# Record of the Cancer Treatments Advisory Committee Meeting held via Zoom on 12 July 2024

Cancer Treatments Advisory Committee records are published in accordance with the Terms of Reference for the Specialist Advisory Committees 2021.

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

The Cancer Treatments Advisory Committee 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.

Pharmac Advisory Committees make recommendations, including priority, within their therapeutic groups of interest.

The record of this Advisory Committee meeting will be reviewed by PTAC at an upcoming meeting.

Specialist Advisory Committees 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 Specialist Advisory Committees, the mix of other applications being assessed, the amount of funding available, the success of commercial negotiations and/or the availability of clinical data.

# Table of Contents

## 1. Attendance

**Present**
Stephen Munn - Chair
Alice Minhinnick
Anne O'Donnell
Chris Frampton
Lochie Teague (until 11:00am)
Matthew Strother
Michelle Wilson

Oliver Brake
Vidya Mathavan

**Apologies**
Alice Loft
Alannah Kilfoyle
Richard Isaacs
Scott Babington

## 2. Summary of recommendations

| Pharmaceutical and Indication | Recommendation |
|---|---|
| • Atezolizumab for the adjuvant treatment of PD-L1 positive non-small cell lung cancer (NSCLC) | Decline |
| • Daratumumab for the treatment of relapsed/refractory multiple myeloma, subject to Special Authority criteria | No formal recommendation |
| • Pembrolizumab for the treatment of biliary tract cancer, within the context of treatment of malignancy, subject to Special Authority criteria | Low priority |
| • Ruxolitinib for the treatment of chronic corticosteroid-refractory graft versus host disease following allogenic haemopoietic stem cell transplant, in the context of the treatment of malignancy, subject to Special Authority criteria | High priority |
| • Dostarlimab for the treatment of advanced or recurrent endometrial cancer, **with deficient mismatch repair** (dMMR) status in the **first line setting,** in the context of treatment of malignancy, subject to Special Authority criteria | High priority |
| • Dostarlimab for the treatment of advanced or recurrent endometrial cancer**, irrespective of deficient mismatch repair** (dMMR) status, in the **first line setting,** in the context of treatment of malignancy, subject to Special Authority criteria | Medium priority |
| • Dostarlimab for the treatment of advanced or recurrent endometrial cancer, **with deficient mismatch repair** (dMMR) status in the **second line setting,** in the context of treatment of malignancy, subject to Special Authority criteria | High priority |
| • Dostarlimab for the treatment of advanced or recurrent endometrial cancer, **irrespective of** | Decline |

**deficient mismatch repair** (dMMR) status, in the **second line setting**

## 3. The role of Specialist Advisory Committees and records of meetings

3.1. This meeting record of the Cancer Treatments Advisory Committee is published in accordance with the Terms of Reference for the Pharmacology and Therapeutics Advisory Committee (PTAC) 2021 and Specialist Advisory Committees 2021 describe, *inter alia*, the establishment, activities, considerations, advice, and the publication of such advice of Specialist Advisory Committees and PTAC.

3.2. Conflicts of Interest are described and managed in accordance with section 6.4 of the SAC Terms of Reference.

3.3. The Cancer Treatments Advisory Committee is a Specialist Advisory Committee of Pharmac. The Cancer Treatments Advisory Committee and PTAC and other Specialist Advisory Committees have complementary roles, expertise, experience, and perspectives. The Cancer Treatments Advisory Committee and other Specialist Advisory Committees may therefore, at times, make recommendations for treatments for Cancer 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 Cancer Treatments that differ from the Cancer Treatments Advisory Committee's, or Specialist Advisory Committees may make recommendations that differ from other Specialist Advisory Committees'.

Pharmac considers the recommendations provided by both the Cancer Treatments Advisory Committee and PTAC and any other relevant Specialist Advisory Committees when assessing applications for treatments for Cancer.

## 4. Welcome and introduction

4.1. The Chair welcomed the Committee with a karakia followed by whakawhanaungatanga.

## 5. Pharmac Update

5.1. The Committee noted the Pharmac | Te Pātaka Whaioranga update.

5.2. The Committee discussed the update on the review of Paediatric Cancer Funding rule 8.1b. Members noted that Pharmac has confirmed it is keeping Rule 8.1b and is working through next steps to improve the way the Rule works.

5.3. The Committee noted the update provided on active cancer treatment funding applications and their current status in the assessment process.

## 6. Matters Arising

### 6.1. Discussion about funding proposals and draft access criteria

6.1.1. The Committee noted the Government had provided additional funding to Pharmac in June 2024 to fund new medicines and widen access to medicines that are already funded. The Committee noted the funding boost covers medicines for both cancer and non-cancer health conditions.

6.1.2. The Committee noted Pharmac had subsequently released a consultation to widen access to immunotherapy for six types of cancer. The Committee noted Pharmac

sought advice on these applications, and other applications ranked on their Options for Investment list.

*'Grandparenting' for second line or later treatment*

6.1.3. The Committee noted that pembrolizumab for metastatic MSI-H/dMMR colorectal cancer, head and neck squamous cell carcinoma and triple-negative breast cancer had been proposed as a first-line treatment in the late stage setting only. The Committee considered there would be a prevalent group of people who have received an alternative first-line (or subsequent) treatment. The Committee noted that under the proposed eligibility criteria, these people would not be eligible for funded treatment with pembrolizumab.

6.1.4. The Committee considered that its recommendations for these funding applications were made on the best evidence at the time to ensure funding was targeted to those who would receive the greatest benefit from treatment. The Committee considered that it would need to first review a funding application, with associated clinical evidence, for the use of immunotherapy in people who have received prior treatments before providing Pharmac with advice and a funding recommendation.

6.1.5. The Committee noted that Pharmac had received consultation feedback with supportive evidence for second-line use of pembrolizumab for metastatic MSI-H/dMMR colorectal cancer. The Committee requested an ad hoc meeting to consider this ahead of any decision by Pharmac.

*Locally advanced, unresectable disease*

General comments

6.1.6. The Committee considered the definition of unresectable disease is often subjective and would be difficult to define through eligibility criteria prior to receipt of immunotherapy.

6.1.7. The Committee noted that relevant clinical trials for immune checkpoint inhibitors were often designed to either assess efficacy in recurrent/metastatic disease with palliative intent (ie where the cancer is not considered curable) or early-stage disease as a peri-operative treatment with curative intent. The Committee considered that in cases where there is evidence of a potential benefit in a curative intent setting as a peri-operative treatment, it would be appropriate to consider locally advanced disease in this context, as this would be how the treatment could be used in clinical practice.

Breast cancer

6.1.8. The Committee noted that pembrolizumab had been proposed to be funded for unresectable recurrent or metastatic breast cancer, based on the outcomes reported in KEYNOTE-355.

6.1.9. The Committee noted that high rates of pathological complete response (pCR) have been reported after neoadjuvant treatment in Stage II or III breast cancer, allowing for surgical resection and adjuvant treatment with curative intent. The Committee considered that most people with locally advanced disease would receive pembrolizumab with curative intent if funded.

6.1.10. The Committee noted it had considered a funding application for pembrolizumab for peri-operative treatment of Stage II or III triple negative breast cancer (P-001883) and recommended funding with a low priority. The Committee considered that this funding application would be the appropriate avenue to consider individuals with locally advanced disease.

6.1.11. The Committee noted feedback from the New Zealand Breast Cancer Special Interest Group and from breast cancer patient advocacy groups that there is a small number of people with locally advanced disease that is unresectable or inoperable who are treated with palliative intent.

6.1.12. The Committee considered that if locally advanced unresectable disease was included in the eligibility criteria for recurrent or metastatic disease, it would be difficult to predict utilisation of treatment and could result in substantial overlap between funding decisions in the early and late-stage setting.

6.1.13. The Committee considered that including a criterion specifying that treatment is with palliative intent would help ensure the intended use of treatment in this setting is in line with the proposed indication.

Head and neck squamous cell carcinoma

6.1.14. The Committee noted that pembrolizumab had been proposed to be funded for recurrent or metastatic head and neck squamous cell carcinoma, based on the outcomes reported in KEYNOTE-048.

6.1.15. The Committee considered it would need to review the evidence for neoadjuvant/adjuvant treatment before recommending funding for people with locally advanced, unresectable disease. The Committee noted KEYNOTE-412 was recently published, evaluating the efficacy of pembrolizumab as a peri-operative treatment for head and neck squamous cell carcinoma. The Committee would welcome a funding application based on the outcomes from this trial.

MSI-H/dMMR colorectal cancer

6.1.16. The Committee noted that pembrolizumab had been proposed to be funded for people with metastatic dMMR/MSI-H colorectal cancer, based on the outcomes reported in KEYNOTE-177.

6.1.17. The Committee noted that clinical responses to immunotherapy in MSI-H/dMMR colorectal cancer can be significant, and requested that further consideration be given to the unresectable group at an ad hoc meeting.

*Genetic testing*

6.1.18. The Committee considered that a comprehensive national testing standard is needed to support equitable implementation of funding options that have a genetic testing component in the eligibility criteria. The Committee noted the clinical community had requested this for a number of years but there has been no progress to date.

6.1.19. The Committee considered it necessary that Pharmac seek advice from pathologists to determine what the current availability of testing is in New Zealand, where relevant to a particular proposal.

*Crizotinib and entrectinib*

6.1.20. The Committee noted entrectinib and crizotinib are ranked on Pharmac's Options for Investment list for treatment of ROS Proto-Oncogene 1, Receptor Tyrosine Kinase (ROS1) mutated non-small cell lung cancer (NSCLC).

6.1.21. The Committee noted that reflex ROS1 testing is available in some regions, however this is not nationally consistent. The Committee considered that consistent nationally available testing would be needed to implement this proposal equitably.

*Osimertinib*

6.1.22. The Committee noted it had previously considered a funding application for osimertinib for the first line treatment of metastatic NSCLC with an epidermal growth factor receptor (EGFR) mutation, and the second line treatment of NSCLC with a T790M mutation in the EGFR gene.

6.1.23. The Committee noted osimertinib is ranked on Pharmac's Options for Investment list for second line treatment of metastatic NSCLC with a T790M mutation of the EGFR gene.

6.1.24. The Committee noted T790M testing does not routinely occur in all regions. The Committee considered that people who progress after gefitinib or erlotinib would need to be tested before being eligible for osimertinib if it was funded.

6.1.25. The Committee noted that where insufficient tissue can be obtained from a biopsy, T790M testing can be done by a liquid biopsy. The Committee noted this is a higher cost test and is not widely available across all regions. The Committee considered liquid biopsy testing would need to be nationally available to support equitable implementation of any osimertinib funding in this setting for the few people who may need this. The Committee considered that if first-line treatment is also funded, this would be time limited as most people with newly diagnosed metastatic EGFR mutated NSCLC would receive osimertinib in the first-line setting.

6.1.26. The Committee noted the radiological and performance status requirements for access and ongoing eligibility for immune checkpoint inhibitors, and considered that these should be consistent with osimertinib if funded.

6.1.27. The Committee recommended the following amendments to the eligibility criteria to ensure that these groups would be included. (Additions in **bold**, deletions in ~~strikethrough~~):

> Initial application – (NSCLC – first line) only from a relevant specialist or any relevant practitioner on the recommendation of a relevant specialist. Approvals valid for 4 months for applications meeting the following criteria:
> All of the following:
> 1. Patient has locally advanced (Stage IIIb) or metastatic (Stage IV), non-squamous Non-Small Cell Lung Cancer (NSCLC); and
> 2. Either
>  2.1. Patient is treatment naïve; or
>  2.2. Both:
>  2.2.1. The patient has discontinued gefitinib or erlotinib due to intolerance; and
>  2.2.2. The cancer did not progress while on gefitinib or erlotinib; and
> 3. There is documentation confirming that the disease expresses activating mutations of EGFR tyrosine kinase; and
> 4. Treatment must be used as monotherapy; and
> 5. Patient has an ECOG performance status 0-2; and
> **6. Baseline measurement of overall tumour burden is documented clinically and radiologically.**
>
> Renewal - only from a relevant specialist or any relevant practitioner on the recommendation of a relevant specialist. Approvals valid for 6 months for applications that meet the following criteria:
> **Both:**
> **1. Response to treatment in target lesions has been determined by comparable radiologic assessment following the most recent treatment period; and**
> 2. No evidence of disease progression
>
> Special Authority for Subsidy – Retail Pharmacy - Specialist
> Initial application - (NSCLC – second line) only from a relevant specialist or any relevant practitioner on the recommendation of a relevant specialist. Approvals valid for 4 months for applications meeting the following criteria:
> All of the following:
> 1. Patient has locally advanced (Stage IIIb) or metastatic (Stage IV), non-squamous Non-Small Cell Lung Cancer (NSCLC); and

2. Patient has an ECOG performance status 0-**2**~~1~~; and
3. The patient must have received previous treatment with erlotinib or gefitinib; and
4. There is documentation confirming that the disease expresses T790M mutation of the EGFR gene following progression on or after erlotinib or gefitinib; and
5. The treatment must be given as monotherapy ~~for a maximum of 3 months~~; and
6. **Baseline measurement of overall tumour burden is documented clinically and radiologically.**

Renewal - only from a relevant specialist or any relevant practitioner on the recommendation of a relevant specialist. Approvals valid for 6 months for applications that meet the following criteria:
**Both:**

1. **Response to treatment in target lesions has been determined by comparable radiologic assessment following the most recent treatment period; and**
2. No evidence of disease progression

*Trastuzumab deruxtecan*

6.1.28. The Committee noted it had previously considered a funding application for trastuzumab deruxtecan for the treatment of human epidermal growth factor receptor (HER-2) positive metastatic breast cancer in April 2023.

