Record of the Cancer Treatments Advisory Committee Meeting held on 12 September 2025

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.

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1. Attendance

Present
Stephen Munn - Chair
Alice Minhinnick
Chris Frampton
Matthew Strother
Michelle Wilson
Richard Isaacs
Vidya Mathavan

Apologies
Allanah Kilfoyle
Lochie Teague
Olivier Brake
Scott Babington

2. Summary of recommendations

	Pharmaceutical and Indication	Recommendation
7.5	Pembrolizumab for the treatment of unresectable or metastatic oesophageal, gastro-oesophageal junction, or gastric cancer	Low priority
7.6	Nivolumab for the treatment of unresectable or metastatic oesophageal, gastro-oesophageal junction, or gastric cancer	Low priority
7.9	Pembrolizumab for the treatment of microsatellite instability high (MSI-H) unresectable or metastatic oesophageal, gastro-oesophageal junction, or gastric cancer	High priority
7.10	Nivolumab for the treatment of microsatellite instability high (MSI-H) unresectable or metastatic oesophageal, gastro-oesophageal junction, or gastric cancer	High priority
8.3	Neoadjuvant nivolumab in combination with ipilimumab for the treatment of resectable cutaneous melanoma	High priority
8.4	Nivolumab for the treatment of resected melanoma (Stage IIIB, IIIC, IIID or Stage IV) adjuvant to complete surgical resection	Cost neutral to pembrolizumab

These recommendations were made within the context of treatments of malignancy.

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'.

3.4. 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 Update.

5.2. The Committee acknowledged the recent changes in Pharmac kaimahi and ongoing leadership and strategic changes, including the new Chief Executive who started at Pharmac in mid-September and the release of the 2025/2026 Letter of Expectations.

5.3. The Committee noted an update about the 5-year organisation reset programme and acknowledged that more information can be found on the Pharmac Website.

5.4. The Committee noted the following updates to the record processes:

5.4.1. 30-day provisional recommendation trial update.

5.4.2. The Committee endorsed the removal of second committee reviews, with targeted reviews to be used as required, and supported the use of direct engagement with Discussion Leads to resolve outstanding issues.

6. Correspondence

Atezolizumab for the adjuvant treatment of PD-L1 positive NSCLC – supplier correspondence

Application

6.1. The Committee reviewed the supplier correspondence for atezolizumab for the adjuvant treatment of PD-L1 positive stage II-IIIA non-small cell lung cancer (NSCLC).

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

Discussion

6.2. The Committee noted it has previously reviewed atezolizumab for the adjuvant treatment of PD-L1 positive stage II-IIIA NSCLC in October 2023 and deferred making a recommendation pending publication of longer-term overall survival (OS) data from the IMpower010 trial. The Committee also requested that the statistical analysis plan (SAP) be included with the submission of any further evidence.

6.3. The supplier consequently provided additional information and the SAP, which were considered by the Committee in July 2024. The Committee recommended the application be declined due to concerns with the methodology of the clinical trial including its statistical methods.

6.4. The Committee noted the supplier correspondence included several concerns regarding the Committee's July 2024 review of the additional information and original application.

6.5. The Committee noted the supplier disagreed with the factual accuracy that '*PD-L1 expression for OS was not mentioned in the statistical analysis plan…and therefore, the Committee considered that statistical testing for PD-L1 groups for OS is a retrospective analysis*'.

6.6. The Committee noted Felip et al J Clin Oncol. 2025;43:2343-49. that reported the 5-year OS results of the IMpower010 trial, The publication reported an unstratified hazard ratio (HR) 0.47 (confidence interval (CI) 0.28-0.77) for individuals with stage II-IIIA PD-L1 TC ≥50% with or without EGFR/ALK alterations. The Committee noted the CI did exceed one in the stage II-IIIA PD-L1 TC ≥1% population and the all randomised stage II to IIIA population.

6.6.1. The Committee noted that for the intention to treat (ITT) population the SAP did note an exploratory analysis of OS for individuals with a PD-L1 TC ≥50% population.

6.6.2. The Committee noted Felip et al. Ann Oncol. 2023;34:907-19. reported that *"Post hoc exploratory analyses of OS in the stage II-IIIA PD-L1 TC ≥50%, stage II-IIIA PD-L1 TC 1%-49%, and stage II-IIIA PD-L1 TC <1% populations were also conducted*".

6.6.3. Therefore, the Committee considered that whilst it didn't specify stage II-IIIA in the July 2024 record, it confirms the previous consideration that the analysis of OS in the stage II-IIIA PD-L1 TC ≥50% was a post hoc analysis. The Committee noted that the majority of the health benefit appears to arise from this population, an observation further supported by the 5-year OS results.

6.7. The Committee noted the supplier disagreed with the Committee concerns that the statistical design and reporting in Impower 010 made it difficult to ascertain benefits to subsets and that specifically DFS data alone for stage II-IIIA PD-L1 >50% is a clear indication of benefit.

6.7.1. The Committee considered that DFS is a surrogate for OS, and when considering health benefit in this population, OS is the primary outcome of interest.

6.7.2. The Committee considered that whilst there appears to be benefit from atezolizumab treatment when considering the 5-year OS for individuals with stage II-IIIA PD-L1 TC ≥50%, it remained a post-hoc evaluation, and the trial was never powered to ensure that the benefit in OS in this population is not due to chance alone. The Committee considered the current data for OS in this population is interesting, and would merit further investigation, ideally through a well powered phase three randomised controlled trial to provide greater certainty that these observations are not due to chance alone.

6.8. The Committee considered that irrespective of the maturity of evidence, there will be uncertainty that any benefit in OS is not due to chance in the stage II-IIIA PD-L1 TC ≥50% population as the trial was not designed to analyse this benefit. The Committee further considered that the SAP provided does not appear to detail this as a pre-defined analysis for which there was a planned alpha expenditure. The Committee

considered that there is not a statistically significant 5-year OS benefit in the ITT population as defined in the SAP.

6.9. The Committee confirmed it does not wish to reconsider its recommendation that atezolizumab for the adjuvant treatment of PD-L1 positive stage II-IIIA non-small cell lung carcinoma be declined. The Committee considered that there is inadequate evidence of an OS benefit at this time, and more mature evidence from the IMpower010 trial, would not confirm if benefit is not due to chance alone.

7. Advanced or metastatic gastric and/or oesophageal cancers, first-line: Pembrolizumab – Oesophagus or gastroesophageal junction; Nivolumab - Oesophageal adenocarcinoma or gastric/gastro-oesophageal junction; Nivolumab Oesophageal squamous cell carcinoma

Application

7.1. The Committee reviewed applications for pembrolizumab and nivolumab for the following unresectable, advanced or metastatic cancers:

- Pembrolizumab in the first-line treatment of:
    - oesophageal or gastroesophageal junction cancer (including squamous cell carcinoma and adenocarcinoma)
    - gastric cancer
- Nivolumab in the first-line treatment of:
    - oesophageal adenocarcinoma or gastric/gastro-oesophageal junction
    - oesophageal squamous cell carcinoma.

7.2. The Committee noted that the scope of its consideration was in all three anatomic locations (oesophageal, gastroesophageal junction and gastric cancer) irrespective of histology (ie both adenocarcinoma and squamous cell carcinoma) with tumours with HER-2 negative or indeterminate status.

7.3. The Committee noted that the following were requested to be considered, however noted that they were out of scope of the current discussion and would be considered at a later date:

- Consideration of nivolumab for the second-line treatment of oesophageal squamous cell carcinomas, (requested in the nivolumab application).
- Consideration of a broader, line-agnostic, listing for nivolumab aligned with the updated Australian PBS listing (following listing of tislelizumab in Australia), (requested in recent communication from the nivolumab supplier).
- Additional first-line clinical trial evidence for pembrolizumab in a HER2+ population, (provided by the pembrolizumab supplier).

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

Recommendation

7.5. The Committee **recommended** that pembrolizumab be listed for the treatment of unresectable or metastatic oesophageal, gastro-oesophageal junction, or gastric cancer with a **low priority** within the context of treatment of malignancy, subject to Special Authority criteria.

7.6. The Committee **recommended** that nivolumab be listed for the treatment of unresectable or metastatic oesophageal, gastro-oesophageal junction, or gastric cancer with a **low priority** within the context of treatment of malignancy, subject to Special Authority criteria.

