PHARMAC
TE PĀTAKA WHAIORANGA

# PHARMACEUTICAL SCHEDULE APPLICATION

**To:** CaTSoP

**From:** Funding Application Advisor

**Date:** October 2020

## Pembrolizumab for the first-line treatment of recurrent or metastatic head and neck cancer

| SUMMARY OF PHARMACEUTICAL | | | |
|---|---|---|---|
| **Brand Name** | Keytruda | **Chemical Name** | Pembrolizumab |
| **Indications** | • In combination with platinum and fluorouracil (5-FU) for the first-line treatment of patients with recurrent or metastatic head and neck squamous cell carcinoma (R/M HNSCC)<br>• As monotherapy for the first-line treatment of patients with R/M HNSCC whose tumors express PD-L1 (CPS ≥1) | **Presentation** | 100 mg / 4 ml liquid vial |
| **Therapeutic Group** | Oncology Agents; Programmed Cell Death-1 (PD-1) Inhibitors | **Dosage** | 200mg IV q.3 weekly; or 400mg IV q.6 weekly |
| **Supplier** | Merch Sharpe and Dohme NZ Ltd | **Application Date** | May 2020 |
| **MOH Restrictions** | Prescription medicine | **Proposal type** | Widen listing |
| **Current Subsidy** | NA | **Proposed Restriction** | Special Authority |
| **Proposed Subsidy** | Withheld* per 100 mg vial (CONFIDENTIAL) | **Manufacturer's Surcharge** | Nil |
| **Market Data** | Year 1 | Year 2 | Year 3 |
| **Number of Patients†** | 84 | 86 | 88 |
| **Net Cost to Schedule†** | Withhel | Withhel | Withhel |
| **Net Cost to DHBs (5-year NPV, 8%)** | Withheld | | |

DHBs, District health board; MOH, Ministry of Health; NPV, Net Present Value.
* Current confidential net price after rebate; equivalent to Withhel per mg. Current list price is $4,680 per 100 mg vial.
†Supplier estimate.



A1427391

## QUESTIONS TO CATSOP

*Note to CaTSoP members: These questions have been identified by PHARMAC staff as being particularly relevant to the application. Please feel free to provide additional information as appropriate.*

### Need

1. How severe is the health need of patients with recurrent or metastatic head and neck squamous cell carcinoma (R/M HNSCC)?
    - Does this health need differ between patients with R/M HNSCC who have PD-L1 combined positive score (CPS) of ≥1 compared with those who have CPS <1? If so, please explain.
2. What is the Subcommittee's view of the patient number estimates by the applicant?
3. Is testing for PD-L1 status routinely performed for New Zealand patients with HNSCC, and if so, when?
4. What are the health needs of families and whānau of people with R/M HNSCC (including long-term effects) or of wider society? How severe are these needs?
5. Does R/M HNSCC cancer disproportionally affect Māori, Pacific people or other groups already experiencing health disparities relative to the wider New Zealand population (eg. NZ Dep 9-10 deprivation, refugees/asylum seekers)?
6. What is the strength and quality of evidence in relation to health needs due to this indication?

### Health benefit

7. Does pembrolizumab provide any additional health benefit or create any additional risks compared with other funded treatment options for R/M HNSCC? If so, what benefits or risks are different from alternative treatments?
    - Do the benefits/risks differ depending on the dosing schedule (ie 200 mg 3-weekly vs 400 mg 6-weekly)?
8. Which patient populations would benefit most from pembrolizumab, as monotherapy and in combination with chemotherapy?
9. What is the strength and quality of evidence, including its relevance to NZ, for health benefits that may be gained from pembrolizumab for R/M HNSCC?
    - What is the Subcommittee's view of the validity and relevance of the network meta-analysis for indirect comparison of the proposed interventions vs NZ standard of care?
10. Would pembrolizumab produce a health benefit for family, whānau or wider society, additional to the health benefits for people with R/M HNSCC? If so how, and what is the strength and quality of evidence for this benefit?
11. If pembrolizumab were to be funded, are there any consequences to the health system that have not been noted in the application?

## Suitability

12. Are there any non-clinical features of pembrolizumab that may impact on use that have not been considered in the application?

## Costs and savings

13. Does the information in the PICO table (Table 3) accurately reflect the intended population, intervention, comparator and outcome, should pembrolizumab be funded for R/M HNSCC? If not, how should this be adjusted?
    - What is the Subcommittee's view of the supplier assumption that 85% of all patients with HNSCC would have PD-L1 combined positive score (CPS) of ≥1?
    - Is the assumption of a 5-year treatment benefit for overall survival (OS) reasonable, per the NICE provisional TA 129, as opposed to 20 years per the supplier's estimate?
        - Or, if neither the provisional NICE nor supplier duration of OS treatment benefit appear reasonable, what duration of treatment benefit for OS does the Subcommittee consider reasonable?
14. With which pharmaceuticals would pembrolizumab be used in combination, and which pharmaceuticals would it replace or displace, in treating the requested indication?
    - What proportion of NZ patients currently receive cisplatin (rather than carboplatin) with 5-FU for first-line chemotherapy as standard of care?
    - Would any patients with CPS of ≥1 opt to receive combination therapy instead of monotherapy? If so, why and in what proportion of patients?
15. Would the use of pembrolizumab create any significant changes in health-sector expenditure other than for direct treatment costs (eg diagnostic testing for PD-L1 CPS, longer duration of chemotherapy treatment, nursing costs or treatment of side-effects)?
    - When would PD-L1 testing be performed? How would it differ from standard of care?
    - What is the Subcommittee's view of the supplier's assumption that oncology clinic visits will increase due to lifespan and that palliative care requirements will decrease?

