

7.09 PEMBROLIZUMAB

Solution concentrate for I.V. infusion 100 mg in 4 mL

Keytruda®

Merck Sharp & Dohme (Australia) Pty Ltd

1 Purpose of submission

- 1.1 The codependent resubmission requested MBS listing of programmed death ligand 1 (PD-L1) testing and PBS listing of pembrolizumab for the targeted treatment of previously untreated recurrent or metastatic (R/M) head and neck squamous cell carcinoma (HNSCC), specifically of the oral cavity, pharynx and larynx in patients with combined positive score (CPS) ≥ 1 . The first submission was in November 2020.
- 1.2 The requested basis for listing was cost-effectiveness compared with standard of care (SoC). SoC was defined as first-line (1L) carboplatin or cisplatin and 5-fluorouracil (5-FU) (i.e. chemotherapy), followed by second-line (2L) nivolumab in 50% of patients.

Table 1: Key components of the clinical issue addressed by the resubmission

Component	Description
Population	R/M HNSCC patients who have not had prior systemic therapy administered in the recurrent or metastatic setting whose tumours express PD-L1 CPS ≥ 1
Intervention	Pembrolizumab (200 mg IV) every 3 weeks in combination with platinum and 5-FU, OR Pembrolizumab (200 mg IV) every 3 weeks as a single agent
Comparator	Carboplatin (AUC 5 mg/m ²) IV or cisplatin (100 mg/m ²) IV and 5-FU (1000 mg/m ² per day for 4 consecutive days) IV every 3 weeks for six cycles followed by second line nivolumab in a proportion of patients
Outcomes	Overall survival, progression free survival, overall response rate, safety and quality of life.
Clinical claim	The clinical evidence presented demonstrates that: <ul style="list-style-type: none"> In R/M HNSCC patients whose tumours express CPS ≥ 1, pembrolizumab monotherapy has superior efficacy and a superior safety profile compared to standard of care in the Australian setting, i.e. platinum based chemotherapy in 1L, followed by 2L nivolumab in a proportion of patients. In R/M HNSCC patients whose tumours express CPS ≥ 1, pembrolizumab plus chemotherapy has superior efficacy and inferior safety, compared to standard of care in the Australian setting, i.e. platinum based chemotherapy in 1L, followed by 2L nivolumab in a proportion of patients.

5-FU = 5-fluorouracil; CPS = combined positive score; PD-L1 = programmed death ligand 1; R/M HNSCC = relapsing/metastatic head and neck squamous cell carcinoma

Source: Table 1.1-1, p7 of the resubmission. Section 2.8.2 pp135-136 of the resubmission (clinical claim).

- 1.3 The Pre-Sub-Committee Response (PSCR) requested using a CPS cut-off of ≥ 20 for patients treated with pembrolizumab monotherapy, but maintained the CPS ≥ 1 cut-off for combination therapy. The PSCR provided several justifications for this change in patient population:
- As previously noted by the PBAC, in “the CPS ≥ 1 subgroup the benefit of pembrolizumab monotherapy... was potentially being driven by the results from

the CPS ≥ 20 subgroup” (paragraph 7.5, pembrolizumab Public Summary Document (PSD), November 2020 PBAC Meeting).

- Restricting pembrolizumab monotherapy to patients with CPS ≥ 20 would allow use where it potentially provides the greatest benefit.
 - As demonstrated by a $>40\%$ reduction in the risk of death compared to cetuximab + chemotherapy (KN048 4 year OS HR of 0.60 (95% CI 0.46, 0.80), compared with 0.74 (95% CI: 0.61, 0.89) in the CPS ≥ 1 subgroup).
 - An ESMO-MCBS score of 5 for pembrolizumab for the treatment of R/M HNSCC patients with CPS ≥ 20 (paragraph 6.4 pembrolizumab PSD, November 2020 PBAC Meeting).
- The risks related to false positive CPS results in patients being offered pembrolizumab monotherapy are significantly reduced.
- The PSCR acknowledged MSAC’s view that the “codependency between PD-L1 status and the clinical benefit from pembrolizumab differed when it was used as monotherapy compared with its use in combination with chemotherapy” (MSAC 1522.1 PSD, November 2020 MSAC meeting).

1.4 The ESCs noted that it was not clear why this change was not proposed in the resubmission. The PBAC also noted that NCCN guidelines recommend use of pembrolizumab monotherapy in patients with CPS ≥ 20 . The PBAC considered that the requested CPS cut-off of ≥ 20 for patients treated with monotherapy appeared appropriate and addressed its previous concerns regarding the clinical effectiveness for monotherapy in patients with low CPS scores (1-20) and the potential for worse outcomes in patients with false positive CPS results.

1.5 The PBAC also recalled its previous advice that NCCN guidelines recommend first-line pembrolizumab plus chemotherapy regardless of PD-L1 status and the CPS < 1 subgroup in KN048 was too small to conclude that pembrolizumab plus chemotherapy had no effect in this subgroup (paragraph 7.9, pembrolizumab PSD, November 2020 PBAC Meeting). The PSCR stated that the NCCN recommendations reflect use in the USA where the FDA recommended pembrolizumab plus chemotherapy for allcomers (that is, regardless of PD-L1 status) based on KN048 interim analysis 2 (13 Jun 2018 data cut), rather than the final analysis (25 Feb 2019 data cut), which was reviewed by the TGA and EMA and resulted in the approval of pembrolizumab plus chemotherapy for CPS ≥ 1 . The PBAC noted that statistical significance for pembrolizumab plus chemotherapy in the ITT population was demonstrated at IA 2, whereas statistical significance for pembrolizumab plus chemotherapy in the CPS ≥ 1 population was not tested until the final analysis as per the statistical analysis plan. The PBAC noted that the OS HR for pembrolizumab plus chemotherapy in the ITT population at the final analysis (0.72 95%CI: 0.60, 0.87) and four year follow up (0.71 95%CI: 0.59, 0.85) were consistent with the primary outcome based on interim analysis 2 (13 Jun 2018 data cut) data (0.71 95% CI: 0.57, 0.88) and therefore the basis for the NCCN’s recommendation was unchanged. Noting the statistically significant OS benefit in the ITT population of KN048, the PBAC considered that a broad listing for pembrolizumab

plus chemotherapy (irrespective of CPS) would be preferable, to ensure subsidised access for all R/M HNSCC patients who would potentially benefit from treatment with pembrolizumab.

- 1.6 The PBAC noted that advice from the MSAC was required regarding the testing component of the codependent submission. Subject to this advice, the PBAC expressed a preference for recommending the CPS ≥ 20 threshold for pembrolizumab monotherapy and an allcomers population for pembrolizumab plus chemotherapy. In particular, the PBAC requested that MSAC provide advice on:
- (1) The practical reasons for any reduced confidence in the results of PD-L1 testing using a CPS threshold of ≥ 1 compared to higher thresholds or no threshold at all.
 - (2) 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 potentially detrimental consequences are minimised in the population receiving pembrolizumab monotherapy?
 - (3) 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 ?
- 1.7 The resubmission estimated that approximately 40% of the eligible treated patients would receive pembrolizumab in combination with platinum and 5-FU (pembrolizumab plus chemotherapy), with the remaining 60% receiving pembrolizumab monotherapy based on input from key scientific leaders. The PBAC previously considered that the proposed weighting in the previous submission (80% use of pembrolizumab monotherapy and 20% of use of pembrolizumab plus chemotherapy) 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).
- 1.8 The ESCs noted that the proposed higher CPS threshold for monotherapy would reduce the number of patients eligible for treatment with pembrolizumab monotherapy and would therefore impact on the relative proportions of patients treated with monotherapy or combination therapy. The ESCs noted that the financial estimates provided with the PSCR assumed 40% monotherapy and 60% combination therapy and considered that this split appeared more reasonable than the split assumed in the resubmission but was not clearly justified. The PBAC considered if PBS listings were to include a CPS ≥ 20 threshold for pembrolizumab monotherapy and CPS ≥ 1 threshold for pembrolizumab plus chemotherapy the proportion of patients treated with monotherapy would be around 40%. However the PBAC considered with a CPS ≥ 20 threshold for pembrolizumab monotherapy and an allcomers listing for pembrolizumab plus chemotherapy, the proportion of patients treated with monotherapy would be expected to be reduced to around 30%. This takes into

consideration the proportion of patients expected to have CPS <20 (56% as per monotherapy population in KN048) who would only be eligible for combination therapy and also the proportion of patients who would be expected to receive combination treatment with chemotherapy for other clinical reasons, e.g. where a more rapid response to treatment is needed.

- 1.9 The resubmission proposed that PD-L1 testing will become a part of the diagnostic workup in patients with newly diagnosed metastatic disease. Patients whose disease has recurred and who are not suitable for local treatment are currently re-biopsied as part of standard treatment. Once PD-L1 status is confirmed pembrolizumab may be considered as a treatment option. The PBAC noted that if the combination treatment listing was for an allcomers population PD-L1 testing may not be required for access to treatment in combination with chemotherapy but may still be considered informative for clinical decision-making.

2 Requested listing

- 2.1 The requested listing with the Secretariat’s suggested amendments in italics and strikethrough is shown below.

Proposed PBS Listing

Name, Restriction, Manner of administration and form	Max. Amount	No. of Rpts	Dispensed Price for Max. Amount	Proprietary Name and Manufacturer
Pembrolizumab 100 mg/4 mL injection, 4 mL vial	200mg	6	Published \$7,880.98 (private) \$7,733.28 (public) Effective (SPA) ^a \$ [REDACTED] (private) \$ [REDACTED] (public)	Keytruda MK

Restriction Summary [new] / Treatment of Concept: [new]	
	Category / Program: Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals (Related Benefits)
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
	Restriction type: <input checked="" type="checkbox"/> Authority Required (STREAMLINED) [new/]
	Administrative Advice: No increase in the maximum quantity or number of units may be authorised.
	Administrative Advice: No increase in the maximum number of repeats may be authorised.
	Administrative Advice: Special Pricing Arrangements apply
	Administrative Advice: Patient should be treated with the recommended dose of pembrolizumab according to the TGA-approved Product Information.
	Indication: Recurrent or metastatic squamous cell carcinoma of the oral cavity, pharynx or larynx
	Treatment Phase: Initial treatment

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	Clinical criteria:
	The condition must be incurable by local therapies in the locally advanced setting
	AND
	Patient must not have had systemic therapy for this condition in the recurrent or metastatic setting prior to initiating PBS-subsidised treatment with this drug for this condition
	AND
	Patient must not have <i>experienced disease</i> recurrence within 6 months of <i>completion of systemic therapy if previously treated</i> in the locally advanced setting
	AND
	Patient must have had a WHO performance status of 0 or 1
	AND
	The treatment must be administered as a single agent (monotherapy); or
	The treatment must be commenced in combination with platinum-based chemotherapy
	AND
	The condition must express programmed cell death ligand 1 (PD-L1) with a combined positive score (CPS) ≥ 1 in the tumour sample
	AND
	Clinical criteria:
	The treatment must not exceed a total of 7 doses under this restriction
	Administrative Advice: In the first few months after start of immunotherapy, some patients can have a transient tumour flare with subsequent disease response. When progression is suspected, this should be confirmed through a confirmatory scan, taken at least 4 weeks later.
Restriction Summary [new] / Treatment of Concept: [new]	
	Treatment Phase: Continuing treatment
	Clinical criteria:
	Patient must have previously received PBS-subsidised treatment with this drug for this condition
	AND
	Clinical criteria:
	Patient must not have developed disease progression while being treated with this drug for this condition
	AND
	Clinical criteria:
	The treatment must not exceed a total of 35 cycles in a lifetime or up to 24 months of treatment under this restriction
Restriction Summary [new] / Treatment of Concept: [new]	
	Treatment Phase: Transitioning from non-PBS to PBS-subsidised supply - Grandfather arrangements
	Clinical criteria:
	Patient must have previously received non-PBS subsidised treatment with this drug for this condition in the recurrent/metastatic setting prior to [listing date]
	AND
	Patient must not have received prior PBS-subsidised treatment with a programmed cell death 1 (PD-1) inhibitor or a programmed cell death ligand 1 (PD-L1) inhibitor for this condition
	AND
	Patient must not have had systemic therapy for this condition in the recurrent or metastatic setting prior to initiating non PBS-subsidised treatment with this drug for this condition;
	AND

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	Patient must not have experienced disease recurrence within 6 months of completion of systemic therapy if treated in the locally advanced setting prior to non-PBS subsidised treatment with this drug for this condition
	AND
	The treatment must be administered as a single agent (monotherapy); or The treatment must be commenced in combination with platinum-based chemotherapy
	AND
	The condition must express programmed cell death ligand 1 (PD-L1) with a combined positive score (CPS) ≥ 1 in the tumour sample
	AND
	Clinical criteria:
	Patient must not have developed disease progression while being treated with this drug for this condition
	AND
	Clinical criteria:
	Patient must have had a WHO performance status of 0 or 1 prior to initiation of non-PBS-subsidised treatment with this drug for this condition
	AND
	The patient must not have evidence of recurrence
	Clinical criteria:
	The treatment must not exceed a total of 35 cycles, or up to 24 months, of combined non-PBS subsidised and PBS-subsidised treatment under the grandfather and continuing treatment restrictions in a lifetime or up to 24 months of treatment under this restriction
	Administrative Advice: In the first few months after start of immunotherapy, some patients can have a transient tumour flare with subsequent disease response. When progression is suspected, this should be confirmed through a confirmatory scan, taken at least 4 weeks later.
	Administrative Advice: This grandfather restriction will cease to operate from 12 months after the date specified in the clinical criteria.
	Administrative Advice: A patient may only qualify for PBS-subsidised treatment under this restriction once.
	Administrative Advice: Following completion of the initial PBS subsidised course, further applications for treatment will be assessed under the continuing treatment restriction.

^a The resubmission proposed two separate prices for pembrolizumab in the economic model depending on the treatment regimen and assumed a 60:40 use of pembrolizumab monotherapy to combination therapy. The price applied for pembrolizumab monotherapy was \$ [redacted]/100mg (\$ [redacted]/200mg) and the price applied for pembrolizumab when used with chemotherapy was \$ [redacted]/100mg (\$ [redacted]/200mg).

Source: p7 of the resubmission

- 2.2 The recommended dose of pembrolizumab is 200 mg administered as an infusion over 30 minutes every 3 weeks, up to a maximum of 35 doses (equivalent to 2 years of continuous treatment).
- 2.3 The resubmission proposed an effective DPMA of \$ [redacted] (private hospital) and \$ [redacted] (public hospital) for 200 mg of pembrolizumab. The resubmission proposed two separate prices for pembrolizumab in the economic model depending on the regimen. The weighted effective DPMA (assuming 40.79% public hospital use) applied for pembrolizumab monotherapy was \$ [redacted]/200 mg (revised to \$ [redacted]/200 mg in the PSCR) and the price applied for pembrolizumab when used with chemotherapy was \$ [redacted]/200 mg (revised to \$ [redacted]/200 mg in the PSCR). The ESCs noted that the revised weighted price for pembrolizumab was unclear as the revised CPS cut-off for monotherapy would affect the relative proportions of monotherapy and combination therapy (see also paragraph 1.8). The pre-PBAC

response revised the price for pembrolizumab to an AEMP of \$ [REDACTED]/100 mg, (weighted public/private DPMA \$ [REDACTED]) for both monotherapy and combination therapy.

- 2.4 While the requested PBS restriction limits use to patients with R/M HNSCC of the oral cavity, pharynx and larynx, the TGA indication does not restrict use to these locations (i.e. may include nasopharynx). The PBAC previously observed that it was unclear whether the requested restriction was sufficient to exclude nasopharyngeal carcinomas (which were excluded in the KN048 trial) as the nasopharynx is part of the pharynx. The previous submission argued that clinicians were unlikely to treat patients with nasopharyngeal SCC with pembrolizumab due to its distinct disease aetiology (paragraph 2.5, pembrolizumab PSD, November 2020 PBAC Meeting). The ESCs agreed with the submission that clinicians are unlikely to treat patients with nasopharyngeal SCC with pembrolizumab, however noted that the restriction could specify treatment of hypopharynx or oropharynx rather than “pharynx”, in order to exclude nasopharyngeal SCC.
- 2.5 The ESCs also noted that the requirement for combination treatment to be commenced in combination with “platinum-based chemotherapy” was broader than the TGA indication, which specifies combination with 5FU (as used in KN048). The PBAC agreed with the ESCs that the restriction should allow use in combination with platinum-based chemotherapy rather than specifying 5FU, as outcomes are unlikely to be affected by the choice of platinum-based chemotherapy.
- 2.6 The PBAC noted that the above criteria concerning PD-L1 CPS would need to be amended to reflect the populations accepted. The PBAC also considered that a single listing (rather than separate listings for monotherapy and combination therapy) was preferable as it would be simpler for prescribers.

For more detail on PBAC’s view, see section 7 PBAC outcome.

3 Background

Registration status

- 3.1 Pembrolizumab was TGA registered on 22 September 2020 for:
- Pembrolizumab as monotherapy or in combination with platinum and 5-fluorouracil (5-FU) chemotherapy, is indicated for the first-line treatment of patients with metastatic or unresectable recurrent HNSCC, and whose tumours express PD-L1 [Combined Positive Score (CPS) ≥ 1] as determined by a validated test.
- 3.2 Pembrolizumab is also TGA approved for the treatment of patients with metastatic or unresectable recurrent HNSCC with disease progression on or after platinum-containing chemotherapy whose tumours express PD-L1 (CPS ≥ 1) and a number of indications including for non small cell lung cancer (NSCLC), melanoma, Hodgkin

lymphoma, urothelial cancer, primary mediastinal B-cell lymphoma and microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) cancers.

Previous PBAC consideration

3.3 There was one previous consideration of pembrolizumab for the 1L treatment of patients with R/M HNSCC in November 2020. Table 2 summarises the outstanding matters of concern and how these matters were addressed in the resubmission.