7.7. The Committee considered that the following Special Authority criteria could be applied to nivolumab and/or pembrolizumab for the treatment of unresectable or metastatic oesophageal, gastro-oesophageal junction, or gastric cancer:

> **[PEMBROLIZUMAB /NIVOLUMAB/]**
> **Initial application (unresectable or metastatic oesophageal, gastro-oesophageal junction, or gastric cancer)**
> Applications only from a relevant specialist or any relevant practitioner on the recommendation of a relevant specialist. Approvals valid for four months.
> All of the following:
> 1. The individual has unresectable or metastatic oesophageal, gastroesophageal junction, or gastric cancer; and
> 2. The cancer is not HER-2 positive; and
> 3. The patient has not had prior systemic therapy administered for their unresectable or metastatic disease; and
> 4. Patient has an ECOG performance status of 0-2; and;
> 5. Treatment with [**pembrolizumab/ nivolumab**] is to be commenced in combination with chemotherapy; and
> 6. Patient has not previously received a PDL-1 inhibitor for the treatment of oesophageal or gastro-oesophageal junction cancer; and
> 7. Baseline measurement of overall tumour burden is documented clinically and radiologically; and
> 8. Patient's disease has a combined positive score (CPS) of 5 or greater.
>
> **Renewal (unresectable or metastatic oesophageal, gastro-oesophageal junction, or gastric cancer)**
> Applications only from a relevant specialist or any relevant practitioner on the recommendation of a relevant specialist. Approvals valid for four months.
> All of the following:
> 1. The individual has no evidence of disease progression; and
> 2. Response to treatment in target lesions has been determined by comparable radiologic assessment following the most recent treatment period; and
> 3. Treatment with [**pembrolizumab/ nivolumab**] is to cease after maximum total duration of 24 months from commencement.

7.8. In making these recommendations, the Committee:

- Considered that pembrolizumab and nivolumab each appeared to offer a modest benefit to people with unresectable or metastatic oesophageal, gastro-oesophageal junction, or gastric cancer
- Noted that there was no New Zealand-specific outcome data for these medicines in this setting which adds uncertainty regarding the relevance of these outcomes to Māori with gastric cancers in New Zealand, who experience higher incidence rates than non-Māori and may have germline mutations not necessarily represented in the key clinical trial evidence.

7.9. The Committee **recommended** that pembrolizumab be listed for the treatment of microsatellite instability high (MSI-H) unresectable or metastatic oesophageal, gastro-oesophageal junction, or gastric cancer with a **high priority** within the context of treatment of malignancy, subject to Special Authority criteria.

7.10. The Committee **recommended** that nivolumab be listed for the treatment of microsatellite instability high (MSI-H) unresectable or metastatic oesophageal, gastro-oesophageal junction, or gastric cancer with a **high priority** within the context of treatment of malignancy, subject to Special Authority criteria.

7.11. The Committee considered that the following Special Authority criteria could be applied to pembrolizumab and/or nivolumab for the treatment of MSI-H unresectable or metastatic oesophageal, gastro-oesophageal junction, or gastric cancer:

> **[PEMBROLIZUMAB /NIVOLUMAB/]**
> **Initial application (microsatellite instability high [MSI-H] unresectable or metastatic oesophageal, gastro-oesophageal junction, or gastric cancer)**
> Applications only from a relevant specialist or any relevant practitioner on the recommendation of a relevant specialist. Approvals valid for four months.
> All of the following:
> 1. The individual has unresectable or metastatic oesophageal, gastroesophageal junction, or gastric cancer; and
> 2. Both:
> 2.1 The cancer is not HER-2 positive; and
> 2.2 The cancer is microsatellite instability high (MSI-H); and
> 3. The patient has not had prior systemic therapy administered for their unresectable or metastatic disease; and
> 4. Patient has an ECOG performance status of 0-2; and;
> 5. Treatment with [**/pembrolizumab/nivolumab**] is to be commenced in combination with chemotherapy; and
> 6. Patient has not previously received a PDL-1 inhibitor for the treatment of oesophageal or gastro-oesophageal junction cancer and
> 7. Baseline measurement of overall tumour burden is documented clinically and radiologically
>
> **Renewal (microsatellite instability high [MSI-H] unresectable or metastatic oesophageal, gastro-oesophageal junction, or gastric cancer)**
> Applications only from a relevant specialist or any relevant practitioner on the recommendation of a relevant specialist. Approvals valid for four months.
> All of the following:
> 4. The patient has no evidence of disease progression; and
> 5. Response to treatment in target lesions has been determined by comparable radiologic assessment following the most recent treatment period; and
> 6. Treatment with [**pembrolizumab/nivolumab**] is to cease after maximum total duration of 24 months from commencement.

7.12. In making these recommendations, the Committee considered that:

- There is a low level of evidence to support defining those with MSI-H disease as a distinct subpopulation at the present time. The Committee acknowledged the level of evidence may not substantially improve with time.
- There is evidence in the CHECKMATE-649 trial from nivolumab, and in the KEYNOTE-062 for pembrolizumab, of a marked benefit in the subgroup with MSI-H disease, despite small numbers (~3-10% of trial population). This likely corresponds to a greater increase in health benefit in this subset than in the overall trial populations with metastatic oesophageal, gastro-oesophageal junction, or gastric cancer.
- Better evidence to inform benefits from pembrolizumab and nivolumab in MSI-H metastatic oesophageal, gastro-oesophageal junction, or gastric cancer from is unlikely to eventuate.

Discussion

Māori impact

7.13. The Committee discussed the impact of funding pembrolizumab and nivolumab for the treatment of unresectable or metastatic oesophageal (OC), gastro-oesophageal junction (GOJ), or gastric cancer (GC) on Māori health areas of focus | Hauora Arotahi and Māori health outcomes. The Committee considered that Māori experience a particularly high impact from these cancers and have a high health need in this setting, and noted the following:

7.13.1. Māori experience higher age-standardised rates of oesophageal cancer (4.95

per 100,000) and much higher rates of GC (11.08 per 100,000) compared to New Zealand Europeans (3.88 per 100,000) and non-Māori (4.76 per 100,000), respectively (Health NZ Cancer Web Tool).

7.13.2. Alongside an increased prevalence of GC in Māori, survival outcomes are also poorer across all disease stages. An analysis of New Zealand Cancer Registry data for the period 2007 to 2016 reported that Māori with stomach cancer were 22% more likely to die than non-Māori (Gurney et al. CO Glob Oncol. 2020;6:766-74).

7.13.3. The higher incidence of GC in Māori is primarily linked to exposure to environmental risk (including *Helicobacter pylori* infection) and lifestyle factors (such as overrepresentation in smoking and alcohol consumption), and germline mutations that are more prevalent in Māori (e.g., E-cadherin/CDH1) (Ellison-Loschmann et al. PLoS One. 2017;12:e0181581; Hakkaart et al. Familial Cancer 2019;18:83-90). A New Zealand study of 94 Māori with gastric cancer included 18% with CDH-1 mutation, causing diffuse GC (Hakkaart et al., 2019). The Committee noted that there is currently no evidence to inform whether there is any relationship between CDH1 and PD-L1.

Populations with high health needs

7.14. The Committee discussed the health need(s) of unresectable or metastatic OC, GOJ, and GC among Māori, Pacific peoples, disabled peoples including tāngata whaikaha Māori, and other populations identified by the Government Policy Statement on Health 2024-2027 to have high health needs. The Committee discussed the impact of funding pembrolizumab and nivolumab in this setting and considered:Highly deprived communities are at a greater risk of developing oesophageal cancer, with quintile 5 having the highest rate per 100,000, at 4.66. In comparison, quintile 1 has a rate of 3.12 per 100,000 (Health NZ Cancer Web Tool). The Committee considered that in the case of squamous cell carcinoma (SCC), this difference may be explained by exposure to environmental risk factors such as smoking, high alcohol use, low fruit and vegetable intake, and poor oral hygiene.

7.14.2. Pacific people experience exposure to environmental risk including Helicobacter pylori infection and lifestyle factors (ie. overrepresentation in smoking and alcohol consumption), however, they are reported to experience lower age-standardised rates of oesophageal cancer at 2.64 per 100,000 compared to New Zealand Europeans (3.88 per 100,000) (Health NZ Cancer Web Tool).

Background

7.15. The Committee noted previous discussions regarding programmed death ligand 1 (PD-L1) measurement and testing considerations in the context of immune checkpoint inhibitors (ICI) including differences in measurement of PD-L1 expression using various scoring systems including the combined positive score (CPS). The Committee considered there is variability in testing access, and reporting thresholds in New Zealand, especially in the context of gastric and oesophageal cancers (GC/OC).

7.16. The Committee noted that CTAC had previously considered an application for pembrolizumab for OC or gastroesophageal junction (GOJ) cancer in October 2022, where the application was deferred pending a review of the entire OC treatment setting.

