 The Subcommittee noted that pembrolizumab for use in the treatment of adult and paediatric patients with unresectable or metastatic, MSI-H/dMMR solid tumours, regardless of tumour site or histology has been approved by the FDA, and that pembrolizumab appears in the NCCN guidelines as a treatment option for MSI-H/dMMR colorectal cancer. The Subcommittee also noted that in 2019, the PBAC recommended pembrolizumab as a second-line treatment for unresectable or

metastatic MSI-H/dMMR colorectal cancer be declined but considered that the evidence reviewed at the time included very early data. The Subcommittee noted SMC and CADTH recommendations for treatment of MSI-H/dMMR colorectal cancer were pending, and NICE had recommended pembrolizumab for first-line MSI-H/dMMR colorectal cancer provided pembrolizumab was provided in line with a commercial agreement with the supplier.

8.21 The Subcommittee considered that the most significant adverse events requiring either hospitalisation or further pharmacological treatment following pembrolizumab therapy are thyroid disorders, pneumonitis, colitis, hepatitis, skin reactions of various types, and type I diabetes.

8.22 The Subcommittee considered that the strength and quality of evidence for use of pembrolizumab in the treatment of MSI-H/dMMR cancers is strongest for colorectal cancer, and that MSI-H/dMMR tumours are a hypervariable, heterogenous population defined only by a single measure. The Subcommittee considered that the summative data of the different tumour type subgroups and the biological plausibility of using an immune checkpoint inhibitor for all MSI-H/dMMR cancers regardless of tumour subtype is not supported by the currently available evidence.

8.23 The Subcommittee considered that the evidence was too immature to indicate strongly which tumour types expressing dMMR would achieve the greatest gain in OS or PFS relative to currently available treatment and prognosis from pembrolizumab. The Subcommittee noted that KEYNOTE-158 results were soon to be published by ASCO as an update and considered it appropriate to wait for these before assessing which tumour types warranted further review. The Subcommittee considered that endometrial cancer seems to be the most promising treatment candidate after colorectal cancer, and that future review of updated data for endometrial cancer is warranted. The Subcommittee considered that extrapolation of the results from the above trials to imply benefit across all treatment arms is inappropriate as not all dMMR cancers have the same prognosis, respond to pembrolizumab in the same way, and some do not respond to pembrolizumab at all.

8.24 The Subcommittee considered that the phenomenon of clinical trial data evaluating biological plausibility by biological and molecular status definition rather than tumour histological organ specific definition (ie tumour agnostic basket studies) was likely to increase in prevalence and presented difficulties with both assessment of evidence, and assessment of cost-effectiveness due to the lack of homogeneity in outcomes and costs.

8.25 The Subcommittee considered oxaliplatin and capecitabine (CAPOX) to be an important part of the mixed comparator in this proposal noting CAPOX is preferred due to resource implications, relative to other treatment options, but folinic acid, fluorouracil and oxaliplatin (FOLFOX) is often used for patients with comorbidities, intolerance to CAPOX or issues swallowing tablets, for example.

8.26 The Subcommittee considered that the below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for pembrolizumab if it were to be funded in New Zealand for unresectable or metastatic, MSI-H or dMMR colorectal cancer. This PICO captures key clinical aspects of the proposal and may be used to frame any future economic assessment by PHARMAC staff. This PICO is based on the Subcommittee's assessment at this time and may differ from that requested by the

applicant. The PICO may change based on new information, additional clinical advice, or further analysis by Pharmac staff.

Population	Treatment of unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer, as per Special Authority criteria.
Intervention	200mg of pembrolizumab (2 x 100mg/4mL vials), administered by 30-minute infusion every three weeks. Treatment will be ceased in the event of disease progression, unacceptable toxicity, or patient withdrawal. Treatment is anticipated to ~17 months for colorectal MSI-H/dMMR cancers (KEYNOTE-117).
Comparator(s) (NZ context)	For patients with metastatic colorectal cancer, chemotherapy is the standard of care where surgical treatment alone is either insufficient or inappropriate. Single-agent chemotherapies used for metastatic colorectal cancer include capecitabine and 5-fluorouracil and combination regimens include the following, with proportions of patients estimated based on clinical advice: • FOLFIRI (40% of patients) o Leucovorin 400mg/m^2 once every 2 weeks o Fluorouracil bolus 400mg/m^2 once every 2 weeks o Fluorouracil infusion 2400mg/m^2 once every 2 weeks o Irinotecan 180mg/m^2 once every 2 weeks • FOLFOX (20% of patients) (mFOLFOX6 was the FOLFOX regimen used in KEYNOTE-177) o Leucovorin 400mg/m^2 once every 2 weeks o Fluorouracil bolus 400mg/m^2 once every 2 weeks o Fluorouracil infusion 2400mg/m^2 once every 2 weeks o Oxaliplatin 85/m^2 once every 2 weeks • CAPOX (40% of patients) o Capecitabine 1000/m^2 twice daily for first 2 weeks, then 1 week off o Oxaliplatin 130/m^2 once every 3 weeks
Outcome(s)	As per KEYNOTE-177: - Overall survival (24 months, 36 months) is a key endpoint, but only 120 of the 190 events required for the final analysis of overall survival had occurred at the data cut-off - Median progression free survival (24 months, 36 months) with pembrolizumab was 16.5 months, while with SOC median PFS was 8.2 months - Grade 3+ adverse events which the supplier included in the CUA. See above for details. - Health-related quality of life improved, as measured by EQ-5D-3L and EORTC QLQ-C30, in the pembrolizumab group and deteriorated to some extent across measures in the SoC group
Table definitions: Population, the target population for the pharmaceutical; Intervention, details of the intervention pharmaceutical; Comparator, details the therapy(s) that the patient population would receive currently (status quo – including best supportive care); Outcomes, details the key therapeutic outcome(s) and source of outcome data.	

9 Niraparib - Ovarian, fallopian tube or primary peritoneal cancer, advanced high-grade, first and second-line, platinum-sensitive – maintenance

Application

9.1. The Subcommittee considered an application from GlaxoSmithKline NZ Limited for niraparib (Zejula) for the following indications:

- First line maintenance for adult patients with newly diagnosed advanced and platinum-sensitive high-grade serous ovarian, fallopian tube or primary peritoneal cancer

- Second-line maintenance for adult patients with newly diagnosed advanced and platinum-sensitive high-grade serous ovarian, fallopian tube or primary peritoneal cancer.

Recommendation

9.2. The Subcommittee **recommended** that niraparib for first-line maintenance of BRCA mutated (BRCAm) ovarian cancer be funded with a **high priority** in the context of treatment of malignancy, subject to Special Authority criteria (see 1.5).

9.2.1 In making this recommendation, the Subcommittee noted the health need of patients with ovarian cancer with respect to disease severity and availability of alternative treatment options, the evidence of a progression-free survival benefit of niraparib in patients with BRCAm disease, the maintenance of quality of life with niraparib treatment compared with placebo, and suitability of niraparib as an oral treatment.

9.3. The Subcommittee **recommended** that niraparib for first-line maintenance of homologous recombination deficient (HRD) ovarian cancer be funded with a **medium priority** in the context of treatment of malignancy, subject to Special Authority criteria (see 1.5).

9.3.1. In making this recommendation, the Subcommittee noted the health need of patients with ovarian cancer with respect to disease severity and availability of alternative treatment options, however, noted the progression-free survival benefit of niraparib in the HRD ovarian cancer population was less than that seen in BRCAm ovarian cancer, and considered the significant cost and impact of HRD testing that is not currently available in New Zealand.

9.4. The Subcommittee **recommended** that niraparib for first-line maintenance of ovarian cancer irrespective of mutation status (ie an ‘all comers’ population) be funded with a **medium priority** in the context of treatment of malignancy, subject to Special Authority criteria (see 1.5).

9.4.1. In making this recommendation, the Subcommittee noted the health need of patients with ovarian cancer with respect to disease severity and availability of alternative treatment options, however, noted that use of niraparib in an ovarian cancer population who were not required to be tested for BRCAm or HRD in order to access funded niraparib treatment would result in some patients receiving a substantial benefit while other patients (those without BRCAm or HRD mutation) would receive less benefit, yet enabling access would remove the requirement for testing and therefore may improve equitable access to treatment.

9.5. The Subcommittee recommended that these niraparib first-line maintenance indications be funded subject to the following Special Authority criteria (note that

these criteria are to be adapted to the recommended patient population; shown in bold and square brackets):

NIRAPARIB
Initial application – (first-line maintenance) only from a medical oncologist 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 advanced high-grade serous* epithelial ovarian, fallopian tube, or primary peritoneal cancer; and
2. **[There is documentation confirming pathogenic BRCA1 or BRCA2 gene mutation/There is documentation confirming homologous recombination deficiency (HRD); and]**
3. Patient has received one line of previous treatment with platinum-based chemotherapy; and
4. Patient's disease must have achieved partial or complete response to the previous treatment with platinum-based chemotherapy; and
5. Patient has not previously received funded treatment with a PARP inhibitor; and
6. Treatment will be commenced within 12 weeks of the patient's last dose of the immediately preceding platinum-based regimen; and
7. Treatment to be administered as maintenance treatment; and
8. Treatment not to be administered in combination with other chemotherapy.

