6.09 PEMBROLIZUMAB, Solution concentrate for I.V. infusion 100mg in 4mL, Keytruda®, Merck, Sharp & Dohme (Australia) Pty Limited.

1 Purpose of Application

1.1 The submission requested a Section 100 (Efficient funding of Chemotherapy) listing for pembrolizumab for the treatment of patients with locally advanced (Stage III) or metastatic (Stage IV) squamous cell carcinoma of the head and neck (SCCHN) who have failed a platinum-containing regimen. This was the first submission to the PBAC for pembrolizumab for this indication.

1.2 The requested listing was based on a cost-minimisation analysis of pembrolizumab compared with nivolumab. The key components of the clinical issues addressed by the submission are summarised below.

Table 1: Key components of the overall clinical claim addressed by the submission.

Component	Description
Population[1]	Patients with recurrent or metastatic squamous cell carcinoma of the head and neck (R/M SCCHN) who have failed prior platinum based chemotherapy. This includes: • Patients who have failed either a platinum-containing regimen in the recurrent / metastatic setting with recurrence or progression at any time during or after platinum based therapy; or • Patients with locally advanced disease, with recurrence or progression within 6 months of platinum-based chemotherapy.
Intervention	Pembrolizumab (200 mg IV) every 3 weeks until disease progression or unacceptable toxicity.
Comparator	Main: Nivolumab (3mg/kg IV every 2 weeks)
Outcomes	OS, PFS, QoL during treatment and AEs.
Clinical claim	In patients with R/M SCCHN who have failed prior platinum-based chemotherapy, pembrolizumab is non-inferior to nivolumab on the basis of OS and PFS, as well as a similar QoL and safety profile.

AEs=adverse events; IV = intravenous; OS = overall survival; PFS = progression-free survival; QoL= quality of life; R/M SCCHN = recurrent or metastatic squamous cell carcinoma of the head and neck

[1] As described in Section 1.4.2, p11 of the submission.

Source: Table 1.1-1, p2 of the submission

2 Requested listing

Suggestions and additions proposed by the Secretariat to the requested listing are added in italics and suggested deletions are crossed out with strikethrough.

Name, Restriction, Manner of administration and form	Max. Amount	№. of Rpts	Dispensed Price for Max. Amount	Proprietary Name and Manufacturer	
PEMBROLIZUMAB 100 mg/4 mL injection; 1 x 4 mL vial	200 mg	~~56~~	$9023.22 (Public, published) $[redacted] (Public, effective) $9186.18 (Private, published) $[redacted] (Private, effective)	Keytruda®	Merck Sharp & Dohme (Australia) Pty Limited

Category / Program :	Section 100 - Efficient funding of Chemotherapy
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐ Midwives
Severity:	Locally advanced (Stage III) or metastatic (Stage IV)
Condition:	*Squamous cell carcinoma of the oral cavity, larynx, oropharynx or hypopharynx* ~~Head and neck cancer~~
PBS Indication:	Locally advanced (Stage III) or metastatic (Stage IV) *squamous cell carcinoma of the oral cavity, larynx, oropharynx or hypopharynx* ~~head and neck cancer~~
Treatment phase:	Initial *treatment*
Restriction Level / Method:	☐Restricted benefit ☐Authority Required - In Writing ☐Authority Required - Telephone ☐Authority Required – Emergency ☐Authority Required - Electronic ☒Streamlined
Clinical criteria:	Treatment must be the sole PBS-subsidised therapy for this condition, AND Patient must have failed a platinum-containing regimen for this condition in the metastatic setting or for inoperable locally advanced disease, AND Patient must have a ~~World Health Organisation (~~WHO~~)/Eastern Cooperative Oncology Group (ECOG)~~ performance status score of 0 or 1~~;~~, *AND* *Patient must not have received prior treatment with a PD-1 (programmed cell death-1) inhibitor for this condition.* ~~Treatment must be discontinued in patients who experience disease progression;~~ ~~AND~~ The treatment must not exceed a total of 6 cycles at a maximum dose of 200 mg every 3 weeks.
Administrative Advice	No increase in the maximum quantity or number of units or number of repeats will be authorised. *Special Pricing Arrangements apply.* 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.

Name, Restriction, Manner of administration and form	Max. Amount	№. of Rpts	Dispensed Price for Max. Amount	Proprietary Name and Manufacturer	
PEMBROLIZUMAB 100 mg/4 mL injection, 1 x 4 mL vial	200 mg	~~76~~	$9,023.83 (Public, published) $[redacted] (Public, effective) $9,187.35 (Private, published) $[redacted] (Private, effective)	Keytruda®	Merck Sharp & Dohme (Australia) Pty Limited

Category / Program :	Section 100 - Efficient funding of Chemotherapy

Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐ Midwives
Severity:	*Locally* advanced (Stage III) or metastatic (Stage IV)
Condition:	*Squamous cell carcinoma of the oral cavity, larynx, oropharynx or hypopharynx* ~~Head and neck cancer~~
PBS Indication:	*Locally* advanced (Stage III) or metastatic (Stage IV) *squamous cell carcinoma of the oral cavity, larynx, oropharynx or hypopharynx* ~~head and neck cancer~~
Treatment phase:	Continuing *treatment*
Restriction Level / Method:	☐Restricted benefit ☐Authority Required - In Writing ☐Authority Required - Telephone ☐Authority Required – Emergency ☐Authority Required - Electronic ☒Streamlined
Clinical criteria:	Patient must have previously been issued with an authority prescription for this drug for this condition, AND Treatment must be the sole PBS-subsidised therapy for this condition, AND Patient must have stable or responding disease, AND The total treatment received, inclusive of initial treatment, must not exceed 35 cycles at a dose of 200 mg every 3 weeks.
Administrative Advice	No increase in the maximum quantity or number of units or number of repeats will be authorised. *Special Pricing Arrangements apply.*

Name, Restriction, Manner of administration and form	Max. Amount	№.of Rpts	Dispensed Price for Max. Amount	Proprietary Name and Manufacturer	
PEMBROLIZUMAB 100 mg/4 mL injection, 1 x 4 mL vial	200 mg	5	$9,023.83 (Public, published) $[redacted] (Public, effective) $9,187.35 (Private, published) $[redacted] (Private, effective)	Keytruda®	Merck Sharp & Dohme (Australia) Pty Limited

Category / Program :	Section 100 - Efficient funding of Chemotherapy
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐ Midwives
Severity:	*Locally* advanced (~~unresectable~~ Stage III) or metastatic (Stage IV)
Condition:	*Squamous cell carcinoma of the oral cavity, larynx, oropharynx or hypopharynx* ~~Head and neck cancer~~
PBS Indication:	*Locally* advanced (~~unresectable~~ Stage III) or metastatic (Stage IV) *squamous cell carcinoma of the oral cavity, larynx, oropharynx or hypopharynx* ~~head and neck cancer~~
Treatment phase:	Grandfathering *treatment*
Restriction Level / Method:	☐Restricted benefit ☐Authority Required - In Writing ☐Authority Required - Telephone ☐Authority Required – Emergency ☐Authority Required - Electronic ☒Streamlined
Clinical criteria:	Patient must have received non-PBS treatment with this drug for this condition prior to [date of PBS listing], AND

	Patient must have failed a platinum-containing regimen for this condition in the metastatic setting or for inoperable locally advanced disease, AND Patient must have stable or responding disease, AND The total treatment received must not exceed 35 cycles at a dose of 200 mg every 3 weeks.
Administrative Advice	No increase in the maximum quantity or number of units or number of repeats will be authorised. *Special Pricing Arrangements apply.*

2.1 The submission stated that the proposed population is restricted to a subset of SCCHN patients with carcinomas in the oral cavity, larynx, oropharynx and hypopharynx. This is reasonable and is consistent with the eligibility criteria of the key pembrolizumab KN040 trial. The Pre-Sub-Committee Response (PSCR) reiterated the sponsor's willingness to align the listing for pembrolizumab with that for nivolumab. The ESC noted that the proposed pembrolizumab restriction wording currently excludes nasopharyngeal tumours but considered it was reasonable to align the proposed PBS indication wording with that of nivolumab.

2.2 The proposed target population is not restricted to patients expressing PD-L1. The PBAC noted that this is inconsistent with a recent pembrolizumab codependent application to the MSAC for use in previously untreated head and neck cancer patients who test positive for PD-L1[1]. The PSCR acknowledged that a different approach is being undertaken for first line therapy and stated that the decision to seek reimbursement in a biomarker driven population compared to an all-comers population is complex with a tumour and treatment-line specific approach needed to determine the most appropriate target population for anti-PD1 therapies.

2.3 The PBAC noted that the target PBS population as described in the requested listing for pembrolizumab appears broader than that for nivolumab. The requested listing for pembrolizumab specifies locally advanced (Stage III) or metastatic (Stage IV) head and neck cancer with no specification of time elapsed between recurrence/progression and prior platinum-based chemotherapy. The requested listing for nivolumab 1) did not specify Stage III or locally advanced disease (Public Summary Document (PSD) - Nivolumab November 2017 PBAC meeting); and 2) specified that recurrent or metastatic (R/M) SCCHN must have progressed within 6 months of receiving prior platinum based chemotherapy.

- The eligibility criteria of the key pembrolizumab trial (KN040) allowed patients with Stage III disease to enrol. However, baseline data for the KN040 trials show that the proportion of patients enrolled with Stage III disease was small ([redacted]% and [redacted]% of patients in the pembrolizumab and comparator arms, respectively).

[1] MSAC (2018) Application No. 1522 PD-L1 immunohistochemistry testing for access to pembrolizumab for patients with R/M SCCHN

- The submission stated that "the target population includes patients who have failed either a platinum-containing regimen in the recurrent/metastatic setting with recurrence or progression at any time during or after the therapy or for locally advanced disease, with recurrence or progression within 6 months after the therapy". This implies that the submission intends to specify a 6-month period, during which progression on a platinum-containing regimen should have occurred, for inoperable locally advanced disease but not for metastatic disease. The wording of the requested listing for pembrolizumab did not specify a 6-month progression period for locally advanced disease.

2.4 R/M SCCHN patients who progress early (for example within 6 months after receiving platinum-based chemotherapy) are likely to have poor prognosis/non-responding disease with a poor performance status. The proportion of R/M SCCHN patients who had progressed within 6 months of receiving platinum-based chemotherapy, prior to enrolment in the KN040 trial (consistent with the ITT population of the nivolumab CM141 trial) could not be identified from the KN040 clinical study report (CSR).