7.17. The Committee noted that Pharmac staff had sought input from the Gastrointestinal Special Interest Group (GISIG) regarding this tumour group, including the first-line treatment of advanced or metastatic GC/OC/ GOJ. The Committee considered the following comments:

- Support for funding an ICI in advanced/metastatic PD-L1 positive GC/OC/GOJ in the first line setting for patients with ECOG performance status of 0-2.
- PD-L1 thresholds are less meaningful and potentially variable, thus distinguishing between PD-L1 positive and negative disease is more relevant. However, FDA and EMA approvals restrict use to PD-L1 CPS ≥1 based on subgroup analyses not scorable by ESMO-MCBS.

Health need

7.18. The Committee noted that GC cause debilitating symptoms (including vomiting, abdominal pain and swelling from ascites and dysphagia) that significantly impact daily life. The Committee considered that hospitalisations are common for people with GC, with many requiring procedures (eg stent placements) or admission for symptom control. The Committee considered that the need for inpatient care increases as the disease advances, but that care moves to a hospice setting.

7.19. The Committee noted that the World Health Organisation estimates the five-year prevalence rate of OC among New Zealanders in 2022 was 10.5 per 100,000, and 14.9 per 100,000 for New Zealanders with GC and GOJ (WHO, 2022). The Committee noted that in New Zealand (NZ), the predominant histology is adenocarcinoma rather than squamous cell carcinoma (SCC), which is not the case internationally, and considered that GC rates vary internationally.

7.20. The Committee noted the Health NZ Cancer Web Tool that reported a much higher age-standardised rate of gastric cancer for Māori (11.08/100,000) versus non-Māori (4.76/100,000) between 2017-2021. In the same period, the rate of death related to gastric cancer was significantly higher for Māori (7.32/100,000) versus non-Māori (2.97/100,000). The Committee noted this was due to environmental (Helicobacter pylori (*H. pylori*) infection, smoking and salt-preserved foods) and hereditary gene mutations. The Committee noted a study reported Māori patients with stomach cancer were 22% more likely to die than non-Māori patients with stomach cancer. Māori patients are reported to have poorer survival across all stages of disease at diagnosis (Gurney et al. J Comorb. 2020;10:2235042X20971168).

7.21. The Committee considered Pacific populations are at an increased likelihood of developing GC due to similar environmental factors as Māori (Gut Cancer Foundation NZ).

7.22. The Committee noted that people with GC/OC have an expected five-year survival rate of 16-17% with currently funded treatments and experience a severely diminished quality of life. The Committee noted that for 67-75% of people curative treatment is not possible due to advanced disease or comorbidities (Dalhammar et al. BMC Cancer. 2022;22:434).

7.23. The Committee considered that those with advanced GC have a high symptom burden and that about ~40-50% of those with GC in New Zealand would have ECOG score of 0-1, and that 50% or more have an ECOG of 2 at presentation.

7.24. The Committee considered that patients with ECOG score of 2 would be likely to receive and benefit from chemotherapy. The Committee noted that most people with GC receive chemotherapy first, with an aim to proceed to surgery which provides a significant benefit regardless of tumour histology.

7.25. The Committee noted that there is a limited range of funded treatments for human epidermal growth factor receptor (HER2)-negative GC, GOJ and OC. The Committee noted the 2024 European Society for Medical Oncology (ESMO) guidelines that suggest a platinum-based chemotherapy doublet or triplet (FOLFOX, XELOX). The Committee considered that oxaliplatin has a superior safety profile in older patients,

compared to cisplatin and may be associated with improved survival. The Committee noted that in New Zealand:

- oral capecitabine is used in combination with oxaliplatin for the ~20% who are able to swallow
- intravenous 5-fluorouracil (5FU) (FOLFOX) is used for the remaining 80%, as the individual has dysphagia or significant gastric involvement
- very few receive 5FU in combination with cisplatin
- trastuzumab is not a relevant comparator treatment in this patient group as this is funded for people with HER-2 positive disease

7.26. The Committee considered microsatellite instability-high (MSI-H) disease as being strongly predictive of outcomes in lower GI tract cancers. The Committee considered individuals with MSI-H GC have high response rates, and excellent long-term outcomes when treated with an anti-PD-L1 monotherapy. The Committee considered MSI-H GC, GOJ and OC are often more resistant to chemotherapy.

7.27. The Committee noted ESMO guidelines recommend nivolumab for OC with PD-L1 ≥1% and advocate for combination treatment with ipilimumab. Pembrolizumab is recommended in those with PD-L1 CPS>10. The Committee noted nivolumab is recommended for GC with any level of PD-L1 expression, although considered the omission of pembrolizumab from this recommendation could be due to publication timing.

Health benefit

Adenocarcinomas

Nivolumab

Attraction 4 trial

7.28. The Committee noted the randomised, multicentre, double-blind, placebo-controlled, phase-III ATTRACTION-4 trial of nivolumab with chemotherapy vs chemotherapy in first line, HER2-negative GC/GOJ adenocarcinoma (n = 724, approximately 15% had a PD-L1 expression ≥1%) (Kang et al. Lancet Oncol. 2022;23:234-47, Boku et al. Gastric Cancer. 2024;27:1287-301).

7.29. The Committee noted the study population were Asian and considered that environmental risks contributing to the development of GC and GOJ adenocarcinoma are different to the New Zealand setting, and that there was uncertainty around of differences in genetic risk.

7.30. The Committee noted the three-year follow up results:

7.30.1. Improvement in median PFS 10.94 vs 8.48 months (HR 0.67 [95% CI 0.55-0.82)] for nivolumab with chemotherapy vs chemotherapy monotherapy but no improvement in OS (HR 0.89 [0.75-1.05)]

7.30.2. The Committee noted that approximately 30% of the chemotherapy monotherapy group went on to receive nivolumab following progression. The Committee considered this differed from other studies discussed where most received chemotherapy on progression, and access to immunotherapy was affected by availability of drugs in the trial participants location. The Committee considered overall approximately 50% of all study participants across trials would have treatment post progression, with approximately 8-9% receiving an immunotherapy.

7.31. The Committee considered the study a relevant source of evidence to represent the benefit of treatment in New Zealand. The Committee noted that the main limitations were recruitment being mostly among Asian patients and that participants may be healthier than individuals with GC and GOJ in New Zealand due to the eligibility criteria specifying a lower ECOG score (0-1).

7.32. Overall, the Committee considered that the ATTRACTION-4 trial was not the most relevant evidence to represent the effect of the treatments under consideration in the New Zealand population.

Checkmate 649 trial

7.33. The Committee noted evidence from the randomised, open-label, phase III CheckMate 649 trial of nivolumab plus chemotherapy in first line, HER2-negative GC/GOJ/ OC adenocarcinoma (N=1851) (Janjigian et al. Lancet. 2021;39:27-40) with follow up after a median of 47.4 months (Janjigian et al. J Clin Oncol. 2024;42).

7.33.1. The Committee noted that the trial design changed during recruitment, including closure of an ipilimumab-nivolumab arm due to greater toxicity and no OS benefit on an interim analysis (IA).

7.33.2. The Committee noted the eligibility criteria was amended to require PD-L1 CPS of ≥5 due to other trials suggesting CPS scoring was associated with better efficacy than tumour cell PD-L1 scoring. The Committee noted that 23% of those with CPS ≥5 had PD-L1 expression ≥1% while 16% of those with any CPS expression had PD-L1 expression ≥1%.

7.33.3. The Committee considered the trial population (who had an ECOG score 0-1) were generally more well than New Zealanders with these cancers. The Committee considered an ECOG score 0-2 would be more appropriate for the New Zealand population

7.33.4. The Committee noted that 3% of participants had MSI-H disease and 12-14% of people had oesophageal adenocarcinoma while the remainder had GC/GOJ adenocarcinoma.

7.33.5. The Committee noted that at three years, OS was modestly improved with nivolumab with chemotherapy vs chemotherapy alone (median OS 13.7 vs 11.6 months; HR, 0.79 [95% CI, 0.71 to 0.88]) in the total population, with a larger difference in OS in the PD-L1 CPS ≥5 population (median 14.4 vs 11.1 months) (HR, 0.70 [95% CI, 0.61 to 0.81]). The Committee noted there was similar trend for PFS.

7.33.6. The Committee noted that OS with nivolumab with chemotherapy was markedly greater in the very small MSI-H population (median 44.8 months; unstratified HR for death, 0.29; 95% CI, 0.12 to 0.71) and considered that this subgroup benefitted most from the treatment.

7.33.7. The Committee noted that subgroup analyses of survival for GOJ and OC showed overlapping CI, which the Committee considered could potentially be attributed to small participant numbers. The Committee considered that censorship of participants at later timepoints would not meaningfully affect confidence in the data due to the small number of participants.