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

Renewal – (first-line maintenance) only from a medical oncologist or medical practitioner on the recommendation of a medical oncologist. Approvals valid for 6 months for applications meeting the following criteria:
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.

9.6. The Subcommittee **recommended** that niraparib for second-line maintenance of germline BRCA mutated (BRCAm) ovarian cancer be funded with a **high priority** in the context of treatment of malignancy, subject to Special Authority criteria (see 1.9).

9.6.1. In making this recommendation, the Subcommittee noted the health need of patients with ovarian cancer with respect to disease severity and availability of alternative treatment options, the evidence of a progression-free survival benefit of niraparib in patients with BRCAm disease, the maintenance of quality of life with niraparib treatment compared with placebo, and suitability of niraparib as an oral treatment.

9.7. The Subcommittee **recommended** that niraparib for second-line maintenance of homologous recombination deficient (HRD) ovarian cancer be funded with a **medium priority** in the context of treatment of malignancy, subject to Special Authority criteria (see 1.9).

9.7.1. In making this recommendation, the Subcommittee noted the health need of patients with ovarian cancer with respect to disease severity and availability of alternative treatment options, however, noted the progression-free survival benefit of niraparib in the HRD ovarian cancer population was less than that seen in BRCAm ovarian cancer, and considered the significant cost and impact of HRD testing that is not currently available in New Zealand.

9.8. The Subcommittee **recommended** that niraparib for second-line maintenance of ovarian cancer (irrespective of mutation status, ie an 'all comers' population) be

funded with a **medium priority** in the context of treatment of malignancy, subject to Special Authority criteria (see 1.9).

9.8.1. In making this recommendation, the Subcommittee noted the health need of patients with ovarian cancer with respect to disease severity and availability of alternative treatment options, however, noted that use of niraparib in an ovarian cancer population who were not required to be tested for BRCAm or HRD in order to access funded niraparib treatment would result in some patients receiving a substantial benefit while other patients (those without BRCAm or HRD mutation) would receive less benefit, yet enabling access would remove the requirement for testing and therefore may improve equitable access to treatment.

9.9. The Subcommittee recommended that these niraparib second-line maintenance indications be funded subject to the following Special Authority criteria (note that these criteria are to be adapted to the recommended patient population; shown in bold and square brackets):

NIRAPARIB
Initial application – (second-line maintenance) only from a medical oncologist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 6 months for applications meeting the following criteria:
All of the following:

1. Patient has a high-grade serous* epithelial ovarian, fallopian tube, or primary peritoneal cancer; and
2. **[There is documentation confirming pathogenic germline BRCA1 or BRCA2 gene mutation/There is documentation confirming homologous recombination deficiency (HRD); and]**
3. Patient has received one line of previous treatment with platinum-based chemotherapy; and
4. Patient's disease must have achieved partial or complete response to the previous treatment with platinum-based chemotherapy; and
5. Patient has not previously received funded treatment with a PARP inhibitor; and
6. Treatment will be commenced within 8 weeks of the patient's last dose of the immediately preceding platinum-based regimen; and
7. Treatment to be administered as maintenance treatment; and
8. Treatment not to be administered in combination with other chemotherapy.

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

Renewal – (second-line maintenance) only from a medical oncologist or medical practitioner on the recommendation of a medical oncologist. Approvals valid for 6 months for applications meeting the following criteria:
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.

Discussion

9.10. The Subcommittee noted that the health need of people with ovarian cancer, including ovarian, primary peritoneal or fallopian tube cancer that is platinum-sensitive (ie disease progression has occurred 6 months or more after the end of chemotherapy) has been previously described, most recently by PTAC in August 2020 and by CaTSoP in February 2021 in relation to an application for the polyadenosine 5'-diphosphoribose polymerase (PARP) inhibitor olaparib. The Subcommittee noted that olaparib is currently funded for the second-line maintenance treatment of platinum-sensitive ovarian cancer with germline BRCA mutation (gBRCA) only, and that olaparib has been considered for first-line maintenance treatment of platinum-sensitive BRCAm ovarian cancer.

9.11. The Subcommittee noted that about 80% of patients with ovarian cancer who receive first-line treatment with platinum-based chemotherapy are platinum-sensitive, and considered that this sensitivity correlates with a response to a PARP inhibitor such as olaparib or niraparib.

9.12. The Subcommittee noted that homologous recombination is a biological process that occurs as part of multistrand DNA repair and that the presence of identifiable errors in this repair process are described as homologous repair deficiency (HRD). The Subcommittee noted that well-known examples of HRD are mutations in breast cancer susceptibility gene 1 or 2 (BRCAm) which can occur either in the germline (gBRCA) as hereditary mutations occurring in about 15% of people with ovarian cancer, or as somatic mutations (sBRCA) that arise within a tumour in about 6% of ovarian cancer cases. The Subcommittee considered that platinum-sensitive disease, in which platinum-induced single-strand DNA breaks are not amended, also has deficiency in this repair pathway. The Subcommittee noted that other types of HRD occur in roughly 20% of ovarian cancers and that the population without HRD, including those without BRCAm (ie those who are HR proficient), account for 38-50% of ovarian cancers (Ngoi & Tan. ESMO Open. 2021;6:100144; Timms et al. J Clin Oncol. 2020;38(15_suppl):1586).

9.13. The Subcommittee noted that patients with gBRCA ovarian cancer are generally diagnosed at a younger age than those ovarian cancer patients without a BRCAm, have an increased risk of other malignancies and may experience added anxiety about mutation inheritance, although members identified no evidence to inform whether there are quality of life or survival differences between ovarian cancer patients with gBRCA and those without gBRCA. In addition, members considered that there is currently no evidence to inform whether there are any quality of life or survival differences between sBRCA, HRD and HR proficient patients with ovarian cancer.

9.14. The Subcommittee noted that there is emerging evidence of a poorly defined population with BRCA-like phenotype where their disease behaves like BRCAm, possibly resulting from non-BRCA gene mutations or other complex changes (ie epigenetics) affecting the HR repair pathway. The Subcommittee noted that this may occur in between 10-22% of ovarian cancers (Ngoi & Tan. 2021; Timms et al. 2020) and that there are multiple approaches seek to objectively and prospectively define this population such as functional tests (eg RAD51), mutation profiling for indicative mutations (eg signature3 or HRDetect), and genomic instability tests (ie germline damage indicating poor HR), although each of these tests has varied and challenging requirements.

9.15. The Subcommittee noted that current tests used internationally for diagnosis of genomic instability (ie HRD) include the FoundationOne CDx (Foundation Medicine) and myChoice CDx (Myriad Genetics) although it is unclear which should be preferred due to biased data and self-chosen thresholds. The Subcommittee noted that these two tests have reasonable agreement in outcomes and high agreement on HR proficient results, although these tests will not capture the proportion of patients with BRCA-like phenotype of epigenetic cause. The Subcommittee noted that neither of these tests are used in New Zealand outside of clinical trials or private testing and that unverified, nominal estimates of these costs could range from $2,000-5,000 per test.

9.16. The Subcommittee noted that the sensitivity of the current BRCAm test is high due to the quality of the reference data but noted that there is less data available for other types of HRD. The Subcommittee considered that the BRCAm reference population data is predominantly from Caucasian patients and therefore its

applicability to various other ethnic groups may overestimate population-level benefits of treatment in those other groups.

9.17. The Subcommittee noted that niraparib is an oral treatment that targets PARP-1 and PARP-2, and that the mechanism by which PARP inhibitors facilitate cancer cell death has been described previously. The Subcommittee noted that niraparib is being assessed under Pharmac's cancer medicines parallel assessment process, as it was submitted to Medsafe in November 2020 for the following indications:

- maintenance treatment of adult patients with advanced high-grade ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy
- monotherapy maintenance treatment of adult patients with platinum-sensitive relapsed high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy.

9.18. The Subcommittee noted that many PARP inhibitors are either under assessment or approved internationally and in most cases, were initially considered or approved for the targeted population with BRCAm disease however these medicines are being targeted at a broader population over time. The Subcommittee noted that niraparib was recommended for funding for first-line maintenance and for second-line maintenance in Canada (CADTH), Scotland (SMC), England & Wales (NICE; within Cancer Drugs Fund); although in all cases, improvement of cost-effectiveness was required.

Niraparib first-line maintenance

9.19. The Subcommittee noted evidence from PRIMA, a multi-centre phase III randomised (2:1), double-blind, placebo-controlled trial of 733 adult patients with newly diagnosed stage III/IV high grade serous or endometrioid ovarian cancer who had complete or partial response to first-line platinum-based chemotherapy, irrespective of HRD status (González-Martín et al. N Engl J Med. 2019;381:2391-2402). The Subcommittee noted that patients received oral niraparib or placebo once daily within 12 weeks after completion of the last dose of platinum-based chemotherapy starting with a fixed dose of 300 mg with the trial protocol subsequently amended to incorporate an individualised starting dose of 200 mg for patients with a baseline body weight of less than 77 kg, a platelet count of less than 150,000 per mm3, or both. The Subcommittee noted that treatment continued for 28-day cycles for 36 months or until disease progression.