2.5 The PSCR provided data estimating that [redacted]% of R/M SCCHN patients had progressed within 6 months of receiving platinum-based chemotherapy prior to enrolment in the KN040 trial and were therefore consistent with the ITT population of the nivolumab CM141 trial (see paragraph 6.11). The median OS outcome for this subpopulation was congruent with the ITT KN040 trial population outcome. The ESC considered that the high proportion of patients who aligned with the CM141 inclusion criteria was reassuring, and acknowledged the comparability of the OS outcome between the KN040 subpopulation and ITT population.

2.6 While the PSCR indicated a willingness to align the listing for pembrolizumab with that of nivolumab it also requested the PBAC to consider broadening the listing to include patients who have progressed more than 6 months after prior platinum based therapy. The PSCR stated that pembrolizumab outcomes are non-inferior to nivolumab despite the inclusion of this relatively small ([redacted]%) patient group in the ITT population. The PSCR estimated that this patient subgroup would equate to approximately [redacted] patients per annum and reasoned that it would be inequitable to deny this subgroup access to a PD-1 inhibitor. The ESC noted the small percentage of the KN040 trial population who progressed more than 6 months after platinum based therapy, and that this subgroup is included within the TGA registration for pembrolizumab. The ESC agreed with the PSCR that there is a potential issue of inequity if these patients cannot access a PD-1 inhibitor.

2.7 To account for pseudo-progression[2] events, the administrative advice in the requested restriction (for both pembrolizumab and nivolumab) specifies that a confirmatory scan be taken at least 4 weeks after progression is suspected. However, evidence from the literature suggests that such events (previously observed in

[2] T-cell infiltration and an apparent increase in tumour size otherwise termed "tumour flare"

melanoma trials) are "very rare" in SCCHN trials[3]. The low incidence of pseudo-progression events in SCCHN should be weighed against the harms of overtreatment with immunotherapy and delayed or missed opportunities for alternative therapeutic options. This issue represents an important quality use of medicines (QUM) issue and applies to nivolumab and other immunotherapy agents in head and neck cancer.

2.8 The submission did not propose any criteria for ascertaining whether a patient has stable or responding disease for the continuation phase (e.g. modified RECIST 1.1 criteria). This would therefore be determined primarily by clinician judgement.

2.9 To be consistent with the restriction for nivolumab, the clinical criteria for initial treatment would need to note that patients must not have received prior treatment with a PD-1 or PD-L1 inhibitor for this condition. There is no evidence presented that demonstrates pembrolizumab is effective in patients who have failed/received prior treatment with a PD-1/PD-L1 inhibitor.

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

3 Background

Registration status

3.1 Pembrolizumab was approved for registration by the TGA on the 20th March 2017 for the treatment of patients with R/M SCCHN with disease progression on or after platinum containing therapy. A note to the indication states that the approval was based on overall response rate and duration of response. Improvements in overall survival (OS), progression-free survival (PFS) or health-related quality of life (QoL) have not been established. The PBAC noted that a condition for registration is to provide the results from the Phase III KN040 trial when they become available. The TGA evaluation was based on Phase I and phase II single pembrolizumab arm data (KN012 and KN055). The submission noted that the KN040 data are currently under review by the TGA.

3.2 Pembrolizumab is PBS listed for the treatment of unresectable stage III or Stage IV malignant melanoma and for relapsed or refractory classical Hodgkin's Lymphoma (rrcHL) in patients who have progressed following autologous stem cell transplant (ASCT), or who are ineligible for ASCT and have progressed on at least two prior systemic therapies. PD-L1 testing is not a pre-requisite for patients accessing pembrolizumab in these PBS listed indications.

[3]Baxi SS, Dunn LA, Burtness BA. Amidst the excitement: a cautionary tale of immunotherapy, pseudoprogression and head and neck squamous cell carcinoma. Oral oncology. 2016;62:147-8.
Chiou VL, Burotto M. Pseudoprogression and immune-related response in solid tumors. Journal of Clinical Oncology. 2015;33(31):3541.
Seiwert TY, Burtness B, Mehra R, Weiss J, Berger R, Eder JP, et al. Safety and clinical activity of pembrolizumab for treatment of recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-012): an open-label, multicentre, phase 1b trial. The Lancet Oncology. 2016;17(7):956-65

Previous PBAC consideration

3.3 This is the first submission to PBAC requesting listing of pembrolizumab for the treatment of R/M SCCHN.

3.4 A co-dependent submission for use of pembrolizumab in the treatment of non-small cell lung cancer (NSCLC) after failure of platinum based initial therapy was considered and rejected at the November 2016 PBAC/December 2016 MSAC meetings. A co-dependent submission for the treatment of NSCLC cancer in patients with no prior chemotherapy was considered and rejected at the March 2017 PBAC/April 2017 MSAC meetings and was considered and deferred at the November 2017 PBAC /December 2017 MSAC meetings. A resubmission was deferred at the March 2018 PBAC meeting. The co-dependent submission proposes use of PD-L1 testing to determine treatment eligibility for pembrolizumab.

3.5 Pembrolizumab was considered and rejected at the November 2017 PBAC meeting for treatment of urothelial cancer in a PD-L1 'all-comers' population. A resubmission is being considered at the July 2018 PBAC meeting.

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

4 Population and disease

4.1 Head and neck cancer represents the 7th most commonly diagnosed cancer in Australia (Australian Institute of Health and Welfare (AIHW, 2017)). The vast majority of head and neck cancers arise from the mucosa of the upper aero-digestive tract and are predominantly squamous cell in origin (Barnes et al., 2005) and are referred to as SCCHN.

4.2 The target population in this submission is restricted to patients with R/M SCCHN who have failed a prior platinum-containing regimen.

5 Comparator

5.1 The submission nominated nivolumab as the main comparator. Nivolumab was recommended by the PBAC (March 2018 meeting) for R/M SCCHN patients who have progressed within 6 months of receiving prior platinum based chemotherapy. The PBAC agreed that nivolumab is the appropriate main comparator. However, the requested restriction for pembrolizumab does not mandate a limit on the elapsed time since receiving platinum-based chemotherapy, at least for patients with metastatic disease, and is therefore broader than the target PBS population for nivolumab. The PBAC agreed with the evaluation that for patients with recurrence/progression more than 6 months after platinum based chemotherapy, pembrolizumab may compete with other therapies such as docetaxel/paclitaxel, capecitabine, or methotrexate.

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

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

6.2 The PBAC noted and welcomed the input from individuals (11) and organisations (2) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with pembrolizumab including reductions in the pain associated with SCCHN and improvements in appetite as a result. Individuals noted the expense associated with pembrolizumab treatment currently and that it was available for other types of cancer on the PBS.

6.3 The PBAC noted Rare Cancers Australia supported the application based on the need for access to pembrolizumab demonstrated by the SCCHN community. The PBAC noted the Rare Cancers Australia letter of support provided an insight into the impact of SCCHN on those with the condition.

6.4 The Medical Oncology Group of Australia (MOGA) also expressed its support for the pembrolizumab for SCCHN submission. The PBAC noted that the MOGA presented the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for pembrolizumab for SCCHN, which was limited to 3 (out of a maximum of 5, where 5 and 4 represent the grades with substantial improvement) [4], based on a comparison with chemotherapy. The PBAC considered that the ESMO-MCBS for pembrolizumab for SCCHN was more likely to be limited to 2, based on a comparison with chemotherapy.

Clinical trials

6.5 The submission was based on an indirect comparison between pembrolizumab (Trial KN040: Pembrolizumab vs. Investigators choice (IC)) and nivolumab (CM141: Nivolumab vs. IC) in R/M SCCHN patients who had progressed on or after platinum-based chemotherapy using IC as the common reference.

- KN040 trial was a randomised, open-label, trial comparing pembrolizumab with IC (in a 1:1 ratio) in R/M SCCHN patients who had progressed on or after platinum-based chemotherapy (N= 495);
- CM141 trial was a randomised, open-label, trial comparing nivolumab with IC (in a 2:1 ratio) in R/M SCCHN patients who had progressed on or after platinum-based chemotherapy (N= 361).

6.6 Details of the trials presented in the submission are provided in the table below.

[4] 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 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Proposed medicine: Pembrolizumab versus investigator's choice (IC).		
KN040	Clinical study report P040V01MK3475: A Phase III Randomized Trial of MK-3475 (Pembrolizumab) versus Standard Treatment in Subjects with Recurrent or Metastatic Head and Neck Cancer.	December 2017
	Publications:	
	Cohen E.E., Harrington K.J., et al. PR Pembrolizumab (pembro) vs standard of care (SOC) for recurrent or metastatic head and neck squamous cell carcinoma (R/M SCCHN): Phase 3 KEYNOTE-040 trial	Annals of Oncology 2017 28 Supplement 5 (v628).
Main comparator: Nivolumab versus investigator's choice (IC).		
CM141	Publications:	
	Ferris, R. L., Blumenschein, G., Fayette, J., Guigay, J., Colevas, A. D., et al. "Nivolumab for recurrent squamous-cell carcinoma of the head and neck."	New England Journal of Medicine 2016; 375(19): 1856-1867.
	Kiyota N., Hasegawa Y., et al. A randomized, open-label, Phase III clinical trial of nivolumab vs. therapy of investigator's choice in recurrent squamous cell carcinoma of the head and neck: A subanalysis of Asian patients versus the global population in checkmate 141.	Oral Oncology 2017; 73 (138-146).
	Harrington K.J., Ferris R.L., et al. Nivolumab versus standard, single-agent therapy of investigator's choice in recurrent or metastatic squamous cell carcinoma of the head and neck (CheckMate 141): health-related quality-of-life results from a randomised, phase 3 trial.	The Lancet Oncology 2017; 18:8 (1104-1115).
	Abstracts	
	Gillison M.L., Blumenschein G., et al. Characterisation of potential predictive biomarkers of response to nivolumab in checkmate 141 in patients with squamous cell carcinoma of the head and neck (SCCHN).	Asia-Pacific Journal of Clinical Oncology 2017; 13 Supplement 4 (141).
	Gillison M.L., Blumenschein G.R., et al. Nivolumab (Nivo) vs investigator's choice (IC) for platinum-refractory (PR) recurrent or metastatic (R/M) squamous cell carcinoma of the head and neck (SCCHN; Checkmate 141): Outcomes in first-line (1L) R/m patients and updated safety and efficacy.	Journal of Clinical Oncology 2017; 35:15 Supplement 1.
	Gillison, M. L., Blumenschein, G., Fayette, J., Guigay, J., Colevas, A. D., et al.. "Nivolumab (nivo) vs investigator's choice (IC) for recurrent or metastatic (R/M) head and neck squamous cell carcinoma (SCCHN): CheckMate-141."	Cancer Research 2016; 76(14).
	Ferris R.L., Licitra L., et al. Nivolumab vs investigator's choice (IC) in patients with recurrent or metastatic (R/M) squamous cell carcinoma of the head and neck (SCCHN): Efficacy and safety in checkmate 141 by prior cetuximab use.	Asia-Pacific Journal of Clinical Oncology 2017; 13 Supplement 4 (143).
	Kasper S., Haddad R., et al. Treatment beyond progression with nivolumab (nivo) in patients with recurrent or metastatic (R/M) Squamous Cell Carcinoma of the Head and Neck (SCCHN) in the phase 3 CheckMate 141 study.	Oncology Research and Treatment 2017; 40 Supplement 3 (250-251).
	Haddad R., Blumenschein G., et al. Treatment beyond progression with nivolumab in patients with recurrent or metastatic (R/M) squamous cell carcinoma of the head and neck (SCCHN) in the phase 3 checkmate 141 study: A biomarker analysis and updated clinical outcomes.	Annals of Oncology 2017; 28 Supplement 5 (v372-v373).
	Licitra L., Ferris R.L., et al. Nivolumab vs investigator's choice (IC) in patients with recurrent or metastatic (R/M) squamous cell carcinoma of the head and neck (SCCHN): Treatment effect on clinical outcomes by best overall response in checkmate 141.	Annals of Oncology 2017; 28 Supplement 5 (v377-v378).
	Simpson S., Cocks K., et al. A quality-adjusted time without symptoms of disease and toxicity (Q-TWIST) analysis comparing nivolumab and therapy of investigator's choice (IC) in patients with recurrent or metastatic (R/M) platinum-refractory squamous cell carcinoma of the head and neck (SCCHN) (checkmate 141).	Value in Health 2017; 20:9 (A450).