7.33.8. The Committee noted that there were no meaningful differences or increases in toxicity with nivolumab compared to chemotherapy monotherapy. The Committee noted a decreased risk of symptom deterioration in the nivolumab with chemotherapy group versus chemotherapy alone in both the PD-L1 CPS ≥5 and total population.

7.33.9. Overall, the Committee considered the study a relevant source of evidence to represent the potential benefit of treatment in New Zealand. The Committee noted that the main limitation of the evidence was that participants may be relatively healthier than in New Zealand due to the eligibility criteria specifying a lower ECOG score (0-1).

Pembrolizumab

Keynote 062 trial

7.34. The Committee noted the randomised, uncontrolled, partially blind, phase III KEYNOTE-062 trial of pembrolizumab monotherapy or in combination with chemotherapy in first line, HER2-negative, GC adenocarcinoma (n = 763) (Shitara et al. JAMA Oncol. 2020;6:1571-80). The Committee noted long term extension follow up to 54 months (Wainberg et al. J Clin Oncol. 2022;40:243).The Committee noted that an average of 36.8% of participants had PD-L1 CPS ≥10. The Committee noted a low proportion of MSI-H disease (5-7%) in each group.

7.34.2. The Committee noted pembrolizumab was noninferior to chemotherapy for OS in PD-L1 CPS ≥1 (HR, 0.91; 99.2% CI, 0.69- 1.18), but did report a statistically unsubstantiated OS benefit in the PD-L1 CPS ≥10 group (HR 0.69 (95% CI, 0.49-0.97). Long term follow-up reported similar results with an OS of 17.4 months pembrolizumab monotherapy vs 10.8 months chemotherapy (HR 0.62, 95% CI 0.45-0.86) in the CPS ≥10 group, with no benefit reported in the CPS ≥1 group (HR 0.90, CI 0.75-1.08).

7.34.3. The Committee noted whilst pembrolizumab provided a clinically meaningful OS benefit, this hypothesis could not be tested per the statistical analysis plan. The Committee noted this was due to a hierarchical testing design.

7.34.4. The Committee noted that there was no OS benefit for pembrolizumab in combination with chemotherapy for either the PD-L1 CPS ≥1 (HR 0.85 [95% CI, 0.70-1.03]) or PD-L1 CPS ≥10 group (HR 0.85 [95% CI, 0.62-1.17]) in the initial trial data or in the long term follow up data (PD-L1 CPS ≥1 [HR 0.85(95% CI, 0.71-1.02], PD-L1 CPS ≥10 group (HR 0.76 [95% CI, 0.56-1.03]). The Committee noted there was a survival benefit in those with MSI-H tumours with a PD-L1 CPS ≥1 for both pembrolizumab monotherapy (HR 0.29 [95% CI, 0.11-0.81]) and pembrolizumab in combination with chemotherapy (HR 0.37 [95% CI, 0.14-0.97]) vs chemotherapy monotherapy, however, that this was a very small group of participants.

7.34.5. The Committee noted that none of the publications considered reported a clinically or statistically significant improvement in PFS with pembrolizumab for any group, and that in the subgroup with CPS ≥10, the numerical reported PFS favoured chemotherapy. The Committee considered that it would not be appropriate for Pharmac to consider an improvement in PFS in its assessment if the results of this study were used.

7.34.6. The Committee noted that grade 3-5 AEs were as expected for pembrolizumab monotherapy, and there was a modest increase in AEs associated with the addition of chemotherapy.

7.35. Overall, the Committee considered the study a relevant source of evidence to represent the benefit of treatment in New Zealand. The Committee noted that the main limitation was that participants may be relatively healthier than in New Zealand due to the eligibility criteria specifying a lower ECOG score (0-1).

Keynote 859 trial

7.36. The Committee noted the randomised, double-blind, multicentre, phase III KEYNOTE-859 trial and 4.5-year follow-up of pembrolizumab plus chemotherapy in first line, HER2-negative GC/GJC adenocarcinoma (n = 1579) (Rha et al. Lancet Oncol. 2023;24:1181-95; Rha et al. J Clin Oncol. 2025; 43 (suppl):Abstract nr 4036). Committee noted participants were recruited more often from European sites than the other studies considered, had an ECOG PS ≤1 and 4.7% had MSI-H disease. The Committee noted that there was a relatively even distribution of PD-L1 CPS scores among the trial population, with the trial allowing enrolment regardless of CPS score. The Committee noted that approximately 35% had CPS ≥10 and considered that the treatment groups appeared well matched on baseline characteristics.

7.36.2. The Committee noted pembrolizumab treated PD-L1 CPS ≥10 population had improved OS (15·7 months [13·8-19·3] vs 11·8 months [10·3-12·7]; 0·65 [0·53-0·79]; p<0·0001), but the CPS ≥1 population did not experience the same magnitude of benefit (13·0 months [11·6-14·2] vs 11·4 months [10·5-12·0]; 0·74 [0·65-0·84]; p<0·0001), a similar effect was seen for PFS, with a moderate improvement in the CPS ≥10, and smaller improvement for CPS ≥1 pembrolizumab treated populations.

7.36.3. The Committee considered that OS with pembrolizumab was still poor for approximately 80% of trial participants, but that the Kaplan-Meier curves had a long tail which may represent both a small proportion of people experiencing most of the benefit and the immunotherapy effect (delayed onset of benefits, diverging Kaplan-Meier curves).

7.36.4. The Committee considered that some increase in response rate that appeared to be correlated with PD-L1 CPS scores.

7.36.5. The Committee noted that AEs in both treatment arms were similar, and not markedly increased by the addition of PEMBRO.

7.37. Overall, the Committee considered the study a relevant source of evidence to represent the benefit of treatment in New Zealand. The Committee noted that the main limitation was that participants may be relatively healthier than in New Zealand due to the eligibility criteria specifying a lower ECOG score (0-1).

Adenocarcinoma and squamous cell carcinoma

Pembrolizumab

Keynote-590 trial

7.38. The Committee noted the KEYNOTE-590 trial (ongoing, randomised, double-blind, placebo-controlled multicenter phase III) that enrolled individuals with OC adenocarcinoma or squamous carcinoma and Siewert type 1 adenocarcinoma of the GEJ (Sun et al. Lancet. 2021;398:759-71, Mansoor et al. Oncologist. 2024;29:e1324–e1335).

7.38.1. The Committee considered the trial had a similar requirement for ECOG PS ≤1 as the other studies considered across tumour types.

7.38.2. The Committee considered the trial included a reasonable number of participants.

7.38.3. The Committee considered the majority of the trial participants had a squamous cell tumour type compared to adenocarcinoma (74% vs 26% respectively). The Committee considered the adenocarcinoma group was a predominantly Asian population. The Committee considered this was not representative of NZ where adenocarcinoma is the predominant tumour type (61% vs 39%

respectively). The Committee considered the study was not powered to assess the effect of pembrolizumab in the adenocarcinoma group.

7.38.4. The Committee noted there was a higher proportion of individuals with a squamous cell carcinoma had a CPS ≥10 compared to the adenocarcinomas.

7.39. The Committee noted the following five year follow up results: An improvement in the PFS (6.3 months vs 5.8 months, HR 0.64 [95% CI 0.54-0.75]) and OS (12.3 months vs 9.8 months, HR 0.72 [95% CI 0.62 -0.84]) in the intention to treat population in the pembrolizumab with chemotherapy vs chemotherapy monotherapy group. The Committee noted improvement in PFS and OS were observed in both the adenocarcinoma and squamous cell groups, however that it was not possible to draw conclusions about the treatment effect in the two groups due to the small number of trial participants.

7.39.2. The Committee noted there was little additional toxicity from the addition of pembrolizumab, with immunotherapy related toxicities uncommon.

7.39.3. The Committee noted there was an improvement in the overall quality of life by the addition of pembrolizumab in terms of pain as measured by EORTC Quality of Life Questionnaire Core Oesophageal cancer module (QLQ-OES18).

7.40. Overall, the Committee considered that the applicability of the study was limited in New Zealand due to the different proportion with adenocarcinoma and inadequate statistical power to draw conclusions about the benefit of treatment in the group with adenocarcinoma.

Squamous cell carcinoma

Nivolumab

Checkmate 648 trial

7.41. The Committee noted the Checkmate 648 trial (global, randomised (1:1:1 to nivolumab with chemo, nivolumab with ipilimumab and chemotherapy), open-label, phase III) that enrolled individuals with squamous-cell OC (N=970).

7.41.1. The Committee noted the study population were predominantly Asian, with an ECOG PS ≤1, which represents a clinically well population. The Committee noted there was a high proportion of individuals with a tumour cell PD-L1 expression ≥1%.