9.20. The Subcommittee noted that patient characteristics were balanced between groups, the trial was powered appropriately for assessment of the primary outcome, and that participants were stratified appropriately according to their response to first-line chemotherapy, use of neoadjuvant therapy and HRD status. The Subcommittee noted that HRD was defined as the presence of a BRCA deleterious mutation, a score of at least 42 on the myChoice CDx (Myriad Genetics) test, or both. The Subcommittee noted that the myChoice test used a combined score of 0-100 with a cutpoint of 42 used to report HRD as positive or negative and that it was assumed that 50% of participants had HRD. The Subcommittee noted that PRIMA included both germline and somatic BRCAm.

9.21. The Subcommittee noted that PRIMA used both RECIST and CA125 to define disease progression with histologic progression or clinical symptoms and

considered this was a slightly different and more sensitive threshold than that used in other ovarian cancer literature. The Subcommittee noted that after median follow-up of 13.8 months, median progression-free survival (PFS), tested hierarchically, in the HRD population was 21.9 months with niraparib compared with 10.4 months with placebo (hazard ratio for disease progression or death, 0.43; 95% confidence interval [CI], 0.31 to 0.59; p<0.001) and in the overall population was 13.8 months with niraparib compared with 8.2 months with placebo (hazard ratio, 0.62; 95% CI, 0.50 to 0.76; p<0.001).

9.22. The Subcommittee noted that overall survival data was immature at the interim analysis with 10.8% of deaths having occurred in the overall population. The Subcommittee noted 177 patients were still on treatment at data cut-off and therefore considered it likely that some continued beyond two years of treatment, however, the Subcommittee considered that there was no evidence to indicate an appropriate duration of treatment for patients in response.

9.23. The Subcommittee noted that post-hoc exploratory subgroup analyses of PFS hazard ratios suggested there was greatest benefit from niraparib in the BRCAm population, a lesser benefit in non-BRCA HRD, and the least benefit in the HR proficient population. The Subcommittee noted that the greatest reported differences in PFS between niraparib and placebo were seen in the non-BRCAm HRD group (11.4 months) and BRCAm only (11.2 months), compared with HR proficient group (2.7 months) although the study was not powered to determine the size of effect in the latter population, therefore it was unclear if a significant benefit occurred in the HR proficient group. However, the Subcommittee noted that stratification imbalances were not correctly accounted for in the Cox regression analyses and considered that the HRD population drove the overall benefit, therefore the actual effect size was uncertain in each group.

9.24. The Subcommittee noted that the PRIMA study design limited its ability to detect the significance of a PFS benefit in the HR proficient group and the trial did not enrol participants from Pacific regions therefore it does not provide efficacy data in Asian populations, in particular, who are more susceptible to metabolic faults in carboxylesterase 1 that may affect PARP inhibitor metabolism and treatment response.

9.25. The Subcommittee considered that, overall, this single high-quality placebo-controlled randomised controlled trial provides evidence of a PFS benefit from niraparib first-line maintenance compared with current standard of care (observation) in the overall trial population, driven by a greater benefit in the HRD population (which included patients with germline and somatic BRCAm). The Subcommittee noted that niraparib first-line maintenance was associated with some toxicities, considered it would be associated with increased clinic requirements, but noted it was not associated with a decrement in quality of life.

Niraparib second-line maintenance

9.26. The Subcommittee noted evidence from NOVA, a phase III randomised (2:1) double-blind placebo-controlled trial of 533 adult patients with platinum-sensitive high-grade serous ovarian cancer in complete or partial response to their last line of platinum-based chemotherapy (Mirza et al. N Engl J Med. 2016;375:2154-64). The Subcommittee noted that patients received oral niraparib 300 mg or placebo once daily commencing no later than 8 weeks after completing their last dose of platinum-based therapy for 28-day cycles until disease progression, and that dose reductions to 200 mg or 100 mg were permitted in cases of toxicity.

9.27. The Subcommittee noted that patient characteristics were generally balanced between groups except prior receipt of ≥3 lines of chemotherapy which was reported in about half of gBRCA patients and about one-third of non-gBRCA patients, and roughly 10-15% of non-gBRCA patients received less prior chemotherapy than gBRCA patients. The Subcommittee considered this may impact the assessment of benefit in non-gBRCA compared with gBRCA populations from NOVA. The Subcommittee noted that the trial grouped patients as either gBRCA or non-gBRCA, the latter of which contained the HRD subgroup.

9.28. The Subcommittee noted that NOVA enrolled patients with gBRCA and sBRCA but participants were not stratified by this status. The Subcommittee noted that patients were stratified by time to progression, use of bevacizumab in prior chemotherapy line (which occurred in about 30%), and response to prior chemotherapy line. The Subcommittee considered that the trial criteria selected for a BRCA-like phenotype. The Subcommittee noted that post-hoc testing of HRD using the myChoice CDx would have grouped patients with sBRCA as HRD rather than as BRCAm.

9.29. The Subcommittee considered that NOVA was powered appropriately for assessment of the primary outcome of PFS using RECIST criteria (NOVA did not allow CA125 in its definition of progression). The Subcommittee noted that after median follow-up of 16.9 months, median PFS in patients with gBRCA was 21.0 months with niraparib compared with 5.5 months with placebo (difference of 15.5 months, HR, 0.27; 95% CI, 0.17 to 0.41); median PFS in the non-gBRCA HRD subgroup was 12.9 months with niraparib compared with 3.8 months with placebo (HR, 0.38; 95% CI, 0.24 to 0.59); and median PFS in the non-gBRCA group was 9.3 months with niraparib compared with 3.9 months with placebo (HR, 0.45; 95% CI, 0.34 to 0.61, p<0.001 in all three primary efficacy populations). The Subcommittee considered that these PFS benefits of even five months' improvement or longer and, by extrapolation, possibly survival benefits were clinically significant, noting that the time not on chemotherapy is important for this patient population in terms of quality of life.

9.30. The Subcommittee noted that the exploratory median PFS in the HR proficient subgroup was 6.9 months with niraparib compared with 3.8 months with placebo (difference of 3.1 months; HR, 0.58; 95% CI, 0.36 to 0.92; p=0.02).

9.31. The Subcommittee noted a post-hoc subgroup analysis of outcomes according to whether patients had received two vs more than two prior lines of chemotherapy (Mirza et al. 2016). The Subcommittee considered it was unclear whether there is a difference in effect for patients with gBRCA who had 2 lines of prior chemotherapy (ie receiving better effect than in those with gBRCA who had >2 lines prior chemotherapy) and patients with non-BRCA HRD who had 2 lines of prior chemotherapy (ie receiving a lesser effect than those with non-BRCA HRD who had >2 lines prior chemotherapy). The Subcommittee considered the post-hoc results did not align with biological rationales, as patients with non-BRCA HRD are generally quite well and are considered a chemotherapy-sensitive population.

9.32. The Subcommittee noted evidence from a conference presentation reporting substantial drop-out in NOVA with 155/553 (28%) of patients discontinuing the study for reasons other than death, resulting in arm imbalances between arms and reduced availability of survival data availability (Matulonis et al. [presentation notes]. Society of Gynecologic Oncology (SGO) Annual Meeting on Women's Cancer (virtual): 2021 March 19-25). The Subcommittee noted that subsequent treatment data and therefore crossover rates were missing for the discontinued

population. The Subcommittee noted that imputed and estimated data, adjusted for subsequent PARP inhibitor use, was used to generate an adjusted overall survival estimate in the context of substantial missing data. The Subcommittee considered that there is a possibility of an overall survival (OS) benefit in the gBRCA population but, as the analysis was based on a small sample with several steps, this could not accurately indicate the magnitude of any OS effect.

9.33. The Subcommittee noted that NOVA did not include low-grade serous or non-serous histology therefore potential benefits in those populations are unknown. The Subcommittee considered that NOVA provided evidence that niraparib second-line maintenance is associated with a PFS benefit for the overall trial population, with the greatest benefit seen in the gBRCAm population followed by the non-gBRCA HRD population. The Subcommittee considered that less benefit was seen in the non-BRCAm population which comprises both HRD (non-BRCAm) and HR-proficient patients, therefore the evidence cannot confirm the magnitude of any benefit for HR-proficient patients.

9.34. The Subcommittee also noted the following evidence:

- Oza et al. Lancet Oncol. 2018;19:1117-25
- Del Campo et al. J Clin Oncol. 2019;37:2968-73
- Fabbro et al. Gynecol Oncol. 2019;152:560-7
- an unpublished indirect treatment comparison provided by the supplier

9.35. The Subcommittee considered that funding niraparib for second-line maintenance would offer no difference in benefits or risks for patients with gBRCA who could otherwise receive funded olaparib maintenance after a response to second-line chemotherapy. However, the Subcommittee considered that niraparib second-line could offer a PFS benefit to patients with sBRCA or HRD and possibly a lesser benefit to patients who are HR-proficient, although accompanied by toxicity compared with observation alone.