	DeRosa M., Cocks K., et al. Association of health-related quality of life (HRQOL) and healthcare resource utilization (HCRU) in checkmate 141, a phase 3 study of nivolumab versus investigator's choice (IC) in patients with recurrent or metastatic (R/M) platinum-refractory squamous cell carcinoma of the head and neck (SCCHN).	Value in Health 2017; 20:9 (A447).
	Venkatachalam M., Bobiak S., et al. Estimated costs of treatment-related adverse events (TRAEs) for recurrent or metastatic (R/M) squamous cell carcinoma of the head and neck (SCCHN) in the checkmate 141 trial.	Annals of Oncology 2017; 28 Supplement 5 (v378-v379).
	Haddad R., Ferris R.L., et al. Treatment beyond progression with nivolumab in patients with recurrent or metastatic squamous cell carcinoma of the head and neck in the phase 3 Checkmate 141 study.	Cancer Research 2017; 77:13 Supplement 1.
	Ferris R.L., Blumenschein G., et al. Evaluation of oral microbiome profiling as a response biomarker in squamous cell carcinoma of the head and neck: Analyses from CheckMate 141.	Cancer Research 2017; 77:13 Supplement 1.
	Ferris R.L., Blumenschein G., et al. Tumor-associated immune cell PD-L1 expression and peripheral immune profiling: Analyses from CheckMate 141.	Cancer Research 2017; 77:13 Supplement 1.
	Ferris R.L., Licitra L., et al. Nivolumab (Nivo) vs investigator's choice (IC) in patients with recurrent or metastatic (R/M) squamous cell carcinoma of the head and neck (SCCHN): Efficacy and safety in CheckMate 141 by prior cetuximab use.	Journal of Clinical Oncology 2017; 35:15 Supplement 1.
	De Rosa M., Cocks K., et al. Analyses of healthcare resource utilization (HCRU) in checkmate 141, a phase 3 study of nivolumab versus investigator's choice (IC) in patients with recurrent or metastatic (R/M) platinum-refractory squamous cell carcinoma of the head and neck (SCCHN).	Value in Health 2017; 20:5 (A113).
	Hasegawa Y., Kiyota N., et al. Efficacy and safety of nivolumab for recurrent or metastatic (R/M) squamous cell carcinoma of the head and neck (SCCHN) in Asia: CheckMate 141 subgroup analysis.	Annals of Oncology 2016; 27 Supplement 9 (ix112-ix113).
	Kiyota N., Harrington K., et al. Patient-reported outcomes (PROs) in recurrent or metastatic (R/M) squamous cell carcinoma of the head and neck (SCCHN) treated with nivolumab (Nivo) or Investigator's Choice (IC): CheckMate 141.	Annals of Oncology 2016; 27 Supplement 9 (ix113).
	Ferris R.L., Blumenschein G.R., et al. Further evaluations of nivolumab (nivo) versus investigator's choice (IC) chemotherapy for recurrent or metastatic (R/M) squamous cell carcinoma of the head and neck (SCCHN): CheckMate 141.	Journal of Clinical Oncology 2016; 34 Supplement 15.
	Harrington K., Ferris R.L., et al. PR Patient-reported outcomes (PROs) in recurrent or metastatic (R/M) squamous cell carcinoma of the head and neck (SCCHN) treated with nivolumab (nivo) or investigator's choice (IC): CheckMate 141	Annals of Oncology 2016; 27 Supplement 6.
	Gillison M.L., Blumenschein G., et al. Nivolumab (nivo) vs investigator's choice (IC) for recurrent or metastatic (R/M) head and neck squamous cell carcinoma (SCCHN): CheckMate-141.	Cancer Research 2016; 76:14 Supplement.

Source: Table 2.2.1, pp22-24 of the submission

6.7 The key features of the randomised trials used in the indirect comparison are summarised in the table below.

Table 3: Key features of the included evidence – indirect comparison

Trial	N	Design/ duration of follow-up[β]	Risk of bias	Patient population	Outcomes[#]
Pembrolizumab vs. chemotherapy					
KN040	495	R, OL 7.3 months	Low*	R/M SCCHN patients who had progressed on or after platinum-based chemotherapy	OS, PFS, AEs
Nivolumab vs. chemotherapy					
CM141	361	R, OL 5.1 months	High**	As above	OS, PFS, AEs

AE = adverse event; PFS = progression-free survival; OL = open label; OS = overall survival; R = randomised; R/M SCCHN = recurrent or metastatic squamous cell carcinoma of the head and neck.

[β] The median duration of treatment with pembrolizumab was 2.8 months (85 days) and that for treatment with nivolumab was 1.9 months (Ferris et al, 2016)

* the risk of bias for KN040 was regarded as low since baseline characteristics of patients were reasonably balanced between the two treatment arms in KN040, and PFS and related treatment decisions were determined by independent central review. The risk of bias for other patient reported outcomes was high, however, given the open-label design of the trial.

** the risk of bias for CM141 was regarded as high since PFS was determined by investigator assessment, and there was a substantial proportion of non-quantifiable/missing baseline data.

[#] The primary outcome of both the KN040 and CM141 trials was OS. Secondary endpoints were PFS, objective response rate (ORR), patient-reported outcomes (PROs) and AEs.

Source: Compiled during the evaluation based on Sections 2.3 and 2.4 of the submission and Ferris et al, 2016[5].

6.8 The PBAC noted that all patients in the KN040 trial had an ECOG performance status of 0 or 1. The majority of patients were less than 65 years of age ([redacted]%) with [redacted]% and [redacted]% of patients in the pembrolizumab and IC arms respectively ≥ 75 years. The PBAC noted that the submission reported the average age of those diagnosed with head and neck cancer in Australia is approximately [redacted] years (GLANCE Clinical Study Report, 2018: AIHW cancer pivot table, 2014). The PBAC was concerned that the trial population were younger and therefore not representative of patients who would be eligible for PBS subsidised treatment.

6.9 The PBAC noted that there were differences in the level of risk of bias for different bias types between the KN040 and CM141 trials. Notwithstanding other inherent caveats associated with an indirect comparison (unknown confounding/non-transitivity factors), the key issues that may impact the indirect treatment effect between pembrolizumab and nivolumab are summarised below:

- Baseline characteristics for the treatment arms of the KN040 trial were reasonably balanced. However, in the IC arm of the CM141 trial, there was a higher proportion of patients who were: >65 years of age (37.2% vs.28.3%), never smokers (25.6% vs. 16.2%), HPV negative status (29.8% vs. 20.8%) and PD-L1 expression tumour proportion score (TPS) ≥1% (50.4% vs. 36.7%), compared to the nivolumab treatment arm. Additionally for the CM141 trial, there was a substantial amount of non-quantifiable/missing baseline data, at least for PD-L1

[5] Ferris RL, Blumenschein Jr G, Fayette J, Guigay J, Colevas AD, Licitra L, et al. Nivolumab for recurrent squamous-cell carcinoma of the head and neck. New England Journal of Medicine. 2016;375(19):1856-67

expression (~30%) and HPV status (~50%). If there are real imbalances between treatment arms within the CM141 trial, in terms of (but not limited to) PD-L1 expression (a treatment effect modifier based on the mechanism of action of PD-1 inhibitors) and HPV positive head and neck cancer (a favourable prognostic factor[6]), the relative treatment effect between nivolumab and chemotherapy would be confounded which would likely impact the indirect treatment effect.

- CM141 trial inclusion criteria specified that tumour progression or recurrence should have occurred within 6 months of the last dose of platinum therapy. However, for the KN040 trial, this 6-month period for progression was specified only for patients in the locally advanced setting. The inclusion criteria for KN040 therefore appear broader than those for CM141. The PSCR acknowledged that this inclusion criteria may have impacted the patients enrolled in each trial, and that any effect due to the difference in the timing of progression criteria likely influenced the efficacy of the SOC arm in each trial, given that time to prior-line progression has been identified as a predictor of subsequent chemo-sensitivity in other tumour types (Brun et al., 2000).

6.10 To validate the extent of potential influence of the inclusion criteria, the PSCR included a post-hoc analysis of the KN040 trial conducted to evaluate the average time to progression and the proportion of patients that align with the CM141 trial criteria of progression within 6 months of prior platinum therapy (Table 4).

