

6.07 NIVOLUMAB,

Injection concentrate for I.V. infusion 40 mg in 4 mL, Injection concentrate for I.V. infusion 100 mg in 10 mL, Opdivo®, Bristol-Myers Squibb Australia Pty Ltd

1 Purpose of application

- 1.1 Section 100, Authority Required (streamlined) listing for nivolumab for treatment of recurrent or metastatic (RM) squamous cell carcinoma of the oral cavity, pharynx or larynx (SCCHN) who have progressed within 6-months after platinum-based chemotherapy. Nivolumab has not been previously considered by the PBAC for this indication.
- 1.2 The basis for the requested listing was a cost-utility analysis compared to Australian standard of care (SOC) (paclitaxel, docetaxel, methotrexate, or capecitabine).

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

Component	Description
Population	Patients with recurrent or metastatic squamous cell carcinoma of the oral cavity, pharynx or larynx who have progressed within 6 months after receiving platinum-based chemotherapy. Patients must have an ECOG performance score of 0 or 1.
Intervention	Nivolumab 3 mg/kg administered as a 60 minute IV infusion every two weeks.
Comparator	Standard of care (docetaxel/paclitaxel/methotrexate/capecitabine)
Outcomes	OS, PFS, objective response rate. Quality of life during treatment. The assessment of safety was based on frequency of deaths, AEs, SAEs, AEs leading to discontinuation.
Clinical claim	Nivolumab is superior in terms of efficacy compared to standard of care and has a favourable safety profile for the treatment of recurrent or metastatic squamous cell carcinoma of the oral cavity, pharynx or larynx in patients who have progressed following treatment with platinum-based therapy.

AEs: adverse events; ECOG: Eastern Cooperative Oncology Group; OS: overall survival; PFS: progression-free survival; RECIST: Response evaluation criteria in solid tumours; SAEs: serious adverse events.

Source: Table 1, p12-13 of the submission

2 Requested listing

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

Public Summary Document – November 2017 PBAC Meeting

Name, Restriction, Manner of administration and form	Max. Amount	No. of Rpts	Dispensed Price for Max. Amount	Proprietary Name and Manufacturer	
NIVOLUMAB nivolumab 40 mg/4 mL injection, 1 x 4 mL vial	360 mg	8	\$7560.13 (Public, published) \$ [REDACTED] (Public, effective)	Opdivo	Bristol Myers Squibb Pty Ltd.
nivolumab 100 mg/10 mL injection, 1 x 10 mL vial	360 mg	8	\$7703.43 (Private, published) \$ [REDACTED] (Private, effective)		
Category / Program :	Section 100 - Efficient funding of Chemotherapy				
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives				
Severity:	Recurrent or metastatic				
Condition:	Squamous cell carcinoma of the oral cavity, pharynx or larynx				
PBS Indication:	Recurrent or metastatic squamous cell carcinoma of the oral cavity, pharynx or larynx				
Treatment phase:	Initial treatment				
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined				
Clinical criteria:	Patient must have a WHO performance status of 0 or 1 AND The treatment must be the sole PBS-subsidised therapy for this condition AND The condition must have progressed within 6 months of receiving prior platinum based chemotherapy. AND <i>Patient must not have received prior treatment with a PD-1 inhibitor for this condition.</i>				
Prescriber Instructions	The patient's body weight must be documented in the patient's medical records at the time treatment is initiated.				
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. No increase in the maximum number of repeats may be authorised. Special Pricing Arrangements apply.				

Name, Restriction, Manner of administration and form	Max. Amount	No. of Rpts	Dispensed Price for Max. Amount	Proprietary Name and Manufacturer
NIVOLUMAB				
nivolumab 40 mg/4 mL injection, 1 x 4 mL vial	360 mg	11	\$7560.13 (Public, published) \$ [REDACTED] (Public, effective)	Opdivo Bristol Myers Squibb Pty Ltd.
nivolumab 100 mg/10 mL injection, 1 x 10 mL vial	360 mg	11	\$7703.43 (Private, published) \$ [REDACTED] (Private, effective)	

Category / Program:	Section 100 - Efficient funding of Chemotherapy
Prescriber type	Medical Practitioners
Severity:	Recurrent or metastatic
Condition:	Squamous cell carcinoma of the oral cavity, pharynx or larynx
PBS Indication:	Recurrent or metastatic squamous cell carcinoma of the oral cavity, pharynx or larynx
Treatment phase:	Continuing treatment
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined
Clinical criteria:	Patient must have previously been issued with an authority prescription for this drug for this condition AND Patient must have stable or responding disease AND The treatment must be the sole PBS-subsidised therapy for this condition
Administrative Advice	No increase in the maximum number of repeats may be authorised. Special Pricing Arrangements apply.

- 2.2 The recommended dose regimen for nivolumab is 3 mg/kg IV over 60 minutes every 2 weeks.
- 2.3 Nivolumab is a human anti-PD-1 monoclonal antibody which binds to programmed cell death 1 receptor (PD-1) inhibiting the interaction between the PD-1 receptor and its ligands, PD-L1 and PD-L2.
- 2.4 The clinical criteria in the proposed PBS continuing restriction states that patients must have stable or responding disease. The submission does not propose any criteria for ascertaining whether a patient has stable or responding disease (e.g. Response Evaluation Criteria In Solid Tumours (RECIST) criteria), rather leaving it to the judgment of clinicians. The submission argued that some patients treated with immune system stimulating agents may develop progression of disease (by conventional response criteria) before demonstrating clinical objective responses and/or stable disease.
- 2.5 The submission proposed an effective price for nivolumab which was [REDACTED] % lower than the published price.

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

3 Background

Registration status

- 3.1 TGA status: nivolumab was TGA registered on 11 July 2017 for the following indication: as monotherapy for the treatment of recurrent or metastatic squamous cell cancer of the head and neck in adults progressing on or after platinum based therapy.
- 3.2 The proposed PBS restriction is narrower than the TGA approved indication. While the TGA approved indication includes treatment for all SCCHN patients, the PBS restriction would only allow for SCCHN in the oral cavity, larynx and pharynx, thereby excluding the paranasal sinuses, nasal cavity and salivary gland subgroups of SCCHN. Additionally, although pharynx as a whole was included in the proposed PBS restriction, the key clinical trial (CA209141) excluded patients with any nasopharyngeal involvement. The DUSC advised that the proposed PBS restriction should specifically exclude treatment of patients with nasopharyngeal cancer, consistent with the inclusion criteria of the trial presented as clinical evidence in the submission.
- 3.3 Nivolumab is PBS listed for unresectable Stage III or Stage IV malignant melanoma, locally advanced or metastatic non-small cell lung cancer, and stage IV clear cell variant renal cell carcinoma (RCC). PD-L1 testing is not a pre-requisite for patients accessing nivolumab in these PBS listed indications.
- 3.4 Co-dependent submissions were considered by the PBAC and MSAC for pembrolizumab (another anti-PD-1 monoclonal antibody) for locally advanced or metastatic non-small cell lung cancer (NSCLC)¹ and treatment naïve patients with locally advanced or metastatic NSCLC². MSAC and PBAC raised the following concerns about PD-L1 expression testing for accessing pembrolizumab in NSCLC³:
- PD-L1 immunohistochemistry (IHC) as a companion diagnostic test has weak evidence of clinical validity (lacks ability to predict response to therapy) and clinical utility (insufficient information to guide treatment).
 - Unlike many other companion tests, PD-L1 has a wide range of expression and hence the results reported are not dichotomous and are challenging to quantify.
 - The issue of the optimum threshold for PD-L1 positivity remained unresolved.
 - If other programmed death 1 (PD-1)/PD-L1 inhibitors become listed in the PBS for NSCLC in the future that also require PD-L1 testing, the required tumour proportion score (TPS) threshold for eligibility may vary.

The ESC considered that the utility of PD-L1 testing was a contentious matter, particularly because the sensitivity and specificity of the available tests were still an

¹ MSAC (2016) Application No. 1414 – PD-L1 testing for access to pembrolizumab for the treatment of locally advanced or metastatic NSCLC

² MSAC (2016) Application No. 1440 – PD-L1 testing for access to pembrolizumab in treatment naïve patients with locally advanced or metastatic NSCLC

³ PBAC (March 2017) Public Summary Document – 6.04 Pembrolizumab

evolving area in molecular pathology. As such, the ESC advised that, at the present time, it was difficult to determine if there was any benefit in stratifying patients based on PD-L1 status for nivolumab for RM SCCHN.

Previous PBAC consideration

3.5 Nivolumab has not been previously considered by the PBAC for this indication.

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

4 Population and disease

4.1 Head and neck cancer refers to a range of malignant tumours that develop in or around the throat (pharynx and larynx), nose, sinuses and mouth. Cancers of the oral cavity, pharynx and larynx are the most common types of head and neck cancer, while cancers of the sinuses and salivary glands are less common. In Australia, head and neck cancers accounted for 3.4% of all cancers diagnosed in 2009. While treatment of small localised cancer results in approximately 80% of patients surviving five years after diagnosis, with more advanced disease, this reduces to 38%.