6.1.29. The Committee noted that the proposed eligibility criteria had not included all the considerations of the Committee, in particular the following:

6.1.29.1. *The Committee considered that there was insufficient evidence to support subsequent treatment of this population group with trastuzumab emtansine following treatment with trastuzumab deruxtecan. However, those who received trastuzumab emtansine in the early breast cancer setting, or are receiving trastuzumab emtansine in the metastatic setting at the time a positive funding decision is made, should be eligible to receive trastuzumab deruxtecan in the metastatic setting upon progression.*

6.1.30. The Committee recommended the following amendments to the eligibility criteria for trastuzumab deruxtecan and trastuzumab emtansine to ensure that these groups would be included. (Additions in **bold**, deletions in ~~strikethrough~~):

**Trastuzumab deruxtecan**

Initial application- (metastatic breast cancer) - Applications only from a relevant specialist or any relevant 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 metastatic breast cancer expressing HER-2 IHC3+ or ISH+ (including FISH or other current technology) and
2. Patient has previously received trastuzumab and chemotherapy, separately or in combination and
3. Either:
   - 3.1. The patient has received prior therapy for metastatic disease; ~~including prior to adjuvant therapy including anthracycline, other chemotherapy, biological drugs, or endocrine therapy~~ or
   - 3.2. The patient developed disease recurrence during, or within six months of completing adjuvant therapy and
4. Patient has a good performance status (ECOG 0-1) and
5. **Both:**
   - **5.1. Patient has not received prior funded trastuzumab deruxtecan treatment; and**
   - **5.2. Any of the following:**
     - **5.2.1. Patient has not previously received trastuzumab emtansine; or**
     - **5.2.2. Patient was receiving trastuzumab emtansine for treatment of their metastatic breast cancer at [*listing date of T-Dxd*]; or**
     - **5.2.3. Patient previously received treatment with trastuzumab emtansine in the early breast cancer setting only; and**
6. Treatment to be discontinued at disease progression.

Renewal – (metastatic breast cancer) Applications only from a relevant specialist or any relevant practitioner on the recommendation of a relevant specialist. Approvals valid for 6 months for people meeting the following criteria:
Both:

1. The cancer has not progressed at any time point during the previous approval period whilst on trastuzumab deruxtecan; and
2. Treatment to be discontinued **if** ~~at~~ disease progression.

**Trastuzumab emtansine**

Initial application — (metastatic breast cancer) only from a relevant specialist or any relevant 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 metastatic breast cancer expressing HER-2 IHC 3+ or ISH+ (including FISH or other current technology); and
2. Patient has previously received trastuzumab and chemotherapy, separately or in combination; and
3. Either:
   3.1. The patient has received prior therapy for metastatic disease*; or
   3.2. The patient developed disease recurrence during, or within six months of completing adjuvant therapy*; and
4. Patient has a good performance status (ECOG 0-1); and
5. Either:
   5.1. Patient does not have symptomatic brain metastases; or
   5.2. Patient has brain metastases and has received prior local CNS therapy; and
6. Patient has not received prior funded trastuzumab emtansine **or trastuzumab deruxtecan** treatment; and
7. Treatment to be discontinued **if** ~~at~~ disease progression.

Renewal — (metastatic breast cancer) 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. The cancer has not progressed at any time point during the previous approval period whilst on trastuzumab emtansine; and
2. Treatment to be discontinued **if** ~~at~~ disease progression;

Note: Prior or adjuvant therapy includes anthracycline, other chemotherapy, biological drugs, or endocrine therapy.

*Inotuzumab for acute lymphoblastic leukaemia (ALL)*

6.1.31. The Committee noted it had previously considered two funding applications for inotuzumab for the treatment of ALL in November 2021. The Committee noted the different recommendations provided for the two applications were based on the treatment outcomes that could be achieved (curative vs non-curative).

6.1.32. The Committee noted that the proposed eligibility criteria for each group included all the considerations of the Committee.

6.1.33. The Committee noted that the key factors in determining transplant eligibility were age, comorbidities, and response to treatment. The Committee considered the intention for people under the age of 70 years old would be to progress to a curative transplant. The Committee noted that ALL in people over 70 years old is rare.

*Venetoclax with azacitidine for acute myeloid leukaemia (AML)*

6.1.34. The Committee noted that the proposed eligibility criteria for both venetoclax and azacitidine for the treatment of AML included all the considerations of the Committee and remained appropriate.

**Venetoclax**

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

1. Patient has previously untreated acute myeloid leukaemia, according to World Health Organization (WHO) Classification; and
2. Patient must not be considered eligible for standard intensive remission induction chemotherapy; and
3. Venetoclax to be used in combination with azacitidine or low dose cytarabine;

Renewal - previously untreated acute myeloid leukaemia. Applications only from a relevant specialist or any other medical practitioner on the recommendation of a relevant specialist. Approvals valid for 6 months for applications meeting the following criteria:
Both:

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

**Azacitidine**
Initial application - only from a haematologist or medical practitioner on the recommendation of a haematologist. Approvals valid for 12 months for applications meeting the following criteria:
All of the following:

1. Any of the following:
   1.1. The patient has International Prognostic Scoring System (IPSS) intermediate-2 or high-risk myelodysplastic syndrome; or
   1.2. The patient has chronic myelomonocytic leukaemia; or
   1.3. The patient has Acute Myeloid Leukaemia; and
2. The patient has performance status (WHO/ECOG) grade 0-2; and
3. The patient does not have secondary myelodysplastic syndrome resulting from chemical injury or prior treatment with chemotherapy and/or radiation for other diseases; and
4. The patient has an estimated life expectancy of at least 3 months.

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

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

*Multiple myeloma*

6.1.35. The Committee noted that it was considering daratumumab as its own item at this meeting, specifically in combination with pomalidomide (funded from 1 August 2024).

6.1.36. The Committee noted the supplier's proposal for access to intravenous daratumumab for those people who received more than one prior line of treatment.

6.1.37. The Committee noted daratumumab fourth line treatment would provide better health outcomes than the status quo, however there is a preference for the subcutaneous formulation, due to the toxicity and adverse events associated with the intravenous formulation.

6.1.38. The Committee noted the eligibility criteria would have to be specifically worded if the subcutaneous formulation were only accessed if the condition progressed after one prior line.

6.1.39. The Committee noted that there would remain a need for carfilzomib if daratumumab were funded, due to the different mechanism of action and evidence of both agents being used in combination. The Committee considered the need for isatuximab would no longer remain if daratumumab were funded, due to their similar mechanism of action.

## 6.2. Ovarian cancer subgroup feedback (olaparib and niraparib)

### Recommendation

6.2.1. The Committee recommended that the eligibility criteria for niraparib be amended to include high-grade endometrioid epithelial ovarian cancer as follows (additions in **bold**; only initial criteria shown):

Special Authority for Subsidy
Initial application from any relevant practitioner. Approvals valid for 6 months for applications meeting the following criteria:
All of the following:

1. Patient has advanced high-grade serous **or endometrioid*** epithelial ovarian, fallopian tube, or primary peritoneal cancer; and
2. Patient has received at least one line** of treatment with platinum-based chemotherapy; and
3. Patient has experienced a partial or complete response to the preceding treatment with platinum-based chemotherapy; and
4. Patient has not previously received funded treatment with a PARP inhibitor; and
5. Either:
    5.1. Treatment will be commenced within 12 weeks of the patient's last dose of the preceding platinum-based regimen; or
    5.2. Patient commenced treatment with niraparib prior to 1 May 2024; and
6. Treatment to be administered as maintenance treatment; and
7. Treatment not to be administered in combination with other chemotherapy.

Notes:
* "high-grade serous **or endometrioid**" includes tumours with high-grade serous **or endometrioid** features or a high-grade serous **or endometrioid** component.
**A line of chemotherapy treatment is considered to comprise a known standard therapeutic chemotherapy regimen and supportive treatments.

6.2.2. The Committee recommended that the eligibility criteria for olaparib be amended to include high-grade endometrioid epithelial ovarian cancer as followings (additions in **bold,** deletions in ~~strikethrough~~, initial criteria shown only):

Special Authority for Subsidy
Initial application - only from a medical oncologist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 12 months for applications meeting the following criteria:
All of the following:

1. Patient has a high-grade serous **or endometrioid*** epithelial ovarian, fallopian tube, or primary peritoneal cancer; and
2. There is documentation confirming pathogenic ~~germline~~ BRCA1 or BRCA2 gene mutation; and
3. Either
    3.1. Patient has newly diagnosed, advanced disease; and
    3.2. Patient has received one line** of previous treatment with platinum-based chemotherapy; and
    3.3. Patient's disease must have experienced a partial or complete response to the first-line platinum-based regimen; or
        3.3.1. Patient has received at least two lines of previous treatment with platinum-based chemotherapy; and
        3.3.2. Patient has platinum sensitive disease defined as disease progression occurring at least 6 months after the last dose of the penultimate line of platinum-based chemotherapy; and
        3.3.3. Patient's disease must have achieved partial or complete response to treatment with the immediately preceding platinum-based regimen; and
        3.3.4. Patient has not previously received funded olaparib treatment; and
4. Treatment will be commenced within 12 weeks of the patient's last dose of the immediately preceding platinum-based regimen; and
5. Treatment to be administered as maintenance treatment; and
6. Treatment not to be administered in combination with other chemotherapy.

Notes
*"high-grade serous **or endometrioid**" includes tumours with high-grade serous **or endometrioid** features or a high-grade serous **or endometrioid** component
**A line of chemotherapy treatment is considered to comprise a known standard therapeutic chemotherapy regimen and supportive treatments

6.2.3. The Committee recommended amendments to the eligibility criteria, noting:

6.2.3.1. the rare but high unmet health need for people with high-grade endometrioid epithelial ovarian cancer

6.2.3.2. people with high-grade endometrioid epithelial ovarian cancer would likely receive the same health benefits from poly (ADP-ribose) polymerase (PARP) inhibitors as those in the funded high-grade serous epithelial ovarian (HGSOC) cancer group, based on good quality phase three clinical trial data

6.2.3.3. there is nationally available testing for somatic BRCA mutations and people with these mutations would be treated with olaparib for a shorter time compared to niraparib.

## Discussion

*Background*

6.2.4. The Committee noted that two PARP inhibitors, olaparib and niraparib, are funded for HGSOC. The Committee noted olaparib was funded as a maintenance treatment only for people with a germline BRCA mutation for up to two years, while niraparib was funded for 'all-comers' for up to three years.

6.2.5. The Committee noted Pharmac had received feedback from the Ovarian Cancer Foundation New Zealand (OCFNZ) requesting the addition of high-grade endometrioid epithelial ovarian cancer (HGEEOC) to the criteria for niraparib. The amendment was requested on the basis that individuals with HGEEOC were included in the study population for PARP inhibitors (i.e. individuals with either endometrioid or serous high-grade epithelial ovarian cancers were eligible) and that there was an unmet health need.

6.2.6. The Committee noted Pharmac staff sought advice on the health need of people with HGEEOC and the health benefits of PARP inhibitors in treating HGEEOC, in response to the feedback received.

*Health need*

6.2.7. The Committee noted that primary epithelial ovarian cancers have various histological subtypes, including serous, clear cell, endometrioid and mucinous. Endometrioid ovarian cancer can be further differentiated into high-grade and low-grade. The Committee noted that endometrioid subtypes comprise around 10% of ovarian cancers (Vaughan et al. 2011).

6.2.8. The Committee noted endometrioid epithelial ovarian cancer is typically diagnosed at an early stage and mostly low grade. When considering high-grade stage III or IV disease, where there is a role for maintenance treatment with PARP inhibitors, the Committee noted that endometrioid subtypes account for between 13 to 17% of the population, with a smaller proportion (between 5 and 16%) being grade 3 (Chen et al. 2021).

6.2.9. The Committee considered that in the New Zealand context, less than 5% of people presenting with stage III or IV ovarian cancer would have HGEEOC. The Committee considered these people would receive surgery and chemotherapy, with additional lines of chemotherapy after relapse. The Committee noted that relapse rates for advanced HGEEOC are around 80%.

6.2.10. The Committee noted that the progression free and overall survival for stage III or IV HGEEOC is similar to that of HGSOC (Mackay et al. 2010), however, currently there are less funded treatments options available for HGEEOC.

*Health benefit*

6.2.11. The Committee noted that PARP inhibitors are indicated for maintenance therapy after initial treatment of ovarian cancer, thereby reducing the likelihood of, and delay the time until, disease relapse.

6.2.12. The Committee noted that the use of PARP inhibitors has only been investigated in HGSOC and HGEEOC. The Committee noted clear cell and mucinous histological subtypes were not included in studies of PARP inhibitors.

6.2.13. The Committee considered that 50% of HGSOC cancers are homologous recombination deficient (HRD), and are most likely to benefit from treatment. The Committee noted the data for HRD rates is less clear for HGEEOC.

6.2.14. The Committee noted it had previously reviewed pivotal trials for olaparib (SOLO1 and SOLO2) and for niraparib (PRIMA and NOVA) at its February 2021 and July 2021 meetings respectively. The Committee noted that all of these trials, except for NOVA, included people with HGEEOC. The Committee considered that people in the NOVA trial may have had a mixed histological subtype, however there was no data to support this assumption.

6.2.14.1. The Committee noted that in the SOLO1 trial, 2.3% of the overall population had HGEEOC. The Committee considered this was too small to undertake subgroup analysis of the health benefits in this group. The Committee considered that because the health benefit of olaparib was driven by the presence of a BRCA mutation, it is reasonable to assume that olaparib would provide a similar benefit for BRCA-mutated HGEEOC as BRCA-mutated HGSOC.

6.2.14.2. The Committee noted the SOLO1 trial included two individuals with a somatic BRCA mutation. For the same reasons as the above, the Committee considered it reasonable to assume they would similarly benefit from olaparib. The Committee noted there was now national screening for somatic BRCA mutations in HGSOC, which was not in place when olaparib was reviewed previously.