Table 4: Time from last platinum therapy to disease progression in the recurrent/metastatic setting in KN040[a] (ITT population)

	Pembrolizumab		IC		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population[a]	[redacted]		[redacted]		[redacted]	
Time from last platinum therapy to disease progression in R/M setting[b]						
≤ 6 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
> 6 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Missing classification	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Note: table excludes those patients that recurred from platinum therapy in locally advanced setting (where inclusion criteria for KN040 aligned with CM141 and specified recurrence/progression must occur within 6 months of last platinum dose).
IC = investigator's choice, R/M = Recurrent/Metastatic
Database Cutoff Date: 15MAY2017

[a] Number of patients: intention-to-treat population with prior platinum therapy in the R/M setting.

[b] Time from end date of last platinum therapy in the R/M setting till the disease progression date. Subjects with no disease progression date are classified as missing.

6.11 The PSCR stated that in the KN040 trial, [redacted] ([redacted]%) of the metastatic patients could have time to progression quantified, and of these [redacted] ([redacted]%) progressed from prior platinum therapy within 6 months. This indicates that [redacted] ([redacted]%) of patients of the ITT population in the KN040 trial (recurrence in locally advanced and metastatic)

[6] Fakhry C, Westra WH, Li S, Cmelak A, Ridge JA, Pinto H, et al. Improved survival of patients with human papillomavirus–positive head and neck squamous cell carcinoma in a prospective clinical trial. Journal of the National Cancer Institute. 2008;100(4):261-9

were aligned with the CM141 criteria. The ESC noted the high proportion of overlap between the KN040 and CM141 trial populations.

6.12 To illustrate non-inferiority, the submission proposed "to show non-significance in overall survival hazard ratios as well as similar absolute efficacy for survival rate, and similar impacts on health-related quality of life (QoL) and AEs". It would not be appropriate for a non-inferiority margin to be based solely on lack of statistical significance. This margin must be specified based on clinical and statistical reasoning. Importantly, the point estimate and confidence intervals should exclude important clinical differences between pembrolizumab and nivolumab. The lack of an adequately justified non-inferiority margin, where results of indirect comparisons are imprecise, makes it difficult to judge true non-inferiority.

Comparative effectiveness

6.13 The OS results and the Kaplan-Meier curves for OS for the KN040 and CM141 intention-to-treat (ITT) population are summarised below.

Table 5: Results of overall survival in KN040[a] and CM141 (ITT population)

KN040 trial				
	KN040 Pembrolizumab (N=247)	**KN040 IC (N=248)**	**KN040 Absolute difference: pembrolizumab minus IC**	**KN040 HR (95% CI) p-value (log rank)**
Events, n (%)	[redacted]	[redacted]	-	-
OS median, months (95% CI)[a]	8.4 (6.4,9.4)	6.9 (5.9,8.0)	+1.5months	0.80 (0.65,0.98) p=0.01605*
OS rate % (95% CI) 6 months 9 months 12 months	[redacted]	[redacted]	[redacted]%	
Post-hoc analysis of KN040 time of last platinum therapy to disease progression in R/M setting ≤ 6 months subgroup [a]				
	Pembrolizumab (N=180)	**IC (N=175)**		**HR (95% CI) p-value (log rank)**
Events, n (%)	[redacted]	[redacted]		
OS median, months (95% CI)	[redacted]	[redacted]		p=[redacted]*
Post-hoc analysis of KN040 time of last platinum therapy to disease progression in R/M setting > 6 months R/M subgroup [a]				
	Pembrolizumab (N=21)	**IC (N=12)**		**HR (95% CI) p-value (log rank)**
Events, n (%)	[redacted]	[redacted]		
OS median, months (95% CI)	[redacted]	[redacted]		p=[redacted]*
CM141				
	Nivolumab (N=240)	**IC (N=121)**	**Absolute difference: Nivolumab minus IC**	**HR (95% CI) Nivolumab vs. IC p-value (log rank)**
Events, n, (%)	133 (55.4)	85 (70.2)	-	-
OS median, months (95% CI)	7.5 (5.5,9.1)	5.1 (4.0,6.0)	+2.4 months	0.70 (0.51,0.96) p=0.01
OS rate % (95% CI) at 12 months	36.0 (28.5,43.4)	16.6 (8.6,26.8)	+19.4%	
Gillison et al., 2017 (abstract; 18 months follow-up)				
OS median, months (95% CI)	7.7 (5.7,8.8)	5.1 (4.0,6.2)	+2.6 months	0.71 (0.55,0.90) p=0.0048
OS rate % (95% CI) at 18 months	21.5 (NR,NR)	8.3% (NR,NR)	+13.2%	

Note: shaded cells represent post-hoc analysis of KM040 ITT subgroup with prior platinum therapy in the R/M setting with an available disease progression date

CI = confidence interval; HR = hazard ratio; IC = investigator's choice; ITT = intention-to-treat; n = number of participants with event; N = total participants in group; NR = not reported; OS = overall survival; *1-sided p-value

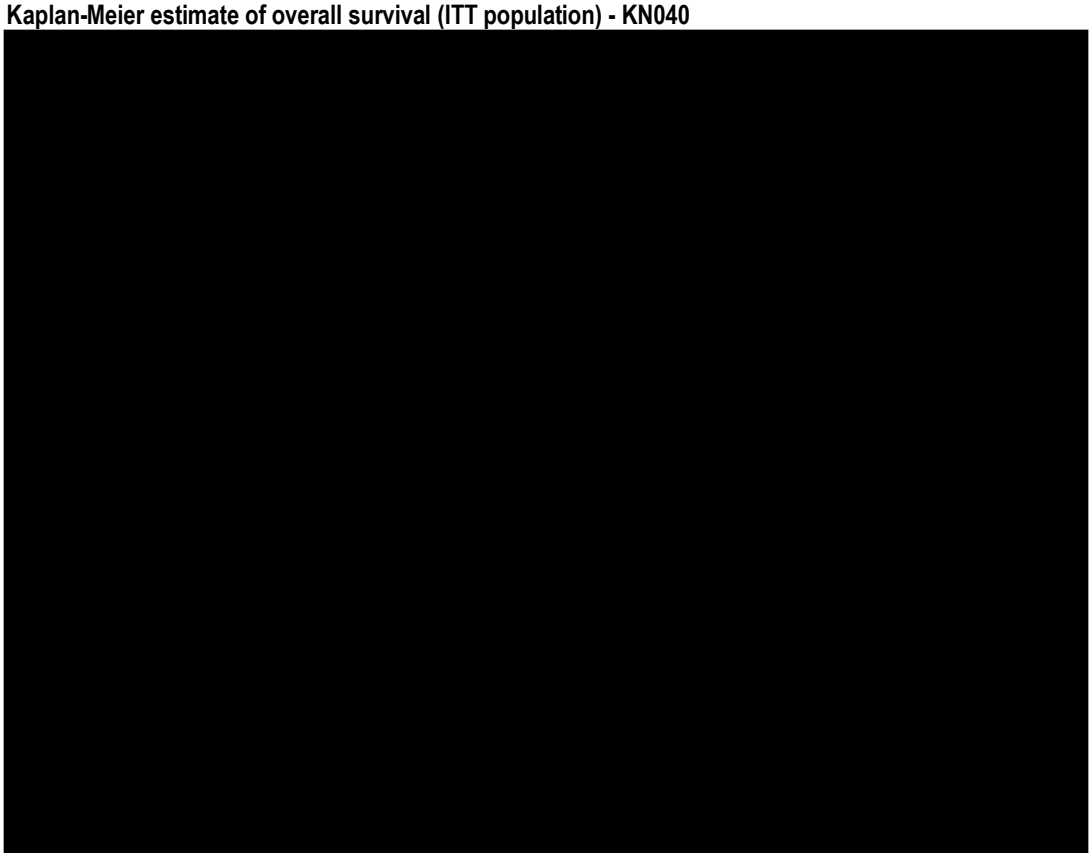
[a] Database cutoff 15 May 2017.

Source: Table 2.5-1, p47 of the submission; and Table 2.5-2, p49 of the submission; (Sources in submission: Ferris et al., 2016)[7]; Gillison

[7] Ferris RL, Blumenschein Jr G, Fayette J, Guigay J, Colevas AD, Licitra L, et al. Nivolumab for recurrent squamous-cell carcinoma of the head and neck. New England Journal of Medicine. 2016;375(19):1856-67

et al (2017)[8]; data in shaded cells from Table 2 PSCR (p6)

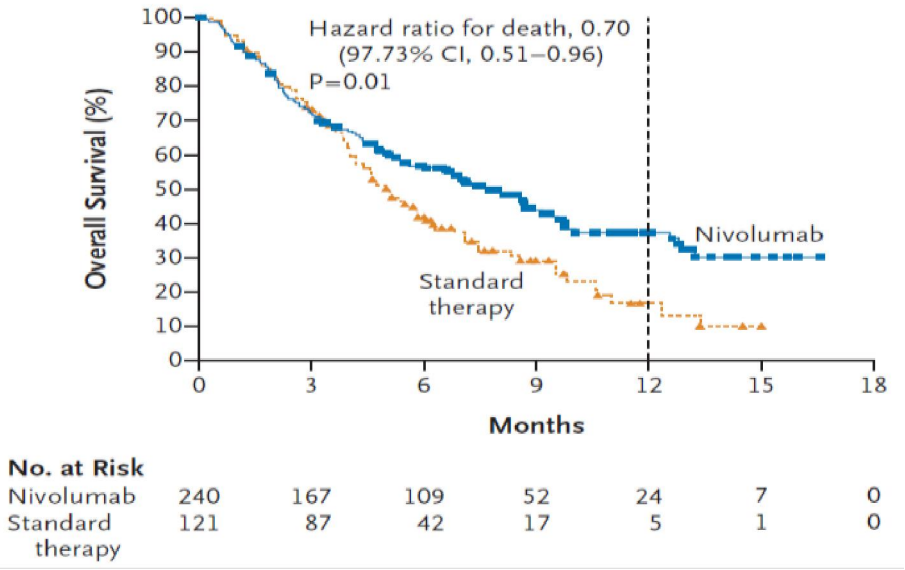
Figure 1: Kaplan-Meier estimate of overall survival (ITT population) - KN040



ITT = intention-to-treat; Q3W = every 3 weeks
Source: Figure 2.5-1, p48 of the submission.