7.41.2. Overall, the Committee considered both nivolumab treatment arms reported an OS advantage compared to chemotherapy alone, with the best OS in the group with PD-L1 ≥1%. However, the Committee noted that a PFS improvement was only observed in the nivolumab with + chemotherapy treated PD-L1 expression ≥1% group, with no benefit in the nivolumab with ipilimumab combination group.

7.41.3. The Committee noted secondary analysis based on CPS scoring, that reported no benefit from nivolumab treatment in individuals with a CPS≤1% (which was approximately 9% of individuals).

7.41.4. The Committee considered the adverse events were highest in the nivolumab with ipilimumab group compared to nivolumab with chemo, and chemotherapy alone. The Committee considered overall all three treatments were well tolerated however there were more frequent serious treatment related AEs in the immunotherapy arms.

7.42. Overall, the Committee considered the study a relevant source of evidence to represent the benefit of treatment in New Zealand. The Committee noted that the main

limitations were recruitment being mostly among Asian patients and that participants may be relatively healthier than in New Zealand due to the eligibility criteria specifying a lower ECOG score.

General

7.43. The Committee considered the studies restricted enrolment to individuals with an ECOG PS ≤1, which represent a clinically well population. The Committee considered this differs from the NZ population, 50% of whom may have ECOG of 2 and currently receive chemotherapy. The Committee considered that chemotherapy already has a relatively high level of toxicity, and that an immunotherapy like pembrolizumab or nivolumab would not confer a much higher level of toxicity than chemotherapy does currently. The Committee considered that for this reason, uptake of an ICI in the population with an ECOG score of 2 would be very high if made available in this group. The Committee considered there was variability in status scoring by clinicians. The Committee further considered that ECOG PS can be modulated by the clinician.

7.44. The Committee overall considered across studies there is evidence of modest benefits in terms of PFS and OS from nivolumab and from pembrolizumab in both adenocarcinoma and squamous cell carcinoma, and in all three anatomic locations. However, the Committee considered that the findings were somewhat inconsistent across the trial evidence, with variability in PFS and OS benefit depending on trial design, including the region in which the study was undertaken, and inclusion criteria relating to CPS/ PD-L1 expression, histology or anatomical location.

7.45. The Committee considered overall the relatively modest benefits, especially OS benefits, are likely driven by a small cohort that gain high levels of health benefit from the immunotherapy component and would benefit most from the treatment.

7.46. The Committee considered the greatest health benefit of either pembrolizumab or nivolumab was observed in individuals with high PD-L1 expression, and in particular MSI-H cancers. The Committee noted that there were very few individuals included that have MSI-H cancers within the trials.

7.47. The Committee noted the paucity of outcome data for the NZ population, which includes differences in frequency of germline mutations in certain groups (eg greater rates of CDH-1 in Māori vs non-Māori). The Committee considered that there is a lack of certainty in the response such individuals might receive from the addition of an ICI, which theoretically could be less than those without the germline mutation.

7.48. The Committee considered current outcomes for individuals with GC/GOJ and OC are poor and there is a high symptom burden. The Committee considered the trials were limited to individuals with an ECOG PS 0-1 which is not representative of patients with advanced disease in New Zealand. The Committee considered individuals with an ECOG PS of two would receive similar clinical benefit to treatment to those with an ECOG PS of 0-1.

7.49. The Committee considered that in New Zealand, people requiring treatment for metastatic OC, GEJ or GC may increasingly receive prior treatments which could alter the benefit they receive from pembrolizumab or NIVO. Specifically, FLOT regimens are used increasingly for people with OC and GEJ, and chemotherapy and radiation are available for people with adenocarcinoma. The Committee considered this may reduce the response to treatment among people in the patient group who would access pembrolizumab and NIVO.

7.50. The Committee considered overall each trial was well designed with adequate patient numbers included and comparator treatments that represented clinical practice in New Zealand, however when considering the data all together that each trial looked at

different populations and therefore potential genetic and environmental variations may affect the overall outcomes.

7.51. The Committee considered the submissions excluded trials that may have conflicting results, and that the SIG should have a more significant role in providing submissions or commentary on new therapeutics.

7.52. The Committee considered that the toxicities of pembrolizumab and nivolumab are low and well known. The Committee considered the addition of either agent to chemotherapy did not increase the risks for this population. The Committee considered both therapeutics were used routinely in practice.

7.53. The Committee considered that an ICI class effect in this setting is supported by the evidence for pembrolizumab, nivolumab and tislelizumab and aligns with known mechanism of action, as well as appraisal of these medicines in other cancers such as melanoma. The Committee considered the results in the studies presented were similar for both agents and could be considered interchangeable in this setting.

7.54. The Committee considered that given the class effect of ICI it was reasonable that Pharmac use the CHECKMATE-649 and CHECKMATE-648 trials to represent the benefits of treatment with any ICI in the combined population with HER-2 negative or indeterminate OC, GEJ and GC in New Zealand. Though the KEYNOTE-590 and KEYNOTE-859 trials were considered to also jointly represent the full relevant treatment group, their applicability was limited by KEYNOTE-590 not accurately representing the New Zealand population.

7.54.1. The Committee considered that 92% of the relevant patient population in New Zealand would be represented by CHECKMATE-649, with just 8% represented by CHECKMATE-648, based on the calculation shown in the PICO table below.

7.54.2. The Committee considered that the subgroup analyses of people with CPS ≥5 were the most applicable to the group represented by the proposed special authority criteria.

7.55. The Committee considered that a particular benefit was seen in MSI-high cancers despite the trials including only small proportions of such cases. The Committee considered there is currently low-quality evidence to consider those with MSI-H disease as a distinct subgroup, however, that this disease characteristic is a predictor of benefit in this setting and better cost-effectiveness would be expected to result in this subgroup.

Suitability

7.56. The Committee noted that there would be resource capacity implications of funding an ICI for combination treatment and subsequent monotherapy for gastric cancers, although this would add about 30 minutes to the total combination treatment infusion time per episode of infusion.

7.57. The Committee noted that pembrolizumab (every three or six weeks) and nivolumab (every two or four weeks) would be administered intravenously in combination with chemotherapy (chemo), and that monotherapy treatment was proposed in both applications to be continued until disease progression or no longer tolerated. Nivolumab was proposed for up to two years in patients without disease progression or intolerance, whilst pembrolizumab was proposed for a maximum of 35 cycles.

Cost and savings

7.58. The Committee considered that economic modelling should represent OS as the primary benefit of treatment. The Committee considered that where evidence of health-related quality of life (HRQOL) over time with an ICI relative to chemotherapy

was available, this should be modelled preferentially over any differences in PFS. The Committee considered that only in the absence of evidence of HRQOL over time with the different treatments, PFS could be used as a proxy for HRQOL.

7.59. The Committee considered the estimate of patient numbers should include both people with advanced and unresectable disease, and that populations would be reduced if only considering advanced disease presenting for first treatment (excluding those treated for pre-operative chemotherapy).

7.60. The Committee considered that uptake of treatment would be high in the group already receiving chemotherapy, due to the high tolerability of immunotherapy. The Committee considered that the majority of people in New Zealand, with adequate performance status, with metastatic or unresectable OC, GC or GEJ would already receive chemotherapy.

7.61. The Committee considered there was PFS benefits observed in all trials (CHECKMATE-648 and KEYNOTE-590 for OC, KEYNOTE-859, CHECKMATE-649 and attraction 4 for GC or GOJ) excluding KEYNOTE-062. The Committee considered the extent and timing of benefit varied between trials, as did the use of PDL-1 scoring. The Committee considered the histology and immunotherapy used did not induce a clear difference.

7.62. The Committee noted that current treatment at second line is irinotecan and taxanes, such as paclitaxel. The Committee considered both treatments have significant potential toxicities and therefore if those with a ECOG PS score of two are included in the funded population, potentially a lower proportion of people in New Zealand would go on to further treatments compared with the trial populations.

Funding criteria

7.63. The Committee considered that there was no reason for the treatment duration to differ between pembrolizumab and nivolumab and that a maximum funded duration of two years would be appropriate. The Committee considered that unlike the evidence for further ICI treatment in melanoma where data supports long-term responses beyond, for example, six to 12 months on treatment, this data is not available in GC and noted that there is a different degree of biological response in melanoma compared with other cancers. The Committee considered it would be appropriate to include renewal for individuals who have a partial response to treatment, as is included in the melanoma Special Authority criteria.

7.64. The Committee considered it would be appropriate to target access to those who did not have HER-2 positive disease (ie HER-2 negative or indeterminate) due to funded trastuzumab being an available option for HER-2 positive disease.