6.2.14.3. The Committee noted that in the PRIMA trial, 2.7% of the overall population had HGEEOC. The Committee considered this was also too small to undertake a subgroup analysis. The Committee noted that 11/20 people with HGEEOC were HRD positive, which was similar to rates of HRD positivity observed in the overall ovarian cancer population. As such, the Committee considered it was reasonable to assume niraparib would provide a similar benefit in HGEEOC as HGSOC.

6.2.14.4. Based on the results of the SOLO2 and NOVA trial, and noting the above considerations, the Committee considered that assumptions of benefit would also apply in the second-line (or later) settings.

6.2.15. Overall, the Committee considered the health benefit of the two PARP inhibitors in high grade ovarian cancer is supported by good quality phase three clinical trial evidence, although noted the small size of the number of people with HGEEOC included in the study populations. The Committee considered that due to the rarity of HGEEOC, there are unlikely to be large phase three trials to clearly demonstrate the efficacy of treatments such as PARP inhibitors for this group. The Committee noted it can be histologically difficult to differentiate between HGEEOC and HGSOC, and considered this likely the reason for including HGEEOC in the clinical trials.

*Cost and savings*

6.2.16. The Committee noted OCFNZ estimated five additional people per year would receive treatment if access were widened to include HGEEOC. The Committee considered this estimate to be reasonable, noting that some people may choose not to have treatment, or be contraindicated.

6.2.17. The Committee considered there may be up to an additional two people per year who would be eligible in the recurrent setting, however this would reduce over time as most people would receive a PARP inhibitor as a first-line maintenance treatment. The Committee considered treatment refusal rates in the recurrent setting are higher than the first-line setting.

6.2.18. The Committee considered that it could be cost saving to the health sector, if somatic BRCA mutations were included in the eligibility criteria for olaparib, as these people would currently be receiving niraparib for up to three years, compared to up to two years on olaparib. This would represent a reduction in health sector costs through less intensive monitoring and clinic resources.

*Funding criteria*

6.2.19. The Committee considered the current HGSOC-based criteria for olaparib and niraparib eligibility were appropriate to define people with HGEEOC who would benefit from a PARP inhibitor, with relevant amendments to include HGEEOC in criterion one of the Special Authority criteria.

6.2.20. The Committee considered the current olaparib eligibility criteria would be appropriate to identify people with somatic mutations who would benefit from a PARP inhibitor, with relevant amendments to include this group in criterion two.

*General*

6.2.21. The Committee considered Pharmac would likely receive NPPA applications for individuals with HGEEOC, given the rarity of the presentation. The Committee noted Pharmac had not received any NPPA applications for HGEEOC to date and considered this is likely due to the rarity of the presentation and the recency of the olaparib and niraparib funding decisions .

6.2.22. The Committee noted that BRCA testing is available for HGEEOC. The Committee considered that it would be equitable to widen access to both niraparib and olaparib, so that people with HGEEOC would have the same level of access to a PARP inhibitor as people with HGSOC.

## 6.3. Atezolizumab - Non-Small Cell Lung Cancer (NSCLC), PD-L1 positive, adjuvant treatment

### Application

6.3.1. The Committee reviewed the application for atezolizumab for the adjuvant treatment of PD-L1 positive non-small cell lung cancer (NSCLC).

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

### Recommendation

6.3.3. The Committee recommended that atezolizumab for the adjuvant treatment of PD-L1 positive non-small cell lung cancer (NSCLC) be **declined**.

6.3.4. The Committee recommended based on the following:

- Concerns with the methodology of the clinical trial including its statistical methods.

## Discussion

*Background*

6.3.5. The Committee noted it reviewed the application for atezolizumab for adjuvant treatment of PD-L1 positive non-small lung cancer (NSCLC) in October 2023. The Committee had concerns that:

6.3.5.1. The majority of the benefit in IMpower010 was in individuals who had PD-L1 expression on ≥50% of tumour cells, where a statistically significant OS benefit was observed. However, this was not a pre-specified endpoint and was instead analysed as a subgroup post-hoc. Without pre-specification there is a risk of a false positive finding, hence this result should be interpreted with caution.

6.3.5.2. From the currently available data, the Committee could not determine whether it was appropriate to restrict access to those with PD-L1 expression on ≥50% of tumour cells. More mature data would be needed to make this determination as well as consideration of the statistical analysis plan.

6.3.5.3. The OS data had not reached statistical significance in the intention to treat population, and median OS was also not reached (noting the data was immature, with further trial results still to be published).

6.3.6. The Committee noted it had therefore deferred a recommendation pending publication of longer-term overall survival data from the IMpower010 trial. The Committee had also requested that the statistical analysis plan be included with the submission of any further evidence.

6.3.7. The Committee noted the supplier had now provided a confidential copy of the Impower010 Statistical Analysis Plan unpublished, dated 30 June 2020) and additional data to support the health benefit.

*Health need*

6.3.8. The Committee reiterated its previous considerations of October 2023 regarding the health need of people with NSCLC.

*Health benefit*

6.3.9. The Committee noted the supplier had provided the statistical analysis plan for the IMpower010 trial as well as additional data with median follow up times in the intention-to-treat (ITT) population of 45 months (Felip et al. Ann Oncol. 2023;34:907-19) and 65 months (Wakelee et al. ASCO. 2024 [poster presentation]).

6.3.9.1. The Committee noted that by design the three populations considered for the primary endpoint (disease free survival (DFS)) were tested in a hierarchical manner. Firstly, DFS in individuals with stage II and III cancer with PD-L1 TC >1%; secondly all randomised individuals, with stage II and IIIA disease, and thirdly the ITT population of Stage IB through to IIIA disease. [redacted] [1]The Committee noted that the population for DFS included individuals with stage II-IIIA cancer only, whilst the OS population included

[1] Redacted text refers to information provided in confidence.

everyone in the intention to treat population including individuals with stage Ib cancer. The Committee noted that in the OS population, people with stage Ib represented 10% of the population. The Committee considered that time to progression would be longest in this group. Thus, predicting OS from the DFS population would not be reliable.

6.3.9.2. The Committee noted the test used to determine PD-L1 expression status was changed from the SP142 to SP263 assay approximately 12 months before the first interim analysis (described in Felip et al. Lancet. 2021;398:1344-57 and its Supplementary Appendix pages 343-4). The Committee noted this changed the number of participants in each of the stratification groups, and the data analysis, but was performed ahead of the interim analysis so was acceptable.

6.3.9.3. The Committee noted the new data reported a median DFS of 68.5 months in the atezolizumab arm and 37.3 months in the control arm [stratified HR 0.7 (95% CI 0.55, 0.91)] in PD-L1 positive tumours (TC≥1%). The Committee noted that the DFS was significant in the previous data reviewed, and remained significant in the new updated data, however the OS was not (OS not estimable in the atezolizumab arm and 87.1 months in the control arm [stratified HR 0.77 (0.56, 1.06)]. [2]

6.3.9.4. [redacted]

6.3.9.5. [redacted]

6.3.9.6. The Committee noted that those with a PD-L1 TC≥50% represented less than 20% of the total group in each arm.

6.3.9.7. The Committee considered that tumours with a PD-L1 score of TC≥50% did not represent a more high-risk group either by histology or stage. [3]

6.3.9.8. [redacted]

6.3.9.9. The Committee considered that the statistical design and reporting in Impower010 reduced the ability to ascertain if there were cohorts that benefited more or less from adjuvant treatment with atezolizumab. The Committee considered that this rendered interpretation of benefit from atezolizumab (particularly in specific cohorts) in this setting to be uncertain.

6.3.10. The Committee noted that event free survival has been correlated with OS after neoadjuvant treatment for NSCLC (Ostoros et al. Expert Rev Anticancer Ther. 2023;23:1305-13). The Committee noted the meta-analysis was performed on data prior to the introduction of immunotherapies for the treatment of NSCLC. The Committee considered this analysis may not accurately reflect the post immunotherapy treatment landscape.

[2] Redacted text refers to information provided in confidence.
[3] Redacted text refers to information provided in confidence.

6.3.11. The Committee noted two different studies that explored the time to recurrence in NSCLC treated with surgery. The Committee noted for individuals with stage I-II NSCLC, the median time to recurrence was 18.8 months (Potter et al. Ann Thorac Surg. 2023;116:684-92), whilst a further study reported that those with stage I NSCLC had 60% recurrence within the first two years, this was 80% for stage II-II, and 90% within five years for all stages (Karacz et al. Clin Lung Cancer. 2020; 21:127-35.e3).The Committee noted that at 65.5 months, 59% of the population in the IMpower010 trial remain in the study.

6.3.12. The Committee considered in clinical care, neoadjuvant treatment provides a potential opportunity to increase rates of cure and may remove the need for adjuvant immunotherapy. In all these trials, this benefit will need to be balanced against long lasting immune related adverse events.

## 7. Daratumumab subcutaneous for multiple myeloma, for people that have received one prior line of myeloma therapy

### Application

7.1. The Committee reviewed the application for daratumumab subcutaneous for multiple myeloma, for people who have received one prior line of myeloma therapy.

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

### Recommendation

7.3. The Committee **recommended** that daratumumab be listed for the treatment of relapsed/refractory multiple myeloma, subject to the following Special Authority criteria:

> Initial application - (Relapsed/refractory multiple myeloma) from any relevant practitioner. 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. Patient has not received prior funded daratumumab.
>
> Renewal application – (Relapsed/refractory multiple myeloma) from any relevant practitioner. Approvals valid for 6 months where there is no evidence of disease progression.

7.4. In making this recommendation, the Committee considered that previously recommended funding criteria were not applicable given the change in paradigm with the decision to fund lenalidomide and pomalidomide.

### Discussion

*Māori impact*

7.5. The Committee discussed the impact of funding daratumumab for the treatment of relapsed and refractory multiple myeloma on Māori health areas of focus and Māori health outcomes. The Committee noted its previous advice in April 2018 that the age-standardised incidence rate for Māori was 7.6 cases per 100,000; or approximately double that of the non-Māori populations (4.9 cases per 100,000), thought to be primarily due to a younger age at diagnosis. This shows that there is a clear health need for Māori.

*Impact on Pacific peoples, disabled people, tāngata whaikaha Māori, and other people who have been underserved by the health system*

7.6. The Committee discussed the impact of funding daratumumab for treatment of relapsed and refractory multiple myeloma on priority populations. The Committee

noted the previous advice from PTAC in February 2019 that incidence of multiple myeloma in Pacific peoples (9.8 per 100,000) was higher than in non-Māori (4.9 per 100,000).

*Background*

7.7. The Committee noted its previous consideration of intravenous daratumumab (IV) for multiple myeloma for people who have received one prior line of therapy in April 2018 and deferred its recommendation pending further data on overall survival. The Committee noted that upon re-reviewing in October 2019 daratumumab IV was recommended with a low priority. The Committee considered that the progression free survival benefit was substantial, but the low priority was due to the high cost and the lengthy infusion time for daratumumab IV treatment (90 minute accelerated IV infusion protocol from week 3 onwards). The Committee noted its review of the subcutaneous (SC) preparation for second-line treatment in July 2021 and the resulting high recommendation.

7.8. The Committee noted its previous advice relating to pomalidomide second-line treatment from April 2021 that, based on clinical practice, almost all people with multiple myeloma will receive first-line treatment, although only about 61% and 38% of people will receive second- and third-line treatments, respectively.

*Health benefit of funded treatments*

7.9. The Committee noted the decision to fund lenalidomide first line and pomalidomide second line in combination with bortezomib and dexamethasone (lenalidomide/bortezomib/dexamethasone (RVd) and pomalidomide/bortezomib/dexamethasone (PVd), respectively). The Committee considered that while this was an improvement on the currently funded options, there was still an unmet need for people with disease that may be refractory to bortezomib (proteasome inhibitor) and lenalidomide (immunomodulator (IMiD)). The Committee noted that people with disease refractory to lenalidomide would be eligible for funded pomalidomide as a further line of treatment. The Committee considered that people with disease refractory to both lenalidomide and bortezomib treated with pomalidomide with dexamethasone (Pd), and with or without bortezomib, would get 4 to 10 months of progression free survival (PFS).

7.10. The Committee considered the following trials evaluating progression-free survival for PVd:

7.10.1. OPTIMISMM trial (Richardson et al. Lancet Oncol. 2019;20:781-94) reported PFS as 11.2 months (median of 2 previous lines of treatment).

7.10.2. DREAMM8 trial (Dimopoulos et al. N Engl J Med. 2024. Epub) reported PFS in the control arm as 12 months

7.11. The Committee noted the following evidence on the efficacy of pomalidomide and dexamethasone (Pd) treatment:

7.11.1. APOLLO (Dimopoulos et al. Lancet Oncol 2021;22:801-12) reported PFS in the control arm as 6.9 months in people with a median of two previous lines of treatment

7.11.2. MM-003 trial (San Miguel et al. Lancet Oncol. 2013;14:1055-66) in people with more two lines of treatment: 31% overall response rate (ORR), 4 month PFS, 12.7 month OS

7.11.3. Richardson et al. Blood. 2014;123:1826-32: 4.2 month PFS, 16 month OS in people with a median of five prior lines of treatment

7.11.4. Lacy et al. Leukemia. 2010;24:1934-9: ORR 47%, 4.8 month PFS, 14 months OS in people with a median of three prior lines of treatment.

7.12. The Committee noted the ENDEAVOR trial comparing carfilzomib and bortezomib in combination with dexamethasone (Dimopoulos et al. Lancet Oncol. 2016;17:27-38). The Committee noted that 54% of the population in this trial was bortezomib-exposed, with 3% refractory to bortezomib. The Committee noted that 38% were lenalidomide exposed, with 24% refractory. The Committee considered it was more likely that people's disease would become refractory to lenalidomide than to bortezomib.