[8] Gillison ML, Blumenschein Jr G, Fayette J, Guigay J, Colevas AD, Licitra L, et al., editors. Nivolumab Versus Investigator's Choice (IC) for Platinum-Refractory Recurrent or Metastatic (R/M) Squamous Cell Carcinoma of the Head and Neck (SCCHN; CHECKMATE 141): Outcomes in First-Line R/M Patients and Updated Safety and Efficacy. Asia-Pacific Journal of Clinical Oncology; 2017

Figure 2: CM141 - Kaplan-Meier estimate of overall survival (ITT population)



CI = confidence interval; ITT = intention-to-treat
Source: Figure 2.5-2, p49 of the submission.

6.14 The PBAC noted that variation in the planned statistical hypothesis boundary values reported for final analysis for OS was evident across the KN040 Trial Protocol and KN040 Clinical Study Report. The PBAC noted that the "by design" and "actual" p-value (one sided) reported in the protocol were p=[redacted] (~Observed HR at boundary [redacted]) and p=[redacted] (~Observed HR at boundary [redacted]) respectively with a boundary of p=[redacted] reported in the Clinical Study Report.

6.15 The PBAC noted that the initial OS analysis based on a database cutoff date of 15 May 2017 with a database lock date of 04 Jun 2017 did not reach statistical significance (HR=[redacted], 95% CI ([redacted]); one sided p-value [redacted]). The KN040 Clinical Study Report stated that the result was considered to be a clinically meaningful improvement in OS for patients with second line R/M SCCHN treated with pembrolizumab, although this result missed the primary statistical hypothesis p-value boundary of [redacted] for OS.

6.16 The PBAC noted that the evaluation had identified some inconsistent OS results from the KN040 trial in the published literature [Abstract LBA45_PR Phase III KEYNOTE-040. HR=0.81, 95% CI (0.66, 0.99)]. These results were described as "not reaching statistical significance" (one sided p-value 0.0204). The abstract also noted that median OS "was only marginally higher in the pembrolizumab compared to standard treatment arm (8.4 versus 7.1 months)". The database cutoff for these results could not be identified from the abstract.

6.17 The PBAC noted that at database cutoff May 2017 for KN040 with a database lock date of 13 October 2017, there was a 1.5 month OS gain associated with pembrolizumab over IC which corresponded to a 20% reduction in risk of death with borderline statistical significance (HR=0.80, 95% CI (0.65, 0.98); p-value=0.01605).

The difference in OS rate at 12 months was 10.5% favouring pembrolizumab. The Kaplan-Meier curves for OS show there was a separation at approximately 5 months favouring pembrolizumab over IC. The PBAC noted that median follow-up period for the KN040 trial was 7.3 months. In addition, the PBAC noted that the statistical significance of the HR was based on a one sided p-value and was concerned that the inconsistency in the OS results reported created uncertainty regarding the statistical significance of the OS benefit. The PBAC considered that pembrolizumab presented at best a modest OS benefit compared with IC.

6.18 The PSCR included post-hoc analysis for the KN040 R/M patient subgroups with progression within (and after) 6 months of prior platinum therapy. The median OS for pembrolizumab treated metastatic patients with progression within 6 months was [redacted]months (HR=[redacted], 95% CI ([redacted])). The PSCR stated that the outcome of this subgroup was congruent with the total ITT population. The ESC noted the high degree of overlap between the median OS for the KN040 population subgroup who progressed within 6 months and the KN040 total ITT population. However, the ESC also noted that given less than [redacted]% of patients were in the group that progressed more than 6 months after prior treatment, such a comparison was likely underpowered.

6.19 The PSCR provided OS data for the PD-L1 TPS <50% subgroup of KN040. The OS analysis indicated that in this subgroup, there was [redacted] in the reduction in risk of death associated with pembrolizumab over IC (HR=[redacted], 95% CI: [redacted]; p=[redacted]) with [redacted] median OS durations between treatment arms of [redacted] months (95% CI: [redacted]) versus [redacted] months (95% CI: [redacted]), respectively. The ESC noted that the overall efficacy of pembrolizumab was greater in the strongly positive PD-L1 expression subgroup (TPS ≥50% PD-L1 expression subgroup HR=0.53, 95% CI: 0.35, 0.81), and considered that PD-L1 expression may predict greater benefit in this group of patients. However, the ESC agreed with the sponsor that pembrolizumab should be available to all-comers if approved. The PBAC agreed with the ESC that overall efficacy of pembrolizumab was greater in the strongly positive PD-L1 expression subgroup.

6.20 Using updated data at 18 months follow-up from Gillison et al (2017)[9], nivolumab demonstrated superior OS benefit compared with IC with a difference in median OS of 2.6 months which corresponded to an approximate 30% reduction in the risk of death (HR=0.71, 95% CI: 0.55, 0.90; stratified log-rank test p-value = 0.0048). The difference in OS rate at 12 and 18 months was 19.4% and 13.2%, respectively, favouring nivolumab over IC. The Kaplan-Meier curves for OS show there was a separation at approximately 4 to 5 months favouring nivolumab over IC. The ESC noted that nivolumab presented a higher OS rate at 12 months compared with

[9] Gillison ML, Blumenschein Jr G, Fayette J, Guigay J, Colevas AD, Licitra L, et al., editors. Nivolumab Versus Investigator's Choice (IC) for Platinum-Refractory Recurrent or Metastatic (R/M) Squamous Cell Carcinoma of the Head and Neck (SCCHN; CHECKMATE 141): Outcomes in First-Line R/M Patients and Updated Safety and Efficacy. Asia-Pacific Journal of Clinical Oncology; 2017

pembrolizumab.

6.21 The PBAC noted that there was no significant difference in median PFS improvement between the pembrolizumab (2.1 months) and IC (2.3 months) treatment arms (HR=0.96, 95% CI: 0.79, 1.16) in KN040. Similarly, there was no statistically significant difference in median PFS between the nivolumab (2.0 months) and IC (2.3 months) treatment arms with a non-statistically significant 11% reduction in risk of progression or death (HR=0.89, 95% CI: 0.70, 1.13; p=0.32). The Kaplan Meier PFS curves for both pembrolizumab and nivolumab compared with IC show a rapid occurrence of progression for both the intervention and IC treatment, with a subsequent delayed separation around 4-5 months favouring pembrolizumab or nivolumab.

6.22 A summary of the results of the indirect comparison for OS and PFS is presented below.

Table 6: Summary of results of the indirect comparison for OS and PFS

Trial type or estimate	Trial ID	HR (95% CI)
Overall survival (OS)		
Pembrolizumab vs. IC	KN040	0.80 (0.65, 0.98)
Nivolumab vs. IC	CM141	0.70 (0.51, 0.97)
Indirect estimate of the OS HR adjusted for the common reference[1]		1.14 (0.78, 1.67)[2]
Progression free survival (PFS)		
Pembrolizumab vs. IC	KN040	0.96 (0.79, 1.16)
Nivolumab vs. IC	CM141	0.89 (0.70, 1.12)
Indirect estimate of the PFS HR adjusted for the common reference[1]		1.08 (0.80, 1.46)[2]

CI = confidence interval; IC = investigator's choice, HR = hazard ratio; CI = confidence interval.

[1] Indirect comparison analysis conducted during the evaluation using a standard approach adjusted for the common reference (Bucher et al)[10]. [redacted]

[2] Indirect comparison approach in the submission using a "network meta-analysis" resulted in an indirect OS HR= [redacted] (95% CI: [redacted]) and in an indirect PFS OS of [redacted] (95% CI: [redacted])

Source: Compiled during the evaluation based on information presented in Section 2.6.1 of the submission.

6.23 The available data provided in the submission and in the public domain indicate that transitivity is of concern for the indirect comparison between the pembrolizumab KN040 and nivolumab CM141 trials. There were imbalances for some baseline characteristics within the CM141 trial whereas for the KN040 trial, baseline characteristics were reasonably equally distributed. Furthermore, there were some differences between the standard care arms across the two trials. The insufficient transitivity between the KN040 and CM141 makes interpretation of the indirect comparison results challenging:

- Differences in the definition of the timing of recurrence /progression as an inclusion criterion, may have resulted in an enrolled CM141 patient population that had non-responding disease, compared with that enrolled into the KN040 trial. In terms of an indirect comparison, this results in an important selection bias, the direction of which is difficult to ascertain given the paucity of data. The PSCR submitted data addressing these concerns; see paragraphs 6.10 and 6.11.

[10] Bucher HC, Guyatt GH, Griffith LE, Walter SD. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. Journal of clinical epidemiology. 1997;50(6):683-91

- A test for interaction across the TPS ≥50% vs. TPS<50% subgroups in the KN040 trial, resulted in a [redacted] ratio of HRs of [redacted] (95% CI: [redacted]). This indicates that PD-L1 expression affects OS benefit with pembrolizumab over IC. Substantial unquantifiable baseline data for PD-L1 expression status in CM141 makes the PD-L1 subgroup analyses of CM141 difficult to interpret. No comparisons can be made for PD-L1 expression between the KN040 and the CM141 studies, as the PD-L1 tumour expression thresholds differed between the two trials.
- There were substantial missing or unquantifiable data for PD-L1 expression status and HPV status in CM141; HR results within these subgroups are at best hypothesis generating.

The PSCR recalled examples (nivolumab indirect comparison to pembrolizumab for unresectable Stage III or Stage IV malignant melanoma and atezolizumab indirect comparison to nivolumab for locally advanced or metastatic non-small cell lung cancer) where the PBAC made non-inferior conclusions in the presence of transitivity issues within indirect comparisons. The PBAC considered that while there are previous examples of this, any decision for such an approach takes into account a number of factors and is therefore context specific.

6.24 Health-related QoL assessments were captured in KN040 and CM141 using the EORTC QLQ-C30 and EQ-5D-3L instruments. The individual trial data for KN040 indicated that the EORTC QLQ-C30 score remained stable for pembrolizumab at week 15 but declined for the IC arm resulting in the LS mean difference of 6.25 (95% CI 1.32 to 11.18). While the submission claimed a mean difference of 4 to 10 points is viewed as clinically significant, the PBAC considered that a difference of less than 10% is modest and may not be clinically meaningful. In CM141, the EORTC QLQ-C30 score remained stable for nivolumab at week 15 (+2.7) but declined for the IC arm (-7.3). The PBAC noted that the submission did not provide a formal indirect comparison of QoL data between pembrolizumab and nivolumab.

Comparative harms

6.25 All cause AEs, AEs leading to discontinuation and most frequent AEs (>10%), by treatment arm, in the KN040 trial, are summarised below.

