**Australian Government**

**Medical Services Advisory Committee**

# Public Summary Document

## *Application 1522.1 – Programmed Cell Death Ligand 1 (PD-L1) immunohistochemistry testing for access to pembrolizumab as first-line therapy for patients with recurrent (not amenable to local treatment) or metastatic head and neck squamous cell carcinoma*

**Applicant:**                              **Merck, Sharp & Dohme (Australia) Pty Limited**

**Date of MSAC consideration: 83rd MSAC Meeting, 25-26 November 2021**

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, visit the MSAC website

## 1.     Purpose of application

The applicant-developed assessment report (ADAR) was received from Merck Sharp & Dohme (MSD) by the Department of Health, which comprised an integrated codependent resubmission for:

- Medicare Benefits Schedule (MBS) listing of an immunohistochemistry test for the evaluation of programmed death ligand 1 (PD-L1) using the combined positive score (CPS) and the 22C3 antibody to determine eligibility for treatment with pembrolizumab in patients with previously untreated recurrent or metastatic (R/M) head and neck squamous cell carcinoma (HNSCC), specifically R/M squamous cell carcinoma (SCC) of the oral cavity, pharynx or larynx; and

- Pharmaceutical Benefits Scheme (PBS) Authority Required listing for treatment with pembrolizumab (as monotherapy or in combination with chemotherapy) for the treatment of previously untreated R/M head and neck HNSCC specifically of the oral cavity, pharynx or larynx in patients who have evidence of PD-L1 expression with a CPS ≥1 in the tumour sample.

The pre-ESC response requested that pembrolizumab monotherapy be limited to patients with CPS ≥20 for whom this therapy was claimed to have the greatest benefit and for whom the risks related to false positive patients being offered pembrolizumab monotherapy are significantly reduced.

## 2.    MSAC's advice to the Minister

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness and cost-effectiveness, MSAC supported amending MBS item 72814 for PD-L1 immunohistochemistry testing to also include testing of tumour material from a patient with recurrent or metastatic squamous cell carcinoma of the oral cavity, pharynx or larynx. MSAC considered that the codependency between varying the PD-L1 CPS and extent of response to pembrolizumab treatment was weak. However, MSAC considered that PD-L1 testing with a CPS threshold of ≥20 has sufficient value in identifying which patients may derive greater benefit from pembrolizumab monotherapy.

MSAC supported the following amended MBS item:

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72814

Immunohistochemical examination by immunoperoxidase or other labelled antibody techniques using the programmed cell death ligand 1 (PD-L1) antibody of tumour material from a patient diagnosed with non-small cell lung cancer <u>or recurrent or metastatic squamous cell carcinoma of the oral cavity, pharynx or larynx</u>.

**Fee:** $74.50          **Benefit:** 75% = $55.90   85% = $63.35

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**Consumer summary**

This application was from Merck, Sharp & Dohme (Australia) Pty Limited for public funding via the Medicare Benefits Schedule (MBS) for programmed cell death ligand 1 (PD-L1) immunohistochemistry testing to inform decisions about a patient's suitability for pembrolizumab as first-line treatment of recurrent or metastatic head and neck squamous cell carcinoma. This was a resubmission.

This application was a codependent application, which means that the applicant also applied to the Pharmaceutical Benefits Advisory Committee (PBAC) to list pembrolizumab on the Pharmaceutical Benefits Scheme (PBS) for those patients shown to be suitable by this immunohistochemistry testing. The PBAC had deferred its recommendation pending advice from MSAC.

Squamous cell carcinoma of the head or neck starts in the cells inside the mouth, nose or throat. Recurrent means the cancer has come back after being treated, and metastatic means the cancer has spread to other parts of the body.

Immunohistochemistry testing in tumours is a way for doctors to know whether a certain protein is in some tumours and how much of it is there (called "expression"). Sometimes, if a patient's tumour is expressing certain proteins, some medicines work better, and testing is needed to show that patients are suitable for these medicines. In this application, the PD-L1 test result is reported as a combined positive score (CPS). The applicant stated that those patients with a CPS of 1 or more could be suitable for treatment with pembrolizumab in combination with chemotherapy, and those with a CPS of 20 or more could be suitable for treatment with pembrolizumab alone.

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**Consumer summary**

As previously, MSAC considered that there is not enough evidence to suggest that a patient's CPS score is linked to pembrolizumab being a better treatment. MSAC also noted that different pathologists may give different CPS scores to the same tumour sample, and there are many reasons why this might happen. However, MSAC considered that the PD-L1 CPS result may usefully add to the information that clinicians may use to determine the best treatment for their patient. Overall, MSAC advised that this testing would be good value for money and may reduce PBS expenditure if the test results guide against using pembrolizumab monotherapy by raising doubts about its benefits for a patient.

**MSAC's advice to the Commonwealth Minister for Health**

MSAC supported changing MBS Item 72814 to also include PD-L1 testing for patients with recurrent or metastatic head and neck squamous cell cancer. MSAC considered a CPS ≥20 threshold may be suitable for guiding access to pembrolizumab monotherapy, and no CPS score is needed for pembrolizumab plus chemotherapy.

## 3.    Summary of consideration and rationale for MSAC's advice

MSAC noted the purpose of this codependent resubmission, from Merck, Sharp & Dohme, was to request MBS listing of an immunohistochemistry (IHC) test for the evaluation of PD-L1 expression using the CPS to determine eligibility for treatment with pembrolizumab in patients with previously untreated recurrent or metastatic (R/M) head and neck squamous cell carcinoma (HNSCC) (specifically of the oral cavity, pharynx or larynx); and to request listing for pembrolizumab (as monotherapy or in combination with chemotherapy) on the PBS for the treatment of the same conditions.

MSAC noted that, for the original submission in November 2020, the Pharmaceutical Benefits Advisory Committee (PBAC) did not recommend listing pembrolizumab for these conditions, and MSAC did not support listing the test. MSAC had considered that the evidence presented did not adequately support the claim of codependency ([Application 1522 Public Summary Document](), page 1).

MSAC noted that the resubmission initially proposed a CPS threshold ≥1 for patients to be eligible for pembrolizumab monotherapy or combination therapy. This was revised in the pre-ESC response to a CPS score ≥20 for eligibility for pembrolizumab monotherapy, and retained the threshold of ≥1 for combination therapy. MSAC noted that the PBAC had deferred its decision at its November 2021 meeting, pending advice from MSAC. The PBAC considered that, based on the data provided, pembrolizumab plus chemotherapy was clinically superior to first-line chemotherapy alone in the CPS ≥1 population and also in the "all-comers" population (that is, regardless of CPS). The PBAC considered that, on this basis, it was preferable that listing of pembrolizumab in combination with chemotherapy not exclude patients with CPS <1. The PBAC expressed a preference for recommending the CPS ≥20 threshold for pembrolizumab monotherapy and an all-comers population for pembrolizumab plus chemotherapy. The PBAC requested that MSAC provide advice on:

- The practical reasons for whether to have reduced confidence in the results of PD-L1 testing using a CPS threshold of ≥1 compared to higher thresholds or no threshold at all.

- More specifically, the practical difference between CPS thresholds of ≥1 and ≥20 in terms of confidence in the results obtained in the context of the codependence with pembrolizumab monotherapy. Would a CPS threshold of ≥20 be expected to ensure that false positives and their negative consequences are minimised in the population receiving pembrolizumab monotherapy?

- The expected differences in population sizes based on the different CPS thresholds (for financials and caps). For patients likely to be treated with pembrolizumab monotherapy what proportion of patients would be expected to have CPS <1 and what proportion would be expected to have CPS <20?

MSAC noted that the ADAR presented results from the Keynote trial (KN048), with an additional 12 months of follow-up. MSAC noted that KN048 was stratified by tumour proportion score (TPS, using the ≥50% threshold), this could have biased the results by recruiting a higher proportion of such patients than would be expected in Australian practice. MSAC noted KN048 had a complex study design and statistical analysis plan. As previously, MSAC considered that this trial does not provide enough evidence to confirm that a patient's CPS score is linked to a variation in the treatment effect of pembrolizumab. Specifically, while the overall survival and PFS of KN048 were analysed by CPS>1 and CPS ≥20, the stratification of KN048 remained on the basis of TPS ≥50% and hence comparisons on the basis of CPS were effectively non-randomised and thus subject to bias.

MSAC noted a publication by Rasmussen (2019)[1] exploring intratumour heterogeneity in PDL1 expression in HNSCC. The study found that no lesions were true negative with a CPS threshold of 1 and that PD-L1 positivity varied markedly within HNSCC tumours. MSAC considered these differences in the PD-L1 positivity within tumours would affect test performance.

MSAC considered the impact of different testing protocols on PD-L1 scoring. MSAC considered that the SP263 antibody was mostly commonly used in Australia whereas the 22C3 antibody was used in the KN048 trial. MSAC considered Crosta (2021)[2] was particularly informative as it compared the clinical utility standard with several other testing protocols. MSAC considered Protocol 4 (SP263 antibody clone and Ventana Benchmark Platform) would be most informative for Australian clinical practice. MSAC highlighted that Crosta (2021) demonstrated that there may be false negatives at the CPS ≥20 threshold using Protocol 4 compared with the clinical utility standard. MSAC considered that this suggested that using CPS ≥20 would lead to more false negatives and very few false positives, which may be an appropriately conservative threshold.

MSAC noted issues relating to discordance in CPS scoring results among pathologists. The resubmission provided the CPS scoring results from pathologist training in Australia in November 2020. MSAC noted that all pathologists demonstrated at least 85% concordance, however all pathologists were discordant from the consensus score in at least one case. MSAC noted that there was high variation in scoring of some tissue samples. MSAC noted

[1]     Rasmussen et al. Intratumor heterogeneity of PD-L1 expression in head and neck squamous cell carcinoma, *British Journal of Cancer* 2019;120:1003–1006.
[2]     Crosta et al. PD-L1 Testing and squamous cell carcinoma of the head and neck: a multicenter study on the diagnostic reproducibility of different protocols, *Cancers* 2021;13:292.

that there were high CPS samples with highly variable scoring as well as samples with low CPS scores (0-2) that were difficult to score.

MSAC noted a range of factors that may affect scoring. PD-L1 assessment requires careful assessment of cells within a sample that could contribute to inter-observer variability of CPS scoring. This includes assessment of individual cells as some do not contribute to the assessment of CPS score, differentiation of granular membrane staining and granular cytoplasmic staining which can be difficult, exclusion of tissue with edge and crush artifacts. MSAC also noted that PD-L1 expression could be affected by inflammation and radiation, and whether samples had undergone appropriate fixation. MSAC noted that NordicQC Immunohistochemical Quality Control were moving towards drug-disease combinations for their quality assurance programs.

MSAC noted that there is also a lack of detail in the PD-L1 IHC 22C3 pharmDx kit Interpretation Manual[3] on how to score borderline cases. The interpretation manual also does not advise on reporting a score between 0 and 1 (i.e. 1 positive cell per 200 tumour cells), meaning that pathologists may be more likely to round up to 1 rather than down to 0. If this is the case, then the proportion of patients given a score of 1 or more would likely be greater than 85%. MSAC also noted the possibility that pathologists may be inclined overestimate CPS scores close to the threshold for treatment eligibility so that patients can access more treatment options. MSAC considered this may also be true for samples with a CPS close to 20 if a CPS score of 20 is defined in a PBS restriction to allow patients to avoid chemotherapy.

MSAC noted the applicant's pre-MSAC response that practices such as peer-to-peer training, quality assurance programs and using the consensus approach for tissue that is difficult to score would reduce inter-observer variability. However, given the many issues that may lead to variability in CPS scoring, MSAC considered that these measures would not sufficiently reduce inter observer variability.

In relation to PD-L1 testing using a CPS threshold of ≥1, MSAC considered there were several practical considerations that limited its confidence in PD-L1 CPS assessment in clinical practice. This was because of variability in assessment due to different test protocols, and inter-observer variability that would occur in clinical practice. MSAC advised against relying on a CPS threshold of ≥1 because all HNSCC tumours are expected to have some sections that would meet this threshold.

MSAC considered there would be a practical difference in testing tumour samples at the CPS threshold of ≥20 to determine eligibility for pembrolizumab monotherapy. MSAC noted the applicant's response that if false positives occur, this would occur in the CPS 15-19 range remote from the CPS threshold of ≥1, and less likely affected by the mosaicism that particularly affects the CPS threshold of ≥1.

In the economic evaluation, MSAC noted that the base case in the original submission assumed that CPS testing had 100% sensitivity and specificity (with 96% used in scenario

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[3] Agilent Technologies. PD-L1 IHC 22C3 pharmDx Interpretation Manual – Head and Neck Squamous Cell Carcinoma (HNSCC). Published June 2019. Accessed November 2021.
https://www.agilent.com/cs/library/usermanuals/public/29314_22c3_pharmDx_hnscc_interpretation_manual_us.pdf

analysis), but that this had been revised to 96% in the base case and 85% in a scenario analysis. Changes to PD-L1 test sensitivity did not substantially impact the incremental cost-effectiveness ratio (ICER).

MSAC noted the financial and budgetary impacts showed a net cost saving to the MBS as a result of cost offsets from administration of chemotherapy. MSAC advised that the estimated proportion of patients expected to have tumours with CPS ≥1 should be unchanged at 85% and that 40-50% of all patients would have tumours with CPS ≥20, with the applicant proposing an estimate of 44.2% from KN048 (Table 11).

MSAC considered that the PD-L1 CPS result may usefully add to the variables that clinicians may use to determine the best treatment for their patient. Overall, MSAC advised that this testing may reduce PBS expenditure if the test results guide against using pembrolizumab by raising doubts about its benefits for a patient. MSAC noted that PD-L1 testing is currently funded under the MBS through item 72814 for non-small cell lung cancer (NSCLC) patients and supported amending the descriptor for this item to include the proposed population for testing. 72814. MSAC advised that an explanatory note should request the pathology report to specify the antibody and technique used and for fine needle aspirates to be excluded as these are not an appropriate sample type.

## 4. Background

MSAC has previously considered PD-L1 testing for access to pembrolizumab as first-line therapy for patients with recurrent (not amendable to local treatment) or metastatic head and neck squamous cell carcinoma.

The original application was considered by MSAC at its November 2020 meeting.