Table 2: Summary of outstanding matters of concern

Component	Matter of concern	How the resubmission addresses it
Clinical issues for PBAC		
Efficacy of 2L nivolumab	The PBAC noted there was no clinical evidence presented in the submission to assess the impact of 2L nivolumab on the incremental efficacy and considered this was inappropriate. (paragraph 7.3, pembrolizumab PSD, November 2020 PBAC Meeting)	A simplified two stage model with no re-censoring based on Latimer 2013 was conducted on the cetuximab plus chemotherapy arm in KN048 to estimate the treatment effect of 2L nivolumab. This was then upscaled to reflect the estimated proportion of 2L use of nivolumab in Australia, effectively raising the hazard rate for the SoC arm. This resulted in OS hazard ratios for pembrolizumab monotherapy (HR=0.767) and pembrolizumab plus chemotherapy (HR=0.658).
Pembrolizumab monotherapy clinical claim	The PBAC did not accept the clinical claim that pembrolizumab monotherapy demonstrated superior clinical effectiveness compared to 1L chemotherapy alone for patients with CPS ≥ 1 . The PBAC noted there was no planned statistical analysis for OS for pembrolizumab monotherapy versus cetuximab plus chemotherapy in the CPS ≥ 1 subgroup. (paragraph 7.5, pembrolizumab PSD, November 2020 PBAC Meeting)	The resubmission stated that the statistical analysis plan required testing of CPS ≥ 20 first, if superiority was shown then CPS ≥ 1 was tested, which was before ITT testing was done. Since superiority was demonstrated in CPS ≥ 20 , testing in CPS ≥ 1 was pre-specified and appropriately conducted. Since superiority was also shown, the clinical claim is valid thereby demonstrating codependence.
Pembrolizumab combination non-inferiority safety claim	The PBAC also noted that KN048 showed that pembrolizumab plus chemotherapy was similar to cetuximab plus chemotherapy in safety, with a similar proportion of patients in both arms reporting any grade 3 to 5 drug related adverse events (71.7% vs 69.3% respectively, RD = 2.4%, 95% CI -6.1, 9.9). On this basis, the PBAC considered that pembrolizumab plus chemotherapy was likely inferior in safety to chemotherapy alone. (paragraph 7.8, pembrolizumab PBAC PSD, November 2020)	The resubmission has revised the safety claim to one of inferior safety. The resubmission stated that this is conservative, as it has not taken into account the additional adverse events that would be seen in Australian patients currently receiving 2L nivolumab.
Economic issues		
Efficacy of 2L nivolumab	The PBAC considered there was a high level of uncertainty with the economic model and interpretation of the ICER for a number of reasons, including inappropriately excluding the effectiveness of 2L nivolumab in the SOC arm which resulted in a significant under-estimate of OS. (paragraph 7.10, pembrolizumab PSD,	The resubmission reported that a conservative approach was undertaken for the economic evaluation using the KN048 pivotal trial SoC arm (1L cetuximab plus chemotherapy) as a proxy for 1L chemotherapy alone. A two-stage adjustment for treatment switching was applied to the SoC arm to estimate the treatment effect of 2L

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	November 2020 PBAC Meeting) The original submission presented an indirect comparison as the primary analysis that used data from KN048 and EXTREME to compare pembrolizumab ± chemotherapy versus chemotherapy alone in the CPS ≥1 population. The OS HRs presented were 0.61 (95% CI: 0.46, 0.80) for pembrolizumab monotherapy and 0.53 (95% CI: 0.40, 0.71) for pembrolizumab + chemotherapy.	nivolumab. This was then upscaled to reflect the estimated 2L use of nivolumab in Australia, effectively raising the hazard rate for the SoC arm, resulting in OS hazard ratios for pembrolizumab monotherapy (HR=0.767) and pembrolizumab plus chemotherapy (HR=0.658).
FP NMA data	Applying the inverse hazard ratio from the FPNMA to the pembrolizumab data as observed in KN048 resulted in increasing treatment benefit over time. (paragraph 7.10, pembrolizumab PSD, November 2020 PBAC Meeting)	FPNMA no longer used, instead KM data from KN048 with extrapolation and upscaling of 2L nivolumab is used to inform economic model.
Adverse events	Applying all cause grade 3-4 adverse events from EXTREME to the SoC arm, but only selectively applying treatment related grade 3-5 adverse events which required hospitalisation from KN048 to the pembrolizumab arms. (paragraph 7.10, pembrolizumab PSD, November 2020 PBAC Meeting)	Despite stating that all-cause adverse events were used to compare pembrolizumab to chemotherapy in this resubmission, the same adverse event rates as used in the previous model were used in the resubmission. During evaluation, a revised base case assuming the weekly rate of AEs for the SoC arm to be the same as used for pembrolizumab plus chemotherapy was constructed.
Financial issues		
Prevalence estimates	Overall, the PBAC considered the prevalence estimates underpinning the financial forecasts were uncertain and likely overestimated. (paragraph 7.14, pembrolizumab PSD, November 2020 PBAC Meeting)	Incidence and prevalence data have been revised using the most recent AIHW data. Patient pathways have been nominally simplified and reduced but in fact the overall estimation method remains unchanged from the previous submission. Overall eligible patient pool has been reduced.
Prevalence of CPS ≥1	As outlined in paragraph 6.78, the PBAC advised that the prevalence of CPS ≥1 should be 80%. (paragraph 7.14, pembrolizumab PSD, November 2020 PBAC Meeting)	The CPS ≥1 prevalence has been altered to 80%.
2L nivolumab estimates	The PBAC further advised that patients who have relapsed within 6 months of curative treatment (and are therefore eligible for nivolumab) should be excluded from the estimates. (paragraph 7.14, pembrolizumab PSD, November 2020 PBAC Meeting)	The estimated use of 2L nivolumab has been adjusted to account for continued use in patients progressing from curative treatment within 6 months, as well as the 20% of patients with CPS <1 who would still be eligible to receive 2L nivolumab.

2L = second line; AIHW = Australian Institute of Health and Welfare; CPS = combined positive score; EA = economic analysis; FPNMA = fractional polynomial network meta-analysis; HR = hazard ratio; OS = overall survival; SoC = standard of care; RD = risk difference
Source: Table 1.1, pages iii-v of the resubmission

For more detail on PBAC's view, see section 7 PBAC outcome.

4 Population and disease

4.1 The target population was patients with R/M HNSCC, specifically the oral cavity, pharynx, and larynx, which was incurable by local therapy, who have not had prior

systemic therapy administered in this setting and whose tumours express PD-L1 CPS ≥ 1 (revised to CPS ≥ 20 for monotherapy in the PSCR). Based on estimates from the Australian Institute of Health and Welfare (AIHW) in 2019, approximately 4,455 Australian patients had SCC of the oral cavity, pharynx or larynx. A majority (73%) were male, with an average age of 65 years (based on 2014 data).

- 4.2 Patients with R/M HNSCC which was incurable by local therapy have significant mortality. The resubmission estimated that the five-year survival was only 5.3%.
- 4.3 Pembrolizumab \pm chemotherapy was expected to replace 1L chemotherapy (and 2L nivolumab in a proportion) in patients with R/M HNSCC who have not previously been treated.
- 4.4 The resubmission proposed the use of PD-L1 biomarker, as detected by the pharmDx 22C3 test using the CPS scoring algorithm, to determine eligibility to pembrolizumab in R/M HNSCC. The 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. Despite its derivation, the CPS is expressed as a value and not a percentage, and although the result can exceed 100, the maximum score is defined as CPS 100. The resubmission estimated that 80% of all R/M HNSCC patients will have CPS ≥ 1 . The PBAC requested that MSAC advise on the proportion of R/M HNSCC patients who will have CPS ≥ 20 (see paragraph 1.6).

For more detail on PBAC's view, see section 7 PBAC outcome.

5 Comparator

- 5.1 As in the previous submission, no PD-L1 testing was the appropriate nominated comparator to the proposed test as PD-L1 testing is not part of treatment with the current standard of care for R/M HNSCC patients.
- 5.2 Pembrolizumab may be used as (i) monotherapy and replace SoC (1L chemotherapy \pm 2L nivolumab) or (ii) together with chemotherapy as 1L therapy and replace 2L nivolumab. The use of 1L pembrolizumab would preclude patients from accessing PBS subsidised 2L nivolumab. Therefore 1L pembrolizumab would directly replace 2L nivolumab use in some patients.
- 5.3 The resubmission nominated SoC, defined as 1L chemotherapy followed by 2L nivolumab in 50% of patients, as the comparator. The PBAC had previously accepted that SoC was the appropriate comparator, and noted that current SoC consists of 1L chemotherapy alone followed by 2L nivolumab for a proportion of patients. The ESCs previously considered that the proportion of patients likely to be treated with 2L nivolumab was uncertain as the sponsor's calculations relied on assumptions regarding the number of patients to be treated with pembrolizumab from the complex

epidemiological approach presented in the financial estimates (paragraphs 5.2 and 7.3, pembrolizumab PSD, November 2020 PBAC Meeting).

5.4 The submission’s derivation of the proportion of patients who would have been treated with 2L nivolumab in SoC is shown in Table 3.

Table 3: Derivation of proportion of patients treated with 2L nivolumab and eligible for pembrolizumab

		Proportion	Number of patients (2019)
a	Using 2L nivolumab	-	1 ^a
b	Assumed to be using 2L nivolumab <u>not</u> in early recurrent setting	80% ^b	1
c	CPS ≥1	80% ^c	1
d	Eligible for, but did not take 2L nivolumab	15%	1
e	Estimated 2019 pembrolizumab patients		2
	Estimate proportion who would be eligible for pembrolizumab who would be eligible for 2L nivolumab	48% [(c+d)÷e] ^d	-
	Estimate proportion who would be eligible for pembrolizumab and would not have used 2L nivolumab (revised in commentary)	42% [c÷e]	-

^aNumber of individual patients who received at least one prescription for nivolumab for the treatment of head and neck cancer in 2019, as provided by DUSC during evaluation of the previous pembrolizumab submission.

^bThe proportion of patients using 2L nivolumab not in early recurrent setting (b) was an assumption and was not further justified.

^cThe proportion of patients who did not take 2L nivolumab (d) was an assumption and was not further justified.

^d rounded up to 50% by resubmission

Source: adapted from p279 of resubmission

The redacted values correspond to the following ranges:

¹ < 500

² 500 to < 5,000

5.5 The resubmission inappropriately included patients who were eligible but did not use 2L nivolumab in its estimates. 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. Based on data provided by DUSC there were < 500 and < 500 incident patients treated with 2L nivolumab in 2019 and 2020, respectively. Assuming this increased to < 500 in 2022 and using the resubmission’s estimates of 500 to < 5,000 incident patients treated with pembrolizumab in 2022, and adjusting for uptake (85%) and prevalence of CPS ≥1 (80%) it was estimated that there would be 500 to < 5,000 incident patients in 2022. This would equate to < 500/500 to < 5,000 (43.7%) patients estimated to use 2L nivolumab in 2022.

5.6 The PBAC considered that the proportion of HNSCC patients treated with 2L nivolumab appears to be underestimated in these calculations. The PBAC considered that the proportion of R/M HNSCC patients receiving 2L nivolumab in practice would be expected to be around 80% as the majority of patients are well enough to receive 2L treatment, especially given the general shift to younger patients who are otherwise well. The PBAC considered that this suggested that the number of patients treated with pembrolizumab from the financial estimates was overestimated, noting that

estimation of incident and prevalent patients was complex and relied on a number of assumptions, where relatively small differences in some steps would result in a large difference in the final patient numbers (see Figure 6).

For more detail on PBAC's view, see section 7 PBAC outcome.

6 Consideration of the evidence

Sponsor hearing

- 6.1 The sponsor requested a hearing for this item. The clinician noted that there is a significant burden of morbidity and mortality from HNSCC. The clinician noted that there has been a shift from older patients with disease related to smoking and alcohol exposure to a younger patient population who are otherwise well, with disease related to exposure to human papilloma virus (HPV). The clinician noted that immune checkpoint inhibitors are PBS listed in the second line setting (nivolumab) but noted that the evidence suggests these treatments are most effective when used earlier. The clinician commented that for any level of PD-L1 expression first line treatment should include a PD-L1 inhibitor and the main decision point is whether to treat with monotherapy or in combination with chemotherapy. The clinician stated for patients with CPS >20, with no significant symptoms, monotherapy is likely to be appropriate. For patients with lower CPS (1-10) monotherapy would not be suitable as chemotherapy is also needed to ensure sufficient speed of response to prevent further problems arising before immunotherapy is likely to produce benefit. For patients with CPS levels in between (10-20) there may be other factors to consider in choosing whether to include chemotherapy such as tumour bulk or the presence of significant symptoms. The clinician noted that many patients are aware of data supporting 1L use of checkpoint inhibitors but the majority of patients are not in a position to afford treatment without PBS reimbursement.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from individuals (3), health care professionals (4) and organisations (4) via the Consumer Comments facility on the PBS website. The comments described the devastating impacts of surgical treatments for HNSCC in terms of physical appearance and the ability to breath, speak, eat and drink. Individuals noted that outcomes from trials of pembrolizumab look promising, however patients are unable to access treatment due to its high cost.
- 6.3 The PBAC noted the advice received from the Australasian College of Dermatologists, Head and Neck Cancers Australia and Rare Cancers Australia in support of the pembrolizumab submission. These groups also noted the profound impact of treatment for head and neck cancer on patients' physical and psychological wellbeing.

Immunotherapy is perceived as effective and well tolerated compared with standard treatments. The PBAC noted the advice from Head and Neck Cancers Australia, concurring with statements in the sponsor hearing, that in the past smoking and alcohol were the most common causes of head and neck cancers, whereas today in Australia many head and neck cancers are due to other causes including HPV which can affect young, otherwise healthy, non-smoking men and women.

- 6.4 The Medical Oncology Group of Australia (MOGA) also expressed its strong support for the pembrolizumab submission, categorising it as one of the therapies of “highest priority for PBS listing” on the basis of the KN048 trial. The PBAC noted that the MOGA presented a European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for KN048, which was limited to 4 (out of a maximum of 5, where 5 and 4 represent the grades with substantial improvement)¹ for patients with CPS \geq 1.

Clinical trials

- 6.5 The approach taken in the resubmission was to present evidence that had been linked to support the contention that targeting of CPS \geq 1 with pembrolizumab will identify patients with R/M HNSCC who may derive the most benefit from immunotherapy.

¹ Cherny NI, Dafni U, Bogaerts J, et al: ESMO-Magnitude of Clinical Benefit Scale version 1.1. *Annals of Oncology* 28:2340-2366, 2017

Table 4: 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.	<input type="checkbox"/> 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.	<input type="checkbox"/> k=5 n=10,203	Risk of bias was not assessed by the resubmission. Significant overlap in the included trials of the systematic reviews.
Change in patient management	Not explicitly assessed. CPS thresholds were based on KN048 results.	<input type="checkbox"/> k=0 n=0	NA
Treatment effectiveness Predictive effect (treatment effect variation)	Based on KN048 with subgroups defined using CPS.	<input type="checkbox"/> k=1 n=477	Overall risk of bias considered low because of the objective nature of the overall survival endpoint. However, 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

6.6 The data available to inform the comparison are summarised in Table 5. The data available were the same as in the previous submission, however in the resubmission only data from KN048 were presented in the main analysis with the cetuximab plus chemotherapy arm used as proxy for chemotherapy.

Table 5: 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.

Comparative effectiveness

6.7 Details of the treatment trials presented in the resubmission are provided in Table 6.

Table 6: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Pembrolizumab (± chemotherapy) versus cetuximab plus chemotherapy		
KN048	A Study of Pembrolizumab (MK-3475) for First Line Treatment of Recurrent or Metastatic Squamous Cell Cancer of the Head and Neck (MK-3475-048/KEYNOTE-048) Pembrolizumab alone or with chemotherapy versus cetuximab with chemotherapy for recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-048): a randomised, open-label, phase 3 study	22 July 2019 Lancet. 2019;394(10212):1915-1928.

Source: Table 2.2-1, p35 of the resubmission

6.8 Unlike in the previous submission in which 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 based the clinical claim and economic model on the results of KN048 alone, using 1L cetuximab + chemotherapy as a proxy for 1L chemotherapy alone, with the indirect comparison of KN048 and EXTREME used as supportive data. Results from an additional 12 months of follow-up from KN048 with data cut off date of 18 February 2020 (referred to as four year follow-up) compared to the previous submission were also presented. Results presented in the previous submission (data cut off date 25 February 2019) reflecting the planned final analysis are also referred to throughout as the final analysis.

Table 7: Key features of the included evidence

Trial	N	Design, median follow up	Patient population	Outcome(s)	Use in modelled evaluation
Pembrolizumab ± chemotherapy vs cetuximab plus chemotherapy					
KN048	882	Randomised, open label, 46 months	Previously untreated R/M HNSCC, disease unsuitable for local therapy with curative intent and ECOG PS 0-1, all PD-L1 status	OS, PFS	Informs OS, PFS, ToT, AE resource use and utilities

R/M = recurrent or metastatic, HNSCC = head and neck squamous cell carcinoma, ECOG = eastern cooperative oncology group, PD-L1 = programmed death ligand 1, OS = overall survival, PFS = progression free survival, ToT = time on treatment, AE = adverse event

Source: constructed during evaluation

6.9 Despite the open label nature of the key clinical trial KN048, the risk of bias for the efficacy outcome of overall survival (OS) was considered low, as it is an objective measure.

6.10 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.
- 6.11 The resubmission acknowledged that ten protocol amendments were made during the KN048 trial, with some of these amendments potentially leading to misunderstandings during the previous submission. The resubmission sought to clarify these issues:
- TPS $\geq 50\%$ was used as a stratification factor during enrolment. During KN048 the primary objectives of the trial were altered to include analysis of OS and progression-free survival by CPS ≥ 1 and CPS ≥ 20 instead of TPS, based on early data from KN012 and KN055 (a non-randomised phase 2 study of pembrolizumab in patients with R/M HNSCC in whom platinum and cetuximab therapy failed). No change was made to the stratification of KN048, and it remained TPS $\geq 50\%$ to maintain the internal validity of the trial (Global amendment 5).
 - While there was a protocol amendment (Global Amendment 1) made to ensure inclusion of additional patients with strongly positive PD-L1 expression, this amendment was subsequently superseded (Global amendment 5) and was not implemented. Consequently, there was no enrichment of TPS $\geq 50\%$ patients.
- 6.12 The resubmission stated that a multiplicity strategy was used in KN048 to determine the statistical significance of analyses whereby the group-sequential approach was used to allocate alpha between the interim and final analyses. The allocation of alpha across the hypotheses changed during KN048. There were substantial changes to the trial from the protocol to interim analysis 2. This included the addition of new hypotheses and reallocating alpha away from PFS outcomes.
- 6.13 The resubmission concluded that, based on the statistical analysis plan, statistical significance for pembrolizumab monotherapy and pembrolizumab plus chemotherapy over SoC was demonstrated for the CPS ≥ 20 and then the CPS ≥ 1 population. The ESCs noted that statistical significance was demonstrated for pembrolizumab monotherapy in the CPS ≥ 20 population based on the statistical analysis plan for KN048 described in the resubmission.
- 6.14 The OS results of patients in KN048 are presented in Table 8 (final analysis), and in Table 9 (four year follow-up). Figure 1 and Figure 2 present the Kaplan Meier curves for KN048 updated with 12 months of additional follow up data. OS HR for the complement to the subgroups and tests for interaction are provided in Table 14 (claim of codependence section).
- 6.15 The PBAC noted that KN048 was not powered to detect a difference between monotherapy and combination therapy.