Table 7: KN040 - Summary of all-cause adverse events and most frequent adverse events of any grade (all patients as treated population)

	Pembrolizumab n=246	IC n=234	Risk difference	Relative risk (95% CI)
All cause AEs, n (%)				
Any grade	[redacted]	[redacted]	[redacted]	[redacted]
Grade 3-5	[redacted]	[redacted]	[redacted]	[redacted]
AEs leading to discontinuation, n (%)				
Any grade	[redacted]	[redacted]	[redacted]	[redacted]
Grade 3-5	[redacted]	[redacted]	[redacted]	[redacted]
Most Frequent AEs, any grade (≥10% of patients), n (%)				
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]
Constipation	[redacted]	[redacted]	[redacted]	[redacted]
Cough	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]	[redacted]	[redacted]
Hypothyroidism	[redacted]	[redacted]	[redacted]	[redacted]
Decreased appetite	[redacted]	[redacted]	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]	[redacted]	[redacted]
Rash	[redacted]	[redacted]	[redacted]	[redacted]
Weight decreased	[redacted]	[redacted]	[redacted]	[redacted]
Mucosal inflammation	[redacted]	[redacted]	[redacted]	[redacted]
Stomatitis	[redacted]	[redacted]	[redacted]	[redacted]
Neutrophil count decreased	[redacted]	[redacted]	[redacted]	[redacted]
Alopecia	[redacted]	[redacted]	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]
Most Frequent AEs, grade 3-5 (≥5% of patients), n (%)				
Pneumonia	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]
Neutrophil count decreased	[redacted]	[redacted]	[redacted]	[redacted]
Febrile Neutropenia	[redacted]	[redacted]	[redacted]	[redacted]

Statistically significant results are bolded
AEs = adverse events; CI =confidence interval; IC = investigator's choice.
Source: Table 2.5-6, p55 of the submission.

6.26 There was a higher proportion of patients with hypothyroidism in the pembrolizumab ([redacted]%) compared to the IC ([redacted]%) treatment arm. In the IC vs. pembrolizumab arm, there was a higher proportion of patients with mucosal inflammation, stomatitis, neutrophil count decreased, febrile neutropenia and alopecia in the IC arm. The ESC considered the comparative toxicity profile of pembrolizumab to be reasonable and similar to AEs observed in clinical practice. However, the ESC considered the higher rate of hypothyroidism reported may be an artefact of the trial sample size. The PBAC agreed with the ESC and noted that there was a slightly higher proportion of AEs leading to discontinuation (any grade and Grade 3-5) in the IC versus the pembrolizumab treatment arm.

6.27 The overall safety data for the CM141 trial (sourced from the NICE appraisal of nivolumab for head and neck cancer during the evaluation) are summarised below. A lower proportion of patients in the nivolumab treatment arm, compared to the IC arm, experienced Grade 3-4 all-causality AEs and SAEs, any-grade and Grade 3-4 drug-related AEs, drug-related serious AEs, and AEs leading to discontinuation were lower in the nivolumab arm.

Table 8: CM141 – Summary of safety analysis in CM141

Adverse event, n (%)[a, b]	Nivolumab (n=236)		IC (n=111)	
Deaths	132 (55.9)		78 (70.3)	
Deaths due to study drug toxicity	2 (0.8)[c]		0[d]	
	Any grade	**Grade 3-4**	**Any grade**	**Grade 3-4**
All causality AEs	229 (97.0)	97 (41.1)	109 (98.2)	58 (52.3)
Drug-related AEs	139 (58.9)	31 (13.1)	86 (77.5)	39 (35.1)
All-causality SAEs	127 (53.8)	66 (28.0)	66 (59.5)	36 (32.4)
Drug-related SAEs	16 (6.8)	11 (4.7)	17 (15.3)	12 (10.8)
All-causality AEs leading to treatment discontinuation	51 (21.6)	27 (11.4)	27 (24.3)	12 (10.8)
Drug-related AEs leading to treatment discontinuation	9 (3.8)	6 (2.5)	11 (9.9)	7 (6.3)

AEs = adverse events; IC = investigator's choice; MedDRA = Medical Dictionary for Regulatory Activities; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; SAEs = serious adverse events.

[a] Analysed in the all-treated population; includes events reported between the first dose and 30 days after the last dose of therapy.

[b] AEs were coded using the MedDRA version 18.1 and were graded for severity according to the NCI CTCAE version 4.0.

[c] Two deaths in the nivolumab arm (Grade 3 pneumonitis and Grade 5 hypocalcaemia) were assessed as related to study drug.

[d] In the IC arm, there was 1 death in a patient with a Grade 5 drug-related AE (lung infection) that was not attributed to study drug toxicity; Database lock of 18th December 2015.

Source: Table 18, p78 of the NICE technology appraisal of nivolumab for treating recurrent or metastatic squamous-cell carcinoma of the head and neck after platinum-based chemotherapy (https://www.nice.org.uk/guidance/ta490)

6.28 The submission provided a descriptive indirect comparison between pembrolizumab and nivolumab, with no formal statistical analysis conducted.

Clinical claim

6.29 The submission described pembrolizumab as non-inferior to nivolumab in terms of efficacy and safety for the treatment of R/M SCCHN in patients who have failed a prior platinum containing regimen. The ESC noted the high point estimate and upper confidence interval in the indirect comparison conducted during the evaluation for OS HR for pembrolizumab versus nivolumab (HR=1.14, 95% CI: 0.78, 1.67), and agreed with the evaluation that the clinical claim of non-inferiority is not adequately supported by the evidence provided. The ESC further considered that the OS HR point estimate and confidence intervals provided do not exclude important clinical differences and hence it was possible that pembrolizumab is inferior to nivolumab in terms of OS. The pre-PBAC response argued that differences in docetaxel dosing schedules, distribution of SOC therapies and subsequent immunotherapy between KN040 and CM141 may favour the nivolumab comparison to IC in CM141. In addition, the pre-PBAC response argued that differences in the level of risk of bias for different bias types between the KN040 and CM141 trials, along with differences in progression criteria and potential impact on chemo-sensitivity suggest that the

higher point estimates for the nivolumab OS HR may be favourably influenced by OS underperformance in the IC arm. The PBAC considered that the pre-PBAC response's claim was unsupported as the differences between the trials did not consistently bias in favour of nivolumab. The PBAC recalled concerns regarding the statistical significance of the OS benefit for the KN040 trial (see paragraph 6.17) and agreed with the ESC that the OS HR point estimate and confidence intervals for the indirect comparison do not exclude important clinical differences, with pembrolizumab possibly inferior to nivolumab in terms of OS.

6.30 The submission did not provide a non-inferiority margin. It would not be appropriate for a non-inferiority margin to be based solely on lack of statistical significance. The PSCR argued that an appropriate non-inferiority margin for the comparison of immunotherapies in R/M SCCHN has not been established, and recalled examples where the PBAC accepted results of indirect comparisons as a basis for non-inferiority. The PBAC considered that the lack of an adequately justified non-inferiority margin, where results of indirect comparisons are imprecise, makes it difficult to judge true non-inferiority. Furthermore, the PBAC considered that a claim of non-inferiority was difficult to support with an upper 95%CI for OS that extended to 1.67.

6.31 There were concerns of transitivity of trials included in the indirect comparison and their comparative efficacy and safety are difficult to interpret. The ESC noted that the additional data provided in the PSCR partially addressed these concerns (see paragraphs 6.10 and 6.11). The PBAC acknowledged that concerns regarding differences in the definition of the timing of recurrence/progression as an inclusion criterion had been partially addressed by the data provided in the PSCR. However, the PBAC considered that due to imbalances in the baseline characteristics of the CM141 trial concerns regarding transitivity remain.

6.32 The PBAC considered that the claim of non-inferior comparative effectiveness was not adequately supported by the data.

6.33 The PBAC considered that the claim of non-inferior comparative safety was reasonable.

Economic analysis

6.34 The submission presented a cost-minimisation analysis. The key components and assumptions of the cost-minimisation analysis are summarised below. The PBAC considered that a cost-minimisation analysis was inappropriate, as the indirect comparison evidence presented did not demonstrate that pembrolizumab is non-inferior to nivolumab in terms of efficacy for the treatment of R/M SCCHN in patients who have failed a prior platinum-containing regimen.

Table 9: Summary of model structure and rationale

Component	Claim or assumption
Therapeutic claim: effectiveness	Based on evidence presented in Section 2, effectiveness of pembrolizumab is assumed to be non-inferior to nivolumab
Therapeutic claim: safety	Based on evidence presented in Section 2, safety of pembrolizumab is assumed to be non-inferior to nivolumab
Evidence base	Indirect comparison of Trials KN040 (pembrolizumab vs methotrexate, docetaxel and cetuximab) and CM141 (nivolumab vs methotrexate, docetaxel and cetuximab)
Equi-effective doses	Pembrolizumab 200mg every 3 weeks and nivolumab 3mg/kg every 2 weeks. The submission assumed the same treatment duration for pembrolizumab and nivolumab.
Direct medicine costs	The proposed drug cost for pembrolizumab is higher than the drug cost for nivolumab to reflect the difference in the frequency of administration for pembrolizumab and nivolumab (every 3 weeks vs every 2 weeks).
Other costs or cost offsets	Yes. The infusion cost has been taken into account in the cost-minimisation analysis due to the differential administration frequency.

Source: Table 3.1.1, pp80-81 of the submission.

6.35 The treatment duration for pembrolizumab and nivolumab was assumed to be comparable and, therefore, not considered in the cost-minimisation analysis. Trial-based treatment duration was reported for pembrolizumab, but not for nivolumab. The PBAC considered that this would be a reasonable assumption if the discontinuation criteria for pembrolizumab is consistent with the PBS restriction for nivolumab and the non-inferiority claim is accepted by the PBAC, but noted that this had not been supported by the data presented in the submission.

6.36 The ESC noted that the average number of 2-weekly nivolumab administrations in the CM141 trial was not provided in the published paper. Unlike the KN040 trial, patients in CM141 were permitted to continue treatment with nivolumab beyond initial investigator assessed progression so long as the subject had investigator assessed clinical benefit and tolerated nivolumab treatment. The ESC noted that the treatment course cost for pembrolizumab in the submission was based on an average of [redacted] infusions per patient per course of therapy in trial KN040. Assuming the treatment duration for nivolumab was the same as that for pembrolizumab, [redacted] cycles were calculated for nivolumab ([redacted] x 2-weekly cycles versus [redacted] x 3-weekly cycles). The PBAC considered that any differences in treatment duration between the KN040 trial and the assumptions used to determine nivolumab utilisation across the nivolumab PBAC submissions for this indication would need to be accounted for in a cost-minimisation analysis.