Table 1    MSAC concerns and how these were addressed in the resubmission

| MSAC issue (MSAC Application 1522, November 2020 PSD) | How it is addressed in the resubmission |
| --- | --- |
| **Biological rationale**<br>MSAC considered that the biological rationale for the proposed codependence was weak. | The resubmission stated that the selection of CPS rather than TPS in HNSCC is based on rigorous scientific analysis of which methodology best predicted response for patients using on 4 clinical trials, including 2 phase 3 trials and over 1300 patients, rather than biological explanation. Therefore, the commentary considered the biological rationale as to why CPS but not TPS would be correlated with pembrolizumab efficacy in R/M HNSCC remains unclear. The results of KN048 further validated that the CPS ≥1 cut point as a treatment effect modification was observed for both pembrolizumab monotherapy and pembrolizumab plus chemotherapy at this cut point. |
| **Sensitivity/specificity**<br>MSAC noted the high sensitivity and low specificity reported for the test at the threshold of CPS ≥1, and that the apparently high sensitivity might be due to the test classifying over 80% of patients as being CPS ≥1 rather than the test accurately identifying patients who will respond to pembrolizumab. | Although no additional studies were noted in the updated literature search, the resubmission argued that at the CPS ≥1 cut-point, the test will capture the broadest pool of patients likely to respond to pembrolizumab due to the high prevalence at this cut point. In this way PD-L1 was an enrichment biomarker, which enriches the population with patients more likely to benefit from pembrolizumab treatment. Furthermore, no clinical benefit was observed in the CPS <1 subgroup in KN048 treated with either pembrolizumab monotherapy and pembrolizumab plus chemotherapy, thought the commentary noted that the CPS <1 subgroup in KN048 lacked statistical power and was not powered to detect statistically significant differences. |

| MSAC issue (MSAC Application 1522, November 2020 PSD) | How it is addressed in the resubmission |
|---|---|
| **Stratification**<br>In KN048, after patient enrolment, but before data analysis, the trial protocol was amended from stratification of PD-L1 status from TPS ≥50 to CPS ≥1. This led to an increase in risk of bias. | The trial stratification remained at TPS>=50% for the entire trial. Hence randomisation by TPS was maintained for the duration of the trial. The definition of the biomarker was changed in the study objectives and statistical analysis plan from TPS to CPS at amendment 5 prior to data analysis, after evidence from KN012/KN055 showed that CPS was more sensitive in HNSCC tissue, especially at low cut points. |
| **Baseline characteristics imbalanced by CPS subgroup**<br>MSAC also noted the baseline characteristics by CPS subgroup were imbalanced – for example, there were more women and fewer patients with larynx cancer in the pembrolizumab plus chemotherapy arm. | Multivariate analyses were conducted adjusting for multiple baseline demographic and disease characteristics for the CPS ≥1 population where there was a ≥5% difference between treatment arms. For participants receiving pembrolizumab monotherapy, the results from the multivariate analysis showed an OS HR for the CPS ≥ 1 population of 0.75 (95% CI: 0.61, 0.93). which was comparable to the interim analysis 2 results (OS HR = 0.78 (95% CI: 0.64, 0.96) and the final analysis result (OS HR = 0.74, 95% CI 0.61, 0.90).<br>For participants receiving pembrolizumab plus chemotherapy, the results from the multivariate analysis showed an OS HR of 0.71 (95% CI: 0.57, 0.88). This was compared to the primary outcome based on interim analysis 2 data showing an OS HR = 0.71 (95% CI: 0.57, 0.88) and the final analysis OS HR = 0.65 (0.53, 0.80). Therefore, it was argued that the minor imbalances in baseline characteristics had no significant effect on the outcomes of this trial. |
| **Proportion of patients with CPS >1**<br>As a result, 85.3% of KN048 patients had CPS ≥1 and the proportion of patients with CPS ≥20 was also disproportionately increased. MSAC noted the PD-L1 CPS >1 prevalence of 45.6% in de Ruiter 2019. | The resubmission uses a CPS ≥1 prevalence of 80%, in line with the PBAC recommendations (paragraph 6.78, pembrolizumab PSD, November 2020 PBAC Meeting). |
| **Antibody concordance**<br>MSAC noted there was poor concordance between 22C3 antibody used to test PD-L1 positivity in the KN048 trial and other PD-L1 IHC antibodies (SP263, SP142 and 28-8). | Consistent with the previous submission and MSAC's previous consideration, there is currently insufficient evidence to support the concordance of the 22C3 antibody and the SP263 antibody. Hence the applicant is recommending that that MBS item number is restricted to the 22C3 antibody. |
| **Tumour samples**<br>MSAC noted the 22C3 antibody has not been validated for use with FNA as raised in the pre-ESC response. MSAC advised that FNA would not be appropriate for CPS testing because CPS testing requires staining of adjacent immune cells which may not be appropriately captured in an FNA. | The applicant supported MSAC's position, given the weak evidence base for use of FNA. MSD proposes that the item descriptor should specify core biopsy or excision, as these tissue types were used in KN048. |
| **Pathologist training**<br>MSAC considered necessary a mechanism to train pathologists on the interpretation of PD-L1 CPS testing in HNSCC and validation of their competency is required. (Section 3 p4, application no. 1522 PSD, November 2020 MSAC Meeting) | The applicant has supported training for four pathologists as trainers in PD-L1 testing for R/M HNSCC and these pathologists have trained 22 pathologists with plans to train an additional 48 in 2021. This was likely to cover the majority of pathologists who will encounter HNSCC PD-L1 testing as HNSCC treatment is relatively centralised. For the pathologists trained to date, all pathologists have passed the training course, achieving at least 85% concordance with index cases, indicating that Australia pathologists can accurately score using the CPS approach. MSD is in regular contact with the RCPAQAP regarding a QAP. |

CPS = combined positive score; FNA = fine needle aspirates; HNSCC = head and neck squamous cell carcinoma; PD-L1 = programmed cell death ligand 1; PSD = public summary document; QAP = Quality Assurance Program; RCPAQAP = Royal College of Pathologists Quality Assurance Programs; TPS = tumour proportion score
Source: Table 1.1, pages ii-iii of the resubmission

## 5. Prerequisites to implementation of any funding advice

The PD-L1 IHC 22C3 pharmDx kit is currently approved for use in identifying patients with NSCLC who would be eligible for pembrolizumab. As pembrolizumab has been approved by the TGA for use in the CPS ≥1 population, the resubmission claimed that the Instructions for Use are in the process of being updated with the proposed text:

"PD-L1 IHC 22C3 pharmDx is indicated as an aid in identifying HNSCC (Head and neck squamous cell carcinoma) patients for treatment with KEYTRUDA® (pembrolizumab) at PD-L1 expression level CPS ≥1."

The TGA classifies all in vitro diagnostic (IVD) companion diagnostics as class 3 IVDs.

## 6. Proposal for public funding

**Table 2    Proposed MBS listing (pre-ESC response)**

| Category 6 – Pathology Services |
| --- |
| MBS item number |
| Immunohistochemical examination by immunoperoxidase or other labelled antibody techniques using the 22C3 PD-L1 antibody of tumour material from *a core biopsy or* ~~excision~~ *resection specimen of a* patient diagnosed with recurrent or metastatic squamous cell carcinoma of the oral cavity, pharynx or larynx incurable by local therapies to determine if the requirements relating to programmed cell death ligand 1 (PD-L1) status for access to pembrolizumab under the Pharmaceutical Benefits Scheme (PBS) are fulfilled. |
| Fee: $74.50  75% = $55.90  85% = $63.35 |

Source: p161 of the resubmission and pp3-4 of the pre-ESC response *(changes from resubmission request in italics).*

The proposed MBS listing was identical to the requested listing in the previous submission however, the pre-ESC response revised the descriptor to specify that testing is to be performed on tumour material from a core biopsy or excision. The ESCs preferred the term "resection" to "excision".

The resubmission sought PBS listing of pembrolizumab for patients whose tumours express PD-L1 CPS ≥1. The pre-ESC response proposed limiting pembrolizumab monotherapy for patients whose tumours express PD-L1 CPS ≥20.

The proposed MBS fee was consistent with the fee for current PD-L1 testing for NSCLC (MBS item 72814).

In considering the previous submission, the ESCs noted that the proposed item descriptor was for squamous cell carcinoma (SCC) of the oral cavity, pharynx or larynx while the TGA indication for pembrolizumab is for head and neck squamous cell carcinoma (HNSCC). The ESCs noted that the requested item descriptor was consistent with the existing PBS listing for nivolumab and the requested restriction for pembrolizumab. The ESCs supported limiting PD-L1 testing to the 22C3 antibody in the item descriptor as there was poor concordance between 22C3 and other antibodies used in PD-L1 testing. (Section 14 p20, application no. 1522 public summary document (PSD), November 2020 MSAC Meeting)

In considering the previous submission, MSAC noted there is some evidence there may be differences in PD-L1 status between resection and core biopsy specimens. The related pre-ESC response also highlighted that the product information for the 22C3 antibody states that fine needle aspirates (FNA) have not been validated and considered that limiting to either

core biopsy or excision would be consistent with tissue samples used in the KN048 trial. (Section 14 p20, application no. 1522 PSD, November 2020 MSAC Meeting).

The commentary for the resubmission highlighted that the ESCs had previously suggested that the proposed item descriptor should specify that PD-L1 CPS testing should occur once per cancer recurrence or metastasis. (p21, application no. 1522 PSD, November 2020 MSAC Meeting)

The resubmission expected that the majority of 22C3 antibody assay tests will be laboratory developed tests conducted on the Ventana BenchMark XT platform as the majority of platforms in Australia are Ventana (approximately 95%). While this is different to the 22C3 pharmDx kit used in the pembrolizumab clinical trials which requires the Autostainer Link 48 platform, there is a high level of concordance between the 22C3 antibody protocols between the two platforms. Therefore, it is likely that the PD-L1 test for R/M HNSCC will be available at any NATA accredited laboratory in Australia.

The resubmission provided some details of the proposed quality assurance program. The applicant has supported training for four pathologists as trainers in PD-L1 testing for R/M HNSCC and these pathologists have trained 22 pathologists with plans to train an additional 48 in 2021. For the pathologists trained to date, all pathologists have passed the training course, achieving at least 85% concordance with index cases. The applicant is in contact with the Royal College of Pathologists Quality Assurance Programs (RCPAQAP) regarding on going plans for PD-L1 testing for their members related to both technical and interpretation modules offered.

## 7.     Summary of public consultation feedback/consumer issues

Consultation feedback was received from one consumer organisation - Head and Neck Cancer Australia. The feedback was supportive of PD-L1 testing and pembrolizumab treatment. The feedback highlighted that head and neck cancer can leave a person unable to speak, it can leave them with devastating facial disfigurements and take away basic abilities such as eating, breathing, speaking, drinking and swallowing all of which can have a profound impact on a patient's physical and psychological wellbeing. The feedback stated there is an unmet clinical need for effective treatments recurrent or metastatic head and neck cancer.

PASC previously noted the following targeted consultation feedback (Ratified PICO confirmation 1522, 2020, p17):

- Royal College of Pathologists of Australasia (RCPA): While supporting this application (1522), the respondent highlighted previously raised issues about the imperfect nature of PD-L1 IHC as a predictive biomarker for selecting patients likely to respond to immunotherapy. The RCPA also highlighted challenges associated with different scoring algorithms for different tumour types, and inter-operability of assays. Despite this, the RCPA acknowledged there is no clear alternative assay or gold standard, and it is the best test currently available. The RCPA also noted 'In the head and neck, the combined positive score is a useful PD-L1 scoring method' of PD-L1 testing to assist in selecting patients who may benefit from immunotherapy. RCPA noted 'the importance of Quality Assurance Programs (QAP) and accurate training in the diagnostic evaluation of PD-L1 positivity in this context. The assessment of PD-L1 is challenging in existing testing contexts, as it can suffer from variability and ambiguities in interpretation. Multiple PD-L1 antibodies are available. There is also

variation in the affinity and staining intensity of the tumour cells and immune infiltrate. However, this can be managed with a high standard of training and QAP involvement.'

- Specialist / medical oncologist — Peter MacCallum Cancer Centre, Melbourne: Supports the application, but declared a conflict of interest as an investigator in KEYNOTE-048.

## 8. Proposed intervention's place in clinical management

*Description of proposed intervention*

The proposed medical service is an immunohistochemical (IHC) test for evaluation of PD-L1 expression to determine eligibility for treatment with pembrolizumab in patients with R/M SCC of the oral cavity, pharynx and larynx incurable by local therapies who have not had prior systemic therapy administered in the recurrent or metastatic setting. Tumour material obtained via a resected biopsy or core biopsy as part of usual care to confirm disease progression will be used for immunohistochemical testing using the 22C3 antibody as part of the PharmDX kit or as a laboratory developed test (LDT). The testing would be done by a pathologist alongside other immunohistochemical tests which are done routinely.

The CPS algorithm was nominated to be used to score PD-L1 IHC staining. CPS measures the number of PD-L1 stained cells, including tumour cells, lymphocytes, and macrophages, divided by the total number of viable tumour cells, multiplied by 100. The Keynote-048 (KN048; the pembrolizumab trial presented in the ADAR), used the 22C3 PharmDX kit which requires the Autostainer Link 48 platform.