General

9.36. The Subcommittee considered that toxicity with niraparib was similar between treatment lines, and that a wide range of any-grade toxicities were associated with niraparib compared with placebo. The Subcommittee noted that quality of life (QOL) data indicates some toxicity, however, the QOL between patients who received niraparib and those who received placebo was the same. The Subcommittee considered that this evidence could be interpreted as there being no adverse impact on QOL with niraparib despite additional toxicities and clinic visits with niraparib and as part of a clinical trial, compared with usual care.

9.37. The Subcommittee considered that the magnitude of benefit from niraparib on the HR proficient ovarian cancer population remains unclear.

9.38. The Subcommittee considered that the available evidence supports the use of one PARP inhibitor in a patient's treatment journey for ovarian cancer, either as a first-line maintenance therapy or as second-line maintenance.

9.39. The Subcommittee considered that the data suggests there may be a class effect among PARP inhibitors for first-line maintenance (ie olaparib, niraparib, veliparib) or second-line maintenance treatment (ie olaparib, niraparib, rucaparib) for ovarian cancer in terms of PFS, however, the clinical trial populations for these medicines differ in their definitions due to use of different companion diagnostics.

The Subcommittee noted that olaparib has not been validated with HRD tests and considered it was uncertain whether the HRD results from niraparib trials could be applied to treatment with olaparib. The Subcommittee considered that the benefits from PARP inhibitors appear greatest in BRCAm disease with lesser benefit in a broader general ovarian cancer population however more thorough review would inform assessment of a class effect of PARP inhibitors in ovarian cancer and what benefits may be expected in which clinical patient populations.

9.40. The Subcommittee noted that currently there is heavy demand on BRCA testing in New Zealand and that there can be significant delays in gaining timely access to genetic counsellors. The Subcommittee considered that funding a PARP inhibitor regardless of BRCA mutation status would potentially reduce the BRCA testing demand, although many clinicians would still test given potential familial implications. The Subcommittee considered that, if funded, niraparib would increase clinical resource use to some extent for the existing population with ovarian cancer (eg genetic testing, monthly blood tests and medical oncology clinic visits, and repeated CT imaging perhaps twice during maintenance treatment). The Subcommittee considered that a similar magnitude of health system impact would occur whether funded for first-line or second-line maintenance, although patients may have a longer duration on maintenance treatment in the first-line setting.

9.41. The Subcommittee noted that HRD testing is costly but quick to interpret given the yes/no result of the Myriad diagnostic. The Subcommittee noted that HRD testing is currently not available in New Zealand. The Subcommittee considered that, if niraparib were funded for somatic BRCAm, this could result in patients seeking a new test of a tumour tissue sample requiring a separate process involving a biopsy.

9.42. The Subcommittee noted that the FoundationOne HRD test is validated only for rucaparib and that olaparib is not validated with any HRD tests, therefore would not be appropriate to test for HRD and treat with olaparib based on HRD results.

9.43. The Subcommittee considered that, whilst evidence of benefit was limited in the HR proficient population, funding niraparib for the wider ovarian cancer population irrespective of mutational status (ie an ‘all comers’ population) would enable access to a PARP inhibitor without the requirement for mutational testing. The Subcommittee considered that funding niraparib without requiring mutational testing may have a benefit for those unable to access costly mutational testing and reduce the health system impact from additional testing in the ovarian cancer patient population. The Subcommittee acknowledged the overall benefit in an ‘all comers’ population would be driven by the BRCAm/HRD population groups, noting HR proficient patient populations in the first-line are expected to have PFS of approximately 2 months. The Subcommittee considered that for these HR proficient patients, the short period of time until treatment progression would likely result in a shortened treatment period and recommended Pharmac undertake analysis to understand the cost of this compared with the costs associated with treating the ‘all comers’ patient population.

9.44. The Subcommittee considered that, if funded, niraparib would not be used in combination with any other anticancer medicines nor would it replace any anticancer medicines although members noted that combination treatment is being investigated in clinical trials. The Subcommittee considered that first-line maintenance with niraparib would provide an additional maintenance treatment option within a line of therapy, and that second-line maintenance irrespective of mutation status would provide an additional option for patients without gBRCA, as

those with gBRCA could access olaparib. The Subcommittee considered that if more than one PARP inhibitor were funded, patients may choose to start treatment with either in a random fashion and that switching from one PARP inhibitor to another would be unlikely unless a patient experienced dose-limiting toxicity with one PARP inhibitor.

9.45. The Subcommittee considered that approximately 30 patients with gBRCA and sBRCA may be eligible for niraparib first-line maintenance per year, and that only patients with gBRCA would be eligible for second-line maintenance. The Subcommittee considered that funding the population with ovarian cancer irrespective of mutation status would result in much higher eligible patient numbers. The Subcommittee considered that a small prevalent pool may occur in both the first-line and second-line due to the timeframe to commence PARP inhibitor treatment post-chemotherapy, however, if not restricted by this timeframe then the prevalent pool would double in both lines.

9.46. The Subcommittee considered that, if funded in the absence of other funded PARPi's, niraparib uptake would be 100% in the populations with gBRCA and sBRCA, respectively, and uptake in the ovarian cancer population irrespective of mutation status would reach 100% within three to six months.

9.47. The Subcommittee considered that, given available evidence supported once-per-patient-lifetime access to a PARP inhibitor, if niraparib were funded, the preference would be for first-line use due to greater evidence for benefits in the first-line setting. However, members considered that some patients would prefer to receive a PARP inhibitor in the second-line maintenance setting rather than first-line due to the risk of possible serious side effects including myelodysplastic syndrome and acute myeloid leukaemia).

9.48. The Subcommittee noted that the supplier had proposed funding criteria that stated niraparib should be commenced with 8 weeks of the last dose of platinum-based chemotherapy for first-line or second-line maintenance. However, the Subcommittee considered that the Special Authority criteria should align with what was used in the clinical trials for niraparib (ie 12 weeks for first-line and 8 weeks for second-line).

9.49. The Committee considered that the below summarises its interpretation of the most appropriate PICOs (population, intervention, comparator, outcomes) information for niraparib if it were to be funded in New Zealand for first-line or second-line maintenance, respectively, for ovarian cancer. These PICOs capture key clinical aspects of the proposals and may be used to frame any future economic assessment by Pharmac staff. These PICOs are based on the Subcommittee's assessment at this time and may differ from that requested by the applicant. These PICOs may change based on new information, additional clinical advice, or further analysis by Pharmac staff.

Populations	Adult patients with newly diagnosed high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who have had a complete response or partial response to **first-line** platinum-based chemotherapy. See proposed special authority for more detail. • Patients with BRCAm (germline and somatic) • Patients with HRD • All comers (ie regardless of BRCA mutation status)
Intervention	Niraparib – treatment commenced within 8 weeks of last platinum-based regimen dose and continued until disease progression or death.

	200 mg once daily – patient <77kg OR have a platelet count of <150,000/μL 300 mg once daily – patient ≥77kg AND have a platelet count ≥150,000/μL Post-relapse, patients will receive salvage chemotherapy.
Comparator(s)	Surveillance following first-line platinum-based chemotherapy, then after relapse, second-line platinum-based chemotherapy with maintenance olaparib therapy for gBRCAm patients, otherwise surveillance.
Outcome(s)	<u>BRCAm (germline and somatic)</u> Improved progression free survival (HR 0.40, 95%CI: 0.27 to 0.62) as per the PRIMA clinical trial. No overall survival data. <u>HRD</u> Improved progression-free survival (HR, 0.43; 95% CI: 0.31 to 0.59; p<0.001) and overall survival (HR, 0.61; 95% CI, 0.27 to 1.39) as per the PRIMA trial. <u>All comers</u> Improved progression free survival (HR 0.62, 95%CI: 0.50 to 0.76) and overall survival (HR 0.70 95%CI: 0.44 to 1.11) as per the PRIMA clinical trial.
Table definitions: Population, the target population for the pharmaceutical; Intervention, details of the intervention pharmaceutical; Comparator, details the therapy(s) that the patient population would receive currently (status quo – including best supportive care); Outcomes, details the key therapeutic outcome(s) and source of outcome data.	

Populations	Adult patients with platinum-sensitive, high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who have had a complete response or partial response to **second-line** platinum-based chemotherapy. See proposed special authority for more detail. • Patients with germline BRCAm • Patients with HRD • All comers (ie regardless of BRCA mutation status)
Intervention	Niraparib – treatment commenced with 8 weeks of last platinum-based regimen dose and continued until disease progression or death. 200mg once daily – patient <77kg OR have a platelet count of <150,000/μL 300mg once daily – patient ≥77kg AND have a platelet count ≥150,000/μL Post relapse patients will receive surveillance or salvage chemotherapy.
Comparator(s)	Second-line platinum-based chemotherapy with either maintenance olaparib therapy (for patients with germline BRCAm only) or surveillance.