6.37 As the nivolumab dosing is weight-based (3mg/kg), the number of vials per patient per administration was estimated on the basis of an average weight of [redacted]kg. This was derived from the GLANCE study, a retrospective chart review capturing data on [redacted] Australian SCCHN patients initiated on systemic therapy between January 2012 and June 2013. It is unclear whether the patient weight of the [redacted] Australian subjects in the GLANCE study are representative of the proposed PBS population. The average dosage of nivolumab was estimated as [redacted]mg (=3mg/kg x [redacted]kg) per administration. The submission assumed that the [redacted]mg of nivolumab would be supplied via 1x40mg vial and 2x100mg vials every 2 weeks. Therefore, the equi-effective dose used to determine the proposed price for pembrolizumab was pembrolizumab 200mg every 3 weeks (Q3W) and nivolumab 240mg every 2 weeks (Q2W). The submission's approach to nivolumab costing has incorporated substantial wastage ([redacted]mg of wastage out of the 40mg vial) which is unlikely to occur in clinical practice. A dose of [redacted]mg could also be achieved using 1x100mg vial and 3x40mg vials, resulting in less drug wastage.

6.38 A fixed 200mg per dose, i.e. 2x100mg vials, for pembrolizumab was used in the cost-minimisation analysis. Currently two vial strengths of pembrolizumab are currently reimbursed on the PBS (100mg and 50mg). The submission indicated that the sponsor would de-list the 50mg vial presentation from the PBS (planned for end of Q3 2018) where by 1 December 2018 (PBS listing date) existing stocks were expected to be exhausted. It is noted that the TGA-approved Product Information recommends a fixed dose (200mg) for treatment of SCCHN, classical Hodgkin lymphoma, urothelial carcinoma or NSCLC and either a fixed dose (200mg) or a weight-based dose (2mg/kg) for treatment of melanoma. Should a weight-based dosing for pembrolizumab (2mg/kg) be used in the proposed R/M SCCHN population in the Australian setting, and when 50mg vials become unavailable, a majority of the proposed target patients would still require 2x100mg vials of pembrolizumab, resulting in considerable wastage.

6.39 The results of the cost-minimisation analysis are presented in the table below.

Table 10: Results of the cost-minimisation analysis

Component	Pembrolizumab	Nivolumab
Ex-manufacturer price	100mg vial: $3,784.16	40mg vial: $830.70 100mg vial: $2,076.75
Number of vials per administration	2 x 100mg vials	1 x 40mg vial + 2 x 100mg vials
Dispensed drug cost per administration[a]	$7,732.88	$5,133.57
Cost of IV infusion per administration	$65.05	
Drug cost + infusion cost per administration	$7,797.93	$5,198.62
Number of administrations every 3 weeks[b]	1	1.5
Drug cost + infusion cost every 3 weeks	$7,797.93	$7,797.93
Difference	**$0.00**	

IV = intravenous

[a] Including the relevant EFC fees and assuming a public/private hospital split of 58%/42%

[b] The administration frequency is every 3 weeks for pembrolizumab and every 2 weeks for nivolumab

Source: Table constructed during the evaluation, based on the "Att 7 – BI model" workbook.

6.40 As noted above, the submission is likely to have overestimated the cost for nivolumab by incorporating substantial wastage for nivolumab, and therefore the price of pembrolizumab is likely to have been inflated. The ESC agreed with the evaluation that at the nivolumab vial combination initially proposed by the submission, the price of pembrolizumab was likely inflated. The PSCR accepted the evaluation's reduced nivolumab cost which translated into an ex-manufacturer price for pembrolizumab of $3,472.64 per 100mg vial. The PBAC agreed with the ESC and noted the revised ex-manufacturer price proposed in the PSCR and reaffirmed in the pre-PBAC response.

Drug cost/patient/course: $[redacted]

6.41 The submission estimated the treatment course cost per patient to be $[redacted]. This was based on an average of [redacted] infusions per patient per course of pembrolizumab therapy in Trial KN040, using the weighted effective price of $7,733 per administration for pembrolizumab. This estimated drug cost/patient/course is based on the original effective price presented in the submission, and does not reflect the revised ex-manufacturer price of $3,472.64 per 100mg vial proposed in the PSCR. The pre-PBAC response stated that the updated price per patient for pembrolizumab was $[redacted].

6.42 The cost of nivolumab was estimated by the submission to be $[redacted] per treatment course, by assuming the treatment duration for nivolumab being the same as that for pembrolizumab ([redacted] x 2-weekly cycles vs [redacted] x 3-weekly cycles) and the weighted published price of $5,134 per administration for nivolumab. The PBAC noted that the actual agreed cost of nivolumab per patient course would need to be accounted for in any cost-minimisation analysis.

Estimated PBS usage & financial implications

6.43 This submission was not considered by DUSC.

6.44 The submission used an epidemiological approach to estimate the extent of use of PD-1 therapies, and then a market share approach to determine the cost implications to the government health budgets.

6.45 The estimated financial implications of pembrolizumab are summarised below.

Table 11: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
No. of patients likely to be treated with PD-1 inhibitor	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No. of patients likely to be treated with pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No. of pembrolizumab administrations[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated financial implications of pembrolizumab[b]						
Dispensed costs[b] (including co-payments)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patient co-payments	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost to the PBS/RPBS[b] (excluding co-payments)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated financial implications for reduction in use of nivolumab[c]						
Dispensed costs (including co-payments)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patient co-payments	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost to the PBS/RPBS (excluding co-payments)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net financial implications						
Net cost to PBS/RPBS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net cost to MBS[d]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net cost to Government	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net financial implications (revised budget impact model[e])						
Net cost to PBS/RPBS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net cost to MBS[d]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net cost to Government	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] Assuming [redacted] administrations per patient

[b] The cost of pembrolizumab to the PBS/RPBS was calculated on the basis of the proposed effective price.

[c] The cost of nivolumab to the PBS/RPBS was calculated on the basis of the published price. The submission assumed that the treatment duration for nivolumab would be same as that for pembrolizumab (ie [redacted] x 2 weekly cycles vs [redacted] x 3-weekly cycles)

[d] Including patient co-payments

[e] Changes made to budget impact model in pre-PBAC response (pp3-4): ex-manufacturer 100 mg vial price for pembrolizumab updated to $3,472.64; vials used per nivolumab course updated to 3 x 40 mg vials and 1 x 100 mg vial; treatment rate altered to [redacted]% in years 1-6; candidate patient population (metastatic/recurrent second line) reduced by [redacted]% to extract the patients not relevant to nivolumab who progress after 6 months.

Source: Table compiled during the evaluation, based on Table 4.2-2, p89, Table 4.3-2, p90, Table 4.4-5, p93, Table 4.5-2, p94, Table 4.5-3, p95, Table 4.6-1, p95, Table 4.6-4, p96, Table 4.6-10, p98, Table 4.6-11, p98, Table 4.6-12, p99 and Table 4.9-3, p101 of the submission; "Budget Impact model updated for pembrolizumab for RMSCCHN – KEYTRUDA – MSD_vF".xlsx submitted in July 2018

The redacted table shows that at year 6, the estimated number of patients was less than 10,000 and the net cost to the PBS would be less than $10 million.

6.46 Overall, the cost of pembrolizumab to the PBS/RPBS could be either greater or lower than the submission's estimate. The main uncertainty is the estimated number of R/M SCCHN patients after failure of prior platinum-containing chemotherapy, which was based on a sponsor commissioned report. Insufficient information on the sponsor commissioned report was available to assess the suitability of this data source or to verify the resulting patient numbers. The submission could have overestimated the treatment rate with PD-1 inhibitors ([redacted]%), given the advanced

disease stage of the candidate population and the requirement for patients to have an ECOG status of 0 or 1 to be eligible for pembrolizumab. The PSCR acknowledged the treatment rate with PD-1 inhibitors may have been overestimated in the submission and suggested adjustment from [redacted]% to [redacted]% in the financial estimates ([redacted] in Year 1 to [redacted] in Year 6), in line with the proportion of ECOG status 0 or 1 patients from the GLANCE study. The ESC considered the estimated number of patients likely to be treated with pembrolizumab remains uncertain.

6.47 In addition, the PBAC considered that the uptake rate of pembrolizumab could be higher than the submission's estimate, given its less frequent administration compared with nivolumab (Q3W vs Q2W) may be beneficial to a small number of patients.

6.48 The cost implications to the PBS/RPBS were assumed to be equivalent to the MBS savings. The overall cost to the Commonwealth is neutral. This is consistent with the cost-minimisation approach taken by the submission. However, if the patient co-payments are removed from the net cost savings to the MBS, the proposed listing of pembrolizumab would result in minimal additional costs to the government health budgets.

6.49 The proposed restriction for pembrolizumab is broader than the PBS listing for nivolumab, and includes patients who experience disease progression greater than 6 months following treatment with chemotherapy. The financial analysis presented in the submission, however, assumed that all patients likely to receive pembrolizumab would otherwise be treated with nivolumab. This did not take into account the additional patients who would be eligible for pembrolizumab, but not for nivolumab and the resulting net cost to the Government associated with the substitution of pembrolizumab for single-agent chemotherapy within this subpopulation.

6.50 An updated budget impact model was provided with the pre-PBAC response with the net financial implications presented in the shaded section of Table 11. The pre-PBAC response stated the following changes were made to the budget impact model: the ex-manufacturer 100 mg vial price for pembrolizumab was updated to $3,472.64; the vials used per nivolumab course was updated to 3 x 40 mg vials and 1 x 100 mg vial; the treatment rate was altered to [redacted]% in years 1-6; and the candidate patient population (metastatic/recurrent second line) was reduced by [redacted]% to extract the patients not relevant to nivolumab who progress after 6 months.

6.51 The PSCR calculated the additional cost of pembrolizumab to the PBS/RPBS in metastatic patients who have progressed more than 6 months after first line treatment (i.e. those patients not currently included in the nivolumab deed) using an [redacted]% treatment rate for PD-1 inhibitors (Table 12).