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Table 8: Overall survival in KN048 by CPS status at final analysis

	Pembrolizumab		Cetuximab + chemotherapy		OS HR (95%CI)	p-value
	Deaths, n/N (%)	Median OS months (95%CI)	Deaths, n/N (%)	Median OS months (95%CI)		
Pembrolizumab + chemotherapy						
ITT (allcomers)	213/281(75.8)	13.0(10.9,14.7)	247/278(88.8)	10.7 (9.3,11.7)	0.72 (0.60, 0.87)	0.00025
CPS <1	36/39 (92.3)	11.3 (9.5, 14.0)	34/43 (79.1)	10.7 (8.5, 15.9)	1.18 (0.73, 1.90)	0.498
CPS ≥1	177/242 (73.1)	13.6(10.7,15.5)	213/235 (90.6)	10.4 (9.1, 11.7)	0.65 (0.53, 0.80)	<0.001
1 ≤ CPS <20	93/116 (80.2)	12.7 (9.4, 15.3)	115/125 (92.0)	9.9 (8.6,11.5)	0.71 (0.54, 0.94)	0.017
CPS ≥20	84/126 (66.7)	14.7 (10.3,19.3)	98/110 (89.1)	11.0 (9.2, 13.0)	0.60 (0.45, 0.82)	<0.001
Pembrolizumab monotherapy						
ITT (allcomers)	237/301 (78.7)	11.5 (10.3, 13.4)	264/300 (88.0)	10.7 (9.3,11.7)	0.83 (0.70, 0.99) ^a	0.01985
CPS <1	40/44 (90.9)	7.9 (4.7, 13.6)	35/45 (77.8)	11.3 (9.1, 15.9)	1.72 (1.06, 2.79)	0.029
CPS ≥1	197/257 (76.7)	12.3(10.8, 14.3)	229/255 (89.8)	10.3 (9.0, 11.5)	0.74 (0.61, 0.90)	0.003
1 ≤ CPS <20	103/124 (83.1)	10.8 (9.0,12.6)	121/133 (91.0)	10.1 (8.7,12.1)	0.92 (0.70,1.20)	0.534
CPS ≥20	94/133 (70.7)	14.8(11.5, 20.6)	108/122 (88.5)	10.7 (8.8,12.8)	0.58 (0.44,0.78)	<0.001

Chemotherapy = cisplatin or carboplatin + 5FU; CPS = combined positive score; NA = not applicable

^a Not statistically significant due to alpha spending requiring lower p-value than 0.05.

Text in bold indicate statistically significant differences

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

Table 9: Overall survival in KN048 by CPS status (four year follow up)

	Pembrolizumab		Cetuximab + chemotherapy		OS HR (95%CI)	p-value
	Deaths, n/N (%)	Median OS months (95%CI) ^b	Deaths, n/N (%)	Median OS months (95%CI)		
Pembrolizumab + chemotherapy						
ITT (allcomers)	213/281(75.8)	13.0 (10.9,14.7)	247/278(88.8)	10.7 (9.3,11.7)	0.71 (0.59, 0.85)	0.00008
CPS <1 ^c	37/39 (94.9)	11.3 (9.5, 14.0)	38/43 (88.4)	10.7 (8.5, 15.9)	1.21 (0.76, 1.94)	0.417
CPS ≥1	189/242 (78.1)	13.6 (10.7,15.5)	221/235 (94.0)	10.6 (9.1, 11.7)	0.64 (0.53, 0.78)	<0.001
1 ≤ CPS <20	99/116 (85.3)	12.7 (9.4, 15.3)	120/125 (96.0)	9.9 (8.6,11.5)	0.68 (0.52, 0.90)	0.006
CPS ≥20 ^c	90/126 (71.4)	14.7 (10.3,19.3)	101/110 (91.8)	11.1 (9.2, 13.0)	0.62 (0.46, 0.83)	0.001
Pembrolizumab monotherapy						
ITT (allcomers)	237/301 (78.7)	11.5 (10.3, 13.4)	264/300 (88.0)	10.7(9.3,11.7)	0.81 (0.68, 0.97) ^a	0.00994
CPS <1 ^c	40/44 (90.9)	7.9 (4.7, 13.6)	35/45 (77.8)	11.3 (9.1, 15.9)	1.53 (0.95, 2.48)	0.083
CPS ≥1	197/257 (76.7)	12.3 (10.8, 14.3)	229/255 (89.8)	10.3 (9.0, 11.5)	0.74 (0.61, 0.89)	0.002
1 ≤ CPS <20	103/124 (83.1)	10.8 (9.0,12.6)	121/133 (91.0)	10.1 (8.7,12.1)	0.91 (0.70,1.19)	0.493
CPS ≥20 ^c	94/133 (70.7)	14.8 (11.5, 20.6)	108/122 (88.5)	10.7 (8.8,12.8)	0.60 (0.46,0.80)	<0.001

Chemotherapy = cisplatin or carboplatin + 5FU; CPS = combined positive score; NA = not applicable

^a Not statistically significant due to alpha spending requiring lower p-value than 0.05.

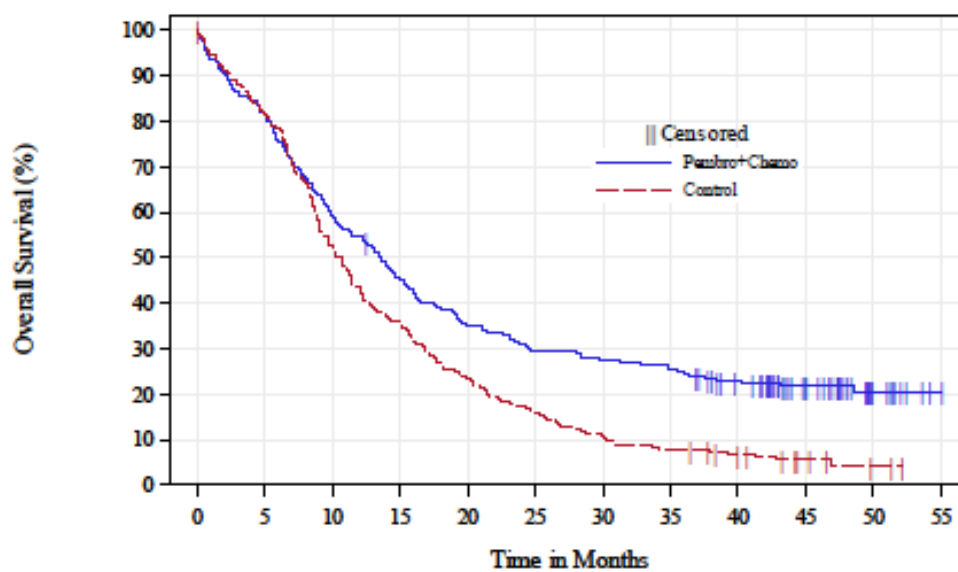
^b Median OS was unchanged from the final data cut

^c Provided in the PSCR

Text in bold indicate statistically significant differences

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; Table 5 and 6 PSCR

Figure 1: Kaplan Meier estimates of OS for pembrolizumab plus chemotherapy in KN048 CPS ≥ 1 (updated with 12 months additional follow up)

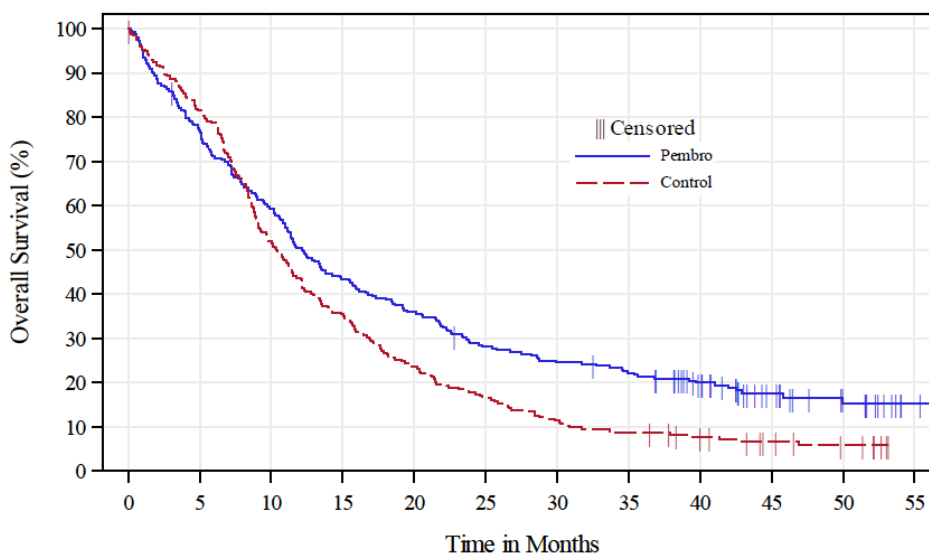


At Risk

Pembro+Chemo	242	197	144	109	84	71	66	61	48	29	9	1
Control	235	191	123	84	55	37	25	18	12	6	2	0

Source: Figure 2.5-2, p71 of the resubmission

Figure 2: Kaplan Meier estimates of OS for pembrolizumab monotherapy in KN048 CPS ≥ 1 (updated with 12 months additional follow up)



At Risk

Pembro	257	197	152	111	92	71	62	55	40	22	12	2
Control	255	207	132	90	60	42	29	22	16	10	6	0

Source: Figure 2.5-1, p70 of the resubmission

- 6.16 The OS HRs reported in the resubmission for the ITT population for pembrolizumab \pm chemotherapy in KN048 at four years were similar in magnitude to the OS HRs reported at three years (final analysis) in the previous submission.
- 6.17 In patients treated with pembrolizumab plus chemotherapy the risk of death was statistically significantly lower in both the ITT population and CPS ≥ 1 population but not in the CPS < 1 population, compared to patients treated with cetuximab plus chemotherapy. A statistically significant survival benefit was observed in the allcomers (ITT) population treated with pembrolizumab plus chemotherapy at the four year follow up (OS HR = 0.71, 95%CI 0.59, 0.85). In the CPS ≥ 1 subgroup, a statistically significant difference in OS favouring pembrolizumab plus chemotherapy was reported at the four year follow up (OS HR = 0.64, 95% CI 0.53, 0.78). Previously 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 . The PBAC also previously noted that the CPS < 1 subgroup in KN048 was too small to conclude that pembrolizumab plus chemotherapy had no effect in this subgroup (paragraph 7.9, pembrolizumab PSD, November 2020 PBAC Meeting). This was unchanged in the resubmission.
- 6.18 In patients treated with pembrolizumab monotherapy, OS was not statistically different to patients treated with cetuximab plus chemotherapy in the ITT population (p-value for significance: 0.0059, observed p-value at four-year follow-up: 0.00994). In

the CPS ≥ 1 subgroup, a statistically significant difference in OS favouring pembrolizumab monotherapy was reported at the four year follow up (OS HR = 0.74, 95% CI 0.61, 0.89, $p=0.00080$). In the CPS ≥ 20 subgroup, a statistically significant difference in OS favouring pembrolizumab monotherapy was reported at the four year follow up (OS HR = 0.60, 95% CI 0.46, 0.80), $p<0.001$). The PBAC recalled that on the basis of the indirect comparison of KN048 with EXTREME, it did not accept the clinical claim for pembrolizumab monotherapy compared to chemotherapy alone in patients with CPS ≥ 1 (paragraphs 7.5 and 7.6, pembrolizumab PSD, November 2020 PBAC Meeting). The PBAC noted that the resubmission provided additional information regarding the statistical analysis plan and its revisions to support the claim that there was a statistically significant OS benefit for patients with CPS ≥ 1 treated with pembrolizumab monotherapy compared with cetuximab plus chemotherapy in KN048.

- 6.19 The PBAC previously noted that the benefit of pembrolizumab monotherapy was likely driven by the CPS ≥ 20 population (paragraph 7.5, pembrolizumab PSD, November 2020 PBAC Meeting). Following changes to the proposed population for pembrolizumab monotherapy in the PSCR, the relevant comparison for pembrolizumab monotherapy is in the CPS ≥ 20 subgroup (OS HR = 0.60, 95%CI 0.46, 0.80 vs cetuximab + chemotherapy, at the four year follow up).
- 6.20 The resubmission stated that in the absence of head to head data comparing pembrolizumab \pm chemotherapy to chemotherapy followed by 2L nivolumab, the impact of 2L nivolumab has been accounted for by using a simplified two stage model with no re-censoring based on Latimer 2013² was conducted on the cetuximab plus chemotherapy arm in KN048, with a separate model for pembrolizumab monotherapy vs cetuximab plus chemotherapy and pembrolizumab plus chemotherapy vs cetuximab plus chemotherapy.
- 6.21 The resubmission used a combination of the observed OS HR from KN048, which reported between 25.18% to 26.67% (depending on comparison and CPS status) of 2L ICI use, which was assumed to be nivolumab, and the adjusted OS HR that represented 0% 2L ICI use to further estimate an upscaled OS HR that includes 50% 2L ICI. The results of the two-stage adjustment and the subsequent upscaling to 50% are summarised in Table 10. The Kaplan-Meier curves with and without adjustment for 2L nivolumab use are presented in Figure 3 and Figure 4. The ESCs considered that using a simplified two stage model with no re-censoring in this way was unconventional but may be a reasonable attempt at adjusting for 2L nivolumab in the absence of other options. The ESCs noted that the inclusion of the adjustment for 2L nivolumab

² Latimer NR, Abrams KR, Lambert PC et al. Adjusting survival time estimates to account for treatment switching in randomised controlled trials: a simulation study. HEDS Discussion Paper 13/06 2013. Available from <https://eprints.whiterose.ac.uk/75249/1/HEDSDP1306.pdf> Accessed 3/8/2021

appeared to make very little difference to the HR for pembrolizumab ± chemotherapy, as demonstrated in Figure 3 and Figure 4 and may have underestimated the benefit from 2L nivolumab (see also Paragraph 6.23). The PBAC considered that the estimate of 50% 2L nivolumab appears to be an underestimate and therefore the clinical benefit from 2L treatment may have been underestimated (see also paragraph 5.6).

Table 10: Results of two-stage model adjusting for 2L immune checkpoint inhibitor

	Median OS (95%CI)	Survival at 12 months %(95%CI)	HR (95% CI)	P-value	Acceleration Factor (95%CI) ^a
Pembrolizumab + chemotherapy (ITT)					
Pembrolizumab +chemotherapy	13.0 (10.9, 14.7)	53.0 (47.0, 58.7)	NA	NA	NA
KN048 SoC	10.7 (9.3, 11.7)	44.0 (38.1, 49.8)	0.71 (0.59, 0.85)	0.0002	NA
Adjusted SoC ^b	10.4 (9.2, 11.5)	43.3 (37.4, 49.1)	0.68 (0.55, 0.83)	0.0002	1.595 (1.178, 2.159)
Upscaled SoC ^c	NR	NR	0.741 (NR)	NR	NA
Pembrolizumab + chemotherapy (CPS ≥1)					
Pembrolizumab +chemotherapy	13.6 (10.7, 15.5)	55.0 (48.5, 61.0)	NA	NA	NA
KN048 SoC	10.6 (9.1, 11.7)	43.6 (37.2, 49.8)	0.64 (0.53, 0.78)	<0.0001	NA
Adjusted SoC ^b	10.4 (9.0, 11.5)	43.2 (36.8, 49.4)	0.62 (0.50, 0.77)	<0.0001	1.502 (1.11, 2.033)
Upscaled SoC ^c	NR	NR	0.658 (NR)	NR	NA
Pembrolizumab monotherapy (ITT)					
Pembrolizumab monotherapy	11.5 (10.3, 13.5)	48.7 (42.9, 54.2)	NA	NA	NA
KN048 SoC	10.7 (9.3, 12.1)	44.5 (38.8, 50.0)	0.81 (0.68, 0.97)	0.0199	NA
Adjusted SoC ^b	10.4 (9.2, 11.7)	43.8 (38.1, 49.3)	0.78 (0.63, 0.96)	0.0199	1.631 (1.218, 2.185)
Upscaled SoC ^c	NR	NR	0.840 (NR)	NR	NA
Pembrolizumab monotherapy (CPS ≥1)					
Pembrolizumab monotherapy	12.3 (10.8, 14.8)	50.4 (44.1, 56.4)	NA	NA	NA
KN048 SoC	10.4 (9.0, 11.7)	43.7 (37.5, 49.7)	0.74 (0.61, 0.89)	0.0016	NA
Adjusted SoC ^b	10.2 (9.0, 11.5)	43.3 (37.2, 49.3)	0.71 (0.57, 0.88)	0.0017	1.541 (1.15, 2.066)
Upscaled SoC ^c	NR	NR	0.767 (NR)	NR	NA

^aAcceleration factor measures the effect of second line immune checkpoint inhibitor. A higher acceleration factor indicates more effective second line treatment

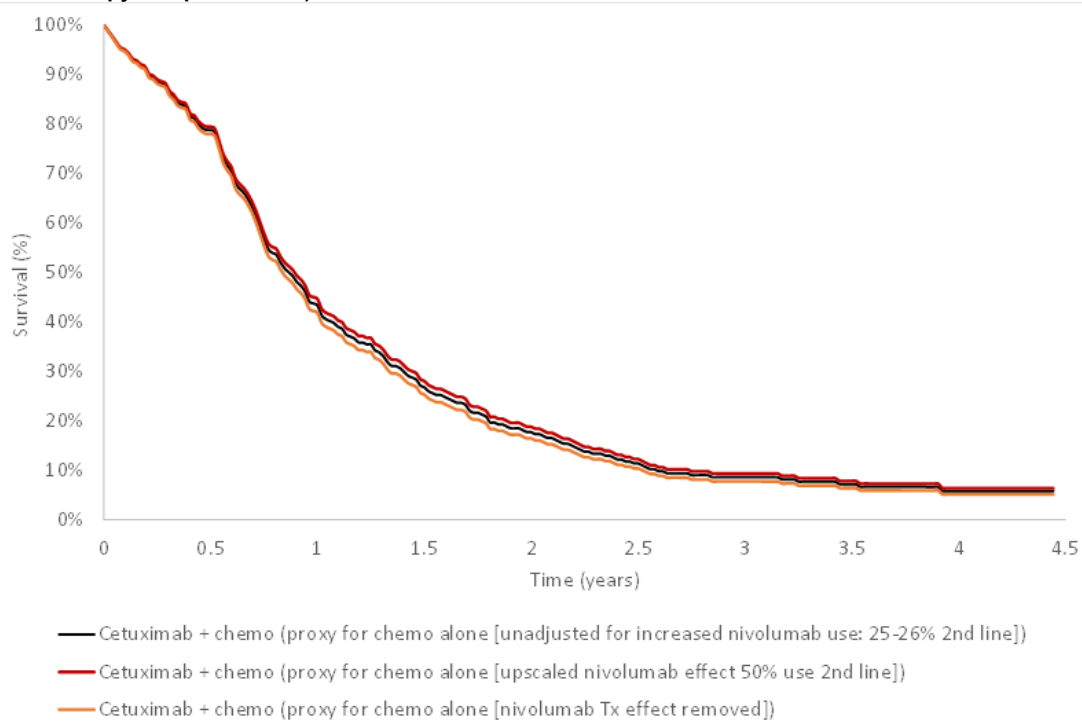
^bAdjusted SoC refers to the estimated survival in patients assuming 0% second line immune checkpoint inhibitor use