Outcome (s)	<u>Germline BRCAm</u> Improved progression free survival (HR 0.27 95%CI: 0.17 to 0.41) and overall survival (HR, 0.66, 95% CI: 0.44 to 0.99) as per the NOVA clinical trial <u>HRD</u> *Germline BRCAm population:* Improved progression free survival (HR 0.27 95%CI: 0.17 to 0.41) and overall survival (HR, 0.66, 95% CI: 0.44 to 0.99) as per the NOVA clinical trial *Non-gBRCA HRD+ subgroup:* Improved progression-free survival (HR, 0.38; 95% CI, 0.24 to 0.59) and overall survival (no difference observed) as per the NOVA clinical trial. <u>All comers</u> *gBRCAm population:* Improved progression free survival and overall survival for the BRCAm population as detailed above *Non-BRCAm population:* Improved progression free survival (HR, 0.45; 95% CI, 0.34 to 0.61) and overall survival (no difference observed) as per the NOVA clinical trial
Table definitions: Population, the target population for the pharmaceutical; Intervention, details of the intervention pharmaceutical; Comparator, details the therapy(s) that the patient population would receive currently (status quo – including best supportive care); Outcomes, details the key therapeutic outcome(s) and source of outcome data.	

10. Pegfilgrastim and lipegfilgrastim clinical equivalence and criteria

Application

10.1. The Subcommittee noted a discussion paper prepared by Pharmac staff seeking advice on the access criteria for long-acting filgrastim, and the potential inclusion of pegfilgrastim, pegfilgrastim biosimilars and lipegfilgrastim in a competitive procurement process.

Recommendation

10.2. The Subcommittee supported a competitive process for long-acting filgrastim, and considered pegfilgrastim, pegfilgrastim biosimilars and lipegfilgrastim to be clinically equivalent with no significant concerns regarding people changing treatments if required.

Discussion

10.3. The Subcommittee noted that lipegfilgrastim is pegylated via conjugation to a glycan moiety and not directly to an amino acid in standard pegylation like that of pegfilgrastim. The Subcommittee noted that lipegfilgrastim binds to the human granulocyte colony-stimulating factor (G-CSF) receptor similarly to filgrastim and pegfilgrastim.

10.4. The Subcommittee noted the current Special Authority criteria for pegfilgrastim. The Subcommittee noted that as part of Pharmac's response to COVID-19, a change was made to widen the access criteria of pegfilgrastim for patients undergoing high risk chemotherapy for cancer to prevent neutropenia and reduce

the risk of hospitalisation, thus reducing the burden on the health sector. This change reduced the threshold for access from a 20% risk of febrile neutropenia to a 5% risk of febrile neutropenia. The Subcommittee considered that if the criteria were changed, those with previous approvals under the wider access criteria would remain eligible for pegfilgrastim.

Clinical criteria

10.5. The Subcommittee noted that the ASCO (Smith et al. J Clin Oncol. 2015;28:3199-212) and EORTC (Aapro et al. Eur J Cancer. 2010;47:8-32) guidelines recommend that prophylaxis with a G-CSF is recommended in patients who have an approximately 20% or higher risk for febrile neutropenia on the basis of patient-disease-, and treatment-related factors. The Subcommittee however noted that it may be appropriate for certain patients with a febrile neutropenia risk of 10-20% to receive treatment if they are at an increased risk of febrile neutropenia due to individual risk factors (eg. age, advanced disease, history of febrile neutropenia etc.).

10.6. The Subcommittee considered that it would be appropriate to amend the current access criteria to reflect international guidelines. The Subcommittee considered that the below criteria would be appropriate for the use of pegfilgrastim:

Special Authority for Subsidy
Initial application only from a relevant specialist, vocationally registered general practitioner or medical practitioner on the recommendation of a relevant specialist. Approvals valid without further renewal unless notified for applications meeting the following criteria:
Both:

1. Treatment is to be used for the prevention of neutropenia; and
2. Either:
   - 2.1. Patient is undergoing high risk chemotherapy for cancer (febrile neutropenia risk greater than or equal to 20%*); or
   - 2.2. Both:
     - 2.2.1. Febrile neutropenia risk greater than or equal to 10%*; and
     - 2.2.2. Patient is treated on a myelosuppressive chemotherapy protocol and is considered to be at excessive risk of febrile neutropenia

Note *Febrile neutropenia risk after taking into account other risk factors as defined by the European Organisation for Research and Treatment of Cancer (EORTC) guidelines

Competitive procurement process

10.7. The Subcommittee noted two meta-analyses (Bond et al. J Oncol. Pharm Practice. 2018;24(6):412-23 and Wang et al. Nature 2019;9:15374), which analysed the incidence of severe and febrile neutropenia, severity of infection, safety, and quality of life in patients after chemotherapy treatment. The Subcommittee noted that there was no difference between lipegfilgrastim, pegfilgrastim and pegfilgrastim biosimilars in these endpoints.

10.8. The Subcommittee noted the results of the AVOID neutropenia study (Hartmut et al. Supp Care Cancer. 2021;29:2519-27), which assessed the efficacy and safety of lipegfilgrastim versus pegfilgrastim in elderly patients with aggressive B cell non-Hodgkin lymphoma receiving myelosuppressive chemotherapy. The Subcommittee noted that lipegfilgrastim was non-inferior to pegfilgrastim for the duration of severe neutropenia with a similar safety profile.

10.9. The Subcommittee noted that in Australia the PBAC considered pegfilgrastim, lipegfilgrastim, and filgrastim should be treated as interchangeable on an individual patient basis.

10.10. The Subcommittee noted that pegfilgrastim, lipegfilgrastim and pegfilgrastim biosimilars had the same dosing and administration, as well as a similar safety profile. The Subcommittee considered there to be no additional benefits or risks associated with the use of pegfilgrastim and lipegfilgrastim or pegfilgrastim biosimilars. The Subcommittee considered lipegfilgrastim, pegfilgrastim and pegfilgrastim biosimilars to be both clinically equivalent, and interchangeable.

10.11. The Subcommittee considered that it would be appropriate for patients to change from pegfilgrastim to either lipegfilgrastim or a biosimilar pegfilgrastim product within a treatment course and considered that a 5 month transition period, as per Pharmac's Annual Invitation to Tender, would be appropriate.

10.12. The Subcommittee considered that they had no concerns with patients changing between pegfilgrastim and either lipegfilgrastim or a pegfilgrastim biosimilar and considered that a competitive procurement process for the long acting filgrastim market could be run that resulted in the listing of one of pegfilgrastim lipegfilgrastim or a pegfilgrastim biosimilar.

11. Nab-paclitaxel - Metastatic breast cancer

Application

11.1. The Subcommittee noted the applications from Specialised Therapeutics Limited in 2010, the New Zealand Breast Cancer Special Interest Group (NZBSIG) in 2013, and additional information provided by the Breast Cancer Aotearoa Coalition (BCAC) in 2018 for the funding of nanoparticle albumin-bound paclitaxel (nab-paclitaxel) for the treatment of metastatic breast cancer (mBC).

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

Recommendation

11.3. The Subcommittee **recommended** that the application for nab-paclitaxel for the treatment of metastatic breast cancer in patients with history of hypersensitivity reactions, or contraindication to paclitaxel be funded with a **high priority**, in the context of treatment of malignancy, subject to the following Special Authority critieria:

Nanoparticle albumin-bound paclitaxel (nab-paclitaxel)

INITIAL APPLICATION – Metastatic breast cancer.

Applications only from an oncology or relevant specialist on the recommendation of an oncologist. Approvals valid for 6 months.

All of the following:

1. Patient has metastatic breast cancer
2. Patient is contraindicated to, or has experienced a grade ≥3 adverse event from, prior treatment with taxane chemotherapy.

Nanoparticle albumin-bound paclitaxel (nab-paclitaxel)

RENEWAL APPLICATION – Metastatic breast cancer.

Applications only from an oncology or relevant specialist on the recommendation of an oncologist. 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.

11.3.1. In making this recommendation, the Subcommittee considered the health need of patients with metastatic breast cancer contraindicated or intolerant to paclitaxel therapy, the likely benefit that could be achieved from nab-paclitaxel therapy in patients contraindicated or intolerant to taxane therapy, the improved toxicity profile and suitability of nab-paclitaxel compared with comparator therapies.

11.4. The Subcommittee **recommended** that the application for nab-paclitaxel for the treatment of metastatic breast cancer be funded with a **medium priority**, in the context of treatment of malignancy.

Nanoparticle albumin-bound paclitaxel (nab-paclitaxel)

INITIAL APPLICATION – Metastatic breast cancer.

Applications only from an oncology or relevant specialist on the recommendation of an oncologist. Approvals valid for 6 months.

1. Patient has metastatic breast cancer

Nanoparticle albumin-bound paclitaxel (nab-paclitaxel)

RENEWAL APPLICATION – Metastatic breast cancer.

Applications only from an oncology or relevant specialist on the recommendation of an oncologist. 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.

11.4.1. In making this recommendation, the Subcommittee considered the reduction in burden on clinical resources from a shorter infusion duration, the likely benefit that could be achieved from nab-paclitaxel therapy compared with paclitaxel therapy, the improved toxicity profile and suitability of nab-paclitaxel compared with comparator therapies.

Discussion

11.5. 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.

11.6. The Subcommittee noted that the application for nab-paclitaxel for treatment of metastatic breast cancer has been considered numerous times, first in November 2010 by PTAC and CaTSoP, and more recently by PTAC in May 2019 where PTAC had recommended nab-paclitaxel be listed if cost-neutral to weekly paclitaxel, taking into account pharmaceutical and administration costs.