7.13. The Committee noted the EQUULEUS/MMY1001 trial evaluating daratumumab in combination with different backbone regimens in people who have trialled two prior lines of therapy (98% RVd exposed, 71% double refractory) (Chari et al. Blood. 2017;130:974-81). The Committee noted that in the daratumumab, pomalidomide and dexamethasone (**DPd**) arm 98% of people were exposed to bortezomib, with 71% bortezomib-refractory, and 100% were lenalidomide exposed with 89% lenalidomide-refractory.

7.14. The Committee noted that in the OPTIMISMM trial the population was 100% lenalidomide-exposed, with 71% refractory, and 72% bortezomib-exposed, with 9% refractory (Richardson et al. Lancet Oncol. 2019;20:781-94). The Committee estimated that 50% of people treated with lenalidomide would have their disease become refractory, and 10-20% of people treated with bortezomib would have their disease become refractory.

7.15. The Committee considered that for newly diagnosed people the standard of care in those aged under 70 years was lenalidomide induction (with bortezomib and dexamethasone) prior to autologous stem cell transplant (ASCT) followed by lenalidomide maintenance, and those aged 70 years and over would be treated with lenalidomide, dexamethasone and bortezomib (without ASCT preceded by lenalidomide induction). The Committee considered that anyone who had been treated with lenalidomide in first line and progressed could trial a higher lenalidomide dose, but their disease would be regarded as lenalidomide-refractory, therefore this would not be their first choice of second-line therapy. The Committee considered that there was an unmet need for these people for an agent in another class as there are not further lines of treatment in the relapsed setting other than re-treatment combinations.

*Health benefit of proposed treatments*

7.16. The Committee considered that there was benefit in using second line DPd. The Committee noted evidence from the APOLLO trial on the relative efficacy of DPd compared to Pd treatment (Dimopoulos et al. 2021; Dimopoulos et al. Lancet Haematol. 2023;10:e813-24). The Committee noted that the median age was 67 years (42 - 86 years), 38% had high risk cytogenetics, the median number of prior treatments was two, 47% had disease refractory to bortezomib, and 42% had disease double refractory to both IMiD and bortezomib. The Committee considered that as DPd is being considered as a second line therapy in New Zealand, the outcomes are likely better than seen in the trial, in both the intervention and the control.

7.16.1. The Committee considered that the population in the APOLLO trial was similar to the New Zealand population as they are heavily pre-treated, with 79% of the study population having disease that was lenalidomide refractory and 60% being ASCT recipients.

7.16.2. The Committee noted that the median PFS reported was 12.4 months for the DPd group compared to 6.9 months for the Pd group (*P*=0.002). The Committee noted the OS reported was 34 months for the DPd group compared to 23.7 months for the Pd group (Hazard ratio (HR): 0.82 [95% CI 0.61, 1.11]). The Committee noted that the ORR was reported as 69% in the DPd group compared to 46% in the Pd group (*P*<0.001).

7.17. The Committee noted the following additional evidence on the efficacy of daratumumab, pomalidomide and dexamethasone treatment:

7.17.1. EQUULEUS/MMY1001 trial (Chari et al. Blood. 2017;130:974-81)

7.17.2. MM-014 trial (Siegel et al. Leukemia. 2020;34:3286-97)

7.18. The Committee noted the evidence from the POLLUX trial (Bahlis et al. Leukemia. 2020;34:1875-84). The Committee noted the PFS reported was 44.5 months for the daratumumab, lenalidomide and dexamethasone (**DRd**) group compared to 17 months for the lenalidomide and dexamethasone group (Rd) (*P*<0.0001). The Committee noted that PFS for people with one prior line of treatment was 44.5 months in the DRd group compared to 17.5 months for the Rd group (*P*<0.0001). The Committee noted that in people previously treated with lenalidomide the reported median PFS was 38.8 months in the DRd group compared to 18.6 months in the Rd group (*P*=0.0004). The Committee noted that in people with disease refractory to bortezomib the reported median PFS was 34.3 months in the DRd compared to 11.3 months in the Rd group (*P*=0.0003). The Committee noted the reported OS was 67.6 months in the DRd group compared to 51.8 months in the Rd group (P=0.0044) (Dimopoulos et al. Clin Oncol. 2023;41:1590-9).

7.19. The Committee noted the CASTOR trial reporting the efficacy of daratumumab, bortezomib and dexamethasone (**DVd**) treatment compared to bortezomib and dexamethasone (**Vd**) (Mateos et al. Clin Lymphoma Myeloma Leuk. 2020;20:509-18. The Committee noted the reported PFS was 16.7 months in the DVd group compared to 7.1 months in the Vd group (P<0.0001)).

7.19.1. The Committee considered DVd to be the least effective of the daratumumab triplet regimens, as suggested by the results of a retrospective study in Canada, comparing DVd, DPd, and DRd (Main et al. Front Oncol. 2022:12:826342). The Committee noted that while the outcomes from CASTOR were appreciable, two thirds of the people were pre-treated with bortezomib and dexamethasone (which is also the control regimen), which would likely inflate the benefit of daratumumab.

7.19.2. The Committee noted additional evidence relating to the efficacy of DVd was available in the DREAMM 7 trial (Mateos et al. N Engl J Med. 2024. Epub.)

7.20. The Committee considered that overall the evidence was of varied quality but was extensive including four very well-designed phase threerandomised controlled trials (RCTs) (the above APOLLO, POLLUX, MMY1001, and CASTOR trials) to support the use of daratumumab. The Committee considered that these trials were conducted during a time where the induction treatment approach was the same as the current treatment in New Zealand. The Committee noted that the intention to treat populations were similar when considering age, prior lines of treatment, distribution of cytogenetic, and other risk factors. The Committee considered that the data was now mature enough with extended follow up including OS for RCTs.

7.21. The Committee noted that the generalisability of the evidence was limited by the strict inclusion and exclusion criteria inherent to controlled clinical trials. The Committee noted that due to the heterogenous nature of multiple myeloma that the populations in controlled clinical trials experienced better outcomes than would be expected in

practice. The Committee considered that this applied to both the control and treatment arms of trials, and that the incremental benefit of the treatment would be similar between control trials and in real-world practice.

7.22. The Committee considered that there could be risks when using daratumumab and pomalidomide or lenalidomide in combination such as increased risk of infection and neutropenia. The Committee considered that current treatments also had risks, including bortezomib re-treatment that is associated with an increased risk of neuropathy (estimated to affect 20-30% of all people re-treated) and cyclophosphamide with myelosuppression.

*Treatment paradigm*

7.23. The Committee noted that when daratumumab was last ranked on the Pharmac Options For Investment (OFI) list it was considered as being in combination with bortezomib and dexamethasone (DVd) in the second-line setting, compared to cyclophosphamide, bortezomib and dexamethasone (**CyBorD**). The Committee considered that if pomalidomide was made available to people from second line as well as daratumumab, clinicians would most likely use these agents in combination as DPd, rather than use the agents sequentially. The Committee considered that DPd would likely be more efficacious than DVd for people on second line treatment, especially as individuals would be exposed to two new agents.

7.24. The Committee considered that first-line treatment would be RVd induction followed by ASCT if eligible, with lenalidomide maintenance until a person's disease relapses or becomes refractory to lenalidomide or bortezomib. The Committee considered that first-line treatment for people who are ineligible for ASCT would usually also be RVd, followed by lenalidomide maintenance. The Committee considered it would only be people who were very frail who would have Rd induction, and for these individuals ongoing maintenance would depend on disease response and treatment toxicity.

7.25. The Committee considered that in New Zealand all people who have already received lenalidomide maintenance and whose disease progresses, would be considered lenalidomide-refractory. The Committee considered that the decision to stop maintenance therapy would usually be based on disease progression or toxicity. The Committee considered that almost all people in New Zealand who require second-line treatment would be considered lenalidomide- refractory.

7.26. The Committee considered the exception to this would be people who were ineligible for ASCT and had received a fixed duration of lenalidomide in first-line treatment. The Committee considered if these people had experienced a good response to first-line treatment, and their disease had not progressed for some years, then at relapse a DRd regimen could be used. However, the Committee considered this unlikely if an untrialled agent (ie pomalidomide) were available. The Committee considered it was reasonable to assume all people, regardless of whether they had received an ASCT, would be treated with DPd in second line.

7.27. The Committee considered that less than 10% of people ineligible for ASCT receiving first-line treatment would not receive a triplet combination in the first line. The Committee considered that these would likely be people who are unable to travel to hospitals, and there would be clinical discussion regarding potentially not offering treatment at all eg to those people with pre-existing neuropathy that is severe.

7.28. The Committee considered that use of cyclophosphamide, thalidomide, melphalan or other cytotoxic combinations available would be low, and at the clinician's discretion. The Committee considered that this would likely be in a very small number of people due to the preference for using more effective treatments in earlier lines of treatment.

7.29. The Committee considered that very few people are likely to receive a second transplant. The Committee considered that in New Zealand if a person is aged under 65 years and receives an ASCT then sufficient cells are collected for two ASCTs. The Committee considered that a second ASCT after relapse or becoming refractory to lenalidomide treatment would be unlikely as most people are older than the threshold for ASCT. The Committee considered that in younger (aged under 65 years) fit people this could be a possibility, but a long duration of remission (PFS of over 3 years) following the first ASCT would be necessary to consider a second transplant. The Committee considered there to be little, if any, evidence to inform clinical practice in this setting, and that internationally second transplants are used less due to the increased access to other pharmaceutical treatments, cellular, and bio-specific therapies as salvage options.

7.30. The Committee noted there is evidence for the use of quadruple therapy (anti-CD38, proteasome inhibitor, IMiD and dexamethasone) in the first line setting (PERSEUS (Sonneveld et al. N Engl J Med. 2024;390:301-13) – daratumumab/ bortezomib/ lenalidomide/ dexamethasone; GMMG-CONCEPT (Leypoldt et al. J Clin Oncol. 2024;42:26-37) –isatuximab/ carfilzomib/ lenalidomide/ dexamethasone; IMROZ (Facon et al. N Engl J Med. 2024 Jun doi: 10.1056/NEJMoa2400712) – isatuximab/ bortezomib/ lenalidomide/ dexamethasone). Additionally, the Committee considered that quadruple therapy was increasingly used in first line internationally.

7.30.1. The Committee considered it possible that quadruple therapy could be used in younger fit people who have experienced disease relapse following first-line treatment, as the second line is the last efficacious line of treatment available in New Zealand, and clinicians may wish to trial all possible options in this line for people who could tolerate it.

7.30.2. The Committee considered that the toxicity of a quadruple regimen would not be much higher than a triplet regimen.

7.31. The Committee considered that as first line bortezomib would be of fixed duration, individuals' disease may not be refractory to it. The Committee considered that this was particularly important as chimeric antigen receptor-T cell therapy (CAR-T) or bio-specifics are not available in New Zealand for these people. The Committee considered that individuals who are fit enough to tolerate quadruplet therapy (based on age, organ function and prior toxicity) would be offered quadruple second-line therapy with DPVd if their disease was not previously refractory to bortezomib.

7.32. The Committee considered that daratumumab is most effective in earlier lines of treatment and that first line treatment would be preferred. The Committee noted that Pharmac has not received an application for daratumumab in first line. The Committee considered that if first line was considered then the budgetary impact could be limited by reducing the number of cycles that are funded to achieve minimal residual disease (MRD) and by restricting the use of maintenance daratumumab with maintenance lenalidomide thereafter. The Committee considered that use in second line means that people treated with daratumumab are treated indefinitely.

*Carfilzomib*

7.33. The Committee noted that carfilzomib is not funded for multiple myeloma. The Committee noted the ENDEAVOR trial comparing bortezomib (Vd) and carfilzomib with dexamethasone (Kd) in people with relapsed and refractory multiple myeloma. The Committee noted that the population in the ENDEAVOR trial were heavily bortezomib treated. The Committee noted that PFS was 18.7 months in the Kd group and 9.4 months in the Vd group ($P$<0.0001) (Dimopoulos et al. Lancet Oncol. 2016;17:27-38). The Committee noted that OS was 47.8 months in the Kd group and

38.8 months in the Vd group (*P*=0.0017) (Orlowski et al. Clin Lymphoma Myeloma Leuk. 2019;19:522-30.e1). The Committee noted that carfilzomib was non-inferior to bortezomib in first-line treatment.

7.34. The Committee considered that carfilzomib would be used in people who are triplet exposed (IMiD, bortezomib and daratumumab) who may have disease that is triplet refractory. The Committee considered that trials evaluating carfilzomib in people who have been treated with anti-CD38 agents are not being conducted and that carfilzomib would be most useful in second line as a triple combination ie anti-CD38 agent, carfilzomib and dexamethasone or IMiD, carfilzomib and dexamethasone, particularly in second line in people who are bortezomib-refractory. The Committee considered that carfilzomib would likely add little health benefit to people in third line (or later) treatment, and there is no evidence that carfilzomib is more efficacious than bortezomib in first line treatment.

*Funding criteria*

7.35. The Committee considered that the previously recommended funding criteria are not applicable, given the change in paradigm with the funding of lenalidomide and pomalidomide. The Committee considered that specifying multiple myeloma with one prior line of treatment with no previous daratumumab treatment sufficiently targets the population intended.