^cUpscaled from around 26% second line immune checkpoint inhibitor in observed SoC from KN048 to 50% assumed by resubmission

CPS = combined positive score, NA = not applicable, NR = not reported

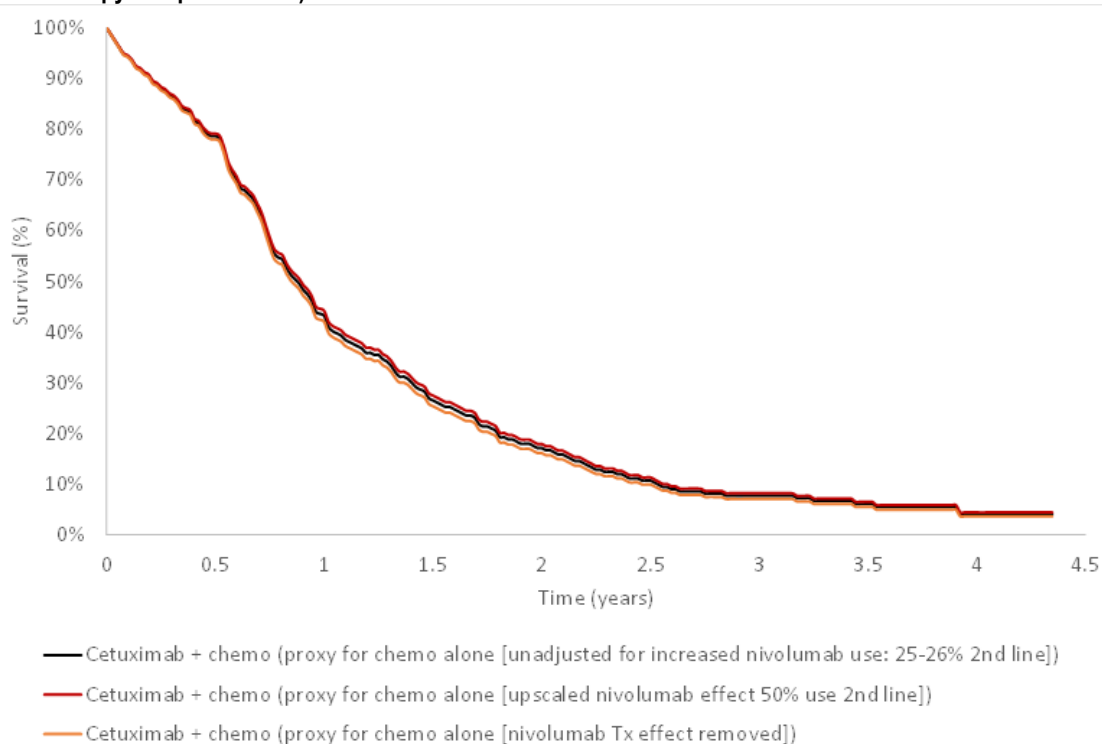
Source: Table 3, p17, table 6, p21, table 7, p23, table 10, p27, table 11, p29, table 14, p33, table 15, p35 and table 18, p39, Attachment 20 to the resubmission and Table 2.6-13, p127 of resubmission

Figure 3: Cetuximab + chemotherapy with and without adjustment for 2L nivolumab use (pembrolizumab monotherapy comparator arm)



Source: Figure 2.6-1, p128

Figure 4: Cetuximab + chemotherapy with and without adjustment for 2L nivolumab (pembrolizumab plus chemotherapy comparator arm)



Source: Figure 2.6-2, p128

6.22 The two-stage model to upscale the proportion of patients with 2L nivolumab use in the comparator arm of the KN048 trial (around 26%) to 50% as assumed by the resubmission resulted in only minor adjustments to the hazard ratios (pembrolizumab monotherapy OS HR=0.74, adjusted OS HR=0.77; pembrolizumab plus chemotherapy OS HR=0.65, adjusted OS HR=0.66). These adjusted HR were not directly applied in the economic model. Instead, an additional HR modifier between the HR of patients who were not treated with 2L nivolumab calculated by the resubmission and the HR reported in KN048 patients was calculated and then applied to the observed KM of the cetuximab plus chemotherapy arm of KN048. For example, in the base case assuming 50% 2L nivolumab use, a HR of 0.972 was applied to the observed KM for 1L cetuximab plus chemotherapy to account for 2L nivolumab use.

6.23 Using the economic model, which allowed manipulation of the proportion of patients using 2L nivolumab, upscaling to 100% 2L nivolumab use resulted in a median OS of 49.5 weeks compared to 43.5 weeks when assuming 0% 2L nivolumab use, inferring an overall OS benefit (across both 1L and 2L treatment) with 2L nivolumab of 6 weeks, or around 1.38 months. Comparatively, Checkmate 141³, which compared 2L

³ Ferris RL, Blumenschein G Jr, Fayette J et al. Nivolumab for recurrent squamous-cell carcinoma of the head and neck. *N Engl J Med* 2016;375:1856–1867.

nivolumab to chemotherapy in R/M HNSCC, reported a difference in median OS of 2.4 months (7.5 months in 2L nivolumab vs 5.1 months in 2L chemotherapy). The ESCs considered this suggested that the resubmission's approach may have underestimated the efficacy of 2L nivolumab.

- 6.24 However, the ESCs considered that the use of 1L cetuximab plus chemotherapy as proxy for 1L chemotherapy overestimated the efficacy of 1L chemotherapy alone. The PSCR argued that this approach overestimated the efficacy of 1L chemotherapy alone for all patients, which offsets the underestimate of the 2L nivolumab treatment effect in the proportion of patients treated with 2L nivolumab (<50%). The ESCs also noted that EGFR inhibitors were used as 2L treatment in 18-24% of patients in the pembrolizumab groups, favouring the estimation of the effectiveness of pembrolizumab.
- 6.25 The PBAC noted that the results of 2-stage adjustment model to account for 2L nivolumab was not provided for the CPS ≥ 20 population (for monotherapy) but the PSCR model assumed that the adjustment factor for the CPS ≥ 1 would be applicable to the CPS ≥ 2 population. Overall, the PBAC agreed with the ESCs that the magnitude of benefit for pembrolizumab \pm chemotherapy, including adjustment for 2L nivolumab, remained uncertain.

Comparative harms

- 6.26 The resubmission made a claim of inferior safety for pembrolizumab plus chemotherapy compared to SoC, consistent with the PBAC's previous advice (paragraph 7.8, pembrolizumab PSD, November 2020).
- 6.27 The PBAC previously noted that the safety profile of pembrolizumab monotherapy (mainly immune related) was different to the profile of chemotherapy alone, but considered that the claim of superior safety was reasonable given the known safety profile and mechanism of action of pembrolizumab (paragraph 7.7, pembrolizumab PSD, November 2020 PBAC Meeting). Accordingly, a claim of superior safety for pembrolizumab monotherapy compared to SoC was presented in the resubmission.
- 6.28 The resubmission stated that as there were no published available data for drug-related adverse events from the EXTREME trial, a formal indirect comparison of pembrolizumab \pm chemotherapy versus chemotherapy was not conducted, however, a naïve side by side comparison using the separate arms of KN048 and EXTREME was presented (Table 11).

Table 11: Naïve indirect comparison of all cause grade 3-5 adverse events pembrolizumab monotherapy and pembrolizumab plus chemotherapy with chemotherapy alone

	KN048		EXTREME	Pembro mono vs chemo alone		Pembro + chemo vs chemo alone	
	Pembro mono	Pembro + chemo	Chemo alone	RR (95%CI)	RD% (95%CI)	RR (95%CI)	RD% (95%CI)
	All grade 3-5 AE	164/300 (54.7)	235/276 (85.1)	171/215 (79.5)	0.69 (0.61,0.78)	-25 (-32, -17)	1.07 (0.98, 1.16)
Drug related grade 3-5 AE	52/300 (17.0)	198/276 (71.7)	NR	NC	NC	NC	NC

AE = adverse events; chemo = chemotherapy; NR = not reported; NC = not calculable; pembro = pembrolizumab; RR = relative risk; RD = risk difference

Source: Table 2.6-12, p126 of the resubmission

- 6.29 The resubmission acknowledged the Committee’s previous comments that analysis of relative risk and risk difference has demonstrated that pembrolizumab plus chemotherapy has a slightly higher incidence of grade 3-5 adverse events than chemotherapy (85.1% vs 79.5%), relative risk (RR) 1.07 (95% CI 0.98, 1.16) (paragraph 6.35, Table 14, pembrolizumab PSD, November 2020 PBAC Meeting). Pembrolizumab combination therapy had slightly more anaemia, mucosal inflammation, stomatitis, hyponatraemia, fatigue and febrile neutropenia; but a lower incidence of neutropenia, decreased neutrophil count, rash and lower white blood cell count.
- 6.30 The safety of 2L nivolumab was not considered, therefore this was not factored into the comparative safety of pembrolizumab ± chemotherapy with SoC.

Benefits and harms

- 6.31 A summary of the comparative benefits and harms for pembrolizumab versus chemotherapy is presented in Table 12.

Table 12: Summary of comparative benefits and harms for pembrolizumab ± chemotherapy and chemotherapy

Benefits^a					
Time-to-event outcome: OS (Upscaled 2L nivolumab to 50%)					
Trial	Median duration of follow up^b	Pembrolizumab Median OS Months (95%CI)	SoC Median OS Months (95%CI)	Absolute difference (%)	HR (95% CI)
KN048 (pembrolizumab plus chemotherapy) – ITT	45.6 months pembro + chemo 45.7 months SoC	13.0 (10.9, 14.7)	NR	NR	0.741 (NR)
KN048 (pembrolizumab plus chemotherapy) – CPS ≥1	45.6 months pembro + chemo 45.7 months SoC	13.6 (10.7, 15.5)	NR	NR	0.658 (NR)
KN048 (pembrolizumab monotherapy) – CPS ≥1	46.3 months pembro 46.2 months SoC	12.3 (10.8, 14.8)	NR	NR	0.767 (NR)
KN048 (pembrolizumab monotherapy) – CPS ≥20	46.3 months pembro 46.2 months SoC	14.9 (11.5, 20.6)	11.1 (9.2, 13.0)	NR	0.62 (0.46, 0.83)^e
Harms: Based on naïve indirect comparison using KN048 and EXTREME data					
Trial	Median duration of follow up (pembro/chemo)	Pembrolizumab n/N (%)^a	SoC n/N (%)	RR (95% CI)	RD % (95% CI)
Pembrolizumab plus chemotherapy (ITT) versus chemotherapy (ITT)					
All cause grade 3+ adverse event	11.5/18.2 months	235/276 (85.1)	171/215 (79.5)	1.07 (0.98, 1.16)	6 (-1, 13)
Pembrolizumab monotherapy (ITT) versus chemotherapy (ITT)					
All cause grade 3+ adverse event	13.0/18.2 months	164/300 (54.7)	171/215 (79.5)	0.69 (0.61, 0.78)	-25 (-32, -17)

Chemo = chemotherapy; CPS = combined positive score; ITT = intention to treat; pembro = pembrolizumab, RD = risk difference; RR = risk ratio; NR = Not Reported

^a n/N reported were likely from final analysis (three year follow-up) but this was not made clear in the resubmission

^b Median follow up in the CPS ≥1 subgroup not reported in KN048, this value reflects the follow up in ITT population and is an approximation only.

^c Updated 4 year data

^d Not statistically significant due to alpha spending requiring lower p-value than 0.05.

^e No adjusted value to account for 2L nivolumab was provided for the CPS≥20 population. The revised model in the PSCR assumed that the HR for CPS≥20 is the same as for the CPS≥1 population (0.767).

Values in bold indicate statistically significant differences

Source: Table 2.6-12, p126, Table 2.6-13, p127 of the resubmission, Table 6, p 21, Table 10, p27, and Table 18, p39, Attachment 20 to the resubmission

6.32 On the basis of the direct comparison presented by the resubmission, the comparison of pembrolizumab plus chemotherapy and SoC (using cetuximab plus chemotherapy as a proxy for chemotherapy and upscaled 2L nivolumab use), resulted in:

- In patients with CPS ≥1, approximately a 34.2% reduction in risk of death (at 46 months follow up); and
- In patients irrespective of CPS, approximately a 25.9% reduction in risk of death (at 46 months follow up).

6.33 On the basis of the direct comparison presented by the resubmission, the comparison of pembrolizumab monotherapy and SoC (using cetuximab plus chemotherapy as a proxy for chemotherapy and upscaled 2L nivolumab use) resulted in:

- In patients with CPS ≥ 1 , approximately a 23.3% reduction in risk of death (at 46 months follow up); and
 - In all patients irrespective of CPS, for every 100 patients treated, 25 fewer patients will experience a grade 3+ adverse event.
- 6.34 False positives from CPS testing would result in patients who should be treated with SoC being exposed to pembrolizumab. If patients receive pembrolizumab monotherapy instead of SoC or pembrolizumab plus chemotherapy, they may have a worse clinical outcome.
- 6.35 With a CPS cut-off of ≥ 1 for pembrolizumab plus chemotherapy false negatives from CPS testing would result in patients who would benefit from pembrolizumab therapy being treated with SoC instead. The PBAC noted this would not be relevant if combination treatment is available to patients irrespective of CPS status. 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).

Clinical claim

- 6.36 The resubmission made the clinical claim that in patients with R/M HNSCC whose tumours express CPS ≥ 1 , pembrolizumab plus chemotherapy has superior efficacy and inferior safety, compared to SoC in the Australian setting, i.e. platinum based chemotherapy in 1L, followed by 2L nivolumab in 50% of patients. The upscaled OS HR results which included 50% use of 2L nivolumab in the resubmission appear to support the claim of superior efficacy of 1L pembrolizumab plus chemotherapy compared to 1L chemotherapy + 50% 2L nivolumab (HR = 0.658). Overall the ESCs considered the clinical claim is likely to be reasonable based on the evidence presented, though the magnitude of benefit remains uncertain. The ESCs considered the claim of inferior safety was appropriate based on the indirect comparison of grade 3-5 adverse events between KN048 and EXTREME presented in the resubmission.
- 6.37 The PBAC recalled it previously accepted the clinical claim of superiority for pembrolizumab plus chemotherapy compared to 1L chemotherapy alone in patients whose tumour express CPS ≥ 1 , however the magnitude of clinical benefit over current SoC was uncertain (paragraph 7.6, pembrolizumab PSD, November 2020 PBAC Meeting). The PBAC also considered that based on results of the KN048 trial pembrolizumab plus chemotherapy is superior to 1L chemotherapy alone in the full population (regardless of CPS status), though there is likely to be a larger effect with higher CPS score. The PBAC considered that the claim of superior comparative effectiveness over SoC was reasonable for both the CPS ≥ 1 and ITT population, but the magnitude of benefit remained uncertain as i) 1L cetuximab plus chemotherapy was used as a proxy for 1L chemotherapy alone which may underestimate the incremental efficacy of pembrolizumab plus chemotherapy but ii) the efficacy of 2L nivolumab was

likely underestimated compared to the literature and iii) the efficacy of pembrolizumab plus chemotherapy was likely overestimated as no adjustment for 2L EGFR treatment was considered.

- 6.38 The PBAC also recalled that it previously considered that pembrolizumab plus chemotherapy was likely inferior in safety to chemotherapy alone and noted that the basis for this conclusion was unchanged.
- 6.39 The resubmission made the clinical claim that in patients with R/M HNSCC whose tumours express CPS ≥ 1 , pembrolizumab monotherapy has superior efficacy and a superior safety profile compared to SoC in the Australian setting, i.e. platinum based chemotherapy in 1L, followed by 2L nivolumab in 50% of patients. Based on the revised proposed population in the PSCR the relevant clinical claim was that in patients with R/M HNSCC whose tumours express CPS ≥ 20 , pembrolizumab monotherapy has superior efficacy and a superior safety profile compared to SoC in the Australian setting. The ESCs considered that this claim is likely to be reasonable based on the data presented, though the magnitude of benefit remains uncertain as the OS HR from KN048 does not account for 2L nivolumab use in the comparator arm or EGFR use in the pembrolizumab arm.
- 6.40 The PBAC considered that the claim of superior comparative effectiveness in the CPS ≥ 20 population was reasonable based on the results of the KN048 trial. The PBAC considered that but the magnitude of benefit over SoC remained uncertain for the same reasons as outlined above for the comparison with pembrolizumab plus chemotherapy.
- 6.41 The PBAC recalled that it had previously noted that the safety profile of pembrolizumab monotherapy (mainly immune related) was different to the profile of chemotherapy alone, but considered that the claim of superior safety was reasonable given the known safety profile and mechanism of action of pembrolizumab (paragraph 7.7, pembrolizumab PSD, November 2020 PBAC Meeting).

Claim of codependence

- 6.42 MSAC previously considered that the biological rationale for the proposed codependency was weak and that there was not enough evidence to suggest that a patient's CPS score is linked to pembrolizumab being a better treatment. MSAC concluded that the trial's problems due to the change in the definitions of PD-L1 assessment, enrichment of patients with TPS $\geq 50\%$, and complex statistical methodology contributed to a complicated trial that was difficult to understand and interpret, and did not fully inform whether PD-L1 CPS testing identified patients most likely to benefit from pembrolizumab treatment (application no. 1522 PSD, November 2020 MSAC Meeting). In response, the resubmission claimed:
- Patients have a better treatment effect when the CPS score is >1 , and that in the CPS <1 population, pembrolizumab is potentially harmful as monotherapy, and

provides no added benefit but potential harm (due to adverse events) in combination with chemotherapy;

- The change in definition of PD-L1 positivity from using TPS to CPS occurred prior to any analysis of results and impacted only the primary objectives and statistical plan, with no change to stratification;
- The KN048 trial stratification (TPS \geq 50%) remained for the entire trial. Hence randomisation by TPS was maintained for the duration of the trial;
- There was no enrichment of TPS \geq 50% patients. While there was a protocol amendment (Global Amendment 1, dated 26 June 2015) made to ensure inclusion of an increased proportion of patients with strongly positive PD-L1 expression, this amendment was superseded (Global amendment 5, dated 5-Aug 2016) and was not implemented;
- The selection of CPS, rather than TPS was based on rigorous scientific analysis of four clinical trials, including two Phase III trials rather than a biological explanation; and
- Any imbalances in baseline characteristics in the CPS \geq 1 population for both pembrolizumab monotherapy and pembrolizumab + chemotherapy had minimal impact on the overall survival hazard ratios, as determined through multivariate analysis.