## General

16. Is there any data or information missing from the application, in particular clinical trial data and commentary?

## Recommendations

17. Should the listing of pembrolizumab in the Pharmaceutical Schedule be extended to the treatment of R/M HNSCC?
    - Name the Factors for Consideration particularly relevant to a positive or negative recommendation and explain why each is relevant.
18. If widened access is recommended, what priority rating would you give to this proposal (within the context of treatment of malignancy)? **[low / medium / high / only if cost-neutral]**?

19. Are the proposed Special Authority criteria appropriate? If not, how should these be amended (eg to specify dose and frequency, tumour location and stage, consent to stopping treatment etc)?

    - If patients with CPS ≥1 may opt to receive combination therapy instead of monotherapy, are any additional clinical criteria required to distinguish those patients suitable for combination therapy from those suitable for monotherapy?

20. Does the Subcommittee have any recommendations additional to the application?

## PURPOSE OF THIS PAPER

The purpose of this paper is to seek advice from the Subcommittee regarding an application from Merck Sharpe and Dohme (NZ) Ltd for pembrolizumab (Keytruda) as first-line treatment of recurrent or metastatic head and neck squamous cell carcinoma (R/M HNSCC), in patients who have not received systemic therapy for recurrent or metastatic disease.[1]

## DISCUSSION

### BACKGROUND

*Previous consideration of treatments for head and neck squamous cell carcinoma*

Cetuximab has been funded for the treatment of locally advanced, non-metastatic squamous cell carcinoma of the head and neck (subject to clinical criteria) since February 2018. PTAC and CaTSoP had earlier considered cetuximab for these head and neck cancers in 2013-2014. A number of chemotherapy agents used in the treatment of head and neck cancers are currently funded without restriction (see *The availability and suitability of existing medicines, medical devices and treatments*).

*Previous consideration of pembrolizumab*

PHARMAC has received several applications for pembrolizumab for the treatment of different indications and regular updates are submitted by the supplier, MSD, regarding this product. The latest pembrolizumab annual information (2018 update) is available on request.

Pembrolizumab has been previously considered for multiple oncology indications, and is currently funded in New Zealand for the treatment of unresectable or metastatic melanoma. Neither PTAC nor PTAC Subcommittees have previously considered pembrolizumab for HNSCC.

[1] Please note that this application is part of the PHARMAC's undertaking of earlier assessments of new medicines applications, under the New Zealand Cancer Action Plan 2019-2029. We note that NICE in the UK has recently suspended its (what is now a provisional) assessment TA 129 (pembrolizumab for untreated metastatic or unresectable recurrent squamous cell head and neck cancer), pending further information from Merck Sharpe and Dohme. However, as this current application here is an earlier assessment of a new cancer medicine, as such PHARMAC staff have accepted the application as is, without seeking further clarification or data from the supplier at this stage, even in light of that July suspension by NICE.

# Need

## Description of the disease

Cancers of the head and neck are malignancies that arise in the upper aerodigestive tract. Of all head and neck cancers, about 90% are of squamous cell carcinoma histology (SCC) and the majority of these occur in the epithelial lining of the oral cavity, larynx, oropharynx and hypopharynx; these cancers are the focus of the current application (World Health Organization. 2014 Review of the Cancer Medicines in the WHO List of Essential Medicines; Locally advanced squamous carcinoma of the head and neck. Available in Appendix 1).

According to UpToDate, clinical presentation of SCC of the head and neck (HNSCC) is highly variable, depending on the site of the primary cancer and exposure to risk factors such as tobacco and alcohol consumption, or the presence of certain human papilloma virus (HPV) strains. Patients may present with a noticeable mass at diagnosis; depending on location of the primary tumour, this may be accompanied by tumour-related symptoms such as dysphagia, hearing loss, otalgia, nasal obstruction, pain, obstructive sleep apnoea, bleeding, non-healing mouth ulcers, weight loss and epistaxis.

Tumour location and disease staging (ie assessment of the primary tumour, regional lymph nodes, and distant metastases) influences treatment and prognosis. More than half of patients present with locally/regionally advanced disease (ie stage III-IVb) disease and distant metastatic disease at diagnosis is uncommon (Grünwald et al. Oral Oncol. 2020;102:104526). According to UpToDate, patients with localised disease (stage I and II) generally receive either surgery or radiation therapy (RT) alone with curative intent, whereas patients with more advanced disease (stage III, IVA, and IVB) may receive both RT and chemotherapy, with therapeutic approaches intended to preserve organ function.

Patients may be monitored for their lifetime due to treatment-related morbidity, but intensive follow-up occurs within the first two to four years post-treatment as the vast majority (80-90%) of disease recurrence occurs within this time, according to UpToDate. Patients are also at risk of developing a second primary malignancy; after three years this risk is higher than the risk of recurrence for most patients.

## Epidemiology

Head and neck cancers affect more males than females at a ratio of from 2:1 to 4:1. Annual incidence of head and neck cancers worldwide is more than 550,000 and the disease results in about 300,000 deaths per year (World Health Organization, 2014).

Five-year prevalence of HNSCC in New Zealand is estimated to be between 1,603-1,734 and 33.82-36.62 per 100,000 in the population (Source: Supplier application, based on WHO 2018 estimates [unable to be accessed by PHARMAC staff]). In 2017, the Ministry of Health recorded 627 registrations for HNSCC (ICD codes C00-06, C09-10, C12-14 and C32; Ministry of Health, 2017). Age-standardised registration rates for all relevant subtypes (except larynx cancer ICD C32) were 11.1 per 100,000 for males and 5 per 100,000 for females, with 7.9 registrations per 100,000 overall in the standardised population.