The clinical management algorithms for current practice and for the intended use of testing for PD-L1 and pembrolizumab for the treatment of R/M HNSCC are presented in Figure 1 and Figure 2.
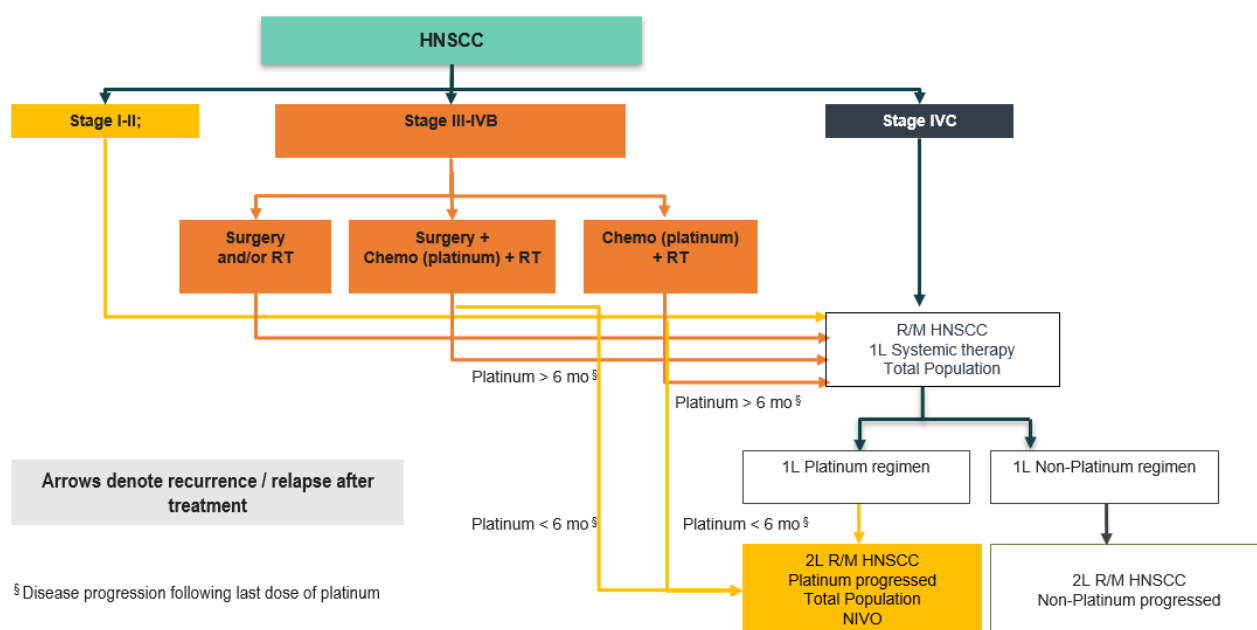


**Figure 1    Current treatment algorithm for patients with R/M HNSCC presented in the resubmission**
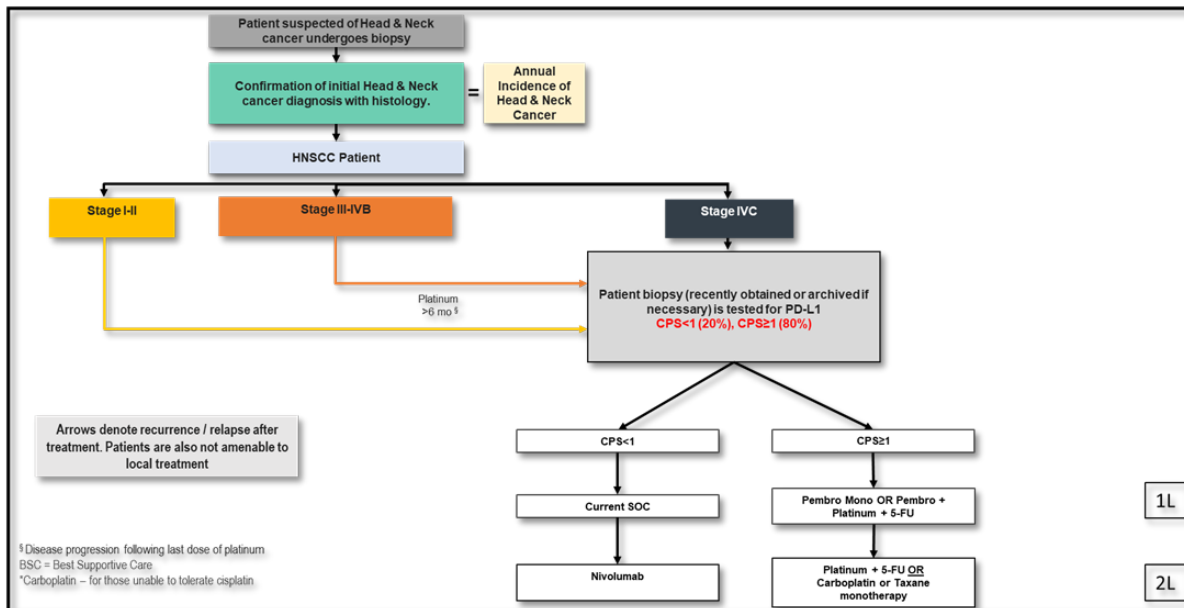Source: Figure 1.2-1, p 7 of the submission

**Figure 2    Proposed treatment algorithm for patients with R/M HNSCC presented in the resubmission**
Source: Figure 1.2-2, p 7 of the submission

The proposed medical service is an IHC test for evaluation of PD-L1 expression to determine eligibility for treatment with pembrolizumab in patients with R/M HNSCC of the oral cavity, pharynx and larynx incurable by local therapies who have not had prior systemic therapy administered in the recurrent or metastatic setting. Tumour material obtained via a resected biopsy or core biopsy as part of usual care to confirm disease progression would be used for IHC testing using the 22C3 antibody as part of the pharmDx kit or as a laboratory developed test (LDT). The testing would be done by a pathologist alongside other IHC tests which are done routinely.

The resubmission claimed that a sample biopsy is currently routinely conducted in the majority of recurrent patients to confirm recurrence. For patients who are unable to be re-biopsied or who have insufficient fresh tissue for testing, archival tissue from their biopsy at the initial diagnosis would be used for PD-L1 testing. Following the previous submission the ESCs agreed that a fresh sample was preferred, though positivity and negativity rates for PD-L1 were similar for archival and fresh tissue in KN048. The ESCs had previously agreed that the evidence presented in the submission suggested that the prevalence of CPS ≥1 was similar between fresh and archival tissue, but did provide evidence that the archival or fresh tissue samples were accurately classified and therefore did not fully support the claim that fresh and archival tissue would be interchangeable. Additionally, the ESCs had previously noted that there is some evidence that PD-L1 expression is dynamic and can vary between the primary tumour and metastases. (Section 14 p21, application no. 1522 PSD, November 2020 MSAC Meeting)

The CPS algorithm was nominated to be used to score PD-L1 IHC staining. CPS measures the number of PD-L1 stained cells, including tumour cells, lymphocytes, and macrophages, divided by the total number of viable tumour cells, multiplied by 100. KN048 used the 22C3 pharmDx kit which requires the Autostainer Link 48 platform.

In the resubmission the proposed treatment algorithm was updated to recommend use of core biopsies or excisional samples if possible. MSAC previously noted the 22C3 antibody has not been validated for use with FNA, and advised that FNA would not be appropriate for CPS

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testing because CPS testing requires staining of adjacent immune cells which may not be appropriately captured in a FNA. (p4, application no. 1522 PSD, November 2020 MSAC Meeting)

MSAC had previously considered that the biological rationale for the proposed codependence was weak and that reflecting this lack of a cohesive rationale, pembrolizumab is approved by the Therapeutic Goods Administration (TGA) for the treatment of several different tumour types with varying requirements of PD-L1 positivity and that the submission to PBAC for second-line pembrolizumab monotherapy for recurrent or metastatic HNSCC (after failure of platinum-based chemotherapy) was not limited to patients whose tumours express PD-L1. (Section 3 p2, application no. 1522 PSD, November 2020 MSAC Meeting)

## 9.     Comparator

As in the previous submission, no PD-L1 testing was the appropriate nominated comparator as PD-L1 testing is not part of the treatment with the current standard of care for R/M HNSCC patients.

Standard of care (SoC), defined as first-line (1L) carboplatin or cisplatin and 5-FU (chemotherapy), followed by second-line (2L) nivolumab in 50% of patients was nominated as the comparator for pembrolizumab ± chemotherapy. In the previous submission 1L chemotherapy followed by 2L nivolumab in 66.7% of patients was nominated as comparator.

The commentary considered that the resubmission inappropriately included patients who were eligible but did not use 2L nivolumab in its estimates. The commentary considered that there was no justification to include these patients in the economic model or financial estimates as they never received 2L nivolumab, and as such, the 50% figure was likely overestimated. Based on the resubmission's assumptions, an overestimate in the proportion of patients treated with 2L nivolumab will lead to an underestimate in the ICER and financial impact of listing pembrolizumab.

## 10.     Comparative safety

*Overview of the evidence base*

Compared to the results presented in the previous submission the following changes were made in the resubmission:

- An additional 12 months of follow up overall survival (OS) data was reported for KN048.

- Unlike in the previous submission where an indirect analysis using data from KN048 and EXTREME (using cetuximab plus chemotherapy as the common comparator) was presented as the main analysis, the resubmission has based the clinical claim and economic model on the results of KN048 alone, using 1L cetuximab plus chemotherapy as proxy for 1L chemotherapy alone, with the indirect comparison of KN048 and EXTREME used as supportive data.

As in the previous submission, the approach taken in the resubmission is to present evidence that has been linked to support the contention that targeting of CPS ≥1 with pembrolizumab will identify patients with R/M HNSCC who may derive the most benefit from immunotherapy.

**Table 3    Summary of the linked evidence approach**

| | Type of evidence supplied | Extent of evidence supplied | Overall risk of bias in clinical trials |
|---|---|---|---|
| Accuracy and performance of the test (analytical validity) | Emancipator 2020 included a portion of patients enrolled in KN012 and KN055 (n=252) and aimed to determine whether CPS or TPS is the preferred PD-L1 scoring method in advanced HNSCC. Cohen 2019 (n=475) reported a similar study with the patients in KN040. No reference standard was identified. | ☐ k=2 n=727 | An updated full QUADAS-2 assessment provided in the resubmission. Overall risk of bias was considered to be high. |
| Prognostic evidence | Five systematic reviews – Lenouvel 2020 (n=2532), Tang 2020 (n=1729), Troiano 2019 (n=1060), Yang 2018 (n=3105) and Peng 2017 (n=1777) – which examined the relationship between PD-L1 and survival in HNSCC were identified by the submission. | ☐ k=5 n=10,203 | Risk of bias was not assessed by the resubmission. There was significant overlap in the included trials of the systematic reviews. |
| Change in patient management | Not explicitly assessed. CPS thresholds were based on KN048 results. | ☒ k=0 n=0 | NA |
| Treatment effectiveness<br><br>Predictive effect (treatment effect variation) | Based on KN048 with subgroups defined using CPS. | ☐ k=1 n=477 | Overall risk of bias was considered low because of the objective nature of the overall survival endpoint. However, the risk of bias may possibly be higher due to the change in protocol from measuring PD-L1 via TPS to CPS. |

CPS = combined positive score, k=number of studies, n=number of patients, NA=not applicable, TPS = tumour proportion score
Source: Table 2.13-1, p164 and Table 2.14-4, p168 of the resubmission

The data available to inform the comparison are summarised in Table 4. The data available was the same as in the previous submission, however in the resubmission only data from KN048 was presented in the main analysis with cetuximab plus chemotherapy arm used as proxy for chemotherapy.

**Table 4    Data availability to inform comparisons**

| Proposed test vs no test | Subgroup analysis of KN048 | |
|---|---|---|
| Proposed test vs alternative test | NA | |
| | **Pembrolizumab** | **Chemotherapy** |
| Biomarker test positive | KN048 | KN048* |
| Biomarker test negative | KN048 | KN048* |

Source: constructed during evaluation
*Cetuximab plus chemotherapy arm used as proxy for chemotherapy.

KN048 underwent many protocol changes. These included:

- OS was moved from a secondary efficacy endpoint to a primary endpoint;

- The definition of the PD-L1 positive subpopulations were updated from TPS to CPS. The resubmission clarified that the KN048 remained stratified by TPS throughout;

- Added hypotheses for PFS and OS superiority in the biomarker-positive subpopulation comparison of pembrolizumab in combination with chemotherapy versus the comparator arm;

- Updates to the statistical methods, power and sample size calculation, multiplicity strategy and analysis plans.

KN048 aimed to control the overall type I error rate at 2.5% (one-sided) by allocating the error rate (alpha) across the primary hypotheses. This consisted of:

- 0.19% allocated to each PFS hypothesis of pembrolizumab monotherapy versus standard treatment (H1) and pembrolizumab plus chemotherapy versus standard treatment (H4) in participants with PD-L1 CPS ≥20;

- 0.02% allocated to PFS hypothesis of pembrolizumab plus chemotherapy versus standard treatment in all participants (H6);

- 0.7% allocated to each OS hypothesis of pembrolizumab monotherapy versus standard treatment (H7) and pembrolizumab plus chemotherapy versus standard treatment (H11) in participants with PD-L1 CPS ≥20; and

- 0.7% allocated to OS non-inferiority hypothesis of pembrolizumab plus chemotherapy versus standard treatment in all participants (H13).

The final multiplicity strategy including the updated efficacy boundaries after taking into consideration of all alpha rollovers are presented in Figure 3 (refer to Predictive evidence).

The resubmission claimed that the use of cetuximab plus chemotherapy efficacy data instead of 1L chemotherapy only underestimated the incremental treatment benefit of pembrolizumab in this line of therapy. Additionally, in the resubmission, the proportion of patients who received 2L nivolumab in the comparator arm of KN048 was inflated to 50% (from 26% in KN048) using a simplified two stage model with no re-censoring based on Latimer 2013 with a corresponding HR adjustment, to approximate the efficacy of SoC in Australia. The commentary considered reasonable the resubmissions' claim that using 1L cetuximab plus chemotherapy data instead of 1L chemotherapy alone data would have underestimated the incremental benefit of pembrolizumab. However, the commentary considered that the resubmission's estimates of 2L nivolumab likely underestimated the benefit of 2L nivolumab in R/M HNSCC.

*Adverse events from testing*

As PD-L1 testing is intended to be done on tissue previously biopsied for confirmation or diagnosis of recurrence or metastasis, it was not anticipated that there will be any additional adverse events from testing.

*Adverse events from changes in clinical management*

The commentary considered that false positives results from CPS testing (at the CPS ≥1 threshold) would result in patients who should be treated with SoC being exposed to pembrolizumab. If patients received pembrolizumab monotherapy instead of SoC, they may have a worse clinical outcome with a lower OS observed for patients with CPS <1 (hazard ratio (HR) 1.72, 95% CI 1.06, 2.79). If a false positive would result in patients receiving pembrolizumab plus chemotherapy instead of SoC, they would be exposed to additional adverse events with no corresponding benefit in efficacy. Additionally, the commentary considered that false positive patients would not be eligible for treatment with PBS-subsidised 2L nivolumab based on the current restrictions, which restricts use to patients who have not received prior treatment with a programmed cell death-1 (PD-1) inhibitor for this condition.

The commentary considered that false negatives from CPS testing would result in patients who would benefit from pembrolizumab therapy being treated with SoC instead. In patients who would have been treated with pembrolizumab monotherapy, a false negative would expose patients to adverse events associated with chemotherapy (such as neutropenia and anaemia) rather than immune related adverse events (such as hypothyroidism and pneumonitis).

## 11.    Comparative effectiveness

*Prognostic evidence*

The resubmission identified five meta-analyses which considered the relationship between PD-L1 and prognosis in patients with HNSCC, including one meta-analysis newly identified in the resubmission (Lenouvel 2020). A further two additional meta-analyses were identified during the evaluation (Li 2017 and Jia 2019). A range of outcomes including OS, PFS, disease free survival (DFS), disease specific survival (DSS) were reported in the included meta-analyses. A summary of the study characteristics in the seven meta-analyses is presented in Table 5.