6.43 Evidence for PD-L1 as a valid biomarker for efficacy of pembrolizumab in R/M HNSCC was first observed in Keynote-012 (KN012), a non-randomised open label phase 1b study of pembrolizumab in R/M HNSCC, which reported a correlation between the degree of PD-L1 expression and overall response and progression-free survival (PFS). A Combined Positive Score (CPS) \geq 1 was proposed as the threshold for eligibility, as subsequent analysis of data from KN012 demonstrated that the CPS scoring was more sensitive than tumour proportion score (TPS) scoring and was more predictive of improved overall survival (OS) and progression free survival (PFS). CPS measures PD-L1 expression by staining tumour cells, lymphocytes and macrophages, whereas TPS restricts PD-L1 staining to tumour cells only.

6.44 Further analysis of data from KN012 (cohort B2) and Keynote-055 (KN055) (a non-randomised phase 2 study of pembrolizumab in patients with R/M HNSCC in whom platinum and cetuximab therapy failed) confirmed that these CPS cut off points should be evaluated (Table 13). The resubmission appeared to define sensitivity and specificity in the context of clinical utility, which was based on a retrospective exploratory analysis where overall response rates to pembrolizumab were compared to the different PD-L1 metrics and thresholds to propose a preferred option. A subset of the CPS thresholds was then further examined in a subsequent analysis in KN048 (with unclear prespecification because the prespecified TPS \geq 50% metric and threshold were changed at some stage).

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Table 13: Clinical utility for CPS and TPS in non-enriched KN012 cohort B2 and KN055 (n=252; 51 responses; ORR = 20.2%)

Scoring and cutoff	Sensitivity %	Specificity %	YI %	PPV %	NPV %	Prevalence %
CPS ≥1	92.2	18.9	11.1	22.4	90.5	83.3
CPS ≥10	74.5	45.8	20.3	25.9	87.6	58.3
CPS ≥20	66.7	54.2	20.9	27.0	86.5	50.0
CPS ≥30	58.8	62.7	21.5	28.6	85.7	41.7
CPS ≥40	49.0	69.7	18.7	29.1	84.3	34.1
CPS ≥50	43.1	74.1	17.3	29.7	83.7	29.4
TPS ≥1%	74.5	32.3	6.8	21.8	83.3	69.0
TPS ≥10%	66.7	52.7	19.4	26.4	86.2	51.2
TPS ≥20%	62.7	59.2	21.9	28.1	86.2	45.2
TPS ≥30%	58.8	65.2	24.0	30.0	86.2	39.7
TPS ≥40%	45.1	71.6	16.7	28.8	83.7	31.7
TPS ≥50%	41.2	75.6	16.8	30.0	83.5	27.8

CPS = combined positive score, NPV = negative predictive value, PPV = positive predictive value, TPS = tumour proportion score, YI = Youden Index

Source: Table 2.9-3, p143 of the resubmission

6.45 The results for OS in the intention to treat (ITT) population and the CPS ≥1 and ≥20 subgroups and their complements in KN048 are presented in Table 14.

Table 14: Overall survival for pembrolizumab ± chemotherapy vs cetuximab plus chemotherapy (KN048)

	Previous submission		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 <1	1.72 (1.06, 2.79)		1.53 (0.95, 2.48) ^b	
CPS <20	1.05 (0.84, 1.32)	0.002	1.02 (0.81, 1.28)	0.004 (87.85 %)
CPS ≥20	0.58 (0.44, 0.78)		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 (83.43%)
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 <1	1.18 (0.73, 1.90)		1.21 (0.76, 1.94)	
CPS <20	0.83 (0.65, 1.05)	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
Chemotherapy = cisplatin or carboplatin + 5FU

^a Not statistically significant due to alpha spending requiring lower p-value than 0.05.

^b As provided in the PSCR

CPS = combined positive score, NA = not applicable, NR = not reported

Text in bold indicate statistically significant differences

- 6.46 The PSCR stated that the tests for interaction at CPS ≥20 for pembrolizumab monotherapy and at CPS ≥1 for pembrolizumab plus chemotherapy have demonstrated a statistically significant treatment effect modification, indicative of a predictive effect of PD-L1 (p-value for interaction test: CPS ≥20 pembrolizumab monotherapy p=0.004; CPS ≥1 pembrolizumab plus chemotherapy p=0.014).
- 6.47 In studies using response rate from clinical trials as the reference standard, PD-L1 testing using the CPS ≥1 threshold reported a high sensitivity (92-94%), but low specificity (19-23%). If a high sensitivity was acceptable at the expense of low specificity, then it would arguably be preferable to not test and just assume all patients respond to a similar extent (100% sensitivity, 0% specificity).
- 6.48 The discordance of the PD-L1 test may lead to unacceptable risks for some patients. False positives from CPS testing (patients with CPS <1 being misclassified as CPS ≥1) would result in patients who should be treated with SoC being exposed to pembrolizumab. If patients receive pembrolizumab monotherapy instead of SoC, they would be expected to have a worse clinical outcome with a lower OS observed for patients with CPS <1 (HR 1.72, 95% CI 1.06, 2.79). In the PSCR the sponsor proposed increasing the threshold for pembrolizumab monotherapy to CPS ≥20 to decrease the likely number of false positives. If a false positive would result in patients receiving pembrolizumab plus chemotherapy instead of SoC, they would be exposed to additional adverse events with reduced corresponding benefit in efficacy and would

be denied treatment with PBS-subsidised 2L nivolumab based on the current restrictions.

- 6.49 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).
- 6.50 MSAC previously queried whether the postulated codependency between PD-L1 status and the clinical benefit from pembrolizumab differed when it was used as monotherapy compared with its use in combination with chemotherapy (application no. 1522 PSD, November 2020 MSAC Meeting). As noted above (paragraphs 1.5-1.6), subject to MSAC's advice, the PBAC expressed a preference for recommending the CPS ≥ 20 threshold for pembrolizumab monotherapy and an allcomers population for pembrolizumab plus chemotherapy. The PBAC considered that this clinical approach may minimise the impact of false negative and false positive CPS test results. The ESCs noted that if pembrolizumab + chemotherapy was to be listed for allcomers (regardless of PD-L1 status) acceptance of PD-L1 testing as a valid biomarker for efficacy of pembrolizumab in this indication would not be required. However, clinicians may still prefer that PD-L1 testing is accessible to inform the treatment decision regarding the inclusion/exclusion and/or extent of chemotherapy.

Economic analysis

- 6.51 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 a CPS ≥ 1 . Both models had the same structure. 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)) which relied on outputs from EA1, EA2 and SA1. Incremental cost-effectiveness ratios (cost per quality-adjusted life-year (QALY) gained [base case] and cost per life-year-saved) were presented for each analysis and a weighted cost-utility estimate was also provided.
- 6.52 The resubmission included a number of additions and alterations that were made to the economic evaluation following the previous submission. The primary changes were:

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- Additional long-term data has been added to the economic model such that median patient follow-up has increased to ~46 months (~55 months/4.6 years maximum follow-up), with a resultant change in the extrapolation of all treatments;
- The base case CEA (CPS ≥ 1) relied on efficacy data taken directly from KN048 comparing pembrolizumab \pm chemotherapy with cetuximab plus chemotherapy (acting as a proxy for chemotherapy alone), not indirect comparisons. The cost of cetuximab was not applied in these analyses;
- While 26-27% of patients in KN048 received nivolumab treatment in the comparator arm after disease progression, it was estimated that around 50% of patients who have disease progression and receive a 2L treatment will receive nivolumab in Australia. The resubmission acknowledged that while it was elementary to capture the costs of these treatments in the economic model, adjusting the survival estimates to capture the effects of increased use of nivolumab is methodologically challenging. A two-stage adjustment for treatment switching was applied to the SoC arm to estimate the treatment effect of nivolumab, which was then upscaled to reflect 50% (revised to 43.7% in the PSCR) estimated 2L use of nivolumab in Australia; and
- In the resubmission, the transition probabilities for SoC were informed directly from the KM curves (and the extrapolations) in KN048, with 1L cetuximab plus chemotherapy serving as a proxy for 1L chemotherapy. Previously the SoC arm was informed by applying an inverse hazard ratio to the results of the pembrolizumab KM curve.

6.53 The summary of the model structure and rationale is presented in Table 15.

Table 15: Summary of model structure and rationale

Component	Description	Justification/comments
Type of analysis	Cost effectiveness analysis (cost utility analysis in the base case)	Appropriate, as used in previous model
Outcomes	Quality-adjusted life years saved (base case), life years gained	Appropriate, as used in previous model
Time horizon	7.5 years in the model base case Sensitivity analysis in resubmission considered a 10 year time horizon.	Same duration as used in previous model. The PBAC previously considered that the use of a base case 7.5 year time horizon was not reasonable based on the currently available evidence but that it may be supported with longer follow up for KN048 (paragraph 7.10, pembrolizumab PSD, November 2020 PBAC Meeting). An additional 12 months of data from KN048 has been provided in the resubmission (median patient follow up of 46 months).
Method used to generate results	Partitioned survival cohort simulation	Appropriate, as used in previous model
Health states	Progression free survival, progressive disease, death	Appropriate, as used in previous model
Cycle length	1 week	Reasonable, as used in previous model
Discount rate	5% per annum	Appropriate
Transition probabilities	No specific transition probabilities are modelled. Health state allocation over time was determined by PFS and OS curves from the KN048 trial (partitioned survival analysis) using cetuximab plus chemotherapy as a proxy for chemotherapy alone plus adjustment for 2L nivolumab use.	Compared to the previous model, different methodology has been used for health state allocation of the SoC arms (previously the HR from a fractional polynomial network meta analysis was used). An adjustment was also incorporated to factor in 2L nivolumab use in the resubmission.
Software package	Excel 2010	Appropriate, as used in previous model

R/M = recurrent or metastatic, HNSCC = head and neck squamous cell carcinoma, HR = hazard ratio, 2L = second line
Source: Table 3.1-1, p201-202 of the resubmission

6.54 In the partitioned survival cohort simulations, all patients enter the model in the progression free survival state. Each cycle (1 week), a proportion of the cohort moved to the progressed disease state (based on PFS curve in KN048) or died (based on OS curve in KN048 and baseline mortality from ABS life tables), and a proportion of the cohort in the progressed disease state died (based on the difference between the PFS and OS curves). Patients who progressed incurred a once off progression cost while patients who died incurred a terminal care cost. OS and PFS curves for pembrolizumab monotherapy and pembrolizumab plus chemotherapy were derived from the KN048 trial (direct Kaplan Meier data used until median follow up, then parametric extrapolation used until 7.5 years, the time horizon for the model). OS and PFS curves for SoC were also derived from the KN048 trial using direct Kaplan Meier data, with the comparator arm (cetuximab plus chemotherapy, upscaled to 50% 2L nivolumab use) of KN048 used as a proxy for chemotherapy alone. Patients in the progression free survival and progressed disease health states accrue health state costs associated with management of disease and utilities depending on the health state. Total life years and QALYs accrued in the cohort over the time horizon were then added

together. The ESCs considered the overall structure of the economic model was generally appropriate, though there were issues with some of the inputs.

- 6.55 The observed time on treatment (ToT) Kaplan-Meier curves from KN048 were applied, with a proportion of patients discontinuing treatment each cycle. A fixed proportion of patients who discontinue treatment each cycle (based on difference in ToT between cycles) and who were alive (based on difference in OS between cycles) were assumed to use subsequent anti-cancer therapy, which differed depending on the initial therapy. Because the use of subsequent therapies was not related to progression the proportion of patients who discontinued and received subsequent treatment was actually higher than the proportion of patients who progressed. For SoC, it was assumed that the ToT data from the cetuximab plus chemotherapy arm in KN048 would apply.
- 6.56 The PBAC previously considered that the use of a base case 7.5 year time horizon was not reasonable, based on the currently available evidence but that it may be supported with longer follow up for KN048 (paragraph 7.10, pembrolizumab PSD, November 2020 PBAC Meeting). In the March 2018 cetuximab submission, the PBAC considered a five year time horizon to be appropriate for 1L R/M HNSCC (paragraph 7.8, cetuximab PSD, March 2018 PBAC Meeting), although this was based on the EXTREME trial having 18.2-19.1 months of follow up. The ESCs also noted that the current model did not include any convergence which increases the uncertainty of the model and favours treatment with pembrolizumab over a long time horizon. While the Kaplan-Meier curves beyond 45 months appeared to suggest that the number of OS responders was beginning to plateau after four years of follow up, the number of patients who remained in the trial was very small (see Figure 1 and Figure 2) with a higher proportion of patients censored between 40 and 55 months of follow-up.
- 6.57 In KN048, around 20% of patients randomised to pembrolizumab ± chemotherapy used 2L EGFR inhibitors (such as cetuximab) and around 6% used 2L immunotherapy (likely nivolumab) after disease progression. The ESCs previously noted that cetuximab is not PBS listed for R/M HNSCC and therefore using unadjusted results from KN048 would overestimate the survival benefit for pembrolizumab in the Australian population (paragraph 6.11, pembrolizumab PSD, November 2020 PBAC Meeting). In addition, PBS subsidised 2L nivolumab would not be available to patients who have received 1L pembrolizumab under the current 2L nivolumab listing. The resubmission did not adjust for the efficacy of these 2L therapies in the pembrolizumab arms, favouring pembrolizumab. However, the PBAC noted that the use of chemotherapy plus cetuximab as a proxy for SoC favoured the comparator arm.
- 6.58 There were significant issues with the application of adverse event costs in the resubmission, these are outlined in Table 16.

Table 16: Application of adverse events associated with chemotherapy in economic model

Analysis	Pembrolizumab ± chemotherapy	SoC
EA1	<p>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.</p> <p>Duration of treatment was overestimated as chemotherapy treatment was continued past 6 cycles, which resulted in AEs being overestimated.</p>	<p>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.</p> <p>Duration of treatment was overestimated as treatment related adverse event was applied past six cycles of treatment, which resulted in AEs being overestimated.</p>
EA2	NA	

AEs = adverse events; TNA = not applicable; RAE = treatment related adverse events; SoC = standard of care

Source: Constructed during evaluation

6.59 A modified base case was constructed during the evaluation with the following adjustments:

- Change 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 and is aligned with the approach of the resubmission which acknowledged that the safety of pembrolizumab plus chemotherapy was inferior to that of SoC; and
- Change ToT for SoC arm in pembrolizumab monotherapy model (EA2) 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 overestimate of adverse events from the chemotherapy use should numerically cancel out between treatment arms and provide an increment that was reasonable (though the adverse event costs in each arm would still be overestimated).

6.60 The key drivers of the economic model identified during the evaluation are presented in Table 17.

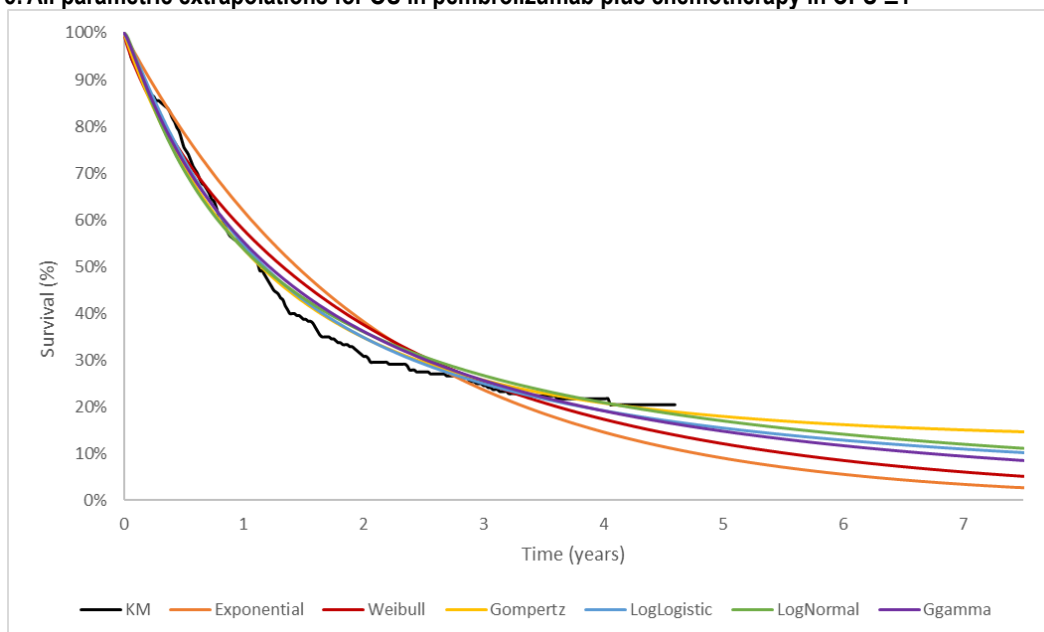
Table 17: Key drivers of the model

Description	Method/Value	Impact
Time horizon	Base case 7.5 years, extrapolated from 46 month median follow up in KN048.	High. Changing to a 5 year time horizon as per cetuximab March 2018 submission increased ICER by 39%. The effect of extrapolation diminishes significantly with shorter time horizon.
Efficacy of pembrolizumab	Extrapolation applied after around 46 months. In EA1, most optimistic extrapolation chosen. No convergence assumed	High. Using exponential function for extrapolation of pembrolizumab ± chemotherapy OS increased ICER by 29%. All alternative extrapolation functions for either pembrolizumab plus chemotherapy or SoC in EA1 increased ICER.
Source of utility	Based on utility analysis in KN048	Moderate, favours pembrolizumab. Using utility values from cetuximab March 2018 submission (PF 0.69, PD 0.52 (base case PF 0.787, PD 0.707) increases ICER by 27%.
Treatment duration of 2L nivolumab use in SoC treatment arm	Assumed 5.56-5.62 months of 2L nivolumab treatment in SoC	Moderate, favours pembrolizumab. Halving duration of 2L nivolumab used increased ICER by 18%.
Proportion of patients using 2L nivolumab in SoC treatment arm	50% use of 2L nivolumab in SoC treatment arm calculated in resubmission.	Moderate. Halving proportion using 2L nivolumab increases ICER by 10%.