The key risk factors for HNSCC, tobacco use and alcohol consumption, contribute to about three-quarters of cases (Mehanna et al. BMJ. 2020;341:c4684).

Testing for programmed death ligand-1 (PD-L1) status is understood not to be routine for patients with HNSCC in New Zealand

**The health need of the person**

The supplier considers that patients with R/M HNSCC have an unmet health due to a lack of clinically meaningful improvement in overall survival and durable response with current funded therapies. Prognosis is poor for patients with R/M HNSCC (Grünwald et al. 2020). In patients whose disease recurs or is metastatic, palliative systemic therapy may be suitable, otherwise treatment approaches would be based on supportive care. In patients with R/M HNSCC who are suitable for first-line systemic treatment, platinum-based chemotherapy is most commonly used. Surgical or radiation salvage and/or re-irradiation may be an option only for carefully selected patients whose disease is confined to the head and neck.

In its application, the supplier notes that HNSCC is a debilitating disease that can impact significantly on a patient's physical, functional and psychosocial health due to the pain and symptoms of the disease that affects patients' communication, nutrition and physical appearance (Wissinger et al. Pharmacoeconomics. 2014;32:1213-29). Patients with head and neck cancer require multidisciplinary care due to the impact of the disease on a patient's appearance and function (eg voice and speech, oral continence, chewing and swallowing, breathing, hearing and sight, and even shoulder function).

The Ministry of Health's 2013 provisional tumour standards note that there is evidence that patients with head and neck cancer generally experience a measurable improvement in quality of life within the first two to three years after treatment, that long-term survival has also been shown to be significantly associated with early quality of life scores in these patients; that patients with head and neck cancer have substantial unmet needs; and that there is great potential for enhanced quality of life and other benefits for individuals if they receive adequate support (2013 Standards of Service Provision for Head and Neck Cancer Patients in New Zealand [Provisional] Available in Appendix 1).

**The availability and suitability of existing medicines, medical devices and treatments**

According to UpToDate, available treatments are associated with functional outcomes and morbidity. The supplier considers that there are limited treatment options for patients with R/M HNSCC and that, based on the GLANCE study (Grünwald et al. 2020) and confirmed with treating clinicians in New Zealand, most patients with R/M HNSCC receive first-line treatment with a platinum-based chemotherapy regimen, typically including cisplatin if tolerable, in combination with fluorouracil (5-FU). In patients who have poor performance status or renal impairment, cisplatin would be unsuitable and carboplatin could be used instead. For patients who are unable to tolerate combination chemotherapy, treatment with a platinum, taxane (eg weekly paclitaxel) or methotrexate could be administered as monotherapy. Carboplatin, cisplatin, fluorouracil and paclitaxel are all funded in New Zealand without restriction. Platinum-based chemotherapy and fluorouracil can result in median overall survival of somewhere in the range of 5.0 to 9 months for patients with R/M HNSCC.

**The health need of family, whānau, and wider society**

Caregivers of patients with HNSCC may experience poorer psychological health, including higher levels of anxious symptoms, compared to HNSCC patients and to the general population. Fear of patient cancer recurrence is evident among caregivers and is associated with poorer psychological health outcomes. (Longacre et al. Oral oncology. 2012;48:18-25).

**The impact on the Māori health areas of focus and Māori health outcomes**

Māori patients with head and neck cancer have, overall, lower one-year (81.6%), five-year (55.9%) and 10 year (45.5%) cumulative relative survival compared to non-Māori (82.9%, 64.7% and 56.6% , respectively); and survival is particularly poor for Māori males (Cancer Patient Survival 1994–2011. Ministry of Health, 2015).

The 2013 Standards of Service Provision for Head and Neck Cancer Patients in New Zealand (provisional) noted cancer is an important contributor to health inequalities between Māori and non-Māori; Māori are less likely to access primary oral health care compared to Pacific people and Europeans; and that Māori males are twice as likely and Māori females three times as likely as non-Māori to have a smoking history (Ministry of Health, 2014).

**The impact on the health outcomes of population groups experiencing health disparities**

New Zealand patients with HNSCC who live in more deprived areas have worse cumulative relative survival than patients living in less deprived areas (Ministry of Health, 2015).

**The impact on Government health priorities**

The supplier considers that the treatment of R/M HNSCC is not a Government heath priority, however, the treatment of cancer is one of the Government health priorities for 2020.

## Health Benefit

**Details of the pharmaceutical under consideration**

*Clinical Pharmacology and Mechanism of Action*

Pembrolizumab is a humanized IgG4 monoclonal antibody PD-1 inhibitor. Pembrolizumab binds to the PD-1 receptor on the surface of T-cells and blocks its interaction with PD-1 and PD-L2 expressed by antigen-presenting cells and other cells such as tumour cells. The PD-1 receptor is a protein located on T-cells and pro-B cells which interacts with its ligands to inhibit T-cell activation and proliferation, thereby down-regulating the immune system. Through this mechanism of action PD-1 inhibitors, like nivolumab and pembrolizumab, have the potential to treat a broad range of tumour types.