7.65. The Committee considered that a PD-L1 threshold, due to variability in testing practice, might exclude some patients who would benefit whilst providing access to a treatment to others who would receive no benefit (likely 70% of the population). The Committee considered there was a poor correlation between different scoring systems and noted it had previously discussed this. It further considered that CPS scoring was not available in all regions in NZ, with relatively few sites in NZ processing samples.

7.66. The Committee considered that using PD-L1 CPS of ≥5 was the most appropriate measure and reasonable threshold for access to a funded ICI in this first line setting. The Committee considered a single testing site would provide more reliability in results.

7.67. The Committee considered that pembrolizumab and nivolumab would be used in the metastatic disease setting. The Committee considered that enabling access to pembrolizumab and nivolumab for first-line treatment of advanced or metastatic gastric and/or oesophageal cancers for those with ECOG PS of 0 to 2 was reasonable despite

the trial evidence not extending to those with ECOG PS of 2. The Committee considered those with ECOG PS of two are generally fit to receive chemotherapy and would likely tolerate the addition of an immunotherapy that would add minimal toxicity. Furthermore, it considered excluding patients with ECOG PS of 2 from the funding criteria would be inappropriate as this would mean that a subset of patients who could otherwise benefit would not be able to access treatment.

7.68. Overall, for this setting, the Committee considered the fitness to receive chemotherapy a more clinically appropriate criteria than an ECOG PS, noting the latter is a more subjective measure.

Summary for assessment

7.69. The Committee considered that the below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for nivolumab if it were to be funded in New Zealand for the first-line treatment of advanced or metastatic gastric and/or oesophageal cancers. 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	HER-2 negative or indeterminate PD-L1 CPS ≥5	
	Unresectable or metastatic gastric (GC), gastro-oesophageal junction (GOJ) or oesophageal adenocarcinoma (OA) (92%)****	Unresectable or metastatic oesophageal squamous cell carcinoma (8%)****
Intervention	Pembrolizumab 200 mg fixed dose administered intravenously (IV) 3-weekly, ceased at the sooner of disease progression or 35 administrations OR Nivolumab 360mg IV 3-weekly OR Nivolumab 240mg IV 2-weekly AND SoC chemotherapy	Pembrolizumab 200 mg fixed dose administered IV 3-weekly, ceased at the sooner of disease progression or 35 administrations OR Nivolumab 240mg IV 2-weekly OR Nivolumab 480 mg IV 4-weekly AND SoC chemotherapy
	Either treatment would be followed by second line treatment for a minority of people (fewer than received 2L treatment in the key trials), with irinotecan or paclitaxel**	
Comparator	SoC (capecitabine and oxaliplatin or Leucovorin, fluorouracil, and oxaliplatin)[b] using CAPOX (20%) or FOLFOX (80%)* regimens 2L treatment for a minority of people (fewer than received 2L treatment in the key trials), with irinotecan or paclitaxel**	
Outcomes	• Improved PFS (possibly resulting in less deterioration in HRQOL from baseline) • Improved OS	
Key study* **	CHECKMATE-649 CPS ≥5 subgroup	CHECKMATE-648 CPS ≥5 subgroup

*Due to only 20% being able to swallow large capecitabine tablets, so requiring an infused 5-FU regimen (FOLFOX)

**This is lower than in the clinical trials due to the inclusion of ECOG 2 in the SA criteria, which would mean fewer people may be well enough to use second line treatment in New Zealand given the toxicity of irinotecan and paclitaxel

***Pembrolizumab studies not preferred due to inclusion of both AC and SCC in the oesophageal cancer trial (KEYNOTE-590) not allowing for representation of the different proportion of AC vs SCC in New Zealand compared to the trials. It is possible to represent the New Zealand split of histologies in Pharmac's assessment using the nivolumab trials. See below.
****Estimate based on 13% of people having oesophageal adenocarcinoma in CHECKMATE-649, implying 13:87 ratio of oesophageal adenocarcinoma to gastric or GOJ tumours. The Committee presented evidence that 61% of oesophageal cancers in New Zealand are adenocarcinoma, so it is assumed that the ratio of oesophageal adenocarcinoma to gastric or GOJ tumours to oesophageal squamous cell carcinoma is 13:87:8 where 8 = 13.(39/61). As a percentage, this split is 80% to 12% to 8%, or 92% to 8% represented by CHECKMATE-649 and CHECKMATE-648 respectively.

8. Stage III/IV melanoma, neoadjuvant and/or adjuvant treatment: Nivolumab monotherapy [P-002085] and nivolumab with ipilimumab

Application

8.1. The Committee reviewed the applications for

8.1.1. neoadjuvant nivolumab in combination with ipilimumab for the treatment of resectable cutaneous melanoma; and

8.1.2. nivolumab monotherapy for the treatment of resected melanoma (Stage IIIB, IIIC, IIID or Stage IV) adjuvant to complete surgical resection.

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 neoadjuvant nivolumab in combination with ipilimumab for the treatment of resectable cutaneous melanoma be listed with a **high priority** within the context of treatment of malignancy subject to the following Special Authority criteria:

Initial application — stage III or IV resectable melanoma - neoadjuvant
Applications only from a relevant specialist or any relevant practitioner on the recommendation of a relevant specialist. Approvals valid for 4 months.
All of the following:
Either
1. The individual is currently on treatment with ipilimumab/nivolumab for neoadjuvant treatment of stage IIIB to IV resectable melanoma and met all remaining criteria prior to commencing treatment; or
2. All of the following:
    2.1. The individual has resectable stage IIIB, IIIC, IIID or IV melanoma (excluding uveal) (see note); and
    2.2. The individual has not received prior funded systemic treatment in the perioperative setting for their stage IIIB, IIIC, IIID or IV melanoma; and
    2.3. Treatment must be prior to complete surgical resection; and
    2.4. Ipilimumab/nivolumab must be administered in combination with nivolumab/ipilimumab; and
    2.5. The individual has ECOG performance score 0-2; and
    2.6. Ipilimumab/nivolumab to be administered for maximum of two cycles prior to surgical resection

Renewal — stage III or IV resectable melanoma - neoadjuvant
Applications only from a relevant specialist or any relevant practitioner on the recommendation of a relevant specialist. Approvals valid for 4 months.
Either:
1. Both:
    1.1. The individual has received neoadjuvant treatment with an immune checkpoint inhibitor; and
    1.2. The individual meets initial application criteria for nivolumab for stage III or IV resected melanoma – adjuvant; or
2. Both:

2.1. The individual has received neoadjuvant and adjuvant treatment with an immune checkpoint inhibitor; and
2.2. The individual meets renewal criteria for nivolumab for stage III or IV resected melanoma – adjuvant; or

3. All of the following:
3.1. The individual has received neoadjuvant and adjuvant treatment with an immune checkpoint inhibitor; and
3.2. The individual has metastatic or unresectable melanoma (excluding uveal) stage III or IV; and
3.3. The individual meets initial application criteria for nivolumab for unresectable or metastatic melanoma; or

4. All of the following:
4.1. The individual has received neoadjuvant and adjuvant treatment with an immune checkpoint inhibitor; and
4.2. The individual has received treatment with an immune checkpoint inhibitor for unresectable or metastatic melanoma; and
4.3. The individual meets renewal criteria for nivolumab for unresectable or metastatic melanoma.

Note:
a) Stage IIIB, IIIC, IIID or IV melanoma defined as per American Joint Committee on Cancer (AJCC) 8th Edition.
b) Disease must be considered to be completely resectable and amenable to curative intent surgery, including stage IV disease
c) Initiating treatment within 13 weeks of complete surgical resection means either 13 weeks after resection (primary or lymphadenectomy) or 13 weeks prior to the scheduled date of the resection (primary or lymphadenectomy).

8.4. The Committee recommended that **nivolumab** for the treatment of resected melanoma (Stage IIIB, IIIC, IIID or Stage IV) adjuvant to complete surgical resection application be listed as **cost neutral to pembrolizumab** within the context of treatment of malignancy subject to the following Special Authority criteria:

Initial application — stage III or IV resected melanoma - adjuvant
Applications only from a relevant specialist or any relevant practitioner on the recommendation of a relevant specialist. Approvals valid for 4 months.
Either

1. The individual is currently on treatment with **nivolumab** and met all remaining criteria prior to commencing treatment; or
2. All of the following:
2.1. The individual has resected stage IIIB, IIIC, IIID or IV melanoma (excluding uveal) (see note a); and
2.2. Adjuvant treatment with nivolumab is required; and
2.3. The individual has not received prior funded systemic treatment in the adjuvant setting for stage IIIB, IIIC, IIID or IV melanoma; and
2.4. Treatment must be in addition to complete surgical resection; and
2.5. Treatment must be initiated within 13 weeks of complete surgical resection, unless delay is necessary due to post-surgery recovery (see note b); and
2.6. Nivolumab must be administered as monotherapy; and
2.7. The individual has ECOG performance score 0-2; and
2.8. Nivolumab to be administered at a dose of 3 mg/kg every two weeks, 240 mg every two weeks, or 480 mg every four weeks.