**Table 5    Summary of meta-analyses on prognostic value of PD-L1**

| Study | Patient population | Number of studies | Number of patients | Conclusion |
|---|---|---|---|---|
| Tang 2020 | HNSCC | 16 | 1729 | No relationship between PD-L1 and prognosis |
| Troiano 2019 | Oral SCC | 11 | 1060 | |
| Yang 2018 | HNSCC | 23 | 3105 | |
| Lenouvel 2020 | OSCC | 26 | 2532 | |
| Peng 2017 | HNSCC | 12 | 1777 | PD-L1 overexpression associated with poor cancer specific survival |
| Li 2017 | HNSCC | 17 | 2869 | Positive expression of PD-L1 could serve as a predictor for poor prognosis of patients with OSCC and Asian patients with HNC, however, the findings still need to be confirmed by large-scale, prospective studies. |
| Jia 2019 | HNSCC | 32 | 4854 | PD-L1 is a potential prognostic predictor in head and neck cancer. |

HNSCC = head and neck squamous cell carcinoma, OSCC = oral squamous cell carcinoma, SCC = squamous cell carcinoma
Grey shaded cells indicate studies included in the previous submission
Source: Table 2.13-1, p164 of the resubmission, Li 2017 and Jia 2019

The commentary highlighted that Yang 2018, which was the largest of the systematic reviews by number of patient and studies, noted that, in the only study in pharyngeal SCC (Vassilakopoulou 2016, n=260), high PD-L1 expression (>59th percentile in automated quantitative protein analysis) was associated with longer OS in multivariate analysis (HR=0.570, 95% CI: 0.333, 0.973, P=0.039). Yang 2018 also found that patients with positive PD-L1 expression had improved PFS compared to patients with negative PD-L1 expression (HR=0.71, 95% CI: 0.55, 0.93, P=0.01) across six studies.

The commentary noted that there were several studies (e.g. Cho 2011, Oliveira-Costa 2015 and Satgunaseelan 2016) which were included in all the identified meta-analyses and a number of other studies which were included in multiple meta-analyses as such, the agreement between the various meta-analyses on the overall HNSCC population should have been expected.

The commentary identified two additional meta-analyses (Li 2017 and Jia 2019) both of which reported statistically significant correlations between PD-L1 expression and OS

outcomes in different subgroups. However the direction of the effect and the subgroups differed, with Li 2017 reporting worse OS outcomes in patients with oral squamous cell carcinoma or from Asian countries/regions and positive PD-L1 expression and Jia 2019 reporting better OS outcomes in nasopharyngeal carcinoma patients with higher expression of PD-L1. The commentary considered that given the potentially contradictory nature of the results it was difficult to draw any additional conclusions regarding the prognostic effect of PD-L1 expression and OS for patients with HNSCC. Nonetheless, there may not be sufficient evidence to conclude that PD-L1 expression has no prognostic impact on overall survival in HNSCC of the oral cavity, pharynx or larynx.

*Predictive evidence*

Figure 3 presents the final multiplicity strategy, including alpha reallocation.
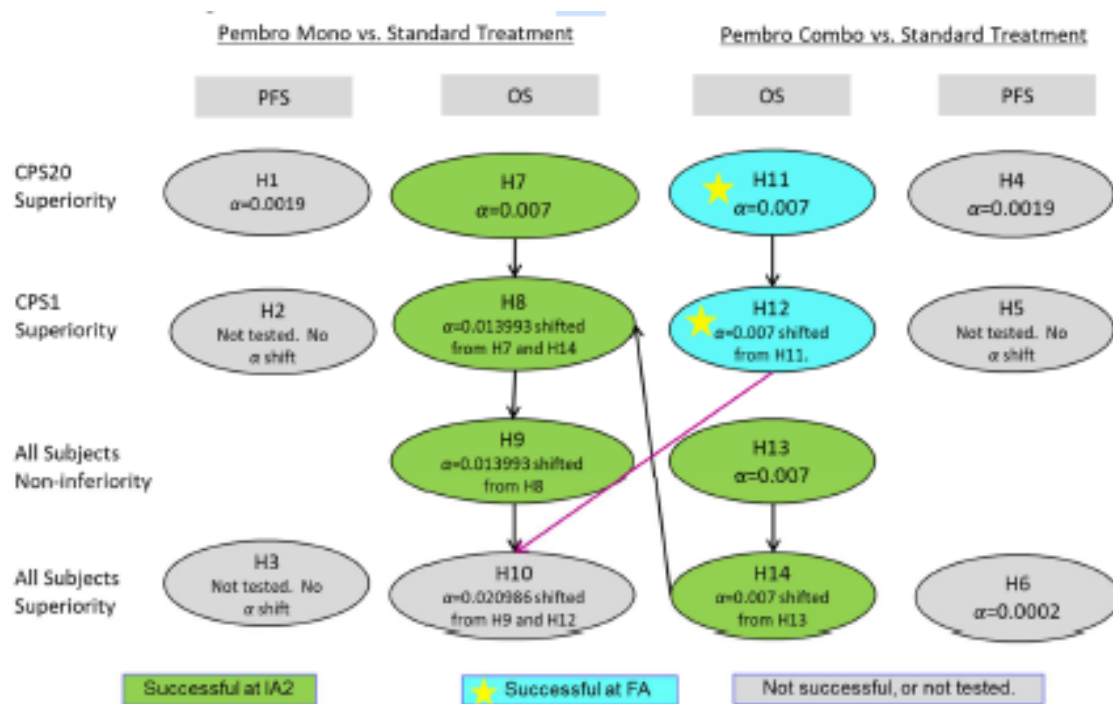


**Figure 3    KEYNOTE-048 multiplicity strategy and alpha reallocation schema**
Source: Figure 9-2, p113 of the KN048 CSR
C = pembrolizumab plus chemotherapy; CPS = combined positive score; CSR = clinical study report; M = pembrolizumab monotherapy; OS = overall survival; PD-L1= programmed death ligand 1; PFS = progression-free survival; S = cetuximab plus chemotherapy (standard treatment)

Not all hypotheses were tested. The final analysis used the remaining Type I error (alpha) not spent at earlier analyses. The KN048 CSR concluded that the major change at final analysis was that statistical superiority for OS was demonstrated for the CPS ≥1 and CPS ≥20 populations for pembrolizumab plus chemotherapy versus standard treatment (H12 and H11 were achieved at the final analysis, respectively).

Several of the hypotheses were successful after reallocation of alpha across the hypotheses. These included:

- Hypothesis 8: Pembrolizumab monotherapy prolongs OS in 1L R/M HNSCC participants with PD-L1 ≥1 CPS compared to standard treatment;

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- Hypothesis 9: Pembrolizumab monotherapy is noninferior to standard treatment in terms of OS in all 1L R/M HNSCC participants;

- Hypothesis 12: Pembrolizumab in combination with chemotherapy prolongs OS in 1L R/M HNSCC participants with PD-L1 ≥1 CPS compared to standard treatment;

- Hypothesis 14: Pembrolizumab in combination with chemotherapy prolongs OS in all 1L R/M HNSCC participants compared to standard treatment.

The overall survival of patients by PD-L1 status in KN048 are reported in Table 6. As in the previous submission, the resubmission claimed that the OS HR results for both pembrolizumab monotherapy and pembrolizumab + chemotherapy indicated an increasing clinical benefit with increasing levels of PD-L1 expression. Also, as in the previous submission, the resubmission acknowledged that the results in the PD-L1 CPS<1 population were based on a small sample size as the trial was not powered to show a difference between CPS ≥1 and CPS <1. (KN048 was powered to show a difference between pembrolizumab monotherapy and pembrolizumab + chemotherapy and SoC in CPS ≥20 and CPS ≥1 populations).

**Table 6    Overall survival in KN048 by CPS status**

| | Previous submission (three-year follow-up) | | Current resubmission (four-year follow-up) | |
|---|---|---|---|---|
| | **OS HR** | **Test for interaction** | **OS HR** | **Test for interaction** |
| Pembrolizumab monotherapy cohort | | | | |
| ITT[a] | 0.83 (0.70, 0.99) [a] | NA | 0.81 (0.68, 0.97) [a] | NA |
| CPS <1 | **1.72 (1.06, 2.79)** | 0.002(89.8%) | 1.53 (0.95, 2.48) [b] | 0.006 (86.93%) |
| CPS ≥1 | **0.74 (0.61, 0.90)** | | **0.74 (0.61, 0.89)** | |
| 1≤ CPS <20 | 0.92 (0.70,1.20) | <0.001 (86.81%) | 0.91 (0.70; 1.19) | 0.003 (82.93%) |
| CPS ≥20 | **0.58 (0.44,0.78)** | | **0.60 (0.46; 0.80)** | |
| CPS <20 | NR | NR | 1.02 (0.81; 1.28) | 0.004 (87.85%) |
| CPS ≥20 | NR | | **0.60 (0.46;0.80)** | |
| Pembrolizumab + chemotherapy cohort | | | | |
| ITT | **0.72 (0.60, 0.87)** | NA | **0.71 (0.59, 0.85)** | NA |
| CPS <1 | 1.18 (0.73, 1.90) | 0.025(80.2%) | 1.21 (0.76, 1.94) [b] | 0.014 (83.4%) |
| CPS ≥1 | **0.65 (0.53, 0.80)** | | **0.64 (0.53, 0.78)** | |
| 1≤ CPS <20 | **0.71 (0.54, 0.94)** | 0.067 (63.08%) | 0.68 (0.52, 0.90) | 0.049 (66.78%) |
| CPS ≥20 | **0.60 (0.45, 0.82)** | | **0.62 (0.46, 0.83)** | |
| CPS <20 | NR | 0.109 | 0.80 (0.63, 1.00) | 0.180 (44.42%) |
| CPS ≥20 | **0.60 (0.45, 0.82)** | | **0.62 (0.46, 0.83)** | |

Source: Table 2.5-4, p75, Table 2.5-12, p89-90, Table 2.6-1, p117 and Table 2.6-2, p118 of the resubmission and p203 of the resubmission; Tables 5 to 6 of the pre-ESC response.
Chemotherapy = cisplatin or carboplatin + 5FU
[a] Not statistically significant due to alpha spending requiring lower p-value than 0.05.
[b] Not clearly indicated by the resubmission (p203) to be four-year follow-up value, but assumed to be so.
CPS = combined positive score, NA = not applicable, NR = not reported
Text in bold indicate statistically significant differences

Figures 4 to 6 present the Kaplan Meier curves for KN048 updated with 12 months of additional follow up data.

**Figure 4**      **Kaplan Meier estimates of overall survival for pembrolizumab plus chemotherapy in KN048 CPS ≥1 (updated with 12 months additional follow up)**

Source: Figure 2.5-2, p71 of the resubmission



**Figure 5**      **Kaplan Meier estimates of overall survival for pembrolizumab monotherapy in KN048 CPS ≥1 (updated with 12 months additional follow up)**
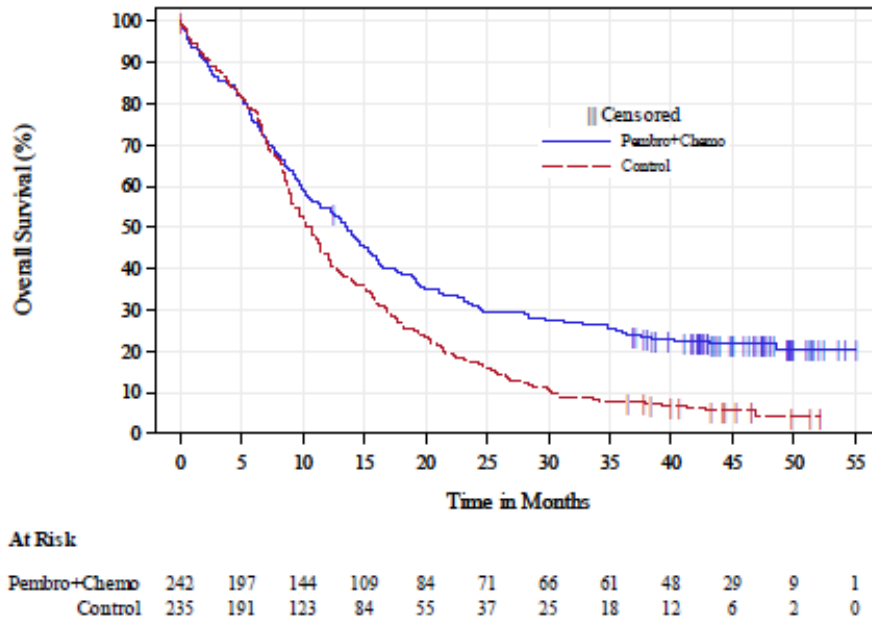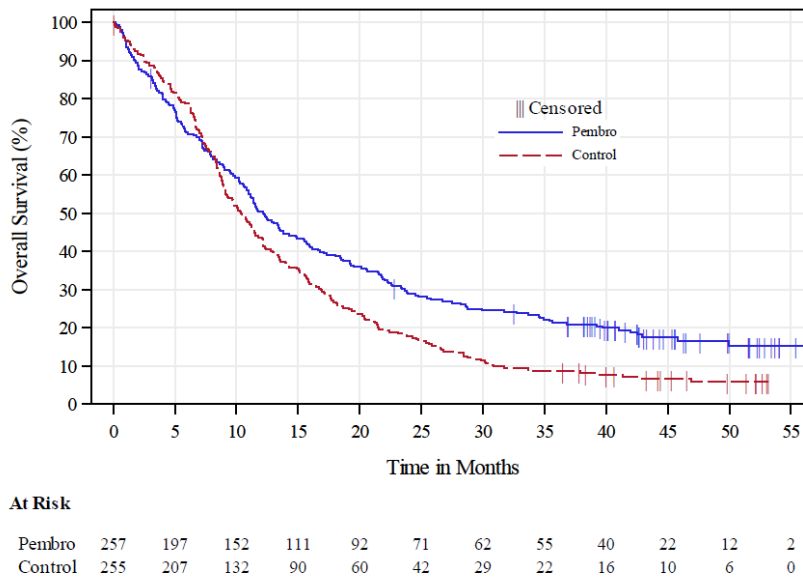
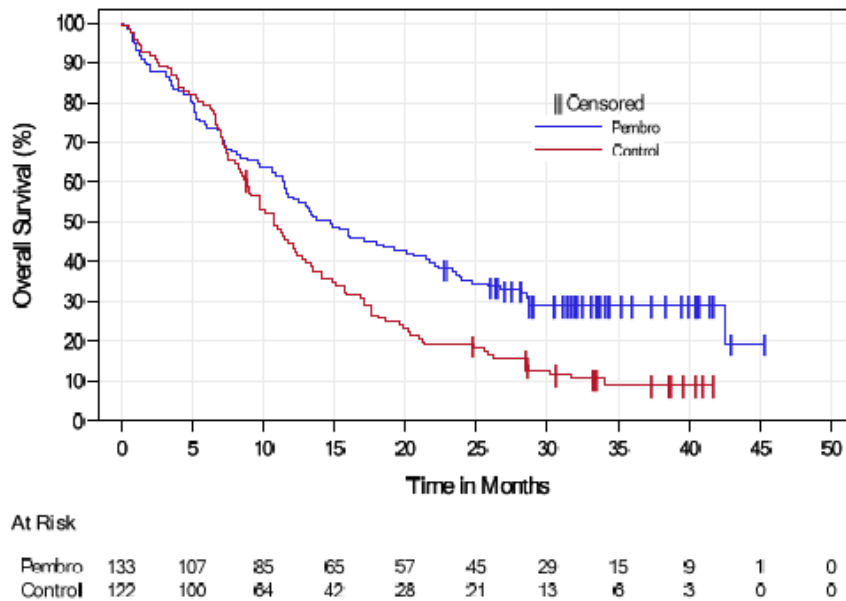Source: Figure 2.5-1, p70 of the resubmission