*New Zealand Regulatory Approval*

Pembrolizumab is approved for a broad range of cancer indications, including the treatment of patients with recurrent or metastatic head and neck squamous cell carcinoma (R/M HNSCC) with disease progression on or after platinum-containing chemotherapy. It is also Medsafe-approved for use in specific settings for the treatment of melanoma, non-small cell lung cancer (NSCLC), classical Hodgkin lymphoma (cHL), urothelial carcinoma, microsatellite instability-high cancers with no satisfactory alternative treatment options (colorectal and non-colorectal cancers) and renal cell carcinoma.

The supplier states that they submitted to Medsafe on 28 April 2020 for pembrolizumab to be registered for the first-line R/M HNSCC indications as follows:

- In combination with platinum and 5-FU for the first-line treatment of patients with metastatic or with unresectable, recurrent HNSCC (R/M HNSCC)
- As monotherapy for the first-line treatment of patients with metastatic or with unresectable, recurrent HNSCC.

Note: The supplier notes that the requested Medsafe monotherapy indication is wider than that requested for PHARMAC funding, the latter of which is for patients with combined positive score (CPS) ≥1, and wider than the approved monotherapy indication for pembrolizumab in the USA (which specifies CPS ≥1) and both the monotherapy and combination indications in Europe (both of which specify CPS ≥1).

Medsafe approval of the new R/M HNSCC indications is expected by 28 February 2021.

Based on the supplier-provided information and information on the Medsafe website, PHARMAC staff consider this application meets the current criteria for parallel assessment.

*Recommended Dosage*

The recommended dosage of pembrolizumab for R/M HNSCC is 200 mg given over a 30-minute intravenous infusion, every three weeks up to a maximum of 24 months. The supplier also proposes the option of a 400 mg dose of pembrolizumab administered every six weeks.

Platinum and fluorouracil (5-FU) is given either three- or four-weekly. For patients receiving pembrolizumab in combination with platinum and 5-FU, treatment would likely be given three-weekly.

*Proposed Treatment Paradigm*

The supplier proposes that pembrolizumab would replace or displace all current first-line standard of care therapies for R/M HNSCC. If pembrolizumab is funded for monotherapy in the CPS ≥1 population, platinum-based chemotherapy treatments would move to second-line. Existing second-line treatments would remain an option or would shift to third-line treatment.

The supplier has proposed a simplified current clinical management algorithm (in light grey) which illustrates the proposed new funding option (in teal) as shown in Figure 1, below.

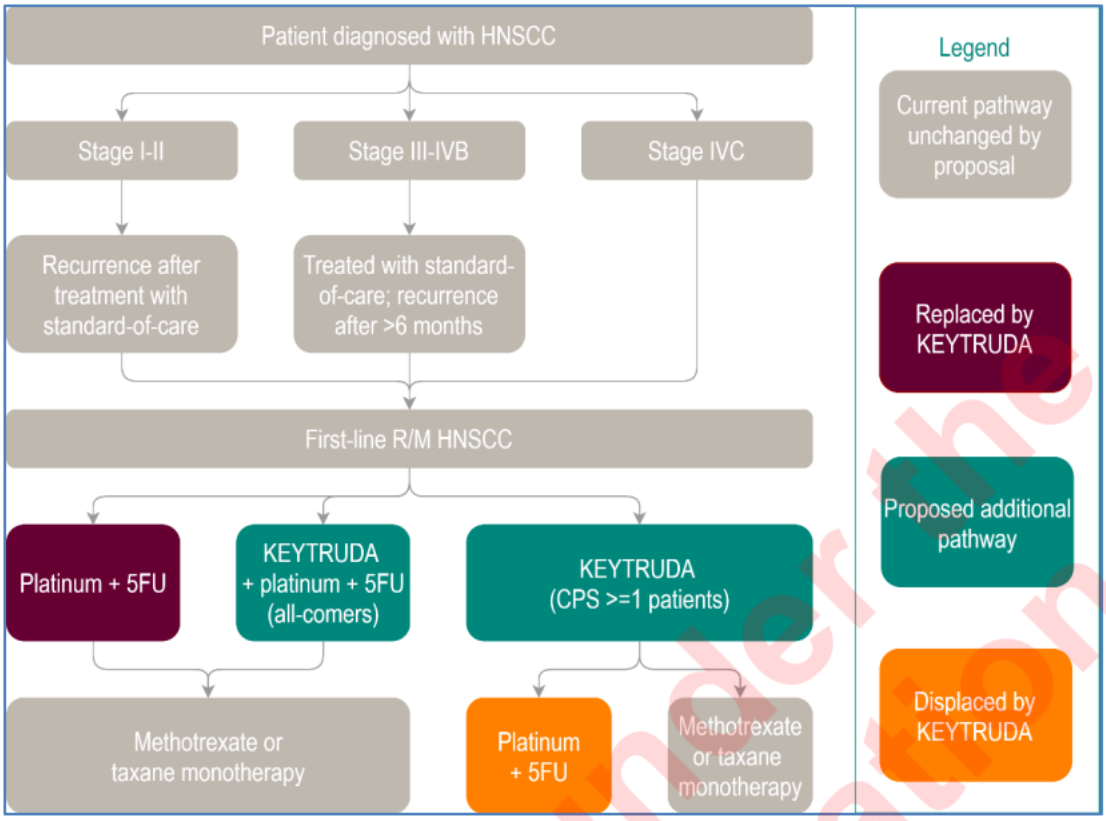


**Figure 1:** Current and proposed funded New Zealand treatment algorithm for R/M HNSCC, per supplier.

*Proposed Special Authority Criteria*

The supplier has provided Special Authority criteria for pembrolizumab as a first-line treatment option for patients with R/M HNSCC, either as monotherapy (PD-L1 CPS ≥1 population) or in combination with chemotherapy for all patients. Patients would not have had prior systemic therapy administered for recurrent or metastatic disease. The target population is described by the supplier as patients with R/M HNSCC in the oral cavity, pharynx and larynx; this includes patients with newly diagnosed metastatic HNSCC (stage IVC) or those with locoregionally recurrent and/or metastatic HNSCC.