2L = second line; EA = economic analysis; ICER = incremental cost effectiveness analysis; SoC = standard of care

6.61 Of all the extrapolations for OS and PFS in pembrolizumab ± chemotherapy, the model was most sensitive to changes in the OS extrapolation in the pembrolizumab plus chemotherapy arm in EA1, which was considered to be more optimistic than the previous submission. All the parametric functions fitted to the OS curve for pembrolizumab + chemotherapy are shown in Figure 5. The resubmission nominated the Gompertz function as the base case, which was the most optimistic extrapolation. The ESCs noted that none of the tested extrapolations appeared to be a good visual fit to the Kaplan-Meier data and all the extrapolations appear to overestimate OS to some degree up to around three years. The choice of the extrapolation function had a large impact on the ICER, with the exponential function estimating an ICER which was 29.5% higher than the base case. However, when the time horizon was reduced to five years this difference reduced to 4.3%, illustrating that the impact and uncertainty of the choice of extrapolation function was also influenced by the time horizon. The impact of the extrapolation of the SoC arm was much smaller than the pembrolizumab plus chemotherapy arm (no more than 6.5% change in ICER). The ESCs also noted that the suitability of extrapolation functions for OS, PFS and ToT for the CPS ≥20 population had not been assessed as these changes were proposed in the PSCR.

Figure 5: All parametric extrapolations for OS in pembrolizumab plus chemotherapy in CPS ≥ 1



KM = Kaplan Meier; CPS = combined positive score; GGamma = generalised gamma function
Source: Figure 3.4-2, p219 of the resubmission

6.62 The results of the adjusted base case of the economic evaluation for patients with R/M HNSCC and CPS ≥ 1 are presented in Table 18.

Table 18: Results of the partitioned survival cohort simulation in patients with CPS ≥1 (adjusted base case)

Component	Pembrolizumab ± chemotherapy	SoC	Increment
Pembrolizumab plus chemotherapy vs SoC (EA1)			
Cost	\$ [redacted]	\$36,760.39	[redacted]
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)			
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%)			
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

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

Text in italics indicate values calculated during the evaluation.

Source: Constructed during evaluation

The redacted values correspond to the following ranges:

¹ \$45,000 to < \$55,000

² \$55,000 to < \$75,000

³ \$75,000 to < \$95,000

- 6.63 The incremental cost per QALY gained for EA1, EA2 and the weighted analysis was higher in the adjusted base case calculated in the commentary compared to the base case presented in the resubmission. The resubmission’s model reported that the base case ICERs were \$55,000 to < \$75,000/QALY gained (EA1), \$55,000 to < \$75,000/QALY gained (EA2) and \$55,000 to < \$75,000/QALY gained (weighted ICER).
- 6.64 The ICERs were uncertain due to uncertainty in the magnitude of OS benefit for pembrolizumab ± chemotherapy compared with chemotherapy because i) 1L cetuximab plus chemotherapy was used as a proxy for 1L chemotherapy alone which may underestimate the incremental efficacy of pembrolizumab plus chemotherapy but ii) the efficacy of 2L nivolumab was likely underestimated compared to the literature and iii) the efficacy of pembrolizumab plus chemotherapy was likely overestimated as no adjustment for 2L EGFR treatment was considered.
- 6.65 The commentary modified base case ICER was likely to be underestimated due to:
- Assumption of no convergence of OS curves. The ESCs noted that the extrapolations chosen assumed a significant proportion of patients had a sustained complete response. The ESCs considered that this may be clinically plausible, though relatively few patients remained at risk in the later parts of the Kaplan-Meier curves from KN048. The ESCs noted that none of the tested extrapolations appeared to be a good visual fit to the Kaplan-Meier data and all the extrapolations appear to

overestimate OS to some degree. The PBAC noted that uncertainty in the extrapolations was somewhat mitigated by the use of a 5 year time horizon;

- The inconsistent QALY gain from SoC arm in EA1 and EA2 may have led to an overestimate of the incremental benefit for pembrolizumab plus chemotherapy. The QALY gain in the SoC arm in EA2 (with all CPS ≥ 1 patients included) was higher than the SoC arm in EA1; and
- The assumption of 100% sensitivity and specificity of CPS ≥ 1 test in the base case appears optimistic and not supported by available evidence.
- The ESCs also noted that assuming 60% monotherapy use in the resubmission may have underestimated the weighted ICER.

6.66 The upscaling of the OS HR used in the model from an increase in 2L nivolumab usage (50%) compared to in KN048 (26.38%) may have underestimated the benefit of 2L nivolumab though this may have been compensated by using 1L cetuximab plus chemotherapy as a proxy for 1L chemotherapy (which applied to the whole population). The ESCs considered that the incremental OS benefit remained uncertain due to these factors.

6.67 As described in paragraph 5.6, the PBAC considered that the basis for the resubmission's estimated proportion of patients receiving 2L nivolumab was unreliable. The PBAC considered that it was likely that closer to 80% of patients would be expected to receive 2L nivolumab in clinical practice. The PBAC noted that this further underestimated the benefit from 2L nivolumab, but also underestimated the cost for 2L nivolumab in the model.

6.68 Compared with the previous submission the requested price for pembrolizumab as monotherapy was lower (from \$ [REDACTED]/100 mg to \$ [REDACTED]/100 mg). Given the inclusion of the efficacy of 2L nivolumab in the SoC arm and the subsequently smaller incremental benefit compared to the previous submission, the lower price was consistent with the result that reported an ICER which was similar to the previous submission. However, the price for pembrolizumab when used in combination with chemotherapy increased from the previous submission (from \$ [REDACTED]/100 mg to \$ [REDACTED]/100 mg) despite the inclusion of the efficacy of 2L nivolumab in the SoC arm, with a less favourable OS HR relative to SoC (0.658 in current resubmission compared to 0.54 in the previous submission). This reflected the more favourable extrapolation assumed in the current submission for pembrolizumab plus chemotherapy. The increase in QALYs from the previous submission for pembrolizumab plus chemotherapy (0.0848) due to the updated data and extrapolation was around half of the gain in the SoC arm ostensibly from the inclusion of 2L nivolumab (0.1713).

6.69 The results of SA1 (CEA conducted in all patients enrolled in KN048 irrespective of CPS) are presented in Table 19.

Table 19: Results of scenario analysis 1, economic evaluation in all patients (adjusted base case, as calculated in the commentary)

	Pembrolizumab ± chemotherapy	SoC	Increment
Pembrolizumab plus chemotherapy vs SoC (EA1)			
Cost	\$ [REDACTED]	\$37,060.01	\$ [REDACTED]
LY	1.8736	1.3281	0.5455
QALY	1.3901	0.9899	0.4002
Weighted incremental cost per LY gained			\$ [REDACTED] ¹
Weighted incremental cost per QALY gained			\$ [REDACTED]²
Pembrolizumab monotherapy vs SoC (EA2)			
Cost	\$ [REDACTED]	\$33,877.88	\$ [REDACTED]
LY	1.7028	1.37	0.3328
QALY	1.2628	1.0226	0.2402
Weighted incremental cost per LY gained			\$ [REDACTED] ¹
Weighted incremental cost per QALY gained			\$ [REDACTED]³
Weighted pembrolizumab monotherapy (60%) and pembrolizumab plus chemotherapy (40%) ^b			
Cost	\$ [REDACTED]	\$35,150.73	\$ [REDACTED]
LY	1.7711	1.3532	0.4179
QALY	1.3137	1.0095	0.3042
Weighted incremental cost per LY gained			\$ [REDACTED] ¹
Weighted incremental cost per QALY gained			\$ [REDACTED]²

LY = life year, QALY = quality adjusted life year

Text in italics indicate values calculated during the evaluation.

Source: Source: Constructed during evaluation

The redacted values correspond to the following ranges:

¹ \$55,000 to < \$75,000

² \$75,000 to < \$95,000

³ \$95,000 to < \$115,000

6.70 In SA2, the economic model results were modified to capture the likely discordance between the diagnostic test used in the pivotal trial and the test employed in Australia for the CPS ≥ 1 measure. The resubmission assumed 96% sensitivity and specificity for the CPS test based on results from Vainer 2019. The PSCR noted that the trial data already captures false positives and false negatives that occur using the 22C3 PharmDx kit employed in the trial and the sensitivity analysis using 96% reflects potential discordance between the 22C3 Pharm Dx Kit and the 22C3 lab developed test likely to be used in Australia. The ESCs noted that the sensitivity and specificity for the CPS ≥ 20 would be different but noted that the sensitivity analyses indicated that the sensitivity and specificity of the test appeared to have a fairly minimal impact on the ICER (4.2% increase when sensitivity and specificity decreased from 96% to 85%). In SA2, the resubmission assumed that any QALY decrement in patients misclassified as false positives would be offset (on a one to one ratio) by any QALY gain in patients correctly identified as CPS >1 and treated with pembrolizumab. This may not be appropriate.

6.71 The results of key additional sensitivity analyses conducted in the commentary for the adjusted model are presented in Table 20.

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Table 20: 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		0.5987		-
	EA2		0.3501		-
	Weighted				-
Time horizon decrease to 5 years (base case 7.5 years)	EA1		0.3901		+46.97%
	EA2		0.2587		+30.55%
	Weighted				+38.83%
Apply SoC QALY from EA2 (n=255, QALY = 0.9962) to SoC in EA1 (n=235, QALY = 0.9111) ^a	EA1		0.5136		+16.57%
	EA2		0.3501		-
	Weighted				+8.19%
Use utilities from cetuximab March 2018 submission, PF 0.69, PD 0.52 (base case PF 0.787, PD 0.707)	EA1		0.4694		+27.55%
	EA2		0.2750		+27.28%
	Weighted				+27.42%
Assume 25% 2L nivolumab use in SoC (base case 50%)	EA1		0.6207		+10.42%
	EA2		0.3854		+9.79%
	Weighted				+10.36%
Halve treatment duration of 2L nivolumab use in SoC	EA1		0.5987		+14.55%
	EA2		0.3501		+20.82%
	Weighted				+17.75%
Discount rate, 0%	EA1		0.7180		-14.04%
	EA2		0.4134		-11.87%
	Weighted				-10.70%
Discount rate, 3.5%	EA1		0.6311		-4.32%
	EA2		0.3674		-3.63%
	Weighted				-1.74%
Use next best fit for parametric distribution for extrapolation	EA1 ^b		0.5596		+6.83%
	EA2 ^c		0.3454		-1.34%
	Weighted				+5.62%
Scenario analysis 2 (including PD-L1 test accuracy)					
Base case	EA1		0.457		-
	EA2		0.267		-
	Weighted				-
Decrease test sensitivity and specificity to 85% (base case 96%) ^d	EA1		0.395		+4.7%
	EA2		0.232		+3.7%
	Weighted				+4.2%

CPS = combined positive score; EA = economic analysis; PF = progression free; PD = progressed disease; QALY = quality adjusted life year; SoC = standard of care

^a Due to enrolment interruption, some SoC patients were excluded in the comparison with pembrolizumab plus chemotherapy whereas the whole SoC cohort was included in the pembrolizumab monotherapy comparison. Costs from SoC in EA2 not applied to EA1 as the estimation of adverse event costs differed between EA1 and EA2 in the modified base case.

^b For EA1, the Gompertz distribution was used to extrapolate the pembrolizumab + chemotherapy curve in the base case. The distribution with the next lowest average AIC BIC, used as the parametric function of next best fit was log logistic.

^c For EA2, the log logistic distribution was used to extrapolate the pembrolizumab monotherapy curve in the base case. The distribution with the next lowest average AIC BIC, used as the parametric function of next best fit was log normal.

^d 85% used as this was the pass mark for the concordance of the Australian pathologists training

Source: Constructed during evaluation using Section 3 workbook.xslm

The redacted values correspond to the following ranges:

¹ \$55,000 to < \$75,000

² \$75,000 to < \$95,000

³ \$95,000 to < \$115,000

- 6.72 Additional univariate sensitivity analyses around the extrapolation of OS for EA1 and EA2 were conducted. In EA1, the extrapolation for OS chosen in the base case was the most favourable for pembrolizumab plus chemotherapy. The impact of varying the extrapolation of pembrolizumab plus chemotherapy (range +2.5% to +33.8%) was higher than SoC (range +13.2% to +20.7%). In EA2, using exponential and Weibull functions for the extrapolation of pembrolizumab monotherapy led to an increase in the ICER, but all other functional forms led to decreases in the ICER. As with EA1, the extrapolation of pembrolizumab monotherapy had a greater impact (-9.4% to +19.2%) compared to SoC (-1.7% to + 8.5%).
- 6.73 A multivariate sensitivity analysis assuming a scenario with 85% test sensitivity/specificity (based on minimum concordance for pathologist training), using SoC QALY from EA2 for EA1 (see paragraph 6.65), assuming 42% 2L nivolumab use (see Table 3) for 4.06 months and 60% use of pembrolizumab plus chemotherapy (assumption) was tested during evaluation. The ICER for EA1, EA2 and the weighted ICER was \$75,000 to < \$95,000/QALY gained (+31.6%), \$75,000 to < \$95,000/QALY gained (+16.4%) and \$75,000 to < \$95,000/QALY gained (+23.1%), respectively.
- 6.74 The PSCR provided a revised economic model which reflected changes in the proposed CPS cut-off (≥ 20), and also incorporated the following additional changes:
- The AE assignment to SoC such that AEs were limited to the 18 week duration of chemotherapy;
 - A reduction of 2L nivolumab use from 50% to 43.7%.
 - The effective price of pembrolizumab was revised to \$ [REDACTED] (combination) and \$ [REDACTED] (monotherapy) per 100 mg vial resulting in a weighted ICER of \$55,000 to < \$75,000/QALY gained.
- 6.75 The results of the PSCR economic model (CPS ≥ 20 for monotherapy), the Commentary respecified base case model (correcting AE costs) with the resubmission prices and PSCR revised prices are shown in Table 21.

Table 21: Comparison of results of economic model across PSCR and resubmission using new and previous price

Incremental component	PSCR model with new price and updated model	Respecified base case constructed during evaluation using new price	Respecified base case constructed during evaluation using previous price ^a
Pembrolizumab plus chemotherapy vs SoC, CPS ≥1 (EA1)			
Cost (\$)	██████████	██████████	██████████
LY	0.8258	0.8178	0.8178
QALY	0.6043	0.5987	0.5987
Cost per LY gained	██████████ ¹	██████████ ¹	██████████ ²
Cost per QALY gained	██████████ ³	██████████ ³	██████████ ³
Pembrolizumab monotherapy vs SoC, CPS ≥20 (EA2)			
Cost (\$)	██████████	██████████	██████████
LY	0.6856	0.6716	0.6716
QALY	0.5163	0.5063	0.5063
Cost per LY gained	██████████ ²	██████████ ²	██████████ ²
Cost per QALY gained	██████████ ³	██████████ ³	██████████ ³

CPS = combined positive score; LY = life year, QALY = quality adjusted life year, SoC = standard of care

^a Results for the pembrolizumab monotherapy model were not presented in the Commentary as model results from the CPS≥20 subgroup were not considered.

Source: Constructed for ESC.

The redacted values correspond to the following ranges:

¹ \$35,000 to < \$45,000

² \$45,000 to < \$55,000

³ \$55,000 to < \$75,000

6.76 The ESCs noted that the revised model had not been fully evaluated as it was provided with the PSCR. The ESCs observed the following regarding the changes to the economic model as provided with the PSCR:

- The revised OS and PFS values would be expected to reduce the ICER, based on more favourable results in the CPS ≥20 subgroup for monotherapy. Incremental QALYs in EA 2 were increased from 0.3501 in the resubmission to 0.5063 as a result of the change in CPS cut-off (based on the respecified base case constructed during the evaluation).
- The revised ToT resulted in increased incremental costs for pembrolizumab (from \$██████████ to \$██████████) as patients in the CPS ≥20 subgroup stayed on treatment longer.
- The reduction in 2L nivolumab from 50% to 43.7% would be expected to reduce costs in the comparator arm and result in a very small reduction in LY/QALY in the comparator arm as the adjustment to the HR for 2L nivolumab was very small.
- Overall, the reduction in price proposed in the PSCR had a relatively small impact on the ICER.

6.77 Although the PSCR model wasn't evaluated, the PBAC considered it reliable for decision-making on the basis of a comparison of the results for the revised and evaluated models. Taking into consideration the effectiveness in the CPS ≥20

population and the safety advantage for monotherapy, the PBAC considered that it is likely that when used as monotherapy for patients with high CPS (≥ 20) pembrolizumab provides a similar level of cost-effectiveness as when used in combination with chemotherapy in the broader population.

- 6.78 The PBAC noted that in the pre-PBAC response the proposed price was reduced for pembrolizumab monotherapy such that it was equal to the proposed price for pembrolizumab when used in combination with chemotherapy. The PBAC noted that the total drug cost/patient/course was similar between monotherapy (in patients with CPS ≥ 20) and combination therapy (in the ITT population) as the small additional cost of chemotherapy was offset by the small difference in treatment duration (see paragraph 6.81). This approach helped to address uncertainty regarding the proportion of patients undergoing monotherapy vs combination therapy and impact on cost-effectiveness.
- 6.79 The PBAC considered that the inputs for the respecified base case model and weighting calculations should be revised in the following ways:
- Assume a cut-off of CPS ≥ 20 for pembrolizumab monotherapy and an allcomers population for pembrolizumab plus chemotherapy as reflects the preferred clinical approach to treatment, as described in paragraphs 1.4-1.5);
 - Reduce the time horizon to five years to address the uncertainty in extrapolations, especially given the additional uncertainty in extrapolations introduced by changing the CPS cut-off for the monotherapy, as described in paragraphs 6.62 and 6.66;
 - Increase the proportion of patients treated with 2L nivolumab to 80% to reflect clinical practice, as described in paragraphs 5.6 and 6.68;
 - Revise the ICER weighting to 30% monotherapy use, as described in paragraph 1.8; and
- 6.80 The PBAC noted that when respecified in this way, and using the price proposed in the pre-PBAC response (\$ [REDACTED]/200 mg), the models resulted in a weighted ICER of \$75,000 to < \$95,000/QALY gained and would require a price reduction of around 17% to reach an ICER of \$55,000 to < \$75,000/QALY gained. The PBAC also noted that using a CPS ≥ 1 threshold for pembrolizumab plus chemotherapy and assuming 40% monotherapy resulted in a weighted ICER of \$55,000 to < \$75,000/QALY gained and would require a price reduction of around 6% to reach an ICER of \$55,000 to < \$75,000/QALY gained.