*Summary for assessment*

7.36. The Committee 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 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 Committee'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.

| | |
|---|---|
| **P**opulation | Multiple myeloma; people with relapsed or refractory disease after one prior line of therapy (ie. second line MM) |
| **I**ntervention | Daratumumab with **pomalidomide** and dexamethasone (+/- bortezomib)<br>*Subsequent treatment:*<br>Bortezomib retreatment |
| **C**omparator(s)<br>(NZ context) | Pomalidomide with dexamethasone (+/- bortezomib)<br>*Subsequent treatment:*<br>Bortezomib retreatment |
| **O**utcome(s) | Longer PFS and improved OS |

*Table definitions:*

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

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

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

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

## 8. Pembrolizumab for the treatment of biliary tract cancer

### Application

8.1. The Committee reviewed the application for pembrolizumab for the treatment of biliary tract cancer.

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

### Recommendation

8.3. The Committee recommended that pembrolizumab for the treatment of biliary tract cancer be recommended with a **low priority** within the context of treatment of malignancy subject to the following Special Authority criteria:

> **Initial application — advanced biliary tract cancer.** Applications from any relevant medical practitioner. Approvals valid for 6 months for applications meeting the following criteria:
> All of the following
> 1. Patient has advanced biliary tract cancer (Locally Advanced, Metastatic, or Recurrent Disease); and
> 2. Patient has an ECOG performance status of 0-2; and
> 3. Either:
>    3.1. Patient has not received prior systemic therapy; or
>    3.2. Patient has recurrent disease after surgery with curative intent or after adjuvant therapy; and
> 4. Pembrolizumab to be given in combination with gemcitabine and cisplatin for up to 8 cycles; and
> 5. Treatment to be used at a maximum dose of 200 mg every three weeks (or equivalent).
>
> **Renewal application - advanced, metastatic, or recurrent metastatic biliary tract cancer.** Applications from any relevant medical practitioner. Approvals valid for 6 months for applications meeting the following criteria:
> All of the following:
> 1. No evidence of disease progression; and
> 2. The treatment remains clinically appropriate, and the individual is benefiting from treatment; and
> 3. Pembrolizumab to be given as monotherapy; and
> 4. Pembrolizumab to be used at a maximum dose of 200mg every three weeks (or equivalent); and
> 5. Treatment with pembrolizumab to cease after a total duration of 24 months from commencement (or equivalent of 35 cycles dosed every 3 weeks).

8.4. The Committee recommended pembrolizumab based on:

- The high unmet health need of those with biliary tract cancer
- Māori are disproportionately affected by biliary tract cancer
- The lack of treatment options for people with biliary tract cancer
- Trial data reports an increase in overall survival for people who receive pembrolizumab in combination with chemotherapy.

8.5. The Committee considered there was a same or similar health benefit amongst immune checkpoint inhibitors for the treatment of advanced biliary tract cancer and considered it would be reasonable for Pharmac to fund any one of these in this setting.

### Discussion

*Māori impact*

8.6. The Committee discussed the impact of funding pembrolizumab for the treatment of locally advanced or metastatic biliary tract cancer on Pharmac's Hauora Arotahi (Māori health areas of focus) and Māori health outcomes.

8.7. The Committee had previously noted a 2015 New Zealand based study that reported the (non-age standardised) incidence rates of gallbladder carcinoma were higher for Māori tāne and wāhine in comparison to the overall population gender-specific age standardised rates (Lilic et al. ANZ J Surg. 2015;85:260-3). The Committee previously noted that the total number of Māori cases were too few to be able to calculate age-standardised incidence rates by ethnicity. The Committee noted the prevalence of *H. pylori* infections, linked to an increased risk of biliary tract cancer, were found to be increased in Māori compared to Europeans (McDonald et al. Helicobacter. 2015;20:139-45).

*Background*

8.8. The Committee previously considered an application for durvalumab for the treatment of biliary tract cancer in October 2023.

*Health need*

8.9. The Committee noted it had previously considered the health need of people with biliary tract carcinoma in October 2023.

- The Committee previously noted that people with biliary tract cancer have a short life expectancy and a high unmet health need.
- The Committee considered that people with biliary tract cancers can have obstructions that may or may not be amenable to stenting. The Committee noted that stents require frequent replacing, and this can result in cholangitis and sepsis which has a high mortality rate. The Committee considered that relieving biliary obstructions significantly improved health outcomes and quality of life.

8.10. The Committee noted that a small proportion of people with biliary tract carcinoma would be microsatellite instability high (MSI-H) or deficient mismatch repair (dMMR). The Committee considered this could confer a higher likelihood of response to immunotherapy. The Committee considered biliary tract cancer is sometimes difficult to biopsy, therefore people with MSI-H or dMMR disease may be difficult to identify.

*Health benefit*

8.11. The Committee noted the KEYNOTE-966 randomised, double-blind, placebo-controlled, phase three study of pembrolizumab compared with placebo, administered together with chemotherapy in individuals with untreated, unresectable, locally advanced or metastatic biliary tract cancer.

- Kelley et al. Lancet. 2023;401:1853-65 reported results at a median duration of follow up of 25.6 months.
  - Median overall survival was 12.7 months (95% CI 11·5-13·6) in the pembrolizumab group versus 10.9 months (9·9-11·6) in the placebo group (hazard ratio 0·83 [95% CI 0·72-0·95]; one-sided p=0·0034 [significance threshold, p=0·0200])
  - Median progression-free survival was 6.5 months (95% CI 5.7–6.9) in the pembrolizumab group and 5.6 months (5.1–6.6) in the placebo group.
  - Grade 3 - 4 adverse events occurred in 79% of people in the pembrolizumab arm vs 75% in placebo.

- Supplier-provided 2023 American Society of Clinical Oncology (ASCO) annual meeting presentation providing information on the health-related quality of life (HRQOL) outcomes of the KEYNOTE-966 trial:
    - HRQoL was maintained with addition of pembrolizumab to first-line gemcitabine/cisplatin in individuals with advanced biliary tract cancer with similar scores across a variety of quality-of-life outcomes.
- Supplier-provided poster (Yau et al. JCO. 2024.42.16 suppl 4097) presented at the ASCO annual meeting in 2024 investigating the impact of hepatitis B viral infection on efficacy and safety in KEYNOTE 966 study.
    - The poster reported overall survival benefit, as well as other efficacy and safety outcomes remained consistent between people positive for the hepatitis B virus and people negative for the virus.
- Supplier-provided poster (Finn et al. JCO. 2024;42.16 suppl 4093) presented at the ASCO annual meeting in 2024 reporting three years follow up data from the KEYNOTE-966 study.
    - Median overall survival of 12.7 months (95% CI 11.5-13.6) in the pembrolizumab arm vs 10.9 months (95% CI 9.9-11.6) in placebo arm (HR 0.86, 95% CI 0.75-0.98, nominal P= 0.0099)
    - At 24 months, the overall survival rate was 24.6% (95% CI 21.0-28.3) in the pembrolizumab arm vs 19.2% (95% CI 16.0-22.6) in the placebo arm.
    - Median progress free survival was 6.5 months (95% CI 5.7-6.9) for the placebo arm vs 5.6 months (95% CI 4.9-6.5) for the pembrolizumab arm (HR 0.85, 95% CI 0.75-0.97).
    - Objective response rate was 28.7% (n = 153) in the pembrolizumab arm vs 28.7% (n = 154) in the placebo arm.
    - Duration of response was longer in pembrolizumab arm (8.3 vs 6.9 months).
- The Committee considered KEYNOTE-966 was a well-designed study including over 1000 participants, which is impressive given the rarity of the cancer.
- The Committee noted there were not large differences between programmed death-ligand 1 (PDL-1) combined positive score (CPS) groups reported hazard ratios (HR) (95% CI): <1% HR 0·84 (0·62–1·14) compared with ≥1% HR 0·85 (0·72–1·00)
- The Committee noted that no individuals from New Zealand were included in the study but considered its results to be relevant to the New Zealand population.

8.12. The Committee also noted Piha-Paul et al. Int J Cancer. 2020;147:2190-8, which reported data from KEYNOTE-158 (phase two, required PD-L1 positive tumours) and KEYNOTE-028 (Phase oneb). The Committee noted the studies reported that overall pembrolizumab provided durable antitumor activity in 6% to 13% with advanced biliary tract cancer, regardless of PD-L1 expression.

8.13. The Committee noted the following studies:

- Monge et al. Oncologist. 2022;27:e273-85
- Marabelle et al. Lancet Oncol. 2020;21:1353-65
- Lee et al. J Clin Med. 2020;9:1769
- Alshari et al. Onco Targets Ther. 2019;12:5293-98
- Habib et al. Cureus. 2023;15 e38332.

8.14. The Committee considered the populations of individuals included in the KEYNOTE-966 and TOPAZ studies were similar. The Committee noted the results were similar in both studies and considered a class effect amongst PD-L1 or PD-1 inhibitors was likely in biliary tract cancer.

8.15. The Committee considered that the majority of individuals would receive pembrolizumab and chemotherapy in combination, unless pembrolizumab was contraindicated for them, there were other auto-immune contraindications, or they had experienced an early immune reaction to pembrolizumab.

8.16. The Committee considered immune related side effects can be challenging to treat and could be long lasting in nature.

8.17. The Committee considered bile duct cancer to be a heterogeneous group of cancers. The Committee considered it was challenging to test biliary cancers as it was difficult to biopsy and that inclusion of different types of cancers can influence interpretation of trial data.

8.18. The Committee considered that the health benefit observed may in part be driven a small population of individuals with dMMR cancers, but this was not tested for in the trial. The Committee considered that this group might possibly benefit to a greater extent from pembrolizumab monotherapy, as has been demonstrated for other dMMR cancers and might be best considered as part of a tumour agnostic indication, which has been considered and deferred by the Committee previously.

*Suitability*

8.19. The Committee noted pembrolizumab is administered as an intravenous infusion which would increase the time an individual must spend at an infusion centre for their administration.

*Cost and savings*

8.20. The Committee noted the funding of pembrolizumab would result in an increase in infusion time, which would put pressure on already overburdened infusion services. Additional nursing time would also be required for administration and monitoring.

8.21. The Committee noted that funding pembrolizumab would result in an increase in the management costs of immunotherapy related side-effects.

*Funding criteria*

8.22. The Committee noted there were minimal differences in the health benefit between PD-L1 expressing groups (CPS <1% and ≥1%). The Committee considered in biliary tract cancer, it is sometimes challenging to isolate a sample for testing, and therefore would be difficult to determine if an individual's cancer had microsatellite instability (MSI) or mismatch repair (MMR) deficiency.

*Summary for assessment*

8.23. The Committee 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 biliary tract 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 Committee'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 | The population indicated in the Special Authority is as follows:<br>• Individuals with advanced biliary tract cancer (locally advanced, metastatic, or recurrent disease) where biliary tract cancer is defined as intrahepatic cholangiocarcinoma, extrahepatic cholangiocarcinoma, or gallbladder cancer.<br>• Has an ECOG performance score of 0-2<br>• Either not received prior systemic therapy or having recurrent disease after surgery with curative intent or after adjuvant therapy. |
| Intervention | • Pembrolizumab with chemotherapy 200 mg IV pembrolizumab infusion on day 1 of every 3-weekls (maximum of 35 cycles)<br>• Gemcitabine 1000 mg/m$^2$ and cisplatin 25 mg/m$^2$ IV infusion, on day 1 and 8 every 3-week cycle (maximum 8 cycles) |
| Comparator(s) | Chemotherapy alone<br>gemcitabine 1000 mg/m$^2$ and cisplatin 25 mg/m$^2$ IV infusion, on day 1 and 8 every 3-week cycle |
| Outcome(s) | Improved overall survival<br>Median overall survival was 12·7 months (95% CI 11·5–13·6) in the pembrolizumab group versus 10·9 months (9·9–11·6) in the placebo group (hazard ratio 0·83 [95% CI 0·72–0·95]; one-sided p=0·0034 [significance threshold, p=0·0200]) (KEYNOTE-966).<br><br>Improved progression-free survival<br>Median progression-free survival was 6·5 months (95% CI 5·7–6·9) in the pembrolizumab group and 5·6 months (5·1–6·6) in the placebo group. (KEYNOTE-966). |
| Table definitions: Population, the target population for the pharmaceutical; Intervention, details of the intervention pharmaceutical; Comparator, details the therapy(s) that the target population would receive currently (status quo – including best supportive care); Outcomes, details the key therapeutic outcome(s) and source of outcome data. | |

## 9. Ruxolitinib for the treatment of graft versus host disease, following allogenic haemopoietic stem cell transplant, chronic corticosteroid-refractory

### Application

9.1. The Committee reviewed the application for ruxolitinib for the treatment of chronic corticosteroid-refractory graft versus host disease following allogenic haemopoietic stem cell transplant (allo-HSCT).

9.2. The Committee noted an application was also received for ruxolitinib for the treatment of acute corticosteroid-refractory graft versus host disease following allo-HSCT, and considered this application should also be reviewed at a future Committee meeting.

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

## Recommendation

9.4. The Committee **recommended** that ruxolitinib for the treatment of chronic corticosteroid-refractory graft versus host disease following allogenic haemopoietic stem cell transplant be listed with a **high priority**, in the context of the treatment of malignancy, to the following Special Authority criteria:

> **Initial application** (**chronic graft versus host disease**) – from any relevant practitioner. Approvals valid for 6 months for applications meeting the following criteria:
> All of the following:
> 1. Person has chronic graft versus host disease following allogenic haemopoietic stem cell transplant; and
> 2. Either:
>  2.1 Person has received insufficient benefit, or their disease has progressed after administration of minimum prednisone 1 mg/kg/day for at least 1 week (or equivalent); or
>  2.2 Disease persists without improvement despite continued treatment with prednisone at > 0.5 mg/ kg/day or 1 mg/kg/every other day for at least 4 weeks (or equivalent); and
> 3. Ruxolitinib will not be used with systemic therapies other than corticosteroids and/or calcineurin inhibitors.
>
> **Renewal (chronic graft versus host disease)** - Approvals valid for 6 months for applications meeting the following criteria:
> Both:
> 1. The treatment remains appropriate; and
> 2. Ruxolitinib will not be used with systemic therapies other than corticosteroids and/or calcineurin inhibitors.

9.5. In making this recommendation, the Committee considered:

- The health needs of people with chronic graft versus host disease (cGvHD) are high due to increased mortality and the impacts on their quality of life, and the limited effective, evidence-based treatments available in those whose cGvHD is refractory to corticosteroids.
- The REACH3 trial was good quality evidence for ruxolitinib being superior to the currently funded treatments available for the treatment of corticosteroid-refractory cGvHD in New Zealand.
- As an orally administered treatment, ruxolitinib has the potential to relieve pressure on infusion services if it is used for people who would otherwise receive treatments administered via intravenous infusion.
- Funding ruxolitinib for the treatment of corticosteroid-refractory cGvHD may reduce long term health sector expenditure through requiring less multi-disciplinary team involvement, reduced hospital stays, and decreased risk of complications associated with current treatments.