11.7. The Subcommittee noted that in October 2020 nab-paclitaxel was included in a proposal to decline inactive funding applications, noting that it was unlikely that cost-neutral pricing of nab-paclitaxel compared with solvent based paclitaxel could be achieved to enable progression. The Subcommittee noted feedback received in response to this consultation from clinicians, patients and the Breast Cancer Aotearoa Coalition, indicating that there is a patient group who cannot tolerate paclitaxel, for whom there are few other treatment choices available in New Zealand, noting that the available chemotherapy options (including paclitaxel) are

comparatively appreciably toxic, reduce quality of life and often result in discontinuation.

11.8. The Subcommittee noted that paclitaxel is a taxane formulated with a cremaphor-based solvent that traps paclitaxel in micelles resulting in nonlinear pharmacokinetics and, whilst considered effective in producing an anti-tumour effect against a range of solid tumours, is frequently associated with toxicity hypersensitivity reactions and neuropathies. The Subcommittee noted that paclitaxel typically requires a 90 minute infusion time due to the requirement for coadministration of corticosteroids and antihistamines.

11.9. The Subcommittee noted evidence that weekly paclitaxel had higher response rates, and increased time to progression than 3 weekly administration and considered that weekly administration of paclitaxel is now standard practice (Gonzalez-Angulo et al. JClinOnc. 2008;26(10):1585-7). Members considered that pre-medication prior to paclitaxel administration could be ceased following a desensitisation phase, typically after the first 3-4 doses, noting however that approximately 1-2% of patients may still develop hypersensitivity reactions.

11.10. The Subcommittee noted that hypersensitivity to paclitaxel can occur in up to 45% of patients, with severe hypersensitivities occurring in 2-5%, noting that whilst the coadministration of steroids and H1 or H2 blockers prior to administration can reduce the frequency of hypersensitivity reaction, severe reactions can still occur in 1-2% of patients despite premedication. The Subcommittee considered that the cremaphor solvent was the likely cause of adverse reactions and can result in either immediate reaction or delayed cutaneous reactions in 10-15% of patients. The Subcommittee noted that the development of neuropathy with solvent based paclitaxel was a concern, occurring in 42-70% of patients, occurring as a grade 3-4 adverse event in approximately 7% (Uptodate; Paclitaxel (conventional): Drug information). The Subcommittee considered that the risk of toxicity from paclitaxel appears to be dose and frequency dependent; however, members noted that it was unclear whether increasing frequency of administration to weekly (with a smaller dose) reduced the impact of all side effects including the frequency of neuropathy.

11.11. The Subcommittee noted the alternative taxane to paclitaxel, docetaxel, is considered more toxic and no more effective than weekly paclitaxel, and its use is typically confined to metastatic disease where there is pre-existing neuropathy.

11.12. The Subcommittee noted that instead, nab-paclitaxel is a colloidal suspension of paclitaxel, bound to human serum albumin as nanoparticles. The Subcommittee noted solid tumours have a high metabolic uptake of albumin, which may result in greater penetration of nab-paclitaxel due to heightened permeability of tumour vasculature.

11.13. The Subcommittee noted that nab-paclitaxel can be infused over a much shorter time period (30 minutes) every three weeks, with reduced risk of hypersensitivity reactions. The Subcommittee considered that the primary benefit of nab-paclitaxel compared to paclitaxel, related to safety and mode of administration, as nab-paclitaxel does not require pre-medication, can be infused over a shorter time period, freeing up clinical resource and infusion capacity, and reduces the risk of hypersensitivity.

11.14. The Subcommittee noted nab-paclitaxel is widely available internationally, can be used with caution in patients with history of prior hypersensitivity reaction to paclitaxel, can be used in a range of other indications such as pancreatic cancer

and ovarian cancer, and is increasingly used as part of combination chemotherapy regimens alongside novel immunotherapy agents.

11.15. The Subcommittee noted the available, updated evidence since nab-paclitaxel was last reviewed:

11.16. A systematic review of five studies including neoadjuvant RCT and cohort studies comparing the efficacy and safety of nab-paclitaxel to solvent-based (sb) taxanes, paclitaxel or docetaxel (Li et al. J Int Med Res. 2020;48(8):300060520943473). The Subcommittee noted that there were differences in the dosing regimens of paclitaxel and nab-paclitaxel in studies included in this review. Neoadjuvant nab-paclitaxel improved both pathologic complete response (pCR) (odds ratio (OR) = 1.39, 95% confidence interval (CI) = 1.16–1.67), and event-free survival (EFS) rates (hazard ratio (HR) = 0.69, 95% CI = 0.57–0.85), but without any significant differences in overall survival (OS). All-grade adverse events of neutropenia, neuropathy, fatigue and rash were more frequent in the nab-paclitaxel arm with no significant difference found in the rates of severe adverse events of neutropenia, rash, vomiting or fatigue; however, grade ≥3 peripheral neuropathy was more frequent with nab-paclitaxel in higher dosing regimens. The Subcommittee considered lower doses than those attributed to neuropathy reactions were typically used in practise.

11.17. Long-term outcome data of GeparSepto trial of 1,206 patients comparing nab-paclitaxel (weekly 150 mg/m^2, then 125mg/m^2) with paclitaxel (weekly 80 mg/m^2) (Untch et al. J Clin Oncol. 2019;37:2226-34). At median follow up (49.6 months) nab-paclitaxel had an improved pathologic complete response (pCR rate) (38 vs 29%) and invasive disease-free survival (IDFS) rate at four years (84.0% vs. 76.3%; HR: 0.66, 95% CI, 0.51 to 0.85, p=0.02), with no OS difference (89.7% *v* 87.2%, respectively; HR, 0.82; 95% CI, 0.59 to 1.16; *P* = .260). Treatment related neuropathy was reported to resolve more rapidly with lower dose nab-paclitaxel, compared with higher doses.

11.17.1. A meta-analysis comparing the efficacy and safety of nab-paclitaxel chemotherapy compared with solvent-based (sb)-taxanes paclitaxel and docetaxel three weekly, or 150 mg/m^2 (Lee et al. Sci Rep. 2020;10:530) in patients with metastatic breast cancer. Of five RCTs identified, nab-paclitaxel reported improved overall response rates (ORR) (OR 2.39, 95% CI 1.69-3.37, p<0.001) and progression-free survival (PFS) (HR 0.75, 95% CI 0.62-0.90, p=0.002), with a small OS benefit compared with docetaxel (HR 0.73, 95% CI 0.54-0.99, p=0.04). The Subcommittee noted hypersensitivity reactions were not reported; however adverse events and discontinuation rates appeared comparable between trials' arms.

11.17.2. A Phase II randomised open-label trial assessing chemotherapy-induced neurotoxicity in different regimens of nab-paclitaxel compared with solvent-based (sb) paclitaxel in first line metastatic breast cancer (Ciruleos et al. Oncologist. 2019;24:1024-33.). Neurotoxicity, as evaluated by total neurotoxicity scores did not differ significantly between groups; however the Subcommittee considered that the study did not include sufficient patients to draw statistically valid conclusions related to safety.

11.18. The Subcommittee noted a clinical review evaluating the clinical experience of nab-paclitaxel as a single agent, or in combination with targeted agents in different populations to assess administration, adverse event profile and standard efficacy points (Martin, M. Breast Cancer Res. 2015; 17(1):81.) The Subcommittee noted the 100mg/m^2 nab-paclitaxel dose was reported to have a more manageable

toxicity profile compared to other regimens including solvent-based (sb) paclitaxel and docetaxel, with lower rates of grade 3 / 4 adverse events, including reduced rates of dose related neuropathy vs higher doses of weekly nab-paclitaxel.

11.18.1. The Subcommittee noted evidence of benefit in patients despite previous taxane use in some patients and considered that whilst numbers were small and response rates appeared similar, neuropathy appeared lower in lower doses, indicating more manageable toxicity with maintained response rates.

11.19. The Subcommittee considered the evidence provided did not indicate significant improvements in OS with nab-paclitaxel compared with the solvent-based taxanes paclitaxel and docetaxel, however it did indicate nab-paclitaxel was at least as clinically effective with also an improved safety and toxicity profile.

11.20. The Subcommittee considered that whilst pathologic complete response (pCR) improvements reported are not directly relevant to the management of metastatic disease, these indicate nab-paclitaxel may be more effective than paclitaxel, particularly when used in combination with novel immunotherapy treatments, and considered that in the metastatic setting, safety, efficacy, quality of life and improved use of clinical resources can be meaningful.

11.21. The Subcommittee considered the patient group likely to derive the greatest benefit from nab-paclitaxel treatment would be patients with histories of hypersensitivity reaction or toxicities meaning they are unable to receive solvent-based taxanes, and considered this may represent approximately 30-50 patients per year. Members noted that access to nab-paclitaxel for the metastatic breast cancer patient population would be preferred, due to the increased tolerability of nab-paclitaxel compared with paclitaxel, reduced need for premedication, and reduced infusion time. Members considered that this may increase the total number of patients receiving taxane treatment by 10-20%.