**Figure 6** Kaplan Meier estimates of overall survival for pembrolizumab monotherapy in KN048 CPS ≥20 (updated with 12 months additional follow up)

Source: Figure 11-27, p260 of the KN048 CSR (v02)

The OS HR reported in the resubmission for the ITT population for both pembrolizumab plus chemotherapy and pembrolizumab monotherapy in KN048 at four years were similar in magnitude to the OS HR reported at three years in the previous submission. Compared to patients treated with cetuximab plus chemotherapy, the risk of death in patients treated with pembrolizumab plus chemotherapy was statistically significantly lower in both the ITT population and CPS ≥1 population but not in the CPS <1 population. The difference in OS between patients treated with pembrolizumab monotherapy was not statistically different to patients treated with cetuximab plus chemotherapy in the ITT population. Comparatively, in the CPS ≥1 population, patients treated with pembrolizumab monotherapy had a statistically significantly lower risk of death compared to patients treated with cetuximab plus chemotherapy.

The resubmission presented a multivariate analysis was conducted adjusting for multiple baseline demographic and disease characteristics for the CPS ≥1 population. For participants receiving pembrolizumab plus chemotherapy, the results from the multivariate analysis showed an OS HR of 0.71 (95% CI: 0.57, 0.88) for the CPS ≥1 population. The resubmission considered that this was consistent with the primary outcome based on Interim Analysis 2 data showing an OS HR of 0.71 (95% CI: 0.57, 0.88). For participants receiving pembrolizumab monotherapy, the results from the multivariate analysis showed an OS HR for the CPS ≥1 population of 0.75 (95% CI: 0.61, 0.93). The resubmission considered that This was consistent with the primary outcome showing an OS HR of 0.78 (95% CI: 0.64, 0.96) for the CPS ≥1 population for Interim Analysis 2.

The commentary noted that the PBAC accepted the claim of superior efficacy for pembrolizumab plus chemotherapy compared to chemotherapy alone in terms of OS in patients with CPS ≥1, but did not accept such a claim for pembrolizumab monotherapy in patients with CPS ≥1. (paragraphs 7.5 and 7.6, pembrolizumab PSD, November 2020 PBAC Meeting). The commentary considered that while this decision was made on the basis of the indirect comparison of KN048 with EXTREME instead of the results of KN048 only as

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presented in the resubmission, given that the OS HR in the indirect comparison in the previous submission (Bucher indirect OS HR = 0.59, 95% CI: 0.44, 0.79) was more favourable towards pembrolizumab monotherapy than in the current resubmission (OS HR = 0.74, 95%C 0.61, 0.90) in patients with CPS ≥1, it may be argued that the resubmission has not provided any further data to demonstrate that pembrolizumab monotherapy was superior in efficacy with regards to OS to SoC in patients with CPS ≥1.

The commentary highlighted that PBAC has previously noted that the benefit of pembrolizumab monotherapy was likely driven by the CPS≥20 population and that the It was also acknowledged (paragraph 7.9, pembrolizumab PSD, November 2020 PBAC Meeting) that the CPS <1 subgroup in KN048 was too small to conclude that pembrolizumab plus chemotherapy had no effect in this subgroup. Similarly, while the results suggest that patients with CPS <1 treated with pembrolizumab monotherapy had a potentially statistically significantly higher risk of death compared to patients treated with cetuximab plus chemotherapy at three years (OS HR = 1.72, 95%CI 1.06, 2.79), the commentary considered the small number of patients in the subgroup may increase the uncertainty of the conclusion.

The pre-ESC response considered restricting pembrolizumab monotherapy to the CPS ≥20 population and would address residual concerns and major barriers related to codependency and allow pembrolizumab monotherapy to be available to the CPS ≥20 population where it provides the greatest benefit. The pre-ESC response provided the following arguments for updating the population eligible for pembrolizumab monotherapy from CPS ≥1 to CPS ≥20 for monotherapy:

- Pembrolizumab monotherapy provides a 40% reduction in death compared to cetuximab + chemotherapy following by 2L nivolumab in 26% of patients and a superior side effect profile (21% absolute reduction in grade 3-5 AEs);

- The tests for interaction at CPS ≥20 for pembrolizumab monotherapy and at CPS ≥1 for pembrolizumab + chemotherapy have demonstrated a statistically significant treatment effect modification, indicative of a predictive effect of PD-L1. The pre-ESC response claimed that this is a more robust evidence base than that presented by prior PD-L1 applications in NSCLC (1440.1) and triple negative breast cancer (1570) that MSAC either approved or was of a mind to approve; and

- The approach was supported by key oncology organisations:

  o The ESMO-MCBS score for the CPS≥20 population was higher than the CPS ≥1 population (5 vs 4) (paragraphs 7.2, and 7.5, pembrolizumab PSD, November 2020 PBAC meeting).
  o The CPS≥ 20 population is included in the NCCN® guidelines (Version 3.2021, p116) as "Category 1" (uniform consensus that this intervention is appropriate).

The pre-ESC response further clarified that whilst the NCCN guidelines "recommend first-line pembrolizumab plus chemotherapy regardless of PD-L1", this recommendation is relevant for the USA where the FDA recommended pembrolizumab + chemotherapy for allcomers based on KN048 interim analysis 2, rather than the final analysis, which was reviewed by the TGA and EMA and resulted in the approval of pembrolizumab + chemotherapy for CPS ≥1.

The clinical claims made by the resubmission were similar to the previous submission with the exception that the safety claim for pembrolizumab plus chemotherapy has changed from similar in safety to chemotherapy to a claim of inferiority.

*Intratumoural concordance*

Three new studies that investigated the 22C3 antibody in PD-L1 testing and intratumoural concordance were presented in the resubmission (Tzoraleftheraki 2020, Kalpakoff 2021 and De Ruiter 2020). Tzoraleftheraki 2020 demonstrated a low level of heterogeneity (9.6%) when assessing the rate of PD-L1 positivity across tumour cores and margins in 228 samples. While de Ruiter 2020 showed moderate to good intratumoural concordance for the 22C3 pharmDx assay and the 22C3 laboratory developed test (LDT) across 147 head and neck tumour specimens, the LDT protocol was developed using the SP263 assay rather than the 22C3 assay, and hence the resubmission (p 171) stated that the LDT was more concordant with the SP263 assay rather than 22C3 assay. The resubmission suggested that an alternative LDT as used in Vainer 2019, which used a 22C3 LDT on the BenchMark XT platform and whole slides, should be used in Australia therefore the concordance from de Ruiter 2020 was not considered applicable to the current resubmission. Kalpakoff 2021 showed high overall agreement in terms of intra-block and intra-case concordance with overall agreements of 97.1% and 100% respectively, though there was a lower concordance between primary and metastatic tissues (88.9%). The resubmission (p186) concluded that based on the available evidence, there is a low to moderate level of intratumour heterogeneity using the 22C3 antibody.

Rasmussen 2019 was presented in the previous submission and examined intratumor heterogeneity of PD-L1 expression in HNSCC. The study used 33 whole surgical specimens from 28 patients with HNSCC. Concordance of PD-L1 expression was assessed in six random core biopsies from each surgical specimen using plat form Autostainer Link 48 and the 28-8 antibody. Rasmussen 2019 reported that no lesions were true negative with a CPS threshold of 1 (Figure 7).
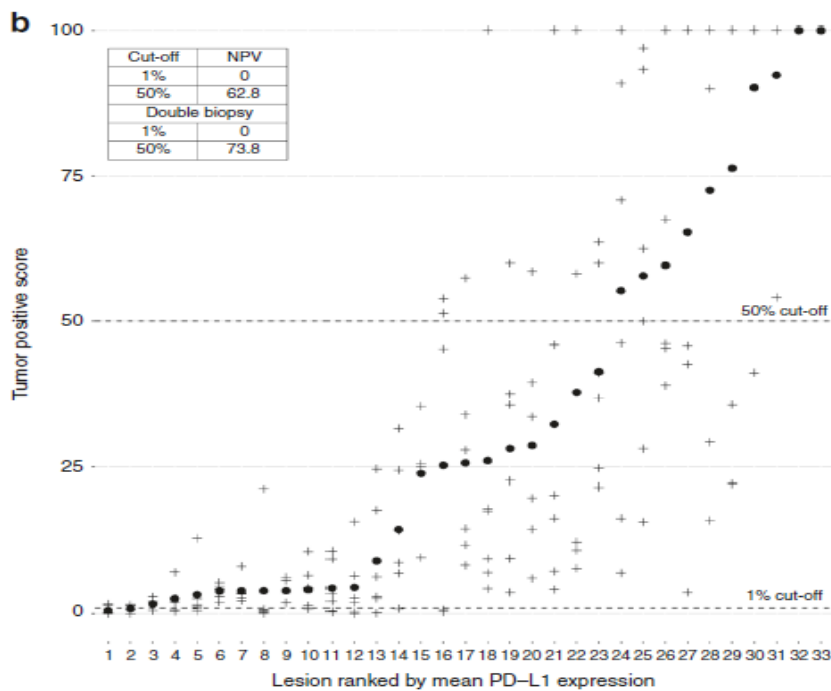
**Figure 7       PD-L1 expression with combined positive score (CPS)**
Note: The y-axis depicts the PD-L1 score from 100%. The x-axis depicts the 33 lesions ranked by mean PD-L1 score.
Source: Figure 2b, Rasmussen 2019

*Histology versus cytology*

One new study (Kandel 2021) was identified that compared histology versus cytology samples from pathology files of 31 patients using FNA cell blocks and matching resections of HNSCCs. Kandel 2021 found that cytology samples did not reliably give similar PD-L1 scoring results as core biopsies or resections. Hence, the resubmission (p190) stated that PD-L1 testing should not be done on cytological samples and that in practice, clinical experts have indicated that cytology is rarely done for this tumour type. The commentary considered that this was consistent with MSAC's previous advice that FNA would not be appropriate for CPS testing because CPS testing requires staining of adjacent immune cells which may not be appropriately captured in an FNA.

*Antibody concordance*

The updated literature search for antibody concordance identified one new study, Crosta 2021. This study used 15 histologic samples from surgical resections of HNSCCs to compare CPS of PD-L1 using alternative methods adopted in routine clinical practice to determine the level of diagnostic agreement and inter-observer reliability (Table 7). Crosta 2021 indicated that, for CPS, the 22C3 pharmDx kit was not strongly concordant with the SP263 antibody, reporting a 96% sensitivity and 50% specificity for the SP263 antibody on the Ventana Benchmark compared to the 22C3 pharmDx, with 86% concordance for positive or negative classifications. Crosta 2021 reported a sensitivity of 88% and specificity of 83%, when comparing the 22C3 on the Ventana platform with the 22C3 kit using tissue microarrays, which were considered to be more susceptible to variability compared to whole slides, and as such the resubmission maintained that the LDT as used in Vainer 2019 which used a 22C3 LDT on the BenchMark XT platform and whole slides, should be used in Australia therefore the concordance from Crosta 2021 was not considered applicable to the current resubmission.

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Based on these results, the resubmission proposed that the MBS item number for testing should be specific to the 22C3 antibody.

**Table 7  CPS extended results from Crosta 2011**

| N | Protocol 1 | Protocol 2* | Protocol 3 | Protocol 4 | Protocol 5 | GS |
|---|---|---|---|---|---|---|
| 1 | 90 | >20 | 80 | 100 | 100 | 100 |
| 2 | ne | ne | ne | ne | ne | ne |
| 3 | 0 | 1–20 | 0 | 1 | 0 | 3 |
| 4 | 0 | <1 | 0 | 0 | ne | 0 |
| 5 | 15 | >20 | 35 | 82 | 40 | 19 |
| 6 | ne | ne | ne | ne | ne | 0 |
| 7 | ne | <1 | ne | ne | 0 | 0 |
| 8 | 60 | >20 | 10 | 26 | 50 | 40 |
| 9 | 50 | >20 | 30 | 14 | 60 | 25 |
| 10 | 80 | 1–20 | 15 | 4 | 5 | 25 |
| 11 | ne | ne | ne | ne | ne | 0 |
| 12 | 80 | >20 | 70 | 100 | 100 | 90 |
| 13 | 5 | 1–20 | 1,5 | 2,5 | 0 | 1–20 |
| 14 | 10 | 1–20 | 8,5 | 10 | 5 | >20 |
| 15 | 15 | >20 | 12,5 | 12,5 | 15 | >20 |
| 16 | 10 | >20 | 11,5 | 12,5 | 25 | 15 |
| 17 | 0 | <1 | 0 | 0 | 0 | 0 |
| 18 | 0 | <1 | 0 | 1 | 0 | 0 |
| 19 | ne | ne | ne | ne | ne | ne |
| 20 | 0 | <1 | 5 | 8 | 0 | 10 |
| 21 | ne | <1 | ne | ne | ne | 0 |
| 22 | 70 | >20 | 80 | 100 | 100 | 100 |
| 23 | 2 | 1–20 | 0 | 0 | 0 | 8 |
| 24 | 10 | <1 | 70 | 100 | 95 | 0 |
| 25 | 85 | >20 | 80 | 100 | 100 | >20 |
| 26 | ne | ne | ne | ne | ne | >20 |
| 27 | ne | ne | ne | ne | ne | ne |
| 28 | 60 | >20 | 45 | 60 | 75 | >20 |
| 29 | 5 | 1–20 | 4 | 20 | 3 | 15 |
| 30 | 10 | 1–20 | 3 | 5 | 1 | 5 |
| 31 | ne | ne | ne | ne | 0 | 1–20 |
| 32 | 18 | >20 | 30 | 30 | 100 | >20 |
| 33 | 5 | >20 | 4 | 60 | 20 | >20 |
| 34 | 0 | 1–20 | 0 | 6 | 7 | >20 |
| 35 | 2 | <1 | 2 | 12 | 3 | 15 |
| 36 | 5 | 1–20 | 9 | 13 | 20 | >20 |
| 37 | 0 | ne | 0 | 0 | 0 | 0 |
| 38 | 0 | ne | 0 | 15 | 0 | 0 |
| 39 | 0 | <1 | 3 | 30 | 1 | ne |
| 40 | 15 | 1–20 | 0 | 2 | 0 | 10 |

*Sensitivity and specificity of 22C3 assay*

No reference standard for PD-L1 testing in R/M HNSCC is available. However, as presented in both the resubmission and the previous submission, two studies (Emancipator 2020 and Cohen 2019) evaluated the sensitivity and specificity of the pharmDx 22C3 antibody in clinical trials (Keynote-012, n=297 and Keynote-055, n=172) using response rate as the reference standard to provide information on the sensitivity and specificity in the context of clinical utility. The results from Emancipator 2020 and Cohen 2019 are presented in Table 8 to Table 10.