## Discussion

*Māori impact*

9.6. The Committee discussed the impact of funding ruxolitinib for the treatment of corticosteroid-refractory cGvHD following allogenic haemopoietic stem cell transplant (allo-HSCT) on Māori health outcomes. The Committee noted graft versus host disease (GvHD) is not one of Pharmac's five Hauora Arotahi - Māori Health Areas of Focus, which were identified by Māori stakeholders as breast cancer, lung cancer, diabetes, respiratory health, mental health, and heart health. The Committee considered that although there is no evidence to suggest GvHD is more prevalent in

Māori, this does not exclude the possibility that Māori with GvHD experience inequitable access to specialist services and/or inequitable health outcomes.

9.7. The Committee considered long term consequences of prolonged corticosteroids and calcineurin inhibitors such as increased cardiovascular risk and development of diabetes, or progression (given corticosteroid impact on diabetic control) may inequitably effect Māori with GvHD , but noted there is currently no published evidence to support this. However, the Committee considered this lack of published evidence in the peer-reviewed literature does not mean that inequities do not exist.

*Impact on Pacific peoples, disabled people, tāngata whaikaha Māori, and other people who have been underserved by the health system*

9.8. The Committee discussed the impact of funding ruxolitinib for the treatment of corticosteroid-refractory cGvHD following allo-HSCT on people who have been underserved by the health system. The Committee did not identify any group with known inequitable health outcomes associated with GvHD but noted that the lack of available evidence did not exclude the possible presence of these inequities.

9.9. The Committee considered that the consequences of cGvHD such as time away from work, time away from home and family (or demands on family or whānau to take the person to a treatment centre) due to the need to be treated in a specialist centre, and long term consequences of prolonged steroids and calcineurin inhibitors may inequitably affect populations who are underserved by the health system, but noted there was no published evidence to support this.

*Background*

9.10. The Committee noted ruxolitinib is currently funded for myelofibrosis in New Zealand, subject to Special Authority criteria.

9.11. Pharmac has not previously considered any other treatments for corticosteroid-refractory cGvHD following HSCT.

9.12. The Committee noted a small number of people are currently receiving funding ruxolitinib for cGvHD through the Named Patient Pharmaceutical Assessment (NPPA) pathway due to being defined as having exceptional clinical circumstances.

*Health need*

9.13. The Committee noted GvHD is a frequent complication of allo-HSCT, which occurs when the transplanted or donor immune system attacks healthy tissues in the recipient (host). The Committee noted acute GvHD (aGvHD) and cGvHD are distinguished by their clinical findings, according to the National Institutes of Health (NIH) consensus criteria (Filipovich et al. Biol Blood Marrow Transplant. 2005;11:945-56). The Committee noted aGvHD and cGvHD were previously distinguished by onset <100 days versus ≥100 days from transplantation, but each condition may occur outside of those time periods. cGvHD is a distinct diagnosis, and not progression of aGvHD (Jagasia et al. Biol Blood Marrow Transplant. 2007;13:1207-15).

9.14. The Committee noted that cGvHD is a multisystem disorder, and that while clinical manifestations may be restricted to a single site/organ, they are often widespread to several sites/organs. The Committee noted common clinical manifestations include skin involvement, dry oral mucosa, gastrointestinal tract ulcerations and sclerosis, elevated serum bilirubin, and bronchiolitis obliterans (Filipovich. Best Pract Res Clin Haematol. 2008;21:251-7). The Committee noted that people with moderate to severe GVHD were often managed in specialist allo-HSCT centres, and this may involve being away from home a number of months.

9.15. The Committee considered the applicant's estimate that approximately 40-50% of people who receive HSCT develop cGvHD to be reasonable, and noted this aligns with the literature where estimates vary from about 30-70% (Baumrin et al. J Am Acad Dermatol. 2024;90:1-16. The Committee noted that approximately 40-50% of people experience an adequate response to first line treatment with corticosteroids, with conversely over half of the group becoming corticosteroid-resistant (refractory) or -dependent within two years (Flowers et al. Blood. 2015;125:606-15, Lee at al. Biol Blood Marrow Transplant. 2003;9:215-33).

9.16. The Committee noted cGvHD is a leading cause of late non-relapse mortality and morbidity following allo-HSCT (Tey et al. The Haematologist. 2019;16), noting that compared with people who did not develop GvHD, the presence of cGvHD has been associated with inferior overall survival (relative risk [RR] of death 1.56; 95% CI 1.41, 1.73) and higher treatment-related mortality (RR 2.43; 95% CI 2.09-2.82) in a registry study of 7489 allo-HSCTs (Boyiadzis et al. Clin Cancer Res. 2015;21:2020-8). The Committee considered the health needs of people with cGvHD to be high due to inferior survival and the impacts on their quality of life (Pidala et al. Cancer Control. 2011;18:268-76, Kurosawa et al. Biol Blood Marrow Transplant. 2017;23:1749-58).

9.17. The Committee considered that for people experiencing an inadequate response or progression on oral corticosteroids with optimised immunosuppression, there is but limited evidence-based, effective, second line funded therapy available in New Zealand, while noting there was a variety of second/third line options (currently considered as second line in the NZ context) that might be used (albeit without much effect), which included mycophenolate mofetil, rituximab, sirolimus, imatinib, methotrexate, and thalidomide. The Committee considered there to be no clear 'best choice' among these agents and that choice may be guided by affected organ systems. The Committee noted there was no head-to-head comparative data between them, and that all evidence for the agents is based on retrospective cohort study or weaker data (Socie et al. Blood. 2014;124:374-84).

9.18. The Committee considered limitations of mycophenolate mofetil, which the applicant stated is often trialled for this indication, include a response rate of 26-64% in retrospective cohorts, and with concerns around post-transplant lymphoproliferative disease and viral reactivations. The Committee noted the studies suggesting efficacy of mycophenolate were small and single arm (Lopez et al. Biol Blood Marrow Transplant. 2005;11:307-13, Baek et al. J Clin Oncol. 2004;22:6631). The Committee noted the applicant's consideration that methotrexate is often trialled for the indication, although complete response rates in retrospective cohorts are approximately 60%. The Committee noted rituximab is funded for corticosteroid-refractory GvHD. However, the Committee noted that support for its efficacy was from small phase two studies, and considered there was concern about infective complications. The Committee considered evidence for pentostatin is limited with a range of responses from 30-60%, and noted results from a small study that reported infective complications and cytopaenias (Jacobsohn et al. J Clin Oncol. 2007;25:4255-51). The Committee agreed with the applicant that there is limited evidence for efficacy of thalidomide, imatinib, and sirolimus in this population, and noted sirolimus and thalidomide are not currently funded for this indication in New Zealand.

9.19. The Committee noted that non-pharmaceutical treatment for corticosteroid refractory cGvHD, extracorporeal photopheresis (ECP), is supported by some prospective evidence, with response rates up to 80%(Couriel et al. Blood. 2006;107:3074-80, Dignan et al. Bone Marrow Transplant. 2012;47:824-30, Flowers et al. Blood. 2008;112:2667-74).The Committee noted that this was a cost to the health system and is expensive, access is limited to Auckland, and few individuals are likely to access this treatment. Members considered Pharmac could follow up with the

applicant to gauge the number of people receiving ECP in New Zealand, and the applicant's views on treatment preference between ECP and ruxolitinib if both were funded.

9.20. The Committee considered that the currently funded treatment options for corticosteroid-refractory cGvhD in New Zealand are poor with limited supporting evidence, and this was contributing to the currently unmet health needs of those with corticosteroid refractory cGvHD.

*Health benefit*

9.21. The Committee noted results of the REACH3 study, a Phase three open-label, randomised controlled trial comparing ruxolitinib 10 mg twice daily (*n* = 165) to an investigator's choice of therapy from a list of 10 commonly used options considered best available care (control) (*n* = 164) in people 12 years or older with moderate or severe glucocorticoid-refractory or -dependent cGvHD, used for 24 weeks (Zeiser at al. N Engl J Med. 2021;385:228-38).

9.21.1. The Committee noted concomitant corticosteroids could be tapered off once a response was reached in all affected organs, and concomitant calcineurin inhibitors, and ruxolitinib could be tapered after six (28-day) cycles. The Committee noted participants in the control group could cross over to the ruxolitinib group if they experienced progressive cGvHD or toxicity on their original therapy.

9.21.2. The Committee noted the overall response at week 24 (the primary end point) was higher with ruxolitinib (82 people, 49.7%) than with control therapy (42 people, 25.6%) (odds ratio, 2.99 [95% confidence interval (CI)}, 1.86, 4.80]; risk ratio, 1.93 [95% CI, 1.44, 2.60]; P<0.001), and a total of 11 people (6.7%) in the ruxolitinib group and 5 (3.0%) in the control group had a complete response. The Committee considered this showed there was a clear difference in favour of ruxolitinib treatment between the two groups.

9.21.3. The Committee noted people who crossed over from control therapy to ruxolitinib (*n* = 61) also had a response, with a best overall response at data cutoff in 78.7% (4 with a complete response and 44 with a partial response.

9.21.4. The Committee noted people receiving ruxolitinib had longer failure free survival than people receiving control therapy (median failure-free survival, >18.6 months vs. 5.7 months; hazard ratio, 0.37; 95% CI, 0.27, 0.51; P<0.001), and the probability of failure-free survival at 6 months, as estimated with the use of the Kaplan–Meier method, was higher with ruxolitinib (74.9%; 95% CI, 67.5 to 80.9) than with control therapy (44.5%; 95% CI, 36.5, 52.1). The Committee noted response on the modified Lee Symptom Scale at 24 weeks was also higher with ruxolitinib than with control therapy (24.2% vs. 11.0%; odds ratio, 2.62 [95% CI, 1.42, 4.82]; P=0.001).

9.21.5. The Committee noted the occurrence adverse events (AEs) of grade 3 or higher was similar in the two groups (in 57.0% of the people who received ruxolitinib and in 57.6% of the people who received control therapy), and AEs led to treatment discontinuation in 27 people (16.4%) who received ruxolitinib and in 11 (7.0%) who received control therapy. The Committee noted that at a median follow up of 57.3 weeks, 83 people were continuing treatment with ruxolitinib, and 42 people continuing treatment with their control therapy.

9.21.6. The Committee considered the results from the REACH3 trial showed good quality evidence for ruxolitinib as a superior treatment to the control group agents for the treatment of cGVHD.

9.22. The Committee considered that the treatment with ruxolitinib of individuals in New Zealand, if funded, would follow the REACH3 protocol.

9.23. The Committee noted the 2023 Australia and New Zealand Transplant and Cellular Therapies (ANZCT) consensus position statement on ruxolitinib in corticosteroid-refractory acute and chronic GvHD (Hamad et al. Intern Med J. 2023;53:2319-29). The Committee noted the statement outlines recommendations for use of ruxolitinib if it were to be available in New Zealand, including dosing and other recommendations using data from the REACH3 trial.

9.24. The Committee also noted results from the following publications regarding the efficacy and safety of ruxolitinib for the treatment of cGvHD:

- Zhang et al. PLoS One. 2022;17:e0271979, a recent systematic review and meta-analysis of randomised and non-randomised studies assessing the efficacy and safety of ruxolitinib for corticosteroid-refractory GvHD (both acute and chronic) which included nineteen studies, totalling 1358 participants.
- White et al. Transplant Cell Ther. 2023;29:120, a multicentre, retrospective study evaluating clinical outcomes of ruxolitinib therapy in heavily pretreated cGvHD people with corticosteroid failure (*N* = 115).
- Fan et al. Front Immunol. 2022;13:954268, a meta-analysis of the efficacy and safety of ruxolitinib in corticosteroid refractory GvHD (acute and chronic) which included 37 studies, totalling 1580 participants.

9.25. The Committee considered that aside from the REACH3 trial, the other supporting evidence for ruxolitinib for the treatment of cGvHD was of poor quality, due to its retrospective nature, and the inclusion of non-randomised and single arm studies.

9.26. The Committee considered that while there was no direct trial evidence, a partial or better response is a good surrogate outcome to model a potential overall survival benefit.

9.27. The Committee noted that there is limited retrospective evidence for the use of ruxolitinib for GvHD in children, and considered Pharmac should seek expert advice from paediatric haematologists if considering funding the treatment for children less than 12 years of age.

*Suitability*

9.28. The Committee noted that as an orally administered treatment, ruxolitinib has the potential to relieve pressure on infusion services, if it is used for people who would otherwise receive treatments administered via intravenous infusion (eg rituximab).

*Cost and savings*

9.29. The Committee considered that people who received a response from treatment would likely have a shorter length of stay in hospital, and therefore it could be extrapolated that ruxolitinib would lead to shorter length of stays in hospital. The Committee also considered that funding ruxolitinib may lead to decreased risk of complications associated with current treatments (eg cardiovascular morbidity, infection risk).

9.30. The Committee considered that up to 50% of individuals who have allo-HSCTs will experience at least moderate cGVHD. Of those with cGVHD, about 50% are likely to

be corticosteroid refractory. Therefore, the eligible patient group is likely to be about 25% of individuals who have allo-SCTs.

