Record of the Cancer Treatments Advisory Committee Ad-Hoc Meeting held via Microsoft Teams on 15 August 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 the Pharmacology and Therapeutics Committee (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.

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1. Attendance

Present
Stephen Munn - Chair
Chris Frampton
Lochie Teague
Matthew Strother
Oliver Brake
Richard Isaacs
Scott Babington

Apologies
Alannah Kilfoyle
Alice Loft
Alice Minhinnick
Michelle Wilson
Vidya Mathavan

2. Summary of recommendations

	Pharmaceutical and Indication	Recommendation
•	Pembrolizumab for the treatment of unresectable dMMR/MSI-H colorectal cancer, within the context of treatment for malignancy, subject to eligibility criteria	High Priority
•	Pembrolizumab for the second line treatment of dMMR/MSI-H metastatic colorectal cancer, within the context of treatment for malignancy, subject to eligibility criteria	Medium Priority

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.Terms of Reference 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 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 karakia followed by whakawhanaungatanga.

5. Pembrolizumab for MSI-H dMMR metastatic colorectal cancer

Application

5.1. The Committee noted that at its July 2024 meeting, it had requested an ad-hoc meeting to review the evidence for pembrolizumab for second line treatment of DNA mismatch repair/microsatellite instability-high (dMMR/MSI-H) metastatic colorectal cancer.

5.2. The Committee noted Pharmac staff also sought advice on inclusion of unresectable dMMR/MSI-H colorectal cancer in the proposed access criteria, following consultation feedback received on a proposal to fund pembrolizumab for first-line treatment of metastatic dMMR/MSI-H colorectal cancer.

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

Recommendation

5.4. The Committee **recommended** that pembrolizumab for the **second line** treatment of dMMR/MSI-H **metastatic** colorectal cancer be listed with a **medium priority**, and for the treatment of **unresectable** dMMR/MSI-H colorectal cancer with a **high priority**, within the context of treatment for malignancy, both priorities subject to the following eligibility criteria:

> Initial application – (MSI-H/dMMR advanced colorectal cancer) 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 deficient mismatch repair (dMMR) or microsatellite instability-high (MSI-H) unresectable or metastatic colorectal cancer; and
2. Patient has not received prior funded treatment with pembrolizumab; and
3. Patient has an ECOG performance score of 0-1; and
4. Baseline measurement of overall tumour burden is document clinically and radiologically; and
5. Pembrolizumab to be used at a maximum dose of 200 mg every three weeks (or equivalent) for a maximum of 16 weeks.

Renewal – (MSI-H/dMMR advanced colorectal cancer) 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:
Both:

1. No evidence of disease progression; and
2. Pembrolizumab to be used at a maximum dose of 200 mg every three weeks (or equivalent); and
3. Treatment with pembrolizumab is to cease after a total duration of 24 months from commencement (or equivalent of 35 cycles dosed every 3 weeks).

5.5. In making these recommendations, the Committee considered the following:

- The high health needs of people with treatment resistant unresectable or metastatic colorectal cancer.
- The likely improvements to overall response rates and outcomes compared to currently funded treatments, although this was based on low quality evidence.
- The reduction in infusion hours associated with pembrolizumab compared to standard care chemotherapy.

Discussion

Background

5.6. The Committee noted its initial July 2021 consideration of pembrolizumab for the first line treatment of metastatic MSI-H/dMMR colorectal cancer.

5.7. The Committee further noted its July 2024 discussions, that:

- Pembrolizumab for metastatic MSI-H/dMMR colorectal cancer [alongside other specific cancers] had been proposed in the late stage setting only as a first-line treatment, based on the outcomes reported in KEYNOTE-177.
- There would be a prevalent group of people who have received an alternative first line (or subsequent) treatment, but under the Special Authority criteria proposed at the time, these people would not be eligible for funded treatment with pembrolizumab.
- Pharmac had received consultation feedback, with supportive evidence for second-line use of pembrolizumab for metastatic MSI-H/dMMR colorectal cancer, and the Committee requested an ad-hoc meeting to consider this ahead of any funding decision, noting clinical responses to immunotherapy in MSI-H/dMMR colorectal cancer can be significant.
- The definition of unresectable disease is often subjective and would be difficult to define through Special Authority criteria prior to receipt of immunotherapy.
- 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.
- 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.

Second line treatment

5.8. The Committee noted that a registry and combined clinical trial pool of individuals with dMMR/MSI-H metastatic colorectal cancer treated with chemotherapy had a reported median overall survival (OS) of 16 months. Median OS from start of first-line treatment was reported as 12.8 months and from start of second-line treatment as 6.2 months (Wensink et al. Br J Cancer. 2021;124:399-406).

5.9. The Committee noted that in Aotearoa New Zealand, most people receive either oxaliplatin with fluorouracil (5-FU), or irinotecan with or without 5-FU, as a second line treatment, depending on the chemotherapy agent used in first line.

5.10. The Committee considered that it was reasonable to assume 73% of people with metastatic colorectal cancer progress on a first line treatment, and therefore could be offered second line treatment.

5.11. The Committee considered Pharmac's estimates of 124 eligible people in year one and 26 in year two to be reasonable. The Committee considered uptake of pembrolizumab in this setting would be at least 85% to 90% of eligible patients, which would equate to 111 people in year one and 23 people subsequently.