PHARMAC staff have drafted the below Special Authority criteria based on the supplier's proposed criteria, adapted for consistency with similar listings. We seek the Subcommittee's view on whether tumour location or stage, a specific dosing regimen, or any other relevant clinical criteria should be included in the funding criteria.

PEMBROLIZUMAB
**Initiation – (head and neck squamous cell carcinoma)**
Applications only from a medical oncologist. Approvals valid for four months.

1. Patient has recurrent or metastatic head and neck squamous cell carcinoma (R/M HNSCC) that is incurable by local therapies; and
2. Patient has not received prior systemic therapy in the recurrent or metastatic setting; and
3. Either:
    a. Pembrolizumab to be used in combination with platinum-based chemotherapy; or
    b. Both:
        i. The patient has a positive PD-L1 combined positive score (CPS) of >1; and
        ii. Pembrolizumab will be used as monotherapy; and
4. The patient has ECOG performance score of 0-2.

**Continuation**

Applications only from a medical oncologist. Approvals valid for four months.

1. No evidence of disease recurrence; and
2. The treatment remains appropriate and the patient is benefitting from treatment; and
3. The total treatment received must not exceed 24 months.

*International Recommendations*

**Table 1:** International recommendations regarding funding of pembrolizumab for the treatment of recurrent or metastatic head and neck cancer.

| **Country (HTA Agency)** | **Meeting Date** | **Outcome** | **Reason** |
|---|---|---|---|
| Australia (PBAC) | No evidence of consideration at the time this paper was written. | | |
| Canada (CADTH - CDEC) | Under review | TBC | TBC |
| Scotland (SMC) | No evidence of consideration at the time this paper was written. | | |
| England/Wales(NICE) | Jan 2020 (provisional) | Not recommended as an option for untreated metastatic or unresectable recurrent HNSCC in adults whose tumours express PD-L1 with a combined positive score (CPS) of 1 or more | Requested clarification on patient characteristics, provision of overall survival data following adjustment and analysis, provision of alternate utility value for progressed disease, and incremental analyses for the two subgroups (ie people whose cancer started inside or outside the oral cavity).<br><br>**Note: Final appraisal document suspended as of 10 July 2020, as Merck is proposing an update.** |

**The health benefits to the person, family, whānau and wider society**

*Evidence Summary*

The supplier has identified one key trial (Keynote-048) that provides the primary evidence for the benefits of pembrolizumab for the treatment of R/M HNSCC. A summary of this trial is provided in the table below (Table 2) and the full publication is available in Appendix 2. The clinical study protocol and clinical study report (CSR) are available on request. PHARMAC staff note that the primary publication describes that the statistical analysis plan for Keynote-048 has evolved (see Supplementary Appendix p. 35-37).

PHARMAC staff note the following additional material available for Keynote-048, also available in Appendix 2:

- Keynote-048: protocol-specified final analysis – conference abstract. Data cut-off 25 Feb 2019. (Rischin et al. J Clin Oncol. 2019;37:6000-6000(suppl 15).

- Keynote-048: conference presentation slides from ASCO May 2020, provided by supplier after application was submitted.

*Systematic review and meta-analysis*

The supplier has also provided the technical report of a systematic review and meta-analysis of pembrolizumab for first-line treatment of R/M HNSCC, which included nine randomised controlled trials (RCTs) in the base case analysis and six RCTs in the sensitivity analysis. This is also available in Appendix 2. The key conclusions in terms of overall survival and safety from the network meta-analysis are summarised as follows:

- Statistically meaningful improvement in OS with pembrolizumab monotherapy in comparisons with both the EXTREME regimen (cetuximab + platinum + 5-FU) and platinum + 5-FU in PD-L1 CPS ≥1 and CPS ≥20 subgroups, with a more enhanced OS benefit seen in the CPS ≥20 subgroup.
- Statistically meaningful improvement in OS in the broader (ie. regardless of CPS status) R/M HNSCC population with pembrolizumab combination therapy compared with both the EXTREME regimen and platinum + 5-FU.

- Safety in the broader R/M HNSCC population showed pembrolizumab monotherapy was associated with statistically lower incidence of grade 3 or 4 adverse events compared with EXTREME regimen and platinum + 5-FU.