4.2 The mechanism of action of nivolumab is to block the interaction between PD-1 and its ligands PD-L1 and PD-L2. An Australian study reported that round 52.7% of primary SCCHN cases and 44.7% of metastatic SCCHN cases had tumour PD-L1 expression $\geq 1\%$ (n=74 and 28, respectively).⁴

4.3 The proposed clinical management algorithm suggested that nivolumab be used as a treatment option for patients with progression within 6 months of receiving platinum based therapy; and as a treatment option for patients who progress after 6 months of platinum based therapy; subsequent to rechallenge with further platinum based therapy.

4.4 It was not clear from the clinical management algorithm whether patients who progressed after 6 months of initial platinum-based therapy and were rechallenged with platinum-based therapy were subsequently eligible for nivolumab following progression within 6 months, or whether they were eligible if progression occurred after 6 months. The Pre-Sub-Committee Response (PSCR) (p2) clarified that the intention of the proposed PBS restriction was for patients to only be eligible for nivolumab treatment if they have progressed within six months of the last dose of platinum therapy. The PSCR further assumed that, upon PBS listing, the majority of patients who progress within 6 months would be treated with nivolumab (■%), while the remaining would receive a single agent (■%) or best supportive care (■%). The PSCR claimed that this was in alignment with the inclusion criteria for the pivotal Study CA209141.

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

⁴ Roper et.al (2017). PD-L1 expression predicts longer disease free survival in high risk head and neck squamous cell carcinoma. Pathology.

5 Comparator

- 5.1 The submission nominated current Australian SOC as the main comparator, specifically one of either paclitaxel, docetaxel, methotrexate, or capecitabine. The comparators are included in the United States' National Comprehensive Cancer Network (NCCN) Head and Neck guidelines provided with the submission, and were supported by minutes from the sponsor-appointed expert advisory board panel meeting consisting of six advisors.
- 5.2 The main comparators nominated by the submission were reasonable. The Commentary on the submission queried whether fluorouracil and gemcitabine should also be considered as relevant comparators. The ESC advised that the nomination of SOC, represented by paclitaxel, docetaxel, methotrexate and capecitabine, was appropriate in the Australian treatment paradigm.
- 5.3 The submission also nominated pembrolizumab as a near market comparator, which is TGA listed for "the treatment of patients with recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) with disease progression on or after platinum containing chemotherapy".
- 5.4 Pembrolizumab has not been considered by the PBAC for this indication. The submission did not provide a formal comparison between nivolumab and pembrolizumab.
- 5.5 Cetuximab could also be considered as a relevant near market comparator. Cetuximab was not recommended by the PBAC for the treatment of *previously untreated* RM SCCHN on the basis of uncertain magnitude of clinical benefit and likely high and unacceptable cost-effectiveness (paragraph 7.1, cetuximab Public Summary Document (PSD), March 2016 PBAC meeting and paragraph 6.1, cetuximab PSD, November 2016 PBAC meeting). The ESC considered that cetuximab was not a relevant comparator, noting that the PBAC's previous consideration of cetuximab was for previously untreated RM SCCHN.

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

6 Consideration of evidence

Sponsor hearing

- 6.1 The sponsor requested a hearing for this item. At the hearing, representatives of the sponsor discussed the benefits of nivolumab treatment in an area of high clinical need, highlighting its effects in improving quality of life in particular. While it was acknowledged that capecitabine is more commonly used in Australia than cetuximab, the sponsor also urged PBAC to consider that Australian clinical experts treating SCCHN have advised that SOC in Australia for treating this condition is varied, and therefore the treatments in the study's comparator arm were representative of the results expected with SOC in Australia. The sponsor also contended against the ESC advice that a multivariate analysis with revised inputs for certain parameters resulted in the more realistic incremental cost-effectiveness ratio (ICER), disagreeing with the

ESC's preferred extrapolation method and assumptions on post-progression utilities, and partially agreeing on the treatment duration (see Table 10 and paragraph 6.40 for further details).

Consumer comments

- 6.2 The PBAC noted and welcomed the input from individuals (1), health professionals (2) and organisations (1) via the Consumer Comments facility on the PBS website. The comments described the benefits and tolerability profile of nivolumab in an aggressive and debilitating malignancy with limited treatment options.
- 6.3 A letter of support from Rare Cancers Australia indicated that the PBS listing of nivolumab would offer SCCHN patients an effective treatment option with fewer side effects.
- 6.4 The Medical Oncology Group of Australia (MOGA) also expressed its support for the nivolumab submission, noting the limited treatment options available for SCCHN. The PBAC noted that the MOGA presented a European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) of 5 for nivolumab for SCCHN (out of a maximum of 5, where 5 and 4 represent the grades with substantial improvement)⁵, based on a comparison against chemotherapy. PBAC considered that an ESMO-MCBS of 3 better reflected the evidence available.

Clinical trials

- 6.5 The submission was based on one direct randomised trial comparing nivolumab to investigator's choice of a single agent therapy consisting of either docetaxel OR methotrexate OR cetuximab (IC) in RM SCCHN (n=361) (Trial CA209141).
- 6.6 Details of the trial presented in the submission are provided in the table below. An independent search located no other relevant trials.

⁵ Cherny NI, Sullivan R, Dafni U, et al: A standardised, generic, validated approach to stratify the magnitude of clinical benefit that can be anticipated from anti-cancer therapies: the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS). *Ann Oncol* 26:1547-73, 2015

Table 2: Trials and associated reports presented in the submission

Trial ID/First Author	Protocol title/ Publication title	Publication citation
Direct randomised trial		
CA209141	An Open Label, Randomised Phase 3 Clinical Trial of Nivolumab vs Therapy of investigator's choice in recurrent or metastatic platinum refractory squamous cell carcinoma of the head and neck (SCCHN). American Association for Cancer Research (2016). "Nivolumab Doubles Survival for Patients with HNSCC." Ferris, R. L., Blumenschein, G., Fayette, J., Guigay, J., Colevas, A. D., et al. (2016). "Nivolumab for recurrent squamous-cell carcinoma of the head and neck." Gillison, M. L., Blumenschein, G., Fayette, J., Guigay, J., Colevas, A. D., et al. (2016). "Nivolumab (nivo) vs investigator's choice (IC) for recurrent or metastatic (R/M) head and neck squamous cell carcinoma (HNSCC): CheckMate-141." Harrington, K., Ferris, R. L., Shaw, J., Taylor, F., Derosa, M., et al. (2016). "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."	07 June 2016 Cancer Discov 6(7): Of3. New England Journal of Medicine 375(19): 1856-7 Cancer Research 76(14). Annals of Oncology 27.

Source: Table 14, p43-44 of the submission

6.7 The key features of the direct randomised trial is summarised in the table below.

Table 3: Key features of the included evidence, nivolumab versus investigator's choice of therapy

Trial	N	Design/ median duration of follow-up	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
CA209141	361	R, OL Nivolumab: ██████████	Medium	RM SCCHN, ECOG 0-1, tumour progression or recurrence within 6 months of last dose of platinum therapy	Primary: OS Secondary: PFS, ORR, EORTC-QLQ-C30, EORTC-QLQ-C30-H&N35, EQ-5D-3L	PFS and OS Kaplan-Meier data used in model

ECOG: Eastern Cooperative Oncology Group; IC: investigator's choice of therapy; OL: open-label; ORR: objective response rate; OS: overall survival; PFS: progression-free survival; R: randomised, RM SCCHN: recurrent or metastatic squamous cell carcinoma of the head and neck.

Source: compiled during the evaluation

6.8 There was no planned cross-over in the trial design, however in the investigator's choice of therapy arm, ██████% of patients received subsequent therapy with an anti-PD-1 pathway agent (nivolumab [█████%] and pembrolizumab [█████%]). This could have biased the OS results in favour of the investigator's choice of therapy arm.

6.9 The overall risk of bias in Trial CA209141 was moderate due to the open-label nature of the trial. This was unlikely to affect the primary endpoint (OS), however the trial did not utilise a blinded independent review committee to assess progression free survival (PFS) and objective response rate (ORR). Consequently, the trial design did not minimise observer bias that may influence the results of the secondary outcomes.

6.10 Treatment with nivolumab was permitted to continue beyond initial investigator assessed progression in Trial CA209141 according to RECIST version 1.1 criteria, so long as the subject had investigator assessed clinical benefit and tolerated nivolumab treatment. A total of ██████% of nivolumab patients continued treatment following progression in Trial CA209141. The proposed PBS restriction stated that a patient continuing treatment with nivolumab must have stable or responding disease. The

proposed PBS restriction did not contain criteria for ascertaining whether a patient has progressed, rather it is left up to the judgement of clinicians.