5.12. The Committee noted the Keynote-164 phase two clinical trial investigating the efficacy of pembrolizumab in people with treatment-refractory dMMR/MSI-H metastatic colorectal cancer (Le et al. J Clin Oncol. 2020;38:11-9). The Committee noted that the objective response rate was reported at 33% (95% CI, 21% to 46%) in people who had received more than one prior line of treatment and 33% (95% CI, 22% to 46%) in people who had received one prior line of treatment. The Committee noted that median progression free survival (PFS) was reported as 2.3 months (95% CI, 2.1 to 8.1 months) and 4.1 months (95% CI, 2.1 to 18.9 months) in the respective cohorts. The Committee noted that OS was reported as 31.4 months (95% CI, 21.4 months to not reached) and not reached (95% CI, 19.2 months to not reached) in the respective cohorts.

5.13. The Committee considered Keynote-164 to be a reasonable estimate of the benefit from second line treatment with pembrolizumab. The Committee noted that while pembrolizumab requires less infusion time than standard of care chemotherapy, there would be additional infusion hours required for those who would not have otherwise received any treatment, and people would also likely remain on pembrolizumab for longer.

5.14. The Committee noted that there were no clinical trials comparing outcomes from pembrolizumab and chemotherapy. The Committee noted OS in metastatic colorectal cancer treated with folinic acid, fluorouracil and oxaliplatin (FOLFOX) sequenced with folinic acid, fluorouracil and irinotecan (FOLFIRI) has been reported as 21.5 months, and with FOLFIRI sequenced with FOLFOX 20.6 months (Tournigand et al. J Clin Oncol. 2004;22(2):228-37). The Committee noted the evidence of benefit from these treatments is not specific to dMMR/MSI-H metastatic colorectal cancer, and considered this relevant as the prognosis of dMMR/MSI-H metastatic colorectal cancer is poorer compared to the MMR proficient population.

5.15. The Committee noted evidence of comparator efficacy wasconsidered by NICE (September 2023) and the Scottish Medical Consortium (January 2024) for indirect treatment comparisons to model efficacy in the second line (Li et al. Future Oncol. 2018;14:2031-44; Giantonio et al. J Clin Oncol. 2007;25:1539-44; Cao et al. Med Oncol. 2015;31:1-5; Moore et al. Ann Oncol. 2016;27:2216-24; Xie et al. Med Oncol. 2014;31:35).

5.16. The Committee considered that most centres would test for dMMR/MSI-H status at diagnosis, however if this had not been performed then archived tissue may need to be tested.

Unresectable disease

5.17. The Committee considered that the health need of people with unresectable colorectal cancer is very similar to metastatic colorectal cancer, including a small number of people with stage III disease.

5.18. The Committee considered that some people with unresectable colorectal cancer can receive a sufficient response from treatment in order for the lesions to change and surgical resection to become a potential treatment option. The Committee considered that the treatment paradigm for rectal cancer in particular was moving towards a total neoadjuvant treatment paradigm. However, there is currently no evidence for this treatment paradigm shift outside of those with rectal cancer.

5.19. The Committee noted that the response to pembrolizumab can be appreciable for some people, which can enable surgical resection and/or treatment cessation. The Committee considered that any clinical decision to stop treatment would be made by the treating clinician, as there was currently insufficient evidence to include specific exit criteria or inform the likely duration of treatment for people who did have a resection after treatment.

5.20. The Committee considered it would be appropriate to include unresectable disease in the eligibility criteria Pharmac staff had proposed for metastatic disease, provided that treatment was with palliative intent. This was considered reasonable on the basis that the evidence for metastatic cancer from KEYNOTE-177 was assumed to be applicable to people with unresectable earlier stage colorectal cancer with MSI-H/dMMR characteristics.

5.20.1. With these considerations, the Committee was made aware of the final OS results for KEYNOTE-177, published in Diaz et al. Lancet Oncol. 2022;23:659-70, where at final analysis (median follow-up 44.5 months) there was no significant difference in OS between first-line treatment with pembrolizumab versus chemotherapy (hazard ratio [HR] 0.74; 95% CI 0.3-1.03; p=0.036). Superiority was not demonstrated because the prespecified one-sided alpha value (significance level) of 0.025 needed for statistical significance was not achieved.

5.20.2. The Committee noted these final OS results, and had previously considered that complexities with the cross-over design of the trial had created challenges for analysis of KEYNOTE-177's OS (CTAC July 2021). The Committee considered these analytical challenges from cross-overs would have increased even further, as at final analysis only two individuals remained on chemotherapy, 56 (36%) of 154 individuals randomised to chemotherapy had met the cross-over criteria and were treated with pembrolizumab, and an additional 37 (24%) people received off-study anti- programmed cell death protein 1 (PD-1)/ programmed death-ligand 1 (PD-L1) therapies; this meant an effective cross over of 60% overall, possibly contributing to an improvement in OS in the chemotherapy group, and possibly diluting true differences.

5.20.3. The Committee considered the final KEYNOTE-177 results continued to support pembrolizumab as effective first-line therapy for the treatment of MSI-H/dMMR metastatic colorectal cancer, and that it was reasonable to extrapolate to the unresectable earlier stage MSI-H/dMMR setting.

5.21. The Committee noted emerging evidence for neoadjuvant immune checkpoint inhibitors in stage II or III colorectal cancer, such as the NEOPRISM-CRC trial (Shiu et al. J Clin Oncol. 2024;42:17).

5.22. The Committee indicated it would welcome the opportunity to consider any funding application for the use of immune checkpoint inhibitors in this setting once the evidence base has developed.