**Table 2**: Summary of evidence for pembrolizumab for the treatment of recurrent or metastatic head and neck cancer.

| Trial | Study Design | Patients Group(s) | No. Patients | Intervention | Duration | Efficacy | Safety | Citation |
|---|---|---|---|---|---|---|---|---|
| Keynote-048 | Open-label, randomised (1:1:1), phase III study | Adult patients with R/M HNSCC that is not curable by local therapies, no prior systemic therapy in R/M setting, ECOG score 0-1, measurable disease (RECIST 1.1), and known p16 status (if oropharyngeal cancer).<br><br>Tumour sample required for PD-L1 testing (IHC 22C3 assay); PD-L1 positivity not required for study eligibility. | N = 882 | Pembrolizumab monotherapy 200 mg 3-weekly (pembro mono, N=301)<br><br>Vs<br><br>Pembrolizumab 200 mg 3-weekly in combination with cisplatin (100 mg/m$^2$) or carboplatin (AUC 5 mg/m$^2$) and 5-FU (1000 mg/m$^2$ per day for 4 days) (pembro + chemo, N=281)<br><br>Vs<br><br>Cetuximab (400 mg/m$^2$ loading dose then 250 mg/m$^2$ weekly) in combination with platinum-based chemotherapy with cisplatin or carboplatin, and 5-FU (cetuximab + chemo, N=300). | Mean follow-up: 11.5 months pembro mono, 13 months pembro + chemo, 10.7 months cetuximab + chemo.<br><br>Treatment until RECIST 1.1-defined disease progression or unacceptable toxicity (max. 35 cycles of pembrolizumab; up to 6 cycles of chemotherapy; cetuximab no max. # cycles).<br><br>Pembrolizumab discontinuation allowed in patients with confirmed CR after at least 24 weeks of therapy incl. 2 doses of pembrolizumab beyond first CR. | Data cut-off 25 Feb 2019.<br><br>Overall survival (OS): Median OS in CPS ≥1 after 383/512 (75%) deaths: 12.3 months pembro mono vs 10.3 months cetuximab + chemo (HR 0.78, 95% CI: 0.64 to 0.96, *P*=0.0086). OS at 12 & 24 months, respectively:<br>• CPS ≥1 (F); pembro + chemo vs cetuximab + chemo: 57% vs 46%, and 35% vs 19%.<br>• Total population (pop'n); pembro mono vs cetuximab + chemo: 49% vs 44%, and 27% vs 19%.<br>• Total pop'n; pembro + chemo vs cetuximab + chemo: 53% vs 44%, and 29% vs 19%.<br><br>Progression-free survival (PFS): Median PFS across populations was 2.3-3.4 months pembro mono, 4.9-5.8 months pembro + chemo, 5.0-5.2 months cetuximab + chemo. Superiority not met in analyses of CPS ≥20; no further tests.<br><br>Objective response in pembro mono vs cetuximab + chemo, respectively:<br>• CPS ≥20: 31 (23%) vs 44 (36%)<br>• CPS ≥1: 49 (19%) vs 89 (35%)<br>• Total pop'n: 51 (17%) vs 108 (36%)<br><br>Change in global health status or quality of life (QOL) not reported in this publication. | Grade ≥3 treatment-related adverse events (AEs) occurred in 51 (17%) pembro mono, 198 (72%) pembro + chemo and 199 (69%) cetuximab + chemo.<br><br>AEs led to death in 25 (8%) pembro mono incl. 1 case of pneumonitis, 32 (12%) pembro + chemo incl. 1 case of pneumonitis, and 28 (10%) cetuximab + chemo; 3 (1%), 11 (4%) and 8 (3%) treatment-related, respectively.<br><br>AEs with pembro mono: fatigue, anaemia most common; increased risk of hypothyroidism. | Burtness et al. Lancet. 2019;394:1915-28<br><br>Also Supplementary Appendix |

**Literature Search**

The supplier had noted that the evidence for pembrolizumab for R/M HNSCC is at an early stage, and had considered that as of June 2019, Keynote-048 was the only trial for pembrolizumab (monotherapy or in combination) as the first-line treatment of R/M HNSCC. Therefore, the supplier did not conduct a systematic literature search as part of their funding application.

PHARMAC staff conducted the following PubMed searches on 22 July 2020 to identify any additional data of relevance:

- Search terms: keynote-048/keynote 048; filtered by type: clinical trial OR randomised controlled trial OR meta-analysis OR systematic review – no additional results of relevance.
- Search terms: pembrolizumab AND squamous cell carcinoma; filtered by type: meta-analysis – no additional results of relevance.
- Search terms: pembrolizumab AND squamous cell carcinoma; filtered by type: clinical trial – one result of relevance, as follows:
    - The Society for Immunotherapy of Cancer consensus statement on immunotherapy for the treatment of squamous cell carcinoma of the head and neck (HNSCC) (Cohen et al. J Immunother Cancer. 2019;7:184). Recommends, based on L1 evidence, first-line pembrolizumab for treatment-naïve R/M HNSCC as monotherapy (if PD-L1 CPS ≥1) or in combination with platinum and fluorouracil chemotherapy (all patients with biomarker-unspecified disease). Consensus that PD-L1 positivity is ≥1 CPS by IHC staining.

Publications relating to the following clinical trials were deemed irrelevant based on eligibility criteria that permitted prior systemic therapy for recurrent or metastatic disease:

- Study of Pembrolizumab (MK-3475) in Participants With Advanced Solid Tumours (MK-3475-012/Keynote-012), which included a cohort of patients with HNSCC
- Pembrolizumab (MK-3475) Versus Standard Treatment for Recurrent or Metastatic Head and Neck Cancer (MK-3475-040/Keynote-040)
- Study of MK-3475 (Pembrolizumab) in Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma After Treatment With Platinum-based and Cetuximab Therapy (MK-3475-055/KEYNOTE-055)

PHARMAC staff are not aware of any additional data of relevance since then.

**Consequences for the health system**

*Duration of treatment administration*

Pembrolizumab would be administered in hospital medical wards and outpatient clinics over a period of 30 minutes, every three weeks or every six weeks. If administered every six weeks, this would reduce overall administration resource and patient travel requirements.