Comparative effectiveness

6.11 The key results of Trial CA209141 are presented in Table 4 and Figures 1 to 3.

Table 4: Results of OS and PFS across the direct randomised trial

Trial ID	Nivolumab, n with event/N (%)	IC, n with event/N (%)	Nivolumab, Median months (95% CI)	IC, Median months (95% CI)	Diff	HR (95% CI)
OS	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Primary definition of PFS ^b	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Secondary definition of PFS ^c	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

a Stratified Log-rank p-value

b The time between the date of randomisation and the first date of documented progression, as determined by the investigator (as per RECIST 1.1 criteria), or death due to any cause, whichever occurs first. Censoring rules:

Patients who did not progress or die were censored on date of last evaluable tumour assessment

Patients who did not have any on study tumour assessments and did not die will be censored on their date of randomisation

Patients who receive subsequent systemic anti-cancer therapy prior to documented progression will be censored at the date of the last tumour assessment prior to the initiation of the new therapy.

c The time between the date of randomisation and the first date of documented progression, as determined by the investigator (as per RECIST 1.1 criteria), or death due to any cause, whichever occurs first. Censoring rules:

Patients who did not progress or die were censored on date of last evaluable tumour assessment

Patients who did not have any on study tumour assessments and did not die will be censored on their date of randomisation

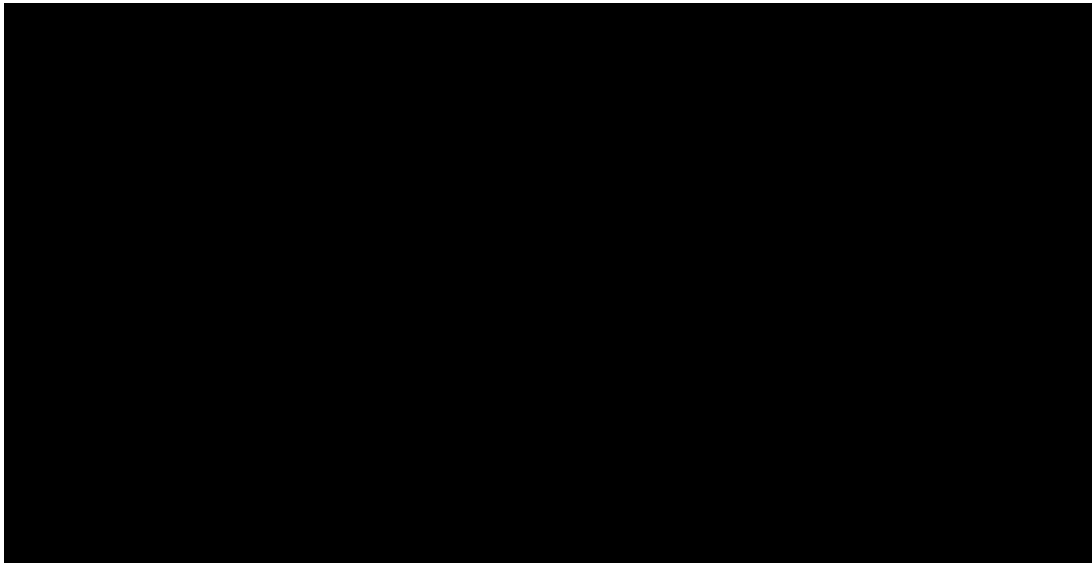
CI: confidence interval; HR: hazard ratio; IC: investigator’s choice of therapy; PFS: progression-free survival; OS: overall survival.

Source: Table 23 p58 and Table 25 p60 of the submission

Figure 1: Kaplan-Meier OS plot – All randomised patients



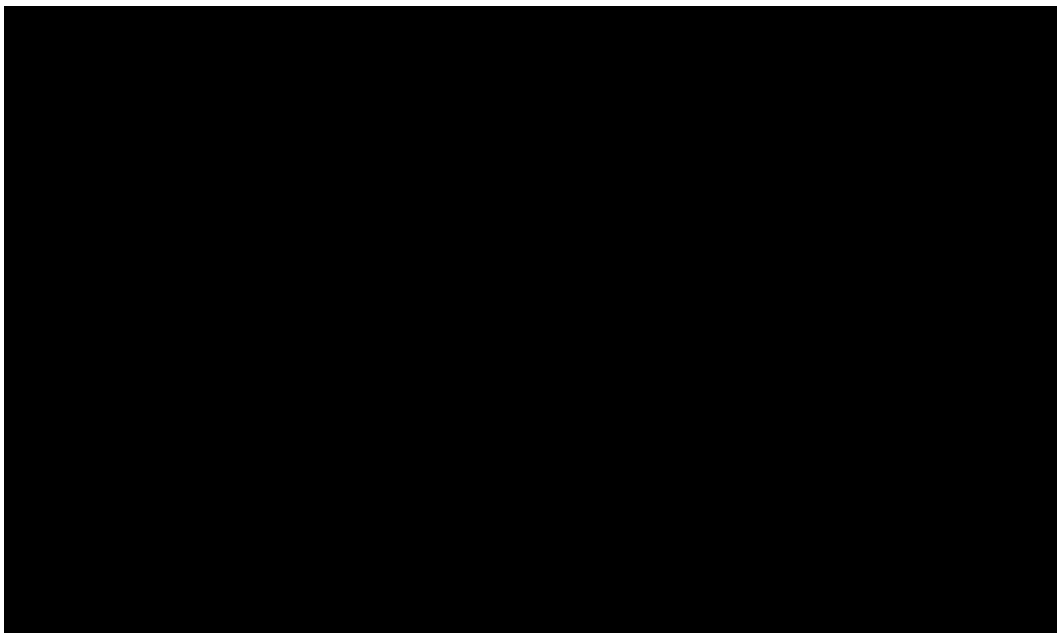
Figure 2: Kaplan-Meier plot of PFS (primary definition) – All randomised patients



INV Choice: investigator's choice of therapy; NIVO: nivolumab.

Source: Figure 7, p61 of the submission

Figure 3: Kaplan-Meier plot of PFS (secondary definition) – All randomised patients



INV Choice: investigator's choice of therapy; NIVO: nivolumab.

Source: Figure 8, p61 of the submission

- 6.12 There was a statistically significant difference in OS between nivolumab and the investigator's choice of therapy (IC), however there was no statistically significant difference in PFS. The median difference in OS was [REDACTED] months.
- 6.13 Initially there was a rapid occurrence of progression observed in both the nivolumab and investigator's choice of therapy arms, however there was a delayed separation of the Kaplan-Meier curves favouring nivolumab. The submission claimed that "the PFS curves were heavily influenced by the steep drop observed within the first 8 weeks of follow-up and the crossing of curves at about 4 months. The steep drop may be an artifact [sic] of the clinical trial design for Study CA209141, whereby the first

assessment of disease progression was conducted 8 weeks after randomisation. However, it is also possible that these curves represent an underlying clinical process such as a delayed effect on PFS for nivolumab". This reason was plausible, although this could also be the result of a subset of patients who respond better to nivolumab.

6.14 Subgroup analyses found that the OS HR was more favourable when nivolumab was compared to cetuximab, than to methotrexate or docetaxel:

- nivolumab vs. cetuximab: [REDACTED]

- nivolumab vs. methotrexate: [REDACTED]

- nivolumab vs. docetaxel: [REDACTED]

However, this analysis was not pre-specified in the trial protocol.

6.15 Pre-specified subgroup analyses also found that patients with PD-L1 tumour expression $\geq 1\%$ experienced a greater gain in OS:

- PD-L1 expression $\geq 1\%$: [REDACTED]

- PD-L1 expression $< 1\%$: [REDACTED]

6.16 The PSCR (p2) stated that the results of subgroup analyses based on nivolumab versus individual IC agents should be interpreted with caution due to the small sample sizes treated with each individual agent (docetaxel n=[REDACTED]; methotrexate n=[REDACTED]; cetuximab n=[REDACTED]) and may be at risk of selection bias for patient characteristics. The ESC acknowledged that the analyses could have been confounded by potential selection bias in the individual IC subgroups; however, the ESC considered that the applicability of the results to the Australian setting remained uncertain. In particular, the ESC advised that it was unclear whether the removal of cetuximab and the addition of capecitabine as a comparator would affect the incremental effectiveness of nivolumab. The pre-PBAC response (p1) reiterated that SOC in Australia for treating this condition is varied, and therefore the treatments in the study's comparator arm were representative of the results expected with SOC in Australia.

6.17 The p-value for the interaction term ([REDACTED]) suggests a possible predictive relationship between PD-L1 expression and OS considering the trial was not powered to detect such an interaction.

6.18 The median gain in OS was [REDACTED] months for patients with PD-L1 expression $\geq 1\%$, compared to [REDACTED] months in patients with PD-L1 expression $< 1\%$.