Drug cost/patient/course

- 6.81 In the resubmission the number of doses per course was 11.71 for pembrolizumab plus chemotherapy (\$ [REDACTED]/200 mg) and 10.49 for pembrolizumab monotherapy

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(\$ [REDACTED]/200 mg), based on the CPS ≥ 1 threshold. In the model the time on treatment was dependent on the patient population assumed. For the revised patient populations the PBAC considered preferable, with revised prices as per the pre-PBAC response the drug cost/patient/course was:

- \$ [REDACTED]/patient/course for use as combination treatment in the ITT population, where the treatment duration in the economic model was 11.41 doses per course, at \$ [REDACTED]/200 mg. The total cost/patient/course including chemotherapy costs was \$ [REDACTED].
- \$ [REDACTED]/patient/course for use as monotherapy in the CPS ≥ 20 population, where the treatment duration was 11.83 doses per course, at \$ [REDACTED]/200 mg.

6.82 There were inconsistencies between the dosages used in the economic evaluation and the financial estimates. A comparison of dosages in the resubmission is presented in Table 22. The PBAC noted that the number of doses of pembrolizumab assumed in the financial estimates reflected the duration for monotherapy in the CPS ≥ 1 population (10.49 doses) and treatment duration would be expected to be higher for use in both the CPS ≥ 20 population (for monotherapy) and the ITT population (for combination therapy).

Table 22: Comparison of dosages of medications used in resubmission (CPS ≥ 1)

	KN048 dosage (no. of doses)		Economic Model dosage (no. of doses)		Financial estimates dosage (no. of doses)	
	Pembro	SoC	Pembro	SoC	Pembro	SoC
Pembrolizumab + chemotherapy						
Pembrolizumab Q3W	200mg (10.87) ^a	-	200mg (11.71)	-	200mg (10.49) ^b	-
Cisplatin Q3W ^c	100mg/m ² (NR) ^d		200mg (4.98)	200mg (4.95)	1600 mg (7.19)	1600 mg (9.52)
Carboplatin Q3W ^c	AUC 5mg/mL/min (NR) ^d		600mg (4.98)	600mg (4.95)	500mg (7.19)	500mg (9.52)
5-FU Q3W	1,000mg/m ² /day, day 1-4 each cycle (NR) ^d		7000mg (4.98)	7000mg (4.95)	6,410 mg (7.19)	6,410 mg (9.52)
2L Nivolumab Q2W	240mg (NR)	240mg (NR)	-	240mg (12.21) ^f	-	240mg (12.05)
Pembrolizumab monotherapy						
Pembrolizumab Q3W	200mg (9.91) ^a	-	200mg (10.49)	-	200mg (10.49) ^b	-
Cisplatin Q3W ^c	-	100mg/m ² (NR) ^e	-	200mg (4.96)	1600 mg (7.19)	1600 mg (9.52)
Carboplatin Q3W ^c	- ^d	AUC 5mg/mL/min (NR) ^e	-	600mg (4.96)	500mg (7.19)	500mg (9.52)
5-FU Q3W	-	1,000mg/m ² /day, day 1-4 each cycle (NR) ^e	-	6500mg (4.96)	6,410 mg (7.19)	6,410 mg (9.52)
2L Nivolumab Q2W	240mg (NR)	240mg (NR)	-	240mg (11.99) ^g	-	240mg (12.05)

Source: Table 2.5-21, p105-106 of resubmission, section 3 workbook.xlsx and section 4 workbook HNSCC.xlsx

NR = not reported; Pembro = pembrolizumab; Q2W = every two weeks; Q3W = every three weeks; SoC = standard of care

^a mean dose reported

^b 5.25 assumed for grandfathered patients

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^c 42% cisplatin and 58% carboplatin assumed

^d Mean dose of chemotherapy not reported in KN048 CSR, and duration of chemotherapy was not reported separate to pembrolizumab or to cetuximab in KN048 CSR. However a maximum of 6 cycles of chemotherapy given as per protocol. Mean BSA 1.74m² in SoC for pembrolizumab plus chemotherapy

^e Mean BSA 1.60m² in SoC for pembrolizumab monotherapy

^f Estimated by dividing 2L nivolumab cost (\$11,271.72) at by \$2645.07 every two weeks, including administration, then divided by proportion receiving 2L nivolumab in SoC (46.21%) and by the sum of newly discontinued patients for SoC (0.7551)

^g Estimated by dividing 2L nivolumab cost (\$11,053.38) at by \$2645.07 every two weeks, including administration then divided by proportion receiving 2L nivolumab in SoC (46.21%) and by the sum of newly discontinued patients for SoC (0.7551)

Estimated PBS usage & financial implications

6.83 This resubmission was not considered by DUSC.

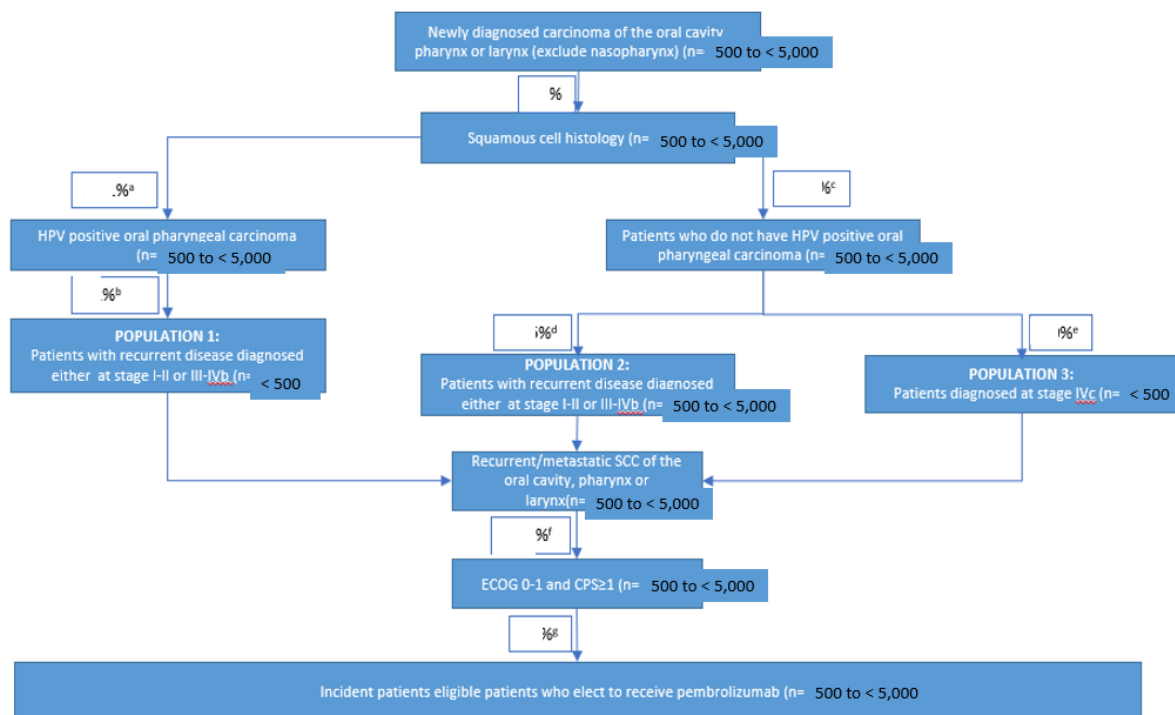
6.84 The resubmission presented an epidemiological approach to estimate the financial impact of listing pembrolizumab ± chemotherapy in patients with previously untreated recurrent or metastatic SCC of oral cavity, pharynx or larynx incurable by local therapies with CPS ≥1 and ECOG 0-1. The resubmission claimed that a total of three possible pathways to treatment initiation in incident patients were presented:

- Pathway 1: Patients recurrent from HPV +ve oropharyngeal carcinoma. While most head and neck cancers result from exposure to tobacco and/or alcohol, 90% of oropharyngeal carcinomas are related to infection with the HPV virus, particularly HPV 16. HPV+ve oropharyngeal cancers have shown to be very responsive to chemotherapy treatment and have a better prognosis than HPV-ve patients.
- Pathway 2: Patients recurrent from HPV-ve head and neck cancers. These are patients with cancers of the oral cavity, hypopharynx and larynx, as well as 10% of patients who have HPV-ve oropharyngeal cancer.
- Pathway 3: Patients initially diagnosed with metastatic (Stage IVc) cancer. Of all patients diagnosed with HPV-ve head and neck cancers, 10% of them are diagnosed with metastatic disease according to KSLs.

6.85 While three pathways were presented in the resubmission rather than the seven pathways presented in the previous submission, overall the pathways were similar. Figure 6 provides a diagram of these pathways, with patient numbers for the first year of listing (2022) for reference. An additional two pathways used to estimate prevalent patients were presented in the resubmission:

- Pathway 4: prevalent R/M HNSCC patients (not currently treated with pembrolizumab); and
- Pathway 5: grandfathered patients (prevalent R/M HNSCC patients already treated with pembrolizumab).

Figure 6: Flowchart of estimation of patient numbers in year one of listing (2022)



- a Assume █% of all SCC being oral pharyngeal carcinomas, of which █% of patients were HPV positive (█% x █% = █%).
- b Assume █% of patients diagnosed with stage I-II disease, then █% having recurrent disease (█% x █% = █%). Assumes █% of patients diagnosed with stage III-IVb disease, then █% having recurrent disease (█% x █% = █%). Total: █% + █% = █%
- c Patients who do not have HPV positive oral pharyngeal carcinoma (█% - █% = █%)
- d Assume █% of patients diagnosed with stage I-II disease, then █% having recurrent disease (█% x █% = █%). Assumes █% of patients diagnosed with stage III-IVb disease, then █% having recurrent disease (█% x █% = █%). In the previous submission, proportion was further split into those treated with radiotherapy ± surgery (█% of patients with █% recurrence) or chemo, radiotherapy ± surgery (█% of patients with █% recurrence) Total: █% + █% = █% Proportions of recurrent patients derived by back calculating figures provided in Table 4.2-3, p269 of the resubmission.
- e Assume █% of patients are diagnosed at stage IV disease
- f Assume proportion of patients with ECOG 0-1 is 77.3% and proportion of patients with CPS ≥ 1 is █%. (█% x █% = █%)
- g Assume █% of eligible patients elect to receive treatment with pembrolizumab.

SCC = squamous cell carcinoma, HPV = Human papillomavirus, ECOG = Eastern Cooperative Oncology Group performance score, CPS = combined positive score

Source: Created during evaluation using information from Table 4.2-1, p266, Table 4.2-2, p267, Table 4.2-3, p269, Table 4.2-4, p269 of the resubmission

6.86 The various sources used to inform the financial impact of listing pembrolizumab were similar to those used in the previous submission and are presented in Table 23.

Table 23: Data sources used to calculate the financial impact of pembrolizumab

Data source	Purpose
AIHW, 2020	Inform incidence and prevalence of head and neck carcinoma in Australia
2014 Review of the Cancer Medicines in the WHO List of Essential Medicines. Locally advanced squamous carcinoma of the head and neck	Inform SCC percentage
GLANCE study	Proportion of ECOG 0 or 1
PBAC (paragraph 6.78, pembrolizumab PSD, November 2020 PBAC Meeting)	Prevalence of CPS \geq 1
KN048	Dosage and usage of medications
Expert opinion (Key Scientific Leaders)	Staging of disease at diagnosis, proportion of patients who are HPV positive, proportion treated with surgery \pm RT or chemo + RT \pm surgery, usage of pembrolizumab (weighting of combination therapy vs monotherapy)
Kolli 2000, Hosal 2000	Recurrence rate with surgery \pm RT in patients with Stage III-IVb cancer
PBS and MBS schedule	Unit costs for drugs and administration

AIHW = Australian Institute of Health and Welfare; CPS = combined proportion score; ECOG = Eastern Cooperative Oncology Group; RT = radiotherapy; SCC = squamous cell carcinoma
Source: constructed during evaluation

6.87 The estimated use and financial implications for listing pembrolizumab in patients with R/M HNSCC CPS \geq 1 are summarised in Table 24.

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Table 24: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Projected SCC of the oral cavity, pharynx, larynx cancers (exclude nasopharyngeal)	■ ¹	■ ¹	■ ¹	■ ¹	■ ¹	■ ¹
Estimated extent of use of pembrolizumab (R/M SCC of oral cavity, pharynx or larynx, ECOG 0-1, CPS ≥1)						
Population 1: HPV positive oral pharyngeal carcinoma	■ ²	■ ²	■ ²	■ ²	■ ²	■ ²
Population 2: Patients recurrent from HPV negative HNSCC	■ ²	■ ²	■ ²	■ ²	■ ²	■ ²
Population 3: Patients diagnosed at stage IVc	■ ²	■ ²	■ ²	■ ²	■ ²	■ ²
Population 4: prevalent R/M HNSCC patients (not currently treated with pembrolizumab)	■ ²	-	-	-	-	-
Pathway 5: grandfathered patients ^a	■ ²	-	-	-	-	-
Total treated patients: incident + prevalent + grandfathered ^b	■ ¹	■ ¹	■ ¹	■ ¹	■ ¹	■ ¹
Estimated financial implications of pembrolizumab ± chemotherapy to the PBS/RPBS						
Cost of pembrolizumab	■ ³	■ ³	■ ³	■ ³	■ ³	■ ³
Cost of chemotherapy ^c	■ ⁴	■ ⁴	■ ⁴	■ ⁴	■ ⁴	■ ⁴
Copayments	■ ⁴	■ ⁴	■ ⁴	■ ⁴	■ ⁴	■ ⁴
Cost to PBS/RPBS less copayments	■ ³	■ ³	■ ³	■ ³	■ ³	■ ³
Estimated financial implications of administration of pembrolizumab ± chemotherapy to the MBS						
Cost to MBS	■ ⁴	■ ⁴	■ ⁴	■ ⁴	■ ⁴	■ ⁴
Estimated financial implications for SoC to the PBS/RPBS						
Cost of 1L chemotherapy offset	■ ⁴	■ ⁴	■ ⁴	■ ⁴	■ ⁴	■ ⁴
Cost of 2L nivolumab offset ^d	■ ⁵	■ ⁴	■ ⁴	■ ⁴	■ ⁴	■ ⁵
Copayments	■ ⁴	■ ⁴	■ ⁴	■ ⁴	■ ⁴	■ ⁴
Total cost offset net copayment	■ ⁵	■ ⁵	■ ⁵	■ ⁵	■ ⁵	■ ⁵
Estimated financial implications of administration offset of SoC to the MBS						
Cost to MBS	■ ⁴	■ ⁴	■ ⁴	■ ⁴	■ ⁴	■ ⁴
Net financial implications						
Net cost to PBS/RPBS	■ ⁵	■ ⁵	■ ⁵	■ ⁵	■ ⁵	■ ⁵
Total cost administration	- ■ ⁴	- ■ ⁴	- ■ ⁴	- ■ ⁴	- ■ ⁴	- ■ ⁴
Cost of CPS testing ^e	■ ⁴	■ ⁴	■ ⁴	■ ⁴	■ ⁴	■ ⁴
Net cost to MBS ^f	- ■ ⁴	- ■ ⁴	- ■ ⁴	- ■ ⁴	- ■ ⁴	- ■ ⁴
Net cost to PBS/RPBS/MBS	■ ⁵	■ ⁵	■ ⁵	■ ⁵	■ ⁵	■ ⁵

^a In year 1 the < 500 grandfathered patients were removed from the prevalent R/M HNSCC population to avoid double counting.

^b Assumes ■% uptake in all eligible patients

^c Assumes ■% of patients use pembrolizumab plus chemotherapy

^d Assumes ■% of patients use 2L nivolumab

^e 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.

^f PD-L1 test and cost of administration for pembrolizumab minus cost of SoC administration

Text in italics indicate values calculated during evaluation

Source: constructed during evaluation using information from Section 4 Workbook (1L HNSCC).xlsx

The redacted values correspond to the following ranges:

¹ 500 to < 5,000

² <500

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³ \$20 million to < \$30 million

⁴ \$0 to < \$10 million

⁵ \$10 million to < \$20 million

- 6.88 At year 6, the estimated number of patients was 500 to < 5,000 and the net cost to the PBS/RPBS would be \$10 million to < \$20 million. This was reduced from the previous submission where at year 6 the estimated number of patients was 500 to < 5,000 and the estimated net cost to PBS/RPBS was \$20 million to < \$30 million. The PBAC noted that the overall estimates were lower than in the previous submission due to the lower unit cost of pembrolizumab and higher offsets. The patient numbers were slightly lower due to a lower CPS ≥ 1 prevalence assumed, and a lower average number of pembrolizumab doses was assumed (10.49 instead of 10.743 in prevalent and incident patients and 5.25 instead of 10.743 in grandfathered patients). However the cost of chemotherapy (when used with pembrolizumab) increased due to increased number of doses assumed (7.19 instead of 4.98). Administration cost also increased due to the change in the MBS item unit costs.
- 6.89 Errors in the estimation of cost offsets from other medicines were corrected during the evaluation, however the following issues remained:
- The proportion of prevalent patients may be underestimated. As in the previous submission, a five-year mortality rate of 5.3% was inappropriately applied to estimate the proportion of prevalent patients who would be alive after two years (and could experience a recurrence), however the PBAC considered that the methods for estimation of the incident population were also uncertain and the overall population appears overestimated;
 - The number of doses of chemotherapy assumed exceeds the recommended number of cycles (six), however chemotherapy costs were relatively small; and
 - The administration cost of nivolumab may be overestimated as the resubmission assumed nivolumab would be given every two weeks instead of every four weeks.
- 6.90 Compared to the previous submission, the cost offsets were of a higher magnitude due to increased number of doses assumed for nivolumab (12.05 every two weeks instead of 4.06 every four weeks) and chemotherapy (9.52 instead of 4.6) and higher administration costs due to updated MBS item numbers, however a lower proportion of patients using nivolumab was assumed (50% instead of 66.7%). The PBAC considered that around 80% of patients would receive nivolumab, therefore the cost offsets from nivolumab are likely to be substantially underestimated.
- 6.91 The financial estimates were sensitive to changes in the number of doses of pembrolizumab and 2L nivolumab assumed. Using the average doses from pembrolizumab plus chemotherapy instead of pembrolizumab monotherapy (11.7 doses, a proportional increase of 11.5% from 10.46 doses in the base case) in KN048, or using the number of 2L nivolumab doses from the previous submission (8.80 doses over 4.06 months) increased expenditure each year by 19-22%. Higher uptake (100%)

or if all patients were considered eligible irrespective of CPS, also increased the financial estimates by at least 17% per annum.