**Table 8        Summary of sensitivity/specificity results of the pharmDx 22C3 assay**

| Cut off | Emancipator 2020 | | | Cohen 2019 | | |
|---|---|---|---|---|---|---|
| | Sensitivity (%) | Specificity (%) | Prevalence (N=252) | Sensitivity (%) | Specificity (%) | Prevalence (N=244) |
| CPS ≥1 | 92.2 | 18.9 | NR (83.3%) | 94 | 23 | 195 (80%) |
| CPS ≥20 | 66.7 | 54.2 | NR (50.0%) | 58 | 64 | 96 (39%) |
| CPS ≥50 | 43.1 | 74.1 | NR (29.4%) | 50 | 78 | 64 (26%) |
| TPS ≥1% | 74.5 | 32.3 | NR (69.0%) | 64 | 44 | 140 (57%) |
| TPS ≥20% | 62.7 | 59.2 | NR (45.2%) | 56 | 64 | 94 (39%) |
| TPS ≥50% | 41.2 | 75.6 | NR (27.8%) | 47 | 77 | 65 (27%) |

Source: Table 2.14-5, p170 of the resubmission, Emancipator 2020 and Cohen 2019

Results of the pharmDx 22C3 assay versus response rate for Emancipator 2020 and Cohen 2019 were reconstructed in the commentary to the previous submission (Tables 2B.6.2 and 2B.6.3). "The Commentary estimated that 20.3% and 17.4% of the total population responded to pembrolizumab in Emancipator 2020 and Cohen 2019, respectively. MSAC agreed with the commentary that this indicated there was a poor correlation between the proposed PD-L1 CPS positivity threshold and extent of response to pembrolizumab" (p3, application no. 1522 PSD, November 2020 MSAC Meeting).

**Table 9        Reconstructed results of pharmDx 22C3 assay versus response rate in Emancipator 2020**

| | Reference | | |
|---|---|---|---|
| CPS | Positive | Negative | Total |
| Positive | 18.7 | 64.6 | 83.3 |
| Negative | 1.6 | 15.1 | 16.7 |
| Total | 20.3 | 79.7 | |

Source: Table 2B.6.2, p109 of first commentary, pembrolizumab 6.08 November 2020

**Table 10        Reconstructed results of pharmDx 22C3 assay versus response rate in Cohen 2019**

| | Reference | | |
|---|---|---|---|
| CPS | Positive | Negative | Total |
| Positive | 16.4 | 63.6 | 80 |
| Negative | 1.0 | 19.0 | 20 |
| Total | 17.4 | 82.6 | |

Source: Table 2B.6.3, p109 of first commentary, pembrolizumab 6.08 November 2020

Following the previous submission "MSAC noted that there is no reference standard for the clinical validity of PD-L1 testing… MSAC noted the high sensitivity and low specificity reported for the test at the threshold of CPS ≥1, and agreed with the ESCs and the Commentary that the apparently high sensitivity might be due to the test classifying over 80% of patients as being CPS ≥1 rather than the test accurately identifying patients who will respond to pembrolizumab." (p3, application no. 1522 PSD, November 2020 MSAC Meeting)

The resubmission (p166) appeared to agree with the comments of MSAC, noting that "at the CPS ≥1 cut-point the test will capture the broadest pool of patients likely to respond to pembrolizumab due to the high prevalence at this cut point. In this way PD-L1, whether scored by TPS or CPS, is an enrichment biomarker, which aims to enrich the population with patients more likely to benefit from pembrolizumab treatment. This is distinct from driver mutation biomarkers such as *EGFR* which are highly predictive of a clinical benefit in response to tyrosine kinase inhibitors in patients with specific driver mutations."

The resubmission (p166) claimed that in MSAC's April 2020 consideration of Application 1570 for PD-L1 testing for access to atezolizumab in triple negative breast cancer does not comment on the sensitivity or specificity. The resubmission considered that this was an

inconsistency in the assessment of the PD-L1 biomarker. The commentary considered that this may not be an appropriate conclusion, as MSAC's assessment of testing and decision to support extends beyond sensitivity and/or specificity. The commentary considered there were numerous differences between the two considerations (but not limited to): different cancers being considered and associated biological plausibility of the PD-L1 measurement, different alternative treatment pathways and potential sequelae for false positives, and different trial designs and alignment to requested listing and PD-L1 threshold. The concordance of different PD-L1 assays as well as all the reasons behind MSAC's considerations for PD-L1 testing for access to atezolizumab in triple negative breast cancer were discussed in MSAC's consideration of Application 1570.

The commentary considered that there remains concerns around the low specificity of CPS at detecting responders, uncertainty around whether prior treatment could affect PD-L1 expression (which may confound the correlation between OS and PD-L1 expression), uncertainty around effect of disease progression on PD-L1 expression and intratumour heterogeneity potentially affecting the rate of false results (both positive and negative). The commentary considered that false positive results beyond the unnecessary economic costs, may have negative consequences for patients and false negative results would result in foregone clinical benefits in misclassified patients.

*Prevalence*

The resubmission adopted the proportion of patients with CPS ≥1 of 80% in line the PBAC comments for the original submission (paragraph 6.78, pembrolizumab PSD, November 2020 PBAC Meeting). This figure is lower than proposed in the original submission which estimated the prevalence of CPS ≥1 in patients with R/M HNSCC, specifically of the oral cavity, pharynx or larynx, to be around 85.3% based on the proportion of patients in KN048. The proportions of patients with PD-L1 CPS ≥1 or ≥20 from studies presented in the resubmission are presented in Table 11.

Table 11    PD-L1 prevalence in KN048, Emancipator (2020) and Cohen (2019)

| | KN048 | | | | | Other studies | |
| --- | --- | --- | --- | --- | --- | --- | --- |
| | Pembro +chemo n (%) | Pembo mono n (%) | Chemo [a] n (%) | Total n (%) | Australian participants n (%) | Emancipator (2020) [b] | Cohen (2019) [c] |
| N | 281 | 301 | 300 | 882 | 64 | 252 | 244 |
| CPS ≥1 | 242 (86.1%) | 257 (85.4%) | 255 (85.0%) | 754 (85.5%) | 52 (81.3%) | NR (83.3%) | 195 (80%) |
| CPS ≥20 | 126 (44.8%) | 133 (44.2%) | 122 (40.7%) | 381 (43.2%) | Not reported | NR (50.0%) | 96 (39%) |

Source: Table 10-9, p137 and Table 10-15, p148 of the KN048 clinical study report, Table 2.7-3, p131 of the resubmission; and calculated by the Department

[a] Full chemotherapy group as reported in Table 10-15. 22 participants in the chemotherapy arm excluded in the comparison with pembrolizumab + chemotherapy due to an enrolment pause in the pembrolizumab plus chemotherapy group

[b] R/M HNSCC patients after failure of platinum-based therapy (Keynote 012 and Keynote 055) using 22C3 PharmDx test.

[c] R/M HNSCC patients after failure of platinum-based therapy (Keynote 040) using 22C3 PharmDx test

*Change in management in practice*

The resubmission (p198) stated that if a patient tests positive for PD-L1 CPS ≥1 it was expected that in the vast majority of cases, clinicians would prescribe pembrolizumab monotherapy or pembrolizumab plus chemotherapy. The only instances where a pembrolizumab-containing regimen would not be prescribed would relate to the regimen being contraindicated for a particular patient (e.g. those with severe autoimmune disease or who have had a heart and lung transplant).

The following updates were made to the clinical management algorithms in the resubmission:

- The proportion of patients expected to test positive for PD-L1 CPS ≥1 who will then be prescribed pembrolizumab monotherapy or pembrolizumab plus chemotherapy was split 80:20 in the original submission. This has been changed to 60% use of pembrolizumab monotherapy and 40% pembrolizumab plus chemotherapy. The PBAC previously considered that the weighting of 80% of use of pembrolizumab monotherapy and 20% of use of pembrolizumab plus chemotherapy used in the original submission was not reasonable given that the combination appeared to be more effective in terms of OS (paragraph 7.13, pembrolizumab PSD, November 2020 PBAC Meeting);

- The future clinical management algorithm was updated to include core biopsy or excisional tissue if possible, which was aligned with the tissue types used in KN048. This incorporated MSAC's comments regarding the inappropriateness of the use of FNA for CPS testing. i.e. The 22C3 antibody has not been validated for use with FNA and FNA would not be appropriate for CPS testing because CPS testing requires staining of adjacent immune cells which may not be appropriately captured in a FNA (p4, application no. 1522 PSD, November 2020 MSAC Meeting).

In order to provide the test in Australia, MSAC considered necessary a mechanism to train pathologists on the interpretation of PD-L1 CPS testing in HNSCC and validation of their competency is required. MSAC noted advice from the National Pathology Accreditation Advisory Council (NPAAC) that PD-L1 CPS testing requires a robust quality assurance framework and few laboratories are currently performing this test (p4, application no. 1522 PSD, November 2020 MSAC Meeting).

The resubmission provided details of the applicant-run training program for PD-L1 testing in Australia. Four pathologists have been trained as trainers in PD-L1 testing for R/M HNSCC having undertaken the TARGOS PD-L1 (22C3) Advanced Professional Expert Course HNSCC for trainer and these trainers training 22 pathologists (20 Australians; 2 New Zealanders) using the TARGOS PD-L1 (22C3) Professional Expert Course in HNSCC. By the end of 2021 the applicant plans to have supported training of pathologists at all major HNSCC treatment centres by training an additional 48 pathologists in 2021, with this likely to cover the majority of pathologists who will encounter HNSCC PD-L1 testing.

Participants in both the Advanced Professional Expert and Professional Expert training courses were required to obtain a CPS concordance of at least 85% to pass when assessing 20 cases. CPS scoring results for 22 participants from the Professional Expert course were provided in the resubmission. The commentary noted that among the 22 participants, 13 out of 20 samples were perfectly concordant. For two of the cases (that both had a consensus score of 0), a significant number of course participants provided discordance classification despite their training, and samples with higher consensus scores appeared to have a higher rate of correct answers. As the requested patient population has a cut point of CPS ≥1, the commentary considered there is uncertainty around whether patients with CPS ≥1 can be distinguished from patients with CPS <1 with a high degree of reproducibility.

## 12. Economic evaluation

The basis of the economic evaluation was a cost effectiveness analysis (CEA). The resubmission presented two modelled economic evaluations, separately comparing

pembrolizumab plus chemotherapy with SoC (economic analysis 1 (EA1)), and pembrolizumab monotherapy with SoC (economic analysis 2 (EA2)), in a population of patients with previously untreated R/M HNSCC with CPS ≥1. In both analyses cetuximab plus chemotherapy was used as a proxy for chemotherapy alone and adjustments were made for increased 2L nivolumab use.

Also presented were additional analyses that considered treating all patients irrespective of CPS (scenario analysis 1 (SA1)), and a wholistic model that accounts for the assumed PD-L1 test accuracy (Scenario analyses 2 (SA2)). Incremental cost-effectiveness ratios (cost per quality-adjusted life-year gained [base case] and cost per life-year-saved) were presented for each analysis and a weighted cost-utility estimate was also provided.

There were significant issues with the application of adverse event costs in the resubmission as outlined in Table 12.

Table 12    Application of adverse events associated with chemotherapy in economic model

| Analysis | Pembrolizumab ± chemotherapy | SoC |
|---|---|---|
| EA1 | AE rates were underestimated based on the new clinical claim of inferior safety to SoC. The AE rates from KN048 applied to the pembrolizumab plus chemotherapy arm were lower than the all cause grade 3-4 AEs from EXTREME applied to SoC. | AE rates were overestimated for the SoC arm as the model used all cause grade 3-4 AEs from EXTREME for SoC, whereas KN048 grade 3-5 TRAE which required hospitalisation were applied to the pembrolizumab plus chemotherapy arm. |
| | Duration of treatment was overestimated as chemotherapy treatment was continued past 6 cycles, which resulted in AEs being overestimated. | Duration of treatment was overestimated as treatment related adverse event was applied past six cycles of treatment, which resulted in AEs being overestimated. |
| EA2 | NA | |

AEs = adverse events; TNA = not applicable; RAE = treatment related adverse events; SoC = standard of care
Source: Constructed during evaluation

Based on the reasons in the above table, the commentary made the following adjustments to the base case of the economic evaluation (Table 15).

EA1 and EA2 assumed 100% sensitivity and specificity. The results of EA1, EA2 and the weighted ICER (assuming 60% pembrolizumab monotherapy and 40% pembrolizumab plus chemotherapy) is presented in Table 15. The results of SA2 which assumed a 96% sensitivity and specificity of the PD-L1 test are presented in Table 14. The commentary highlighted that in SA2, the resubmission assumed that any QALY loss in patients who were misclassified would be compensated for by QALY gain in patients with CPS ≥1 who were treated with pembrolizumab on a one to one basis. The commentary concluded that it was unclear if this was a reasonable assumption.