Comparative harms

6.19 Table 5 presents an overview of the all cause AEs, drug related AEs and deaths in Trial CA209141.

Table 5: Summary of key AEs in the direct randomised trial

	Nivolumab n with event/N (%)	IC n with event/N (%)	RR (95% CI)	RD (95% CI)
All cause				
AEs	██████████	██████████	██████████	██████████
Grade 3-4 AEs	██████████	██████████	██████████	██████████
SAEs	██████████	██████████	██████████	██████████
Grade 3-4 SAEs	██████████	██████████	██████████	██████████
AEs leading to discontinuation	██████████	██████████	██████████	██████████
Drug related				
AEs	██████████	██████████	██████████	██████████
Grade 3-4 AEs	██████████	██████████	██████████	██████████
SAEs	██████████	██████████	██████████	██████████
Grade 3-4 SAEs	██████████	██████████	██████████	██████████
AEs leading to discontinuation	██████████	██████████	██████████	██████████
Deaths				
Overall	██████████	██████████	██████████	██████████
Within 30 days of last dose	██████████	██████████	██████████	██████████
Within 100 days of last dose	██████████	██████████	██████████	██████████

AE: adverse event; CI: confidence interval; IC: investigator's choice of therapy; RD: risk difference, RR: relative risk; SAE: serious adverse event.

Source: Table 30, pp.68-69 of the submission

Benefits and harms

6.20 A summary of the comparative benefits and harms for nivolumab versus investigator's choice of therapy is presented in the table below.

Table 6: Summary of comparative benefits and harms for nivolumab and investigator's choice of therapy

Benefits						
Outcome	Nivolumab	IC	RD	HR (95% CI)		
Alive at 12 months, n (%)	██████	██████	████	████████████████████		
Harms						
Outcome	Nivolumab	IC	RR (95% CI)	Events/100 patients*		RD (95% CI)
				Nivolumab	IC	
Drug related grade≥3 AEs	██████	██████	██████████	████	████	██████████
Drug related SAEs	██████	██████	██████████	████	████	██████████

* Median duration of follow-up was █████ months with nivolumab and █████ months with IC.

a The time between the date of randomisation and the first date of documented progression, as determined by the investigator (as per RECIST 1.1 criteria), or death due to any cause, whichever occurs first. Censoring rules:

Patients who did not progress or die were censored on date of last evaluable tumour assessment

Patients who did not have any on study tumour assessments and did not die will be censored on their date of randomisation

Patients who receive subsequent systemic anti-cancer therapy prior to documented progression will be censored at the date of the last tumour assessment prior to the initiation of the new therapy

b The time between the date of randomisation and the first date of documented progression, as determined by the investigator (as per RECIST 1.1 criteria), or death due to any cause, whichever occurs first. Censoring rules:

Patients who did not progress or die were censored on date of last evaluable tumour assessment

Patients who did not have any on study tumour assessments and did not die will be censored on their date of randomisation

AE: adverse events; HR: hazard ratio; IC: investigator's choice of therapy; NR: not reported; RD: risk difference; RR: risk ratio; SAE: serious adverse event.

Source: Table 23 p58 and Table 25 p60 of the submission, Attachment 13 – Study CA209141 CSR addendum, Table s.5.2 p116 and Table s.5.12 p123, and Compiled during the evaluation

6.21 On the basis of direct evidence presented by the submission, for every 100 patients treated with nivolumab in comparison to investigator's choice of therapy:

- approximately 14 additional patients would be alive at 12 months
- approximately 21 fewer patients would experience a drug-related grade≥3 adverse event
- approximately 8 fewer patients would experience a drug-related serious adverse event.

Interpretation of clinical evidence

6.22 The submission claimed that nivolumab is superior in terms of effectiveness and favourable in terms of safety compared with single agent SOC in the treatment of patients with recurrent and metastatic SCCHN who have progressed within six months of receiving platinum based chemotherapy.

6.23 The clinical claim of superior effectiveness was adequately supported. However, the following issues were raised in relation to this claim:

- The OS gain in the ITT population was statistically significant, although the magnitude of benefit was small (median survival gain of █████ months). The OS gain was similar in magnitude to that previously considered by the PBAC with regards to cetuximab for the treatment of RM SCCHN.⁶ However, the ESC noted that the cetuximab submission previously considered by PBAC was for the treatment of previously untreated RM SCCHN, not after progression on platinum based chemotherapy. The gain in PFS was not statistically significant in either

⁶ PBAC (2016) Public summary document: CETUXIMAB, solution for intravenous (IV) infusion, 100 mg in 20 mL & 500 mg in 100 mL, Erbitux, Merck Serono Australia Pty Ltd.

the primary and secondary definitions. The PSCR (p2) claimed that the observation of long term survival benefit from nivolumab, despite the lack of overall differences in RECIST defined PFS, was consistent with the hypothesis of sustained immunological disease control in a subset of patients who respond to nivolumab.

- The comparators differed between those included in the investigator's choice of therapy arm of Trial CA209141, and SOC in the Australian setting. Subgroup analysis found that the HR for OS was more favourable when nivolumab was compared to cetuximab, than to methotrexate or docetaxel. However, the ESC noted that these subgroup analyses were not pre-specified. Notwithstanding the PSCR's arguments (see paragraph 6.16), the ESC maintained that it was unclear whether the removal of cetuximab and the addition of capecitabine as a comparator would affect the incremental effectiveness of nivolumab.
- Pre-specified exploratory subgroup analyses found that patients with PD-L1 tumour expression $\geq 1\%$ experienced a greater gain in OS. The median gain in OS was [REDACTED] for patients with PD-L1 expression $\geq 1\%$, compared to [REDACTED] in patients with PD-L1 expression $< 1\%$. Although these subgroup analyses suggest that nivolumab may be more effective and more cost-effective for patients with tumour PD-L1 expression $\geq 1\%$, both MSAC and PBAC have previously raised several concerns regarding test accuracy in the context of integrated co-dependent submissions for pembrolizumab (another anti-PD-1 monoclonal antibody) for treatment naïve, locally advanced NSCLC patients (see paragraph 3.4). The ESC considered that the role of PD-L1-based histological stratification of subgroups remained unclear, for reasons discussed earlier (see paragraph 3.4).

6.24 Overall, the ESC considered that the submission's claim of superior effectiveness over SOC was reasonable. However, the ESC advised that the extent of incremental benefit of nivolumab treatment was marginal, and was further confounded by the use of cetuximab, instead of capecitabine, in the IC arm of the analysis.

6.25 The ESC considered that the submission's claim of favourable safety, implying superiority over SOC, was adequately supported by the evidence presented in the submission.

6.26 The PBAC accepted that nivolumab treatment resulted in modest clinical benefit, and the magnitude of incremental benefit in Australian clinical practice was confounded by the disparity in comparator choice.

6.27 The PBAC noted that nivolumab treatment resulted in fewer drug-related AEs, but there was minimal difference in all-cause AEs. On balance, the PBAC considered that a conclusion of superior safety over SOC was reasonable.

Economic analysis

6.28 The submission conducted cost-effectiveness (cost per life year gained) and cost-utility (cost per QALY gained) analyses comparing nivolumab to current SOC for the treatment of patients with recurrent or metastatic SCCHN.

6.29 A summary of the model structure is presented in the table below.

Table 7: Summary of model structure and rationale

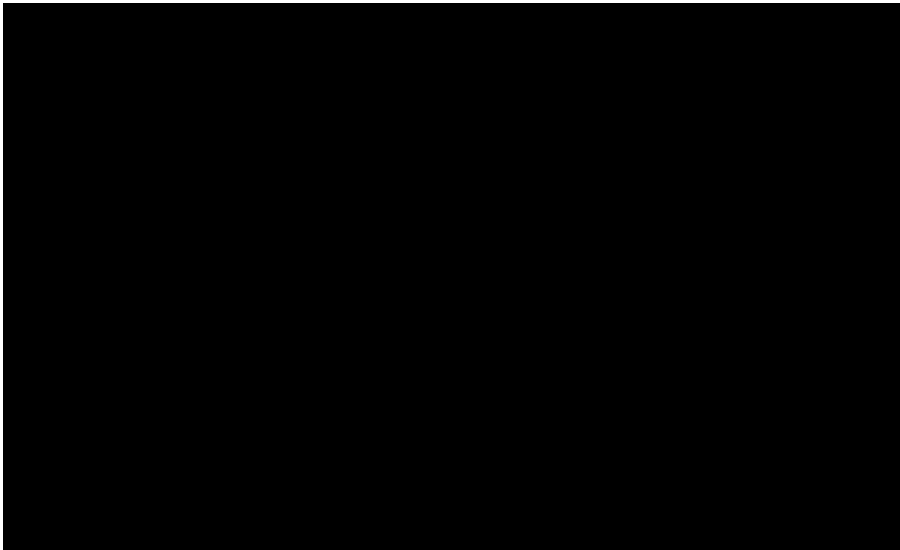
Component	Summary
Time horizon	[REDACTED]
Outcomes	PFS, OS, QALYs and Lys
Methods used to generate results	Partitioned survival model
Health states	'Alive Without Progression' 'Alive Following Progression' Dead
Utilities	<p>Mean utilities were estimated for the health states of 'Alive Without Progression' and 'Alive Following Progression' using the EQ-5D-3L questionnaire in Trial CA209141. Responses to the EQ-5D-3L were converted to EQ-5D utility values using the Australian-specific scoring algorithm published by Viney et al. (2011).</p> <p>The submission did not provide any patient level data or STATA code/output to verify the utility values.</p> <p>The submission did not report how the results were adjusted for differences in utility values across the treatment arms at baseline, or questionnaires that had missing domain scores or were missing in their entirety.</p> <p>It is not known how many observations were used to estimate the utility value in the 'Alive Following Progression' health state, and whether these were driven by one or two end of treatment follow-up visits. It is possible that the utility value for the 'Alive Following Progression' health state is over-estimated.</p> <p>The results may be subject to bias as Trial CA209141 was an open-label trial.</p> <p>It is questionable whether there should be any ongoing difference in the utility values post-progression if the AEs are short-term.</p> <p>The utilities derived from patient level data pick up the impact on AEs, however this does not reflect what would be experienced in clinical practice due to a difference in chemotherapies in Trial CA209141 and medicines typically used in Australian practice. It is not clear whether this bias favours the investigator's choice of therapy or nivolumab arms.</p>
Cycle length	3 weeks
Survival rates	<p>Investigator assessed PFS and OS rates were used to quantify the proportions of patients in the 'Alive Without Progression' and 'Dead' health states, respectively. The chemotherapies included in the investigator's choice of therapy (docetaxel, methotrexate or cetuximab) arm in Trial CA209141 differ from the comparator medicines used in Australian practice. The impact on the results was uncertain.</p> <p>PFS and OS data from Trial CA209141 were extrapolated to [REDACTED]. The point of extrapolation was reasonable. The log-logistic function had the best goodness-of-fit compared to other functions tested for both PFS and OS. However, the fit of the parametric functions to PFS was poor and the submission should have considered alternative approaches to extrapolating PFS. Regarding OS, there was very little difference in the AIC and BIC between the log-logistic ([REDACTED]) and exponential ([REDACTED]) functions fitted to the nivolumab arm, however the application of the log-logistic function had a substantial impact on the ICER, mainly due to the long tail.</p> <p>Treatment continuation was based on PFS in Trial CA209141 (and thus also extrapolated to [REDACTED]). Around [REDACTED] of nivolumab patients continued treatment following progression in Trial CA209141.</p> <p>Treatment costs were underestimated in the model.</p> <p>Convergence of health outcomes between the two treatment arms was modelled from the 3rd year of the base projection. This is reasonable.</p>