If used in combination with chemotherapy, pembrolizumab would increase the total time required for each treatment administration. However, if used as monotherapy instead of chemotherapy, there would be resource savings of up to 4 hours depending on the standard of care chemotherapy regimen that is replaced. Likely standard of care treatment regimens and their administration durations are as follows (obtained from eviQ):

- Cisplatin (60-minute IV infusion, total of about 4.5 hours administration) and fluorouracil (continuous infusion via pump over 96 hours, 30 minutes for pump disconnection on day 5) – every 21 days for up to 6 cycles.
- Carboplatin (30 to 60-minute IV infusion, total of ~90 minutes administration) and fluorouracil (continuous infusion via pump over 96 hours, 30 minutes for pump disconnection on day 5) – every 21 or every 28 days for up to 6 cycles.
- Paclitaxel (60-minute IV infusion, total of ~90 minutes administration) – every 7 days until disease progression or unacceptable toxicity.
- Methotrexate (3 to 15-minute IV infusion via bolus or minibag, total of ~30 minutes administration) – every 7 days until disease progression or unacceptable toxicity.
- Monotherapy with cisplatin or carboplatin is also an option; assumed to be administered over the same duration and at the same frequencies as listed above.

*Overall duration of chemotherapy treatment*

According to the supplier, the duration of chemotherapy treatment may be increased for patients receiving pembrolizumab in combination with chemotherapy, as patients would live longer and therefore be expected to remain on treatment for longer than if they received chemotherapy alone. This increase in chemotherapy treatment duration is considered to be immaterial by the supplier (PHARMAC staff note that in the Keynote-048 trial, patients received a median of 8 pembrolizumab and chemotherapy administrations).

*Oncology clinic visits and palliative care*

The supplier considers that, as a result of improved survival from treatment with pembrolizumab, patients with R/M HNCC would require additional oncology clinic visits due to having a longer lifespan. However, the supplier considers that this would be associated with a decrease in palliative care requirements for these patients.

*PD-L1 testing*

If pembrolizumab were funded for the treatment of patients with PD-L1 positive disease (CPS≥1), this testing would need to be introduced as part of the patient management algorithm and would incur a cost to DHBs. It is possible that all patients with R/M HNSCC could be tested in order to determine whether monotherapy with pembrolizumab, rather than treatment in combination with chemotherapy, would be more suitable for a given patient.

## Suitability

**The features of the medicine or medical device that impact on use**

Pembrolizumab can be prepared for administration by any qualified person and no special handling is required, as it is not cytotoxic. The supplier considers that the fixed 200 mg (or

400 mg) dose (regardless of body weight) can delay infusion preparation until the last moment, helping to avoid potential wastage if a planned treatment does not occur.

## Costs and Savings

### PICO (Population, Intervention, Comparator, Outcome)

Table **3** below summarises PHARMAC staff's interpretation of the PICO for pembrolizumab if the listing were widened to include the treatment of patients with recurrent or metastatic squamous cell carcinoma of the head and neck (R/M HNSCC) in New Zealand.

This PICO captures key clinical contexts, helping review the proposal and frame any future economic assessment by PHARMAC. We seek the Subcommittee's advice on the content in the table below.

Note that the PICO may change as clinical and other features evolve.

**Table 3:** PICO for pembrolizumab if listing were to be widened to include the treatment of patients with recurrent or metastatic head and neck squamous cell carcinoma (R/M HNSCC).

| | |
|---|---|
| **P**opulation | Two populations identified in supplier application:<br>1. 1st line R/M HNSCC (all patients)<br>2. 1st line R/M HNSCC where tumours express PD-L1 (combined positive score [CPS]≥1) – approx. 85% of R/M HNSCC patients, based on the Keynote-048 patient population. |
| **I**ntervention | Pembrolizumab 200mg IV q.3weekly or 400mg IV q.6weekly up to maximum of 24 months, as either:<br>- combination therapy with platinum and 5-FU (all patients with R/M HNSCC), or<br>- monotherapy (for tumours with PD-L1 expression) |
| **C**omparator(s) (NZ context) | **Either:**<br>In most cases; Cisplatin 75 mg/m2 IV on day 1 of each 21 day cycle administered over 4.5 hours (including considerable pre and post treatment therapy; EVIQ)<br>**Or:**<br>If cisplatin is not suitable; Carboplatin 5 AUC on day 1 of each 21 day cycle administered over 30-60 mins (EVIQ)<br>**And:**<br>Fluorouracil 4,000 mg/m2 (equivalent to 1,000 mg/m2/day) via CIV via pump over 96 hours beginning on day 1 of each 21 day cycle (EVIQ) |

| | |
|---|---|
| **O**utcome(s) | As per KEYNOTE-048:<br>- Overall survival gain for patients treated with pembrolizumab, assuming a 5-year treatment benefit (as assumed by NICE provisional TA 129) (noting indirect comparison required for the NZ clinical context as cetuximab is not funded for R/M HNSCC)<br>Based on indirect comparison between KEYNOTE-048 and historical trial data comparing cetuximab with platinum and 5-FU vs platinum and 5-FU:<br>- Progression free survival gain for patients treated with pembrolizumab<br>As per KEYNOTE-048:<br>- No difference in serious adverse events between intervention and comparator treatments |

*Table definitions:*

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

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

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

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

### Costs and savings to pharmaceutical expenditure

### Cost per patient

The supplier estimates the average cost of treatment per patient to be Withheld under. This is based on each patient receiving on average ~11 cycles of pembrolizumab. Time on treatment has been informed from the results of the KEYNOTE-048 study.