*Summary for assessment*

9.31. The Committee considered that the below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for ruxolitinib if it were to be funded in New Zealand for chronic corticosteroid-refractory GvHD following allo-HSCT.

| | |
|---|---|
| **P**opulation | People aged 12 and older treated with allogeneic stem cell transplant who have developed chronic graft-versus-host disease (GvHD) and received an inadequate response to corticosteroids. |
| **I**ntervention | Ruxolitinib (tablet) at starting dose of 10mg twice daily (BD), for at least 6 cycles (28 days per cycle) unless the individual has unacceptable side effects or progression of chronic GVHD.<br><br>If a response is experienced, then taper systemic corticosteroids first. If the response is sustained after 6 cycles of ruxolitinib – start tapering ruxolitinib and/or calcineurin inhibitor.<br><br>Adjunctive to corticosteroids with or without calcineurin inhibitors |
| **C**omparator(s) (NZ context) | Any of the following:<br>• mycophenolate mofetil<br>• rituximab,<br>• imatinib,<br>• methotrexate<br><br>Adjunctive to corticosteroids with or without calcineurin inhibitors |
| **O**utcome(s) | REACH3 trial (Zeiser at al. 2021):<br>• Overall response rate at 24 weeks (49.7% ruxolitinib vs 25.6% best available therapy (OR 2.38; 95% CI, 1.43 to 3.94; P<0.001).<br>• Median failure-free survival (>18.6 months vs. 5.7 months; HR 0.37; P<0.001).<br>➔ These outcomes likely lead to an overall survival benefit and/or HRQOL benefits, as well as shorter length of stay in hospital.<br><br>• Lee Symptom Scale responses (24.2% vs. 11.0%; OR 2.62; P=0.001).<br>➔ Likely to translate to improvement in HRQoL for the duration of the disease.<br><br>Ruxolitinib may shorten the duration of stay in hospital, however Pharmac staff have not found empirical evidence to support this. |
| *Table definitions:*<br>**P**opulation: The target population for the pharmaceutical, including any population defining characteristics (eg line of therapy, disease subgroup)<br>**I**ntervention: Details of the intervention pharmaceutical (dose, frequency, treatment duration/conditions for treatment cessation).<br>**C**omparator: Details the therapy(s) that the target population would receive currently (status quo – including best supportive care; dose, frequency, treatment duration/conditions for treatment cessation).<br>**O**utcomes: Details the key therapeutic outcome(s), including therapeutic intent, outcome definitions, timeframes to achieve outcome(s), and source of outcome data. | |

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 Committee's assessment at this time and may differ from that requested by the applicant.

## 10. Dostarlimab for the treatment of advanced or recurrent endometrial cancer, with or without deficient mismatch repair (dMMR) status.

### Application

10.1. The Committee reviewed the application for dostarlimab for the treatment of advanced or recurrent endometrial cancer, with or without deficient mismatch repair (dMMR) status

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

### Recommendation

10.3. The Committee recommended that the application for dostarlimab for the treatment of advanced or recurrent endometrial cancer, **with deficient mismatch repair** (dMMR) status in the **first line setting** be recommended with a **high priority** in the context of treatment of malignancy, subject to the following Special Authority criteria:

> **Initial application (endometrial cancer, primary advanced or first recurrent).** Applications from relevant medical practitioner. Approvals valid for 12 months.
> All of the following:
> 1. Patient has primary advanced or recurrent endometrial cancer; and
> 2. The disease is unsuitable for curative surgical resection and or curative radiotherapy; and
> 3. Patient has an ECOG performance score of 0-2; and
> 4. Patient has not received prior systemic therapy in the advanced or recurrent setting; and
> 5. Patient has deficient mismatch repair (dMMR) endometrial cancer, as determined by immunohistochemistry test; and
> 6. Treatment to be administered in combination with platinum-based chemotherapy.
>
> **Renewal application (endometrial cancer, primary advanced or first recurrent).**
> Applications from relevant medical practitioner. Approvals valid for 4 months.
> Both:
> 1. No evidence of disease progression; and
> 2. Dostarlimab is to be discontinued after a maximum of 36 months of treatment.

10.4. The Committee recommended that the application for dostarlimab for the treatment of advanced or recurrent endometrial cancer**, irrespective of deficient mismatch repair** (dMMR) status, in the **first line setting** be recommended with a **medium priority** in the context of treatment of malignancy subject, to the following Special Authority criteria:

> **Initial application (endometrial cancer, primary advanced or first recurrent).** Applications from relevant medical practitioner. Approvals valid for 12 months.
> All of the following:
> 1. Patient has primary advanced or recurrent endometrial cancer; and
> 2. The disease is unsuitable for curative surgical resection and or curative radiotherapy; and
> 3. Patient has an ECOG performance score of 0 or 2; and
> 4. Patient has not received prior systemic therapy in the advanced or recurrent setting; and
> 5. Treatment to be administered in combination with platinum-based chemotherapy.
>
> **Renewal application (endometrial cancer, primary advanced or first recurrent).**
> Applications from relevant medical practitioner. Approvals valid for 4 months.
> Both:
> 1. No evidence of disease progression; and
> 2. Dostarlimab is to be discontinued after a maximum of 36 months of treatment.

10.5. The Committee recommended that the application for dostarlimab for the treatment of advanced or recurrent endometrial cancer, **with deficient mismatch repair** (dMMR) status in the **second line setting** be recommended with a **high priority** in the context of treatment of malignancy, subject to the following Special Authority criteria:

**Initial application (endometrial cancer, primary advanced or first recurrent).** Applications from relevant medical practitioner. Approvals valid for 12 months.
All of the following:

1. Patient has primary advanced or recurrent endometrial cancer; and
2. The disease is unsuitable for curative surgical resection and or curative radiotherapy; and
3. Patient has an ECOG performance score of 0-2; and
4. Patient has deficient mismatch repair (dMMR) endometrial cancer, as determined by immunohistochemistry test; and
5. Patient has had prior systemic therapy fin the advanced or recurrent setting.

**Renewal application (endometrial cancer, primary advanced or first recurrent).**
Applications from relevant medical practitioner. Approvals valid for 4 months.
Both:

1. No evidence of disease progression; and
2. Dostarlimab is to be discontinued after a maximum of 24 months of treatment.

10.6. The Committee recommended that application dostarlimab for the treatment of advanced or recurrent endometrial cancer, **irrespective of deficient mismatch repair** (dMMR) status, in the **second line setting** be **declined**.

10.7. In making these recommendations, the Committee considered:

- The high unmet health need of people with endometrial cancer
- Endometrial cancer disproportionally affects Māori and Pacific peoples.
- Dostarlimab is a targeted medicine that has the greatest health benefit in people whose cancer has deficient mismatch repair (dMMR) status.
- The evidence for the use of dostarlimab in second line treatment, particularly where the cancer is proficient mismatch repair (pMMR), to be of poor quality.

## Discussion

*Māori impact*

10.8. The Committee discussed the impact of funding dostarlimab for the treatment of endometrial cancer on Māori health areas of focus and Māori health outcomes. The Committee noted Māori are more likely to be diagnosed with endometrial cancer at a younger age, higher grade and have poorer survival.

*Background*

10.9. No applications for the treatment of endometrial cancer have been considered by the Committee. The Committee has previously reviewed pembrolizumab for the treatment of microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal and pancreatic cancer in July 2021 and July 2023 respectively. In addition, the Committee has considered pembrolizumab for dMMR tumours that have progressed after previous treatments, including endometrial tumours.

*Health need*

10.10. The Committee noted endometrial cancer is a malignancy of the inner epithelial lining of the uterus, with an increasing incidence and disease-associated mortality, worldwide. Most cases of endometrial cancer occur between 65 and 75 years of age. Several risk factors including increased age, certain ethnicities, higher body mass index (BMI), endogenous or exogenous oestrogenic exposure, tamoxifen use, early menarche, late menopause, lower parity, metabolic syndrome, family history and genetic predisposition have been associated with an increased risk of endometrial cancer development. By contrast, a lower risk is associated with normal BMI and oral contraception use (Makker et al. Nat Rev Dis Primers. 2021; 7: 88).

10.11. The Committee noted that:

10.11.1. the classification of endometrial cancer has changed from type I and type II to a molecular classification (Cancer Genome Atlas Research Network, Nature. 2013; 497:67-73) Oaknin et al. Ann Oncol. 2022;33:860-77).

10.11.2. among perimenopausal and postmenopausal women, postmenopausal bleeding is a common symptom of endometrial cancer present in approximately 70% to 90% of individuals (Seebacher et al. BMC Cancer. 2009;9:460)

10.11.3. in advanced stages of endometrial cancer, other symptoms may be present, including pelvic pain, often during urination or intercourse, back pain, the presence of a mass, or unintentional weight loss (Riedinger et al. Gynecol Oncol. 2022;167:174-80)

10.11.4. early diagnosis is associated with an improved prognosis; the 5-year survival rate for those diagnosed with localised disease is 95%, with survival rates decreasing to 18% in people with advanced or metastatic disease (Makker et al. Gynecol Oncol Res Pract. 2017;4:19, Tuninetti et al. Cancers (Basel). 2023;15:3639)

10.11.5. a study of 259 individuals with endometrial cancer in the USA reported endometrial cancer survivors with high-grade disease reporting significantly lower quality of life (QOL) compared to survivors with low-grade disease (85 vs. 91, respectively, p value = 0.025) as assessed by the Functional Assessment of Cancer Therapy-General (FACT-G) survey (Banning et al. Cancer Med. 2023;12:13675-86)

10.11.6. a metanalysis in individuals with gynaecological cancers reported 23% experienced depression (Krebber et al. Psychooncology. 2014;23:121–30). In addition, a study has reported that over 50% of individuals with gynaecological cancer will experience either temporary or persistent sexual difficulties. Those who undergo hysterectomies, a surgical treatment option for endometrial cancer, have also reported experiencing a sense of loss after a hysterectomy, which affected their emotional state (Goudarzi et al. BMC Womens Health. 2022; 22: 40)

10.11.7. in addition to the psychological effects, individuals may have early physiological postmenopausal changes, either pre-existing or as a result of oophorectomy, depending on age and menopausal status at the time of diagnosis. Additionally, a high proportion of individuals with early-stage disease will be cured of their cancer, making longer-term QoL issues more pertinent. Following bilateral oophorectomy, premenopausal women may develop significant and debilitating menopausal symptoms (Edey et al. Cochrane Database Syst Rev. 2018;2018(5):CD008830)

10.11.8. a study reported that over 50% of individuals with gynaecological cancer will have either temporary or persistent sexual difficulties (Hopkins et al. Climacteric. 2015;18:94-8), A further study reported that individuals who had surgery for endometrial cancer had no differences in their own sexual experience postoperatively, but compared with healthy controls, they had more sexual difficulties overall (Carr et al. Int J Gynaecol Obstet. 2015:131 Suppl 2:S159-63)

10.11.9. a recent study of individuals who had undergone a hysterectomy, one of the surgical treatment options for endometrial cancer, reported individuals after hysterectomy describing physical limitations, especially in the workplace and in life, and considered therefore could limit some individuals participating

fully outside of the home and in their communities (Goudarzi et al. BMC Womens Health. 2022;22:40).

*Māori impact*

10.12. The Committee noted that Māori are more likely to be diagnosed with endometrial cancer at a younger age, higher grade and have poorer survival. This in part could be due to increased barriers to healthcare. Late presentation can be due to reported barriers to accessing care, such as costs, overbooked clinics, low-quality health care and appropriate cultural respect of the healthcare provider (Henry et al. Aust N Z J Obstet Gynaecol. 2019;59:874-6).

*Impact on Pacific peoples, disabled people, tāngata whaikaha Māori, and other people who have been underserved by the health system*

10.13. The Committee noted a survey that reported higher incidence rates of endometrial cancer in Pacific peoples, that were also more likely to be affected by other variables including higher BMI and cardiovascular comorbidities (Williams et al. Aust N Z J Obstet Gynaecol. 2024). A 2012 study also reported Pacific women had 2.61 (95 % CI 2.22, 3.05) times the endometrial cancer rate of European/Other women pooled over time, and the most rapidly increasing rates over time with the rate ratio increasing from 1.96 (1.14-3.37) in 1981/1986 to 3.78 (3.03-4.71) in 2001/2004 (p for trend = 0.14) (Meredith et al. Cancer Causes Control. 2012;23:875-85).

10.14. The Committee noted Pacific people are also more likely to be diagnosed with endometrial cancer at a younger age, higher grade and have poorer survival. Similar barriers to healthcare access have been identified for Pacific people as for Māori, including costs of accessing care, and appropriate cultural respect and culturally safe care (Henry et al. 2019).

10.15. Socioeconomic deprivation has been linked both to increased obesity (1.5 times increase in people living in the most deprived compared with the least deprived areas), and to overall cancer incidence, where the most socioeconomically deprived quintile shows a 25% higher rate for all cancers than the least deprived group (Bigby et al. Aust N Z J Obstet Gynaecol. 2020;60:250-7).

10.16. About 20-30% of endometrial cancers are caused by dMMR or MSI-H. Of these, about 3-5% are hereditary (Lynch syndrome) while the remainder are somatic (double somatic mutation or epigenetic silencing of the MLH1 gene) (Corr et al. BMJ Med. 2022; 1: e000152).

10.17. The Committee previously noted in 2021 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*'. The Committee considered there was evidence to show immunohistochemistry testing for dMMR results to be consistent irrespective of assay or laboratory used for testing.

10.18. The Committee noted data that suggested there is a reduced enrichment of people with advanced endometrial cancer who are dMMR positive in later lines of treatment compared with first line treatment (Kelkar et al.Arch Gynecol Obstet. 2024;309:2833-41).

10.19. The Committee noted a study in 1024 endometrial tumour samples reported progression-free survival was worse for women whose tumours had epigenetic MMR defects compared with the MMR normal group (hazard ratio, 1.37; P < 0.05; 95% CI, 1.00 to 1.86) (McMeekin et al. J Clin Oncol. 2016;34:3062–68).

10.20. The Committee noted the 2022 ESMO guidelines (Oaknin et al. Ann Oncol. 2022;33:860-77) for the treatment of endometrial cancer. The Committee considered

that development of treatments for endometrial cancer is an active space with many trials ongoing, therefore currently guidelines may not reflect the most up to date data. The Committee considered that therapeutics considered now for the treatment of endometrial cancer should be compared with the treatment landscape when new evidence is published.