AE: adverse event; IC: investigator's choice of therapy; LY: life year; OS: overall survival; OR: overall response; PFS: progression-free survival; QALY: quality adjusted life year; SD: stable disease.

Source: Table 39, p93 of the submission

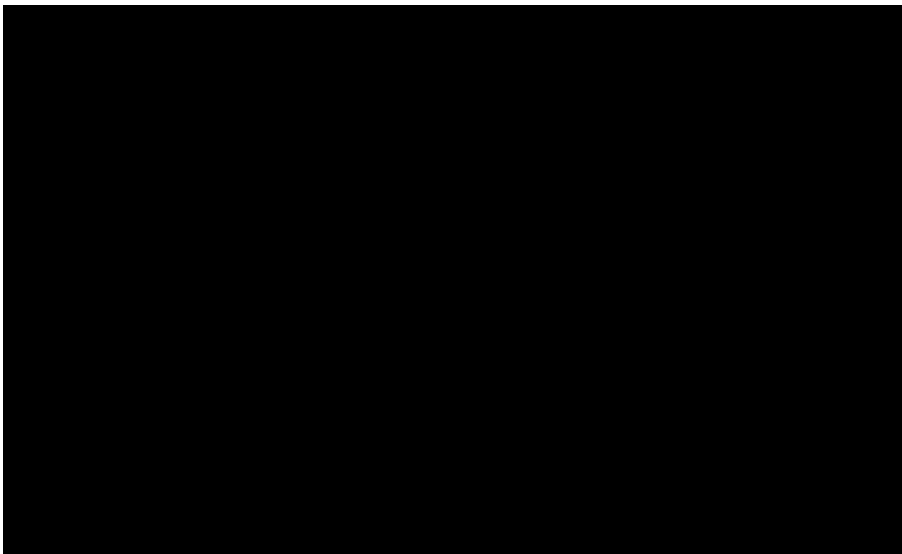
6.30 Figures 4 to 7 present the extrapolation of PFS and OS in the model using different parametric functions.

Figure 4: Extrapolation of PFS in the nivolumab arm using different parametric functions (base case = log-logistic)



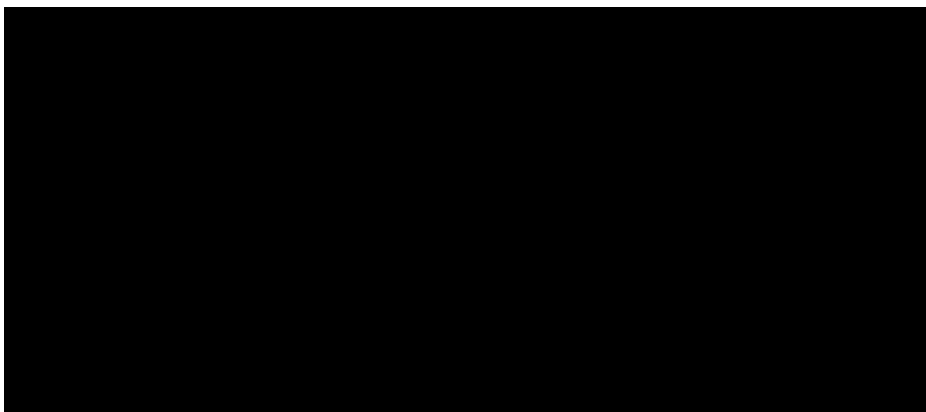
PFS: progression-free survival; IC: investigator's choice of therapy.
Source: App_1_nivo SCCHN economic evaluation.xlsx. The observed curve was added by the Evaluator using data in the Excel workbook.

Figure 5: Extrapolation of PFS in the IC arm using different parametric functions (base case = log logistic)



PFS: progression-free survival; IC: investigator's choice of therapy.
Source: App_1_nivo SCCHN economic evaluation.xlsx. The observed curve was added by the Evaluator using data in the Excel workbook.

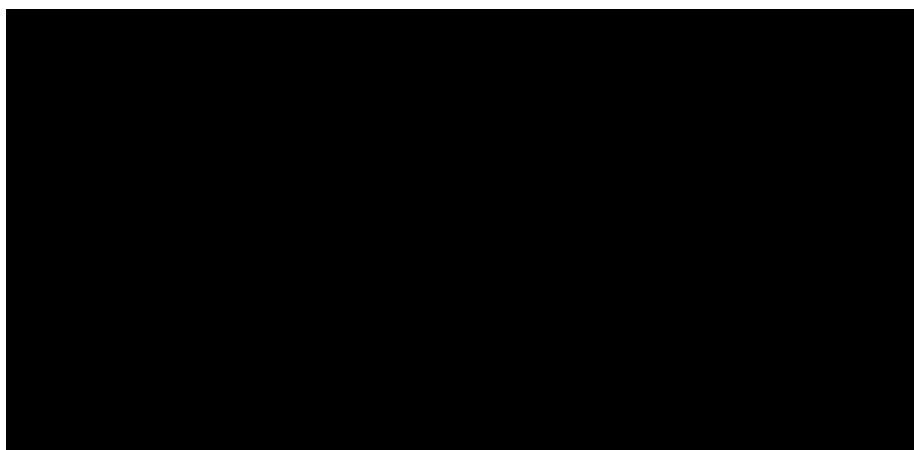
Figure 6: Extrapolation of OS in the nivolumab arm of Trial CA209141 using different parametric function (base case = log logistic)



OS: overall survival; IC: investigator's choice of therapy.

Source: App_1_nivo SCCHN economic evaluation.xlsx. The observed curve was added by the Evaluator using data in the Excel workbook.

Figure 7: Extrapolation of OS in the IC arm of Trial CA209141 using different parametric functions (base case = log logistic)



OS: overall survival; IC: investigator's choice of therapy.

Source: App_1_nivo SCCHN economic evaluation.xlsx. The observed curve was added by the Evaluator using data in the Excel workbook.

6.31 A summary of the key drivers of the model is presented in the table below.

Table 8: Key drivers of the model

Description	Method/Value	Impact
Use of PFS for treatment duration	Around [REDACTED] of nivolumab patients continued treatment following progression in Trial CA209141. Treatment costs were underestimated in the model. Duration of treatment is not truncated in the base case.	High. Favours nivolumab.
Log-logistic model used for extrapolation of OS	[REDACTED]	High. Favours nivolumab
Utilities applied Following progression	Utilities were based on CA209141. It is questionable whether there should be any ongoing difference in the utility values in the 'Alive Following Progression' health state if the AEs are short-term.	Moderate. Favours nivolumab
Costs for subsequent therapies	Costs associated with subsequent therapies were not included in the economic model. Even though patients in each arm are on a similar balance of therapies, they are on the therapies for a longer period on the nivolumab arm due to improved survival.	Likely to favour nivolumab.

AE: adverse event; PFS: progression-free survival.