The pre-ESC response presented a new economic model (Table 13). The new economic model could not be fully evaluated. The new economic model incorporated the following changes:
- Patient population for pembrolizumab monotherapy has been restricted to CPS ≥20. This resulted in changes to inputs including OS, progression free survival (PFS) and time on treatment (ToT), as well as the patient characteristics and subsequent treatment data used to inform the model;

- The AE assignment to SoC such that AE costs and utilities were limited to the 18-week duration of chemotherapy. In the resubmission model AE assignment continued beyond the duration of chemotherapy resulting in the base case ICER being underestimated for both economic analysis 1 (EA1 - pembrolizumab plus

chemotherapy versus chemotherapy) and economic analysis 2 (EA2 - pembrolizumab monotherapy versus chemotherapy);

- A reduction of 2L nivolumab use from 50% to 43.7%. This was consistent with calculations presented during the evaluation (paragraph 5.5, PBAC executive summary of the commentary); and

- The effective price of pembrolizumab has been reduced from $redacted to $redacted (-8.9%) for use with chemotherapy and from $redacted to $redacted (-2.0%) for use as monotherapy.

The pre-ESC response's economic model reported an ICER of $55,000 to < $75,000 /QALY for both pembrolizumab plus chemotherapy and pembrolizumab monotherapy.

The pre-ESC response contended that the economic model only explores the potential discordance between the 22C3 Pharm Dx Kit and the 22C3 lab developed test because:
- the clinical trial data already captures any false positives and false negatives that would occur when using the 22C3 PharmDx kit; and

- 22C3 lab developed test is likely to be used in Australia and has a high level of concordance (96% with Vainer et al, 2019).

The pre-ESC response considered that the impact of this 96% discordance was minimal, increasing the weighted ICER from $55,000 to < $75,000 to $55,000 to < $75,000 /QALY.

The updated economic evaluation in the pre-ESC response also included investigation of diagnostic concordance, assuming 85% sensitivity and specificity. This resulted in an ICER of $55,000 to < $75,000 /QALY in the pembrolizumab + chemotherapy arm, using a threshold of CPS ≥1. This was a decrease from the $55,000 to < $75,000 /QALY reported using the adjusted base case and assuming 85% sensitivity and specificity in the commentary.

**Table 13   Results of the partitioned survival cohort simulation in patients with CPS ≥1 (adjusted base case) [a]**

| Component | Pembrolizumab ± chemotherapy | SoC | Increment |
|---|---|---|---|
| **Resubmission (adjusted base case)** | | | |
| Pembrolizumab plus chemotherapy vs SoC (EA1 - CPS≥ 1) | | | |
| Cost | $redacted | $36,760.39 | $redacted[4] |
| LY | 2.0331 | 1.2153 | 0.8178 |
| QALY | 1.5099 | 0.9111 | 0.5987 |
| | | Incremental cost per LY gained | $redacted [1] |
| | | **Incremental cost per QALY gained** | **$redacted [2]** |
| Pembrolizumab monotherapy vs SoC (EA2 - CPS≥ 1) | | | |
| Cost | $redacted | $33,755.29 | $redacted |
| LY | 1.7935 | 1.3224 | 0.4711 |
| QALY | 1.3463 | 0.9962 | 0.3501 |
| | | Incremental cost per LY gained | $redacted [2] |
| | | **Incremental cost per QALY gained** | **$redacted [3]** |
| Weighted pembrolizumab monotherapy (60%) and pembrolizumab plus chemotherapy (40%) [b] | | | |
| Cost | $redacted | $34,957.33 | $redacted |
| LY | 1.8893 | 1.2796 | 0.6098 |
| QALY | 1.4117 | 0.9622 | 0.4495 |
| | | Weighted incremental cost per LY gained | $redacted [1] |
| | | **Weighted incremental cost per QALY gained** | **$redacted [2]** |
| **Pre-ESC response** | | | |
| Pembrolizumab plus chemotherapy vs SoC (CPS≥ 1) | | | |
| Cost | - | - | $redacted |
| LY | - | - | 0.8258 |
| QALY | - | - | 0.6043 |
| | | Weighted incremental cost per LY gained | $redacted [4] |
| | | **Weighted incremental cost per QALY gained** | **$redacted [2]** |
| Pembrolizumab monotherapy vs SoC (CPS ≥20) | | | |
| Cost | - | - | $redacted |
| LY | - | - | 0.6856 |
| QALY | - | - | 0.5163 |
| | | Weighted incremental cost per LY gained | $redacted [1] |
| | | **Weighted incremental cost per QALY gained** | **$redacted [2]** |

LY = life year, QALY = quality adjusted life year, SoC = standard of care

Text in italics indicate values calculated during the evaluation.

Source: Table MSAC.14, p30 of the commentary and extracted from the pre-ESC response economic model

[a] Changes applied include changing the weekly rate of AEs for SoC arm in EA1 and EA2 to be the same as used for pembrolizumab plus chemotherapy. This addresses the inconsistency with the non-inferior clinical claim for EA2. This approach provides a conservative estimate for EA1 (favouring pembrolizumab) as the resubmission acknowledged that the safety of pembrolizumab plus chemotherapy was inferior to that of SoC but the adverse event rates have been made equal for the two treatment arms. The time on treatment (ToT) for SoC arm in pembrolizumab monotherapy model (EA2) was changed to account for the overestimate in duration of treatment, thereby limiting the duration of chemotherapy treatment to six cycles. This was not done in EA1 as the adverse events from the chemotherapy use should cancel out between treatment arms. Ideally, pembrolizumab and chemotherapy adverse events would be estimated separately in EA1, with chemotherapy related adverse events limited to 18 weeks/six cycles and pembrolizumab related adverse events applied for up to two years/35 cycles (maximum duration of therapy).

*The redacted values correspond to the following ranges:*

[1] *$45,000 to < $55,000*

[2] *$55,000 to < $75,000*

[3] *$75,000 to < $95,00*

[4] *$35,000 to < $45,000*

**Table 14    Scenario Analysis 2 – EA1 and EA2 weighted results (resubmission)**

| Outcome | Incremental cost | Incremental QALY | Treatment weighting* | Incremental cost per QALY gained |
|---|---|---|---|---|
| **EA1 (CPS ≥1; pembrolizumab plus chemotherapy versus SOC)** | $redacted | 0.457 | 40% | $redacted [1] |
| **EA2 (CPS ≥1; pembrolizumab monotherapy versus SOC)** | $redacted | 0.267 | 60% | $redacted [1] |
| **Weighted ICER** | | | | **$redacted**[1] |

CPS = combined positive score; EA = Economic Analysis; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year
Source: Table 3.8-15, p257 of the resubmission
*The redacted values correspond to the following ranges:*
[1] *$55,000 to < $75,000*

The key univariate sensitivity analyses around testing thresholds and accuracy of the test are presented in Table 15. The sensitivity analyses presented in the pre-ESC response are presented in Table 16.

**Table 15    Key sensitivity analyses conducted during evaluation**

| Univariate analyses | Model/ comparison | Incremental costs | Incremental effectiveness (QALY) | Incremental cost-effectiveness ($/QALY) | % change from base case |
|---|---|---|---|---|---|
| **Base case** | **EA1** | $redacted | **0.5987** | **$redacted** [1] | - |
| | **EA2** | $redacted | **0.3501** | **$redacted** [2] | - |
| | **Weighted** | | | **$redacted** [1] | - |
| Patient inclusion threshold CPS ≥20 (base case CPS ≥1) | EA1 | $redacted | 0.7397 | **$redacted** [1] | -3.06% |
| | EA2 | $redacted | 0.5063 | **$redacted** [1] | -13.36% |
| | Weighted | | | **$redacted** [1] | -8.10% |
| No CPS testing in model, all patients treated (base case CPS ≥1) i.e. SA1 | EA1 | $redacted | 0.4002 | **$redacted** [2] | +40.91% |
| | EA2 | $redacted | 0.2401 | **$redacted** [2] | +30.72% |
| | Weighted | | | **$redacted** [2] | +35.80% |
| **Scenario analysis 2 (including PD-L1 test accuracy)** | | | | | |
| **Base case** | **EA1** | $redacted | **0.457** | **$redacted** [1] | - |
| | **EA2** | $redacted | **0.267** | **$redacted** [2] | - |
| | **Weighted** | | | **$redacted** [1] | - |
| Decrease test sensitivity and specificity to 85% (base case 96%) | EA1 | $redacted | 0.395 | **$redacted** [1] | +4.7% |
| | EA2 | $redacted | 0.232 | **$redacted** [2] | +3.7% |
| | Weighted | | | **$redacted** [2] | +4.2% |

CPS = combined positive score; EA = economic analysis; QALY = quality adjusted life year
Source: Constructed during evaluation using Section 3 workbook.xslm
*The redacted values correspond to the following ranges:*
[1] *$55,000 to < $75,000/QALY gained*
[2] *$75,000 to < $95,000*

**Table 16    Key sensitivity analyses presented in the pre-ESC response**

| Univariate analyses | Model/ comparison | Incremental costs | Incremental effectiveness (QALY) | Incremental cost-effectiveness ($/QALY) | % change from base case |
|---|---|---|---|---|---|
| **Base case** | **Chemotherapy** | $redacted | **0.6043** | **$redacted** [1] | - |
| | **Monotherapy** | $redacted | **0.5163** | **$redacted** [1] | - |
| | **Weighted** | | | **$redacted** [1] | - |
| Decrease test sensitivity and specificity to 85% (base case 100%) | Chemotherapy | $redacted | 0.395 | **$redacted** [1] | NR |
| | Monotherapy | $redacted | 0.232 | **$redacted** [1] | NR |
| | Weighted | | | **$redacted** [1] | NR |
| Decrease test sensitivity and specificity to 96% (base case 100%) | Chemotherapy | $redacted | NR | $redacted | NR |
| | Monotherapy | $redacted | NR | $redacted | NR |
| | Weighted | | | **$redacted** [1] | NR |

*The redacted values correspond to the following ranges:*
[1] *$55,000 to < $75,000*

## 13.    Financial/budgetary impacts

The resubmission presented an updated epidemiological approach to estimate the expected cost to the MBS of listing the PD-L1 test. The resubmission simplified the incident population treatment pathways, reducing the number of incident pathways from five to three. The estimated proportion of 2L nivolumab patients and the price of pembrolizumab were also revised.

The estimated use and financial implications are summarised in Table 17. Resubmission erroneously applied the cost of PD-L1 testing only to patients treated with pembrolizumab instead of all patients diagnosed with R/M HNSCC. The number and cost of PD-L1 tests were recalculated in the commentary. The commentary noted that there were several errors in the calculation of the resubmission's financial estimates and as such the results presented differed to the resubmission's estimates.

The pre-ESC response provided updated financial estimates. These could not be fully evaluated. Key changes included:

- Incorporating the updated population for pembrolizumab monotherapy. The updated financial estimates did not incorporate an estimated prevalence of CPS ≥20. Instead an assumption has been made that 40% of all patients who were CPS ≥1 would use pembrolizumab monotherapy.

- Recalculating the eligible prevalent patients using 2-year survival (27%), rather than 5-year survival (5.3%). This increased the pembrolizumab eligible treatment pool from <500 patients to <500 patients.

- Changing the nivolumab administration frequency to 4-weekly for continuing treatment (2-weekly in the resubmission). The pre-ESC response considered that it is extremely unlikely that any clinician would initiate a patient who has just progressed within 6 months of platinum-based chemotherapy, onto a 4-weekly regimen as they have a high risk of progression and would want to see them more frequently.

- Increasing the mean number of pembrolizumab doses from 10.49 to 11.22 to account for 60% of patients using pembrolizumab with chemotherapy).

**Table 17    Estimated use and financial implications**

| Parameter/source | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 | Year 6 |
|---|---|---|---|---|---|---|
| **Resubmission/commentary** | | | | | | |
| Projected HNSCC | redacted [1] | redacted [1] | redacted [1] | redacted [1] | redacted [1] | redacted [1] |
| R/M HNSCC (CPS tests) [a] | redacted [1] | redacted [1] | redacted [1] | redacted [1] | redacted [1] | redacted [1] |
| Cost of CPS testing [a] | $redacted [2] | $redacted [2] | $redacted [2] | $redacted [2] | $redacted [2] | $redacted [2] |
| Pembrolizumab ± chemotherapy administration costs | $redacted [2] | $redacted [2] | $redacted [2] | $redacted [2] | $redacted [2] | $redacted [2] |
| Administration costs offset [b] | $redacted [2] | $redacted [2] | $redacted [2] | $redacted [2] | $redacted [2] | $redacted [2] |
| Net administration cost | $redacted [3] | $redacted [3] | $redacted [3] | $redacted [3] | $redacted [3] | $redacted [3] |
| Net cost to MBS [c] | $redacted [3] | $redacted [3] | $redacted [3] | $redacted [3] | $redacted [3] | $redacted [3] |
| Net cost to PBS/RPBS | $redacted [5] | $redacted [5] | $redacted [5] | $redacted [5] | $redacted [5] | $redacted [5] |
| Net cost to PBS/RPBS/MBS | $redacted [5] | $redacted [5] | $redacted [5] | $redacted [5] | $redacted [5] | $redacted [5] |
| **Pre-ESC response** | | | | | | |
| CPS tests | redacted [1] | redacted [1] | redacted [1] | redacted [1] | redacted [1] | redacted [1] |
| Cost of CPS testing | $redacted [2] | $redacted [2] | $redacted [2] | $redacted [2] | $redacted [2] | $redacted [2] |
| Pembrolizumab ± chemotherapy administration costs | $redacted [2] | $redacted [2] | $redacted [2] | $redacted [2] | $redacted [2] | $redacted [2] |
| Administration costs offset | $redacted [3] | $redacted [3] | $redacted [3] | $redacted [3] | $redacted [3] | $redacted [3] |
| Net administration cost | $redacted [3] | $redacted [3] | $redacted [3] | $redacted [3] | $redacted [3] | $redacted [3] |
| Net cost to MBS [c] | $redacted [3] | $redacted [3] | $redacted [3] | $redacted [3] | $redacted [3] | $redacted [3] |
| Net cost to PBS/RPBS | $redacted [4] | $redacted [5] | $redacted [5] | $redacted [5] | $redacted [5] | $redacted [5] |
| Net cost to PBS/RPBS/MBS | $redacted [4] | $redacted [5] | $redacted [5] | $redacted [5] | $redacted [5] | $redacted [5] |
| **November 2020 submission** | | | | | | |
| Projected SCC | redacted [1] | redacted [1] | redacted [1] | redacted [1] | redacted [1] | redacted [1] |
| R/M HNSCC (CPS tests) | redacted [1] | redacted [1] | redacted [1] | redacted [1] | redacted [1] | redacted [1] |
| Cost of CPS testing | $redacted [2] | $redacted [2] | $redacted [2] | $redacted [2] | $redacted [2] | $redacted [2] |
| Pembrolizumab ± chemotherapy administration costs | $redacted [2] | $redacted [2] | $redacted [2] | $redacted [2] | $redacted [2] | $redacted [2] |
| Administration costs offset | $redacted [2] | $redacted [2] | $redacted [2] | $redacted [2] | $redacted [2] | $redacted [2] |
| Net administration cost | $redacted [3] | $redacted [3] | $redacted [3] | $redacted [3] | $redacted [3] | $redacted [3] |
| Net cost to MBS | $redacted [3] | $redacted [3] | $redacted [3] | $redacted [3] | $redacted [3] | $redacted [3] |

[a]   Resubmission erroneously applied cost of PD-L1 testing only to patients treated with pembrolizumab instead of all patients diagnosed with R/M HNSCC. Number of patients with R/M HNSCC crudely estimated by taking number of patients treated with pembrolizumab divided by the prevalence of CPS ≥1 (80%) and the uptake rate (85%). Cost of CPS testing= $59.60 × number of patients with R/M HNSCC.