11.22. The Subcommittee considered that the below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for nab-paclitaxel if it were to be funded in New Zealand for metastatic breast cancer. This PICO captures key clinical aspects of the proposal and may be used to frame any future economic assessment by Pharmac staff. This PICO is based on the Subcommittee's assessment at this time and may differ from that requested by the applicant. The PICO may change based on new information, additional clinical advice, or further analysis by Pharmac staff.

Population	1. Patients with metastatic breast cancer, or 2. Patients with metastatic breast cancer with a history of hypersensitivity reactions, or contraindication to paclitaxel
Intervention	Nab-paclitaxel at dose of 100 mg/m^2 every 7 days
Comparator(s) (NZ context)	If funded for all metastatic breast cancer: paclitaxel, administered weekly at a dose of 80 mg/m^2 If restricted to use in patients who have a history of hypersensitivity reactions: best supportive care or weekly paclitaxel at a dose of 80 mg/m^2

Outcome(s)	If funded for all metastatic breast cancer: no significant difference in overall survival, progression-free survival or quality of life for patients administered nab-paclitaxel compared to paclitaxel*;* increased persistence on therapy If restricted to use in patients who have a history of hypersensitivity reactions: increased overall survival and progression free survival vs best supportive care in patients who need to discontinue paclitaxel due to hypersensitivity reactions

Table definitions:

Population: The target population for the pharmaceutical, including any population defining characteristics (eg. line of therapy, disease subgroup)

Intervention: Details of the intervention pharmaceutical (dose, frequency, treatment duration/conditions for treatment cessation).

Comparator: Details the therapy(s) that the patient population would receive currently (status quo – including best supportive care; dose, frequency, treatment duration/conditions for treatment cessation).

Outcomes: Details the key therapeutic outcome(s), including therapeutic intent, outcome definitions, timeframes to achieve outcome(s), and source of outcome data.

12. Atezolizumab in combination with bevacizumab for the treatment of patients with unresectable hepatocellular carcinoma (HCC) who have not received prior systemic therapy

Reviewed via Zoom on 23rd July 2021

Application

12.1. The Subcommittee considered an application from Roche for the use of atezolizumab in combination with bevacizumab for the treatment of advanced, unresectable hepatocellular carcinoma (HCC) which has not been previously treated with systemic therapy.

Recommendation

12.2. The Subcommittee **recommended** that atezolizumab in combination with bevacizumab for the treatment of patients with unresectable hepatocellular carcinoma (HCC) who have not received prior systemic therapy be funded with a **high priority** within the context of treatments for malignancies subject to the following Special Authority criteria:

> **Initial application** – (hepatocellular carcinoma) only from an oncologist, gastroenterologist or hepatologist, or Practitioner on the recommendation of an oncologist, gastroenterologist or hepatologist. Approvals valid for 6 months for applications meeting the following criteria:
> All of the following:
> 1. Patient has locally advanced or metastatic, unresectable hepatocellular carcinoma; and
> 2. Patient has preserved liver function (Child-Pugh Classification score of 5-6)); and
> 3. Patient has not received prior systemic therapy for the treatment of HCC, and
> 4. Patient has ECOG performance score of 0-1, and
>
> Renewal – (hepatocellular carcinoma) only from a relevant oncologist, gastroenterologist or hepatologist.
> 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 the patient is benefiting from treatment

12.3. In making its recommendation the Subcommittee considered the high health need and lack of alternative funded treatments for patients with unresectable

hepatocellular carcinoma, high incidence and health need of hepatocellular carcinoma in Māori and Pacific, and populations experiencing socioeconomic depravation, and the evidence of a likely survival advantage compared to the current standard of care.

Discussion

12.4. The Subcommittee noted that, in October 2020, it had reviewed an application from Eisai for lenvatinib mesilate for the first-line treatment of unresectable HCC and recommended it for funding with a low priority. The Subcommittee noted that the health need of patients with unresectable HCC was described in depth at that meeting and considered these health need considerations remained accurate and would apply to the patient population considered for the atezolizumab in combination with bevacizumab application. The Subcommittee reiterated its comments noting an unmet need for effective treatment options for patients with unresectable HCC and noted there is a disproportionately high incidence of this disease in Māori and Pacific people with incidence three times higher amongst the Māori population when compared with the non-Māori population (Cancer – New Registrations and Deaths. 2013. Ministry of Health) and also associated with an increased rate of mortality.

12.5. The Subcommittee noted that, compared with reported international incidence rates, New Zealand has a high incidence of HCC and considered this may be associated with high rates of non-alcoholic steatohepatitis (NASH) and fatty liver related HCC, compounded by increasing rates of metabolic disease.

12.6. The Subcommittee noted that there are no funded systemic treatment options for patients with advanced unresectable HCC in New Zealand beyond palliative care, with a median overall survival of HCC secondary to hepatitis B and hepatitis C of 5.2 and 8.3 months respectively (Shauer et al. N Z Med J. 2020;133:25-34).

12.7. The Subcommittee noted that international guidelines recommend atezolizumab in combination with bevacizumab for the first-line treatment of intermediate and advanced HCC, with tyrosine kinase inhibitors sorafenib and lenvatinib then recommended in the second line setting or in patients ineligible for immunotherapy (Llovet et al. Nat Rev Gastroenterol Hepatol. 2021;18:293-313).

12.8. The Subcommittee noted a lack of randomised controlled trials comparing atezolizumab with bevacizumab directly with best supportive care as is available in the New Zealand setting and considered indirect comparisons would be required to evaluate likely benefit in the New Zealand patient population. The Subcommittee noted two trials evaluating sorafenib (a tyrosine kinase inhibitor therapeutic agent) as first line treatment of HCC compared to placebo:

12.8.1. A phase III randomised, double-blind, placebo-controlled trial of sorafenib compared with placebo for the treatment of advanced hepatocellular carcinoma (Cheng et al. Lancet Oncol. 2009;10:25-34). The Subcommittee noted that overall survival (OS) with sorafenib was 6.5 months, compared with the 4.2 months with placebo (hazard ratio (HR) 0.68; p=0.014) with a time to progression of 2.8 months compared with 1.4 months with placebo (HR 0.57; p=0.0005).

12.8.2. A multi-centre phase III, double-blind, placebo controlled trial of sorafenib compared with placebo in the treatment of HCC (the SHARP trial; Llovet et al. N Engl J Med. 2008;359:378-90), where the median overall survival for sorafenib was 10.7 months versus 7.9 months with placebo (HR 0.69;

p<0.001). The Subcommittee noted it has previously reviewed both trials in its assessment of sorafenib for the treatment of HCC (April 2010) and at the time did not consider treatment with sorafenib to result in a meaningful change in progression-free or overall survival.

12.9. The Subcommittee noted that atezolizumab and bevacizumab are recommended to be used in combination for HCC (Vogel et al. Ann Oncol. 2021;36:801-5) and considered this reflected their complementary activity through efficient tumour cells apoptosis secondary to bevacizumab usage combined with the ability of atezolizumab to enable efficient presentation of tumour antigens culminating in improved priming and activation of immune cells which can then travel to the tumour to perpetuate the cancer immunity cycle. The Subcommittee noted that various combinations of immunotherapy and angiogenic agents are being used and evaluated in cancer treatment and considered the combination of atezolizumab and bevacizumab for HCC to have the most mature data to date. The Subcommittee noted other trials comparing immunotherapy alone with sorafenib for HCC did not report clinically significant improvements in progression-free survival:

12.9.1. CheckMate 459 (Yau et al. Ann Oncol. 2019;30:874-5) compared nivolumab with sorafenib and reported median progression free survival (PFS) of 3.7 months (95% CI 3.1 to 3.9) and 3.8 months (95% CI 3.7 to 4.5) respectively (HR 0.93; P = 'not reached')

12.9.2. KEYNOTE-240 (Finn et al. J Clin Oncol. 2020;38:193-202) compared pembrolizumab with placebo and reported median PFS of 3.0 months and 2.8 months respectively (HR 0.718, 95% CI, 0.570 to 0.904; p=0.0022)

12.9.3. The Subcommittee noted a phase Ib multi-centre, open-label, multi-arm trial of atezolizumab with or without bevacizumab in unresectable HCC (Lee et al. Lancet Oncol. 2020;21:808-20).

12.9.4. The Subcommittee noted that patients in "Group A" (n=104) received atezolizumab (1200 mg) and bevacizumab (15 mg/kg) intravenously every 3 weeks, with patients in "Group F" randomly assigned (1:1) to receive intravenous atezolizumab (1200 mg) plus intravenous bevacizumab (15 mg/kg) every 3 weeks or atezolizumab alone (n=119; 60 to atezolizumab plus bevacizumab; 59 to atezolizumab monotherapy). The Subcommittee noted the primary endpoints differed between the two treatment arms; with the primary end point for Group A of objective response rate (ORR) and the primary endpoint for Group F of PFS.

12.9.5. The Subcommittee noted that in Group A, 37 (36%; 95% CI 26 to 46) patients achieved a confirmed objective response, and in Group F, median PFS was 5·6 months (95% CI 3·6 to 7·4) in the combination group, versus 3·4 months (95% CI 1·9 to 5·2) in the atezolizumab monotherapy group (HR 0·55; 80% CI 0·40 to 0·74; p=0·011). The Subcommittee noted that in Group A there was an apparent overall response rate benefit across all subgroups and noted that in Group F the PFS hazard ratios consistently favoured atezolizumab in combination with bevacizumab, as opposed to atezolizumab monotherapy, across all subgroups investigated.