Source: compiled during the evaluation (reference sections/tables/spreadsheets within the submission)

6.32 The results of the economic evaluation are presented in the table below.

Table 9: Results of the stepped economic evaluation

Step and component	Nivolumab	IC	Increment
Step 1: Cost per life year gained over the Trial CA209141 trial period (approximately 24 months) was estimated.			
Costs	[REDACTED]	[REDACTED]	[REDACTED]
LYG	[REDACTED]	[REDACTED]	[REDACTED]
Incremental cost/extra LYG gained			[REDACTED]
Step 2: Trial period data was transformed by QALYs (clinical outcome) and cost per QALY estimated over the trial period			
Costs	[REDACTED]	[REDACTED]	[REDACTED]
QALYs	[REDACTED]	[REDACTED]	[REDACTED]
Incremental cost/extra QALYs gained			[REDACTED]
Step 3: Trial CA209141 outcomes were transformed to QALYs and extrapolated to a [REDACTED]-year horizon			
Costs	[REDACTED]	[REDACTED]	[REDACTED]
QALYs	[REDACTED]	[REDACTED]	[REDACTED]
Incremental cost/extra QALYs gained			[REDACTED]
Step 4: Trial CA209141 results were transformed and extrapolated over a [REDACTED]-year horizon, with convergence included in extrapolations from 3 years			
Costs	[REDACTED]	[REDACTED]	[REDACTED]
QALYs	[REDACTED]	[REDACTED]	[REDACTED]
Incremental cost/extra QALYs gained			[REDACTED]

LY: life years; QALYs: quality adjusted life years. IC: investigator's choice of therapy; ICER: incremental cost-effectiveness ratio.

Source: Table 67 p139 of the submission

6.33 The economic evaluation presented in the submission should be considered with caution. The following issues were identified during the evaluation:

- The ESC noted that no evidence was provided regarding the impact of the differences in the comparators used to estimate the incremental benefit with nivolumab over the SOC in Australian practice. In particular, no evidence was provided on the comparative effectiveness of cetuximab and capecitabine. Although the PSCR (p4) argued that all of the drugs included in the IC arm were equally ineffective, the ESC noted that sensitivity analysis was not conducted on the impact of applying the costs of the drugs included in the IC arm (docetaxel, methotrexate, or cetuximab). Consequently, the ESC advised that impact of any differences on the cost-effectiveness of nivolumab was uncertain.
- The fit of the parametric functions to PFS was poor and the submission should have considered other, more flexible approaches to extrapolating PFS (e.g. generalised gamma, generalised F, and spline-based functions). The impacts on the results are uncertain.
- The log-logistic function was used to extrapolate OS. The PSCR (p3) contended that the application of the log-logistic model to extrapolate OS was appropriate, arguing that the mathematical properties of the log-logistic distribution matches the underlying scientific assumptions of immunotherapy agents, as it allows a clinically plausible plateau in survival. The ESC considered that fitting log-logistic model to the OS curves was the least conservative choice in this instance. Further, the ESC considered that, although the Weibull method was the most conservative choice, it was not a good fit. As such, the ESC advised that exponential curves would have been the most appropriate method of extrapolation.
- Treatment duration was based on PFS. However, around [REDACTED] of nivolumab patients continued treatment following progression in Trial CA209141. The PSCR (p3) argued that it was reasonable to use PFS to estimate the duration of treatment, noting that the PBAC had considered the use of PFS to inform costs twice in the past for nivolumab (paragraph 7.5, nivolumab PSD, July 2016 and paragraph 6.39, nivolumab PSD for RCC, March 2017). The ESC considered that, as [REDACTED] of nivolumab patients continued treatment following progression, treatment costs were underestimated in the model, and these had a substantial impact on the ICER.
- The utility estimates were unable to be verified. It was unclear whether there should be any ongoing difference in the utility values of the 'Alive Following Progression' health state if the AEs are short-term (these utilities may also be overestimated if they were based on a single end-of-treatment visit). It was also unclear whether the utilities for the comparator in the 'Alive Without Progression' health state reflect the chemotherapies used in Australian clinical practice.
- Costs associated with subsequent therapies were not included in the economic model. Even though patients in each arm were on a similar balance of therapies, they underwent treatment for a longer period on the nivolumab arm due to improved survival. Consequently, treatment costs were likely to be higher in the nivolumab arm. This approach was likely to favour nivolumab.

6.34 Table 10 presents the results of the key univariate sensitivity analyses conducted by the submission and during the evaluation.

Table 10: Results of scenario and univariate sensitivity analyses

Variable	Base case	Sensitivity analysis		Cost/LY	Cost/QALY
Base case					
Time & convergence	█; converge from █	SA.1	5 years; no convergence	█	█
		SA.2	7 years; no convergence	█	█
		SA.3	10 years; no convergence	█	█
		SA.4	10 years; converge from 3 yrs	█	█
Parametric function	Log-logistic PFS and OS	SA.5	Exponential PFS and OS	█	█
			Weibull PFS and OS	█	█
			Exponential OS	█	█
			Weibull OS	█	█
			Exponential PFS	█	█
Kaplan-Meier estimates	Median time to follow-up		Weibull PFS	█	█
		SA.6	Full extrapolation	█	█
		SA.7	No extrapolation (within trial analysis)	█	█
			End Kaplan-Meier data	█	█
Utilities	CA209141 per arm		Minimum follow-up OS	█	█
		SA.8	Overall results – average used for both arms	█	█
			Same utilities for 'Following Progression' applied in each arm (e.g. 0.696)	█	█
Weight	█		Same utilities for 'Following Progression' applied in each arm (e.g. █) and – █%	█	█
		SA.9		█	█
Maximum DOT	Modelled DOT	SA.10		█	█
			Modelled nivolumab PFS DOT + █ ^a	█	█
		SA.11	Modelled nivolumab OS used as proxy	█	█
Multivariate analysis	Exponential OS curves, equal utilities post-progression, and modelled nivolumab PFS DOT + █ ^a		█	█	

PFS: progression-free survival; OS overall survival; DOT: duration of therapy.

^a Increased cost of nivolumab to proxy the proportion of patients in CA209141 who progressed and remained on treatment.

Source: Table 74, p. 145 of the submission

The redacted table shows ICERs in the range of \$45,000/QALY - \$200,000/QALY.

6.35 Overall, the ICER was most sensitive to whether extrapolation was included, the modelling approach used to extrapolate OS and the inclusion of additional nivolumab costs on the treatment arm to reflect the higher proportion of patients that received treatment in Trial CA209141 than that reflected using the PFS. In addition, applying the same utility in both treatment arms in the 'Alive Following Progression' health state increased the ICER.

6.36 The ICER increased to \$105,000/QALY - \$200,000/QALY gained when a within trial analysis was conducted.

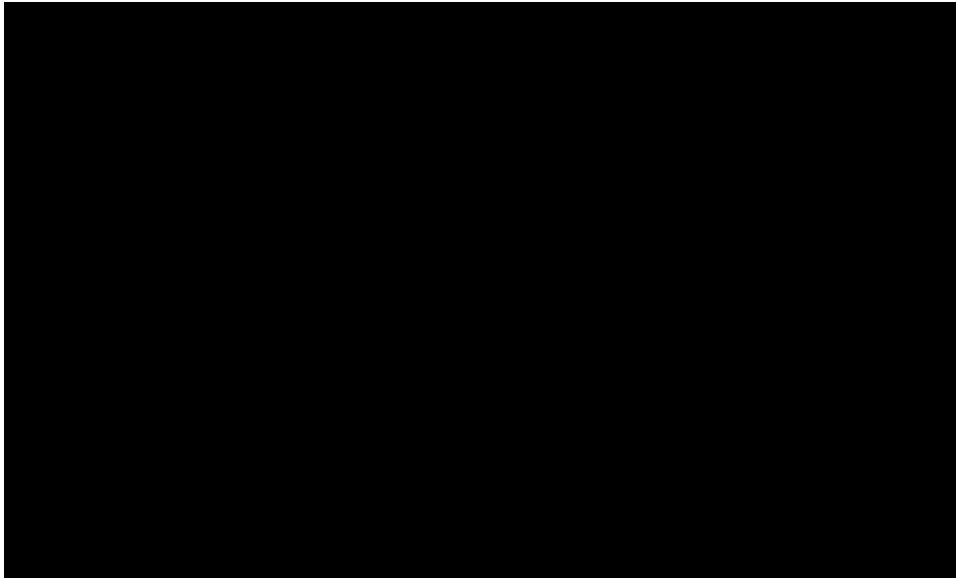
6.37 The selection of extrapolation function for OS had a large impact on ICER. There was very little difference in the AIC and BIC between the log-logistic and exponential functions fitted to OS in the nivolumab arm. Applying an exponential function to OS, instead of a log-logistic function, increased the ICER to \$105,000/QALY - \$200,000/QALY gained.

6.38 Figure 8 presents the ICERs for Weibull, exponential and log-logistic (OS and PFS) extrapolations by month of follow-up, along with the ICER for the within-trial analysis.