6.92 The PSCR provided updated financial estimates incorporating the following changes:

- Revised pembrolizumab prices;
- Revised split of monotherapy to combination therapy to reflect the increased CPS threshold for CPS monotherapy (from 60% to 40% monotherapy), which the ESCs considered was not well-justified;
- Decrease in the duration of nivolumab (from 24.09 weeks to ~16.6 weeks);
- Increase in the number of pembrolizumab doses assumed (from 10.49 up to 11.22);
- Increase in the number of patients in year 1 due to changes in prevalent patient estimate to use the 2-year survival of 27% (estimated from the SoC arm of EXTREME) from the previous 5-year survival of 5.3%. This increased the eligible patient pool in year 1 from < 500 to < 500 and
- Changes to chemotherapy use so that it did not exceed six cycles (18 weeks) for both pembrolizumab + chemotherapy (resubmission: 21.58 weeks) and for offsets (resubmission: 28.58 weeks, PSCR 14.28 weeks assumed).

6.93 The revised financial estimates are shown in Table 25. The ESCs noted that the net cost to the PBS for pembrolizumab ± chemotherapy was increased in the PSCR's revised financial estimates.

Table 25: Overall net cost to PBS/RPBS with 1L chemotherapy and 2L nivolumab offset included

	2022	2023	2024	2025	2026	2027
Cost to PBS/RPBS of 1L pembrolizumab listing PSCR (no offsets for SoC)	██████████ ¹	██████████ ²	██████████ ²	██████████ ²	██████████ ²	██████████ ²
SoC offsets to PBS/RPBS PSCR	██████████ ³	██████████ ³	██████████ ³	██████████ ³	██████████ ³	██████████ ³
Net cost to PBS/RPBS (PSCR)	██████████ ²	██████████ ⁴	██████████ ⁴	██████████ ⁴	██████████ ⁴	██████████ ⁴

1L = first line; 2L = second line

Source: Table 3 of the PSCR, Table PBAC.23, MSAC 1522.1/PBAC 7.09.COM.72, PSCR revised financial estimates worksheet

The redacted values correspond to the following ranges:

¹ \$30 million to < \$40 million

² \$20 million to < \$30 million

³ \$0 to < \$10 million

⁴ \$10 million to < \$20 million

6.94 Due to the complicated nature of the epidemiological approach and the large number of assumptions (many of which could not be independently verified), the PBAC considered that the net financial impact of listing pembrolizumab as presented in the resubmission was highly uncertain. The PBAC considered that a more reliable approach would be to estimate the proportion of HNSCC patients treated with 2L

nivolumab and apply this to the 2L nivolumab PBS patient numbers to estimate the 1L population eligible for treatment with pembrolizumab. The PBAC considered that based on the number of patients treated with nivolumab as second line treatment for R/M HNSCC the number of incident patients appeared to be substantially overestimated.

- 6.95 The PBAC noted that values from DUSC indicated that < 500 patients were treated with nivolumab for HNSCC in 2019. Assuming 20% (<500) of these patients were in the early recurrent setting, < 500 patients (< 500x80%) would be receiving nivolumab in the 2L R/M HNSCC setting. Assuming 80% of 1L R/M HNSCC patients would be treated with 2L nivolumab the number of 1L R/M HNSCC patients eligible for pembrolizumab treatment (without applying a PD-L1 cut-off) would be < 500 (< 500/80%). The PBAC considered that this would be the maximum number of patients eligible for pembrolizumab treatment and the financial estimates should be revised to reflect this, with adjustment for annual changes to patient numbers. However, not all patients would be suitable for treatment with pembrolizumab plus chemotherapy and the number of patients eligible for monotherapy with pembrolizumab would be dependent on the proportion of patients with CPS ≥ 20 and requested that the MSAC provide advice regarding the population size based on the different CPS thresholds (see paragraph 1.6).
- 6.96 The PBAC considered that on this basis a small increase in the caps for 2L nivolumab would be warranted to account for: (1) up to 20% total additional patients (including 1L pembrolizumab patients + early relapse patients treated with nivolumab) and (2) a longer treatment duration expected in the 1L setting. The PBAC noted that the increase to caps would be reduced if the listing for pembrolizumab plus chemotherapy is restricted to the CPS ≥ 1 population.

Quality use of medicines

- 6.97 The resubmission stated that as pembrolizumab belongs to a new immunotherapy class it is important that resources are devoted to ensuring appropriate use in clinical practice. The sponsor noted that it will develop education materials on how to identify and manage adverse events, with educational programs and activities including face to face workshop sessions at conferences and also a medical information service hotline.

Financial management – risk sharing arrangements

- 6.98 The resubmission indicated that the sponsor is willing to enter into a risk sharing arrangement (RSA) with the Commonwealth to manage any risks to the overall costs to the PBS. The sponsor noted that there is currently an RSA in place for nivolumab for the 2L treatment of HNSCC and the sponsor proposed joining this RSA whereby the current annual subsidisation caps are increased to reflect the additional number of

patients receiving pembrolizumab and the increased cost of treatment with pembrolizumab net of the nivolumab offset. The expanded annual subsidisation caps would then be shared between nivolumab and pembrolizumab in their relevant lines of therapy. The resubmission stated that for the purpose of the RSA, the sponsor has agreed to reimburse the Commonwealth with a “considerable proportion of the treatment costs of pembrolizumab, should use exceed the subsidisation cap in that year”. The PBAC considered that a small increase in the existing caps for nivolumab would be justified as outlined in paragraph 6.96.

For more detail on PBAC’s view, see section 7 PBAC outcome.

7 PBAC Outcome

- 7.1 The PBAC deferred its decision regarding pembrolizumab for first line treatment of R/M SCCN. 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 allcomers population (regardless of PD-L1 status). The PBAC considered that, based on the results of the Keynote 048 trial, it is not possible to conclude that patients with CPS < 1 derive no benefit from pembrolizumab plus chemotherapy. A statistically significant survival benefit was observed in the allcomers population treated with pembrolizumab plus chemotherapy at the interim analysis, final analysis and at four years follow-up. The PBAC advised that, on this basis, it was preferable that listing of pembrolizumab in combination with chemotherapy not exclude patients with CPS < 1 . The PBAC considered that the claim of superior comparative effectiveness for pembrolizumab monotherapy was adequately supported by the data for patients with CPS ≥ 20 . The PBAC was of a mind to recommend listing of pembrolizumab for these populations as the committee considered that the incremental cost-effectiveness ratios could be brought into an acceptable range with a price reduction, noting that the areas of uncertainty in the economic model had been somewhat reduced by the resubmission. The PBAC noted that advice from the Medical Services Advisory Committee (MSAC) was required regarding the PD-L1 testing component of the codependent submission. Subject to this advice, the PBAC expressed a preference for recommending the CPS ≥ 20 threshold for pembrolizumab monotherapy and an allcomers population for pembrolizumab plus chemotherapy, noting that a greater price reduction would be required for the latter broader population compared to restricting to a CPS ≥ 1 threshold.
- 7.2 The PBAC considered there is a high clinical need for a first-line immunotherapy treatment option for this difficult to treat cancer. The PBAC noted advice from the sponsor hearing and from Head and Neck Cancers Australia indicating that there has been a shift from older patients with disease related to smoking and alcohol exposure to a younger patient population who are otherwise well, with disease related to exposure to HPV.

- 7.3 The PBAC noted that the resubmission requested PBS listing for 1L treatment of R/M HNSCC in patients whose tumours express PD-L1 CPS ≥ 1 . In the PSCR, the requested population was revised to patients whose tumours express PD-L1 CPS ≥ 20 for pembrolizumab monotherapy. The PBAC recalled that the NCCN guidelines recommend use of pembrolizumab monotherapy in patients with CPS ≥ 20 . The PBAC considered that the requested CPS cut-off of ≥ 20 for patients treated with monotherapy appeared appropriate and addressed its previous concerns regarding the clinical effectiveness for monotherapy in patients with low CPS scores (1-20) and the potential for worse outcomes in patients with false positive CPS results. The PBAC requested advice from MSAC regarding the PD-L1 testing prerequisite, specifically around the practical difference between CPS thresholds of ≥ 1 and ≥ 20 .
- 7.4 The PBAC also recalled it had previously noted that the NCCN guidelines recommend first-line pembrolizumab plus chemotherapy regardless of PD-L1 status and the CPS < 1 subgroup in KN048 was too small to conclude that pembrolizumab plus chemotherapy had no effect in this subgroup (paragraph 7.9, pembrolizumab PSD, November 2020 PBAC Meeting). The PBAC noted that the OS HR for pembrolizumab plus chemotherapy in the ITT population at the final analysis (0.72 95%CI: 0.60, 0.87) and four year follow up (0.71 95%CI: 0.59, 0.85) were consistent with the statistically significant primary outcome based on IA2 data (0.71 95% CI: 0.57, 0.88). Noting the statistically significant OS benefit in the ITT population of KN048, the PBAC considered that a broad listing for pembrolizumab plus chemotherapy (irrespective of CPS) would be preferable, to ensure subsidised access for all R/M HNSCC patients who would potentially benefit from treatment with pembrolizumab, and to avoid any delay to starting treatment whilst waiting for the test results.
- 7.5 The PBAC considered that the indication “recurrent or metastatic squamous cell carcinoma of the oral cavity, pharynx or larynx” was appropriate and consistent with the indication for nivolumab in the 2L setting. The PBAC noted that the requested restrictions concerning PD-L1 CPS would need to be amended to reflect the revised populations. The PBAC also considered that a single listing (rather than separate listings for monotherapy and combination therapy) was preferable as it would be simpler for prescribers.
- 7.6 The resubmission nominated SoC, defined as 1L chemotherapy followed by 2L nivolumab in 50% of patients, as the comparator. The PBAC had previously accepted that SoC was the appropriate comparator, and noted that current SoC consists of 1L chemotherapy alone followed by 2L nivolumab for a proportion of patients. The PBAC considered that the use of 2L nivolumab appears to be underestimated in the resubmission’s calculations. The PBAC considered that the resubmission’s estimated proportion of R/M HNSCC patients treated with 2L nivolumab was highly uncertain as the sponsor’s calculations relied on assumptions regarding the number of patients to be treated with pembrolizumab from the complicated epidemiological approach presented in the financial estimates. The PBAC considered that the proportion of R/M HNSCC patients receiving 2L nivolumab in practice would be expected to be closer to

80% as the majority of patients are well enough to receive 2L treatment, especially given the general shift to younger patients who are otherwise well.

- 7.7 The PBAC noted that the resubmission based the clinical claim and clinical outcomes in the economic model on the results of KN048 alone, using 1L cetuximab + chemotherapy as a proxy for 1L chemotherapy alone. The PBAC noted that the resubmission also sought to address previous concerns regarding protocol amendments, TPS stratification and the multiplicity strategy for testing statistical significance applied in KN048. Results from an additional 12 months of follow-up from KN048 with data cut off date of 18 February 2020 (referred to as four year follow-up) compared to the previous submission were also presented. The PBAC noted that these results were consistent with outcomes reported at the interim analysis and final analysis.
- 7.8 In addition, the resubmission sought to address the PBAC's previous concern that the impact of 2L nivolumab on the incremental efficacy estimates should be considered to reflect current SoC. In the absence of head to head data comparing pembrolizumab ± chemotherapy to chemotherapy followed by 2L nivolumab, the impact of 2L nivolumab was accounted for using a two-stage model to upscale the proportion of patients with 2L nivolumab use in the comparator arm of the KN048 trial (around 26%). The PBAC noted that when upscaled to 50% as assumed by the resubmission, the adjustment resulted in only minor changes to the hazard ratios (pembrolizumab monotherapy OS HR=0.74, adjusted OS HR=0.77; pembrolizumab plus chemotherapy OS HR=0.65, adjusted OS HR=0.66). The PBAC considered that this adjustment appeared to have underestimated the benefit from 2L nivolumab (see paragraph 6.23) and, as the proportion of 2L nivolumab use was underestimated, the benefit was further underestimated. In addition, no adjustment was made for EGFR inhibitors which were used as 2L treatment in 18-24% of patients in the pembrolizumab arms, which potentially favoured pembrolizumab. However, the PBAC considered that overall these factors may have been somewhat balanced by the use of chemotherapy plus cetuximab as a proxy for SoC. Overall the PBAC considered that there remains uncertainty regarding the magnitude of incremental benefit for pembrolizumab ± chemotherapy.
- 7.9 The PBAC recalled it had previously accepted the clinical claim of superiority for pembrolizumab plus chemotherapy compared to 1L chemotherapy alone in patients whose tumour express CPS ≥ 1 (paragraph 7.6, pembrolizumab PSD, November 2020 PBAC Meeting). The PBAC also considered that based on results of the KN048 trial pembrolizumab plus chemotherapy is superior to 1L chemotherapy alone in the full population (regardless of CPS status), though there is likely to be a larger effect with higher CPS score. The PBAC also recalled that it previously considered that pembrolizumab plus chemotherapy was likely inferior in safety to chemotherapy alone and noted that the basis for this conclusion was unchanged.

- 7.10 The PBAC considered that the claim of superior comparative effectiveness in the CPS ≥ 20 population was reasonable based on the results of the KN048 trial. The PBAC recalled that it previously noted that the safety profile of pembrolizumab monotherapy (mainly immune related) was different to the profile of chemotherapy alone, but considered that the claim of superior safety was reasonable given the known safety profile and mechanism of action of pembrolizumab (paragraph 7.7, pembrolizumab PSD, November 2020 PBAC Meeting).
- 7.11 The PBAC noted that the resubmission's economic analysis addressed a number of its previous concerns by using the KM curves from KN048 and including both costs and outcomes from 2L nivolumab treatment. However, the PBAC considered that the economic analysis was limited by the uncertainty in the magnitude of clinical benefit for pembrolizumab \pm chemotherapy. The PBAC noted that use of the CPS ≥ 20 population for monotherapy reduced the ICER as pembrolizumab was assumed to have improved efficacy in this group relative to the CPS ≥ 1 population. Conversely the use of the ITT population for combination therapy increased the ICER as efficacy in the broader population was lower.
- 7.12 The PBAC noted that none of the tested extrapolations appeared to be a good visual fit to the Kaplan-Meier data and the choice of the extrapolation function had a large impact on the ICER. The Gompertz function chosen in the base case was the most favourable for pembrolizumab. The model did not include any convergence which increased the uncertainty of the model over a longer time horizon. The PBAC also noted that extrapolation functions for the CPS ≥ 20 and ITT populations had not been assessed in detail as the resubmission initially requested the CPS ≥ 1 population for pembrolizumab \pm chemotherapy.
- 7.13 The PBAC recalled it previously considered that, based on the currently available evidence, the use of a base case 7.5 year time horizon was not reasonable, but that it may be supported with longer follow up for KN048 (paragraph 7.10, pembrolizumab PSD, November 2020 PBAC Meeting). Although additional follow-up was provided from KN048, the PBAC noted that the sensitivity of the model to the choice of extrapolation function was dependent on the time horizon and the impact of the extrapolation function was substantially reduced when a time horizon of 5 years was used.
- 7.14 The PBAC considered that, to reflect its preferred eligible populations, the inputs for the respecified base case model and weighting calculations should be revised in the following ways:
- Assume a cut-off of CPS ≥ 20 for pembrolizumab monotherapy and an allcomers population for pembrolizumab plus chemotherapy as reflects the preferred clinical approach to treatment, as described in paragraphs 1.4-1.5);
 - Reduce the time horizon to five years to address the uncertainty in extrapolations, especially given the additional uncertainty in extrapolations introduced by

changing the CPS cut-off for the monotherapy population, as described in paragraphs 6.62 and 6.66;

- Increase the proportion of patients treated with 2L nivolumab to 80% to reflect clinical practice, as described in paragraphs 5.6 and 6.68; and
- Revise the ICER weighting to 30% monotherapy use, as described in paragraph 1.8.

- 7.15 The PBAC noted that when respecified in this way, and using the price proposed in the pre-PBAC response (\$ [REDACTED]/200 mg), the models resulted in a weighted ICER of \$75,000 to < \$95,000/QALY gained. A further reduction in the pembrolizumab price of around 17% would be required to reach an ICER of \$55,000 to < \$75,000/QALY gained. The PBAC also noted that if a CPS ≥ 1 threshold was used for pembrolizumab plus chemotherapy and assuming 40% monotherapy, a weighted ICER of \$55,000 to < \$75,000/QALY gained resulted. With these inputs a price reduction for pembrolizumab of around 6% would be required to reach an ICER of \$55,000 to < \$75,000/QALY gained. Therefore the PBAC considered that a further price reduction from the pre-PBAC proposed price (\$ [REDACTED]/200 mg DPMA) of 10% would result in a weighted ICER that is within an acceptable cost-effectiveness range for the PBAC's preferred population (CPS ≥ 20 for pembrolizumab monotherapy and allcomers for pembrolizumab plus chemotherapy).
- 7.16 The PBAC considered the epidemiological approach was not reliable and the net financial impact of listing pembrolizumab as presented in the resubmission was highly uncertain. The PBAC considered that a more reliable approach would be to estimate the proportion of HNSCC patients treated with 2L nivolumab and apply this to the 2L nivolumab PBS patient numbers to estimate the 1L population eligible for treatment with pembrolizumab (as described in paragraph 6.95). The PBAC considered that based on the number of patients treated with nivolumab as second line treatment for R/M HNSCC the number of incident patients appeared to be substantially overestimated in the resubmission. The PBAC considered that the patient numbers should be revised in the financial estimates to reflect this. The PBAC also noted that the financial estimates were sensitive to the duration of treatment, which is impacted by the CPS cut-off for the PBS population.
- 7.17 The PBAC considered it would be appropriate for there to be a combined RSA for both pembrolizumab and nivolumab for HNSCC. The PBAC considered that a small increase in the existing financial caps for 2L nivolumab would be warranted to account for: (1) up to [REDACTED]% total additional patients (including 1L pembrolizumab patients + early relapse patients treated with nivolumab) and (2) a longer treatment duration expected in the 1L setting. The PBAC considered that not all patients would be suitable for treatment with combination therapy and the number of patients eligible for monotherapy with pembrolizumab would be dependent on the proportion of patients with CPS ≥ 20 . The PBAC requested that the MSAC provide advice regarding the population size based on the different CPS thresholds (see paragraph 1.6). The PBAC

noted that the increase to caps would be reduced if the listing for pembrolizumab plus chemotherapy is restricted to the CPS ≥ 1 population.

7.18 The PBAC noted that this submission is not eligible for an Independent Review.

Outcome:

Deferred

8 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

9 Sponsor's Comment

MSD welcomes the opportunity to work with PBAC and MSAC to expedite availability of pembrolizumab for patients with recurrent or metastatic squamous cell carcinoma of the head and neck.