12.10. The Subcommittee noted the global open-label phase III trial of atezolizumab plus bevacizumab versus sorafenib in the treatment of unresectable HCC (IMbrave150; Finn et al. N Engl J Med. 2020;382:1894-1905).

12.10.1. The Subcommittee noted the trial had a median follow up of 8.6 months at time of publishing, with a patient sample size of 501 and considered that the sample size was sufficient to enable power to detect a hazard ratio for overall survival of 0.71 using a log-rank test at a two-sided 0.048 significance level.

12.10.2. The Subcommittee noted that there were no significant differences between the patient cohorts in the two treatment arms, and that all participants in the trial had an ECOG score of 0-1 with well-compensated disease and Child-Pugh Class A scores.

12.10.3. The Subcommittee noted that the median overall survival (OS) for the atezolizumab with bevacizumab group was not reached, with an OS at six months of 84.4% of participants. The Subcommittee noted that the median OS for the sorafenib group was 13.2 months (95% CI 10.4 to 'not reached') with an OS at six months of 72.2% of participants, which the Subcommittee noted was longer than the OS observed in sorafenib treatment arms in other trials. The Subcommittee considered that the longer OS for sorafenib observed in IMBrave 150 compared with SHARP was likely due to be related to subsequent systemic lines of treatments taken by sorafenib patients in IMBrave 150 (including tyrosine inhibitors and immunotherapy), which are not funded for patients in New Zealand with HCC. The Subcommittee also considered that best supportive care has improved over time, and that this may have an impact on prolonging OS in more recent studies compared to historical data. The Subcommittee considered the progression-free survival benefit in IMbrave 150 to be encouraging but considered the greatest benefit to be the prolonged overall survival with atezolizumab with bevacizumab.

12.10.4. The Subcommittee noted that the stratified hazard ratio for death was 0.58 (95% CI 0.42 to 0.79). The Subcommittee noted that the median progression free survival was 6.8 months for the atezolizumab with bevacizumab treated group (95% CI 5.7 to 8.3) compared with 4.3 months for the sorafenib group (95% CI 4.0 to 5.6). The Subcommittee noted that the stratified hazard ratio for progression or death was 0.59 (95% CI 0.47 to 0.76; p<0.001).

12.10.5. The Subcommittee was made aware of a 2021 update of IMbrave150 (Finn et al. J Clin Oncol. 2021;39:267[no. 3 suppl]), which had a median follow-up of 15.6 months. The Subcommittee noted that the median overall survival was 19.2 months with atezolizumab with bevacizumab compared to 13.4 months with sorafenib (HR for death 0.66; 95% CI 0.52 to 0.85; p=0.0009). The Subcommittee noted that at 18 months OS was 52% in the atezolizumab with bevacizumab group and 40% in the sorafenib group, with no new safety signals were reported.

12.11. The Subcommittee noted that confirmed objective response rates (ORRs) were higher in the atezolizumab with bevacizumab group (ORR 27.3%, 95% CI 22.5 to 32.5) compared with the sorafenib group (11.9%, 95% CI 7.4 to 18.0) according to RECIST 1.1 criteria (p<0.001). The Subcommittee noted that the confirmed ORR for HCC-Specific mRECIST criteria was also higher for those receiving atezolizumab with bevacizumab (33.2%, 95% CI 28.1 to 38.6) compared with sorafenib (13.3%, 95% CI 8.4 to 19.6; p<0.001). The Subcommittee noted that the ongoing ORR at data cut-off was higher in the atezolizumab with bevacizumab group (86.5%) compared with the sorafenib group (68.4%) according to RECIST 1.1 criteria.

12.12. The Subcommittee noted that the IMbrave 150 trial measured quality-of-life as reported by the patient with deterioration defined as a decrease from baseline of

10 points or more on the EORTC QLQ–C30 maintained for two consecutive assessments or a decrease of 10 points or more in one assessment followed by death from any cause within 3 weeks.

12.12.1. The Subcommittee noted that the mean time to deterioration of quality of life in the atezolizumab combination group was longer than for the sorafenib group, at 13.1 months versus 4.9 months respectively for physical functioning (HR 0.53; 95% CI 0.39 to 0.73), and 9.1 months and 3.6 months respectively for role functioning (HR 0.62; 95% CI 0.46 to 0.84).

12.12.2. The Subcommittee considered quality of life measurements had clearly defined endpoints from the start of the trial and considered that the improvement in quality of life alongside the survival benefit adds validity to the quality-of-life results indicating patients without disease progression experience better quality of life; however, considered that declines in HR-QoL in this patient population are also likely to be attributed to other comorbidities associated with severe liver disease or cirrhosis, probably independent of treatment efficacy.

12.13. The Subcommittee noted that serious adverse events were more common with atezolizumab and bevacizumab therapy than with sorafenib (38.0% and 30.8%, respectively), and that there were more events leading to withdrawal of trial drug in the combination therapy group compared to the sorafenib group (15.5% and 10.3%, respectively). The Subcommittee noted that the median duration of treatment was 7.4 months for atezolizumab, 6.9 months with bevacizumab, and 2.8 months with sorafenib. The Subcommittee also noted that there was a higher incidence and severity of liver toxicities in the combination treated group.

12.14. The Subcommittee considered that although the IMbrave 150 trial reported a statistically significant benefit of atezolizumab with bevacizumab over sorafenib, that the true comparator for the New Zealand population is ‘no treatment’, and so the magnitude of potential incremental benefit of atezolizumab and bevacizumab treatment in the New Zealand HCC patient population is unknown., but likely to be improved. The Subcommittee considered, however, the IMbrave 150 patient population to be similar to the HCC patient population in New Zealand.

12.15. The Subcommittee considered that patients would be screened for eligibility for trans-arterial chemoembolization (TACE) when first presenting with HCC with localised disease, and that a majority of patients eligible for TACE would receive this prior to systemic therapy. The Subcommittee considered that systemic therapy would therefore be targeted towards patients who are ineligible or unsuitable for TACE. The Subcommittee considered that TACE would therefore not be an appropriate comparator for this patient population.

12.16. The Subcommittee considered that HCC patients may live longer and with a better quality of life if atezolizumab with bevacizumab were to be funded, but that treatment related toxicities may lead to an increase in hospital visits. The Subcommittee considered that treatment frequencies requiring three weekly infusions would mean that patients would have to visit infusion centres and clinics more often than they would with current standard of care, which can be difficult for patients living rurally or experiencing socioeconomic depravation. The Subcommittee noted that patients would also require restaging scans, which have been indicated to be approximately 3 monthly, with half of patients having at least an additional two scans, in addition to 3-weekly blood testing for safety monitoring. The Subcommittee considered noted that, when bevacizumab is used for the treatment of other malignancies, clinicians typically use a lower dose than what

was proposed for this indication, and considered this dose modification may be a way to mitigate the toxicity related to the combination therapy in HCC patients.

12.17. The Subcommittee considered that if atezolizumab in combination with bevacizumab were to be funded for the requested indication that there would likely be between 60 and 70 new patients per year eligible for treatment, with a small prevalent influx of approximately 30 patients in the first year due to the short median survival of these patients.

12.18. The Subcommittee noted that in the IMbrave 150 trial, patients were permitted to remain on treatment after disease progression, but that the proposed Special Authority criteria require treatment to be discontinued on progression. The Subcommittee considered that in clinical practice it may be difficult to accurately assess disease progression due to liver related changes seen on diagnostic imaging and noted that international practice typically also requires treatment to stop at progression.

12.19. The Subcommittee considered that the below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for atezolizumab with bevacizumab if it were to be funded in New Zealand for the treatment of HCC. This PICO captures key clinical aspects of the proposal and may be used to frame any future economic assessment by PHARMAC staff. This PICO is based on the Subcommittee's assessment at this time and may differ from that requested by the applicant. The PICO may change based on new information, additional clinical advice, or further analysis by PHARMAC staff.

Population	Intermediate/advanced, systemic treatment-naïve HCC
Intervention	1200mg atezolizumab + 15mg/kg bevacizumab 3-weekly Treatment administered until unacceptable toxicity, loss of clinical benefit or disease progression Median treatment duration in IMBrave 150: 7.4 months with atezolizumab and 6.9 months with bevacizumab (vs PFS on atezolizumab/bevacizumab of 6.8 months).
Comparator(s) (NZ context)	Best supportive/palliative care
Outcome(s)	• Gain in PFS and OS vs sorafenib • Extrapolated gain in PFS and OS vs best supportive care (magnitude uncertain, though in sorafenib vs placebo trial, sorafenib associated with improved OS and time to radiologic progression but not symptomatic progression) • Delay in time to quality-of-life deterioration vs sorafenib (hazard ratio 0.63)
Table definitions: Population, the target population for the pharmaceutical; Intervention, details of the intervention pharmaceutical; Comparator, details the therapy(s) that the patient population would receive currently (status quo – including best supportive care); Outcomes, details the key therapeutic outcome(s) and source of outcome data.	