The ICERs for the projections stabilise at around 35-40 months, which was outside the follow-up for observed data in Trial CA209141 (around 24 months). The ICER for the observed data was between the log-logistic and exponential functions, reflecting the small difference in the goodness-of-fit for these functions.

- 6.39 The results were not sensitive to the selection of extrapolation function for PFS, however only a limited range of functions were explored and all functions fitted poorly.

Figure 8: ICERs for different time frames (0-84 months) and extrapolation functions



Source: Excel model and analyses undertaken by evaluator

- 6.40 The ESC noted that a multivariate sensitivity analysis (i) applying an exponential model to extrapolate OS, (ii) equal utility values post-progression (██████), and (iii) nivolumab treatment duration increased by ██████ (i.e. PFS DOT + ██████) resulted in an ICER of \$105,000/QALY - \$200,000/QALY, compared to the base case of \$75,000/QALY - \$105,000/QALY presented in the submission. The ESC therefore advised that, assuming all other model inputs remained the same, \$105,000/QALY - \$200,000/QALY would be the more realistic ICER. The pre-PBAC response (p2) disagreed with the use of the log-logistic method of extrapolation and application of the same utility values post progression, arguing that this was against precedents set in previous nivolumab considerations for second-line NSCLC (March 2016, November 2016 and March 2017 PBAC meetings) and RCC (July 2016, November 2016 and March 2017 PBAC meetings). The pre-PBAC response (p2) then claimed that assuming all other model inputs remaining the same, a reduced ██████ (i.e. PFS DOT + ██████) increase in nivolumab treatment duration would be addressed by a reduced requested price of \$ ██████ per 100 mg vial (which represented a ██████% price reduction) to result in an ICER that was identical to the base case presented in the submission (\$75,000/QALY - \$105,000/QALY). The pre-PBAC response (p2) stated that this estimate of ██████ was “based on the mean additional infusions received per patient treated beyond progression”, but this was not independently verified, including whether this was an underestimate due to truncated follow-up.

Drug cost/patient/course: \$ [REDACTED]

6.41 The submission assumed a cost of \$ [REDACTED] per infusion and patients would receive [REDACTED] infusions of nivolumab, based on the mean number of doses received by patients in the nivolumab arm of Trial CA209141. The mean duration of therapy in Australian practice may be underestimated as [REDACTED]% of patients treated with nivolumab were still being treated at data cut-off. The PBAC noted that these costs were revised, but not independently verified, after a [REDACTED]% price reduction was proposed in the pre-PBAC response (p2).

Estimated PBS usage & financial implications

6.42 The submission took an epidemiological approach to develop its financial estimates. The submission included patients who progressed after 6 months of platinum-based therapy and those subsequently rechallenged with platinum-based therapy.

Table 11: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of patients treated	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Number of scripts dispensed / infusions ^a	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Estimated financial implications of nivolumab						
Cost to PBS/RPBS	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Copayments	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Cost to PBS/RPBS less copayments	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Estimated financial implications for other PBS-listed drug						
Cost to PBS/RPBS	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Copayments	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Cost to PBS/RPBS less copayments	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Net financial implications						
Net cost to PBS/RPBS	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Net cost to MBS	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Net cost to PBS/RPBS/MBS/DHS	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

^a Assuming [REDACTED] infusions per year as estimated by the submission.

Source: Table 77, p153; Table 78, p154; and Table 79, p155, Table 81 p15, Table 82 p159, Table 85, p162 of the submission, and App_2_nivo SCCHN BIM.xlsx

The redacted table shows that at year 5, the estimated number of patients was less than 10,000 and the net cost to the PBS would be \$30 - \$60 million.

- 6.43 The PBAC noted that revised financial estimates were provided along with the pre-PBAC response accounting for the [REDACTED] % price reduction offered; however, these estimates were not independently verified (see paragraph 6.40).
- 6.44 The DUSC considered that many assumptions in the utilisation estimates, including nivolumab uptake rates of [REDACTED] % of patients following PBS listing, were based on expert opinion provided by the sponsor-appointed, six member clinical advisory panel. The submission did not indicate how this six member clinical advisory panel was selected, nor was it noted whether any member had a conflict of interest. The DUSC noted that the PSCR (p5) stated that the financial estimates provide a robust estimate for the number of patients likely to be treated with nivolumab for this patient population, and noted that the sponsor is committed to working with the PBAC to address any financial uncertainties associated with listing nivolumab on the PBS for the treatment of SCCHN.
- 6.45 The DUSC considered that it was unclear if the projected eligible population accounted for the proposed PBS restriction for patients to have an ECOG performance status of 0 or 1. The DUSC considered that if only patients with ECOG performance statuses of 0 or 1 were included, the estimated cost would decrease by [REDACTED] % (i.e. based on the sponsor's estimate of [REDACTED] % of patients with an ECOG performance status of 2 in the Australian setting presented in the submission).
- 6.46 The submission estimated that [REDACTED] % of patients who progressed after more than six months would be retreated with platinum doublet chemotherapy. The DUSC considered that many patients would not be routinely rechallenged with platinum chemotherapy, and considered this proportion was overestimated.
- 6.47 The submission estimated that [REDACTED] % of patients who progressed within six months would be treated with nivolumab. The submission also estimated [REDACTED] % of patients who progressed after more than six months and were rechallenged with platinum chemotherapy, would then be treated with nivolumab. These estimates were based on advice from the sponsor-appointed clinical advisory panel. The DUSC considered that these rates were overestimated, and noted that if only the proportion of patients with ECOG 0 or 1 was included, this uptake may be still overestimated. The pre-PBAC response (p3) argued that it was reasonable to assume that uptake rate would be high with a new standard of care in this difficult to treat patient population.
- 6.48 The submission assumed that patients would receive [REDACTED] infusions of nivolumab, based on the mean number of doses received by patients in the nivolumab arm of Trial CA209141. The DUSC considered that the assumption of [REDACTED] infusions of nivolumab may underestimate use if there is a high rate of post-progression treatment. The pre-PBAC response (p3) stated that, in accepting the application of additional nivolumab costs to account for treatment beyond progression by applying modelled nivolumab PFS plus [REDACTED] % to the base case (see paragraph 6.40), the sponsor concurrently accepted an increase in mean duration of treatment from [REDACTED] infusions to [REDACTED] infusions per patient.
- 6.49 The submission assumed that patients would weigh [REDACTED] kg and have a height of [REDACTED] cm, based on Trial CA209141. The DUSC considered that the patient weights in the clinical study seemed lower than expected for the Australian setting, noting that the

average 55-64 year old Australian weighs 89.2 kg⁷. The DUSC considered that although weight loss is common in patients with this condition, weight loss would be minimal in patients with ECOG of 0 or 1. The DUSC considered that, in practice, patients are likely to weigh 10% more than estimated in the submission. The pre-PBAC response (p3) maintained that in the absence of Australian data specific to SCCHN patients, it was appropriate to use the mean patient weight from study CA209141 to inform mean dose per patient.

- 6.50 The DUSC advised that a large proportion of patients with stage IV (metastatic) head and neck cancer will have an ECOG status greater than 1, and will therefore have significant functional impairment. The DUSC therefore considered that there is a high risk of nivolumab use beyond the PBS restriction to treat these patients.

Quality use of medicines

- 6.51 The submission proposed that the sponsor would provide continued support and education to practitioners and patients who have not used nivolumab, through an education, information and adverse effect awareness program.

Financial management – risk sharing arrangements

- 6.52 The submission indicated that the sponsor would be willing to consider addressing residual uncertainty identified by the PBAC through a risk-sharing arrangement; however, details of a risk-sharing arrangement were not proposed. A risk-sharing arrangement to address the uncertainty due to the duration of nivolumab therapy could be considered.

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

7 PBAC outcome

- 7.1 The PBAC decided not to recommend the Section 100 (Efficient Funding of Chemotherapy - Public and Private Hospital) Authority Required (STREAMLINED) listing of nivolumab for the treatment of SCCHN. The PBAC advised that there was uncertainty in the nature and magnitude of its incremental clinical benefit in Australian clinical practice, and a high and overoptimistic estimated incremental cost effectiveness ratio at the price proposed by the submission.
- 7.2 Consistent with the clinical evidence presented in the submission and advice received from DUSC (see paragraph 3.2), the PBAC advised that the "PBS indication" component of any PBS restriction should exclude the nasopharyngeal subgroup of SCCHN. The PBAC advised that all remaining aspects of the proposed restriction were appropriate and consistent with the current listing of nivolumab for unresectable Stage III or Stage IV malignant melanoma, NSCLC, and RCC.
- 7.3 The PBAC considered that the proposed place of nivolumab in clinical therapy was appropriate, and advised that subsidised access to nivolumab should not be made conditional on PD-L1 expression status, consistent with the current PBS listing of

⁷ ABS statistics. Accessed at: <http://www.abs.gov.au/ausstats/abs@.nsf/Lookup/4338.0main+features212011-13>

nivolumab for unresectable Stage III or Stage IV malignant melanoma, NSCLC, and RCC.