Note:
a) Stage IIIB, IIIC, IIID or IV melanoma defined as per American Joint Committee on Cancer (AJCC) 8th Edition.
b) Disease must have been considered to be completely resectable and amenable to curative intent surgery, including stage IV disease
c) Initiating treatment within 13 weeks of complete surgical resection means 13 weeks after resection (primary or lymphadenectomy).

Renewal — stage III or IV resectable melanoma - adjuvant
Applications only from a relevant specialist or any relevant practitioner on the recommendation of a relevant specialist. Approvals valid for 4 months.
Any of the following:

1. All of the following:
1.1. No evidence of disease recurrence; and
1.2. Nivolumab must be administered as monotherapy; and

1.3. Nivolumab to be administered at a fixed dose of 3 mg/kg every two weeks, 240 mg every two weeks, or 480 mg every four weeks; and
1.4. Treatment to be discontinued at signs of disease recurrence or at completion of 12 months total treatment including any systemic neoadjuvant treatment; or

2. All of the following:
2.1. The individual has received adjuvant treatment with an immune checkpoint inhibitor; and
2.2. The individual has metastatic or unresectable melanoma (excluding uveal) stage III or IV; and
2.3. The individual meets initial application criteria for nivolumab for unresectable or metastatic melanoma; or

3. All of the following:
3.1. The individual has received adjuvant treatment with an immune checkpoint inhibitor; and
3.2. The individual has received treatment with an immune checkpoint inhibitor for unresectable or metastatic melanoma; and
3.3. The individual meets renewal criteria for nivolumab for unresectable or metastatic melanoma.

8.5. In making these recommendations the Committee considered:

- Good quality trial evidence of efficacy in the neoadjuvant and adjuvant setting
- The potential reduced resource utilisation and long-term treatment time in individuals who have a major pathologic response following neoadjuvant treatment with nivolumab and ipilimumab
- Lack of head-to-head data comparing nivolumab to pembrolizumab in the adjuvant setting
- The high health need of individuals with stage IIIb-IV melanoma.

Discussion

Māori impact

8.6. The Committee discussed the impact of funding neoadjuvant nivolumab in combination with ipilimumab, and adjuvant nivolumab treatment of stage IIIb to IV melanoma on Māori health areas of focus | Hauora Arotahi and Māori health outcomes. The Committee noted it had previously considered the health need of this population when considering pembrolizumab in April 2024. The Committee considered the impacts of funding nivolumab would be similar.

Populations with high health needs

8.7. The Committee discussed the health need(s) of stage IIIb to IV melanoma among Māori, Pacific peoples, disabled peoples including tāngata whaikaha Māori, and other populations identified by the Government Policy Statement on Health 2024-2027 to have high health needs. The Committee discussed the impact of funding neoadjuvant nivolumab in combination with ipilimumab, and adjuvant nivolumab and considered:

8.7.1. The potential reduction in long-term treatment time in individuals who have a major pathologic response would be especially beneficially for rural populations. The Committee considered reduced treatment time would likely result in a reduction in the cost of travel and time away from whānau.

8.7.2. The potential reduction in long-term treatment time in individuals who have a major pathologic response would also be beneficial for individuals from high deprivation quintiles, as it would reduce time away from paid employment, as well as a reduction in cost of travel.

Background

8.8. The Committee noted it had recently reviewed applications for pembrolizumab and dabrafenib and trametinib for resected/resectable stage IIIB to IV melanoma.

Health need

8.9. The Committee noted it had recently discussed the health need of individuals with stage IIIb to IV melanoma in April 2024.

Health benefit

8.10. The Committee noted the NADINA study (Blank et al. N Engl J Med.2024;391:1696-1708) that investigated the use of nivolumab in combination with ipilimumab as neoadjuvant therapy compared with adjuvant nivolumab monotherapy for resectable Stage III melanoma.

8.10.1. The Committee considered neoadjuvant treatment (as used in the NADINA trial) is associated with reduced resource utilisation and long-term treatment time in individuals who have a major pathologic response (MPR) (≤ 10% viable tumour) as approximately 60% of individuals do not progress to adjuvant therapy.

8.10.2. The Committee noted that the specific AJCC staging version was not included in the protocol for the study. The Committee considered the transition between AJCC versions has previously influenced the outcome of other trials for this stage of disease.

8.10.3. The Committee considered anecdotal evidence that the evaluation of pathological response as per the NADINA study was not routinely performed in New Zealand, however this may be performed in the future.

8.10.4. The Committee considered MPR was a novel surrogate marker for event free survival, and it is not comparable to other trial endpoints.

8.10.5. The Committee considered the baseline characteristics of the population looked balanced, with Australian participants comprising 33% of the trial population. The Committee considered that there may be biological differences between melanoma that originates in the northern and southern hemisphere.

8.10.6. The Committee noted MPR was high and concordant between the local assessment and central review (56.6% -59%). The Committee noted that individuals with a MPR experienced good recurrence free survival in comparison to those who had a partial pathological response and underwent adjuvant treatment.

8.10.7. The Committee noted that median duration of follow up was 10.6 months for the experimental arm and 9.9 months for the control arm. The Committee noted that overall survival results will not be available until 2027.

8.10.8. The Committee considered that the individuals in the neoadjuvant group experienced high levels of toxicity, noting the number of ≥grade 3 events was higher in the neoadjuvant group compared to the adjuvant group (47.2% vs 34.1% respectively). Serious adverse events were also higher in the neoadjuvant group compared to the adjuvant (36.3% vs 23.6%). The Committee considered this did not increase the risk of surgery and noted there were more surgical related adverse events in the adjuvant group.

8.10.9. The Committee considered that it was unclear whether the treatment related adverse events observed in the NADINA study were more likely to be caused by neoadjuvant treatment or subsequent adjuvant nivolumab or BRAF/MEK inhibitor therapy.

8.10.10. The Committee considered there was a lack of evidence to determine if there was less toxicity in individuals (n=119) who had neoadjuvant treatment and no adjuvant treatment. The Committee considered this would be helpful to determine healthcare resource use and patient management.

8.11. The Committee considered there was an absence of head-to-head comparisons between the NADINA trial and trials involving neo(adjuvant) pembrolizumab and therefore it is not possible to evaluate comparative efficacy fully at this time. The Committee considered meta-analysis comparing these treatments may be available in the future.

8.12. The Committee considered in the metastatic setting PFS is likely a surrogate for OS based on trial and patient level data however there are conflicting analyses. The Committee considered there was a lack of evidence for a correlation between relapse free survival and/or event free survival and OS.

8.13. The Committee noted the Menzies et al Nat Med. 2021;27:301-9. study that reported pathological complete response (pCR) does correlate with improved RFS and OS for immunotherapy. The Committee noted that the trial population was small and consisted of mainly phase one or phase two trial data. The Committee noted a further study that supported the pCR as a surrogate for RFS when considering immunotherapy treatment of melanoma (Meyers et al. Curr Opin Oncol. 2025;37:116-20). Overall, the Committee considered there is weak to moderate evidence to suggest pCR is a surrogate for OS, however further evidence would be required to strengthen this conclusion.

8.14. The Committee considered evidence regarding the need for surgery and adjuvant treatment following neoadjuvant treatment. The Committee noted results from the OpACIN-neo study that reported total lymph node dissection may potentially be omitted in individuals with MPR post neoadjuvant immunotherapy, without affecting RFS. Whilst the PRADO trial reported that adjuvant treatment is helpful in improving RFS in individuals with pathologic nonresponse following neoadjuvant immunotherapy (Reijers et al. Eur J Cancer. 2025:214:115141).

8.15. The Committee overall considered neoadjuvant nivolumab and ipilimumab treatment did provide a health benefit in the trial population however was associated with an increase in toxicity in the neoadjuvant setting. The Committee considered this benefit is based on the use of event free survival as a surrogate for OS. The Committee also considered that the evidence on the use of MPR for determining future treatment options was weak to moderate.

8.16. The Committee considered the trial was good quality, despite being open-label by design, however additional evidence is needed to support RFS as a surrogate endpoint.

Adjuvant

8.17. The Committee noted the Checkmate 238 trial investigated the effect of adjuvant nivolumab compared with adjuvant ipilimumab.