### Estimated Incremental Total Cost of Listing

The supplier has undertaken modelling of estimated patient numbers, using a combination of NZ cancer registry data for head and neck cancer (2015 data) and additional data sources to inform the estimated incremental total cost of listing. This modelling is complex and draws on multiple strands of information to quantify eligibility (including commissioned market research undertaken in USA and clinical advice provided to the supplier). PHARMAC staff caution that the generalisability of the BIA assumptions to the New Zealand context might be inaccurate, affecting the estimated incremental total cost of listing. A condensed version of the workings is shown below; full version available on request.

**Table 4:** Supplier estimate (condensed) of potentially eligible patients with recurrent or metastatic head and neck squamous cell carcinoma (R/M HNSCC).

Withheld under section 9(2)(b)(ii) and 9(2)(ba)(i)

Evidence used by supplier to support extrapolation of estimated patient numbers:

1. WHO. Union of International Cancer Control. 2014 Review of the Cancer Medicines in the WHO List of Essential Medicines. Locally advanced squamous carcinoma of the head and neck. 2014. Available at: www.who.int/selection_medicines/committees/expert/20/applications/HeadNeck.pdf. Accessed: March 2016.
2. NCI, Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence - SEER 18 Regs Research Data + Hurricane Katrina Impacted Louisiana Cases, Nov 2017 Sub (2000-2015) <Katrina/Rita Population Adjustment> - Linked To County Attributes - Total U.S., 1969-2016 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, released April 2018, based on the November 2017 submission. April 3, 2019. Data on file, 2019.
3. Clinician advised.

**Costs and savings to the rest of the health system**

As outlined in the supplier application, patients are anticipated to live longer if pembrolizumab is funded, and therefore additional visits to specialist medical oncologists are likely to be incurred. However, PHARMAC staff suspect this cost would likely be immaterial to the overall value of this proposal.

**Cost Effectiveness (combining the Health Benefits and Costs quadrants)**

The supplier application refers to economic modelling undertaken by the supplier to estimate the cost-effectiveness of pembrolizumab with or without chemotherapy for the proposed head and neck indications. While the economic model itself has not been shared with PHARMAC at this time, a detailed technical report has (see pp.151-232 of the supplier application).

The supplier claims that for patients treated with pembrolizumab monotherapy, the incremental cost of treatment is Withheld, with incremental benefit of Withhel QALYs per patient. This equates to an ICER of Withheld per QALY (or Wit QALYs per $1m discounted net incremental health sector funds invested).

PHARMAC staff note that one of the major drivers of the base case is the extrapolation of the overall survival benefit for pembrolizumab over the 20-year horizon of the model. The supplier acknowledges uncertainty surrounding this OS extrapolation in their report, by highlighting the impact on the economic model should the horizon be limited to 10 years (Wit QALYs per $1m invested) or where the treatment effect of pembrolizumab is considered to wane after 3 years (W QALYs per $1m invested) or 5 years (Wit QALYs per $1m invested). Recent provisional guidance provided by NICE in January 2020 has indicated that a 5-year treatment benefit for pembrolizumab is appropriate for UK decision making purposes (see p.12 of NICE provisional appraisal).

PHARMAC staff also note concerns raised in this recent provisional NICE guidance regarding the method used by the supplier (fractional polynomial network meta-analysis indirect comparison) to indirectly compare pembrolizumab versus platinum + 5-FU, suggesting the

supplier may have overestimated the true benefit of pembrolizumab in this setting (see p.11 of NICE provisional appraisal).

PHARMAC staff would request the original CUA modelling from the supplier and undertake de novo modelling, should a positive clinical recommendation be provided for this application.

## APPENDICES

**Appendix 1:** Health need of R/M HNSCC

- 2014 Review of the Cancer Medicines in the WHO List of Essential Medicines; Locally advanced squamous carcinoma of the head and neck
- GLANCE study (Grünwald et al. Oral Oncol. 2020;102:104526)
- 2013 Standards of Service Provision for Head and Neck Cancer Patients in New Zealand (Provisional)

**Appendix 2:** Evidence

- Keynote-048: Primary publication (Burtness et al. Lancet. 2019;394:1915-28)
- Keynote-048: Supplementary Appendix
- Keynote-048: Protocol-specified final analysis – conference abstract (Rischin et al. J Clin Oncol. 2019;37:6000-6000(suppl_15)
- Keynote-048: Conference presentation slides from ASCO May 2020
- Network Meta-analysis of Pembrolizumab for the First-line Treatment of Recurrent/Metastatic Head and Neck Squamous Cell Carcinoma (R/M HNSCC) – technical report
- The Society for Immunotherapy of Cancer consensus statement on immunotherapy for the treatment of squamous cell carcinoma of the head and neck (HNSCC) (Cohen et al. J Immunother Cancer. 2019;7:184)

## THE FACTORS FOR CONSIDERATION

Factors are presented here in the order they appear in the paper, without implying any ranking or relative importance.

### NEED

- The health need of the person
- The availability and suitability of existing medicines, medical devices and treatments
- The health need of family, whānau, and wider society
- The impact on the Māori health areas of focus and Māori health outcomes
- The impact on the health outcomes of population groups experiencing health disparities
- The impact on Government health priorities

### HEALTH BENEFITS

- The health benefit to the person
- The health benefit to family, whānau and wider society
- Consequences for the health system

### SUITABILITY

- The features of the medicine or medical device that impact on use by the person
- The features of the medicine or medical device that impact on use by family, whānau and wider society
- The features of the medicine or medical device that impact on use by the health workforce

### COSTS AND SAVINGS

- Health-related costs and savings to the person
- Health-related costs and savings to the family, whānau and wider society
- Costs and savings to pharmaceutical expenditure
- Costs and savings to the rest of the health system