- 7.4 The PBAC noted that the comparators differed between those included in the investigator's choice of therapy arm of Trial CA209141 (docetaxel, methotrexate, or cetuximab) and SOC in the Australian setting (paclitaxel, docetaxel, methotrexate, or capecitabine). Although the PSCR (p2) and pre-PBAC response (p1) argued that SOC in Australia for treating this condition is varied, and therefore the treatments in the study's comparator arm were representative of the results expected with SOC in Australia, the PBAC agreed with ESC, and advised that the applicability of the results to the Australian setting remained uncertain. The PBAC remained particularly uncertain about the consequence of replacing cetuximab with capecitabine as a comparator on the incremental effectiveness of nivolumab.
- 7.5 The PBAC noted that the submission was based on a direct randomised trial comparing nivolumab to investigator's choice of a single agent therapy consisting of either docetaxel or methotrexate or cetuximab (n=361) (Trial CA209141), with OS as the primary outcome, and ORR and PFS as secondary outcomes. The PBAC noted that the trial demonstrated a [REDACTED] month improvement in median OS, with a median duration of follow-up of [REDACTED] months in a relatively mature dataset of more than [REDACTED]% survival events. The PBAC also noted that there was no statistically significant difference in PFS, which the Committee considered was unusual as PFS is widely advocated as an informative predictor of OS outcomes across a wide range of cancers and their treatment options. The PBAC considered that there was (i) a moderate risk of bias due to the study being open-label, potentially affecting the secondary ORR and PFS outcomes; (ii) a potential bias against detecting an incremental nivolumab effect on OS as [REDACTED]% of patients in the IC arm received subsequent therapy with an anti-PD-1 pathway agent; and (iii) uncertainty in the applicability of the OS results to a proposed PBS restriction to cease nivolumab following progression, as [REDACTED]% patients in the nivolumab arm were treated beyond progression.
- 7.6 The PBAC was concerned that the results of a subgroup analysis showed that OS HR ([REDACTED] (95% CI: [REDACTED])) was more favourable when nivolumab was compared to cetuximab, than to methotrexate or docetaxel, noting that this disparity in comparators contributed to uncertainty in estimating the magnitude of incremental clinical benefit derived with nivolumab in the Australian clinical setting.
- 7.7 The PBAC was also concerned regarding the likely reduced effectiveness of nivolumab in the older patient population (>75 years). The PBAC noted that the median age in the trial was 60 years, with [REDACTED]% of patients below the age of 65 years and only [REDACTED]% over the age of 75 years. The PBAC recalled that this concern was first raised with the reduced effectiveness of nivolumab in the older patient population (>75 years) in its NSCLC submissions (nivolumab PSDs, March 2016, November 2016 and March 2017 PBAC meetings).
- 7.8 The PBAC acknowledged that SCCHN is a particularly debilitating malignancy, and noted that there was a trend to slower deterioration in global health (as a surrogate

- for overall quality of life) after starting nivolumab compared to investigator's choice of chemotherapy treatment in Trial CA209141⁸.
- 7.9 Overall, the PBAC accepted that nivolumab treatment resulted in modest clinical benefit, but estimating the magnitude of incremental benefit in Australian clinical practice from Trial CA209141 was confounded.
- 7.10 The PBAC noted that nivolumab treatment resulted in lesser drug-related AEs but there was minimal difference in all-cause AEs. On balance, the PBAC considered that a conclusion of superior safety over SOC was reasonable.
- 7.11 The PBAC noted that the submission presented a partitioned survival model with a [REDACTED]-year time horizon to estimate the cost-effectiveness of nivolumab. The PBAC considered that a number of key drivers in the economic model favoured nivolumab. These included (i) use of a log-logistic model to extrapolate OS; (ii) application of different utility values across the model's arms for the post-progression health state; (iii) the use of PFS to estimate treatment duration (noting that [REDACTED]% of nivolumab patients were treated beyond disease progression); and (iv) the exclusion of costs associated with subsequent therapies in the economic model.
- 7.12 The PBAC noted that a multivariate sensitivity analysis applying (i) an exponential model to extrapolate OS, (ii) equal utility values post-progression ([REDACTED]), and (iii) a [REDACTED]% (i.e. PFS DOT + [REDACTED]%) increase in nivolumab treatment duration resulted in an ICER of \$105,000/QALY - \$200,000/QALY, compared to the base case of \$75,000/QALY - \$105,000/QALY presented in the submission.
- 7.13 The PBAC also noted that, while ESC advised that this was the more realistic ICER, the pre-PBAC response (p2) and the sponsor hearing disagreed with the use of the log-logistic method of extrapolation and application of the same utility values post progression, arguing that this was against precedents set in previous nivolumab considerations for second-line NSCLC (March 2016, November 2016 and March 2017 PBAC meetings), and RCC (July 2016, November 2016 and March 2017 PBAC meetings).
- 7.14 The pre-PBAC response (p2) and the sponsor hearing then claimed that assuming all other model inputs remaining the same, an [REDACTED]% (i.e. PFS DOT + [REDACTED]%) increase in nivolumab treatment duration (compared with the [REDACTED]% increase in the sensitivity analysis) would be addressed by a reduced requested price of \$[REDACTED] per 100 mg vial (which represented a [REDACTED]% price reduction) to result in an ICER that was identical to the base case presented in the submission (\$75,000/QALY - \$105,000/QALY).
- 7.15 Although the pre-PBAC response (p2) stated that this estimate of [REDACTED]% was "based on the mean additional infusions received per patient treated beyond progression", the PBAC considered that this estimate was not independently verified, and could be an underestimate of treatment duration due to truncated follow-up.
- 7.16 The PBAC considered that the choice of the method of extrapolation of OS and of different post-progression utilities depended on the nature of the clinical evidence,

⁸ 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 Harrington, Kevin J et al. The Lancet Oncology , Volume 18 , Issue 8 , 1104 - 1115

and therefore what was deemed appropriate in one cancer setting was not necessarily predictive of other cancer settings.

7.17 The PBAC also considered that the sponsor's presentation of precedents was incomplete on several counts, as:

- The PBAC recalled that the commentary for the July 2016 submission for RCC stated that "... the utility values are significantly different between the nivolumab and everolimus treatment arms, except for the health state of clinical DP [disease progression]." Further, the PBAC recalled that, in that instance, "...utility estimates have a relatively minor impact on the final ICER." (July 2016 nivolumab (RCC) COM, page 51-52). In contrast, post-progression utility values were a key driver of the model results in this submission. Additionally, in case of the RCC submission, the PBAC relied on a statistically significant difference in PFS, which was not the case in this SCCHN submission.
- Similarly, the PBAC recalled that, for the squamous NSCLC population, "The original submission argued that it seemed implausible that patients in the nivolumab treatment arm should have a lower progressive disease utility value. Therefore, the observed utility value for progressive disease in the docetaxel treatment arm was applied to both treatment arms in the base case". Similar to the RCC model, the post-progression utilities had a minimal impact on the ICER in this case as well (November 2016 PSD, page 15, Table 8).
- The PBAC acknowledged that while the post-progression utilities were indeed different in the non-squamous NSCLC population, the difference had a modest impact on the ICER (November 2016 nivolumab commentary, pages 89 and 94).

Overall, the PBAC considered that on balance, even if a difference in post-progression utilities could be adequately supported from the trial evidence for the early stages of the SCCHN model, there is no basis to accept that this difference would be maintained until death.

7.18 The PBAC considered that the estimated financial cost to the PBS was high, and that there were significant uncertainties in the financial estimates presented in the submission, noting the concerns raised by DUSC regarding potential (i) overestimation of the eligible patient population; (ii) overestimation of the uptake rate; (iii) underestimation of the treatment duration due to risk of post-progression treatment; and (iv) underestimation of the average Australian body weight.

7.19 The PBAC acknowledged the clinical need in the proposed PBS population and advised that a future major resubmission should include:

- any further evidence that may be available to demonstrate the comparative effectiveness of nivolumab in the proposed PBS population, to compensate for the disparity in comparator choice;
- any additional quality of life data, if available, including to provide direct evidence to support an early difference in post-progression utilities between nivolumab and SOC;

- an updated economic model based on more realistic post-progression utilities in modelled arms, and either methods of extrapolation and estimates of nivolumab treatment duration which are less favourable to nivolumab, or which are based on more persuasive justifications of the log-logistic method of extrapolating OS and the █████% increase in nivolumab treatment duration for the base case of the updated economic model;
- a base case ICER of \$45,000/QALY - \$75,000/QALY, which the PBAC considered would be a relevant incremental cost-effectiveness target to account for the current context given the uncertainties from the clinical evidence in estimating the extent to which nivolumab would address the unmet clinical need in Australian patients and also in the economic model;
- amended utilisation estimates addressing the concerns raised by DUSC; and
- a proposal for a risk-share agreement with 100% rebate beyond the agreed subsidisation caps to mitigate the uncertainties raised by DUSC, including the risk of nivolumab use beyond disease progression.

7.20 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

The sponsor is committed to working with the PBAC to ensure the earliest possible PBS listing of nivolumab for all eligible SCCHN patients, who have progressed within 6 months after platinum based chemotherapy.