8.17.1. The Committee noted the primary endpoint was RFS, with OS as a key secondary end point. The Committee noted the trial was not powered to evaluate OS, however, would be tested for, if RFS was statistically significant.

8.17.2. The Committee noted the baseline characteristics of the population looked balanced.

8.17.3. The Committee noted Weber, et al. N Eng J Med. 2017;377:1824-35) that reported results at 18 months of follow up. The Committee noted nivolumab improved RFS compared to ipilimumab (HR 0.65 (95% CI 0.51-0.83) in the intention to treat population. This improvement was consistent across stage three and stage four subgroups.

8.17.4. The Committee noted Larkin et al. N Engl J Med 2019;381:1535-46 that reported results at five years of follow up. The Committee considered nivolumab appeared numerically better than ipilimumab for OS (HR 0.86 (95% CI 0.66-1.12). The Committee considered the RFS remained consistent between the 18 month and five-year analysis.

8.18. The Committee considered that overall, the trial was good quality, despite being open label, however additional evidence is needed to support RFS as a surrogate endpoint.

Overall

8.19. The Committee considered whilst the three-year event free survival data appeared similar there was a lack of head-to-head data comparing nivolumab and pembrolizumab and further noted Prasad et al Transl Oncol. 2024:45:101959 that reported concerns regarding the pembrolizumab trial design. Overall, the Committee considered there was insufficient evidence to suggest (neo)adjuvant nivolumab is superior to pembrolizumab.

8.20. The Committee considered the health benefit of adjuvant nivolumab was similar to adjuvant pembrolizumab and considered there to be a class effect among immune checkpoint inhibitors for the adjuvant treatment of resectable melanoma

8.21. The Committee noted that approximately 60% of individuals with MPR in the NADINA trial did not proceed to additional therapy. The Committee considered this would be a significant health benefit to the individual through prevention of additional treatment time. The Committee did consider there may be additional ongoing management of toxicity events following treatment.

8.22. The Committee considered that this reduction in further treatment would be of particular benefit to individuals who live rurally or are in higher deprivation quintiles due to travel costs and time associated with treatment.

Suitability

8.23. The Committee considered nivolumab to have a similar suitability to other treatments in this setting including pembrolizumab.

Cost and savings

8.24. The Committee considered it was uncertain based on current available evidence if the observed pathological response rates observed in the NADINA trial would be relevant to the New Zealand setting, however considered that current outcomes in the metastatic setting were consistent with trial reported outcomes for immune checkpoint inhibitor therapies.

8.25. The Committee considered that other studies had reported melanoma stage specific responses to treatment, with resectable stage four disease populations having worse outcomes in the Checkmate 238 trial. The Committee considered in practice individuals with resectable or oligometastatic stage four cancer would receive treatment similar to those with resectable stage three however it is likely they would have worse outcomes.

8.26. The Committee considered in New Zealand most individuals with BRAF-mutated melanoma would receive treatment with an adjuvant immune checkpoint inhibitor, before receiving BRAF-MEK inhibitor treatment in the metastatic setting if their disease progressed. Therefore, if nivolumab were funded in the neoadjuvant setting, individuals who do not experience MPR may be offered BRAF-MEK inhibitor treatment in the adjuvant setting, moving BRAF-MEK inhibitors earlier in the treatment paradigm.

8.27. The Committee considered that additional advice from a pathologist would be needed to determine if MPR testing would require additional resources or would need

services to be trained in this type of testing and uniformity of reporting. The Committee considered there would still be significant resource saving if those who experienced MPR did not go onto further treatment. The Committee considered there would be additional pressure on the healthcare system to provide earlier treatment in the neoadjuvant setting.

8.28. The Committee considered there would be a preference to receive neoadjuvant nivolumab with ipilimumab over neoadjuvant pembrolizumab or adjuvant BRAK/MEK inhibitor treatment. The Committee considered the majority of individuals would receive neoadjuvant nivolumab and ipilimumab with adjuvant nivolumab as necessary. The Committee considered anecdotal evidence of individuals whose disease has not had a MPR following private neoadjuvant nivolumab with ipilimumab treatment being referred to public hospitals in New Zealand for adjuvant pembrolizumab or BRAF/MEK inhibitor treatment. The Committee considered this would not happen if nivolumab and ipilimumab were funded. The Committee further considered in the adjuvant setting, clinicians may prescribe either nivolumab or pembrolizumab as these are often considered interchangeable by clinicians, and pembrolizumab is administered less frequently (every 6 weeks rather than every 4 weeks).

8.29. The Committee considered there would be a small number who might have an infusion reaction to either nivolumab or pembrolizumab who may benefit from switching between treatments. The Committee considered this would be approximately 1 individual per 200 treated. The Committee considered individuals would not swap between treatments if there was no adverse reaction.

8.30. The Committee considered there would not be a preference for weight based or flat dosing. The Committee considered it was likely many clinicians would be following the NADINA protocol for the neoadjuvant treatment and may extend the dose interval for the adjuvant component (to the maximum dose interval of four weeks). The Committee considered there is similar efficacy between weight and flat dosing regimens. The Committee considered there was no supporting information in the neoadjuvant setting.

8.31. The Committee considered there would be no reason to assume difference in median time on treatment between adjuvant pembrolizumab and adjuvant nivolumab.

Funding criteria

8.32. The Committee considered that treatment should be for individuals undergoing surgery with curative intent, rather than defining the population by individuals undergoing therapeutic lymph node dissection. The Committee considered surgical interventions for this population had recently been amended, with a change in the need for nodal dissection. However, the Committee considered there may be alterations in the surgical landscape if nivolumab and ipilimumab were funded with the requirement for larger surgical resection to document MPR for the NADINA protocol.

8.33. The Committee considered that given service level constraints on access to treatment in New Zealand it would be inappropriate to place an absolute restriction on the time between surgery and initiation of adjuvant treatment.

Summary for assessment

Neoadjuvant plus adjuvant

8.34. The Committee considered that the below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for neoadjuvant nivolumab in combination with ipilimumab if it were to be funded in New Zealand for the treatment of resectable cutaneous melanoma. 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	People with resectable stage IIIB, IIIC, IIID or IV melanoma (excluding uveal), prior to surgical resection.
Intervention	Neoadjuvant treatment in a regimen as follows: • Two cycles of neoadjuvant ipilimumab (at a dose of 80 mg) plus nivolumab (at a dose of 240 mg) every 3 weeks Followed by a therapeutic lymph-node dissection and, if applicable, resection of the in-transit metastases in week 6. Followed by adjuvant treatment in a regimen as follows (among cases without pathologic complete response): • An additional 11 cycles of adjuvant nivolumab (at a dose of 480 mg) every 4 weeks if the melanoma does not have a *BRAF v600E or V600K mutation*; OR Dabrafenib (at a dose of 150 mg twice daily) plus trametinib (at a dose of 2 mg once daily) for 46 weeks if the melanoma had a *BRAF* V600E or V600K mutation
Comparator(s)	Neoadjuvant and/or adjuvant pembrolizumab (at a dose of 200 mg every 3 weeks)
Outcome(s)	Improved event free survival (EFS) Increased toxicity Reduced need for adjuvant treatment
Table definitions: Population, the target population for the pharmaceutical; Intervention, details of the intervention pharmaceutical; Comparator, details the therapy(s) that the patient population would receive currently (status quo – including best supportive care); Outcomes, details the key therapeutic outcome(s) and source of outcome data.	

8.35. The Committee considered that the below summarises its interpretation of the most appropriate PICO for adjuvant nivolumab for the treatment of resected melanoma. 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	Patients with resected Stage IIIB, IIIC, IIID or IV malignant melanoma who have undergone surgical resection within the last 13 weeks.
Intervention	Adjuvant nivolumab therapy in one of the following regimens: • 3 mg/kg every 2 weeks (30-minute intravenous infusion) OR • 240 mg every 2 weeks (30-minute intravenous infusion) OR • 480 mg every 4 weeks (30-minute intravenous infusion). Treatment should be continued as long as clinical benefit is observed or until treatment is no longer tolerated to maximum duration of 12 months.
Comparator(s)	Adjuvant pembrolizumab at a fixed dose of 200 mg every 3 weeks for a maximum of 12 months or 18 cycles.
Outcome(s)	No evidence of a difference in benefits or risks compared to pembrolizumab.
Table definitions: Population, the target population for the pharmaceutical; Intervention, details of the intervention pharmaceutical; Comparator, details the therapy(s) that the patient population would receive currently (status quo – including best supportive care); Outcomes, details the key therapeutic outcome(s) and source of outcome data.	