[b]   Resubmission erroneously assumed that for each patient treated with pembrolizumab, the offset administration costs would be 26 services per patient for nivolumab and 17.33 services per patient for chemotherapy, which exceeds the number of doses assumed (12.05 for nivolumab and 9.17 for chemotherapy, respectively). This was corrected during evaluation by changing the basis of delivery (cell L254:L255) in Sheet 7 to 'per script' and number of services per script (cell N254) to 1 (cell N255 should remain as 0). This is consistent with the method of estimating injections in the pembrolizumab arm.

[c]   PD-L1 test and cost of administration for pembrolizumab minus cost of SoC administration

Source: Table MSAC.19, p32 of the commentary; Tables 4.3.1 to 4.4.1, pp222-223 of the commentary; Table MSAC.16, p28 of the previous commentary; and extracted from the pre-ESC response financial estimates spreadsheet.

*The redacted values correspond to the following ranges:*

[1] *500 <5,000*

[2] *$0 to < $10 million*

[3] *Net cost savings*

[4] *$20 million to < $30 million*

[5] *$10 million to < $20 million*

The net cost to the MBS of listing the PD-L1 test was cost saving, as found in the previous submission. Cost of CPS testing was less in the resubmission was lower than in the previous submission due to a lower proportion of patients projected to access PD-L1 testing. The net cost saving to the MBS was lower in the pre-ESC response.

The commentary considered main uncertainty with the financial estimates relate to the estimated usage of chemotherapy and its duration of use, as well the frequency of nivolumab administration and the expected number of doses used which may have resulted in the estimated cost offsets being overestimated in the resubmission. MBS item 13950 for chemotherapy administration is for parenteral administration of one or more antineoplastic agents for one or more episodes of administration. The explanatory notes state that whilst it is not expected that there would be multiple claims for item 13950 on the one day, there are clinical instances where this might occur. In these circumstances, the medical practitioner will need to assure themselves that these instances represent separate and distinctly relevant services.

The commentary highlighted that the financial estimates applied an administration cost to each prescription of pembrolizumab, cisplatin, carboplatin or 5-FU in pembrolizumab arm. Further, the commentary highlighted that the financial estimates assumed 43.33 (26 for nivolumab, 17.33 for chemotherapies) administrations per patient treated with pembrolizumab would be offset. This was corrected in the commentary to 12.05 for nivolumab and 9.17 for chemotherapy, respectively. The commentary noted this cost offset was applied to all patients rather than 50% of patients estimated to use nivolumab.

The commentary noted that assuming nivolumab was administered every four weeks (as in the previous submission) instead of every two weeks (as in the resubmission) decreased the net savings to MBS by 36%.

## 14.     Key issues from ESCs to MSAC

| ESCs key issue | ESCs advice to MSAC |
|---|---|
| Rationale for codependency | The ESCs considered the rationale for codependency remained weak for PD-L1 expression (CPS ≥1) identifying patients who would benefit differently from pembrolizumab either as monotherapy or in combination with chemotherapy. The resubmission presented tests for interaction to support the predictive value of CPS testing using updated data from the Keynote-048 trial. The ESCs considered the results of the KN048 trial were difficult to interpret and queried their reliability due to the change in PD-L1 measurement (from TPS to CPS), changes to primary and secondary outcomes, updates to the statistical methods, and the complex multiplicity strategy in both the statistical plan and the subsequent analyses. The ESCs considered the pre-ESC response's request to limit pembrolizumab monotherapy to patients with CPS ≥20 did not strengthen the biological basis of the claim of codependency. |
| Variability of PD-L1 classification | The ESCs considered there is uncertainty around whether patients with CPS ≥1 can be distinguished from patients with CPS <1 with a high degree of reproducibility. This was supported by data from the pathologist training program where there was substantial discordance in pathologists' classification of two samples that had a consensus CPS score of zero. There may also be uncertainty around whether patients with CPS ≥20 can be distinguished from patients with CPS <20 with a high degree of reproducibility. The ESCs also noted there may be some heterogeneity of PD-L1 expression between primary tumours and metastases. |
| Pembrolizumab monotherapy limited to CPS ≥20 | The pre-ESC response requested that pembrolizumab monotherapy be limited to patients with CPS ≥ 20. The ESCs considered that there was merit to this approach. The updated economic evaluation and financial estimates included in the pre-ESC response could not be fully evaluated. The revisions to the economic model were complex and would require re-evaluation. |

| CPS test sensitivity in the economic modelling | The economic model assumed PD-L1 CPS testing had 100% sensitivity and specificity. The pre-ESC response claimed that trial data already captures false positives and false negatives that occur using the clinical utility standard. The pre-ESC response considered 96% concordance reflects potential discordance between the 22C3 Pharm Dx Kit and the 22C3 lab developed test likely to be used in Australia. This increased the ICER from $55,000 to < $75,000 to $55,000 to < $75,000/QALY. An additional sensitivity analysis estimated that 85% concordance (consistent with the proposed pathologist training program) would increase the weighted ICER to $55,000 to < $75,000. |
| --- | --- |
| Net costs to MBS | The resubmission estimated net savings to the MBS. The savings were uncertain as they were dependent on the assumptions around comparator treatment administration. |

**ESCs discussion**

The ESCs noted that this is a resubmission requesting Medicare Benefits Schedule (MBS) listing of a test for the evaluation of programmed death ligand 1 (PD-L1) using the combined positive score (CPS) and the 22C3 antibody to determine eligibility for treatment with pembrolizumab in patients with previously untreated recurrent or metastatic (R/M) head and neck squamous cell carcinoma (HNSCC), specifically R/M squamous cell carcinoma (SCC) of the oral cavity, pharynx or larynx. The ESCs advised that SCC of the nasopharynx should be excluded from PD-L1 testing and pembrolizumab treatment as there is limited evidence to support pembrolizumab treatment in this population.

The pre-ESC response updated the MBS item descriptor to specify that tumour material should be from a core biopsy or excision specimen. The ESCs considered that this should a resection specimen rather than an excision specimen.

The resubmission proposed that the test would report a combined positive score (CPS) to help determine eligibility for pembrolizumab (whether as monotherapy or combination therapy) on the Pharmaceutical Benefits Scheme (PBS). The resubmission proposed pembrolizumab treatment patients who also have a PD-L1 CPS ≥1. This was consistent with the Therapeutic Goods Administration (TGA) indication for pembrolizumab.

The ESCs noted that the pre-ESC response proposed further limiting pembrolizumab monotherapy on the PBS to patients with a PD-L1 CPS ≥20 as this would limit subsidy to patients most likely to benefit from pembrolizumab monotherapy. The pre-ESC response considered that this would reduce the risks from false positive (FP) patients using pembrolizumab monotherapy as patients with CPS <1 would not be incorrectly classified as CPS ≥20 and incorrectly classified patients with CPS 1-19 will gain an efficacy benefit that is at least comparable to chemotherapy + cetuximab followed by 2L nivolumab in 26% of patients based on 4-year overall survival data from the Keynote-048 (KN048) trial with fewer side effects. The pre-ESC response considered that this approach was supported by key oncology organisations. This included:
- A European Society for Medical Oncology -Magnitude of Clinical Benefit Scale (ESMO-MCBS) score of 5. The ESCs noted that this is the highest magnitude of clinical benefit for a non-curative therapy; and

- Inclusion of this population in the United States National Comprehensive Cancer Network® (NCCN®), Guidelines as "Category 1" (uniform consensus that this intervention is appropriate).

The ESCs considered that the rationale for limiting pembrolizumab monotherapy to the CPS ≥20 population had merit, this did not strengthen the claim of codependency.

The ESCs noted consumer feedback from Head and Neck Cancer Australia that was supportive of the resubmission. The ESCs considered that consumers would value the option of a potentially better treatment for HNSCC. The ESCs noted feedback from the Royal College of Pathologists of Australasia highlight that imperfect nature of PD-L1 IHC as a predictive biomarker for selecting patients likely to respond to immunotherapy in a range of malignancies. The RCPA acknowledged that there is no clear alternative assay or gold standard and that PD-L1 IHC it is the best test currently available.

The ESCs noted the additional studies presenting prognostic evidence. The ESCs considered noted that two new studies (Li 2017 and Jia 2019) identified during the evaluation presented potentially contradictory conclusions. The ESCs considered that the evidence presented may not be sufficient to conclude that PD-L1 expression has no prognostic impact on OS.

The resubmission presented multivariate analyses examining baseline characteristics in KN048 that were not balanced by CPS subgroups. The ESCs noted the resulting hazard ratios for overall survival were similar. The ESCs considered that this helped partially address the impact of these imbalances which MSAC considered could be independent predictors of variation in prognosis and the extent of effectiveness of pembrolizumab.

The ESCs recalled that MSAC had previously considered the evidence presented did not adequately support the claim of codependency. The ESCs noted that the predictive evidence to support that PD-L1 CPS scoring predicted the treatment effect with pembrolizumab was largely unchanged from the previous submission. The resubmission provided an additional 12 months follow-up from KN048. The ESCs noted that the resubmission addressed several aspects of the KN048 trial conduct that MSAC previously considered did not support the claim of codependency. The resubmission clarified that KN048:

- Remained stratified for TPS ≥50% throughout the trial;

- Was not enriched for TPS ≥50% as the protocol was amended again prior to the enrichment being implemented; and

- The definition of PD-L1 positivity was altered in amendment 5 from TPS to CPS prior to any analysis of results. The resubmission stated that this impacted the primary objectives and statistical plan, but there was no change to stratification.

The resubmission claimed that there was rigorous evidence supporting that CPS, not TPS, predicted treatment effect with pembrolizumab in HNSCC. The ESCs considered that the biological rationale for CPS was not strong.

The ESCs considered that the results of the KN048 trial remained difficult to interpret due to the change in PD-L1 measurement (from TPS to CPS), changes to primary and secondary outcomes, updates to statistical methods, and the complex multiplicity strategy. The ESCs considered these factors reduced the reliability of the results from KN048.

The ESCs noted that additional studies had been presented to address intratumoural concordance. These generally supported a good concordance, however, the ESCs highlighted that concordance may be lower between the primary tumour and metastases.

The resubmission noted the results from pathologist training program and highlighted the commentary's concerns that there was substantial discordance in pathologists' classification of two samples that had a consensus CPS score of zero. The ESCs considered that there is uncertainty around whether patients with CPS ≥1 can be distinguished from patients with

CPS <1 with a high degree of reproducibility. This was supported by data from the pathologist training program where there was substantial discordance in pathologists' classification of two samples that had a consensus CPS score of zero. There may also be uncertainty around whether patients with CPS ≥20 can be distinguished from patients with CPS <20 with a high degree of reproducibility. The ESCs noted advice from NPAAC that a quality assurance program for interpretative proficiency testing may be available this year as part of its 'Head and Neck diagnostic' program, but are awaiting for the applicant's training to take place first which was delayed due to COVID-19.

The ESCs noted that the pre-ESC response provided a revised economic model and financial estimates reflecting the request to limit pembrolizumab monotherapy for patients with CPS ≥20. As these were provided with the pre-ESC response and include numerous changes, they have not been independently evaluated given the timing of their provision. The ESCs noted that the pre-ESC response reaffirmed that concordance between the 22C3 Pharm Dx Kit and the 22C3 lab developed test likely to be used in Australia is high (96%), though not 100% as assumed in the economic model. In the pre-ESC response's economic model, decreasing concordance to 96% increased the weighted ICER from $55,000 to < $75,000 to $55,000 to <$75,000/QALY. An additional sensitivity analysis estimated that 85% concordance would increase the weighted ICER to $55,000 to < $75,000 .

The ESCs considered the pre-ESC response's revised weighting of 60% pembrolizumab combination therapy and 40% as monotherapy to be more appropriate than the weighting used in the previous submission and resubmission, though it remains uncertain given proposed changes to CPS ≥20 for monotherapy. The ESCs noted the following issues may lead to underestimating the ICER:

- The extrapolation of outcomes which appeared to overestimate OS to some degree;

- Overestimation of adverse event costs in the resubmission's base case;

- Inconsistent QALY gain in the SoC arm in monotherapy and combination therapy arms that was not justified in the resubmission. Using the QALY gain in the SoC arm in EA2 to inform EA1 increased the ICER in EA1 by 16%; and

- The OS curves did not converge which was inconsistent with the 2L nivolumab for R/M HNSCC model previously considered by the PBAC.

The ESCs noted that the revised financial estimates did not incorporate the estimated prevalence of CPS ≥20, rather it assumed fewer (40%) of patients with CPS ≥1 would use pembrolizumab monotherapy. The ESCs noted that using the patient demographics in KN048, 43% (257/601) of patients had CPS ≥1 but <20 compared to 85% (512/601) of patients who had CPS ≥1. These ratios indicate that 50.5% of all patients with CPS ≥1 would have CPS <20 (i.e. would not be eligible for pembrolizumab monotherapy). The pre-ESC response's financial estimates also updated the calculation of the eligible population.

The ESCs considered the financial impact to the MBS were uncertain as estimates were dependent on the assumptions around comparator treatment administration. The ESCs noted that MBS costs had increased in the pre-ESC response, resulting in a smaller net saving to the MBS. These were not fully evaluated. The changes appeared to be due to more patients using pembrolizumab with chemotherapy (fewer administration cost offsets for chemotherapy), lower cost offsets for nivolumab administration (shorter duration of nivolumab use and some 4-weekly administration), and changes to chemotherapy use.

## 15. Other significant factors

Nil.

## 16. Applicant comments on MSAC's Public Summary Document

The Sponsor is pleased that MSAC supports the use of the PD-L1 test for access to pembrolizumab for HNSCC.

## 17. Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website: visit the MSAC website