Table 12: Financial implications of patient population outside nivolumab deed

	Year 1	*Year 2*	*Year 3*	*Year 4*	*Year 5*	*Year 6*
Candidate population (oral cavity, oropharyngeal, hypopharyngeal, laryngeal, pharyngeal) - Metastatic/recurrent second line, first line failed (Plan A Data_JCP)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
% progressed after 6 months (based on KN040 data)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No. pts progressed after 6 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment rate in those who progressed after 6 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No. treated pts progressed after 6 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab market share	100%	100%	100%	100%	100%	100%
No. pembrolizumab treated pts	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Average Pembrolizumab Cost per patient (from submission Budget Impact model)[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Revised[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Additional pembrolizumab cost to government	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Revised[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] Estimates based on per patient cost for nivolumab sourced from the submission
[b] Revised estimates based on per patient cost for pembrolizumab sourced from the submission
Source: Table 5 PSCR

The redacted table shows that at year 6, the estimated number of patients was less than 10,000 and the net cost to the PBS would be less than $10 million.

6.52 The PSCR estimated that [redacted]% of metastatic patients progress more than 6 months after first line treatment and calculated that this equates to approximately [redacted] additional patients each year outside the current nivolumab restriction. The PSCR assumed an identical average patient cost for this population to the populations already included in the nivolumab restriction (i.e. $[redacted]) and estimated an additional cost to the PBS/RPBS of $10 – $20 million over the first 6 years. Using the submission's estimate of cost per patient for pembrolizumab, instead of cost per patient for nivolumab as used in the PSCR, the cost implications of pembrolizumab to the PBS/RPBS (including co-payments) would be $10 – $20 million over the first 6 years of listing. The pre-PBAC response stated that using an average patient cost of $[redacted] the cost implication of pembrolizumab to the PBS/RPBS for these 40-45 additional patients would be $10 – $20 million over the first 6 years of listing. While this estimated proportion of patients was consistent with the population in the trial that progressed after 6 months, the applicability of this proportion or the assumptions regarding treatment duration to the Australian population could not be evaluated because it was provided in the PSCR.

Quality Use of Medicines (QUM)

6.53 Although the administrative advice in the requested restrictions for pembrolizumab and nivolumab specify that a confirmatory scan be taken at least 4 weeks after progression is suspected, evidence from the literature suggests that such events previously reported in melanoma are very rare in SCCHN[11]. The rarity of pseudo-progression events in solid tumours (beyond melanoma) may need to be weighed against the harms of overtreatment with immunotherapy and delayed or missed opportunities for alternate therapeutic options including SOC[12]. This issue represents an important QUM issue.

6.54 A minor submission to the March 2018 PBAC meeting requested a change to the pembrolizumab dosing for malignant melanoma from 2 mg/kg to a fixed dose of 200mg per infusion. The PBAC recommended an amendment to the existing PBS restrictions to allow either a weight-based dose of 2 mg/kg or a fixed dose of 200 mg Q3W. However, because the submission argued that there was a flat relationship between pembrolizumab exposure and efficacy or safety within the dose range of 2 to 10mg/kg, the PBAC concluded that, for patients who are currently on a weight-based dose of less than 200mg, there is no extra clinical benefit achieved by increasing to the fixed 200mg dose, but there could potentially be more toxicity (Paragraph 5.2, 6.13 pembrolizumab (melanoma) PBAC PSD, March 2018 meeting).

6.55 There is a potential leakage to pembrolizumab use outside of the PBS restriction for treatment of patients with performance status greater than 1. Although a Risk Sharing Arrangement (RSA) would limit the financial risk to government health budgets of these patients with accessing pembrolizumab, there is also a QUM issue in treating these patients.

Financial Management – Risk Sharing Arrangements

6.56 The submission proposed a Special Pricing Arrangement (SPA) where the published price is greater than the effective price.

6.57 It was noted that a RSA would apply to the comparator nivolumab, once PBS listed. The submission acknowledged that pembrolizumab would become part of the same deed, should it be recommended by the PBAC. As commented previously, the proposed restriction for pembrolizumab is broader than that for nivolumab (without vs with a limit on the elapsed time for progression after platinum-based chemotherapy), which might have implications for the RSA if pembrolizumab shares the same deed with nivolumab. The PSCR and pre-PBAC response reiterated the sponsor's willingness to enter into the RSA for nivolumab, with amendments to

[11] Baxi SS, Dunn LA, Burtness BA. Amidst the excitement: a cautionary tale of immunotherapy, pseudoprogression and head and neck squamous cell carcinoma. Oral oncology. 2016;62:147-8.
Chiou VL, Burotto M. Pseudoprogression and immune-related response in solid tumors. Journal of Clinical Oncology. 2015;33(31):3541.

[12] Baxi SS, Dunn LA, Burtness BA. Amidst the excitement: a cautionary tale of immunotherapy, pseudoprogression and head and neck squamous cell carcinoma. Oral oncology. 2016;62:147-8.

account for the additional patients relevant to the broader proposed pembrolizumab restriction. The PBAC considered that given the limited data relating to the treatment of patients who have progressed after six months, it may be more appropriate for this listing, including the additional patient population, to be cost-neutral to the PBS.

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

7 PBAC Outcome

7.1 The PBAC decided not to recommend pembrolizumab for the treatment of patients with locally advanced (Stage III) or metastatic (Stage IV) squamous cell carcinoma of the head and neck (SCCHN) who have failed a platinum-containing regimen. The PBAC considered that the clinical need was low due to the availability of alternative treatments, and that the magnitude of clinical benefit was uncertain. In addition, the PBAC considered that the clinical evidence provided did not adequately support the claim of non-inferior efficacy to nivolumab as the nominated comparator. As such, the PBAC considered that the cost-minimisation analysis presented was inappropriate.

7.2 The PBAC welcomed the input from individuals and organisations which described the potential benefits of treatment with pembrolizumab.

7.3 The PBAC considered that the clinical need for the requested listing was low following the recommendation of nivolumab for SCCHN at the March 2018 meeting. The PBAC considered that the advantages of pembrolizumab compared with nivolumab would likely be limited to a very small population (patients with Stage III SCCHN, and patients who experience disease progression greater than 6 months following treatment with platinum-based chemotherapy) or to the modest benefit associated with a lower frequency in dosing (Q3W compared with nivolumab's Q2W).

7.4 The PBAC accepted nivolumab as the main comparator, however also considered second line chemotherapy to be an appropriate secondary comparator for the population with disease progression greater than 6 months following treatment with platinum-based chemotherapy.

7.5 The PBAC noted that the proposed pembrolizumab population was slightly broader than for nivolumab but considered it may be appropriate to include this group of patients.

7.6 The submission was based on an indirect comparison between pembrolizumab (KN040 trial) and nivolumab (CM141 trial) in R/M SCCHN patients who had progressed on or after platinum-based chemotherapy using IC as the common reference. The PBAC noted that for KN040, there was a 1.5 month OS gain associated with pembrolizumab over IC which corresponded to a 20% reduction in risk of death (HR=0.80, 95% CI (0.65, 0.98); p-value=0.01605). The PBAC noted that the statistical

significance of the HR was based on a one sided p-value, and it was concerned that the inconsistency in the OS results reported across analyses created uncertainty regarding the statistical significance of the OS benefit. The PBAC considered that pembrolizumab presented at best a modest OS benefit, and no benefit in PFS, compared with IC.

7.7 The PBAC was also concerned regarding the generalisability of the KN040 trial results to the intended Australian population. The PBAC considered that the trial population were younger than patients who would be eligible for PBS subsidised treatment and hence trial benefits may not be realised in clinical practice.

7.8 The PBAC noted that a difference of less than 10% in EORTC QLQ-C30 score, favouring pembrolizumab, was reported in the KN040 trial. The PBAC considered that the impact of pembrolizumab on QoL was modest and may not be clinically meaningful. The PBAC considered that the KN040 trial indicated the comparative toxicity profile of pembrolizumab with IC was reasonable and noted the slight reduction in AEs leading to discontinuation (any grade and grade 3-5) in the pembrolizumab arm.

7.9 The PBAC considered that concerns regarding transitivity of trials and the lack of an adequately justified non-inferiority margin made interpretation of the indirect comparison difficult. The PBAC noted the high point estimate and upper confidence interval in the indirect comparison OS HR for pembrolizumab versus nivolumab (HR=1.14, 95% CI: 0.78, 1.67), and considered that the clinical claim of non-inferior comparative effectiveness was not adequately supported by the evidence provided. The PBAC considered that important clinical differences are not excluded in the indirect comparison, with pembrolizumab possibly inferior to nivolumab in terms of OS.

7.10 The PBAC considered that the claim of non-inferior safety compared with nivolumab was reasonable.

7.11 The PBAC considered that a cost-minimisation analysis was inappropriate, as the indirect comparison evidence presented did not demonstrate that pembrolizumab is non-inferior to nivolumab in terms of efficacy for the treatment of R/M SCCHN in patients who have failed a prior platinum-containing regimen.

7.12 The PBAC noted that the submission estimated the overall cost to the Commonwealth to be neutral. However, the PBAC considered the financial impact of listing pembrolizumab for this indication was uncertain due to:

- uncertainty in the estimated number of patients treated with PD-1 inhibitors;
- the inclusion of patients who experience disease progression greater than 6 months following treatment with chemotherapy (not included in the PBS listing for nivolumab);

- a potentially higher uptake rate than the submission estimate, given its less frequent administration compared with nivolumab may be beneficial to a small number of patients.

7.13 The PBAC considered that a RSA would be required to address the sources of uncertainty identified in the financial estimates.

7.14 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:
Rejected

8 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

9 Sponsor's Comment

MSD is disappointed in this PBAC outcome but will work towards obtaining funded treatment options for patients with squamous cell carcinoma of the head and neck at the earliest opportunity.

MSD also wishes to note the complexities in evaluating a claim of non-inferiority for pembrolizumab with nivolumab across the KN040 and CM141 trials, respectively.

- Within KN040: As noted in the submission, despite well-balanced baseline characteristics, a high degree of cross-over from the comparator arm to an immune-oncology therapy likely confounded the evaluation of over-all survival, negatively impacting the HR.
- Across KN040 & CM141: As noted in paragraph 6.23, there are inherent risks in comparing across trials, which may have confounded any indirect comparison of pembrolizumab and nivolumab. Indirect comparisons with wide confidence intervals that range either side of 1 indicate that a therapy may have a likelihood of being superior or inferior.