10.21. The Committee considered there were limited effective second line treatment options and that clinicians must balance the toxicity and previous treatments when deciding second line treatment options.

10.22. The Committee noted the incidence of endometrial cancer is increasing globally, this trend has also been observed in New Zealand with a 59% increase in cases in the last ten years (New Zealand Cancer Registry, 2022).

10.23. The Committee stated it would welcome applications for other immunotherapies for the treatment of endometrial cancer.

*Health benefit*

10.24. The Committee noted the RUBY study, a phase three, global, double-blind, randomised, placebo-controlled trial in 494 people with primary advanced stage III or IV, or first recurrent endometrial cancer. Individuals were treated with either dostarlimab (500 mg) or placebo, plus carboplatin and paclitaxel every 3 weeks (six cycles), followed by dostarlimab (1000 mg) or placebo every 6 weeks for up to 3 years.

10.24.1. The study reported first interim analysis results at 24 months' follow up (Mirza et al. N Engl J Med 2023;388:2145-58):

- Around one quarter (23.9%) of participants randomised had mismatch repair–deficient (dMMR), microsatellite instability–high (MSI-H) tumours.
- In the dMMR–MSI-H population: estimated progression-free survival (PFS) at 24 months was 61.4% (95% confidence interval [CI], 46.3 to 73.4) in the dostarlimab group and 15.7% (95% CI, 7.2 to 27.0) in the placebo group (hazard ratio (HR) for progression or death, 0.28; 95% CI, 0.16 to 0.50; P<0.001).
- In the overall population: PFS at 24 months was 36.1% (95% CI, 29.3 to 42.9) in the dostarlimab group vs 18.1% (95% CI, 13.0 to 23.9) in the placebo group (HR 0.64; 95% CI, 0.51 to 0.80; P<0.001). OS at 24 months was 71.3% (95% CI, 64.5 to 77.1) with dostarlimab and 56.0% (95% CI, 48.9 to 62.5) with placebo (HR for death, 0.64; 95% CI, 0.46 to 0.87).
- The most common adverse events (AE) that occurred or worsened during treatment were nausea (53.9% dostarlimab group vs 45.9% placebo group), alopecia (53.5% vs 50.0%), and fatigue (51.9% vs 54.5%). Severe and serious AEs were more frequent in the dostarlimab group than in the placebo group.
- Although at the time of this first interim analysis 65 of all 245 individuals treated with dostarlimab (26.5%) and 100 of all 249 placebo (40.2%) had died (with the above 0.64 HR for death, this result did not reach the level of statistical significance for OS overall established prospectively as the trial's stopping rule (P value stopping boundary of 0.00177).

10.24.2. The study subsequently reported results of the protocol-determined second interim analysis at a median duration of follow up of 37.2 months (Powell et al. Ann Oncol. 2024;35:728-38):

- In the overall population, with 51% maturity, RUBY now met the dual-primary endpoint for OS at this further interim analysis, with a statistically significant reduction in the risk of death (HR = 0.69; 95% CI, 0.54-0.89; P = 0.0020) in dostarlimab plus carboplatin-paclitaxel vs carboplatin-paclitaxel alone, with now sufficient precision to meet the trial's stopping rule.
- In the all-comer population, the above reduction in death was an improvement of 16.4 months in median OS for dostarlimab plus carboplatin-paclitaxel vs carboplatin-paclitaxel alone (median OS of 44.6 months vs 28.2 months), with the Kaplan-Meier probability of survival at 24 months of 70.1% (95% CI, 63.8%-75.5%) in the dostarlimab arm and 54.3% (95% CI, 47.8%-60.3%) in the placebo arm.
- In prespecified exploratory analysis, the risk of death was significantly lower in the dMMR/MSI-H population (HR = 0.32; 95% CI, 0.17-0.63; nominal P = 0.0002), and a trend in favour of dostarlimab was seen in the pMMR/MSS population (HR = 0.79; 95% CI, 0.60-1.04; nominal P = 0.0493).

10.24.3. The Committee noted that both PFS and now OS were statistically significantly higher in both the dMMR population and the overall population when comparing the treatment versus placebo group.

10.24.3.1. The Committee noted that the adjusted alpha p values were recalculated for the second interim analysis based on a different number of events. The Committee considered this was appropriate although not commonly undertaken.

10.24.3.2. The Committee considered the results in PFS and OS were stable between the first and second interim analysis, and suggested improvements in both endpoints for the dostarlimab arm compared to placebo.

10.24.4. The Committee noted patient-reported health rated quality of life results were similar in both the overall population and the dMMR population. The Committee considered results indicated that those that received dostarlimab had a better patient reported outcomes, however the error bars did overlap between the groups.

10.24.5. The Committee noted that the demographics of people who were randomised between the two trial arms were similar, however there were slightly more people in the placebo arm for the dMMR population who were aged 65 years or older. The Committee considered previous data has reported age as a predictor of poor outcome, which might provide some bias against the placebo dMMR arm, but not for the overall group, for outcomes.

10.24.6. The Committee noted that most people experienced an AE, with immune related AE (IRAE) more common in the dostarlimab compared to placebo treatment groups. The Committee considered the rates of IRAE similar to other agents in combination with carboplatin and paclitaxel.

10.24.7. The Committee considered that the proportion of cancers that were dMMR would be similar in New Zealand. The Committee considered anecdotal evidence that Māori and Pacific peoples have similar dMMR rates to New Zealand Europeans.

10.25. The Committee noted the GARNET trial, single- arm, open-label, phase one trial in 290 people with advanced and recurrent endometrial cancer that progressed on or

after platinum doublet therapy: ≤2 prior lines of treatment for recurrent or advanced disease.

10.25.1. The study reported the following data at 16.3 months (Oaknin et al. J Immunother Cancer 2022;10:e003777):

- In individuals with dMMR the objective response rate (ORR) was 43.5% (95% CI 34.0% to 53.4%) with 11 complete responses and 36 partial responses.
- In people with proficient MMR, ORR was 14.1% (95% CI 9.1% to 20.6%) with three complete responses and 19 partial responses.
- Median duration of response was not reached in either cohort.

10.25.2. The Committee also noted Oaknin et al JAMA Oncol. 2020;6:1766-72 reporting data at a median follow up of 11.2 months.

10.25.3. The Committee noted Kristeleit et al. Int J Gynecol Cancer 2022;0:1-8 reporting the Patient reported outcomes (PRO) from the GARNET trial.

- Assessment completion was >95.5% throughout cycle 7 of the trial, with no individual domain completion <90.9%. Quality of life, emotional functioning, and social functioning showed improvement compared with baseline. All symptom scores showed either improvement or stability from baseline through cycle 7. Categorical change in response across all symptom scales and single-item response scores showed stability or improvement for most individuals.
- For individuals who saw a worsening of their categorical change in response, ≤7.4% experienced a 2- category worsening and ≤2.5% experienced a 3-category worsening.

10.25.4. The Committee considered that the majority of health benefit was found in individuals whose cancers are dMMR in second line treatment.

10.26. The Committee noted Goulden et al. J Health Econ Outcomes Res. 2023;10:53-61, a propensity score matched study that compared individuals on the GARNET trial with a standard of care cohort. The Committee noted that 12.6% of the standard of care cohort received carboplatin and paclitaxel, which is the standard of care in New Zealand. The Committee noted the study reported a hazard ratio of 0.48, however the authors did note that the assumption of proportional hazards was violated.

10.27. The Committee noted Matthews et al. Oncologist. 2022;27:1058-66, an indirect comparison of the efficacy and safety of dostarlimab and doxorubicin. The Committee noted the authors of the publication considered that while the dMMR status of people in the control arm was unknown, that this would not affect survival estimates. The authors further noted that that assessments were carried out at different timepoints and therefore data had to be interpolated to match the two arms of the study.

10.28. The Committee noted the following studies:

- Oaknin et al. Clin Cancer Res. 2023;29:4564-74
- Andre et al. JAMA Netw Open. 2023;6:e2341165
- Rodrigues et al. Bull Cancer. 2023;110:1041-50
- Goulden et al. J Health Econ Outcomes Res. 2023;10:53-61
- Goulden et al. Int J Gynecol Cancer. 2023;33:1715-23
- Bartoletti et al. Curr Oncol. 2022;29:5209-12

- Bartoletti et al. Cancer Treat Rev. 2024:125:102701.

10.29. The Committee considered overall the evidence for dostarlimab for second line treatment to be of poor quality.

*Suitability*

10.30. The Committee noted dostarlimab infusions would require individuals to travel to infusion centres, and considered this is particularly difficult for those in rural areas. The Committee considered additional help from whānau, or carers may be needed for individuals to attend these appointments, as well as treatment impacting on an individual's time away from work and whānau.

*Cost and savings*

10.31. The Committee considered that IRAEs, associated with dostarlimab, would typically be managed in a hospital setting, and would be associated with incremental costs to the health sector.

10.32. The Committee noted that each dose of dostarlimab is infused over a 30- minute period and this incremental infusion time per treatment cycle, alongside longer treatment durations overall due to people experiencing longer progression-free intervals, would be associated with additional demand on infusions services, where capacity is already limited.

10.33. The Committee considered that if dostarlimab were to be funded for those with dMMR endometrial cancer, there were unlikely to be incremental costs to health system budgets related to MMR testing, as this testing is already routine in the setting of endometrial cancer.

10.34. The Committee considered that if dostarlimab were to be funded in both the first-line and second-line setting, most people would opt to receive dostarlimab in the first-line setting and as such, there would be very few people initiating second-line treatment beyond the first year of funding.

10.35. The Committee considered that based on the available international evidence, between 20% to 30% of recurrent and advanced endometrial cancer cases in New Zealand would be dMMR.

*Summary for assessment*

10.36. The Committee considered that the below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for dostarlimab if it were to be funded in New Zealand for advanced or recurrent endometrial cancer with dMMR status. 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 Committee'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.

| | | |
|---|---|---|
| **P**opulation | People with advanced or recurrent endometrial cancer (EC) **with dMMR status,** whose disease is unsuitable for resection or radiation, and **have not received systemic treatment** in the advanced or recurrent setting (ie first-line). | People with advanced or recurrent endometrial cancer (EC) **with dMMR status,** whose disease is unsuitable for resection or radiation, and **have received prior systemic treatment** in the advanced or recurrent setting (ie second-line). |
| **I**ntervention | Dostarlimab 500mg administered via 30-min IV infusion in combination with carboplatin AUC 5mg/ml/min and | Dostarlimab 500mg administered via 30-min IV infusion every three weeks for 4 cycles followed by 1000 mg dostarlimab |

| | | |
|---|---|---|
| | paclitaxel 175mg/m2 IV infusions (5 hours for the chemotherapy component - Eviq) every three weeks for six cycles, followed by 1000 mg dostarlimab every 6 weeks until disease progression or unacceptable toxicity, for a maximum of three years. | every 6 weeks until disease progression or unacceptable toxicity, for a maximum of two years. |
| **C**omparator(s) (NZ context) | Carboplatin AUC 5mg/ml/min and paclitaxel 175mg/m2 IV infusions every three weeks for six cycles, | |
| **O**utcome(s) | Improved progression-free survival (PFS)<br><br>• At 24 months follow-up, PFS was reported to be 61.4% (median was not reached) in the dostarlimab-chemotherapy arm and 15.7% (median PFS 7.7 months) in the placebo-chemotherapy arm, with HR 0.28 (95% CI 0.16-0.50) in the first interim analysis of the RUBY trial (Mirza et al. 2023)<br><br>Improved overall survival (OS)<br><br>• The second interim analysis results from the RUBY trial reported an estimated OS of 82.8% at 24 months in the dostarlimab-chemotherapy arm and 57.5% in the placebo-chemotherapy arm, with HR 0.32 (95% CI 0.17-0.63) (Powell et al. 2024) | Improved PFS<br><br>Improved OS<br><br>• Synthetic control analyses report an HRs for OS of roughly 0.4 to 0.5 for dostarlimab-chemotherapy compared to chemotherapy. OS estimates violate use of the Cox proportional hazards model as the hazard for OS were non-proportional.<br><br>The evidence to support use of dostarlimab in the 2L setting is of very low strength and quality.<br><br>However this is of limited materiality to economic assessment, as the group receiving 2L treatment would be small and there would be very few initiations beyond the first year of funding. |

10.37. The Committee considered that the below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for dostarlimab if it were to be funded in New Zealand for advanced or recurrent endometrial cancer regardless of dMMR status. 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 Committee'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.

| | |
|---|---|
| **P**opulation | People with advanced or recurrent endometrial cancer (EC) whose disease is unsuitable for resection or radiation, regardless of dMMR status, and have not received systemic treatment in the advanced or recurrent setting. |
| **I**ntervention | Dostarlimab 500mg administered via 30-min IV infusion in combination with carboplatin AUC 5mg/ml/min and paclitaxel 175mg/m2 IV infusions (5 hours for the chemotherapy component - Eviq) every three weeks for six cycles, followed by 1000 mg dostarlimab every 6 weeks until disease progression or unacceptable toxicity, for a maximum of three years. |
| **C**omparator(s) (NZ context) | Carboplatin AUC 5mg/ml/min and paclitaxel 175mg/m2 IV infusions every three weeks for six cycles |
| **O**utcome(s) | Improved progression-free survival (PFS)<br>• The second interim analysis of the RUBY trial reported that the median PFS was 11.8 months in the dostarlimab-chemotherapy arm and 7.9 months in the placebo-chemotherapy arm (HR 0.64, 95% CI 0.51-0.80) (Mirza et al. 2023).<br>Improved overall survival (OS)<br>The second interim analysis results from the RUBY trial reported a median OS of 44.6 months in the dostarlimab-chemotherapy arm and 28.2 in the placebo-chemotherapy arm (HR 0.69, 95% CI 0.54-0.89) (Mirza et al. 2023). |

*Table definitions:*

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

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

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

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